Tissue Adaptation and Repair

Understanding of Pathophysiological Processes and Discovery of Medical Technology Seeds through Spatiotemporal Research of Tissue Adaptation and Repair Mechanisms

Research and Development Objectives

Investigations into life phenomena and the discovery of medical technology seeds based on spatiotemporal insights into biological tissue adaptation and repair mechanisms

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The goal of this R&D area is to significantly accelerate the discovery of technology seeds that contribute to health and medical care by deepening the spatiotemporal understanding of biological tissue adaptation and repair mechanisms.

The body maintains its functions through tissue adaptation and repair against various types of tissue injury or excessive stress. It remains to be elucidated how the organism responds to the damages from the inside and outside of the living body, what types of cells in the tissues are involved in adaptation and repair, and what kind of interactions proceed during adaptation and repair. When the regulatory mechanisms for the tissue adaptation and repair become dysfunctional, tissue homeostasis is broken down, thereby eventually leading to the onset of serious diseases. These processes are also not fully understood. The aim of this R&D area is the elucidation of mechanisms of tissue adaptation and repair, their maintenance and broken-down. We will develop new technologies to obtain greater spatiotemporal insights, and will discover the seeds for preventive, diagnostic, and therapeutic technologies.

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AMED-CREST Started in 2018 · 1st period

Dissecting intestinal fibrogenic diseases by a newly developed 4D disease model system (*)

SATO Toshiro
Professor,
Keio University School of Medicine

Epithelial injury is healed by prompt epithelial regeneration and stromal responses, whereas impaired epithelial healing system leads to fibrotic diseases through aberrant activation of stromal cells. Thus far, owing to a lack of tractable epithelial-stromal functional assay system, the mechanism underlying the impaired epithelial healing and fibrotic diseases remains elusive. In this project, we seek to establish an organoid-based spatio-temporal analysis system and elucidate the molecular basis of how intestinal epithelium orchestrate tissue healing and whether its disorder leads to gut fibrotic diseases.

Study of the regulatory mechanisms of cell-cell interaction underlying liver remodeling in NASH for the development of therapeutic and diagnostic procedures (*)

TANAKA Minoru
Laboratory Head, Research Institute, National Center for Global Health and Medicine

The liver is known to possess high capacity of regeneration upon injury. However, inadequate regeneration in chronic hepatitis often causes fibrosis and carcinogenesis in the liver. The research objective is to elucidate the regulatory mechanisms underlying the pathogenesis and progression of chronic liver diseases, especially non-alcoholic steatohepatitis (NASH) for the development of diagnostic and therapeutic methods. We focus on two representative liver remodeling (i.e. fibrosis and regeneration) from a perspective of cell death, tissue stem cell and cell-cell interaction.

Elucidation of the pathophysiology of tissue remodeling fibrosis in the airway; towards the development of a new strategy for treating fibrotic diseases (*)

NAKAYAMA Toshinori
President,
Chiba University

The aim of this project is to investigate the cellular and molecular mechanisms underlying pathological tissue remodeling (fibrotic changes) and elucidate the pathogenesis of chronic intractable diseases with tissue fibrosis. We focus on fibrotic changes in the airway. We will use our established techniques together with new cutting-edge technologies to define how epigenetic pathways, fibrosis-inducing pathogenic Th2 (Tpath2) cells, inflammatory eosinophils and inducible bronchus-associated lymphoid tissues (iBALT) can control development of fibrotic diseases. Our final goal is to establish a comprehensive and multidisciplinary research platform of immunology, pathology and regenerative science.

Stem cell system-based four dimensional ocular tissue remodeling in homeostatic and pathological states (*)

NISHIDA Kohji
Professor, Graduate School of Medicine,
Osaka University

Our hypothesis is that specialized cells such as vascular and neural cells which were thought to be quiescent are constantly being replaced by newly emerged cells originated from somatic stem cells with different timespans. Moreover, disruption of those physiological remodeling may lead to pathological change. Based on the fact that eye ball is a unique organ which contains multiple component of tissue such as vascular, nervous and epithelial system, we aim to elucidate whether time-dependent remodeling of these specialized cells are involved in disease model in the eye which is constantly exposed by various external stress (e.g. light exposure) or internal stress (e.g. high glucose).

