



Review Article



Role of Gut Microbiota in Immune System Regulation

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ABSTRACT

The human gut is a densely populated organ system that bears hundreds of microbial species, including bacteria, viruses, and various protozoans. The gut microbiome expresses enormous functional diversity based on microbial community collection. However, this has remained unexplored for a long time, but in the recent past various researches have revealed its immense significance in host metabolism and immunity. Gut microbiota metabolize undigested substances and release various metabolites in response to microbial metabolism that have a significant effect on the immune system. The balance and stability of the immune system within the body are achieved and maintained through the complex interaction between the gut microbiota and the host mucosal immune system. Upon loss of control by the immune system, dysbiosis occurs, the modulation of the microbial community, which leads to different disorders, including inflammatory bowel disease and colorectal cancer. Moreover, dysbiosis is also associated with various autoimmune diseases such as rheumatoid arthritis, diabetes mellitus, and multiple sclerosis. Despite its intricate mechanism in autoimmune diseases, various therapeutic strategies are utilized to treat chronic diseases, including prebiotics treatment, personalized probiotics therapy, fecal microbiome transplantation, and narrow-spectrum antibiotic treatment. This review discusses the interaction of gut microbiome with the immune system, how this association becomes dysregulated, its various outcomes in the form of autoimmune diseases, and therapeutic interventions to cope with it.

INTRODUCTION

The microbial community in the mammalian gut consists of a diverse range of microorganisms such as bacteria, viruses, fungi, and other microbes. The information obtained from analyzing 16S rRNA sequencing indicates that Firmicutes and Bacteroidetes account for around 92% of the human microbiome, while the total number of bacterial species in the gut microbiota is estimated to be between 1,000 and 1,500 [1]. However, an individual typically harbors around 160 bacterial species [2]. Environmental factors and genetic inheritance also influence the composition and functioning of the gut

microbiome. Mice with identical genotypes exhibit distinct microbiota configurations, influenced by diet, age, and inflammation [3]. The intestinal microbiome is influenced by both the host's genetic makeup and developmental processes, with synchronized interactions affecting intestinal balance and immune system function [4]. The gut's immune system has multiple components that foster symbiotic relationships. The host provides nourishment for the microbiome, while gut microbiota strengthens the intestinal immune system. It produces immunoglobulin A (IgA), develops gut structures, and promotes tolerance to



dietary antigens [5]. Additionally, it maintains beneficial bacteria and protects against harmful pathogens through secretory IgA (SIgA) on mucosal surfaces. IgA functions as a primary barrier, preventing microorganisms from entering the epithelium [6]. It supports the complex interplay between commensal organisms, the epithelium, and the immune system. The gut microbiome and the immune system are responsible for regulating the mucosal ecosystem, but the disruption may have adverse effects on the gastrointestinal tract. Microbial colonization is crucial in the maturation of the immune system, as shown by studies on germ-free (GF) mice. These studies have demonstrated that the absence of gut microbiota leads to a notable impairment of the immune system [7, 8]. Moreover, the imbalance of gut microbiota has been strongly associated with various disorders, including obesity, type 2 diabetes, hypertension, necrotizing enterocolitis (NEC), and inflammatory bowel diseases (IBD), among others [9]. Moreover, various studies depict the involvement of gut microbiome in different autoimmune diseases. For example a reduction in the ratio of gut *Firmicutes* to *Bacteroidetes* in patients with systemic lupus erythematosus (SLE) [10]. Similarly, *Porphyromonas gingivalis* seems to be a potential initiator of anticitrullinated protein antibodies (ACPAs) from rheumatoid factor (RA) and a notable increase in the concentration of *Lactobacillus* in stool, while a decrease in *Bacteroidetes* [11].

In this article, we have focused on the interaction between the gut microbiome and the immune system of humans. Additionally, we explore the association of gut dysbiosis with the different autoimmune diseases and significant fluctuations in the gut microbiome.

Mechanisms of Microbiota-Immune System Interaction

The relationship between gut microbiota and the immune system is a mutual and multifaceted process that implies the use of various pathways and mechanisms.

