Postbiotics Conference2025

1st International Symposium on Postbiotics

Organized by the Postbiotics Conference Committee

Date	March 11, 2025
Venue	Maskawa Building for Education and Research, Kyoto University
Chairman	Jun Ogawa (Graduate School of Agriculture, Kyoto University)

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Gut microbiome research is emerging as a new frontier in interdisciplinary science. "Postbiotics" are bioactive compounds produced during microbial metabolism that provide a wide range of health benefits to the host. This conference aims to bring together leading experts at the forefront of postbiotics research, fostering knowledge sharing and in-depth discussions to pave the way for further advancements in this exciting field.

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15:15 15:45 16:15	**Invited Lectures** **Hiroshi Itoh ○ (Center for Preventive Medicine, Keio University), Jun-ichiro Irie (Department of Medicine, Kansai Medical University) and Ikuo Kimura (Graduate School of Biostudies, Kyoto University)** Effects of Exopolysaccharides from *Leuconostoc mesenteroides* on The Gut Environment and Metabolic Parameters in Humans **Makoto Arita (Faculty of Pharmacy, Keio University/Riken)** Advanced Lipidomics to Illuminate The Functional Postbiotics in Host-Microbiome Interactions **Wataru Ogawa (Graduate School of Medicine, Kobe University)** Regulation of Immobilization-Induced Muscle Atrophy via the Neuro-Gut Axis: The Potential of HYA-Based Intervention	- - Page 13-14 - - Page 15-16 - - Page 17-18
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Postbiotics Pioneering New Gut Microbial Sciences and Providing Novel Tools for Health Promotion

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Key words: postbiotics, gut microbiota, metabolisms, metabolites, food, health

The host intestine is inhabited by a microbiota with rich diversity. The host, in its inner ecosystem, has a mutual relationship with the gut microbiota. The host provides habitat and nutrition to the gut microbiota. The microbiota also affects the host's metabolism, immune and organ development, and behavior. The composition of the gut microbiota is known to be considerably stable. However, its alteration has been discovered to lead to chronic diseases, such as irritable bowel syndrome, inflammatory bowel disease, colorectal cancer, obesity, and type 2 diabetes. Therefore, scientific understanding of the mutualistic relationship between the host and the gut microorganisms are key factors for the health of the host.

With the progress of genome science, the study of gut microorganisms has shifted from isolation and identification of microorganisms to a bird's eye view of the microbiota and microbiome. In the future, the knowledge of intestinal microbiota and diseases and health will be further deepened through genomic analysis at the single-cell level, metabolomics analysis of a vast number of molecules, and information science such as cohort studies to reveal the relationship between health conditions and diseases and intestinal microbiota.

Even with the above scientific progress, the reason why the health-promoting effects come out from gut microorganisms is still obscure. One of the key substances connecting the function of microbiota and human health is now revealed to belong with metabolites generated by gut microorganisms. Such gut microbial metabolites are now recognized as "Postbiotcs" and the research on postbiotics function now open a new science in our inner ecosystem. The recent findings bring a new concept that intestinal bacterial metabolites "Postbiotics" could be a dual controller that simultaneously controls disease state and intestinal flora and contribute future drug discovery. The gene information on the enzymes generating "Postbiotics" will contribute to make the new scientific aera of "Precision nutrition" being more reliable.

In this conference, we would like to establish a research community focusing on "Postbiotics" sciences to open new gut microbial sciences and develop novel tools for health promotion.

Postbiotics Linking Food and Human Health
- Examples of Gut Microbial Metabolites of Food Components-

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Key words: postbiotics, gut microbiota, metabolisms, metabolites, food, health, fatty acids

Food components and physiological functions derived from food components and microorganisms and microbial functions support each other in terms of health promotion. How intestinal bacteria can elicit physiological functions from food components is becoming clear. The metabolism of intestinal bacteria induces molecules from food components that cannot be produced by the host, and that these molecules create new physiological functions that have not been discovered before, as found in gut microbial metabolism of polyunsaturated fatty acids and plant-derived bioactive compounds such as glucosinolates, polyphenols, and glycosylated flavonoids. These metabolites produced from food components by gut microorganisms, which is now recognized as “Postbiotcs”, have vast potential as materials for functional food and pharmaceuticals. Here, we introduce an example of gut microbial polyunsaturated fatty acids metabolites as “Postbiotics”.

