Microbiome

Understanding the Interactions and Symbiosis between the Microbiome and the Host Organism, Leading to an Understanding of the Mechanisms of Disease Onset

Research and Development Objectives

Understanding the crosstalk and symbiosis between the microbiome and host, and the applications to health and healthcare

In this R&D area, we aim to achieve a better understanding of microbiome-host interactions and symbiosis and use these findings to elucidate the mechanisms involved in disease onset, thereby contributing to the development of new concepts for health and healthcare through the control of the human microbiome.

Various different microorganisms—bacteria, fungi, viruses—live in the parts of the human body that come into direct contact with the external environment, such as the digestive tract, skin, oral cavity, nasal cavity, respiratory organs, and reproductive organs. These microorganisms form microbiomes with different characteristics specific to each location. Research has started to show that the microbiomes of healthy individuals differ from those in diseased individuals in a wide range of diseases and conditions, suggesting that the microbiome plays an important role in health and disease. However, we still have a lot to learn about the mechanisms involved in host-microbiome interactions, symbiosis, and disease onset in terms of how these microbiomes form or change and how they affect human health, disease onset, or disease progression.

In this R&D area, we aim to gain a comprehensive understanding of the processes involved and develop new strategies for health promotion and healthcare technologies based on novel mechanisms for host-microbiome interactions.

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Started in 2016 • • • 1st period

Development of therapeutic strategies to inflammatory diseases based on comprehensive understanding on skin microbiome and host relationship (*)

AMAGAI Masayuki
Professor and Chair, Department of Dermatology, Keio University School of Medicine

Our team will clarify how skin microbiome affects immune system in a healthy condition, and how dysbiosis is involved in the cause of skin inflammation, such as atopic dermatitis in mice and human. Furthermore, we will clarify the homeostatic mechanism of stratum corneum, which is highly regulated to maintain 10-15 layers of dead keratinocytes and provides niche for skin microbiome. The goal of our study is to develop a novel therapeutic strategy to inflammatory and allergic skin diseases by regulating skin microbiome through manipulating the microenvironment of stratum corneum.

Started in 2016 • • • 1st period

Clarifying the role of microbiome in cancer immunity for application into cancer therapy (*)

NISHIKAWA Hiroyoshi
Chief, Division of Cancer Immunology, Research Institute/ EPOC, National Cancer Center

Immune checkpoint blockade provides clinical success in various types of cancers. Yet, more than half of treated patients do not respond to immune checkpoint blockade therapy, even in combination. It is therefore required to define biomarkers to properly evaluate phenotypes of both immune responses and cancer cells in cancer patients for detecting responders. In this study, we focus on the diversity of metabolism and microbiome of cancer tissues in each cancer patient, clarifying their contribution to cancer immunity. Moreover, the role of the microbiome in immune tolerance and surveillance is addressed from the view of cancer immunity.

Started in 2016 • • • 1st period

Elucidation of causal association of intestinal dysbiosis in abnormal intestinal aggregation of alpha-synuclein in Parkinson's disease (*)

OHNO Kinji
Professor, Nagoya University Graduate School of Medicine

Accumulating knowledge indicates that abnormally aggregated α-synuclein in the intestine behaves like a prion and causes Parkinson's disease (PD). It is subsequently inferred that intestinal microbiota is causally associated with the development of PD. Specific aims of our current studies are to obtain temporal profiles of clinical features, biomarkers, and intestinal microbiota in patients with PD and dementia with Lewy bodies (DLB), and to perform cross-sectional and longitudinal analyses using machine learning techniques to elucidate the possible roles of intestinal dysbiosis in the development of PD and DLB.