Comprehensive study of resilience control by interaction between the nervous system and the biological system (*)

YAMASHITA Toshihide
Professor, Graduate School of Medicine,
Osaka University

We will conduct research to elucidate a maintenance mechanism of the central nervous system with the focus on “resilience control by biological system network”, in order to develop methods for the prevention, delay, and recovery from neurological diseases. In neurological diseases, the bi-directional functional interaction between the nerves and the biological system deteriorates, causing exacerbation of pathological conditions as a result of the attenuated recuperative and restorative ability of nervous tissue or its decreased resilience. Our goal is to elucidate the mechanism of resilience controlled by biological system interactions and the neurological conditions caused by its failure.

AMED-CREST Started in 2019 · 2nd period

Adaptation and repair of skin barrier via multi-cellular interactions

KABASHIMA Kenji
Professor, Graduate School of Medicine
Kyoto University

We would like to perform research focusing on the skin barrier function, which is deeply involved in the onset of skin immunity and allergy. To this end, we set three objectives: I, Elucidation of the skin barrier formation and failure by keratinocyte crosstalk; II, Elucidation of the mechanism of the skin barrier by peripheral nerves and immunity; III, Forming foundation of clinical application. These results are expected to overcome atopic dermatitis and other skin barrier dysfunction-mediated diseases, including other allergies, which lead to improving the QOL of allergic patients and reducing medical costs in the future.

Neuronal migration: strategies for adaption and endogenous repair in the injured brain

SAWAMOTO Kazunobu
Professor, Nagoya City University
Graduate School of Medical Sciences

There are still no promising strategies for regenerating lost neurons at the appropriate positions in the injured brain, which will be necessary for functional recovery. In this project, we focus on the migration of new neurons generated from neural stem cells (NSCs) in the postnatal ventricular-subventricular zone (V-SVZ), and seek to understand the molecular mechanisms for “adaptation” and “repair” of the injured brain. Since the postnatal human brain also contains NSCs in the V-SVZ, these endogenous mechanisms of neuronal regeneration will provide bases for novel strategies for treating brain diseases such as neonatal hypoxia/ischemia and adult stroke.

Discovery of tissue repairing immune cells for the development of therapeutic strategy

TAKAYANAGI Hiroshi
Professor, Graduate School of Medicine,
The University of Tokyo

The immune system contributes to not only host defense but also tissue repair throughout the body. Activation of immune cell subsets specific for tissue repair and the proper cooperation with the mesenchymal cells and parenchymal cells within the injured tissue is necessary for tissue regeneration. In this study, during various external and internal injuries, we identify immune cell subsets that specifically direct the tissue repair. We will understand the entire process of tissue repair mediated by the tissue repairing immune cells, aiming at the development of tissue regeneration technology by targeting tissue-repairing immune cells.

Identification of cellular and molecular constituents in unique microenvironments regulating tissue damage and repair to prevent chronic kidney disease

YANAGITA Motoko
Professor and Chair, Graduate School of Medicine Kyoto University

Kidney injury and repair are dynamically controlled depending on the disease condition, however, precise molecular mechanisms regulating these processes remain unclear. In kidney injury, proximal tubules, the most vulnerable segment in the nephrons, are frequently damaged. Proximal tubule injury subsequently alters the pre-existing intercellular interaction between proximal tubules and surrounding cells, and recruit hematopoietic cells to form new distinct “microenvironments”, which act as driving engines for tissue remodeling. In this proposed research, we identify the cellular and molecular targets orchestrating kidney injury and repair, particularly focusing on above-mentioned unique “microenvironments” regulating dynamic tissue remodeling after injury.

