

Biology

Gut Microbiota and Immune Responses**Tobin Lee***

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The gut is the body's largest immune organ, consisting of both hematopoietic (macrophages, dendritic cells, and T cells) and non-hematopoietic cells (epithelial cells, Paneth cells, and goblet cells). It is home to hundreds of millions of microorganisms, which collaborate with the host immune system to maintain the internal environment's homeostasis. The gut microbiome plays a critical role in the development of inflammatory responses (including autoimmune diseases, allergies, etc.). The gut microbiota has a direct effect on the maturation of the host immune system, inducing immunoglobulin A (IgA), and regulating CD4⁺ T cells, including Th1, Th17, and regulatory T cells (CD4⁺, CD25⁺, Foxp3⁺). Along with the expression of antimicrobial peptides (AMPs), numerous molecules produced by flora may influence these immune responses. Numerous basic and clinical studies have established that controlling the gut microbiota is an effective method for treating and controlling disease. Once these mechanisms are fully understood, probiotics/prebiotics may be used to regulate the gut microbiota in order to treat diseases.

Keywords: Gut; Microbiota; Host Immunity; Homeostasis; Diseases
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THE human body contains between 10¹² and 10¹⁴ gut microbiota, with an average mass of roughly 1.5 kg (1, 2) and approximately 6-10 groups (3,000 species) of bacteria (3, 4). Infants populate the gut with microorganisms immediately after birth, and this process continues until the gut microbiota stabilizes to a commensal state (5). The host benefits from the gut microbiome. The gut microbiota is critical for human development (6), intestinal barrier function (7), immunological modulation (8), material metabolism (9), nutrient absorption (10), toxin excretion (11) and disease incidence and development (12). Disruptions in the gut microbiota can result in a variety of disorders, including obesity, cirrhosis of the liver, diabetes, cardiovascular disease, and autism. The primary role of the gut microbiota is to aid the host metabolism by optimizing

the utilization of energy and nutrients, providing nutrition to intestinal epithelial cells, enhancing host immunological function, and assisting the host in resisting harmful bacteria (13).

Studies have demonstrated that the gut microbiota's metabolic role is critical, and its efficiency much exceeds that of the liver. For instance, the gut microbiota not only influences the fatty acid content of the retina and the density of the eye lens, bone, and intestinal blood vessels (14, 15); but also delivers vital nutrients (biotin, vitamin K, butyric acid, and so on) and digests edible cellulose (16). The immune system's regular operation (fighting against bacterial infections) is dependent on the gut microbiota (17). Simultaneously, the gut microbiota plays a critical role in the maturation of the "mucosal immune system" and "systemic immune system" (18, 19). The composition and

metabolites of the gut microbiota have been shown to have a significant effect on immunological and inflammatory responses in experimental experiments. When the immune system of the gut fails, chronic enteritis disorders such as Crohn's disease and ulcerative colitis can result (20). However, because the commensal gut microbiota is so diverse, it is difficult to distinguish between commensal and opportunistically pathogenic bacteria, immunological regulation of the gut microbiota colonization response is a complicated system.

Gut Microbiota Induces Regulatory T Cells

CD4⁺ T cells, particularly Th1, Th17, and regulatory T cells (CD4⁺, CD25⁺, Foxp3⁺), are crucial for maintaining intestinal immunological homeostasis in the presence of commensal microflora that are not pathogenic (21). Only when a complex microbial flora exists in the stomach will more Th1 and Th17 regulatory T cells be generated, and their numbers are extremely low in germ-free animals (8, 22). A single bacterial population, such as segmented filamentous, can also trigger regulatory T cell responses, such as Th17 cell responses (23, 24). Additionally, Foxp3⁺ regulatory T cells persist in the intestinal mucosa and lymphoid tissues linked with the intestinal mucosa, which is critical for the intestinal inflammatory response (25). Mucosal regulatory T cells can be constantly created by retinoic acid-induced particular axonal cells (26, 27). Clostridia in the gut play a critical role in the development of mucosal and systemic immune systems (28). Experiments were undertaken to compare germ-free and germ-free mice colonized with ASF (altered Schaedler flora), and it was discovered that germ-free animals colonized with ASF activate and regenerate immunological regulatory T cells in the colonic lamina propria mucosa (29, 30). Without mucosal Th17 or Th1 cell responses, regulatory T cell induction is critical for CD4⁺ T cell homeostasis (31, 32). MyD88, a Toll-like receptor adaptor, and Ticam-1 are necessary for effective T cell activation regulation (33).

