東北大学
未来型医療創造
卓越大学院プログラム

THE KICK-OFF SYMPOSIUM OF ADVANCED GRADUATE PROGRAM FOR

FUTURE MEDICINE & HEALTH CARE

MARCH 5TH (TUE) - 7TH (THU), 2019

SEIRYO AUDITORIUM, TOHOKU UNIVERSITY, SENDAI JAPAN

TOHOKU FORUM for CREATIVITY

This symposium is also a pre-event of the
Tohoku Forum for Creativity Thematic Program 2019
"Cancer - from Biology to Acceptance"

www.fmhc.tohoku.ac.jp

Contents

Greeting from Program Coordinator, Keiko Nakayama

I am delighted to announce that the Kick-off Symposium of the Advanced Graduate Program for Future Medicine and Health Care will be held during the three days from Tuesday, March 5 through Thursday, March 7, 2019.

This April, we will start our program, the Advanced Graduate Program for Future Medicine and Health Care. At this symposium, we would like to share the latest discoveries in biological sciences, and discuss necessary undertakings for medicine of the future.

We have set the definition of the term “Future Medicine” as medicine supported by Data Science, Technology and Society (DTS) in our program. We are expecting to meet and cultivate talented people who have strong determination to study Future Medicine.

Our program is characterized by the following two points: students with diverse backgrounds will gather in the classroom or during fieldwork and strive to develop their abilities by learning from others; and students will learn beyond the classroom at the cutting-edge of the medical front or at local clinics located at super-aging areas. Students will realize a future society, identify problems, and seek solutions to them. These processes are facilitated by brainstorming among faculty members and students pursuing work in various fields.

At this symposium, Professor Yoshiaki Ito, an alumnus of our university, will give us a plenary lecture. I have great regard for him because he has maintained a fresh interest in oncogenesis, and has been at the front line of cancer research. I am sure that we will be greatly impressed by his enthusiastic talk and encouraged by his many years of effort in pursuit of science.

At the special session, we would like to discuss how to train young scientists and develop new technologies simultaneously. Business-academia collaboration is expected to make increasingly important contributions to a less-disruptive transition from scientific knowledge at the laboratory to manufactured products. We would like to ponder how we, academia scientists, can address this issue.

I hope that every participant will learn a great deal, enjoy discussion, and deepen scientific exchange. Furthermore, I appreciate your support of this program and hope to develop future medicine together with all of you.

Time Table

March 5 (Tue) – The 1st Day (Venue: Seiryo Auditorium)

9:00 Registration

9:30–10:00
Opening Session
9:30– 9:40 **Opening Remarks**
Keiko Nakayama, Program Coordinator, Tohoku Univ.
9:40–10:00 **Opening Address**
Hiroo Yugami, Associate Executive Vice President, Tohoku Univ.
(photograph)

10:00–12:00
Special Session (Chair: Nobuhiro Takahashi)
Advanced Graduate Program in Future Medicine
・Christopher Peck (Univ. of Sydney)
・Jianmin Han (Peking Univ.)
・Wataru Uchida (Tohoku Univ.)

12:00–13:00 (lunch break)

13:00–13:50
Plenary Lecture (Chair: Hozumi Motohashi)
Yoshiaki Ito (National Univ. of Singapore)

13:50–14:00 (coffee break)

14:00–15:35
Scientific Session 1 – Inflammation and Immune Response
(Chair: Akihiko Muto)
14:00–14:30 SS1.1 Junken Aoki (Tohoku Univ.)
14:30–15:05 SS1.2 Johan Garaude (INSERM U1211)
15:05–15:35 SS1.3 Takehiko Yokomizo (Juntendo Univ.)

15:35–15:50 (coffee break)

15:50–17:30
Scientific Session 2 – Redox Biology 1
(Chair: Norio Suzuki)
15:50–16:25 SS2.1 James R. Mitchell (Harvard School of Public Health)
16:25–16:55 SS2.2 Takaaki Akaike (Tohoku Univ.)
16:55–17:30 SS2.3 Yvonne Janssen-Heininger (Univ. of Vermont)

17:40–19:30
Poster Presentation and Discussion
Poster view (17:40–18:20)
Entrance Hall, Seiryo Auditorium (free talk)

March 6 (Wed) – The 2nd Day (Venue: Seiryo Auditorium)

8:30 Registration

9:00–10:30
Scientific Session 3 – Redox Biology 2
(Chair: Atsushi Matsuzawa)
9:00– 9:30 SS3.1 Masayuki Yamamoto (Tohoku Univ.)
9:30–10:00 SS3.2 Hiroaki Miki (Osaka Univ.)
10:00–10:30 SS3.3 Yoshiaki Kubota (Keio Univ.)

10:30–10:40 (coffee break)

10:40–12:20
Scientific Session 4 – Neuroscience
(Chair: Hiromu Tanimoto)
10:40–11:15 SS4.1 Luca Peruzzotti-Jametti (Univ. of Cambridge)
11:15–11:45 SS4.2 Ken-Ichiro Tsutsui (Tohoku Univ.)
11:45–12:20 SS4.3 Martin A. Giese (Univ. of Tuebingen)

12:20–13:00 (lunch break)

13:00–17:40
Young Scientists Oral Sessions
13:00–14:30 **Session 1 – Oncology & Chromosome**
14:30–14:40 (coffee break)
14:40–16:15 **Session 2 – Neuroscience & Pharmacology**
16:15–16:25 (coffee break)
16:25–17:40 **Session 3 – Stem Cell & Differentiation**

17:45–19:15
Workshop on Global Career Development in Future Medicine
・Panel discussion with NIH, NUS, JNCASR and Tohoku University young scientists
・Global career opportunities & future medicine

March 7 (Thu) – The 3rd Day (Venue: Seiryo Auditorium)

8:30 Registration

9:00–10:40
Scientific Session 5 – Epigenetic Regulation
(Chair: Yasuhisa Matsui)

9:00– 9:35 SS5.1 Tapas Kumar Kundu (JNCASR)
9:35–10:05 SS5.2 Kazuhiko Igarashi (Tohoku Univ.)
10:05–10:40 SS5.3 Reshma Taneja (National Univ. of Singapore)

10:40–10:55 (coffee break)

10:55–12:30
Scientific Session 6 – Carcinogenesis
(Chair: Natsuko Chiba)

10:55–11:25 SS6.1 Susumu Kobayashi (National Cancer Center)
11:25–11:55 SS6.2 Hiroyuki Inuzuka (Tohoku Univ.)
11:55–12:30 SS6.3 Wenyi Wei (Harvard Medical School)

12:30–12:40 Closing Remarks
Kazuhiko Igarashi, Dean, Graduate School of Medicine, Tohoku Univ.

12:40–13:30 (lunch break)

13:30–14:30
Tour of Tohoku Medical Megabank Organization (ToMMo) in Tohoku University

Program

Program

Day 1 March 5 (Tue), 2019

Registration (9:00 –)

Opening Session (9:30 – 10:00)

Opening remarks

Keiko Nakayama

Program Coordinator, Advanced Graduate Program for Future Medicine and Health, Tohoku University

Opening Address

Hiroo Yugami

Associate Executive Vice President for Graduate School Reform, Tohoku University

(Photograph)

Special Session – Advanced Graduate Program in Future Medicine (10:00 – 12:00)

Chair: Nobuhiro Takahashi, Tohoku University Graduate School of Dentistry

FM1 **Improving health and wellbeing through co-design: the Westmead Living Lab**

Christopher Peck, Director, The University of Sydney Westmead Initiative, Australia

FM2 **Chinese Medical Device Regulation Update**

Jianmin Han, Associate Professor, Peking University School and Hospital of Stomatology, China

FM3 **Aiming for Future Medicine and Healthcare: Tohoku University Open Innovation**

Wataru Uchida, General Creative Manger, Specially Appointed Professor, Head Office for Open Innovation Strategy, Tohoku University

(Lunch Break 12:00-13:00)

Plenary Lecture (13:00 – 13:50)

Chair: Hozumi Motohashi, Institute of Development, Aging and Cancer, Tohoku University

PL1 **Roles of RUNX genes in tissue stem cells**

Yoshiaki Ito

Senior Principal Investigator, Cancer Science Institute of Singapore, National University of Singapore, Singapore

(Coffee Break 13:50-14:00)

Scientific Session 1 – Inflammation and Immune Response (14:00 – 15:35)

Chair: Akihiko Muto, Tohoku University Graduate School of Medicine

SS1.1 (14:00–14:30)

Lipidomics revealed a novel role of omega-3-containing lysophospholipid in activating vagal nerve via LPA_3 receptor to protect heart from ischemic damage

Junken Aoki, Graduate School of Pharmaceutical Sciences, Tohoku University

SS1.2 (14:30–15:05)

Regulation of mitochondrial respiratory chain by innate immunity

Johan Garaude, INSERM U1211, France

SS1.3 (15:05–15:35)

The roles of leukotriene B4 receptor in macrophage and dendritic cell

Takehiko Yokomizo, Graduate School of Medicine, Juntendo University

(Coffee Break 15:35–15:50)

Scientific Session 2 – Redox Biology 1 (15:50 – 17:30)

Chair: Norio Suzuki, Tohoku University Graduate School of Medicine

SS2.1 (15:50–16:25)

Hydrogen sulfide in oxidative stress resistance, metabolic fitness and longevity

James R. Michell, Harvard T. H. Chan School of Public Health, USA

SS2.2 (16:25–16:55)

Cysteine persulfide synthases mediate sulfur respiration and energy metabolism

Takaaki Akaike, Tohoku University Graduate School of Medicine

SS2.3 (16:55–17:30)

Causal role for glutathione-induced protein oxidation in tissue fibrosis: New avenues for redox-based therapeutics?

Yvonne M.W. Janssen-Heininger, Larner College of Medicine, University of Vermont, USA

Poster Presentation and Discussion (17:40 – 19:30)

Poster view (17:40–18:20) at Entrance Hall, Seiryo Auditorium

Day 2 March 6 (Wed), 2019

Registration (8:30 –)

Scientific Session 3 – Redox Biology 2 (9:00 – 10:30)

Chair: Atsushi Matsuzawa, Graduate School of Pharmaceutical Sciences, Tohoku University

SS3.1 (9:00–9:30)

KEAP1–NRF2 System and Its Future

Masayuki Yamamoto, Tohoku University Graduate School of Medicine

SS3.2 (9:30–10:00)

Regulation of Mg^{2+} levels and ROS generation by PRL/CNNM protein complexes

Hiroaki Miki, Research Institute for Microbial Diseases, Osaka University

SS3.3 (10:00–10:30)

Intrinsic mechanism for separating blood and lymphatic vascular systems in development and cancer

Yoshiaki Kubota, Keio University School of Medicine

(Coffee Break 10:30–10:40)

Scientific Session 4 – Neuroscience (10:40 – 12:20)

Chair: Hiromu Tanimoto, Tohoku University Graduate School of Life Sciences

SS4.1 (10:40–11:15)

Targeting the metabolism of innate immune cells as a therapeutic strategy for progressive multiple sclerosis

Luca Peruzzotti-Jametti, University of Cambridge, UK

SS4.2 (11:15–11:45)

Trans-cranial magnetic stimulation (TMS): a powerful tool for neuromodulation and functional mapping of the cerebral cortex

Ken-Ichiro Tsutsui, Tohoku University Graduate School of Life Sciences

SS4.3 (11:45–12:20)

Computational approaches in action vision and control and implications in basic and clinical research

Martin A. Giese, University Clinic Tübingen, Germany

(Lunch Break 12:20–13:00)

Young Scientists Oral Sessions (13:00 – 17:40)

Session 1 – Oncology & Chromosome (13:00 – 14:30)

Session 2 – Neuroscience & Pharmacology (14:40 – 16:15)

Session 3 – Stem Cell & Differentiation (16:25 – 17:40)

Workshop on Global Career Development in Future Medicine (17:45 – 19:15)

Panel discussion with NIH, NUS, JNCASR and Tohoku University young scientists
Global career opportunities & Future Medicine

Day 3 March 7 (Thu), 2019

Registration (8:30 –)

Scientific Session 5 – Epigenetic Regulation (9:00 – 10:40)

Chair: Yasuhisa Matsui, Institute of Development, Aging and Cancer, Tohoku University

SS5.1 (9:00–9:35)

Master Epigenetic Enzyme p300 in Life and Death

Tapas Kumar Kundu, Jawaharlal Nehru Centre for Advanced Scientific Research, India

SS5.2 (9:35–10:05)

Gene regulatory network for hematopoietic stem and progenitor cell differentiation

Kazuhiko Igarashi, Tohoku University Graduate School of Medicine

SS5.3 (10:05–10:40)

Identifying epigenetic regulators for targeted therapy in rhabdomyosarcoma

Reshma Taneja, National University of Singapore, Singapore

(Coffee Break 10:40–10:55)

Scientific Session 6 – Carcinogenesis (10:55 – 12:30)

Chair: Natsuko Chiba, Institute of Development, Aging and Cancer, Tohoku University

SS6.1 (10:55–11:25)

Resistance to EGFR Tyrosine Kinase Inhibitors

Susumu Kobayashi, National Cancer Center, Japan

SS6.2 (11:25–11:55)

Regulation of cell survival through post-translational modifications of MCL-1 in tumorigenesis

Hiroyuki Inuzuka, Tohoku University Graduate School of Dentistry

SS6.3 (11:55–12:30)

CRL3/SPOP promotes Nanog destruction to suppress stem cell traits and prostate cancer progression

Wenyi Wei, Beth Israel Deaconess Medical Center, Harvard Medical School, USA

Closing remarks (12:30 – 12:40)

Kazuhiko Igarashi, Dean, Tohoku University Graduate School of Medicine

(Lunch Break 12:40–13:30)

Tour of Tohoku Medical Megabank Organization (ToMMo) in Tohoku University

■ Young Scientists Oral Sessions (13:00 – 17:40 on March 6 (Wed))

Young Scientists Oral Session 1 – Oncology & Chromosome (13:00 – 14:30)

YSOS1-1

Analysis of the *CDKN2A* gene in FAMMM Syndrome families reveals early age of onset for additional syndromic cancers

Candace Middlebrooks, National Human Genome Research Institute, NIH, USA

YSOS1-2

Pathways of Progression from Intraductal Papillary Mucinous Neoplasm to Pancreatic Ductal Adenocarcinoma Based on Molecular Features

Yuko Omori, Tohoku University Graduate School of Medicine

YSOS1-3

The mitochondria gain-of-function phenotype in oncogenic Ras-driven metastatic breast cancer

May Yin Lee, Genome Institute of Singapore, National University of Singapore, Singapore

YSOS1-4

Regulation of chromatin dynamics and autophagy by non-histone chromatin protein PC4: Implications in Breast cancer

Sweta Sikder, Jawaharlal Nehru Centre for Advanced Scientific Research, India

YSOS1-5

Quantifying transcription at Single Molecule level reveals linked cycles of chromatin remodeling and transcription factor binding at gene promoter

Gunjan Mehta, National Cancer Institute, NIH, USA

YSOS1-6

A novel machinery for maintenance of faithful chromosome segregation

Kenji Iemura, Institute of Development, Aging and Cancer, Tohoku University

(Coffee Break 14:30-14:40)

Young Scientists Oral Session 2- Neuroscience & Pharmacology (14:40 – 16:15)

YSOS2-1

***In vitro* and *in vivo* knock-out system labelled by fluorescent protein via microhomology-mediated end joining**

Shota Katayama, Tohoku University Graduate School of Medicine

YSOS2-2

Categorizing Autism Spectrum Disorder Candidate Genes

Victoria Heigh, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, USA

YSOS2-3

Multifunctional fibers for elucidating astroglial basis of anxiety

Yuanyuan Guo, Tohoku University Graduate School of Life Sciences

YSOS2-4

Association of Amyloid Positivity with Volume Loss in Temporal Lobes Differs between Men and Women in Cognitively Normal Older Adults

Nicole Armstrong, National Institute on Aging, NIH, USA

YSOS2-5

Structural biology of β-sheet ligand-type PET probes and monoamine oxidase

Ryuichi Harada, Tohoku University Graduate School of Medicine

YSOS2-6

Interactions of synthetic cannabinoids with the 5HT1A receptor

Hideaki Yano, National Institute on Drug Abuse, NIH, USA

YSOS2-7

A Novel Allosteric Drug That Stimulates Insulin Secretion by Acting on β-Cell M3 Muscarinic Acetylcholine Receptors

Jonathan Pham, National Institute of Diabetes and Digestive and Kidney Diseases, NIH, USA

