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

Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title Project : Gaining Integrative Understanding of Gastrointestinal Disease Phenotypes through Establishment of an Organoid Library

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Research Project Number : 17H06176 Researcher Number : 70365245
Research Area : Gastroenterology
Keyword : Lower gastroenterology (small intestine, colon)

【Purpose and Background of the Research】

Our gastrointestinal epithelium accumulates genetic mutations along with age, which eventually lead to tumorigenesis. The advance in molecular biology has enabled to identify a number of oncogenic mutations. Recent development of next generation sequencing further deepened our understanding of genetic contribution to the cancer. Nevertheless, we still have little understanding of life-threatening malignant cellular behaviors, such as tumor invasion and metastasis. The long-standing challenge prompted us to shift our focus on conventional genome analysis using “dead cells” to the cell biological analysis using “living cells” from patients (Figure 1).

We recently succeeded in establishing organoid culture technology that enabled growth of stereotypic structures from human gastrointestinal tissue in vitro. By combining with genome editing technology, the organoid technology has revealed genotype-phenotype correlations during human tumorigenesis and has become a valuable a biological platform.

In this study, using the latest version of organoid technology, we establish a gastrointestinal organoid library with each organoid characterized by comprehensive molecular analyses and drug screening tests. The established organoids will be provided to research community, in order to gain deeper biological insights into malignant transformation of gastrointestinal cancer.

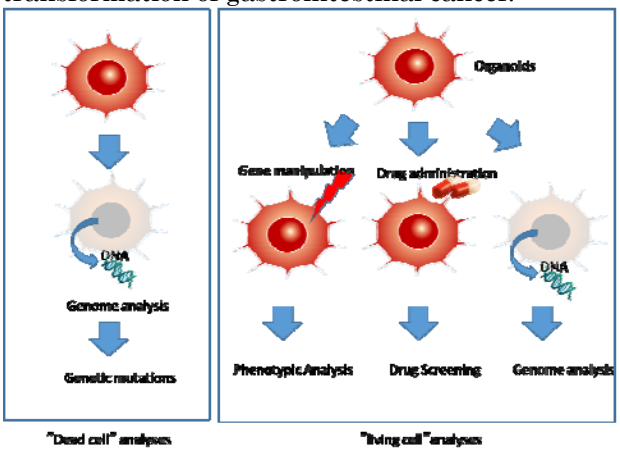

Figure 1. Organod technology realizes “Living Cell” analyses

【Research Methods】

To efficiently propagate patient-derived diseased tissues, we refine the organoid culture protocol and establish an organoid library. The established organoids are subjected to comprehensive molecular analyses encompassing whole exome analysis, gene expression analysis, epigenetic analysis and high throughput drug screening tests. These data sets are systemically analyzed to reveal relationships between genotypes and phenotypes. We also reconstruct genetic mutations into organoids in order to understand the oncogenic contribution of ill-defined genetic mutations that are highlighted by above analyses. We streamline the system for organoid biobanking to distribute the established organoids to research community.

【Expected Research Achievements and Scientific Significance】

This study can provide novel cell biological insights into malignant cell behavior of cancer cells, which may not be achieved by conventional genomic analyses. Furthermore, distribution of organoids to research community will promote multidisciplinary research.

【Publications Relevant to the Project】

・Matano M, Date S, Shimokawa M, Takano A, Fujii M, Ohta Y, Watanabe T, Kanai T, Sato T*. Modeling colorectal cancer using CRISPR-Cas9-mediated engineering of human intestinal organoids. Nature Medicine. 2015;21:256-62.
・Fujii M, Shimokawa M, Date S, Takano A, Matano M, Ohta Y, Nanki K, Kawasaki K, Nakazato Y, Uraoka T, Watanabe T, Kanai T, Sato T*. A colorectal tumor organoid library demonstrates progressive loss of niche factor requirements. Cell Stem Cell 2016:18:827-38.

【Term of Project】 FY2017-2021

【Budget Allocation】 159,000 Thousand Yen

【Homepage Address and Other Contact Information】

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