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REVIEW

Gut Microbiota and Autoimmune Diseases: Mechanisms, Treatment, Challenges, and Future Recommendations

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Abstract

Purpose of Review This review provides an overview of the role of dysbiosis (imbalanced gut microbiota) in the maintenance of host homeostasis and immune function and summarizes recent evidence connecting gut microbiota dysbiosis to the development of autoimmune diseases (ADs) (such as rheumatoid arthritis, type 1 diabetes, systemic lupus erythematosus, multiple sclerosis, spondyloarthritis, and irritable bowel syndrome). The potential mechanisms that underlie the host-microbiota interaction are also discussed to evaluate the manipulation of the gut microbiota as a potential therapeutic approach to managing ADs. Additionally, this review addresses current challenges in gut microbiota-host research and provides future recommendations.

Recent Findings Recent findings suggested that the pathogenesis of ADs appears to be multifaceted involving both genetic and environmental factors. Dysbiosis or imbalanced gut microbiota has been increasingly identified as one of the main environmental factors that can modulate immune responses and contribute to the development of ADs.

Summary New research has highlighted the significance of gut microbial dysbiosis in the etiology of numerous diseases. Understanding the relationship between the gut microbiota and the host, however, goes beyond taxonomic concerns, demanding multidisciplinary efforts to design new therapeutic approaches that take individual variances into account.

Keywords Autoimmune diseases · Gut microbiota · Dysbiosis · Immune system

Introduction

Autoimmune diseases are a group of disorders in which the immune system targets and attacks healthy tissues and cells. These diseases show a wide range of clinical manifestations, impacting various organs in the body [1]. Prominent examples of ADs include inflammatory autoimmune diseases like rheumatoid arthritis (RA) and spondyloarthritis (SpA), primarily affecting the musculoskeletal system, leading to joint inflammation [2]. Additionally, systemic lupus erythematosus (SLE) is known for its systemic nature, affecting multiple organs, including the skin, joints, kidneys, and nervous system [3]. Furthermore, type 1 diabetes (T1D) which targets the insulin-producing beta cells in the pancreas and results in insulin deficiency and associated consequences is another example of ADs [4].

Neuroinflammatory autoimmune diseases such as multiple sclerosis (MS) represent another class of ADs that affect the central nervous system, leading to demyelination, neural damage, and a range of neurological symptoms [5]. Moreover, gastrointestinal autoimmune disorders like irritable bowel syndrome (IBS) which affects 15% of the global population can significantly impact the functionality of the gastrointestinal tract and the overall quality of life of individuals by causing abdominal pain, bloating, diarrhea, and constipation among others [6].

Recent studies have highlighted that certain microbial taxon and their metabolites are linked to the development of ADs [7]. This comprehensive review explores the intricate relationship between gut microbiota and ADs, shedding light on the pathways through which the immune system and gut microbiota dysbiosis are associated. This review also investigates the therapeutic methods that have shown promise in mitigating the impact of ADs by modulating the gut microbiota composition. Additionally, the manuscript discusses the existing challenges faced in microbiota studies and presents strategies to address these challenges.

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Gut Microbiota

The human gut harbors a complex community of microorganisms known as the gut microbiota, which plays a significant role in maintaining the host's physiology [8]. The study of the gut microbiota has gained considerable attention in recent years, particularly with the development of new terms such as the gut-brain, gut-skin, gut-mouth, gut-immunity axes, and other yet-to-be-discovered. The gut microbiota contributes to the development of the immune system through different mechanisms, including the maintenance of the intestinal barrier and the maturation and regulation of immune cells through the production of short-chain fatty acids (SCFAs). SCFA-producing bacteria have the ability to regulate immune cell differentiation and the development of regulatory T cells (Tregs), which are critical for maintaining immune homeostasis and controlling immune responses [9].

The initial evidence of the role of gut microbiota dysbiosis in the pathogenesis of ADs developed from germ-free models that lacked gut microbe composition and did not develop ADs [10]. Follow-up studies on transferring fecal microbiota from AD individuals to healthy mice, which triggered the development of autoimmune responses, and antibiotic treatments, which prevented the growth of beneficial bacteria, underlined the significance of gut microbiota in the overall health [11, 12].

Dysbiosis can lead to the loss of immune tolerance, over-activation of T cells, and the production of several pro-inflammatory cytokines. These can activate autoimmune responses and contribute to the development of various diseases, including ADs [13]. The prevalence of ADs has been increasing worldwide in recent decades, with over 80 ADs currently recognized, including RA, T1D, SLE, MS, and SpA [14].

Recent findings have shown an association between specific microbial taxa and their metabolites with the development of ADs. For instance, in patients with RA, an overgrowth of *Prevotella* spp. (such as *P. copri*) and a reduction in the abundance of *Bacteroides*, *Bifidobacterium*, and butyrate-producing bacteria was associated with the production of pro-inflammatory molecules and activation of autoreactive immune cells [7]. Also, high abundance of *Ruminococcus gnavus*, a microorganism that degrades mucin, has been detected in stool of individuals affected by RA, SpA, and SLE [15, 16]. Moreover, its presence in the ileum has been linked to RA susceptibility associated with specific HLA-DRB1 alleles [17].

