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Role of Gut Microbiota in Autoimmune Diseases: A Review

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Abstract

The gut microbiota represents the symbiotically living microorganisms in the host gastrointestinal tract. The human gastrointestinal tract is one of the largest interfaces in human body for microbial colonization. The gut microbiota plays a significant role in human health as well as in disease, particularly in autoimmune diseases. In a diseased condition, the gut microbiota composition becomes altered (dysbiosis), causing improper interaction between immune cells and microbiota resulting in infectious diseases and triggering autoimmune conditions. Various factors such as diet, age, geographical location, mode of delivery, use of antibiotics or probiotics and various disease conditions influence the gut microbiota. Several human studies and animal autoimmune models have reported on alterations in gut microbiota in comparison to healthy controls. This comprehensive review will elucidate the data on role of gut microbiota in various autoimmune diseases such as systemic lupus erythematosus, type-1 diabetes, rheumatoid arthritis, multiple sclerosis, autoimmune liver disease, Graves's disease, Hashimoto's thyroiditis, psoriasis, psoriatic arthritis, other skin related autoimmune pathologies and psychiatric disorders, etc. This will help to discover new biotherapies targeting the gut microbiota and in establishing highly personalized management for patients with autoimmune diseases.

Keywords: Autoimmune diseases; Autoimmune liver disease; Crohn's disease; Gut microbiot; Inflammatory bowel disease; Multiple sclerosis; Rheumatoid arthritis; Systemic lupus erythematosus; type 1 diabetes; Ulcerative colitis

Abbreviations: SLE: Systemic Lupus Erythematosus; RA: Rheumatoid Arthritis; T1D: Type-1 Diabetes; MS: Multiple Sclerosis; RRMS: Relapsing-Remitting MS; AILD: Autoimmune Liver Disease; PBC: Primary Biliary Cholangitis; AIH: Autoimmune Hepatitis; IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis; CD: Crohn's Disease; GD: Graves's Disease; HT: Hashimoto's Thyroiditis; APS: Antiphospholipid Syndrome; SS: Sjogren's Syndrome; GI tract: Gastrointestinal Tract; MetaHit: Metagenomics Of The Human Intestinal Tract; SCFAs: Short-Chain Fatty Acids; MACs: Microbiota-Accessible Carbohydrates; LPS: Lipopolysaccharide; SIgA: Secretory IgA; SFB: Segmented Filamentous Bacteria; TLRs: Toll-Like Receptors; GF: Germ-Free; CIA: Collagen-Induced Arthritis; DC: Dendritic Cells; NOD: Non-Obese Diabetic; CNS: Central Nervous System; PSA: Polysaccharide A; LTA: Lipoteichoic Acid; EAE: Experimental Autoimmune Encephalomyelitis; Treg Cells: Regulatory T Cells; BDNF: Brain Derived Neurotrophic Factor; DSS: Dextran Sodium Sulphate; FMD: Fasting-Mimicking Diet

Introduction

The microbiota represents a collective terminology used for the microorganisms that live symbiotically with the mammalian host. The human body harbors trillions of such microorganisms which consist of bacteria, archaea, viruses and eukaryotic microbes etc. The microbiota imposes a tremendous influence on human physiology both in health and in disease. The human Gastrointestinal (GI) tract is one of the largest interfaces in the human body for microbial colonization. Over 10^{14} microorganisms are estimated to inhabit the GI tract, and have co-evolved over thousands of years to establish a symbiotic relationship with the host. In this symbiotic relationship, the microbiota provides several advantages to the host by synthesizing essential amino acids and vitamins that the human body cannot produce (e.g., vitamin B12 by lactobacilli, folate by bifidobacteria required for DNA synthesis and repair, vitamin K, riboflavin, biotin, nicotinic acid, panthotenic acid, pyridoxine and thiamine). The microbiota also aid in carbohydrate fermentation and digestion, gut associated lymphoid tissue development, strengthening gut integrity, shaping the intestinal epithelium, harvesting energy, protection against pathogens by preventing colonization, and regulating host immunity etc. In return, the gut microbiota gets place and nutrients

for survival. This symbiotic relationship is crucial to maintain gut homeostasis. However, in diseased conditions this symbiotic relationship is disrupted due to altered microbial composition known as dysbiosis, which causes altered interaction between immune cells and microbiota, resulting in infectious diseases and triggering autoimmune conditions [1-5]. In this review, we have summarized the role of gut microbiota in various autoimmune diseases.