Novel polyunsaturated fatty acid (PUFA) metabolism, anaerobic saturation metabolism, was found in gut bacteria. Through the metabolism, hydrated (hydroxy), oxo, enone, conjugated, and non-methylene-interrupted fatty acids were produced by the enzyme system consisting of hydratase, dehydrogenase, isomerase, and enone reductase[1)]. Enzymatic method to prepare these unique metabolites was established. The existence of these metabolites in host tissues depending on gut bacteria was revealed. The metabolites showed unique physiological activities. For example, a linoleic acid-derived metabolite 10-hydroxy-*cis*-12-octadecenoic acid (HYA) showed the following unique physiological activities.

1) HYA ameliorates sulfate sodium-induced colitis in mice by recovering the damage of intestinal epithelial barrier[2)]. 2) HYA ameliorates periodontal pathogen-induced gingival epithelial barrier disruption via GPR40 signaling. 3) Oral administration of HYA induced insulin secretion by increasing GLP-1 level[3)]. 4) HYA elicited anti-inflammatory effects in vitro in murine enterocytes. 5) HYA showed protective efficacy against gastric Helicobacter infections.

Not only HYA, various gut microbial fatty acid metabolites were found to have health-promoting activities[4-6)]. These results suggested that the dietary fatty acid metabolites by gut microbiota can influence the health of the host. Gut microbial fatty acid metabolites as “Postbiotics” might have potential as novel functional foods and pharmaceuticals.

1) S. Kishino et al, *Proc. Natl. Acad. Sci. USA*, 110, 17808-17813 (2013).
2) J. Miyamoto et al, *J. Biol. Chem.*, 290, 2902-2918 (2015).
3) J. Miyamoto et al, *Nat. Commun.*, 10, 4007 (2019).
4) T. Nagatake et al, *Mucosal Immunol.*, 15, 289-300 (2022).

5) M. Noguchi, et al, *J. Biol. Chem.*, 298, 102534 (2022).
6) A. Saika, et al, *Front. Cell. Infect. Microbiol.*, 14:1355679 (2024).

Jun Ogawa
Professor, Division of Applied Life Sciences, Graduate School of Agriculture, Kyoto University

Jun Ogawa completed his doctorate in applied microbiology at Kyoto University in 1995 and began his academic career there as an assistant professor. He was a visiting researcher at the French National Institute for Agricultural Research (INRA) from 2006 to 2007 and was appointed as a full professor in 2009. His research focuses on bioprocess development and microbial metabolism analysis, with over 350 published papers. He has received multiple awards, including the Chevreul Medal (2021) and the Society Award of the Japan Society for Bioscience, Biotechnology, and Agrochemistry (2025).

Anti-Allergic and Anti-Inflammatory Effects of Postbiotics for Application to Precision Nutrition

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Key words: Postbiotics, Precision Nutrition, Omega-3 Fatty Acids, Gut Microbiota

As interest in health continues to grow, the role of the gut has been drawing significant attention. As the impact of diet on health has long been recognized, research on the role of gut microbiota has been advancing rapidly. In this context, new concepts leveraging beneficial bacteria have emerged. In particular, attention has recently been directed toward bioactive compounds produced by bacteria, leading to the emergence of the term "postbiotics." As research based on these concepts progresses, it is becoming possible to explain individual differences in the health benefits obtained from diet, paving the way for a new approach known as "personalized and stratified nutrition." In this talk, I will introduce the mechanisms of the anti-allergic and anti-inflammatory effects of lipids, with a focus on omega-3 fatty acids, as well as the involvement of gut microbiota. Furthermore, I will discuss the potential of precision nutrition based on the diversity of gut microbiota and dietary habits in the Japanese population.

Jun Kunisawa
Deputy Director, General of National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN), Microbial Research Center for Health and Medicine

Jun Kunisawa received his Ph.D. from Osaka University in 2001. He is the Deputy Director General of the National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN) and the Director of the Microbial Research Center for Health and Medicine. He completed postdoctoral training at the University of California, Berkeley, before joining The University of Tokyo as an Assistant and Associate Professor. In 2013, he moved to NIBIOHN to establish a new laboratory and was later promoted to Director in 2019 and Deputy Director General in 2024. His research focuses on immune regulation by the gut environment and its implications for immune diseases and health.