Similarly, patients with inflammatory bowel disease (IBD) exhibit a reduced abundance of anti-inflammatory bacteria, such as *Faecalibacterium prausnitzii*, and an overgrowth of pro-inflammatory bacteria, such as *Escherichia coli* [18]. Decreased abundance of *Lachnospiraceae* and *Faecalibacterium* (involved in the production of anti-inflammatory molecules) and increased abundance of pro-inflammatory bacteria such as *Akkermansia* spp. have also been implicated in the pathogenesis of multiple sclerosis (MS) [19]. Induction of pro-inflammatory responses by *Akkermansia muciniphila* and *Acinetobacter calcoaceticus* isolated from MS patients in monocolonized mice and stimulation of anti-inflammatory IL-10-expressing human $CD4^+CD25^+$ T cells and $IL\text{-}10^+FoxP3^+$ Tregs by *Parabacteroides distasonis* have also shown the important role of gut microbiota in modulating immune responses [20].

The abundance of specific microbial taxa may also reflect disease severity and could potentially be used as biomarkers to assess the progression and activity of these ADs. For instance, an increased abundance of *Lactobacillus salivarius* in RA or SLE has been closely associated with higher clinical disease activity scores [21, 22].

Gut microbiota can also regulate other organs remotely by its signals and metabolites. An example of this is the remote control of gut microbial metabolites on the permeability of blood–brain barrier and the development of neuroinflammation in patients with MS [23]. However, relying only on the taxonomy of bacterial communities is insufficient to understand the complex role of gut microbiota dysbiosis in ADs. Recent findings have highlighted the importance of studying microbial metabolites and their interactions with humans using multi-omics methods. Multi-omics approaches offer detailed insight into the gut microbiota-host crosstalk and its impact on ADs (Table 2). For instance, metabolomic profiling has revealed distinct microbial patterns in RA and MS compared to healthy controls [24]. Combining multi-omics data can also pave the way for designing targeted therapeutic interventions aimed at modulating the gut microbiota and improving the health of patients with ADs.

The Complex Interplay

Our current understanding of gut microbiota-associated diseases indicates a complex network that is not fully understood. While evidence has suggested a correlation between dysbiosis and the development of ADs, it is essential to note that this association does not necessarily establish a "cause and effect" relationship, particularly as many of these studies have been conducted on animal models, and the applicability of these models to humans remains unclear [14].

A summary of the most common pathways through which gut microbiota can contribute to the development of ADs is discussed as follows:

Activation of Immune Responses

The dysregulation of immune pathways is the primary mechanism through which gut microbiota dysbiosis can lead to the development and progression of ADs [25]. The gut-associated lymphoid tissue (GALT), comprising different immune cells such as dendritic cells (DCs), macrophages, and innate lymphocytes, serves as the first line of defense. Dysbiosis can trigger abnormal activation of different immune pathways, resulting in the upregulation of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, IL-17, IL-12, IFN-γ, etc.) and the reduction of anti-inflammatory cytokines (IL-10, IL-4, IL-13, TGF-β, IL-1ra, etc.) [26].

One common pathway in the development of some ADs is the dysregulated function of Th17 cells and the production of IL-17. This pathway contributes to joint inflammation in RA, glandular inflammation and autoantibody production in Sjögren's syndrome, and neuroinflammation in MS [27].

In T1D, activation of TNF-α, IL-1β, and IL-6 cytokines can lead to beta-cell destruction and disease progression. Furthermore, autoreactive T cells can target beta-cells in T1D and damage the intestinal epithelial cells in celiac disease [28].

Activation of toll-like receptors (TLRs) on DCs and macrophages, leading to the release of IFN-α, IFN-β, IL-6, and IL-23 cytokines, have also a significant role in the development and progression of SLE [29, 30]. In vitro and ex vivo findings have shown that dysbiosis in SLE patients can promote lymphocyte activation and Th17 differentiation, while *Bifidobacterium bifidum* supplementation can balance the Treg/Th17/Th1 ratio and prevent over-activation of $CD4^+$ lymphocyte [31]. Also, decreased bacterial diversity with a fivefold greater representation of *R. gnavus* and serum antibodies against *Ruminococcus* antigens in SLE patients suggest the contribution of gut microbiota dysbiosis in the pathogenesis of lupus nephritis [32]. Similarly, decreased gut microbial diversity and a high abundance of *Collinsella* (correlated with pro-inflammatory cytokine IL-17A) were associated with RA duration and autoantibody levels, which suggests the potential application of these variations for predicting RA disease status [33]. Also, in RA patients with positive tests for anti-citrullinated protein antibody (ACPA), a decreased microbial diversity and enrichment of *Blautia*, *Akkermansia*, and *Clostridiales* were noted when compared to ACPA-negative individuals [34].

The potential role of gut microbiota on the immune system can also be seen in healthy animal models that received fecal microbiota transplantation (FMT) from lupus-prone mice which led to abnormal activation of plasmacytoid DCs and to the production of pro-inflammatory cytokines [35].

