

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

Biological Sciences (Medicine, Dentistry, and Pharmacy)



Title of Project : Designing and Developing Innovative Use of Newly Discovered Colonic Epithelial Culture Method Applicable to Clinical Medicine

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Research Area : Medical Science

Keyword : Gastrointestinal Disease, Colonic Disease

【Purpose and Background of the Research】

The failure of intestinal environment due to the malfunction of the intestinal epithelial cells is suggested with an intractable cause for the inflammatory bowel disease (IBD). In this study, we thought that the improvement of intestinal environment in IBD by controlling the fate of intestinal epithelial stem cells could reset the homeostasis, resulting in the fundamental healing of IBD. We therefore aimed to develop primary culture method of intestinal epithelial stem cells and the stem cell transplantation model for the elucidation of the relationship between intestinal environment and whole-body homeostasis. Moreover, we propose a new concept to be able to control not only the intestinal diseases but also lifestyle-related diseases due to the intestinal epithelial stem cells.

【Research Methods】

Using primary culture system of the intestinal epithelial stem cells originally established, visible and diachronic evaluation system would be constructed for the stem cell functions such as the cell division, lifespan and differentiation. Furthermore, we would build an in vitro intestinal model including stem cells and enterobacterial flora to assess the mutual relations with the intestinal environment including hormone secretion and mucosal immunity. Specifically, we perform the following analysis.

1) Construction of the in vitro intestinal model by the primary culture organoids.

- a) The establishment of the co-culture system between intestinal organoid with dendritic cell (DC) or intraepithelial lymphocyte (IEL).
- b) The establishment of the enterobacterial flora model by the injection of the bacteria into the organoid lumen.
- c) Construction of high fat diet model in organoid

2) Establishment of the functional analysis for intestinal epithelial stem cells.

- a) The analysis of stem cell dynamics by single stem cell visualization.
- b) Signal analysis in the intestinal epithelial stem cells.
- c) The regulation for the determination of stem cell

fate.

3) The analysis for the abnormality of intestinal epithelial stem cell in whole body diseases.

- a) Construction of the high efficiency epithelium cell transplantation model.
- b) Dysfunction of the intestinal epithelial stem cell in the chronic disease model mouse.
- c) Intestinal epithelial stem cell culture in the patients with lifestyle-related diseases.

【Expected Research Achievements and Scientific Significance】

In late years, it has been suggested that the pathogenesis of lifestyle-related diseases as well as a chronic gastrointestinal disease, is due to the intestinal epithelial function including mucosal immunity, intestinal hormone and the enterobacterial flora. We generate the ex vivo model of the intestine with complicated environment, which can exhibit the mutual relations of various factors in the intestinal tract. Finally, we hope that resetting intestinal environment by controlling the fate of an intestinal epithelial stem cell could cut off the malignant circulation in the chronic disease.

【Publications Relevant to the Project】

- 1) Yui S, Nakamura T, Sato T, Nemoto Y, Mizutani T, Zheng X, Ichinose S, Nagaishi T, Okamoto R, Tsuchiya K, Clevers H, Watanabe M: Functional engraftment of colon epithelium expanded in vitro from a single adult Lgr5+ stem cell. *Nature Medicine* 18: 618-623, 2012.
- 2) Fordham RP, Yui S, Hannan NRF, Madgwick A, Vallier L, Pedersen RA, Nakamura T, Watanabe M, Jensen KB: Transplantation of expanded fetal intestinal progenitors contributes to colon regeneration after injury. *Cell Stem Cell*. 13:734-744, 2013.

【Term of Project】 FY2014-2018

【Budget Allocation】 150,100 Thousand Yen

【Homepage Address and Other Contact Information】