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THE ROLE OF GUT MICROBIOTA IN IMMUNOMODULATION AND AUTOIMMUNE DISEASES: A COMPREHENSIVE REVIEW

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ABSTRACT

The investigation into autoimmune conditions, particularly the intricate interplay between the gut microbiome and the immune response, has emerged as a critical domain of scholarly scrutiny. This review article provides a comprehensive analysis of prevailing views on the role of the gut microbiota in immune regulation and the development of autoimmune diseases. We begin this study by explaining the basic interactions of gut microorganisms and their relationship with the immune system. We then discuss dysbacteriosis and its implications for immune dysfunction, thus understanding the initiation of autoimmune reactions.

Next, we delve into a section examining and reviewing clinical research findings identifying associations between differences in gut microbial compositions and various autoimmune diseases such as inflammatory bowel disease, rheumatoid arthritis, type 1 diabetes.

In conclusion, this review addresses the methodological challenges that currently impede progress in this field and suggests approaches and plans for future research that may advance our understanding of the critical role played by the gut microbiota in the prevention, diagnosis, and treatment of autoimmune diseases. The article emphasizes the need to combine strategies to improve patient prognosis in cases of autoimmune diseases.

INTRODUCTION

The gastrointestinal (GI) tract has one of the largest interfaces (250–400 m2) in the indivigual body between the host, environmental factors, and antigens. During the course of an individual's lifespan, the gastrointestinal (GI) tract undertakes the remarkable task of processing a staggering amount of food, totaling over 60 tons, while simultaneously contending with a multitude of environmental microbes that pose a significant risk to gut integrity. Referred to as the "gut microbiota," this intricate assemblage comprises a diverse range of microorganisms, including bacteria, archaea, and eukarya, which have mutually evolved with the host over millennia, establishing a highly intricate and mutually beneficial symbiotic association. An estimated 10 times as many bacterial cells as human cells and over 100 times the quantity of genetic material (microbiome) as the human genome are found in the GI tract, where there are over 1014 microorganisms. A recently updated study suggests that the ratio of human to bacterial cells may really be closer to 1:1. The large number of bacterial cells in the host's body has led to the term "superorganism" being used to describe both the microbes and the host itself. The microbiota provides the host with various benefits through a range of physiological functions, such as enhancing intestinal integrity or the growth of the intestinal epithelium, energy harvesting, defense against infections, and host immunity modulation. Disruption of these mechanisms is possible, though, as dysbiosis—a state characterized by altered microbial composition—increases the probability. The importance of microbes in a wide range of intestinal and extra-intestinal disorders has become more evident with the advent of more complicated techniques to detect and describe complex ecosystems. The complex network of innate and adaptive components that make up the immune system is remarkably capable of reacting to a variety of stimuli. In the presence of microbial and environmental interactions, this intricate cellular network collaboratively operates as a powerful controller of host balance, facilitating the maintenance and restoration of tissue functionality. The establishment of a sophisticated microbiota and the maturation of various branches of the immune system, notably those associated with adaptive immunity, provide compelling evidence that a substantial component of this system has developed to maintain mutually beneficial relationships with these incredibly varied microbial communities. All facets of the immune system are subsequently supported and adjusted by the microbiota [1-3].

In the context of this comprehensive review, we want to provide a deep dive into the present comprehension of the relationships between the immune system and gut microbiota, as well as the

consequences for autoimmune disorders. We will discuss potential therapeutic treatments and clarify the processes by which the gut microbiota influences immunomodulation through an examination of preclinical and clinical research findings. The difficulties in studying the gut microbiota will also be covered in this review, along with suggestions for future lines of inquiry to further this area of study.

