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LITERATURE REVIEW

Evidence on the importance of gut microbiota for the immune system

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Abstract

Vital to the health of the host is maintaining a delicate balance in the immune system by eliminating harmful pathogens while preserving self-tolerance to prevent autoimmunity. By regulating immune homeostasis, the gut microbiota in the gastrointestinal tract provides vital health benefits to its host. It has been demonstrated conclusively that dysbiosis of these gut microbial communities can cause immune dysregulation and autoimmunity. We attempt to examine the relationship between the gut microbiota and the regulation of the innate and adaptive immune homeostasis, which can influence the development of certain disease. This literature review of recently published research and newly discovered scientific information is intended to increase awareness of the importance of maintaining a microbiota balance in the gut for immune health of the host.

Keywords: gut microbiota, innate immunity, adaptive immunity, immune system, disease

Introduction

The digestive system plays an important role in the human body's physiology and anatomy, to absorb nutrients and maintain immune homeostasis (to protect the body from potentially harmful microbes). It has a dual function that can maximize nutrient absorption while also controlling and organizing mucosal immune responses in the human digestive system.[1] When exposed to many of foreign antigens, the digestive system develops a unique and complex network of immunological and non-immunological mechanisms that act as a mucosal barrier to protect the host from pathogens while also hosting other residents microbes that perform their digestive system functions.[1,2]

The digestive system comprises of gut, organs that produce digestive secretions (liver, pancreas, and gall bladder), as well as the digestant, microflora and immune systems that are associated with it. To contribute to mucosal immune defense, the gut can be divided into three physically distinct components: the intestinal epithelial barriers, the lamina propria and gut-associated lymphoid tissue (GALT). Specialized immune cells in the digestive system promote tolerance for oral antigens (dendritic cells (DCs) and regulatory T cells (TR)). Additionally, secretory IgA on mucosal surfaces can contribute to establishing an anti-inflammatory

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environment by neutralizing immune-stimulatory antigens.[1,3,4] This process will reduce the likelihood of inflammatory responses to potentially harmful stimuli in the digestive system.

The development of the digestive system's microbiome began during the uterine phase and is constantly changing due to various factors such as prematurity, diet, hygiene and the use of medication.[5–7] Maturation of the intestinal immune system in line with the development of the gut microbiome is being observed. In order to activate their ability to ensure proper differentiation and specification, as well as the complete development of adaptive immunity, components of GALT must interact with their gut microbiome.[8,9] As a multifaceted and complex system, the immune system in the digestive system involves the interaction of multiple components, which maintain a state of non-responsiveness to non-pathogenic commensal bacteria, self-antigens and food antigens, while protecting the host against pathogenic organisms and maintaining the integrity of the intestinal mucosa. A disruption in gut homeostasis can lead to persistent or severe gastrointestinal infections, food allergies, celiac disease and inflammatory bowel disease (IBD), among other conditions.[10,11]

The complexity of this system makes it more interesting to discuss because the firm effect mechanism toward the effect of defined gut microbiota and specific immune cell function still need more clarify. In this review, we will discuss the role that the microbiota intestinal system plays in immunity and how it can be affected by both the innate and adaptive immune system pathways.

Methods

This article described the balance of gut microbiota and its correlation with immune system via innate and adaptive pathways that can impact to physical health. This literature review was built by looking for many published relevant articles from electronic databases (ex : Pubmed and Medline) in the last ten years. Variants of “gut microbiota” “innate immunity” “adaptive immunity” “immune system” “disease” were included in the research terms. Further papers were found in English, through manual search from the manual references cited in the corresponding reviews.

The balance of gut microbiota

The term "gut microbiota" refers to a community of microorganisms that are found throughout the entirety of the gastrointestinal tract and which are present in greater numbers than human body cells. Various studies indicate that gut microbiota is directly associated with both the health of the host and the regulation of host immunity, which can influence the immune response to certain diseases. This is because of the diversity of microorganisms, which makes them the most important environmental agent in the human body.[12–15]

Microorganism colonization of mucosal tissues throughout infancy is crucial for the maturity of the host immune system. These episodes in early life can have long-lasting consequences, such as promoting tolerance to environmental exposures or contributing to the development of disease later in life.[13] Due to the fact that bacteria may be isolated from the meconium of preterm infants, the host's exposure to microbiota begins in gestation and expands rapidly after delivery.