Gut Barrier Function and Permeability

Dysbiosis can also increase gut permeability by affecting the protein complex in tight junctions (occludins and claudins) between the epithelial cells in the gut [36]. To assess the gut permeability, lactulose/mannitol or lactulose/rhamnose tests are mostly used, which measure the urinary excretion of these molecules. A low lactulose/mannitol or lactulose/rhamnose ratio in healthy individuals shows a well-functioning gut barrier with minimal lactulose passage. While an increased ratio observed in patients with MS, RA, T1D, or celiac disease suggests increased gut permeability and impaired intestinal barrier function [36–38]. Increased intestinal permeability, known as leaky gut syndrome, allows the entry of microbial products into the bloodstream, disturbs immune homeostasis, and triggers systemic inflammation [39]. For instance, bacterial lipopolysaccharides (LPS) and flagellin can activate toll-like receptors (TLRs), inducing a pro-inflammatory environment characterized by the production of interleukins (IL-1β, IL-6), tumor necrosis factor-alpha (TNF-α), and an imbalanced Th17/Treg ratio [40–42]. This pro-inflammatory environment in the gut can lead to development of different ADs.

It is worth noting that some gut microbial communities involved in ADs may have originated from the oral cavity. For instance, *Porphyromonas gingivalis*, a significant periodontal pathogen, is known to express peptidylarginine deiminase and to produce citrullinated epitopes, which are recognized by ACPA (anti-citrullinated protein antibodies) in patients with RA. However, the exact mechanism is still unidentified, and further research in this area is being conducted [43].

Molecular Mimicry

Sharing similar structural components between gut microbiota and self-antigens, known as molecular mimicry, can lead to the activation of unnecessary immune responses and cross-reactivity. For instance, some peptides originated from bacterial communities such as *Bacteroides fragilis*, *P. copri*, *Candida albicans*, and *Streptococcus sanguis* can mimic collagen and synovial/ribosomal peptides, and induce cross-reactive immune responses and lead to the development of ADs [44].

A high degree of resemblance between citrullinated fibrinogen peptides commonly found in synovial tissue and bacterial antigens in RA patients, and demyelination (loss of myelin sheath-protecting nerves) caused by molecular mimicry between myelin and certain microbial

communities, have also suggested a significant role of autoimmune responses triggered by microbial communities in the pathogenesis of ADs [18, 45].

Recent studies have shown a growing collection of microbial peptides that exhibit molecular mimicry with host self-antigens, leading to autoimmune responses. For instance, specific peptides originated from gut microbial species such as *A. muciniphila* and *R. gnavus* have been found to mimic pancreatic beta-cell antigens and link these bacteria to the development of T1D [46]. Similarly, certain strains of *Klebsiella pneumoniae* can mimic HLA-B27, having shared structural features with these strains, which can lead to autoimmunity, inflammation, and tissue damage in ankylosing spondylitis [47].

Although dysbiosis can influence host immune responses, host susceptibility determined by HLA-DR genotypes (human leukocyte antigen-DR) seems to be one of the primary factors in the AD development. For instance, the association of HLA-DR2 and HLA-DR3 with SLE [48, 49], HLA-DRB1*04 with RA [50, 51], and HLA-DR3 and HLA-DR4 genotypes with T1D [52] show the significant role of genetic-gut microbiota interaction in AD development.

Epitope Spreading

The impact of gut microbiota on host immunity extends beyond molecular mimicry. Specific microbial taxa can convert host self-proteins using their enzymes and generate neoepitopes that are modified version of host antigens. These neoepitopes can be recognized by the immune system and activate autoimmune responses (epitope spreading) [51, 53]. For instance, some bacterial enzymes can convert arginine residues to citrulline and produce citrullinated self-antigens which are associated with RA [54]. A high abundance of *P. copri* have been associated with increased protein citrullination, induction of pro-inflammatory cytokines, and led to tissue damage and the release of self-antigens. This dysregulation may potentially activate epitope spreading and contribute to the expansion of autoimmune responses in ADs [55] (Fig. 1 and Table 1).

Gut Microbiota-Targeted Therapies

The importance of the gut microbiota's function in host physiology and its role in regulating immune responses have created new opportunities for adapted and targeted therapeutic approaches. Several strategies have been proposed for the treatment of ADs by modulating the composition of the gut microbiota. These include probiotics, prebiotics, postbiotics, diet adjustments, fecal microbiota transplantation, and engineered bacteria, which are discussed as follows:

Probiotics

As per the definition provided by the Food and Agriculture Organization and the World Health Organization (FAO/WHO), probiotics are live microorganisms that, when administered in sufficient quantities, confer a health benefit to the host [110]. These beneficial probiotic strains can play a vital role in restructuring the gut microbiota composition, regulating the immune system, and improving disease outcomes. Several studies have shown promising results of using probiotics in the management of ADs.

According to a randomized double-blind clinical trial, *Lactobacillus casei 01* supplementation in women reduced inflammation (decreased IL-10, IL-12, TNF-α, and hs-CRP levels), improved disease activity (tender and swollen joint counts), and a positive treatment effect based on EULAR criteria (European League Against Rheumatism criteria) [111]. Furthermore, patients with RA demonstrated notable improvements after 8 weeks of probiotic supplementation (*L. casei*, *Acidophilus*, and *Bifidobacterium*), with reduced Disease Activity Score, enhanced B cell function, and decreased high-sensitivity C-reactive protein concentrations, suggesting potential benefits of probiotics in managing clinical and metabolic status of RA [112]. However, a meta-analysis of nine studies with 361 patients indicated that although probiotics significantly lowered the pro-inflammatory cytokine IL-6 compared to the placebo group in RA patients, there was no significant difference in disease activity score [113].

