GUNMA UNIVERSITY

Graduate School of Medicine

Admission guidance 2018

Course of Medical Sciences

〔 Doctoral Program 〕

Gunma University Graduate School of Medicine
Institute for Molecular and Cellular Regulation, Gunma University

3-39-22 Showa-machi, Maebashi City, Gunma 371-8511, JAPAN
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Dean, Graduate School of Medicine

Gunma University Graduate School of Medicine was originally founded as Maebashi Medical College in 1943. It became Maebashi College of Medical Science in 1948, and then Gunma University School of Medicine, Faculty of Medicine in 1947. In 2003, we launched a new restructuring program, and School of Medicine was transformed to Graduate School of Medicine, Course of Medical Sciences. In addition, Sections in Gunma University Hospital, Departments in Institute for Molecular and Cellular Regulation Gunma University and Divisions in Takasaki Radiation Chemistry Research Establishment, Japan Atomic Energy Research Institute (JAERI) (presently Takasaki Advanced Radiation Research Institute, Japan Atomic Energy Agency) were incorporated in Course of Medical Sciences as Cooperative Sections.

Graduate School of Medicine is made up of 1) Course of Medical Sciences (Doctor Program) in medicine and biomedical sciences and 2) Course of Biomedical Sciences (Master Program) in biomedical sciences. We pursue the missions through a comprehensive approach to human health. We serve the scientific community in promoting biomedical sciences.

Since the establishment of Maebashi Medical College, Gunma University School of Medicine has been a center for research and education of medicine and health sciences in Japan. We have also played a central role in the health care of more than two million people in the Northern Kanto area. We have been awarded from MEXT prestigious 21st Century COE (Center of Excellence) Programs "Processing of biosignals: Receptor activation, signal transduction, functional expression and animal behaviors"(2002-2007), and "Biomedical research using accelerator technology" (2004-2009), and recently Global COE Program "Signal transduction in the regulatory system and its disorders" (2007-2012).

Gunma University is the only Japanese university that has Heavy Ion Irradiation Facility for the revolutionary cancer therapy. From the start of the first treatment in 2010, we have treated more than 1,000 cancer patients already.

Now, we have following special programs in Graduate School of Medicine: “Cultivating Global Leaders in Heavy Ion Therapeutics and Engineering”, “Asian Nuclear Medicine Graduate Program”, and “Local Are Open Innovation R&D Human Resources”.

We offer modern and comprehensive programs in medicine and biomedical sciences to pursue Doctor's and Master's degrees. Eagerly we are waiting for bright, sincere and imaginative young people to join us in our endeavor to create a center of medical and biomedical sciences for the 21st century.

Educational Policy for Course of Medical Sciences in Graduate School of Medicine, Gunma University (Doctoral Program)

Admission Policy
～The Medical Sciences course is looking for the following candidates.～

〈Aim of Our Doctoral Program〉
We aim to train students to be leaders in the medical world, who, based on the integration of Science, Ethics, and Skill, play active roles for research, education, and clinical practice.
〈Ability and Quality of Applicants〉
We consider applicants who possess academic knowledge, the ability to learn and conduct research, and who hold the following aspirations:
1. The aspiration to contribute to human and social development though research in advanced biology and medicine.
2. The aspiration to contribute to human and social development as a medical practitioner with high ethical standards and excellent clinic skills.
3. The aspiration to contribute to human and social development as an educator dedicated to the training and development of first-rate medical practitioners.
〈Selection of Candidates〉
We conduct the entrance examination for Working Member of Society in addition to General Selection to select the applicants who possess academic knowledge, the ability to learn and conduct research, and the aspirations mentioned above.
Furthermore, we have a system for enrollment in October in order to expand learning opportunities. In the entrance examination for October enrollment, applicants are evaluated by their ability in English, an interview test, and their past academic record.

Curriculum Policy
～The Medical Sciences course is doing the following education and research.～

Doctoral programs in our course of studies aim to train and develop researchers in advanced medicine and medical practitioners in possession of high ethical standards and excellent clinical skills. As such, our programs are designed specifically to meet the following learning objectives:
1. Programs to master systematically basic knowledge and research skills indispensable for research in advanced biology and medicine, elucidation of pathogenesis of illnesses, and development of novel therapeutic strategies.
2. Programs to acquire high ethical standards necessary for research and education in medical sciences and to experience social contribution activities.
3. Programs to learn how to plan and conduct research autonomously, how to disseminate academic achievements worldwide, and to master professional knowledge and skills required for specific fields of medicine.

Diploma Policy
～The Medical Sciences course grow the following candidates.～

We confer the degree of Doctor of Medical Sciences to candidates who have successfully fulfilled all graduation requirements and who have acquired the following abilities:
1. The ability to contribute to global and local societies by playing an important role in medical research and practices, and in the area of social welfare with high ethical standards and a sense of mission.
2. The ability to conduct advanced research and to educate researchers and practitioners in the medical sciences with wide and profound scholarly knowledge.
3. The ability to elucidate pathogenesis of illnesses and to develop novel therapeutic strategies with excellent technical skills.

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Graduate School of Medicine

Contents

Research Projects of each Major Field and Basic Policy of Graduate School Education

Department of Anatomy

(1) Staff

Professor: Hiroshi Yorifuji, M.D., Ph.D.

Associate Professor: Tohru Murakami, M.D., Ph.D.

Lecturer: Yuki Tajika, Ph.D.

Assistant Professor: Hitoshi Ueno, Ph.D.

Technicians: Mitsuaki Shikada, Yoshihiro Morimura, Harumi Matsuda

(2) Research subject

We are carrying out research on the following subjects:

1) Cytoskeletal architecture of the skeletal muscle with special reference to muscular dystrophies.
2) Investigation into the proteins that control vesicle fusion
3) Investigation into the expressions and functions of cell adhesion proteins during early development of vertebrates
4) Development of new educational systems of human anatomy

For the study of 1)-3), we use not only morphological but also molecular cell biological methods. Both of the methods can be applicable to various cells, tissues and organs. So we can offer various ways of solution to your own subjects.

(3) Participation to our laboratory

Anyone who wants to study some subject using morphological and molecular cell biological method and can pass the entrance examination will be welcomed.

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REVIEW ARTICLE

Organization of organelles and VAMP-associated vesicular transport systems in differentiating skeletal muscle cells

Yuki Tajika · Maiko Takahashi · Hitoshi Ueno · Tohru Murakami · Hiroshi Yorifuji

Received: 24 August 2014 / Accepted: 19 November 2014 / Published online: 5 December 2014

Abstract Vesicular transport plays an important role in the regulation of cellular function and differentiation of the cell, and intracellular vesicles play a role in the delivery of membrane components and in sorting membrane proteins to appropriate domains in organelles and the plasma membrane. Research on vesicular transport in differentiating cells has mostly focused on neurons and epithelial cells, and few such studies have been carried out on skeletal muscle cells. Skeletal muscle cells have specialized organelles and plasma membrane domains, including T-tubules, sarcoplasmic reticulum, neuromuscular junctions, and myotendinous junctions. The differentiation of skeletal muscle cells is achieved by multiple steps, i.e., proliferation of myoblasts, formation of myotubes by cell–cell fusion, and maturation of myotubes into myofibers. Systematic vesicular transport is expected to play a role in the maintenance and development of skeletal muscle cells. Here, we review a map of the vesicular transport system during the differentiation of skeletal muscle cells. The characteristics of organelle arrangement in myotubes are described according to morphological studies. Vesicular transport in myotubes is explained by the expression profiles of soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor proteins.

Keywords Muscle · Myoblast · Myotube · SNARE protein · VAMP

Y. Tajika (✉) · M. Takahashi · H. Ueno · T. Murakami · H. Yorifuji
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Introduction

Skeletal muscle cells are multinuclear cells with a very long cylindrical appearance, with the longest human skeletal muscle cells having a length of up to 14 cm (Paul 2001). Even the smallest human skeletal muscle cells found in the stapedius muscle are 2 mm in length, which is 100-fold longer than the average mononucleated cell (10–20 μm) (Grounds and Shavlakadze 2011). Skeletal muscle cells have contraction ability and are equipped with a specialized plasma membrane and intracellular structures, such as neuromuscular junctions, myotendinous or myo–myo junctions, myofibrils, T-system, and sarcoplasmic reticulum (SR). These specialized structures of skeletal muscle cells develop in a multiple-step process that consists of (1) the proliferation of mononuclear myoblasts, (2) the fusion of myoblasts to form multinuclear myotubes, and (3) the maturation of myotubes. Systematic vesicular transport is expected to play a role in the differentiation of skeletal muscle cells from myoblasts through to myotubes and for the maintenance of the mature skeletal muscle cells (Towler et al. 2004). However, most of the research on vesicular transport in differentiating cells has been performed on neurons and epithelial cells, and few such studies have focused on skeletal muscle cells. Here, we review recent information on the distribution of organelles and the vesicular transport system in myotubes.

Organelles in myoblasts and myotubes

In the early 1960s satellite cells were identified as resident myoblasts in adult muscular tissue (Mauro 1961), and subsequent ultrastructural studies in the 1960s and 1970s described the morphological characteristics of these

Department of Anatomy and Cell Biology

（1）Staff

Professor: Toshiyuki Matsuzaki, MD, PhD

Assoc. Prof.: Hiroshi Kogo, PhD

Assist. Prof.s: Akiko Kogo, PhD

Nobuhiko Sawai, PhD

Research Technician: Yukiko Tajika

（2）Research Projects

We are trying to reveal the physiological importance of functional proteins in the body and their relationships to diseases with the use of morphological techniques including histochemistry and molecular biology techniques. Currently we focus on the membrane water channel proteins, aquaporins. So far, thirteen aquaporin isoforms have been isolated in mammals. We analyze functional importance of each isoform detailed to understand the water metabolism and eventually we aim possible clinical applications. We especially focus on aquaporin-2 (AQP2), AQP11 and AQP5. AQP2 is localized in the kidney collecting duct cells and has an important role in urine concentration. AQP2 traffics between intracellular vesicles and surface membrane via vesicular trafficking to regulate the water permeability of surface membrane under the control of vasopressin. We are interested in the control mechanism of AQP2 trafficking by vasopressin signaling. AQP11 is also expressed in the kidney and polycystic kidneys were found in its knockout mice. We are interested in the functional role of AQP11 and the mechanisms causing polycystic kidneys. AQP5 is expressed in the salivary glands and play an important role in saliva secretion. We study the basic mechanisms of xerostomia caused by radiotherapy for head and neck cancer.

We usually use and we can teach immunofluorescence microscopy, laser confocal microscopy, immunoelectron microscopy, and molecular biology techniques.

（3）Enrollment in Graduate Course

Anybody who meets the requirements for enrollment

（4）Current Students

1 student

（5）Career Paths after Graduation

It depends on individual hope.

（6）Message from Research Supervisor

We accept students who are interested in molecules, cells, tissues, organs, and human bodies.

JSHC
Japan Society of
Histochemistry and Cytochemistry
Established 1959

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Effects of Repeated Administration of Pilocarpine and Isoproterenol on Aquaporin-5 Expression in Rat Salivary Glands

Taketo Susa[1,2], Nobuhiko Sawai[2], Takeo Aoki[2], Akiko Iizuka-Kogo[2], Hiroshi Kogo[2], Akihide Negishi[1], Satoshi Yokoo[1], Kuniaki Takata[2] and Toshiyuki Matsuzaki[2]

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Aquaporins are water channel proteins which enable rapid water movement across the plasma membrane. Aquaporin-5 (AQP5) is the major aquaporin and is expressed on the apical membrane of salivary gland acinar cells. We examined the effects of repeated administration of pilocarpine, a clinically useful stimulant for salivary fluid secretion, and isoproterenol (IPR), a stimulant for salivary protein secretion, on the abundance of AQP5 protein in rat salivary glands by immunofluorescence microscopy and semi-quantitative immunoblotting. Unexpectedly AQP5 was decreased in pilocarpine-administered salivary glands, in which fluid secretion must be highly stimulated, implying that AQP5 might not be required for fluid secretion at least in pilocarpine-administered state. The abundance of AQP5, on the other hand, was found to be significantly increased in IPR-administered submandibular and parotid glands. To address the possible mechanism of the elevation of AQP5 abundance in IPR-administered animals, changes of AQP5 level in fasting animals, in which the exocytotic events are reduced, were examined. AQP5 was found to be decreased in fasting animals as expected. These results suggested that the elevation of cAMP and/or frequent exocytotic events could increase AQP5 protein. AQP5 expression seems to be easily changed by salivary stimulants, although these changes do not always reflect the ability in salivary fluid secretion.

Key words: aquaporin-5 (AQP5), pilocarpine, isoproterenol, repeated administration, salivary gland

I. Introduction

The major components of saliva are water, ions, and proteins secreted by salivary glands. Salivary glands receive variable innervations from both the sympathetic and parasympathetic nervous system [22]. Acetylcholine released from the parasympathetic nerves acts on M_3 and M_1 muscarinic cholinergic receptors which basically evokes fluid secretion [22]. Norepinephrine released from sympathetic nerves affects both fluid secretion and salivary protein secretion via granular exocytosis through α1- and β1-adorenoreceptors, respectively [22].

Membrane water channel aquaporins provide specific pathway for transcellular water transfer in water-handling organs and tissues, such as kidney and salivary glands [11, 12, 14, 15, 29]. Aquaporin-5 (AQP5), which is predominantly found in the glandular tissues, is present in the luminal surface membrane of salivary gland acinar cells and provides a transcellular water transfer pathway for salivary fluid secretion [10, 16, 23]. There have been some studies focused on AQP5 as a possible molecular target for the treatment of xerostomia [1, 18, 28]. In the present study, we focused on the effect of two drugs, pilocarpine and isoproterenol (IPR), on AQP5 expression. Pilocarpine is a commonly used and effective medicine to treat mouth

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Department of Molecular and Cellular Neurobiology

(1) Members

Professor:	Yasuki Ishizaki, MD, PhD
Associate Professor:	Koji Shibasaki, PhD
Assistant Professors:	Masashi Kurachi, PhD Masae Naruse, PhD Hanako Yamamoto, PhD
Postdoctoral fellow:	Shouta Sugio, PhD
Graduate Student:	Hiroya Ohtaki, MD, Sho Osawa, MD (from Department of Neurosurgery)
MD-PhD Students:	Keisuke Nakano, Hiroaki Kawamichi, Saori Shimizu, and Yuki Shima

(2) Research Projects

Control of neural precursor cell survival, proliferation, and differentiation

We are studying the cells in the CNS from their birth to death. We aim at the elucidation of molecular basis for the control of proliferation, differentiation, and survival of neural precursor cells, hoping that our results will contribute to the treatment of intractable CNS diseases in the near future. We found that p27/Kip1 plays an important role in the control of cerebellar granule cell precursor proliferation. We also found that these cells can differentiate into astroglial cells at least *in vitro*. Furthermore, we recently identified CD44-positive cells as astrocyte precursor cells and succeeded in purifying these cells from developing mouse cerebellum. We also found that BMPs act as survival factors for these cells.

Interaction between vascular cells and neural cells

We found that transplantation of cerebral microvascular endothelial cells ameliorates ischemic white matter damage. We are studying the interaction between vascular cells and neural cells (neurons, astrocytes, oligodendrocytes, and their precursor cells).

Mechanisms of neural circuit formation and neuronal excitability

Physiological body temperature is an important determinant for neural functions, and it is well established that changes in temperature have dynamic influences on hippocampal neural activities. We found that hippocampal neurons strongly express functional TRPV4 (activated >34°C). We found that TRPV4 is activated by physiological temperature in hippocampal neurons and thereby controls their excitability. We also revealed that endogenous TRPV2 is activated in a membrane stretch dependent manner in developing neurons, and the channel is important for axon outgrowth regulation. Currently, we are trying to develop new cures for epilepsy and injured axons through our new findings.

(3) Joining Our Lab

We welcome anyone who is interested in our research projects. We also welcome anyone who is interested in the effects of heavy ion irradiation on the central nervous system. Please don't hesitate to contact us.

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PLOS | ONE

RESEARCH ARTICLE

Extracellular Vesicles from Vascular Endothelial Cells Promote Survival, Proliferation and Motility of Oligodendrocyte Precursor Cells

Masashi Kurachi[1], **Masahiko Mikuni**[2], **Yasuki Ishizaki**[1]*

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Abstract

We previously examined the effect of brain microvascular endothelial cell (MVEC) transplantation on rat white matter infarction, and found that MVEC transplantation promoted remyelination of demyelinated axons in the infarct region and reduced apoptotic death of oligodendrocyte precursor cells (OPCs). We also found that the conditioned medium (CM) from cultured MVECs inhibited apoptosis of cultured OPCs. In this study, we examined contribution of extracellular vesicles (EVs) contained in the CM to its inhibitory effect on OPC apoptosis. Removal of EVs from the CM by ultracentrifugation reduced its inhibitory effect on OPC apoptosis. To confirm whether EVs derived from MVECs are taken up by cultured OPCs, we labeled EVs with PKH67, a fluorescent dye, and added them to OPC cultures. Many vesicular structures labeled with PKH67 were found within OPCs immediately after their addition. Next we examined the effect of MVEC-derived EVs on OPC behaviors. After 2 days in culture with EVs, there was significantly less pyknotic and more BrdU-positive OPCs when compared to control. We also examined the effect of EVs on motility of OPCs. OPCs migrated longer in the presence of EVs when compared to control. To examine whether these effects on cultured OPCs are shared by EVs from endothelial cells, we prepared EVs from conditioned media of several types of endothelial cells, and tested their effects on cultured OPCs. EVs from all types of endothelial cells we examined reduced apoptosis of OPCs and promoted their motility. Identification of the molecules contained in EVs from endothelial cells may prove helpful for establishment of effective therapies for demyelinating diseases.

Introduction

Demyelination as a result of white matter ischemia causes loss of brain functions [1,2], but there is no specific treatment so far. We previously showed that transplantation of brain microvascular endothelial cells (MVECs) greatly stimulated remyelination in the white matter infarct

Department of Biochemistry

1. Outline

Bioactive lipids are produced from membrane phospholipids upon various stimuli, and act on their specific cell-surface receptors (G-protein coupled receptor; GPCR) of neighborhood cells. They are involved in most life activity such as nervous system, respiration, circulation, reproduction, and cell differentiation. In our department, biochemical research on **phospholipid metabolism**, **lipid mediator** and **DNA-damage signal** is conducted.

2. Members

Title	Name
Professor	Takashi Izumi, M.D., Ph.D.
Associate Professor	Kazuaki Tatei, Ph.D.
	Hideru Obinata, Ph.D.
	Akimitsu Konishi, M.D., Ph.D.
Assiatant Professor	Noriyasu Ohshima, Ph.D.
	Hiraku Suzuki, D.D.S., Ph.D.

3. Research

Our research projects aim to clarify turnover of cell membrane phospholipids on various kinds of stimulation, production of bioactive lipids, signal transduction through their GPCRs, and function of these bioactive lipids, such as leukotrienes, Sphingosine-1-phosphate, and 9-HODE.

We also want to clarify the molecular mechanism that involves cellular responses caused by DNA damage in cancer, radiation, lifestyle diseases and various oxidative stresses.

4. Special Courses

We participate in following special courses of graduate School of medicine under the support of Japanese Government.

#1 Program for Cultivating Global Leaders in Heavy Ion Therapeutics and Engineering

#2 Local Area Open Innovation R&D Human Resources

We carry out our research in the close relationship with Gunma University Initiative for Advanced Research (GIAR), such as **Karolinska Open Laboratory** and **Big Data Center**.

⌘ *Author's Choice*

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TRF2 Protein Interacts with Core Histones to Stabilize Chromosome Ends*

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From the [‡]*Department of Pathological Cell Biology and* [§]*Medical Top Track Program, Medical Research Institute, Tokyo Medical and Dental University, Yushima, Bunkyo-ku, Tokyo 113-8510, Japan, the* [¶]*Department of Biochemistry, Gunma University Graduate School of Medicine, 3-39-22 Showa, Maebashi, Gunma 371-8511, Japan, and the* [‖]*Laboratory of Cell Biology and Genetics, The Rockefeller University, New York, New York 10065*

Mammalian chromosome ends are protected by a specialized nucleoprotein complex called telomeres. Both shelterin, a telomere-specific multi-protein complex, and higher order telomeric chromatin structures combine to stabilize the chromosome ends. Here, we showed that TRF2, a component of shelterin, binds to core histones to protect chromosome ends from inappropriate DNA damage response and loss of telomeric DNA. The N-terminal Gly/Arg-rich domain (GAR domain) of TRF2 directly binds to the globular domain of core histones. The conserved arginine residues in the GAR domain of TRF2 are required for this interaction. A TRF2 mutant with these arginine residues substituted by alanine lost the ability to protect telomeres and induced rapid telomere shortening caused by the cleavage of a loop structure of the telomeric chromatin. These findings showed a previously unnoticed interaction between the shelterin complex and nucleosomal histones to stabilize the chromosome ends.

The ends of eukaryotic chromosomes are stabilized by specialized structures called telomeres. Failure of the proper function of telomeres leads to a DNA damage response and inappropriate DNA repair at chromosome ends (1). Mammalian telomeres comprise a long array of tandem TTAGGG repeat DNA and shelterin, a telomere-specific protein complex (2). Electron microscopy analysis revealed that telomeres are organized in a large lasso-like structure called a t-loop (3, 4). Recently, t-loops were also detected by a super-resolution fluorescence imaging method (5). t-loops are believed to be formed through strand invasion of duplex telomeric repeat by the 3′ overhang, and their formation requires both homologous recombination (HR)[2] and shelterin components (6). It has been proposed that t-loops protect the telomere terminus from DNA damage response and the DNA repair machinery.

Telomeric nucleosomes have a similar composition to non-telomeric nucleosomes: they contain core histones H2A, H2B, H3, H4, and linker histone H1 (4). However, the higher order structure of telomeric chromatin is different from bulk nuclear chromatin. Telomeric nucleosomes have shorter repeat sizes than bulk nucleosomes and are hypersensitive to micrococcal nuclease (7, 8). Reconstituted nucleosomes on TTAGGG repeats show higher mobility than on other sequences (9). Moreover, telomeric chromatin is enriched for heterochromatin modification, such as tri-methylation of H3K9 and H4K20, and loss of these marks affects telomere length regulation (10).

Telomere function is critically dependent on the shelterin complex. TRF2 is a component of the shelterin complex that localizes at telomeres to protect chromosome ends from inappropriate DNA damage response and the DNA repair machinery (11). Deletion of TRF2 leads to ataxia telangiectasia-mutated (ATM)-dependent DNA damage response at chromosome ends, detected as the occurrence of telomere dysfunction-induced foci (TIFs), which results in end-to-end telomere fusions mediated by non-homologous end joining (NHEJ) (12, 13). TRF2 consists of three domains, the TRF homology (TRFH) domain, a C-terminal Myb/SANT DNA-binding domain, and the Gly/Arg-rich domain (GAR domain; previously referred to as the basic domain).

The GAR domain, which is located at the N terminus of TRF2, is rich in Gly/Arg residues and highly basic, and is important to stabilize the chromosome ends by repressing cleavage of the t-loop. Ectopic expression of TRF2 lacking the GAR domain (TRF2ΔB) induces stochastic telomere deletions and accumulation of circular telomeric DNA (t-circle), as expected from excision of the t-loop mediated by the HR machinery (14). Recent biochemical analyses showed that the GAR domain binds to a Holliday junction, suggesting that the GAR domain prevents t-loop cleavage by physically blocking the junction structure (15, 16). Another group has reported that the GAR

* This work was supported by the Program for Improvement of Research Environment for Young Researchers from Special Coordination Funds for Promoting Science and Technology (SCF) commissioned by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan. The authors declare that they have no conflicts of interest with the contents of this article.

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[2] The abbreviations used are: HR, homologous recombination; TRF2, telomeric repeat-binding factor2; TRF2ts, temperature-sensitive TRF2 mutant; TIF, telomere dysfunction-induced foci; GAR domain, Gly/Arg-rich domain; TERRA, telomere repeat-encoding RNA; PLA, proximity ligation assay; FL, full-length; LANA, latency-associated nuclear antigen; NLS, nuclear localization signal; EGFP, enhanced green fluorescent protein; PRMT1, protein arginine methyltransferase 1; SA-β-gal, senescence-associated β-galactosidase; FKBP, FK506-binding protein; FRB, FKBP12-rapamycin-binding; MEF, mouse embryonic fibroblast; HJ, Holliday junction; aa, amino acids; ANOVA, analysis of variance; IF-FISH, immunofluorescence-fluorescent *in situ* hybridization; TBE, Tris-borate-EDTA; PNA, peptide nucleic acid; DIG, digoxigenin; CBB, Coomassie Brilliant Blue; CHEF, contour-clamped homogenous electric field; IP, immunoprecipitation; h, human; m, mouse.

Department of Integrative Physiology

(1) Staff and Subspecialty

Professor	Noriyuki Koibuchi, M.D., Ph.D.	Endocrine Physiology Environmental Physiology
Assoc. Prof	Yusuke Takatsuru, M.D., Ph.D.	Neurophysiology
Assoc. Prof	Wataru Miyazaki, PhD.	Hygiene･Toxicology
Assist. Prof.	Izuki Amano, M.D., Ph.D.	Endocrine Physiology (studying abroad)
Assist. Prof.	Diana Vargas, Ph.D.	Endocrinology and Metabolism
Assist. Prof.	Asahi Haijima, Ph.D.	Behavioral Science

(2) Research Themes

Effects of environmental factors (i.e., endocrine disruptors, stress, exercise, diseases) on endocrine and paracrine trophic factor-regulated biological function. Special focus is made on neuronal development and plasticity.

Research techniques that we are using are:

Behavioral analysis, microscopy including multi-photon laser microscopy, electrophysiology, and other cellular and molecular biological techniques.

(3) Funding

KAKENHI (MEXT grant) and several other private funding.

(4) Contribution to the Society

Research practical courses for middle- and high- school students (partly supported by MEXT grant), and seminars for regional teachers, are regularly held.

(5) Enrollment of Graduate Course

Ask Prof. Koibuchi directly (nkoibuch@gunma-u.ac.jp) for detail. Foreign and women researchers are encouraged to apply. Both Master's and PhD course are available.

(6) Current Students

Master 2, PhD 7 and 2-3 active MD-PhD course students.

(7) Career Path after Graduation

Graduates are encouraged to apply postdoc at foreign country. Postdoctoral position is sometimes available, but no guarantee.

(8) Message from the Director

Our main key word in research is "environment". Particularly, the effect of environmental factors on biological function has been intensively studied. Research includes from cellular/molecular level to behavior level. These data are integrated to clarify "whole view" of a system. We seek for applicants who have a passion to cultivate a new research field. Having results is not always important. Rather, those who can enjoy a process of making a hypothesis, designing experiments and analyzing data, are encouraged to join our laboratory.

In addition, we seek for applicants who are also interested in students' education. A good researcher should be also a good educator.

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Aberrant Cerebellar Development in Mice Lacking Dual Oxidase Maturation Factors

Izuki Amano,[1] Yusuke Takatsuru,[1] Syutaro Toya,[1] Asahi Haijima,[1] Toshiharu Iwasaki,[1] Helmut Grasberger,[2,3] Samuel Refetoff,[2,4,5] and Noriyuki Koibuchi[1]

Background: Thyroid hormone (TH) plays a key role in the developing brain, including the cerebellum. TH deficiency induces organizational changes of the cerebellum, causing cerebellar ataxia. However, the mechanisms causing these abnormalities are poorly understood. Various animal models have been used to study the mechanism. Lacking dual oxidase (DUOX) and its maturation factor (DUOXA) are major inducers of congenital hypothyroidism. Thus, this study examined the organizational changes of the cerebellum using knockout mice of the *Duoxa* gene (*Duoxa–/–*).
Methods: The morphological, behavioral, and electrophysiological changes were analyzed in wild type (*Wt*) and Duoxa-deficient (*Duoxa–/–*) mice from postnatal day (P) 10 to P30. To detect the changes in the expression levels of presynaptic proteins, Western blot analysis was performed.
Results: The proliferation and migration of granule cells was delayed after P15 in *Duoxa–/–* mice. However, these changes disappeared by P25. Although the cerebellar structure of *Duoxa–/–* mice was not significantly different from that of *Wt* mice at P25, motor coordination was impaired. It was also found that the amplitude of paired-pulse facilitation at parallel fiber–Purkinje cell synapses decreased in *Duoxa–/–* mice, particularly at P15. There were no differences between expression levels of presynaptic proteins regulating neurotransmitter release at P25.
Conclusions: These results indicate that the anatomical catch-up growth of the cerebellum did not normalize its function because of the disturbance of neuronal circuits by the combined effect of hypothyroidism and functional disruption of the DUOX/DUOXA complex.

Introduction

Thyroid hormone (TH) is essential for the normal development of the brain (1). TH deficiency during the postnatal period causes congenital hypothyroidism in humans. The typical findings in cretinism are mental retardation, ataxia, and deafness, together with impaired body growth (2,3). TH deficiency in developing rodents induces organizational changes of the cerebellum, causing cerebellar ataxia (4). However, the mechanisms causing this abnormality are poorly understood.

Perinatal hypothyroidism causes various anatomical changes of the rat cerebellum such as reduction of growth and dendritic arborization of Purkinje cells (5,6), reduction of synaptogenesis between Purkinje and granule cells (6,7), delayed myelination (8), and changes in synaptic connections between cerebellar neurons and afferent neuronal fibers (9). These aberrant phenotypes can be rescued only if TH replacement is instituted by postnatal week 2 in rats (5).

Some of the rate-limiting steps of TH synthesis take place at the apical cell membrane of the thyroid follicular cell. To generate hydrogen peroxide (H_2O_2), dual oxidase (DUOX) 2 requires the maturation factor (DUOXA) (10,11). To iodinate thyroglobulin (TG), thyroid peroxidase (TPO) requires H_2O_2 as the final electron acceptor in two steps (12–14). The first step is oxidation of iodide, which is then covalently linked to selected tyrosine residues of TG (12–14). The second step is coupling of two iodotyrosine residues to form iodothyronines (12–14). A defect of DUOX2 or DUOXA2 decreases TH synthesis, causing congenital hypothyroidism in both humans and mice (15–17).

To evaluate the effect of dyshormonogenesis caused by the absence of DUOXA in cerebellar development, the study used *Duoxa* gene knockout mice (*Duoxa–/–*), in which part of both *Duoxa1* and *Duoxa2* exons were deleted (10). *Duoxa+/–* mice were used as dams. Since the TH status of *Duoxa+/–* mice is euthyroid (10), the involvement of an altered maternal TH status on fetal or neonatal development can be

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[3]Division of Gastroenterology, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan

Department of Neurophysiology and Neural Repair

One of our research subjects is elucidation of molecular mechanisms underlying motor learning. In addition, we are studying practical methods of gene therapy and stem cell therapy to cure spinocerebellar ataxias, for which there are no effective treatments to date. We perform preclinical studies in view of future clinical applications, based on the molecular mechanisms we clarify.

(1) Research Themes

① Development of cell-type specific gene delivery methods using viral vectors

Considering applications of the methods to clinical gene therapy as well as basic research, we are developing efficient ways of neuron-specific gene expression with lentiviral vectors and adeno-associated viral vectors.

② Development of gene / cell therapy for spinocerebellar ataxias

Targeting on spinocerebellar ataxias, which the Japanese government classified as rare and intractable diseases and the government supports the patients, we are making model mice of the diseases and developing methods of gene therapy and stem cell therapy to treat the diseases.

③ Elucidation of mechanisms underlying synapse formation and synaptic plasticity

Using genetically modified mice and techniques of viral vector-mediated gene delivery selectively into neurons or glia, we analyze the effects of the gene transfer both on a cellular level and a behavioral level.

(3) To enter the graduate school

We accept students, who are motivated and interested in the themes above. Academic backgrounds of the current students in the lab are diverse.

(4) Lab life of the current students

The students have to report progress which they made last week in their project in a lab meeting every Monday morning. They are required to give a progress report and to discuss their project with the lab members approximately every 4 months. In addition, every week, we have a journal club in which recent, highly evaluated papers will be introduced. The graduate students are organizing a lab excursion this year.

(5) Career path after graduation

Some got jobs in a pharmaceutical company or an academic publisher. If you want to study abroad as a postdoc, we can help you to find a suitable lab in a foreign country. The lab staffs can give you various information about studying abroad.

(6) Et cetera

Prof. Hirai was also appointed Director of Gunma University Biosignal Genome Resource Center, Member of Science Council of Japan, Gunma University Graduate School of Medicine, and Director of the Japan Neuroscience Society.

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JPn Neuroscience

The Journal of Physiology

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Progressive impairment of cerebellar mGluR signalling and its therapeutic potential for cerebellar ataxia in spinocerebellar ataxia type 1 model mice

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[2]*Department of Life Sciences, Graduate School of Arts and Sciences, University of Tokyo, Tokyo, 153-8902, Japan*
[3]*Research Institute of Molecular Medicine and Pathobiochemistry, Krasnoyarsk State Medical University named after Prof. V. F. Voino-Yasenetsky, Krasnoyarsk 660022, Russia*
[4]*Research Program for Neural Signalling, Division of Endocrinology, Metabolism and Signal Research, Gunma University Initiative for Advanced Research, Maebashi, Gunma 371-8511, Japan*

Key points

- Spinocerebellar ataxia type 1 (SCA1) is a progressive neurodegenerative disease caused by a gene defect, leading to movement disorder such as cerebellar ataxia.
- It remains largely unknown which functional defect contributes to the cerebellar ataxic phenotype in SCA1.
- In this study, we report progressive dysfunction of metabotropic glutamate receptor (mGluR) signalling, which leads to smaller slow synaptic responses, reduced dendritic Ca^{2+} signals and impaired synaptic plasticity at cerebellar synapses, in the early disease stage of SCA1 model mice.
- We also show that enhancement of mGluR signalling by a clinically available drug, baclofen, leads to improvement of motor performance in SCA1 mice.
- SCA1 is an incurable disease with no effective treatment, and our results may provide mechanistic grounds for targeting mGluRs and a novel drug therapy with baclofen to treat SCA1 patients in the future.

Abstract Spinocerebellar ataxia type 1 (SCA1) is a progressive neurodegenerative disease that presents with cerebellar ataxia and motor learning defects. Previous studies have indicated that the pathology of SCA1, as well as other ataxic diseases, is related to signalling pathways mediated by the metabotropic glutamate receptor type 1 (mGluR1), which is indispensable for proper motor coordination and learning. However, the functional contribution of mGluR signalling to SCA1 pathology is unclear. In the present study, we show that SCA1 model mice develop a functional impairment of mGluR signalling which mediates slow synaptic responses, dendritic Ca^{2+} signals, and short- and long-term synaptic plasticity at parallel fibre (PF)–Purkinje cell (PC) synapses in a progressive manner from the early disease stage (5 postnatal weeks) prior to PC death. Notably, impairment of mGluR-mediated dendritic Ca^{2+} signals linearly correlated with a reduction of PC capacitance (cell surface area) in disease progression. Enhancement of mGluR signalling by baclofen, a clinically available $GABA_B$ receptor agonist, led to an improvement of motor performance in SCA1 mice and the improvement lasted ∼1 week after a single application of baclofen. Moreover, the restoration of motor performance in baclofen-treated SCA1 mice matched the functional recovery of mGluR-mediated slow synaptic currents and mGluR-dependent

A. N. Shuvaev and N. Hosoi contributed equally to this work.

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Department of Neurobiology and Behavior

（1）Lab members

Professor and Chairman: Tomoaki Shirao　Adjunct professor: Yuko Sekino

Assistant professor: Hiroyuki Yamazaki, Kenji Hanamura, Noriko Koganezawa

（2）Projects：Synapse formation and function are regulated by both genetic program and sensory input from environment in an activity-dependent manner. We are studying about the molecular mechanisms of synapse formation and function mediated by actin cytoskeleton in postsynaptic sites. In addition, we are also focusing on the mechanisms underlying pathology of psychiatric and neurological diseases induced by synaptic dysfunction (dementia, depression, radiation-induced synaptopathy, etc.). Furthermore, we are developing high-throughput screening system to detect the status of synapses using synaptic marker in postsynaptic sites in combination with human iPS cell-derived neurons for in vitro safety pharmacology testing. We use primary neuronal culture, genetically modified mice and various approaches including molecular and cellular biology, electrophysiology, behavioral analysis, pharmacology and imaging techniques for researches.

（3）Entrance requirements: Students with high motivation, not only from medical background, but also from science and technology background are very welcome. Before application, you need to contact us and have an interview.

（4）Laboratory activities: Each students will have different projects. Journal club is held every other week and each student will present progress report every month. Students will be paid as a teaching assistant or a research assistant.

（5）Career options: Assistant professor, researcher, post-doctoral researcher, etc.

（6）Others：More information is available in our lab website:
http://neuro.dept.med.gunma-u.ac.jp/

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The role of drebrin in dendritic spines

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ABSTRACT

Dendritic spines form typical excitatory synapses in the brain and their shapes vary depending on synaptic inputs. It has been suggested that the morphological changes of dendritic spines play an important role in synaptic plasticity. Dendritic spines contain a high concentration of actin, which has a central role in supporting cell motility, and polymerization of actin filaments (F-actin) is most likely involved in spine shape changes. Drebrin is an actin-binding protein that forms stable F-actin and is highly accumulated within dendritic spines. Drebrin has two isoforms, embryonic-type drebrin E and adult-type drebrin A, that change during development from E to A. Inhibition of drebrin A expression results in a delay of synapse formation and inhibition of postsynaptic protein accumulation, suggesting that drebrin A has an important role in spine maturation. In mature synapses, glutamate stimulation induces rapid spine-head enlargement during long-term potentiation (LTP) formation. LTP stimulation induces Ca^{2+} entry through *N*-methyl-D-aspartate (NMDA) receptors, which causes drebrin exodus from dendritic spines. Once drebrin exits from dendritic spine heads, the dynamic actin pool increases in spine heads to facilitate F-actin polymerization. To maintain enlarged spine heads, drebrin-decorated F-actin is thought to reform within the spine heads. Thus, drebrin plays a pivotal role in spine plasticity through regulation of F-actin.

Contents

1. Introduction

Dendritic spines are small protrusions sticking out from the dendritic shaft, typically consisting of a head (approximately 5.1×10^{-20} m^3) and neck (approximately 1.2×10^{-20} m^3) (Harris and Stevens 1989).

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Department of Genetic and Behavioral Neuroscience

Research Interests

Functional roles of GABA in the CNS,
Characteristics of inhibitory neurons,
Pathophysiology of neuropsychiatric disorders using knockout rodents

Neurons are classified into two major subgroups, excitatory and inhibitory neurons. Inhibitory neurons play an important role in the regulation and stabilization of network activities. These neurons are also essential for a number of brain functions such as cognition, perception, movement, and emotion. GABAergic neurons are a representative inhibitory neuron. GABA is involved in the pathophysiology of diseases such as epilepsy and anxiety. Research in my laboratory focuses on clarifying the role of GABA in brain functions and characterizing GABAergic neurons.

1: In order to clarify the roles of GABA or GABAergic transmission in movement, perception and emotion, we have generated and analyzed conditional knockout mice of glutamate decarboxylase 67 and vesicular GABA transporter.
2: Rats are a useful experimental animal for studying cognition and its dysfunction. In order to clarify a link between GABA and cognition, we have generated knockout rats using genome editing method.
3: We generated transgenic mice and transgenic rats specifically expressing a fluorescent protein, GFP or Venus in inhibitory neurons. GFP expression in inhibitory neurons allows us to visually target them for electrophysiological and morphological studies. Our transgenic rodents have used in a number of laboratories and the use has greatly facilitated modern neuroscience research.

Selected Publications

Egashira Y et al., Unique pH dynamics in GABAergic synaptic vesicles illuminates the mechanism and kinetics of GABA loading. Proc Natl Acad Sci USA 113, 10702-7, 2016
Fujihara K et al., Glutamate decarboxylase 67 deficiency in a subset of GABAergic neurons induces schizophrenia-related phenotypes. Neuropsychopharmacology 2015
Kayakabe M et al., Motor dysfunction in cerebellar Purkinje cell-specific vesicular GABA transporter knockout mice. Front Cell Neurosci. 7, 286, 2014

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Unique pH dynamics in GABAergic synaptic vesicles illuminates the mechanism and kinetics of GABA loading

Yoshihiro Egashira[a], Miki Takase[a,1], Shoji Watanabe[b], Junji Ishida[c], Akiyoshi Fukamizu[c], Ryosuke Kaneko[d], Yuchio Yanagawa[d], and Shigeo Takamori[a,2]

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GABA acts as the major inhibitory neurotransmitter in the mammalian brain, shaping neuronal and circuit activity. For sustained synaptic transmission, synaptic vesicles (SVs) are required to be recycled and refilled with neurotransmitters using an H^+ electrochemical gradient. However, neither the mechanism underlying vesicular GABA uptake nor the kinetics of GABA loading in living neurons have been fully elucidated. To characterize the process of GABA uptake into SVs in functional synapses, we monitored luminal pH of GABAergic SVs separately from that of excitatory glutamatergic SVs in cultured hippocampal neurons. By using a pH sensor optimal for the SV lumen, we found that GABAergic SVs exhibited an unexpectedly higher resting pH (~6.4) than glutamatergic SVs (pH ~5.8). Moreover, unlike glutamatergic SVs, GABAergic SVs displayed unique pH dynamics after endocytosis that involved initial overacidification and subsequent alkalization that restored their resting pH. GABAergic SVs that lacked the vesicular GABA transporter (VGAT) did not show the pH overshoot and acidified further to ~6.0. Comparison of luminal pH dynamics in the presence or absence of VGAT showed that VGAT operates as a GABA/H^+ exchanger, which is continuously required to offset GABA leakage. Furthermore, the kinetics of GABA transport was slower ($\tau > 20$ s at physiological temperature) than that of glutamate uptake and may exceed the time required for reuse of exocytosed SVs, allowing reuse of incompletely filled vesicles in the presence of high demand for inhibitory transmission.

synaptic vesicle | VGAT | inhibitory neuron

Synaptic transmission is mediated by quantal release of neurotransmitters stored in synaptic vesicles (SVs) that are locally recycled at the presynaptic terminals (1). Because vesicular transport of classical transmitters depends on an H^+ electrochemical gradient ($\Delta\mu H^+$) generated by the vacuolar-type H^+ ATPase (V-ATPase), the rate and extent of $\Delta\mu H^+$ formation can influence quantal size (2). Recent characterization of net proton influx into excitatory glutamatergic SVs in cultured neurons (3) revealed kinetics similar to that of glutamate uptake (4) and thus, highlighted possible temporal coupling between luminal proton dynamics and transmitter uptake. However, how H^+ accumulates and how much accumulates in inhibitory GABAergic SVs remain unknown.

Because the molecular composition of inhibitory SVs is almost identical to that of excitatory SVs, except for the respective vesicular neurotransmitter transporters (5, 6), any differences in luminal $[H^+]$ could be explained, in part, by differences in the H^+ coupling to their respective vesicular neurotransmitter transport. Indeed, biochemical studies using SVs isolated from brains have indicated that the contribution of $\Delta\mu H^+$ on uptake differs substantially (2). Vesicular glutamate transport predominantly relies on the electrical gradient ($\Delta\psi$) and results in an enhanced chemical gradient ΔpH (7, 8). In comparison, vesicular GABA transport is equally dependent on both $\Delta\psi$ and ΔpH, which is thought to result from a concomitant H^+ exchange (9, 10). However, a study using proteoliposomes reconstituted with vesicular GABA transporter (VGAT) (11, 12) proposed that VGAT operates a $\Delta\psi$-driven GABA/2Cl^- cotransporter without the need for ΔpH (13). Clarification of the enigmatic GABA transport mechanism was recently provided by Farsi et al. (14), who imaged the pH-sensitive superecliptic pHluorin in isolated single SVs and found evidence that VGAT functions through a GABA/H^+ antiport mechanism. However, no evidence has been obtained that shows any changes in luminal $[H^+]$ associated with V-ATPase–dependent GABA uptake. In addition, acidification of isolated or reconstituted vesicles does not necessarily reflect the situation in SVs in living neurons, particularly because the ionic composition in isolated vesicles is altered during the isolation procedure (15). Therefore, to gain a more accurate understanding of the vesicular loading mechanism for GABA, examination of luminal pH dynamics linked to GABA uptake in functional synapses is important.

Molecules that are pH sensitive, such as pHluorin and CypHer, have been targeted to the SV lumen and used to track vesicle exo-/endocytosis in culture preparations (16, 17). To date, no diversity in SV acidity across neurotransmitter phenotypes has been reported. These pH sensors, however, have a $pK_a > 7$, which has likely hindered the detection of differences in SV pH, particularly

Significance

Neurotransmitters are stored in synaptic vesicles (SVs) depending on the energy provided by an H^+ gradient. The inhibitory transmitter GABA is critical for coordinated neuronal activity of the brain, and vesicular transport of GABA is essential for its release. However, the transport process has been characterized primarily in isolated or reconstituted vesicle preparations, and we know little about its properties at functional synapses. Here, by monitoring the pH of SVs in GABAergic neurons apart from excitatory glutamatergic neurons, we show that GABA transport into SVs is tightly coupled to SV alkalization in living neurons, which occurs at an unexpectedly slow rate, suggesting a possible contribution of incompletely filled vesicles during sustained stimulation at GABAergic synapses.

Author contributions: Y.E. and S.T. designed research; Y.E. and M.T. performed research; S.W., J.I., A.F., R.K., and Y.Y. contributed new reagents/analytic tools; Y.E. analyzed data; and Y.E. and S.T. wrote the paper.

The authors declare no conflict of interest.

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Department of Molecular Pharmacology and Oncology

【Staffs】 Professor: Masahiko NISHIYAMA, M.D., Ph.D.
Associate Professor: Akio NAKAMURA, Ph.D.
Susumu ROKUDAI, Ph.D.
Assistant Professor: Reika KAWABATA, Ph.D.

【Missions】

Cancer is one of the most critical contemporary issues in global health. The “Cancer Professionals Promoting Program” of The Ministry of Education, Culture, Sports, Science and Technology of Japan led us to organize as Department of Molecular Pharmacology and Oncology (DMPO), which aims to realize cancer medical innovation (http://ocd.med.gunma-u.ac.jp/). Our department is home to research focused on (1) understanding biology of cancer to discover novel medical seeds, (2) understanding the mechanism of drug actions, (3) developing new molecular diagnostics and (4) developing new cancer therapeutics including drug discovery and personalized medicine. The DMPO offers a broad range of basic and clinical research topics to educate professionals to become international leaders in the field of cancer pharmacology and translational research and R&D management specialists who can promote an innovation (the new Graduate Course Program adopted by MEXT “Local Area Open Innovation R&D Human Resources, New Paradigms-Establishing Centers for Fostering Medical Researchers of the Future” (http://mirai.showa.gunma-u.ac.jp/).

【Ongoing Research subjects】

① Cancer Drug discovery based on Omics Science（main targets: p53 family, geriatric cancers, triple negative breast cancer, hepatocellular carcinoma, and liver metastasis）
② Predictive biomarkers of anticancer drug therapy for personalized medicine
③ Bioinformatics to develop an algorithm for treatment strategy in elderly cancer patients
④ Peripheral neuropathy caused by anticancer drug therapy: The mechanisms and determinants
⑤ Development of novel cancer diagnostics based on understanding biology of cancer
⑥ Development of novel therapeutics to overcome tumor resistance to irradiation and anticancer agents
⑦ Genetic basis in dedifferentiated vascular smooth muscle cell associated with arteriosclerosis
⑧ Influences of gestational diabetes on cardiovascular system and heart: Transgenerational genetics and epigenetics

【Application】 In accordance with application requirements of Gunma University Graduate School of Medicine.

【Current students】 Doctoral course, 3 students and MD-PhD program, 2 students

【After graduation】 Post-docs and/or staffs in labs, M.D., etc.

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Biology of Human Tumors

Clinical Cancer Research

STXBP4 Drives Tumor Growth and Is Associated with Poor Prognosis through PDGF Receptor Signaling in Lung Squamous Cell Carcinoma

Yukihiro Otaka[1,2], Susumu Rokudai[1,3], Kyoichi Kaira[4], Michiru Fujieda[1], Ikuko Horikoshi[1], Reika Iwakawa-Kawabata[1,5], Shinji Yoshiyama[5], Takehiko Yokobori[1,5], Yoichi Ohtaki[6], Kimihiro Shimizu[6], Tetsunari Oyama[7], Jun'ichi Tamura[2], Carol Prives[3], and Masahiko Nishiyama[1,5]

Abstract

Purpose: Expression of the ΔN isoform of p63 (ΔNp63) is a diagnostic marker highly specific for lung squamous cell carcinoma (SCC). We previously found that Syntaxin Binding Protein 4 (STXBP4) regulates ΔNp63 ubiquitination, suggesting that STXBP4 may also be an SCC biomarker. To address this issue, we investigated the role of STXBP4 expression in SCC biology and the impact of STXBP4 expression on SCC prognosis.

Experimental Design: We carried out a clinicopathologic analysis of STXBP4 expression in 87 lung SCC patients. Whole transcriptome analysis using RNA-seq was performed in STXBP4-positive and STXBP4-negative tumors of lung SCC. Soft-agar assay and xenograft assay were performed using overexpressing or knockdown SCC cells.

Results: Significantly higher levels of STXBP4 expression were correlated with accumulations of ΔNp63 in clinical lung SCC specimens (Spearman rank correlation $\rho = 0.219$). Notably, STXBP4-positive tumors correlated with three important clinical parameters: T factor ($P < 0.001$), disease stage ($P = 0.030$), and pleural involvement ($P = 0.028$). Whole transcriptome sequencing followed by pathway analysis indicated that STXBP4 is involved in functional gene networks that regulate cell growth, proliferation, cell death, and survival in cancer. Platelet-derived growth factor receptor alpha (PDGFRα) was a key downstream mediator of STXBP4 function. In line with this, shRNA mediated *STXBP4* and *PDGFRA* knockdown suppressed tumor growth in soft-agar and xenograft assays.

Conclusions: STXBP4 plays a crucial role in driving SCC growth and is an independent prognostic factor for predicting worse outcome in lung SCC. These data suggest that STXBP4 is a relevant therapeutic target for patients with lung SCC. *Clin Cancer Res; 1–11. ©2017 AACR.*

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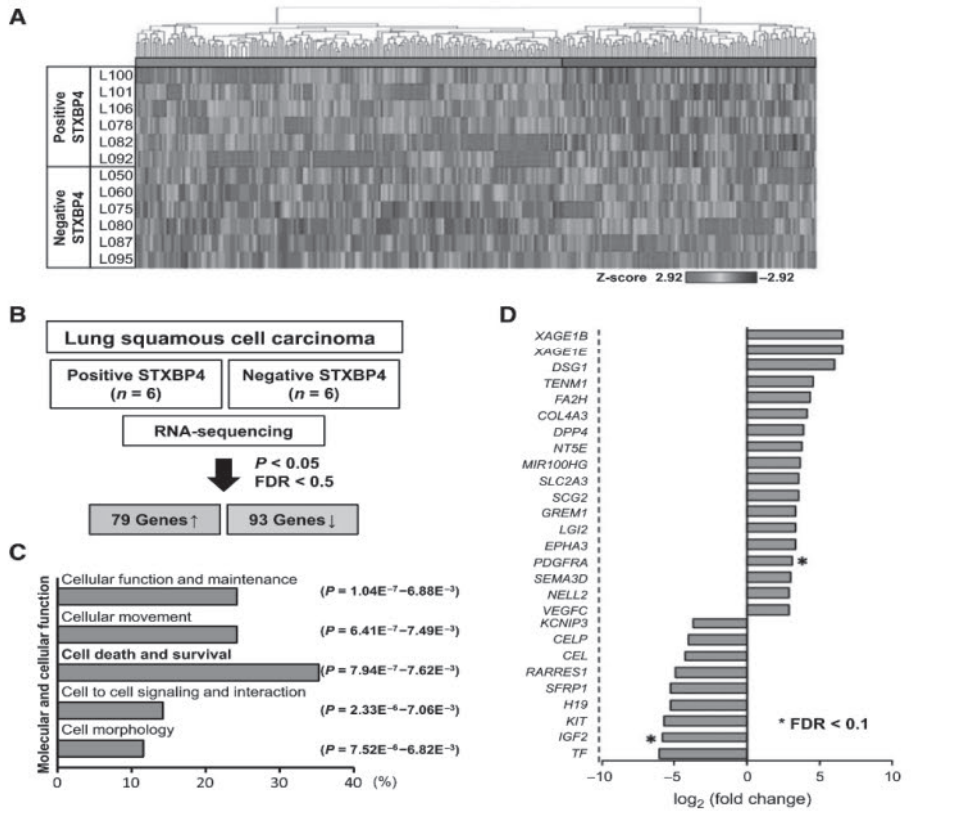
STXBP4 as a Key Regulator of Lung SCC Pathogenesis



Department of Bacteriology/Laboratory of Bacterial Drug Resistance

(1) Members

Bacteriology:

Professor; 1, Researcher; 1, Research technician; 1, Graduate student; 1

Laboratory of Bacterial Drug Resistance:

Associate Professor; 1, Post-doctoral fellow; 1, Lab technician; 2

(2) Projects

1. Molecular genetics of the bacterial pathogenesis (adherence, bacteriocin, cytolysin, drug resistances, UV-resistance)
2. Analysis of enterococcal pheromone-independent highly conjugative plasmid.
3. Analysis of enterococcal pheromone-responsive highly conjugative plasmid.
4. Molecular epidemiology of multidrug resistant bacteria (vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Clostridium difficile*, *Acinetobactor baumanni*, ESBL-producing bacteria, carbapenem-resistant enterobacteriaceae, etc).
5. Epidemiological study of the nosocomial infections.
6. Mechanisms of the multi-drug resistance of *Pseudomonous aeruginosa*.
7. Development of techniques for the bacterial epidemiology, molecular genetics, biological chemistry.

