International Research and Development Center for Mucosal Vaccines

Division of Mucosal Symbiosis
粘膜共生学分野

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The gastrointestinal tract is a unique organ that is constitutively exposed by various antigens, including commensal microbiota. In order to create a symbiotic environment for non-pathogenic luminal microorganisms, epithelial cells (ECs) and immune cells cooperatively establish homeostasis of the intestinal microenvironment. We aim to identify the mechanisms of epithelial α1, 2-fucosylation, one of the symbiotic factors between host and microbiota, and uncover the role of ECs-immune cell network in the establishment of intestinal homeostasis. We also aim to understand host-microbe as well as microbe-microbe interaction in the gut.

1. Innate lymphoid cells govern intestinal epithelial α1, 2-fucosylation

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α1, 2-fucosyl linkages located to terminal carbohydrate moiety expressed on intestinal epithelial cells is catalyzed by fucosyltransferase 2 (Fut2). Epithelial α1, 2-fucose is one of the symbiotic factors that mediate host–microbiota interaction. For example, epithelial α1, 2-fucose is utilized as a dietary carbohydrate by various symbiotic bacteria such as *Bacteroides*. Therefore, disruption of Fut2 leads to dysbiosis both in mice and humans and predisposed to the development of inflammatory diseases such as Crohn's disease. Despite the importance of intestinal and systemic homeostasis, the molecular and cellular mechanisms of the induction of epithelial Fut2, and subsequent α1, 2-fucosylation remains unknown. We found that group 3 innate lymphoid cells (ILC3) are critical inducers of intestinal epithelial Fut2 expression and fucosylation that is mediated by the production of interleukin 22 and lymphotoxin from ILC3 in a commensal bacteria–dependent and -independent manner, respectively. Fut2-deficient mice are susceptible to the infection by pathogenic microorganisms. These data unveil a novel function of ILC3 in creating the appropriate symbiotic environment and protective platform against pathogenic microorganisms through regulating the epithelial α1, 2-fucosylation.

2. Commensal microbiota prevent fungi from colonizing the gastrointestinal tract.

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Intestinal epithelial cells are the first line of defense against infection by pathogenic microorganisms. *Candida albicans* are one of the commensal fungi reside in the mucosal surface including the gastrointestinal tract. However, *C. albicans* also have been reported to exert pathogenic effects in the immunocompromised host and expand to the systemic compartments, which is called invasive candidiasis. Invasive candidiasis triggered by *C. albicans* colonization in the gut is one of the serious infectious diseases in the world. So far, it is unclear what kind of factors which regulate *C. albicans* colonization in the gut. To investigate this, we focused on the role of commensal bacteria against colonization by *C. albicans*. We found that germfree and several antibiotic-treated mice allow colonization of *C. albicans* in the gut. Furthermore, oral administration of feces isolated from normal mice excluded *C. albicans* from the gut. This data suggests that commensal bacteria prevent the colonization of *C. albicans* in the gut, and commensal bacteria may be a useful therapeutic target for protection against *C. albicans* infection.

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