Laboratory of Cellular Regulation

Research Institute for Microbial Diseases

Professor Hiroaki MIKI hmiki @biken.osaka-u.ac.jp

Associate Professor Yosuke FUNATO Yfunato @biken.osaka-u.ac.jp

Assistant Professor Osamu HASHIZUME ohashizume @biken.osaka-u.ac.jp

URL: http://www.biken.osaka-u.ac.jp/lab/cellreg/

Cancers mostly originate from epithelial cells that are tightly connected with each other. Malignant transformation occurs when genetic mutations accumulate in normal epithelial cells, which then break away from the original epithelial layer, expand their territory, and metastasize to other organs via blood vessels, making treatment difficult. While many oncogenes and tumor suppressor genes, which are involved in cell proliferation, survival, etc., have been identified, the mechanism of epithelial cell trait changes in the three-dimensional architecture, such as invasion and metastasis, is not well understood. Many mysteries remain as to how cells in the epithelial tissue leave the original site and how they expand their territory by invading other adjacent tissues. In our laboratory, we are analyzing the process of malignant transformation of cancer cells, using experimental animals, such as mice, and cultured mammalian cells.

CNNM, the target molecule for PRL that causes cancer malignancy

PRL is a tumorigenic molecule that is highly expressed in metastases of human colorectal cancers. We have identified a membrane protein, CNNM, as a target molecule for PRL and have shown that it is a membrane transporter of Mg2+. In particular, we found that CNNM4 functions in the absorption of magnesium from food by analyzing mice lacking the gene for CNNM4, which is expressed in the intestinal epithelium. Furthermore, we have shown that deletion of the CNNM4 gene in mice that spontaneously form intestinal polyps results in the formation of numerous malignant carcinomas that invade from the epithelial layer to the muscle layer (Fig. 1). We are further analyzing the functional relationship between Mg2+ dysregulation and malignant transformation of cancer.

Function of PRL through epithelial cell-cell interactions

To analyze the function of PRL in epithelial cells in detail, we induced expression of PRL in MDCK cells, which are commonly used for experiments in culture systems, and found that cell morphology changed significantly specifically when surrounded by normal cells. Some cells were also observed to invade into the matrix gel from the basolateral side. This suggests that some kind of interaction (communication) occurs between PRL-expressing and non-expressing cells, which may induce phenomena such as invasion. We are now investigating the molecular mechanism.

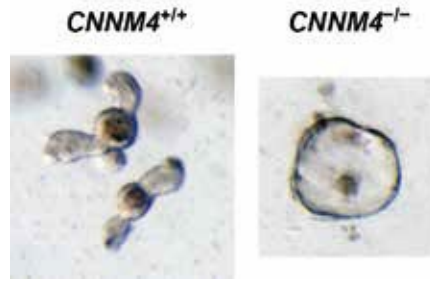

Figure 2: Intestinal organoid culture from a genetically engineered mouse. Deletion of the CNNM4 gene results in abnormal organoid morphology (right panel).

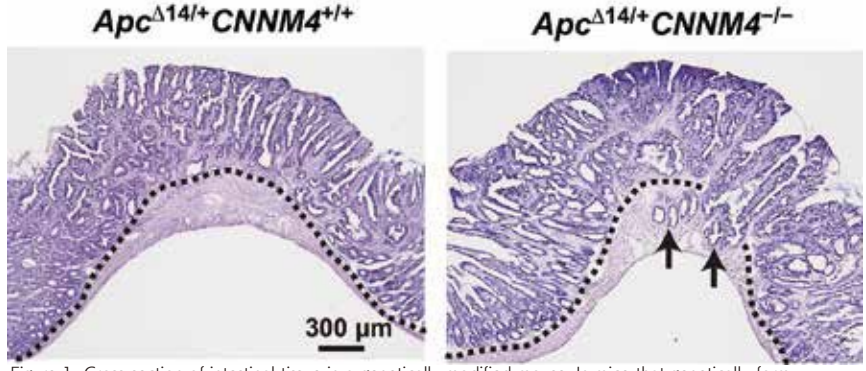

Figure 1: Cross-section of intestinal tissue in a genetically modified mouse. In mice that genetically form numerous polyps in the intestinal epithelium, deletion of the CNNM4 gene results in malignant transformation of polyp cells that had remained in the epithelial layer into cancerous cells that have invaded the muscle layer (arrows in the right photo).

Functional analysis of PRL/CNNM using intestinal organoid culture

In vitro culture of multicellular organisms is generally difficult. However, a method of 3-dimensional culture for intestinal epithelial tissue in an extracellular matrix gel that mimics in vivo situation (organoid culture) has recently been developed. In this intestinal organoid culture, cells are differentiated as in vivo and cultured in a single layer of tissue, forming three-dimensional structures (Figure 2). Using this organoid culture system, we are analyzing the function of PRL/CNNM in cell proliferation and differentiation within intestinal epithelial tissue and its role in cancer transformation from the intestinal epithelium.

We are investigating the behavior of individual cells in the multicellular society by focusing on the characteristic features of cancers, which spread in the three-dimensional tissue structure.

Research Institute for Microbial Diseases,
Osaka University, 3-1 Yamadaoka, Suita, Osaka
565-0871, Japan

TEL: +81-6-6879-8293
FAX : +81-6-6879-8295

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