Review Article

The Role of Microbiota on the Gut Immunology

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ABSTRACT

Purpose: The human gut contains >100 trillion microbes. This microbiota plays a crucial role in the gut homeostasis. Importantly, the microbiota contributes to the development and regulation of the gut immune system. Dysbiosis of the gut microbiota could also cause several intestinal and extraintestinal diseases. Many experimental studies help us to understand the complex interplay between the host and microbiota.

Methods: This review presents our current understanding of the mucosal immune system and the role of gut microbiota for the development and functionality of the mucosal immunity, with a particular focus on gut-associated lymphoid tissues, mucosal barrier, T_H17 cells, regulatory T cells, innate lymphoid cells, dendritic cells, and IgA-producing B cells and plasma cells.

Findings: Comparative studies using germ-free and conventionally-raised animals reveal that the presence of microbiota is important for the development and regulation of innate and adaptive immune systems. The host-microbial symbiosis seems necessary for gut homeostasis. However, the precise mechanisms by which microbiota contributes to development and functionality of the immune system remain to be elucidated.

Implications: Understanding the complex interplay between the host and microbiota and further investigation of the host-microbiota relationship could provide us the insight into the therapeutic and/or preventive strategy for the disorders related to dysbiosis of the gut microbiota. (*Clin Ther*. 2015;37:968–975)

Key words: gut, immune system, microbiota, mucosal.

INTRODUCTION

The human gut harbors >100 trillion microbes referred to as the gut microbiota, and most of these microbes reside in the colon, where densities approach 10^{11} to 10^{12} cells/mL.[1,2] The gut microbiota plays an important role in health and disease in humans.[3] Although the gut provides a rich environment for supporting microbial survival, the microbiota also contributes to the well-being of the host. The main benefits of the microbiota include metabolic, trophic, and immunologic functions.[4–7] The microbiota degrades undigested carbohydrates to produce important energy sources (eg, short-chain fatty acids [SCFAs])[8] and synthesizes essential vitamins.[9] Perhaps even more importantly, the microbiota contributes to the development and regulation of the gut immune system.[10–16] Studies with germ-free (GF) animals reveal that the microbiota is necessary for the development of the gut mucosal immunity. In addition, microbiota-driven immune response can prevent the development of inappropriate inflammation, which in turn allows the microbiota to survive in the absence of unnecessary inflammation. Therefore, the host-microbial symbiosis is necessary for the gut homeostasis. On the contrary, dysbiosis of the gut microbiota could cause immune-related disorders,[17] diabetes,[18] allergies,[19] and even obesity.[20] In this review, we discuss the mucosal

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immune system and the role of gut microbiota for the development and functionality of the mucosal immunity.

THE MICROBIOTA INFLUENCES THE DEVELOPMENT OF THE GUT MUCOSAL IMMUNE SYSTEM

Gut-Associated Lymphoid Tissues and Mucosal Barrier

Gut-associated lymphoid tissues (GALTs) are lymphoid structures and aggregates that line the gut, such as the tonsils, Peyer patches (PPs), isolated lymphoid follicles (ILFs), and mesenteric lymph nodes (MLNs).[21] PPs are the most recognizable immune structure in the small intestine and appear as clusters of ≥ 3 large lymphoid aggregates with an overlying follicle-associated epithelium, a T-cell zone, and a subepithelial dome containing dendritic cells (DCs).[22,23] The follicle-associated epithelium contains M cells, which are specialized epithelial cells that facilitate the uptake of antigen and microbes from the gut lumen and its delivery to underlying lymphoid tissue.[24,25] Although ILFs are structurally and functionally similar to PPs, they are smaller, lack a T-cell zone, and are also present in the large intestine.[26,27] DCs within PPs promote the production of IgA from B cells,[28] and IgA^+ B cells are prevalent in the germinal centers of PPs.[29]

The intestinal epithelium is a single layer of cells derived from the epithelial stem cells within the crypt.[30] Epithelial cells are responsible for the mucosal barrier function, participating in immunologic surveillance and direction of the host responses in the gut. Epithelial cells produce mucus to inhibit pathogen invasion by separating the gut lumen from the surface of the intestinal epithelium[31,32] and also produce antimicrobial peptides, such as regenerating islet-derived protein 3β (REGIIIβ) and REGIIIγ in response to stimulation with interleukin (IL) 22.[33,34] Epithelial cells can express numerous pattern recognition receptors (PRRs), including Toll-like receptor (TLRs) and nucleotide oligomerization domain-like receptors.[35–37] PRRs are germline-encoded receptors in the epithelial and innate immune cells to recognize microbial particles, such as DNA, lipopolysaccharides, peptidoglycans, flagellin, and metabolites.[21,38,39] PRRs have crucial roles in innate immunity because they can sense pathogen-associated molecular patterns and initiate signaling cascades that lead to innate immune response.[21]

Intraepithelial lymphocytes (IELs) are composed of $CD8^+$ T cells and reside within the epithelium of the intestine.[40] IELs have both protective and pathogenic roles during inflammation. IELs help preserve the integrity of damaged epithelial surfaces by providing the localized delivery of an epithelial cell growth factor, such as keratinocyte growth factor.[41,42] On the other hand, IELs capable of interferon γ production have been associated with the development of inflammatory bowel disease.[43]

Studies with GF animals reveal that the microbiota contributes to the development of GALT and promotes mucosal barrier function. PPs in GF mice are less active and contain small germinal zones than those in conventionally raised mice.[44] In mice that are deficient in PRRs, maturation of ileal and colonic ILFs is incomplete.[45] These observations indicate that the generation of the intestinal lymphoid tissues is induced by the microbiota through an innate detection system. GF animals also have lower levels of antimicrobial peptides[46] and smaller numbers of IELs than conventional animals.[47] However, intestinal microbial stimulation in GF animals can restore the proper organization of the intestinal immune system.[46,48] Likewise, the colonic adherent mucous layer in GF mice is significantly thinner than that in conventional mice, but when exposed to bacterial products, such as lipopolysaccharide and peptidoglycan, the thickness of the adherent mucous layer is restored to levels observed in conventional mice.[49] Production of antimicrobial peptides REGIIIγ and REGIIIβ is impaired in mice that lack myeloid differentiation factor 88, a signaling adaptor for several TLRs, resulting in the increased susceptibility of mice to infection by enteric pathogens.[34,50,51] Thus, microbiota can contribute to enhance the innate immunity through the regulation of mucous secretion and production of antimicrobial peptides. In addition, the microbiota can enhance mucosal barrier function through the production of metabolic by-products. SCFAs, such as acetate, propionate, and butyrate, are by-products of fermentation of dietary fiber by colonic bacteria.[8] *Bifidobacteria* inhibit the translocation of the *Escherichia coli* O157:H7 Shiga toxin from the gut lumen to the blood through the production of acetate.[52] Butyrate also reduces T-cell–mediated immune reaction via modulating