Microbiota and Immune System During Development: Insights and Mechanisms

The relationship that exists throughout the formative stage between the immune system and the microbiota In physiological conditions, it is widely accepted that the embryonic gastrointestinal tract remains devoid of microbial presence, with the birth canal serving as the initial encounter between commensal microorganisms and the immune system. As time progresses, these initial interactions are believed to shape both the mucosal and systemic immune systems. It is postulated that certain reactions to commensal microbes during this early period may be influenced by constituents present in breast milk; however, the precise mechanisms underlying the adaptation of neonatal tissues to the profound stress of microbial colonization remain incompletely elucidated. In actuality, colostrum and breast milk contain live bacteria, metabolites, IgA, immune cells, and cytokines. Together, these factors influence the microbiota of breastfed infants and the host's reaction to these microorganisms. Maternal IgA, for example, binds nutritional and microbial antigens to limit immune activation and microbial attachment. Moreover, metabolites, such as oligosaccharides, in the mother's milk facilitate the growth of certain microbiota members, such as Bifidobacterium. Pregnancy and breastfeeding increase the number of bacteria that translocate from the mouse gut, and it has been suggested that bacterium-loaded dendritic cells in breast milk affect the type of immunological response that newborns have to commensal antigens, which in turn contributes to immune imprinting [3-7].

The recognition and identification of MAMPs, or conserved microbial associated molecular patterns, represent a crucial mechanism by which the host and microbiota establish communication. During neonatal development, the innate immune system incorporates these signals in a unique manner to support optimal microbial colonization. Notably, neonatal innate cells exhibit distinct responses to microbial ligands compared to adult cells, characterized by the differential expression of Toll Like Receptors (TLR) ligands. They exhibit increased synthesis of IL-10 and other regulating cytokines, while displaying a remarkable reduction in the synthesis of mediators of inflammation such as oxygen radicals. This distinctive behavior is partially attributed to the influence of the microbiota itself. Particularly, during early encounters with

microbial ligands such as lipopolysaccharide (LPS), The outer membrane of gram-negative bacteria contains an endotoxin, gut epithelial cells undergo conditioning that renders them less susceptible to Toll Like Receptor (TLR) activation in subsequent interactions. Despite lingering uncertainties regarding the integration of microbial signals by the innate immune system, emerging evidence suggests that the regulation of commensal-dependent intestinal homeostasis may rely on the expression of specific enzymes by epithelial cells, thereby inducing epigenetic modifications [8, 9].

Role of the microbiota in chronic diseases

According to the concept of the ideal microbiota-host interaction, immunity may grow without jeopardizing the host's ability to remain resistant to harmless antigens if stimulatory and regulatory signals were balanced. But in westernized countries, antibiotic overuse, dietary changes, and the elimination of chronic parasitic infections—like whipworm, hookworm, or roundworm infections— might have chosen a microbiome lacking in the resilience required to create a balanced immune response. For example, as late as 1940, up to 70% of children in certain rural parts of the United States had helminthic worm infection. Additionally, the use of antibiotics and dietary modifications have led to the long-term and occasionally severe loss of potentially important human microbiota components. Significant alterations in the microbiota and, therefore, the immune system are thought to be a factor in the sharp rise in autoimmune and chronic inflammatory diseases observed in affluent nations. In fact, a common theme throughout inflammatory disorders appears to be the substantial changes in the resident microbiota from a "healthy" to a "pathogenic" state. Each inflammatory disease is linked to distinct genetic and biological pathways. A compelling theory suggests that the partly penetrant character of genetic variants linked to several complex illnesses stems from the microbiota's requirement for alterations before sickness manifests. This idea has the concerning side effect of suggesting that the random acquisition of particular commensal microbes may contribute to a person's vulnerability to certain illnesses. It's interesting to see that comparable "opportunists" are linked to several illness states. Thus, the cause of autoimmune and inflammatory diseases may represent and be significantly influenced by the latest appearance of a specific group of inflammatory clades of bacteria. Consequently, certain bacteria may be particularly skilled at living in and contributing to inflammation. We'll talk about a variety of illnesses and how the microbiome is related to them below [2, 8, 10].