(3) Admissions

Necessities for diligence, integrity, enthusiasm for the medical science, and proficient in English

(4) Status

A graduate student (1st degree) from the clinical department (internal medicine) studies in molecular genetics of the enterococcal pheromone-independent highly conjugative plasmid.

(5) Prospective positions

Companies (research, quality control), post-doctoral fellows (Japan, USA, EU), academic stuffs (basic researcher), clinical doctors

(6) Activities

Lab seminar and meeting (data presentation or journal club) once a week (Mon)

Research discussion with professor once a week (Fri)

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Bacteriology

Partial Diversity Generates Effector Immunity Specificity of the Bac41-Like Bacteriocins of *Enterococcus faecalis* Clinical Strains

Jun Kurushima,[a] Yasuyoshi Ike,[c] Haruyoshi Tomita[a,b]

Department of Bacteriology, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan[a]; Laboratory of Bacterial Drug Resistance, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan[b]; Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan[c]

ABSTRACT

Bacteriocin 41 (Bac41) is the plasmid-encoded bacteriocin produced by the opportunistic pathogen *Enterococcus faecalis*. Its genetic determinant consists of $bacL_1$ (effector), $bacL_2$ (regulator), *bacA* (effector), and *bacI* (immunity). The secreted effectors $BacL_1$ and BacA coordinate to induce the lytic cell death of *E. faecalis*. Meanwhile, the immunity factor BacI provides self-resistance to the Bac41 producer, *E. faecalis*, against the action of $BacL_1$ and BacA. In this study, we demonstrated that more than half of the 327 clinical strains of *E. faecalis* screened had functional Bac41 genes. Analysis of the genetic structure of the Bac41 genes in the DNA sequences of the *E. faecalis* strains revealed that the Bac41-like genes consist of a relatively conserved region and a variable region located downstream from *bacA*. Based on similarities in the variable region, the Bac41-like genes could be classified into type I, type IIa, and type IIb. Interestingly, the distinct Bac41 types had specific immunity factors for self-resistance, BacI1 or BacI2, and did not show cross-immunity to the other type of effector. We also demonstrated experimentally that the specificity of the immunity was determined by the combination of the C-terminal region of BacA and the presence of the unique BacI1 or BacI2 factor. These observations suggested that Bac41-like bacteriocin genes are extensively disseminated among *E. faecalis* strains in the clinical environment and can be grouped into at least three types. It was also indicated that the partial diversity results in specificity of self-resistance which may offer these strains a competitive advantage.

IMPORTANCE

Bacteriocins are antibacterial effectors produced by bacteria. In general, a bacteriocin-coding gene is accompanied by a cognate immunity gene that confers self-resistance on the bacteriocin-producing bacterium itself. We demonstrated that one of the bacteriocins, Bac41, is disseminated among *E. faecalis* clinical strains and the Bac41 subtypes with partial diversity. The Bac41-like bacteriocins were found to be classified into type I, type IIa, and type IIb by variation of the cognate immunity factors. The antibacterial activity of the respective effectors was specifically inhibited by the immunity factor from the same type of Bac41 but not the other types. This specificity of effector-immunity pairs suggests that bacteriocin genes might have evolved to change the immunity specificity to acquire an advantage in interbacterial competition.

Enterococcus faecalis is a Gram-positive commensal bacterium present in the intestinal tract of healthy humans or animals, but it is also a causative agent of opportunistic infectious diseases, including urinary infectious disease, bacteremia, infective endocarditis, and others (1–4). As represented by the development of drug resistance, the acquisition of new genes via mobile genetic elements (MGEs), such as plasmids, raises the concern of increased severity of these enterococcal diseases (5). Enterococcal plasmids also encode various bacteriocins, which are bactericidal peptides or proteins produced by bacteria (6). Enterococcal bacteriocins are generally divided into three classes (7, 8). Heat- and acid-stable bacteriocin peptides are called class I and class II (6). Class I bacteriocin peptides are referred to as lantibiotics, and this class contains nonproteinogenic amino acids generated by post-translational modification. Only two class I bacteriocins, beta-hemolysin/bacteriocin (cytolysin) and enterocin W, have been identified in enterococci (1, 3, 6, 9–11). Class II bacteriocin peptides are not posttranscriptionally modified and include most enterococcal bacteriocins, such as AS-48, enterocin A, bacteriocin 21 (Bac21), Bac31, Bac32, Bac43, and Bac51, which were isolated from clinical strains of *E. faecalis* or *Enterococcus faecium* (6, 7, 12–18). In contrast, class III bacteriocins, which are also referred to as bacteriolysins, are heat-labile antimicrobial proteins showing enzymatic bactericidal activity (7, 19, 20). To date, the only enterococcal bacteriolysins to be identified are enterolysin A and bacteriocin 41 (Bac41) (21–23).

Bac41 was originally cloned from the pheromone-responsive plasmid pYI14 of the clinical strain *E. faecalis* YI714 (21). Like other common bacteriocins, the bactericidal activity of Bac41 has a narrow spectrum against *E. faecalis* but is not active against *E. faecium*, *Enterococcus hirae*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, or *Listeria monocytogenes* (21, 24). The determinant genetic element of Bac41 consists of six open reading frames (ORFs), including the four characterized genes $bacL_1$, $bacL_2$, *bacA*, and *bacI* (Fig. 1) (21). The Bac41 lytic system has a classical antimicrobial effector/immunity module acting in

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Department of Parasitology

More than 80 % people are at risk of parasitic infections worldwide, although parasitic diseases have been eradicated in advanced countries. The reasons why parasitic infections are still problematic are; 1) antibiotics are not effective because parasites are eukaryotic pathogens, 2) there is no vaccine available to any parasites undergoing a complicated lifecycle. Among many parasitic diseases, malaria, our research interests, is one of the three biggest infections and produces 200 million patients and 600 thousand deaths every year (1.1 persons per minute). Researches in our laboratory focus on host-parasite relationship during malaria, whose final goal is to control this disastrous disease.

1. Staffs

Hajime HISAEDA, MD. PhD, Professor & Chairman, Kazutomo SUZUE, PhD, Associate Professor, Chikako SHIMOAKAWA, PhD, Assistant Professor, Alex OLIA, Assistant Professor, Tomoyo TANIGUCHI, Assistant Professor, Wakana MIZUTANI, Lab. Technician

2. Research Topics

Host-malaria parasite relationship is analyzed from host and parasite side, using animal experiments in laboratory and field studies for malaria patients in Uganda. Specifically,

1) Mechanisms for immune evasion or immune suppression by malaria parasites
2) Genuine protective immunity against blood-stage malaria
3) Interactions between malaria, immunity, and intestinal microbiota
4) Development of malaria vaccine

3. To Join Our Lab as Graduate Student

Any way including entering MD-PhD course is welcome. MD students are encouraged to finish a two-year clinical training.

4. How Graduate Students Work in This Lab

Students individually perform their own projects under our supervision. MD students may work hospital outside to earn life. We have provided financial supports (50 - 100K JPY/month) to non-MD student by hiring them as research assistants.

5. After Graduation

Almost students became post-docs at domestic and foreign labs and continued research. Some got research jobs at pharmaceutical companies.

6. Others

Medical students with outstanding academic results should contribute to science by mastering basic research, which leads to clinical or social benefits for all over the world.

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RESEARCH ARTICLE

Cytotoxic activities of CD8$^+$ T cells collaborate with macrophages to protect against blood-stage murine malaria

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Abstract The protective immunity afforded by CD8$^+$ T cells against blood-stage malaria remains controversial because no MHC class I molecules are displayed on parasite-infected human erythrocytes. We recently reported that rodent malaria parasites infect erythroblasts that express major histocompatibility complex (MHC) class I antigens, which are recognized by CD8$^+$ T cells. In this study, we demonstrate that the cytotoxic activity of CD8$^+$ T cells contributes to the protection of mice against blood-stage malaria in a Fas ligand (FasL)-dependent manner. Erythroblasts infected with malarial parasites express the death receptor Fas. CD8$^+$ T cells induce the externalization of phosphatidylserine (PS) on the infected erythroblasts in a cell-to-cell contact-dependent manner. PS enhances the engulfment of the infected erythroid cells by phagocytes. As a PS receptor, T-cell immunoglobulin-domain and mucin-domain-containing molecule 4 (Tim-4) contributes to the phagocytosis of malaria-parasite-infected cells. Our findings provide insight into the molecular mechanisms underlying the protective immunity exerted by CD8$^+$ T cells in collaboration with phagocytes.
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Introduction

Malaria is one of the world's three major infectious diseases, together with AIDS and tuberculosis, accounting for approximately 200 million cases annually, with 600,000 deaths (***Snow et al., 2005***; ***Murray et al., 2012***). With the spread of drug-resistant parasites and the lack of effective vaccines, malaria is a serious global health problem, especially in developing countries. To develop malarial vaccines, it is necessary to understand the protective immune response against malaria. However, because the malaria parasite successfully evades the host immune responses (***Hisaeda et al., 2004***), it is difficult to identify the truly important immune responses, hindering the development of a malarial vaccine (***Good and Engwerda, 2011***).

Antibodies play a major role in the protective immunity directed against the blood-stage malaria parasite. CD4$^+$ T cells contribute to protection against blood-stage malaria though induction of antibody production and macrophage activation (***Good and Doolan, 1999***; ***Marsh and Kinyanjui, 2006***; ***Jafarshad et al., 2007***; ***Langhorne et al., 2008***). However, the contribution of CD8$^+$ T cells to this protection remains controversial because there are no major histocompatibility complex (MHC) class I antigens on human erythrocytes infected with the malaria parasite. Some studies have shown that infection of BALB/c mice with non-lethal *Plasmodium yoelii* was controlled even after depletion of CD8$^+$ T cells comparable to control mice (***Vinetz et al., 1990***). Moreover, MHC class I null mice (beta 2-microglobulin-deficient mice) recovered from infection with *Plasmodium chabaudi chabaudi* AS or *Plasmodium chabaudi adami* (***van der Heyde et al., 1993b***). Other studies have reported that

2. Department of Public Health

Human health can be determined by the surrounding ecological conditions. Various physical, chemical and biological factors have direct or indirect associations with human health. In addition, various sociocultural factors including medical systems, social systems, laws and environmental standards, which are created by human-beings themselves, also play important roles in maintenance and promotion of health. We are studying about how those conditions support human health, based on epidemiological findings.

1) Staffs

Professor	Hiroshi Koyama, M.D., Ph.D.
Associate professor	Ken Inoue, M.D., Ph.D.
Assistant Professor	Satomi Kameo, Ph.D. (Env. Sci.)
	Chiho Yamazaki, Ph.D.
Secretary	Chiho Yoshizawa

2) Study topics

We, including graduate and foreign students, are engaged in a broad range of research works from the ecological viewpoint. Our missions are to promote the health and welfare of the people and to prevent diseases through the effort of creating the healthy social environment.

1. Nutritional epidemiology of essential trace elements

Essential trace elements such as zinc, copper, and selenium have been demonstrated to play important roles in the regulation and homeostasis of various biological functions. We examine the influence of essential trace elements deficiency on health and try to investigate the effect of additional supplementation of these elements.

2. Analytical chemistry of selenoproteins

We have developed an analytical method that determines several selenoproteins simultaneously using ICP-MS combined with a chromatographic separation.

3. Komo-Ise Study: a cohort study

We conduct a large-scale epidemiological research to clarify risk factors of cancer, stroke, cardiovascular diseases, and aging-related disability.

4. Health and Medical Information Management System

5. Screening and causal inference of depression for suicide prevention

6. Development of selenium fortified foods.

Puspitasari et al. Radiation Oncology 2014, 9:125
http://www.ro-journal.com/content/9/1/125

RADIATION ONCOLOGY

REVIEW Open Access

Updates on clinical studies of selenium supplementation in radiotherapy

Irma M Puspitasari[1,2], Rizky Abdulah[1,2], Chiho Yamazaki[1], Satomi Kameo[1], Takashi Nakano[3] and Hiroshi Koyama[1*]

Abstract

To establish guidelines for the selenium supplementation in radiotherapy we assessed the benefits and risks of selenium supplementation in radiotherapy. Clinical studies on the use of selenium in radiotherapy were searched in the PubMed electronic database in January 2013. Sixteen clinical studies were identified among the 167 articles selected in the initial search. Ten articles were observational studies, and the other 6 articles reported studies on the effects of selenium supplementation in patients with cancer who underwent radiotherapy. The studies were conducted worldwide including European, American and Asian countries between 1987 and 2012. Plasma, serum or whole blood selenium levels were common parameters used to assess the effects of radiotherapy and the selenium supplementation status. Selenium supplementation improved the general conditions of the patients, improved their quality of life and reduced the side effects of radiotherapy. At the dose of selenium used in these studies (200–500 μg/day), selenium supplementation did not reduce the effectiveness of radiotherapy, and no toxicities were reported. Selenium supplementation may offer specific benefits for several types of cancer patients who undergo radiotherapy. Because high-dose selenium and long-term supplementation may be unsafe due to selenium toxicity, more evidence-based information and additional research are needed to ensure the therapeutic benefits of selenium supplementation.

Keywords: Selenium, Supplementation, Clinical studies, Radiotherapy

Introduction

Radiotherapy is one of the most common and effective treatments for cancer [1]. Radiation damages cancer cells by direct ionization of DNA and by indirect effects caused by reactive oxygen species (ROS) [2]. Ionizing radiation consists of electromagnetic radiations, including X-rays and gamma rays, and particulate radiation such as electrons, protons and neutrons [2]. Exposure to ionizing radiation produces ROS in the tissue environment; including hydroxyl radicals (the most damaging), superoxide anion radicals and other oxidants such as hydrogen peroxide [2]. Although radiotherapy is effective in killing cancer cells, ROS produced in radiotherapy may threaten the integrity and survival of the surrounding normal cells and may cause late side effects of radiotherapy [1-3]. The administration of radioprotective agents, which are supposed to scavenge radiation-induced radicals and reduce the effects of radiation at an early stage, has been suggested as one approach for prophylaxis of radiation effects in normal tissues [4,5].

Selenium, a trace element, is an essential nutrient of fundamental importance in human biology [6] and as a preventive approach to ROS detoxification, which activates and stimulates the endogenous system [4,7,8]. Some of the most fundamental cellular processes, such as DNA synthesis, depend on the presence of selenium within the catalytic site of thioredoxin reductases (TrxR) [9,10]. A moderate deficiency of selenium has been linked to many conditions, such as an increased risk of cancer, infections and male infertility; a decrease in immune and thyroid function; and several neurological conditions [6,9]. A review paper reported that in prospective studies published in the 1980s and early 1990s involving 8,000 to 11,000 individuals, low selenium status was associated with significantly increased risks of cancer incidence and mortality [6].

A number of mechanisms have been suggested to explain the anti-cancer effects of selenium [11]. Selenium

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Department of Legal Medicine

1) Members of Legal Medicine: Our group is composed of four researches including a professor and two senior investigators. The members can help a graduate student achieve genetic pathological research in the field of forensic sciences. Since autopsy cases have been increased, forensic pathologists are required. Thus, a graduate student with Japanese medical doctor license is employed by Gunma University.
2) Research:
(1) ABO blood group; Fundamental studies on human ABO genes. We have studied the transcriptional regulation of the ABO genes with the identification of cell-specific transcriptional regulatory elements, and found that deletion and mutation of the elements are associated with variant phenotypes, leading to genetic determination of ABO genes.
(2) Postmortem imaging; Postmortem CTs have been carried out prior to autopsies and we have validated the usefulness of the postmortem CT. We are trying to develop a new application of the postmortem CT to investigate the cause of death.
3) Entrance examination; Mutual agreement
4) Enrollment of current graduate students; none
5) Carrier path after graduation; The graduate will be employed as a staff in this department. Those can apply for a position in other institutes including those overseas.
6) History of this department; Professor Shoei Iseki (1944–1972) carried out the research on the genetic conversion of bacterial somatic antigen as well as the molecular structure of ABO blood group antigens, and was twice honored for the achievements of those studies by the Japan Academy, followed by application to the Novel Prize. Those studies were performed in cooperation with the succeeding professor Ken Furukawa (1972–1995), who developed the biochemical and genetic studies on ABO blood group substances. The next professor Koichiro Kishi (1995–2006), who worked with Shoei Iseki at Gunma University and the National Research Institute of Police Science in Japan for 18 years, established a novel research field“Urogenetics” in which DNases I and II were demonstrated as a new genetic marker, and carried out the research ranging from their molecular genetic basis to clinical applications. The present professor Yoshihiko Kominato (2006–), who worked in the laboratory under one of Iseki’s colleagues at Toyama University for 16 years, has studied the transcriptional regulation of the ABO genes with the findings of cis/trans-elements and epigenetics, and demonstrated that the deletion or mutation of the enhancer is associated with variant phenotype Bm.

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Epithelial Expression of Human ABO Blood Group Genes Is Dependent upon a Downstream Regulatory Element Functioning through an Epithelial Cell-specific Transcription Factor, Elf5*

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The human ABO blood group system is of great importance in blood transfusion and organ transplantation. The ABO system is composed of complex carbohydrate structures that are biosynthesized by A- and B-transferases encoded by the *ABO* gene. However, the mechanisms regulating *ABO* gene expression in epithelial cells remain obscure. On the basis of DNase I-hypersensitive sites in and around ABO in epithelial cells, we prepared reporter plasmid constructs including these sites. Subsequent luciferase assays and histone modifications indicated a novel positive regulatory element, designated the +22.6-kb site, downstream from *ABO*, and this was shown to enhance *ABO* promoter activity in an epithelial cell-specific manner. Expression of *ABO* and B-antigen was reduced in gastric cancer KATOIII cells by biallelic deletion of the +22.6-kb site using the CRISPR/Cas9 system. Electrophoretic mobility shift assay and chromatin immunoprecipitation assay demonstrated that the site bound to an epithelial cell-specific transcription factor, Elf5. Mutation of the Ets binding motifs to abrogate binding of this factor reduced the regulatory activity of the +22.6-kb site. Furthermore, *ELF5* knockdown with shRNA reduced both endogenous transcription from *ABO* and B-antigen expression in KATOIII cells. Thus, Elf5 appeared to be involved in the enhancer potential of the +22.6-kb site. These results support the contention that *ABO* expression is dependent upon a downstream positive regulatory element functioning through a tissue-restricted transcription factor, Elf5, in epithelial cells.

The human ABO blood group system is of great importance in blood transfusion and organ transplantation. The system comprises complex carbohydrate structures that are biosynthesized by the A- and B-transferases encoded by the *A* and *B* genes, respectively (1). The ABO genes consist of seven exons spanning more than 20 kb of genomic DNA, and two critical single-base substitutions in the last coding exon result in amino acid substitutions responsible for the difference in donor nucleotide sugar substrate specificity between A- and B-transferases (2). A single base deletion in exon 6 has been ascribed to a shift in the reading frame of codons and abolition of A-transferase activity in most *O* alleles. On the other hand, the distribution of the A- and B-antigens is cell type-specific; for example, the antigens are expressed on red blood cells and epithelial cells, as well as in salivary glands, although they are absent from the central nervous system, muscle, and connective tissue. Moreover, ABH antigens are known to be expressed during the maturation of erythroid and epithelial cells; for example, when erythroid cells differentiate *in vitro*, ABO is expressed at an undetectable level in the early phase, increases subsequently, and then decreases later (3, 4). In addition to the normal cell differentiation process, changes in ABH antigen expression have also been documented in abnormal processes such as tumorigenesis (1). Reduction or complete deletion of A/B antigen expression in primary lung, bladder, and colorectal carcinomas has been reported. This phenotypic change was well correlated with the invasive and metastatic potential of the tumors and with patient 5- or 10-year mortality rates (5, 6).

The DNA sequences in and around specific genes provide the code that dictates when, where, and at what level specific genes are transcribed. This code comprises three parts: the core promoter, the region proximal to the core promoter, and the more distant enhancer sequences. It has become obvious that enhancers usually work in groups (*i.e.* the locus control region and super enhancers), each being bound by several transcription factors (TFs),[2] forming a so-called enhanceosome. These enhanceosomes are nucleated by pioneer TFs early during differentiation and are subsequently replaced by other TFs that trigger polymerase II recruitment. Enhancers recruit the preinitiation complex and TFs and interact with each other through a multilooped structure (7, 8).

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† This author is deceased.

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[2] The abbreviations used are: TF, transcription factor; qPCR, quantitative real time PCR; CGI, CpG island; HMM, hidden Markov model; HMEC, human mammary epithelial cell; NHLF, normal human lung fibroblast; EMT, epithelial-mesenchymal transition; TK, thymidine kinase; TMM, trimmed mean of *M* value; MFI, median fluorescence intensity; CTCF, CCCTC-binding factor.

Department of Medical Philosophy and Ethics

1. Our Basic Orientation

Very easy is it, even for a high school student, to hold and mention some opinions about bio-medical ethics issues and to write essays down in a pseudo-academic style. Producing such self-proclaimed bioethicists is out of our missions. This department is the first and only one lab in Japan, with "medical philosophy" in its official name. We do hate a rough-and ready approach to medical ethics. We are rather developing our speculative and reflective abilities as well as literary sensitivities and imagination, through close reading of, if eastern or western, classical or modern, texts on not only theoretical and practical philosophy, but other human and social sciences in addition to literary works.

We have been awarded *Grants-in-Aid for Scientific Research* on the following subjects: "Modern romantic hermeneutics as the basis of hermeneutical clinical ethics"(2016-20, 42,5000USD); "Establishment and evaluation of the hermeneutic approach to clinical ethics education" (2013-16, 35,000USD); "Elementary doctrines and methodology of clinical ethics" (2011-13, 35,000USD); "Ethical problems about interventions in the field of infectious diseases" (2012-14, 25,000USD); "Methodology of clinical ethics" (2008-10, 28,000USD); "Ethical problems about autonomy and paternalism in preventive medicine" (2005-7, 30,000USD). Also one *Health-and-Labour-Sciences Research Grant*: "Effective and ethically desirable strategy for HIV infection prevention among vulnerable" (2008-10, 192,500USD).

The collaborative relationships with Prof. Daniel Tsai (National Taiwan University), Prof. Ivo Kwon (Ewha Womans University, Korea), Prof. G. Widdershoven (Free University, Amsterdam), and Prof. J. Kole (Radboud University, Nijmegen) have been broadening our perspectives and activities.

2. Research Topic

You can choose and tackle any particular research topics of your own accord. You are not expected to take over any portion of the other members' or staffs' research projects. Though the teaching staffs would be pleased to help your academic endeavors by constructive discussion, reading club and the like, they will decline to be co-authors of your original papers, as is usual in the fields of human and social sciences. Your autonomy should be duly respected and you should be one and only responsible author of your own papers.

3. Application Requirements

You are challenged to improve your reading comprehension level through our rather hard training at weekly reading clubs. We read Levinas' *Time and Others* (2011), Kant's *Critique of Judgment and* Dilthey's *Comparative Psychology*(2012), Kant's *Critique of Pure Reason* and Habermas' *Post-metaphysical Thinking* (2013), Hegel's *Phenomenology of Mind* and Jacobs's *Dimensions of Moral Theory* (2014-).

4. Actual Current Situations

One graduate student earned her PhD degree (2013). One is enrolled in doctoral, one master program.

5. Contact

Our lab is located on the 4th floor of the Common Building at the Showa Campus.

medphilosophie@gmail.com or hattorik@gunma-u.ac.jp (Prof. HATTORI Kenji, MD DMedSc MA)

Learner's Attitudes to be Cultivated through Clinical Ethics Case Studies: with Reference to the Method of Psychotherapy Diagnostic Interview

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Abstract

Clinical ethics aims to provide practical approaches identifying, analyzing and solving moral problems in clinical settings. Educators of clinical ethics commonly do case studies as a useful educational method. Some authors have recently advocated a specific and unique way of case study, which regards a clinical ethics case as a literary story that should be interpreted by making full use of literary imagination. Based on this standpoint, we explore what kinds of attitudes learners should build through clinical ethics case study course. It seems helpful to refer to the method of psychotherapeutic interview at the first contact, core characteristics of which are placing importance on individuality and creating a hypothetical interpretation of the aspects of the patient. These two hold true of working of the clinical ethics case study. Clinical ethics case studies involve drawing a hypothetical image of the case by interpreting the characters of all the people involved and the circumstances in the case. Thus from an analogy between the way of psychotherapeutic interview and perusing cases in clinical ethics case study, we realize that learners of clinical ethics should attempt to throw imaginative light on and depict the case by focusing on the life history of characters in the case and by detecting what they do not understood yet in the given case, without eliminating their own subjective impressions. Through such touch working learners, at the same time, must effort to look deep inside and objectify themselves.

1. Background

Clinical ethics is a practical discipline of systematically identifying, analyzing, and solving ethical issues in clinical settings. Its methods vary from the top-down method that deductively applies ethical principles to cases, to the case approach conducting probable, tentative moral judgments by taking the specific state of each case into consideration in accordance with individual context.

To organize and examine the state of individual cases based on the case approach, Jonsen's four topics method sheet or something similar is widely used (Jonsen, 2010). This method is also often used in clinical ethics education case studies for students and health care providers. Yet, another method has been proposed that regards a clinical ethics case as a literary story that should be interpreted using literary imagination, rather than thinking of the case description as a collection of facts (Hattori, 2010). However, not enough debate has been conducted on this specific method. The author will closely examine it from the standpoint of interpreting cases using literary imagination and explore what attitudes learners should built in clinical ethics case studies. The method of psychotherapy diagnostic interview (PDI) broadly used in the field of clinical psychiatry and the attitudes it requires in therapists seem to be useful for our study as analogical references. While it has long been asserted as necessary to incorporate human understandings in the field of psychiatry into clinical settings (Noble, 1932), there has been no specific discussion of how this relates to case study methods in clinical ethics.

2. Case Understanding Ability

The study of clinical ethics does not deal with cases to illustrate general and abstract issues; rather, it always considers cases as an intricately intertwined complex of individual specific circumstances regarding the patients and their families with proper names. Hattori (2010, p.53) maintains that the essence of clinical ethics education is fostering the ability to understand cases. The ability to understand cases involves "before conducting moral judgment [...], participants perusing, comprehending and interpreting cases while using their imagination to search for the true motives and connections of those involved in specific contexts and situations." In effect, to properly make a moral judgment in individual cases, it is vital to focus on, peruse, and comprehend individual contexts. The contexts include the feelings, personality, history, and values behind the words of people who appear in the case before conducting rational reasoning based on ethical theories and principles. Any discrepancies in this first step will be amplified by the time one reaches the final judgment stage, causing significantly distorted reasoning (Hattori, 2012, p.88). Identifying and examining the ethical issues in a case requires the ability to understand that case.

3. Perusing Cases and the Method of Psychotherapy Diagnostic Interview in the Field of Psychiatric Interview

What does case understanding ability entail? The method of PDI seems suggestive and helpful as a reference in order to identify this ability. Psychiatrists usually conduct PDIs on patients to accurately understand their status, comprehend the relationship between the patients and their environment, identify how much their illness is impeding their lifestyle, and closely examine attitudes of patient and family to regarding treatment. It does not aim to dissect and examine patients, but to gain an overall understanding of them in their most natural state as a unique human being (Doi, 1996, p.119; Sullivan, 1970, pp.16-17). Proper PDI can provide an outlook for diagnosis, prognosis and treatment. A similar concept called case formulation exists in the field of clinical psychology (McWilliams, 1999). However, it differs from PDI as it provides a systemized framework and procedure for understanding patients.

PDIs are basically the similar as medical interviews for physical illnesses. At the initial examination, before moving onto detailed testing after medical interviews and examining physical findings, a differential diagnosis is

Department of Cardiovascular Medicine

(1) Research Interests

The major research interest in this department is to understand the molecular basis of the cardiovascular disease and to develop the new concept. Maladaptation or the inadequate response of the cardiovascular/respiratory system to the extracellular stimuli is responsible for the development of the disease. From these view points, the research in this department focuses on the molecular mechanisms of the gene expression in response to the extracellular signals that are relevant to the pathophysiology in vascular cells, myocardial cells, macrophages and alveolar cells. Furthermore, our research is aiming at the development of the new strategies to prevent the fatal arrhythmia associated with acute myocardial infaction which is the major cause of suden death. Recently, we starrted to use next generation sequencers to identify the novel genes that contribute to sudden cardiac death due to unknown cause.

(2) Research Projects

Atherosclerosis and heart failure are the leading causes of mortality world wide. We are aiming at the identification of the biomarkers that contribute to the early detection of the atherosclerosis and acute myocardial infarction. We are focusing to investigate stress-response mechanism in cardiovascular system using gene-manipulated mouse models. Furthermore, we are investigating the molecular approach to life threatening arrhythmias, such as Brugada syndrome, long QT sundrome, and idiopathic ventricular fibrillation, using next generation sequensers. In addition, we are investigating the novel mechanisms of heart failure by using the animal models of pressure overlaod, or mice with defective utilization of long-chain fatty acids.

(3) Admission to the Department

Applicants are eligible to enter this department after graduation of medical school and pass the English examination.

(4) Curent Fellows from Abroad

We have tthree post-doctoral fellows.

(5) After PhD-course Finishes

Post-doctoral fellows will be able to continue research activity if they receive followship to support the staying in Japan.

(6) Others

We are aiming at the high quality research with highly relevant to clinical medicine. Please join our research.

ORIGINAL RESEARCH

Elongation of Long-Chain Fatty Acid Family Member 6 (Elovl6)-Driven Fatty Acid Metabolism Regulates Vascular Smooth Muscle Cell Phenotype Through AMP-Activated Protein Kinase/Krüppel-Like Factor 4 (AMPK/KLF4) Signaling

Hiroaki Sunaga, PhD;* Hiroki Matsui, PhD;* Saki Anjo, MS; Mas Risky A. A. Syamsunarno, MD, PhD; Norimichi Koitabashi, MD, PhD; Tatsuya Iso, MD, PhD; Takashi Matsuzaka, PhD; Hitoshi Shimano, MD, PhD; Tomoyuki Yokoyama, MD, PhD; Masahiko Kurabayashi, MD, PhD

***Background*—**Fatty acids constitute the critical components of cell structure and function, and dysregulation of fatty acid composition may exert diverging vascular effects including proliferation, migration, and differentiation of vascular smooth muscle cells (VSMCs). However, direct evidence for this hypothesis has been lacking. We investigated the role of elongation of long-chain fatty acid member 6 (Elovl6), a rate-limiting enzyme catalyzing the elongation of saturated and monounsaturated long-chain fatty acid, in the regulation of phenotypic switching of VSMC.

***Methods and Results*—**Neointima formation following wire injury was markedly inhibited in Elovl6-null (Elovl6$^{-/-}$) mice, and cultured VSMCs with siRNA-mediated knockdown of Elovl6 was barely responsive to PDGF-BB. Elovl6 inhibition induced cell cycle suppressors p53 and p21 and reduced the mammalian targets of rapamycin (mTOR) phosphorylation and VSMC marker expression. These changes are ascribed to increased palmitate levels and reduced oleate levels, changes that lead to reactive oxygen species (ROS) production and resulting AMP-activated protein kinase (AMPK) activation. Notably, Elovl6 inhibition robustly induced the pluripotency gene Krüppel-like factor 4 (KLF4) expression in VSMC, and KLF4 knockdown significantly attenuated AMPK-induced phenotypic switching of VSMC, indicating that KLF4 is a bona fide target of AMPK.

***Conclusions*—**We demonstrate for the first time that dysregulation of Elovl6-driven long-chain fatty acid metabolism induces phenotypic switching of VSMC via ROS production and AMPK/KLF4 signaling that leads to growth arrest and downregulation of VSMC marker expression. The modulation of Elovl6-mediated cellular processes may provide an intriguing approach for tackling atherosclerosis and postangioplasty restenosis. **(*J Am Heart Assoc.* 2016;5:e004014 doi: 10.1161/JAHA.116.004014)**

Key Words: Elovl6 • fatty acid • neointimal hyperplasia • proliferation • smooth muscle cell

Phenotypic modulation of vascular smooth muscle cells (VSMCs) is a critical process that regulates the progression of proliferative vascular disease including atherosclerosis and postangioplasty restenosis.[1-4] There have been extensive studies demonstrating that various growth factors, such as platelet-derived growth factor (PDGF) and fibroblast growth factor-2, promote phenotypic switching characterized by the downregulation of expression of differentiation marker genes such as smooth muscle α-actin (SMα-actin) and smooth muscle myosin heavy chain and the induction of proliferative capacity

From the Department of Laboratory Sciences, Gunma University Graduate School of Health Sciences, Maebashi, Japan (H. Sunaga, H.M., S.A., T.Y.); Department of Medicine and Biological Sciences, Gunma University Graduate School of Medicine, Maebashi, Japan (H. Sunaga, M.R.A.A.S., N.K., T.I., M.K.); Department of Biochemistry, Faculty of Medicine Universitas Padjadjaran, Jatinangor, Indonesia (M.R.A.A.S.); Department of Internal Medicine (Endocrinology and Metabolism), Faculty of Medicine, University of Tsukuba, Japan (T.M., H. Shimano); Graduate School of Comprehensive Human Sciences International Institute for Integrative Sleep Medicine (WPI-IIIS), Tsukuba, Japan (H. Shimano).

Accompanying Data S1, Figures S1 through S10, and Tables S1 and S2 are available at http://jaha.ahajournals.org/content/5/12/e004014/DC1/embed/inline-supplementary-material-1.pdf

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Department of Respiratory Medicine

(1) General information

Department of Respiratory medicine has been working on the basic research to contribute to clinical matters. We are keenly performing clinical studies collaborating with affiliated hospitals. To foster Physician Scientists, medical doctors maintaining research minds, is one of goals we aiming.

(2) Research Projects

1) Analyses of pathogenesis relevant to asthma, especially severe refractory asthma, using molecular technique.
2) To elucidate the molecular mechanisms of lung fibrosis and COPD. To approach to these issues, we are investigating the cellular response to oxidative stress and hypoxia.
3) To elucidate molecular signal transduction systems relevant to lung cancer with *kras* mutation positive. Also, to develop new therapeutic techniques targeting amino acid transporter, LAT1.

(3) Admission to this PhD course

Fellows can apply for admission after they have completed their mandatory two-year clinical training. Before starting graduate student course, several fellows have been trained for additional years in their clinical specialties.

(4) Current fellow

We have currently five post-graduated PhD students.

(5) Course after PhD student

Graduates re-start clinical profession and/or continue research work. Many graduates experience overseas research work.

(6) Others

Clinical and basic researches for allergy and respiratory diseases are needed more than ever in our aging society. We try to investigate the pathogenesis of these diseases to make them clear and we would like to give our research work contribution to the medical development.

Int J Clin Oncol
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ORIGINAL ARTICLE

High expression of GRP78/BiP as a novel predictor of favorable outcomes in patients with advanced thymic carcinoma

Yosuke Miura[1,2] · Kyoichi Kaira[2,3] · Reiko Sakurai[2,4] · Hisao Imai[1] · Yoshio Tomizawa[4] · Noriaki Sunaga[2,5] · Koichi Minato[1] · Takeshi Hisada[2] · Tetsunari Oyama[6] · Masanobu Yamada[2]

Received: 24 February 2017 / Accepted: 14 May 2017

Abstract
Background Glucose-regulated protein (GRP) 78/immunoglobulin heavy chain binding protein (BiP) is a member of the endoplasmic reticulum chaperone family, and its role in various types of human malignancies has recently been investigated. However, the clinicopathological characteristics of GRP78/BiP in advanced thymic carcinoma (ATC) remain unknown. We aimed to examine the relationship between GRP78/BiP expression and the clinical outcomes of ATC patients.
Methods Thirty-four patients with ATC receiving combination chemotherapy at three institutions between April 1998 and April 2014 were enrolled in this study. We retrospectively collected patient characteristics such as therapeutic efficacy, pathological findings, and survival data from their medical records. We performed immunohistochemical analysis to evaluate the expression of GRP78/BiP in tumor specimens obtained from surgical resection or biopsy.
Results This study included 21 men (68%) and 13 women (32%) with a median age of 62 years (range 36–75 years). GRP78/BiP overexpression was observed in 65% of the patients (22 of 34 patients). There was no correlation between GRP78/BiP expression and any patient characteristic. Patients with a high level of GRP78/BiP expression had significantly longer overall survival (OS) compared to those with a low level (46.2 vs. 16.8 months, $p = 0.04$). Multivariate analysis demonstrated that a high level of GRP78/BiP expression was an independent prognostic factor for prolonged OS.
Conclusions Our findings indicate that the overexpression of GRP78/BiP is a novel predictor of favorable outcomes in patients with ATC who receive combination chemotherapy.

Keywords Thymic carcinoma · Glucose-regulated protein 78/immunoglobulin heavy chain binding protein · Endoplasmic reticulum stress · Prognostic factor · Biomarker

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Introduction

Thymic carcinoma (TC) is a rare malignancy in the anterior mediastinum with an annual incidence of 0.13 cases/100,000 population [1], and it constitutes approximately 5% of all thymic epithelial tumors (TETs) [2]. TC has a propensity to invade surrounding tissues and metastasize, and approximately two-thirds of all patients with TC are diagnosed with locally advanced or systemic disease [3]. These aggressive features lead to a poor prognosis in the Japanese inoperable population, with a 5-year survival rate of 24% [4].

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Department of Internal Med, Division of Gastroenterology and Hepatology

1） Introduction

Our department performs the basic and clinical study to make contributions to the clinical progression of gastroenterology and hepatology. As well as basic sciences, the clinical studies including multi-institution joint research are performed actively. We aim to develop physician scientists who are keeping research mind even after graduation.

2） Current Research Topics

【1】**Upper GI Group**：Investigation of pathophysiology and development of new therapy for functional gastrointestinal disorders, including functional dyspepsia (FD) and esophageal motility disorders. Research of pathophysiology of gastroesophageal reflux disease (GERD) and its complications: sleep disturbance, supraesophageal GERD, and so on. Application of photodynamic therapy (PDT) with newly developed photosensitizer to the treatment for early gastric cancer. Development of new equipment for gastrointestinal motility recording.

【2】**Pancreato-biliary and Duodenal Group**：Our group accumulates a large number of pancreato-biliary cases by multicenter study and analyzes clinical data associated with endoscopic technique.

【3】**Large intestine Group**： The large intestine and small intestine disease cases are collected multi-institution joint research, clinical study, etc., and the clinical data about the large intestine and a small intestine disease is analyzed.

【4】**Hepatology Group**：We investigate the mechanisms of liver fibrosis, hepatocarcinogenesis, innate immunity, metabolic disorders including nonalcoholic steatohepatitis and drug metabolism.

3） Entrance Way to Graduate School

Fellows can apply for admission anytime after they have completed their mandatory two-year clinical training. Before starting graduate student course, several fellows have been trained for additional one to two years in their clinical specialties.

4） The Number of Students in Our Graduate School Course

We have currently 5 students working in our division and a laboratory in the Institute for Molecular and Cellular Regulation, Gunma University.

5） Course after Graduation

After graduation, a number of doctors have studied abroad as a post-doctoral fellow mainly in the United States and also have extended their research careers while working as a clinical stuff in our department or group hospitals.

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The Japanese Society of Gastroenterology

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Prevalence of nonalcoholic steatohepatitis in Japanese patients with morbid obesity undergoing bariatric surgery

Yosuke Seki[1] · Satoru Kakizaki[2] · Norio Horiguchi[2] · Hiroaki Hashizume[2] · Hiroki Tojima[2] · Yuichi Yamazaki[2] · Ken Sato[2] · Motoyasu Kusano[2] · Masanobu Yamada[2] · Kazunori Kasama[1]

Received: 26 May 2015 / Accepted: 3 August 2015 / Published online: 28 August 2015

Abstract
Background Patients with morbid obesity selected for bariatric surgery have a high prevalence of nonalcoholic steatohepatitis (NASH); however, the incidence is varied and depends on race. The prevalence of NASH in obese Japanese patients is unknown. We evaluated the prevalence of NASH in a prospective cohort of Japanese patients with morbid obesity.
Methods From October 2009 to July 2011, consecutive patients requiring bariatric surgery underwent a liver biopsy during the operation. The indications for bariatric surgery followed the guidelines of the Asia–Pacific Metabolic and Bariatric Surgery Society.
Results One hundred two patients (55 males and 47 females, age 42.7 ± 10.7 years) were analyzed. The mean body mass index was 42.1 ± 8.2 kg/m^2. Among the 102 patients, 84 patients (82.4 %) had nonalcoholic fatty liver disease and 79 patients (77.5 %) had NASH. The grading and staging of NASH by Brunt's classification were as follows: grade 0 steatosis, one patient; grade 1 steatosis, 35 patients; grade 2 steatosis, 32 patients; grade 3 steatosis, 11 patients; stage 1 fibrosis, 25 patients; stage 2 fibrosis, 38 patients; stage 3 fibrosis, 16 patients, stage 4 fibrosis, no patients. The body weight, waist–hip ratio, visceral fat area, and aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, fasting plasma glucose, fasting plasma insulin, C peptide, hemoglobin A_{1c}, and homeostasis model assessment insulin resistance levels were significantly elevated in the NASH group in comparison with the non-NASH group. The platelet count was significantly decreased in the NASH group. The waist–hip ratio and the alanine aminotransferase, fasting plasma glucose, and homeostasis model assessment insulin resistance levels were found to be independent predictors of NASH in a multivariate analysis.
Conclusion The prevalence of NASH was 77.5 % in this prospective Japanese cohort. The prevalence of NASH in Japanese morbidly obese patients was extremely high, and early intervention should be undertaken.

Keywords Nonalcoholic steatohepatitis · Morbidly obesity · Bariatric surgery

Abbreviations

ALT	Alanine aminotransferase
BMI	Body mass index
HAIR	Hypertension, alanine aminotransferase, and insulin resistance
HOMA-IR	Homeostasis model assessment insulin resistance
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis

Introduction

The number of obese patients is increasing worldwide, and the increase in the number of patients with morbid obesity is a major social problem [1]. Morbid obesity tends to be

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Introduction of the Department of Endocrinology and Metabolism

(1) Subgroup

Our department is consisted of two subgroups; the Endocrinology and Metabolism group and the Diabetes group.

(2) Current research topics

The Endocrinology and Metabolism group: Disruption of endocrine and metabolic homeostasis causes many life-style diseases. We mainly investigate regulation of gene transcription and mRNA splicing by nuclear hormone receptors and co-regulators and the molecular mechanism underlying tumorigenesis of endocrine tumors caused by mutations of ion channels and transcription factors.

Diabetes group:

Our research focus is insulin resistance, autophagy, sarcopenia, and cancer. We are tyrying to understand the mechanism of each pathological condition and create new treatments. Our final goal is to cure patients.

(3) The entrance to the Graduate School

Graduate students can enter the course anytime after finishing their initial clinical training.

(4) The number of current Graduate School students

Eight students including one in the night course are currently studying in our department.

(5) The future activity after graduation

After graduation, some doctors study abroad, mainly in the United States, to extend their experimental carriers. Others continue clinical research in the University Hospital or city hospitals.

Whole-Exome Sequencing Study of Thyrotropin-Secreting Pituitary Adenomas

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Context: Thyrotropin (TSH)-secreting pituitary adenomas (TSHomas) are a rare cause of hyperthyroidism, and the genetic aberrations responsible remain unknown.

Objective: To identify somatic genetic abnormalities in TSHomas.

Design and Setting: A single-nucleotide polymorphism (SNP) array analysis was performed on 8 TSHomas. Four tumors with no allelic losses or limited loss of heterozygosity were selected, and whole-exome sequencing was performed, including their corresponding blood samples. Somatic variants were confirmed by Sanger sequencing. A set of 8 tumors was also assessed to validate candidate genes.

Patients: Twelve patients with sporadic TSHomas were examined.

Results: The overall performance of whole-exome sequencing was good, with an average coverage of each base in the targeted region of 97.6%. Six DNA variants were confirmed as candidate driver mutations, with an average of 1.5 somatic mutations per tumor. No mutations were recurrent. Two of these mutations were found in genes with an established role in malignant tumorigenesis (*SMOX* and *SYTL3*), and 4 had unknown roles (*ZSCAN23*, *ASTN2*, *R3HDM2*, and *CWH43*). Similarly, an SNP array analysis revealed frequent chromosomal regions of copy number gains, including recurrent gains at loci harboring 4 of these 6 genes.

Conclusions: Several candidate somatic mutations and changes in copy numbers for TSHomas were identified. The results showed no recurrence of mutations in the tumors studied but a low number of mutations, thereby highlighting their benign nature. Further studies on a larger cohort of TSHomas, along with the use of epigenetic and transcriptomic approaches, may reveal the underlying genetic lesions. (***J Clin Endocrinol Metab*** **102: 566–575, 2017)**

Thyrotropin (TSH)-secreting pituitary adenomas (TSHomas) account for 0.5% to 2.8% of all pituitary adenomas, and an increasing number of these tumors have been reported during the last decade (1, 2). Although goiter and hyperthyroidism are hallmark features in patients with these tumors, many plurihormonal tumors also present with the features of excess growth hormone and prolactin (3, 4). Similarly, because most of these tumors are macroadenomas and are invasive, neurologic features, such as ocular symptoms and headaches due to mass effects, also cause considerable morbidity (4). Surgery remains the treatment of choice; however, surgical resection is often incomplete for macroadenomas, and, consequently, most research recently performed has focused on medical management (5–7). Therefore, elucidating the genetic events that underlie TSHomas could lead to advances in their management.

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Abbreviations: cnLOH, copy number-neutral loss of heterozygosity; LOH, loss of heterozygosity; SNP, single-nucleotide polymorphism; SNV, single-nucleotide variant; TSG, tumor suppressor gene; TSH, thyrotropin; TSHoma, thyrotropin-secreting pituitary adenoma; WES, whole-exome sequencing.

Department of Nephrology and Rheumatology

(1) Introduction

Members of our department are engaged in basic and clinical research in the field of nephrology and rheumatology to clarify the mechanisms of each disease and to develop new diagnostic and treatment methods. Research teams are organized based on the research projects and are actively collaborating with other academic institutions.

(2) Research interests

- Mechanisms of renal tubular regeneration and tubulointerstitial fibrosis.
- Discovery of urinary biomarkers to predict histological diagnosis, response to treatment and renal prognosis.
- Role of dendritic cells in autoimmune diseases and renal diseases.
- Role of podocytes and glomerular parietal cells as a glomerular filtration barrier.
- Clinical study of pathophysiology and treatment of SLE and ANCA-associated vasculitis.

(3) How to start graduate course

It is recommended to start the graduate course after finishing 2 years of initial clinical training and at least 1 year of additional clinical training. Evening graduate students are also accepted. If the new internal medicine residency program starts next year, the graduate course will be provided, in which students can start research after 2 years of clinical training for internal medicine.

(4) Current situation of graduate students

Seven graduate students, including 4 evening graduate students, are currently studying at our department. Students are engaged in multiple projects of both basic and clinical research. Students are expected to improve their clinical ability through attending clinical conferences, clinical journal clubs and outpatient clinics.

(5) After finishing graduate course.

Most post-graduate students become physicians at our department or its affiliated hospitals and undergo clinical training for a board certified nephrologist and rheumatologist, together with executing clinical research. Some students go abroad to continue and extend basic research. During the last 10 years, 2 post-graduate students studied in NIH of USA and 1 post-graduate student currently studies at University of Washington in USA.

Am J Physiol Renal Physiol 312: F297–F304, 2017.
First published November 23, 2016; doi:10.1152/ajprenal.00191.2016.

RESEARCH ARTICLE

Involvement of infiltrating macrophage-derived activin A in the progression of renal damage in MRL-*lpr* mice

Anastasie Tshilela Kadiombo, Akito Maeshima, Ken Kayakabe, Hidekazu Ikeuchi, Toru Sakairi, Yoriaki Kaneko, Keiju Hiromura, and Yoshihisa Nojima

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Submitted 28 March 2016; accepted in final form 20 November 2016

Kadiombo AT, Maeshima A, Kayakabe K, Ikeuchi H, Sakairi T, Kaneko Y, Hiromura K, Nojima Y. Involvement of infiltrating macrophage-derived activin A in the progression of renal damage in MRL-*lpr* mice. *Am J Physiol Renal Physiol* 312: F297–F304, 2017. First published November 23, 2016; doi:10.1152/ajprenal.00191.2016.—Lupus nephritis is a life-threatening complication of systemic lupus erythematosus (SLE). Various growth factors, cytokines, and chemokines are implicated in the development of SLE. However, the pathophysiological processes involved in the development of lupus nephritis still remain unclear. In this study, we examined the involvement of activin A, a member of the transforming growth factor β (TGF-β) superfamily, in the progression of renal damage in lupus-prone MRL-*lpr* mice. Activin A was not expressed in the kidneys of control MRL-MpJ mice but was detectable in perivascular infiltrating cluster of differentiation 68 (CD68)-positive cells in the kidneys of MRL-*lpr* mice. Urinary activin A, which was also absent in MRL-MpJ mice, was detectable in MRL-*lpr* mice from 16 wk onward. Urinary activin A levels were significantly correlated with the number of perivascular inflammatory cell layers, the number of crescentic glomeruli, and the percentage of Elastica van Gieson (EVG)-positive fibrotic areas, but not with urinary protein levels or serum activin A. When activin action was blocked in vivo by the intraperitoneal administration of an activin antagonist, follistatin, the number of crescentic glomeruli, percentage of EVG-positive fibrotic areas, CD68-positive cell infiltration, and proteinuria were significantly reduced in a dose-dependent manner. These data suggest that infiltrating macrophage-derived activin A is involved in the progression of renal damage in MRL-*lpr* mice.

activin; lupus nephritis; urinary biomarker

LUPUS NEPHRITIS is a life-threatening complication of systemic lupus erythematosus (SLE), an autoimmune disease characterized by the production of autoantibodies to various nuclear components which results in complement activation and immune complex deposition in several organs (21). Deregulated cytokine production is considered to contribute to immune dysfunction and mediate tissue inflammation and organ damage in SLE. Multiple proinflammatory cytokines including type I and II interferons, IL-6, IL-1, and TNF-α have been reported to be involved in the development of SLE (44). Immunomodulatory cytokines such as IL-10 and transforming growth factor β (TGF-β) have also been identified as key players in this disease (42, 49).

Activin is a multifunctional cytokine belonging to the TGF-β superfamily which regulates the growth and differentiation of cells in various organs (51). Its action is modulated by an endogenous activin antagonist, follistatin (34). Activin signals are mediated by two types of cell surface serine/threonine receptors. Activin first binds to the type II receptor (ActRII or ActRIIB), which leads to recruitment and phosphorylation of the type I receptor (ActRI or ActRIB) and formation of receptor complexes. The activated type I receptor then phosphorylates Smad proteins, which are subsequently translocated to the nucleus and regulate target gene expression (11).

A series of recent studies suggest that activin A is a critical regulator of inflammation (4) and plays a major role in controlling the cytokine cascade that drives the inflammatory response (14). For example, increased activin expression was observed in inflammatory arthropathies (40, 48). Activin expression was correlated with the degree of inflammation in inflammatory bowel disease in mice (5). In vitro studies have also demonstrated strong induction of activin A expression by proinflammatory cytokines (12). Activin A is released by proinflammatory M1 macrophages and suppresses the production of the anti-inflammatory cytokine, IL-10, by lipopolysaccharide-stimulated M2 macrophages (47). In contrast, it is also recognized that activin A stimulates monocyte/macrophages to produce several inflammatory cytokines, including IL-1β, TNF-α, and IL-6 (36, 37, 52). The release of activin into the circulation precedes the release of proinflammatory cytokines after lipopolysaccharide treatment (13). These data suggest a proinflammatory action for activin. Recently, it has been reported that serum levels of activin A, which was significantly higher in SLE, correlated positively with disease activity of SLE (6). However, little is known about the role of activin A in the development and progression of renal damage in lupus nephritis.

In this study, we examined the role of activin A in MRL-*lpr* mice which develop a kidney disease resembling human lupus nephritis (22). We found that activin A was produced by the macrophages infiltrating in the interstitium of the kidney in these mice. Inactivation of activin A by follistatin significantly reduced renal damage, proteinuria, and macrophage infiltration in a dose-dependent manner, suggesting that activin A might be an attractive target for the treatment of lupus nephritis.