E. coli as a vaccine adjuvant to enhance mucosal IgA antibodies

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Key words: IgA, mucosal vaccine, intestinal bacteria

In the mucosa, IgA antibodies are secreted as multimeric antibodies, which play important roles in normal flora control as well as in infection control. In contrast to IgG antibodies, which are predominantly specific for a single antigen, these mucosal IgA antibodies are known to be broadly antigen-specific, allowing a single type of antibody to respond to multiple antigens.

For SARS-CoV2, it has been shown that multimeric IgM and IgA antibodies can cope with more variants than IgG antibodies. Thus, the development of an effective mucosal vaccine adjuvant that induces mucosal polymeric IgA antibodies provides strong mucosal protection against bacterial and viral infections. This is very different from the conventional vaccine that stimulates the increase of antibody in the serum by intramuscular injection and targets the pathogen after invasion into the body. We believe that it is important for B cells activated by antigens to efficiently migrate to germinal centers in order to induce high-affinity antibodies on mucosal surfaces. We have therefore found a marker for pre-germinal center B cells and are conducting research on substances that induce this marker on B cells as novel mucosal vaccine adjuvants. We identified that heat-killed *E. coli* induced CD11b on B cells *in vitro* and functioned as an effective mucosal adjuvant *in vivo*. We discuss the evaluation of mucosal immunity of vaccine adjuvants based on intestinal germinal center B cell responses.

Reiko Shinkura
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Reiko Shinkura earned her M.D. from the Medical School of Kyoto University in 1986 and her Ph.D. in Medicine from the Graduate School of Kyoto University in 1996. She conducted postdoctoral research at Kyoto University under Professor Tasuku Honjo (1996–1999) and later as an HHMI Research Associate at Children's Hospital Boston under Professor Frederick W. Alt (1999–2003). She then held faculty positions at Kyoto University (2004–2010), the Nagahama Institute of Bio-Science and Technology (2010–2016), and the Nara Institute of Science and Technology (2016–2017). Since 2017, she has been a Professor at the Institute for Quantitative Biosciences, The University of Tokyo, specializing in immunology and molecular biology.

Therapeutic Applications of the Bacterial Metabolite *p*-Cresol in Cardiometabolic Diseases

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Key words: Metabolome, animal models, diabetes, obesity

Metabolome profiling of biofluids in human cohorts provides opportunities to identify microbial metabolites involved in chronic diseases. Among products of bacterial metabolism that we found associated with cardiometabolic diseases through ^{1}H-NMR or MS metabolomics (e.g. TMAO, indolelactate, hippurate), *p*-cresol was inversely correlated with type 2 diabetes and showed pleiotropic effects on symptoms relevant to other diseases. Results from chronic administration of *p*-cresol in preclinical models of type 2 diabetes confirmed its beneficial role in glucose homeostasis, as well as obesity and fatty liver disease. *p*-cresol is a promising candidate to develop both pharmaceutical and probiotic-based solutions in cardiometabolic diseases.

Dominique Gauguier
Director, Research at INSERM, University Paris Cité, France

Dominique Gauguier earned his *Doctorat d'Université* (Ph.D.) in Physiology and Physiopathology of Human Nutrition from the University of Paris 7 in 1991. He was a Research Scientist at the Wellcome Trust Centre for Human Genetics, University of Oxford (1991–1999), where he studied genetic models of multifactorial diseases, before becoming a Professor of Mammalian Genetics and Wellcome Trust Senior Fellow at Oxford (1999–2010). Since 2007, he has been Director of Research at INSERM, University Paris Cité. He also holds adjunct positions at McGill University and Kyoto University. In 2023, he co-founded the startup Metabolica Health.

