論文の内容の要旨

論文題目　Critical role of host immune cells for the induction and regulation of Paneth cells
（宿主免疫細胞によるパネート細胞の分化・機能調節機構の解明）

神岡　真理子

The gastrointestinal tract is constantly exposed to numerous foreign antigens. Intestinal epithelial cell (IEC) layer acts as a first line of defense and is divided into villi and crypt regions. In the crypts, epithelial stem cells and Paneth cells are preferentially located. Paneth cells release granules containing a variety of antimicrobial peptides as a major part of the host innate immune system. α-defensin is most abundant and highly bactericidal peptide specifically produced by Paneth cells. Paneth cells also produce and secrete Delta-like 1/4, epidermal growth factor and Wnt to constitute the niche for epithelial stem cells. Defects of Paneth cells cause the disturbance of epithelial cell differentiation, dysbiosis and/or aggravation of gastrointestinal disorders.

IECs create a co-habitation niche for commensal bacteria by using α(1,2)fucosylation, one of glycosylation system. α(1,2)fucosylation of IECs is regulated by two fucosyltransferases, Fut1 and Fut2. A previous study has shown that segmented filamentous bacteria induce Fut2 expression in villus epithelial cells. Interleukin 22 (IL-22) produced by type3 innate lymphoid cells is another stimulator for the induction of Fut2 in IECs. It has been also shown that α(1,2)fucose is expressed not only in columnar epithelial cells

but also in crypts, where Paneth cells are preferentially localized. However, the mechanism and functional significance of α(1,2)fucosylation in Paneth cells has been unrevealed.

In this study, I aimed to elucidate the mechanism underlying α(1,2)fucosylation in Paneth cells and the significance of α(1,2)fucosylation for Paneth cells development and function. Especially, I focused on Fut2-induced α(1,2)fucosylation in Paneth cells, because FUT2 nonsense polymorphisms are found to be related with Crohn's disease. Further, there is a possibility that Fut2-induced α(1,2)fucosylation has important roles in the functions of Paneth cells for creating and maintaining healthy intestinal environment. My study was also aimed to understand the regulation mechanism of $Fut2^{+}$Paneth cells by intestinal immune cells. Several previous studies have demonstrated that innate immune cells such as innate lymphoid cells regulate the IEC development and function. However, limited information is currently available for our understanding of whether intestinal immune cells regulate Paneth cell development and functions. In this study, I thus analyzed possible roles of innate and adaptive immune systems for the induction and regulation of Paneth cells, especially those of Fut2 harboring cells.

By analyzing Fut1-deficient mice, Fut2-deficient mice and wild type mice, I found two subtypes of Paneth cells that are classified on the basis of their expression of Fut2. Fut2-positive ($Fut2^{+}$) Paneth cells were preferentially located in ileum, whereas large portion of Fut2-negative ($Fut2^{-}$) Paneth cells was

located in duodenum. Since the preferential localization of Fut2^{+} Paneth cells in ileal crypts is correlated with the bacterial load of commensal microbiota (duodenum: 10^{2}–10^{3} microorganisms, ileum: 10^{7}–10^{8} microorganisms), my results suggested that Fut2^{+} Paneth cells are committed to the eradication of luminal microbiota by producing antimicrobial peptides. Indeed, the production of antimicrobial peptides was higher in ileal Paneth cells which were mainly composed of Fut2^{+} Paneth cells than duodenal Paneth cells. I further found a possibility that Fut2^{-} Paneth cells have higher ability to constitute the niche for epithelial stem cells when compared with Fut2^{+} Paneth cells.

I next examined possible molecular mechanisms involved in the induction of Fut2^{+} Paneth cell development. I found that IL-22 signaling, known as a part of innate immune system, induced the development of Fut2^{+} but not Fut2^{-}, Paneth cells with mature granules containing α-defensin. I further analyzed ileal Paneth cells in Rag1-deficient mice which lack both T and B cells to elucidate the involvement of adaptive immune system for governing Fut2^{+} Paneth cell. I found a possibility that the adaptive immune system is involved in the granule release from Fut2^{+} Paneth cells.

In summary, Paneth cells can be separated into two subsets based on their utilization of Fut2. Fut2^{+} Paneth cells are preferentially located in ileum, whereas Fut2^{-} Paneth cells are in duodenum. My current study has indicated a possibility that Fut2^{+} and Fut2^{-} Paneth cells have critical roles in host defense

and constitution of stem cells niche respectively. It has been also suggested that both innate and adaptive immune systems are essential for Fut2^{+} Paneth cell development and functional expression, respectively. Further molecular and cellular analyses of Fut2^{+} and Fut2^{-} Paneth cells will reveal how Paneth cells contribute to the creation of healthy gastrointestinal environment.