Institute of
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Institute of Integrated Research
Medical Research Laboratory

22ND SURUGADAI INTERNATIONAL SYMPOSIUM
Immune-and Inflammatiom-
Related Diseases and Homeostasis

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Welcome to the Institute of Science Tokyo
Medical Research Laboratory

Prof. Takehiko Sasaki, Ph.D.
Director
Medical Research Laboratory
Institute of Integrated Research
Institute of Science Tokyo, Japan

The Medical Research Laboratory, now part of the newly established university, 'Institute of Science Tokyo,' via the merger of Tokyo Medical and Dental University and Tokyo Institute of Technology, is dedicated to addressing the challenges in biomedical sciences. Our mission is to unravel the fundamental mechanisms underlying human health and the pathogenesis of intractable diseases. We also aim to develop innovative diagnostic and therapeutic approaches. To achieve these goals, we leverage state-of-the-art life science techniques. These include molecular and cellular studies, model animal systems, clinical research with patient samples, computational approaches such as molecular simulations, and bioinformatics approaches utilizing machine learning for data-driven life science research.

Our commitment to acquiring and disseminating cutting-edge knowledge, along with advancing research based on novel methodologies, is exemplified by the regular organization of international symposiums and seminars and the allocation of research funding to support over a dozen international collaborative research projects annually under the International Joint Usage/Research Program.

As we host the 22nd Surugadai International Symposium, entitled 'Immune- and Inflammation-Related Diseases and Homeostasis,' we warmly welcome all participants. This symposium serves as a valuable platform to share the latest advancements in immune- and inflammation-related diseases, fostering discussions that could lead to new collaborations and groundbreaking therapeutic innovations. Together, we aspire to uncover novel strategies for treating patients with intractable diseases by revealing the profound mysteries of diseases and the natural mechanisms of life.

22nd Surugadai International Symposium Program
"Immune- and Inflammation-Related Diseases and Homeostasis"

Thursday, November 21, 2024 12:50-17:30

Akio Suzuki Memorial Hall M&D Tower 2nd floor

12:50-13:00 **Opening Remarks**
Dr. Takehiko Sasaki (Director, Medical Research Laboratory, Institute of Science Tokyo)

Moderated by Dr. Fumiko Ozaki (Institute of Science Tokyo)

Session1
13:00-14:55
Chaired by Dr. Hitoshi Okazawa and Dr. Takashi Shichita (Institute of Science Tokyo)

13:00-13:40 Dr. Sumit Chanda (The Scripps Research Institute) by Zoom
Title: Innate Immune Sensing of HIV-1
13:40-14:05 Dr. Hitoshi Okazawa (Institute of Science Tokyo)
Title: Neuroimmune induction by tau via PQBP1-cGAS-STING pathway
14:05-14:30 Dr. Yumiko Oishi (Institute of Science Tokyo)
Title: Identification of a novel subset of macrophages that regulate muscle regeneration
14:30-14:55 Dr. Makoto Murakami (The University of Tokyo)
Title: Lipid-driven immune regulation in health and disease

14:55-15:25 **Coffee Break including group photo**

Session2
15:25-17:30
Chaired by Dr. Noriko Komatsu and Dr. Toshiaki Ohteki (Institute of Science Tokyo)

15:25-16:05 Dr. Nicolas Chevrier (The University of Chicago)
Title: Decoding the body language of immunity
16:05-16:30 Dr. Noriko Komatsu (Institute of Science Tokyo)
Title: Breakdown of joint homeostasis in autoimmune arthritis
16:30-16:55 Dr. Satoshi Uematsu (Osaka Metropolitan University)
Title: An enterococcal phage-derived enzyme suppresses graft-versus-host disease
16:55-17:20 Dr. Sho Yamasaki (Osaka University)
Title: Recognition of metabolites by the immune system
17:20-17:30 **Closing Remarks**
Dr. Toshiaki Ohteki (Division Chief, Medical Research Laboratory, Institute of Science Tokyo)