(Coffee Break 16:15-16:25)

Young Scientists Oral Session 3 - Stem Cell & Differentiation (16:25 - 17:40)

YSOS3-1

Surprise at tissue-resident macrophages in development: brain-resident macrophages control radial glia and cortex development

Chang Liu, National Heart, Lung, and Blood Institute, NIH, USA

YSOS3-2

How TLR9 Signaling shapes the survival, differentiation and the metabolism of B cells

Munir Akkaya, National Institutes of Allergy and Infectious Diseases, NIH, USA

YSOS3-3

PRMT5 Modulates Splicing for Genome Integrity and Preserves Proteostasis of Hematopoietic Stem Cells

Darren Qiancheng Tan, Cancer Science Institute of Singapore, National University of Singapore, Singapore

YSOS3-4

Identification of the tooth-specific novel transcription factor AmeloD and its role during tooth development

Yuta Chiba, Tohoku University Graduate School of Dentistry

YSOS3-5

The transcription factor Foxc1 is necessary for Ihh-Gli2-regulated endochondral ossification

Michiko Yoshida, Tohoku University Graduate School of Dentistry

■ Poster Session (17:40 – 19:30 on March 5 (Tue))

Presenters of Young Scientists Oral Sessions (March 6) also mount their posters in this session

PS1

Tyrosine kinase receptor TIE-1 serves as a novel therapeutic target in PI3K highly expressing ovarian cancer

Xuewei Zhang, Tohoku University Graduate School of Medicine

PS2

The mechanism of epigenetic regulation by the interaction between nuclear FABP7 and ACLY

Yoshiteru Kagawa, Tohoku University Graduate School of Medicine

PS3

Cortical processing of prediction error and self-agency in patients with schizophrenia

Koichi Abe, Institute of Development, Aging and Cancer, Tohoku University

PS4

Chronic poor condition enhances preference to rewarding substances through dopamine system

Toshiharu Ichinose, Tohoku University Graduate School of Life Sciences

PS5

The involvement of fatty acid-binding protein 5 in the blood-brain barrier transport of docosahexaenoic acid and cognition

Yijun Pan, Tohoku University Graduate School of Medicine

PS6

The effect of UGT1A9, CYP2B6, CYP2C9 genes polymorphism on individual differences in propofol pharmacokinetics among Japanese patients

Akihiro Kanaya, Tohoku University Graduate School of Medicine

PS7

Blood Pressure Correlates with 90-Day Mortality in Sepsis Patients: A Retrospective Multicenter Derivation and Validation Study Using High-Frequency Continuous Data

Naoya Kobayashi, Tohoku University Graduate School of Medicine

PS8

Functions of a cancer/testis antigen gene, Tekt5 in cancer cells and male germ cells

Nana Aoki, Institute of Development, Aging and Cancer, Tohoku University

Abstracts

FM1

Improving health and wellbeing through co-design: the Westmead Living Lab

Christopher Peck
Vice Chancellor's Office, University of Sydney

Abstract

Many health systems around the world face serious challenges to quality and financial sustainability due to growing consumer expectations, increasing costs, the ageing of the population and its growing burden of chronic diseases. In western Sydney, these challenges are compounded because it has one of the most culturally diverse populations in Australia including the largest urban Indigenous population, and it is where much of Sydney's projected population growth will occur. The Westmead Health Precinct serves Western Sydney with four hospitals including quaternary adult and children's hospitals, statewide dental and pathology services, three major research institutes, and two major universities. This Precinct requires different approaches to health and wellbeing and the University of Sydney, in collaboration with other Precinct members, industry, government and community, has developed a novel environment for our collaborations: the Westmead Living Lab. This Living Lab will provide a shared environment to co-create implementable and scalable solutions to real world problems. The University has committed to involving all disciplines, not just those that are health related, to contribute to this venture. The Living Lab is founded on four pillars: Collaborative decision making with our community and partners; Inter-disciplinary problem solving and knowledge translation; Mobilising data capacity to enable digital transformations in health; and research and education projects focused on Western Sydney needs. The initial focus is in the areas of Diagnostic Sciences and Technologies, Person Centred Care and Sustainable Health. This collaborative venture is expected to ensure Westmead becomes a global centre of excellence in integrated education, research and healthcare to advance the wellbeing of the people of western Sydney and beyond.

Christopher Peck

Director, The University of Sydney Westmead Initiative

Professor Chris Peck is a prominent pain expert. A strong advocate for multidisciplinary patient management, he is internationally renowned for his leadership and contributions to translational research in orofacial pain and leading the clinical arm of projects involving researchers from biomedicine to mathematics. Research outcomes have focussed on pain classification and screening, pain–muscle activity interactions, nervous system changes and the transition from acute to disabling chronic pain conditions. This research has led to improvements in pain diagnoses, management of impaired jaw function and in our understanding of central nervous system changes and perpetuating factors with persistent pain. He is a senior facial pain expert in the State's public health care system in Sydney at the Royal North Shore Hospital's Pain Management Research Institute, involved in patient care, clinical supervision and research.

Professor Peck is the Director of the University of Sydney's Westmead Initiative, leading the development of academic activities across the multi-billion dollar precinct which includes four hospitals and three medical research institutes. Professor Peck's role as Dean of Dentistry, for the past eight years comprised developing and leading the multidisciplinary strategy integrating dental and systemic health; curriculum reform and the introduction of innovative education programs including the Doctor of Dental Medicine and the first Australian postgraduate orofacial pain program. He also led the NSW Ministerial Taskforce into Oral Health, leading to the Oral Health Strategic Plan 2020 and led the NSW Health Specialist Services Review.

FM2

Chinese Medical Device Regulation Update

Jianmin Han[1,2]

[1] Department of Dental Materials, Peking University School and Hospital of Stomotology

[2] CFDA Medical Devices Quality Supervision and Testing Center of Peking University

Abstract

Recently, medical device technology evolves quickly. The Chinese Medical Device Regulation has been changed a lot aim to scientific supervision and aid medical device development. For example, new regulation for the supervision and administration of medical devices (No.650) was released by China's State Council on March 3, 2014, and the modified version (NO.680) was issued on May 4, 2017, after that, more than 20 rules and 200 normative documents on registration and manufacture had been issued by CFDA. This topic will briefly introduce the China's New Regulatory System, the background of regulatory changes, the main features of regulatory changes and the CFDA's new "Breakthrough Devices Program".

There are three main features for the modified regulations. The first is strengthen the risk management on the Medical device supervision, the classification system of medical device was modified, the Class I device record registration and Class II and III devices approval registration.The second feature is protrude the whole life span supervision of medical device, the measures about the labels and packaging of medical device, medical device registration, clinical evaluation of medical Devices, manufacturing supervision, business supervision, usage quality supervision, network sales Supervision and management, adverse event monitoring and re-evaluation, and measures of medical device Recall have been issued. The third feature is emphasize the responsibility of corporation, the degree of daily inspection has been improved.

The CFDA has also released new guidance documents related to breakthrough medical devices and custom medical devices, the new trend and challenge of Chinese Medical devices Regulation will also discussed in this topic. The new regulation system had been established, but CFDA still has a lot work to do to improve the whole system, including revision of more regulations and deal with the problem accompany with the implementation of new regulations.

Jianmin HAN

Associate Professor of Dental Materials Laboratory of Peking University School and Hospital of Stomatology
Director of Biological Evaluation Laboratory of CFDA Dental Devices Testing and Supervision Center.

[Research Interest]

Biological safety and effectivity evaluation of dental materials
Metal-free dental implant development and surface modification

[Biographical Sketch]

Jianmin Han, Associate Professor of Dental Materials Laboratory of Peking University School and Hospital of Stomatology, the Director of Biological Evaluation Laboratory of CFDA Dental Devices Testing and Supervision Center. He is an Advisory Committee member of NPMA (China Medical Device Evaluation Center). He is also a member of China Dental Materials Committee, Secretary of Beijing Dental Materials Committee, Member of Regulatory Toxicology and Risk Assessment, Chinese Society of Toxicology.

FM3

Aiming for Future Medicine and Healthcare: Tohoku University Open Innovation

WATARU UCHIDA, Ph.D.
General Creative Manager,
Specially Appointed Professor
Head Office for Open Innovation Strategy
Tohoku University

Abstract

Healthcare today is the result of rapid growth and advances in science and technology. For example, recent progress in basic technologies such as gene editing and vector technologies are leading to innovative modalities such as gene therapy and nucleic acid-based medicines becoming more widespread. Furthermore, with the recent rapid progress in engineering technologies, including artificial intelligence (AI), advances in new medical approaches by the fusion of engineering and big data, are leading to the possibility that medical care itself will change in terms of medicine and medical solutions. In this changing environment, it is not realistic that a single company can execute on all R&D aspects in-house and a new collaboration model involving academia, biopharma companies and contract research organizations is developing. On the other hand, many innovative techniques are being reported in technical areas such as sensor imaging and materials, but fusion of these advances with medical care is still immature. Therefore, for creation of future medical care solutions, an effective open innovation (OI) model to promote the fusion of companies and innovative science and engineering into innovative medicines has become very important. From such a point of view, many pharma companies, as well as companies from other industries are participating from last December in the creation of the Tohoku University OI ecosystem, which aims to develop and create advanced innovation. In the activities of the Open Innovation Strategy Organization, a center of industry-academia collaboration, we are challenging to create revolutionary medical solutions and to contribute to the training and education of researchers who will open-up new frontiers in future medicine and healthcare.

WATARU UCHIDA, Ph.D
General Creative Manager
Specially Appointed Professor
Head Office for Open Innovation Strategy
Tohoku University

I am the General Creative Manager for the Head Office for Open Innovation Strategy. I joined Yamanouchi Pharmaceutical Co., Ltd. in 1984, and became Senior Director of Cardiovascular Research in 2004, and was in charge of the Cardiovascular and Urology Research fields. Astellas Pharma Inc. formed in April 2005 from the merger of Yamanouchi Pharmaceutical Co., Ltd. and Fujisawa Pharmaceutical Co., Ltd. From that time, I was Senior Director of Urology Research in the Pharmacology Research Labs. In 2009, I was transferred to the Development Division as Vice President of Clinical Pharmacology. In 2010, he returned to the Drug Discovery Division as Division SVP for the Pharmacology Research Labs. From 2014, I was in charge of the Drug Discovery Research Division as SVP and Division Head. In 2018, I retired from Astellas Pharma Inc. and joined Tohoku University. I hold a PhD in Pharmacology from Tohoku University and was a Visiting Pharmacology Scientist at Oxford University from 1998 to 1999.

PL1

Roles of RUNX genes in tissue stem cells

Yoshiaki Ito
Cancer Science Institute of Singapore, National University of Singapore

Abstract

RUNX genes are evolutionarily old developmental regulator. Mammals have three genes, RUNX1, RUNX2 and RUNX3 and are heavily involved in cancer. RUNX1 is essential for the emergence of hematopoietic stem cells (HSC) from endothelial cells. RUNX1 has two promoters. Between these two promoters, there are multiple enhancer elements. One of them, 270 bp enhancer element, termed eR1, is responsible for inducing RUNX1 expression in HSC. We have been characterizing stomach epithelia stem cells. There are at least two types of stem cells, reserve stem cells and rapidly growing stem cells. Rapidly proliferating stem cells have been predicted to be present in isthmus of stomach corpus. These rapidly proliferating cells express RUNX1 whose expression is regulated by eR1 (1). It turned out that eR1 is functional in tissue stem cells of multiple organs. eR1 is, therefore, an excellent tool to detect tissue stem cells. We recently identified a protein specifically expressed in rapidly proliferating isthmus stem cells, termed here as Isthmus Factor (IF). IF interacts with GTP-bound form of Ras and strongly stimulates cell proliferation through Ras-MAPK signaling pathway. We found that SRF is responsible for stem cell specific expression of IF. We are testing whether expression of SRF in differentiated cell would induce stem cells. IF is also widely expressed in gastric cancer together with Ki67 proliferation marker. Relationship between IF expressing cancer cells and cancer stem cells is important subject to study. We reported RUNX3 as a tumor suppressor in gastric cancer. From a gastric cancer patient sample, we identified mutation, R122C, which converted tumor suppressor to oncogene (2). We generated R122C knock-in mouse that shows dramatic increase of isthmus stem cells. RNA sequence analysis shows the expression of a set of genes expressed in leukemia initiating genes. Studies of wild type and R122C mutant stem cells will be excellent model to study cell of origin and early stages of gastric cancer.

(1) Matsuo et al, Gastroenterology, 2017, 152:218-231.
(2) Li et al, Cell , 2002, 109: 113-124.

Yoshiaki Ito, MD PhD
Yong Loo Lin Professor in Medical Oncology
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[Research Interest]
I am one of the first to identify RUNX genes as developmental regulators often involved in cancer. Since then I have been working on the mechanism of carcinogenesis of sold tumors caused by RUNX genes, especially gastric cancer. It is now commonly understood that RUNX genes have dual functions: oncogenic or tumor suppressive. Initially, we inactivated the genes to study gene function. By this approach, we reported tumor suppressor roles of RUNX3. This approach allowed us to study only tumor suppressor side of RUNX function. More recently, gastric and other cancer cells are found to be expressing RUNX genes. By analyzing RUNX genes in cancer cells, we are characterizing oncogenic roles of RUNX genes including metastasis promoting activity. Most recently, we found the roles of RUNX genes in adult or tissue stem cell. RUNX genes appear to be regulating the emergence of tissue stem cells by inducing a set of tissue specific transcription factors, which in turn induce a stem cell specific factor. This study is important to identify the cell of origin of cancer.

Accomplishment
Discovered middle T antigen of polyomavirus, the major onco protein of the virus.
Discovered RUNX family of genes important for developmental regulators and cancers.

[Biographical Sketch]
Education:
1964 – 1968 Tohoku University, Graduate School of Medical Sciences, Sendai, Japan, PhD
1957 – 1963 Tohoku University, School of Medicine, Sendai, Japan, MD

Past positions
2008 – Current position
2002 – 2008 Principal Investigator, Professor, Institute of Molecular and Cell Biology, Director, Oncology Research Institute, National University of Singapore
1995 – 2001 Director, Institute for Virus Research, Kyoto University, Kyoto, Japan
1984 – 2002 Professor, Laboratory of Cell Regulation, Department of Viral Oncology Institute for Virus Research, Kyoto University, Kyoto, Japan
1983 – 1984 Head, Cell Transformation Section, Basic Research Program, Frederick Cancer Research Facility, NCI, Frederick, Maryland, USA
1979 – 1983 Visiting Scientist, NIAID, NIH, Bethesda, Maryland, USA
1975 – 1979 Scientific Staff, Department of Cell Regulation Imperial Cancer Research Fund Laboratories, London, England
1972 – 1975 Research Associate, Department of Cell Regulation Imperial Cancer Research Fund Laboratories, London, England
1969 – 1972 Research Associate, Department of Microbiology and Immunology Duke University Medical Center, North Carolina, USA

SS1.1

Lipidomics revealed a novel role of omega-3-containing lysophospholipid in activating vagal nerve via LPA_3 receptor to protect heart from ischemic damage

Junken Aoki and Kuniyuki Kano

Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3, Aoba, Aramaki, Aoba-ku, Sendai, 980-8578, Japan

Abstract

Both vagal nerve and omega-3 fatty acids protect heart from myocardial infarction (MI). However, the underlying molecular mechanism has been obscure. We recently showed that lysophosphatidic acid (LPA) with docosahexaenoic acid (DHA) was elevated in the plasma of acute coronary syndrome patients. Here we show that the LPA species was produced specifically in the ischemic region in mouse MI model and protect heart from ischemic damage through the activation of vagal nerve via *sn*-2 PUFA LPA-preferring LPA receptor, LPA_3. In mice deficient in LPA_3, MI-induced heart damage was significantly advanced. Conversely, administration of an LPA_3 agonist or DHA-LPA significantly reduced the damage. The LPA_3 agonist also activated vagal nerve as manifested by decrease in the heart rate, deep breathing and enhanced the baroreflex, one of the most prominent vagal responses. In LPA_3 knockout mice, the baroleflex response was significantly weakened and as a result the mice showed hypertension. Our present data showed that in pathological condition such as MI DHA-LPA behaves like a beneficial DAMPs with a potent cardioprotective role and that in physiological condition it behaves as a stimulator of baroreceptor, all of which were mediated though a G protein-coupled receptor, LPA_3.

Junken Aoki
Position and Affiliation:Graduate School of pharmacyeutical Sciences, Tohoku University

[Research Interest]
Lipid biology, especially in the field of bioactive lipids.