Microbiota composition is first defined by opportunistic colonization by the first types of bacteria to which a newborn is exposed. This, along with other environmental factors like food, can considerably influence the subsequent admission of microbial species into the various mucosal niches. Therefore, the mode of delivery and subsequent environmental exposures have a significant impact on the microbiota makeup of infants.[16] *Lactobacilli* are abundant in the microbiome of vaginally delivered newborns throughout their first few days of life.[17] In contrast, the microbiota of newborns whose mothers gave birth by cesarean section is depleted, and there is a delay in the colonization of the *Bacteroides* genus in these infants. On the other hand, these newborns are already colonized by facultative anaerobes, such as species of *Clostridium*.[18] It may be more difficult to establish a stable gut microbiota during an essential period of time for the development of the immune system if fewer early colonizing bacteria, particularly *Bifidobacteria*, are present.[19]

According to research published in 2016 by Odamaki et al.[20] the composition of the gut microbiota shifts with age. They discovered that the composition of the microbiome remained unchanged throughout adulthood until it reaches a point of equilibrium that, so long as it is not disturbed by external factors, can be expected to remain relatively constant throughout adulthood.[21] The phylum *Firmicutes*, which also includes *Lactobacilles* and *Clostridiales*, was found to be the most prevalent in the gut microbiota of adults, whereas the phylum *Actinobacteria*, which also includes *Bifidobacteriales*, was found to be more prevalent in samples from one year old children. After children were weaned, the relative abundance of *Actinobacteria* in their guts decreased, and by the age of three, the children's gut microbiota had developed into something more similar to an adult's gut microbiota.[21]

It has become clear that the balance of the gut microbiota in early life plays an important role in human health, and that its imbalance, also known as dysbiosis, is linked to the development of a variety of diseases. As the relationship between the gut microbiota and a variety of human health issues has become better understood, it has become clear that the gut microbiota plays an important role in human health.[22] Dysbiosis that begins in the infant stage of a person's life has a good chance of persisting into adulthood.[20]

It is of the utmost importance to take into consideration the mechanisms that contribute to the formation and maintenance of a dysbiotic state. ***Infection and inflammation****:* Dysbiosis can happen in inflammation state because it can reduces the ability of the microbiota to provide resistance to colonization by microorganisms that are invading the body. These changes happens by inflammation that was brought on a genetic lack of interleukin-10 (IL-10).[23] ***Diet and xenobiotics:*** Diet can changes composition microbiota that lives in the intestines, significantly impacted both in the short term and the long term. Other factors, such as familial transmission, pregnancy and physical injury, genetics play a role in determining the composition of the microbiota that live in the gut.[23,24] All these factors have significant contribution in maintaining health and stability immune system in gut.

Role of gut microbiota in immunity

The gut microbiota provides numerous benefits and functions to its host, such as digestion, the production of nutrients, detoxification, protection from pathogens and the regulation of the immune system, among others.[25] It is believed that the enormous and complex intestinal microbiota components play a critical role in the immune system, not only in the local intestinal immune system but also in the systemic immune response.[26] Later, these components elicit inhibitory regulatory mechanisms that are intended to maintain both mucosal and systemic immunity in balance. The presence of commensal microbes is a significant factor in the maturation of the immune system.[27]

The GALT protects us from the gut-dwelling microorganisms. The gastrointestinal system consists of the mesenteric lymph nodes, Peyer's patches, and isolated lymphoid follicles in the small intestine and colon, immune cells dispersed across the mucosal lamina propria, and intraepithelial lymphocytes. In contrast, bacteria promote robust immunity, healthy nutrition, systemic antigen tolerance, also known as mucosal tolerance, and other positive consequences. The existence of a complex microbiota is necessary for this immune response to function correctly.[2] The gut microbiota plays a critical role as a regulator in the development and function of both the innate and adaptive immune systems. It is important to understand how it works.[28] The innate immune responses signal the activation of the adaptive immune responses, and both work in tandem to eliminate the pathogens.[29]