Session 1 13:00–13:40

Innate Immune Sensing of HIV-1

Dr. Sumit Chanda
The Scripps Research Institute

Abstract

Structural regulation on PQBP1 sensing of HIV-1 capsid and innate immune activation.
Most new HIV-1 infections are initiated by a single variant out of a quasi-species deposited at a mucosal site, and transmission is determined by the host-virus interface. Recent studies in the Rhesus model found that immature dendritic cells (DC) in the mucosa become infected, and it remains to be determined why their innate responses sometimes fail to prevent viral spread. HIV-1 infection of DCs triggers expression of antiviral factors and type I interferons as well as proinflammatory cytokines through the cyclic GAMP synthase (cGAS) pathway. Paradoxically, while induction of antiviral genes by cGAS inhibits replication, proinflammatory cytokines can activate resting CD4+ T cells and may promote infection. Thus, the understanding of how this initial sensing of HIV-1 infection by cGAS is regulated and how that will shape the mucosal lymphoid environment to control viral transmission will be a great importance. We discovered that polyglutamine binding protein 1 (PQBP1) is an adaptor required for cGAS sensing of HIV-1 DNA. This two-factor authentication system enables the immune system to respond to a transient, low-abundance pathogen associated molecular pattern (PAMP) encoded by retroviruses. Recently, we reported that PQBP1 decorates the capsids of incoming viruses and, at the onset of capsid disassembly, recruits cGAS to the site of viral DNA synthesis. Whereas PQBP1 seems to facilitate capsid disassembly, the capsid may in turn control PQBP1 assembly on its surface, including the creation of a platform for cGAS capture and release onto the emerging DNA. We identified both naturally occurring and genetically engineered capsid variants that activate cGAS to different levels, suggesting that the capsid is a determinant of cGAS sensing. A critical gap in our knowledge is how this interplay of multi-molecular interactions, rearrangements and assembly-disassembly events facilitates recognition of retroviral PAMPs and governs innate immune activation. We hypothesize that initial binding to the capsid disrupts intramolecular bonds in PQBP1, allowing it to dimerize and consolidate its binding to the capsid. Multiple, arrayed PQBP1 dimers may provide the mechanical strain to disrupt the capsid lattice, thereby facilitating exposure of nascent viral DNA. Further rearrangements of PQBP1 would create a platform for cGAS capture. We are utilizing both biochemical and structural approaches coupled with PQBP1 mutagenesis and capsid variants with a range of cGAS activation potential to test this hypothesis.

Keywards HIV, PQBP1, Immunology, Virology, Pharmacology

Short biography

Sumit Chanda earned his Ph.D. from Stanford University in 2001 and received his post-doctoral training at the Genomics Institute of the Novartis Research Foundation (GNF). He subsequently transitioned to a Group Leader position and established his research group in the Division of Cellular Genomics at GNF. In 2007, he joined the Infectious and Inflammatory Disease Center at Sanford-Burnham Medical Research Institute as an Associate Professor. Dr. Chanda was promoted to Professor in 2013. In 2015, he was appointed Director of the Immunity and Pathogenesis Program at Sanford Burnham Prebys Medical Discovery Institute. He joined Scripps in 2021 as Professor of Immunology and Microbiology. In his free time, Sumit enjoys soccer, scuba-diving, hiking and trying new restaurants.

Session 1　　13:40–14:05

Neuroimmune induction by tau via PQBP1-cGAS-STING pathway

Dr. Hitoshi Okazawa
Institute of Science Tokyo

Abstract

Brain inflammation generally accompanies and accelerates neurodegeneration. Here we report a microglial mechanism in which polyglutamine binding protein 1 (PQBP1) senses extrinsic tau 3R/4R proteins, the key molecule for Alzheimer's disease and other neurodegenerative diseases, by direct interaction and triggers an innate immune response by activating a cyclic GMP-AMP synthase (cGAS)-Stimulator of interferon genes (STING) pathway. Tamoxifen-inducible and microglia-specific depletion of PQBP1 in primary culture in vitro and mouse brain in vivo show that PQBP1 is essential for sensing-tau to induce nuclear translocation of nuclear factor □B (NF□B), NF□B-dependent transcription of inflammation genes, brain inflammation in vivo, and eventually mouse cognitive impairment. Collectively, PQBP1 is an intracellular receptor in the cGAS-STING pathway not only for cDNA of human immunodeficiency virus (HIV) but also for the transmissible neurodegenerative disease protein tau. This study characterizes a mechanism of brain inflammation that is common to virus infection and neurodegenerative disorders.