Moreover, evidence from animal studies demonstrated that oral administration of *L. casei* to Lewis rats suppressed RA progression by reducing pro-inflammatory molecules and promoting immunoregulatory IL-10 levels in $CD4^+$ T cells [31]. *L. casei* intervention in adjuvant-induced arthritis (AIA) rats also inhibited joint swelling, reduced arthritis scores, and prevented bone destruction, suggesting that probiotics like *L. casei* could be a promising strategy for treating RA, especially in the early stages of the disease [114].

In the context of SLE, an in vitro culture study on microbiota isolated from SLE patients' stool demonstrated that SLE-associated microbiota promoted lymphocyte activation and Th17 differentiation from naive $CD4^+$ lymphocytes, while probiotics with Treg-inducer strains showed potential in rebalancing Treg/Th17/Th1 ratio [115]. Additionally, in murine experimental autoimmune encephalomyelitis (EAE), a model for MS, probiotic *Lactobacillus reuteri DSM 17938* reduced TH1/TH17 cells and other associated cytokines, restored gut microbiota diversity, and altered the abundance of EAE-associated bacterial taxa [116]. Furthermore, the gut commensal bacterium *Prevotella histicola* suppressed EAE in mice by modulating systemic immune responses, including reducing pro-inflammatory Th1 and Th17 cells, while increasing $CD4^+FoxP3^+$ Treg cells, tolerogenic DCs, and suppressive macrophages [117].

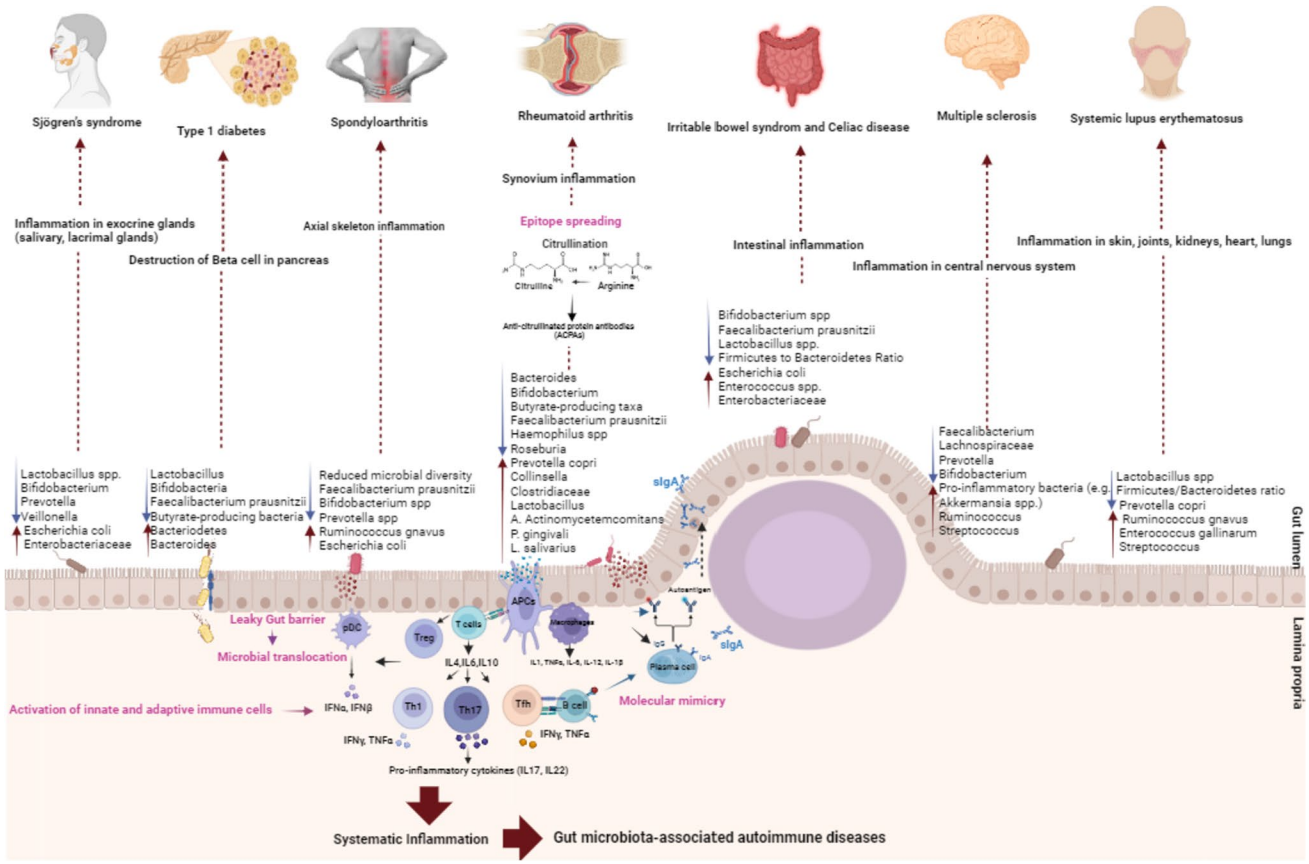

Fig. 1 Potential mechanisms by which disturbed gut microbiota contributes to development of ADs. In patients with ADs, a leaky gut barrier can lead to the translocation of microbes and microbial products from the gut lumen into gut tissues and even into the circulation. The imbalanced gut microbiota can promote the activation of both innate and adaptive immunity, and the activation of pro-inflammatory cytokines, resulting in systemic immune dysregulation. Innate immune cells, like plasmacytoid DCs, become activated and secrete inflammatory cytokines, including type I interferons (IFNs). Moreover, microbial antigens can be presented to $CD4^+$ T cells by DCs and macrophages, leading to the differentiation of inflammatory T cell subtypes such as T helper (Th)1, Th17, and T follicular helper (Tfh) cells. B cells can also be activated directly by microbial antigens or with Tfh cells, differentiating into plasma cells that produce protective secretory IgA (sIgA) and pathogenic autoantibodies. Microbial antigens can also trigger autoimmunity by mimicking self-antigens and lead to the development of ADs

Probiotics have also shown promising results in the management of T1D. Early probiotic administration in children at high genetic risk of T1D, particularly in those with the DR3/4 genotype, suggested a beneficial impact in reducing the risk of islet autoimmunity [118].

