Lipid Molecules

Studies on Specific Activities and Functions of Lipid Molecules to Develop Innovative Medical Technologies

【Research and Development Objectives】
Comprehensive elucidation of functional lipid which contributes to breakthrough medicines

Program Supervisor (PS)

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Program Officer (PO)

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Lipids carry fundamental functions in living organisms as major components of biomembranes and energy-storage molecules. Numbers of their derivatives also play specific roles in regulating metabolism, immunity/inflammation, reproduction, circulation, neural network, etc, and are involved in pathogenesis of various disorders and diseases related to these systems. The objective of this research and development R&D area is to investigate novel biological functions of lipids and develop new technologies for their analysis, to elucidate molecular mechanism of lipid-associated various diseases, and finally to exploit novel developmental seeds for compounds and technologies to overcome these diseases, i.e. chemical compounds relevant to pre-clinical stage, target materials and reactions promising medical application in near future, or innovative diagnostic methods that may construct new clinical benefits, etc.

Lipid research has advanced along with numbers of discovery of new biological activities and exploitation of new analytic technologies. Therefore, more innovative research and exploitation should also be necessary in order to accomplish the goal of this program and initiatively dispatch the novel results toward the world. It should be also important to gather ideas of researchers in various different fields and disciplines, such as the scientists in clinical medicine, pharmaceutical sciences, synthetic chemistry, biophysics and bioengineering, and information engineering, as well as those in lipid biology and biochemistry who have carried mainstream of lipid research. Broad viewpoints based on our interdisciplinary research team works will be indispensable for advancement of research and development in lipid research field to strengthen our international competitiveness.

We would like the program members to conduct their researches with practical translational outputs always in their mind. However, it does not necessarily mean that all the members are obliged to produce practical seeds within the term. We consider it is also important to promote fundamental basic studies that would possibly become the basis for generation of innovative technologies, diagnostics, and medicines only in not-remote future, for development and enforcement of international competitiveness of our lipid research. The research field of biological activities of lipids is continuously expanding, and this R&D area is expected to lead the world in innovative and explorative research in this field.

Because of expected medical application, target lipids are primarily set as the molecules originating in mammalian cells. However, the molecules closely related to human disorders and of nutritional importance may be included, such as omega-3 fatty acids and ceramide.
In this research project, we aim to reveal how membrane proteins and lipids interact in order to emerge signaling functions on plasma membrane. We attempt to develop a new correlative microscope (MULTUM-PALM) by which membrane proteins can be observed at single-molecule level with super resolution (PALM) and lipid molecules can be observed with mass spectroscopy (MULTUM). We will apply this MULTUM-PALM to various membrane proteins including GPCRs and components of phosphatidylinositol lipids signaling pathway on plasma membrane. Through the development of both statistical analysis methods for characterizing lipid/protein distributions and their mathematical modeling, we will try to reconstruct spatiotemporal dynamics of lipid/protein interactions in silico.

Lipids form a barrier in the body surface (epidermis and eyes) and prevent invasion of pathogens and allergens. Barrier abnormality causes various cutaneous disorders (ichthyosis, atopic dermatitis etc.) and eye diseases (dry eye etc.). However, molecular mechanisms producing the barrier lipids are still largely unknown. In this research, we aim to elucidate these problems and create a foundation for drug discovery that enables cause treatment for the skin and eye diseases.

In mammalian cells, fatty acid elongases and desaturases play critical roles in regulating the length and degree of unsaturation of fatty acids and thereby their functions and metabolic fates. We have shown that not only the quantity but also the quality of lipid is important for our health. Our goal is to elucidate the molecular mechanism of diseases such as metabolic syndrome and cancer and develop new strategies for the diagnosis and treatment of these diseases by focusing on the chain-length of fatty acids as a novel qualitative aspect of lipid.

This project aims to create a novel technology “Optolipidomics” to identify, control and observe functional lipids using light; By improvement of the mass microscope in mass resolution and sensitivity, we will try to identify important lipids in human diseases using imaging mass spectrometry. Additionally, we will develop the optically controllable modules and florescent probes to regulate the candidate lipids spatiotemporally and to observe the results of control, respectively. This seamless system to study the functional lipids will be a basis of the lipidome editing technology, leading to a new concept of drug discovery by targeting lipids in the future.

