【Grant-in-Aid for Scientific Research (S)】

Elucidating a role of niche construction in pathophysiological mechanism of human digestive diseases

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Purpose and Background of the Research

●Outline of the Research

The gastrointestinal tract is layered with epithelial cells that prevent the entry of foreign substances. The environment of diet, viruses, bacteria, etc. differs greatly among individuals. The digestive organs may become chronically damaged, or develop tumor cells as a result of genetic mutations. Gastrointestinal epithelium accumulates genetic mutations at a constant rate not only from the external environment but also from cell division and aging itself, which contributes to carcinogenesis. We found that the rate of gene mutation acquisition is accelerated in the epithelial cells of ulcerative colitis, which is characterized by chronic inflammation of the gastrointestinal tract. Furthermore, we found that epithelial cells exposed to inflammation acquire genetic mutations that allow them to tolerate inflammation and selectively amplify progeny cells (Nanki et al Nature 2020). Interestingly, the accumulation of such mutant cells not only tolerates inflammation, but also alters the intestinal immune response and the regulatory mechanisms of the intestinal microbiota, suggesting that the intestinal environment is altered. In other words, the mutant epithelial cells create a new intestinal environment, unfolding a vicious cycle of environment → mutation → environment → mutation. This sequence of environmental change, genetic mutation, and disease onset reminds us of the linkage between ecological environment, molecular genetic evolution, and speciation in biology. Furthermore, in ecology, there is the concept of "niche construction," in which beavers and ants link biological evolution with the creation of new environments. In this study, we will analyze how microevolution and environmental changes, as well as disease onset and progression, are linked in gastrointestinal tissues to gain insight into new disease biology.

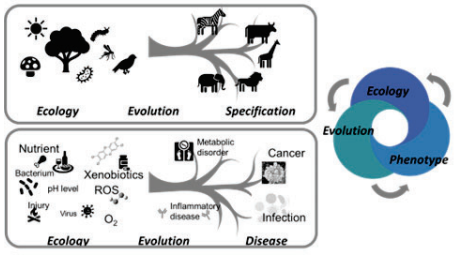
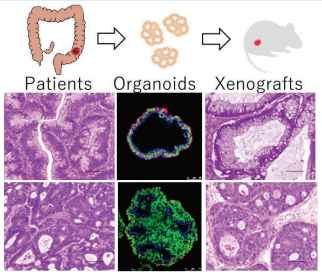


Figure 1: Similarities between biology. Eecological environment/biological evolution/ speciation, and disease biology microenvironment/microevolution/disease onset and progression. The figure depicts the complex intertwining of various changes in information such as environmental changes, genetic mutations, and cellular functions that lead to the onset and progression of disease.

We have developed and applied "organoid technology" to patient-derived tissues, and reconstruct tissue structures in a culture dish (Sato et al Nature 2009, 2011, Shimokawa et al Nature 2017, Nanki et al Cell 2018, Kawasaki et al Cell 2020, Sugimoto et al Nature 2021) (Figure 2). In this study, we will utilize this organoid technology to reveal the true nature of "niche construction" in our body, which repeats environment → mutation → environment.

In this research plan, we will collect various human gastrointestinal disease tissues and analyzed their genetic mutation/expression patterns. We will also use organoids to analyze their biological phenotype, including their in vivo behavior. Using patient-derived tissues, organoids, and organoid-based xenografts, we will analyze biological characteristics, and energy metabolism to associate genetic lesions and disease phenotypes. In addition, we will engineer these characteristics (gene mutations and changes in gene expression) to normal tissue cells to verify whether the disease can be artificially reproduced from normal cells. Furthermore, using organoids, xenografts, and engineered disease models, we will elucidate the mechanisms of how diseased tissues evelome under the presence of certain environments.



Fujii et al ***Cell Stem Cell*** 2016

Figure 2. Patient-derived tissues (left) recapitulate original tissue morphology in vitro organoids (middle) and xenografts (right)

Expected Research Achievements

The ultimate goal of this study is to understand gene mutation accumulation and disease tissue environment architecture in gastrointestinal diseases. We believe that four bottleneck technical issues need to be cleared in order to achieve this goal. Therefore, we will tackle the following four issues and clarify the entire picture of disease tissue environment construction (niche construction).

I. Collection and analysis of patient disease tissues and establishment of an organoid biobank

We will collect and analyze various gastrointestinal disease tissues, establish organoids from the tissues, and generate in vitro disease models. The generated organoids will be distributed to researchers as a biobank for promoting international research.

II. Development of biological model systems using organoids and analysis of disease environment formation

Previous organoid models have been optimized using proliferation, yet insufficient to reflect various morphologies and functions in vivo. Therefore, we will improve model performance to mimic a wide range of biological traits, including digestion, absorption, and metabolism of the digestive epithelium. Through these improvements, we will build models that allow for comprehensive analysis of the disease environment.

III. Establishment of advanced organoid analysis platform

The organoid-based analytical platforms, such as genetic information analysis, tissue morphology imaging analysis, and energy metabolism analysis, will be established.

IV. Development of artificial disease reproduction models

We will construct new artificial disease reproduction models by utilizing state-of-the-art technologies such as organoids, genome editing, and novel perturbation techniques.

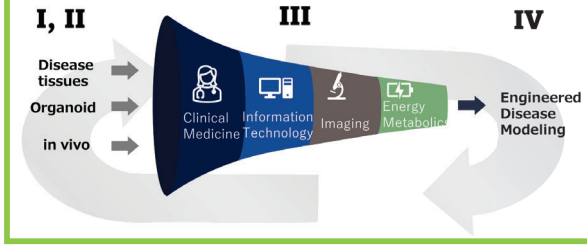


Figure 3. We will obtain a new understanding of disease biology by repeating the I-IV research cycle: the collection of patient-derived samples, organoids, and xenografts (I, II), bed-to-bench data analyses (III), and the engineered disease modeling (IV).

Homepage Address, etc.	https://organoidmed.org/