MATERIALS AND METHODS

Mice. Eight-week-old female MRL-*lpr* and control MRL-MpJ mice (The Jackson Laboratory, Bar Harbor, ME) were housed under specific pathogen-free conditions and provided with autoclaved food and sterile water ad libitum. Mice were randomly tested and documented to be serologically negative for common murine pathogens. For

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Department of Hematology

(1) Introduction

Our research area is comprised of groups studying hematologic malignancies, blood-coagulation disorder, and HIV infection. Each group performs translational research to clarify the cause of the disease and to find out the optimal therapy. Also, we push forward clinical studies in cooperation with affiliated hospitals and domestic and foreign various study groups.

(2) Research Interest

- Whole exome analysis of hereditary blood coagulation disorder
- Establishing the therapy for acquired blood-coagulation disorder
- Analysis of role of glucose transporters in malignant lymphoma
- Genetic search related to extramedullary mass formation of hematological malignancies
- Analysis of the role of the non-coding RNA in multiple myeloma
- Pneumocystis pneumonia risk and genetic polymorphism in HIV patients

(3) How to start graduate course

It is recommended to receive 2 years of post-graduate clinical training before starting graduate course. Evening graduate students are also accepted. If the new internal medicine residency program starts next year, the graduate course will be provided, in which students can start research after 2 years of clinical training for internal medicine.

(4) Current situation of graduate students.

Three graduate students, including 2 students who are now studying at other domestic or foreign institutions. Students are expected to improve their clinical ability through attending clinical conferences and journal club. Some students are taking a medical oncologist training course of cancer professional training plan.

(5) After finishing graduate course

After finishing graduate course, most students become a physician at our department or the affiliated hospitals and undergo clinical training for a board certified physician together with executing clinical research. Some students go abroad or to other institutions in Japan to expand basic research.

3. Presentive Research for Department of Hematology

BCL6 Overexpression Alters Gene Expression Profile in a Myeloma Cell Line and Is Associated with Decreased DNA Damage Response.

Tahara K, Takizawa M, Yamane A, Osaki Y, Ishizaki T, Mitsui T, Yokohama A, Saitoh T, Tsukamoto N, Matsumoto M, Murakami H, Nojima Y, Handa H.

Cancer Sci. 2017 May 23. doi: 10.1111/cas.13283. [Epub ahead of print]

Abstract
BCL6 attenuates DNA damage response (DDR) through gene repression and facilitates tolerance to genomic instability during immunoglobulin affinity maturation in germinal center (GC) B cells. Although BCL6 expression is repressed through normal differentiation of GC B cells into plasma cells, a recent study showed the ectopic expression of BCL6 in primary multiple myeloma (MM) cells. However, the functional roles of BCL6 in MM cells are largely unknown. Here, we report that overexpression of BCL6 in a MM cell line, KMS12PE, induced transcriptional repression of ataxia telangiectasia mutated (ATM), a DDR signaling kinase, which was associated with a reduction in γH2AX formation after DNA damage. In contrast, transcription of known targets of BCL6 in GC B cells was not affected, suggesting a cell type-specific function of BCL6. To further investigate the effects of BCL6 overexpression on the MM cell line, we performed mRNA-sequence analysis and found an up-regulation in the genomic mutator activation-induced cytidine deaminase (AID) with alteration in the gene expression profile, which is suggestive of de-differentiation from plasma cells. Moreover, IL-6-exposure to KMS12PE led to up-regulation of BCL6 and AID, down-regulation of ATM, and attenuation of DDR, which were consistent with the effects of BCL6 overexpression in this MM cell line. Taken together, these results indicated that overexpression of BCL6 alters gene expression profile and confers decreased DDR in MM cells. This phenotypic change could be reproduced by IL-6 stimulation, suggesting an important role of external stimuli in inducing genomic instability, which is a hallmark of MM cells.

Neurology

(1) Members

Professor: Yoshio Ikeda

Associate professor: Masaki Ikeda

Senior assistant professor: Yukio Fujita

Assistant professor: Kazuaki Nagashima, Kouki Makioka, Kimitoshi Hirayanagi, Natsumi Furuta, Setsuki Tsukagoshi, Hiroo Kasahara

(2) Current research projects

1. To develop early diagnostic tools and establish biomarkers for Alzheimer disease (AD)
   Number of elderly people suffering from AD is increasing, and early development of effective disease-modifying therapy is expected. We are establishing diagnostic tools such as Aβ-amyloid imaging (PIB-PET) and CSF biomarkers which are useful for early diagnosis of AD.
2. To unravel a pathogenesis of amyotrophic lateral sclerosis (ALS)
   The biggest intractable neurological disease, ALS, is the most prioritized target for early development of effective therapy. To explore a pathogenesis of ALS, we are investigating the autopsy brain tissues of ALS subjects, and clarified the pathological molecules causing ALS.
3. To elucidate a pathogenesis of microsatellite-repeat expansion disorders including SCAs
   Microsatellite expansions of CAG, CTG, or GGCCTG repeat units are common genetic mutations of the hereditary neurological disorders such as spinocerebellar ataxia (SCA). We are trying to establish cell culture or animal models which are affected by these mutations. We hope to develop a novel disease-modifying therapy for SCA by analyzing these models.
4. To identify a responsible gene for the hereditary neurological disorders
   By using techniques such as conventional positional cloning or high throughput DNA sequencing, we are trying to identify a responsible gene for unknown hereditary neurological disorders.
5. To develop support systems for intractable neurological disorders
   By collaborating with specialists in other departments, we are developing the better care systems to support patients suffering from intractable neurological disorders.

(3) Eligibility

Most postgraduate students enter after a 5-6 years carrier of clinical activities and obtaining a license for neurological specialist. Students who do not have a license for medical doctor also can enter the postgraduate school.

(4) Current postgraduate students

1st grade; 1 student, 2nd grade; 1 student, 3rd grade; 1 student, 4th grade; 1 student

Research project of each student is decided by their interests or professor's suggestion.

Postgraduate students with a license of medical doctor can obtain their living expenses by a part time job in clinical section.

(5) A course after graduation

The former postgraduate students are working as a researcher, or a physician scientist of the university hospital or satellite hospitals. Overseas study is greatly encouraged.

NEUROPATHOLOGY

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Original Article

Hypersialylation is a common feature of neurofibrillary tangles and granulovacuolar degenerations in Alzheimer's disease and tauopathy brains

Shun Nagamine,[1] Tsuneo Yamazaki,[2] Kouki Makioka,[1] Yukio Fujita,[1] Masaki Ikeda,[1] Masamitsu Takatama,[3] Koichi Okamoto,[3] Hideaki Yokoo[4] and Yoshio Ikeda[1]

[1]Department of Neurology, Gunma University Graduate School of Medicine, [2]Department of Rehabilitation, Gunma University Graduate School of Health Sciences, [3]Geriatrics Research Institute and Hospital, and [4]Department of Human Pathology, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

Glycosylation is one of the major post-translational modifications of proteins. The status of sialylation of the neuropathological hallmarks of various neurodegenerative disorders was investigated in this study. Here, we report the novel findings that two phosphorylated tau (p-tau)-containing structures associated with Alzheimer's disease (AD), that is, neurofibrillary tangles (NFTs) and granulovacuolar degenerations (GVDs), were hypersialylated. The NFTs, GVDs and dystrophic neurites of senile plaques (SPs) in AD hippocampi were clearly visualized by immunohistochemistry using an anti-sialic acid (SA) antibody. In contrast, the amyloid core of SPs was not sialylated at all. Interestingly, other p-tau-containing structures, that is, globose-type NFTs in progressive supranuclear palsy and Pick bodies and ballooned neurons in frontotemporal lobar degeneration with Pick bodies, were also hypersialylated. Unlike the p-tau-containing structures observed in tauopathies, the hallmarks of other neurodegenerative disorders, such as Lewy bodies in Parkinson's disease, glial cytoplasmic inclusions in multiple system atrophy, Bunina bodies, skein-like inclusions and round inclusions in amyotrophic lateral sclerosis, intranuclear inclusions in neuronal intranuclear inclusion disease and physiological bodies or granules (lipofuscin granules, corpora amylacea and melanin granules), were not immunolabeled by the anti-SA antibody. Because this antibody specifically identified NFTs and GVDs, immunostaining for sialylation represents a useful tool to screen these structures in a diagnostic setting. These results clearly indicate that the pathological hallmarks of various tauopathies are commonly hypersialylated, and that sialylation plays an important role in the process of p-tau accumulation in AD and other tauopathies.

Key words: Alzheimer's disease, granulovacuolar degeneration, hypersialylation, neurofibrillary tangle, tauopathy.

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INTRODUCTION

Tau is a major component of neurofibrillary tangles (NFT), which are one of the neuropathological hallmarks of Alzheimer's disease (AD) brains.[1] Hyperphosphorylation of tau promotes its self-assembly into paired helical filaments (PHFs).[2] In AD brains, tau is aberrantly glycosylated with various oligosaccharides, including N-acetylneuraminic acid (NeuAc), which is a major member of the sialic acid (SA) family.[3–5] In contrast, deglycosylation by glycosidases depresses the phosphorylation of tau.[6] These findings suggest that aberrant glycosylation in AD brains facilitates the hyperphosphorylation of tau, resulting in the formation of NFTs.[5] In support of this hypothesis, some biological changes of SAs and sialyltransferases have been reported in AD patients.[7–10]

With regard to the relationship between sialylation and amyloid β (Aβ) pathology of AD, it has been reported that the β-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE-1) can cleave not only APP but the sialyltransferase ST6Gal-I, thus downregulating its transferase activity.[11] In addition, a genome-wide association study of AD identified that the common variant of CD33, also known as Siglec-3 and a member of the sialic acid-binding immunoglobulin-like lectins, is a genetic risk factor for AD.[12,13] The uptake and clearance of Aβ due to microglias

Division of cardiovascular surgery, Department of General Surgical Science

(1) Introduction of the medical laboratory

Our research laboratory belongs to the Department of General Surgical Science, and we are collaborating on our studies with other laboratories.

(2) Recent our studies

We studies mainly about the organ protection during the surgery. In cardiovascular surgery, many important organs suffer ischemic stress and ischemia-reperfusion injury, then falling into critical organ failure. Brain and heart protection is our long lasting themes of studies, especially.

(3) Admission to the post graduate school

Any candidates can admit to the post graduate course after the graduation of the medical school.

(4) Daily life of the post graduate course

There are no students in our post graduate course. After admission to the post graduate course, students may research mainly and write papers as soon as they can.

(5) Career path after the graduation

Working in the hospital or going abroad to study.

The comparison of mitogen-activated protein kinases that become activated within the left ventricular and right atrial tissues following heart transplantation in canine model.

Koike N, Takeyoshi I, Ohki S, Tokumine M, Morishita Y.

Abstract :
The activation of p38 mitogen-activated protein kinase (MAPK) plays an important role in ischemia/reperfusion injury. Some reports have documented MAPKs activation of the myocardium in human models, using right atrial (RA) tissue for samples. This study compared the activation of MAPKs in left ventricle (LV) and RA tissues in canine heart transplantation. Four dogs were used as baseline data at two points, before and 20 min after warm ischemia (baseline model), and eight dogs (four pairs of donor and recipient) were used at other points: 4 h after cold ischemia, and at 10, 60, and 180 min after reperfusion (transplantation model). In the transplantation model, donor hearts were left in situ for 20 min after cardiac arrest, and were immersed in Celsior solution for 4 h after coronary flushing. Orthotopic heart transplantation was then performed. Two groups were created: the LV and RA groups (n = 4 in each group). Heart tissue was harvested from the left ventricular wall in the LV group and from the right atrial appendage in the RA group. The activation of MAPKs, including p38 MAPK, c-Jun N-terminal protein kinase (JNK), and extracellular signal-regulated protein kinase (ERK), was evaluated at each point. The activation patterns of p38 MAPK and ERK were similar in the RA and LV groups, but JNK activation was different in the two groups, after ischemia and reperfusion. Thus, RA tissue may be deliberately used as a substitute for LV tissue when investigating the activation of MAPKs in a human model. (J Invest Surg. 20:105-11, 2007)

General Surgical Science –Thoracic Group-

(1) Thoracic research group

The Thoracic Group is a branch of the General Surgical Science Department. Our team consist of 10 members: 8 members working in the clinics and 2 graduate students. There is active cooperation within the team from bench to bedside, which provides an ideal environment for translational research.

(2) Ongoing research themes

Our group focus on a wide range of thoracic diseases, except for esophageal, cardiac, and breast disease. Basic research themes are: (1) carcinogenesis of squamous cell lung cancer, (2) detection methods for driver gene mutations in lung cancer, (3) impact of single nucleotide polymorphisms (SNPs) in lung cancer, (4) bystander effect as a mechanism of EGFR-TKI resistance, (5) generation and maintenance of tumor antigen-specific CD8 T cells. Clinical research themes are: (1) analysis of segmental anatomy based on three-dimensional computed tomography (3D-CT) images, and (2) tumor doubling time in lung cancer.

(3) How to work with us

Graduates from medical school are welcome to join our research team at any time in their career; whether before or after finishing surgical training.

(4) Graduate students in the Thoracic Group

Graduate students can basically commit to research on a full-time basis and do not have clinical obligations. However, in order to promote translational research, they are encouraged to attend at cancer board meetings, pathological conferences, and journal clubs which are held every week.

(5) Career options for postgraduates

Postgraduate students may either continue their research in our group in parallel to clinical work or extend their research field in other laboratories, both domestic and abroad. Recently, two postgraduates have gone to other laboratories: one member went at Dana-Faber Cancer Institute (Massachusetts, USA) for three years, and another member is actually at The University of Texas Southwestern Medical Center (Texas, USA).

Gen Thorac Cardiovasc Surg. 2017 Jun;65(6):343-349. doi: 10.1007/s11748-017-0754-4. Epub 2017 Feb 14.

Analysis of variation in bronchovascular pattern of the right middle and lower lobes of the lung using three-dimensional CT angiography and bronchography.

Nagashima T, Shimizu K, Ohtaki Y, Obayashi K, Nakazawa S, Mogi A, Kuwano H.

Abstract
OBJECTIVES:
General thoracic surgeons must be familiar with anatomical variation in the pulmonary vessels and bronchi. Here, we analyzed the bronchovascular pattern of the right middle lobe (RML) and right lower lobe (RLL) of the lung using three-dimensional CT angiography and bronchography (3DCTAB).
METHODS:
We reviewed the anatomical patterns of the pulmonary vessels and bronchi in 270 patients using 3DCTAB images.
RESULTS:
The branching patterns of vessels and bronchi of RML and S6 were classified according to the number of stems. The single-stem type was the most common, except in the artery of the RML, for which the two-stem type was the most common. The artery and bronchus of S*, which is an independent segment between S6 and S10, were observed in 20.4% of cases. The branching pattern of A7 (B7) was classified into four types. The A7a (B7a) type was observed in 74.8% of cases, and was the most common. The branching pattern of the artery and bronchus of S8-10 was classified into five and three types, respectively. The A8 and A9 + A10 type, and the B8 and B9 + B10 type, were observed in 68.1 and 80.4% of cases, respectively, and were the most common types. The branching pattern of V8-10 was more complex than that of A8-10 and B8-10.
CONCLUSION:
We explored the bronchovascular patterns of RML and RLL and their frequencies using a large number of 3DCTAB images. Our data can be used by thoracic surgeons to perform safe and precise lung resections.

Department of General Surgical Science, Division of Gastroenterological Surgery

1) Staff

Professor: Hiroyuki KUWANO
Associate Professors: Tatsuya MIYAZAKI
Assistant Professors: Makoto SOHDA, Hiroomi Ogawa, Kyoichi OGATA, Makoto SAKAI, Kiyoto IWAMATSU, Akiharu KIMURA, Takahiro TAKADA

Our division consists of three clinical groups: such as the esophagus, stomach and small and large bowel surgery. Graduate students belong to one of the groups upon the admission; however, you can focus on the research subject that they interested in whichever groups you belong. We held a research conference in the morning on every Tuesday and discussed everything to solve the research problems with our professor. We presented 27 papers published and have 11 in press in 2016.

2) Research Subject

- Field carcinogenesis
- Bystander effect in cancer
- Research using the model of peritoneal dissemination
- Cancer chemotherapy and Anticancer drug resistance
- Research of circulating tumor cell
- Tumor Immunity
- Gastrointestinal motility
- Carcinogenesis and Metastasis

3) Admission Regulation
In principal, you can apply for enrollment any time after the early stage of residency for two years.

4) Current Graduate Students
1st Year: 3, 2nd Year: 3, 3rd Year: 2, 4th Year: 5, 6th Year: 1,

5) After Graduation (Graduates in the year 2016)
Affiliated Hospital: 1, Gunma University Hospital: 2,

6) Other
We try to work on streamlining surgical training and foreshortening training period. You may be able to start your graduate course as soon as you reach for minimum admission requirements

Nuclear heat shock protein 110 expression is associated with poor prognosis and chemotherapy resistance in gastric cancer

Akiharu Kimura[1], Kyoichi Ogata[1], Bolag Altan[1], Takehiko Yokobori[1], Munenori Ide[2], Erito Mochiki[3], Yoshitaka Toyomasu[1], Norimichi Kogure[1], Toru Yanoma[1], Masaki Suzuki[1], Tuya Bai[1], Tetsunari Oyama[2], Hiroyuki Kuwano[1]

[1]Department of General Surgical Science, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

[2]Department of Diagnostic Pathology, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

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Keywords: *cancer progression, drug resistance, gastric cancer, heat shock protein, heat shock protein 110*

Received: *September 25, 2015* ***Accepted:*** *January 23, 2016* ***Published:*** *March 01, 2016*

ABSTRACT

Heat shock protein (HSP) expression is induced by the exposure to stress, such as fever, oxidative stress, chemical exposure, and irradiation. In cancer, HSP promotes the survival of malignant cells by inhibiting the induction of apoptosis. In colorectal cancer, a loss-of-function mutation of HSP110 (HSP110ΔE9) has been identified. HSP110ΔE9 inhibits the nuclear translocation of wild-type HSP110, which is important for its chaperone activity and anti-apoptotic effects. The patients carrying HSP110ΔE9 mutation exhibit high sensitivity to anticancer agents, such as oxaliplatin and 5-fluorouracil.There is still insufficient information about HSP110 localization, the clinicopathological significance of HSP110 expression, and its association with chemotherapy resistance in gastric cancer. Here, we found that high nuclear expression of HSP110 in gastric cancer tissues is associated with cancer progression, poor prognosis, and recurrence after adjuvant chemotherapy. *In vitro* results showed that HSP110 suppression increases the sensitivity to 5-fluorouracil and cisplatin of human gastric cancer cell lines. Our results suggest that nuclear HSP110 may be a new drug sensitivity marker for gastric cancer and a potential molecular therapeutic target for the treatment of gastric cancer patients with acquired anticancer drug resistance.

INTRODUCTION

Gastric cancer is one of the most common cancers worldwide and it is particularly prevalent in Asia [1]. Patients with early-stage gastric cancer have a good prognosis following endoscopic or surgical treatment [2], but advanced or recurrent gastric cancer patients have high mortality rates, due to chemotherapy resistance [3]. Therefore, the investigations of the mechanisms of chemotherapy resistance are necessary, in order to improve patient outcomes.

Heat shock proteins (HSPs) are molecular chaperones that facilitate the proper folding and function of proteins. The expression of HSPs is induced by the exposure to stress, such as fever, oxidative stress, chemical exposure, and irradiation [4, 5]. HSPs provide protection against protein aggregation, facilitate folding of nascent polypeptides, participate in the refolding of proteins that have been damaged, and sequester damaged proteins and target them for degradation [6, 7]. Mammalian HSPs are classified into several protein families based on their molecular weight, namely HSP25/HSP27, HSP40, HSP60, HSP70, HSP90, and HSP110 (also called HSP105) families [8, 9]. HSP70 family proteins are expressed in the cytoplasm and nucleus of mammalian cells [10]. HSP105α and HSP105β, the alternatively spliced products of HSP110 family, are expressed in the cytoplasm (HSP105α) and in nucleus (HSP105β) [11]. Previously, it was reported that nuclear HSPs behave as molecular chaperones in cells [10].

HSPs were shown to be overexpressed in a wide range of human carcinomas, including both solid tumors and hematological malignancies [7, 12, 13]. In cancer, HSP promotes the survival of malignant cells by

Division of Breast and Endocrine Surgery

（1）Staff

Director/Associate Professor: Takaaki FUJII
Assistant Professors: Reina YAJIMA, Tomoko HIRAKATA, Sayaka OBAYASHI, Sasagu KUROZUMI
Clinical Fellows: Yuko NAKAZAWA, Naoko TOKUDA, Keiko YANAI
Associate Professor (Medical Education Center): Mami KIKUCHI

Breast Cancer is the highest incidence disease among female malignant neoplasm. We review diagnosis and treatment of breast cancer and endocrine disorders. Basic research includes 1) mechanism of therapy resistance in breast cancer, 2) tumor angiogenesis, 3) biomarker of sensitivity for breast cancer treatment, 4) an exhaustive analysis of breast cancer prognostic factors. In addition, clinical study includes 1) additional usefulness of FDG-PET in breast cancer, 2) Mechanism of lymph node metastasis, 3) analysis of navigation surgery for identification of parathyroid glands and sentinel lymph nodes.
It is not necessary to focus on the specific research subject, which you belong to. We held a research conference every week and discuss everything to solve the research problems with our professor.

（2）Research Themes

1. Mechanism of therapy resistance in breast cancer, 2. Tumor angiogenesis, 3. Biomarker of sensitivity for breast cancer treatment, 4. An exhaustive analysis of breast cancer prognostic factors, 5. Additional usefulness of FDG-PET in breast cancer, 6. Mechanism of lymph node metastasis, 7. Analysis of navigation surgery for identification of parathyroid glands and sentinel lymph nodes.

（3） Admission Regulation

In principal, you can apply for enrollment anytime after the early stage of residency for 2 years.

（4） Current Graduate Students

3rd Year: 2, 4th Year: 1, 6th Year: 1.

（5） After Graduation

Working at Gunma University or affiliated hospitals. You can also research at the university or study abroad.

（6）Other

We try to work on streamlining surgical training and foreshortening training period. You may be able to start your graduate course as soon as you reach for minimum admission requirement.

ANTICANCER RESEARCH *36*: 5481-5486 (2016)
doi:10.21873/anticanres.11129

Clinical Significance of ^{18}F-FDG-PET in Invasive Lobular Carcinoma

TAKAAKI FUJII[1,2], REINA YAJIMA[1,2], SASAGU KUROZUMI[2], TORU HIGUCHI[2], SAYAKA OBAYASHI[2], HIDEAKI TOKINIWA[2], RIN NAGAOKA[2], DAISUKE TAKATA[2], JUN HORIGUCHI[2] and HIROYUKI KUWANO[1]

[1]*Department of General Surgical Science, Graduate School of Medicine, Gunma University, Gunma, Japan;*
[2]*Breast and Endocrine Surgery, Gunma University Hospital, Gunma, Japan*

Abstract. *The diagnostic utility of ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) for breast cancer is controversial. The histological type or tumor size of breast cancer has been reported to be associated with a greater likelihood of positive FDG uptake. Compared to invasive ductal carcinomas (IDCs), invasive lobular carcinomas (ILCs) have a lower level of FDG uptake and are detected at a significantly lower sensitivity. The role of preoperative FDG-PET for ILCs may, thus, be limited. Few data evaluating the significance of FDG-PET in ILCs are available. Here, we evaluated the clinical significance of FDG-PET for ILC patients. We retrospectively investigated the cases of 196 consecutive patients with primary breast cancer who were diagnosed as having ILC (n=15) or IDC (n=181) and underwent FDG-PET preoperatively. Fifteen (7.7%) of patients were histopathologically diagnosed as ILC. A univariate analysis revealed that tumor size, extent of tumor, estrogen receptor (ER) expression and progesterone receptor (PgR) expression were significantly different between the ILC and IDC groups. The maximum standardized uptake value (SUV_{max}) values of the primary tumors were not significantly different between the two groups but, regardless of the larger size of tumor or ductal spread, the SUV_{max} was relatively lower in the ILC group compared to the IDC group. The tumors in two ILC cases showed no FDG uptake. Among the ILC cases, there were linear associations between SUV_{max} and tumor size and between SUV_{max} and the nuclear grade by Pearson correlation (r=0.447, p=0.048 and r=0.519, p=0.024, respectively). Our findings imply that the preoperative FDG uptake in ILC may be reflective of the tumor size and the nuclear grade of the tumor. FDG uptake may be useful and predictive of aggressive features or prognosis in ILC patients.*

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Key Words: FDG-PET, invasive lobular carcinoma, breast cancer, size, nuclear grade.

^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) has been widely used for diagnosing the stage or recurrence in breast cancer; however, the diagnostic utility of FDG-PET for breast cancer is controversial (1-9). FDG-PET has high specificity but mediocre sensitivity for identifying primary breast cancer; it can detect breast cancers with a sensitivity of 66%-96% and a specificity of 83%-100% (1-5). In our previous study, the overall sensitivity for the detection of all breast cancers was 88.6% and the false-negative rate of the FDG-PET evaluation of primary breast cancer was 11.4% (5).

Many studies have evaluated factors associated with the FDG avidity of the primary tumor in breast cancer and the tumor size or histological type of breast cancer has been reported to be associated with a greater likelihood of FDG uptake (5). Invasive lobular carcinomas (ILCs) have a lower level of FDG uptake and are detected at significantly lower sensitivity than invasive ductal carcinomas (IDCs) (10-15). Several studies reported that ILCs showed a limited FDG uptake and that the role of preoperative FDG-PET in ILC may, thus, be limited (11). Few data evaluating the significance and usefulness of FDG-PET in ILC are available in the existing literature.

Our previous study revealed that small-size tumor invasion and lower nuclear grade were significant factors associated with FDG uptake in primary breast cancers, including IDCs and ILCs (5). That study revealed that histological type, including ILC, was not significantly associated with FDG uptake in the primary tumor (5). In the present study, we evaluated the clinical significance and usefulness of FDG-PET in ILC.

Introduction: Department of Hepatobiliary and Pancreatic Surgery, Gunma University Graduate School of Medicine

1.Member

Professor　Ken Shirabe

Assistant professor Kenichirou Araki　　Graduate student　Norihiro Ishii

Assistant professor　Norio Kubo　　Graduate student　Takahiro Yamanaka

Assistant professor　Akira Watanabe　　Graduate student　Kei Hagiwara

Assistant professor　Takamichi Igarashi　　Foreign student　Dolgormaa Gantumur

Clinical fellow Mariko Tsukagoshi

2. Research Subject

The development of new treatment to target Cancer-associated fibroblasts

The significant of Sarcopenia on perioperative state

The investigation of development mechanism on malignant tumor

3. Admission to the graduate school

It is always possible to enter the graduate school after postgraduate clinical training.

4. The places where graduate school students work

Graduate school students mainly work in laboratories and have few clinical duties on Gunma University Hospital. It is as follow table:

<table>
<tr><th></th><th>Mon</th><th>Tue</th><th>Wed</th><th>Thu</th><th>Fri</th><th>Sat</th><th>Sun</th></tr>
<tr><td rowspan="2">AM</td><td rowspan="3">Working
Away</td><td rowspan="2">Reserch</td><td>Reserch
conference</td><td rowspan="2">Working
Away</td><td rowspan="2">outpatient
service</td><td rowspan="3">Reserch
or
Working
Away</td><td rowspan="3"></td></tr>
<tr><td rowspan="2">Operation</td></tr>
<tr><td>PM</td><td>Reserch
conference</td><td>Reserch</td><td>Reserch</td><td>Reserch</td></tr>
</table>

5. After the graduate school

Some students stay in gunma university graduate school of medicine for specialized training. The other students move to other institutes for the further research.

Overexpression of karyopherin-α2 in cholangiocarcinoma correlates with poor prognosis and gemcitabine sensitivity via nuclear translocation of DNA repair proteins

Mariko Tsukagoshi[1,3], Kenichiro Araki[1,3], Takehiko Yokobori[4], Bolag Altan[1], Hideki Suzuki[1], Norio Kubo[1,3], Akira Watanabe[1,3], Norihiro Ishii[1], Yasuo Hosouchi[5], Masahiko Nishiyama[4], Ken Shirabe[2,3], Hiroyuki Kuwano[1,3]

[1]Department of General Surgical Science, Gunma University Graduate School of Medicine, Maebashi Gunma 371-8511, Japan

[2]Department of Hepatobiliary and Pancreatic Surgery, Gunma University Graduate School of Medicine, Maebashi Gunma 371-8511, Japan

[3]Division of Hepatobiliary and Pancreatic Surgery, Integrative Center of General Surgery, Gunma University Hospital, Maebashi Gunma 371-8511, Japan

[4]Department of Molecular Pharmacology and Oncology, Gunma University Graduate School of Medicine, Maebashi Gunma 371-8511, Japan

[5]Department of Surgery and Laparoscopic Surgery, Gunma Prefecture Saiseikai-Maebashi Hospital, Maebashi Gunma 371-0821, Japan

Correspondence to: *Hiroyuki Kuwano,* ***email:*** *hkuwano@gunma-u.ac.jp*

Keywords: *KPNA2, cholangiocarcinoma, gemcitabine, MRN complex, DNA repair*

Received: *August 10, 2016* ***Accepted:*** *January 04, 2017* ***Published:*** *February 02, 2017*

ABSTRACT

Cholangiocarcinoma is a highly malignant tumor, and the development of new therapeutic strategies is critical. Karyopherin-α2 (KPNA2) functions as an adaptor that mediates nucleocytoplasmic transport. Specifically, KPNA2 transports one of the important DNA repair machineries, the MRE11-RAD50-NBS1 (MRN) complex, to the nucleus. In this study, we clarified the significance of KPNA2 in cholangiocarcinoma. KPNA2 expression evaluated by immunohistochemical analysis was common in malignant tissue but rare in adjacent noncancerous tissues. KPNA2 overexpression was significantly correlated with poor prognosis and was an independent prognostic factor after surgery. In patients with cholangiocarcinoma who received gemcitabine after surgery, KPNA2 overexpression tended to be a prognostic indicator of poor overall survival. In KPNA2-depleted cholangiocarcinoma cells, proliferation was significantly decreased and gemcitabine sensitivity was enhanced *in vitro* and *in vivo*. Expression of KPNA2 and the MRN complex displayed colocalization in the nucleus. In addition, nuclear localization of the MRN complex was regulated by KPNA2 *in vitro*. These results suggest that KPNA2 expression may be a useful prognostic and predictive marker of gemcitabine sensitivity and survival. The regulation of KPNA2 expression may be a new therapeutic strategy for cholangiocarcinoma.

INTRODUCTION

Cholangiocarcinoma is a malignant tumor originating from the bile duct epithelial cells that is classified as intrahepatic or extrahepatic depending on location [1, 2]. Although extrahepatic cholangiocarcinoma (EHCC) is relatively uncommon in Western countries, the incidence and mortality rate of cholangiocarcinoma continue to increase worldwide [3, 4]. In Japan in particular, it was reported that cholangiocarcinoma was responsible for approximately 12,000 deaths in 2013 [5]. Surgical resection is currently the only curative treatment for cholangiocarcinoma. However, the majority of patients are inoperable because most are diagnosed at an advanced stage [6–8]. Despite recent advances in surgical techniques and chemotherapy, the post-resection 5-year survival rate is only 20%–30% [9].

Division of Pediatric Surgery, Department of General Surgical Science

(1) Staff

Associate Professor: Makoto SUZUKI

Our department consists of six divisions: such as Gastroenterological Surgery, Hepato-biliary-pancreatic Surgery, General Thoracic Surgery, Breast & Endocrine Surgery, Cardiovascular Surgery and Pediatric Surgery. Even when graduate students belong to our division, it is not necessary to focus on the specific research subjects which you belong to. We hold a research conference in the morning on every Wednesday and discuss everything to solve the research problems with all surgical staffs.

(2) Research Subjects

① Establishment of non-invasive diagnosis with Circulating Tumor Cell
② Relationship between intestinal flora and pathological change after total colectomy
③ Investigation of hepatic fibrogenesis inhibitors for biliary atresia
④ Assessment of surgical performance in limited space model

(3) Admission Regulation

In principal, you can apply for enrollment after the early stage of residency for 2 years.

(4) Current Graduate Student

4th year : Sayaka OTAKE

(5) After Graduation

You can work as a pediatric surgical specialist at Gunma University Hospital and affiliated hospitals. And also, we encourage studying abroad and other institutes.

(6) Others

We try to work on streamlining surgical training and foreshortening training period. You may be able to start your graduate course as soon as you reach for minimum admission requirements.

Contact address: suzuki-m@gunma-u.ac.jp (Makoto SUZUKI)

Pediatr Surg Int
DOI 10.1007/s00383-014-3494-x

ORIGINAL ARTICLE

Safety and efficacy of selective sac extraction method of inguinal hernia repair in children: results of a prospective study

Makoto Suzuki · Masahiro Hatanaka · Junko Fujino · Akihiro Igarashi · Mariko Hasegawa · Kazunori Tahara · Yuki Ishimaru · Hitoshi Ikeda

Accepted: 27 February 2014

Abstracts
Purpose A prospective study was conducted to confirm the safety and efficacy of the selective sac extraction method (SSEM) of inguinal hernia repairs in children.
Methods Primary endpoints of the study were the incidence of any complication related to the SSEM, or hernia recurrence. Secondary endpoints included the success rate of the SSEM, length of incision at the end of operation, and duration of operation. The incidence of contralateral manifestation of hernia was also examined.
Results Between October 2009 and December 2011, a total of 317 repairs, 145 male repairs and 172 female repairs, were performed by applying the SSEM. There were three operative conversions, and the success rate of the SSEM was 99 % in both male and female patients. The length of incision ranged from 4.0 to 12.5 mm (median 6.0 mm) and was ≤7.0 mm in 93 % repairs. The incisional length for male repairs ranged from 4.0 to 12.5 mm (median 6.0 mm) and was ≤7.0 mm in 86 % repairs, while it ranged from 4.0 to 9.0 mm (median 5.5 mm) in female repairs and was ≤6.5 mm in 96 % repairs. The duration of the operation for unilateral repair ranged from 9 to 66 min (median 21 min). Eighty percent of repairs were examined 6–44 months (median 12 months) after the operation. There was one (0.4 %) recurrence among 250 repairs and two (1.7 %) cases of testicular dislocation among 115 male repairs. Contralateral hernia presented in 19 (9.5 %) of 199 patients with unilateral hernia who underwent the follow-up.
Conclusions The feasibility of the SSEM was reconfirmed, and it was revealed that the complication and recurrence rates were low and acceptable. The SSEM is safe and effective, and should be a standard method for repairing inguinal hernia in children.

Keywords Inguinal hernia repair · Selective sac extraction method (SSEM)

M. Suzuki · M. Hatanaka · J. Fujino · A. Igarashi · M. Hasegawa · K. Tahara · Y. Ishimaru · H. Ikeda (✉)
Department of Pediatric Surgery, Dokkyo Medical University Koshigaya Hospital, 2-1-50, Minami-Koshigaya, Koshigaya, Saitama 343-8555, Japan
e-mail: hike@dokkyomed.ac.jp

M. Suzuki
Division of Pediatric Surgery, Department of General Surgical Science, Gunma University Graduate School of Medicine, Maebashi, Japan

Introduction

We previously reported a novel technique for inguinal hernia repair in children, the selective sac extraction method (SSEM), by which satisfactory surgical and cosmetic results could be achieved without laparoscopic assistance [1, 2]. The SSEM is a technique of minimal surgical invasiveness in which only the hernia sac is selectively extracted from an extremely small skin incision instead of elevating the entire cord structures in male hernias. In female hernias, the round ligament is elevated and the hernia sac is extracted without pulling the surrounding muscular and fascial tissues out of the wound. In a retrospective study, the technical feasibility of the SSEM was examined, and the success rates were 88 % in male and 96 % in female repairs [1]. Follow-up interviews revealed no adverse events such as postoperative complications or hernia recurrence, while excellent parental satisfaction with wound cosmesis was evident.

Since it is essential to confirm the safety and efficacy of the SSEM in a prospective manner before it is used as a

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Introduction of Graduate Program in the Department of Radiation Oncology

(1) Research scope

The main research scope of the department is as following:

1 Development of heavy particle beam radiation therapy to overcome X-ray-resistant tumors, and development of the micro-beam radio-surgery technology using the heavy particle beams.

2 Development of advanced techniques to overcome late toxicity induced by radiation therapy with applying regenerative medicine.

3 Research of combination of radiation therapy with molecular-targeting therapy and/or immunotherapy to overcome X-ray-resistant tumors.

(2) Current research theme

In the fiscal year 2011-2017, we promote cutting-edge research in radiation medicine and cultivate world-class leaders in the field of radiation therapy through "Heavy particle beam biomedical engineering global leader training program" which is adopted as the national program conducted by the Ministry of Education, Culture, Sports, Science and Technology, with taking over the achievement of the 21st Century COE program "Biomedical research by accelerator technology".

Basic research

1) Cutting-edge basic research in radiation biology and medical physics using heavy particle beams

2) Radiosensitization of cancer cells targeting proteins involved in the regulation of cell cycle, cellular adhesion and growth factor receptors, and those resulting from cancer-related gene aberrations

3) Basic research of immuno-radiotherapy and elucidation of the radiosensitizing mechanisms of chemoradiotherapy

4) Detection of hypoxic cells *in vivo* using hypoxia markers and sensitization of hypoxic tumor cells

5) Research on the effect of modulation of vascular regenerative factors on the tissue reaction after ionizing irradiation

Clinical research

1) Clinicopathological studies on the outcome of heavy particle beam radiation therapy

2) Development of the Micro-beam radio-surgery technology using heavy particle beams

3) Analysis of dose distribution in heavy particle beam radiation therapy using the 3D CdTel Compton quantum camera

4) Clinical research on the utility of immuno-radiothrapy and hyperthermia in cancer

5) Clinical research to improve the accuracy of the remote-after-loading intracavitary/interstitial brachytherapy

(3) How to admission

Regarding the general selection, in principle, we accept admission after finishing the internship. Admission to the nearest four years after graduation is appropriate.

Regarding the selection for the working members of society (i.e. graduate course at night time), we accept admission after finishing the internship.

(4) Current status of the graduate students in our department

We currently have 6,3,5,2 graduate students in the 1st, 2nd, 3rd and 4th grade, respectively. We guarantee sufficient income as a medical doctor.

(5) Career path after graduation

The graduates can work as a radiation oncologist at the Gunma University Hospital and the satellite hospitals. Regarding studying abroad, we have much experience on sending our staffs to foreign institutes including National Institutes of Health, and do support the graduates to study abroad.

(6) Other

We are currently offering a opportunity to administrate the graduate program of ″Heavy particle beam biomedical engineering global leader training program″ during 2011-2017. Our department, along with the Gunma University Heavy Ion Medical Center, launched heavy particle beam radiation therapy of the world's leading science and technology in March 2010, and thus do hope that the graduate students will participate in this graduate program with passion.

J. Radiat. Res., 51, 1–8 (2010)

Current Advancement in Radiation Therapy for Uterine Cervical Cancer

Takashi NAKANO*, Tatsuya OHNO, Hitoshi ISHIKAWA, Yoshiyuki SUZUKI and Takeo TAKAHASHI

Radiation therapy/Uterine cervix/Brachytherapy/Heavy ion.

Radiation therapy is one of the effective curative treatments for uterine cervical cancer. However poor clinical results for the advanced stages require further improvement of the treatment. Intensive studies on basic and clinical research have been made to improve local control, primarily important for long term survival in radiation therapy. Regarding current advancement in radiation therapy for uterine cervical cancer, the following three major subjects are pointed out; technological development to improve dose distribution by image guided radiation therapy technology, the concomitant anticancer chemotherapy with combination of radiation therapy, and radiation biological assessment of the radiation resistance of tumors. The biological factors overviewed in this article include hypoxia relating factors of HIF-1α, SOD, cell cycle parameters of pMI, proliferation factors of Ki67, EGFR, cerbB2, COX-2, cycle regulation proteins p53, p21, apoptosis regulation proteins Bcl2 and Bax and so on. Especially, the variety of these radiation biological factors is important for the selection of an effective treatment method for each patient to maximize the treatment benefit.

INTRODUCTION

Cervical cancer is a significant cause of death in women worldwide. The combination of external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) is considered the standard treatment for uterine cervical cancer.[1] ICBT has the advantage of delivering a very high dose to the central tumor and a lower dose to the surrounding normal structures, such as the bladder and rectum, resulting in high local control while minimizing normal tissue damage.

In the early stage of the disease, cervical cancer is highly curable by radiotherapy alone. However, the treatment results of locally advanced disease have been poor, with 5-year survival rates of 30–55% for stage IIIB, and 4–20% for stage IVA disease.[1–7] One of the major causes of death for the locally advanced disease is persistent or recurrent pelvic disease. The analyses of failure patterns following radiotherapy in locally advanced disease showed locoregional recurrence of 50–70% of the patients treated, and this proportion increased with increasing tumor bulk.[1,2,5,7]

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Hence further successful treatment strategy should be explored to obtain better outcomes for the locally advanced disease, and three major subjects are depicted: 1) technology development to attain improvement of dose distribution, 2) the use of more attractive anticancer agents than standard chemotherapeutic drags to enhance tumor response to RT, and 3) advance in radiation biology to determine tumor radiosensitivity before the initiation of RT.

Image guided brachytherapy for improvement of the dose distribution

Although three-dimensional (3D) imaging technique using computed tomography (CT) and 3D dose-volume assessment in dose distribution is usually adopt for EBRT, ICBT is still coordinated by doses to reference points and doses of organs at risk (OARs), that is, the rectum and the bladder, are also assessed not by dose volume but by point dose in the treatment for cervical cancer.[8] To assess the dose to irregular shaped tumors and to optimize the dose based on the dose constrains at every session of ICBT using CT or magnetic resonance imaging (MRI) can give a sufficient irradiation dose to the target with the minimal dose to the OARs at the same time.

Recently, the effectiveness of 3D technique on ICBT for cervical cancer has been proven by several investigators. The first promising clinical result of 3D image-based adaptive ICBT has triggered off its establishment in a large number

Department of Diagnostic Radiology and Nuclear Medicine
(Asian Nuclear Medicine Graduate Program)

Our department has three main sections:

A. **Diagnostic Imaging** (CT, MRI, US, Interventional Radiology, etc.)

B. **Nuclear Medicine** (PET, SPECT, radioisotope therapy, etc.)

C. **Molecular Imaging**

Current research topics include:

A. **Diagnostic Imaging**

Functional imaging using MRI, CT, and US

New technologies and techniques in interventional radiology

B. **Nuclear Medicine**

PET and SPECT for malignancies and CNS and cardiac disease

Tumor-specific radioisotope labeled monoclonal antibody therapy

Radioisotope therapy technology for endocrine disorders

C. **Molecular Imaging**

New diagnostic radiologic pharmaceuticals

New therapeutic radiologic pharmaceuticals

Our Graduate Program

We prefer students who have prior training in diagnostic radiology and/or nuclear medicine. Most of our international students receive scholarships from the Japanese Ministry of Education, Science and Technology (MEXT) or other organizations. Students will learn research techniques and experience clinical radiology and nuclear medicine in a Japanese university hospital. Our graduate students are a fun, close-knit group. They enjoy academics and research as well as extracurricular activities.

Postgraduate career

We hope students will return to their home countries and become leading clinicians and researchers in this field.

Effects of Intratumoral Inflammatory Process on ^{18}F-FDG Uptake: Pathologic and Comparative Study with ^{18}F-Fluoro-α-Methyltyrosine PET/CT in Oral Squamous Cell Carcinoma

Mai Kim[1,2], Arifudin Achmad[2–4], Tetsuya Higuchi[2], Yukiko Arisaka[2], Hideaki Yokoo[5], Satoshi Yokoo[1], and Yoshito Tsushima[2]

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The accurate depiction of both biologic and anatomic profiles of tumors has long been a challenge in PET imaging. An inflammation, which is innate in the carcinogenesis of oral squamous cell carcinoma (OSCC), frequently complicates the image analysis because of the limitations of ^{18}F-FDG and maximum standardized uptake values (SUV_{max}). New PET parameters, metabolic tumor volume (MTV) and total lesion glycolysis (TLG), as well as ^{18}F-fluoro-α-methyltyrosine (^{18}F-FAMT), a malignancy-specific amino acid–based PET radiotracer, are considered more comprehensive in tumor image analysis. Here, we showed the substantial effects of the intratumoral inflammatory process on ^{18}F-FDG uptake and further study the possibility of MTV and TLG to predict both tumor biology (proliferation activity) and anatomy (pathologic tumor volume). **Methods:** ^{18}F-FDG and ^{18}F-FAMT PET images from 25 OSCC patients were analyzed. SUV_{max} on the tumor site was obtained. PET volume computerized-assisted reporting was used to generate a volume of interest to obtain MTV and TLG for ^{18}F-FDG and total lesion retention (TLR) for ^{18}F-FAMT. The whole tumor dissected from surgery was measured and sectioned for pathologic analysis of tumor inflammation grade and Ki-67 labeling index. **Results:** The high SUV_{max} of ^{18}F-FDG was related to the high inflammation grade. The SUV_{max} ratio of ^{18}F-FDG to ^{18}F-FAMT was higher in inflammatory tumors ($P < 0.05$) whereas the corresponding value in tumors with a low inflammation grade was kept low. All ^{18}F-FAMT parameters were correlated with Ki-67 labeling index ($P < 0.01$). Pathologic tumor volume predicted from MTV of ^{18}F-FAMT was more accurate ($R = 0.90$, bias = 3.4 ± 6.42 cm^3, 95% confidence interval = 0.77–6.09 cm^3) than that of ^{18}F-FDG ($R = 0.77$, bias = 8.1 ± 11.17 cm^3, 95% confidence interval = 3.45–12.67 cm^3). **Conclusion:** ^{18}F-FDG uptake was overestimated by additional uptake related to the intratumoral inflammatory process, whereas ^{18}F-FAMT simply accumulated in tumors according to tumor activity as evaluated by Ki-67 labeling index in OSCC.

Key Words: inflammation; MTV; OSCC; ^{18}F-FAMT; ^{18}F-FDG

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DOI: 10.2967/jnumed.114.144014

A worldwide estimation of newly diagnosed oral cavity cancer in 2008 was more than 250,000, with an estimated mortality number reaching 128,000 (*1*). Ninety percent of oral cavity cancer is oral squamous cell carcinoma (OSCC) derived from mucosal lining (*2*), which is directly exposed to the external environment. Despite the advancement of diagnostic imaging and detection of biologic markers, no significant improvement in survival rate was obtained over the past 40 y (*3*).

OSCC PET imaging using ^{18}F-FDG and maximum standardized uptake value (SUV_{max}) assessment is helpful for pretreatment staging and improved TNM classification (*4,5*). Even though it has been considered as an independent prognostic factor (*6*), the shortcoming of semiquantitative SUV_{max} is its dependency on a mere single pixel (*7*), which may not represent the whole tumor entity (*8*). Moreover, several major limitations of the standardized uptake value (SUV) concept affect its reliability as a surrogate of the targeted quantity, the metabolic rate of ^{18}F-FDG (*9*).

Because ^{18}F-FDG accumulation in tumor cells depends on glucose metabolism, PET is a sensitive modality for malignancy but lacks the specificity and ability to depict the true tumor biology. To address this, the amino acid–based PET radiotracer ^{18}F-fluoro-α-methyltyrosine (^{18}F-FAMT), which accumulates exclusively in malignant tumor cells through the L-type amino acid transporter 1, was developed (*10–12*). In previous OSCC studies, ^{18}F-FAMT was better than ^{18}F-FDG in its correlation with tumor proliferation activity, represented by Ki-67 labeling index (Ki-67 LI) (*13,14*). Moreover, significant false-positive accumulation of ^{18}F-FDG in inflammatory lesions, other nonmalignant lesions, and some normal organs due to physiologic activity contributes to the lower specificity of ^{18}F-FDG for malignancy.

Recently, metabolic tumor volume (MTV) and total lesion glycolysis (TLG), which quantify both anatomic and pathophysiologic aspects of the entire tumor, have been introduced as new

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Department of ***Psychiatry and Neuroscience***

Pathophysiological studies

- neurodevelopmental study
- Brain structure (MRI)
- Brain function (SPECT / NIRS)
- neurophysiology (MEG)
- analysis of brain oscillations and working memory (MRS collaborative project)
- GABA and the reward system
- Retrieval of the self-efficacy in educational stuff
- Education sleep hygiene using questionnaire method

Therapeutic studies

- Investigation the CBT effectiveness with brain imaging methods
- Effects of electroconvulsive therapy
- Pharmacotherapeutic studies, Clozapine for schizophrenia Drug augument therapy in depression
- transcranial magnetic stimulation
- Availability of family therapy to the Autism spectrum disorder

Nation-wide research project

Study for biomarkers and molecular pathophysiology of depression diversity
Development of new treatments for depression based on neural mechanisms of depressive symptoms
Establishment of clinical stages of psychiatric disorders based on neuroimaging
Early diagnosis of psychiatric disorders using NIRS
Adolescent mind and self-regulation
Science of personalized value development through adolescence

Published monographs

The Science of Adolescence (2015)
Case conference on neuroimaging data of psychiatric disorders (2014)
Textbook of schizophrenia (2013)
Clinical Examinations of Brain Structure and Function for Psychiatric Disorders (2012)
Practical Guidebook for NIRS Examination as the Advanced Medical Technology (2011)

For admission

MD-PhD course: usually enter this course after at least certificated one year junior residency.

Post-doctoral course

Graduates are generally carrying over their study as medical/research staff in Gunma university Hospital, or other affiliated hospital / laboratory.

Information

There are 7 members current postgraduates (2016), and 29 members/11 years. Generally they are working on their studies at 5 days/week.

Qualify

- Certified Psychiatrist of the Japanese Board of Psychiatry
- A designated psychiatrist by Japanese Ministry of Health Welfare and Labor

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journal homepage: www.elsevier.com/locate/ynimg

The inhibition/excitation ratio related to task-induced oscillatory modulations during a working memory task: A multtimodal-imaging study using MEG and MRS

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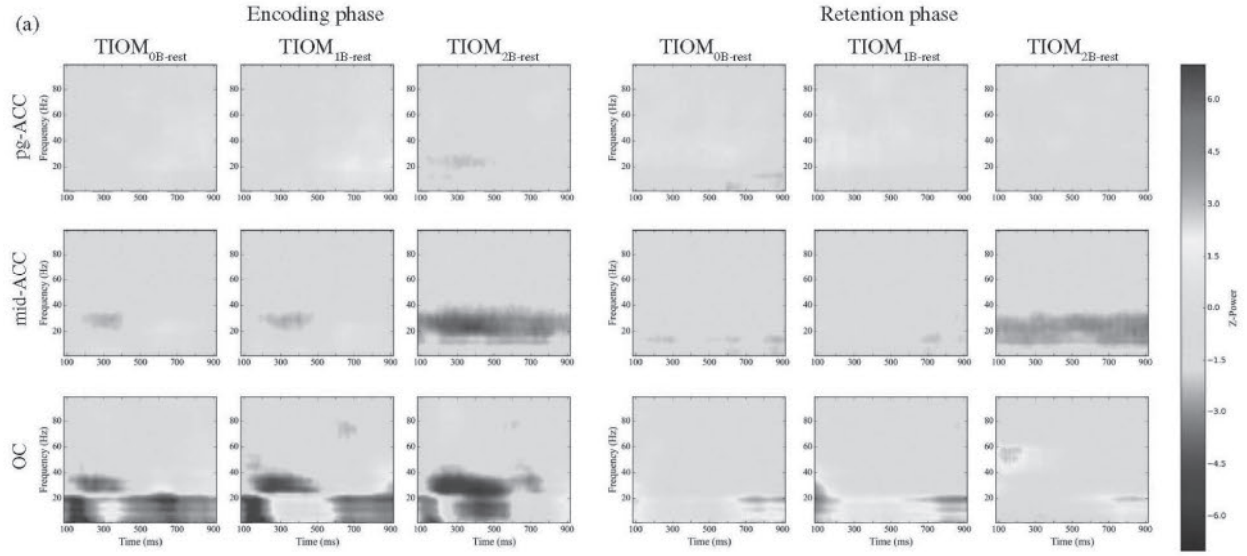
Magnetic resonance spectroscopy

ABSTRACT

Detailed studies on the association between neural oscillations and the neurotransmitters gamma aminobutyric acid (GABA) and glutamate have been performed *in vitro*. In addition, recent functional magnetic resonance imaging studies have characterized these neurotransmitters in task induced deactivation processes during a working memory (WM) task. However, few studies have investigated the relationship between these neurotransmitters and task induced oscillatory changes in the human brain. Here, using combined magnetoencephalography (MEG) and magnetic resonance spectroscopy (MRS), we investigated the modulation of GABA and glutamate + glutamine (Glx) concentrations related to task-induced oscillations in neural activity during a WM task. We first acquired resting-state MRS and MEG data from 20 healthy male volunteers using the n-back task. Time-frequency analysis was employed to determine the power induced during the encoding and retention phases in perigenual anterior cingulate cortex (pg-ACC), mid-ACC, and occipital cortex (OC). Statistical analysis showed that increased WM load was associated with task-induced oscillatory modulations (TIOMs) of the theta-gamma band relative to the zero-back condition ($TIOM_{0B}$) in each volume of interest during the encoding phase of the n-back task. The task-induced oscillatory modulations in the two-back condition relative to the zero-back condition ($TIOM_{2B\text{-}0B}$) were negatively correlated with the percent rate change of the correct hit rate for 2B–0B, but positively correlated with GABA/Glx. The positive correlation between $TIOM_{2B\text{-}0B}$ and GABA/Glx during the WM task indicates the importance of the inhibition/excitation ratio. In particular, a low inhibition/excitation ratio is essential for the efficient inhibition of irrelevant neural activity, thus producing precise task performance.