The microbiota's role in autoimmune diseases like IBD

Gastrointestinal (GI) tract, housing the biggest microbial the population of every pathogen sites in the individual body, also serves as a distinctive milieu for a specialized array of immunoregulatory mechanisms. These processes function to stop the immune system from being unnecessarily activated against harmless antigens, such as those that the microbiota presents. The term "inflammatory bowel disease" (IBD) encompasses a spectrum of chronic inflammatory disorders that arise from dysfunctions within these interwoven regulatory pathways. The intricate connection between mucosal immune dysfunction and inflammatory bowel disease (IBD) is exemplified by the identification of common genetic factors involved in preserving epithelial barrier integrity and regulating immune responses. This underscores the complexity of understanding this relationship [2, 11-13]. Several research investigations have demonstrated the detrimental impact of smoking on human health, as well as its role as a risk factor for the onset of several pathological states and diseases including autoimmune disorders [14].

The development of inflammatory bowel disease (IBD) has been consistently linked to major disruptions in the makeup of the gut microbiota, underscoring the critical role that the microbiota plays in the pathophysiology of disease. Remarkably, a number of investigations have offered strong proof that Crohn's disease (CD) and ulcerative colitis (UC) are related to long-lasting changes in the microbial consortiums, marked by a move toward a dysbiotic condition and a decrease in the intricacy of the commensal microbiota. For instance, both CD and UC exhibit an overgrowth of the phylum Proteobacteria, particularly within the Enterobacteriaceae family, mirroring patterns observed during acute mucosal infections. Notably, commensals that blur the boundary between commensal and pathogen and are inherently inflammatory have been linked to Crohn's disease. For instance, Yersinia, Clostridium difficile, and adherent-invasive E. coli are significantly more prevalent in Crohn's disease patients than in healthy persons, and they have been demonstrated in some animal models to be important contributors to the illness [15, 16]. Known commensals like Bacteroides or Helicobacter hepaticus are sufficient to produce colitis. The susceptibility of mice lacking IL-10 or IL-10 in combination with TGF-β to the illness is noteworthy. These mice can activate both innate and adaptive immune responses upon exposure to harmless food antigens and commensal organisms, thus suggesting a theoretical mechanism for their vulnerability, these commensal bacteria have heightened inflammatory potential and cause illness. People with Crohn's disease does, in fact, share increased blood antibody responses to microbiome-derived antigens. It is simple to see why certain commensal organisms

can "bloom" during inflammation given their close relationship to obligatory pathogens; these organisms have survival modules that enable them to withstand the extreme conditions of immune activation. In fact, commensal E. coli may have a significant growth advantage by employing the immune response's produced inflammatory nitric oxides as a source of energy [17, 18]. Commensal E. coli is benign under homeostatic settings by leveraging food induced bile acids to take over the gut, other organisms like Bilophila Wadsworth can cause illness in mice strains that are prone to colitis, offering an insight into how diet can cause IBD due to its significant influence on the microbiota. The innate immune system's lack of T-bet causes dendritic cells to produce more tumor necrosis factor alpha (TNF-α), which when combined with Treg deficiency results in a chronic inflammatory state that alters the microflora's makeup and ultimately causes colorectal cancer. It's interesting to note that colitis is also transferred when the microbiota from TRUC mice is given to recipients who are wild-type [19, 20]. Certain commensal organisms, such Helicobacter typhlonius, Klebsiella pneumoniae, and Proteus mirabilis, are more frequently detected in TRUC mice and have the ability to infect wild-type mice. Further proof that colitis might become "contagious," at least in lab settings, was demonstrated in numerous animal models where aberrant reactions to commensals were brought on by innate immune deficits in IL-22 or inflammasome components. Colonic cells devoid of the NLRP6 inflammasome component show decreased levels of IL-18 and a changed microbiota composition with more Bacteroidetes (especially the Prevotellaceae family) and TM7. These mice develop intestinal hyperplasia spontaneously following microbial change, making them more vulnerable to chemically induced colitis and colon cancer. [8, 21-23]. It is worth mentioning that TRUC mice exhibit less severe colitis. However, the colitic phenotype can be transferred from TRUC mice to adult or neonatal wild-type mice without innate immune deficits through the microbiota. Understanding how viral and dysbiotic microbiota impact human illnesses is still an ongoing area of research, but it is of utmost importance in order to gain insights into the recent rise in the prevalence of IBD.