Identification and Characterization of Human Intestinal Microbiota

Around a decade ago, the research on identification and characterization of human intestinal microbiota was largely restricted due to the fact that, most of the laboratories were dependent on the labour intensive culture-based methods. However, this restriction was overcome by the advancement of culture-independent, high-throughput and low-cost sequencing methods such as sequencing of the entire 16S rRNA gene. This approach was popular because of presence of this gene in all bacteria and archaea, which contain nine highly variable regions (V1 to V9) to easily distinguish the species. However, using this technique only 24% of the rRNA sequences were correlated with the known database sequences, while 76% sequences were from unknown and uncharacterized species. Another approach of sequencing and analysing shorter gene regions was also found to be less useful as it introduced errors [4]. The recent advancement of whole-genome shotgun metagenomics has opened the doors for research on the human microbiota. Due to its high resolution and sensitivity, the composition and diversity of the microbiota can be estimated more reliably. The two large collaborative projects MetaHit (METAgenomics of the Human Intestinal Tract) and the Human Microbiome Project have provided the most comprehensive view of the human microbiota to date [6,7]. Combined data of these two projects revealed 2172 microbial species, belonging to 12 different phyla, and most of which (93.5%) are Proteobacteria, Firmicutes, Actinobacteria and Bacteroidetes. The study also revealed identification of *Akkermansia muciniphila,* an intestinal species from 3 phyla, and 386 of 2172 strictly anaerobic species generally found in mucosal regions such as the oral cavity and the GI tract [6].

Factors Affecting the Gut Microbiota

In terms of diversity and functionality, the human gut microbiota became less divergent than microbiota from other body sites and showed high level of functional redundancy [8-10]. An extensive data on functionality of human gut microbiota revealed country wise microbial signatures suggesting the role of environmental factors such as diet and also host genetics in shaping the gut microbiota composition. Breast-fed infants show a *Bifidobacterium spp*. rich gut. The gut microbiota in formula-fed infants has shown increased diversity including organisms such as *E. coli*, *Clostridium difficile*, *Bacteroides fragilis* and *lactobacilli* [11-15]. The gut of malnourished infants shows dysbiotic microbiota and largely consists of enteropathogens, such as Enterobacteriaceae [16]. The gut microbiota of rural African infants, whose diet is rich in starch, fibre and plant polysaccharides, was found to consist of Actinobacteria (10.1%) and Bacteroidetes (57.7%) phyla. However, this microbiota was reduced to 6.7 and 22.4% respectively in European children, whose diet is rich in sugar, starch and animal protein [17]. The other factors such as mode of delivery, age, sex, geographical location, use of antibiotics or probiotics and various disease conditions also influence the gut microbiota. In vaginally delivered infants, high abundance of lactobacilli was observed during first few days. In contrast, the microbiota in infants delivered by C-section were depleted and delayed colonized by *Bacteroides spp.* and *Clostridium spp.* were observed [4,18]. The microbiota in the early stages of development is generally less divergent and commonly dominated by two main phyla, Actinobacteria and Proteobacteria. At approximately 2.5 years of age, the diversity and composition of the microbiota changes to adult-like profile and becomes unique. In adulthood, the microbiota is relatively stable. However, the microbiota in individuals above 65 years of age tends to shift to Bacteroidetes phyla and Clostridium cluster IV [4].

Role of Gut Microbiota in Health

Carbohydrate-active enzymes produced by colon microbiota ferments complex carbohydrates generating metabolites such as short-chain fatty acids (SCFAs) [19]. *Prevotella*, a SCFA producer, is an exclusive gut microbiota seen in African children. Gut microbiota rich in *Prevotella* and other SCFA producers have also been detected in healthy individuals consuming high amounts of carbohydrates and simple sugars [20]. A decrease in SCFAs is associated with consumption of a low Microbiota-Accessible Carbohydrate (MAC) diet. Reduction of MACs was seen in Western diet. Reduced microbial diversity has been observed in mice administered with a low MAC diet [21]. SCFAs have an important role in host health via, for example, anti-inflammatory mechanisms [22]. In the elderly population, reduction in metabolic processes such as SCFA production, amylolysis and increase in proteolytic activity has been reported. Thus, it is postulated that decrease in SCFAs may induce the inflamm-ageing process in the GI tract of elderly individuals [23,24]. In chow diet-fed mice, a supplementation of *A. Muciniphila* significantly alleviated body weight gain and reduced fat mass by relieving metabolic inflammation [25]. Thus, *A. Muciniphila* could be a potential therapeutic option to target human obesity and associated disorders. The GI organisms, *Lactobacillus rhamnosus* GG, are known to promote cell renewal and wound healing [26]. The GI microbiota is crucial for the development of both the intestinal mucosal and systemic immune system. In germ-free animals, development of several immune cell types and lymphoid structures were hampered

due to the absence of GI microbiota [27].