Department of Anesthesiology

General Information:

Department of Anesthesiology has been working on perioperative patient care. Recently, the responsibility is expanding in complicated pain management, intensive care and hyperbaric oxygen therapy. Research topics of our department are also corresponding this trend and are extending from pharmacology and mechanism of anesthesia to pain conducting mechanism. Staff members are working on these topics clinically and experimentally by using most brand-new and innovative approaches.

Research Projects:

Current research activities of our members are summarized as follows:

1) Analysis of anesthetic action on intercellular and intracellular signal transduction
2) Pharmacological analysis of neuropathic pain models
3) Vascular responses evoked by non-adrenergic non-cholinergic transmission
4) Actions of anesthetics on growing and regenerating nervous system
5) Multi-modal therapy for peripheral circulation

Admission to Graduate Course:

Following the clinical experience, applicants should make contact with head of department to consult the potential research projects. Applicants should pass the language examination and an interview with professors of the department.

Graduate School Life:

Educational activities of our Department is consists of college students education, graduate school research, clinical bed side teachings for medical students and residents. Graduate students are involved in such activities.

Post-doctoral course:

Following the certification of Medical Doctor degree, graduates restart clinical profession and/or continue research work. Many graduates experience oversea research activities both in clinical field and basic science.

Research Article

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Brain morphological alternation in chronic pain patients with neuropathic characteristics

Satomi Sugimine, MD[1], Yuichi Ogino, MD, PhD[1], Hiroaki Kawamichi, PhD[2], Hideaki Obata, MD, PhD[3,4] and Shigeru Saito, MD, PhD[1]

Abstract

Background: Neuropathic characteristics are highly involved in the development of chronic pain both physically and psychologically. However, little is known about the relationship between neuropathic characteristics and brain morphological alteration.

Objectives: The aim of this study is to investigate the mechanisms of chronic pain development by examining the above-mentioned relationships by voxel-based morphometry in patients with chronic pain.

Methods: First, we assessed neuropathic characteristics using the painDETECT Questionnaire in 12 chronic pain patients. Second, to assess the gray matter volume changes by voxel-based morphometry, we conducted magnetic resonance imaging of the brain. We applied multiregression analysis of these two assessment methods.

Results: There were significant positive correlations between painDETECT Questionnaire scores and the gray matter volume in the bilateral anterior cingulate cortex and right posterior cingulate cortex.

Conclusions: Our findings suggest that neuropathic characteristics strongly affect the brain regions related to modulation of pain in patients with chronic pain and, therefore, contribute to the severity of chronic pain.

Keywords

Brain, chronic pain, voxel-based morphometry, anterior cingulate cortex, painDETECT Questionnaire, posterior cingulate cortex, neuropathic characteristics

Date received: 15 February 2016; revised: 18 April 2016; accepted: 4 May 2016

Introduction

Chronic pain is complicated because of its effects on various physical, emotional, and cognitive functions.[1] Therefore, the treatment of chronic pain requires multiple approaches, such as pharmacological therapy, interventional therapy, exercise, rehabilitation, and psychological therapy.

In clinical practice, neuropathic pain is regarded as group of disorders characterized by nerve damage including diabetic polyneuropathy, postherpetic neuralgia, and poststroke syndromes[2] and defined by the International Association for the Study of Pain as "Pain caused by a lesion or disease of the somatosensory nervous system." Under this definition, chronic pain has been classified into neuropathic pain or non-neuropathic pain. However, Attal[3] provided a novel concept that there are various degrees of neuropathic characteristics in chronic pain, that is, overlapping symptoms such as neuropathic pain and nociceptive pain in various chronic

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Department of Emergency Medicine

(1) Staffs

Professor: Kiyohiro Oshima MD, PhD

Senior Lecturer: Shuichi Hagiwara, MD, PhD

Assistant Professor: Makoto Aoki, MD

Clinical Fellow: Yusuke Sawada, MD, PhD, Jun Nakajima, MD

Senior Resident: Yuta Isshiki, MD, Yumi Ichikawa, MD

(2) Research

(Basic research)

Experimental study for the brain prevention following cardiopulmonary resuscitation (CPR)

Experimental study to clarify the mechanism of ischemia-reperfusion injury following CPR and to reduce its injury

(Clinical research)

Study of clinical factors to predict the prognosis in patients with cardiopulmonary arrest

Study of clinical factors to predict the injury severity in patients with multiple traumas

Study of clinical factors to predict the prognosis in elderly emergent patients

Study of clinical factors to predict blood transfusion in patients with pelvic fracture

(3) Admission to Graduate School

Physicians who belong to our department after the completion of 2-year residency are able to admit to graduate school of medicine.

(4) Current situation of the graduate students

They conduct the clinical studies mentioned above while engaging themselves in emergency practice in the Emergency Medical Center of Gunma University Hospital.

(5) Courses after the completion of graduate school

They basically engage themselves in emergency practice in our hospital and/or other hospital in Gunma Prefecture. The training and studying at home and abroad are possible if they hope so.

(6) Others

Our hospital was authorized as Emergency Medical Center by Gunma prefecture on April 1, 2016. We are able to deal with diverse patients from walk-in patients to critical ill patients, and the themes of clinical studies thereby increase

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FDP/fibrinogen ratio reflects the requirement of packed red blood cell transfusion in patients with blunt trauma

Shuichi Hagiwara, MD, PhD [a,c,*], Makoto Aoki, MD [a,c], Masato Murata, MD [a,c], Minoru Kaneko, MD [a,c], Yumi Ichikawa, MD [a,c], Jun Nakajima, MD [a,c], Yuta Isshiki, MD [a,c], Yusuke Sawada, MD, PhD [a,c], Jun'ichi Tamura, MD, PhD [b,c], Kiyohiro Oshima, MD, PhD [a,c]

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Emergency department

ABSTRACT

Purpose: To find factors that predict the requirement of packed red blood cells (pRBC) transfusion in patients with blunt trauma on arrival at the hospital.
Methods: We conducted blood tests in trauma patients whose trauma severity was suspected as being 3 and over in the Abbreviated Injury Scale. Patients were divided into the blood transfusion (BT) and control groups according to the requirement of pRBC transfusion within 24 h after arrival.
Results: We analyzed 347 patients (BT group, n = 14; control group, n = 333). On univariate analysis, there were significant differences in Glasgow Coma Scale (GCS), rate of positive FAST (focused assessment with sonography for trauma) finding, hematocrit, international normalized ratio of prothrombin time, activated partial thromboplastin time, fibrinogen (Fib), and level of fibrin degradation products (FDP). On multivariable analysis, positive FAST finding, GCS, Fib, and FDP influenced the requirement of pRBC transfusion. In the area under the receiver operating characteristic curve analysis, Fib and FDP were markers that predicted the requirement of pRBC transfusion. The FDP/Fib ratio had a better correlation with the requirement of pRBC transfusion than FDP or Fib.
Conclusions: The FDP/Fib ratio can be easily measured and may be a predictor of the need for pRBC transfusion.

1. Introduction

Prediction of massive blood transfusion requirement in patients with trauma is one of the greatest problems in traumatology. Recently, many investigators have reported scoring systems that activate massive blood transfusion protocols in patients with trauma [1-6]. The assessment of blood consumption score (ABC) [1] and trauma-associated severe hemorrhage score (TASH) [2] are the most well-known, well-designed scoring systems and are widely used. Especially, the ABC is a helpful scoring system in the emergency department to predict the need for massive blood transfusion because the ABC can be easily calculated with only 4 parameters: penetrating or blunt, systolic blood pressure (90 mm Hg or less), heart rate (120/min or greater), and finding of focused assessment with sonography for trauma (FAST) [7]. However, the ABC has some weak points. For example, the ABC does not adjust for the pediatric population [8], and the ABC is not designed to detect the need for blood transfusion. In addition, the usefulness of ABC may be limited in regions in which penetrating trauma is extremely rare compared with blunt trauma such as in Japan (the 2015 Japan Trauma Data Bank Report showed that the incidence of penetrating trauma was only 2.7% in Japan) [9]. Furthermore, not all hospitals have sufficient stocks of packed red blood cells (pRBC), and trauma patients are not always transferred to a hospital that has sufficient stocks of pRBC. Therefore, prediction of the need for pRBC transfusion, and whether a patient needs massive blood transfusion or not, is useful in emergency situations.

The purpose of this study was to identify a useful predictor of the need for pRBC transfusion from vital signs, clinical findings, and results of blood tests in blood samples obtained at arrival in patients with trauma.

2. Methods

The protocol of this study was approved without the need for informed consent by the research ethics board of The Gunma University Hospital (Maebashi, Gunma, Japan). This single-center, prospective, and observational study was conducted at Gunma University Hospital

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1．　Department of Social and Environmental Medicine.
Division on General Practice Medicine

（1）Study groups

① study group for gerontology
② study group for general medicine and oriental medicine, “Kampo”
③ study group for medical education

（2）Research theme

① We are studying to improve feeding methods for elderly patients in hospital. We are interested in a balance of trace elements such as zinc, because the lack of them frequently cause some kinds of complications, pressure ulcer, dermatitis and fracture.

② We are studying about general medicine, especially from field of oriental Medicine. “Kampo”is very effective for treatment of many patients who have a lot of complaints. We are trying to develop more effective care system using traditional oriental medicine.

③ Some of our staff are not only clinician in our hospital but also a staff of medical education group of Gunma University Faculty of Medicine. Our division has key role in education of undergraduate, graduate students and residents in university hospital.

（3）Entrance to graduate school

Medical doctor after two years official medical training is needed. Foreign candidate can ask us.

（4）Present students

Two graduate students are studying presently. Two students are working as clinicians in Maebashi Red Cross Hospital in day time.

（5）After Graduate

Among 5 doctors, 4 doctors are working as clinician of some hospitals after taking of degree. One is director of her clinic.

（6）その他

2　Presentive Research of General Practice Medicine（abstract）

Middle-aged and elderly outpatients show lower body temperature responses than the young, even with the same C-reactive protein levels.

J Int Med Res 2007 35:329-37

The variation of body temperature response and C-reactive protein (CRP) levels with age was investigated. A cross-sectional study on new outpatients between January 2004 and June 2005 was carried out. Body temperature and serum CRP levels were examined for screening purposes in 1081 patients. Mean axillary body temperature was maintained at around 36.7 degrees C in early adulthood, and gradually declined in middle age. Middle-aged and elderly outpatients tended to show a lower body temperature response than the young, even with the same CRP levels. The critical age (boundary age) was assumed to be when the relationship between body temperature response and CRP level changed. This study suggests that the boundary age is about 40 years old.

Department of Rehabilitation Medicine

(1) Staff

Professor: Naoki Wada MD, PhD

Associate Professor: Masayuki Tazawa MD, PhD

Assistant Professor: Minori Kurosaki MD, Tomotaka Inoue MD, PhD, Jyunichi Tomono MD, PhD

(2) Ongoing Research

- Study of 3-dementional motion analyses in the patients with disorders of musculoskeletal organs and central nervous system.
- Building of return to work support system for patients with higher brain dysfunction.
- Development of Japanese functional capacity evaluation.
- Development of novel ice massage device for patients with dysphagia.
- Study of the effect of exercise on the stress in patients with psychiatry. (Analysis of the change of free cortisol in saliva.)
- Determination of vagal baroreflex sensitivity by using Valsalva maneuver.
- Development of virtual reality rehabilitation system for patients with stroke.
- Building of a driving support program for patients with higher brain dysfunction.

(3) Qualification for Admission

Medical doctors can admit to graduate school after the completion of two years junior residency. Non-MDs can admit to graduate school if they completed a master's course. We positively accept the student of working member of society.

(4) Current graduate students

There are currently four graduate students and seven students had completed a doctoral program in our laboratory.

(5) After graduation

Most students return to work at our university hospital or our affiliates hospital. We can help you to study abroad.

Hashimoto et al. BioPsychoSocial Medicine (2015) 9:19
DOI 10.1186/s13030-015-0046-0

BIOPSYCHOSOCIAL MEDICINE

RESEARCH Open Access

Physical activity of elderly patients with rheumatoid arthritis and healthy individuals: an actigraphy study

Toshihide Hashimoto[1,2*], Kazuhiro Yoshiuchi[2], Shyuji Inada[2], Kenji Shirakura[1], Naoki Wada[1], Kimihiko Takeuchi[3] and Masatoshi Matsushita[3]

Abstract

Background: Most people with rheumatoid arthritis (RA) are physically inactive. An accelerometer worn on the waist has been used to evaluate physical activity in people with chronic conditions. It is useful for evaluating moderate to vigorous activity, although it tends to underestimate light or mild activities such as housework or family duties. An accelerometer worn on the wrist (i.e., actigraph) has recently been used to capture daily physical activity in inactive individuals. The purposes of this study were to investigate physical activity measured by an actigraph in patients with RA and in healthy individuals and to investigate the association between actigraphic data and self-reported physical function.

Methods: The subjects were 20 RA patients and 20 healthy individuals. All participants wore an actigraph on their wrist for 6–7 consecutive days. They also completed the Health Assessment Questionnaire disability index (HAQ-DI) and the Medical Outcomes Study (MOS) 36-item short form health survey (SF-36). We extracted three parameters from the actigraphic data: mean activity count (MAC), peak activity count (PAC), and low activity ratio (LAR). These three parameters were compared between the RA patients and healthy individuals and with the self-reported questionnaires.

Results: The MAC was significantly lower and the LAR was significantly higher in RA patients than in healthy individuals. The PAC was not different between the two groups. The LAR was negatively correlated with the MAC for the RA patients and for the healthy individuals. The decrease ratio of the LAR with the increase of the MAC for the RA patients was twice that of the healthy participants. In the RA patients, the LAR was significantly and moderately correlated with the HAQ-DI score and two dimensions of the SF-36 (i.e., "physical functioning" and "bodily pain").

Conclusion: Investigation of the proportion of low activity count using an actigraph may be useful to identify characteristics of the physical function in RA patients.

Background

Rheumatoid arthritis (RA) is a chronic, systemic, progressive inflammatory disease characterized by swelling, pain, and deformity of the joints. RA affects synovial joints, many tissues, and organs. As a result, patients with RA experience functional disability because of multiple joint pain, general symptoms (e.g., anemia, fatigue, low-grade fever, or sleep disorders), and psychosocial disorders [1].

Recent studies indicate that most patients with RA are physically inactive. Based on data from 21 countries, only 13.8 % of patients with RA reported participating in regular exercise, which could provide health benefits in the general population [2]. The benefits of engaging in physical activity are well established for maintaining joint health and functional ability and for decreasing the severity of other chronic health conditions in RA patients [2, 3]. Even engaging in light-intensity and short-

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Full list of author information is available at the end of the article

Introduction of Clinical Laboratory Medicine

(1) Research groups and themes

1) Study on the dyslipidemia and atherosclerosis: Search for new biomarkers and elucidation of the pathophysiology of dyslipidemia. Analysis of the mechanism of action of the new lipid mediators on the endothelium and smooth muscle cells. Analysis of blood rheology in atherosclerotic disease.
2) Study on the lifestyle-related diseases including obesity and diabetes mellitus: The analysis of indicators for glycemic control and pathology of diabetes. The analysis of insulin secretion regulatory mechanism and insulin resistance. The analysis of brown adipose tissue in obesity. The study of primary prevention of lifestyle-related diseases.
3) Study on the endocrine diseases: The development of new diagnostics and treatments of thyroid disease. The elucidation of role of thyroid hormone in lifestyle-related diseases.
4) Study on the sports medicine: Analysis of biomarkers that vary depending on weight reduction and exercise.
5) Study on the infectious diseases: The study of infection control in the hospital and drug resistance bacteria. Studies on the pathogenesis and prevention of virus infection.

(2) Admission method of the graduate school

Candidates are evaluated by the results of the entrance examination and their past academic record. You refer to the admission guidelines. We are accepted for admission at any time. There is no limited number. You can choose freely the research theme.

(3) Graduate students enrolled

There are 2 fourth-year students, 3 third-year students, 2 second-year students and 1 first-year student enrollment. Graduate students for working members of society of various occupations doctor, pharmacist, clinical laboratory technicians and athletes have enrolled.

(4) Course of graduate school after graduation

We recommend the foreign and domestic studying abroad actively upon request of the person. Currently, one person has been studying abroad in the United States. Graduates have been the teaching professions, the executives of health administration and hospitals doctors.

(5) Characteristic of Clinical Laboratory Medicine

The biggest characteristic of Clinical Laboratory Medicine is that you are obtained the cooperation of laboratory technicians and doctors of the infection control center and the department of clinical laboratory. You would like to the various other course of future research and themes. Let's study together by all means.

ORIGINAL ARTICLE

Autoantibodies against GPIHBP1 as a Cause of Hypertriglyceridemia

A.P. Beigneux, K. Miyashita, M. Ploug, D.J. Blom, M. Ai, M.R.F. Linton, W. Khovidhunkit, R. Dufour, A. Garg, M.A. McMahon, C.R. Pullinger, N.P. Sandoval, X. Hu, C.M. Allan, M. Larsson, T. Machida, M. Murakami, K. Reue, P. Tontonoz, I.J. Goldberg, P. Moulin, S. Charrière, L.G. Fong, K. Nakajima, and S.G. Young

ABSTRACT

BACKGROUND

A protein that is expressed on capillary endothelial cells, called GPIHBP1 (glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1), binds lipoprotein lipase and shuttles it to its site of action in the capillary lumen. A deficiency in GPIHBP1 prevents lipoprotein lipase from reaching the capillary lumen. Patients with GPIHBP1 deficiency have low plasma levels of lipoprotein lipase, impaired intravascular hydrolysis of triglycerides, and severe hypertriglyceridemia (chylomicronemia). During the characterization of a monoclonal antibody–based immunoassay for GPIHBP1, we encountered two plasma samples (both from patients with chylomicronemia) that contained an interfering substance that made it impossible to measure GPIHBP1. That finding raised the possibility that those samples might contain GPIHBP1 autoantibodies.

METHODS

Using a combination of immunoassays, Western blot analyses, and immunocytochemical studies, we tested the two plasma samples (as well as samples from other patients with chylomicronemia) for the presence of GPIHBP1 autoantibodies. We also tested the ability of GPIHBP1 autoantibodies to block the binding of lipoprotein lipase to GPIHBP1.

RESULTS

We identified GPIHBP1 autoantibodies in six patients with chylomicronemia and found that these autoantibodies blocked the binding of lipoprotein lipase to GPIHBP1. As in patients with GPIHBP1 deficiency, those with GPIHBP1 autoantibodies had low plasma levels of lipoprotein lipase. Three of the six patients had systemic lupus erythematosus. One of these patients who had GPIHBP1 autoantibodies delivered a baby with plasma containing maternal GPIHBP1 autoantibodies; the infant had severe but transient chylomicronemia. Two of the patients with chylomicronemia and GPIHBP1 autoantibodies had a response to treatment with immunosuppressive agents.

CONCLUSIONS

In six patients with chylomicronemia, GPIHBP1 autoantibodies blocked the ability of GPIHBP1 to bind and transport lipoprotein lipase, thereby interfering with lipoprotein lipase–mediated processing of triglyceride-rich lipoproteins and causing severe hypertriglyceridemia. (Funded by the National Heart, Lung, and Blood Institute and the Leducq Foundation.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Beigneux or Dr. Young at the Department of Medicine, University of California, Los Angeles, 4506 Gonda Bldg., 695 Charles E. Young Dr. S., Los Angeles, CA 90095, or at abeigneux@mednet.ucla.edu or sgyoung@mednet.ucla.edu.

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Department of Human Pathology
Gunma University Graduate School of Medicine

1. Staff

Professor: Hideaki Yokoo, MD, PhD
Associate professor: Hayato Ikota, MD, PhD
Research associate: Sumihito Nobusawa, MD, PhD
Nozomi Matsumura, MD, PhD
Postgraduate students: 5 members (all MD license holders)

2. Outline and research activity

Our department handles all aspects of human pathology, and our ultimate goal is the best contribution to medical education (under- and post- graduates), research activity (especially neuropathology) and local medical practice (diagnostic pathology). Training of diagnostic pathology, including autopsy, histopathology, cytology is our main works. We especially focus on research of brain tumors and neural diseases.

3. Eligibility

Holders of Japanese medical licenses are desirable, but the others are also acceptable.

4. Postgraduate students

Five students belong to the department now, all of them are medical doctors and trainees to be pathologist.

5. After graduation

Pathologists, researchers, clinicians, and post-doctoral fellows of foreign and domestic research institutes.

6. Contact

Hideaki Yokoo, MD, PhD, hyokoo@gunma-u.ac.jp ext. 7970

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ORIGINAL ARTICLE

Immunophenotypic features of immaturity of neural elements in ovarian teratoma

Yoshiyasu Takayama[1] · Nozomi Matsumura[1] · Sumihito Nobusawa[1] · Hayato Ikota[1] · Takashi Minegishi[2] · Hideaki Yokoo[1]

Received: 7 September 2015 / Revised: 8 November 2015 / Accepted: 23 November 2015 / Published online: 5 December 2015

Abstract Neural components in mature teratomas are common and the general assumption is that they are quite similar to those in the mature central nervous system (CNS). We investigated 44 ovarian teratomas by immunohistochemistry to determine cellular and structural immaturity of neural elements. Most teratomas contained cells differentiating into astrocytes positive for nestin, a neural stem cell marker. These nestin-positive astrocytes generally co-expressed glial fibrillary acidic protein-delta, an immature astrocyte marker. Olig2-positive cells were randomly scattered. Areas comprising cells that differentiated into neurons were positive for NeuN and synaptophysin. The border between white and gray matter was ill-defined and more NeuN-positive cells were distributed in areas that were positive for myelin basic protein, indicating that the distribution of neurons and glial cells was disturbed. Peripheral nerve bundles positive for Schwann/2E, an antigen specific for myelinating Schwann cells, were mixed within CNS-like tissues. These results show that apparently mature teratomas are not in fact mature, at least in terms of neural elements, as they harbor immature cells and structural abnormalities. The neural elements of surgically resected teratomas might represent a premature state of the human CNS, and thus be potentially useful for studies of developmental neurobiology as well as gliomagenesis.

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Keywords Mature teratoma · Immature teratoma · Maturity · Neural element

Introduction

Rudolf Virchow initially described a monstrous intraspinal tumor as a *teratoma* based on the Greek words *teras* meaning monster, and *onkoma* meaning swelling or tumor [1]. Almost a century later, Rupert A. Willis defined teratoma as "a true tumor or neoplasm composed of multiple tissues of kinds foreign to the part in which it arises" [2].

Mature teratomas are common ovarian tumors composed exclusively of mature tissues derived from two or three germ layers (ectoderm, mesoderm, and endoderm) and they constitute about 20 % of all ovarian tumors [3, 4]. The most abundant components of ectodermal derivatives are squamous epithelium and brain tissue (glia, ependymal tubules, and cerebellum). Mesodermal derivatives contain bone, cartilage, smooth muscle, and adipose tissue. Gastrointestinal and respiratory/bronchial epithelium, thyroid, and salivary glands are endodermal derivatives. Caruso et al. found ectodermal derivatives, mesodermal structures, and endodermal derivatives in 99.3, 73.3 and 31.9 % of mature teratomas, respectively, and neural elements 32.3 % of them [5]. Another study found a 33.3 % frequency of nervous tissue in mature teratomas [6].

On the other hand, immature teratomas are composed of variable amounts of immature embryonal-type tissues, mostly in the form of neuroectodermal tubules and rosettes, admixed with mature tissues [4, 7]. Immature teratomas have been classified into three grades based on relative amounts of immature neuroectodermal components [4, 7]. Thus, the differentiation of neural components in teratomas has been a good indicator of the overall status of tumor maturity [8]. However, little is known about the status of cellular and structural

Diagnostic Pathology　(formerly known by The Second department of Pathology)

Staffs:
Professor, Tetsunari OYAMA, M.D., Ph.D., Associate Professor, Takaaki Sano, M.D., Ph.D., Assistant Professor, Hiromi Koshi, M.D., PhD and Mai Seki, D.D.S

The main work in the Diagnostic Pathology is surgical pathology, cancer research and pathology education.

Research & Education

1. In surgical pathological work, we pathologists have a common mind similar to clinician, that is, "we see a patient through microscope". Our staff and post-graduate students partly shear the diagnostic and autopsy work in Gunma University Hospital. Social contribution in our department is carried out to providing various pathological works to many hospitals in Gunma Prefecture.
2. In our department, we are clinicopathologically studying the mechanism of carcinogenesis and cancer progression and the problems about cancer therapy. We are focusing human carcinogenesis by genetic abnormality with molecular biological techniques and immunohistochemistry in various cancers, for example, breast cancer, cervical cancer, gastric cancer, oral cancer, and bone and soft tissue tumor. In alimentary tract cancers, we have studied correlation between human carcinogenesis including multi-step carcinogenesis and genetic abnormalities occurred in various oncogenes and tumor suppressor genes. HPV infection and p16 protein expression has been investigated on cervical cancers. Recently, we are studying the expression of L-type amino acid transporter 1 (LAT1), which is a major transporter for essential amino acids, with relation of carcinogenesis in various organs such as breast, lung, and prostate and are trying to find several new biomarkers or new therapeutic taget protein, using next-generation sequencer.

The admission requirements:
A person who has graduated or will graduate from a university (which has a course in medical science or dental science, or a 6-year course in pharmaceutical science or veterinary science). The person who aims to be a pathologists in the future is required to have completed clinical residential training in hospital or MD-PhD integrated course. If you wish to senior resident of the University Hospital, Division of Diagnostic Pathology, it is also possible to enroll as a working member of society.
Current students:
Currently, Second grade: Ordinary course, two person, Third grade: Ordinary course, three person Fourth grade: MD-PhD integrated course, one person, In addition, undergraduate students are enrolled four person as MD-PhD course. If you aim a pathologist, in our department, post-graduate students learn diagnostic pathology including autopsy with learning the techniques of research in the first and/or second year, and followed by research work focusing on studies using clinical specimens in after second year.
After completing the post-graduate course:
Various options such as researchers, pathologists, or clinical physician for subsequent career path is possible after completing our graduate school. Diagnostic pathology has been positioned as clinical medicine also in Japan. The Division of Diagnostic Pathology was established in 2016 as a clinical department in Gunma University Hospital. We make a special effort to supporting a qualification of the pathology specialist of the Japanese society of pathology and of the cytopathologist of the Japanese society of clinical cytology.

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Tumor Biol.
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ORIGINAL ARTICLE

Clinical significance of β2-adrenergic receptor expression in patients with surgically resected gastric adenocarcinoma

Kengo Takahashi[1] · Kyoichi Kaira[2] · Akira Shimizu[3] · Taisuke Sato[1] · Norifumi Takahashi[1] · Ogawa Hiroomi[1] · Daisuke Yoshinari[1] · Takehiko Yokobori[4] · Takayuki Asao[2] · Izumi Takeyoshi[1] · Tetsunari Oyama[5]

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Abstract The β2-adrenergic receptor (β2-AR) is highly expressed in various human neoplasms and has been considered a novel therapeutic target of cancer treatment. However, the clinicopathological significance of β2-AR expression in patients with gastric cancer (GC) remains unclear. The aim of this study was to explore β2-AR expression and its prognostic significance. A total of 331 patients with surgically resected GC were evaluated. Tumor sections were stained immunohistochemically for β2-AR. β2-AR was highly expressed in 30.2 % of GC patients. Expression was significantly associated with age, T factor, tumor differentiation, histology of non-signet cells, lymphatic permeation, and vascular invasion. On univariate analysis, age, disease stage, T factor, N factor, lymphatic permeation, vascular invasion, and β2-AR expression were significantly associated with overall survival. Although the multivariate analysis did not indicate that β2-AR expression was independently prognostic of survival, high-level β2-AR expression was associated with significantly poorer survival of GC patients with well or moderately differentiated tumors. β2-AR expression was a significant predictor of tumor aggressiveness in, and poorer survival of, patients with GC.

Keywords β2-adrenergic receptor · Gastric cancer · Prognosis · Immunohistochemistry · β2-blocker

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Introduction

Gastric cancer (GC) is the fourth most common malignant disease and the second most common cause of cancer-related death worldwide, especially in East Asian countries such as Japan, China, and South Korea [1]. Curative gastrectomy with regional lymphadenectomy remains the standard treatment for patients with stages I–III GC, but approximately 20–30 % of patients develop local or distant recurrences and die of progressive disease, despite a seemingly favorable prognosis after surgery [1]. Disease staging is the most important consideration in predicting the prognosis of patients with GC. Although novel drugs targeting HER2 and VEGFR-2 have been developed and administered clinically, no established biomarker has yet been associated with the prognosis or therapeutic response of patients with GC and the discovery of some promising biomarkers is expected to improve the survival of GC. Thus, more research is required to discover the molecular mechanisms associated with the identification of more promising biomarkers for patients with GC.

Beta-blockers are commonly used for the treatment of heart disease [2]. The β2-adrenergic receptor (β2-AR), a member of the transmembrane G protein-coupled receptor (GPCR) family, triggers multiple signaling cascades and regulates cell proliferation through a classical cyclic adenosine monophosphate

Introduction of pediatrics in graduate school of medicine

Introduction and laboratory configuration
Organized 10 research and clinical group (Please see below for more details) are established. We are working for improving the QOL and developing new treatment to lead to the health of children. Most important goal is to reveal the pathophysiology of the refractory disease especially in pediatric disease and use them for treatment.

Current research topics
A) Allergy, Immunology and Pulmonology
- Elucidation of the molecular mechanisms involved the onset of pediatric allergic airway disease, the factors involved the pathogenesis of airway hyper responsiveness, mechanistic oral immunotherapy for food allergy

B) Cardiology
- Study of new treatment strategies and immunological treatment of Kawasaki disease
- Postoperative study of long-term prognosis and new treatment for co-morbidities in heart disease

C) Endocrinology
- Study of the functional role of the sweet taste receptor in pancreatic be-ta cells as well as in human enteroendocrine cells and bronchial epithelial cells
- Investigation of the molecular mechanism by which plasma glucagon levels elevate in pediatric diabetes

D) Gastroenterology
- Basic, translational, and epidemiologic studies on pathogenesis and clinical fatures of autoimmune intestinal diseases
- Epidemiological and functional studies on pediatric functional gastrointestinal disorders

E) Hematology
- Molecular genetic elucidation of prognostic factors in child leukemia
- Drug susceptibility and analysis of acquired drug resistance mechanism in tumor cell

F) Neonatology
- Colonization/infection with drug-resistant Escherichia coli and its mechanisms in preterm infant s
- The role of hepcidin in iron metabolism in low birth weight infants

G) Nephrology
- Development of a diagnostic tool for pathophysiological state in minimal change nephrotic syndrome with DNA methylation anaylysis
- Creating a new model of glomerular tuft wall using microfluidics
- Establishment of a treatment sensitivity prediction system for nephrotic syndrome in children using podocyte cell line

H) Neurology and developmental medicine
- Development of new therapies and pathogenesis with iPS cells of autophagy-related neurodegenerative diseases
- Elucidation of pathogenesis of restless legs syndrome by animal model
- Clinical research for congenital central hypoventilation syndrome

How to way to graduate school
You can acquire the pediatrics specialist qualification of the Japan pediatrics society when you finish the initial clinical training for two years and the university hospital or affiliated hospitals for further three years after acquiring medical knowledge, examination and treatment. We have the system entering the graduate school after the specialist acquisition as a general rule, because this is able to wrestle with a study with a clinical viewpoint with a carrier of graduate student yourself.

The situation of the graduate student
Several people enter it every year. We prepare for the curriculum which did cooperation with the laboratory of basic science for acquiring new experiment techniques or medical examination and treatment. We consider compensation of the life by a system to employ to a medical doctor for the day-time graduate student.

After course of graduate school
You engage in medical staff in pediatrics. We can provide the opportunity of the studying abroad to develop the own research and also tell you how to write English article.

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Original article

Suppression of *MUC5AC* expression in human bronchial epithelial cells by interferon-γ

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Sp1

Abbreviations:
IFN-γ, interferon-γ; TGF-α, transforming growth factor-α; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; IL-4, interleukin-4 IL-13, interleukin-13; NHBE, normal human bronchial epithelial; Th2, T helper 2; FBS, fetal bovine serum; ChIP, chromatin immunoprecipitation

ABSTRACT

Background: Excessive mucin secretion in the airway is an important feature of airway inflammatory diseases. MUC5AC expression is regulated by a variety of stimuli such as cytokines. Little is known about the role of interferon (IFN)-γ in MUC5AC expression in human bronchial epithelial cells.
Methods: Human pulmonary mucoepidermoid carcinoma cell line (NCI-H292) and normal human bronchial epithelial (NHBE) cells were used to assess the effects of IFN-γ on *MUC5AC* transcription.
Results: Transforming growth factor (TGF)-α and double-stranded RNA (polyI:C)-induced MUC5AC mRNA and protein expression was repressed by IFN-γ in a concentration-dependent manner. IFN-γ showed limited effects on TGF-α and polyI:C-induced activation of epidermal growth factor receptor (EGFR) and extracellular signal-regulated kinase (ERK). A chromatin immunoprecipitation assay indicated that Sp1 bound to its cognate sequence located on the *MUC5AC* promoter. The Sp1 inhibitor mithramycin A inhibited MUC5AC mRNA expression, implying a critical role for Sp1 in MUC5AC induction. Importantly, IFN-γ impeded Sp1 binding to the MUC5AC promoter.
Conclusions: These results suggest that IFN-γ represses MUC5AC expression, disturbing binding of Sp1 to its target sequences.

Introduction

Mucus production by bronchial epithelial cells plays an important role in the clearance of pathogens from the lungs. However, excessive secretion of mucus in some disease states can generate mucus plugs, leading to impaired respiration and possibly, death.[1,2] Therefore, fine control of mucus secretion is important for the physiological functions of the airways.

MUC5AC, which is secreted mainly from goblet cells, is a major component of airway mucins.[3] MUC5AC is upregulated in response to inflammation of the lungs caused by disorders such as bronchial asthma and airway infections.[4] MUC5AC expression and secretion are induced by pro-inflammatory cytokines such as interleukin (IL)-4, IL-13, and transforming growth factor (TGF)-α,[5] and by external agents such as viruses and cigarette smoke. In inflamed tissues, different stimuli can function simultaneously in the same locale while having diverse and interacting functions. Some costimuli initiate common effects, whereas others negatively regulate or synergize with each other. polyI:C, a mimic of viral double-stranded RNA, has been observed to enhance the effects of TGF-α, a ligand for the epidermal growth factor receptor (EGFR).[6] These two stimuli synergistically induce the production of MUC5AC. An underlying mechanism for this synergism is that polyI:C suppresses the expression of dual specificity phosphatase 6 (DUSP6), a negative regulator of extracellular signal-regulated kinase (ERK)1/2, which augments MAPK signaling pathways that are required for *MUC5AC* expression.[6] As another example, CCL20 has also been shown to

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Department of Obstetrics and Gynecology

I. Departmental research

a. Reproductive Endocrinology

b. Oncology

c. Obstetrics

II. Current subject of Research

a. Structure and function of FSH and LH receptor

Since we cloned human FSH-R and LH-R, we have been studying the regulatory mechanisms of regulation of these receptors in the ovary.

Moreover, we have studied the relationship between the mutation of these receptors and the dysfunction of gonad in human.

b. Molecular mechanisms of onset and growth of ovarian and endometrial cancer

We aim to clarify the molecular mechanisms of onset of cancer by using malignant cell line. If we could identify the novel oncogenes, these genes might become the therapeutical target for these cancers.

c. In vitro fertilization and embryo transfer

To prevent multiple pregnancies and ovarian hyper-stimulation syndrome, we are investigating the application and establishment of embryo culture system.

III. Entrance to graduate school.

It is recommended for candidate to apply for entrance to graduate school after three years clinical training. There is a course in graduate school for the student who works in hospital and concurrently studies at night in school.

IV. Current graduate students.

By a part-time job of obstetrics and gynecology hospital, life is stable even if student has a family.

V. Course of graduate school after completing

After completion of course, doctors can continue some basic research in our hospital or the others (The University of British Columbia, Iowa University, NIH and so on). Almost all candidates participate in the ob/gyn clinical duties after graduation.

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Retinoic acid enhances progesterone production via the cAMP/PKA signaling pathway in immature rat granulosa cells

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Protein kinase A

ABSTRACT

Retinoic acid (RA) is a metabolite of vitamin A and has important roles in development, differentiation, and reproduction. Activin has been shown to regulate the RA pathway and affect granulosa cell (GC) proliferation, suggesting that RA is important for early follicle development. However, little is known about the effects of RA on GC functions, particularly steroidogenesis, during the early follicle stage. The aim of this study was to investigate the effects of all-*trans*-RA (atRA) on progesterone production in immature rat GCs cultured without gonadotropin. Our results demonstrated that atRA enhanced progesterone production by upregulating the levels of steroidogenic acute regulatory protein (*StAR*) and cytochrome P450scc (*Cyp11a1*) mRNAs, but not 3β-hydroxysteroid dehydrogenase mRNA in immature rat GCs. Additionally, analysis of the mechanisms through which atRA upregulated *StAR* and *Cyp11a1* mRNAs revealed that atRA enhanced intracellular cAMP accumulation and phosphorylation of cAMP response-element binding protein (CREB). In addition, H-89, an inhibitor of protein kinase A (PKA), abolished the stimulatory effects of atRA, indicating that atRA enhanced progesterone synthesis through cAMP/PKA signaling. In conclusion, our data demonstrated that atRA has a crucial role in progesterone synthesis in rat GCs during the early follicle stage.

1. Introduction

Ovarian functions are regulated by many factors, including gonadotropin, transforming growth factor β (TGFβ), various cytokines, and retinoic acid (RA). RA is the active metabolite of vitamin A and is synthesized from retinol by retinol dehydrogenase (RDH) and retinaldehyde dehydrogenase (RALDH) [1]. RA exerts its activity by acting as a ligand for RA receptors (RARs) and retinoid X receptors (RXRs). RA mediates many physiological functions, including embryogenesis [2] and reproduction. In female rats, severe vitamin A deficiency prior to mating leads to reproductive failure prior to implantation [3]. Maternal vitamin A also plays a role in placental development and maintenance [4]. In addition, several studies have indicated that retinoids have important effects on oocyte maturation and function [5,6].

Previous studies have reported that RA enhances steroid production in several different cell types. For example, in MA-10 mouse Leydig cells, RA increases progesterone production by upregulation of steroidogenic acute regulatory protein (StAR) expression [7], and in rat hippocampal slice cultures, RA increases 17β-estradiol and testosterone levels through upregulation of cytochrome $P450_{17\alpha}$ expression [8]. In the ovary, Bagavandoss et al. reported that retinoids increase luteinized granulosa cell (GC) progesterone accumulation in gonadotropin-primed rat ovaries [9]. In a recent study, Kipp et al. reported that activin regulates the RA pathway to modulate GC proliferation and ovarian functions [10]. Because activin plays a key role in early follicle development [11], it has been hypothesized that RA may affect GC function, including steroidogenesis, during the early follicle stage. However, the effects of RA on steroidogenesis in GCs during the early follicle stage are still unclear.

In the present study, we investigated the effects of all-*trans*-RA (atRA) on progesterone production in immature rat GCs cultured without gonadotropin. Our results indicated that atRA enhanced progesterone synthesis through cAMP/protein kinase A (PKA)/cAMP response element-binding protein (CREB) signaling in GCs during the early follicle stage. Thus, these results provide important insights into the mechanisms of RA signaling in GCs.

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Department of Urology

1 Research group and interests

(1) Prostate diseases

Epidemiology, screening, diagnosis, treatment, molecular biology, genetic analysis

(2) Renal transplantation group

Clinical work as surgeons

(3)Renal cell cancer group

Clinical study, molecular biology

2 Admission policy

After training of urological clinical training, graduate students are encouraged to pursuit the research activities. During the research training, graduate students can participate in the clinical work in Gunma University Hospital or its affiliated hospitals.

3. Post-doctoral course

After graduation, students can continue to work as urologists or scientific surgeon in the university. They can work in the international collaborated laboratories based on their interests in urological sciences.

Simvastatin Up-Regulates Annexin A10 That Can Inhibit the Proliferation, Migration, and Invasion in Androgen-Independent Human Prostate Cancer Cells

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BACKGROUND. Statins have recently been studied for their proapoptotic and antimetastatic effects. However, the exact mechanisms of their anticancer actions remain unclear. Using microarrays, we discovered up-regulation of annexin A10 (ANXA10) in PC-3 cells after simvastatin treatment. ANXA10 reportedly has antitumor effects. In this study, we evaluated the effects of simvastatin on ANXA10 signaling in androgen-independent prostate cancer cells.
METHODS. PC-3, LNCaP-LA (which were derived from LNCaP cells and cultured in 10% charcoal-stripped fetal bovine serum for 3 months), and DU145 human prostate cancer cell lines were used. Prostate tissues were collected from 60 patients (benign prostatic hyperplasia [BPH], n = 20; prostate cancer with a Gleason score of 7, n = 20; prostate cancer with a Gleason score of 8–10, n = 20) at the time of prostate biopsies performed. We used a nude mouse tumor xenograft model with administration of simvastatin or phosphate-buffered saline via intraperitoneal injection.
RESULTS. Simvastatin inhibited the proliferation, migration, and invasion of PC-3, LNCaP-LA, and DU145 cells. The expression level of ANXA10 was up-regulated by simvastatin in PC-3, LNCaP-LA, and DU145 cells. Transfection with ANXA10 inhibited PC-3 and LNCaP-LA cells proliferation, migration, and invasion. Knockdown of ANXA10 by siRNA increased the proliferation of PC-3 and LNCaP-LA cells. In a nude mouse xenograft model of PC-3 cells, simvastatin induced both reduction in the tumor size and up-regulation of ANXA10 expression. In human prostate biopsy samples, ANXA10 mRNA expression was significantly lower in the prostate cancer group than in the BPH group. Next, we found that up-regulation of ANXA10 in PC-3 resulted in down-regulation of S100 calcium binding protein A4 (S100A4), which is reportedly correlated with aggressiveness and a worse prognosis for patients with different types of carcinomas. Expression of S100A4 was down-regulated by simvastatin. In PC-3 cells, knockdown of S100A4 by siRNA inhibited the proliferation, migration, and invasion of PC-3 cells.
CONCLUSION. Our results suggest that statins inhibit the proliferation, migration, and invasion of androgen-independent prostate cancer cells by up-regulation of ANXA10. Additionally, it is possible that S100A4 plays a role in these effects. Statins may be beneficial in the prevention and/or treatment of prostate cancer. *Prostate* © 2016 Wiley Periodicals, Inc.

KEY WORDS: **prostate cancer; statin; annexin A10; S100 calcium binding protein A4**

INTRODUCTION

Prostate cancer is the most commonly diagnosed malignancy and one of the leading causes of cancer death in the United States. Prostate cancer accounts for approximately 27% (233,000 new cases) of incident cases in the United States. Additionally, prostate cancer accounts for 10% (29,480 cases) of the total cancer deaths among men in the United States [1]. Prostate cancer has also been on the rise in Japan in

Conflicts of interest: No potential conflicts of interest were disclosed

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Introduction ; Department of Neurosurgery, Graduate School of Medicine

1) Research conference

Research conference is held once per month. All our members in department of neurosurgery discuss about the details of each research projects. Research projects are not divided into any research groups in our institute. The staffs teach methods of research to each researcher.

2) Subjects of research

A mathematical model of treatment for stroke
Imaging diagnosis, genomic analysis, and treatment in brain tumors
Pathophisiological analysis of Parkinson's disease
Imaging diagnosis of neurological diseases
Pathophisiology of brain ischemia, and treatment with neuroregeneration
Development of intraoperative monitoring for safe and exact neurosurgery
Acute complications after neurosurgery: diagnosis and treatment

3) Admission to the graduate school

It may be better to enter the graduate school as soon as possible after the end of an postgraduate clinical training. However, it is always possible to enter the graduate school.

4) The places where graduate school students work

Graduate school students mainly work in laboratories of Neurosurgery. In clinical study, they work in gunma university affiliated hospital. Some students work in basic research institutes of gunma university graduate school of medicine for instruction of basic researches.

5) After the graduate school

Some students stay in gunma university graduate school of medicine. The other students move to other institutes for the further research.

Risk Profile of Intracranial Aneurysms
Rupture Rate Is Not Constant After Formation

Koji Sato, MD; Yuhei Yoshimoto, MD

Background and Purpose—Management of asymptomatic unruptured intracranial aneurysms remains controversial, and recent prospective follow-up studies showed that the rupture rate of small aneurysms is very low. These results are inconsistent with the finding that the majority of ruptured aneurysms in patients with subarachnoid hemorrhage are small.

Methods—A Markov model was constructed to simulate the natural history of intracranial aneurysms. All epidemiological and statistical data obtained from the Portal Site of Official Statistics of Japan (e-Stat) were adjusted to the standardized age distribution. From the selected data of aneurysm formation, the prevalence of unruptured aneurysms was estimated as 1.45% and the incidence of subarachnoid hemorrhage calculated to be 19.7/100 000/year in the whole standardized population.

Results—The function for rupture rate constant with time was first analyzed. Selected values for annual rupture rates of 0.3%, 0.5%, 0.7%, and 1.0% showed inconsistencies in the relationship between the prevalence of unruptured aneurysm and the incidence of subarachnoid hemorrhage. Next, the function for a short period of high risk followed by a long period of low risk was considered. Annual rupture rates of 0.5%, 0.7%, and 1.0% indicated epidemiological compatibility with additional early rupture rates of 20%, 15%, and 10%, respectively.

Conclusions—This study suggests that some aneurysms bleed shortly after formation and thus are rarely detected as unruptured aneurysms. Most aneurysms without early rupture remain stable for the remainder of life through some healing process, and prophylactic treatment for incidentally identified small unruptured aneurysms has no rationale. (***Stroke*. 2011;42:3376-3381.)**

Key Words: aneurysms ■ Markov model ■ subarachnoid hemorrhage

Incidental detection of brain abnormalities has increased in recent years with the introduction of MRI and poses various practical and ethical issues. The clinical relevance and natural course of such asymptomatic abnormalities are largely unknown and may differ markedly from those of similar symptomatic lesions. In particular, the management of asymptomatic unruptured intracranial aneurysms remains controversial, so identifying the subset of patients likely to have problems with untreated aneurysms is an important clinical issue.

The International Study of Unruptured Intracranial Aneurysms (ISUIA) showed that the size of intracranial aneurysms is a primary determinant of the likelihood of rupture and that the rupture rate of small aneurysms is very low.[1] However, these findings of the natural history of intracranial aneurysms seem to conflict with the well-known epidemiological data that the majority of ruptured aneurysms in patients with subarachnoid hemorrhage (SAH) had diameters of <10 mm.[2,3] The prevalence of unruptured aneurysms will also influence the management strategy. The prevalence in the general population combined with the annual risk of rupture should equal the incidence of SAH, so "higher prevalence" would imply "lower risk." Previous studies used life-table analysis to calculate the lifetime risk of unruptured aneurysms.[4] However, the clinical situation may be different from simple rupture risk analysis based on assumptions of unchanging rupture rate. Therefore, a model of the natural history must incorporate changes in the rupture rate with time.

The present study constructed a mathematical model of the natural history of unruptured aneurysms and used the model to speculate about the risk profile of intracranial aneurysms.

Methods

Standardized Population Pyramid

All statistical data used in this study were obtained from the Portal Site of Official Statistics of Japan (e-Stat, www.e-stat.go.jp). The e-Stat site, developed by the Statistics Bureau, Ministry of Internal Affairs and Communications with the collaboration of other ministries and agencies, is managed by the Incorporated Administrative Agency National Statistics Center. The Statistics Bureau and the Director-General for Policy Planning of Japan are central in the official statistical system in producing and disseminating basic official statistics and coordinating statistical work under the Statistics Act and other legislation.

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Stroke is available at http://stroke.ahajournals.org

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Department of Ophthalmology

(1) Research groups

① Vitreous and Vitreoretinal interface

② Age- related macular degeneration

③ Glaucoma

④ Strabismus and Amblyopia

⑤ Corneal transplant・Ocular surface

⑥ Uveitis

⑦ Basic Research

(2) Research project

① “Histology in vivo” using optical coherence tomography (OCT) in vitreous and vitreoretinal disease. Development of treatment for retinoschisis, macular hole and vitreoreinal traction syndrome.

② Imaging and treatment for age-related macular degeneration.

③ Development of treatment using tube-shunt operation for glaucoma

④ Treatment of strabismus using prism glasses

⑤ Medical and surgical therapy for several corneal and ocular surface diseases

⑥ Molecular biological examinations of uveitis using PCR

⑦ Imaging of retinal hypoxia in animal experiment using phosphorescent lightemitting iridium

(3) Admission of the postgraduate school We recommend entering a postgraduate school after 2 years residency in ophthalmology. Postgraduate students can start a clinical research during residency in ophthalmology.

(4) The current status of postgraduate students in ophthalmology Students can choose a fully-day or a night time course. In a fully-day course, they can participate in a basic research for a whole week except a day for extra job. Students who take ophthalmology mainly perform clinical research , but they can collaborate with basic research laboratories. Students who take night-time course have to practice ophthalmology in day for research and have a day for an extra job in a week.

(5) The course after postgraduate school Students seek a posdoc position in abroad or continue research at Gunma University. They are expected to be valuable staffs in the department.

PLOS ONE

RESEARCH ARTICLE

Evaluation of Fundus Blood Flow in Normal Individuals and Patients with Internal Carotid Artery Obstruction Using Laser Speckle Flowgraphy

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Competing Interests: The authors have declared that no competing interests exist.

Abstract

Purpose

We investigated whether laser speckle flowgraphy (LSFG) results are comparable in both eyes and whether it is useful in the diagnosis of disparity in ocular ischemic syndrome (OIS) patients.

Methods

We compared the mean blur rate (MBR) value for various fundus regions in both eyes of 41 healthy subjects and 15 internal carotid artery occlusion (ICAO) cases. We calculated the standard value of the Laterality Index (LI), which was the MBR comparison of both eyes in each of the regions, in the control subjects. We then investigated the correlation between both eyes for the LIs in the entire fundus, the degree of ICAO and visual function.

Results

The disparity of the LIs in both eyes was least in the entire area of the fundus in control subjects and there was a significant correlation between both eyes of the 41 healthy individuals (P = 0.019). Significant correlations were found for the LI, visual acuity and degree of ICAO. The specificity and sensitivity of LI in the entire area was 93.8% and 100%, respectively.

Conclusions

LSFG revealed normal individuals have symmetrical fundus blood flow. LSFG could detect OIS and might be a useful tool for detecting disparities in fundus blood flow.

Department of Otolaryngology-Head and Neck Surgery

(1) Research groups

① Neuroscience group: Drs. K. Takahashi, Takayasu, Shino, Murata & Kayakabe

② Oncology group: Drs. Chikamatsu, Sakakura, H. Takahashi, Okamoto & Kuwabara

(2) Research themes

① Neuroscience group

1. Neurophysiology of equilibrium in the central pathway
2. Signal transduction of the inner ear
3. Oxidative and reduction stress in nervous disease
4. Relationship between Meniere's disease and human herpes virus

② Oncology group

1. Interaction between the immune system and cancer cells
2. Immunosuppressive mechanisms in head and neck cancers
3. Tumor microenvironment in head and neck cancers
4. Development of cancer vaccines
5. Development of novel biomarkers for head and neck cancers

(3) Admission procedures

Most students enter graduate school after completion of senior residency programs.

(4) The actual situation of graduate school students

Besides research works, most students perform not only outpatient care, but also jobs in affiliated hospitals, and will be eligible to acquire board certificated otolaryngologist. Thus there is nothing to worry about clinical skills and living expenses. Female students can be managed both their career and family. In addition, we have sufficient facilities to undergo researches, while students also can be temporarily transferred to other labs of basic medical science.

(5) The courses after graduation

Most students return to work at a university hospital or an affiliated hospital. Continuation of research works is always considered, and studying in domestic or foreign research institutes is also possible, if desired.

