

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

Biological Sciences (Medicine, dentistry, and pharmacy II)



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】

Progress in gastrointestinal stem cell research and its clinical application have been hampered by the lack of suitable in vitro culture technique for gastrointestinal epithelial cells. Recently we have developed a novel methodology to isolate and maintain normal colonic epithelial cells in vitro under serum- and mesenchyme-free conditions. In this project, we will apply this new technology to investigate the functional properties of normal colonic epithelium, and also to develop strategies for clinical use of these cultured colonic epithelial cells.

【Research Methods】

The culture method that we have established allows us to maintain and expand non-transformed murine colonic epithelial cells over a long time period under serum- and mesenchyme-free conditions. We will take advantage of this technology for the following projects by combining various methods of molecular biology and cellular biology.

1) Establishment of a culture system for pure colonic epithelial stem cells

We will advance our technology to establish a method that allows us to isolate and expand pure colonic stem cells. For this, we will devise a tool to visualize the stem cell populations employing a fluorescent reporter system in combination with the lentiviral vector technologies.

2) Functional analysis of normal colonic epithelial cells in vitro

To date, transformed cells or the cells derived from human colorectal cancer tissues have been the only materials by which cellular functions of colonic epithelium can be investigated. Our culture method will for the first time provide experimental systems to analyze important functions of normal colonic epithelial cells. We will study the feasibility of assessing the physiological colonic epithelial functions such as absorption/secretion, cytokine production, and so forth.

3) Development of a cell based therapy to treat colonic epithelial injuries

We will assess the feasibility of a cell-based

therapy by transplanting cultured colonic epithelial cells into various animal models of colonic diseases.

4) Establishment of an equivalent culture method for human colonic epithelial cells

To develop strategies for clinical use of this methodology, we will try to create the technical basis of in vitro culture for the human colonic epithelial cells.

【Expected Research Achievements and Scientific Significance】

Our research project seeks to analyze the functional properties of colonic epithelial cells that contain stem cell populations. We expect that the output of this project will have significant impacts on our understanding of how colonic stem cells behave under physiological and pathological conditions from a new standpoint. In addition, our project is also expected to stimulate research toward clinical applications of in vitro cultured colonic cells. What we will achieve in this project will suggest realistic scenarios for therapeutic use of these cells in cell-based therapies to colonic epithelial injuries in humans, or their diagnostic use as a tool for the personalized medicine.

【Publications Relevant to the Project】

1) Okamoto R, Yajima T, Yamazaki M, Kanai T, Mukai M, Okamoto S, Ikeda Y, Hibi T, Inazawa J, Watanabe M: Damaged epithelia regenerated by bone marrow-derived cells in the human gastrointestinal tract. *Nature Med.* 8: 1011-1017, 2002.

2) Tsuchiya K, Nakamura T, Okamoto R, Kanai T, Watanabe M: Reciprocal targeting of H_h1 and β -catenin by Wnt-glycogen synthase kinase 3 β in human colon cancer. *Gastroenterology.* 132: 208-220, 2007.

【Term of Project】 FY2010-2014

【Budget Allocation】 166, 900 Thousand Yen

【Homepage Address and Other Contact Information】