Gut Microbiota and Host Immune System

The host immune system also plays an important role in shaping the GI microbiota. The GI tract is protected from injury and maintains homeostasis by recruiting the barriers such as epithelial and mucus layers, enzymes and antimicrobial proteins, IgA and epithelia-associated immune cells so as to diminish exposure of the microbiota to the host immune system [28]. Various antimicrobials like angiogenin 4, α-defensins, cathelicidins, collectins, histatins, lipopolysaccharide (LPS)-binding protein, lysozymes, secretory phospholipase A2 and lectins such as REGIIIα/γ secreted by Paneth cells in the GI tract kills bacteria [28,29]. Reduced expression of mucosal α-defensin was observed in patients with ileal Crohn's disease (CD), highlighting the importance of these proteins [30,31]. Secretory IgA (SIgA) along with gut microbiota co-localize in the outer mucus layer and produce bacterial biofilm, thereby reducing the exposure of the epithelial cell surface to pathogenic bacteria [29,32]. In IgA deficient mice, the Segmented Filamentous Bacteria (SFB) can damage the GI tract by strongly adhering to the epithelium and activating the immune system [33].

Gut Microbiota and Autoimmune Diseases

The interaction between the gut microbiota and immune system is crucial in healthy individuals to maintain tissue homeostasis, provide protection from injury and pathogenic organisms etc. The changes in the composition of the host gut microbiota are often observed in the diseased state. Perturbation of gut microbiota has been associated with many diseases including autoimmune diseases such as Systemic Lupus Erythematosus (SLE), type-1 diabetes (T1D), [34-37], Rheumatoid Arthritis (RA) [38-41], Multiple Sclerosis (MS) [42,43], Autoimmune Liver Disease (AILD), Graves's disease (GD), Hashimoto's thyroiditis (HT), psoriasis, psoriatic arthritis, other skin related autoimmune pathologies, psychiatric disorders [44,45], Inflammatory Bowel Disease (IBD),etc. Various factors such as altered Toll-Like Receptors (TLRs) expression, which results in abnormal signaling; cross reactivity between microbial epitopes and self-proteins, a phenomenon known as "molecular mimicry" (can cause generation of autoantibodies and activation of effector cells), bystander T-cell activation, defective post-translational modification of luminal proteins (may form neoepitopes that could be immunogenic and can cause autoimmune disease) etc. have been implicated in the development of autoimmune diseases [5,46,47].

Role of Gut Microbiota in Systemic Lupus Erythematosus

SLE is a systemic autoimmune disease characterized by production of hyperactive and aberrant autoantibodies against nuclear and cytoplasmic antigens, recruitment of auto reactive or inflammatory T cells, and an unusual production of pro-inflammatory cytokines [48-49]. The disease is commonly seen in women than in men. The disease has unknown etiology. However, various environmental and genetic factors have been implicated in its development. The signs and symptoms are not definite and outcome of the disease is severe. There is persistent inflammation, which results in tissue damage in multiple organs, including the kidneys, lungs, joints, heart, and brain [48]. The disease has no cure. The treatment and prevention depends on long-term use of immunosuppressive drugs that can increase the susceptibility to infections [50]. The association of gut microbiota with SLE has been shown in a lupus-prone mice model by Zhang, *et al.* In this model, a severe diminution of *lactobacilli*, an increase in *Lachnospiraceae* and *Clostridiaceae*, both butyrate-producing genera, and an overall diversity in gut micorbiota were observed when compared to the age-matched healthy controls. In addition, differences in gut microbiota were observed in lupus-prone male and female mice. An increase in Lachnospiraceae in lupus-prone female mice was found to be associated with early disease onset and more severe symptoms. It has also been observed that retinoic acid, as a dietary intervention, re-established lactobacilli in the gut of lupus-prone mice, which resulted in improved outcomes. Metagenomic analysis showed a significant augmentation of bacterial motility and sporulation-related pathways [44]. A dietary intervention such as caloric restriction in NZB/W F1 mice altered the gut microbiota and halted disease progression [51]. In a similar study, Johnson, *et al.* also reported an alteration in the gut microbiota, decrease in antinuclear antibodies and slow development of nephritis in SWR 9 NZB F1 mice provided with drinking water having a low pH. These findings suggested that modulation of the gut microbiota could influence the disease progression [52]. In Germ-free (GF) lymphotoxin-deficient mice, Van Praet, *et al.* reported the role of intestinal microbiota in antinuclear antibody induction that could be related to the colonization of Segmented Filamentous Bacteria (SFB) and IL-17 receptor signaling [53].