Keywords　PQBP1, Tau, Alzheimer's disease, neurodegeneration, neuroinflammation

Short biography

Dr. Hitoshi Okazawa graduated from The University of Tokyo and received M.D. in 1984. After clinical training of Neurology at The University of Tokyo, he became a staff member of The University of Tokyo in 1986. He started research of molecular biology at Department of Biochemistry The University of Tokyo in 1988, and received Ph.D. by discovery of Oct-3/Oct-4, the most essential factor for ES cell and iPS cell, in 1991. He became a staff in Department of Neurobiochemistry of Max-Planck Institute of Psychiatry at Munich in Germany, where he discovered a receptor for brain-derived neurotrophic factor. He became an assistant professor of The University of Tokyo in 1993, then Department Chair of Tokyo Metropolitan Institute for Neuroscience in 2001. He has been Professor and Chair of Neuropathology from 2003, and Director of Center for Brain Integration Research at TMDU from 2012-2022, and directing researches of neurodegeneration and related fields based on molecular biology.

Specialty and present interests

Neurodegeneration

References

Waragai M, Lammers CH, Takeuchi S, Imafuku I, Udagawa Y, Kanazawa I, Kawabata M, Mouradian MM and Okazawa H. PQBP-1, a novel polyglutamine tract-binding protein, inhibits transcription activation by Brn-2 and affects cell survival. Hum Mol Genet. 1999.06; 8 (6): 977-987.

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Jin M, Shiwaku H, Tanaka H, Obita T, Ohuchi S, Yoshioka Y, Jin X, Kondo K, Fujita K, Homma H, Nakajima K, Mizuguchi M and Okazawa H. Tau activates microglia via the PQBP1-cGAS-STING pathway to promote brain inflammation. Nature Commun. 2021.11; 12 (1): 6565.

Jin X, Tanaka H, Jin M, Fujita K, Homma H, Inotsume M, Yong H, Umeda K, Kodera N, Ando T and Okazawa H. PQBP5/NOL10 maintains and anchors the nucleolus under physiological and osmotic stress conditions. Nature Commun. 2023.01; 14 (1): 9.

Session 1 14:05–14:30

Identification of a novel subset of macrophages that regulate muscle regeneration

Dr. Yumiko Oishi
Institute of Science Tokyo

Abstract

Skeletal muscle, the dominant organ for locomotion and energy metabolism, has a remarkable capacity for repair and regeneration in response to injury. Sarcopenia, characterized by a generalized loss of skeletal muscle mass and strength in the elderly, is becoming a serious problem in aging societies. Impaired regeneration has been suggested as a key pathological mechanism of sarcopenia. Recent studies suggest that inflammation and regeneration processes are intimately linked and that macrophages are critical for these processes. Accordingly, dysregulation of macrophages during inflammation/regeneration processes is a possible cause leading to sarcopenia. However, it remains unclear how macrophages coordinately regulate inflammation, regeneration and tissue repair during muscle injury and how macrophage functions are modulated during the aging process.

In this study, we analyzed the diversity of the macrophage population during muscle repair. Using single-cell transcriptome analysis of muscle tissue before and after injury, I found that injured skeletal muscle contains 1000 times more macrophages than uninjured muscle and can be divided into at least eight subpopulations, each of which interacts with other interstitial cells, such as satellite cells and fibroblasts, to promote regeneration and repair. Of these, the novel macrophage subpopulation with HGF-producing capacity (HGF^+) promotes the proliferation and differentiation of satellite cells (expressing the HGF receptor) and is essential for muscle regeneration. Furthermore, HGF-mediated macrophage-satellite cell interaction was significantly reduced by aging. These data strongly suggest that impaired differentiation of HGF^+ macrophages and modulation of macrophage-satellite cell communication may contribute to the age-related decline in muscle regenerative capacity and the development of sarcopenia.

Keywords Macrophage, regeneration, muscle repair, sarcopenia, frailty

Short biography

Professor and Chair, Department of Medical Biochemistry, Graduate school of Medical and Dental Sciences, Institute of Science Tokyo

Education and Degree

1992– 1998	Gunma University, (Maebashi, Japan) M.D. (summa cum laude), Gunma University
2002 – 2006 (Tokyo, Japan)	University of Tokyo Graduate School of medicine Ph.D., Tokyo University

Professional Experience

1998-1999 Resident, Internal Medicine, Department of Internal Medicine, Gunma University Hospital, Maebashi

1999- 2000 Resident, Department of Internal Medicine, Takasaki National Hospital,

2000- 2001 Attending Physician, Department of Cardiovascular Medicine, Sakakibara Heart Institute, Tokyo