Started in 2017 • • • 2nd period

Elucidation of host energy regulation by gut microbial metabolites and the development of preventive and therapeutic strategies for the related metabolic disorders (*)

KIMURA Ikuo
Professor, Graduate School of Biostudies, Kyoto University

Gut microbiota has emerged as a pivotal, multifactorial mediator in metabolic disorders as it remarkably regulates host energy acquisition and metabolism while being modified by diet. Short-chain fatty acids represent an essential subset of gut microbial metabolites derived from the fermentation of the otherwise indigestible dietary fiber. This research aims at elucidating the molecular interplay between host energy metabolism and these metabolites of gut microbiota that underlies the pathogenesis of metabolic disorders with further exploration of novel interventions including drugs and functional foods.

Started in 2016 • • • 1st period

Understanding of disease mechanisms between microbiota and host intestinal epithelium (*)

KANAI Takanori
Professor, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine

Previous studies have revealed the intestinal microbiota is implicated in numerous aspects of health and disease based on their interaction with host epithelium. In this project, we use both an gnotobiotic mouse model using human patients-derived feces and a novel ex vivo intestinal epithelium culture system to understand the mechanism of communication between gut microbes and host intestinal epithelium. The goal of our study will establish basic roles of the effect of microbes for entire body of human thought gut-liver-brain axis that could have implications for therapy and generate new drugs of diseases such as cancer and inflammation of gut or liver that demonstrate poor healing.

Started in 2017 • • • 2nd period

Elucidation of molecular mechanisms of gut microbiota regulation by intestinal IgA (*)

SHINKURA Reiko
Professor, Institute for Quantitative Biosciences, The University of Tokyo

As a modulator of the intestinal microbiota, we isolated a mouse monoclonal IgA antibody (clone W27) with high affinities for multiple commensal bacteria, but not for beneficial bacteria such as *Lactobacillus casei*. By modulating the gut microbiota *in vivo*, oral administration of W27 IgA effectively prevented development of colitis in several mouse models. In this research, we will clarify how intestinal IgA interacts and regulates human gut microbiota. The elucidation of precise molecular mechanism of IgA function leads to a new solution for treatment of dysbiosis.

Started in 2016 • • • 1st period

Analysis on the mechanisms for commensalism and interplay of intestinal microbiota and the host (*)

TAKEDA Kiyoshi
Professor, Graduate School of Medicine, Osaka University

The mechanisms by which commensal microorganisms colonize in the intestine and thereby influence our health condition remain unknown. In this research project, we will analyze the mechanism by which human microbiota and mycobiota help each other to colonize in the intestine. Will also analyze the mechanisms how commensal microorganisms influence our health condition by identifying their metabolites, which act on the host cells.

Started in 2017 • • • 2nd period

Development of metagenomics, metabolomics, and bioinformatics hub to promote human microbiome research and development (*)

TOYODA Atsushi
Project Professor, Departnient of Genomics and Evolutionary Biology, National Institute of Genetics

We aim to establish a new research and development facility to enhance metagenomics, metabolomics, and bioinformatics approaches for human microbiome research in this project. Our missions are to (i) support sequencing and bioinformatics analyses for shotgun metagenomics and amplicon sequencing, (ii) develop advanced technologies by taking advantage of achievements in human microbiome, (iii) propose ethical guidelines for human microbiome research and the recommended protocols for both experiments and bioinformatics analyses (iv) build a human metagenomics data sharing system and (v) create a new integrated metagenomics and metabolomics database including search/browse information and comparative analysis results.

Started in 2018 • • • 3rd period

AMED-CREST

The mechanism and the regulation of liver diseases involved in gut-liver axis-mediated intestinal microbiota

OHTANI Naoko

Professor, Department of Pathophysiology, Osaka Metropolitan University, Graduate School of Medicine

As a modulator of the intestinal microbiota, we isolated a mouse monoclonal IgA antibody (clone W27) with high affinities for multiple commensal bacteria, but not for beneficial bacteria such as *Lactobacillus casei*. By modulating the gut microbiota *in vivo*, oral administration of W27 IgA effectively prevented development of colitis in several mouse models. In this research, we will clarify how intestinal IgA interacts and regulates human gut microbiota. The elucidation of precise molecular mechanism of IgA function leads to a new solution for treatment of dysbiosis.