(6) Others

Similar to clinical works, research works are also conducted together with a number of staffs as a team. Through the course of graduate school, students can learn not only scientific methods for research skills and writing articles, but also logical and flexible thinking. Such results are helpful for moving up the career ladder as a clinician. We are now looking forward to seeing enthusiastic students.

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Research Paper

Cancer-associated fibroblasts promote an immunosuppressive microenvironment through the induction and accumulation of protumoral macrophages

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Keywords: *cancer-associated fibroblast (CAF), tumor-associated macrophage (TAM), tumor microenvironment (TME), immunomodulation, immunosuppression*

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ABSTRACT

Stromal cells in the tumor microenvironment (TME) closely interact with tumor cells and affect tumor cell behavior in diverse manners. We herein investigated the mechanisms by which cancer-associated fibroblasts (CAFs) affect the functional polarization of tumor-associated macrophages (TAMs) in oral squamous cell carcinoma (OSCC) *in vitro* and in human cancer samples. The expression of CD68, CD14, CD163, CD200R, CD206, HLA-G, CD80, and CD86 was higher in CD14-positive cells co-cultured with the culture supernatants of CAFs established from OSCC specimens (CAF-educated cells) than in control cells. The gene expression level of *ARG1*, *IL10*, and *TGFB1* was increased in CAF-educated cells. CAF-educated cells suppressed T cell proliferation more strongly than control cells, and the neutralization of TGF-β IL-10, or arginase I significantly restored T cell proliferation. We then investigated the relationship between the infiltration of CAFs and TAMs using tissue samples obtained from patients with OSCC. The infiltration of CAFs was associated with the numbers of CD68-positive and CD163-positive macrophages. It also correlated with lymphatic invasion, vascular invasion, lymph node involvement, and the TNM stage. The infiltration of CAFs was identified as an independent prognostic factor in OSCC. Our results indicate that CAFs play important roles in shaping the tumor immunosuppressive microenvironment in OSCC by inducing the protumoral phenotype of TAMs. Therapeutic strategies to reverse CAF-mediated immunosuppression need to be considered.

INTRODUCTION

Stromal cells in the tumor microenvironment (TME) closely interact with tumor cells and affect tumor cell behavior in diverse manners; for example, they promote tumor growth, invasion, and metastasis, in addition to treatment resistance [1, 2]. However, the relationship between the TME and the immune system is more complex and has not yet been elucidated. Tumor tissue is infiltrated by a number of immune cells that show functional plasticity and may adopt antitumor or protumor activity. Emerging evidence suggests that stromal cells, including fibroblasts, endothelial cells, and mesenchymal stem cells, play pivotal roles in shaping the tumor immune environment [3, 4]. Fibroblasts have been identified as one of the most active cell types of the tumor stroma [1, 2, 5]. In the TME, fibroblasts transdifferentiate into activated phenotype myofibroblasts through transforming growth factor beta (TGF-β) and interleukin (IL)-1 beta signaling [6, 7], and are known as cancer-associated fibroblasts (CAFs). We recently demonstrated that CAFs in squamous cell carcinoma of the head and neck directly and indirectly modulate effector T cell function during antitumor immune responses [8]. CAFs exhibit greater suppressor activity on T cell proliferation through co-regulatory molecules and immunosuppressive cytokines than normal fibroblasts. Moreover, CAFs preferentially induce T cell apoptosis and regulatory T cells. Similar findings have

(1) **Introduction of Laboratory**

Our research goal is “Bedside to Bench and Bench to Bedside” to cure and care patients suffering from diseases of unknown etiology or intractable diseases. Our experienced staffs , professor Ishikawa O, and assistant professors Shimizu A, Motegi S, Yasuda M and assistant Kishi C, supervise and assist you to publish the high quality paper to the world. Our main research themes are as follows; ①autoimmune rheumatic diseases such as systemic sclerosis, SLE, dermatomyositis (Drs. Motegi and Shimizu, Kishi), ② pathogenesis of skin tumors and clinical pathology (Drs. Motegi, Shimizu, Yasuda), ③ wound healing (Dr. Motegi), ④viral infection and skin diseases (Dr. Shimizu) and ⑤ immune disturbance in skin diseases (Dr. Kishi),

【Recent papers of graduate school students】

1. Uehara A, et al.. Mechanistic insight into the norepinephrine-induced fibrosis in systemic sclerosis. Sci Rep UK, 2016 Sep 21; 6:34012. doi: 10.1038/srep34012.2016 (IF=5.288)
2. Yamada K, et al. MFG-E8 drives melanoma growth by stimulating mesenchymal stromal cell-induced angiogenesis and M2 polarization of tumor-associated macrophages. Cancer Res. **76**(14): 4283-492, 2016 (IF=8.556)
3. Kato M, et al. A novel autosomal recessive mutation of DSG4 causes monilethrix through the ER stress response. J Invest Dermatol **135**(5):1253-1260, 2015 (IF=6.915)

(2) **Present Research Themes**

① Roles of IL-6 and epinephrine, apelin or ATP in systemic sclerosis
② Roles of MFG-E8 in wound healing and Ischemic/Reperfusion injury
③ Pathogenesis of atopic dermatitis and itching skin diseases in the elderly
④ Roles of mesenchymal stem cell in angiogenesis of malignant melanoma
⑤ Human papilloma virus and skin tumors
⑥ Innate immunity and autoimmune rheumatic diseases
⑦ Roles of transposon in autoimmune rheumatic diseases
⑧ Gene analyses of hereditary systemic and skin diseases
⑨ ER stress and hereditary diseases
⑩ Cancer stem cell
⑪ Keratin expression and skin diseases

(3) **Graduate School Admission**

From the clinical point of view, it is desirable for Japanese applicants of medical school graduate to experience a few two years’ clinical practice in dermatology prior to graduate school. The foreign applicant is not required to be a physician. Most important is the interest and the curiosity in human health and diseases.

Tumor and Stem Cell Biology

Cancer Research

MFG-E8 Drives Melanoma Growth by Stimulating Mesenchymal Stromal Cell–Induced Angiogenesis and M2 Polarization of Tumor-Associated Macrophages

Kazuya Yamada[1], Akihiko Uchiyama[1], Akihito Uehara[1], Buddhini Perera[1], Sachiko Ogino[1], Yoko Yokoyama[1], Yuko Takeuchi[1], Mark C. Udey[2], Osamu Ishikawa[1], and Sei-ichiro Motegi[1]

Abstract

Secretion of the powerful angiogenic factor MFG-E8 by pericytes can bypass the therapeutic effects of anti-VEGF therapy, but the mechanisms by which MFG-E8 acts are not fully understood. In this study, we investigated how this factor acts to promote the growth of melanomas that express it. We found that mouse bone marrow–derived mesenchymal stromal cells (MSC) expressed a substantial amount of MFG-E8. To assess its expression from this cell type, we implanted melanoma cells and MSC derived from wild type (WT) or MFG-E8 deficient [knockout (KO)] into mice and monitored tumor growth. Tumor growth and M2 macrophages were each attenuated in subjects coimplanted with KO-MSC compared with WT-MSC. In both xenograft tumors and clinical specimens of melanoma, we found that MFG-E8 expression was heightened near blood vessels where MSC could be found. Through *in vitro* assays, we confirmed that WT-MSC–conditioned medium was more potent at inducing M2 macrophage polarization, compared with KO-MSC–conditioned medium. VEGF and ET-1 expression in KO-MSC was significantly lower than in WT-MSC, correlating *in vivo* with reduced tumor growth and numbers of pericytes and M2 macrophages within tumors. Overall, our results suggested that MFG-E8 acts at two levels, by increasing VEGF and ET-1 expression in MSC and by enhancing M2 polarization of macrophages, to increase tumor angiogenesis. *Cancer Res; 76(14); 1–10. ©2016 AACR.*

Introduction

Mesenchymal stromal cells (MSC) are bone marrow–derived nonhematopoietic pluripotent progenitor cells with the capacity to differentiate into various cell types, including chondrocytes, adipocytes, and osteocytes (1–3). Recent evidence indicates that pericytes and MSC are similar cells that are located external to the vasculature and are involved in angiogenesis, repair, and tissue maintenance (4–6). It has been reported that malignant tumor cells, such as malignant glioma and melanoma, can recruit MSC from surrounding tissue or the circulation and stimulate the growth of MSC by the secretion of soluble factors, including platelet-derived growth factor (PDGF; refs. 7–9). These tumor-associated MSCs secrete growth factors or cytokines, resulting in the promotion of angiogenesis (7–9). In addition, several studies have reported that MSC can differentiate into fibroblasts, myofibroblasts, or pericyte-like cells and enhance angiogenesis, resulting in tumor progression and metastasis *in vivo* (10–14). MSCs also have an immunosuppressive function and may help tumor escape from immune surveillance (11). Tumor-resident and injected MSCs have been demonstrated to promote the recruitment of tumor-associated macrophages (TAM; refs. 15, 16). These findings have led to an increased interest in understanding the role of MSC in tumor growth and the potential of MSC to serve as therapeutic targets in melanoma.

Milk fat globule EGF factor 8 (MFG-E8) is a secreted glycoprotein and consists of two EGF-like domains and two discoidin-like domains with sequence homology to the blood coagulation factors V and VIII (17, 18). The second EGF-like domain contains an RGD motif that binds to integrin αvβ3/5 (18, 19). The carboxy-terminal domains of MFG-E8 can bind to negatively charged phospholipids (20), resulting in the opsonization of apoptotic cells for uptake by phagocytes (19, 21). In addition, interactions between MFG-E8 and integrin αv have been implicated in the enhancement of angiogenesis in mice (22–24).

Many studies have indicated that MFG-E8 enhances tumor cell survival, invasion, and angiogenesis and contributes to local immune suppression (23, 25–29). In a murine melanoma model, MFG-E8 enhanced the tumorigenicity and metastatic capacity through Akt and Twist-dependent pathways (26). In addition, MFG-E8 produced by TAM in melanomas activated STAT3 and sonic hedgehog pathways in cancer stem cells (27). Furthermore, systemic MFG-E8 blockade using an anti-MFG-E8 antibody cooperates with cytotoxic chemotherapy, molecular targeted therapy, and radiation to induce the destruction of murine tumors, including melanoma (28).

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Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

K. Yamada and A. Uchiyama contributed equally to this article.

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Department of Oral and Maxillofacial Surgery・Plastic Surgery

(1) Members and fields

Professor Satoshi Yokoo, DMD, DMSc (oral cancer, oral and maxillofacial reconstruction, jaw deformity, and maxillary sinus disease), Associate professor Takaya Makiguchi, MD, PhD (plastic surgery, cranio-maxillofacial trauma, and facial reconstructive surgery), Assistant professor Yu Takayama, DMD, DMSc (oral surgery, jaw deformity, and maxillary sinus disease), Assistant professor Masaru Ogawa, DDS (oral surgery and endodontic microsurgery), Assistant professor Jun Kurihara, DDS, PhD (oral surgery, bone metabolism, general medicine), Yuki Kanno, DDS, PhD (oral surgry), Kumiko Kurabayashi (oral care), Atsushi Musya, DDS, PhD (heavy ion therapy) and Mai Seki DMD, DMSc (oral pathology).
These members play a central role in performing translational research for clinical practice.

(2) Present research theme

1) Epithelialization in oral mucous wound healing in terms of energy metabolism.
2) Cytological evaluation in odontogenic cyst-lining keratinocyte.
3) Oral and maxillofacial reconstruction with vascularised free flaps.
4) Evaluation of treatment strategy of oral cancer.
5) Effects of pilocarpine and isoproterenol on aquaporin-5 expression in salivary gland
6) Clinical and experimental study of endodontic microsurgery for extensive radicular cyst.
7) Surgical study of jaw deformity
8) Heavy ion therapy of head and neck malignancy

(3) Eligibility requirements for admission to the graduate school

The requirements are graduation from the Department of Dentistry/Medicine, completion of the compulsory 3-year training period (2 years as a resident and 1 year as a medical staff member).

(4) Present status of graduate students

Research is being performed by 3 fourth-year, 1 third-year, and 1 first-year graduate student in our department. When necessary, temporary transfer to research institutions inside or outside the university is permitted.

Graduate students are required to perform clinical practice in the first year, and concentrate on research from the second year. Thus, graduate

students gain remuneration as part-timers and research/education assistants of our university.

(5) Course after the completion of the graduate school program

Graduates of the graduate school are required to give research instruction to successors, and perform clinical practice and research, aiming to become board-certificated specialists.

Motor Nerve Preservation and Muscle Atrophy After Pectoralis Major Musculocutaneous Flap Surgery for Oromandibular Reconstruction

Yu Takayama, DMD, Satoshi Yokoo, DMD, DMSc,**
Takaya Makiguchi, MD, PhD, and Takahide Komori, DDS, PhD†*

Objective: The authors investigated the clinical and histopathologic significance of medial pectoral nerve preservation/reinnervation of pectoralis major musculocutaneous flap for oromandibular reconstruction.

Materials and Methods: The authors compared 13 patients treated with pectoralis major musculocutaneous flap reconstruction and 6 control patients treated by rectus abdominis musculocutaneous flap reconstruction without motor nerve restoration. Subjective awareness was scored to evaluate changes in the facial contour due to muscle atrophy, and objective evaluation was performed in few patients. In addition, the authors performed histopathologic analysis of both muscle atrophy and nerve regeneration in 20 patients from whom samples were available.

Results: Subjective awareness of changes in the facial contour induced by muscle atrophy was low among patients with nerve preservation/reinnervation, but there were objective changes at 3 months after surgery among patients who underwent nerve resection. In the patients who had medial pectoral nerve preservation or nerve restoration by nerve suture, favorable facial symmetry was retained at 5 years after surgery. Even though the motor nerve was preserved or restored, fatty degeneration and fibrosis were noted in approximately 30% of the total surface area of the muscle, and type I fibers had decreased to 36% that of control at 7 years after surgery. However, regressive changes were inhibited for 1 year after surgery; in contrast, changes corresponding to those noted at 7 years after surgery were observed by 3 months in the patients with nerve resection.

Conclusion: Thus, the authors showed that preservation or restoration of nerves can delay muscle and have highlighted the potential benefits of this approach.

Key Words: Motor nerve, muscle atrophy, neural regeneration, oromandibular reconstruction, pectoralis major musculocutaneous flap

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Although free flap transfer is the preferred approach in most major oromandibular reconstruction procedures, the pectoralis major musculocutaneous (PMMC) flap is often used in the salvage of necrotic free flaps and is the first choice for patients who are not suitable for free flaps. The PMMC flap is associated with a high incidence of distal skin necrosis due to vascular insufficiency, which can result in partial or total flap loss as well as fistula formation.[1] This flap is known to cause early muscle atrophy and decreased fat volume that can result in compromised postoperative function and aesthetics.[2] It is widely reported from clinical and animal experiments that the preservation or restoration of the motor nerves (reinnervation) limits the reduction of muscle volume to within 50%.[3] Therefore, to order to prevent significant muscle atrophy with PMMC flaps, we preserve the medial pectoral nerve supplying motor function to the pectoralis major (PM) muscle. Even when the nerve is resected, attempts are made to reconstruct it using nerve sutures whenever possible.[4–8]

The purpose of this study is to examine the clinical and histopathologic effects of the medial pectoral nerve preservation or reinnervation on muscle atrophy as an outcome after oromandibular reconstruction with a PMMC flap.

Musculocutaneous Flap Procedures for Reconstructive Surgery of Mandibular Defect

The protocol for mandibular reconstruction at the Department of Oral and Maxillofacial Surgery of Gunma University Hospital is as follows. Segmental defects of ≤5 cm are treated with a graft comprising a combination of a nonvascularized iliac bone and particulate cancellous bone marrow (PCBM) of from the iliac bone. For segmental defects >5 cm, a vascularized free fibula or scapular bone graft is applied. In 2003, we used a wrap-around procedure with a titanium reconstruction plate and a musculocutaneous flap before secondary reconstruction with PCBM transplantation for regenerative mandibular reconstruction.[9] For hemi- and posterior mandibular defects, we used the methods described by Kroll et al[10] and Butler and Lewin.[11] However, instead of free-end reconstruction with either a bone flap or a reconstruction plate, we carry out aesthetic contour restoration with a musculocutaneous flap alone.

After a wrap-around reconstruction in patients with segmental defects, postoperative muscle atrophy might affect the facial contours and cause plate exposure. In this setting, rectus abdominis musculocutaneous (RAM) flaps are advantageous for several reasons: the reduction in total tissue volume is small because atrophy of subcutaneous fat and muscle with fatty change is limited due to the direct blood supply from the deep inferior epigastric artery, and muscle atrophy is delayed by restoration of the intercostal nerves by nerve suturing. Thus, a RAM flap is used as the established standard for this type of reconstruction. If a RAM flap cannot be used, a PMMC flap is selected, but preservation or

Department of Orthopaedic Surgery

Our department has five main groups: Upper extremities, Rheumatoid arthritis, Spine, Musculoskeletal tumor, and Lower extremities. Each group has several projects and some projects were performed by all members of our department.

① Upper extremities

・Comprehensive study of tendon healing in model rats.

・Quantitative imaging assessment for muscle atrophy and fatty infiltration in rotator cuff muscles.

・Quantitative assessment of muscle atrophy by ultrasound in peripheral nerve palsy

② Rheumatoid arthritis

・Imaging analysis of rheumatoid arthritis using FDG-PET/CT

・Pathological investigation in patients with rheumatoid arthritis

・Osteoporosis in rheumatoid arthritis

③ Spine

・Comprehensive analysis of gene expression in the lumbar spine of congenital kyphoscoliosis

・Clinical anatomy of subaxial cervical foramens

・Functional correlations between the brain and spinal cord during motor tasks using a developed simultaneous Recording technique of the functional magnetic resonance imaging data

④ Tumor

・Morphological changes of tumor cells by glucose metabolism related molecules

・Regulation of lymphatic metastasis of malignant bone and soft-tissue tumors

・Characterization of proteins interacting with autocrine motility factor

⑤ Lower extremities

・Research of Electrical skeletal Muscle Stimulation (EMS) with Positron Emission Tomography

・FDG-PET imaging of lower extremity muscular activity before and after total knee arthroplasty in patients with osteoarthritis

⑥ the others

・Analysis of risk factors of sports disorders among young baseball players

・Practical application of promotion of exercise and learning and neural rehabilitation by non-invasive brain stimulation in old people with locomotive syndrome

・Bone metabolism in atypical femoral fractures

・Investigation of osteoporosis in psychiatric patient

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Compensatory hypertrophy of the teres minor muscle after large rotator cuff tear model in adult male rat

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Background: Rotator cuff tear (RCT) is a common musculoskeletal disorder in the elderly. The large RCT is often irreparable due to the retraction and degeneration of the rotator cuff muscle. The integrity of the teres minor (TM) muscle is thought to affect postoperative functional recovery in some surgical treatments. Hypertrophy of the TM is found in some patients with large RCTs; however, the process underlying this hypertrophy is still unclear. The objective of this study was to determine if compensatory hypertrophy of the TM muscle occurs in a large RCT rat model.

Methods: Twelve Wistar rats underwent transection of the suprascapular nerve and the supraspinatus and infraspinatus tendons in the left shoulder. The rats were euthanized 4 weeks after the surgery, and the cuff muscles were collected and weighed. The cross-sectional area and the involvement of Akt/mammalian target of rapamycin (mTOR) signaling were examined in the remaining TM muscle.

Results: The weight and cross-sectional area of the TM muscle was higher in the operated-on side than in the control side. The phosphorylated Akt/Akt protein ratio was not significantly different between these sides. The phosphorylated-mTOR/mTOR protein ratio was significantly higher on the operated-on side.

Conclusion: Transection of the suprascapular nerve and the supraspinatus and infraspinatus tendons activates mTOR signaling in the TM muscle, which results in muscle hypertrophy. The Akt-signaling pathway may not be involved in this process. Nevertheless, activation of mTOR signaling in the TM muscle after RCT may be an effective therapeutic target of a large RCT.

Level of evidence: Basic Science Study, Physiology, Animal Model.

Keywords: Shoulder joint; rotator cuff tear; muscle hypertrophy; animal study; functional compensation

Rotator cuff tear (RCT) is a common musculoskeletal disorder in the elderly that results in the impairment of daily life due to intolerable shoulder pain or decreased muscle strength, or both. Previous epidemiologic studies have tried to reveal its prevalence and factors that may be

The Gunma University Animal Care and Experimentation Committee approved this study (14-043).

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Gunma University Graduate School of Medicine

Department of Clinical Pharmacology

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Doctoral course student: **12**

SUMMARY

Recently, many new drugs with novel mechanisms have produced to improve the clinical efficacy of drug therapy, however, the development of new drugs also have produced a lot of new problems to be solved. In the pharmacotherapy, the choice of appropriate therapy or drugs for each individual patient is imperative. To establish safe and effective pharmacotherapy, we focus the variation factors for clinical efficacy or expression of adverse drug reaction of drug therapy for several diseases with gene analysis, pharmacokinetic approaches and other fundamental research approaches.

RESEARCH THEME

1. Clinical Pharmacokinetic study for investigation of factors affecting drug efficacy
   Key words: drug concentration in plasma, intracellular concentration of drugs, transporters, intracellular pharmacokinetic, peripheral blood mononuclear cell, cardiovascular disease, acquired immune deficiency syndrome

2. Development of methodology for predicting drug efficacy and expression of drug resistance using genetic analysis, pharmaceutical approach and biomarker analytic approach
   Key words: disposition of biological protein, genetic variation, mRNA, biomarker analysis, antineoplastic drug, antibody drug, antimicrobial drug, LC-MS/MS

3. Study of individual variation of drug efficacy and cause of side effects of drugs with basic study using human liver microsome
   Kew words: anticoagulant drug, vitamin K

Eur J Clin Pharmacol (2013) 69:395–405
DOI 10.1007/s00228-012-1356-9

PHARMACOGENETICS

Responsiveness to low-dose warfarin associated with genetic variants of *VKORC1*, *CYP2C9*, *CYP2C19*, and *CYP4F2* in an Indonesian population

T. Rusdiana · T. Araki · T. Nakamura · A. Subarnas · K. Yamamoto

Received: 7 February 2012 / Accepted: 11 July 2012 / Published online: 2 August 2012

Abstract
Purpose The aim of this study was to assess the pharmacokinetics and pharmacodynamics of warfarin associated with genetic polymorphisms in *VKORC1*, *CYP2C9*, *CYP2C19*, and *CYP4F2* in Indonesian patients treated with low-dose warfarin.
Methods Genotyping of *VKORC1*, *CYP2C9*, *CYP2C19*, and *CYP4F2* was carried out in 103 patients treated with a daily dose of 1–2 mg warfarin, 89 of whom were treated with a fixed daily dose of warfarin (1 mg). The plasma concentrations of *S*- and *R*-warfarin and *S*- and *R*-7-hydroxywarfarin were used as pharmacokinetic indices, while prothrombin time expressed as the international normalized ratio (PT-INR) was used as a pharmacodynamic index.
Results In patients treated with a fixed daily dose of warfarin (1 mg), a higher PT-INR was associated with *VKORC1*-1639 AA [median 1.35; interquartile range (IQR) 1.21–1.50] than with the GA (1.18; IQR 1.12–1.32; $p<0.01$) and GG (1.02; IQR=1.02–1.06; $p<0.01$) polymorphisms, and with *CYP2C9**1/*3 (1.63; IQR 1.45–1.85) compared to *1/*1 (1.23; IQR 1.13–1.43; $p<0.05$). The *S*-warfarin concentration was significantly higher in patients with *CYP2C9**1/*3 than in those with *1/*1 ($p<0.05$). With low-dose warfarin administration, there was no significant difference in the concentrations of warfarin metabolites among any of the genotype variants. The genotype variations of *CYP2C19* and *CYP4F2* were not significantly associated with the PT-INR.
Conclusion For low dose warfarin treatment, the *VKORC1*-1639 G>A and *CYP2C9* genotype variations affected the pharmacokinetics and pharmacodynamics of warfarin, while we could not find significant effects of *CYP4F2* or *CYP2C19* genotype variations on warfarin (metabolite) concentrations or PT-INR.

Keywords Warfarin · Pharmacogenetics · *VKORC1* · *CYP2C9* · *CYP4F2*

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Introduction

Warfarin (WF) is used as an oral anticoagulant drug for the treatment and prevention of thromboembolic disorders [1]. Bleeding is one of the serious adverse reactions in anticoagulant therapy, and it still remains a risk factor during long-term therapy with low-dose WF [2, 3]. Due to the large individual variability in WF response, drug therapy with WF requires frequent and regular monitoring by measurement of the prothrombin time expressed as the international

Clinical Trials and Regulatory Science

Professor: Tetsuya Nakamura, M.D., Ph.D.
Associate Professor: Yuki Date, DDS, Ph.D.
Assistant Professor: Miho Oue, Ph.D.
Assistant Professor: Yoshiaki Ohyama, M.D., Ph.D.

Clinical trials and research are advanced very rapidly and changed dramatically in recent years. We conduct and support a variety of clinical trials in our hospital and in our community to establish highly qualified clinical evidence. Our research interest is also on the development of new medicine or medical devices.

We started Clinical Investigation and Research Unit in Gunma University Hospital in April 2001 for the first time in national university hospital in Japan. Since then, we have built a long history of adopting a policy of GCP for all clinical trials and research for both investigator- and company-initiated. We have not separated or distinguished clinical trials and research, depending upon investigator- or sponsor-based in IRB consideration and data-management. Our department now includes twelve clinical research coordinators, eight data-managers and a specialist of pharmaceutical affairs.

We continuously improve our knowledge and skills about trial design, data management, statistical methods, regulatory science or ethical issues in daily practice. We are trying to open a door for new world of clinical science.

Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial

Tohru Kobayashi, Tsutomu Saji, Tetsuya Otani, Kazuo Takeuchi, Tetsuya Nakamura, Hirokazu Arakawa, Taichi Kato, Toshiro Hara, Kenji Hamaoka, Shunichi Ogawa, Masaru Miura, Yuichi Nomura, Shigeto Fuse, Fukiko Ichida, Mitsuru Seki, Ryuji Fukazawa, Chitose Ogawa, Kenji Furuno, Hirohide Tokunaga, Shinichi Takatsuki, Shinya Hara, Akihiro Morikawa, on behalf of the RAISE study group investigators

Summary

Background **Evidence indicates that corticosteroid therapy might be beneficial for the primary treatment of severe Kawasaki disease. We assessed whether addition of prednisolone to intravenous immunoglobulin with aspirin would reduce the incidence of coronary artery abnormalities in patients with severe Kawasaki disease.**

Methods **We did a multicentre, prospective, randomised, open-label, blinded-endpoints trial at 74 hospitals in Japan between Sept 29, 2008, and Dec 2, 2010. Patients with severe Kawasaki disease were randomly assigned by a minimisation method to receive either intravenous immunoglobulin (2 g/kg for 24 h and aspirin 30 mg/kg per day) or intravenous immunoglobulin plus prednisolone (the same intravenous immunoglobulin regimen as the intravenous immunoglobulin group plus prednisolone 2 mg/kg per day given over 15 days after concentrations of C-reactive protein normalised). Patients and treating physicians were unmasked to group allocation. The primary endpoint was incidence of coronary artery abnormalities during the study period. Analysis was by intention to treat. This trial is registered with the University Hospital Medical Information Network clinical trials registry, number UMIN000000940.**

Findings **We randomly assigned 125 patients to the intravenous immunoglobulin plus prednisolone group and 123 to the intravenous immunoglobulin group. Incidence of coronary artery abnormalities was significantly lower in the intravenous immunoglobulin plus prednisolone group than in the intravenous immunoglobulin group during the study period (four patients [3%] *vs* 28 patients [23%]; risk difference 0·20, 95% CI 0·12–0·28, p<0·0001). Serious adverse events were similar between both groups: two patients had high total cholesterol and one neutropenia in the intravenous immunoglobulin plus prednisolone group, and one had high total cholesterol and another non-occlusive thrombus in the intravenous immunoglobulin group.**

Interpretation **Addition of prednisolone to the standard regimen of intravenous immunoglobulin improves coronary artery outcomes in patients with severe Kawasaki disease in Japan. Further study of intensified primary treatment for this disease in a mixed ethnic population is warranted.**

Funding **Japanese Ministry of Health, Labour and Welfare.**

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Introduction

Kawasaki disease is an acute systemic vasculitis of unknown cause that affects mainly infants and children and is a major cause of acquired heart disease in developed countries.[1] Treatment with high-dose intravenous immunoglobulin plus aspirin resolves inflammation and reduces the occurrence of coronary artery abnormalities.[2–4] However, about 20% of patients have persistent or recurrent fever after completion of intravenous immunoglobulin[5] and these patients have a particularly high risk of developing coronary artery abnormalities.[6–8]

Although corticosteroids are a useful treatment option for various forms of vasculitis, many physicians have hesitated to use them because a report[9] showed a high incidence of coronary artery abnormalities in patients who received a prolonged course of oral prednisolone alone. However, findings from a subsequent retrospective study[10] of the effects of corticosteroids in Kawasaki disease showed possible benefits. In a meta-analysis,[11] inclusion of corticosteroids in regimens containing aspirin for primary treatment of Kawasaki disease reduced the incidence of coronary artery abnormalities. In 2007, findings from a randomised, placebo-controlled trial[12] of the efficacy of a single dose of pulsed intravenous methylprednisolone added to conventional therapy showed that pulsed corticosteroid treatment did not improve coronary artery outcomes. In a randomised, open-label, non-blinded trial,[13] intravenous immunoglobulin plus prednisolone decreased the incidence of coronary artery abnormalities and treatment failure; however, the trial had potential methodological flaws.[14] We subsequently noted in a retrospective analysis[15] that primary treatment with intravenous immunoglobulin plus prednisolone improved

Department of Medical informatics

(1) Stuff

Associate Professor Yuichiro Saito
Associate Professor Kota Torikai
Assistant Professor Ryoji Suzuki
Assistant Professor Shinichi Tsujimura

(2) Research

Deta warehouse and database for hospital information system
Radio frequency identification for hospital management
Analysis of workflow

(3) Admission

We welcome students who aspire to become an educator of medical informatics and have the ability to carry out research and academic studies in the course of medical informatics.

(4) Number of students

Doctoral program; 1
Master's program; none

(5) After graduation

Teacher in a medical school
Stuff of a hospital (medical assistant)
Office worker in software design

指示出し／指示受けの電子化に伴う指示内容の統一化のための機能追加と運用評価

鳥飼 幸太　鈴木 亮二　高木 理　辻村 真一　岡 めぐみ　高橋 功二　茂木 勇次
斎藤 勇一郎
群馬大学医学部附属病院　システム統合センター

Development of electric medical instruction / receiving system with standardizing instruction procedure and operational evaluatuion

Torikai Kota　Suzuki Ryoji　Takaki Osamu　Tsujimura Shinichi　Oka Megumi
Takahashi Kouji　Mogi Yuji　Saito Yuichiro
Gunma University Hospital System Integration Center

[Background] Currently, in most of hospitals, prescription and drip infusion (= medicine) orders are checked revised and executed by “order-book”. One of disadvantage of the “order-book” type order-control process is a difficulty of sharing the updated information. An electric medicine order and direction management tool has been developed for overcoming the disadvantage. [Objective] The aim of this study is to start “electric medical direction notification and response” (e-direction) operation in Gunma University Hospital. [Methods] A specially-formed working group, including all departments’ doctors and nurses, report the differences of the medicine orders (prescription frequency, number of drip roots, kinds of descriptions, duration etc.). After collection and classification of the medical direction patterns, input and viewing form of the e-direction was designed and implemented the electric ordering tool. [Result] Our survey revealed that there are 7 patterns of the prescription direction and 7 patterns of the infusion descriptions. And these pattern can be safely communicated between the medical staffs with the 3 input forms. Our hospital starts the operation test of e-direction from this September.

Keywords: medical description, prescription, infusion, electric carte, electric ordering

1.【背景】

現在、群馬大学医学部附属病院（以下本院）における処方／注射の投与コメント、服薬／投与条件等の、医師の指示出しならびに看護師の指示受け（以下指示出し指示受け）は、紙の指示簿を用いて運用を行っている。本院では、紙の指示簿を病棟ごとに1冊とし、既に電子化されている処方ならびに注射のオーダは電子カルテ上で入力した後、指示簿上で処方／注射に関する医学的指示を行う運用としていた。本方式は1冊の指示簿に伝達を集約するため、メモや付箋紙の運用で生じやすい紛失が避けられる利点がある。また、電子カルテ上のオーダリングと比較して、カレンダー形式で処方／注射が一覧できるため、重複投与や禁忌の気付きに繋がる利点がある。しかしながら、細部にわたる指示を限られた指示簿の紙面に手書き記入することは、書き直しを含めて判読間違いを生じるリスクがあること、繁忙な時間帯では、記入、確認を複数人で行うことが困難となるため、業務ロスが生じていることが問題点として挙げられていた。電子カルテ上で指示内容の電子化伝達を含めた指示運用を行うためには、診療科が統一した指示運用を行う必要があるが、特に注射／処方の指示内容や方法が診療科で大きく異なっていた。このため、医療安全の観点から、電子カルテのオーダ機能と連動した指示運用を行うことが要請された。

2.【目的】

平成27年9月より本院で運用している電子カルテ（NEC製MegaOAK ver8.0）上には処方カレンダー／注射カレンダー機能が実装されている[1]。本研究は、これらカレンダー機能を基礎として、処方指示／注射指示を一体化できるかについて検討することを第1の目標とした。処方／注射における指示ペーパーレス電子化運用のためには、指示内容の伝達に必要十分な医療指示パターンの分類を行う必要があった。次に、分類された医療指示パターンを、異なる診療科であっても共通のフォーマットで記載できるかを検討することを第2の目標とした。このため、既存の処方カレンダー／注射カレンダーで集約できていなかったケース（不定期、イベント後、時間厳守など）を適切な箇所に表現するための機能追加を行う必要があった。また、増量／減量といった指示とともに、隔日投与や不定期投与についても適切に入力／変更／表示できる、”WYSIWYG”（表示の通りに処方／注射を実施する運用）の確実化が必要であることが分かった。

3.【方法】

指示内容の共通化は院内全体の協力が要請される大規模な運用変更であるため、病院長の指揮のもと、指示内容の共通化についての院内ワーキンググループ（以下WG）を組織した。WGでは、診療科で指示方法（ルート／薬剤、投与方法）がどの程度集約できるかを調査した。また、指示コメントの記載が統一化できるかを調査した。調査に参加した診療科は、血液内科、整形外科、泌尿器科、小児科、消化器・肝臓内科、小児外科、内分泌糖尿病内科、乳腺・内分泌外科、皮膚科、精神科、核医学科、放射線部、呼吸器・アレルギー内科、脳神経内科、循環器内科、耳鼻咽喉科、放射線科、産婦人科、眼科、脳神経外科（順不同）であった。これらの診療科・診療部から、医師および看護師に参画いただき、紙帳簿での指示内容についてアンケート調査を行った。この調査で得られた指

Institute for Molecular and Cellular Regulation

Laboratory of Molecular Traffic

(1) Staff

Professor: Ken Sato, Associate Professor: Taichi Hara

Assistant Professor: Aisa Sakaguchi, Technical Officer: Hisae Kobayashi

(2) Research projects:

We are studying molecular mechanisms of LDL (low density lipoprotein) trafficking in *C. elegans.* In addition, we are also studying physiological functions and molecular mechanisms of membrane trafficking during development. We are studying the molecular mechanisms of the biogenesis and exocytosis of the cortical granules as a model of the regulated secretion. Recently, we have revealed that fertilization-induced autophagy is responsible for selective degradation of paternal mitochondria and thereby maternal inheritance of mitochondrial DNA. We are now studying the molecular mechanism of paternal mitochondria degradation by fertilization-induced autophagy.

To study physiological functions of membrane trafficking in mammal, we are generating knockout mice of the genes, which we have identified by *C. elegans* genetics. We are going to investigate these knockout mice by various cell biological methods. (See our Homepage).

(3) Enrollment in Graduate Course

Anyone who is interested in our study will be welcome. Please contact Ken Sato.

(4) Current students

Master 1, PhD 1, and MD-PhD course Students, Medical Students 5.

In our laboratory, 1 Doctor course student and 1 Master course student are studying our projects using *C .elegans* and mice. They receive a scholarship and also work as a Teaching or Research assistant.

(5) Career Paths after Graduation

Two master course students have graduated and they are now working in the companies.

(6) Message from Research Supervisor

We have found novel molecular mechanisms and physiological functions of membrane trafficking in multicellular organisms using use the nematode *Caenorhabditis elegans* and mice as model systems. You can learn the basic science more deeply because our staffs have a lot of experiences and look after students kindly.

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SCIENTIFIC REPORTS

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Rer1 and calnexin regulate endoplasmic reticulum retention of a peripheral myelin protein 22 mutant that causes type 1A Charcot-Marie-Tooth disease

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Laboratory of Molecular Traffic, Institute for Molecular and Cellular Regulation, Gunma University, Maebashi, Gunma 371-8512, Japan.

Peripheral myelin protein 22 (PMP22) resides in the plasma membrane and is required for myelin formation in the peripheral nervous system. Many PMP22 mutants accumulate in excess in the endoplasmic reticulum (ER) and lead to the inherited neuropathies of Charcot-Marie-Tooth (CMT) disease. However, the mechanism through which PMP22 mutants accumulate in the ER is unknown. Here, we studied the quality control mechanisms for the PMP22 mutants L16P and G150D, which were originally identified in mice and patients with CMT. We found that the ER-localised ubiquitin ligase Hrd1/SYVN1 mediates ER-associated degradation (ERAD) of PMP22(L16P) and PMP22(G150D), and another ubiquitin ligase, gp78/AMFR, mediates ERAD of PMP22(G150D) as well. We also found that PMP22(L16P), but not PMP22(G150D), is partly released from the ER by loss of Rer1, which is a Golgi-localised sorting receptor for ER retrieval. Rer1 interacts with the wild-type and mutant forms of PMP22. Interestingly, release of PMP22(L16P) from the ER was more prominent with simultaneous knockdown of *Rer1* and the ER-localised chaperone *calnexin* than with the knockdown of each gene. These results suggest that CMT disease-related PMP22(L16P) is trapped in the ER by calnexin-dependent ER retention and Rer1-mediated early Golgi retrieval systems and partly degraded by the Hrd1-mediated ERAD system.

Charcot-Marie-Tooth disease (CMT) is the most commonly inherited neurological disorder of the peripheral nervous system and has an estimated frequency of 1/2,500[1,2]. CMT is classified into types 1 and 2[1,2]. CMT type 1A (CMT1A) is an autosomal dominant demyelinating neuropathy that accounts for approximately 70% of CMT cases. Approximately 70% of patients with CMT1A harbour the duplication of a 1.4-Mb region of chromosome 17p11.2-12, which comprises the gene encoding peripheral myelin protein 22 (*PMP22*)[3]. PMP22 is a tetraspan membrane protein expressed at high levels by the myelinating Schwann cells of peripheral neurons, and it plays crucial roles in the development and maintenance of compact myelin sheaths[4]. Overproduction of wild-type (WT) PMP22 caused by gene duplication induces the apoptotic death of Schwann cells and demyelination of peripheral nerves[5–7]. Loss of PMP22 causes hereditary neuropathy with predisposition to pressure palsies, which are mild variants of peripheral neuropathy[8]. Approximately 20 missense mutations in *PMP22* have also been identified in patients with CMT1A, and many of these mutants harbour an amino acid residue substitution in the transmembrane domain (TMD)[2,9]. These point mutations often cause more severe effects than those resulting from gene duplication or nonsense mutations of *PMP22*[10]. Interestingly, these mutations lead to high levels of mutant proteins that mainly localize to the endoplasmic reticulum (ER), indicating that misfolded PMP22 in the ER correlates with neuropathy[11–14].

A substantial number of studies have focused on the missense mutations L16P and G150D[9], which were originally identified in the spontaneously occurring mouse models of CMT1, Trembler J (*TrJ*) and Trembler (*Tr*), respectively, and subsequently in patients with CMT1A or the more severe Dejerine-Sottas syndrome, respectively[1,15]. These mutant proteins exert a dominant gain-of-function or dominant-negative effect on their cognate WT alleles and lead to severe neuropathies[10,13,16]. PMP22(L16P) is primarily retained in the ER in Schwann cells[12,14], and when it is expressed in cultured cells, it localizes to the ER-Golgi intermediate compartment (ERGIC) as well as the ER[13]. PMP22(G150D) localizes mainly to the ER in Schwann cells and cultured cells[11,12,14]. The transcription of unfolding protein response-related genes is up-regulated in the sciatic nerves of

Lab of Medical Neuroscience

(1) Specific aims: Drug discovery in neuropsychiatry has been limited to chemical modifications of compounds originally discovered serendipitously. Therefore, more mechanism-oriented strategies of drug discovery for neuropsychiatric disorders are awaited. The deterioration of the neuronal circuit has attracted attention as the pathophysiology of these disorders, and aberrant responses against the stress, such as oxidative stress, is now being considered as a possible causal signaling in these diseases. Thus, we aim to elucidate the disease-relevant signaling pathway by utilizing state-of-art imaging technique, eventually challenging to identify a novel therapeutic target for neuropsychiatric disorders.

(2) On-going projects:

(i) Examination of neuronal stress response for the drug discovery of neuropsychiatric disorders: We are performing the high throughput in vitro screening system as well as in vivo 2-photon brain imaging of disease model so that quantitative measurement of the synaptic deterioration and stress-related metabolites are now being investigated.

(ii) Visualization of the disease-relevant neurocircuits in the neuropsychiatric model mice: We are engineering a novel synaptic optoprobe AS-PaRac1, which specifically visualizes the recently "written" synapse, and "written trace" can be erased by blue light (Hayashi-Takagi A *et al*, ***Nature***, 2015). This novel light-dependent tool of "Synaptic optogenetics" should open up new areas of brain research, and by extension, shed light on the neural networks that determine who we are.

(3) Eligibility: As long as you are interested in our research, anyone who fulfill the eligibility for enrollment are welcome.

(4) Current grad students: We currently have two grad student, who indulges in their research deeply.

(5) Carrier paths after graduation: Oversea research activity is highly encouraged to foster the broad perspective view for science.

(6) Contact information: Full professor, Akiko HAYASHI-TAKAGI, hashitakagi@gunma-u.ac.jp, http://medical-neuro.imcr.gunma-u.ac.jp/

ARTICLE

doi:10.1038/nature15257

Labelling and optical erasure of synaptic memory traces in the motor cortex

Akiko Hayashi-Takagi[1,2], Sho Yagishita[1,3], Mayumi Nakamura[1], Fukutoshi Shirai[1], Yi I. Wu[4], Amanda L. Loshbaugh[5,6], Brian Kuhlman[5,6], Klaus M. Hahn[5,7] & Haruo Kasai[1,3]

Dendritic spines are the major loci of synaptic plasticity and are considered as possible structural correlates of memory. Nonetheless, systematic manipulation of specific subsets of spines in the cortex has been unattainable, and thus, the link between spines and memory has been correlational. We developed a novel synaptic optoprobe, AS-PaRac1 (activated synapse targeting photoactivatable Rac1), that can label recently potentiated spines specifically, and induce the selective shrinkage of AS-PaRac1-containing spines. *In vivo* imaging of AS-PaRac1 revealed that a motor learning task induced substantial synaptic remodelling in a small subset of neurons. The acquired motor learning was disrupted by the optical shrinkage of the potentiated spines, whereas it was not affected by the identical manipulation of spines evoked by a distinct motor task in the same cortical region. Taken together, our results demonstrate that a newly acquired motor skill depends on the formation of a task-specific dense synaptic ensemble.

Optogenetics is a powerful tool for controlling neuronal action potentials[1,2], and has been used to demonstrate the crucial role of cell assemblies in representing memory traces[3]. However, owing to the limitations of spatial resolution of probes currently available, manipulation of individual dendritic spines, the major sites of excitatory synapses[4–6], has been unfeasible, hindering the comprehensive understanding of synaptic reorganization during learning. Thus, for spine-specific light control, we took advantage of the structural properties of spines: the tight correlation between spine volume and function[4–7]. Because the prolonged activation of the small GTPase Rac1 induces spine shrinkage[8–11], we used a photoactivatable form of Rac1 (PaRac1)[12] to induce spine shrinkage, which allowed us to control synaptic transmission with light. Moreover, since it has been suggested for a long time that the memory trace is allocated to specific neurons and spines of neurocircuits[13,14], here we targeted PaRac1 to the activated synapses (activated synapse targeting PaRac1, AS-PaRac1) to establish a novel method, termed 'synaptic optogenetics', to visualize and manipulate the memory trace.

AS-PaRac1 labels the potentiated spines

We first re-engineered the original PaRac1 construct[12] to optimize its properties for synaptic manipulation. Introduction of L514K and L531E mutations into the original construct markedly reduced the undesirable Rac1 background activity in the dark, as shown by isothermal titration calorimetry (ITC), the neuronal morphology, and co-immunoprecipitation (Extended Data Fig. 1a–c). Next, PaRac1 was fused with a deletion mutant of PSD-95 (PSDΔ1.2)[15], which is known to concentrate at the postsynaptic site, but cannot bind with the major PDZ binding proteins, thus minimizing the undesirable effects of PSD-95 overexpression. An enrichment index, quantitative ratio of synaptic localization compared to that of the dendritic shaft (see Methods), supported the effective accumulation of PSD–PaRac1 to the synapse, especially at the tip of the spine (Fig. 1a, construct B), where it was highly co-localized with the endogenous PSD-95, but not with an axonal marker (Extended Data Fig.

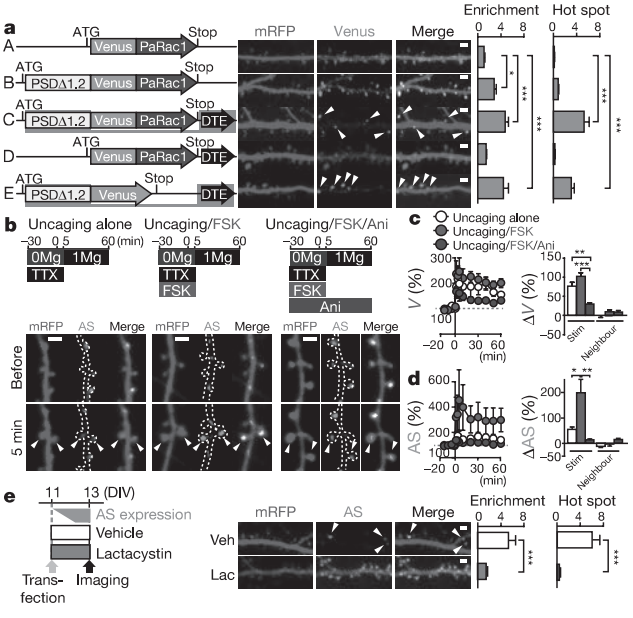

Figure 1 | Potentiation-dependent accumulation of AS-PaRac1 to the dendritic spines in hippocampal slice cultures. **a**, Mapping for essential domains for the discrete distribution of the probe (arrowheads). Enrichment and hot spot index are plotted as arbitrary units. **b**, Representative images of single spine potentiations by glutamate uncaging (arrowheads) in the presence or absence of forskolin (FSK) and anisomycin (Ani). 0Mg, no Mg^{2+}; 1Mg, 1 mM $MgCl_2$. **c**, **d**, Time courses of spine head volume (*V*, **c**) and AS-PaRac1 accumulation (AS, **d**), both measured by fluorescence intensity. The mean change 60 min after uncaging in the stimulated or neighbouring spines. **e**, The effect of lactacystin on the discrete accumulation of AS-PaRac1 (arrowheads). DIV, days *in vitro*. Scale bars, 2 μm. Error bars represent s.e.m. Detailed information on statistical methods/results are described in Extended Data Table 1.

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Institute for Molecular and Cellular Regulation
Biosignal Research Center, **Laboratory of Secretion Biology**

（１）Lab Member

Associate Professor：Seiji Torii
Post-doctoral researcher (1), Graduate student (1), Visiting collaborator (Researchers, Students)

（２）Research Project

① **Study on regulated function and survival/death of neuroendocrine cells**

To understand fundamental mechanisms on a variety of human diseases, we investigate the biosynthesis and secretion of peptide hormones, and the regulation of cell survival and death of neuroendocrine cells, with use of molecular and cellular technical approaches.

② **Imaging of pathological states and cellular functions with new fluorescent probes**

In a collaborative study with some engineering researchers, we are developing new fluorescent or luminescent probes for analyzing cancer, diabetes, and ischemia.

（３）Admission to Laboratory

Graduates of schools of medicine, dentistry or pharmaceutical sciences, or those who has completed master's course in science. Regardless of age, sex, or nationality.
Some students has studied at this lab and finished their courses, while being members of other labs or graduate schools. (as minor/sub-major)

（４）Life of Graduate students

Basically, our students study at the daytime on weekdays. It can be flexible by circumstances of each student.
Graduate students may receive support for living expenses by Research Assistant program.

（５）Post-graduation Course

Students will aim to become Research Fellowship (DC: doctoral course student) of JSPS (Japan Society for the Promotion of Science) while in graduate school.
After completion, they continue to study as our collaborative researcher, or work as a post-doctoral researcher at the basic lab or the pharmaceutical company.

（６）Others

We thoroughly teach the processes, techniques, and assessments of the life medical science.
Our lab has produced two recipients of Gunma university science awards.

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Kyota Aoyagi,[1] Mica Ohara-Imaizumi,[1] Makoto Itakura,[2] Seiji Torii,[3] Yoshihiro Akimoto,[4] Chiyono Nishiwaki,[1] Yoko Nakamichi,[1] Takuma Kishimoto,[1] Hayato Kawakami,[4] Akihiro Harada,[5] Masami Takahashi,[2] and Shinya Nagamatsu[1]

VAMP7 Regulates Autophagy to Maintain Mitochondrial Homeostasis and to Control Insulin Secretion in Pancreatic β-Cells

Diabetes 2016;65:1648–1659 | DOI: 10.2337/db15-1207

ISLET STUDIES

VAMP7 is a SNARE protein that mediates specific membrane fusions in intracellular trafficking and was recently reported to regulate autophagosome formation. However, its function in pancreatic β-cells is largely unknown. To elucidate the physiological role of VAMP7 in β-cells, we generated pancreatic β-cell–specific VAMP7 knockout (*Vamp7$^{flox/Y}$;Cre*) mice. VAMP7 deletion impaired glucose-stimulated ATP production and insulin secretion, though VAMP7 was not localized to insulin granules. VAMP7-deficient β-cells showed defective autophagosome formation and reduced mitochondrial function. p62/SQSTM1, a marker protein for defective autophagy, was selectively accumulated on mitochondria in VAMP7-deficient β-cells. These findings suggest that accumulation of dysfunctional mitochondria that are degraded by autophagy caused impairment of glucose-stimulated ATP production and insulin secretion in *Vamp7$^{flox/Y}$;Cre* β-cells. Feeding a high-fat diet to *Vamp7$^{flox/Y}$;Cre* mice exacerbated mitochondrial dysfunction, further decreased ATP production and insulin secretion, and consequently induced glucose intolerance. Moreover, we found upregulated VAMP7 expression in wild-type mice fed a high-fat diet and in *db/db* mice, a model for diabetes. Thus our data indicate that VAMP7 regulates autophagy to maintain mitochondrial quality and insulin secretion in response to pathological stress in β-cells.

Intracellular membrane fusion events within eukaryotic cells are mediated by members of the soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor (SNARE) protein family. All SNAREs contain a characteristic coiled-coil SNARE motif, through which SNAREs interact with one another. Functionally, SNAREs can be divided into vesicular (v-SNARE) and target membrane SNAREs, which are associated with intracellular trafficking vesicles and their target compartments, respectively. The formation of a functional complex between cognate v-SNAREs and target membrane SNAREs brings the opposing membranes close together and eventually catalyzes membrane fusion. Because each SNARE protein shows distinct tissue expression and intracellular localization patterns, the assembly of a functional SNARE complex is remarkably important for both specifying membrane fusion and coordinating different membrane trafficking pathways (1,2).

Vesicle-associated membrane proteins (VAMPs) function as v-SNAREs. In studies with pancreatic β-cells, among seven VAMP family proteins (VAMP1–5, 7, and 8), VAMP2, 3, 4, and 8 were expressed. VAMP2 and VAMP3/cellubrevin were localized to insulin granules and synaptic-like microvesicles and regulated glucose-stimulated insulin secretion (3,4). VAMP4 was expressed in β-cell–derived Min6 cells (5) and was implicated in post-Golgi vesicular trafficking (6,7). VAMP8/endobrevin was localized to endosomes, insulin granules, and synaptic-like microvesicles and was reported to regulate insulin and γ-aminobutyric acid secretion in pancreatic β-cells (8). VAMP8 was also recently found to participate in β-cell proliferation by regulating mitosis (9). VAMP7, however, has not yet been studied in pancreatic β-cells.