2001-2002 Fellow in cardiovascular medicine, University of Tokyo Graduate School of Medicine, Tokyo

2007-2008 Japan Society for the Promotion of Science (JSPS) Fellow

2008-2009 Project Assistant Professor, Department of Cardiovascular Medicine, The University of Tokyo

2009-2013 Postdoctoral Research scholar, Department of Cellular and Molecular Medicine, School of Medicine, University of California, San Diego, Laboratory of Dr. Christopher K. Glass

2013-2018 Associate Professor, Medical Research Institute, Tokyo Medical and Dental University

2017-2024 Principal Investigator of the PRIME, Advanced Research & Development Programs for Medical Innovation program, Japan Agency for Medical Research and development

2018-2023 Professor and Chair, Department of Biochemistry and Molecular Biology, Nippon Medical School

2023-present Professor and Chair, Department of Medical Biochemistry, Graduate school of Medical and Dental Sciences, Institute of Science Tokyo

2018-2020 Program Officer, Grants-in-Aid for Scientific Research

2022-present Program Officer, Japan Society for the Promotion of Science

Licensure and Certification:

1996 National Board for Medical Practice

2002 Board Certified Member of the Japanese Society of Internal Medicine

2007 Fellow of the Japanese Circulation Society

2019 Fellow of the Japanese Society of Internal Medicine (FJSIM)

Awards and Honors:

1. Research Award for Women investigators, Japanese Cardiology Society (2018)
2. Research Award, Academic-industrial alliance, TMDU (2018)

3. The 39th Annual Meeting of the Molecular Biology Society of Japan, Best Poster award (2016)
4. Young Investigator Award, TMDU (2016)
5. Young Investigator Award, TMDU (2015)
6. The 4th Banyu Medical research Award (2015)
7. The 4th Molecular Cardiovascular Conference II Best abstract award (2013)
8. The 73th Annual meeting for the Japanese Circulation Society, Yagi Award (2009)
9. The 9th US-Japan Asia Dialogue on Cardiovascular Diseases (2008) Best presenter award
10. Keystone Symposia scholarship, Molecular Control of Adipogenesis and Obesity (2008)
11. The 23rd Okamoto Award for Young investigators (2008)
12. The 45th Japanese Society of Molecular Medicine Young Investigator Award (2008)
13. American Heart Association 2007, ATVB Merit Award for Young Investigators (2007)
14. The 79th Japan endocrine society meeting Young Investigator Award (2006)
15. XIVth International Vascular biology Meeting Young Investigator Award (2006)
16. 5th Asian Pacific Society of Atherosclerosis and Vascular Disease Young Investigator Award, 1st prize (2006)
17. Tokyo Medical Association Medical Research Award (2006)
18. 7th European Congress of Endocrinology EFES Young Investigator Award (2005)
19. XIIIth International Vascular biology Meeting Young Investigator Award (2005)

Specialty and present interests

Immune cell diversity and Multiple cellular communication in tissue regeneration and repair

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Session 1 14:30–14:55

Lipid-driven immune regulation in health and disease

Dr. Makoto Murakami
The University of Tokyo

Abstract

Lipids play fundamental roles in life. In essence, "phospholipase A_2" (PLA_2) means a group of enzymes that release fatty acids and lysophospholipids by hydrolyzing the *sn*-2 position of glycerophospholipids. To date, more than 50 enzymes that possess PLA_2 or related lipid-metabolizing activities have been identified in mammals, and these are subdivided into several families in terms of their structures, catalytic mechanisms, tissue/cellular localizations, and evolutionary relationships. From a functional viewpoint, the PLA_2 superfamily has mainly been implicated in signal transduction, driving the production of a wide variety of bioactive lipid mediators. However, a growing body of evidence indicates that PLA_2s also contribute to phospholipid remodeling or recycling for membrane homeostasis, fatty acid b-oxidation for energy production, and barrier lipid formation on the body surface. Accordingly, PLA_2 enzymes are considered one of the key regulators of a broad range of lipid metabolism, and perturbation of specific PLA_2-driven lipid pathways often disrupts tissue and cellular homeostasis and may be associated with a variety of diseases. Among the PLA_2 superfamily, the secreted PLA_2 ($sPLA_2$) family contains 11 isoforms in mammals, which have unique enzymatic specificity toward fatty acids and polar heads of phospholipid substrates and display distinct tissue/cellular distributions. Recent studies using knockout and/or transgenic mice for a full set of $sPLA_2$s have revealed their diverse roles in immunity and metabolism. Application of mass spectrometric lipidomics to these mice has enabled us to identify target substrates and products of individual $sPLA_2$s in given tissue microenvironments. $sPLA_2$s hydrolyze not only phospholipids in the plasma membrane of activated, damaged or dying mammalian cells, but also extracellular phospholipids such as those in extracellular vesicles, microbe membranes, lipoproteins, surfactants, and dietary phospholipids, thereby exacerbating or ameliorating various diseases. The actions of $sPLA_2$s are dependent on, or independent of, the generation of fatty acid- or lysophospholipid-derived lipid mediators according to pathophysiological situations. In this talk, I will make an overview of our recent findings on the unexplored immunoregulatory roles of $sPLA_2$s and their underlying lipid pathways, particularly focusing on their unique actions on exosomes and gut microbiota.