AMED-CREST Started in 2020 ······ 3rd period

Achieving sustainable reconstruction of damaged neural network toward complete recovery in stroke and dementia

SHICHITA Takashi
Professor, Medical Research Laboratory,
Institute of Integrated Research, Institute of Science Tokyo

The pathologies of cerebrovascular diseases and dementia often co-exist and worsen each other in the aged brain, leading to the progression of neurological dysfunction and cognitive decline. There are few established therapeutic drugs that improve the brain function of patients with stroke and dementia which have become major causes of reduced healthy life expectancy in an aging society. In this study, we will identify the key genes that regulate neural network reconstruction and will develop innovative therapeutic drugs that enable neural network reconstruction to be sustained until complete recovery from the neurological deficits caused by stroke and dementia is achieved.

Metabolic reprogramming driving hematological aging

TAKUBO Keiyo
Professor,
Tohoku University Graduate School of Medicine

The functional and populational changes in hematopoietic stem cell (HSC) have been implicated in the rise of infections, cancers, rheumatoid, and cardiovascular diseases. Little is known about inducers and changes affecting the metabolic program in HSC aging. Our primary objective is to define mechanisms that underlie aging-related metabolic reprogramming of HSCs, and consequently, defects in the blood system. We will evaluate the effect of environmental factors on metabolic reprogramming of HSCs during aging. We will also identify transcriptional, epigenetic, and metabolic alterations that induce aging-related changes and methods to reverse these changes in HSCs and the blood system.

Mechanism of endocrine dysregulation in hepatic inflammation and fibrosis using patient-derived organoids

TAKEBE Takanori
Professor, Graduate School of Medicine,
Faulty of Medicine, Osaka University

Emerging evidence suggest that endocrine dysregulation involving insulin like growth factor 1 correlates to liver inflammation and fibrosis. We have pioneered multicellular liver organoid technology, establishing a novel inflammatory disease model in human. Here, we propose to investigate endocrine interaction mediated mechanisms governing liver inflammation and fibrosis using human organoids. At the conclusion, the proposed study will delineate the humanistic mechanisms mediating hepatic inflammation, and will identify compounds to attenuate fibrosis via patient-relevant disease model. Our proposal will establish the foundation for future personalized mechanistic testing, thus facilitating novel diagnostic and drug discovery tools against diseases with no approved treatments.

New mechanisms of tissue adaptation and repair based on disease-associated lipid metabolism and their applications to novel medical seeds

MURAKAMI Makoto
Professor, Graduate School of Medicine,
The University of Tokyo

Disturbed lipid metabolism often hampers tissue adaptation and repair, thereby leading to various diseases. The purpose of this research project is to identify novel PLA_2-driven lipid pathways that are linked to tissue adaptation and repair, putting a specific focus on those in skin diseases, fibrosis, and multi-organ failure. Using gene-manipulated mice for various phospholipid-metabolizing enzymes and clinical specimens, in combination with comprehensive metabolomics, we aim to clarify the molecular mechanisms of disorders associated with lipid failure toward development of novel treatment, prevention and diagnosis of the diseases.

PRIME Started in 2018 ······ 1st period

Study on the roles and mechanisms of adaptive remodeling of the intrahepatic biliary epithelial tissue that supports liver regeneration (*)

ITOH Tohru
Project Associate Professor, Institute for
Quantitative Biosciences, The University of Tokyo

The liver is an essential organ for life with multiple important functions, and is renowned for its tremendous regenerative activity. We have recently revealed that the intrahepatic biliary epithelial tissue possesses a unique and unprecedented structural flexibility and that its dynamic and adaptive remodeling likely constitutes the basis for robust liver regeneration. The aim of this R&D project is to elucidate the cellular and molecular frameworks as well as the modes of action of the biliary remodeling, thereby contributing to our understanding of the mechanisms for liver regeneration and future development of diagnostic and therapeutic strategies to tackle liver diseases.