Role of the microbiota in cancer

The finding that a present of single type of bacterium, Helicobacter pylori, was the cause of stomach ulcers and subsequent stomach cancer may have been the first clue that the commensal microbiota might cause cancer. The host's reaction to Helicobacter pylori colonization determines the occurrence of chronic inflammation and carcinogenesis. This phenomenon extends to other host-microbe interactions and the development of malignancies at barrier surfaces like the colon. However, H. pylori is linked to resistance to different forms of cancer, emphasizing the functional contextuality of commensal even further. The etiology

of intestinal cancer is closely associated with GI tract inflammation, and commensal-driven immune activation plays a significant role in this relationship. Notably, there is a correlation between the onset of colon cancer and IBD, specifically Crohn's disease. The microbiota has also been connected to liver cancer through the production of certain bile acids that harm the DNA in the liver. Numerous investigations have endeavored to establish a connection between the disease in mice models of colorectal cancer and signaling through innate immune receptors in the GI tract; nevertheless, the outcomes have been inconsistent, possibly because of the confounding influence of the microbiota. Microbiota dysbiosis appears to have a significant role in deciding whether the immune system helps in the development of cancer or acts as a preventative measure. For instance, dysbiosis, which is closely linked to immunological dysfunction, is linked to colorectal cancer susceptibility in TRUC and NLRP6 defective mice, who lack a crucial component of the inflammasome. Furthermore, the ability of the commensal microbiota to transmit disease susceptibility to healthy mice serves as a clear demonstration of the role the microbiota plays in colon cancer [24-26].

Prevotella is more prevalent in patient microbiomes in humans with colorectal cancer, which is also mildly disturbed. Furthermore, certain bacterial strains have been demonstrated to aggravate colorectal cancer in mouse models.Microbiota dysbiosis appears to have a significant role in deciding whether the immune system helps in the development of cancer or acts as a preventative measure. For instance, dysbiosis, which is closely linked to immunological dysfunction, is linked to colorectal cancer susceptibility in TRUC and NLRP6 defective mice, who lack a crucial component of the inflammasome. Furthermore, the ability of the commensal microbiota to transmit disease susceptibility to healthy mice serves as a clear demonstration of the role the microbiota plays in colon cancer. Prevotella is more prevalent in the microbiome of humans with colorectal cancer, which is also mildly disturbed. Furthermore, certain bacterial strains have been demonstrated to aggravate colorectal cancer in mouse models. For instance, E. Coli that produces the genotoxic island of polyketide synthase can stimulate carcinogenesis in specific models of colon cancer, and individuals with colon cancer often have E. Coli that expresses the same gene module. Fusobacteria are a phylum of bacteria that are frequently detected living in tumor tissue and play a crucial role in stimulating the migration of myeloid cells that promote tumor growth. Tumorigenesis is thought to be largely driven by immune cells infiltrating gut cancers due to commensal forces. Research has demonstrated that colonic cancers have a weakened mucous layer, making them more vulnerable to Th17 cell infiltration and bacterial translocation. Associated to this, persistent colonization with the enterotoxigenic Bacteroides fragilis bacterium, which induces Th17, leads to increased carcinogenesis in the animal model of multiple intestinal

neoplasia. Consequently, colon cancer may arise from an overreactive immune response against a dysbiotic commensal microbiota, much such IBD and stomach cancer. It should be remembered, nevertheless, that inflammation brought on by commensals has "double-edged sword" effects on the host. As was previously mentioned, in the context of immunotherapy and chemotherapy, the microbiota plays a crucial role in the host's ability to regulate the tumor. As a result, the precise composition of the microbiota as well as the health of a host immune system play a critical and highly contextual role in the formation and control of tumors [27-29].