Keywords Phospholipase A2, Lipid metabolism, Lipidomics, Phospholipid, Fatty acid

Short biography

M.S. (1988), The University of Tokyo, Japan

Ph.D. (1991), The University of Tokyo, Japan

Postdoctoral Fellow (1991-1993), The University of Tokyo, Japan

Postdoctoral Fellow (1993-1995), Harvard Medical School, Boston, USA

Assistant Professor (1995-1997), Showa University, Japan

Associate Professor (1997-2005), Showa University, Japan

Project Leader (2005-2016), Tokyo Metropolitan Institute of Medical Science, Japan

Professor (2017-Present), The University of Tokyo, Japan

Specialty and present interests

Lipid Biology, Biochemistry, Molecular Biology, Immunology

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2.Sato H et al, ***Cell Reports***, 243, 114752, 2024.
3.Endo Y et al, ***Sci Immunol***, 8, eadd4346, 2023
4.Nakamura A et al, ***Neuron***, 111, 2995-3010.e9, 2023
5.Miki Y et al, ***JCI Insight***, 7, e152638, 2022

Session 2 15:25–16:05

Decoding the body language of immunity

Dr. Nicolas Chevrier
The University of Chicago

Abstract

Sepsis is a systemic response to infection with life-threatening consequences. Our understanding of the molecular and cellular impact of sepsis across organs remains rudimentary. Here, we characterize the pathogenesis of sepsis by measuring dynamic changes in gene expression across organs. To pinpoint molecules controlling organ states in sepsis, we compare the effects of sepsis on organ gene expression to those of 6 singles and 15 pairs of recombinant cytokines. Strikingly, we find that the pairwise effects of tumor necrosis factor plus interleukin (IL)-18, interferon-gamma or IL-1β suffice to mirror the impact of sepsis across tissues. Mechanistically, we map the cellular effects of sepsis and cytokines by computing changes in the abundance of 195 cell types across 9 organs, which we validate by whole-mouse spatial profiling. Our work decodes the cytokine cacophony in sepsis into a pairwise cytokine message capturing the gene, cell and tissue responses of the host to the disease.

Short biography

ACADEMIC APOINTMENTS
Jul 2024-present Associate Professor (with tenure) in Molecular Engineering
Jul 2024-present Scientific Director, France's National Centre for Scientific Research (CNRS)-
UChicago International Research Center (IRC) for Fundamental Discovery
2017-2024 Assistant Professor in Molecular Engineering
Member, Committee on Immunology
Member, Graduate Program in Biophysical Sciences
Member, UChicago Medicine Comprehensive Cancer Center
Pritzker School of Molecular Engineering**,** The University of Chicago, Chicago IL, USA
2012-2017 Bauer Fellow, Faculty of Arts and Science Center for Systems Biology
Harvard University, Cambridge MA, USA

EDUCATION & TRAINING
2007-2012 Ph.D. in Immunology
Harvard Medical School, Boston MA, USA
Boehringer Ingelheim Fonds Fellow
Advisor: Nir Hacohen (Broad Institute of Harvard and MIT)
2005-2007 M.S. in Biochemistry & Immunology

Universite de la Mediterranee, Marseille, France
Universite de Bourgogne, Dijon, France
Advisors: Jean-Pierre Gorvel & Eric Vivier (Centre d'Immunologie Marseille-Luminy)
2002-2005 B.S. in Biochemistry
Universite de Bourgogne, Dijon, France
Other research and training experiences:
Summer of 2013 Cold Spring Harbor Laboratory, Course in Programming for Biology
Summer of 2006 The Scripps Research Institute, La Jolla, USA (Bruce Beutler)
Summer of 2005 Research Institute for Microbial Diseases, Osaka, Japan (Shizuo Akira)
Summer of 2004 National Institute for Agricultural Research, Dijon, France (Philippe Lemanceau)