In a cross-sectional study, Hevia, *et al.* showed intestinal dysbiosis related to the decrease in the Firmicutes and an increase in the Bacteroides phyla in the stool samples of SLE patients when compared with healthy controls. In addition, in silico analysis data of these patients suggested the role of intestinal microbiota in dysbiosis that could be correlated to an increase in oxidative phosphorylation and the glycan metabolism pathways induced by patients' intestinal microbiota [54]. Similar findings (decrease in the Firmicutes and an increase in the Bacteroides members) were also reported in patients with SLE in another cross-sectional study. Furthermore, the prevalence of other microbes such as *Rhodococcus*, *Eggerthella*, *Klebsiella*, *Prevotella*, *Eubacterium*, *Flavonifractor* and Incertae sedis genera have been reported in these patients, which suggested the profile of gut microbiota of patients with SLE [55]. Lopez, *et al.* assessed the role of the dysbiosed gut in SLE patients and that in healthy controls for *in vitro* differentiation of Treg, Th1 and Th17 cells. The authors

reported induction of Th17 differentiation and significant decrease in the Th17/Th1 balance after providing Treg-inducing bacteria to the dysbiosed gut of SLE patients. This supports the use of these strains as therapeutic probiotics for autoimmune diseases. A hormone dependent role of gut microbiota in male lupus nephritis patients has been reported. In these patients, clinical manifestation and blood levels of interleukins was found to improve significantly after administration of a mix of *Lactobacillus spp.* [56].

Role of Gut Microbiota in Rheumatoid Arthritis

RA is a chronic systemic inflammatory autoimmune disease that causes pain and inflammation of multiple joints, bone erosion, joint deformity and cartilage destruction. In addition, internal organs such as the lungs, heart and kidneys can also be affected. Various factors are presumed to be involved in the pathogenesis of RA, such as immune and resident cells (chondrocytes and fibroblasts), pro-inflammatory cytokines (TNF-alpha, IL-1 released by activated macrophages and other activated T cells), and autoantibodies such as anti-cyclic citrullinated antibody (IgA) and/or rheumatoid factor. These factors can be found before disease onset in RA patients [57]. Women are three times more prone to RA than men. The interaction between HLA genes and environmental factors such as smoking, infections and dysbiosis etc. are considered the triggering factors for autoimmunity in RA patients [58,59]. Experiments in animal models have suggested the role of gut microbiota in influencing the local and systemic immunity as well as the possibility of triggering joint inflammation [59,60]. In a Collagen-Induced Arthritis (CIA) mice model, exacerbation of disease and induction of pro-inflammatory cytokines such as IL-6, IFNγ, and IL-17 has been reported. In addition, in CIA-susceptible and CIA-resistant mice models, the differences in the gut microbiota composition has been noted with a prevalence of *Desulfovibrio*, *Prevotella*, *Parabacteroides*, *Odoribacter*, *Acetatifactor*, *Blautia*, *Coprococcus* and *Ruminococcus* genera in CIA-susceptible mice along with increased levels of serum IL-17 and CD4 Th17 cells in the spleen [61].