VAMP7 was originally identified as a tetanus neurotoxin–insensitive VAMP regulating vesicular transport to apical

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Molecular Membrane Biology Laboratory, IMCR

(1) Staff

Associate Professor: Miyuki Sato

Technician: 1

(2) Research Projects

1. Selective autophagy of paternal mitochondria in *C. elegans* embryos
2. Endocytic degradation of maternal membrane proteins in *C. elegans* embryos

Eukaryotic cells are composed of several membrane-bound organelles. The shape and composition of cells are dynamically regulated during cell differentiation and are also influenced by various changes in the extracellular environment. We are interested in the regulation of organelle dynamics during animal development and use *C. elegans* as a model system. In particular, we explore the mechanisms and physiological roles of autophagy and endocytosis in fertilized eggs by using genetic and cell biological approaches.

(3) Enrollment in Graduate Course

We will welcome whoever is interested in our research.

(4) Current Students

No students belong to this laboratory now.

(5) Career Paths after Graduation

We aim to educate students to become independent scientists who can work in basic medical science fields.

(6) Message from Research Supervisor

If you are interested in our research, please contact to Miyuki Sato (e-mail: m-sato@gunma-u.ac.jp).

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RESEARCH ARTICLE

Fertilization-induced K63-linked ubiquitylation mediates clearance of maternal membrane proteins

Miyuki Sato[1,2,*], Ryosuke Konuma[1], Katsuya Sato[1], Kotone Tomura[1] and Ken Sato[1,*]

ABSTRACT

In *Caenorhabditis elegans*, fertilization triggers endocytosis and rapid turnover of maternal surface membrane proteins in lysosomes, although the precise mechanism of this inducible endocytosis is unknown. We found that high levels of K63-linked ubiquitin chains transiently accumulated on endosomes upon fertilization. Endocytosis and the endosomal accumulation of ubiquitin were both regulated downstream of the anaphase-promoting complex, which drives the oocyte's meiotic cell cycle after fertilization. The clearance of maternal membrane proteins and the accumulation of K63-linked ubiquitin on endosomes depended on UBC-13 and UEV-1, which function as an E2 complex that specifically mediates chain elongation of K63-linked polyubiquitin. CAV-1-GFP, an endocytic cargo protein, was modified with K63-linked polyubiquitin in a UBC-13/UEV-1-dependent manner. In *ubc-13* or *uev-1* mutants, CAV-1-GFP and other membrane proteins were internalized from the plasma membrane normally after fertilization. However, they were not efficiently targeted to the multivesicular body (MVB) pathway but recycled to the cell surface. Our results suggest that UBC-13-dependent K63-linked ubiquitylation is required for proper MVB sorting rather than for internalization. These results also demonstrate a developmentally controlled function of K63-linked ubiquitylation.

KEY WORDS: Endocytosis, Oocyte-to-zygote transition, K63-linked ubiquitin chains, Ubc13, Multivesicular body (MVB) pathway

INTRODUCTION

The oocyte-to-zygote (embryo) transition is the process by which oocytes transform to totipotent zygotes. It is one of the most dramatic examples of cellular remodeling in animals, and the active degradation of pre-existing materials is an essential part of this transition (Stitzel and Seydoux, 2007; Sato and Sato, 2013). The importance of the ubiquitin-proteasome system in this process has been established. Some oocyte meiotic proteins are harmful for mitosis, and they must be degraded by the proteasome for normal mitotic cell division (Bowerman and Kurz, 2006). The proteasome also mediates the degradation of germ cell-specific proteins in somatic lineages, starting as early as the two-cell-stage embryo (Spike and Strome, 2003). Additionally, autophagy is induced upon sperm entry to deliver paternal (allogeneic) organelles, including mitochondria and membranous organelles (MOs), to the lysosomes for degradation (allophagy) (Sato and Sato, 2011; Al Rawi et al., 2011). We have previously shown that endocytosis is highly upregulated during this period, leading to the rapid turnover of maternal plasma membrane (PM) proteins in *Caenorhabditis elegans* embryos (Sato et al., 2006; Sato and Sato, 2013). This was first visualized by using CAV-1 (a worm caveolin homolog) fused with GFP (CAV-1-GFP) (Sato et al., 2006). In oocytes, CAV-1-GFP accumulates on cortical granules (CGs). Shortly after fertilization, CAV-1-GFP is delivered to the PM by CG exocytosis. CAV-1-GFP targeted to the PM is then quickly endocytosed and degraded in lysosomes before the first mitotic division. In addition to CAV-1-GFP, several maternal membrane proteins, including the yolk receptor RME-2 and the putative sperm receptor EGG-1, are downregulated with a similar time course (Kadandale et al., 2005; Audhya et al., 2007; Balklava et al., 2007). The degradation of maternal membrane proteins is a selective process because GFP fusions of SNB-1 (a synaptobrevin homolog) and SYN-4 (a syntaxin1 homolog), which also localize to the PM of fertilized embryos, are not degraded (Sato et al., 2008).

Ubiquitylation is a post-translational modification involved in proteasomal degradation and various other cellular processes, including endocytosis. Proteins can be modified with a single ubiquitin molecule or a chain of ubiquitins, which are linked through one of the seven lysine residues or the N-terminus of ubiquitin. The diverse types of ubiquitin modifications are thought to have specific functions. Among them, K63-linked polyubiquitylation is involved in DNA repair, various signaling pathways and the endocytosis of membrane proteins (Pickart and Fushman, 2004; Kerscher et al., 2006; Mukhopadhyay and Riezman, 2007). K63- and K48-linked ubiquitylation are induced on paternal MOs in worm embryos before allophagy (Sato and Sato, 2011; Al Rawi et al., 2011). Ubiquitylation is mediated by the sequential action of ubiquitin-activating enzymes (Uba or E1), ubiquitin-conjugating enzymes (Ubc or E2), and ubiquitin ligases (E3) (Kerscher et al., 2006). Substrate recognition largely depends on E3 enzymes, whereas E2 enzymes determine the topology of the ubiquitin modification. Some E2 enzymes mediate the attachment of the first ubiquitin to the lysine residues of the target protein (chain initiation), and others mediate further chain elongation (Ye and Rape, 2009). To date, Ubc13 is the only E2 shown to specifically mediate the elongation of K63-linked polyubiquitin chains. Ubc13 functions in a dimeric complex with the non-catalytic E2 variant Uev1A or Mms2 (Hofmann and Pickart, 1999; Deng et al., 2000; Eddins et al., 2006). In mice, knockout of Ubc13 results in early embryonic lethality, and conditional knockout in myeloid cells or heterozygosity produces defects in the immune response and hematopoiesis (Yamamoto et al., 2006; Fukushima et al., 2007; Wu et al., 2009). In *C. elegans*, UEV-1 is involved in the trafficking of glutamate receptor GLR-1 in neurons (Kramer et al., 2010). However, our understanding of the physiological roles of K63-linked ubiquitylation in animals is still limited.

Ubiquitylation can regulate different steps of endocytosis (Mukhopadhyay and Riezman, 2007; Traub and Lukacs, 2007; Lauwers et al., 2010). Monoubiquitylation (single or multiple) or K63-linked polyubiquitylation of cargo molecules has been reported

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(1) Members

Professor: Tetsuro Izumi

Associate Professor: Katsuhide Okunishi

Assistant Professor: Kohichi Matsunaga, Kouichi Mizuno, Hao Wang

(2) Research themes

To understand the physiopathology of multicellular organisms, it is important to know how differentiated cells communicate each other to regulate their function as a whole body. Regulated exocytosis is one of the major means for cell-cell communication, and its impairment leads to many diseases. Among highly differentiated secretory cells, we particularly focus on pancreatic beta cells, adipocytes, and immune cells, the disorders of which result in the development of endocrine, metabolic, and allergic diseases such as diabetes, obesity, and asthma. We investigate the basic biology and pathology of these cells both in vitro and in vivo by using varying techniques of genetics, molecular biology, biochemistry, cell biology, histochemistry, and physiology. You can see more details at our home page (http://molend.showa.gunma-u.ac.jp/).

Ongoing projects

1) Relationship between secretory granule recruitment docking and fusion. We morphologically analyze intracellular trafficking, docking, and fusion of secretory granules in living cells by using confocal, total internal reflection fluorescence, super-resolution, and electron microscopes.

2) Mechanism for regulated exocytosis of secretory granules. We investigate in vitro and in vivo function of the small GTPases, Rab27a and Rab27b, and their effectors, exophilins, in regulated secretory pathways in endocrine, exocrine, immune, and respiratory cells.

3) Genetic analysis of diabetes and obesity in rodent models. We currently focus on molecular mechanism of adipose fat accumulation involving the ALK7-signaling pathway.

(3) How to apply

If you are interested to apply for either a master or doctor course, please feel free to visit our laboratory or contact Prof. Izumi : tizumi@gunma-u.ac.jp

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RESEARCH ARTICLE

Rab2a and Rab27a cooperatively regulate the transition from granule maturation to exocytosis through the dual effector Noc2

Kohichi Matsunaga[1], Masato Taoka[3], Toshiaki Isobe[3] and Tetsuro Izumi[1,2,*]

ABSTRACT

Exocytosis of secretory granules entails budding from the *trans*-Golgi network, sorting and maturation of cargo proteins, and trafficking and fusion to the plasma membrane. Rab27a regulates the late steps in this process, such as granule recruitment to the fusion site, whereas Rab2a functions in the early steps, such as granule biogenesis and maturation. Here, we demonstrate that these two small GTPases simultaneously bind to Noc2 (also known as RPH3AL) in a GTP-dependent manner, although Rab2a binds only after Rab27a has bound. In pancreatic β-cells, the ternary Rab2a–Noc2–Rab27a complex specifically localizes on perinuclear immature granules, whereas the binary Noc2–Rab27a complex localizes on peripheral mature granules. In contrast to the wild type, Noc2 mutants defective in binding to Rab2a or Rab27a fail to promote glucose-stimulated insulin secretion. Although knockdown of any component of the ternary complex markedly inhibits insulin secretion, only knockdown of Rab2a or Noc2, and not that of Rab27a, impairs cargo processing from proinsulin to insulin. These results suggest that the dual effector, Noc2, regulates the transition from Rab2a-mediated granule biogenesis to Rab27a-mediated granule exocytosis.

KEY WORDS: Small GTPase, Secretory granule, Regulated exocytosis, Insulin, Pancreatic β-cell, Diabetes

INTRODUCTION

Regulated secretion is a main pathway in the delivery of the bioactive molecules of a cell to the extracellular environment. The pathway comprises coordinated sequential steps, such as secretory vesicle biogenesis, maturation, trafficking and fusion with the plasma membrane. Although the molecular machinery for these individual processes has been characterized, the precise mechanisms connecting each process remain poorly understood. Previous studies have shown that the small GTPase Rab27 (of which there are two isoforms, Rab27a and Rab27b), regulates the late steps of this pathway through its multiple effector proteins (Izumi et al., 2003; Fukuda, 2006). For example, in pancreatic β-cells, Rab27a localizes on insulin granules (Yi et al., 2002) and forms a complex with its effectors, such as granuphilin (also known as Slp4) (Wang et al., 1999; Gomi et al., 2005), exophilin 7 (also known as JFC1, Slp1 and SYTL1) (Wang et al., 2013), exophilin 8 (also known as MyRIP and Slac2c) (Waselle et al., 2003; Mizuno et al., 2011) and Noc2 (also known as RPH3AL) (Kotake et al., 1997; Cheviet et al., 2004), and it regulates a specific step of insulin granule trafficking and exocytosis. Namely, granuphilin and exophilin 7 control exocytosis of granules that are docked or undocked to the plasma membrane, respectively, whereas exophilin 8 retains granules in the cortical actin network for subsequent release. However, it remains unknown at which step or by what mechanism Noc2 functions, despite the finding that Noc2-knockout mice exhibit impaired insulin secretion when under acute stress (Matsumoto et al., 2004). This is partly because Noc2 is a relatively small protein compared with other Rab27 effectors, and it appears to lack functional domains other than the Rab27-binding domain. In the present study, we show that Noc2 binds to another GTPase, Rab2a, in addition to Rab27a. The ternary Rab2a–Noc2–Rab27a complex specifically localizes on immature granules, and interference in the complex formation inhibits cargo processing and granule exocytosis. We present evidence that this new complex regulates the transition from Rab2a-mediated granule biogenesis to Rab27a-mediated granule exocytosis in the regulated secretory pathway.

RESULTS

Rab2a binds to Rab27a via Noc2 in a GTP-dependent manner

To identify Rab27a-interacting proteins more comprehensively, we stably expressed Rab27a in the β-cell line MIN6, that was tagged with MEF (Myc-TEV-FLAG), which consists of Myc and FLAG epitope tags connected by a spacer sequence containing a TEV protease cleavage site, and then performed tandem affinity purification (Ichimura et al., 2005; Matsunaga et al., 2009). The protein bands specific to the Rab27a immunoprecipitate were then analyzed by a liquid chromatography (LC)-tandem mass spectrometry (MS/MS) system (Fig. S1A; Table S1). In addition to the known Rab27-interacting proteins, such as granuphilin, exophilin 9 (also known as Slp5 and SYTL5) (Kuroda et al., 2002), and Noc2, two Rab GTPases, Rab2 (which has an a and b isoform) and Rab18, were also identified. Co-immunoprecipitation experiments showed that Rab2a, but not Rab18, interacts with Rab27a in MIN6 cells (Fig. S1C). Because the Rab2a-immunoprecipitate also contained Noc2, but not granuphilin (Fig. S1C,D), we performed similar tandem purification in MIN6 cells stably expressing MEF–Noc2, and found Rab2a to be a Noc2-interacting protein, as is Rab27a (Fig. S1B; Table S2). Furthermore, Noc2 formed an endogenous complex with Rab2a in both of the β-cell lines, mouse MIN6 and rat INS1 832/13 (Fig. 1A,B). Noc2 specifically bound to the Rab2a Q65L mutant mimicking the GTP-bound form, but not with the S20N mutant mimicking the GDP-bound form (Fig. 1C). As previously reported (Fukuda et al., 2004), Noc2 interacted with the corresponding Rab27a Q78L mutant, but not with the T23N mutant (Fig. S1E). Although Noc2 also forms a complex with Rab3a (Fig. 1B), as

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(2) Research Aims

The dysfunction of pancreatic β cells, brown adipocytes, and enterocytes can cause diabetes and metabolic syndrome. Our goal is to elucidate the molecular mechanism involved in the maintenance of homeostasis of these higher-order function cells, which is the key to glucose metabolism. We aim to elucidate the mechanism of cellular homeostasis, from a variety of viewpoints, including developmental biology, zinc biology, autophagy, and cell polarity, by effectively utilizing genetically engineered mice. Furthermore, using our findings from basic medical research, we aim to establish a groundbreaking treatment for diabetes and obesity. You can see more details at our home page (http://tou-taisha.imcr.gunma-u.ac.jp/index.html).

Ongoing Projects

1) Research on the developmental biology of pancreatic β cells
2) Functional analysis of autophagy in lifestyle-associated diseases
3) Analysis of zinc transporters involved in the browning of adipocytes
4) Screening and functional analysis of molecules involved in the regulation of enterocytes

(3) Access

If you are interested in applying to a doctor course, contact Prof. Fujitani: fujitani@gunma-u.ac.jp

RESEARCH ARTICLE The Journal of Clinical Investigation

Human IAPP–induced pancreatic β cell toxicity and its regulation by autophagy

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Pancreatic islets in patients with type 2 diabetes mellitus (T2DM) are characterized by loss of β cells and formation of amyloid deposits derived from islet amyloid polypeptide (IAPP). Here we demonstrated that treatment of INS-1 cells with human IAPP (hIAPP) enhances cell death, inhibits cytoproliferation, and increases autophagosome formation. Furthermore, inhibition of autophagy increased the vulnerability of β cells to the cytotoxic effects of hIAPP. Based on these in vitro findings, we examined the pathogenic role of hIAPP and its relation to autophagy in hIAPP-knockin mice. In animals fed a standard diet, hIAPP had no toxic effects on β cell function; however, hIAPP-knockin mice did not exhibit a high-fat-diet–induced compensatory increase in β cell mass, which was due to limited β cell proliferation and enhanced β cell apoptosis. Importantly, expression of hIAPP in mice with a β cell–specific autophagy defect resulted in substantial deterioration of glucose tolerance and dispersed cytoplasmic expression of p62-associated toxic oligomers, which were otherwise sequestrated within p62-positive inclusions. Together, our results indicate that increased insulin resistance in combination with reduced autophagy may enhance the toxic potential of hIAPP and enhance β cell dysfunction and progression of T2DM.

Introduction

Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance and β cell failure (1); the latter is caused by reduction in β cell function (2, 3) and β cell mass (4–6). One of the characteristic morphological changes in pancreatic islets of human T2DM is amyloid deposition (7–9). Pancreatic islet amyloid is found in approximately 90% of patients with T2DM, and the extent of its deposition correlates negatively with β cell mass (8). The major constituent of islet amyloid in humans is derived from islet amyloid polypeptide (IAPP; also known as amylin), a 37–amino acid polypeptide synthesized in pancreatic β cells and coreleased with insulin in response to a rise in blood glucose level (8, 10). IAPP exhibits close amino acid homology in the N- and C-terminal regions in all species studied (9, 11). In addition, the 20–29 region is homologous among humans, cats, and monkeys and is hydrophobic and amyloidogenic (8, 9, 11). In contrast, in mouse IAPP, the 20–29 region has proline substitutions compared with human IAPP (hIAPP), and, as a result, mouse IAPP is soluble and nonamyloidogenic (8, 9, 11, 12). Rodent IAPP, which lacks β sheet structure, does not form aggregates, and thus the commonly used rodent models of diabetes do not recapitulate islet pathology in humans. To investigate the role of hIAPP, several mouse models and a rat model transgenic for hIAPP have been developed (13–16). Studies in these models have shown that overexpression of hIAPP exhibits toxic effects on β cells by inducing apoptosis and amyloidogenesis in a context-dependent manner. However, these traditional transgenic approaches resulted in large phenotypic variations, presumably due to multiple copy insertions that affect the expression levels and integration of genes near other transcriptional control elements that can adversely modulate expression (17). Expression of hIAPP driven by rat insulin promoter (RIP) is expected to be largely different from that regulated by the endogenous murine *Iapp* gene. To minimize these variations and explore the physiological roles of hIAPP in β cell deficit, a knockin mouse was generated in which the endogenous murine *Iapp* coding region was genetically replaced with that of *hIAPP* (17). In contrast to the results obtained by in vitro overexpression and transgenic overexpression of hIAPP (15, 18, 19), expression of WT hIAPP in the knockin mouse model failed to induce islet amyloid formation; rather, it induced mild glucose intolerance (17), which suggests that hIAPP-knockin mice represent a useful model for pathogenic characterization of hIAPP in a physiological setting.

▶ Related Commentary: p. 3292

Authorship note: Nayumi Shigihara, Ayako Fukunaka, Akemi Hara, and Yoshio Fujitani contributed equally to this work.

Conflict of interest: Yoshio Fujitani has received lecture fees from Novartis and Eli Lilly and research funding from MSD, Eli Lilly, and Takeda. Hirotaka Watada has received lecture fees from Daiichi Sankyo, Takeda, MSD, Sanofi-Aventis, Ono, Novartis, Astellas, Dainippon Sumitomo, Tanabe Mitsubishi, Novo Nordisk, and Sanwakagaku and research funding from Sanofi-Aventis, Novo Nordisk, Novartis, AstraZeneca, Sanwakagaku, Ono, MSD, Boehringer Ingelheim, Kissei, Takeda, Daiichi Sankyo, and Eli Lilly.

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Graduate Student(D)	Takayoshi Suga, Eri Wada
MD,PhD course Student(4)	Naoko Fujikawa
MD,PhD course Student(3)	Yuri Numata

（2） Research

1） Clarifying the molecular mechanism of pancreatic beta cell dysfunction in type 2 diabetes

2） Elucidating how “metabolic signals” regulate energy homeostasis in the hypothalamus at the molecular level

3） Investigating the molecular mechanism by which plasma glucagon levels elevate in type 2 diabetes

4） Developing a new glucagon sandwich ELISA system and re-evaluating plasma glucagon levels

5） Investigating molecular mechanism for the extra beneficial effects of anti-diabetes drugs toward controlling body weight and glucagon secretion

（3） Access

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（4） Situation of the graduate students

This is the laboratory started from 2007.

（5） Course after the graduate school

We basically respect the intention of the person. We introduce studying abroad mainly to the United States to an applicant. One who will return to clinical medicine can utilize a way of thinking obtained in the basic research at the clinical place. One who will continue basic research can get academic position as a fellow of the Japan Society for the Promotion of Science or other post-doctoral positions.

The role of FOXO1 in β-cell failure and type 2 diabetes mellitus

Tadahiro Kitamura

Abstract | Over the past two decades, insulin resistance has been considered essential to the aetiology of type 2 diabetes mellitus (T2DM). However, insulin resistance does not lead to T2DM unless it is accompanied by pancreatic β-cell dysfunction, because healthy β cells can compensate for insulin resistance by increasing in number and functional output. Furthermore, β-cell mass is decreased in patients with diabetes mellitus, suggesting a primary role for β-cell dysfunction in the pathogenesis of T2DM. The dysfunction of β cells can develop through various mechanisms, including oxidative, endoplasmic reticulum or hypoxic stress, as well as via induction of cytokines; these processes lead to apoptosis, uncontrolled autophagy and failure to proliferate. Transdifferentiation between β cells and α cells occurs under certain pathological conditions, and emerging evidence suggests that β-cell dedifferentiation or transdifferentiation might account for the reduction in β-cell mass observed in patients with severe T2DM. FOXO1, a key transcription factor in insulin signalling, is implicated in these mechanisms. This Review discusses advances in our understanding of the contribution of FOXO1 signalling to the development of β-cell failure in T2DM.

Kitamura, T. *Nat. Rev. Endocrinol.* **9**, 615–623 (2013); published online 20 August 2013; doi:10.1038/nrendo.2013.157

Introduction

Insulin resistance and impaired β-cell function are hallmarks of type 2 diabetes mellitus (T2DM). The concept of insulin resistance emerged in the 1980s and 1990s and has been recognized as the most fundamental pathological state of T2DM, with less attention given to β-cell failure. However, insulin resistance does not cause T2DM unless β-cell failure also occurs. Many more people have insulin resistance than have T2DM, suggesting that insulin resistance is necessary but not sufficient to induce the onset of diabetes mellitus.[1] Genome-wide association studies have identified many susceptibility genes linked to diabetes mellitus, most of which are expressed in pancreatic β cells and are thought to have roles in their function and growth.[2–5] Furthermore, studies of postmortem and surgical pancreas specimens describe a 63% loss of β-cell mass in obese patients with T2DM, and a 41% loss in lean patients with T2DM, compared with weight-matched healthy individuals.[6] β-cell dysfunction is, therefore, thought to have a primary role in the pathogenesis of T2DM.

Emerging evidence shows that mediators and effectors of insulin–IGF-1 signalling, including insulin receptor substrate 2 (IRS2), PI3K, 3-phosphoinositide-dependent protein kinase 1 (PDPK1), forkhead box protein O1 (FOXO1) and AKT kinases, have important roles in β-cell growth and function.[7–12] Mammalian cells express four FOXO isoforms: FOXO1, FOXO3, FOXO4 and FOXO6,[13] of which FOXO1 is the most abundant isoform in liver, adipose tissue and pancreatic β cells.[14,15] FOXO1 is phosphorylated by AKT kinases, leading to its translocation from the nucleus to the cytoplasm, which in turn inactivates *FOXO1* transcriptional activity.[16–18] However, FOXO1 is also phosphorylated by other kinases, including mitogen-activated protein kinases (also known as JNKs), inhibitor of nuclear factor κB kinase (NFκB), and cyclin-dependent kinase 2.[19–21] The stability and activity of FOXO1 can also be altered by acetylation, ubiquitination, glycosylation and methylation.[22–26] *FOXO1* is ubiquitously expressed, and its product has multiple functions in various tissues, such as the liver, muscle, adipose tissue and the pancreas. Many different transgenic and conditional knockout mice have, therefore, been generated to analyse the pancreas-specific effects of *FoxO1 in vivo*.

This Review summarizes the proposed molecular mechanisms underlying β-cell failure in T2DM. We describe advances in understanding the role of FOXO1 in insulin–IGF-1 signalling, including the functions of FOXO1 in β cells, and the contribution of this transcription factor to β-cell failure in patients with T2DM.

β-cell dysfunction and loss in T2DM

Patients with a long clinical history of T2DM commonly present with decreased β-cell function and number,[27] often (somewhat vaguely) referred to as 'β-cell exhaustion'. Numerous efforts have been made to elucidate the precise mechanisms by which β-cell numbers and function decline in patients with severe T2DM. Oxidative, endoplasmic reticulum (ER) and hypoxic stress, and exposure to proinflammatory cytokines, are all thought to be involved in β-cell dysfunction. In response to these stressors, β cells can fail to proliferate or undergo

Competing interests
The author declares no competing interests.

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1. Staff

Takeshi Inagaki（Professor, PI）, Hiroshi Shibata（Associate Professor）, Masahiro Nagasawa（Assistant Professor）, Tomohiro Suzuki（Assistant Professor）

2. Research Projects

We seek to understand the molecular mechanisms which will provide novel approaches for the treatment of lifestyle-related diseases such as obesity and diabetes mellitus. Transcription factors and epigenetic factors are the two main focuses of our study. These factors regulate gene expression in response to chronic changes of environmental conditions as well as acute stimuli from outside of the body. We try to elucidate how lifestyle affects future development of metabolic diseases through epigenetic memory of environmental changes.

One of our on-going projects is translating multivalent histone codes written in adipocytes in response to extracellular stimuli or differentiation. We speculate that some of extracellular stimuli result in the changes of concentration of intra-cellular metabolites, which affect the enzyme activity of histone modifiers. Thus, the certain metabolic state is memorized as physical constitution through modulating histone mark. We seek to establish a new technique to re-write epigenetic memory and reduce the risk of future development of metabolic diseases.

3. Admission to Our Laboratory

If you have any questions, or would like to join our laboratory, please contact our PI at inagaki@gunma-u.ac.jp.

4. Current Students

Our laboratory just started in October, 2016. We currently do not have any student and you would be the first one!

5. Career Options after the Course

We hope you would be successful in the field of academic research, industry, clinical works or starting new business.

6. Message from PI

We welcome new passionate and patient members to join our laboratory for advancing our research together.

Transcriptional and epigenetic control of brown and beige adipose cell fate and function

Takeshi Inagaki[1,2], Juro Sakai[1,2] and Shingo Kajimura[3]

Abstract | White adipocytes store excess energy in the form of triglycerides, whereas brown and beige adipocytes dissipate energy in the form of heat. This thermogenic function relies on the activation of brown and beige adipocyte-specific gene programmes that are coordinately regulated by adipose-selective chromatin architectures and by a set of unique transcriptional and epigenetic regulators. A number of transcriptional and epigenetic regulators are also required for promoting beige adipocyte biogenesis in response to various environmental stimuli. A better understanding of the molecular mechanisms governing the generation and function of brown and beige adipocytes is necessary to allow us to control adipose cell fate and stimulate thermogenesis. This may provide a therapeutic approach for the treatment of obesity and obesity-associated diseases, such as type 2 diabetes.

Interscapular BAT
Brown adipose tissue (BAT) is a specialized organ that produces heat. BAT is localized in the interscapular and perirenal regions of rodents and infants.

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Adipose tissue has a central role in whole-body energy homeostasis. White adipose tissue (WAT) is the major adipose organ in mammals. It represents 10% or more of the body weight of healthy adult humans and is specialized for the storage of excess energy. Humans and rodents, however, possess an additional form of adipose tissue, known as brown adipose tissue (BAT), which is specialized to dissipate chemical energy in the form of heat. Evolutionarily, BAT functions as a defence mechanism against hypothermia, particularly in infants, small mammals and hibernating animals.

The best-known function of BAT is its thermogenic capacity, enabled by the BAT-selective expression of uncoupling protein 1 (UCP1), which stimulates thermogenesis by uncoupling cellular respiration and mitochondrial ATP synthesis. This thermogenic capacity of BAT has gained significant attention owing to its potential application in the amelioration of obesity and obesity-related diseases, such as insulin resistance, type 2 diabetes and fatty liver diseases (reviewed in REF. 1). Several human studies with ^{18}fluoro-labelled 2-deoxy-glucose positron emission tomography (^{18}FDG-PET) scanning indicate that the increased mass of ^{18}FDG-PET-positive BAT (which may result from, for example, increased BAT mass or thermogenic activity of existing BAT) is inversely correlated with body mass index (BMI), adiposity or fasting plasma glucose level in adult humans[2–5]. Recent studies in adult humans further demonstrated that chronic cold exposure stimulates the recruitment of new ^{18}FDG-PET-positive BAT even in subjects who had previously lacked detectable BAT depots before cold exposure, presumably owing to the emergence of new thermogenic adipocytes. This, then, leads to an increase in non-shivering thermogenesis and/or an improvement in insulin sensitivity[6–9]. These findings collectively support the significance of BAT in the regulation of energy expenditure and glucose homeostasis in adult humans.

Recent studies indicate that at least two distinct types of thermogenic adipocyte exist in mammals: a pre-existing form established during development, termed classical brown adipocytes; and an inducible form, termed beige (or brite) adipocytes. Classical brown adipocytes develop prenatally from a subset of dermomyotome cells and are localized predominantly in dedicated BAT depots, such as in the interscapular regions of rodents and human infants. The infant interscapular BAT depots eventually disappear in adult humans[10,11]. By contrast, beige adipocytes emerge postnatally from WAT, but the exact origin of these cells is much less well understood. A notable feature of beige fat is that beige adipocyte biogenesis is highly inducible by various environmental cues, such as chronic cold exposure, exercise and treatment with the agonist of the major regulator of adipogenesis, peroxisome proliferator-activated receptor-γ (PPARγ; discussed in more detail below), in a process referred to as the 'browning' or 'beige-ing' of white fat (reviewed in REF. 12). Notably, UCP1-positive adipocytes from adult human BAT in the supraclavicular region possess

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Undergraduate student (Dpt of Health Science) Miyako Matsuda, Ruri Nakamura

(2) Research interest

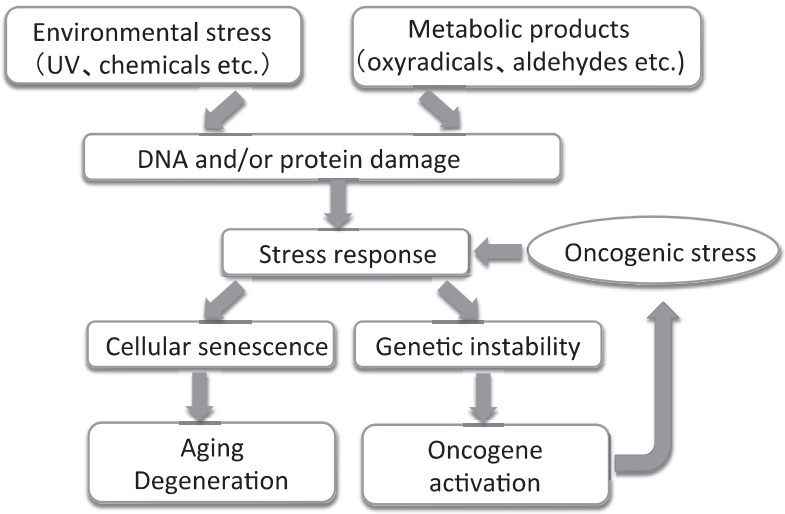
We are interested in the molecular mechanism of cellular stress responses and its role in carcinogenesis and aging.

Increasing attention has focused on the role of cellular stress response mechanisms in aging-related disorders and tumor development. Cells are constantly exposed to extrinsic and intrinsic stressors causing a variety of DNA and protein damages. While cells have diverse anti-stress and repair mechanisms to keep themselves healthy, strong and long-term stress enhances irreversible growth arrest (cellular senescence) and cell death. In addition, DNA damage causes errors in DNA repair/replication (genetic instability), leading to oncogene activation. Of note, activated oncogenes generate “oncogenic stress” signals which have paradoxical effects: cellular senescence/tumor suppression and genetic instability/tumor progression.

(3) Current projects

1) Oncogenic stress-induced replication stress

In these processes, cellular responses to oncogene-induced abnormal DNA replication and subsequent DNA damage play a major role. We have found specialized DNA polymerases involved in the cellular responses.



2) Role of heat shock response in the regulation of cellular senescence

Heat sock factor 1 (HSF1) is a central regulator of heat shock response, the major system coping with protein damages. We found that HSF1 regulates cellular senescence and are studying the underlying molecular mechanisms.

(4) Future Course

We will help students find post-doctoral positions and fellowship.

(5) Contact

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Both High-Fidelity Replicative and Low-Fidelity Y-Family Polymerases Are Involved in DNA Rereplication

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DNA rereplication is a major form of aberrant replication that causes genomic instabilities, such as gene amplification. However, little is known about which DNA polymerases are involved in the process. Here, we report that low-fidelity Y-family polymerases (Y-Pols), Pol η, Pol ι, Pol κ, and REV1, significantly contribute to DNA synthesis during rereplication, while the replicative polymerases, Pol δ and Pol ε, play an important role in rereplication, as expected. When rereplication was induced by depletion of geminin, these polymerases were recruited to rereplication sites in human cell lines. This finding was supported by RNA interference (RNAi)-mediated knockdown of the polymerases, which suppressed rereplication induced by geminin depletion. Interestingly, epistatic analysis indicated that Y-Pols collaborate in a common pathway, independently of replicative polymerases. We also provide evidence for a catalytic role for Pol η and the involvement of Pol η and Pol κ in cyclin E-induced rereplication. Collectively, our findings indicate that, unlike normal S-phase replication, rereplication induced by geminin depletion and oncogene activation requires significant contributions of both Y-Pols and replicative polymerases. These findings offer important mechanistic insights into cancer genomic instability.

Eukaryotic cells contain regulatory mechanisms to ensure that chromosomal DNA is duplicated exactly once per cell cycle (1–3). In late mitosis and early G_1 phase, replication origins are "licensed" through the formation of the prereplicative complex by sequential recruitment of the origin recognition complex, the loading factors Cdt1 and CDC6, and the minichromosome maintenance (MCM) 2-7 replicative helicase complex (MCM complex). At the onset of S phase, cyclin-dependent kinase 2 (CDK2)- and CDC7-mediated phosphorylation activates the MCM complex to unwind DNA, followed by loading of replication machinery to initiate DNA replication. Once cells enter S phase, the MCM complex is depleted from origins, and licensing of origins is inhibited during the S and G_2 phases by multiple mechanisms, including degradation of Cdt1 and CDC6 and expression of geminin, a specific inhibitor of Cdt1.

Growing evidence indicates that DNA rereplication plays a major role in genomic instability during tumor development and progression (2–4). Importantly, expression of various oncoproteins in cultured cells induces rereplication, partly through the increased expression of Cdt1 and/or CDC6, causing copy number changes and genomic rearrangements (5–7). Furthermore, a recent study documented that overexpression of KDM4A demethylase causes rereplication, resulting in site-specific gene amplification in human tumors (8). Although the molecular mechanisms for rereplication-induced genomic instability are not fully understood, it is proposed that rereplication induces double-strand breaks (DSBs) through fork collapse and collisions, leading to copy number variations and genomic rearrangements (2–4). While numerous studies have focused on the causes and consequences of rereplication, little is known about which DNA polymerases drive fork progression in rereplication.

Mammals have 15 different DNA polymerases (9–11). Polymerase δ (Pol δ) and Pol ε catalyze the high-fidelity duplication of the genome, whereas many others lack proofreading activity and have low stringency of catalytic sites. The major function of these polymerases is to bypass replication blocks at sites of DNA damage, i.e., translesion synthesis (TLS) (12–16). Y-family polymerases (Y-Pols), including Pol η, Pol ι, Pol κ, and REV1, are the major group of TLS polymerases. The previous observations that rereplication induces replication stress and DNA damage prompted us to investigate the roles of Y-Pols and replicative polymerases in rereplication in the present study (17–22). We found that rereplication induced by geminin depletion causes slowing down of fork progression, inducing Rad18-mediated monoubiquitination of proliferating cell nuclear antigen (PCNA), resulting in recruitment of Y-Pols to rereplication sites, and that Y-Pols, together with replicative polymerases, contribute to rereplication. We also obtained evidence indicating that Y-Pols are involved in cyclin E-induced rereplication. These findings provide new insights into the molecular basis underlying genomic instabilities during tumorigenesis.

MATERIALS AND METHODS

Plasmids. cDNAs encoding N-terminally green fluorescent protein (GFP)-tagged full-length human Pol η, Pol ι, Pol κ (cDNAs of Pol ι and Pol κ were kindly provided by H. Ohmori, Kyoto University), REV1, and a Pol η mutant carrying two missense mutations (D115A and E116A) in the catalytic domain (GFP-dead Pol η) (23) were inserted into a blasticidin-selectable lentiviral vector, CSII-CMV-MCS-IRES2-Bsd (kindly provided by H. Miyoshi, RIKEN). The cDNA encoding GFP-Pol η was also inserted into a hygromycin-selectable lentiviral vector, CSII-CMV-MCS-

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T.S. and T.O. contributed equally to this work.

doi:10.1128/MCB.01153-14

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(1) Members

Professor (Izuho Hatada)、Assistant Professor (Takuro Horii)、Research Assistant Professor (2), Assistant Technicians (2), Graduate Students (2)

(2) On-going projects

Epigenome analysis of diseases

Aberrant changes of epigenome caused by environments results in several diseases like cancers, obese and diabetes. We are going to clarify the causative genes for these by massive analysis of the epigenome. Functional analysis of identified candidate genes are performed by making knockout mice and human iPS cells using CRISPR/Cas genome editing technique.

Development of tumor-free pluripotent stem cells – New choice of regenerative medicine

Differentiated tissues derived from pluripotent stem cells (ES & iPS cells) unfortunately form tumors with considerable frequency after transplantation therapy. In most cases, oncogenes are epigenetically activated in these tumors. We established new pluripotent stem cells that are resistant to epigenetic activation of oncogenes. These cells do not form tumors after transplantation.

Epigenetic anomalies in assisted reproductive technology and regenerative medicine

A lot of couples have children by the favor of assisted reproductive technology (ART); however, epigenetic anomalies are often seen in these in vitro manipulated embryos . Methylation anomalies increase the risk of diseases such as Beckwith-Wiedemann Syndrome (BWS). ES cells and iPS cells cultured for a long term in vitro also show methylation anomalies. We are now studying why these anomalies occurred in vitro.

(3) Qualifications for admission

According to the rule of Gunma University Medical School.

(4) Graduate students

Two graduate students are in our laboratory.

(5) After graduation

Professional scientist

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nature biotechnology

Targeted DNA demethylation *in vivo* using dCas9–peptide repeat and scFv–TET1 catalytic domain fusions

Sumiyo Morita[1], Hirofumi Noguchi[2,5], Takuro Horii[1,5], Kazuhiko Nakabayashi[3], Mika Kimura[1], Kohji Okamura[4], Atsuhiko Sakai[2], Hideyuki Nakashima[2], Kenichiro Hata[3], Kinichi Nakashima[2] & Izuho Hatada[1]

Despite the importance of DNA methylation in health and disease, technologies to readily manipulate methylation of specific sequences for functional analysis and therapeutic purposes are lacking. Here we adapt the previously described dCas9–SunTag for efficient, targeted demethylation of specific DNA loci. The original SunTag consists of ten copies of the GCN4 peptide separated by 5-amino-acid linkers. To achieve efficient recruitment of an anti-GCN4 scFv fused to the ten-eleven (TET) 1 hydroxylase, which induces demethylation, we changed the linker length to 22 amino acids. The system attains demethylation efficiencies >50% in seven out of nine loci tested. Four of these seven loci showed demethylation of >90%. We demonstrate targeted demethylation of CpGs in regulatory regions and demethylation-dependent 1.7- to 50-fold upregulation of associated genes both in cell culture (embryonic stem cells, cancer cell lines, primary neural precursor cells) and *in vivo* in mouse fetuses.

In mammalian genomes, ~70% of cytosine residues in the sequence 5′-CpG-3′ are methylated[1]. DNA methylation regulates many biological processes[2,3], and deregulation of DNA methylation has been implicated in the etiology of several diseases such as cancer and imprinting diseases[4]. Methylation of cytosines is catalyzed by DNA methyltransferases, whereas the TET family of proteins catalyzes oxidation of methylated cytosine to 5-hydroxymethylcytosine, the initial step of the demethylation pathway[5]. Although DNA methylation is thought to play important roles in several processes, in many cases its causative effects are unclear because of a lack of widely applicable techniques for adding and removing DNA methylation at specific loci. In principle, such technologies could find application in targeted epigenetic therapy. Nonspecific methods for erasure of methylation by inhibitors of DNA methyltransferases such as 5-aza-2′ -deoxycytidine have been commonly used to study the effects of demethylation on specific gene promoters[6]. However, as these reagents demethylate genomes globally, it is difficult to study the effect of specific DNA methylation events, and there is the risk of side effects in therapeutic use.

Recently, genome editing technologies, such as zinc-finger nucleases (ZFNs)[7], transcription activator-like effector nucleases (TALENs)[8], and CRISPR–Cas9 (refs. 9–11) have been adapted to recruit catalytic activity to specific loci by fusion to catalytically inactive endonucleases. Zinc fingers (ZFs)[12] and transcription activator-like effectors (TALEs)[13] fused to TET family fusion proteins were reported to hydroxylate specific loci to activate demethylation in cultured cells, but the extent of demethylation was limited in this system. In addition, in ZFN and TALEN systems, the design and protein engineering of endonucleases are required for each locus, which is time-consuming. On the other hand, CRISPR RNA-guided Cas9 nucleases use small base-pairing guide RNAs (gRNAs) to target and cleave foreign DNA elements in a sequence-specific manner. Therefore, only alteration of the target sequence in small gRNAs is required to generate new endonucleases for new loci in the CRISPR–Cas9 system. Here, we show that a catalytically inactive Cas9 (dCas9) fused to the catalytic domain of TET1 (TET1CD) hydroxylates specific loci and activates site-specific demethylation. TET1 is a dioxygenase that catalyzes the hydroxylation of 5-methylcytosine to 5-hydroxymethylcytosine and the subsequent generation of 5-formylcytosine and 5-carboxylcytosine. These modified bases are either diluted by replication or removed by thymine DNA glycosylase and base-excision repair. This activity is greatly enhanced by fusion of dCas9 to a peptide repeat sequence to recruit multiple copies of an antibody-fused TET1 hydroxylase. We also show that our system is applicable to *in vivo* manipulation of methylation of specific loci in mouse fetuses.

First, we used a simple design to manipulate methylation, a direct fusion protein of an inactive Cas9 nuclease (dCas9) and TET1. TET1 has a conserved catalytic domain at the C terminus, which has a higher catalytic activity than the full-length protein[14]. Therefore, we fused TET1CD to the catalytically inactive dCas9 (system 1, **Fig. 1a** and **Supplementary Fig. 1**). A cytosine residue within the STAT3-binding site upstream of the gene (*Gfap*) encoding the astrocyte-specific marker glial fibrillary acidic protein (GFAP) was used as a target[15]. This site is methylated in most cell types, except for astrocytes, and demethylation of this site plays a critical role in the differentiation of neural precursor cells (NPCs) into astrocytes. We designed three targets around the STAT3-binding site (**Fig. 1b**), generated gRNA vectors for them, and transiently introduced these gRNA vectors into embryonic stem cells (ESCs) with the dCas9-TET1CD fusion

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Institute for Molecular & Cellular Regulation
Lab of Integrated Signaling Systems

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(2) Research Project

In our body, cells recognize its position and roles via cell-cell communication and behave appropriately. Such cell behavior supports tissue morphogenesis and homeostasis, and its dysregulation is involved in a variety of diseases, including cancer and diabetes. We investigate the molecular basis of cell-cell communication and behavior in animal body, using *in vivo* imaging, molecular genetics, molecular and cell biology, and biochemistry.

On-going projects:

1. Cell competition and its roles in animal development and cancer.

2. Function and regulation of nemo-like kinase (NLK) in cancer, metabolic diseases, and neurodegenerative disease.

3. Mechanisms that regulate Wnt signaling in tissue morphogenesis and homeostasis.

(3) Enrollment in Graduate Course

We will welcome anyone who is interested in our study.

(4) Graduate students in our lab

We recently moved from Kyushu University to Gunma University. Therefore, three master course students belonging to Kyushu University are studying in our team. One of them is a foreign student.

(5) Career Path after graduation

Two doctor course students have graduated. They are now researching as post-docs in USA or Kyushu Univ. Two master course students have also graduated and they are now working in the medical instrument company or agricultural company.

(6) Message

We are challenging to reveal the molecular basis of cell-cell communication and behavior in tissue morphogenesis, homeostasis, and diseases, using a variety of methods, including *in vivo* imaging, molecular genetics, molecular and cell biology, and biochemistry. You can acquire various knowledges and skills. Shall we have an enjoyable and exciting time in our lab?

Contact: Tohru Ishitani, Tel: 027-220-8892, e-mail: ishitani@gunma-u.ac.jp

Lab HP： http://www.imcr.gunma-u.ac.jp/?organization=個体制御システム分野 integrated-signaling-systems&lan=en

Cell Reports
Article

Hipk2 and PP1c Cooperate to Maintain Dvl Protein Levels Required for Wnt Signal Transduction

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SUMMARY

The phosphoprotein Dishevelled (Dvl) is a common essential component of Wnt/β-catenin and Wnt/planar cell polarity (PCP) signaling pathways. However, the regulation and significance of Dvl phosphorylation are not fully understood. Here, we show that homeodomain-interacting protein kinase 2 (Hipk2) facilitates protein phosphatase 1 catalytic subunit (PP1c)-mediated dephosphorylation of Dvl via its C-terminal domain and that this dephosphorylation blocks ubiquitination and consequent degradation mediated by the E3 ubiquitin ligase Itch, which targets the phosphorylated form of Dvl proteins. Inhibition of Hipk2 or PP1c function reduces Dvl protein levels and suppresses Wnt/β-catenin and Wnt/PCP pathway-dependent events in mammalian cells and zebrafish embryos, suggesting that Hipk2 and PP1c are essential for maintaining Dvl protein levels that are sufficient to activate Wnt signaling. We also show that Wnt-3a, a Wnt/β-catenin ligand, induces dissociation of the Dvl-Hipk2-PP1c complex and Dvl degradation under high-cell-density conditions. This regulation may be a negative feedback mechanism that fine-tunes Wnt/β-catenin signaling.

INTRODUCTION

Members of the Wnt family of secreted proteins transduce their signals through multiple pathways, including the β-catenin and planar cell polarity (PCP) pathways. In the β-catenin pathway, Wnt binds to the cell-surface receptor Frizzled and its coreceptor, LRP5/6. This Wnt-bound receptor complex recruits the cytoplasmic phosphoprotein Dishevelled (Dvl1, Dvl2, and Dvl3 in vertebrates) and induces phosphorylation of LRP6. Phosphorylated LRP6 then promotes the disassembly of the β-catenin degradation complex, leading to the stabilization of cytoplasmic β-catenin (MacDonald et al., 2011; Niehrs and Shen, 2010). β-Catenin then migrates into the nucleus, where it forms complexes with Tcf/Lef proteins and activates gene expression. Regulation of this pathway controls cell proliferation and fate determination (Clevers, 2006; Logan and Nusse, 2004). In the PCP pathway, which regulates cell movement and polarity, Wnt signals via Dvl to activate members of the Rho family of small G proteins. The activated G proteins then regulate the remodeling of actin filaments (Angers and Moon, 2009). Thus, Wnt proteins transduce their signals through Dvl in both the β-catenin and PCP pathways.

Dvl is phosphorylated by various kinases, including CK1δ, CK1ε, CK2, Par1, Plk1, and RIPK4 (Bryja et al., 2007; Cong et al., 2004; Huang et al., 2013; Kishida et al., 2001; Ossipova et al., 2005; Willert et al., 1997), and is dephosphorylated by protein phosphatase-2A (PP2A) (Yokoyama and Malbon, 2007). This kinase- and phosphatase-mediated regulation of Dvl plays both positive and negative roles in Wnt signal transduction. Although the regulation and significance of Dvl phosphorylation are not fully understood, a recent report showed that the E3 ubiquitin (Ub) ligase Itch ubiquitinates and destabilizes the phosphorylated form of Dvl regardless of whether Wnt signaling is active (Wei et al., 2012), indicating that Dvl is constitutively destabilized by phosphorylation. These findings also suggest that the destabilizing-phosphorylation of Dvl must be kept at low levels to maintain a pool of Dvl proteins available to respond to Wnt stimulation. However, the mechanism that controls this phosphorylation is unclear.

Protein phosphatase 1 catalytic subunit (PP1c) is a member of the PPP family of serine/threonine phosphatases that regulates a diverse array of cellular functions (Cohen, 2002). Recently, PP1c was identified as a positive regulator of Wnt/β-catenin signaling by two independent functional screenings using cultured cells (Kim et al., 2013; Luo et al., 2007). Inhibition of PP1c by treatment with PP1c chemical inhibitors, or overexpression of PP1c negative regulators, induced the phosphorylation of Axin and promoted its interaction with GSK-3β (Luo et al., 2007). However, the role of PP1c in regulating Wnt signal transduction is not fully understood.

Homeodomain-interacting protein kinase 2 (Hipk2) is an evolutionarily conserved serine/threonine kinase that phosphorylates and regulates several transcription factors, including p53, CtBP, and c-Myb (Rinaldo et al., 2007). Recent studies show that Hipk2 and its family proteins bind to and phosphorylate β-catenin, the E3 Ub ligase βTrCP/Slimb, and Tcf/Lef to modulate Wnt/β-catenin signaling in mammalian cell cultures, mouse

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1. Staff

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Professor:	Masami Torikoshi	Akihisa Takahashi
Research Professor:	Tatsuaki Kanai	
Visiting Professor:	Kazuo Arakawa	Koichi Ando, Yasuhiko Kobayashi
Assistant Professor:	Ken Yusa, Hirofumi Shimada, Yoshiki Kubota, Akihiko Matsumura, Motohiro Kawashima, Hikaru Souda, Makoto Sakai, Yoshiyuki Hirano	Yukari Yoshida

2. Research Activities

In Gunma University, patients suffered by various cancers have been treated by radiotherapies using carbon beam as well as x-ray. Although carbon ions have successfully been applied to clinical treatments of radiotherapy in Japan, many subjects have been still remained to be studied in the application of ions to radiotherapy. In this course, we aim to nurture researchers in the field of medical physics who are indispensable for ensuring the reliability of radiotherapy and developing technology of therapy through sophisticated research and credible study of heavy ion and x-ray radiotherapies. To improve radiotherapy, we carry out *in vitro* and *in vivo* experiments regarding a variety of radiation-induced biological phenomena. Another important purpose of this course is to increase the expertise of those radiobiology specialists involved in radiotherapy and space science.

3. Requirements of admission

This course aims to develop the medical physicist and radiation biologists for radiotherapy and space science. We accept students who are motivated and interested in ion therapy and space science. We are actively working to meet the needs by doctors and therapists, pursuing research and development for the heavy ion therapy and advanced photon therapy while undertaking operations.

4. Present student

4th year student	3	It is all student of Program for Cultivating Global Leaders in Heavy Ion Therapeutics and Engineering. 4 persons are abroad students. 3 persons entered Doctoral Program in October.
3rd year student	3	
2nd year student	1	
1st year student	0	

5. Career course

Researcher (Gunma University Initiative for Advanced Research)
Accelerator Engineering Corporation
Mitsubishi Electric Corporation

6. Other

This course is one of course in Program for Cultivating Global Leaders in Heavy Ion Therapeutics and Engineering.

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Development and performance evaluation of a three-dimensional clinostat synchronized heavy-ion irradiation system

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ABSTRACT

Outer space is an environment characterized by microgravity and space radiation, including high-energy charged particles. Astronauts are constantly exposed to both microgravity and radiation during long-term stays in space. However, many aspects of the biological effects of combined microgravity and space radiation remain unclear. We developed a new three-dimensional (3D) clinostat synchronized heavy-ion irradiation system for use in ground-based studies of the combined exposures. Our new system uses a particle accelerator and a respiratory gating system from heavy-ion radiotherapy to irradiate samples being rotated in the 3D clinostat with carbon-ion beams only when the samples are in the horizontal position. A Peltier module and special sample holder were loaded on a static stage (standing condition) and the 3D clinostat (rotation condition) to maintain a suitable temperature under atmospheric conditions. The performance of the new device was investigated with normal human fibroblasts 1BR-hTERT in a disposable closed cell culture chamber. Live imaging revealed that cellular adhesion and growth were almost the same for the standing control sample and rotation sample over 48 h. Dose flatness and symmetry were judged according to the relative density of Gafchromic films along the X-axis and Y-axis of the positions of the irradiated sample to confirm irradiation accuracy. Doses calculated using the carbon-ion calibration curve were almost the same for standing and rotation conditions, with the difference being less than 5% at 1 Gy carbon-ion irradiation. Our new device can accurately synchronize carbon-ion irradiation and simulated microgravity while maintaining the temperature under atmospheric conditions at ground level.