Gut Microbiota and Autoimmunity

It is not unexpected that some microbiome components have been connected to autoimmune diseases, considering the gut microbiota's significant impact on both the innate and adaptive immune systems. The part that gut bacteria play in GI-related autoimmune illnesses has received a lot of attention. As previously mentioned, it is noteworthy that the gut microbiota affects numerous systemic immunological components and plays a role that extends beyond the gut immune system. In light of this, current research has also uncovered the role that gut bacteria plays in extraintestinal disorders. This article will address the involvement of intestinal microbiota in autoimmune diseases that affect organs other than the gut. We specifically concentrate on research that demonstrates how modifications to a single microbial species and/or worldwide commensal populations can shift the balance between a protective and a pathogenic immune response, hence influencing the course of autoimmune disorders. GI-associated autoimmune diseases and gut microbiota [10, 30].

Inflammatory bowel disease (IBD):

IBD is an autoimmune disease that mostly affects the gastrointestinal system. It can manifest as ulcerative colitis or Crohn's disease. Numerous strong lines of evidence suggest that bacteria are essential to the pathophysiology of inflammatory bowel disease. For instance, antibiotic therapy is frequently beneficial for both IBD patients and animal models of the disease. Furthermore, there are significant differences in the phyla of gut microbiota between individuals with IBD and healthy adults. Crucially, after GF rederivation, many IBD animal models either exhibit a milder form of the disease (like the IL-22/2 IBD model) or are protected against it (like the IL-102/2 or T-cell receptor a/β2/2 IBD models). This suggests that the normal gut microbiota plays a role in the inflammatory state of IBD. Identification of the dysbiosis of certain microbiota in IBD patients has advanced recently. IBD patients have been shown to have an excess of proteobacteria

and a decrease in Firmicutes and Bacteroides species. Fascinatingly, comparable alterations in the microbial communities were discovered in a mouse model of severe colitis, where transgenic CD8+ T lymphocytes that attacked the intestinal epithelium were adopted and caused inflammation.69 It is challenging to identify host predisposing variables that produce dysbiosis, despite strong data showing dysbiosis in IBD patients and animals [31, 32].

Rheumatoid arthritis (RA). Rheumatoid arthritis (RA) is an inflammatory illness that affects about 1% of people worldwide and results in persistent joint inflammation. Given that other autoimmune illnesses, including type I diabetes, have concordance rates of approximately 50%, the low concordance rate of 15% for RA in monozygotic twins implies that environmental variables are likely to be important in the etiopathogenesis of RA.78,79 The bacteria we come into contact with every day are a prime contender as environmental causes of RA. Until recently, the majority of attention has been focused on the relationship between infectious microbes and disease. However, a dysbiosis of the gut microbial communities has been observed in patients with early-stage RA (6 months duration) when compared to patients with fibromyalgia, as determined by the 16S rRNA composition of fecal samples. Furthermore, since certain antibiotics (such as minocycline and sulfasalazine) are probably altering gut microbiota, their bactericidal activity may be connected to the therapeutic benefit of these drugs for a subset of RA patients. Early GF research utilizing several RA models revealed that the microbiota had a variable impact on the severity of the disease, ranging from augmentation to inhibition [33-38].

Type 1 diabetes (T1D): T1D is an autoimmune illness caused by T lymphocytes destroying the pancreatic β-cells that produce insulin. Intestinal Tregs were shown to be significantly lower in T1D patients, indicating a potential link between T1D and the gut flora. While many of the autoimmune models previously discussed exhibit a milder disease manifestation in the GF environment, T1D clearly defies this "rule," particularly in the form of the prototypical spontaneous NOD mouse model. When compared to their SPF counterparts, the diabetes incidence of NOD mice in the GF facility is frequently much greater. This fact aligns with the conclusion that T1D is more common in nations with strict hygiene regulations. Disease incidence under non-GF circumstances varies by facility, although it is often higher in the NOD females than males [12, 39, 40].