Started in 2016 • • • 1st period

PRIME

Tracking intercellular electrochemical interaction in human bacterial flora by gene expression mapping method (*)

OKAMOTO Akihiro

Group leader, International Center for Materials Nanoarchitectonics, National Institute for Material Sciences

In the natural environment, certain bacterial consortia live on electricity by transporting respiratory electrons though biofilm and sharing energy. Such “electric symbiosis” has not been known in human or disease-related microbiome. We recently revealed by electrochemical assay that some pathogenic strains have the potential for the electronic symbiosis. In this project, we study the intercellular electrical interaction in in-vivo biofilms by tracking gene expression level of individual bacteria, and challenge to develop technologies to control the activity of human bacterial flora.

Started in 2018 • • • 3rd period

AMED-CREST

Exploring the molecular mechanisms of the systemic changes caused by the oral microbial dysbiosis in association with periodontal disease

MURAKAMI Shinya

Professor, Department of Periodontology, Osaka University Graduate School of Dentistry

Periodontal disease is a condition in which periodontal tissues supporting the teeth are destroyed by bacteria in the oral cavity. Our study examines the deterioration of the oral bacterial flora that accompanies the progression of periodontal disease and includes a detailed analysis of the resulting changes in intestinal bacterial flora and metabolites produced through host-bacteria interactions. Thereby, our study aimed to clarify the etiopathology of periodontal disease from a new perspective and to elucidate the molecular mechanisms involved in the altering effects of periodontal disease on the overall physical condition of the patient.

Started in 2016 • • • 1st period

PRIME

High-resolution metagenomics for intra-species variations based on assembly of the comprehensive draft genomes (*)

KAJITANI Rei

Assistant Professor, School of Life Science and Technology, Tokyo Institute of Technology

To investigate genomic composition of microbiomes, the methods based on marker sequences such as 16S rRNAs are widely utilized and the valuable knowledge associated with health and disease have been accumulated. However, it was also reported that the fine-scale mutations critically changed the characteristics of the microbes, including resistances for medicines, as the results of studies of isolated microbes for decades. In this study, the whole sequence of each microbe genome in a microbiome is thoroughly analyzed and I intend to elucidate the nature of microbiomes that are not targeted in marker sequences-based analysis, mainly developing the informatics methods.

Started in 2018 • • • 3rd period

AMED-CREST

Study of microbiota-mediated modulation of neuroinflammation, neurodegeneration and neural development

YAMAMURA Takashi

Director, National Institute of Neuroscience, NCNP

As recent study has indicated, chronic inflammation accompanied by activated glia cells may play a critical role in neurodegenerative and neurodevelopmental disorders. Given the recent concept on gut-brain axis, we explore the role of gut microbiota in neurodegenerative and neural development disorders. We will analyze the microbiota and gut immunity in new animal models relevant for study of such disorders, and further conduct translational research dependent on human fecal samples. Our unique approaches will lead us to obtain new insights into the pathogenesis and new possible therapeutic strategies.

Started in 2016 • • • 1st period

PRIME

Microbiota regulates IgE-mediated allergic responses (*)

KIM Yun-Gi

Professor, Research Center for Drug Discovery, Faculty of Pharmacy, Keio University

Prenatal or early-life antibiotic exposures are known to increase the risk of allergic diseases, suggesting that exposure to environmental microorganisms in this period is important event to develop and maintain balanced immune systems. Several mouse studies have shown that germ free and antibiotic-treated mice have increased serum IgE level and enhanced disease severity such as allergic airway inflammation and food antigen-induced anaphylaxis. In this study, I try to find gut bacteria which have an ability to reduce serum IgE level. Also, I will elucidate the mechanisms by which the bacteria reduce serum IgE level.