[Biographical Sketch]

Degrees

B. D. The University of Tokyo, Faculty of Pharmaceutical Sciences, 1987
M.S. The University of Tokyo, Faculty of Pharmaceutical Sciences, 1989
Ph.D. The University of Tokyo, Faculty of Pharmaceutical Sciences, 1992

Academic Background

1992 Researcher in Tokyo Metropolitan Institute of Medical Science
1994 Research Associate in The University of Tokyo,
Graduate School of Pharmaceutical Sciences
2000 Associate Professor in The University of Tokyo,
Graduate School of Pharmaceutical Sciences
2006 Researcher of PREST (Sakigake), JST Japan
2007 Professor in Tohoku University,
Graduate School of Pharmaceutical Sciences
2018– Research Professor in Tohoku University

SS1.2

Regulation of mitochondrial respiratory chain by innate immunity

Johan Garaude
Laboratory for Rare Diseases: Genetics and Metabolism – INSERM U1211, Bordeaux, France

Abstract
Innate immune cell activation critically relies on cellular metabolism reprogramming. At the core of this reprogramming is the mitochondrion, the main bioenergetics organelle that also serves as an innate immune signaling plateform. While fluctuations of mitochondrial metabolites during innate immune receptor engagement have received most of the attention, the precise contribution of the mitochondrial electron transport chain (ETC) is poorly defined. Our research nevertheless indicates a strong link between the nature of the infecting bacteria, the ETC structural and functional re-arrangement and antimicrobial immunity. Our current work is exploring how signaling pathways emerging from innate immune receptors intertwin with mitochondrial respiratory chain–mediated control of energetic metabolism in macrophages.

Johan Garaude

Assistant researcher – Laboratoire Maladies Rares: Génétique et Métabolisme, INSERM U1211, Bordeaux, France

[Research Interest]

Our work aims at unraveling the structural and functional adaptations of the respiratory chain and their relevance for innate immune cells contribution to antibacterial immunity. We specifically assess the connection between innate immune receptors engagement by microbial products and the electron transport chain regulation. In turn, we evaluate the innate immune consequences of cellular metabolism and mitochondrial respiratory chain disorders.

[Biographical Sketch]

Johan Garaude got his Ph.D. in Moleclular Endocrinology in 2007 from the University of Montpellier, France for his work on mitogen-activated protein kinases (MAPK) and activating-protein 1 (AP-1) in leukemogenesis and T cell activation. In 2008, he joined the laboratory of Julie Magarian Blander at the Mount Sinai School of Medicine in New York where he investigated how a dual ligand for innate immune receptors can be use to generate potent antitumor immune responses and contributed to the discovery that infected apoptotic cell consistute a natural inducer of TH17 cell differentiation. In 2011, he got a permanent position at INSERM, France, and started investigating the metabolic adapatations and mitochondrial bilology in innate immune cells and how this contributes to antimicrobial responses.

SS1.3

The roles of leukotriene B4 receptor in macrophage and dendritic cell

Takehiko Yokomizo
Department of Biochemistry, Graduate School of Medicine, Juntendo University

Abstract

Leukotriene B4 (LTB4), a classically known inflammatory lipid mediator derived from arachidonic acid, binds and activates a G-protein coupled receptor BLT1 (1) expressed on phagocytes. The roles of LTB4/BLT1 axis has been explored using global BLT1 knockout mice (2), and BLT1 deficiency resulted in the amelioration of bronchial asthma (3), contact dermatitis, and osteoporosis (4) in mice. However, cell-specific roles of BLT1 has not been clarified. We recently established an anti-BLT1 monoclonal antibody (5) and $BLT1^{flox/flox}$ mice, which allowed us to clarify the cell-specific roles of BLT1. In macrophages, BLT1 is expressed only in M2-type macrophages, and LTB4 stimulation strongly induced cell-migration and expression of various angiogenic factors in M2 macrophages. In murine age-related macular degeneration (AMD) model, BLT1-deficiency almost completely abolished choroidal neovascularization (CNV) after retinal injury with much reduced accumulation of M2 macrophages in the injured retina. A selective BLT1 antagonist and inhibitors of LTB4 biosynthesis reduced CNV and inhibited the accumulation of BLT1+ M2 macrophages. Thus, the LTB4-BLT1 axis is a potentially novel therapeutic target for CNV of wet-type AMD (6). We also found a unique subset of dendritic cells defined by the expression of BLT1 (7), which will be mentioned in my lecture. We recently succeeded in crystallization of BLT1(8), which will enable us to develop structure-oriented antagonists and inverse agonists for BLT1.

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Takehiko Yokomizo
Professor, Department of Biochemistry, Graduate School of Medicine, Juntendo University

[Research Interest]

- Structure, signal transduction and in vivo roles of G-protein coupled receptors (GPCRs) for lipid mediators.
- Relationship between membrane lipid composition and intracellular signaling from GPCRs.

[Biographical Sketch]

1988	M.D., Tokyo University
1988–1991	Clinical training as a gynecologist
1991–1995	Graduate School of Medicine, Tokyo University
1995	Ph.D. of Biochemistry, Tokyo University
1995	JSPS postdoctoral fellow, Department of Biochemistry, Tokyo University
1998	Research associate, Department of Biochemistry, Tokyo University
2000	Associate Professor, Department of Biochemistry, Tokyo University
2006–2012	Professor, Department of Medical Biochemistry, Faculty of Medical Sciences, Kyushu University
2010–2012	Distinguished Professor, Kyushu University
2012–present	Professor of Biochemistry, Juntendo University School of Medicine
2018–present	Program Officer, AMED CREST “Tissue Adaptation and Repair”
2018–present	Researcher, JSPS Research Center for Science Systems

SS2.1

Hydrogen sulfide in oxidative stress resistance, metabolic fitness and longevity

James R. Mitchell
Harvard T. H. Chan School of Public Health, Boston MA, USA

Abstract

Dietary restriction (DR), defined loosely as reduced nutrient/calorie intake without malnutrition, is associated with extended longevity, improved metabolic fitness and increased resistance to mulitple forms of stress (oxidative, heat shock, etc.) across evolutionary boundaries. However, downstream effector mechanisms of DR remain poorly characterized, particularly in mammals. We have reported that restriction of calorie or sulfur amino acid intake increases endogenous production of the gas hydrogen sulfide (H_2S) and that this can confer some benefits of DR, including protection from the acute stress of ischemica reperfusion injury in liver and increased angiogenesis in skeletal muscle. Here, I will discuss the nutrient sensing pathways involved in regulation of endogenous H_2S production, as well as the molecular mechanisms by which increased H_2S can exert its biological effects. Finally, I will present new data on a screen for compounds that activate endogenous H_2S production, with implications for clinical translation.

James R. Mitchell
Professor of Genetics and Complex Diseases, Harvard T. H. Chan School of Public Health

[Research Interest]

The Mitchell lab is focused on elucidating the underlying mechanisms of the phenomenon known as dietary restriction, an intervention involving reduced nutrient/energy intake that slows aging, improves metabolic fitness and increases resistance to a variety of clinically relevant acute stressors, including major surgery. Recent work has focused on the beneficial role of increased endogenous production of hydrogen sulfide gas, and its regulation by nutrient and neuroendocrine mechanisms. Dr. Mitchell's long-term goal is to translate knowledge of these anti-aging mechanisms towards improving human health.

[Biographical Sketch]

James R. Mitchell completed his doctoral training at UC Berkeley on human telomerase biochemistry and his post-doctoral studies at Erasmus University in Rotterdam, the Netherlands on the genetics of DNA repair and aging. He is currently a Professor in the Department of Genetics & Complex Diseases at the Harvard T. H. Chan School of Public Health where he works on nutrition and aging.

SS2.2

Cysteine persulfide synthases mediate sulfur respiration and energy metabolism

Takaaki Akaike[1], Tomoaki Ida[1], Hozumi Motohashi[2]

[1]Department of Environmental Medicine and Molecular Toxicology, Tohoku University Graduate School of Medicine, Sendai 980-8575, Japan; Department of [2]Gene Expression Regulation, Institute of Development, Aging and Cancer, Tohoku University, Japan

Abstract

Reactive sulfur species such as cysteine hydropersulfide (CysSSH) and its related polysulfides can act as antioxidant and redox signaling molecules. The chemical properties and abundance of these species suggest a pivotal role for reactive persulfides in cell-regulatory processes. However, how these reactive sulfur molecules are formed was not fully understood. Here, we have identified cysteinyl-tRNA synthetases (CARSs) as the primary and principal persulfide synthases (CPERSs) occurring ubiquitously in all organisms. The CARS/CPERS is involved in protein polysulfidation that is coupled with translation. Also, mitochondrial functions in biogenesis and bioenergetics are supported and up-regulated by cysteine persulfide derived from mitochondrial CARS/CPERS. Targeted and functional disruption of a gene encoding mitochondrial CARS (CARS2) and sulfide-quinone reductase (SQR) in mice revealed that persulfides produced by CARS2 (mitochondrial CPERS) directly mediate mitochondrial energy metabolism in cooperation with SQR, which is known for a long time as sulfur respiration in anaerobic microorganisms. Investigating CARS/CPERS-dependent persulfide production, therefore, may clarify the novel sulfur-based biology and energy metabolism in various cells in diverse organisms including mammals. CARS/CPERS- and SQR-dependent sulfur respiration may extend lifespan and improve the quality of life, and may provide a new venue for diagnosis, prevention and treatment of many diseases including cancer. In fact, reactive sulfur species are likely to contribute to hypoxic response and cytoprotection against oxidative stress, which will confer malignant progression and drug resistance in cancer chemotherapy.

Takaaki Akaike
Professor, Department of Environmental Medicine and Molecular Toxicology, Tohoku University Graduate School of Medicine, Sendai 980-8575, Japan

[Research Interest]

Takaaki Akaike has more than 30 years of active research experience and has the major research interest in redox biology. His group discovered in 2007 a unique second messenger (8-nitro-cGMP) that mediates electrophilic signal transduction during oxidative stress and other cellular redox signaling. In 2014, he reported that reactive persulfide species abundantly produced in vivo regulates electrophilic and redox signaling pathways, and most recently, Akaike's group identified in 2017 a new persulfide synthase that is responsible for most of cysteine persulfide and its related sulfur metabolites endogenously generated.

[Biographical Sketch]

Takaaki Akaike graduated from the Kumamoto University Medical School in Japan, and earned his MD, PhD degree from the Graduate School of Medicine, Kumamoto University in 1991. He then joined the Department of Microbiology at Kumamoto University School of Medicine where he was appointed to several faculty positions and was promoted to Full Professor in 2005. In 2013, he moved to Tohoku University Graduate School of Medicine as Professor & Chairman of the Department of Environmental Medicine and Molecular Toxicology. He held concurrent appointments as Visiting Professors at Thomas Jefferson University (1993) and at University of Alabama at Birmingham (2001), Program Officer at the Ministry of Education, Science, Sports and Culture (MEXT) of Japan (2003-2005), and Vice Dean & Director of Center for Medical Education and Research at Kumamoto University Medical School (2011-2012). He received the Society for the Free Radical Research Japan Prize (2014) and ASAKAWA Award from the Japanese Society for Bacteriology (2015). He was the president of the International/Japanese Nitric Oxide Society (~2011).

SS2.3

Causal role for glutathione-induced protein oxidation in tissue fibrosis: New avenues for redox-based therapeutics?

Yvonne M.W. Janssen-Heininger, Vikas Anathy, Shi B. Chia, Reem Aboushousha, Jos L.J. van der Velden, Evan Elko, David J. Seward, and Albert van der Vliet

Department of Pathology and Laboratory Medicine, University of Vermont, Burlington VT 05445, USA

Abstract

Tissue fibrosis is a major cause of overall mortality, and lung fibrosis each year claims the lives of 40,000 people in the USA alone. Oxidative stress, or changes in the redox environment, are believed to be critical in this disease pathogenesis. Protein S-glutathionylation (PSSG) is a posttranslational modification of proteins via the covalent attachment of glutathione to reactive cysteines within proteins. S-glutathionylation elicits changes in the structure and function of proteins, and is regulated via glutaredoxin (GLRX), a highly specific enzyme that reverses PSSG. I will be describing data demonstrating that GLRX enzymatic activity was strongly decreased in lungs from patients with lung fibrosis, in association with oxidative inactivation, in accordance with increases in PSSG. I will also show that mice globally lacking Glrx were far more susceptible to bleomycin- or adenovirus encoding active transforming growth factor beta-1 (AdTGFB1)-induced pulmonary fibrosis, while conversely, transgenic overexpression of Glrx in the lung epithelium attenuated fibrosis. Direct administration of Glrx protein into airways augmented Glrx activity and reversed increases in collagen in mice with TGFB1- or bleomycin-induced fibrosis, even when administered to fibrotic, aged animals. These findings suggest the therapeutic potential of exogenous GLRX in treating lung fibrosis. l will be touching upon the potential target proteins for GLRX-mediated deglutathionylation in fibrotic tissues. Lastly, I will be describing the steps that were are taking to advance GLRX commercially as a potential therapy for lung fibrosis, and the hurdles that we face.

Supported by grant R35HL135828 from the National Institutes of Health, Heart Lung and Blood Institute

Conflict of interest: YJH and VA hold US patents: 8,679,811 “Treatments Involving Glutaredoxins and Similar Agents”, 8,877,447 “Detection of Glutathionylated Proteins”, They are scientific founders of Celdara Medical LLC, and have received consulting fees.

Yvonne Janssen-Heininger
Professor and vice-chair for Research
Department of Pathology and Laboratory Medicine
Larner College of Medicine, University of Vermont
Burlington VT 05405 USA

[Research Interest]

Dr. Janssen-Heininger has a long standing interest in understanding the biochemical events that promote scarring (fibrosis) in the lung. She is interested in understanding the role changes in the oxidative environment (redox) play in promoting fibrogenesis. Dr. Janssen-Heininger has spent considerable effort in addressing the role of S-glutathionylation chemistry in fibrosis, and has demonstrated roles of glutathione S transferase P and glutaredoxin, two enzyme systems that regulate S-glutathionylation in fibrosis. She also has described an approach to visualize S-glutathionylation in fibrotic tissues and has published these studies in the American Journal of Pathology, the Journal of Clinical Investigation Insight and Nature Medicine among others. Dr. Janssen-Heininger also is working to develop these approaches commercially with the goal to have an improved treatment for pulmonary fibrosis. She will be sharing some of this work at this conference

[Biographical Sketch]

Dr. Janssen-Heininger received her PhD degree and Maastricht University Medical Center in the Netherlands, the country where she was born. From 1993 to 1996, she performed post-doctoral studies in the Department of Pathology and Laboratory Medicine at the University of Vermont. Dr. Janssen-Heininger has remained at the University of Vermont, where she is currently Professor and Vice Chair for Research i the Department of Pathology and Laboratory Medicine. She has published over 130 manuscripts in peer-reviewed journals, received numerous NIH R01 grants. She was inducted at University Scholar 2018-2019 earlier this year. She holds four US patents, and currently is the recipient of a prestigious NIH R35 Outstanding Investigator Award.

SS3.1

KEAP1-NRF2 System and Its Future

Masayuki Yamamoto
Tohoku University Graduate School of Medicine

Abstract

Our body has an ability to sense environmental insults, including oxidative stress, and activate cellular defense enzymes. Transcription factor NRF2 is essential for the coordinated induction of cellular defense enzymes and protection of tissues. This notion has been supported by the experiments with animal models, showing that NRF2-null mice and rats are sensitive to a wide variety of toxic electrophiles and reactive oxygen species (ROS). We found KEAP1 that acts as a subunit of ubiquitin-E3 ligase and degrades NRF2 constitutively, and also acts as a sensor for oxidative and electrophilic (toxic chemical) stresses. Covalent modifications of the cysteine residues of KEAP1 abrogate the ubiquitin ligase activity and stabilize NRF2. We have been referring this system to as the Floodgate system. The Cysteine Code and the Two-site Recognition / Hinge-and-Latch model have been proposed for molecular basis of the KEAP1-NRF2 system. Disruption of the Two-site Recognition model explains the mechanism of nuclear accumulation of NRF2 in a CUL3-KEAP1 E3 ubiquitin ligase-dependent manner. We have verified this model through structure biology, mouse genetics, and human disease analyses. These analyses provide solid basis for the development of drugs that induce NRF2. In fact, genetic as well as pharmacological induction of NRF2 nicely protect tissues from oxidative injury. NRF2 inducers are now actively developed for kidney diseases, neurodegenerative disorders and many more diseases. Meanwhile, many somatic missense mutations have been identified in *KEAP1* and *NRF2* genes of human cancers. These mutations disrupt the KEAP1-NRF2 complex and result in constitutive activation of NRF2, and elevated expression of NRF2 target genes confers advantages on the growth of cancer cells through the metabolic reprogramming and induction of cellular defense enzymes. These cancer cells are referred to as "the NRF2-addicted cancers". We need NRF2 inhibitors for the efficient treatment of the NRF2-addicted cancers. The KEAP1-NRF2 system opens a new avenue to the understanding of the regulatory processes underlying the stress response and cancer progression, and to the development of new drugs and therapies.