Experimental autoimmune encephalomyelitis (EAE): is a widely utilized murine model to study the pathogenesis of multiple sclerosis (MS), a chronic inflammatory disease characterized by demyelination of the central nervous system (CNS) due to an autoimmune response. Even though EAE is widely recognized as a murine model of multiple sclerosis (MS), the pathogenic mechanism of experimental autoimmune

encephalomyelitis (EAE) may differ significantly from that of multiple sclerosis (MS) in humans. This distinction arises from the fact that EAE is not a spontaneous model and necessitates the utilization of the bacterial adjuvant CFA to induce the disease manifestations. Despite these criticisms, the EAE model continues to yield useful data, and numerous studies have suggested a role for microbiota in EAE. Modification of the gut flora by antibiotics can considerably reduce the severity of the disease. The illness phenotype of GF mice induced with EAE was diminished, which is consistent with their decreased production of pro-inflammatory cytokines such IL-17. Ultimately, GF mice that were monocolonized with SFB showed elevated CNS Th17 cell counts and restored EAE development and progression, indicating a pathogenic role for SFB in EAE. On the other hand, certain commensals may be advantageous for the development of EAE. The introduction of human commensal Bacteroides fragilis expressing polysaccharide A (PSA) has shown efficacy in treating illness. Treatment with B. fragilis resulted in increased Treg cells and CD5+ B cells, which correlated with the observed protection [41, 42].

Microbiota-independent autoimmune disease: There are several exceptions to the general rule that autoimmune illnesses are mostly caused by the combination of environmental and hereditary factors. Sometimes the development of a disease is solely due to hereditary factors. Therefore, it's crucial to remember that, in certain cases, The presence or lack of commensal bacteria has little effect on the severity of autoimmune disorders, as demonstrated by autoimmune regulator (Aire) deficient mice. The Aire2/2 mouse is an animal model of human autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). Mutations in the Aire protein, a transcriptional regulator essential for the thymus's induction of T cell tolerance, result in the polyendocrine autoimmune illness known as APECED [43, 44].

Future Directions in Gut Microbiota, Challenges and Considerations

Table 1. Future Directions in Gut Microbiota and Challenges

Future Directions	Challenges and Considerations
1. Identify specific microbial species associated with autoimmune diseases and study their role in disease development.	- Need for large-scale, well-designed studies to establish causal relationships between specific microbial species and autoimmune diseases.
2. Investigate the mechanisms by which gut microbiota influence immune system function and autoimmune disease progression.	- Complexity of the gut microbiota-immune system interaction requires sophisticated

	computational models that accurately capture the dynamic nature of the system.
3. Explore the potential of modulating gut microbiota composition through probiotics, prebiotics, or fecal microbiota transplantation as a therapeutic approach for autoimmune diseases.	- Standardization of interventions and optimal dosing strategies for consistent therapeutic outcomes.
4. Examine the impact of diet and lifestyle factors on gut microbiota composition and its relevance to autoimmune diseases.	- Challenges in accurately capturing and quantifying dietary and lifestyle factors due to individual variations and self-reporting biases.
5. Investigate the crosstalk between gut microbiota and other organ systems to understand the systemic effects of microbial dysbiosis on autoimmune diseases.	- Integration of multi-omics data from different organ systems requires standardized analytical pipelines and improved data sharing practices.
6. Study the role of gut microbiota in the efficacy and response to immunomodulatory therapies for autoimmune diseases.	- Challenges in patient recruitment, variability in treatment response, and long-term monitoring of microbiota dynamics during therapy.
7. Develop personalized approaches for manipulating gut microbiota to prevent or treat autoimmune diseases based on individual microbial profiles.	- Need for robust validation studies to ensure the accuracy, reliability, and clinical utility of AI-driven precision medicine approaches.

CONCLUSION

In summary, the field of gut microbiota research in autoimmune diseases holds great promise for advancing our understanding and developing personalized therapeutic strategies. Despite the complex challenges involved, researchers are well-positioned to tackle knowledge gaps and drive the field forward. Future prospects include utilizing multi-omics methodologies, conducting longitudinal studies, exploring microbial metabolites, developing precision microbiota engineering, conducting clinical trials, establishing microbiota-centered diagnostics, addressing ethical and regulatory concerns, and promoting translational research. These avenues offer exciting opportunities to unravel the intricate interplay between gut microbiota and immune dysregulation.

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