Intestinal Epithelial Cells (IECs) and Short-Chain Fatty Acids (SCFAs)

Intestinal epithelial cells (IECs) control the immune response by passive and active methods and modify the nearby surroundings by recognizing and absorbing short-chain fatty acids (SCFAs) [12]. The balance of the gut ecosystem is maintained by the predominance of *Firmicutes* and *Bifidobacteriaceae*, which are obligate anaerobic bacteria. On the other hand, an increase in *Enterobacteriaceae*, which are facultative anaerobic bacteria, is a common indicator of gut dysbiosis, and unhealthy gut microbial composition. [13]. SCFAs facilitate the intracellular acidity of pathogens, hence protecting against pathogen infection. An essential role of propionate (It is a SCFA derived from the fermentation of dietary fiber by the gut microbiota mainly identified as butyrate-

producing bacteria) is to restrict the growth of pathogens by promoting the acidification of the cytoplasm in *Shigella* and *Salmonella*, which modulates the intracellular pH equilibrium of the pathogens. [14]. The increase in concentration of SCFAs results in a decrease in pH that impedes the process of oxygen (O₂) and nitrate (NO₃) respiration, which in turn reduces the growth of facultative anaerobic bacteria such as *Enterobacteriaceae* [15].

Role of Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ)

During normal conditions of gut homeostasis, the IEC produces peroxisome proliferator-activated receptor gamma (PPAR-γ), which is activated by butyrate [16]. The butyrate produced by commensal bacteria is metabolized by IECs that promote the production of transforming growth factor β (TGF-β) and ultimately the accumulation of regulatory T cells (Treg cells) in the gut [17]. PPAR-γ facilitated the maintenance of a localized oxygen-deprived state by promoting the process of oxidative phosphorylation in colon cells [18] and the breakdown of SCFAs by the mitochondria through β-oxidation. SCFAs are produced by obligate anaerobic bacteria to make a suitable microenvironment for their growth, while the facultative anaerobic enteric pathogens experience inhibited growth [19]. Simultaneously, the activation of PPAR-γ reduces the levels of NOS2 in IEC, disrupting the production of both nitrate and inducible NO synthase, which are crucial energy sources for facultative anaerobic pathogens [20]. Furthermore, propionate confers resistance to the proliferation of harmful bacteria in a PPAR-γ independent manner, suggesting a parallel action of SCFAs [21].

Consequences of PPAR-γ Pathway Disruption

In contrast, blocking the PPAR-γ signaling pathway triggers changes in metabolism, disruption of the microbial balance in the gut, and depletion of SCFAs. This reprogramming stimulated the metabolic activity of colonocytes to shift towards anaerobic glycolysis, a phenomenon known as the Warburg effect [22]. As a result, the utilization of oxidative metabolism was restricted, leading to higher levels of lactate, nitrate, and oxygen in the lumen of the gut [23]. In addition, common virulence factors of *Salmonella* and *Shigella*, induce the recruitment of neutrophils across the epithelium, thus, decreasing SCFA levels [24]. It creates a detrimental feedback loop, promoting the proliferation of pathogens, and illustrating a cause-and-effect relationship between the metabolic activities of microbiota and the well-being of the gut epithelium [25].

The relationship between the gut microbiota and both the immune system and the development of autoimmunity. Many commensal bacterial-derived metabolites including SCFAs modulate the functionality of immune cells. Derangements in the composition of the gut microbiota

(e.g., higher levels of competitive gut pathogens) increase the permeability of the gut wall and thereafter, microbial antigens and microbial metabolites are translocated to system circulation. Such factors in combination with genetic and environmental factors, can underlie an abnormal immune reaction where there is activation of Th17 cells, B cell differentiation into plasma cells, and the production of autoantibodies. Some of the signaling species and pathways that are involved with this process encompass; IL-6, TGF- β , IL-10, PPAR- γ , AhR ligands, NOD, TLR ligands, and molecular mimicry (Figure 1)