Diet-Microbe-Host Interactions in Lipid Metabolism

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Key words: Nutrition, Microbiome, Metabolism, Lipid

Dietary intake of ω-6 and ω-3 polyunsaturated fatty acids (PUFA) can promote human health via both lipid lowering and anti-inflammatory effects. Although dietary PUFA supplementation can strongly impact host lipid metabolic pathways in the liver, it is often overlooked that gut microbiota can also synthesize and degrade diverse lipids. Although there is a wealth of knowledge regarding diet-microbe-host interactions on carbohydrate and protein co-metabolism, comparatively little is known regarding meta-organismal metabolism of dietary fatty acids. Here, we hypothesized that the ability of dietary PUFAs to protects against diet-induced metabolic disturbance dependent on microbe and host co-metabolism of lipids. To test this, we fed either conventionally-raised or germ-free C57BL6/N mice six sterile diets with well-defined levels of either saturated monounsaturated, ω6 PUFAs, or ω3 PUFAs and comprehensively examined the diet-microbe-host interactions as they relate to cardiometabolic phenotypes. Compared to a SFA control diet (palm oil with lard), which effectively promoted obesity and NASH, both ω-6 (borage oil) and ω-3 PUFAs (fish oil) reduced body weight and liver weight in conventional, but not germ-free mice. Furthermore, the ability of dietary SFA, MUFA, and PUFAs to uniquely alter the hepatic lipidome was clearly altered in germ-free versus conventional mice. Of particular interest, the ability of dietary PUFAs to reshape pro-inflammatory and pro-resolving lipid mediators is profoundly impacted by the presence of gut microbe. Collectively, this study provides a comprehensive lipidomic analysis defining unique dietary fatty acid-microbe-host interactions and have uncovered new insights into how meta-organismal metabolism impacts cardiometabolic disease.

Mark Brown

Director, Research in the Center for Microbiome and Human Health, Cleveland Clinic, USA

Mark Brown received his Ph.D. in adipocyte biology and nutrition from the University of North Carolina in 2004. He subsequently conducted postdoctoral research at Wake Forest University, focusing on animal models of atherosclerosis and lipoprotein metabolism. He is currently a research fellow in the Department of Cancer Biology at the Cleveland Clinic and serves as the Director of Research at the Center for Microbiome and Human Health.

Novel Strategies for the Analysis of Microbial-Derived Octadecanoids

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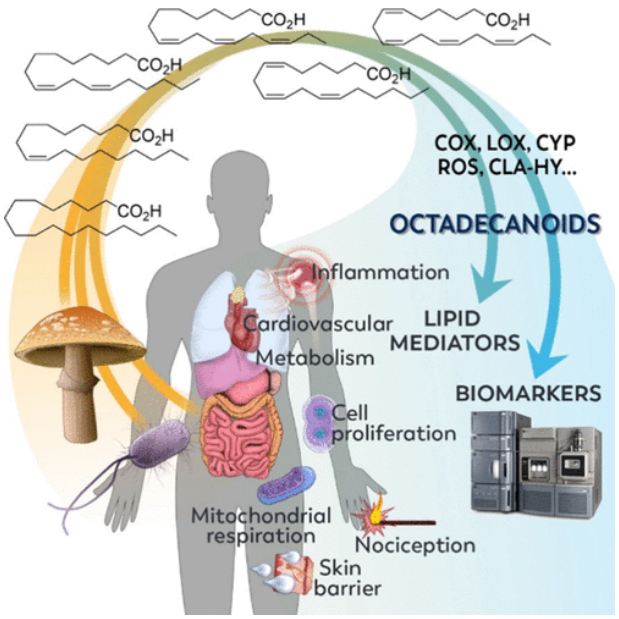
Key words: octadecanoid, lipid mediator, mass spectrometry, inflammation.

Oxylipins are a group of oxygenated lipids formed from fatty acids. The most studied class of oxylipins is the eicosanoids, which are derived from the 20-carbon fatty acids *via* cyclooxygenase, lipoxygenase and cytochrome P450 activity. However, 18-carbon fatty acids including oleic, linoleic, alpha-linolenic, and gamma-linolenic acid can be metabolized by these same enzymes, resulting in a combination of structurally heterogenous 18-carbon oxylipins, collectively defined as octadecanoids.[1] More recently, the gut microbiome has been shown to be a significant source of octadecanoid biosynthesis, providing additional biosynthetic routes including hydratase activity (*e.g.,* CLA-HY, FA-HY1).[2] Octadecanoids are involved in multiple disease processes including regulation of inflammation and immune function, with microbial-derived octadecanoids affecting host energy metabolism.[3] Our research efforts focus on developing methods to analyze octadecanoids. We established an analytical workflow combining chiral separation by supercritical fluid chromatography (SFC) and reversed-phase liquid chromatography (LC) coupled to tandem-MS detection for quantification of a broad panel of octadecanoids.[4] The platform includes >100 custom-synthesized standards. We can separate >230 octadecanoids by chiral SFC and complex enantioseparations can be performed in <12 minutes.