AWARDS & HONORS
• Duckworth Family Commercial Promise Award 2023
• Robert Lavichant Faculty Innovation Award, UChicago PME 2023
• Janet Rowley Discovery Fund Award, UChicago Comprehensive Cancer Center 2020
• NIH Director's New Innovator Award 2018
• Elliott and Ruth Sigal Melanoma Research Alliance Young Investigator Award 2018
• Harvard University Center for AIDS Research Scholar Award 2015
Nicolas Chevrier – Curriculum Vitae (08/17/2024) Page 2 of 3
• The William F. Milton Fund Award, Harvard Medical School 2015
• Bauer Fellowship, Harvard University 2012-2017
• Harold M. Weintraub Graduate Student Award, Fred Hutchinson Cancer Center 2012
• Jeffrey Modell Award in Immunology, Harvard Medical School 2012
• Ph.D. Fellowship, Boehringer Ingelheim Fonds 2009-2011
• Graduate Fellowship, Harvard Medical School 2007-2009
• National Ph.D. Fellowship, French Government – declined 2007
• RIKEN RCAI International Summer Program, Japan 2007
• National Scholarship for Master Studies, French Government 2006-2007
• Undergraduate Summer Research Fellowship, Region of Burgundy, France 2005 & 2006
• Undergraduate Summer Research Fellowship, University of Burgundy, France 2005 & 2006

PEER-REVIEWED PUBLICATIONS
Independent Research (* = equal contribution; ‡ = undergraduate co-author)
20. Cipurko D, Ueda T, Mei L, **Chevrier N**. (**2024**) Repurposing Large-Format Microarrays for Scalable Spatial
Transcriptomics. *Nature Methods* in press.
19. Takahama M, Patil A, Richey G, Cipurko D, Johnson K, Carbonetto P, Plaster M, Pandey S, Cheronis K,
Ueda T, Gruenbaum A, Kawamoto T, Stephens M, **Chevrier N**. (**2024**) A Pairwise Cytokine Code Explains the Organism-Wide Response to Sepsis. *Nature Immunology* in press. DOI: https://doi.org/10.1038/s41590-023-01722-8. Featured in: Research Briefing.
18. Pandey S, Gruenbaum A, Kanashova T, Mertins P, Cluzel P*, **Chevrier N***. (**2020**) Pairwise Stimulations
of Pathogen-Sensing Pathways Predict Immune Responses to Multi-Adjuvant Combinations. *Cell Systems*

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17. Pandey S, Takahama M, Gruenbaum A, Zewde M, Cheronis K, **Chevrier N**. (**2020**) A whole-tissue RNAseq
toolkit for organism-wide studies of gene expression. *Nature Protocols* 15(4):1459-1483. DOI: https://doi.org/10.1038/s41596-019-0291-y.
16. **Chevrier N**. (**2019**) Decoding the Body Language of Immunity: Tackling the Immune System at the Organism Level. *Current Opinion in Systems Biology* 18, 19-26. DOI: https://doi.org/10.1016/j.coisb.2019.10.010.
15. Kadoki M, Patil A, Thaiss C‡, Brooks DJ‡, Pandey S, Deep D‡, Alvarez D, von Andrian UH, Wagers AJ, Nakai K, Mikkelsen T, Soumillon M, **Chevrier N**. (**2017**) Organism-level analysis of vaccination reveals networks of protection across tissues. *Cell* 171(2):398-413. DOI: https://doi.org/10.1016/j.cell.2017.08.024.
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14. Sage PT, Ron-Harel N, Juneja V, Sen D, Maleri S, Sungnak W, Kuchroo V, Haining N, **Chevrier N**, Haigis
M, Sharpe A. (**2016**) Suppression by TFR cells leads to durable and selective inhibition of B cell effector functions. *Nature Immunology* 17(12):1436-1446. DOI: https://doi.org/10.1038/ni.3578.
Graduate and Undergraduate Research (* = equal contribution)
15. Mertins P, Przybylski D, Yosef N, Qiao J, Clauser K, Raychowdhury R, Eisenhaure TM, Maritzen T, Haucke
V, Satoh T, Akira S, Carr SA, Regev A*, Hacohen N*, **Chevrier N***. (**2017**) An Integrative Framework Reveals Signaling-to-Transcription Events in Toll-like Receptor Signaling. *Cell Reports* 19(13):2853-2866. DOI: https://doi.org/10.1016/j.celrep.2017.06.016.
13. Mostafavi S, Yoshida H, Moodley D, LeBoite H, Rothamel K, Raj T, Ye CJ, **Chevrier N**, Zhang SY, Feng T, Lee M, Casanova JL, Clark JD, Hegen M, Telliez JB, Hacohen N, De Jager PL, Regev A, Mathis D, Benoist C; Immunological Genome Project Consortium. (**2016**). Parsing the Interferon Transcriptional Network and Its Disease Associations. *Cell* 164(3):564-78. DOI: https://doi.org/10.1016/j.cell.2015.12.032.
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Session 2 16:05–16:30