Despite all the beneficial effects of probiotic administration, it is important to note that the strain-specific effects of probiotics require further research to evaluate the most beneficial and effective strains for each autoimmune condition. Additionally, more research is needed to assess the long-term effects and therapeutic effectiveness of probiotics in human trials.

Prebiotics

Non-digestible dietary fibers that selectively stimulate the growth and activity of beneficial microbes in the gut are known as prebiotics. Prebiotics provides a suitable growth environment for microbial communities which positively influence the gut microbiota structure [119]. Recent studies have shown the potential of prebiotics in modulating immune responses and reducing disease severity.

Studies focusing on RA have shown that prebiotics promoted the growth of beneficial bacteria and reduced the abundance of pro-inflammatory bacteria and disease severity. For instance, the administration of *Bacillus coagulans* and prebiotic inulin (either alone or in combination) significantly reduced pro-inflammatory cytokines, serum amyloid A (SAA), and fibronectin (Fn); inhibited RA progression; and improved its clinical parameters [120]. Furthermore, the combination of prebiotics, a specific diet (known as synbiotics), and beneficial probiotic strains enhance positive effects through synergistic interactions. For instance, *L. casei 01* combined with prebiotic oligofructose-enriched

Table 1 Commonly identified microorganisms and mechanisms in development of ADs

Disease	Increased	Decreased	Metabolites/dysbiosis mechanism	Ref
Rheumatoid arthritis	*P. copri* *P. gingivalis* *A. actinomycetemcomitans* *Collinsella* *Lactobacillus* *Bacteroidaceae* *Lachnospiraceae* *Bacteroidetes* *Clostridiaceae* *L. salivarius*	Butyrate-producing bacteria Firmicutes *Bacteroides* *Bifidobacterium* *F. prausnitzii* *Haemophilus* spp. *Roseburia*	• Short-chain fatty acids • Peptidoglycan • Lipopolysaccharide • Imbalance immune responses, particularly Th17 cell activation • TLR2 and TLR4 signaling triggered by intestinal bacterial substances (some oral bacteria) • TNF-α, IL-6 pathways, pro-inflammatory cytokines • Immune dysregulation/Tfh + autoantibodies • Chronic inflammation and joint damage	[51, 53, 53, 55–65]
Systemic lupus erythematosus (SLE)	*Lactobacillus* *L. reuteri* *E. gallinarum* *R. gnavus* *Bacteroides* *Streptococcus* *Lachnospiraceae* *A. muciniphila* *Enterococcus* spp. *Enterobacteriaceae* *Bacteroidaceae*	Firmicutes *Bacteroidetes* *Proteobacteria* *Lactobacillus* spp. Firmicutes/Bacteroidetes ratio *Bifidobacterium* *F. prausnitzii* *Faecalibacterium*	• Short-chain fatty acids • Lipopolysaccharide • Flagellin • Peptidoglycan • Polysaccharide • Aromatic amino acids • Triggers immune responses via TLRs and NOD-like receptors • Immune dysregulation/AhR (tryptophan derivatives) • Molecular mimicry/autoantibodies	[48, 62, 66–72]
Type 1 diabetes	*Bacteriodetes* *Bacteroides* *Bacteroidaceae*	Butyrate-producing bacteria *F. prausnitzii* *Roseburia* spp. *B. dorei* *R. gnavus* *Akkermansia* (mucin-degrading bacteria) *Lactobacillus* *Bifidobacteria* Firmicutes *Lachnospiraceae*	• Short-chain fatty acids (butyrate) • Lipopolysaccharide • Impairs gut barrier function • Loss of immune tolerance • β cell destruction	[73–79]
Multiple sclerosis	Pro-inflammatory bacteria *A. muciniphila Methanobrevibacter Ruminococcus* spp. *Streptococcus* spp.	Anti-inflammatory bacteria *F. prausnitzii* *Methanobrevibacter smithii* *Lachnospiraceae* *Prevotella* *Bifidobacterium* *Bacteroides* Firmicutes/Bacteroidetes ratio	• Short-chain fatty acids • Tryptophan metabolites • Alters blood–brain barrier permeability • Molecular mimicry • Induces neuroinflammation • T cell responses (activation of Th1, Th17, and TLR2 (TNF-α, IFN-γ, IL-17) • Suppression of Treg and low expression of IL-10	[80–90]
Spondyloarthritis	*R. gnavus* *E. coli* *Lachnospiraceae* *A. muciniphila*	*Lactobacillus* spp. *Bifidobacterium* spp. *Bacteroides* *F. prausnitzii* *Prevotella* spp.	• Short-chain fatty acids • Polysaccharide A • Indole derivatives • Bile acid metabolism • Alters gut barrier function • Modulates the host immune response • Inflammation	[91–95]