Started in 2016 • • • 1st period

PRIME

Crosstalk among microbiome, host, disease, and drug discovery enhanced by statistical genetics (*)

OKADA Yukinori

Professor, Graduate School of Medicine, Osaka University

Statistical genetics is a research field that evaluates causality of human genetic variations on diseases, using statistical and bioinformatics approaches. In this project, we integrate high-throughput omics data related to human microbiome generated by next generation sequencer. We focus on variations in human genome and metagenome sequences, and their relationships in host-microbiome interaction. Based on the newly developed statistical genetic approaches, our project aims elucidation of novel disease biology and identification of drug discovery seeds.

Started in 2016 • • • 1st period

PRIME

Regulation of intestinal microbiota through carbohydrate chain expressed on intestinal epithelial cells (*)

GOTO Yoshiyuki

Associate Professor, Division of Molecular Immunology, Medical Mycology Research Center, Chiba University

Numerous numbers of microorganisms colonize in our intestine. Epithelial cells covering the intestinal tract directly face to these microorganisms and create a symbiotic environment with microorganisms by expressing α1, 2-fucose, a kind of sugar chain, on their cell surface. In this project, we aim to clarify regulation mechanism of the homeostasis of commensal microbiota by symbiotic and immunological factors including carbohydrate chain produced by epithelial cells in each intestinal tract. We further investigate mechanism of the development of inflammatory bowel disease and metabolic disorders caused by dysbiosis.

Started in 2016 • • • 1st period

PRIME

Development of metatranscriptome analysis method based on megagenome assembly and its application to metatranscriptome map of commom marmoset (*)

SAKAKIBARA Yasubumi
Professor,
Keio University

We develop a bioinformatics method for high-precision meta-transcriptome analysis that can deeply detect bacteria species with high sensitivity and low abundance by applying the MetaVelvet, an assembler specialized for metagenomes developed in our laboratory. Next, we construct the meta-transcriptome map in the intestine including rectal and vermiform that forms the common bacterial flora using common marmoset as a target preclinical primate model of human.

Started in 2017 • • • 2nd period

PRIME

Elucidation of DOHaD mechanisms driven by gut microbiota (*)

OBATA Fumiaki
Team Leader, Laboratory for Nutritional Biology, RIKEN center for Biosystems Dyamics Research

Early-life environment can influence the adult health throughout life. However, mechanism(s) of this phenomenon known as “The Developmental Origins of Health and Disease (DOHaD)” is poorly understood. The present study elucidates the mechanism of DOHaD driven by gut microbiota, based on a hypothesis that developmental environment triggers irreversible reprogramming of gut microbiome to affect the organismal healthspan. Taking advantages of shorter lifespans of fruit flies *Drosophila melanogaster* enables to promote the rapid progress of the unique research.

Started in 2016 • • • 1st period

PRIME

Isolation of yet-uncultured microorganisms and elucidation of symbiosis mechanism between the microbe (*)

SAKAMOTO Mitsuo
Senior Research Scientist, Japan Collection of Microorganisms,
RIKEN BioResource Research Center

Human intestinal microbiota is composed of a wide variety of species, many of which have been found to be yet-uncultured or unclassified bacteria. In this study, we aim to establish a new culture system and co-cultivation system by multiple species in order to isolate yet-uncultured microorganisms. Furthermore, by clarifying the characteristics of the isolates and co-culturing them with multiple species based on the obtained information, it is possible to clarify the mechanisms of the interaction between the microbiota and the host.

Started in 2017 • • • 2nd period

PRIME

Elucidation of the relationship between microbiota and enteroendocrine cells (*)

KURAISHI Takayuki
Associate Professor,
Kanazawa University

Intestinal enteroendocrine cells are specialized minority cells of the gastrointestinal tract with endocrine function. They produce peptide hormones in response to various stimuli, such as amino acids and lipids of ingested foods, in order to modulate host metabolism. In a sense, enteroendocrine cells are considered as chemosensors for host internal environment that are responsible for the control of host physiology. We hypothesized that enteroendocrine cells could recognized bacterial metabolites derived from intestinal microbes so as to adjust their production of peptide hormones. In this study, we try to identify bacterial subsets that induce the expression of the intestinal peptide hormones, and clarify its molecular mechanisms.