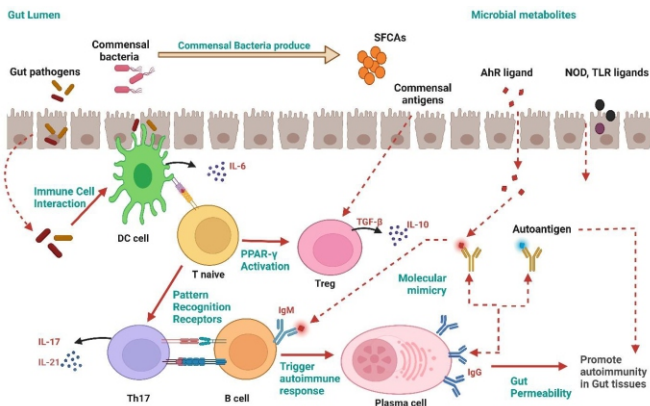


Figure 1: Relationship Between the Gut Microbiota and the Development of Autoimmunity

Pattern Recognition Receptors (PRRs) and Immune Response

Host immune systems employ various strategies to prevent the colonization of pathogens. Generally, the bacteria are recognized in the host by two pattern recognition receptor (PRR) systems: the toll-like receptors and nucleotide-binding oligomerization domain receptors (NODs) [26]. Various cells in the guts, like, IECs, macrophages, and dendritic cells express higher levels of PRR expression that can detect molecular patterns of pathogens and symbiotic microbes [27]. Once a microorganism has invaded the epithelium, the immune system initiates a specific immune response directed against the microorganism. When PAMPs are detected, pattern recognition receptors (PRRs) initiate multiple intracellular signaling pathways involving transcription factors, ligands, and kinases to evaluate the presence of infection in the host [28]. This signaling leads to modifications in gene expression, resulting in changes in the levels of various anti-microbial and pro-inflammatory cytokines, chemokines, and immunoreceptors [29]. The protective benefits seen were attributed to a reduction in the levels of pro-inflammatory cytokines, specifically IL-8, IL-12, and IL-23 [30]. This reduction was accompanied by an increase in the levels of anti-inflammatory cytokines, particularly IL-1s produced by Treg cells. Dendritic cells present the antigen to naive T-cells which provoke the generation of anti-inflammatory cytokines, leading to the

establishment of both systemic and local tolerance [31].

Gut Permeability and Immune System Interaction

The composition of gut microbial communities varies throughout the gastrointestinal tract and different mucus layers. The immunological activity in the duodenum is significantly lower than in the ileum and colon [32]. However, the presence of enteric microorganisms in the gut evokes an increase in permeability, allowing large molecules and antigens to be absorbed from the gut into the bloodstream [33]. The permeability of the gut is strongly associated with both the commensal microbiota and components of the mucosal immune system [34]. It is affected by various causes, such as modifications to mucus layers, injury to the epithelial cells, and abnormalities in the composition of gut bacteria [35]. The products of fermentation by gut microbes and the components of cells are crucial in the immunological responses of the host that help preserve the integrity of the epithelium [36]. Flagellin is the primary constituent of bacterial flagellum which is recognized by TLR-5. In response to the recognition, bacteria enhance the expression of TLR-5 agonist which is further recognized by the B cells and CD4+ T-cells [37]. The activation of naive B cells stimulates the differentiation into mature B lymphocytes that produce higher titers of IgA. Fully differentiated IgA specifically attached to microbial antigens and efficiently neutralizes the pathogens [38].

Pathogen Recognition and Response

Pathogenic bacteria inhibit the movement of phagocytes, which leads to the transmission of bacterial antigens to surrounding lymphoid tissues that trigger B-cell and T-cell activation [39]. Furthermore, pathogens stimulate dendritic cells and macrophages to generate pro-inflammatory cytokines. Consequently, the activation of pro-inflammatory immune responses occurs via the differentiation of naive T cells [40]. The activation of various Toll-like receptor (TLR) members is associated with the recognition of lipopolysaccharide (LPS) in gram-negative bacteria. Mammalian cells recognize LPS as a sign of bacterial invasion and use it to trigger innate immune responses [41]. The polysaccharide component of LPS serves as a protective strategy for bacteria, aiding in the prevention of complement assaults and allowing them to camouflage themselves among the carbohydrate residues of the host [42]. The TLR4/MD-2 complex after recognizing LPS, triggers various signal transduction pathways to activate the innate immune response in the host [43]. Nevertheless, the proliferation of probiotics that produce SFCAs had a considerable effect on the population of gram-negative bacteria, resulting in a subsequent reduction in LPS [44].