A germ-free mice study reported that TLR-2 deficiency (TLR activation depends on status of microbiota of mice) leads to reduced Foxp3 expression and Treg suppressive activity, resulting in arthritis. TLR4 was also found to contribute to Severe Arthritis By Modulating IL-17 production and Th17 cell proliferation [62]. The gut-residing segmented filamentous bacteria (SFB) also contribute by stimulating IL-1β and IL-6 production and Th17 development. Thus, a fine balance in TLR mediated discrimination of gut microbiota is important to maintain homeostasis and prevent RA and certain other autoimmune diseases. Spontaneous development of arthritis was observed in IL-1RA deficient mice. In IL-RA$^{-/-}$ GF mice, there was decrease in the IL-17 and IL-1β secretion as well as TLR-2 and TLR-4 stimulation and was associated with attenuation of RA. Furthermore, when these mice were colonized with *Bifidobacterium bifidum* an increase in clinical scores compared with conventionally housed mice were noted [63-65]. Gomez A, *et al*. studied the gut microbiota composition of genetically arthritis-susceptible transgenic mice *0401 and genetically resistant transgenic mice *0402. The prevalence of *Clostridia* in genetically arthritis-susceptible transgenic mice and dominance of Porphyromonadaceae and Bifidobacteriaceae families in the genetically resistant transgenic mice were observed. In addition, an increase in the intestinal permeability and a Th17profile was observed in genetically arthritis-susceptible transgenic mice, which indicate the role of genetic background in influencing the individual's microbiota profile [66]. Maeda, *et al.* transplanted the gut microbiota from RA patients to GF arthritis-prone SKG mice and observed the increase in the number of Th17 cells in the gut and development of severe arthritis. The researchers also co-cultured the SKG dendritic cells with *Prevotella copri* in the presence of RA autoantigens and observed increased IL-17 secretion. These findings indicate the role of RA gut microbiota in the induction of autoreactive cells in the gut and promotion of joint inflammation [67].

The introduction of SFB in GF K/BxN mice induced Th17 cells in the intestinal lamina propria and reinstated the production of autoantibodies and arthritis. The possible mechanism suggested is the production of pro-inflammatory cytokines such as IL-1β and IL-6, by induced Dendritic Cells (DC) and macrophage that facilitate Th17 differentiation and trigger the onset of arthritis. The same signal i.e. IL-1β and IL-6 triggered by the microbiome induced IL-10-producing Breg cells in mice. This indicates that the gut microbiota plays a dual role in establishing both pro-inflammatory and regulatory immune responses [65]. The dominance of Gram-negative *Prevotella* members, especially *Prevotella copri* has been reported in the intestinal microbiota of newly diagnosed RA patients when compared with healthy individuals. *Prevotella copri* initiates the RA by activating helper T cells [67,68]. Using quantitative real-time PCR, Liu, *et al*. investigated the Lactobacillus community in recently diagnosed RA patients and observed an increase in copy numbers of *Lactobacillus salivarius*, *Lactobacillus iners* and *Lactobacillus ruminis* in untreated RA patients compared with healthy controls [69]. Chen, *et al*. reported decreased species richness (α-diversity) and increased rheumatoid factor and disease progression in RA patients.

The gut microbiota of people with RA was enriched with *Eggerthella*, *Actinomyces*, *Turibacter*, *Streptococcus* and *Collinsela spp*., which was positively correlated with the pro-inflammatory cytokine IL-17. Furthermore, the study showed the correlation of rheumatoid factor, C-reactive protein, disease progression and methotrexate treatment with β-diversity found in the gut microbiota of RA patients [70]. The role of SFB in expanding Th17 cells expressing dual T cell receptors (TCRs) recognizing SFB as well as self-antigens and their recruitment to the lungs through the CCL20–CCR6 axis caused RA-related

lung pathology. This dual TCR mechanism was different than the previously suggested molecular mimicry or bystander activation mechanisms and provides new information about modulation of host immunity by the gut microbiota. Molecular mimicry mechanism in RA was supported by the presence of two auto antigens, N-acetylglucosamine-6-sulfatase (GNS) and filamin A (FLNA) sharing sequence homology to the epitopes of gut microbes, such as *Prevotella spp* [71,72].

Role of Gut Microbiota in Type-1 Diabetes

T1D is a chronic autoimmune disease in which immune cells destroy the insulin producing cells known as beta cells in the pancreas, which results in increased blood glucose level that affects various organs like eyes, heart, kidney etc. Insulin, GAD65 (glutamic acid decarboxylase, 65 kDa isoform), and IA2 (Insulin autoantigen 2) are the three major auto antigens found to be associated with T1D and presence of antibodies against these autoantigens were reported in the serum of T1D patients [73]. The typical characteristic symptoms of T1D include polydipsia, polyphagia, and polyuria, accompanied by overt hypoglycaemia and are the diagnostic parameters in high-risk individuals, such as children and adolescents [74]. The role of gut microbiota as a causative agent in T1D was the matter of research in last decade to prove its role in disease development and determine preventive measures such as diet manipulation and probiotic administration. One of the first studies in MyD88-deficient non-obese diabetic (MyD88_/NOD) mice indicates the role of gut microbiota composition in modulation of innate and adaptive immune functions and causing the disease.