Additionally, interleukin-10 receptor (IL-10R) signaling is required for the formation of CD4⁺ T cell homeostasis in the gut. IL-10R signaling, on the other hand, cannot impact the production and activation of regulatory T cells, as activation of regulatory T cells can result in mucosal immunological bias (to carry out Th1 and Th17 cell responses), which requires wild-type regulatory T cells to compensate. As a result, the activation of regulatory T cells by the symbiotic gut microbiota is critical (34). Whether functional regulatory T cells are activated or not, ASF has a constant composition and non-invasive features. This data suggests that in the absence of sex T cell responses, the immunological bias was toward Th17 cell responses in non-commensal regulatory T cells, a finding consistent with the absence of filamentous bacteria in the gut (35). Thus, symbiotic stimulation of intestinal regulatory T cells is a critical strategy for maintaining intestinal immunological homeostasis following microbial colonization of the gut, laying the groundwork for the creation of a cascade of immune responses.

Gut Microbiota Induces IgA Protein

Immunoglobulin A (IgA) is a kind of antibody that is required for mucosal immunity. IgA is produced in greater quantities than other types of antibodies in the mucosa (36), and approximately

3-5 g of IgA is secreted into the gut daily (37), accounting for 15% of all immunoglobulins produced by the human body (38). Numerous immunological illnesses can be caused by abnormal IgA, including IgA nephropathy, celiac disease, Henoch-Schönlein purpura, linear IgA bullous skin diseases, and IgA pemphigus (39). Given the difficulty of curing these disorders, it is critical to understand the mechanism through which the gut microbiota affects IgA.

It has been demonstrated through the use of germ-free animals with commensal bacteria in the gut that the mucosa is extremely adaptable to commensal microbes (40). Although the complete functional importance of these modifications is unknown, when commensal microorganisms are present, the total intestinal IgA released by the intestinal mucosa accounts for more than 70% of the total immune proteins secreted in the human body (41-43). However, it is unknown whether the secreted IgA simply inhibits the growth of commensal microorganisms in the gut or whether commensal microorganisms that express IgA are prevented from penetrating the superficial epithelium. Like other pathogenic bacteria, commensal microorganisms express substances that can be detected by systemic immune system Toll-like receptors (44, 45). While commensal microbes and their metabolites can stimulate B and T cells, they do not induce pathogenic infection features (neutrophil infiltration and usual inflammatory responses) (46). By administering *Enterobacter cloacae* and other commensal microorganisms to mice, an experiment demonstrated how commensal microbes reach intestinal dendritic cells to stimulate IgA synthesis (47). The stomachs of C5BL/6 wild-type mice were injected with a specific dose of *E. cloacae*, and after culture for a length of time, the bacteria were retrieved by washing the mesenteric lymph node (MLN) (48). Between 200 and 800 species were maintained, and no bacteria were detected in the spleen cells or other systemic tissues of mice (49). Following bacterial culture, it was determined that living commensal bacteria existed in dendritic cells (DCs) but not in macrophages via fluorescence-activated cell sorting, as macrophages can efficiently kill infiltrating commensal microorganisms (50), whereas dendritic cells are relatively inefficient at killing bacteria (51).

Salmonella typhimurium was injected into mice and cultivated for 18 hours, and it was discovered that *Salmonella* could be isolated from spleen cells, dendritic cells, and macrophages in intestinal lymph nodes (52). Commensal bacteria, on the other hand, are distinct from pathogens. Because macrophages can effectively eliminate symbiotic bacteria, just a few commensal bacteria can survive in dendritic cells (52). The intestinal examination of mice revealed that commensal bacteria were carried by dendritic cells and moved to the intestinal lymph nodes with them, and that dendritic cells were activated following *Enterobacter cloacae* phagocytosis (53). IgA was selectively produced in the mucous membrane and serum of mice following repeated intragastric instillation with *Enterobacter cloacae*, whereas non-mucosal and serum IgA were not found (54). B cells release IgA, and IgA⁺ B cells are induced exclusively in the presence of dendritic cells containing *Enterobacter cloacae* (55). Thus, while most symbiotic microorganisms are rapidly killed by macrophages, a few can enter dendritic cells and survive for a few days, when dendritic cells containing symbiotic microor-

ganisms can selectively induce large amounts of IgA to defend against commensal microorganisms penetrating the mucosa. Adults treated with prebiotics (oligosaccharides) indicated that: (i) Prebiotics have the potential to alter the makeup of gut commensal microorganisms; and (ii) The rise in fecal IgA is directly tied to gut commensal microbes (56). These findings demonstrate that the gut microbiota has a role in IgA modulation, implying novel therapeutic strategies for IgA-related illnesses.