Dysbiosis and Immune Dysregulation

The gut microbiota of any individual is constantly changing

due to factors such as age, nutrition, medication, and geographical location. The majority of bacteria are introduced into the body by exposure to the environment [45]. However, certain bacteria are temporary and cannot permanently establish themselves in the intestinal environment. These bacteria are either unable to compete with other beneficial microbes or are unable to adapt to the conditions of the intestines [46].

Assessment of Gut Microbiota Health

The assessment of the health of the microbiota in an individual can be determined based on its diversity, stability, resilience, and resistance [47]. So, it assesses the biodiversity of the ecosystem, its susceptibility to changes in composition and function, and its ability to restore itself to its initial condition [48]. Consequently, the equilibrium of the microbial ecology might be disrupted due to a decrease in variety, proliferation of harmful microorganisms, or decline of beneficial microorganisms [49].

Characteristics and Causes of Dysbiosis

Gut dysbiosis is characterized by alterations in the composition and functional capacity of the gut bacteria, resulting in detrimental consequences on the overall health of the host [50]. Commensal bacteria suppress the growth of opportunistic infections by producing SCFAs, which modify the pH of the intestines [51]. For instance, *Bifidobacterium* decreased the pH in the intestines while fermenting lactose, therefore inhibiting the growth of harmful *Escherichia coli* [52]. Various causes can contribute to dysbiosis, such as the presence of invasive intestinal pathogens, the use of antibiotics, physical harm to the mucosa, dietary choices, and genetic factors in the host [53].

Effects of Dysbiosis

Dysbiosis has increased vulnerability to enteric infection, and disruption of the commensal microbiota composition caused inflammation when antibiotics were used [54]. Commensal bacteria not only limit the virulence of diseases by altering the environment, but they also directly inhibit the expression of virulence genes in pathogens by releasing various metabolites [55]. *Shigella flexneri* relies on oxygen to effectively release virulence factors, but the other bacteria that live in the gut, take up the remaining oxygen [56]. As a result, the levels of *Shigella* virulence factors in the gut are reduced. In cases of gut dysbiosis in humans and mice, there is typically a drop in the prevalence of obligatory anaerobes, while the presence of potentially harmful facultative anaerobes such as *Shigella*, *Salmonella*, *E. coli*, *Proteus*, and *Klebsiella* [57] tends to increase. Dysbiosis does not necessarily entail an escalation in the prevalence of pathogens, as the absence of crucial commensal bacteria alone might have detrimental effects [58].

Dysbiosis Without Pathogen Increase

Dysbiosis commonly arises when bacterial proliferation is reduced, in contrast to the growth of potentially harmful bacteria. Depleted commensals play significant roles, and restoring the absent microorganisms or their metabolites can potentially modify the characteristics linked to the disturbed gut [59]. The interaction between the immune system and gut microbiota is highly significant, as commensal bacteria strengthen the protective lining of the gut and stimulate the natural defense mechanisms of the body against harmful pathogens [60].

Interaction Between the Immune System and Gut Microbiota

The significance of diversity and abundance of gut microbiota in maintaining the health of the host has been confirmed, and alterations in diversity have been associated with several human disorders [61]. The extent to which the microbiota directly contributes to the development of all related disorders is yet uncertain.

Dysbiosis and Disease Correlation

Numerous studies have demonstrated that gut bacteria play a direct role in the development and progression of some diseases using an intricate network that connects metabolism and the immune systems of the host [62]. The correlation between mucosal inflammation and gut dysbiosis may be confined to dysbiosis only, or its associated disease, or simultaneous effect on both. The gut microbiota exhibited a significant correlation with the initiation and progression of inflammation in the mucosal layers of mice that were devoid of microorganisms [63].