Administration of antibiotics and GF condition in these mice abolished the protection against diabetes, suggesting that the gut microbiota may be important in reducing disease susceptibility in these mice [75]. Wen, *et al*. reported that MyD88-deficient NOD GF mice did not develop T1D and this protection was associated with the presence of gut microbiota. It was also observed that MyD88-deficiency changed the gut microbiota composition in MyD88-deficient NOD GF mice and attenuated T1D by colonization with bacterial community known as "altered Schedler's flora" (ASF) which is normally present in healthy mouse gut. However, receptors and signaling pathways associated with microbiota-dependent protection against the development of T1D remains unclear. It has been postulated that involvement of TRIF signalling in TLR-3 and TLR-4 mediated discrimination of gut microbiota contribute in the protection against the development of T1D in MyD88-deficient NOD GF mice through tolerance mechanisms. *Bacteroides*, *Ruminococcus* and *Eubacterium spp*. were abundant in stool samples of bio-breeding diabetes-prone rats, while *Bifidobacterium* and *Lactobacillus spp*. were abundant in stool samples of bio-breeding diabetes-resistant rats [76].

The altered gut microbiota (increase in *Bacteroidetes spp*.) associated with increased intestinal permeability and clinical onset of T1D in animal models and pre-diabetic and diabetic patients. Lee, *et al*. showed higher intestinal permeability, earlier insulitis and increased lymphocytic infiltration at the pancreas Langerhan's islets in pre diabetic young NOD mice infected by an oral gavage with wild type *C. Rodentium.* These authors also reported inability of mutant strain of *C. Rodentium*, lacking ability to disrupt the intestinal barrier, to induce insulitis [77]. *Akkermansia muciniphila*, a symbiont, when transferred to NOD mice alone instead of whole microbiota significantly reduced the incidence of T1D due to its multiple immunologic and metabolic signalling remodelling effects [78].

The association of gut microbiota and T1D has been suggested since 1987. The first human study was conducted in Finland in children having T1D. The study reported decrease in gut microbiota diversity and reduction in the Firmicutes: Bacteroidetes ratio in T1D children as compared to matched healthy controls [79]. Altered gut microbiota and autoantibodies against β-cells were observed in genetically susceptible pre-diabetic children [80,81]. De Goffau and colleagues observed increased *Bacteroidetes spp*. and decreased lactate and butyrate-producing bacteria in the feces of children having autoantibodies against β-cells [80]. Similar findings were also reported by Brown, *et al*. who showed decreased mucin-degrading and butyrate-producing microbiota in T1D patients than healthy controls [82]. Endesfelder, *et al*. reported no significant difference in gut microbiota diversity in children with positive islet autoantibodies compared with controls. In addition, in children with T1D, decreased numbers of *Bifidobacterium longum*, subspecies *infantis*, lactate-producing bacteria, were noted [83]. Murri, *et al.* reported increase in *Clostridium*, *Bacteroides* and *Veillonella* spp. and decrease in Firmicutes: Bacteroidetes ratio and *Lactobacillus*, *Bifidobacterium* and *Prevotella spp*. in children with T1D compared with controls in a cohort study [84]. Davis-Richardson,*et al.* observed increased numbers of *Bacteroides dorei* and *Bacteroides vulgatus* in stool samples of seroconverted patients with T1D 8 months before β-cell autoimmunity, which suggest that early dysbiosis may envisage T1D in genetically predisposed individuals [85]. Maffeis, *et al.* reported a correlation between altered microbiota composition and increased intestinal permeability along with dominance of three microbial species (*D. invisus*, *G. sanguinis*, and *B. longum*) in T1D affected Italian children as compared to healthy controls [86].

Role of Gut Microbiota in Multiple Sclerosis

Multiple Sclerosis (MS) is an immune-mediated chronic inflammatory disease of the brain and spinal cord (central nervous system). The immune system attacks myelin, a protective layer around nerve fibers, and axons causing destruction of both structures to variable degrees resulting in significant physical disability. In MS, there is a communication problem (messaging)

between brain and rest of body due to inflammation and scar tissue, or lesions in the CNS. The messaging is either altered or stopped completely. Infiltration of myelin-specific auto-reactive Th1 and Th17 cells, in either relapsing or progressive condition, into the CNS has been seen in MS patients [87,88]. In MS, both CNS and microbiota influence each other. The CNS influences the gut microbiota composition by its peptides such as melanocortin Antagonist Agouti-Related Peptide (AgRP) and neuropeptide Y (NPY) that can modulate food intake and physiological processes controlling nutrient absorption. The gut microbiota releases SCFAs, lipopolysaccharides (LPS), polysaccharide A (PSA) and LTA that can modulate brain functions [89]. It has been observed that SFB colonization increased the number of Th17 cells in the lamina propria and CNS, thereby worsening the disease severity in an experimental autoimmune encephalomyelitis (EAE) animal model for MS [87]. *Bacteroides fragilis* colonization and PSA, which induces Foxp3+ Treg cell differentiation, reduced the disease severity in same animals [90]. Antibiotic-treated mice reconstituted with *Bacteroides fragilis* gut microbiota get protected from EAE through PSA-induced TLR2 signalling dependent induction of Treg cells producing IL-10 and reduced IL-17 levels [91].