Although infectious diseases represent a major threat to humans, the repertoire of anti-viral therapeutic drugs available currently remains very limited. Recent studies, including our own, demonstrated that various intracellular pathogens hijack the lipid transport proteins (LTPs) of host cells in order to use host lipids for their own proliferation. Thus, in this research and development project, we aim to elucidate the molecular mechanisms by which a pathogen utilizes the lipids of host cells for its own proliferation, and to develop an inhibitor of this lipid-utilizing process.
Understanding disease mechanisms based on glucosylated lipid functions

Hiroyuki Kamiguchi
Deputy Director,
RIKEN Center for Brain Science

Novel glucosylated lipids present in small amounts in the human body have been discovered as intercellular signal messengers that regulate the formation of neural networks. It has also been suggested that glucosylated lipid signaling mediated by G protein-coupled receptor participates in pathological states not only of the nervous system but also of the blood and metabolic systems. In this project, we will elucidate structure-function relationship and disease-associated mechanisms of glucosylated lipids, with the aim of establishing new strategies for the development of disease biomarkers and therapeutics.

Development of innovative technology for structure-based drug design targeting prostanoid receptor

Takuya Kobayashi-Shimizu
Professor, Department of Medical Chemistry,
Kansai Medical University
Associate Professor,
Graduate School of Medicine, Kyoto University

We have recently succeeded in developing antibodies against native GPCRs using this technology in combination with our improved immunization and screening methods. In this project, we have been trying to develop innovative technologies using a successful example of prostaglandin E2 receptor (one of the GPCRs) with an inhibitory antibody structure. To avoid several adverse effects of current therapeutics, it is essential to understand the molecular mechanism of GPCR signal transduction to selectively regulate GPCR signaling via functional antibodies, which are developed by our methods, and/or the designed small organic molecules depending on the GPCR structures.

Elucidation of metabolic control by oxysterols and disease molecular mechanism

Ryuichiro Sato
Professor, Graduate School of Agricultural and Life Sciences, The University of Tokyo

Metabolic disorder of cholesterol, a fundamental structural component of biological membranes, causes the onset of various diseases. Although the most potent regulatory factor of sterol metabolism is oxysterols, their synthetic mode, intracellular distribution, and function of their mediator molecules remain relatively unknown. In this study, we aim at analyzing the multi-layer regulatory system controlled by oxysterols and making a proposal for next-generation drug discovery together with elucidation of molecular disease mechanisms.

Creation of a novel approach for drug development by elucidation of the regulation mechanism of cell migration with S1P transporters

Tsuyoshi Nishi
Associate Professor, ISIR,
Osaka University

Sphingosine 1-phosphate (S1P) is an intercellular signaling molecule that is produced inside the cells by phosphorylation of sphingosine and is exported outside the cells by its specific transporters. In this experiment, we are trying to understand the pharmacokinetics of S1P comprehensively through identifying all S1P transporters in mammalians and to clarify the role of the S1P transporters in various diseases. Based on these findings we will establish a strategy to develop a novel transporter oriented drugs.

Development of novel anti-infective drugs targeting lipid metabolism

Sho Yamasaki
Professor, Research Institute for Microbial Diseases, Osaka University

Infectious diseases are one of the leading causes of death. Successful control of global infectious diseases is therefore a common and critical issue worldwide. Immune receptors can recognize pathogens via their characteristic lipids to trigger host defense responses. However, some pathogens degrade/modify these lipids to evade host immune responses. In this project, we aim to identify novel immunostimulatory lipids and their metabolic pathways in pathogens, which will lead to the development of novel anti-infective drugs that confer ‘immunological susceptibility’ on pathogens by preventing their immune-evading strategies.
Innovative research by control and visualization of cellular membrane phospholipids

Hideo Shindou
Vice Project Leader, National Center for Global Health and Medicine (NCGM)

Cellular membranes contain several classes of glycerophospholipids, which have functional roles in cells. Glycerophospholipids contain two fatty acids and one polar head group, and the compositions vary across cell and tissue types. Little is known about how the phospholipid compositions impact their cellular functions; therefore, we utilize lysophospholipid acyltransferase knock-out mice to control membrane phospholipid compositions and uncover novel lipid functions. Additionally, we will observe phospholipids spatiotemporally at the subcellular level to gain new understanding about physiological roles of phospholipids. This project will contribute to finding novel lipid functions and establishing novel therapeutic strategies.