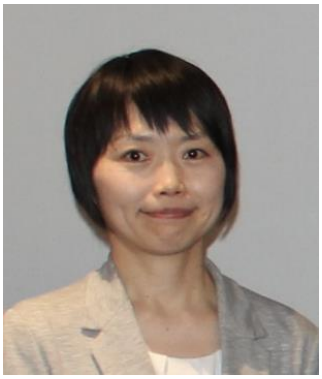
Breakdown of joint homeostasis in autoimmune arthritis

Dr. Noriko Komatsu
Institute of Science Tokyo

Abstract

The interaction of immune cells and non-immune cells, such as mesenchymal cells, is important for maintenance of tissue homeostasis as well as formation of various diseases including autoimmune diseases. In rheumatoid arthritis, one of the most common autoimmune diseases, various types of immune cells including T cells, B cells and macrophages, synergize with synovial fibroblasts, the tissue-specific mesenchymal cells in joints. We previously identified that plastic T cells convert into pathogenic T cells which exacerbate inflammation and bone destruction under arthritic conditions. Synovial fibroblasts promote the conversion into the arthritogenic T cells, which in turn, promote the activation of synovial fibroblasts. Recent single cell-RNA seq analysis revealed the functional heterogeneity of synovial fibroblasts. There are two representative subsets, inflammatory and tissue-destructive subsets. Although mechanisms that govern the polarization of each subset remain to be fully understood, we reported that the transcription factor, Ets1, governs the polarization of tissue-destructive fibroblasts. Ets1 promotes receptor activator for nuclear factor-kappa B ligand (RANKL) and matrix metalloproteinases (MMPs) in synovial fibroblasts, which induce bone destruction and cartilage degradation, respectively. It is suggested that inflammatory conditions as well as hypoxic conditions may be important for the formation of tissue-destructive fibroblasts. We recently elucidated one of the important immune-mesenchymal interactions by clarifying the mode of action of JAK inhibitors in vivo. Here, I would like to introduce the recent advances in studies regarding the immune-mesenchymal interaction in the breakdown of joint homeostasis in autoimmune arthritis and discuss the potential impacts on the development of new therapeutic strategies.

Keywords Autoimmune disease, arthritis, fibroblast, T cell, macrophage



Short biography

Noriko Komatsu PhD is Professor of Medical Research Laboratory, Institute of Science Tokyo (April 2024~). She graduated from The University of Tokyo (Faculty of Pharmaceutical Sciences) in 2003 and got PhD at Chiba University in 2008. After RIKEN Special Postdoctoral Researcher (SPDR) and JSPS PD, she became Assistant Professor and then, Associate professor at the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo (~March, 2024).

Specialty and present interests

She is an immunologist who has been studied for elucidating the mechanism of autoimmunity. Her research interests lie in the area of bone biology with specific interest in the immune-mesenchymal-bone interaction in autoimmune arthritis.

