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

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.
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.

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.

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).

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.
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.

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.

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.

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.

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.
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.

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.

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.

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.

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.