Table 1 (continued)

Disease	Increased	Decreased	Metabolites/dysbiosis mechanism	Ref
Sjögren's syndrome	*Streptococcus* *Rothia mucilaginosa* *Bacteroidetes* *E. coli* Enterobacteriaceae	*Proteobacteria* *Lactobacillus* spp. *Bifidobacterium* *Prevotella* *Veillonella* *F. prausnitzii*	• Triggers autoimmunity via molecular mimicry • Inflammation • Altering salivary gland function	[96–103]
Irritable bowel syndrome and celiac disease	IBD:*Bacteroides* Enterobacteriaceae *E. coli* *Enterococcus* spp.	Firmicutes *F. prausnitzii* Firmicutes to Bacteroidetes ratio *Bifidobacterium* spp. *Lactobacillus* spp. *Lachnospiraceae*	• Short-chain fatty acids • Activation of Th1, Th2, Th17 (TNF-α, IFN-γ, IL-17) • Suppression of Treg cells • Low expression of IL-10	[104–109]

inulin promoted anti-inflammatory responses, reduced colonic damage, increased *lactobacilli* counts in feces, and improved myeloperoxidase activity in rat colitis models [121]. By providing a favorable environment for probiotic activity, synbiotic can optimize the symbiotic relationship between probiotic strains and the gut microbiota, which ultimately leads to improved health outcomes [122].

Postbiotics

Postbiotics are bioactive compounds produced by the metabolic activity of probiotic strains. These include bacterial lysates and enzymes, cell wall fragments, SCFAs, antimicrobial peptides, exopolysaccharides, and cell-free supernatants [123]. Postbiotics have emerged as potential alternatives to live microorganisms, as they offer a safer and more stable option for therapeutic use [124]. Studies have shown the immunomodulatory effects of postbiotics in several autoimmune diseases. For instance, *Propionibacterium freudenreichii MJ2*, a bacterium with postbiotic and probiotic properties, could inhibit osteoclast differentiation and improve RA in collagen-induced arthritis mice. It also reduced bone erosion, joint damage, and inflammation, offering potential therapeutic benefits for RA [125]. Similarly, *L. casei DG* (LC-DG) and its postbiotic (PB) could reduce the inflammatory mucosal response in ex-vivo cultures of mucosa from postinfectious irritable bowel syndrome (PI-IBS) patients. The results showed that LC-DG and PB reduced pro-inflammatory cytokines and TLR-4 expression, while increasing IL-10 levels after stimulation. This indicates the protective role of LC-DG and its PB in regulating the inflammatory response in PI-IBS [126]. Emerging research on postbiotics presents a promising therapeutic strategy for managing ADs. Their stable and well-defined properties, along with their immunomodulatory and anti-inflammatory effects, make them suitable candidates for clinical applications.

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) involves transferring healthy fecal material to a recipient's gastrointestinal tract to restore a balanced gut microbiota composition. Although FMT has gained significant attention for its high efficiency in the treatment of *Clostridium difficile* infections [127], the impact of FMT on the management of ADs still is under investigation.

In a recent study, it was found that the FMT from SLE mice could trigger autoimmune responses in germ-free C57BL/6J mice. This was demonstrated by inflammatory responses, production of anti-dsDNA antibodies, and an increased susceptibility to the effects of genes associated with SLE [128]. In a similar study, FMT from SLE patients to germ-free mice (GF C57/B6J) resulted in the development of lupus-like features and pro-inflammatory responses, characterized by elevated levels of SLE-related autoantibodies, serum cytokines (IL-6, IL-8, TNF-α, and INF-γ), increased B-lymphocyte subsets in the intestinal lamina propria, and expanded peripheral Th-17 and $CD4^+$ $CXCR3^+$ cells with reduced immunomodulatory Treg cells compared to mice receiving healthy controls' gut microbiota [129].

Also, RA fecal samples introduced into arthritis-prone SKG mice increased intestinal Th17 cells and caused severe arthritis when treated with zymosan. Lymphocytes in the colon and regional lymph nodes, but not the spleen, displayed enhanced IL-17 responses to RPL23A. Additionally, naive SKG mouse T cells co-cultured with *P. copri*-stimulated DCs induced IL-17 production and rapid arthritis development [58].

Mice colonized with IBD donor-derived microbiota also exhibited an abundance of mucosal Th17 cells, a deficit in tolerogenic $ROR\gamma t^+$ Treg cells and increased susceptibility to colitis, while transplanting healthy donor-derived microbiota induced $ROR\gamma t^+$ Treg cells and improved disease outcomes [130].

Another study on the role of isolated bacteria from individuals with MS in influencing human T cells and exacerbating MS symptoms in mouse models showed that MS fecal bacteria can induce pro-inflammatory responses and T cell differentiation leading to an exacerbation of MS-like symptoms in mice [81].

In the context of metabolic disorders, FMT in recently diagnosed T1D patients could prevent the decline in endogenous insulin production over 12 months. Patients who received autologous FMT (from their fecal samples) had significantly preserved stimulated C peptide levels compared to those who received allogenic FMT (from a healthy donor) with detected associations between specific bacteria taxa, plasma metabolites, and the preservation of residual beta cell function [131].