Started in 2016 • • • 1st period

PRIME

Investigation of the mechanism for forming neonatal gut microbiota (*)

SAWA Shinichiro
Professor, Medical Institute of Bioregulation, Kyushu University

Neonate is a critical period for colonizing bacteria in mammals. However, it has been unclear by which mechanism particular species of bacteria colonize in the neonatal gut. In this project, I am investigating mechanism for forming intestinal microbiota and for shaping immune system, particularly focusing on the newly identified lymphoid population termed innate lymphoid cells. This study will bring us a new knowledge that helps us to understand relationship between the dysbiosis and the necrotizing colitis (NEC) that occur in neonates. Moreover, this study might help us to develop new strategy to prevent dysbiosis occasionally observed in adult patients suffering from obesity and inflammatory bowel disease.

Started in 2017 • • • 2nd period

PRIME

Elucidation of crosstalk between the enteric nervous system and commensal microbiota for gut mucosal health and disease (*)

KURASHIMA Yosuke
Associate Professor,
Graduate School of Medicine, Department of Innovative Medicine, Chiba University

The enteric nervous system is comprised of two separate plexuses, the Meissner's and Auerbach's plexuses. The Meissner's plexus is in the intestinal submucosa while the Auerbach's plexus is located between the longitudinal and circular intestinal muscle layers. Both plexuses promote peristalsis and digestive activity through myenteron stimulation. The plexuses, particularly Meissner's plexus, have also been shown to alter epithelial cell function such as hormone and mucous secretion; however, the precise mechanisms are not well elucidated. We aim to detail mechanisms of gut mucosal health and disease, to elucidate the body's environmental maintenance mechanisms.

Started in 2017 • • • 2nd period

PRIME

Developing mouse intestine infection model against enteric pathogens through the study of microbiota-bacterial pathogens interplay and its application (*)

ASHIDA Hiroshi
Associate Professor,
Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University

Enteric infectious diseases caused by enteric bacterial pathogens are one of the leading infectious killers. Furthermore, since many enteric pathogens are highly human adapted and unable to colonize mice intestine, lack of appropriate animal infection models are becoming bottleneck for in vivo pathogenic analysis and developing vaccine and novel drugs. Therefore I am trying to develop mouse intestinal infection model that would be suitable to in vivo pathogenic analysis and develop vaccine and novel drug through the analysis of microbiota-bacterial pathogens interplay.

Started in 2017 • • • 2nd period

PRIME

Research for the mechanism of human gut microbiota mediated induction of immune cells and cancer immunity (*)

TANOUE Takeshi
Assistant Professor,
Department of Microbiology and Immunology, Keio University School of Medicine

There are mounting evidences showing that gut microbiota affects various physiological responses of the host. A control or reproduce of these effects is promising strategies for disease control and health maintenance in clinical fields. In this study. I focus on the immunological effect and try to investigate the molecular mechanism of human gut microbiota mediated induction of immune cells, mainly search for bacteria-derived antigen that can drive the activation of immune cells. And I also try to address the effect of microbiota on cancer immunity.

Started in 2017 • • • 2nd period

PRIME

Elucidation of the inflammation regulating mechanism by skin resident commensals in the pathogenesis of inflammatory skin diseases (*)

NAKAJIMA Saeko
Program-Specific Associate Professor,
Graduate School of Medicine, Kyoto University

Shifts in skin microbiota composition have been shown in the context of skin inflammatory disorders, however, the precise role of cutaneous commensals in the control or promotion of skin inflammatory states remains unclear.
I will identify the skin commensals which regulate the inflammation and will evaluate local immune responses in inflammatory skin diseases such as psoriasis vulgaris and atopic dermatitis. I will clarify the molecular mechanism which is regulated by skin commensals. I will use microbiological and immunological approaches to assess these questions by using human skin models and murine dermatitis models.