Effects of Gut Microbiota on the Expression of Immune Antimicrobial Peptides

Almost all plants and animals contain antimicrobial peptides (AMPs). In mammals, AMPs are expressed by both epithelial cells in the steady state and immune cells during inflammatory responses (57, 58). Antimicrobial peptides are positively charged polypeptides that have the ability to kill microorganisms by interfering with the integrity of their cell membranes (59, 60). Apart from their antibacterial properties, antimicrobial peptides have pro/anti-inflammatory properties in the immune system (61, 62). It has been reported that antimicrobial peptide cathelicidins play a significant role in the development of autoimmune diseases (systemic lupus erythematosus, vasculitis, and psoriasis, among others) (63), which are all caused by excessive cathelicidin expression on neutrophils, and the onset of non-obese autoimmune diseases follows the same mechanism (64, 65). Via injecting the antimicrobial peptide cathelicidins into normal mice and non-obese diabetic mice, we discovered that the gut microbiota regulates the production of cathelicidins in mouse pancreatic endocrine cells by regulating the synthesis of short-chain fatty acids (66). It can maintain immunological homeostasis and exert positive immune regulation on pancreatic macrophages and common dendritic cells via the generation of regulatory T cells (67). Thus, the concentration of pancreatic antimicrobial peptide cathelicidins was found to be extremely low in female non-obese diabetic mice with faulty short-chain fatty acid synthesis, indicating that the mice will develop pancreatitis and autoimmune disorders (68). Cathelicidins, which are antibacterial peptides, exhibit direct chemotaxis toward a variety of innate immune cells (neutrophils, macrophages, common dendritic cells, etc.). When antimicrobial peptide cathelicidins fight an infection, they first employ innate immune cells and then rely on their viability to avoid immuno-pathological tissue damage (69).

Endocrine cells use short-chain unsaturated fatty acids and their associated receptors GPR41 and GPR43 to synthesize antimicrobial peptide cathelicidins. Beta cells express these receptors (70). By virtue of short-chain fatty acids generating an immunological milieu in the pancreas, the gut microbiota controls autoimmune disorders. Due to the fact that the gut microbiota can influence the connection between the colonic epithelium and the intestinal immune system, it plays a role in a variety of autoimmune illnesses, including type 1 diabetes (T1DM) (71). By decreasing the number of butyrate-producing bacteria in the gut microbiota of type 1 diabetic patients, the condition can be improved (72). The gut microbiota of male mice was transferred into the intestines of female mice with non-obese diabetes in an experiment, and it was discovered to have a protective effect against diabetes; at the same time, the proportion of butyr-

ate-producing bacteria in the intestines of female mice with non-obese diabetes increased. This finding implies that by supplementing with short-chain fatty acids, the gut microbiota may be able to modify non-obese diabetes mellitus (73). The gut microbiota has the ability to regulate the production of antimicrobial peptides via the short-chain fatty acid synthesis pathway, hence preserving immunological homeostasis and preventing the development of autoimmune disorders.

Impact of Gut Microbiota on IgE

IgA production is dependent on the gut bacteria, whereas IgE production is the inverse. Although germ-free mice secrete more IgE than the reference level, the amount of IgE falls with commensal bacterium colonization (74, 75). Within one week after weaning, germ-free mice developed 1,000-10,000 times the level of IgE compared to traditionally reared 64-day-old mice (76). It is worth mentioning that when only one or two species were colonized in the intestinal tract, even a large dose of a single strain (10^9 - 10^{10} CFU) administered via gavage was unable to suppress excessive IgE expression (77). However, when fed to germ-free mice, a more diversified intestinal flora, such as seven to forty distinct groups of intestinal flora, can restore normal IgE levels in mice (78). Additionally, high levels of germ-free murine IgE are dependent on CD4⁺ T cells, IL-4, and mucosal lymphoid tissue, but are unaffected by dietary antigens (79). The decrease in IgE levels induced by microorganisms is dependent on direct interaction between B cells and microorganisms and on the intracellular myd88 signaling pathway (80).

Although the explanation for the increased IgE levels in sterile mice is unknown, it is determined that the increased IgE levels encourage the occurrence of Th2-type inflammatory responses (81, 82). Under antibiotic stress or sterile culture conditions, reducing the amount of commensal bacteria colonizing mice enhanced the number of IgE antibody-dependent circulating basophils and the activation of Th2-type T cells. Increased IgE expression also increases basophil IL-3 expression, promoting the maturation of basophil precursors (83, 84), and the state of mast cells is also regulated by IgE levels (85), and increased IgE expression under sterile conditions results in an increase in the amount of IgE bound to the surface of mast cells, resulting in systemic allergic reactions (86). As a result, the gut microbiota not only affects the production of intestinal IgA, but also the expression of IgE.

Conclusions

The gut microbiota is critical for the development of gastrointestinal and immunological illnesses, as commensal microorganisms can send signals that encourage appropriate immune responses and can influence subsequent immune responses. However, the method by which commensal bacteria in the gut interact with the immune system remains unknown. It is possible that commensal microorganisms communicate with the immune system via the chemicals they create. Once these mechanisms are elucidated, the therapy of immune-associated disorders will focus on controlling these bacteria through the examination of the gut microbiota and the use of prebiotics and probiotics. Additionally, the gut microbiota of healthy persons can be used to treat certain disorders. Meanwhile, for symbiotic bacte-

ria, the host is merely a complicated habitat that varies between healthy and diseased states. The challenge is to determine whether sickness directly affects symbiotic microorganisms or whether disease directly affects the host environment, causing

the symbiotic bacteria to adapt to the new environment. We can only maintain a mutualistic relationship with the gut microbiota if we comprehend the relationship between the symbiotic microbial structure and the host. ■

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