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腸粘膜表層と腸管組織内における免疫共生システム

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腸管には，外界から進入してくる有害な病原体に対する生体防御と食餌性物質や常在細菌などの有益な異物に対する免疫学的寛容という相反する免疫応答を巧みに制御するためのシステムが発達している．無菌マウス等を用いた古くからの研究より，腸管免疫の発達には腸管に存在する常在細菌からの刺激が必要であることが知られている．一方で，近年のゲノム技術をもとにした腸内細菌の解析技術の発展に伴い，これまで多くが未解明であった腸内細菌の実体が明らかとなってきた．

腸管組織に点在するパイエル板は，腸管組織における主要な免疫誘導組織として機能しているが，無菌マウスにおいてその組織形成・機能不全を起こしていることからも分かるようにその発達に腸内細菌からの刺激を必要とする．我々は，宿主免疫系と直接相互作用し得るパイエル板組織内において存在する共生細菌の解析を行い，その代表的共生細菌として*Alcaligenes*を同定した．*Alcaligenes*はパイエル板組織内部に生存，定着しているだけではなく，特に樹状細胞の内部に存在することで，パイエル板を介した免疫制御に関与していることを見いだしている．

本発表においては，*Alcaligenes*によるパイエル板組織内共生の免疫学的機能の詳細を発表すると共に，最近我々が見いだした腸内細菌を介した上皮細胞の糖鎖修飾における宿主免疫系の関与や，腸内細菌を介した刺激により誘導されるユニークなIgA産生細胞など，腸管表層における免疫共生システムについても紹介したい．

New Mutualism for the Regulation of Intestinal Immune System at the Surface and Inside of Gut

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The mutual communication with commensal bacteria plays an important role in the regulation of the host immune responses, especially in the gut. The current advanced technology in the genetic analysis of commensal bacteria has revealed the complex interaction between host and commensal bacteria in health and disease. These studies were mainly performed using feces, while the nature of commensal bacteria in different parts of the gastrointestinal tract including the gut-associated lymphoid tissue and epithelium is still not well understood. In this talk, I will show our recent findings on the novel immunological crosstalk with commensal bacteria neighboring the surface and inside of gut.

As commensal bacteria at the inside of gut, we identified Alcaligenes species specifically inhabit Peyer's patches (PPs), with the associated induction of antigen-specific IgA antibodies in the intestine. The dominant presence of Alcaligenes in the PPs were observed not only in mice, but also in human and monkey. Oral transfer of Alcaligenes into germ-free mice resulted in the presence and growth of Alcaligenes inside the PPs of recipients. Some Alcaligenes localized in the dendritic cells (DCs) in the PPs, where they promoted the production of antibody-enhancing cytokines (e.g., TGF-β, BAFF and IL-6). These DCs did not migrate beyond the draining mesenteric lymph nodes, leading to the predominant induction of IgA-producing cells in the PPs. Intriguingly, the presence of Alcaligenes in PPs was greatly diminished in the absence of intestinal antibodies.

We also found that glycosylation, especially fucosylation, of epithelial cells (ECs) was induced by commensal bacteria and reciprocally fucosylation of ECs determined the composition of commensal bacteria at the intestinal epithelium. Interestingly, direct interaction between commensal bacteria and ECs was not sufficient to induce the fucosylation, and MyD88-mediated recognition of commensal bacteria by innate immunocompetent cells was essentially involved in this pathway. Thus, microbial composition at the intestinal epithelium was changed in mice lacking fucosyltransferase 2, a key enzyme in the fucosylation of ECs, or MyD88. MyD88-mediated recognition of commensal bacteria was also involved in the induction of unique subset of IgA-producing plasma cells in the gut. The commensal bacteria-dependent IgA plasma cells produced high amounts of IgA and mediated the early phase of IgA production against orally immunized antigens. Taken together, these studies show some molecular and cellular mechanisms underlying unique communications between commensal bacteria and intestinal immune system, which potentially involves in the creation of an optimal symbiotic environment on the interior and surface of the gut.