Innate immunity

The innate immunity is a rapid and non-specific response to an infectious pathogen. Additionally, it is called the initial line of defense.[29] Physical barriers like the skin and mucous membranes, chemical barriers like enzymes and antimicrobial proteins, and innate immune cells like granulocytes, macrophages and natural killer cells

all contribute to the non-specific protection afforded by the innate immune system.[30]

Innate immune cells in GALTs identify pathogens non-specifically, begin an innate immune response, and deliver antigens to activate the adaptive immune system farther downstream. Moreover, GALTs are crucial for maintaining immunological tolerance to commensal bacteria. The dual function of GALTs is crucial for maintaining the equilibrium between the gut microbiota and the human immune system.[31] Stanisavljevic et al.[32] demonstrated that variable baseline levels of pro-inflammatory cytokines produced by GALTs from different mouse strains with distinct species of gut microbiota may contribute to the vulnerability to autoimmune disorders.

Recent investigations have demonstrated that memory is present not just in T cells, but also in monocytes/macrophages and natural killer (NK) cells.[33] Gut innate immunity is initiated by a single layer of intestinal epithelial cells (IECs) directly exposed to luminal contents and microbial metabolites.[28] Peyer's patches, which are responsible for the production of antimicrobial peptides, are activated by the gut commensal flora through the toll-like receptor (TLR) pathway. It is possible that inhibiting molecules related to the TLR pathway will make a person more susceptible to infection by enteric pathogens.[34]

In the gut, commensals produce short-chain fatty acids (SCFAs) such as butyrate, acetate and propionate. Commensals are microorganisms that help the body fight infection. When SCFAs are present in the body, they increase the number of myeloid precursors and provide protection against infection, which is necessary for immune homeostasis. This finding supports the notion that the microbiota can function as an epigenetic regulator of host physiology and as an energy source for the intestinal epithelium, both of which can influence immune responses.[31,32,35] The majority of the bacteria that produce butyrate, including *Bacteroidetes* and *Clostridia*, are anaerobes, and the low levels of oxygen found in the colon provide them with an ideal environment to thrive in.[33] SCFAs suppress inflammatory responses in human monocytes by activating pertussis toxin-sensitive (PTX-sensitive) G protein-coupled receptors (GPCRs), which results in the release of the anti-inflammatory cytokine IL-10 and the release of prostaglandin E2, both of which limit inflammatory responses.[36]

By increasing the expression of antimicrobial peptides, IL-22, IL-17 and IL-10 while simultaneously activating the inflammasome, the gut microbiota hinders the colonization and growth of invading pathogens.[37] Yao et al.[38] reported the immunological memory profile and protective actions of alveolar macrophages following infection with a respiratory virus.

Induction of immunological memory by commensal bacteria may be influenced by host genetic differences in microbiota makeup as well as pathogen exposure. While the process of intrinsic memory development should be viewed as an effective method for enhancing the host's defense, it must be carefully managed to prevent negative side effects while staying useful to the host.[39]

Adaptive immunity

Instead of being generalized to any pathogen, adaptive immunity is highly specific to a single pathogen and provides long-term protection against that pathogen. Adaptive immune responses, which are a form of defense, eliminate invading infections and any hazardous compounds they produce. Because these reactions are destructive in nature, it is crucial that they are solely specific to molecules that are foreign to the host and not to molecules that are native to the host. White blood cells known as lymphocytes, B cells and T cells are responsible for adaptive immune responses. Antibodies (immunoglobulins) are secreted by activated B cells to prevent pathogens from attaching to receptors on host cells. In response to microbes hiding inside host cells, T cells react by either killing the infected cells or assisting other cells in eliminating the microbes from the body.[29] Collaboration between commensal microbiota, intestinal adaptive immune cells, and secretory IgA facilitates tolerance for symbiotic bacteria and a mutualistic interaction between the host and the microbiota (sIgA). This ultimately leads in the preservation of intestinal homeostasis and the

capacity to mount an effective immune response against invading pathogens.[40]