Elucidation of neuronal signal-regulated cell proliferation for tissue adaptation and repair (*)

IMAI Junta
Associate Professor,
Tohoku University Graduate School of Medicine

When organs are damaged, cells proliferate to repair the organs. On the other hand, pancreatic β-cells adaptively proliferate in insulin-resistant states to increase insulin production. Therefore, these proliferations are compensatory mechanisms aiming at maintaining whole body homeostasis and survival. In this project, we aim to clarify the mechanisms by which neuronal signals regulate compensatory cell proliferation in tissue adaptation and repair processes. These research efforts are anticipated to enhance our understanding of adaptation and recovery systems of organs/tissues as well as clarifying pathogenesis of several diseases attributable to impaired adaptive tissue proliferation. Furthermore, these researches may provide novel clues for developing tissue regeneration strategies based on endogenous biological systems.

Study of the central nervous system regeneration by regulating glial scar (*)

OKADA Seiji
Professor, Graduate School of Medicine, Osaka University

The glial scar is a main cause of the limited regenerative capability in the mammalian central nervous system. Although the glial scar has been studied for more than half a century, the cellular and molecular mechanisms of glial scar formation remain unclear. In this project, we will examine the reversibility of glial scar formation and possibility of novel therapeutic strategy for the injured central nervous system by regulating the glial scar formation.

Study of the cellular and cell adhesion molecule mechanisms underlying peripheral nerve axon regeneration (*)

KADOYA Ken
Associate Professor, Faculty of Medicine and Graduate School of Medicine, Hokkaido University

In spite of the fact that peripheral nerve can regenerate, the clinical outcomes of peripheral nerve injuries are not satisfactory. To induce meaningful recovery, novel therapy to promote axon regeneration needs to be developed. However, the cellular and molecular mechanisms underlying axon regeneration remains to be fully clarified. Therefore, to generate the evidence contributing to the development of effective therapy for peripheral nerve injury, the current study aims to elucidate the cellular and molecular interactions among axons, Schwann cells, and macrophages, with special focuses on cell surface molecules.

4D multi-scale imaging study sheds light on the tissue remodeling mechanism (*)

KIKUTA Junichi
Associate Professor, Graduate School of Medicine, Osaka University

When the tissue is damaged, it is repaired through the dynamic interaction of organs. If an error occurs during the repair process, the affected organ will undergo fibrosis. In this study, using an advanced 4D imaging technology, I will observe the pathogenesis of fibrosis in multiple organs, and analyze the time-course of the complex cell-cell interactions and function of different cell populations. This approach will yield compelling insights into the common molecular mechanisms underlying fibrosis, which could also serve as the basis for developing novel anti-fibrotic therapies.

Molecular mechanisms underlying resilient system for organogenesis during development (*)

SHINDO Asako
Associate Professor, Institute of Molecular Embryology and Genetics, Kumamoto University

In nature, oviparous embryos develop normally despite unfavorable extrinsic stressors. This fact implies that embryos are equipped with molecular machinery to resist and repair the impact of such stresses. This may be accounted for by their active gene expression and diverse cellular behaviors. In this study, I focus on nutrient-dependent organogenesis in *Xenopus* as a model to investigate the molecular and cellular strategies for surviving adverse conditions. I aim to uncover possible mechanisms for controlling organ shape by exploring this unique ability of developing animals.

The cellular and molecular basis of lymphoid tissue remodeling by adrenergic nerves (*)

SUZUKI Kazuhiro
Professor, Immunology Frontier Research Center, Osaka University

Excessive immune responses sometimes destroy highly organized microenvironments in lymphoid organs, leading to an immunodeficient condition. Reacquisition of immunocompetence requires restoration of the lymphoid microarchitecture. However, the mechanisms of the lymphoid tissue remodeling are incompletely understood. We found that inputs from adrenergic nerves promote restructuring of lymphoid tissues after virus infection. In this study, we aim to clarify the cellular and molecular basis for lymphoid tissue remodeling by investigating how adrenergic nerves control immune cell functions to restore the integrity of lymphoid tissues. This study would lead to the development of a useful therapeutic approach for immune disorders targeting lymphoid tissue remodeling.