1. Introduction

Astronauts can now stay in space longer than before because of scientific advances, such as the construction of the International Space Station (ISS). The ISS orbits the Earth at an altitude of about 400 km, and astronauts are exposed to high-energy radiation originating from space. Exposure doses in the ISS have been estimated at about 1 mSv/day, which is about 100 times the dose received on the ground. There is thus an urgent need to obtain basic data of the effects of space radiation for the assessment and management of health risks in space. Several space agencies (i.e., the Russian Space Agency, European Space Agency, and Canadian Space Agency) have established their own maximum allowable effective doses for an astronaut's lifetime, which are generally 1 Sv (Zeitlin et al., 2013). Continuous area radiation monitoring has been performed within the Japanese experiment module Kibo on board the ISS (Nagamatsu et al., 2013).

To further human activity in space, it is necessary to study biological effects of combined microgravity and space radiation. In previous space experiments, there was no appreciable difference in results between space and ground samples because the time spent in space was short and samples were thus exposed to space radiation at a low dose (Bender et al., 1968). Although various organisms were pre-irradiated before space flight to test the effect of microgravity on the repair of radiation-induced damage, there was again no appreciable difference in results (Horneck et

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Heavy Ion Clinical Medicine

（１） We have a close relationship with Department of Radiation Oncology in terms of research on biology, physics, and heavy ion oncology.

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Associate Professor: Hiroshi Matsui

Assistant Professor: Masahiko Okamoto

Assistant Professor: Takuya Kaminuma

（２） Heavy ion clinical medicine includes radiobiology, medical physics and engineering, tumor pathology, clinical oncology, radiation diagnosis, and heavy ion radiotherapy technology to realize sophisticated radiation therapy. Research topic includes optimization of treatment planning, high precision beam delivering, adaptive treatment, 4-dimention irradiation system, multimodality approach, dose-volume-fractionation effect, scanning beam irradiation, socioeconomic issues, quality of life, and patient's survivor ship.

（３） After completion of residency training

（４） None. Applicants have admitted in department of Radiation Oncology because we share the opportunity for study.

（５） Radiation oncologist (majority)

（６） Our center is first facility operating carbon ion therapy at University in Japan. Heavy ion radiotherapy is a new exciting field of radiation oncology. We have a MOU with distinguished international particle/conventional radiotherapy centers (MGH (Boston), Mayo clinic (Rochester), GSI (Darmstadt), Medical University of Vienna (Vienna), and KIRAMS (Seoul)), which will promote our future collaboration.

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Original article

A multi-institutional analysis of prospective studies of carbon ion radiotherapy for prostate cancer: A report from the Japan Carbon ion Radiation Oncology Study Group (J-CROS)

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ABSTRACT

Background and purpose: A multi-institutional observational study (J-CROS1501PR) has been carried out to analyze outcomes of carbon-ion radiotherapy (CIRT) for patients with prostate cancer.
Patients and methods: Data of the patients enrolled in prospective studies of following 3 CIRT institutions were analyzed: National Institute of Radiological Sciences (NIRS; Chiba, Japan), Gunma University Heavy Ion Medical Center (GHMC; Gunma, Japan), and Ion Beam Therapy Center, SAGA HIMAT Foundation (HIMAT; Saga, Japan). Endpoints of the clinical trial are biochemical recurrence-free survival (bRFS), overall survival (OS), cause-specific survival (CSS), local control rate (LCR), and acute/late adverse effects.
Results: A total of 2157 patients' data were collected from NIRS ($n = 1432$), GHMC ($n = 515$), and HIMAT ($n = 210$). The number of patients in low-risk, intermediate-risk, and high-risk groups was 263 (12%), 679 (31%), and 1215 (56%), respectively. The five-year bRFS in low-risk, intermediate-risk, and high-risk patients was 92%, 89%, and 92%, respectively. The five-year CSS in low-risk, intermediate-risk, and high-risk patients was 100%, 100%, and 99%, respectively. The incidence of grade 2 late GU/GI toxicities was 4.6% and 0.4%, respectively, and the incidence of ⩾G3 toxicities were 0%.
Conclusions: Favorable overall outcomes of CIRT for prostate cancer were suggested by the analysis of the first multi-institutional data.

The incidence and mortality of prostate cancer have been reported to be 14.8% and 7.8%, respectively, according to the worldwide cancer database [1]. The outcomes of radiotherapy (RT) for prostate cancer have improved over the years due to the introduction of new treatment modalities, such as conventional RT, three dimensional conformal RT, and intensity-modulated RT (IMRT) [2–4]. The outcomes of RT for prostate cancer are suggested to be equal to or better than surgery [5]. Recently, robot-associate radical prostatectomy has been developed. Although the problem of surgical margin and learning curve are remaining, the outcomes of the surgery has been improving [6,7]. Besides that, low-dose rate (LDR) or high-dose rate (HDR) brachytherapy, combination of brachytherapy and IMRT, and proton beam therapy are also available for patients with prostate cancer [8–10]. Heavy ion (carbon ion) RT (CIRT) for cancer treatment in humans has been started in Japan in 1994, and the first CIRT clinical trial for prostate cancer was started in 1995 in Japan [11]. The advantages of CI beam are the focused dose distribution by an energy surge known as a spread-out Bragg-peak (SOBP) at a certain depth and its high biological effectiveness. Because these advantages have been extensively discussed in the literature, the characteristics and mechanism of CI beam will not be described in detail here [12,13].

Since its implementation >20 years ago, CIRT is currently available in eight institutions across four countries [14]. There are many challenges to conduct multi-institutional studies of CIRT due to the small number of CIRT institutions, almost all of which are specialized centers rather than general hospitals. However, due to the evidence of favorable outcomes with low incidence of adverse effects reported by CIRT studies, the number of CIRT institutions has been steadily increasing [11,14–18].

Here, we report the results of the first multi-institutional study of its kind that analyzed the data on the outcomes of CIRT for prostate cancer conducted in three institutions in Japan.

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Reference Materials

Contact Information and Main contents (contact number: +81-27-220-the extension number)

Region	Major Field	Contact Information	Main contents of research and key words
Basic Medicine	Anatomy	Hiroshi Yorifuji※ Ext. 7910 yorifuji@gunma-u.ac.jp	Research themes of our laboratory are 1) molecular cell biology of functional proteins of the skeletal muscle and 2) expression and function of cell adhesion molecules during early development. For the former, we are now concentrating on studying cytoskeletal anchoring systems to the sarcolemma and vesicular sorting systems. For the latter, we are studying cadherin-superfamily proteins with in situ hybridization technique using zebrafish embryos that are characterized by transparency in early development. 【Keywords】 skeletal muscle, cytoskeleton, vesicular sorting system, embryogenesis, cell adhesion
	Anatomy and Cell Biology	Toshiyuki Matsuzaki Ext. 7900 matoshi@gunma-u.ac.jp	We are studying the function of cellular molecules and their relations to cell function and structure. We especially focus on membrane channels and transporters in the kidney, such as water channel aquaporins. We are studying the regulation of water channels and relations to polycystic kidney. To understand these molecules, we use bio-imaging techniques such as immunofluorescence microscopy and immunoelectron microscopy, as well as molecular biology techniques. We are also working on functional molecules in meiosis and cellular polarity. 【Keywords】 cell membrane, water channels, transporters, microscopy, immunohistochemistry, electron microscopy
	Molecular and Cellular Neurobiology	Yasuki Ishizaki Ext. 7950 yasukiishizaki@gunma-u.ac.jp	We are studying the cells in the CNS from their birth to death. We aim at elucidation of molecular basis for the control of proliferation, differentiation, and survival of neural precursor cells, hoping that our results will contribute to the treatment of intractable CNS diseases in the near future. We are also studying the interaction between neural cells (especially oligodendrocyte precursor cells) and vascular cells (especially endothelial cells). 【Keywords】 neural stem cells, neuronal precursor cells, oligodendrocyte precursor cells, glial cells, endothelial cells, regenerative medicine
	Biochemistry	Takashi Izumi※ Ext. 7940 takashi_izumi@gunma-u.ac.jp	Our research projects aim to clarify turnover of cell membrane phospholipids on various kinds of stimulation, production of bioactive lipids (lipid mediators), signal transduction through their receptors, function of these bioactive lipids, and signal transduction after DNA damage, using methods of biochemistry, molecular biology and cell biology. Lipid mediators are involved in various pathological processes such as inflammation, allergy, cancer, neurological disorders. We are also working on omics analysis of protein and metabolite by mass spectrometry. 【Keywords】 Lipid mediator, Receptor, Signal transduction, DNA damage, Omics analysis
	Integrative Physiology	Noriyuki Koibuchi Ext. 7920 nkoibuch@gunma-u.ac.jp	Small lipophilic hormones such as steroid and thyroid hormones play a crucial role in the development and functional maintenance of various organs including the central nervous system. On the other hand, there are drugs and environmental chemicals whose structures are similar to those of these hormones. Such chemicals may disrupt endogenous hormone actions as either an agonist or antagonist. We study the effect of small lipophilic hormones on organ development and plasticity, and modulation by environmental chemicals and drugs on such process, using various techniques including behavioral analysis with gene modified animals, and cellular and molecular biological techniques. 【Keywords】 hormone, development, plasticity, regeneration, environmental factors, endocrine disruption

※ Due to retire in March 2018

Region	Major Field	Contact Information	Main contents of research and key words
Basic Medicine	Neurophysiology and Neural Repair	Hirokazu Hirai Ext. 7930 hirai@gunma-u.ac.jp	We are studying the mechanism underlying memory, learning and motor control as well as brain disorders and aging in terms of molecular, cellular, network and behavioral aspects. Our challenge includes development of novel therapies effective for the brain disorders. To pursue these aims, we are developing cutting-edge techniques such as novel viral vectors, genome editing technology and disease model non-human primates. Our laboratory has sufficient experimental setup to perform world top-level research. 【Keywords】 Memory, Learning, Motor control, Regenerative medicine, Viral vector, Neurodegenerative disease, Marmoset, Non-human primate model, Aging, Stem cell therapy, Gene therapy, Patch clamp.
	Neurobiology and Behavior	Tomoaki Shirao Ext. 8050 tshirao@gunma-u.ac.jp	To understand the regulatory mechanisms of synapse morphology and function, we have studied the actin cytoskeleton in postsynaptic sites. For this research, primary cultured neurons, human iPS cells-derived neurons and knockout mice have been used with various experimental techniques including cell biology, biochemistry, molecular biology, neuronal cell culture, histochemistry, imaging and behavioral analysis. In addition, we have also studied about the effects of radiation on the synapses. These studies will shed light on the mechanisms of brain function and development of new diagnostic and therapeutic methods for neurological and psychiatric disorders. 【Keywords】 Synaptic morphology and function, Actin cytoskeleton, Imaging techniques, Human iPS cells-derived neurons, Radiation damage, High-throughput
	Genetic and Behavioral Neuroscience	Yuchio Yanagawa Ext. 8040 yuchio@gunma-u.ac.jp	We are studying the role of neurotransmitter GABA in brain functions such as emotion and the properties of GABAergic neurons through the generation and analyses of genetically engineered rodents such as conditional knockout mice and transgenic rats. We are also interested in the relationship between the deficits in GABAergic neurons and neuropsychiatric disorders. We have established model mice for schizophrenia or epilepsy and are characterizing them to elucidate the pathogenesis and/or pathophysiology of these disorders. 【Keywords】 neurotransmitter, GABA, knockout mice, transgenic rats, neuropsychiatric disorders, model mouse
	Molecular Pharmacology and Oncology	Masahiko Nishiyama Ext. 7960 m.nishiyama@gunma-u.ac.jp	Our department is home to research focused on (1) understanding biology of cancer to discover novel medical seeds (Basic Oncology), (2) understanding the mechanism of drug actions (Cancer Pharmacology), (3) developing new molecular diagnostics and cancer therapeutics including drug discovery and personalized medicine (Cancer Translational Research), based on the fundamental biology and OMICS research, which offers a broad range of basic and clinical research topics to educate professionals to become leaders in the fields of cancer pharmacology, translational research and R&D management specialists. 【Keywords】 Cancer Pharmacology, Basic Oncology, Cancer Translational Research, Drug Action Mechanism, Genome-based Cancer Drug Discovery, Cancer Biomarker
	Bacteriology	Haruyoshi Tomita Ext. 7990 tomitaha@gunma-u.ac.jp	Nosocomial infections caused by multi-drug resistant (MDR) bacteria have increased and become a worldwide social problem. Our research is focused on the major causative MDR bacteria including methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), MDR *Pseudomonas aeruginosa*, and MDR *Acinetobactor baumanni*. The drug resistances and pathogenecities of MDR bacteria are examined by molecular biological methodology. The molecular mechanisms of bacterial genetic exchange system which is a significant factor for the spread of drug resistance and virulence genes are also studied. 【Keywords】 multi-drug resistant bacteria, VRE, MDRP, enterococcus, bacteriocin, conjugative plasmid, transposon

Region	Major Field	Contact Information	Main contents of research and key words
Basic Medicine	Parasitology	Hajime Hisaeda Ext. 8024 hisa@gunma-u.ac.jp	Malaria is one of the most life-threatening infections like AIDS and tuberculosis. Our research interest is host-parasite relationship in malaria. Specifically, immune responses to malaria parasites and pathogenesis of malaria parasites are analyzed in detail. We aim to develop vaccines and drugs to control malaria by revealing host-parasite relationship from both host and parasite points of view. 【Keywords】 Malaria, host-parasite relationship, immunity, vaccine
	Public Health	Hiroshi Koyama Ext. 8010 hkoyama@gunma-u.ac.jp	Public Health is the art and science to delineate the environmental and social determinants of health, and to reduce the harmful factors and to promote the supportive factors for health through the organized community efforts. Our research topics include, the protective effect of trace elements on the development of cancer and metabolic syndrome, analytical studies of trace elements using HPLC-ICP-MS method, depression screening-test for the suicide prevention, and the epidemiology of the relationship between QOL and insurance system and community organization. We also examine health equity and public health ethics. 【Keywords】 trace element, selenium, cancer prevention, depression screening, and epidemiology, public health ethics
	Legal Medicine	Yoshihiko Kominato Ext. 8030 kominato@gunma-u.ac.jp	Legal medicine is essentially the application of scientific methods and techniques to matters involving the public: that covers a lot of ground. Every science from chemistry to medicine, from biology to statistics, from dentistry to anthropology, can be a forensic science if it has some applications to the law or public matter. Especially, our group has been focusing on personal identification, which is one of the important matters of legal medicine in Japan. We have performed researches on ABO blood group, which is one of the important genetic markers in human identification. Based on experimental procedures and human genetic analysis of weak phenotypes, we have investigated transcriptional regulation of the ABO gene. 【Keywords】 Legal medicine, personal identification, ABO blood group, transcription
	Medical Philosophy and Ethics	Kenji Hattori Ext. 8037 hattorik@gunma-u.ac.jp	Medical practices in the clinical setting as one of existential situations are fraught with troublesome problems in terms of actual human ways of life. Clinical ethics is tackling them by, not applying some general principles or abstract doctrines mechanically to every case, but paying close attention to the individual circumstances of each case. We have been involved in the groundwork for the methodology of clinical ethics from the perspective of hermeneutics and philosophy of literature. Ethical problems in preventive medicine, the method of teaching medical ethics, meta-ethical approaches to medical ethics, and critically examining the fundamental concepts such as health and disease, are also of our core concern. 【Keywords】 clinical ethics, medical ethics, philosophy of medicine, medical ethics education
Clinical Medicine	Cardiovascular Medicine	Masahiko Kurabayashi Ext. 8140 mkuraba@gunma-u.ac.jp	This department aims to elucidate the molecular mechanisms for a variety of cardiovascular disease, including atherosclerosis, arrhythmia, and heart failure.In particular, we have been interested in the identification of biomarkers that have incremental value for prevention of cardiovascular disease, and key molecules that are targetable by drugs. Furthermore, with the advent of human genome science as well as cell biology, we seek for the development of novel therapeutic strategies for atherosclerosis, fatal arrhythmia, and heart failure. 【Keywords】 vascular biology, atherosclerosis, heart failure, arrhythmia, myocardial infarction, transcription factors

Region	Major Field	Contact Information	Main contents of research and key words
Clinical Medicine	Respiratory Medicine	Takeshi Hisada Ext. 8123 hisadat@gunma-u.ac.jp	Clinical and basic researches for allergy and respiratory diseases are needed more than ever in our aging society. We try to investigate the pathogenesis of these diseases to make them clear. Our oncology unit is focusing on the basic and clinical research for lung cancer. Using genetically modified mice, research for refractory respiratory diseases such as asthma, COPD and lung fibrosis have been investigated. [Keywords] lung cancer, allergic respiratory disease, COPD, lung fibrosis, infectious lung disease
	Gastroenterology and Hepatology	Satoru Kakizaki Ext. 8127 kakizaki@gunma-u.ac.jp	In Gastroenterology Unit, we investigate pathophysiology and evaluate therapy of gastroesophageal reflux disease (GERD), gastrointestinal motility disorder including esophageal motility disorder, using high resolution manometry (HRM), intraluminal impedance & pH monitoring, gastric emptying assessed by ^{13}C breath test, and frequency score for the symptom of GERD (FSSG). We started the new study entitled “association between inflammatory bowel disease and cellular stress response". In Hepatology Unit, main research themes are viral hepatitis, hepatocarcinogenesis, liver fibrosis and non-alcoholic steatohepatitis. We have investigated the pathogenesis of these disorders using animal models such as knockout mice, and analyzed clinical samples to establish new methods of the diagnosis and therapy. 【Keywords】 GERD, esophageal motility disorder, high resolution manometry, hepatocarcinogenesis, non-alcoholic steatohepatitis, knockout mice
	Endocrinology and Metabolism	Masanobu Yamada Ext. 8120 myamada@gunma-u.ac.jp	Endocrine metabolic system is an important biological signal transduction system, which transmits changes in a living body inside and outside to the target organ for eliciting appropriate biological responses. Collapse of this endocrine-metabolic system causes a variety of endocrine disorders, diabetes, and obesity, which reduces the patient's quality of life and leads to life-threatening cardiovascular disorders and malignant tumor. We are aiming to gain new insight into the pathogenesis of these disorders and develop new diagnostic methods and treatment by using genetically modified animal models, human gene analyses of surgical specimen and analyses of intracellular signaling system using molecular biology techniques. 【Keywords】 Lifestyle-related diseases, endocrine-metabolic disorders, diabetes mellitus, hypothalamus-pituitary-thyroid axis, adrenal gland, endocrine tumor
	Nephrology and Rheumatology	Keiji Hiromura Ext. 8166 hiromura@gunma-u.ac.jp	We are studying the molecular mechanisms of glomerular and tubulointerstitial injuries and renal tubular regeneration and trying to develop how to control renal injuries and regeneration. We are also examining the role of dendritic cells in renal diseases and autoimmune diseases. To investigate these research questions, we are using genetically modified animals and animal models of human diseases in vivo and several kinds of cultured cells in vitro. In addition, we are exploring and evaluating biomarkers for diagnosis or prognosis of renal and rheumatic diseases, using patients’ urine and tissue samples. 【Keywords】 nephrology, rheumatology, autoimmune disease, regeneration medicine, biomarkers
	Hematology	Hiroshi Handa Ext. 8166 handahiroshi@gunma-u.ac.jp	We study genetic polymorphism and epigenome, comprehensive analysis of RNA, non-coding RNA, microRNA by Next Generation Sequencing (NGS), the carbohydrate metabolism to elucidate the mechanism of the development and the progression of hematologic malignancies. We also conduct study about genetic polymorphism relevant to opportunistic infection in HIV patients, genome wide analysis in congenital coagulation disorder in cooperation with other institutions including in foreign countries. Student will learn NGS, gene introduction into tumor cells and methods of clinical statistics to search a factor associated with disease development, taking advantage of hematologic disorder to be easy to obtain a specimen from human. 【Keywords】 hematologic malignancy, genome, epigenome, coagulation disorder, HIV, Next Generation Sequencer

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Clinical Medicine	Neurology	Yoshio Ikeda Ext. 8060 ikeday006@gunma-u.ac.jp	To develop early diagnostic tools and establish useful biomarkers for Alzheimer disease, we are investigating the A β -amyloid imaging (PIB-PET) and CSF biomarkers. To unravel a pathogenesis of the biggest intractable neurological disease, amyotrophic lateral sclerosis (ALS), we are investigating the autopsy tissues of ALS subjects. Microsatellite-repeat expansions of CAG, CTG, or GGCCTG repeat units are common genetic mutations of the hereditary neurological disorders such as spinocerebellar ataxia (SCA). We are trying to establish cell culture or animal models which are affected by these mutations. We hope to develop a novel disease-modifying therapy for SCA by analyzing these models. 【Keywords】 Alzheimer disease, dementia, amyotrophic lateral sclerosis (ALS), spinocerebellar ataxia (SCA), microsatellite-repeat
	Cardiovascular Surgery	Toru Takahashi Ext. 8245 torutaka@gunma-u.ac.jp	According to an increase in aged population, the prevalence of arteriosclerotic diseases and heart failure are rapidly increasing, and part of such patients need surgical treatment. In cardiovascular surgery, organ ischemia occurs in almost all patients, and then the reduction of the ischemia-reperfusion injury is important to the surgical results. It is still controversial in the methods of myocardial protection and brain protection, and we study more effective methods for organ protection. 【Keywords】 surgery, heart, brain, ischemia, reperfusion injury, organ protection
	General Thoracic Surgery	Akira Mogi Ext. 8224 akmogi@gunma-u.ac.jp	The understanding of fundamental knowledge and concept of malignant diseases in thoracic surgical oncology, in particular, lung cancer, metastatic lung tumor, and thymic epithelial tumor is most important. The various factors related in each stage of carcinogenesis, proliferation, local invasion and also metastasis of tumor are reviewed with the latest knowledge. Furthermore, we make the students understands in the importance of the recent advances in the diagnosis and treatment to patients with thoracic malignant disease. After clarifying the clinical problems, the students will learn the basic experimental techniques necessary for development of new diagnostic method and therapy in surgical science of future. 【Keywords】 Surgical oncology, mechanism of proliferation, invasion and metastasis, driver gene, diagnosis and treatment
	Gastroenterological Surgery	Hiroyuki Kuwano※ Ext. 8220 hkuwano@gunma-u.ac.jp	In Division of Gastroenterological Surgery, researches for whole digestive tract are included. A wide variety of research, which including mechanism of carcinogenesis, growth and invasion of tumor, metastasis of tumor, suppressive research of malignancy and gastrointestinal motility research with conscious dogs, it will read to new therapeutic treatment have been energetically performed. Moreover, several clinical researches including development of excellent diagnostic method and therapeutic method have been performed continuously for the future. 【Keywords】 gastrointestinal surgery, carcinogenesis, gastrointestinal motility, excellent diagnostic method, development of therapeutic method
	Breast and Endocrine Surgery	Takaaki Fujii Ext. 8224 ftakaaki@gunma-u.ac.jp	Breast Cancer is the highest incidence disease among female malignant neoplasm. We review diagnosis and treatment of breast cancer and endocrine disorders. Basic research includes 1) mechanism of therapy resistance in breast cancer, 2) tumor angiogenesis, 3) biomarker of sensitivity for breast cancer treatment, 4) an exhaustive analysis of breast cancer prognostic factors. In addition, clinical study includes 1) additional usefulness of FDG-PET in breast cancer, 2) Mechanism of lymph node metastasis, 3) analysis of navigation surgery for identification of parathyroid glands and sentinel lymph nodes. It is not necessary to focus on the specific research subject, which you belong to. We held a research conference every week and discuss everything to solve the research problems with our professor. 【Keywords】 breast cancer, biomarkers, lymph node metastasis, TILs, microRNA, PET

※ Due to retire in March 2018

Region	Major Field	Contact Information	Main contents of research and key words
Clinical Medicine	Hepatobiliary and Pancreatic Surgery	Ken Shirabe Ext. 8800 kshirabe@gunma-u.ac.jp	In Department of Hepatobiliary and Pancreatic Surgery, main theme in basic research field, for overcoming refractory cancer, such as hepatobiliary and pancreatic cancer is microenvironment of cancer. In the clinical research field, important theme is new evaluation for liver function, sarcopenia, and laparoscopic surgery in hepatobiliary and pancreatic surgery in safe manner. For developing research, we will send young surgeons to outstanding research center. 【Keywords】 cancer microenvironment, hepato-biliary and pancreatic cancer, liver transplantation, sarcopenia, and laparoscopic surgery for hepato-biliary and pancreatic disease.
	Pediatric Surgery	Makoto Suzuki Ext. 8224 suzuki-m@gunma-u.ac.jp	We cooperate with other divisions of surgery and organize multidisciplinary research. Our main research subjects are development of new diagnostic and treatment methods with minimally invasive approach. In particular, we study the minimally invasive diagnosis using circulating tumor cells for childhood cancer, the development of new instruments in minimally invasive surgery, and the relation between gastro-intestinal motility and enterobacterial flora after total colectomy for ulcerative colitis. 【Keywords】 Surgical oncology, Circulating tumor cells, Minimally invasive surgery, Gastro-intestinal motility, Enterobacterial flora
	Radiation Oncology	Takashi Nakano Ext. 8380 tnakano@gunma-u.ac.jp	The Department of Radiation Oncology practices radiation therapy for various cancers comprehensively. It undertakes basic research on radiation induced apoptosis, modulation of radiation sensitivity by cell cycle regulatory proteins, hypoxia, cell- proliferation proteins, oncogenes, and cancer vasculature. In addition, clinical researches on heavy ion radiotherapy, combination of molecular targeted therapy with radiation, image based brachytherapy, and high precision radiotherapy (IMRT,SBRT, etc) are extensively conducted and promoted. 【Keywords】 radiation therapy, heavy ion therapy, radiation biology, radiation oncology, radiation pathology
	Diagnostic Radiology and Nuclear Medicine	Yoshito Tsushima Ext. 8400 yoshitotsushima@gunma-u.ac.jp	Incredible advances in medical imaging technology have followed the discovery of X-ray. CT, PET and SPECT use radiation. MRI and Ultrasound do not. All of these modalities are widely used in modern medicine. Interventional radiology and radioisotope therapy use image-guided, minimally invasive techniques to contribute to patient care. This field researches new imaging technology such as combining morphological and functional imaging, and develops “patient-friendly” treatment methods such as those in interventional radiology and radioisotope therapy. 【Keywords】 Diagnostic Radiology, Nuclear Medicine, CT, MRI, US, SPECT, PET, Interventional Radiology
	Psychiatry and Neuroscience	Masato Fukuda Ext. 8180 fukuda-psy@gunma-u.ac.jp	Development in neurosciences and brain sciences is just revealing brain dysfunctions for etiology and pathophysiology of psychiatric disorders using neuroimaging and genetic studies. Department of Psychiatry and Neuroscience endeavors to clarify etiology and pathophysiology of “mental dysfunction” employing structural neuroimaging such as MRI, functional neuroimaging such as PET and NIRS, neurophysiology such as MEG, neuroendocrine stress responses such as DST, and animal model of psychiatric disorders. 【Keywords】 psychiatric disorder, neuroimaging, stress, mental illness, brain function

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Clinical Medicine	Anesthesiology	Shigeru Saito Ext. 8450 shigerus@gunma-u.ac.jp	Development in neurosciences and brain sciences is just revealing consciousness, pain sensation, and brain dysfunctions objectively by using neuroimaging and/or genetic studies. Department of Anesthesiology endeavors to clarify origin of consciousness and pain perception, and to modify such neuronal functions pharmacologically. In addition to classical biochemical, physiological and anatomical strategies, modern genetic and fMRI methods are employed to investigate Anesthesiology topics. Pharmaceutical, pharmacodynamic and behavioral approaches are also adopted for both of clinical and basic pain researches. 【Keywords】 anesthesia, neuroimaging, consciousness, pain, brain function
	Emergency Medicine	Kiyohiro Oshima Ext. 8541 kiyohiro@gunma-u.ac.jp	(Basic research) ・Experimental study for the investigation and the inhibition of reperfusion injury in multi-organs following cardiopulmonary resuscitation (CPR) ・Experimental study of the coagulation in severe emergent conditions (Clinical research) ・Study of clinical factors to predict the prognosis in patients with cardiopulmonary arrest ・Study of clinical factors to predict the injury severity in patients with severe trauma ・Study of clinical factors to predict the prognosis in elderly emergent patients ・Study of clinical factors to predict blood transfusion in patients with severe trauma 【Keywords】 cardiopulmonary arrest, cardiopulmonary resuscitation, severe trauma, reperfusion injury, coagulation
	General Practice Medicine	Junichi Tamura Ext. 8665 jtamura@gunma-u.ac.jp	In our department, we are going to study about many problems in gerontology, especially methods of nutrition for old people. We are interested in the effects of the lack of trace elements on immune systems or protection to infectious disease. 【Keywords】 general medicine, gerontology, primary care, nutrition
	Rehabilitation Medicine	Naoki Wada Ext. 8655 nwada@gunma-u.ac.jp	Rehabilitation medicine is a transverse field of diagnostic as well as therapeutic medicine for infant-to-elder patients with a great variety of diseases. The course of rehabilitation medicine consists of basic knowledge of rehabilitation medicine, which are kineology, central and peripheral nerve system, respiratory, cardiac systems and psychiatry. The students discuss the methods for evaluation of disabilities and the equipment for the measurements. The indications of scales, rating scores and other evaluation methods for functional and mental disorders will be studied. Biological and cytological methods are also applied to the analysis, and the cellular reaction by physical stimulation will be observed. Statistical analysis will be indicated for the measurements and evaluations. Investigation of the results and publishing some conclusions in the journal is the purpose of the courses. 【Keywords】 disability medicine, diagnostic medicine, therapeutic medicine, kinesiology

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Clinical Medicine	Clinical Laboratory Medicine	Masami Murakami Ext. 8550 mmurakam@gunma-u.ac.jp	The following studies are conducted in our department. 1) Studies on the genetic analysis and preventive medicine: The development and clinical application of new methods for clinical laboratory testing including genetic analysis. 2) Studies on the lifestyle-related diseases and atherosclerosis: The clinical and basic studies of lifestyle-related diseases including obesity, diabetes mellitus and dyslipidemia that result in atherosclerosis, especially focusing on energy expenditure, glucose metabolism, lipid metabolism, and insulin and thyroid hormone actions. 3) Studies on the sports medicine: The application of novel biomarkers to support training of athletes. 4) Studies on the infection control: The study of infection control in the hospital, including the detection of drug resistant bacteria and the prevention of viral infection. 【Keyword】 genetic analysis, preventive medicine, lifestyle-related diseases, atherosclerosis, sports medicine, infection control
	Human Pathology	Hideaki Yokoo Ext. 7970 hyokoo@gunma-u.ac.jp	Pathology has dual aspects, one is basic science, and the other is clinical medicine practicing diagnostic works. Currently, the Department of Human Pathology is positioned in the clinical group. We routinely carry out pathological diagnosis (biopsy, cytology, autopsy), and also explore pathologic basis of diseases as well as novel therapy. Especially, our research group consistently plays a central role of brain tumor pathology of Japan for decades. 【Keywords】 human pathology, neuropathology, molecular pathology, diagnostic pathology, brain tumor, translational research
	Diagnostic Pathology	Tetsunari Oyama Ext. 7980 oyama@gunma-u.ac.jp	Our department has focused on “cancer”, especially on tumor pathology and diagnostic pathology. Various organs, for example, breast, uterine cervix, oral and head and neck, bone and soft tissue, prostate and digestive organs are our subjects of research. Clinicopathological approach with surgical specimens is our main method about carcinogenesis, cancer progression and cancer therapy. Recent projects in our department are as to mutation of oncogene and suppressor gene and expression of cancer related proteins. We have been studying on HPV infection and carcinogenesis. 【Keywords】 cancer, tumor pathology, oncogene, tumor progression, protein expression, breast
	Pediatrics	Hirokazu Arakawa Ext. 8200 harakawa@gunma-u.ac.jp	Various diseases in children are closely related to the growth and development of individuals. In addition, the diseases may be caused by breakdown of defense mechanism and homeostasis in response to ambient stimuli. Our aim is to reveal the mechanisms of mucosal immunity related to several infections, the role of autophagy needed to maintenance of intracellular homeostasis, and new genetic mutation and epigenetics related to development of diseases. 【Keywords】 Allergic diseases, neurodegenerative disorder, acute leukemia, nephrosis, inflammatory bowel diseases.
	Obstetrics and Gynecology	Hiroshi Kishi (Associate Professor) Ext. 8423 hrskishi@gunma-u.ac.jp	The understanding of hormonal effects and interactions on the hypothalamo-pituitary-ovarian axis is important for comprehending reproductive physiology and pathophysiology. The hormones work on the axis in a well-coordinated way and maintain physiological homeostasis. The aim of our research is to understand the functions of hormones at the molecular level, leading to the discovery of biologically active substances such as hormones and growth factors and their functional mechanisms. Our research involves the interrelationship between structures and functions of hormone receptors to elucidate the functions and mechanisms of actions of gonadotropin receptors 【Keywords】 LH receptor, FSH receptor, mutation, intracellular signal transduction, Vitamin A

Region	Major Field	Contact Information	Main contents of research and key words
Clinical Medicine	Urology	Kazuhiro Suzuki Ext. 8300 kazu@gunma-u.ac.jp	Our department has focused on understanding of the pathophysiology of prostate cancer. Basic studies cover genetic analysis, the role of lipids and intratumoral hormonal environments. Clinical studies cover the role of the tumor marker PSA and screening of prostate cancer. 【Keywords】 Urological tumor, prostate cancer, androgen dependency, screening, urological disease
	Neurosurgery	Yuhei Yoshimoto Ext. 8510 yyoshimo@gunma-u.ac.jp	Neurosurgical science had been evolved remarkably for recent 10 years with the introduction of new devices, including an endovascular catheter, an endoscope, and intraoperative monitoring systems, etc. These technical innovations make it possible to approach neurosurgical diseases with minimally invasive way. We will understand more deeply central nervous system, anatomically, pathologically, and biochemically, and develop pre, and intraoperative neurophysiological, and imaging studies. Then, we pursue the truly sophisticated treatment for neurosurgical diseases. 【Keywords】 micro-neurosurgery, interventional radiology, endoscopic neurosurgery, intraoperative imaging, intraoperative neurophysiology
	Ophthalmology	Hideo Akiyama Ext. 8338 akiyamah47@gunma-u.ac.jp	We are investigating 1) the mechanisms of pathogenesis in fundus diseases with optical coherence tomography (OCT) and 2) the lifetime of phosphorescence from iridium complex to develop a new system which can measure oxygen partial pressure in retinal tissue. Furthermore, our concern is also 3) the molecular mechanisms of damages in photoreceptor after retinal detachment using animal models. 【Keywords】 hematologic malignancy, genome, epigenome, coagulation disorder, HIV, Next Generation Sequencer
	Otolaryngology Head and Neck Surgery	Kazuaki Chikamatsu Ext. 8350 tikamatu@gunma-u.ac.jp	Antitumor immunity plays an important role in protection against the development of malignancy. However, with a developing tumor, tumor cells acquire various mechanisms to corrupt the host antitumor responses, escape from immune surveillance system, and grow in the host. The followings are current studies being conducted.1) Immunological analysis of T cells in patients with head and neck cancer 2) Analysis of interaction between tumor cells and stromal cells in head and neck cancer 【Keywords】 Head and neck cancer, immunosuppression, cancer vaccine, tumor microenvironment
	Dermatology	Osamu Ishikawa Ext. 8280 osamuishi@gunma-u.ac.jp	Our research goal is "Bedside to Bench and Bench to Bedside" to cure and care patients suffering from diseases of unknown etiology or intractable diseases. Our experienced staff supervises and assists you to publish the high quality paper to the world. Our main research themes are as follows: systemic sclerosis, dermatomyositis, viral infection, wound healing, cutaneous malignant neoplasms, and hereditary disease. 【Keywords】 Skin, autoimmune rheumatic disease, cutaneous malignant neoplasms, wound healing, hereditary diseases
	Plastic Surgery	Takaya Makiguchi Ext. 8484 tmakiguchi@gunma-u.ac.jp	We are investigating in collaboration with department of Oral and Maxillofacial Surgery and Dermatology. Present research theme are 1) Clinical and experimental study wound healing. 2) Clinical and experimental study of free flap reconstruction. 3) Evaluation of breast, head and neck reconstruction with brain science using MRI images. 【Keywords】 reconstruction, free flap, wound healing, breast reconstruction

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Clinical Medicine	Orthopaedic Surgery	Hirotaka Chikuda Ext. 8260 chikudah@gunma-u.ac.jp	Nowadays, it is important to facilitate the maintenance and improvement of bone and joint function. The aim of our department contributes further to the development of musculoskeletal medicine through research, maintenance of health, prevention of diseases, development of public health in both mind and body mainly through sports medicine, support for the handicapped, and extension of social welfare services for the aged. 【Keywords】 Osteoarthritis, spondylotic deformans, joint arthroplasty, sports injury, musuclo-skeletal tumor
	Clinical Pharmacology	Koujirou Yamamoto Ext. 8743 koujirou@gunma-u.ac.jp	Recently, many new drugs with novel mechanisms have produced to improve the clinical efficacy of drug therapy, however, the development of new drugs also have produced a lot of new problems to be solved. In the pharmacotherapy, the choice of appropriate therapy or drug for each individual patient is imperative. To establish safe and effective pharmacotherapy, we focus the variation factors for clinical efficacy of drug therapy for several diseases with gene analysis and pharmacokinetic approaches. 【Keywords】 Clinical pharmacology, pharmacokinetics, genetic polymorphisms, individualization of drug therapy
	Oral and Maxillofacial Surgery	Satoshi Yokoo Ext. 8480 syokoo@gunma-u.ac.jp	Present research theme 1) Epithelialization in oral mucous wound healing in terms of energy metabolism. 2) Cytological evaluation in odontogenic cyst-lining keratinocyte. 3) Oral and maxillofacial reconstruction with vascularised free flaps. 4) Evaluation of treatment strategy of oral cancer. 5) Effects of pilocarpine and isoproterenol on aquaporin-5 expression in salivary gland 6) Clinical and experimental study of endodontic microsurgery for extensive radicular cyst. 7) Surgical study of jaw deformity 【Keywords】 oral mucous wound healing, oral and maxillofacial reconstruction, oral cancer, salivary gland, .jaw deformity
	Quality and Safety in Healthcare (tentative)	Yasuki Ishizaki（Dean） (Ext.)：7950 yasukiishizaki@gunma-u.ac.jp	This department was newly founded in April of 2017 to study and promote quality and safety in healthcare, cooperating with international organizations such as WHO, etc. We are now selecting a candidate for the professor of this department. Refer to Professor Ishizaki, Dean of Graduate School of Medicine, for further information.
Cooperative Department and Joint Department	Clinical Trials and Regulatory Science	Tetsuya Nakamura Ext. 8740 nakamurt@gunma-u.ac.jp	Clinical trials and research are advanced very rapidly and changed dramatically in recent years. We conduct and support a variety of clinical trials in our hospital and in our community to establish highly qualified clinical evidence. We continuously improve our knowledge and skills about trial design, data management, statistical methods, regulatory science or ethical issues in daily practice. We are trying to open a door for new world of clinical research science. 【Keywords】 clinical research, study design, statistics
	Medical Informatics	Yuichiro Saito (Associate Professor) Ext. 8771 saitoyui@gunma-u.ac.jp	Today's rapid growth of hospital information systems produces huge amount of data and excellent infrastructure to let clinicians to access them. This seminar aims to learn methodology contributing human health care using medical information system. It has been exploring and presenting required data via hospital information system using ubiquitous computing technologies. 【Keywords】 medical information, health care, hospital information system

Region	Major Field	Contact Information	Main contents of research and key words
Cooperative Department and Joint Department	Molecular Traffic	Ken Sato Ext. 8840 sato-ken@gunma-u.ac.jp	Membrane trafficking plays essential roles not only in secretion and nutrient uptake but also in various physiological processes such as those involving the endocrine system, metabolic system, and nervous system in animals. In our laboratory, we study the molecular mechanisms and physiological functions of membrane trafficking in multicellular organisms by using the nematode Caenorhabditis elegans and mice as model systems. In addition, we study the molecular mechanisms underlying protein-misfolding diseases, in which abnormal membrane proteins accumulate in the endoplasmic reticulum (ER), in order to discover new targets for the treatment of such diseases. 【Keywords】 Membrane trafficking, Secretion, Metabolism, Development, Model animal
	Medical Neuroscience	Akiko Hayashi-Takagi Ext. 8850 hayashitakagi@gunma-u.ac.jp	The deterioration of the synapses has attracted attention as the pathophysiology of neuropsychiatric disorders. Thus, we examine the relationship between the structural and functional property of synapse and behavioral manifestations by utilizing in vivo 2-photon imaging. Furthermore, we also utilize novel optogenetic tools, which can manipulate the plasticity of the synapse in order to alter neurocircuits by extension changing the behaviors. By these two strategies, we pursue the cellular mechanism of neuropsychiatric disorders to identify a novel therapeutic target for disorders. 【Keywords】 Neuropsychiatric disorders, synapse, 2-photon imaging, signal transduction, drug discovery
	Secretion Biology	Seiji Torii (Associate Professor) Ext. 8859 storii@gunma-u.ac.jp	With the decrease of neuroendocrine function, a variety of diseases increase, which include metabolic syndrome and neuronal disorders. To understand fundamental mechanisms on such human diseases, we investigate the biosynthesis and secretion of peptide hormones, and the regulation of cell survival and death, with use of molecular and cellular technical approaches. In a collaborative study with some engineering researchers, we are developing new compounds or fluorescent probes for analyzing cancer, diabetes, and ischemia. 【Keyword】 Endocrine cells, Peptide hormones, Insulin, Molecular imaging, Reactive oxygen species, Ferroptosis
	Molecular Membrane Biology	Miyuki Sato (Associate Professor) Ext. 8843 m-sato@gunma-u.ac.jp	Eukaryotic cells are composed of several membrane-bound organelles. The shape and composition of organelles are dynamically regulated during cell differentiation and are also influenced by various changes in the extracellular environment. We are interested in the regulation of organelle dynamics during animal development and use C. elegans as a model system. In particular, we explore the mechanisms and physiological roles of autophagy and endocytosis in fertilized eggs by using genetic and cell biological approaches. 【Keywords】 C. elegans, embryonic development, organelle, autophagy, endocytosis
	Molecular Endocrinology and Metabolism	Tetsuro Izumi Ext. 8856 tizumi@gunma-u.ac.jp	To understand the physiopathology of multicellular organisms, it is important to know how diff erentiated cells communicate with each other to regulate their function as a whole body. We especially focus on the basic biology of pancreatic beta cells, adipocytes, and immune cells, because of their involvement in the pathogenesis of endocrine, metabolic, and allergic diseases such as diabetes, obesity and asthma. We approach these themes at multiple levels from molecules to whole body, and by using varying techniques of molecular biology, biochemistry, cell biology, and genetics. 【Keywords】 genetically modified mouse, regulated exocytosis, endocrine, metabolic, and allergic disease, live cell imaging, cell sorting

Region	Major Field	Contact Information	Main contents of research and key words
Cooperative Department and Joint Department	Developmental Biology and Metabolism	Yoshio Fujitani Ext. 8855 fujitani@gunma-u.ac.jp	The dysfunction of pancreatic beta cells, brown adipocytes, and enterocytes can cause diabetes and metabolic syndrome. Our goal is to elucidate the molecular mechanism involved in the maintenance of homeostasis of these higher-order function cells, which is the key to glucose metabolism. We aim to elucidate the mechanism of cellular homeostasis, from a variety of viewpoints, including developmental biology, zinc biology, autophagy, and cell polarity, by effectively utilizing genetically engineered mice. Furthermore, using our findings from basic medical research, we aim to establish a groundbreaking treatment for diabetes and obesity. 【Keywords】 diabetes, glucose metabolism, developmental biology, pancreatic beta cells, genetically engineered mice, brown adipocytes, zinc biology, autophagy
	Metabolic Signaling	Tadahiro Kitamura Ext. 8845 kitamura@gunma-u.ac.jp	In this laboratory, we are trying to elucidate the molecular mechanism by which metabolic syndrome occurs, using genetically manipulated animal models, such as knockout mice or transgenic mice. We hope that our research will contribute to the development of new strategies to treat or prevent diabetes and obesity. 【Keywords】 diabetes, obesity, metabolic syndrome, transcription factor, knockout mouse, insulin glucagon
	Laboratory of Epigenetics and Metabolism	Takeshi Inagaki Ext. 8835 inagaki@gunma-u.ac.jp	Epigenetic regulation of gene expression is independent of genomic sequence and therefore can flexibly respond to environmental factors. We are currently investigating various epigenetic mechanisms by which the environmental factors are linked to metabolic diseases. Main focus of our research is histone modification which regulates gene expression through changing chromatin structure and cofactor recruitment. Using techniques of transcriptomics, epigenetics, proteomics and animal models, we intend to elucidate the detail mechanisms of epigenetic regulations of energy metabolism and adipose cell development. 【Keywords】 Epigenome, metabolic diseases, energy metabolism, transcription, chromatin structure
	Molecular Genetics	Takayuki Yamashita Ext. 8830 y-taka@gunma-u.ac.jp	Cells are constantly exposed to diverse genotoxic and proteotoxic stresses derived from environmental and intrinsic sources. Cellular responses to these stresses play essential roles in oncogenesis, degeneration and aging. Our research focuses on the molecular mechanisms underlying the cellular responses to DNA replication stress and heat shock and their pathological functions in cellular senescence and oncogenic transformation. 【Keywords】 DNA replication stresses, Heat shock response, Cellular senescence, Genomic instability, Oncogenesis
	Genome Sciences	Izuho Hatada Ext. 8057 hatada@gunma-u.ac.jp	Epigenetics is the study of heritable codes other than genetic codes written in A,G, C, and T. Monozygotic twins have the same genetic information; however, they have different epigenetic information and phenotype. DNA methylation and histone modifcations (acetylation and methylation) serve as epigenetic code. Epigenetic status, namely, epignome, is thought to be influenced by the environment, such as food, infection, and chemicals. This reprogramming of the epigenome by the environment could cause diseases such as cancer, and diabetes. We are going to clarify the role of epigenetic anomalies in diseases such as cancer, diabetes and obesity. 【Keywords】 epigenetics, epigenome, DNA methylation, microarray, genome-wide analysis

Region	Major Field	Contact Information	Main contents of research and key words
Cooperative Department and Joint Department	Laboratory of Integrated Signaling Systems	Tohru Ishitani Ext. 8892 ishitani@gunma-u.ac.jp	Morphogen signaling systems, such as Wnt signaling, plays crucial roles in animal tissue morphogenesis and homeostasis, and dysregulation of morphogen signaling causes a variety of diseases, including cancer, metabolic diseases, and neurological diseases. Our laboratory investigates the regulatory mechanisms of morphogen signaling systems and also searches for unknown signaling systems that regulate tissue morphogenesis and homeostasis, using in vivo imaging, biochemistry, and molecular genetics. Especially, we are now focusing on "cell competition", a new system supporting animal tissue homeostasis. 【Keywords】 signal transduction, morphogen, cell competition, in vivo imaging, disease model
	Medical Physics and Biology for Ion Therapy	Masami Torikoshi Ext. 8378 torikosi@gunma-u.ac.jp Akihisa Takahashi Ext. 7917 a-takahashi@gunma-u.ac.jp	In this course, we aim to nurture researchers in the field of medical physics who are indispensable for ensuring the reliability of radiotherapy through sophisticated research and credible study of heavy ion and x-ray radiotherapies. To improve radiotherapy and to use space environment, we carry out *in vitro* and *in vivo* experiments regarding a variety of radiation-induced biological phenomena. Another important purpose of this course is to increase the expertise of those radiobiology specialists involved in radiotherapy and space science. 【Keywords】 Radiotherapy, heavy ion radiotherapy, medical physics, accelerator, radiation biology, effect of space radiation
	Heavy Ion Clinical Medicine	Tatsuya Ohno Ext. 8378 tohno@gunma-u.ac.jp	Heavy ion radiotherapy for malignant tumors has several biophysical advantages compared with photon therapy. Heavy ion clinical medicine includes clinical oncology, tumor pathology, radiobiology, medical physics and engineering, diagnostic radiology, and image-guided therapy. This course is implemented to understand that the radiation oncology including heavy ion radiotherapy is comprehensive medical science which integrates and systematizes these wide varieties of scientific subfields to attain successful cancer treatment. 【Keywords】 Heavy ion radiotherapy, Multimodality cancer therapy, Biological response, high LET, Hypofractionation, Image-guided adaptive radiotherapy
	Quantum Biology	Takasaki Advanced Radiation Research Institute, National Institutes for Quantum and Radiological Science and Technology Yasuyuki Ishii Yasuhiko Kobayashi Contact to Admissions Section, Educational Affairs office	Using the features of physical and biological effects of ion beam, the new method for analyzing biofunction which was very difficult to be analyzed in conventional technology will be developed to perform the functional analysis at each level of a molecule, a cell, and an organ. The following analysis methods will be established: analysis of cell function based on the element distribution in the cell using micro-PIXE (Particle Induced X-ray Emission) or measurement of dynamics of trace elements contained in drugs, contaminants, or substances transmitting information inside and outside the cell; analysis of inactivation of specific organ in the cell by microbeam irradiation of body tissues / cultured cell line and crosstalk within the cell; analysis of crosstalk between cells by inactivation of specific cell in living tissue. Also, the influence of irradiating living cells with an ion (single ion irradiation) will be analyzed at the molecular level. The mechanism of cell response under stress or by exposure to radiation such as apoptosis, genome instability, mutagenesis, and carcinogenesis will be elucidated with those analysis methods aiming to nurture the researchers who play a leading role in advanced medical research. 【Keywords】 ion beam, cell metabolic function, micro-PIXE, crosstalk between cells, single ion irradiation, stress damage, cell response mechanism

Admission Guidelines (Excerpts)

***Regarding the number of pages, refer to that of Admission Guidelines.**

Admission Guidelines for general selection

1 Number of Students to be Admitted

Basic Medicine	Clinical Medicine		Cooperative and Joint Department	
Anatomy	(Internal Medicine)	Radiation Oncology	(University Hospital)	The number of students to be admitte is 57
Anatomy and Cell Biology	Cardiovascular Medicine	Diagnostic Radiology and Nuclear Medicine		
Molecular and Cellular Neurobiology	Division of Pulmonary Medicine	Psychiatry and Neuroscience	Clinical Trials and Regulatory Science	
Biochemistry	Gastroenterology and Hepatology	Anesthesiology	Medical Informatics	
Integrative Physiology	Endocrinology and Metabolism	Emergency Medicine		
Neurophysiology and Neural Repair	Nephrology and Rheumatology	General Practice Medicine	(Institute for Molecular and Cellular Regulation)	
Neurobiology and Behavior	Hematology	Rehabilitation Medicine	Molecular Traffic	
Genetic and Behavioral Neuroscience	Neurology	Clinical Laboratory Medicine	Medical Neuroscience	
Molecular Pharmacology and Oncology	(General Surgical Science)	Human Pathology	Secretion Biology	
Bacteriology	Cardiovascular Surgery	Diagnostic Pathology	Molecular Membrane Biology	
Parasitology	General Thoracic Surgery	Pediatrics	Molecular Endocrinology and Metabolism	
Public Health	Gastroenterological Surgery	Obstetrics and Gynecology	Developmental Biology and Metabolism	
Legal Medicine	Breast and Endocrine Surgery	Urology	Metabolic Signaling	
Medical Philosophy and Ethics	Hepatobiliary and Pancreatic Surgery	Neurosurgery	Laboratory of Epigenetics and Metabolism	
	Pediatric Surgery	Ophthalmology	Molecular Genetics	
		Otolaryngology-Head and NeckSurgery	Genome Sciences	
		Dermatology	Laboratory of Integrated Signaling Systems	
		Plastic Surgery	(Heavy Ion Clinical Medicine)	
		Orthopaedic Surgery	Medical Physics and Biology for Ion Therapy	
		Clinical Pharmacology	Heavy Ion Clinical Medicine	
		Oral and Maxillofacial Surgery	(Takasaki Advanced Radiation Research Institute, National Institutes for Quantum and Radiological Science and Technology)	
		Quality and Safety in Healthcare (tentative)	Quantum Biology	

Notes: 1. The number of students to be admitted includes that of the selection for working members of society.
2. When applying, be sure to contact the supervisor (see page 55) of major field of your choice about research, guidance, etc.
3. There is a special course as shown below in our Course of Medical Sciences.
A person who desires to take the cooperative course on heavy ion medical engineering must submit the application form (Form-7) at the time of application.
A person who desires to take the other course should consult his /her Academic Advisor and submit the application after enrollment.
Furthermore, for more information about the Special Course, please confirm it by visiting our Course of Medical Sciences in Graduate School of Medicine and Faculty of Medicine at website at http://www.med.gunma-u.ac.jp/.