Alternative methods, such as oral capsules and sterile fecal filtrate transfer, have also shown success in managing microbiota-associated diseases [131, 132]. However, careful screening of these intervention methods targeting gut microbiota composition is crucial to prevent any potential adverse effects in recipients. Also, there are several challenges in terms of donor selection, standardization of FMT procedures, and potential long-term effects that need to be addressed in preclinical and clinical trials [133].

Beside recently introduced gut-microbiota associated therapies, synthetic or genetically modified bacteria, known as engineered bacteria, have also introduced a new therapeutic approach. Modification of microbial genetic properties enables specialized abilities beyond the natural features of microorganisms, which have been utilized across various fields, from agriculture to healthcare and industrial applications and holds great promise for future improvements in biotechnology and medicine [134].

Discussion

Gut microbiota dysbiosis has been linked to the pathophysiology and development of ADs [135]. In this review, the complex interactions between the gut microbiota and the host immune system in several ADs have been discussed.

Dysbiosis can result in an unbalanced immune response that is characterized by increased pro-inflammatory activities and impaired immunological tolerance [44]. Gut microbiota not only affects the immune response but also produces metabolites, such as SCFAs, that can regulate various organs and functions in the body [136]. SCFAs (acetate, propionate, and butyrate), in particular, have immunomodulatory properties which regulate the balance between pro-inflammatory and anti-inflammatory responses. Numerous studies have shown the association between altered gut microbiota composition and lower microbial diversity with autoimmune diseases. These variations have been linked to abnormal microbial translocation, increased intestinal permeability, cross-reactivity of microbial components with autoantigens, inflammatory responses, and dysregulated immune cell activation.

In recent years, studies examining the relationship between gut microbiota and different human disorders have attracted significant attention. However, despite the growing body of research in this area, the field is still in its early stages and have several gaps and challenges which are summarized as follows:

Existing Challenges and Strategies in Microbiota-Associated Studies

Definition of a Healthy Microbiota

Traditionally, researchers have defined a "healthy microbiota" based on the presence or absence of certain microbial taxa or species [137]. However, the gut microbiota structure may vary between individuals without necessarily indicating poor health. Therefore, a healthy gut microbiota should be defined based on the microbial functions and its interaction with the host, rather than merely relying on microbial taxonomical information. Also, the gut microbiota composition is influenced by several confounding factors, such as genetics and environmental factors over time. Therefore, it is difficult to define a "one-size-fits-all" solution for a healthy gut microbiota [138].

Study Design

Inappropriate study design and small sample size, which are seen in many microbiome studies, can significantly influence the conclusions of microbiota findings. The design of study depends on the study question and hypotheses of the research. For instance, cross-sectional studies are useful for identifying associations between microbial communities and clinical outcomes, while case–control studies are suitable for identification of potential biomarkers. Longitudinal studies can provide insight into the changes of the gut microbiota over time and the influence of confounding factors on gut microbiota composition and overall health. Moreover, randomized controlled trials can found causality between the microbiota findings and disease outcomes [139]. Strengths and limitations of each design should also be considered when interpreting the findings.

Methodology

The lack of standardized guidelines regarding sample collection, storage conditions, DNA extraction, sequencing platforms, and data analysis pipelines has made it challenging

to draw clear conclusions and identify consistent patterns of gut microbiota involved in human diseases. A standardized approach enables comparability between studies and increases the reliability and reproducibility of results in the microbiota field [140, 141].

Model System

Although mouse models are commonly used in microbiota research, they are a few issues that need to be taken into account. These include the absence of standardized experimental protocols, the genetic similarity of laboratory mice, differences between mouse and human microbiota, and coprophagia habit which can significantly influence the gut microbiota composition in mouse models [142]. To overcome these challenges, it is necessary to develop mouse models that more accurately reflect the human gut microbiota and to adhere to standardized protocols when working with these animal models.

From Laboratory to Human Studies

Since most of our knowledge is limited to preclinical studies on animal models, long-term clinical studies are required to assess the safety, effectiveness, and long-term effects of in vivo and in vitro findings.

Ethics

Manipulation of the gut microbiota using different methods of interventions such as FMT requires considering different ethical considerations, such as informed consent, selection of appropriate donors, and safety of protocols, which might be very challenging in microbiota studies [143]. Transparency and open communication with participants must be prioritized in order to address these challenges, and strict guidelines for donor selection and risk assessments must also be implemented in order to guarantee the health and safety of study participants (Fig. 2).