Elucidation of roles and functions of bioactive lipids underlying stress-related dysfunctions and foundation of novel technology platforms for bioactive lipid-targeting clinical applications

Tomoyuki Furuyashiki
Professor, Graduate School of Medicine, Kobe University

Stress due to social environments and lifestyle habits can promote the onset and pathophysiology of various mental and physical illnesses. Recent studies have suggested that the regulation of inflammation by multiple bioactive lipids is involved in stress-induced changes in mental and physical functions. In this research, we will identify bioactive lipids underlying stress-related dysfunctions and elucidate their roles, regulations and actions, and will develop tools for measuring and visualizing these bioactive lipids. Through this strategy, we aim to develop novel technology platforms targeting bioactive lipids for preventing and curing stress-related dysfunctions.

Elucidation of disease mechanism and study of drug discovery targeted for oxidized lipids

Kenichi Yamada
Professor, Faculty of Pharmaceutical Sciences, Kyushu University

Lipids are easily oxidized by reactive oxygen species (ROS), resulting in lipid peroxidation and metabolic products such as lipid-derived electrophiles. Lipid peroxidation products and lipid-derived electrophiles have been reported to bind to protein or DNA and induce inflammation and apoptosis. However, such oxidized lipids have high reactivity, appropriate detection technologies is limited. Here, in this study, we aim to develop the detection technique, elucidate disease mechanism, and study drug discovery targeted for oxidized lipids

Development of milieu-lipidomics platform for grasping metabolic crosstalk between host and intestinal bacteria

Kazutaka Ikeda
Deputy Team Leader, Laboratory for Metabolomics, RIKEN Center for Integrative Medical Sciences (IMS)

Lipid metabolites consist of a wide variety of hydrophobic molecular species. Some of them are metabolized by intestinal bacteria, and function to regulate host immune response and intestinal homeostasis. Mass spectrometry-based metabolomics is an effective method to grasp metabolic interplay between intestinal bacteria and host metabolism. However, it remains insufficient to measure these metabolites comprehensively because conventional analytical methods are focused on the host metabolites with a limited search range. In this study, we designed a new non-targeted lipidomics, namely milieu-lipidomics, to search lipid metabolites derived from the symbiotic relationship using LC/Q-TOF MS and in-house lipid screening software “Lipidiscovery”. Our advanced lipidomics platform has a strong potential to understand the interplay between intestinal bacteria and host metabolism unbiasedly. Also this system could lead to the identification of bioactive metabolites that control intestinal tissue homeostasis.

Elucidation of roles of lipids in the epithelial-mesenchymal transition

Junichi Ikenouchi
Professor, Faculty of Sciences, Kyushu University

Epithelial cells adhere between adjacent cells and form a cell sheet that covers the surface of organs such as the digestive tract. Epithelial cells play an essential role in maintaining life, such as absorption of nutrients from the outside world. On the other hand, epithelial cells lose adhesion and convert to mesenchymal cells in pathological conditions such as invasive cancer and fibrosis. I aim to develop innovative medicines by clarifying the roles of lipids in the pathological conditions associated with the epithelial-mesenchymal transition.
Lipid Molecules

Mechanisms of lipid dynamics on plasma membranes and their application

Jun Suzuki
Professor, Institute for Integrated Cell-Material Sciences (iCeMS), Kyoto University

Phospholipids on plasma membranes are asymmetrically distributed. Among the lipids, Phosphatidylserine (PS) is maintained to the inner side of the membranes. However, this asymmetry is collapsed by the action of scramblases and exposed PS functions as a signaling molecule. Therefore, I would like to reveal that PIP3 can be a key target for drug development for the mental diseases using a brand new technology, lipid optogenetics.