Special Course	Course for Promotion of Research Based on the Alliance between Basic and Clinical Medicine Translational Research Course
	Course for Program for Cultivating Global Leaders in Heavy Ion Therapeutics and Engineering
	Course for Cultivating Globally Co-operative Experts in Clinical Oncology ○Course for Experts in Surgical Oncology ○Course for Experts in Multidisciplinary Oncology ○Course for Experts in Radiation Oncology ○Course for Experts of Research on Pharmaceutical Sciences of Cancer ○Course for Experts in Basic and Translational Research
	Asian Nuclear Medicine Graduate Course
	Integrated medicine training course

2 Qualifications for Application（A person who falls under any of the following provisions）

(1) A person who has graduated or will graduate from a university (which has a course in medical science or dental science, or a 6-year course in pharmaceutical science or veterinary science) by March 2018.

(2) A person who has completed or will complete an 18-year course (final course has to be the course in medical science, dental science, pharmaceutical science, or veterinary science) of school education in a foreign country by March 2018.

(3) A person who has completed or will complete an 18-year course (final course has to be the course in medical science, dental science, pharmaceutical science, or veterinary science) in a foreign country's school education by taking class subjects in Japan through correspondence courses run by the said foreign educational establishments by March 2018.

(4) A person who has completed a foreign country's university course or is expected conferred by March 2018 at an educational institution in Japan (limited to the person who has completed an 18-year course of school education (including the doctoral course to study medical science, dental science, pharmaceutical science, or veterinary science) in the said foreign country's school education) which is designated in the said foreign country's education system as having a foreign university's curriculum and specifically designated by the Minister of Education, Culture, Sports, Science and Technology, Japan.

(5) A person who has completed five or more years of study (the course in medical science, dental science, pharmaceutical science, or veterinary science)at a foreign university, or foreign educational establishment (including a person who, while residing in Japan, has completed the program of education provided by a foreign university or foreign educational establishment through correspondence or distance education courses) and who received or is expected conferred by March 2018 a degree certificate that is recognized by the Japanese Ministry of Education, Culture, Sports, Science and Technology.

(6) A person designated by the Minister of Education, Culture, Sports, Science and Technology, Japan. (Notification No. 39 of the Ministry of Education, 1955)

(Note) The designated person above refers to a person who falls under any of the following provisions:

(a) A person who has completed medical science or dental science at the faculty of medicine or dentistry of a university under the old University Ordinance (Imperial Ordinance No. 388 of 1918), and who has graduated from these faculties.

(b) A person who has graduated or will graduate from National Defense Medical College by March 2018 under the Act for Establishment of the Ministry of Defense (Act No. 164 of 1954)

(c) A person who has completed a master's course, a person who can be awarded a master's degree, or a person who has been enrolled in the doctoral course with no separation of a 2 year- first semester and a 3 year-second semester for 2 years or longer acquiring 30 credits or more under the necessary research guidance (including a person who falls under Article 6-1 of the Degree regulations (Ordinance of the Ministry of Education, Science, Culture No. 9 of 1953) prior to version by Ministerial Ordinance (Ordinance of the Ministry of Education, Science, Culture No. 29 of 1974) that revises part of the Degree regulations), in addition to the above-described premises, a person who has been recognized by our Graduate School as having academic ability equivalent or superior to a university graduate who has completed the course to study medical science, dental science, pharmaceutical science, or veterinary science.

(d) A person who has graduated from a university (excluding the course to study medical science or dental science, or a 6-year course in pharmaceutical science or veterinary science), or a person who has been engaged in research for 2 years or longer at university or institute, etc. after having completed 16 years of a school education in a foreign country (including a person who will engage in research for 2 years or longer by March 31, 2018), in addition to the above-described premises, a person who has been recognized by our Graduate School as having academic ability equivalent or superior to a university graduate who has completed the course in medical science, dental science, pharmaceutical science, or veterinary science based on the said research's results etc.

(7) A person who entered a graduate school other than our Graduate School (limited to the course to study medical science, dental science, pharmaceutical science, or veterinary science) based on the provisions of Article 102-2 of the School Education Act (Act No. 26 of 1947) and who has been recognized by our Graduate School as having academic abilities appropriate for receiving graduate school education.

(8) A person who has been recognized by our Graduate School as having academic abilities equivalent or superior to a person who has graduated a university (which has a course in medical science or dental science, or a 6-year course in pharmaceutical science or veterinary science) based on the results of individual examination of the applicant's qualifications, and who will be 24 years of age by March 31, 2018.

(9) A person who has been enrolled at a university for 4 years or longer taking the course in medical science or dental science, or the 6-year course in pharmaceutical science/ veterinary science (including a person who is specified by the Minister of Education, Culture, Sports, Science and Technology, Japan as any other person equivalent thereto) by March 2018 and who has been recognized by Gunma University as having completed the required units with excellent results.

3 Screening etc. of "Qualifications for Application" (only for the people concerned)

(1) A person who intends to apply under the provisions of Qualifications for Application (6)－(c)(d), (7) or (8) must undergo the screening of requirements for admission of our Graduate School before applying under the following

conditions, and after that the only person who is proved that he/she has Qualifications for Application can apply. Furthermore, the result of the qualification screening will be notified to each applicant by August 15 (Tue.), 2017.

(a) Application period
August 1 (Tue.), 2017

(b) Application documents

① In the case of the screening concerning Qualifications for Application (6)-(c)(d):

Ⅰ Application for the screening of admission requirements (The form attached to our admission guidelines must be used.[Form-8])

Ⅱ Certificate of Research Activities (The form attached to our admission guidelines must be used.[Form-9])

Ⅲ Research achievements in medicine and medical treatment (Papers etc.)

Ⅳ Profile of the research institute to which the applicant has belonged to in order to produce the above research achievements.

Ⅴ Letter of recommendation prepared by the supervisor of the research area of your choice (form : free)

Ⅵ Graduation Certificate or Completion Certificate issued by the final educational establishment from which the applicant graduated.

Ⅶ Academic transcript issued by the final educational establishment from which the applicant graduated.

② In the case of the screening concerning Qualifications for Application (7):

Ⅰ Application for the screening of admission requirements (The form attached to our admission guidelines must be used.[Form-8])

Ⅱ Academic transcript (faculty results and the document showing the curriculum of the faculty (e.g. syllabus))

Ⅲ Certificate of student status (issued by the president of the university (graduate school) you are in and with the date of your entrance). If you completed or quit the graduate school, submit the document with the date of your entrance (e.g. the transcript from the graduate school).

Ⅳ Published academic papers etc. on research achievements, if any.

③ In the case of the screening concerning Qualifications for Application (8):

Ⅰ Application for the screening of admission requirements (The form attached to our admission guidelines must be used.[Form-8])

Ⅱ Certificate of Research Activities (The form attached to our admission guidelines must be used.[Form-9])

Ⅲ Research achievements equivalent to master's thesis (Papers etc.)

Ⅳ Profile of the research institute to which the applicant has belonged in order to produce the above research achievements.

Ⅴ Graduation Certificate or Completion Certificate issued by the final educational establishment from which the applicant graduated.

Ⅵ Academic transcript issued by the final educational establishment from which the applicant graduated.

(c) Application documents should be sent to:
Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University, 3-39-22 Showa-machi, Maebashi City, Gunma 371-8511, JAPAN
TEL. +81-27-220-7797

(2) A person who intends to apply under the provisions of Qualifications for Application (9) must inquire at the office described in (1)-(c) before applying.

4 Acceptance of Application

(1) Application Period
August 16 (Wed.) to August 23 (Wed.), 2017 (**without fail**)

(2) Submission Procedures of Application documents
Application documents must be submitted by bringing them by the applicant in person or by mail within the application period.

① Submitting the documents in person will be accepted at Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University described in (3) from 9:00 a.m. to 4:00 p.m.

② When mailing the documents, be sure to use **registered mail** and write "Application form for Graduate School of Medicine enclosed" in red on the front of the envelope and send it to Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University described in (3).

Notes:

1. Application documents will not be accepted after the designated the application period. The documents should be sent early taking mailing conditions / mailing period into consideration. When special circumstances need to be taken into consideration, please contact "Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University" described in (3) by August 16 (Wed.), 2017 at 4:00 p.m.
2. If the application documents are sent by ordinary mail, Gunma University will not be responsible for it no matter what happens to the documents.

(3) Submitted address and Reference for Application documents etc.
Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University,
3-39-22 Showa-machi, Maebashi City, Gunma 371-8511, JAPAN
TEL. +81-27-220-7797

(4) Application Documents, etc. (The form is also available through the website of the Graduate School of Medicine and the Faculty of Medicine, Gunma University (http:// www.med.gunma-u.ac.jp/))

Documents		Outline
1	Application Form and Curriculum Vitae [Form-1]	Fill out the form attached to our admission guidelines or obtained from the homepage. The person who has graduated or will graduate from a school in foreign countries must fill in his/her curriculum vitae.
2	Entrance Examination Fee	¥30,000 (Examination Fee: JPY 30,000) Please select one from the following four payment methods. 1. Payment at a bank in Japan (the payment cannot be made at post office). (1) The examination fee transfer form provided must be used and the payment should be made at a teller' s window of your nearest bank. Bank transfer fees are chargeable on the person who pays the fees. [Form 2] (2) Confirm that the "Certificate of Transfer Receipt" is sealed by the bank (financial institution) and paste it on the prescribed place in the "Sheet for Certificate of Transfer Receipt" [Form 3]. (3) The transfer payment receipt should be kept with good care as your own duplicate. (4) Transfer payment period: August 7 (Mon.) to 3:00 p.m. (Japan time) of August 23 (Wed.), 2017. (5) We do not accept the "Certificate of Transfer Receipt" without a seal by financial institution, one with the amended amount of money, or one written with a pencil. Payment by using ATM (Automated Teller Machine), cell phone or personal computer should not be made. 2. Payment at a convenience store (make sure that you have a personal computer or cell phone with you). (1) Refer to the page 54 when you pay at a convenience store. Payment commissions are chargeable on the person who pays the fees. (2) After payment, receive the "Application Fee Statement", detach the "Certificate of Payment" (receipt) portion from it, and paste it on the prescribed place in the "Sheet for Certificate of Transfer Receipt" [Form 3]. (3) Payment period: August 7 (Mon.) to 3:00 p.m. (Japan time) of August 23 (Wed.), 2017. When you make payment via the web site, you have to pay 30 minutes before the end of payment period. 3. Payment by credit card (make sure that you have a personal computer or cell phone connected to a printer with A4 paper with you). (1) Refer to the page 54 when you pay by credit card. Payment commissions are chargeable on the person who pays the fees. (2) After payment, print the "Application Fee Statement", detach the "Certificate of Payment" (receipt) portion from it, and paste it on the prescribed place in the "Sheet for Certificate of Transfer Receipt" [Form 3]. (3) Payment period: August 7 (Mon.) to 3:00 p.m. (Japan time) of August 23 (Wed.), 2017. 4. Remittance from abroad (1) Please make a remittance on a yen basis from a bank teller's window to the Following bank account (a bank transfer fee and an overseas remittance fee will be borne by an applicant in person). (2) Paste the receipt (the copy of it is also valid) you receive from a bank on the prescribed place in the "Sheet for Certificate of Transfer Receipt [Form3]". In addition, if an excess or a deficiency arises in amount of remittance, please note that it cannot be deal with. (3) When you make a remittance, please contact a person in charge of Gunma University as below. At which time, be sure to specify your name, the name of the nation from which you remit, and your planning to apply for our Doctoral Program. 〔E-mail: kk-mgakumu5@jimu.gunma-u.ac.jp〕 ○Bank Account Bank: The Towa Bank, LDT (Bank Code: 0516) Branch: Maebashi Kita Branch (Branch Code: 012) Address: 1-5-2 Kokuryo-cho, Maebashi City, Gunma, 371-0033, JAPAN TEL: +81-27-231-6789 Swift Code: TOWAJPJT Account number: 3169574 (Savings Account) Name of account: Gunma daigaku Address of AC Holder: 4-2 Aramaki-machi, Maebashi City, Gunma, 371-8510, JAPAN TEL: +81-27-220-7062 (4) Transfer Payment period: August 7 (Mon.) to 3:00 p.m. (Japan time) of August 23 (Wed.), 2017. (5) Payment by using ATM (Automated Teller Machine), cell phone or personal computer should not be made. 【Concerning the return of the entrance examination fee (common notes to both remittances)】 ※In principle, the entrance examination fee will not be returned, but it will be returned in the following cases according to the designated procedures. ①When an application is not made after paying the entrance examination fee. ②When the entrance examination fee is paid twice, or more than the amount of fixed money accidentally. ③When application documents are not accepted after submission. We will return the entrance examination fee later.

Documents		Outline
2	Entrance Examination Fee	Declaration of claiming back the Entrance Examination Fee (Doctral Program) 1. The reason why you want to claim back the fee. 2. Name 3. Postal Code. Present Address 4. Phone Number or E-mail Address Address for sending the declaration form: Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University, 3-39-22 Showa-machi, Maebashi City, Gunma 371-8511, JAPAN ※When performing the procedures of the return of the entrance examination fee, the transfer payment receipt will be needed (When performing the procedures abroad, the original transfer payment receipt you receive from a bank will be needed.). Any processing fees will be deducted from the amount to be returned. For inquiries regarding the return of the entrance examination fees, please contact: Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University TEL. +81-27-220-7797 ※If the applicant is receiving the Japanese Government (MEXT) Scholarship at the time of application, the examination fee payment is not required. Please submit the document certifying that you are the recipient of the scholarship. ※ Applicants who suffered from the Great East Japan Earthquake and disaster from storm and flood will be exempted from the total amount of examination fee as special measures. 〈Eligible applicants for exemption from entrance examination fee〉 1. Special measures for the Great East Japan Earthquake (1)The applicants who suffered in the areas where the Disaster Relief Act in the Great East Japan Earthquake has been applied, and who fall under any of the following categories. ①Applicants whose houses, which are owned by payers of school expenses, were completely destroyed, largely half-destroyed, partially destroyed, or washed away. ②Applicants whose payers of school expenses are dead or missing. (2)Applicants whose payers of school expenses are recognized that their domiciles were designated as warning areas, deliberate evacuation areas, areas where it is expected that the residents have difficulties in returning for a long time, areas in which the residents are not permitted to live, and areas to which evacuation orders are ready to be lifted due to the Fukushima Daiichi nuclear disaster. 2. Special measures for the disaster from storm and flood (1)The applicants who suffered in the areas where the Disaster Relief Act in the disaster from storm and flood within one year before the application period has been applied, and who fall under any of the following categories. ①Applicants whose houses, which are owned by payers of school expenses, were completely destroyed, largely half-destroyed, partially destroyed, or washed away. ②Applicants whose payers of school expenses are dead or missing. (2)For further information, please contact the following. Inquiries should be directed to: Admissions Office, Educational Division, Gunma University TEL. +81-27-220-71493
3	Sheet for Certificate of Transfer Receipt or Certificate of Payment [Form-3]	Paste the "Certificate of Transfer Receipt" or "Certificate of Payment" on the space for paste-up in the sheet attached to the Admission Guidelines or obtained from the homepage and submit it.
4	Photograph Card [Form-4] Examination Card [Form-5]	Fill out the form attached to the Admission Guidelines or obtained from the homepage. Furthermore, write your name on the back of the photograph (waist-up, full-face and uncovered head (L4 cm x W3 cm)) taken within three month prior to the application and paste it on the prescribed column in the Photograph Card. In addition, Photograph Card and Examination Card must be submitted without cutting apart.
5	Certificate of Graduation (or expected graduation)	The certificate issued by the presidents of the university and the graduate school from which you graduated. If the applicant have completed or is expected to complete Master's Course, submit the certificate of completion (or expected completion) issued by the Dean of the said graduate school. However, those who have passed the screening of admission requirements by our Graduate School under Qualifications for Application (6)-(c)(d) or (8), and who have graduated from Faculty of Medicine of Gunma University are not required to submit it.
6	Certificate of Bachelor's Degree	Attach the diploma or other certificate of Bachelor' s Degree which is conferred from the university of educational establishment. This item 6 applies to a person who falls under "Qualifications for Application (5)"
7	Academic transcript	The certificate issued by the presidents of the university and the graduate school from which you graduated and sealed tightly. If the applicant have completed or is expected to complete Master's Course, he/she must submit the Academic Transcript issued by the Dean of the said graduate school as well. However, those who have passed the screening of admission requirements by our Graduate School under Qualifications for Application (6)-(c)(d),(7) or (8), and who have graduated from Faculty of Medicine of Gunma University are not required to submit it.
8	Name and Address Card [Form-10]	Fill out the form attached to the Admission Guidelines or obtained from the homepage.
9	Self-addressed envelop (size No. 3)	The self-addressed envelop with the applicant's name, address, and postal code written and a ¥362 (JPY 362) stamp pasted on it must be attached. In addition, an applicant from overseas is not required to submit it.
10	Written approval for taking examination [Form-6]	A working person must submit the written approval for taking examination (form attached to the Admission Guidelines is designated) issued by supervisor or appointer of workplace. [Form 6]

Documents		Outline
11	Certificate confirming 'Qualifications for Application' (A copy of it is acceptable.)	A person who has undergone the screening of admission requirements conducted by our Graduate School about whether he/she falls under Qualifications for Application (6) − (c)(d), (7) or (8) before applying and has also been proved to have qualifications for application must submit it.
12	Application form for Program for Cultivating Global Leaders in Heavy Ion Therapeutics and Engineering [Form-7]	A person who desires to take the course for this program must submit this application. Fill in the form attached to our admission guidelines or obtained from the homepage.
13	Score report in TOEFL, TOEIC Listening & Reading Test (open test) or IELTS (Academic Module)	The foreign applicant in hope of a foreign language (English) examination by TOEFL, the TOEIC Listening & Reading Test (open test) or IELTS (Academic Module), please submit either one score among TOEFL-PBT, TOEFL-iBT, TOEFL-ITP, TOEIC Listening & Reading Test (open test), and IELTS (Academic Module). The score report is limited to the original (which has been issued in less than 2 years). The copy of it is unacceptable. The original will be returned with the examination card.

Notes: 1. Alteration to the contents of the application documents will not be accepted after the acceptance of the application documents.
2. Whatever the reason may be, the application documents accepted will not be returned.
3. When it turns out that matters described in the application documents do not agree with the facts, the success in the examination and the admission may be revoked.
4. When confirming the qualifications for application, an applicant may be requested to submit the documents other than the Application Documents, etc. on the above if our University deems it necessary.
5. When your former name is used in each certificate, an official document (family register, etc.) to be able to prove the relation between your current name and former name must be attached.
6. TOEIC Test (Open Test) is also acceptable.

(5) Sending of Examination Card etc.

Examination Card etc. will be sent to the applicant after paperwork following the acceptance of Application documents. If Examination Card etc. should not be sent by September 5 (Tue.), 2017, apply to Admissions Section, Educational Affairs Office, Administration Division, Showa Campus (TEL. +81-27-220-7797, E-mail : kk-mgakumu5@jimu.gunma-u.ac.jp).

5 Preliminary Consultation for Applicants with Disabilities etc.

Gunma University provides academic support to students with disabilities etc.

When you have a disability and need consideration in examination and your study, prior to an application, please consult with our university beforehand.

(1) When to consult

As due date of consultation is August 1 (Tue.), 2017, please consult as soon as possible.

(2) How to consult

Please submit a consultation document (its format is optional) by attaching required documents including a doctor's certificate.

When necessary, the interview with the persons concerned with the school from which an applicant graduated, or his/her family etc. who can speak for the applicant or his/her position is performed in our university.

(3) Consultation document should be sent to:

Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University,
3-39-22 Showa-machi, Maebashi City, Gunma 371-8511, Japan
TEL. +81-27-220-7797

6 Selection Method

Selection will be made by making a comprehensive judgment on the scholastic ability tests and the academic transcript issued by the president of the university etc. from which you graduated.

※Notes for foreign applicants

① For a person who has the nationality of the country where English is used as major language (or official language), the selection except the above written examination can be done.

② A foreign applicant who submits the score in TOEFL-PBT (Paper Based Test), TOEFL-iBT (internet Based Test), TOEIC Listening & Reading Test (open test) or IELTS (Academic Module) at the time of application can convert the submitted score into the score on the foreign language examination (English) based on the following conversion table for the foreign language examination (English) instead of the written examination. The score in TOEFL-ITP (TOEFL Institutional Testing Program) will also be the subject of evaluation in the same way as the score in TOEFL- PBT.

Furthermore, even the applicant who submits the score in TOEFL, TOEIC Listening & Reading Test (open test) or IELTS (Academic Module) at the time of application can take the foreign language examination

(English) if he/she wishes. In that case, the better results will be used for the judgment.

The score report of TOEFL, TOEIC Listening & Reading Test (open test) or IELTS (Academic Module) which has been issued in less than 2 years shall be valid. The submitted the score report, score card or official score certificate of TOEFL or TOEIC Listening & Reading Test (open test), or test report form of IELTS (Academic Module) shall be the original and a copy of it is unacceptable. The original will be returned with the Examination Card.

③ Example of conversion table for foreign language examination (English)

Example of conversion table for TOEFL and TOEIC Listening & Reading Test (open test) and IELTS (Academic Module)

Conversion of English examination	49	56	60	69	80	89	100
TOEFL-PBT	471	489	499	521	549	571	599
TOEFL-iBT	52	57	61	69	79	89	100
TOEIC Listening & Reading Test (open test)	505	555	585	650	730	790	870

Conversion of English examination	41	60	80	95	100
IELTS (Academic Module)	5.5	6	6.5	7	7.5

※ TOEIC Test (Open Test) is also acceptable.

7 Date and Locations for Examination

Date	Time	Examination Subject	Location
September 10 (Sun.), 2017	10:00-12:00	Foreign Language (English)	Graduate School of Medicine, Gunma University etc.
	13:00-15:00	Desired Major Field (Oral Examination)	

8 The Aim of Each Examination Subject

Foreign language (English) ……The comprehension of English documents and English composition ability will be examined.

Desired Major Field (Oral examination)…… In engaging in his/her studies, basic academic ability necessary for his/her major field and willingness to study will be examined.

9 Exam Instructions

(1) The examination card must be brought with you on taking the entrance examination.

(2) Examinees must enter the prescribed examination room by 9:30 a.m. Late arrivals for the examination will be accepted to take the examination within 30 minutes after the start of the examination, but the test time shall not be extended.

(3) Examinees must take all tests on the examination subjects assigned, or he/she will be disqualified.

(4) When a delay occurs on the public transport on the examination day, please refer to:
Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University (TEL. +81-27-220-7797)

(5) If unexpected incidents (a disaster, an accident, etc.) happen on the day of examination, visit our website (http://www.med.gunma-u.ac.jp/) for your reference. In principle, we will not conduct supplementary examinations.

10 Announcement of Screening Result

Letters of acceptance will be mailed to successful applicants on September 29 (Fri.), 2017. At the same time, successful applicants' numbers will be posted on the website of "the Graduate School of Medicine and the Faculty of

Medicine, Gunma University" on and after 10:00 a.m. to the date for admission procedures. Notice about announcement of selection results will not be posted in Gunma University campus.

Additionally, any inquiries about selection results by telephone will not be accepted.

11 Admission Procedures

Successful applicant is required to read the enclosed “admissions guide” with “the letter of acceptance” carefully and must complete (1) the preparations for the admission procedures, and (3) during the period of the admission procedures, “mail” or “bring” them to (4) the place for the admission procedures.

(1) Fees and documents for admission procedures

① Admission fee: ¥282,000 (JPY 282,000)

Notes: (a) Any revisions to admission fee on admission during enrollment shall be applied.

(b) Methods for payment of the admission fee will be informed separately.

(c) Admission fee paid shall not be returned under any circumstances.

② Examination Card

③ Any additional documents instructed in the admissions guide.

(2) Fees for after entrance.

Tuition fee: (first-semester) ¥267,900 (JPY 267,900) (Annual tuition fee : ¥535,800 (JPY 535,800))

Notes: (a) Any revisions to tuition fees during enrollment shall be applied.

(b) Methods for payment of the tuition fee will be informed separately.

(c) Tuition fee including the tuition fee second-semester can be paid at the time of paying the tuition fee for first-semester according to the successful applicant’s wishes.

(d) If a person who completes the admission procedures declines the admission by March 31 (Sat.), 2018, the amount equivalent to the tuition fee paid shall be returned based on his/her request by following the prescribed procedures.

(3) Period of Admission Procedures

○By mail: The necessary documents must be reached to the university no later than October 20 (Fri.), 2017.

○In person: The necessary documents must be brought no later than October 20 (Fri.), 2017. (until 5:00p.m.)

Note: Whether it is “By mail” or “In person”, he/she will be regarded as a person who declines the admission if the admission procedures have not been completed by the above deadline.

(4) Places for the admission procedures

○By mail: Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University, 3-39-22 Showa-machi, Maebashi City, Gunma 371-8511, JAPAN

○In person: Educational Affairs Office, Administration Division, Showa Campus of Gunma University (The third floor of Common Building)

12 Exemption and Postponement of Admission Fee and Tuition Fee

There is a system that the admission fee or the tuition fee can be exempted in full or by half for a person who is admitted that it is very difficult to pay the tuition owing to special circumstances.

Also, the collection of admission fee or tuition fee can be postponed for a certain period for a person who is admitted that it is very difficult to pay the admission fee or the tuition fee by the specified deadline.

Inquiries should be directed to:

Education and Student Support Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University TEL. +81-27-220-7796

Gunma University has a system of exemption from admission fee or tuition fee for those recognized as having difficulty in paying due to suffering from the Great East Japan Earthquake.

Inquiries should be directed to:

Student Life Section, Student Support Office, Educational Division, Aramaki Campus of Gunma University TEL. +81-27-220-7136

13 Scholarship

There is the scholastic loan and benefit system for learning support provided by Japan Student Services Organization (JASSO) for a person who has difficulty in paying the tuition fee, and who has his/her great academic performance as well as a fine personality.

Also, graduate scholarship system of Japan Student Services Organization includes Post-entry Applications (system to apply for scholarship after enrollment) and Prior Applications (system to make a reservation for applying

for scholarship before enrollment). Those who wish for Prior Applications can apply before announcement of selection results, but should make an inquiry below by the end of September allowing for recruitment period.

Inquiries should be directed to:

Education and Student Support Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University　TEL. +81-27-220-7792

14　Disclosure of Admission Information

Admission Information will be disclosed in the following way:

(1)　Disclosed on the website of Graduate School of Medicine/School of Medicine, Faculty of Medicine on and after May 1 (Tue.), 2018. (http://www.med.gunma-u.ac.jp/)

The above information contains number of applicants, number of examinees, number of successful applicants, number of newly enrolled students, the proportion of men to women in the newly enrolled students etc., the highest totaled scores that one of the successful applicants got, the average score of the totaled scores that the successful applicants got.

Furthermore, the highest totaled scores that one of the successful applicants got and the average score of the totaled scores that the successful applicants got will not be provided if the personal information about the applicant is likely to be specified.

(2)　Disclosed by the examinee's request in written form.

The said examinee's totaled scores on the entrance examination will be disclosed in written form.

○Period for acceptance of disclosure request

From May 1 (Tue.) to May 31 (Thu.), 2018

15　Protection of the Personal Information about the Applicants for Admission etc.

Gunma University will acquire the personal information about the applicants etc. through the application documents submitted and the personal information about the examinees by carrying out the entrance examination, but the personal information described above will be used only for the following operations based on "Act on the Protection of Personal Informaition Held by Indipendent Administrative Agencies in Gunma University".

(1)　For the operations (including subordinate operation, such as statistical treatment) concerning the selection of newly enrolled students.

(2)　For the operations concerning the student advising, the student support, and the tuition fee collection after enrollment as the data on the newly enrolled student in the case of a person who has completed the admission procedures.

In addition, our university may be mentioned like above operations to an external company after concluding the contract concerning the appropriate handling of personal information.

Admission Guidelines for working members of society

1 Aim

With the rapid development of medical science and medical treatment, the development of human resources with the special ability, knowledge, and technique of more advanced medical science and medical treatment is socially requested.

Our Graduate School introduces the Day/Evening lecture course system based on the special divisions on education methods by Article 14 of the Standards Act for Establishment of Graduate School and conducts the selection for a working member who is active in the field connected with medical science and medical treatment in local society in order to give him/her an opportunity to learn the ability, knowledge, and technique of advanced medical science and medical treatment.

2 Number of Students to be Admitted

The number of the students to be admitted for the selection for working members of society is included in the number of students to be admitted described in the Admission Guidelines for general selection.

Note: When applying, inquire of the supervisor of the desired major field (see page 55) about research and guidance, etc.

3 Qualifications for Application

A person who can apply for admission shall fall under any of the following, and who has been working for a hospital, a clinic, a research institute, an educational institution, or a health center etc. on applying. Furthermore, after entering our graduate school, he/she shall retain his/her status with the excellent work performance and be approved to take entrance examination and attend school by the supervisor or appointer of the workplace.

(1) A person who has graduated from a university (which has a course in medical science or dental science, or a 6-year course in pharmaceutical science or veterinary science).

(2) A person who completed an 18-year course (its final course has to be the course in medical science, dental science, pharmaceutical science, or veterinary science) of school education in a foreign country.

(3) A person who completed an 18-year course (its final course has to be the course in medical science, dental science, pharmaceutical science, or veterinary science) in a foreign country's school education by taking class subjects in Japan through correspondence courses run by the said foreign educational establishments.

(4) A person who completed a foreign country's university course at an educational institution in Japan (limited to the person who has completed an 18-year course of school education (including the doctoral course to study medical science, dental science, pharmaceutical science, or veterinary science) in the said foreign country's school education) which is designated in the said foreign country's education system as having a foreign university's curriculum and specifically designated by the Minister of Education, Culture, Sports, Science and Technology, Japan.

(5) A person who has completed five or more years of study (the course in medical science, dental science, pharmaceutical science, or veterinary science)at a foreign university, or foreign educational establishment (including a person who, while residing in Japan, has completed the program of education provided by a foreign university or foreign educational establishment through correspondence or distance education courses) and who received a degree certificate by March 2018 that is recognized by the Japanese Ministry of Education, Culture, Sports, Science and Technology.

(6) A person designated by the Minister of Education, Culture, Sports, Science and Technology, Japan. (Notification No. 39 of the Ministry of Education, 1955)

(Note) The designated person above refers to a person who falls under any of the following provisions:

(a) A person who completed medical science or dental science at the faculty of medicine or dentistry of a university under the old University Ordinance (Imperial Ordinance No. 388 of 1918), and who graduated from these faculties.

(b) A person who graduated from National Defense Medical College under the Act for Establishment of the Ministry of Defense (Act No. 164 of 1954)

(c) A person who completed a master's course, a person who can be awarded a master's degree, or a person who had been enrolled in the doctoral course without dividing the course between 2 years' first semester and 3 years' second semester for 2 years or longer acquiring 30 credits or more under the necessary research guidance (including a person who falls under Article 6-1 of the Degree regulations (Ordinance of the Ministry of Education, Science, Culture No. 9 of 1953) prior to version by Ministerial Ordinance (Ordinance of the Ministry of Education, Science, Culture No. 29 of 1974) that revises part of the Degree regulations), in addition to the above-described premises, a person who has been recognized by our Graduate School as having academic ability equivalent or superior to a university graduate who has completed the course to study medical science, dental science, pharmaceutical science, or veterinary science.

(d) A person who graduated from a university (excluding the course to study medical science or dental science, or a 6-year course in pharmaceutical science or veterinary science), or a person who has been engaged in research for 2 years or longer at university or institute, etc. after having completed 16 years of a school education in a foreign country (including a person who will engage in research for 2 years or longer by March 31, 2018), in addition to the above-described premises, a person who has been recognized by our Graduate

School as having academic ability equivalent or superior to a university graduate who has completed the course in medical science, dental science, pharmaceutical science, or veterinary science based on the said research's results etc.

(7) A person who has been recognized by our Graduate School as having academic abilities equivalent or superior to a person who has graduated a university (which has a course in medical science or dental science, or a 6-year course in pharmaceutical science or veterinary science) based on the results of individual examination of the applicant's qualifications, and who will be 24 years of age by March 31, 2018.

4 Screening etc. of "Qualifications for Application" (only for the people concerned)

(1) A person who intends to apply under the provisions of Qualifications for Application (6) - (c)(d) or (7) must undergo the screening of requirements for admission of our Graduate School before applying under the following conditions, and after that the only person who is proved that he/she has Qualifications for Application can apply.

Furthermore, the result of the qualification screening will be notified to each applicant by August 15 (Tue.), 2017.

(a) Application period
August 1 (Tue.), 2017

(b) Application documents

① In the case of the screening concerning Qualifications for Application (6)-(c)(d):

Ⅰ Application for the screening of admission requirements (The form attached to our admission guidelines must be used. [Form-8])

Ⅱ Certificate of Research Activities (The form attached to our admission guidelines must be used. [Form-9])

Ⅲ Research achievements in medicine and medical treatment (Papers etc.)

Ⅳ Profile of the research institute to which the applicant has belonged to in order to produce the above research achievements.

Ⅴ Letter of recommendation prepared by the supervisor of the research area of your choice (form : free)

Ⅵ Graduation Certificate or Completion Certificate issued by the final educational establishment from which the applicant graduated.

Ⅶ Academic transcript issued by the final educational establishment from which the applicant graduated.

② In the case of the screening concerning Qualifications for Application (7):

Ⅰ Application for the screening of admission requirements (The form attached to our admission guidelines must be used.[Form-8])

Ⅱ Certificate of Research Activities (The form attached to our admission guidelines must be used. [Form-9])

Ⅲ Research achievements equivalent to master's thesis (Papers etc.)

Ⅳ Profile of the research institute to which the applicant has belonged in order to produce the above research achievements.

Ⅴ Graduation Certificate or Completion Certificate issued by the final educational establishment from which the applicant graduated.

Ⅵ Academic transcript issued by the final educational establishment from which the applicant graduated.

(c) Application documents should be sent to:
Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University, 3-39-22 Showa-machi, Maebashi City, Gunma 371-8511, JAPAN
TEL. +81-27-220-7797

5 Acceptance of Application

(1) Application Period
August 16 (Wed.) to August 23 (Wed.), 2017 **(without fail)**

(2) Submission Procedures of Application documents
Application documents must be submitted by bringing them by the applicant in person or by mail within the application period.

① Submitting the documents in person will be accepted at Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University described in (3) from 9:00 a.m. to 4:00 p.m.

② When mailing the documents, be sure to use **registered mail** and write "Application form for Graduate School of Medicine enclosed" in red on the front of the envelope and send it to Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University described in (3).

Notes:

1. Application documents will not be accepted after the designated the application period. The documents should be sent early taking mailing conditions / mailing period into consideration. When special circumstances need to be taken into consideration, please contact "Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University" described in (3) by August 16 (Wed.), 2017 at 4:00 p.m.
2. If the application documents are sent by ordinary mail, Gunma University will not be responsible for it no matter what happens to the documents.

(3) Submitted address and Reference for Application documents etc.
Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University,
3-39-22 Showa-machi, Maebashi City, Gunma 371-8511, JAPAN
TEL. +81-27-220-7797

(4) Application Documents, etc. (The form is also available through the website of the Graduate school of Medicine and the Faculty of Medicine, Gunma University (http:// www.med.gunma-u.ac.jp/))

Documents		Outline
1	Application Form and Curriculum Vitae [Form-11]	Fill out the form attached to our admission guidelines or obtained from the homepage. The person who has graduated or will graduate from a school in foreign countries must fill in his/her curriculum vitae.
2	Entrance Examination Fee	¥30,000 (Examination Fee : JPY 30,000) Please select one from the following four payment methods. 1. Payment at a bank in Japan (the payment cannot be made at post office). (1) The examination fee transfer form provided must be used and the payment should be made at a teller's window of your nearest bank. Bank transfer fees are chargeable on the person who pays the fees. [Form 2] (2) Confirm that the "Certificate of Transfer Receipt" is sealed by the bank (financial institution) and paste it on the prescribed place in the "Sheet for Certificate of Transfer Receipt" [Form 3]. (3) The transfer payment receipt should be kept with good care as your own duplicate. (4) Transfer payment period: August 7 (Mon.) to 3:00 p.m. (Japan time) of August 23 (Wed.), 2017. (5) We do not accept the "Certificate of Transfer Receipt" without a seal by financial institution, one with the amended amount of money, or one written with a pencil. Payment by using ATM (Automated Teller Machine), cell phone or personal computer should not be made. 2. Payment at a convenience store (make sure that you have a personal computer or cell phone with you). (1) Refer to the page 54 when you pay at a convenience store. Payment commissions are chargeable on the person who pays the fees. (2) After payment, receive the "Application Fee Statement", detach the "Certificate of Payment" (receipt) portion from it, and paste it on the prescribed place in the "Sheet for Certificate of Transfer Receipt" [Form 3]. (3) Payment period: August 7 (Mon.) to 3:00 p.m. (Japan time) of August 23 (Wed.), 2017. When you make payment via the web site, you have to pay 30 minutes before the end of payment period. 3. Payment by credit card (make sure that you have a personal computer or cell phone connected to a printer with A4 paper with you). (1) Refer to the page 54 when you pay by credit card. Payment commissions are chargeable on the person who pays the fees. (2) After payment, print the "Application Fee Statement", detach the "Certificate of Payment" (receipt) portion from it, and paste it on the prescribed place in the "Sheet for Certificate of Transfer Receipt" [Form 3]. (3) Payment period: August 7 (Mon.) to 3:00 p.m. (Japan time) of August 23 (Wed.), 2017. 4. Remittance from abroad (1) Please make a remittance on a yen basis from a bank teller's window to the Following bank account (a bank transfer fee and an overseas remittance fee will be borne by an applicant in person). (2) Paste the receipt (the copy of it is also valid) you receive from a bank on the prescribed place in the "Sheet for Certificate of Transfer Receipt [Form 3]". In addition, if an excess or a deficiency arises in amount of remittance, please note that it cannot be deal with. (3) When you make a remittance, please contact a person in charge of Gunma University as below. At which time, be sure to specify your name, the name of the nation from which you remit, and your planning to apply for our Doctoral Program. 〔E-mail: kk-mgakumu5@jimu.gunma-u.ac.jp〕 ○Bank Account Bank: The Towa Bank, LDT (Bank Code: 0516) Branch: Maebashi Kita Branch (Branch Code: 012) Address: 1-5-2 Kokuryo-cho, Maebashi City, Gunma, 371-0033, JAPAN TEL: +81-27-231-6789 Swift Code: TOWAJPJT Account number: 3169574 (Savings Account) Name of account: Gunma daigaku Address of AC Holder: 4-2 Aramaki-machi, Maebashi City, Gunma, 371-8510, JAPAN TEL: +81-27-220-7062 (4) Transfer Payment period: August 7 (Mon.) to 3:00 p.m. (Japan time) of August 23 (Wed.), 2017. (5) Payment by using ATM (Automated Teller Machine), cell phone or personal computer should not be made. 【Concerning the return of the entrance examination fee (common notes to both remittances)】 ※In principle, the entrance examination fee will not be returned, but it will be returned in the following cases according to the designated procedures. ①When an application is not made after paying the entrance examination fee. ②When the entrance examination fee is paid twice, or more than the amount of fixed money accidentally. ③When application documents are not accepted after submission.

Documents		Outline
2	Entrance Examination Fee	We will return the entrance examination fee later. Declaration of claiming back the Entrance Examination Fee (Doctral Program) 1. The reason why you want to claim back the fee. 2. Name 3. Postal Code. Present Address 4. Phone Number or E-mail Address Address for sending the declaration form: Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University, 3-39-22 Showa-machi, Maebashi City, Gunma 371-8511, JAPAN ※When performing the procedures of the return of the entrance examination fee, the transfer payment receipt will be needed (When performing the procedures abroad, the original transfer payment receipt you receive from a bank will be needed.). Any processing fees will be deducted from the amount to be returned. For inquiries regarding the return of the entrance examination fees, please contact: Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University TEL. +81-27-220-7797 ※If the applicant is receiving the Japanese Government (MEXT) Scholarship at the time of application, the examination fee payment is not required. Please submit the document certifying that you are the recipient of the scholarship. ※ Applicants who suffered from the Great East Japan Earthquake and disaster from storm and flood will be exempted from the total amount of examination fee as special measures. 〈Eligible applicants for exemption from entrance examination fee〉 1. Special measures for the Great East Japan Earthquake (1)The applicants who suffered in the areas where the Disaster Relief Act in the Great East Japan Earthquake has been applied, and who fall under any of the following categories. ①Applicants whose houses, which are owned by payers of school expenses, were completely destroyed, largely half-destroyed, partially destroyed, or washed away. ②Applicants whose payers of school expenses are dead or missing. (2)Applicants whose payers of school expenses are recognized that their domiciles were designated as warning areas, deliberate evacuation areas, areas where it is expected that the residents have difficulties in returning for a long time, areas in which the residents are not permitted to live, and areas to which evacuation orders are ready to be lifted due to the Fukushima Daiichi nuclear disaster. 2. Special measures for the disaster from storm and flood (1)The applicants who suffered in the areas where the Disaster Relief Act in the disaster from storm and flood within one year before the application period has been applied, and who fall under any of the following categories. ①Applicants whose houses, which are owned by payers of school expenses, were completely destroyed, largely half-destroyed, partially destroyed, or washed away. ②Applicants whose payers of school expenses are dead or missing. (2)For further information, please contact the following. Inquiries should be directed to: Admissions Office, Educational Division, Gunma University TEL. +81-27-220-7149
3	Sheet for Certificate of Transfer Receipt or Certificate of Payment [Form-3]	Paste the "Certificate of Transfer Receipt" or "Certificate of Payment" on the space for paste-up in the sheet attached to the Admission Guidelines or obtained from the homepage and submit it.
4	Photograph Card [Form-12] Examination Card [Form-13]	Fill out the form attached to the Admission Guidelines or obtained from the homepage. Furthermore, write your name on the back of the photograph (waist-up, full-face and uncovered head (L4 cm x W3 cm)) taken within three month prior to the application and paste it on the prescribed column in the Photograph Card. In addition, Photograph Card and Examination Card must be submitted without cutting apart.
5	Certificate of Graduation	The certificate issued by the presidents of the university and the graduate school from which you graduated. If the applicant have completed or is expected to complete Master's Course, submit the certificate of completion issued by the Dean of the said graduate school. However, those who have passed the screening of admission requirements by our Graduate School under Qualifications for Application (6)-(c)(d) or (7), and who have graduated from Faculty of Medicine of Gunma University are not required to submit it.
6	Certificate of Bachelor's Degree	Attach the diploma or other certificate of Bachelor' s Degree which is conferred from the university of educational establishment. This item 6 applies to a person who falls under "Qualifications for Application (5)"
7	Academic transcript	The certificate issued by the presidents of the university and the graduate school from which you graduated and sealed tightly. If the applicant have completed or is expected to complete Master's Course, he/she must submit the Academic Transcript issued by the Dean of the said graduate school as well. However, those who have passed the screening of admission requirements by our Graduate School under Qualifications for Application (6)-(c)(d) or (7), and who have graduated from Faculty of Medicine of Gunma University are not required to submit it.
8	Name and Address Card [Form-10]	Fill out the form attached to the Admission Guidelines or obtained from the homepage.
9	Self-addressed envelop (size No. 3)	The self-addressed envelop with the applicant's name, address, and postal code written and a ¥362 (JPY 362) stamp pasted on it must be attached. In addition, an applicant from overseas is not required to submit it.
10	Written approval for taking examination and school attendance[Form-14]	The written approval for taking examination and school attendance (the form attached to our admission guidelines must be used) issued by the supervisor or appointer of your workplace must be submitted. [Form 14]

Documents		Outline
11	Certificate confirming 'Qualifications for Application' (A copy of it is acceptable.)	A person who has undergone the screening of admission requirements conducted by our Graduate School about whether he/she falls under Qualifications for Application (6) – (c)(d) or (7) before applying and has also been proved to have qualifications for application must submit it.
12	Application form for Program for Cultivating Global Leaders in Heavy Ion Therapeutics and Engineering [Form-7]	A person who desires to take the course for this program must submit this application. Fill in the form attached to our admission guidelines or obtained from the homepage.

Notes: 1. Alteration to the contents of the application documents will not be accepted after the acceptance of the application documents.
2. Whatever the reason may be, the application documents accepted will not be returned.
3. When it turns out that matters described in the application documents do not agree with the facts, the success in the examination and the admission may be revoked.
4. When confirming the qualifications for application, an applicant may be requested to submit the documents other than the Application Documents, etc. on the above if our University deems it necessary.
5. Application documents for selection for working members of society are colored pink, and please be careful not to confuse them with others. (An applicant who has obtained the form through the homepage must write "Application documents for selection for working members of society enclosed" on the front of the envelope for sending application documents).
6. When your former name is used in each certificate, an official document (family register, etc.) to be able to prove the relation between your current name and former name must be attached.

(5) Sending of Examination Card etc.

Examination Card etc. will be sent to the applicant after paperwork following the acceptance of Application documents. If Examination Card etc. should not be sent by September 5 (Tue.), 2017, apply to Admissions Section, Educational Affairs Office, Administration Division, Showa Campus (TEL. +81-27-220-7797, E-mail : kk-mgakumu5@jimu.gunma-u.ac.jp).

6 Preliminary Consultation for Applicants with Disabilities etc.

Gunma University provides academic support to students with disabilities etc.

When you have a disability and need consideration in examination and your study, prior to an application, please consult with our university beforehand.

(1) When to consult

As due date of consultation is August 1 (Tue.), 2017, please consult as soon as possible.

(2) How to consult

Please submit a consultation document (its format is optional) by attaching required documents including a doctor's certificate.

When necessary, the interview with the persons concerned with the school from which an applicant graduated, or his/her family etc. who can speak for the applicant or his/her position is performed in our university.

(3) Consultation document should be sent to:

Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University,
3-39-22 Showa-machi, Maebashi City, Gunma 371-8511, Japan
TEL. +81-27-220-7797

7 Selection Method

Selection will be made by making a comprehensive judgment on the scholastic ability tests and the academic transcript issued by the president of the university etc. from which you graduated.

8 Date and Locations for Examination

Date	Time	Examination Subject	Location
September 10 (Sun.), 2017	10:00–12:00	Foreign Language (English)	Graduate School of Medicine, Gunma University etc.
	13:00–15:00	Desired Major Field (Oral Examination)	

9 The Aim of Each Examination Subject

Foreign language (English) ……The comprehension of English documents and English composition ability will be examined.

Desired major field (Oral examination)…… In engaging in his/her studies, basic academic ability necessary for his/her major field and the willingness to study will be examined.

10 Exam Instructions

(1) The examination card must be brought with you on taking the entrance examination.

(2) Examinees must enter the prescribed examination room by 9:30 a.m. Late arrivals for the examination will be accepted to take the examination within 30 minutes after the start of the examination, but the test time shall not be extended.

(3) Examinees must take all tests on the examination subjects assigned, or he/she will be disqualified.

(4) When a delay occurs on the public transport on the examination day, please refer to:
Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University (TEL. +81-27-220-7797)

(5) If unexpected incidents (a disaster, an accident, etc.) happen on the day of examination, visit our website (http://www.med.gunma-u.ac.jp/) for your reference. In principle, we will not conduct supplementary examinations.

11 Announcement of Screening Result

Letters of acceptance will be mailed to successful applicants on September 29 (Fri.), 2017. At the same time, successful applicants' numbers will be posted on the website of "the Graduate School of Medicine and the Faculty of Medicine, Gunma University" on and after 10:00 a.m. to the date for admission procedures. Notice about announcement of selection results will not be posted in Gunma University campus.

Additionally, any inquiries about selection results by telephone will not be accepted.

12 Admission Procedures

Successful applicant is required to read the enclosed "admissions guide" with "the letter of acceptance" carefully and must complete (1) the preparations for the admission procedures, and (3) during the period of the admission procedures, "mail" or "bring" them to (4) the place for the admission procedures.

(1) Fees and documents for admission procedures

① Admission fee: ¥282,000 (JPY 282,000)

Notes: (a) Any revisions to admission fee on admission during enrollment shall be applied.
(b) Methods for payment of the admission fee will be informed separately.
(c) Admission fee paid shall not be returned under any circumstances.

② Examination Card

③ Any additional documents instructed in the admissions guide.

(2) Fees for after entrance.

Tuition fee: (first-semester) ¥267,900 (JPY 267,900) (Annual tuition fee : ¥535,800 (JPY 535,800))

Notes: (a) Any revisions to tuition fees during enrollment shall be applied.
(b) Methods for payment of the tuition fee will be informed separately.
(c) Tuition fee including the tuition fee second-semester can be paid at the time of paying the tuition fee for first-semester according to the successful applicant's wishes.
(d) If a person who completes the admission procedures declines the admission by March 31 (Sat.), 2018, the amount equivalent to the tuition fee paid shall be returned based on his/her request by following the prescribed procedures.

(3) Period of Admission Procedures

○By mail: The necessary documents must be reached to the university no later than October 20 (Fri.), 2017.

○In person: The necessary documents must be brought no later than October 20 (Fri.), 2017 (until 5:00p.m.).

Note: Whether it is "By mail" or "In person", he/she will be regarded as a person who declines the admission if

the admission procedures have not been completed by the above deadline.

(4) Places for the admission procedures

○By mail: Admissions Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University, 3-39-22 Showa-machi, Maebashi City, Gunma 371-8511, JAPAN

○In person: Educational Affairs Office, Administration Division, Showa Campus of Gunma University (The third floor of Common Building)

13 Exemption and Postponement of Admission Fee and Tuition Fee

There is a system that the admission fee or the tuition fee can be exempted in full or by half for a person who is admitted that it is very difficult to pay the tuition owing to special circumstances.

Also, the collection of admission fee or tuition fee can be postponed for a certain period for a person who is admitted that it is very difficult to pay the admission fee or the tuition fee by the specified deadline.

Inquiries should be directed to:

Education and Student Support Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University TEL. +81-27-220-7796

Gunma University has a system of exemption from admission fee or tuition fee for those recognized as having difficulty in paying due to suffering from the Great East Japan Earthquake.

Inquiries should be directed to:

Student Life Section, Student Support Office, Educational Division, Aramaki Campus of Gunma University TEL. +81-27-220-7136

14 Scholarship

There is a scholastic loan and benefit system for learning support provided by Japan Student Services Organization (JASSO) for a person who has difficulty in paying the tuition fee, and who has his/her great academic performance as well as a fine personality.

Also, graduate scholarship system of Japan Student Services Organization includes Post-entry Applications (system to apply for scholarship after enrollment) and Prior Applications (system to make a reservation for applying for scholarship before enrollment). Those who wish for Prior Applications can apply before announcement of selection results, but should make an inquiry below by the end of September allowing for recruitment period.

Inquiries should be directed to:

Education and Student Support Section, Educational Affairs Office, Administration Division, Showa Campus of Gunma University TEL. +81-27-220-7792

15 Special Provisions for Education Methods

The education based on the Day/Evening lecture course system will be implemented for a student who enters our Graduate School by passing the entrance examination designed for working people.

The education based on the Day/Evening lecture course system will be implemented in the evening (5:30 p.m.-8:35 p.m.), on Saturdays, on Sundays, on national holidays and during the period of absence from work, for example in summer. However, 5 credits or more in the major class subjects shall be acquired from the class subjects in the Day lecture course.

16 Disclosure of Admission Information

Admission Information will be disclosed in the following way:

(1) Disclosed on the website of Graduate School of Medicine / School of Medicine, Faculty of Medicine on and after May 1 (Tue.), 2018. (http://www.med.gunma-u.ac.jp/)

The above information contains number of applicants, number of examinees, number of successful applicants, number of newly enrolled students, the proportion of men to women in the newly enrolled students etc., the highest totaled scores that one of the successful applicants got, the average score of the totaled scores that the successful applicants got.

Furthermore, the highest totaled scores that one of the successful applicants got and the average score of the

totaled scores that the successful applicants got will not be provided if the personal information about the applicant is likely to be specified.

(2) Disclosed by the examinee's request in written form.

The said examinee's totaled scores on the entrance examination will be disclosed in written form.

○Period for acceptance of disclosure request

From May 1 (Tue.) to May 31 (Thu.), 2018

17 Protection of the Personal Information about the Applicants for Admission etc.

Gunma University will acquire the personal information about the applicants etc. through the application documents submitted and the personal information about the examinees by carrying out the entrance examination, but the personal information described above will be used only for the following operations based on "Act on the Protection of Personal Informaition Held by Indipendent Administrative Agencies in Gunma University".

(1) For the operations (including subordinate operation, such as statistical treatment) concerning the selection of newly enrolled students.

(2) For the operations concerning the student advising, the student support, and the tuition fee collection after enrollment as the data on the newly enrolled student in the case of a person who has completed the admission procedures.

In addition, our university may be mentioned like above operations to an external company after concluding the contract concerning the appropriate handling of personal information.