Masayuki Yamamoto
Tohoku University Graduate School of Medicine
Tohoku Medical Megabank Organization

[Research Interest]

1) Elucidation of molecular mechanisms regulating the NRF2-KEAP1 pathway that regulates the cellular response against electrophilic and oxidative stresses
2) Elucidation of the regulatory mechanisms of *Gata1* and *Gata2* gene expression during hematopoiesis and their link to the *GATA-related leukemia*
3) Elucidation of the regulatory mechanisms of mouse *erythropoietin* gene expression and identification of Renal Epo Producing (REP) cells.

[Biographical Sketch]

Masayuki Yamamoto was graduated from Tohoku University School of Medicine and from Tohoku University Graduate School of Medicine. In 1983, he obtained Doctor of Medical Sciences (PhD). In 1983-1986, Yamamoto was a postdoctoral fellow at Northwestern University with Professor Doug Engel. During this period, he cloned erythroid-type 5-aminllevulinate synthase (*ALAS2 or ALAS-E*) cDNA. In 1989, Yamamoto revisited the Engel laboratory and in collaboration identified the GATA family of transcription factors, which is one of the prototype transcription factor families regulating lineage commitment and cell differentiation. In 1991, Yamamoto returned to Japan and starts analyses on the regulation of *Gata1* and *Gata2* genes during hematopoiesis. In 1995, Yamamoto became a Professor at University of Tsukuba and started a series of analyses on CNC and Maf family of transcription factors. He identified the KEAP1-NRF2 system regulating the cellular response against electrophilic and oxidative stresses. A series of his papers on this topic awarded Medal with Purple Ribbon (2012) and the Japan Academy Prize (2014). In 2007, he returned to Tohoku University and served as a Dean of Medical School and Vice president of the University. In 2012, he started Tohoku Medical Megabank Project for the creative reconstruction from the devastating earthquake and tsunami in March 11, 2011.

SS3.2

Regulation of Mg^{2+} levels and ROS generation by PRL/CNNM protein complexes

Hiroaki Miki
Research Institute for Microbial Diseases, Osaka University

Abstract
Phosphatase of regenerating liver (PRL) is a tyrosine phosphatase that is overexpressed in metastatic cancers and actively promotes cancer malignancy. We found that PRL directly binds to cyclin M (CNNM), an evolutionarily conserved membrane protein. CNNM proteins can extrude intracellular Mg^{2+}, which was inhibited by the interaction with PRL. It has been reported that PRL overexpression in B16 mouse melanoma cells greatly augments their lung metastasis. Using this experimental model, we investigated the effects of various single amino acid substitutions in PRL and found that the interaction with CNNM, not the intrinsic phosphatase activity, was essential for the promotion of metastasis. Moreover, intestinal polyps spontaneously formed in *APC* hetero-deficient mice were confined within the mucosa, but they developed into invasive carcinoma by additional deletion of *CNNM*. Therefore, the inhibition of *CNNM* protein functions is considered to be crucial for PRL to stimulate cancer malignancy. To explore the mechanistic details, we isolated *C. elegans* mutants for *cnnm* family genes and performed their phenotypic analyses. As a result, we found that double mutant worms for *cnnm-1* and *cnnm-3* were sterile and had shortened lifespan. Investigations of the cause of this shortened lifespan phenotype revealed that mitochondrion-derived ROS levels were significantly increased in the intestinal cells of the double mutant worms. Indeed, treatment of the mutant worms with an antioxidant, NAC, restored their lifespan to the levels of wild-type worms. Moreover, we found that ATP levels were also increased in the mutant worms, thus indicating the occurrence of alterations in mitochondrial energy metabolism utilizing oxygen. Similar increases of both ATP levels and ROS levels were observed in human cultured cells lacking CNNM functions. In this symposium, I will describe the biomedical importance of Mg^{2+} in energy metabolism, centering on our latest research results on these intriguing protein complexes.

Hiroaki Miki
Professor, Research Institute for Microbial Diseases, Osaka University

[Research Interest]
Regulatory mechanism of Mg^{2+} levels and its biomedical importance

[Biographical Sketch]

Education
B.Sc. March 1993, School of Sciences, The University of Tokyo
Ph.D. March 1998, Graduate School of Sciences, The University of Tokyo

Work Experience
1998–2002: Research Associate, Institute of Medical Science, The University of Tokyo
2002–2007: Associate Professor, Institute of Medical Science, The University of Tokyo
2007–2011: Professor, Institute for Protein Research, Osaka University
2011– : Professor, Research Institute for Microbial Diseases, Osaka University

SS3.3

Intrinsic mechanism for separating blood and lymphatic vascular systems in development and cancer

Yoshiaki Kubota
Department of Anatomy, Keio University School of Medicine

Abstract
Blood and lymphatic vessels structurally bear a strong resemblance, but never share the lumen in the periphery to keep their distinct functions. During embryogenesis, lymphatic vessels arise mainly from preexisting veins; lymphatic endothelial progenitors bud from the cardinal vein through the function of Prox1, a master transcription factor of lymphatic specification. However, it is not elucidated how these two tubular structures remain separated throughout life. Here we found a tumor suppressor, which pathway ultimately governs the expressions of Prox1, separates blood and lymphatic vascular systems in mice and humans. Our data implicate some common mechanisms govern oncogenesis and lympogenous metastasis, which may extend our knowledge about the molecular mechanism for cancer progression.

Yoshiaki Kubota
Professor, Department of Anatomy, Keio University School of Medicine

[Research Interest]

The vascular network is formed throughout the body to meet the tissue requirements for oxygen and nutrients. Our lab is exploring the molecular and cellular mechanism how this network is established, primarily using the model of mouse retina.

[Biographical Sketch]

1994–2000	MD Keio University School of Medicine
2000–2002	Fellow in Plastic Surgery, Keio University School of Medicine
2003–2006	PhD Dept of Cell Differentiation, Keio University School of Medicine
2006–2008	Instructor, Dept of Cell Differentiation, Keio University
2008–2011	Tenure track assistant professor, Keio Kanrinmaru Project
2012	Visiting researcher in Dept of Stem Cell and Neuro-vascular biology, National Institutes of Health
2013–2014	Principal Investigator (Associate professor), The Laboratory of Vascular Biology, Keio University School of Medicine
2015– 2017	Professor, Department of Vascular Biology, The Sakaguchi laboratory, Keio University School of Medicine
2017–	Professor, Department of Anatomy, Keio University School of Medicine

SS4.1

Targeting the metabolism of innate immune cells as a therapeutic strategy for progressive multiple sclerosis

Luca Peruzzotti-Jametti[1], Aletta van den Bosch[1], Sarah Gehrke[2], Ana Sofia Henriques Costa[3], Daniel Trajkovski[1], Carlo Viscomi[4], Michael P. Murphy[4], Christian Frezza[3], Angelo D'Alessandro[2], Stefano Pluchino[1]

[1]Dept of Clinical Neurosciences, University of Cambridge, UK; [2]University of Colorado, Denver, USA; [3]MRC Cancer Unit, University of Cambridge, UK; [4]MRC Mitochondrial Biology Unit, University of Cambridge, UK

Abstract

The introduction of disease modifying agents has transformed the management of relapsing remitting multiple sclerosis (MS), but has not yet provided substantial benefits for patients with progressive forms of disease. The scarcity of effective treatment options for progressive MS highlights the need to re-evaluate disease pathophysiology to identify novel therapeutic targets.

In progressive MS, a diffuse chronic activation of inflammatory mononuclear phagocytes (MPs), including microglia and macrophages, is one of the main processes associated to irreversible tissue damage in the central nervous system (CNS). Metabolism influences the activity of MPs by guiding their inflammatory function, and several metabolites produced by MPs have key signaling roles in inflammation. However, how innate immune cell metabolism sustains a chronic state of inflammation in the CNS is not fully understood.

Herein, we provide evidence suggesting that novel molecular and cellular therapies for progressive MS should be designed to target the metabolism in innate immune cells. Our aim is to modulate mitochondrial function in MPs during chronic neuroinflammation to lessen secondary neurological damage and prevent the accumulation of disability in progressive MS patients.

Luca Peruzzotti-Jametti
Clinical Research Associate and Neurology Consultant
Dep. of Clinical Neurosciences, University of Cambridge, UK

[Research Interest]

Luca's work has been focusing on the application of molecular and cellular therapies to acute and chronic disorders of the Central Nervous System (including ischemic stroke and multiple sclerosis).
Currently, he is studying how progression works in multiple sclerosis by focusing on the link between immune cell metabolism and chronic neuroinflammation (thanks to a Fondazione Italiana Sclerosi Multipla-FISM Senior Research Fellowship).

[Biographical Sketch]

After receiving his MD (2007) from the University Vita-Salute San Raffaele of Milan (Italy), Luca completed a residency program in Neurology at the same University in 2013. He then successfully obtained a Wellcome Trust research training fellowship and completed a PhD in Clinical Neurosciences at the University of Cambridge (2018).
During the past years, Luca has worked as visiting scientist in major European universities, such as the University Hospital in Zürich (Switzerland), the University of Aarhus (Denmark), the Laboratory of Stem Cells and Restorative Neurology of Lund (Sweden) and the University of Innsbruck (Austria).

SS4.2

Trans-cranial magnetic stimulation (TMS): a powerful tool for neuromodulation and functional mapping of the cerebral cortex

Ken-Ichiro Tsutsui
Laboratory of Systems Neuroscience, Tohoku University Graduate School of Life Sciences

Abstract
TMS is expected to be a powerful tool in manipulating the brain activity. In order to investigate its working mechanisms, we recorded electrocorticogram (ECoG) before and after repetitive trans-cranial magnetic stimulation (rTMS). We also recorded motor evoked potential (MEP) induced by single-pulse TMS before and after rTMS. When the MEP amplitude was supressed after low-frequency (1 Hz) rTMS, we observed the decrease of beta-band power in ECoG; when the MEP amplitude was enhanced after high-frequency (10 Hz) rTMS, we observed the increase of gamma-band power in ECoG. These result indicate the systematic change of cortical neural activity induced by low-frequency and high-frequency rTMS.
We then explored the function of the medial cortical surface by applying low-frequency rTMS inhibiting the local neural activity (intensity: 120% of the MI motor threshold, duration of stimulation: 20 minutes, total number of pulses: 1200). In addition to the figure-of-eight coil, double cone coil was used to stimulate deeper regions on the medial cortical surface. We observed clear and profound impact on behaviour only when the low-frequency rTMS was targeted on the anterior part of the medial prefrontal cortex with a double-cone coil. After the stimulation, the monkey exhibited changes in physiological and behavioural measures that indicated sustained depression of mood and emotion, such as elevated cortisol level in the blood, decreased within-cage spontaneous activity, social withdrawal (unwillingness to interact with research staffs taking care of them), and decreased motivation for performing tasks to acquire food. These results indicate the critical involvement of the medial frontal cortex in the regulation of mood and emotion.

Ken-Ichiro Tsutsui
Professor, Tohoku University Graduate School of Life Sciences

[Research Interest]

Systems neuroscience of higher brain function:
The brain recognizes, makes judgments on, and commands the behavior. The brain is an outstanding device for information processing, and is also considered to be the entity of the "mind". The understanding of higher brain function is the central theme of science in the 21st century. I consider that, in order to unveil the mechanisms that realize higher brain function, we need to understand the functional architecture of the brain. We therefore aim to understand the mechanisms of higher brain function on the systems level, from the aspects of how the brain is formed and how it works. 1) Understanding the structure of the brain: We investigate the structure of the brain, which realizes higher brain function, on a multiscale level, namely on the cellular, local circuit, and inter-regional circuit levels. We therefore develop and use novel research tools, such as visualization of neural circuits based on circuit-specific tracing using plasmid or virus vectors. 2) Understanding the dynamics of the brain: We investigate the neuronal representation of various information, information processing on the local circuit level, and the inter-regional synchronization of neuronal activity by recording and analyzing the functional dynamics of the brain, using multiple-unit recording, circuit-specific functional imaging, transcranial magnetic stimulation (TMS), and functional magnetic resonance imaging (fMRI) technologies. On the basis of these, we aim to understand the entity that realizes higher brain function on a systems level.

[Biographical Sketch]

Ken-Ichiro Tsutsui graduated, and received his Ph.D. in Experimental Psychology, from the University of Tokyo. Since then he has been studying the neural mechanisms of higher cognitive functions, first as a JSPS Fellow in the Department of Physiology, Nihon University School of Medicine, next as a Research Associate in the Department of Anatomy, University of Cambridge, and then as an Associate Professor and later as a Professor in the Tohoku University Graduate School of Life Sciences.

SS4.3

Computational approaches in action vision and control and implications in basic and clinical research

M.A. Giese
Section Computational Sensomotorics, CIN & HIH, Department of Cognitive Neurology, University Clinic Tübingen, Germany

Abstract

In modern research computational models provide a new tool for the development of a deeper understanding of brain function. At the same time, computational methods can support the clinical diagnosis and therapeutic interventions in neurological diseases, such as Parkinson's disease or cerebellar ataxia. The talk will discuss approaches how biologically-inspired computational methods can support basic research in neuroscience and clinical applications.

First, we present a physiologically-inspired neural model of action recognition, which accounts for a variety of properties of mirror neurons. The model predicts and motivated new electrophysiological experiments that found the first neural correlate of the visual perception of causality in primate cortex. Second, we demonstrate how a computational method that allows to separate spatial and temporal variability of movements helped to devise efficient training procedures with substantial benefits for patients with cerebellar ataxia. It is shown how such methods can support the preclinical diagnosis of this disease, opening the possibility to preclinical interventions by rehabilitation training which is supported by computer games and VR technology. Finally, it is demonstrated how the concept of movement primitives, derived from biological motor control, helps to develop efficient technical algorithms for movement synthesis that can be exploited in humanoid robots and computer games for rehabilitation training.

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Martin A. Giese
Prof. for Computational Sensomotorics
Department of Cognitive Neurology
CIN & HIH
University Clinic Tübingen
Germany

[Research interests]

Theoretical neuroscience, biomedical engineering in neurology, biologically-inspired technology

[Biographical Sketch]

Martin A. Giese (PhD in Electrical Engineering) was a postdoc at CBCL (M.I.T.), and then headed the HONDA Cambridge Research Laboratory. In 2001, he founded the Laboratory for Action Representation and Learning at the Hertie Institute for Clinical Brain Research in Tübingen (Germany).

In 2007 he became Senior Lecturer at the Department of Psychology at the University of Bangor (UK), and since 2008 he is Professor for Computational Sensomotorics at the Hertie Institute and the Centre for Integrative Neuroscience at the University Clinic Tübingen, Germany. His research addresses the role of learning in action recognition and control, underlying neural mechanisms, and related biomedical applications in neurology.

SS5.1

Master Epigenetic Enzyme p300 in Life and Death

Tapas K. Kundu
CSIR-Central Drug Research Institute, Lucknow
and
Transcription and Disease Laboratory, Molecular Biology and Genetics Unit,
Jawaharlal Nehru Centre for Advanced Scientific Research, Jakkur Post, Jakkur, Bangalore-64, INDIA.

Abstract
Lysine acetyltransferase (KAT) p300 play pivotal role in the diverse physiological processes of higher eukaryotes. As a transcriptional coactivator it interacts with large array of transcription factors. However, its acetyltransferase catalytic activity is regulated by both post-translational modifications and interacting partners. We have discovered p53 allosterically activates the acetyltransferase activity of p300 through the enhancement of p300 autoacetylation. Cryo-electron microscopy revealed that the domain organization of p300 is substantially altered upon binding of p53, suggesting that a structural switch may underpin the activation. Acetylated p300 accumulates near the transcription start sites accompanied by a similar enrichment of activating histone marks near those sites. Abrogation of p53-p300 interaction by a site-directed peptide inhibitor, abolished p300-mediated histone acetylation, suggesting a crucial role played by the allosteric activation in p53-mediated gene regulation. Our results suggest that the allosteric activation of p300 by p53 plays a crucial role to modify epigenetic landscape and thereby in p53-depedent gene regulation. The KAT activity of p300 could also be activated by small molecule activator, which possess tremendous potential to be a new class of epigenetic therapeutics. The modulation of the p300 KAT activity thus to be explored for therapeutic interventions. Our recent findings on these phenomenons will be presented.