Study on the mechanism of inflammatory memory in intestinal regeneration (*)

TANIGUCHI Koji
Professor, Hokkaido University Graduate School of Medicine

Previously, it was thought that cellular memory for inflammation and infection occurs only in immune cells. However, recent studies reported that not only immune cells but also epithelial stem cells remember inflammation in the skin, and respond quickly to the next stimulus to promote wound healing. Like the skin, the intestines also function as a barrier between the human body and the outside world, but inflammatory memory has not been studied in the intestines. In this research, we aim to elucidate the mechanism of inflammatory memory in intestinal regeneration.

Study of endothelial stem cell and vascular homeostasis (*)

NAITO Hisamichi
Professor, Graduate School of Medical Sciences, Kanazawa University

Blood vessels delivering oxygen and essential molecules are critical for maintaining homeostasis in all tissues of the body and for recovery from the injury. We recently identified a stem cell population in the endothelial cells which cover the inner surface of the blood vessels. However, little is known about their physiological role and cell regulatory mechanisms. The aim of this project is to understand, through analysis of endothelial stem cells, how blood vessels are repaired and tissue homeostasis maintained.

Organism-level single-cell 4D dynamics in cardiac stress response (*)

NOMURA Seitaro
Assistant Professor, The University of Tokyo Hospital

Hemodynamic overload to the heart induces heart failure and ischemia to the heart causes myocardial infarction. During these processes, various cells and/or molecules are considered to show spatio-temporal dynamics for adaptation and repair, but its whole picture remains unclear. In this study, by analyzing multi-organ communications in cardiac stress responses at the single-cell level, we will address the question how cells exert their functions in adaptation and repair processes and what cells/molecules interact with each other to contribute to these processes, providing new avenues for the development of novel therapeutic strategies for heart diseases.

Study of how beige fat induction by environmental thermal stress adaptation and how aging affects beige fat induction (*)

IKEDA Kenji
Associate professor, Tokyo Medical and Dental University

Mammal has adaptive mechanism against environmental thermal cold stress. Thermogenic fat, Beige fat is induced by cold stress and induced beige fat makes heat. Though aging strongly inhibits the induction of beige adipocytes, it is poorly understood for molecular mechanism. In this study, we focused on the subtypes of beige adipocytes, we will identify all subtypes of beige adipocytes and then analyze the molecular control mechanisms of each subtype. We will elucidate the mechanism of how aging affects beige adipocytes induction. Finally, we will identify new treatment targets, which can induce beige adipocytes, even under aging condition. These targets will lead to novel treatment to obesity and type2 diabetes.

Elucidation of neural repair mechanism by immune cells in the brain injury (*)

ITO Minako
Associate Professor, Medical Institute of Bioregulation, Kyushu University

In brain inflammation by ischemic stroke, multiple sclerosis, and Alzheimer's disease, acquired immune system and natural immune system interacts with brain cells, which is involved in repair of brain tissue and nerve system. In this study, we aim to clarify the developmental mechanism of brain-specific lymphocytes and repairing macrophages by analyzing such interactions in the brain, and further elucidate the contribution of such interactions to tissue repair and nerve regeneration.

Elucidation of cell interaction mechanism in suppression of chronic kidney disease progression through nervous and immune systems (*)

INOUE Tsuyoshi
Professor, Graduate School of Biomedical Sciences, Nagasaki University

It is known that there are many different cells in the kidney. We have found that the kidney is protected from injury through the nervous-immune systems. Therefore, in this study, I will focus on how immune cells activated by nerve stimulation protect the kidney (cell interaction) and whether there is a direct protective effect on the kidney through the nerve (organ interaction). I hope that this study reveals a new renal protection mechanism.

Study of the epithelial repair mechanism by the new bioactive peptide (*)

ODA Yukako
Associate Professor, Center for iPS Cell Research & Application, Kyoto University

Tight junctions (TJ) are cell–cell adhesion structures that function as a barrier between epithelial cells to avoid dehydration, regulate ion permeability and prevent invasion of bacteria and viruses. Despite the fact that restoration of TJ integrity is critical for a treatment of the diseases, coordinated mechanism that directly promotes TJ formation in vivo is unknown. We recently succeeded in identifying the new peptides that induce TJ formation. In this project, we will dissect the repairing mechanism of epithelia by the peptide in inflammation.