References

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Session 2 16:30–16:55

An enterococcal phage-derived enzyme suppresses graft-versus-host disease

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Dr. Satoshi Uematsu
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Abstract

With recent improvements in genome analysis technology, it has become clear that dysbiosis is found in a variety of diseases. In organ transplantation, immune cells attack the transplanted organ as a foreign body, resulting in rejection. In hematopoietic stem cell transplantation for the treatment of leukemia and other diseases, immune cells derived from the transplanted hematopoietic stem cells may develop graft-versus-host disease (GVHD), in which they attack the transplant recipient's organ as if it were a foreign body. Previous studies have reported that GVHD is exacerbated when the balance of the intestinal microflora is disturbed with *Enterococcus spp.* domination during the treatment process of hematopoietic stem cell transplantation. We performed a metagenomic analysis of fecal samples from 46 hematopoietic stem cell transplant patients (allogeneic transplantation) at Osaka Metropolitan University Hospital, and found not only an increase in *Enterococcus spp.* in 30 of the 46 patients, but also the presence of highly toxic *Enterococcus faecalis* with cytolysin. It was thought that the highly virulent *E. faecalis* may be involved in the pathogenesis of GVHD. During the treatment of hematopoietic stem cell transplantation, antimicrobial agents are used to protect against infection. However, highly toxic *E. faecalis* escaped from the antimicrobial agents by forming biofilms in the intestinal tract, thereby proliferating. It was also found that GVHD worsened in gnotobiotic mice transplanted with cytolysin-positive *E. faecalis*. We then attempted to eliminate this bacteria. We performed a metagenomic analysis of clinical isolates of *E. faecalis* and identified phage genome sequences inserted as prophage. We further found phage-derived bacteriolysis enzyme “endolysin” that can act specifically on *E. faecalis* and destory biofilms from those sequences. When this endolysin was administered to GVHD model mice, the aggravation of GVHD was inhibited and the mortality rate was greatly improved. The phage-derived endolysin obtained in this study is expected to lead to the development of new therapeutic agents for GVHD in the future.

Keywords GVHD dysbiosis Enterococcus faecalis Bacteriophage Biofilm

Short biography

1991-1997: Medical School, Osaka City University, Osaka, Japan
1997-1999: Residency of Medical Doctor, Internal Medicine II at Hospital of Osaka City University Medical School (Prof. Hirotoshi Morii)
2000-2004: Graduate School of Medicine, Osaka University, Osaka, Japan (Prof. Shizuo Akira)
2004-2009: Assistant Professor, Department of Host Defense, Research Institute for Microbial Diseases, Osaka University
2009-2012: Project Associate Professor, Laboratory of Host Defense, Immunology Frontier Research Center, Osaka University
2012-2022: Project Professor, Division of Innate Immune Regulation, International Research and Development Center for Mucosal Vaccines, Institute of Medical Science, The University of Tokyo
2014-2018: Professor, Department of Mucosal Immunology, Graduate School of Medicine and School of Medicine, Chiba University
2018- 2022: Professor, Department of Immunology and Genomics, Osaka City University Graduate School of Medicine
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Specialty and present interests

Innate Immunity, Metagenomics, Phage therapy

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Session 2 **16:55–17:20**

Recognition of metabolites by the immune system

Dr. Sho Yamasaki
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Abstract

While the immune system has developed to eliminate foreign pathogens, the principles underlying self-recognition are not fully understood. It is recently acknowledged that self-reactivity is not necessarily detrimental; instead, it connotes beneficial outcomes for the host. Indeed, innate and acquired immune receptors broadly recognize self components, thereby sensing the perturbation of host equilibrium to drive homeostatic responses. In particular, we recently found that receptor families lying between innate and acquired immunity, such as ITAM-coupled innate receptors and unconventional TCRs, recognize various host-derived metabolites. In this workshop, I will present our recent study on the self-recognition via MAIT cells, iNKT cells and other unconventional T cells and discuss their physiological relevance in immune homeostasis.

Short biography

Sho Yamasaki is Professor and head of the division of Molecular Immunology. After graduation from Kyoto University (Ms) in 1993, he started immunology research in Mitsubishi Chemical Corporation (1993-1999). In 1999, he received his PhD from Kyoto University for his study with Makio Iwashima on T cell antigen receptor signaling. Then he worked with Takashi Saito at Chiba University and RIKEN RCAI on the signal transduction of immune receptors. In 2009, he started the Molecular Immunology Laboratory at Kyushu University, where he holds the position of professor (2009-2017). He took his current position at Osaka University from 2017. His laboratory focuses on understanding the molecular mechanisms underlying the recognition of internal and external insults through ITAM-coupled immune receptors, such as C-type lection receptors and innate-type T cell receptors. His laboratory is also developing a platform analyzing human T cell clonotypes specific for pathogens.

Specialty and present interests

C-type lectin receptors
Unconventional T cell receptors
Clonotypic analysis of T cell receptors and antigens

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