Projects started in 2015

The role of lipid in the exosome derived from the inflammatory cancer

Ai Kotani
Professor, Institute of Medical Science, Tokai University

Exosome is a kind of vesicles which work as intercellular communicator. It has been recently reported that several lipids are enriched in exosome. Exosome contains nucleic acid whose functions we found to be enhanced in the macrophages specifically taking it in the EBV related lymphoma. Accordingly we hypothesized that lipids amplify the function of nucleic acid in the exosome. We will test the hypothesis and try to find the novel lipid therapeutic target for the EBV related lymphoma.

Projects started in 2015

Development of basic technologies for medical application based on oxidized phospholipid-derived bioactive fatty acids

Nozomu Kono
Associate Professor, Graduate School of Pharmaceutical Sciences, The University of Tokyo

Membrane phospholipids abundantly contain polyunsaturated fatty acids such as arachidonic acid and docosahexaenoic acid. These polyunsaturated fatty acyl chains in membrane phospholipids are easily oxidized to form oxidized phospholipids. Although oxidized phospholipids have been suggested to be associated with various pathological conditions, its molecular mechanisms remain to be clarified. The aim of this project is to elucidate the mechanism of production and action of oxidized phospholipid-derived bioactive fatty acids and the role of the bioactive fatty acids in metabolic diseases.

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Dendritic spines in neurons play important roles in synapse plasticity underling learning and memory. Mental diseases such as Autism Spectrum Disorder, Fragile X syndrome, and Cowden syndrome often exhibit abnormal spine morphology. My previous study shows that a functional lipid, phosphatidylinositol 3,4,5-trisphosphate (PIP3) regulates spine morphology. Therefore, I would like to reveal that PIP3 can be a key target for drug development for the mental diseases using a brand new technology, lipid optogenetics.

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Unraveling a novel metabolic system orchestrated by a metabolic sensor toward development of therapeutics

Motohiro Sekiya
Assistant Professor, Department of Internal Medicine, Endocrinology and Metabolism, Tsukuba University

We identified a novel metabolic system orchestrated by a metabolite sensor. The system governs global metabolism including lipid, glucose and inflammation by sensing multiple metabolic intermediates and could play a critical role in the pathogenesis of metabolic diseases. The sensor molecule accommodates metabolic intermediates in its pocket which can be targeted by small molecules. We will unravel molecular basis of the system toward development of novel therapeutics.

Projects started in 2015

Control of functional lipids using optogenetics

Yoshibumi Ueda
Specially Appointed Researcher, Department of General Systems Studies, Graduate School of Arts and Sciences, The University of Tokyo

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Physiological and pathological roles of cholesterol in primary cilia

Tatsuo Miyamoto
Lecturer, Research Institute for Radiation Biology and Medicine, Hiroshima University

The primary cilium formed on the surface of quiescent human cells functions as a sensor for receiving the extracellular signals. Ciliary dysfunction is causally linked to the group of human hereditary disorders and cancers.

The goals of this study are to elucidate the physiological roles of cholesterol in the ciliary membrane, and to establish the pathological concept of cilia-related diseases from the aspect of impaired cholesterol metabolism. This study also attempts to create the pharmaceutical seeds of ciliary cholesterol regulation.

Identification of lipid metabolites controlling physiological function of the uterus

Yasushi Hirota
Lecturer, Department of Obstetrics and Gynecology, Graduate School of Medicine, The University of Tokyo

Recurrent implantation failure is one of the major clinical issues in the field of reproductive medicine. Previous studies indicate that the enzymes associated with polyunsaturated fatty acid metabolism have key roles in embryo implantation, but it remains unclear which lipid metabolites are critical for this event.

The aim of this project is to elucidate the mechanism of embryo implantation and the pathogenesis of recurrent implantation failure by using lipidomics analysis and mice lacking enzymes involved in polyunsaturated fatty acid metabolism. The ultimate goal of the project is to discover novel therapeutic approach to recurrent implantation failure by focusing on lipid metabolites and their metabolizing enzymes.