Covariation network analysis for neural differentiation in disease iPS cells (*)

KANO Fumi
Associate Professor, Institute of Innovative Research, Tokyo Institute of Technology

Alzheimer's disease (AD) is an irreversible neurodegenerative disorder, which usually progress slowly. To prevent the aggravation, detecting the symptoms of disease before the cells enter the severe irreversible pathological state would be effective. The aim of this study is to develop the innovative image-based covariation network analysis to reveal the key molecules and disease biomarkers at the early stage of disease progression. We apply this analysis to the neural differentiation of disease iPS cells derived from AD patients, elucidate the molecular mechanisms underlying the pathological phenotypes of AD-derived cells, and regulate the cell fate in neural differentiation.

Study on the crosstalk between stromal cells and immune cells in intestinal homeostasis (*)

KAYAMA Hisako
Associate Professor, Institute for Advanced Co-Creation Studies, Osaka University

In the intestinal mucosa, a refined balance is maintained between tolerance and inflammatory responses against multiple environmental factors. This is because aberrant inflammatory responses can cause tissue damage. In patients with inflammatory bowel diseases, composition of stromal cell subsets is altered. However, whether stromal cells are implicated in either the maintenance of gut homeostasis or the pathogenesis of IBD by interacting with immune cells remains unknown. Therefore, I will examine effects of interactions between stromal cells and immune cells on intestinal inflammation, tissue repair, and fibrosis, thereby promoting advances in diagnostic and therapeutic approaches for IBD.

Regulatory mechanism segregating blood and lymphatic vascular systems (*)

KUBOTA Yoshiaki
Professor, Keio University School of Medicine

Vascular and lymphatic systems are two major circulatory systems distributed throughout the body. The structures of these two are histologically very similar but anatomically never share the lumen with except for the "venous angle", the final junction of collecting lymph ducts and subclavian veins. In this research, we will uncover the fundamental mechanisms segregating blood and lymphatic vascular systems mainly using genetically modified mice. The resultant data may pave the way to treat the secondary lymphedema, which frequently occurs after extensive lymph node dissection associated with cancer surgery, and is currently a big social issue related to cancer survivors.

Exploring and exploiting regulatory T cell-dependent mechanisms of tissue homeostasis (*)

HORI Shohei
Professor, Graduate School of Pharmaceutical Sciences, The University of Tokyo

Regulatory T (Treg) cells exhibiting anti-inflammatory functions play an essential role in the maintenance of tissue homeostasis. We have hypothesized that impaired differentiation, homeostasis, and/or function of tissue-resident Treg cells contributes to pathological tissue remodeling (e.g., fibrosis) and that tissue Treg cell-dependent mechanisms of tissue homeostasis may be exploited for therapeutic conversion of pathological tissue repair into physiological tissue regeneration. This project aims at testing this hypothesis and thereby contributing to future development of therapeutic strategies to cure many fibrosis-associated diseases.

Removal repair of pre-cancerous cells by spatiotemporally sensing suboptimal cells (*)

MARUYAMA Takeshi
Associate Professor, Waseda Institute for Advanced Study, Waseda University

Spatiotemporal recognition of suboptimal cells triggers the elimination force of surrounding normal cells against transformed cells and induces the repair of the apportionment space. However, it was largely unknown how to recognize these transformed cells and evoke the eliminating force. We have found the alteration of antigen presentation on the transformed cells are recognized by surrounding normal cells. In this study, we will elucidate the whole mechanism of suboptimal cell recognition; elucidate the whole mechanism of multilateral and precise recognition mechanisms against suboptimal cell development.