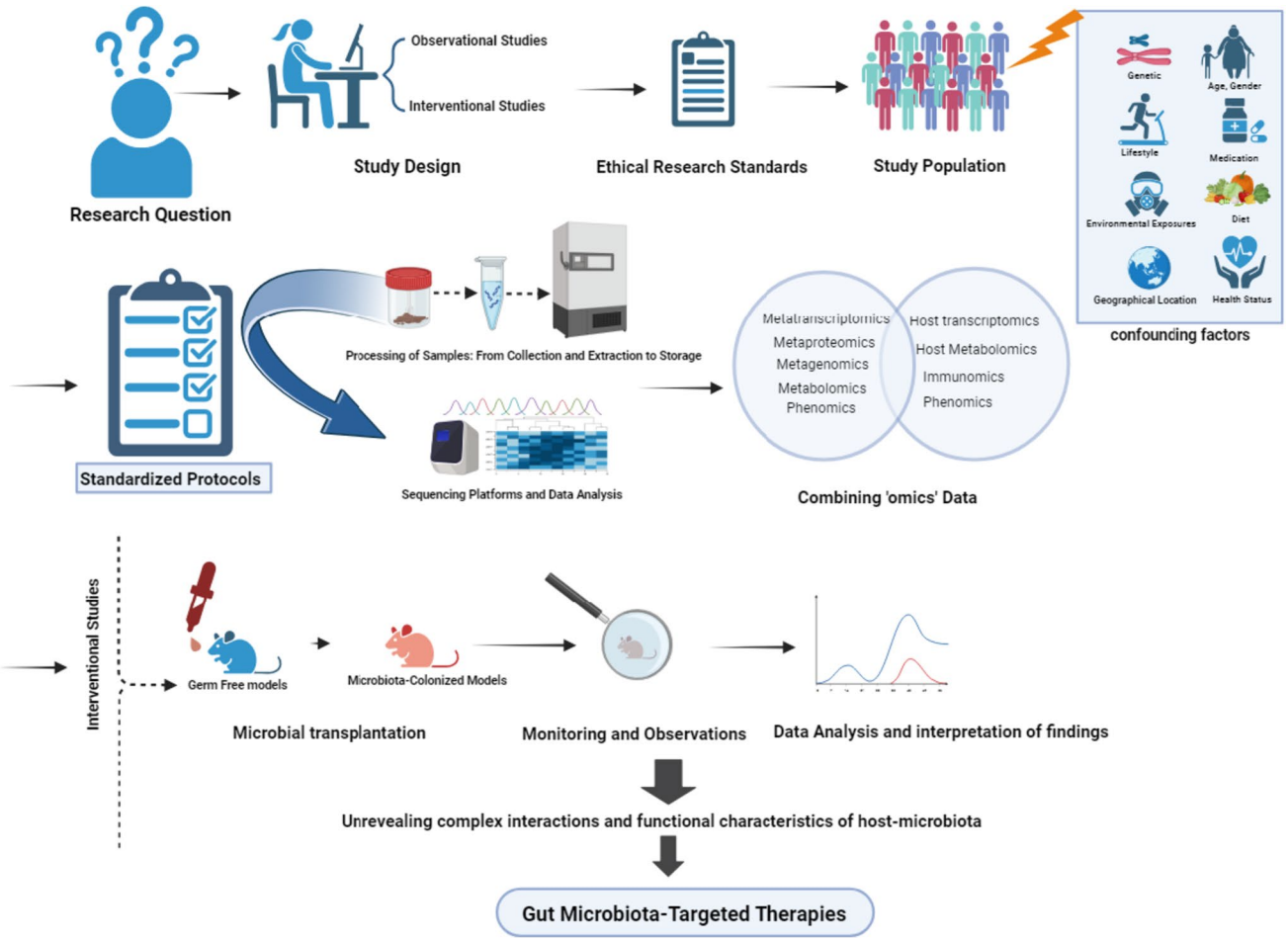

Fig. 2 A workflow from study question to omics data integration in microbiome studies

Table 2 Definitions of terms

Term	Definition
Multi-omics	Combination of data from multiple "omics" technologies [145]
Metagenomics	Study of genetic material directly from samples [146]
Meta-transcriptomics	Analysis of RNA transcripts in a microbial community [147]
Transcriptomics	Study of the entire RNA transcripts in a cell or microorganism [148]
Metaproteomics	Study of the entire set of proteins expressed by a microbial community in a specific sample [149]
Metabolomics	Analysis of small molecules (metabolites) in a sample [150]
Proteomics	Study of all proteins present in a cell, tissue, or microorganism [151]
Glycomics	Study of the structure and function of carbohydrates [152]
Lipidomics	Analysis of lipids in a sample [153]
Epigenomics	Study of changes in gene expression or cellular phenotype [154]

Conclusion

Dysbiosis has been associated with the development of several gut-microbiota-associated diseases in humans. It has been shown that the abundance of several beneficial microbial communities decreases, while pathogenic and opportunistic pathogens increase. Therefore, targeting the gut microbiota composition through various human interventions with the aim of balancing the ratio of different microbial communities and their influence on host physiology seems to be a promising approach. However, it is important to note that the host-gut microbiota interaction is a complex network, and dysbiosis is not the only contributing factor in the development of several diseases. Recent advancements in omics approaches have shed light on the complex interactions between the host-microbiota interaction. Meta-transcriptomics, metagenomics, proteomics, metabolomics, transcriptomics, glycomics, lipidomics, and epigenomics have revealed that microbial metabolites, genes, and transcripts may provide more comprehensive insights than microbial taxa alone. These advancements have enabled researchers to go beyond the identification of microbial taxonomy and explore microbiota functions and their interactions with the host, which are essential in designing new therapeutical approaches. Also, it is worth pointing out that the non-bacterial communities of the gut, including viruses (virome), fungi (mycobiome), archaea, and protozoa, also play a significant role in shaping gut microbiota composition and influencing host physiology [144]. Although there is little information now available on these topics, gaining an understanding of the intricate relationships that exist between these bacteria and their hosts may help develop novel therapeutic approaches that focus on the entire gut ecology and pave the way for more personalized therapy (Table 2).

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Data Availability All data is available in the manuscript.

Declarations

Conflict of Interest The author declares no competing interests.

Human and Animal Rights and Informed Consent This article contains no studies with human or animal subjects performed by the author.

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- • Of importance
- •• Of major importance

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