Infections and Dysbiosis

Infections are a frequently reported factor that can lead to gut dysbiosis, as seen in both human and animal studies. Infectious diseases and their treatments have an impact on the human gut microbiota, leading to feedback loops that modify the nearby surroundings [64] and eventually, determine the influence of the infection on the host bacteria. Multiple investigations have confirmed the strong associations between infection and gut dysbiosis, establishing links with both gut bacteria and resident viruses [65]. For instance, patients with *Clostridium difficile* infection had substantial changes in their gut microbiota, which actively facilitated the advancement of the hepatitis B virus (HBV), the human immunodeficiency virus (HIV), and various other infectious disorders [66].

Gut-microbiota and Autoimmune Diseases

Autoimmune disorders are distinguished by the abnormal generation of autoantibodies. The immune system is influenced by both genetic and environmental variables, which result in the abnormal development of B cells that produce autoantibodies, T cells that react against the body's cells, and the excessive production of proinflammatory cytokines [67]. Various studies depict

that the increase in the prevalence of autoimmune diseases can be attributed to significant alterations in the gut microbiota [68], which are caused by several factors such as extensive use of antibiotics and an imbalanced diet [69].

A Complex Relationship between Gut Microbiota and Autoimmune Disorders

The gut microbiota has a significant role in starting and intensifying the progression of disease in individuals with autoimmune disorders. Possible processes encompass molecular mimicry, effects on the mucosal permeability of the gut, the microbiota-stimulated immunological response, and antigenic mimicry [70]. Therefore, changes and fluctuations in microbial communities are always associated with host health and their significant involvement in autoimmune disorders [71]. The gut microbiome can impact immunological sense in distinguishing between self and non-self, perhaps playing a role in the development of autoimmune disorders [72]. Individuals suffering from autoimmune disorders frequently exhibit indications of compromised intestinal barriers, leading to potential immune system exposure to beneficial gut flora [73]. Furthermore, a disruption in the body's ability to tolerate the presence of the gut microbiota results in abnormal and harmful immunological reactions, ultimately worsening the severity of the disease [74].

Table 1: Gut Microbiota associated with various Autoimmune Diseases

Autoimmune Disease	Gut Microbiota Involved	References
Rheumatoid Arthritis	<i>Prevotella copri</i> , <i>Lactobacillus spp.</i>	[75]
Multiple Sclerosis	<i>Akkermansia muciniphila</i> , <i>Acinetobacter calcoaceticus</i>	[76]
Inflammatory Bowel Disease (IBD)	<i>Bacteroides fragilis</i> , <i>Faecalibacterium prausnitzii</i>	[77]
Type 1 Diabetes	<i>Bifidobacterium spp.</i> , <i>Firmicutes</i>	[78]
Systemic Lupus Erythematosus	<i>Lactobacillus reuteri</i> , <i>Ruminococcus gnavus</i>	[79]

Molecular Mechanisms

Genetic and Environmental Influences

Autoimmune diseases are influenced by both genetic and environmental variables, such as complicated geographical location, genetic elements, immunologic derangement, patient exposure, and viral infections [80].

Aryl Hydrocarbon Receptor (AhR)

Aryl hydrocarbon receptor (AhR) may have a role in autoimmune diseases by attaching various cellular, dietary, and microbe-derived substances and converting external and internal signals into cellular responses [81]. Likewise, lower levels of innate IL-22 in AhR-deficient animal models led to an increase in commensal segmented filamentous bacteria (SFB) (an immune activator) and the growth of Th17 cells [82]. The inherent manifestation of AhR has a defensive function in T-cell-driven experimental

colitis by inhibiting the development of harmful Th17 cells [83]. Various AhR ligands, such as 2,3,7,8-tetrachloro dibenzo-p-dioxin (TCDD) cause changes [84] in the microbial communities of *Bacteroides fragilis* (an immune suppressor) and SFB in mice when compared to levels observed in a typical gut microbiota [85]. Furthermore, the host response triggered by TCDD was greatly influenced by the presence of SFB in the gut microbiome, indicating a potential therapeutic relationship between AhR ligands and important commensal microorganisms [86].