Restoration of regenerative system in the aged central nervous system (*)

MURAMATSU Rieko
Director, National Institute of Neuroscience, National Center of Neurology and Psychiatry

The goal of this study is identification of molecular target for treating demyelinating diseases. White matter atrophy is a promising feature of many central nervous system diseases. White matter is composed by oligodendrocytes, which are generated from their precursor cells (oligodendrocyte precursor cells, OPCs). White matter atrophy in aging brain is caused by the impairment of OPC differentiation into the mature oligodendrocyte around the lesion; however, the mechanism of impairment of OPC differentiation in aged animal has not been clarified. This study unveils the molecular mechanism that restore the OPC differentiation potential to regenerate white matter in the aged brain.

PRIME Started in 2020 ····· 3rd period

Spatiotemporal-functional analysis of the enteric nervous system in tissue remodeling. (*)

ISHIGAME Harumichi
Associate Professor, Near InfraRed Photo-ImmunoTherapy Research Institute, Kansai Medical University

The enteric nervous system and immune system continuously sense luminal environmental changes to maintain tissue homeostasis. Their dysregulation is associated with human pathologies including defective motor function and chronic inflammation. This proposal will establish a genetic strategy that is capable of targeting a molecularly defined subtype of enteric neurons and manipulating its neuronal activity. The experiments proposed will incorporate the gene expression profiling of enteric neurons and immune cells as well as 4D intravital imaging techniques in order to identify specific neuronal cell types involved in intestinal tissue remodeling and elucidate their molecular mechanisms during intestinal inflammation.

Clarifying and Targeting Integrated Network of Hematopoiesis under Age-related Stress (*)

INOUE Daichi
Professor, Institute of Biomedical Research and Innovation, Foundation for Biomedical Research and Innovation at Kobe

In the bone marrow, hematopoietic stem cells (HSCs) utilize support from the microenvironment's niche cells. On the other hand, functionally impaired HSCs by aging or genetic alteration also adapt and repair themselves through the surrounding environment. Our study will mainly focus on the role of extracellular vesicles derived from HSCs in altering the multiple systems in and out of the bone marrow. We will seek to elucidate the complicated network changing the systemic organ functions as well as the hematopoiesis and create medical seeds by using single-cell omics and spatio-temporal imaging at the single-cell level.

Mechanisms of skeletal muscle regeneration mediated by increased macrophage diversity (*)

OISHI Yumiko
Professor, Graduate School of Medicine, Tokyo Medical and Dental University

Skeletal muscle, the dominant organ for locomotion and energy metabolism, has a remarkable capacity for repair and regeneration upon injury. Recent studies indicate that inflammation and regeneration processes are intricately linked in injured muscle, macrophages are crucial for both processes. In this study, I test the idea that increased macrophage diversity leads muscle regeneration and tissue restoration by rewiring intercellular communication networks and that macrophage diversity is driven by metabolic reprogramming. My long term aim is to contribute to our society by uncovering the mechanisms and providing novel therapeutic strategy for sarcopemia.

Enteric Mesenchymal-Neural Circuit for the Mucosal Regeneration and Fibrogenesis (*)

KURASHIMA Yosuke
Associate Professor, Chiba University Department of Innovative Medicine

Mesenchymal cells such as fibroblasts and myofibroblasts are deeply involved in tissue repair and fibrosis. However, in order to target these cells distributed in various organs and tissues of our body as therapeutic strategies for fibrotic diseases, it is necessary to find organ and disease specific traits and target molecules. In this research, we focus on the histological characteristics of mucosal tissues and elucidate the mechanisms of fibrogenesis caused by inflammatory bowel diseases and develop new treatment strategies from the viewpoint of enteric mesenchymal-neural circuits.

Study of the mechanism of lung repair in interstitial lung diseases by temporal cellular network analysis (*)

SHICHINO Shigeyuki
Lecturer, Research Institute of Biomedical Science, Tokyo University of Science

Impairment of lung resolution results in pulmonary fibrosis. However, little is known about the starting point of the cell-cell interaction (CCI) network which promote lung resolution. To address this question, we will evaluate the alterations of cellular composition/states in the resolution stage of various murine lung injury/fibrosis models by using our novel single-cell RNA-seq method—TAS-Seq. Next, we will establish novel analysis framework for re-construction of pseudotemporal CCI network based on the TAS-Seq data, and identify/validate the starting point of the network that highly propagates to the network structure of lung resolution. We believe resulting data will provide novel insights in lung fibrosis treatment and the framework for analyzing temporal changes of CCI network in various injured organs.