Started in 2018 • • • 3rd period

PRIME

Comprehensive analysis of microbiome by single cell glycomics (*)

TATENO Hiroaki
Group Leader, Cellular and Moleclar Biotechnology Research Institute, National Institute of Advanced Industrial Science and Technology(AIST)

Not only mammalian cells, but also microorganisms are also coated with glycans at the outermost cell surface, which play roles as “starting point” of the crosstalk with host cells. However, there has been no method to analyze the glycome of microbiome and its roles have not been understood at all. In this study, I will develop a novel technology to analyze the glycome of microbiome in a high-throughput manner and pioneer a new breakthrough in microbiome researches.

Started in 2017 • • • 2nd period

PRIME

The role of gastric dysbiosis in gastrointestinal diseases and its relationship to nerve-dependent regulation of gastrointestinal stem cells (*)

HAYAKAWA Yoku
Assistant Professor, Department of Gastroenterology, The University of Tokyo

Changes in gastric microbiome during gastritis and gastric cancer progression have been recently reported, but the details and mechanisms of gastric dysbiosis remain unclear. In this proposal, we focus on gastric dysbiosis during gastric disease progression, and their role in gastritis, intestinal metaplasia, and gastric cancer. We will investigate the possible relationship between gastric microbiome and small intestinal and colon diseases. We will also explore how gastric microbiome affects gastrointestinal stem cell activity and influences nerve-dependent regulation of gastrointestinal homeostasis. This proposal would contribute to provide new insights for understanding the pathogenesis of gastrointestinal diseases, and help to establish novel therapeutic approaches such as probiotics treatment.

Started in 2018 • • • 3rd period

PRIME

The occurrence and control of diabetes and obesity: exploring the multidimensional interaction between host, antagonist bacteria, and protagonist viruses (*)

TAMAKI Hideyuki
Group Leader, Bioproduction Research Institute, National Institute of Advanced Industrial Science and Technology (AIST)

In this work, we aim to investigate the interaction between uncultured intestinal flora and two widespread health conditions of major concern-diabetes and obesity. In particular, we will cultivate and identify diabetes and obesity causing bacteira (DIB) and DIB-targeting viruses (DIB-V), and perform a concerted investigation of the three-way interaction between the host, DIB, and DIB-V to address the main questions at hand: cause, mechanism, and solution. This work will provide major steps forward in our comprehension of the relationship between human diseases, GIT microbiota, and even viruses and, most importantly, essential insight into unprecedented microbiology-based bottom-up development of innovative disease prevention and treatment.

Started in 2017 • • • 2nd period

PRIME

Identification of the mechanism responsible for the evolutionary changes of *S. aureus*-genome controlled by normal skin microbiome (*)

MATSUOKA-NAKAMURA Yuumi
Associate Professor, Immunology Frontier Research Center, Osaka University

Atopic dermatitis (AD) and CA-MRSA infection are associated with the skin colonization with *Staphylococcus aureus*. In this study, we will analyze the mechanism responsible for this evolutionary change of *S. aureus*-genome that regulates *S. aureus* adaptation to the skin by using whole genomic analysis of *S. aureus* and skin microbiome analysis. This study can contribute a more detailed understanding of the role of *S. aureus* in skin disease pathogenesis and provide the new therapeutic target for AD and *S. aureus*-associated cutaneous infections.

Started in 2018 • • • 3rd period

PRIME

Mechanism for acceleration of T cell senescence and transformation by intestinal flora (*)

NAKATSUKASA Hiroko
Associate Professor, Laboratory of Microbiology and Immunology, Graduate School of Pharmaceutical Sciences, Chiba University

Aging-dependent dysbiosis is related to susceptibility to infection and cancer and contributes to the development of various diseases, such as chronic inflammation, autoimmune diseases, diabetes, and cardiovascular diseases, through T cell senescence and dysfunction of immune systems. In this study, we will clarify the effect of intestinal bacteria-dependent epigenetic modification on T cell homeostasis including senescence and tumorigenesis. We will also try to identify the intestinal bacteria species or their metabolites responsible for T cell senescence and tumorigenesis, and to develop therapeutic strategy for aging-related diseases.