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Functional elucidation of bioactive alkenyl-type lysophospholipids

Kei Yamamoto
Associate Professor, Graduate School of Technology, Industrial and Social Science, Tokushima University

Recently, lipid metabolomics analyses using mice gene-manipulated for lipid metabolism-related enzymes have revealed that they display diverse functions by driving unique diseases pathways. In this research, we elucidate the possible mechanism of metabolic and dynamic action of alkenyl-type lysophospholipids (P-LPEs) as a novel bioactive lipid for exacerbation of epidermal hyperplastic diseases. Based on the knowledge, this project is aiming to contribute to improvement of healthy longevity society through development of new biomarkers and drug discovery.

It has been difficult to determine individual lipid species in live tissues or iPSC cells derived from patients, because the conventional lipid labeling techniques usually disrupted the physiological condition and it could not keep spatial distributions of lipids in tissues untouched. In this study, we measure intrinsic molecular vibrations in order to identify lipid species. Vibrational spectroscopy provides vibrational information characteristic of chemical groups in a molecule without any labeling procedures. Using this technique, we develop a new vibrational microspectroscopy which locates and quantitates specific lipid species in molecular specific manner. In addition, we aim to propose an application strategy which benefits researchers working on diagnosis and treatment of lipid metabolism disorders.
Understanding lipid-related orphan G protein-coupled receptors using activating GPCR mutations

**Asuka Inoue**
Associate Professor, Graduate School of Pharmaceutical Sciences, Tohoku University

G protein-coupled receptors (GPCRs) represent the most promising targets for drug development. Currently, there are approximately 20 orphan (ligand-unknown) GPCRs that are phylogenetically located near lipid-recognizing receptors. In general, orphan GPCRs are poorly characterized and thus excluded from drug development because of lack of pharmacological methods to activate these receptors. In this project, the PI will develop a strategy to analyze orphan GPCRs by introducing an activating amino acid mutation. Expression of such an activating GPCR is expected to mimic ligand-induced activation of the native GPCR. The project will enable a genetic approach to induce orphan GPCR signaling and possibly expand orphan GPCR as next-generation drug targets.

Development of novel treatment strategies by regulating functional lipids involved in the pathogenesis of pulmonary hypertension

**Jin Endo**
Assistant Professor, Department of Cardiology, Keio University School of Medicine

Pulmonary artery hypertension (PAH) characterized by stenosis of pulmonary blood vessels and right heart failure is one of the intractable diseases whose pathology and pathogenic mechanisms are still unclear. Bioactive lipids that control cardiovascular function positively or negatively in vivo are drawing attention as a therapeutic target for PAH. In this study, we aim to create new therapeutic strategies via appropriate quantitative and qualitative control of the lipids by clarifying the role of various functional lipids in PAH and changes in lipid metabolism in failure hearts.

Functional analysis on cholesterol metabolizing enzyme that defines a novel T cell subset and the clinical application for disease control

**Hayato Takahashi**
Assistant Professor, Department of Dermatology, Keio University School of Medicine

CD4+ T cell is a crucial immune cell that is involved in various infections and allergic diseases. The aim of this project is to identify the T cell with new functions. We assumed that the T cells might be armed with a sort of cholesterol metabolizing enzyme based on our data. That nature has not been seen in the known helper T cell subsets. The metabolite produced by the enzyme is estimated to regulate immune reaction. Intensive investigation on the mechanism of the metabolite action would be helpful to develop new therapeutic strategies and drugs in the future.

Molecular mechanism and physiological role of PI4P-driven lipid countertransport system

**Fubito Nakatsu**
Associate Professor, Department of Neurochemistry and Molecular Cell Biology, Graduate School of Medical and Dental Sciences, Niigata University

Lipids exert their function properly only when transported correctly in cells. A variety of human diseases involve malfunction of cellular lipid transport systems, whose underlying mechanisms are still largely unknown. Our study is focused on to clarify how cellular lipids are specifically recognized and exchanged at a region (termed “membrane contact sites”) where two cellular membranes come close each other. Understanding the regulation and dysregulation of the lipid countertransport systems will help developing new strategies to treat and prevent human diseases.