Tapas K. Kundu
Director
CSIR-Central Drug Research Institute, Lucknow
and
Transcription and Disease Laboratory, Molecular Biology and Genetics Unit,
Jawaharlal Nehru Centre for Advanced Scientific Research, Jakkur Post, Jakkur, Bangalore-64, INDIA.

[Research Interest]

Focus of Prof. Tapas K Kundu's group is to understand the different aspects of functional chromatin dynamics which are responsible for the gene regulation and its link to cellular physiology, differentiation and pathobiology. Apart from cell cycle regulation, muscle differentiation and neuroglial differentiation, they are investigating two different diseases in this context, namely cancer (oral cancer and breast cancer) and neurodegenerative disorders. Prof. Kundu's laboratory has also been actively working on the small molecule modulators of chromatin modifying enzymes. Apart from several small molecule inhibitors of lysine acetyltransferases and arginine methyltransferase, they have also discovered the first known small molecule activator of p300/CBP lysine acetyltransferase, which could activate histone acetylation in mice brain and thereby enhance the neurogenesis process and spatial memory.

[Biographical Sketch]

Prof. Tapas K. Kundu was awarded his PhD from the Indian Institute of Science, Bangalore, in the year 1995 with the best thesis award. Following his PhD, he had a short stint as a visiting foreign research associate in the National Institute of Genetics, Mishima, Japan, followed by a post-doctoral fellowship at the Rockefeller University, USA (1996-99). He joined Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Bengaluru as assistant Professor in 1999 and served as a Professor until 2018. Recently he has joined CSIR-Central Drug Research Institute as Director in August 2018.

Prof. Kundu has made significant contributions in the area of regulation of gene expression and its link to disease and therapeutics. He is not only elucidating the mechanisms of transcription regulation through the epigenetic modifications, but also targeting them to design new generation diagnostics, as well as therapeutics. Over the years, he has published several research papers in many international journals. Several patent applications from the laboratory have been granted and some are under process, which includes several academically important research reagents with potential commercial values, some of which have already been commercialized by renowned companies. He is the recipient of several awards, noteworthy among which are: the Shanti Swarup Bhatnagar prize from CSIR Government of India (2005), the National Academy of Science, India- Reliance Industries Platinum Jubilee Award (2008), the Sir JC Bose National Fellowship from DST Government of India (2010), the GD Birla award for scientific research (2011), The Ranbaxy Research Award 2011 in the field of Medical Sciences – Basic Research and India Innovation Award 2012 given by Merck Millipore 2012 (First place). He is the fellow of three major national academies of India and served as an editorial board member of the *Journal of Biological Chemistry (JBC) from 2011-2016*. He was instrumental to establish the *Asian Forum for Chromatin and Chromosome Biology and Chemical Biology Society, India*. Besides fundamental research, Prof. Kundu is also involved in teaching and organizing science outreach programs.

SS5.2

Gene regulatory network for hematopoietic stem and progenitor cell differentiation

Kazuhiko Igarashi[1,2], Hiroki Kato[1,3], Ari Itoh-Nakadai[4], Mitsuyo Matsumoto[1,2], Hideo Harigae[3]

[1]Department of Biochemistry, [2]Center for Regulatory Epigenome and Diseases, [3]Department of Hematology and Rheumatology, Tohoku University Graduate School of Medicine, Sendai, Japan. [4]Laboratory for Human Disease Models, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan

Abstract

Differentiation of hematopoietic stem and progenitor cells (HSPCs) is dependent on the functions of a set of transcription factors. While stochastic fluctuations in the expression of such transcription factors are likely involved in the initiation of differentiation of HSPCs (i.e. lineage commitment), it cannot explain the homeostasis of hematopoiesis nor "on-demand" hematopoiesis in response to environmental changes. We have found that transcription factors BACH1 and BACH2 regulate both commitment and on-demand hematopoiesis. BACH factors promote commitment to erythroid or lymphoid lineages by repressing the myeloid program of gene expression in HSPCs, whereas their activities are repressed in response to infectious and inflammatory conditions. We discuss possible mechanisms of lineage commitment of HSPCs, focusing on the gene regulatory network (GRN) composed of genes encoding key transcription factors, including BACH. The suggested GRN of BACH factors sheds light on the myeloid-based model of hematopoiesis as a guide to understanding the tuning of hematopoiesis in higher eukaryotes under homeostatic as well as infectious and inflammatory conditions, the evolutional history of the system, and aging and disease states, such as anemia due to inflammation and myelodysplastic syndrome.

Kazuhiko Igarashi
Professor, Department of Biochemistry, Tohoku University Graduate School of Medicine

[Research Interest]

My interest is in how transcription factors regulate biological phenomena such as differentiation, proliferation, and stress responses. Currently, my group is focusing on two transcription factors Bach1 and Bach2. Bach1 connects heme metabolism and the regulation of globin gene and oxidative stress-inducible genes. Bach2 regulates oxidative stress response and immune response. Our major discoveries include the regulation of antibody class switch and somatic hypermutation in B cells by Bach2 (Nature 2004, EMBO J 2010), regulation of the lung homeostasis and alveolar macrophages by Bach2 (J. Exp. Med. 2013, J. Biol. Chem. 2017), and the resolution of lymphoid, erythroid, and myeloid gene expression programs by the concerted functions of Bach1 and Bach2 (Nature Immunol. 2014, 2018; Cell Rep 2017). We are also working on how the synthesis of S-adenosylmethionine, the methyl group donor for methylation of histone, DNA, and RNA, is coupled with epigenomic and epitranscriptome regulation (Mol. Cell 2011, JBC 2013, Cell Rep 2017).

[Biographical Sketch]

1993-1995, Assistant Professor, Department of Biochemistry, Tohoku University School of Medicine
1995-1998, Lecturer, Institute of Basic Medical Sciences, University of Tsukuba
1998-1999, Associate Professor, Department of Biochemistry, Tohoku University School of Medicine
1999-2005, Professor, Department of Biochemistry, Hiroshima University School of Medicine and Graduate School of Biomedical Sciences
2005-present, Professor, Department of Biochemistry, Tohoku University Graduate School of Medicine
2017-present, Dean, Tohoku University Graduate School of Medicine

SS5.3

Identifying epigenetic regulators for targeted therapy in rhabdomyosarcoma

Reshma Taneja
Department of Physiology, National University of Singapore, Singapore

Abstract

Rhabdomyosarcoma is the most common soft-tissue sarcoma in children in which myogenic precursor cells fail to undergo differentiation. There are two major subtypes: alveolar rhabdomyosarcoma characterized by expression of PAX3-FOXO1 fusion protein; and the embryonal type, which is fusion-negative. Current standard of care is ineffective in high risk disease. Epigenetic de-regulation is a hallmark of cancer. To identify chromatin modifiers that sustain tumor growth and underlie the myogenic differentiation defect in RMS, we performed an epigenetic screen and found that inhibitors of G9a, a lysine methyltransferase that mediates histone H3 lysine 9 di-methylation significantly impact viability of ARMS cell lines. Targeting G9a expression or activity reduced cellular proliferation and motility *in vitro* and tumor growth *in vivo*. Using transcriptome and chromatin immunoprecipitation-sequencing analysis, we have identified a G9a-dependent epigenetic program that regulates tumor growth and inhibits myogenic differentiation. I will discuss our ongoing efforts to identify novel druggable targets by examining the altered epigenetic landscape in RMS.

Reshma Taneja
Associate Professor and Deputy Head, Department of Physiology, National University of Singapore

[Research Interest]
Epigenetic regulation of skeletal myogenesis; epigenetic alterations in human myopathies

[Biographical Sketch]
Reshma Taneja got her Ph.D. degree from the Indian Institute of Science. She did her postdoctoral training in the laboratory of Prof Pierre Chambon at the IGBMC in France. Her own laboratory, initially at the Mount Sinai School of Medicine in New York and currently at the National University of Singapore, has a long-standing interest in understanding the epigenetic landscape during skeletal muscle differentiation and its de-regulation in human myopathies. She has received multiple awards including a Scholar Award from the Leukemia and Lymphoma Society and the Basil O'Connor Award in the USA; as well as Faculty Research Excellence and Teaching Commendation Awards in Singapore.

SS6.1

Resistance to EGFR Tyrosine Kinase Inhibitors

Susumu Kobayashi, M.D., Ph.D.
Exploratory Oncology Research & Clinical Trial Center
National Cancer Center, Japan

Beth Israel Deaconess Medical Center,
Harvard Medical School, Boston, MA, USA

Abstract

The discovery of somatic mutations in *epidermal growth factor receptor (EGFR)* and development of EGFR tyrosine kinase inhibitors (TKIs) have revolutionized treatment for non-small cell lung cancer (NSCLC) with *EGFR* mutations. These oncogenic EGFR mutations trigger both pro-survival and anti-apoptotic signals, and inhibition of these aberrant signals causes massive apoptosis of tumor cells and tumor regression. Recently, it has been shown that osimertinib, a third-generation EGFR inhibitor that was originally developed to target the gatekeeper *EGFR*-T790M mutation, can be used as first-line therapy for advanced NSCLC with *EGFR* mutations. However, intrinsic and acquired resistance to osimertinib remains a serious problem in clinic. In this presentation, I will summarize the current knowledge about mechanisms of resistance to osimertinib and other EGFR TKIs. In addition, I will share our recent data demonstrating that β-catenin may contribute to the emergence of drug-tolerant cells in the presence of EGFR TKIs. Targeting these critical signaling pathways downstream of mutant EGFR may provide novel strategies to prevent lung cancer development or overcome resistance to EGFR TKIs.

Susumu Kobayashi, M.D., Ph.D.

Associate Professor, Harvard Medical School, Boston, MA
Chief, Division of Translational Genomics (Kashiwa), Exploratory Oncology Research & Clinical Trial Center, National Cancer Center Japan

[Research Interest]

Lung cancer. Myeloproliferative neoplasms. Acute leukemias. Oncogenic mutations. Apoptosis and Bcl-2 family proteins. Drug resistance, Differentiation therapy.

[Biographical Sketch]

Educational History

1994. 4.28 M.D. (Japan), Kyoto University, School of Medicine, Kyoto, Japan
1997-2001 Kyoto University, Graduate School of Medicine, Kyoto, Japan
2001-2002 Research Fellow, Kyoto University, Graduate School of Medicine, Kyoto, Japan
2003.3.24 Ph.D., Kyoto University, Graduate School of Medicine, Kyoto, Japan

Positions and Employment

1994-1995 Internship: Internal Medicine, Kyoto University Hospital, Kyoto, Japan
1995-1997 Residency: Internal Medicine, Hyogo Prefectural Amagasaki Hospital, Hyogo, Japan
2002-2006 Postdoctoral Fellow, Department of Medicine, Hematology/Oncology Division, Beth Israel Deaconess Medical Center, Boston, MA
2006-2009 Instructor in Medicine, Harvard Medical School, Boston, MA
2009-2016 Assistant Professor, Harvard Medical School, Boston, MA
2016-present Co-Director, Lung Cancer Research Program, Cancer Research Institute at Beth Israel Deaconess Medical Center, Boston, MA
2017-present Associate Professor, Harvard Medical School, Boston, MA
2018-present Chief, Division of Translational Genomics (Kashiwa), Exploratory Oncology Research & Clinical Trial Center, National Cancer Center Japan

Awards and Honors

2005 Research Fellowship award, Uehara Memorial Foundation, Japan.
2006 AACR-Merck Scholar-in-Training Award, American Association for Cancer Research
2009 Joan's Legacy/Michael R. Pascucci Lung Cancer Association Award, Uniting Against Lung Cancer
2010 Team Science Award/American Association for Cancer Research

SS6.2

Regulation of cell survival through post-translational modifications of MCL-1 in tumorigenesis

Kouhei Shimizu[1], Mitsuki Chiba[1], Satoshi Fukumoto[1], Wenyi Wei[2], Hiroyuki Inuzuka[1]

[1] Center for Advanced Stem Cell and Regenerative Research, Tohoku University Graduate School of Dentistry, Sendai, Japan

[2] Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Abstract

MCL-1 is an anti-apoptotic protein belonging to the pro-survival BCL-2 family. It is frequently amplified in a variety of cancers, and increased levels of MCL-1 contribute to apoptotic evasion through binding to, and sequestering, the pro-apoptotic BCL-2 family of proteins such as Bax and Bak. Therefore, MCL-1 is often regarded as a critical mediator of cell survival and therapeutic resistance. Emerging evidence has elucidated a crucial oncogenic role of MCL-1 in various cancers; however, the detailed molecular mechanisms by which MCL-1 oncogenic activity is regulated have not been fully understood. MCL-1 is a highly unstable protein, and we found that its stability is controlled by the SCF^{FBW7} E3 ubiquitin ligase complex. We have further demonstrated that MCL-1 is targeted for acetylation, leading to MCL-1 stabilization, thereby enhancing its oncogenic activity. These findings suggest that a crosstalk between two post-translational modifications, ubiquitination and acetylation, is a critical regulatory mechanism underlying MCL-1 oncogenic function.

Hiroyuki Inuzuka

Associate Professor, Tohoku University Graduate School of Dentistry

[Research Interest]

Dr. Inuzuka's main research interest is in understanding the molecular mechanisms of how dysregulations of protein degradation pathways lead to human malignancies and bone diseases.

[Biographical Sketch]

Dr. Hiroyuki Inuzuka is an Associate Professor at Tohoku University Graduate School of Dentistry. He received a Ph.D. in applied animal science from the University of Tokyo and performed his postdoctoral studies in the laboratory of Dr. Wenyi Wei on the regulation of SCF E3 ubiquitin ligases in cancer.

SS6.3

CRL3/SPOP promotes Nanog destruction to suppress stem cell traits and prostate cancer progression

Jinfang Zhang[1], Ming Chen[2],, Yasheng Zhu[3],, Xiangpeng Dai[1], Yinghao Sun[3], Xu Gao[3],, Pier Paolo Pandolfi[2],, Wenyi Wei[1]

[1] Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA.

[2] Cancer Research Institute, Beth Israel Deaconess Cancer Center, Department of Medicine and Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA.

[3] Department of Urology, Shanghai Changhai Hospital, Second Military Medical University, Shanghai, 200433, China.

Abstract

Frequent SPOP mutation defines the molecular feature underlying one of seven subtypes of human Prostate Cancer (PrCa). However, it remains largely elusive how SPOP functions as a tumor suppressor in PrCa. Here, we report that SPOP suppresses stem cell traits of both embryonic stem cells and PrCa cells through promoting Nanog polyubiquitination and subsequent degradation.

Mechanistically, Nanog, but not other pluripotency-determining factors including Oct4, Sox2 and Klf4, specifically interacts with SPOP via a conservative degron motif. Importantly, cancer-derived mutations in SPOP, or at the Nanog-degron (S68Y), disrupt SPOP-mediated destruction of Nanog, leading to elevated cancer stem cell traits and PrCa progression. Notably, we identify the Pin1 oncoprotein as an upstream Nanog regulator that impairs its recognition by SPOP and thereby stabilizes Nanog. Thus, Pin1 inhibitors promote SPOP-mediated destruction of Nanog, which provides the molecular insight and rationale to use Pin1 inhibitor(s) for targeted therapies of PrCa patients with wild type-SPOP.

Wenyi Wei
Professor, Beth Israel Deaconess Medical Center, Harvard Medical School

[Research Interest]

The major focus of research in my laboratory is aimed at understanding how APC and SCF activities contribute towards cell cycle regulation and subsequent tumor formation. More specifically, I am interested in elucidating the underlying mechanisms that define the oscillation of APC and SCF activity in different cell cycle phases. Currently I am pursuing the underlying mechanisms that timely regulate APC/Cdh1 activity in different cell cycle phases. Additionally, I am also interested in understanding whether other layers of crosstalk between the APC and SCF complex exist. Furthermore, I would like to identify novel downstream targets for both APC and SCF complexes, which will help pinpoint their functions in both cell cycle control and tumor formation. To this end, I have developed biochemical purification approaches that would allow me to identify novel downstream targets for APC/Cdh1 and SCF/Fbw7 complexes. In addition, I am also interested in defining the tumor suppressor function of Cdh1 utilizing conditional Cdh1 knockout mice. To achieve these goals, my lab will use multidisciplinary approaches including biochemical and genetic analysis. In the long term, I hope that a better understanding of the multilayer regulation of the delicate proteolysis pathways will lead us to the design of more efficient intervention strategies to combat cancer, cardiovascular disorders and other human diseases

[Biographical Sketch]

Dr. Wei received his B.A. degree from Shandong University in 1993 and then obtained his M.S. training in Chinese Academy of Science in 1996. Afterwards, Dr. Wei received his Ph.D. training in the MCB department at Brown University and his postdoctoral training in the laboratory of Dr. William Kaelin, Jr. at DFCI, Harvard Medical School. Dr. Wei became independent from 2006 in Department Pathology at BIDMC, Harvard Medical School. The major focus of the WEI laboratory is aimed at understanding how aberrant cell signaling events contribute to cell cycle dysregulation and tumorigenesis, which offer the molecular basis and the rationale to develop novel anti-cancer therapies targeting specific cell signaling pathways.