Caption 1: 18-carbon fatty acids are metabolized into a suite of downstream oxygenated lipids collectively called octadecanoids. These lipids include dietary linoleic and alpha-linolenic acid, which are transformed into a range of compounds that can exert multiple biochemical functions. In addition to mammalian metabolism, the gut microbiome can produce octadecanoids that exert a range of biological functions in maintaining homeostasis and the onset of

We expanded these efforts with imaging mass spectrometry to spatially map octadecanoids in tissue.[5] To investigate octadecanoid function, we developed a zebra fish model to examine the role of octadecanoids in gut barrier integrity. These tools will enable studies of the biological role of octadecanoids, with a focus on microbial-derived compounds. These efforts will collectively assist in demonstrating that these dietary fat-derived compounds are potent bioactive lipid mediators that constitute an interesting new field of study.

References

1) A. Quaranta, J. Revol-Cavalier, C.E. Wheelock: Biochem. Soc. Trans., 50(6), 1569-1582, (2022).
2) J. Revol-Cavalier, A. Quaranta, J.W. Newman, A.R. Brash, M. Hamberg, C.E. Wheelock: Chem. Rev., 125(1), 1-90, (2025).
3) J. Miyamoto, M. Igarashi, K. Watanabe, S. Karaki, H. Mukouyama, S. Kishino, X. Li, A. Ichimura, J. Irie, Y. Sugimoto, T. Mizutani, T. Sugawara, T. Miki, J. Ogawa, D.J. Drucker, M. Arita, H. Itoh, I. Kimura: Nat. Comms., 10(4007), (2019).
4) A. Quaranta, B. Zöhrer, J. Revol-Cavalier, K. Benkestock, L. Balas, C. Oger, G.S. Keyes, Å.M. Wheelock, T. Durand, J.M. Galano, C.E. Ramsden, M. Hamberg, C.E. Wheelock: Anal. Chem., 94(42), 14618-14626, (2022).
5) M.J. Smith, M. Nie, M. Adner, J. Säfholm, C.E. Wheelock: Anal. Chem., 96(45), 17950-17959, (2024).

Craig Wheelock

Associate Professor, Karolinska Institutet, Sweden

Craig Wheelock earned his Ph.D. in Agricultural and Environmental Chemistry from the University of California, Davis, under the mentorship of Dr. Bruce Hammock. After completing a postdoctoral fellowship in the Hammock laboratory, he relocated to Kyoto, Japan, in 2004 to conduct postdoctoral research at the Bioinformatics Center, Institute for Chemical Research, Kyoto University. In 2006, he joined the Karolinska Institute in Sweden, where he currently leads the Integrative Molecular Phenotyping Laboratory.

Special Lecture

Holden Thorp

Editor-in-Chief of the *Science* Family of Journals

Holden Thorp became Editor-in-Chief of the *Science* family of journals on October 28, 2019. Prior to this role, he served as Provost at Washington University from 2013 to 2019 and was a professor there from 2013 to 2023.

He is currently a professor at George Washington University and is on leave to serve as Editor-in-Chief at *Science*.

Effects of Exopolysaccharides from *Leuconostoc mesenteroides* on The Gut Environment and Metabolic Parameters in Humans

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Key words: exopolysaccharide, intestinal hormones, type 2 diabetes

Type 2 diabetes and obesity are major risk factors for cardiovascular diseases and are increasing globally. To date, modification of diet and behavior has been the primary therapeutic strategy, but more effective treatments are needed. Recent clinical trials have shown that therapies acting through intestinal hormones can significantly reduce body fat mass and improve glycemic control in individuals with diabetes and obesity. New treatments leveraging intestinal hormones are currently under investigation.