Understanding pathogenic mechanisms of skin diseases by focusing on polyphosphoinositide metabolism

**Yoshikazu Nakamura**
Associate Professor, School of Life Sciences, Tokyo University of Pharmacy and Life Sciences

Some inflammatory skin diseases, including atopic dermatitis and psoriasis have a significant negative impact on quality of life of patients by chronic itch and changes in skin appearance. The aim of this project is to contribute to understanding the mechanisms of pathogenesis and exacerbation of these inflammatory skin diseases through clarification of the relationship between inflammatory skin diseases and abnormal phospholipid metabolism.
Elucidation of the immune-metabolic-regeneration systems network linked by fatty acids

Yumiko Oishi
Professor, Department of Biochemistry & Molecular Biology, Nippon Medical School

Obesity, physical inactivity, and aging are the leading causes of the noncommunicable diseases (NCDs), such as cardiovascular disease, diabetes and cancer. Recent studies indicate that chronic inflammation crucially underlies NCDs, alterations in systemic metabolism due to obesity also greatly contribute to the progression of NCDs, suggesting the link between chronic inflammation and metabolic dysfunction. Moreover, insufficient regeneration prolongs inflammation, further accelerating tissue remodeling. In this study, I will elucidate the immune-metabolic-regeneration systems network linked by unsaturated fatty acids and signal-epigenome regulatory pathways in the maintenance of tissue homeostasis and development of NCDs.

Projects started in 2017

Development of novel microsystems for highly sensitive analysis of lipid transport proteins

Rikiya Watanabe
Chief Scientist, Molecular Physiology Laboratory, RIKEN

The asymmetric phospholipid distribution on biological-membrane is a key feature of living cells. The disruption of lipid asymmetry, involved in physiological processes, is mediated by phospholipid scramblases, promoting bidirectional lipid transport across membranes. In this study, we attempt to analyze at the single-molecule level the phospholipid transport of scramblases by developing a microsystem equipped with asymmetric lipid membrane arrays. The findings from single molecule analysis will provide a molecular insight into how scramblases transport phospholipids, and moreover a versatile strategy for single-molecule analysis of other phospholipid-transport proteins, e.g. flippase and floppase.

Projects started in 2016

Identification of functional lipid metabolites to control purinergic chemical transmission, and the molecular mechanism-based drug discovery research

Takaaki Miyaji
Associate Professor, Advanced Science Research Center, Okayama University

Vesicular nucleotide transporter (VNUT) is responsible for vesicular storage of ATP, and is essential for purinergic chemical transmission. Recently, we demonstrated that VNUT-mediated ATP transport is allosterically activated by Cl–, and this activation is inhibited by lipid metabolites. Regulation of the metabolic anion switch improved the major factors of lifestyle-related disease without side effects. In this study, we aim to identify functional lipid metabolites to selectively inhibit VNUT, develop the preventive drug of lifestyle-related disease, and establish the molecular mechanism-based drug discovery platform.

Projects started in 2016

Development of molecular tools for the clarification of metabolism and molecular interaction of glycolipids

Go Hirai
Professor, Graduate School of Pharmaceutical Science, Kyushu University

We aim to develop molecular tools contributing to functional analysis of glycolipids, which control several cellular events at plasma membrane and so on. Function of glycolipids is considered to differ by carbohydrate structures and length of lipid chains, and degradation of carbohydrate structure by glycohydrolases also causes change of glycolipids structure. We address the design and development of molecules capable of analyzing “binding partners” and “metabolism” of “particular glycolipids in interest”, based on the knowledge of organic chemistry and bioorganic chemistry.