Miyake, *et al*. studied gut microbiota composition in relapsing MS and healthy individuals. A significant difference was observed in the relative abundance of archaea and butyrate producing bacteria. Furthermore, a decrease in *Clostridial spp.* in MS patients has been observed. However, no overlapping of these decreased *Clostridial spp.* with other spore forming *Clostridial spp.*, capable of inducing colonic regulatory T cells and thus protecting from autoimmunity and allergies have been observed [92]. Untreated MS patients showed augmentation in *Methanobrevibacter smithii* and decrease in *Firmicutes* and *Butyricimonas*, butyrate-producing members of the microbiota [93]. Alterations in the gut microbiota of RRMS patients showed decrease in *Clostridia* XIVa and IV groups, *Firmicutes*, *Bacteroidetes* and *Proteobacteria* members [94,95]. In another study on RRMS patients, a decrease in *Faecalibacterium spp.* and augmentation in *Akkermansia*, *Coprococcus* and *Faecalibacterium* was reported after vitamin D supplementation [96]. *Methanobrevibacter* has a role in recruitment of macrophages and activation of dendritic cells involved in inflammatory conditions [97]. *Akkermansia spp.* has a role in immunoregulation by converting mucin into SCFAs; however, they are also involved in promoting inflammation by degrading the mucus layer [98,99]. *Butyricimonas spp.* (butyrate-producing bacteria) has a role in immunomodulation by inducing Treg cells in the gut. *Prevotella* was found to be associated with high-fibre ingestion and plays a role in immunoregulation by butyrate generation. Chen, *et al.* compared stool samples from RRMS patients and healthy controls and reported gut dysbiosis in the former group. They noted an increase in the *Pseudomonas*, *Mycoplasma*, *Haemophilus*, *Blautia* and *Dorei* genera in RRMS patients compared with healthy controls, who showed a dominance of *Prevotella* and *Parabacteroides* [100].

Role of Gut Microbiota in Inflammatory Bowel Disease

The term IBD represents a group of disorders characterized by intestinal disorders that can cause chronic inflammation of the digestive tract. The causative factors of IBD include genetic susceptibility of individual, immune responses, gut microbiota and environmental stimuli. Ulcerative colitis (UC) and Crohn's Disease (CD) are the two major types of IBD. UC is characterized by inflammation and ulcers in the superficial lining of the colon and rectum, whereas CD is associated with inflammation of deeper layers of GI tract. Omori, *et al.* showed an increase in *Paraprevotellaceae* and *Porphyromonas spp.* in dogs with IBD compared to healthy dogs by analyzing fecal samples by 16S rRNA gene next-generation sequencing [101]. Kawashima, *et al*. showed a protective role of TLR signaling and microbiota in an experimental colitis mice model. They showed that the dsRNA of lactobacilli triggering interferon beta production through TLR3 activation pathway offered protection to mice from experimental colitis [102].

IELs are T cells that are most closely in contact with intestinal micorbiota and may be influenced by the alterations in intestinal micorbiota in distinct subtypes of IBD. It has been observed that IELs from UC patients secreted significantly higher quantity of IL-1β, and those from CD patients secreted significantly higher quantity of IL-17A, IFN-γ, and TNF-α as compared to healthy controls [103]. The gut microbiota of IBD patients has been found to be altered than in healthy controls, showing a predominance of *Enterococcus* and *Bacteroids spp.* and decrease in *Bifidobacterium* and *Lactobacillus spp.,* thereby suggesting the important role of gut microbiota in intestinal inflammatory diseases. Cario and Podolsky showed variations in the expression of some TLRs in UC and CD patients. They observed less expression of TLR2 and TLR4 on IECs and lamina propria cells during homeostasis to minimize microbiota recognition and maintain tolerance [104,105], and high expression of TLR2, TLR3, TLR4 and TLR5 in UC and CD patients. On the other hand, pathogenic bacteria contain less dsRNA than lactobacilli and induce much less IFN- β production. Thus, TLR3 acts as a sensor to microbiota and contributes to the anti-inflammatory and protective immune responses. It has been suggested that the alterations in the intestinal extracellular vesicle proteins might cause abnormal host-microbiota interactions in pediatric patients with IBD [106].