Intestinal hormones, including GLP-1 and GIP, are secreted in response to nutrient signals in the intestinal lumen. These hormones slow gastrointestinal motility, lower blood glucose levels, and suppress appetite, making them a key focus in clinical research. Their secretion is stimulated by intestinal metabolites such as short-chain fatty acids (SCFAs), which are produced by intestinal microbiota. Dietary fiber intake, commonly recommended for patients with type 2 diabetes and obesity, has been shown to improve metabolic disorders partially due to SCFA action. We have demonstrated that SCFAs not only serve as an energy source for the host but also improve glucose intolerance and obesity by promoting intestinal hormone secretion and inhibiting fat accumulation in adipocytes via GPR41 and GPR43. Developing therapies that increase intestinal SCFA levels represents an attractive strategy for managing obesity and type 2 diabetes.

Therefore, we conducted research focusing on postbiotics, specifically exopolysaccharides (EPS), which are polysaccharides produced by bacteria. Our research revealed that individuals with obesity had a lower abundance of *Streptococcus salivarius*, an EPS-producing bacterium, and lower fecal EPS levels. Additionally, individuals with obesity exhibited reduced fecal SCFA concentrations. When EPS derived from *Streptococcus salivarius* was administered to mice, SCFA levels in the gut increased, accompanied by an enrichment of Bacteroides species, enhanced intestinal hormone secretion, and suppressed obesity and diabetes. These findings suggest that EPS may serve as a potential treatment for obesity and diabetes by modulating intestinal microbiota-derived metabolites.

We next investigated EPS produced by *Leuconostoc mesenteroides* (LmEPS), a bacterium found in fermented foods and human feces. LmEPS administration increased fecal SCFA levels, stimulated intestinal hormone secretion, and improved glycemic control and obesity in mice. These results prompted us to conduct the first-in-human trial of LmEPS. In healthy participants, a single dose of LmEPS increased fecal acetate levels and plasma intestinal hormone concentrations without any adverse effects (n = 9–10 in placebo, 0.5 g, 2.5 g and 5 g of LmEPS groups, respectively; mean age 44.7 years, mean body mass index (BMI) 22.7 kg/m^2). Subsequently, a 12-week daily administration study in healthy individuals showed a sustained increase in fecal propionate levels, enhanced intestinal hormone secretion, and reduced postprandial hyperglycemia with no severe adverse events (n = 10; mean age 51.3 years, mean BMI 22.9 kg/m^2). Finally, a randomized, placebo-controlled trial was conducted in patients with obesity over four weeks (placebo vs. 5 g of LmEPS daily; n = 10, respectively; mean age 47.2

years, mean BMI 35.0 kg/m^2). LmEPS administration significantly increased fecal propionate and plasma intestinal hormone levels, with a correlation between fecal propionate and intestinal hormone secretion (Participants with a BMI >30 kg/m² exhibited increased serum HDL cholesterol levels (placebo; n = 5, LmEPS; n = 9). Additionally, LmEPS administration promoted the growth of Bacteroidetes species in the intestinal microbiota. No significant adverse effects were observed in the EPS-treated group.
Our findings suggest that EPS represents a novel therapeutic approach for obesity and type 2 diabetes. Postbiotics, such as EPS, have the potential to be developed into new treatments for metabolic disorders.

Hiroshi Itoh
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Hiroshi Itoh received his Ph.D. from Kyoto University School of Medicine in 1989. He is currently a Specially Appointed Professor at the Center for Preventive Medicine, Keio University, and the Director of the Research Support Center at Shizuoka General Hospital. He previously served as a Professor and Chairman of the Department of Endocrinology, Metabolism, and Nephrology at Keio University. His research focuses on hypertension, endocrinology, and metabolism, and he has held leadership roles in several medical societies. He has received multiple awards, including the Japanese Society of Endocrinology Award in 2020.

Advanced lipidomics to illuminate the functional postbiotics in host-microbiome interactions

Makoto Arita[1-5]

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Key words: untargeted lipidomics, mass spectrometry imaging, lipidome atlas, postbiotics

Abnormal lipid metabolism is often a background factor of diseases, which may lead to the discovery of new seeds for drug discovery and medical applications such as early diagnosis and treatment. Recent advances in mass spectrometry have provided a major impact on lipid biology, suggesting that the lipid molecules analyzed in the past are only the tip of the iceberg. Host-microbiome interactions create a unique metabolic milieu that modulates intestinal environments. By combining non-targeted mass spectrometry with feature-based molecular spectrum networking technology, we revealed that lipids with complex structures are produced by gut microbiota. Correctly capturing such molecular groups that have been overlooked by conventional targeted analysis will lead to understanding the significance of bacterial species that correlate with various diseases. The method developed in this study is a technology that enables us to view such changes in the bacterial flora as changes in the lipidome environment from a bird's eye view, and is expected to contribute to the discovery of functional metabolites (i.e. postbiotics) that mediate the host-microbiome interactions.