Projects started in 2016

Characterization of the early steps of high-density lipoprotein (HDL) formation

Yasuhisa Kimura
Assistant Professor, Graduate School of Agriculture, Kyoto University

High-density lipoprotein (HDL) is thought to play important roles in prevention of atherosclerosis by removing excess cholesterol from peripheral tissues and transporting it to the liver. It is widely accepted that HDL is formed by an ATP-dependent lipid transporter (ABCA1), however, the detailed mechanisms are still controversial. The aim of this research is a clarification of the early steps of ABCA1-mediated HDL formation in molecular level to provide the useful information for the development of novel antiatherogenic drugs.
Lipid Molecules

Dissecting intracellular phospholipid traffic for understanding mitochondrial functional integrity

Yasushi Tamura
Associate Professor, Faculty of Science, Yamagata University

In order to understand functional integrity of mitochondria, it is essential to elucidate phospholipid traffic via mitochondria since phospholipids are major constituents of mitochondrial membranes. However, it is still largely unknown how phospholipids travel among cellular membranes. In addition, how cardiolipin, the mitochondria-specific phospholipid, is synthesized in mitochondria is still enigmatic. In this research, we will elucidate these mysteries and aim to develop innovative drugs to overcome diseases causing compromised phospholipid metabolism.

Development and application of the phosphatidylinositol-specific nucleic acid drug

Futoshi Suizu
Associate Professor, Institute for Genetic Medicine, Hokkaido University

Projects started in 2017

This project aims at the development of the simple chase technology as well as manipulating technology of cellular phosphoinositide that was relative difficulty until now. I am planning to isolate nucleic acid drugs harboring three character with a small, stable, and high cell membrane permeability, and finally apply to develop drugs for an early diagnosis or a novel treatment of diseases that phosphoinositide abnormality is concerned with, such as cancer or neurodegenerative diseases.

The clarification of lipid-mediated mechanisms in the inflammatory and repairing process after stroke

Takashi Shichita
Project Leader, Stroke Renaissance Project, Tokyo Metropolitan Institute of Medical Science

Recently, the number of stroke or dementia patients is increasing in Japan; however, the therapeutic agents which improve the neurological deficits of these patients has not been developed. We have clarified that retinoids enhance the expression of scavenger receptors in infiltrating microglia and macrophages after ischemic stroke, and this leads to the acceleration of the resolution of cerebral post-ischemic inflammation. Based on these findings, this research aims at developing novel therapeutic agents which improve the functional prognosis of stroke and dementia patients through the identification of specific lipids which regulate the inflammatory and repairing process after stroke.

Intracellular organelles of eukaryotic cells have distinct lipid compositions, however, its significance has not been well understood. In this study, by exploiting the proximity-dependent biotinylation method with phospholipid-specific probes in living cells, proteins that are in close proximity to specific phospholipids will be identified. I expect that, through this approach, the novel function of organelle membranes and phospholipids will be revealed. Diseases that are caused by dysregulated function of organelle membranes will also be identified.

The molecular mechanism that regulates cellular signaling pathways through organelle-specific lipid domains

Tomohiko Taguchi
Professor, Graduate School of Life Sciences, Tohoku University

Projects started in 2017

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Development of enzymatic fluorometric assays for quantifying phospholipids, sphingolipids and acylglycerols and for evaluating asymmetrical distribution of membrane lipids

Shin-ya Morita
Associate Professor, Shiga University of Medical Science

Projects started in 2017

Phospholipids, sphingolipids and acylglycerols act as cell membrane components, energy sources and signaling molecules, and are associated with various diseases including coronary heart disease, neurodegenerative diseases and cancers. However, there are no sensitive and simple methods for measuring these lipids. In this study, by using specific enzymes and fluorescent compounds, I develop new simple assays for quantifying phospholipids, sphingolipids and acylglycerols and for evaluating asymmetrical distribution of membrane lipids. These enzymatic fluorometric assays will be helpful for understanding of the pathogenesis of various diseases and for early detection of diseases.
Although there are many reports on the relationship between diets and infertility, detailed mechanisms of the diet-induced infertility remain largely unknown. In this research project, focusing on an interesting finding that female mice genetically deficient in an intestinal lipid transporter exhibit diet-induced infertility, we will identify dietary lipids causing female infertility and clarify their clinical relevance and molecular mechanisms of the lipids-induced reproductive dysfunction. The outcome of this research project will lead to the development of new therapeutic strategies, drugs, and biomarkers for female infertility.