Spatiotemporal effects of a novel signaling molecule, bicarbonate, in neurovascular unit reconstruction (*)

JO-WATANABE Airi
Project Associate Professor, Juntendo University, Faculty of Medicine

The goal of this research proposal is to elucidate the cellular and molecular mechanisms of tissue adaptation and repair in brain ischemia-reperfusion injury from the viewpoint of the bicarbonate-induced intracellular signaling and intercellular communication within Neurovascular Unit (NVU). I am going to reveal the spatiotemporal effects of bicarbonate ion in the NVU after middle cerebral artery occlusion and reperfusion. The achievement of this research could lead to the development of novel therapeutic strategies for cerebrovascular diseases based on the molecular understanding of bicarbonate effects, and will allow us the identification of 'bicarbonate signaling defects' in acid-base imbalance in a variety of disorders.

Analysis of sparse and hidden tissue remodeling regions indicated by active astrocytes (*)

SUSAKI Etsuo A.
Professor, Juntendo University School of Medicine

This project aims to elucidate the hidden tissue damage and repair processes and their molecular mechanisms in the very early stages of disease that have been difficult to target in previous biomedical studies. In particular, we will investigate the function of the early activated astrocytic foci reported by the principal investigator and analyze their association with age and age-related diseases of the central nervous system. We will use advanced 3D tissue visualization and cellular perturbation techniques being developed by the principal investigator.

The roles of oxygen environment on the pathogenesis of cardiac fibrosis (*)

TAKEDA Norihiko
Visiting Researcher, Center for Molecular Medicine, Jichi Medical University

Excessive cardiac fibrosis elicits the development of heart failure with preserved ejection fraction (HFpEF), a form of congestive heart failure in which the fraction of blood ejected from the left ventricle is within normal thresholds. Therefore, elucidation of the molecular processes by which fibroblasts are activated or deactivated is critically important for the development of therapeutic approaches in the management of heart diseases.
In this project, we will identify the metabolic profiles of cardiac fibroblasts, which produces extracellular matrixes in hypoxic environment. These approaches will uncover a previously unidentified therapeutic target of cardiac fibrosis.

Modeling and studying cholestatic liver diseases using a novel hepato-biliary organoid system (*)

TANIMIZU Naoki
Assistant Professor, The Institute of Medical Science, The University of Tokyo

Neighboring epithelial tissues establish a functional connection for the transport of substances and metabolites. In the liver, bile canaliculi of hepatocytes and bile ducts consisting of cholangiocytes form the biliary system, whose destruction causes cholestasis resulting in fatal liver diseases. We recently established a novel hepatobiliary tubular organoid (HBTO) in which bile secreted from hepatocytes is transported to biliary tubules. In this project, we introduce hepatic stellate cells and Kupffer cells to HBTO and then induce cholestasis by disrupting the bile excretion system. We aim to identify molecular mechanisms modulating cellular communications at the onset of cholestasis-induced liver failure.

A challenge to reveal and regulate multi-cellular networks that remove abnormal cells and maintain tissue homeostasis (*)

MOROISHI Toshiro
Professor, Faculty of Life Sciences, Kumamoto University

Increasing amounts of abnormal cells, such as over-proliferating cells, will impair organ functions by destroying the tissue architecture. Those abnormal cells are removed by a multicellular network, mainly the immune system, to ensure tissue homeostasis, otherwise those cells contribute to chronic inflammation, organ fibrosis, and cancer progression. In this study, we aim to elucidate the molecular and cellular mechanisms of tissue adaptation by uncovering a multicellular network involved in the removal of abnormal cells. We also try to open up new avenues for future drug discovery for the prevention and treatment of diseases related to fibrosis and cancer.

(*) indicates completed R&D projects.
Institution names, affiliations, and titles are as of the final year.