References

1. Tsugawa H, Ishihara T, Ogasa K, Iwanami S, Hori A, Takahashi M, Yamada Y, Satoh-Takayama N, Ohno H, Minoda A, Arita M. A lipidome landscape of aging in mice. ***Nature Aging*** 4, 709-726 (2024)
2. Yasuda S, Okahashi N, Tsugawa H, Ogata Y, Ikeda K, Suda W, Arai H, Hattori M, Arita M. Elucidation of gut microbiota-associated lipids using LC-MS/MS and 16S rRNA sequence analyses. ***iScience*** 23, 101841 (2020)
3. Tsugawa H, Ikeda K, Takahashi M, Satoh A, Mori Y, Uchino H, Okahashi N, Yamada Y, Tada I, Bonini P, Higashi Y, Okazaki Y, Zhou Z, Zhu Z, Koelmel J, Cajka T, Fiehn O, Saito K, Arita M, Arita M. A lipidome atlas in MS-DIAL 4. ***Nature Biotechnol*** 38, 1159-1163 (2020)

Makoto Arita

Professor, Physiological Chemistry and Metabolism, Faculty of Pharmacy, Keio University, and RIKEN Center for Integrative Medical Sciences

Makoto Arita earned his Ph.D. from the Graduate School of Pharmaceutical Sciences, University of Tokyo, in 1997. He is the Dean of the Faculty of Pharmacy and a Professor of Physiological Chemistry and Metabolism at Keio University, as well as a Team Leader at the RIKEN Center for Integrative Medical Sciences. He has led multidisciplinary research projects, including the JSPS-funded "Biology of LipoQuality" program. Currently, he directs the JST-ERATO Lipidome Atlas Project (2021–2026) and serves as Core Director of Keio University's WPI-Bio2Q initiative (2022–2032), integrating human biology, microbiome research, and quantum computing to advance healthy longevity.

Regulation of Immobilization-Induced Muscle Atrophy via the Neuro-Gut Axis: The Potential of HYA-Based Intervention

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Key words: Muscle atrophy, Immobilization, Neuro-Gut Axis, HYA, Macrophage

Skeletal muscle mass is an important determinant of whole-body metabolism, and reductions in muscle mass are associated with various metabolic disorders. Whereas immobility is a common cause of skeletal muscle mass reduction, the underlying mechanisms of this process have remained unclear.

We have now found that immobilization-induced muscle atrophy is accompanied by muscle inflammation that is associated with the infiltration of activated macrophages, and that the chemokine CXCL10 plays a key role in such inflammation. Unexpectedly, limb immobilization was also found to trigger changes to the gut microbiota and intestinal inflammation, and sterilization of the intestine by oral administration of antibiotics prevented the immobilization-induced inflammation and atrophy of muscle. Furthermore, oral administration of a linoleic acid–derived gut microbial metabolite, 10-hydroxy-cis-12- octadecenoic acid (HYA), prevented both intestinal and muscle inflammation as well as muscle atrophy elicited by limb immobilization, highlighting the importance of intestinal inflammation in immobilization-induced muscle atrophy.

We also found that limb immobilization increased both sympathetic nerve activity and expression of the β2-adrenergic receptor gene (*Adrb2*) selectively in the lower intestine. Single-cell RNA sequencing analysis revealed that *Adrb2* was expressed in both pro-inflammatory and anti-inflammatory macrophages of the colon, and that macrophage-specific ablation of *Adrb2* increased the number of anti-inflammatory macrophages and reduced that of proinflammatory macrophages in this tissue of immobilized mice. Finally, pharmacological inhibition or macrophage-specific genetic ablation of *Adrb2* prevented immobilization-induced inflammation of the intestine and muscle. Thus, our study has revealed a previously unrecognized neuro-gut axis that plays a key role in the development of immobilization-induced muscle atrophy.

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