YSOS1-1/PS

Analysis of the *CDKN2A* gene in FAMMM Syndrome families reveals early age of onset for additional syndromic cancers

Candace D. Middlebrooks[1], Mark Stacey[2], Qing Li[1], Carrie Snyder[2], Trudy Shaw[2], Marc Rendell[3], Claire Ferguson[2], Theresa Townley[4], Peter Silberstein[5], Murray Joseph Casey[2,6], Stephen Lanspa[7], Joan E. Bailey-Wilson[1], Henry T. Lynch[2]

[1] Computational and Statistical Genomics Branch, National Human Genome Research Institute, National Institutes of Health, Baltimore, MD
[2] Hereditary Cancer Center, Creighton University, Omaha, NE
[3] The Rose Salter Medical Research Foundation, Newport Coast, CA
[4] Internal Medicine Department, Creighton University, Omaha, NE
[5] Department of Hematology/Oncology, Creighton University, Omaha, NE
[6] Department of Obstetrics and Gynecology, Creighton University, Omaha, NE
[7] Internal Medicine Department - Gastrointestinal Division, Creighton University, Omaha, NE

Familial atypical multiple mole melanoma (FAMMM) syndrome is a hereditary cancer syndrome that results from mutations in several genes including the *CDKN2A* gene. The syndrome is currently comprised of dysplastic nevi as well as melanoma, breast, pancreatic and lung cancer which are referred to as "concordant" cancers. As families with known *CDKN2A* mutations have been studied longitudinally, clinicians observed an abundance of other cancers or "discordant cancers." However, it was unknown whether these cancers were related to the syndrome. We sought to determine whether these discordant cancers also occur at higher frequencies and at earlier age of onset in carriers than non-carriers.

We studied 10 FAMMM syndrome families (N = 1085 individuals) in which a causal mutation in the *CDKN2A* gene was identified. We performed survival analysis as well as a mixed effects cox regression with age at follow-up or cancer event as our time variable and presence or absence of a concordant or discordant cancer as our censoring variable. The survival curves showed a significant age effect with carriers having a younger age at cancer onset for concordant (as expected) as well as discordant cancers than that of non-carriers. The cox regression models were also highly significant (P = 1.24E-27 and P = 5.00E-13 for the concordant and discordant cancers, respectively).

As melanoma screening in these high risk families identify non-melanoma skin cancers but not the other discordant cancers observed here, we sought to determine if there was evidence that new sites should also be commonly screened. Hence, we repeated the discordant cancer analysis with non-melanoma skin cancers removed to ensure that this group was not driving the effects seen. The result was still highly significant. These analyses support the hypothesis that carriers of mutations in *CDKN2A* in FAMMM syndrome have increased risk for early onset of several additional cancer types, suggesting that early screening for these cancers would be beneficial to carriers. The analysis of discordant cancers with the non-melanoma skin cancers removed indicate that additional anatomical sites should be screened in these families and clinical guidelines may need to be updated.

YSOS1-2/PS

Pathways of Progression from Intraductal Papillary Mucinous Neoplasm to Pancreatic Ductal Adenocarcinoma Based on Molecular Features

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[1] Department of Histopathology, Tohoku University Graduate School of Medicine, [2] Department of Cancer Pathology, Hokkaido University Graduate School of Medicine, [3] Department of Pathology, Teine-Keijinkai Hospital. [4] Institute of Biomedical Research, Sapporo Higashi Tokushukai Hospital [5] Department of Medicine, Asahikawa Medical University. [6] Division of Diagnostic Pathology, Tokyo Medical University [7] Center for Advanced Research and Education, Asahikawa Medical University [8] Diagnostic Partnering, Clinical Sequencing Division, Thermo Fisher Scientific [9] Center for Gastroenterology, Teine-Keijinkai Hospital [10] Department of Surgery, Teine-Keijinkai Hospital [11] Cancer Center, Keio University Hospital

Intraductal papillary mucinous neoplasms (IPMNs) are regarded as precursors of pancreatic ductal adenocarcinomas (PDACs), however, the mechanism of the progression is not well understood, which may intervene precise assessment of a cancer risk in patients with IPMNs. We investigated associations of IPMNs with concurrent PDACs by histologic and genetic analyses. In 30 pancreatectomy specimens concurrently with PDAs and IPMNs, 168 lesions of PDAs and IPMNs, including incipient foci, were mapped, microdissected, and examined for mutations in 18 PDAC-associated genes and protein expression of tumor suppressors. By clonal relatedness determined by shared driver mutations between PDAC and concurrent IPMN, the examined cases were classifiable into three distinct subtypes of molecular progression of IPMN toward PDAC. 12 PDACs harbored driver mutations shared by concurrent IPMNs, which was coined as sequential subtype. This subtype was characterized by less *KRAS* diversity in incipient foci with frequent *GNAS* mutations. 11 PDACs harbored driver mutations partially shared by concurrent IPMNs, which was coined as branch-off subtype. In this subtype, PDAC and concurrent IPMN harbored identical *KRAS* mutations but different *GNAS* profile although they are closely located. Additional whole-exome sequencing and methylation analysis for these lesions indicated clonal with divergent progression, i.e., fork-like relatedness. 10 PDACs harbored distinct driver mutations compared to concurrent IPMNs, which was coined as de novo subtype. Notably, the branch-off and the de novo subtype were related to the substantial heterogeneity in early clones marked by various *KRAS* mutations. Furthermore, patients with PDACs of the branch-off subtype were found to have longer disease-free survival than patients with PDACs of the de novo or the sequential subtypes. Detailed histologic and genetic analysis of PDACs and concurrent IPMNs uncovered three different ways of molecular progression of IPMNs toward PDAs, namely, sequential, branch-off, and de novo subtypes. This subtype classification may be associated with clinicopathological features and serve for designing an efficient surveillance program of patients with IPMN.

YSOS1-3/PS

The mitochondria gain-of-function phenotype in oncogenic Ras-driven metastatic breast cancer

May Yin Lee[1], Yanzhe Li[1], Jason Tham[1], Esther Peh[2], Ying Swan Ho[2], Salanne Lee[3], Kah Min Ang[3], Ivy Low[3], Siming Ma[1], Cheryl Phua[1], Edwin Lim[1], Wai Leong Tam[1,4]

[1] Genome Institute of Singapore, A*STAR

[2] Bioprocessing Technology Institute, A*STAR

[3] Flow Cytometry Core, Singapore Immunology Network, A*STAR

[4] Cancer Science Institute, Singapore

Metastasis is the cause of death in 90% of breast cancer cases. The dysregulation of cellular energetics and in particular, the dysregulation of mitochondria, the energy generating organelle of the cell has been linked closely to the metastatic phenotype. However, how and when exactly does the mitochondria confer a malignant phenotype to the cell requires greater clarification. We established a panel of cell lines harbouring mutations that frequently occur in breast cancers and found that amongst these, KRas G12V and HRas G12V-transformed cell lines give rise to aggressive basal subtype breast cancers and metastasis in the lungs. Preliminary studies show that compared to the primary tumor, lung metastatic cells upregulate mitochondria oxidative phosphorylation complexes mRNA, mitochondria DNA copy number, membrane potential and reactive oxygen species. While tumor and metastatic cells upregulate autophagy compared to wildtype cells, we show that metastatic cells may accumulate mitochondria by downregulating autophagy. Serial transplantation of primary tumor and lung metastatic cell lines lead to the formation of more aggressive primary tumors and lung metastasis at a shorter latency and with increased mitochondria DNA copy number. Metabolomics analyses show the differential regulation of glycerolphospholipid, pyrimidine, and amino sugar and nucleotide metabolism in lung metastatic cells. Together, we propose that mitochondria gain-of-function and the balance of glycerolphospholipids and other metabolites may govern the metastatic potential of cells. A clearer picture of the above would enable the more precise identification of targets and therapeutic strategies to target malignant mitochondria and inhibit metastasis.

YSOS1-4/PS

Regulation of chromatin dynamics and autophagy by non-histone chromatin protein PC4: Implications in Breast cancer

Sweta Sikder[1], Sujata Kumari[1], Manoj Kumar[1], Srikumar Chellapan[2], K.S. Gopinath[3], Ravi Manjithaya[4], Tapas K Kundu[1]

[1] Transcription and Disease laboratory, Molecular Biology and Genetics Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore, India

[2] Department of Tumour Biology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida

[3] Bangalore Institute of Oncology, Bangalore, India.

[4] Autophagy Laboratory, Molecular Biology and Genetics Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore, Karnataka, India

The highly abundant multifunctional nuclear protein PC4 is an integral chromatin component involved in the genome compaction and its 3-dimmensional organization. PC4 is an essential protein for mammalian life, downregulating its expression induces rapid proliferation and induction of autophagy. Knocking down of PC4 alters the epigenetic landscape dramatically and confers radiation resistance to the cells. In this study, we elucidate the detailed mechanism of regulation of autophagy through chromatin dynamics altered by PC4 knockdown. Validating its important role in various other physiological functions of the cell, PC4 has been reported to be aberrantly expressed in different cancers. Quite contrary to the upregulated expression of PC4 in other cancers, we find that it is significantly downregulated in Breast Cancer tissues derived from patient samples and also in some of the highly invasive Breast cancer cell lines. Stable knockdown of PC4 in Breast cancer line enhances its tumorigenic properties. To elucidate the molecular mechanism we have identified a family of miRNA which directly bind to the 3'UTR region of PC4 and mediate its downregulation. Correlating with patient samples, where PC4 was found to be significantly down regulated in breast cancer tissues and cell lines, the expression analysis of these candidate miRNAs were found to be negatively correlated to PC4 expression. Downregulation of PC4 led to the uniform progression of Breast tumor in invivo mice model. The underlying gene signature and the pathway leading to enhanced tumor formation upon PC4 knockdown are being investigated.

YSOS1-5/PS

Quantifying transcription at Single Molecule level reveals linked cycles of chromatin remodeling and transcription factor binding at gene promoter

Gunjan Mehta[1], David Ball[1], James McNally[2], Tatiana Karpova[1]

[1] CCR/LRBGE Optical Microscopy Core, National Cancer Institute, National Institutes of Health, Bethesda, MD

[2] Institute for Soft Matter and Functional Materials, Helmholtz Center Berlin, Berlin, Germany

Transcription is a dynamic process and binding of transcription factors (TFs) to gene promoters is a transient process, often in the range of seconds. It is unknown how the dynamic binding of transcription factors is molecularly linked to chromatin remodeling and transcription. We have developed a Single-Molecule Tracking (SMT) method to visualize and quantify the binding of individual molecules of the TFs (Ace1) at specific gene promoters (*CUP1*) in yeast S. cerevisiae. Using SMT, we show that the chromatin remodeler RSC speeds up the search process of the TF Ace1p for *CUP1* promoter. We quantified *CUP1* transcription parameters using smFISH and computational modelling (gene bursting model) to demonstrate that RSC regulates transcription bursts of *CUP1* only by modulating TF occupancy but does not affect initiation and elongation rates. We show by SMT that RSC binds to activated promoters transiently. Therefore, transient binding of Ace1p and rapid bursts of transcription at *CUP1* may be dependent on short repetitive cycles of chromatin remodeling and nucleosome mobilization. This type of regulation reduces the transcriptional noise and ensures a homogeneous response of the cell population to heavy metal stress.

YSOS1-6/PS

A novel machinery for maintenance of faithful chromosome segregation

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Most of the cancer cells show abnormal number of chromosomes. The chromosome number is maintained by equal chromosome segregation in mitosis. The rate of chromosome missegregation in cancer cells is generally higher than that in normal cells, suggesting that a robust system maintaining faithful chromosome segregation is defective in cancer cells. Proper attachment of kinetochores to spindle microtubules is a prerequisite for faithful chromosome segregation, and phosphorylation of kinetochores by Aurora B kinase, which localizes to inner centromere, is known as a mechanism for the correction of erroneous kinetochore-microtubule attachments. Through careful observation, we found that the kinetochore phosphorylation disappeared in metaphase in cancer cell lines, but remained in normal cell lines. The finding prompted us to pursue the possibility that the kinetochore phosphorylation in metaphase as a novel mechanism for the maintenance of faithful chromosome segregation. We addressed how kinetochores are phosphorylated in metaphase, and found that Aurora A kinase that resides in centrosomes, but not Aurora B, is responsible for the phosphorylation. Although centrosomes are distant from kinetochores in metaphase, Aurora A distributed on the spindle supposedly phosphorylates kinetochores, which is facilitated by chromosome oscillation, a continuous chromosome motion around the spindle equator in metaphase. Interestingly, chromosome oscillation was reduced in cancer cell lines, and enhancing the oscillation resulted in the increased kinetochore phosphorylation, indicating the correlation between Aurora A-mediated kinetochore phosphorylation and chromosome oscillation. Furthermore, inhibition of Aurora A in normal cell lines in metaphase caused an increase in the rate of erroneous kinetochore-microtubule attachments and chromosome missegregation. Our data suggest that Aurora A phosphorylates metaphase kinetochores in normal cells depending on chromosome oscillation, which is required for proper kinetochore-microtubule attachment and equal chromosome segregation. We found that phosphorylation level of metaphase kinetochores and chromosome oscillation are decreased in various cancer cell lines. We propose that Aurora A-mediated kinetochore phosphorylation through chromosome oscillation in metaphase is a novel mechanism for the maintenance of faithful chromosome segregation, which eliminates the remaining erroneous kinetochore-microtubule attachments after general error correction by Aurora B during prometaphase. Reduced kinetochore phosphorylation in metaphase may be a cause of the increased chromosome missegregation in cancer cells.

YSOS2-1/PS

In vitro and in vivo knock-out system labelled by fluorescent protein via microhomology-mediated end joining

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Gene knock-out is important for understanding its function and genetic disorders. CRISPR/Cas9 has great potential to achieve this purpose. However, we cannot analyze only in knock-out cells among cell populations since knock-out cells by CRISPR/Cas9 would not be labelled with fluorescence. Here, we developed a new system which enables the knock-out cells label with fluorescent protein through microhomology-mediated end joining (MMEJ)-based knock-in. Moreover, we have succeeded in cell-type specific knock-out by the shorten *Brn3b* promoter-driven *Staphylococcus aureus* Cas9. Combination with recombinant adeno-associated virus (rAAV), we delivered our system to retina, knocked out *Carnitine acetyltransferase* (*CAT*) only in retina ganglion cells (RGCs) and evaluated fluorescent-labelled RGCs.