Started in 2018 • • • 3rd period

PRIME

Mucosal immunity developed by microbe-host interaction through D-amino acids and its pathological role in the immunological diseases (*)

SASABE Jumpei
Assistant Professor,
Keio University School of Medicine

While microbiota is increasingly associated with the host physiology and pathology, molecular mechanisms that link between microbiota and its host are less understood. In this project, we focus on D-amino acids, chiral forms of L-amino acids, originated in bacteria as interkingdom signaling molecules. We aim to understand the immunological and pathological significance of microbe-host relationship through D-amino acids and a host metabolic enzyme, D-amino acid oxidase.

Started in 2018 • • • 3rd period

PRIME

Elucidation of inhibitory receptor-microbiome interaction in health and disease (*)

HIRAYASU Kouyuki
Associate Professor, Kanazawa University Advanced Preventive Medical Sciences Research Center

Host-commensal bacteria relationships can impact host immunity, the mechanism of which is not fully understood. Considering that not only microbial pathogens but also tumor cells exploit host inhibitory receptors to act on host immune system, the host microbiome is also likely to interact with immune inhibitory receptors to establish the host-microbe symbiosis. Therefore, this study aims to elucidate the host-microbiome interaction in health and disease by focusing on the immune inhibitory receptors.

Started in 2018 • • • 3rd period

PRIME

Elucidation of mechanism of pancreatic cancer initiation based on the interaction between microbial flora and host (*)

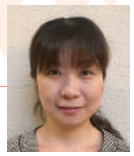
FUKUDA Akihisa
Lecturer, Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University

This study aims to investigate the mechanism by which pancreatic ductal adenocarcinoma (PDAC) is developed in the context of the interaction between microbial flora and host. We will investigate how innate immune response to intestinal microbial flora affects inflammation, dedifferentiation of pancreatic epithelial cells, formation of pancreatic precancerous lesions and PDAC, and pancreatic cancer stem cells. To this end, we will use genetically engineered mouse models of PDAC and ex vivo 3D culture system of PDAC spheroids of mouse and human.

Started in 2018 • • • 3rd period

PRIME

Understanding of immunity and metabolism network through nutrient-specific intestinal microbial control and bacterial metabolites (*)



FUJISAKA Shiho
Associate Professor, Faculty of Medicine, Academic Assembly, University of Toyama

Diet is the major driver that controls the gut microbiota which is known to be involved in the onset of various diseases such as obesity and type 2 diabetes. Microbiota produces various metabolites from dietary nutrients. However, it is poorly understood what nutrients affect bacterial composition that produces biologically active metabolites and how they affect the host metabolism. The aim of this study is to elucidate the crosstalk between nutrient-specific microbiota control and bacterial metabolites, and clarify the relation with host metabolism and immunity.

Started in 2018 • • • 3rd period

PRIME

Unraveling the anti-inflammatory mechanisms of human 2 *Bacteroides* species and their application for treating chronic inflammatory diseases (*)

YAMASHITA Tomoya
Professor, Advanced Medical Science, Graduate School of Science, Technolgy and Innovation, Kobe University

Our clinical studies demonstrated *Bacteroides vulgatus* and *Bacteroides dorei* were decreased in coronary artery disease patients compared with controls. Further, oral administration of the *Bacteroides* 2 species were shown to reduce the cytokine and chemokine production *in vivo*, and to inhibit the progression of atherosclerotic lesion formation in atherosclerosis-mouse model. The aims of this research are to clarify the anti-inflammatory mechanisms of *Bacteroides* 2 species *in vivo* (1), to verify the effects of them on several inflammation-related disease mouse models (2), and finally to establish the basis for clinical application of them as microbial drugs.

(*) indicates completed R&D projects.