Immunoglobulin (Ig) A-secreting plasma cells make up the majority of gut-associated B cells found in Peyer's patches. IgA, an immunoglobulin produced by the adaptive immune system, contributes to the diversification and balance of gut microbiota, which is necessary for immune homeostasis to be maintained.[41] Thus, the gut microbiota is a major driving force for mucosal IgA production.[42] Pathogens typically engage with antigen-presenting cells and trigger adaptive B cell and T cell responses, resulting in the generation of antigen-specific sIgAs, after entering the mucus layer.[43,44]

Adaptive T cells are the primary defenders of the host's homeostasis against immune-mediated inflammatory diseases in cellular immunity. The intestinal microbiome may promote the differentiation of T cells to initiate adaptive immune responses rapidly in response to signals from the intestinal lumen environment.[45]

The microbiota of the intestines plays a crucial role in the development of $CD4^+$ T cells both inside and outside the intestine. $CD4^+$ T cells are essential to the adaptive immune system. $CD4^+$ T cells can differentiate into four major subtypes upon stimulation: T helper 1 (Th1), Th2, Th17 and regulatory T cell (Treg). The regulation and equilibrium of T-cell subtypes are crucial in determining a person's health status. Th1 cells, for instance, are essential for the host's defense against intracellular microbial infection, whereas Th2 cells are essential for eliminating parasite infections. Th1 and Th17 responses have been associated with autoimmune diseases, whereas Th2 responses have been linked to allergic reactions.[42] *Bacteroides fragilis*, *Bifidobacterium longum* and *B. pseudolongum* can increase T cells and then triggers Th1 responses.[46,47] There is also a direct connection between *B. adolescentis*, a common commensal bacteria found in the human colon, and the production of homologous Th17s.[48]

Regulatory T cells (Tregs) are a crucial mediator of immune tolerance; their dysfunction can result in autoimmune diseases.[49] Tregs target the majority of immune cells to induce antigen-specific or non-specific immune tolerance via contact-dependent mechanisms, immunomodulatory cytokines (e.g., IL-10, TGF- and IL-35), or metabolic disruption of target cells.[50] *Clostridium* species induce both healthy and inflamed colonic Tregs. Other researchers have discovered that any of the five Bacteroides (*B. intestinalis, B. caccae, B. thetaiotaomicron, B. vulgatus, and B. massiliensis*) effectively induces colonic T regulatory cells (Tregs).[51,52] The development of dysbiosis and intestinal immunological abnormalities results in the development of chronic local and systemic inflammatory and autoimmune diseases.[40]

Evidence of gut microbiota influence on health and diseases

As previously stated, the intestinal microbiota plays an important role in the immune system. When the microbiota is complete and diverse, it can affect host homeostasis and make the host less susceptible to disease. The gut mucosal immune system functions normally, differentiates, functions and regulates itself as a result of proper bacterial colonization. Based on this mechanism, we may have a different perspective on microbiota and their impact on host health.[53]

Inflammatory bowel disease (IBD)

In susceptible hosts, an aberrant mucosal immune response to a commensal microbial antigen might generate an inflammatory bowel disease (IBD). It is determined by the genetically determined innate immunological responsiveness of intestinal tissue to components of the commensal microbiota, and following this process, T cells and B cells create IgG antibodies that can cause chronic inflammation in intestinal tissue and can be prevented by removing the commensal microbiota from our bodies.[53] In addition, numerous studies have demonstrated that specific gut microbiota drive the differentiation of Th17 cells that secreted IL-17 and IL-22 which have really strong impact in stimulating immune damage and autoimmune

disease by producing a potent pro-inflammatory factor.[54]