Dysbiosis and Immune Dysregulation

The presence of an imbalanced gut microbiota has been recognized as a potential cause of autoimmune disorders [87]. These diseases are believed to be influenced by various variables in humans, although the specific role of the gut microbiota is still not fully understood. The association between an imbalance in gut microbiota and autoimmune diseases can be ascribed to various mechanisms that can impact the operation and reaction of the human immune system [88]. With the stimulation of antigen-presenting cells and host immune responses, it is possible to induce antigen presentation and the generation of cytokines, which can then impact the differentiation and function of T cells [89]. In addition, this influence disturbs the balance between T regulatory cells (Tregs) and T helper 17 (Th17) cells in homeostasis [90]. The gut microbiota contributes to autoimmunity by modifying autoantigens at the molecular level through posttranslational modification and exhibiting cross-reactivity with autoantigens [91]. The movement of living gut bacteria through a malfunctioning gut barrier at the cellular level leads to direct contact with immunological and tissue cells, which in turn triggers systemic autoimmunity [92].

Molecular Mimicry and Antigen Presentation

Antigenic mimicry can cause foreign antigens to resemble self-antigens, leading to the activation of autoreactive T and B lymphocytes generated by infections [93]. This activation has the potential to facilitate the progression of autoimmunity [94]. However, the permeability of the intestinal mucosa is altered as a result of the modification of tight junction protein expression [95].

Therapeutic Approaches and Implications

Based on several researches, the administration of prebiotics, probiotics, antimicrobial compounds, and fecal microbiota transplantation (FMT) can effectively control the composition of the gut microbiota [96]. Nevertheless, there is a correlation between improper antibiotic usage and the alteration of gut microbiota composition. This correlation also extends to non-antibiotic medications that are intended for human use [97]. Accumulating empirical and medical evidence has indicated that the persistent inflammatory reaction caused by an imbalance in gut microbiota might significantly contribute to the onset of

autoimmune disorders [98]. In general, germ-free animal models are better suited for investigating the impact of the host microbiome on the progression and formation of various illnesses [99]. Overall, the microbiota can either initiate autoimmune in individuals with genetic susceptibility or protect against autoimmunity in others [100].

Future Recommendations

Extensive research has been performed on gut microbiome but still, it contains multiple research gaps that demand further research on gut microbiota. Currently, detailed molecular mechanisms by which gut microbiota influence the immune system remain incompletely understood. Moreover, Identification of specific microbial species that play a crucial role in modulating immune responses. Similarly, the role of microbiota-derived metabolites (such as short-chain fatty acids) in immune modulation and autoimmunity. Importantly, the mechanism and identification of short-chain fatty acids in immune system modulation is more important. The understanding of variations in microbial composition and its contribution to the development or prevention of autoimmune diseases. The microbial influence on the differentiation and function of various immune cell types should be investigated. The impact of early life microbiota colonization on the development of the immune system and its long-term effects on autoimmunity. The mechanism of host genetics interacts with gut microbiota to influence immune responses and autoimmune disease susceptibility. The role of environmental factors (such as diet, antibiotics, and infections) in shaping gut microbiota and their subsequent effects on immune function and autoimmunity. These are the various research gaps that should be studied in later research.

CONCLUSIONS

The gut microbiome also plays a critical role in shaping and regulating immune system development and function. Healthy gut bacteria release SCFAs that help in immune regulation of the colon, and altered bacterial ecology of the gastrointestinal tract termed dysbiosis can potentially result in autoimmune disorders. Thus, therapeutic modification of the composition of gut microbiota has been considered as a perspective direction for the treatment of autoimmune diseases, so further study of the relationships between the gut microbiome, immune system, genetic factors, and the environment is needed.

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Methodology: TA, AFA, SK, FN, IH, RA, HKK

Formal analysis: MS

Writing-review and editing: SS, FF

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

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