YOS2-2/PS

Categorizing Autism Spectrum Disorder Candidate Genes

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by behaviors such as social deficits, difficulties with communication, repetitive motor movements, and abnormal responses to sensory stimuli. Previous research has shown that these behaviors are caused by an imbalance in glutamatergic and GABAergic neural activity. Additionally, recent genomic studies have yielded a list of candidate genes that may be implicated in ASD. However, ASD is a broad diagnosis encompassing distinct behavioral phenotypes. Furthermore, the candidate genes are predominantly undefined, and it is expected that they underly different aspects of the disorder. Understanding the effects that each candidate gene has on neurodevelopment is necessary for future genetic studies of autism, and it will allow for improved therapeutics. Therefore, our goal is to link ASD candidate genes to particular neurodevelopmental phenotypes and, consequently, be able to categorize the genes according to similarities between their phenotypes. Zebrafish are an effective model organism in ASD research because they are transparent as larvae which enables live imaging of their developing brains. They also have a high genetic homology to mammals, develop rapidly, and show high fecundity. For those reasons, we knockdown ASD candidate genes in zebrafish using the CRISPR/cas9 system. Following gene knockdown, we study abnormal responses to sensory stimuli and whole brain structure imaging in mutant zebrafish. Zebrafish, when exposed to a startling stimulus, will display escape responses. Prepulse inhibition (PPI) occurs when an organism has a decreased startle response if a weaker stimulus is followed by the stronger startling stimulus. Since ASD patients display an abnormal response to sensory stimuli, and PPI has been shown to be altered in other neurodevelopmental disorders, we expect to see an atypical PPI in the mutant zebrafish.
CRISPR injections at the one-cell stage are performed to make mutations in autism candidate genes. At six days post-fertilization, zebrafish larvae are individually tested to analyze their escape response to acoustic stimuli. They are exposed to stimuli of various strengths with different interstimulus intervals in a pseudo-random pattern. They are then analyzed for how frequently they display escape responses, and the strength, duration, and speed of their responses. In parallel, CRISPR injected larvae are imaged using confocal microscopy to examine glutamatergic and GABAergic neuronal activity. We have currently screened seven of the known autism candidate genes. Most notable of our behavioral results were the G0 screen of scn1lab, which is a gene implicated in forming a voltage-gated sodium channel. Compared to the control group, the scn1lab mutants exhibited little to no PPI; this may indicate decreased GABAergic activity. We also completed the G0 screen of mecp2 which is a gene that assists in gene regulation by means of DNA methylation. The mecp2 mutant zebrafish larvae presented with increased responsiveness; we theorize that it may be due to abnormal glycinergic activity. SThus far, we have screened CRISPR injected G0s exclusively. While we will continue to screen G0s, we will also confirm our initial findings with stable mutant lines. Therefore, as we obtain more results, we can accurately begin to categorize the ASD candidate genes by their phenotypes. Ultimately, this project will deepen our understanding of the link between the genes that are hypothesized to be implicated in ASD and the behaviors associated with the disorder.

YSOS2-3/PS

Multifunctional fibers for elucidating astroglial basis of anxiety

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Brain makes us human. To fully understand how our brain works, we need technologies that can interface with delicate brain tissues with minimal elicited tissue response and probe brain activities across their multiple signaling mechanisms. Leveraging the thermal drawing process, conventionally used in the telecommunication industry to produce optical fibers, we have pioneered multifunctional fibers that have integrated with optical, electrical and chemical modalities, yet maintained its flexibility and overall size comparable to human hairs. Such innovation in interfacing with brain opens a new window that allows us to look into its functions in unprecedented detail.
Here engineering innovations will be discussed first, which is about the pioneer work of multimaterial and multifunctional fibers as a collaborative effort between our university, MIT and Virginia Tech. Then further deployment of these fibers in resolving particular biological questions will be discussed in detail. Such fibers are of great usefulness in studying glial modulation on neural circuits from amygdala to medial prefrontal cortex and its mediation on the anxiety behaviors, via the combination with transgenic mouse models.

YSOS2-4/PS

Association of Amyloid Positivity with Volume Loss in Temporal Lobes Differs between Men and Women in Cognitively Normal Older Adults

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Amyloid positivity is a biomarker of AD pathology, yet the associations between amyloid positivity and brain volumetric changes, especially in the hippocampus, are inconsistent. We hypothesize that sex differences in associations may contribute to inconsistent findings among cognitively normal older adults. Using linear mixed effects models with random intercepts and slopes, we examined sex differences in the association of amyloid positivity with prospective volumetric changes (mean=3.3 visits) of parahippocampal gyrus (phg), hippocampus, entorhinal cortex (erc), precuneus, and fusiform among 171 Baltimore Longitudinal Study of Aging participants aged ≥55 years. Amyloid positivity was defined by a mean 11C-Pittsburgh Compound B (PiB) distribution volume ratio (DVR) cut-off of 1.062. All analyses included age, race, sex, education, APOE e4 carrier status, two-way interactions of these covariates with time, a two-way interaction between sex and PiB+ status, and three-way interaction of sex and PiB+ status with time. Sex modified the association of PiB+ status and rates of volumetric declines in occipital GM (β=-0.409, SE=0.218, p=0.062), the fusiform (β=-0.117, SE=0.049, p=0.019), and parahippocampal gyrus (β=-0.037, SE=0.019, p=0.053), with PiB+ men having steeper rates of decline. PiB+ men had steeper rates of volumetric declines in phg (β=-0.051, SE=0.013, p<0.001) and erc (β=-0.029, SE=0.012, p=0.014) than PiB- men, while there was no difference in rates of volumetric change between PiB+ and PiB- women. Amyloid positivity is a predictor of volume loss in brain regions affected by early AD pathology in men, but not women, among cognitively normal older adults.

YSOS2-5/PS

Structural biology of β-sheet ligand-type PET probes and monoamine oxidase

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Several neurodegenerative diseases are characterised by the deposition of protein aggregates such as amyloid plaques and tau tangles found in the brain of patients with Alzheimer's disease (AD), termed 'proteinopathies'. These protein aggregates share cross-β-sheet structures in which individual β-strands run perpendicular to the fibre axis. For the imaging of these protein aggregates, the most common approach was to develop a positron emission tomography (PET) ligand that bound selectively to cross β-sheet structures of protein aggregates. Recent advances in the development of PET radiopharmaceuticals have enabled the successful visualisation of amyloid plaques and tau tangles in living individuals. However, recent studies have shown the off-target binding of these kinds of PET ligands to monoamine oxidase-B (MAO-B). On the structural point of view, MAO-B contains well-ordered β-sheet structures creating substrate cavity and entrance cavities. Based on this evidence, we have hypothesized that β-sheet ligands are a potential binder for MAO-B. First, we investigated the binding ability of various β-sheet ligands including amyloid and tau PET tracers. Now, we are trying X-ray crystallography to better understanding of the binding nature between β-sheet ligands and MAO-B as off-target interaction to develop new selective PET tracers.

YSOS2-6/PS

Interactions of synthetic cannabinoids with the 5HT1A receptor

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Synthetic cannabinoid (SC) use among recreational drug users has continued to increase worldwide, often leading to serious adverse effects including hallucinations, disorientation, coma and death. Many SCs contain an indole moiety in their structure unlike the naturally occurring Δ9-tetrahydrocannabinol (Δ9-THC), the primary psychoactive component of cannabis. Compared to Δ9-THC, SCs are associated with a greater incidence of serious adverse effects, leading to speculation that non-CB1R sites of action could be involved. Serotonin (5-HT) receptors represent logical "off target" candidate sites for SC interaction, as many indole ring-containing molecules exhibit binding at these 5-HT receptors. Here, we examined the interactions of SCs at 5-HT receptor subtypes to evaluate possible non-CB1R mechanisms of action. Using bioluminescence resonance energy transfer (BRET) receptor function assays, indole-containing SCs were screened against various monoaminergic receptors associated with disorders of the central nervous system. We found that the SCs AM2201 and JWH018 displayed minimal orthosteric interactions with the tested monoaminergic receptors, but exhibited positive allosteric modulation of the 5HT1A receptor (5HT1AR). This allosteric modulation of the 5-HT1AR was not observed with Δ9-THC. Consistently, molecular dynamics simulations showed more stable binding of 5HT in the orthosteric site of the 5HT1AR when AM2201 occupied an allosteric cavity in the extracellular vestibule of the receptor. In support of this model, in vitro electrophysiology experiments in mice lacking the CB1R (CB1R-/-) showed that G protein-coupled inwardly-rectifying potassium channel (GIRK) currents, activated by 5-HT1AR agonists, were enhanced by AM2201. Moreover, the hypothermic response to 5HT1AR stimulation in CB1R-/- mice was also significantly potentiated by AM2201.
Together, these results suggest that positive allosteric modulation of the 5HT1AR represents a novel off-target mechanism of action for indole ring-containing synthetic cannabinoids, and we hypothesize that this modulation mediates some adverse effects of these illicit drugs.

YSOS2-7/PS

A Novel Allosteric Drug That Stimulates Insulin Secretion by Acting on β-Cell M3 Muscarinic Acetylcholine Receptors

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Type 2 diabetes (T2D) has emerged as a global threat to human health worldwide. The key hallmarks of T2D are insulin resistance of peripheral tissues and insufficient insulin secretion by pancreatic β-cells. We recently demonstrated that the M3 muscarinic acetylcholine (ACh) receptor (M3R), a G-protein coupled receptor that is selectively linked to Gq-type G proteins, plays a key role in promoting insulin release. Stimulation of β-cell M3Rs leads to increases in intracellular calcium levels, thereby stimulating glucose-induced insulin release. Until now, no M3R-specific agonists have been developed, primarily due to the conserved nature of the primary (orthosteric) binding sites found throughout the muscarinic receptor family (M1-M5 receptors). Interestingly, a novel small molecule drug, VU0119498, has been developed recently that selectively acts on a secondary (allosteric) binding sites on the M3R. This allosteric site varies considerably in sequence between the M1-M5 receptors, allowing the devolvement of novel, receptor subtype-selective muscarinic drugs. Specifically, VU0119498 acts as a positive allosteric modulator (PAM) at the M3R, enhancing ACh-induced signaling at this receptor subtype. Our aim was to study whether VU0119498 stimulates M3R-mediated insulin release and has beneficial metabolic effects in a mouse model of diabetes. We found that VU0119498, an M3R PAM, enhances ACh-mediated insulin secretion in vitro and in vivo by acting on β-cell M3Rs. Metabolic studies with WT and mutant mice demonstrated that VU0119498 greatly improves glucose tolerance and insulin resistance in obese mice. Our data strongly suggest that VU0119498 and other M3 PAMs may become therapeutically useful as novel antidiabetic drugs.

YSOS3-1/PS

Surprise at tissue-resident macrophages in development: brain-resident macrophages control radial glia and cortex development

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The central nervous system (CNS) and its meninges host a diverse populations of macrophages with fundamental significance to both CNS health and disease. Although the importance of these cells is recognized, their phylogenetic basis and exact functions in the CNS continue to be explored. Here, we describe the interrelationships of multiple subpopulations of embryonic macrophages in the CNS with distinct spatial, cellular and molecular characteristics. We uncover a homogenous LYVE1+/F4/80+ macrophage progenitors located on the CNS meningeal coverings. These cells retain differentiation potential to give rise to several LYVE1-/F4/80+ macrophage subpopulations inside the CNS with unique positioning and molecular identify to that of perivascular macrophages and microglia. We further found that the LYVE1+/F4/80+ meningeal macrophages, but not the LYVE1-/F4/80+ macrophages/microglia, are in direct cell-cell contact with the endfeet of radial glial cells through IGF1-Akt signaling. Elimination of macrophages in the developing CNS results in dilated ventricles and significantly diminished cortical neuronal layers, coincident with a markedly reduction in the radial glial endfeet. These defects in the embryonic brains are due to a decrease in the mitotic divisions of radial glial cells and an increase in cell apoptosis. Conversely, administration of SC79, a small molecule Akt activator, to the macrophage-depleted brains restore the proper ventricle size and replenish the neuronal layers of the neocortex. Our results provide a comprehensive atlas of embryonic macrophages in the CNS and highlight a meningeal macrophage-radial glia interaction through IGF1-Akt signaling that is indispensable for the formation of neocortex in the developing brain.

YSOS3-2/PS

How TLR9 Signaling shapes the survival, differentiation and the metabolism of B cells

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The signaling cascades initiated by the binding of the antigen to the B cell receptor (BCR) leads to rapid increases in cellular respiration, nutrient uptake and expression of various activation markers. These early changes prepare the B cell to further differentiate into professional antibody producing cells. However, unless a second, independent stimulus is received soon after antigen binding, BCR signaling does not lead to B cell proliferation and differentiation. Instead, in the absence of a second signals, antigen binding to the BCR leads to a dysregulation of cellular calcium homeostasis which in turn leads to mitochondrial dysfunction and a phenomenon called activation induced cell death. The second signal can be provided by Toll like receptor (TLR) signaling to pathogen products, indicating the presence of an acute infection or through B cell-T cell interactions that rules out that the initial antigen was a prohibited self-antigen that would lead to autoimmunity. Additionally, there is an interplay between TLR versus T cell mediated second signals, namely that TLR signaling trumped the need for the antigen-stimulated B cell to interact with T cells to receive a 'go' signal. TLR stimulation decreased B cells' ability to capture, process and present antigens to solicit help from T cells. Rather TLRs directly boosted B cell antibody and cytokine secretion and proliferation. Thus, TLR signals drive B cells toward rapid T cell-independent differentiation to plasma cells providing rapid neutralizing antibody production to fight off infections quickly. In contrast B cells that receive their survival signals from T cells are induced to undergo a time-consuming process that is necessary for antibody affinity maturation and long-lasting immune memory. Therefore, the TLR driven shortcut to quick antibody comes with a price which is the absence of "crème de la crème" antibodies that would protect the body from subsequent infections for years to come.

YSOS3-3/PS

PRMT5 Modulates Splicing for Genome Integrity and Preserves Proteostasis of Hematopoietic Stem Cells

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Protein arginine methyltransferase 5 (PRMT5) has been identified as a promising therapeutic target in various solid and hematologic cancers, while clinically-favorable PRMT5 inhibitors have been developed. Functionally, PRMT5 has a well-established role in regulating splicing, and is essential for hematopoiesis. However, the requirement for PRMT5 in the hematopoietic stem cell (HSC) compartment remains unclear.

Here, we demonstrate that HSC quiescence and viability are severely perturbed upon PRMT5 depletion. Interestingly, depletion of PRMT5 activity also increases HSC size, PI3K/AKT/mTOR pathway activity, and protein synthesis rate; thus, highlighting a potential role for PRMT5 in regulating HSC proteostasis. We further uncover a critical role for PRMT5 in maintaining HSC genomic integrity by modulating splicing of genes involved in DNA repair. We found that reducing PRMT5 activity upregulates exon skipping and intron retention events that impair gene expression. Notably, genes across multiple DNA repair pathways are affected. Consequently, loss of PRMT5 activity leads to oxidative DNA damage that triggers p53 activation, induces apoptosis, and culminates in rapid HSC exhaustion; which is significantly delayed by co-depletion of p53. Collectively, these findings establish PRMT5-mediated splicing as a major determinant of HSC fate, and highlight the need to maintain an adequate level of PRMT5 activity in HSCs.

YSOS3-4/PS

Identification of the tooth-specific novel transcription factor AmeloD and its role during tooth development

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Tooth is a unique organ that not only mesenchyme- but also epithelium-derived tissue will be mineralized to form proper shape. The regulation of size and shape is essential for the development of functional teeth, however, its molecular mechanisms are poorly understood.We have previously identified several novel genes using tooth germ cDNA library to identify the mechanism of tooth development. In this study, we focused on a tissue-specific basic-helix-loop-helix(bHLH) transcription factor during tooth development. Tissue-specific bHLH transcription factors are known to be important for organ development, however, tooth-specific bHLH factors have not reported. Here, we aim to identify a novel bHLH factor from a tooth germ cDNA library. We screened a rat tooth germ cDNA library using the yeast-two-hybrid system with the bHLH factor E12 fused protein as a bait. We isolated one of the bHLH factors that is originally registered as a pseudogene and cloned its full-length cDNA by 5'RACE method. We registered it to Genebank as a functional novel gene and named it as "AmeloD". We first examined the expression of AmeloD in various tissues by northern blotting and found that AmeloD was highly expressed in teeth. We then analyzed its expression pattern during tooth development by immunostaining. AmeloD was specifically expressed in the inner enamel epithelium (IEE) but not mesenchymal tissue. To determine the role of AmeloD during tooth development, we created AmeloD knockout (KO) mice. Micro-CT analysis showed that AmeloD KO mice developed smaller size and volume of molars than that of wild-type. By immunostaining of developing tooth germs, we found that the expression of E-cadherin, a cell adhesion molecule, was increased in AmeloD KO IEE cells. Next, we examined the effect of AmeloD in a mouse-derived dental epithelial cell line CLDE. RT-qPCR revealed that overexpression of AmeloD suppressed E-cadherin expression in CLDE cells. Further, we analyzed the effect of AmeloD on E-cadherin promoter region by ChIP assay and luciferase reporter assay. AmeloD bound to E-cadherin promoter region and suppressed its transcriptional activity. In addition, overexpression of AmeloD promoted cell migration in wound healing assay. Thus, AmeloD is one of the morphogenic factor of teeth development by suppressing E-cadherin to promote IEE cell migration. The novel transcription factor AmeloD stimulates dental epithelial cell motility by suppressing E-cadherin expression during tooth development.

YSOS3-5/PS

The transcription factor Foxc1 is necessary for Ihh-Gli2-regulated endochondral ossification.