In contrast, intestinal bacteria can increase anti-inflammatory activity. *Clostridium spp, B. fragilis* and *F. prausnitzii* play a significant protective role in IBD.[55–57] Finally, an unbalanced level of several cytokines, dysbiosis from gut microbiota and impairment of the mucosal barrier can lead to mucosal inflammation and potential IBD progression.[58]

Diarrhea

Dysbiosis characterized by pathogen dominance is prevalent in diarrheal people and animals, and the interaction with gut microbiota is currently attracting a great deal of research in the field of diarrhea. Invading pathogenic bacteria inhibit the growth of normal bacteria, which results in a decrease in the total number of helpful bacteria in the digestive system.[59] Then, pathogen-produced toxic substances further cause abnormal gut function and immune responses, leading to the occurrence of diarrhea.[60] *Escherichia coli* (*E. coli*), *Shigella*, *Salmonella*, *Campylobacter*, *Clostridium difficile* (*C. difficile*) and *Aeromonas* are mainly considered to be the pathogens of diarrhea.[61]

According to the findings of a study conducted by Qin et al.[62] the abundance of *E. coli* and *Enterococcus* in children suffering from diarrhea was found to have a positive correlation with serum levels of IL-1, IL-6, IL-17 and TNF-⟨. On the other hand, the findings showed that the abundance of *Bifidobacterium* and lactic acid bacteria had a negative correlation with serum levels of IL-1, IL-6, IL-17, and TNF-⟨. Based on these findings, it was hypothesized that alterations in the composition of the gut flora could affect the release of inflammatory factors in vivo.[62]

Atopy and asthma

Atopy and asthma are complicated disorders that are influenced by the populations of microorganisms that populate the gut and respiratory systems. These communities are influenced by a range of environmental factors, including food, the administration of antimicrobials and early life exposures to local microorganisms.[63] According to the findings of a number of studies, early life is the most important period during which a microbiota dysbiosis in the gut may lead to the development of a number of respiratory diseases, because the gut microbiota has a significant influence on immune cell maturation and resistance to pathogens.[64] Colonization by *Clostridium difficile* at one month of age was associated with wheeze in the first six to seven years of life and asthma at six to seven years of age.[65]

Decrease in *Lachnospira* and an increase in *Clostridium* spp , these particular gut bacteria may prevent or promote the development of an asthmatic phenotype in pre-schoolers. In children at risk of asthma, *Lachnospira*, *Veillonella*, *Faecalibacterium* and *Rothia* levels were reduced.[66] Using methacholine challenge, Arnold et al.[67] demonstrate that *Helicobacter pylori* can also alleviate the symptoms of allergic airways disease by reducing the amount of air resistance in the stomach. *Lactobacillus* supplemetation can promote the maturation of the gut microbiota in infants at high risk of asthma. It may be a useful strategy to prevent the onset and exacerbation of asthma.[68]

Food allergy

Several bacteria, including *Lactobacilus*, *Bifidobacterium* and *Faecalibacterium*, have a protective effect on the host when it comes to mucosal inflammation.[69] When the flora is absent or limited to a single bacterial strain, an impaired tolerance response is observed, which prevents the development of autoimmunity (i.e., IBD) and food allergy. As a result of intestinal microbe colonization, the immune system appears to be stimulated to produce a non-allergic Th1 response, whereas IgE synthesis appears to be downregulated, which may reduce the risk of developing a food allergy.[70]

The presence of high levels of *Bacteroides fragilis* in the early stages of colonization was also associated with decreased lipopolysaccharide (LPS) responsiveness, indicating that *Bacteroides*

fragilis may have an impact on the systemic immune response.[71] Lack of *Bacteroides fragilis* and *Bifidobacteria* colonization in the gut, which is required from maternal bacteria (during the delivery process), is considered to have poor immune recognition of food, which can result in food allergy.[72] Guénolée et al.[73,74] discovered that *Lacticaseibacillus paracasei* strains could be used to induce and maintain oral tolerance in mice. This suggests that *L. paracasei* strains could be used as a probiotic to prevent infants from developing allergies, such as milk allergies.