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Endochondral bone formation is an essential process for skeletal development. It consists of series of events including an aggregation of mesenchymal cells, their differentiation into chondrocytes, followed by chondrocyte proliferation, hypertrophy and apoptosis. These processes are very complicated but well-organized and various transcription factors assemble into transcriptional networks that orchestrate the endochondral bone formation. To understand the molecular mechanism underlying endochondral bone formation, we previously identified several transcription factors using a high-throughput assay system and RNA-seq analysis. So far we have used chondrogenic cell lines for the identification of transcription factors. However, these cloning strategy has limitations because cell lines are not physiological chondrocytes and the biological characteristics is completely different from natural chondrocytes. Cartilage tissue is very unique tissue characterized by abundant extracellular matrix, avascular and hypoxia and it is very difficult to identify functional and physiological transcription factors using cell lines. Thus, to identify physiological and functional transcription factors involved in chondrogenesis, it is necessary to establish novel cloning system using chondrocytes which was directly isolated from growth plate. We performed FACS-assisted microarray using reporter mice, in which chondrocytes are fluorescently labelled with Venus driven by *Col2a1*-gene promoter, and identified Forkhead box c1 (Foxc1) as a transcription factor selectively expressed in chondrocytes. We found Foxc1 regulates endochondral bone formation through functional interaction with Ihh-Gli2 signaling. It should be noted that this functional collaboration is significantly impaired in the pathological *FOXC1* missense mutation (F112S) observed in Axenfeld-Rieger syndrome characterized by skeletal malformations. We identified a novel function for Foxc1 as a critical transcription factor for endochondral ossification. This function modulates the expression of chondrogenic genes through its physical and functional interaction with Ihh-Gli2 signalling. Our findings suggest a novel molecular mechanism underlying endochondral bone formation that has clinical relevance during skeletal development.

PS1

Tyrosine kinase receptor TIE-1 serves as a novel therapeutic target in PI3K highly expressing ovarian cancer

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Tyrosine kinase receptor TIE-1 is a cell surface protein expressed exclusively in endothelial cells. The only function of TIE-1 is known for playing a critical role in angiogenesis and blood-vessel stability. In recent years, increased TIE-1 expression was observed in many types of cancers, however the biological significance and mechanism remain unknown and further research is needed. Thus, in the present study, we investigated the tumor biological functions of TIE-1 in refractory ovarian cancer.

Ovarian cancer cells were cultured in Dulbecco's modified Eagle's medium (DMEM), supplemented with 10% fetal bovine serum (FBS) at 37°C in a humidified incubator containing 5% CO_2. Cells were transfected with 5 nM of siRNAs using Lipofectamine RNAiMAX transfection reagent. Living cell number was measured by trypan blue-exclusion test. The specific proteins were detected by immunostaining.

Treatment of ovarian cancer cells with siRNA against TIE-1 decreased the expression of key molecules in PI3K/Akt signaling pathway, such as p110 α , phospho-Akt, suggesting TIE-1 seems to be related with the PI3K/Akt pathway. Furthermore, knock-down of TIE-1, significantly decreased cell proliferation in PI3K highly expressing cell lines (SKOV3, JHOC7), but not in PI3K-low-expressing cell lines (TOV112D, A2780). These results suggest that inhibition of TIE-1 decreases cell growth in PI3K highly expressing cells. Mechanistically, TIE-1 participates in cell growth, cell proliferation by regulating PI3K/Akt signaling pathway.

Taken together, our findings strongly implicate that TIE-1 could represent as a novel therapeutic target in PI3K highly expressing ovarian cancer cells.

PS2

The mechanism of epigenetic regulation by the interaction between nuclear FABP7 and ACLY

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Intracellular lipid dynamics is involved in the epigenetic status including DNA methylation and histone modification. Fatty acid-binding proteins (FABPs) bind and solubilize long chain fatty acids, controlling lipid homeostasis. FABP7 has high affinity with n-3 PUFAs, and it is expressed by astrocytes in the brain and oligodendrocyte progenitor cells during brain development. FABP7 is highly expressed by several malignant tumors such as glioblastoma and melanoma, we previously reported that FABP7 regulates lipid raft function; the main source of cellular activity in response to external stimuli, through the expression of caveolin-1, a scaffold protein of lipid raft. In this study, we sought to examine how FABP7 regulated the caveolin-1 gene expression focusing on epigenetic modification.

The expression of caveolin-1 (*Cav1*) was increased in FABP7- overexpressed NIH-3T3 cells. CHIP assay revealed that FABP7-overexpression increased the level of histone-H3 lysine27 acetylation on *Cav1* promoter in NIH-3T3 cells. Overexpression of NLS (nuclear localization signal)-tagged FABP7 further increased *Cav1* expression, but NES (nuclear export signal)-tagged FABP7 did not affect it. Mass spectrometry analysis revealed that FABP7 strongly binds to ATP citrate lyase (ACLY), which is essential enzyme for the production of nuclear acetyl CoA. Quantitation experiments showed that the level of nuclear acetyl CoA was higher in NLS-tagged FABP7-overexpressed cells compared with control, but there was no difference between NES-tagged FABP7-overexpressed cells and control. Furthermore, the assay using malate dehydrogenase coupled method revealed that recombinant FABP7 protein increased ACLY activity in dose-dependent manner.

The interaction between nuclear FABP7 and ACLY is likely critical for the modification of nuclear acetyl CoA levels, thereby epigenetically regulates *Cav1* expression.

PS3

Cortical processing of prediction error and self-agency in patients with schizophrenia

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Schizophrenia is associated with deficits in a broad range of cognitive domains including working memory, selective attention, reward, salience processing, and theory of mind that can be measured at both behavioral and neuroimaging levels. Among them, abnormality of sense of agency has been studied in cognitive neuroscience as capturing self-disturbance which is a core symptom of schizophrenia. Dysfunction of prediction and inference may be involved in misattribution of agency, for which several models have been proposed, with different assumed functional abnormalities. Some models assume functional abnormality in detection of prediction error dependent on action (i.e., forward model) or independent of action (i.e., sensory gating); other models assume functional abnormality in the inference of attribution of detected prediction error. However, these models have never been verified systematically. The purpose of this research was to compare and verify these three models. For that purpose, we conducted fMRI on both patients with schizophrenia and HC using prediction violating auditory input dependent on / independent of action. Eighteen schizophrenia patients (9 males and 9 females) and nineteen matched healthy controls (7 males and 12 females) participated in the study. Patients' positive symptoms were well controlled. Using functional magnetic resonance imaging (fMRI), we examined brain responses to both action-dependent and independent prediction errors in brain regions implicated in action-dependent prediction error (temporoparietal junction, TPJ) and action-independent prediction error (superior temporal gyrus, STG). The brain responses in TPJ to action-dependent error and those in STG to action dependent / independent error were normal in patients. Brain responses to action-independent error were also observed in TPJ in patients, unlike in healthy controls. These patterns of TPJ and STG activation are consistent with the abnormal attribution inference model. We observed that patients did not have deficits in error detection, but action-independent error was misattributed as action-dependent-error (i.e., inference process), an observation well explained by the abnormal attribution inference model. Given that patients' positive symptoms were well controlled, the abnormalities we identified may persist even if positive symptoms are controlled. Investigating when these abnormalities will occur can contribute to the early intervention of schizophrenia. If they precede the symptoms, it may be useful for predicting the onset of schizophrenia, narrowing down of high-risk individuals, or for differential diagnosis. This latent pathological factor may be a key target for diagnosis and early intervention.

PS4

Chronic poor condition enhances preference to rewarding substances through dopamine system

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Sub-optimal environment is a risk factor for the development of substance abuse. However, how the inferior condition alters behavior is still poorly understood. Using a genetically-tractable model organism Drosophila melanogaster, we aimed to establish a behavioral model system and examine the underling neural mechanisms.

We found that chronic poor nutritional status remarkably enhances preference to multiple rewarding stimuli, e.g. sugar, alcohol and methamphetamine, without changing sweet- or bitter- taste sensitivity. Because simply starved flies do not show this behavioral alteration, long-term experience is a key component. Dopamine release and D1-type dopamine receptor are critical for this change. Moreover, we found that dopamine synapses were sensitized after the chronic poor condition. Overexpression of the D1-type dopamine receptor mimics the poor-effect. We will discuss how the brain adapts to environments and changes behaviors.

PS5

The involvement of fatty acid-binding protein 5 in the blood-brain barrier transport of docosahexaenoic acid and cognition

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Docosahexaenoic acid (DHA) is beneficial for cognitive function, however, the brain has limited ability to synthesize its own DHA. Plasma-derived DHA has to be transported across the blood-brain barrier (BBB) to reach the brain parenchyma. The mechanism governing BBB transport of DHA is not clearly understood. The current study aims to investigate if fatty acid-binding protein 5 (FABP5) mediates the BBB transport of DHA and whether FABP5 deficiency leads to cognitive impairment.

The uptake of ^{14}C-DHA was measured in human brain microvascular endothelial cells (hCMEC/D3) with and without FABP5 genetic silencing and BBB transport of ^{14}C-DHA assessed in wild-type (FABP5$^{+/+}$) and FABP5 deficient (FABP5$^{-/-}$) mice using an *in situ* transcardiac perfusion technique. Endogenous brain concentrations of DHA were measured using gas chromatography with flame ionization detection, and cognitive function was assessed using water maze, novel object recognition (NOR), Y-maze, and T-maze memory paradigms.

FABP5 siRNA knockdown in hCMEC/D3 cells was associated with a reduction in ^{14}C-DHA cellular uptake. DHA brain transport decreased in FABP5$^{-/-}$ mice, and this was associated with a reduction in endogenous brain DHA levels. Moreover, FABP5 deficiency generally induced deficits in memory paradigms assessed. FABP5$^{-/-}$ mice showed impaired spatial learning in the water maze and increased latency to escape in the probe test. In NOR tests, the FABP5$^{-/-}$ mice failed to discriminate novel object from familiar object. FABP5$^{-/-}$ mice also showed a decrease in spontaneous alternations in the T-maze paradigm.

This study has demonstrated that FABP5 mediates the BBB transport of DHA *in vitro* and *in vivo*. A reduction in DHA brain access is associated with impaired cognitive function, suggesting a crucial role of FABP5 at the BBB in maintaining DHA brain concentrations and consequently normal cognitive function.

PS6

The effect of UGT1A9, CYP2B6, CYP2C9 genes polymorphism on individual differences in propofol pharmacokinetics among Japanese patients

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Propofol is one of the most widely used fast-acting intravenously administered anesthetics. However, large interindividual differences in dose requirements and recovery time have been observed. For minimizing adverse effects, pharmacogenetic investigation is suggested. In this study, we aimed to investigate the relationship between UDP-glucuronosyltransferase 1A9 (UGT1A9), cytochrome P450 2B6 (CYP2B6), and cytochrome P450 2C9 (CYP2C9) gene for single-nucleotide polymorphisms (SNPs) and propofol pharmacokinetics profile in Japanese patients. Ninety-four patients were enrolled and their blood samples were collected 1, 5, 10, and 15 min after administering a single intravenous bolus of propofol at a dose of 2.0 ml/kg for measuring propofol plasma concentration. Propofol concentration in the plasma was determined by high-performance liquid chromatography. The area under the time-plasma concentration curve from zero to the last measurable time point (AUC_{15min}) was determined from the concentration data. Genomic DNA was extracted from the leukocytes of the peripheral blood, and SNPs of UGT1A9 (rs2741049, rs2741045, and rs13418420); CYP2B6 (rs3745274, rs2279343, rs8192709, and rs3211371); and CYP2C9 (rs1057910) were amplified using polymerase chain reaction, directly sequenced, and genotyped. The interindividual variability of propofol pharmacokinetics was evaluated by investigating relationships between AUC_{15min} and genotypes of UGT1A9, CYP2B6, and CYP2C9. For statistical analysis, the Mann–Whitney U test was used for examining the effect of polymorphism on propofol pharmacokinetics. All SNPs appeared to conform to Hardy–Weinberg equilibrium ($p > 0.05$). Although no significant association was found between the studied SNPs of UGT1A9 (rs2741049 and rs2741045); CYP2B6 (rs3745274, rs2279343, rs8192709, and rs3211371); CYP2C9 (rs1057910); and AUC15min, UGT1A9 (rs13418420) showed significant association with AUC15min. The distribution of UGT1A9 (rs13418420:1818C > T) genotypes and alleles was CC = 43, CT = 43, TT = 8, and the career of the T allele was associated with higher AUC_{15min} ($p = 0.0181$). From all the analyzed SNPs, only polymorphism rs13418420 in UGT1A9 influences propofol pharmacokinetics after its single intravenous injection, and it may play an important role in the optimization of propofol anesthesia.

PS7

Blood Pressure Correlates with 90-Day Mortality in Sepsis Patients: A Retrospective Multicenter Derivation and Validation Study Using High-Frequency Continuous Data

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High-frequency arterial pressure data of the period and extent of blood pressure depression can be useful in predicting the outcome of patients with sepsis. In this study, we aimed to study the influence of high-frequency continuous arterial blood pressure that takes the frequency and duration of the low blood pressure into consideration on the outcomes for patients with sepsis.

This retrospective observational study was conducted at a university hospital intensive care unit (derivation study) and at two urban hospitals (validation study) with data from adult sepsis patients that visited the centers during the same period. The area under the curve (AUC) of blood pressure falling below threshold was calculated. The predictive 90-day mortality (primary endpoint) area under threshold (AUT) and critical blood pressure were calculated as the maximum area under the curve of the receiver operating characteristic (AUCROC) and the threshold minus average AUT (derivation study), respectively. For the validation study, the derived 90-day mortality AUCROC (using critical blood pressure) was compared with SOFA, SAPS II, APACHE II, and III.

Derivation cohort (N=137): the drop area from the mean blood pressure of 70 mmHg at 24-48 h most accurately predicted 90-day mortality (critical blood pressure: 67.8 mmHg, AUCROC: 0.763, 95%CI: 0.653-0.890). Validation cohort (N=141): the 90-day mortality AUCROC (0.776) compared with AUCROC for SOFA (0.711), SAPSII (0.771), APACHE II (0.745), and APACHE III (0.710), was not significantly different from the critical blood pressure 67.8 mmHg ($p = 0.420$).

High-frequency arterial pressure data of the period and extent of blood pressure depression can be useful in predicting the outcome of patients with sepsis.

PS8

Functions of a cancer/testis antigen gene, Tekt5 in cancer cells and male germ cells

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Tektin5 (Tekt5) gene is one of the cancer/testis antigen (CTA) genes, and is preferentially expressed in cancer cells and in testis. Although TEKT5 is localized in the mid-piece of sperm, its detailed functions are unknown in sperm as well as in cancer cells. In this study, we attempted to clarify the functions of *Tekt5* both in cancer cells and in male germ cells.

Tekt5 is highly expressed in ovarian granulosa cancer cell line, OV3121. *Tekt5* KD by siRNA in OV3121 cells caused G1 arrest and apoptosis, and p27, a negative cell cycle regulator was concomitantly upregulated. Although Tektin family members are considered as structural components of the outer doublet microtubules in cilia and flagella, we found that it was not co-localized with tubulin. However, down-regulation of acetylated- α -tubulin and subsequent fragmentation of β-III-tubulin as well as up-regulation of HDAC6 which deacetylates α-tubulin was observed in *Tekt5* KD OV3121 cells. We also found that *Tekt5* KD resulted in nuclear accumulation of SMAD3 which is known to induces p27 expression. Because depolymerization of tubulin causes translocation of SMAD3 to nucleus, the results together suggest that TEKT5 represses *Hdac6* expression and consequently enhances cell cycle and cell survival via stabilization of tubulin.

In testis, TEKT5 expression increases after late pachytene spermatocyte. We carried out microinjection of *Tekt5* siRNA into seminiferous tubules of mouse testis in order to study the function of *Tekt5* during mouse spermatogenesis. In *Tekt5* KD testes, the expression of *Tekt5* was down-regulated and number of spermatids were significantly decreased. The results suggest that differentiation of spermatid was impaired in *Tekt5* KD testes. Because *Tekt5* expression increases and *Hdac6* expression decreases during spermatogenesis, and previous studies indicated that acetylated α-tubulin was required for sperm morphogenesis, the results suggest that TEKT5 is necessary for spermiogenesis via maintaining acetylated α-tubulin by repression of HDAC6.

In this study, we examined functions of *Tekt5* in cancer cells and in testis. Our data suggest that *Tekt5* is involved in stabilization of tubulin through repression of HDAC6 both in cancer cells and in male germ cells. These finding may be helpful for understanding functions of CTA genes.