Symbiotic microbes impact on the induction of Tregs, which suggests that there is a link between our environment and our susceptibility to allergic conditions. Mazmanian et al.[46] discovered that *Bacteroides fragilis* could maintain a healthy balance of Th1/Th2, thereby preventing the allergy process.

The influence of commensals on health and disease through the control of immune function has arisen as a topic of scientific and therapeutic importance. Preserving a delicate balance in the immune system by removing invading pathogens while maintaining self-tolerance to prevent autoimmunity is vital to the health of the body. By controlling immunological homeostasis, the gut microbiota that inhabits the gastrointestinal system confers significant health benefits on its host. Additionally, it has become clear in recent years that modifications of these gut microbial communities/dysbiosis can result in immunological dysregulation and illness (Fig.1).[26]

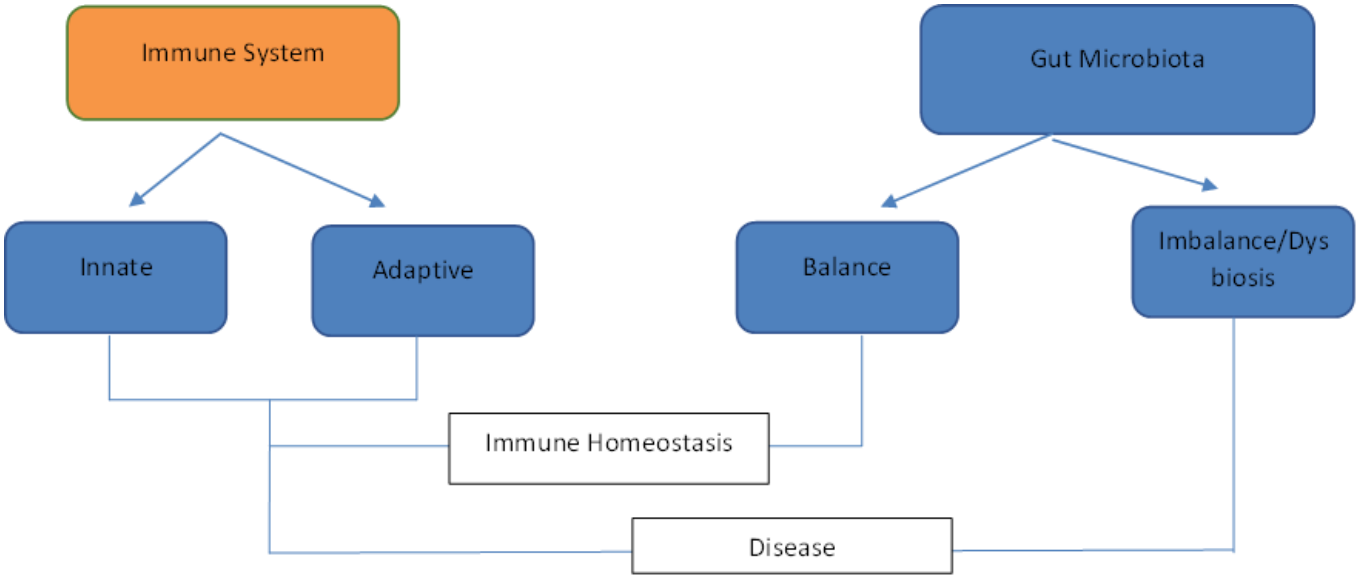

Figure 1. Relationship between immune system and gut microbiota.

Conclusions

Gut microbiota plays a very crucial part in the development of the immune system because they have strong relation each other by influencing the function. The immune system consists of two components: the innate immune system and the adaptive immune system, which can control microbes and various harmless and dangerous microbes. The digestive tract is an entry point for numerous pathogens and toxins present in the food we digest. Creating a balanced microbiome community in the gastrointestinal tract can boost immune defense. Dysbiosis can cause immunological reactions such as allergy, food allergy, inflammatory bowel disease and asthma. Physicians must be concerned about the balance

of gut microbes in the digestive system, which can induce robust immunity in their patients.

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