A decrease in the genus *Roseburia* has been observed in the healthy individuals having a high genetic risk for IBD. Also, the gut microbiota in patients with ileal CD showed a decreased α-diversity compared to those with colonic CD [107]. Zhou, *et al*. conducted a meta-analysis and reported similar gut microbiota alteration patterns in IBD among Chinese and Western populations.

These authors also reported association between augmentation of *Actinobacteria* and *Proteobacteria* (*Enterobacteriaceae*) and reduction of *Firmicutes* (Clostridiales) and IBD severity [108]. Altomare, *et al.* reported a statistically significant increase in *Proteobacteria* and a reduction in Firmicutes and *Actinobacteria* in mucosal-associated microbiota of IBD patients compared to those of healthy controls [109]. Sokol, *et al.*, using 16S sequencing, reported that the presence of *Clostridium difficile* infection (CDI) in IBD patients resulted in poor outcomes. Authors showed IBD patients having CDI infection had higher levels of RG and *Enterococcus* OTUs and lower levels of *Blautia* and *Dorea* OTUs than did IBD patients without CDI infection [110]. A significant reduction in *Eubacterium rectale* and *Faecalibacterium prausnitzii* and an increase in *Escherichia coli* was observed in children with UC [111].

Role of Gut Microbiota in Antiphospholipid Syndrome

Antiphospholipid Syndrome (APS) or Hughes syndrome is an autoimmune disease characterized by generation of antibodies against phospholipids of the cell membrane that causes an increased risk of thrombosis. The thrombosis can occur in the legs, kidneys, lungs and brain. APS in pregnant women may lead to miscarriage and stillbirth. The cause of APS remains unclear; however, it is believed that the genetic predisposition along with environmental factors play an important role in its development. There are two types of disease i.e. primary APS and secondary APS. Primary APS occurs alone without any other related disease, while secondary APS arises with other autoimmune diseases such as SLE.

It has been suggested that the alterations in the gut such as infections or inflammation acts as triggers in APS development. The role of molecular mimicry has been suggested in APS. The presence of *Roseburia intestinalis, a* Gram-positive, anaerobic bacterium, in the gut microbiota of APS patients leads to chronic activation of Th CD4+ lymphocytes due to sharing of common epitopes as those of T and B-cells [112].

Role of Gut Microbiota in Sjögren's Syndrome

Sjögren's Syndrome (SS) is a chronic autoimmune inflammatory disease characterized by dryness of the mouth and eyes. In SS, inflammation and dysfunction of the lacrimal and salivary glands, including the parotid gland, result in reduced production of tears and saliva respectively. The disease is predominantly seen in women. Complications of SS include infections of the eyes, breathing passages, and mouth. In SS, there is infiltration of CD4+ T cells, DCs and B cells, hyperactivity of polyclonal B cells and production of autoantibodies (anti-SSA/Ro60 antibodies). The gut microbiota (*B. finegoldii*, *B. intestinalis*, *B. fragilis* and *Alistipes finegoldii*) also plays an important role in the pathogenesis of SS. Peptides derived from gut microbiota may stimulate the immune response by activation of Ro60- reactive T cells. In SS patients, an increase in Firmicutes, specifically *Streptococcus* and *Veillonella*, and a decrease in *Synergistete*s and *Spirochaetes* has been observed [113]. Additionally, approximately 50% decrease in the genus *Faecalibacterium*, including *F. prausnitzii*, one of the predominant butyrate producers in the intestine, has been reported by de Paiva, *et al*. [114]. Augmentation of enteric pathogens, such as *Escherichia/Shigella* and *Enterobacter* has been observed. There was no significant difference in the gut microbial composition between control and SS patients, except for a rise in *Streptococcus* and diminution of *Leptotrichia* and *Fusobacterium*. SS patients with severe dysbiosis (reduced *Bifidobacterium* and *Alistipes* genera) were found to experience high disease severity, reduced levels of complement component and higher levels of faecal calprotectin [115].

Role of Gut Microbiota in Graves's Disease And Hashimoto's Thyroiditis

Grave's Disease (GD) is an autoimmune disease characterized by over production of thyroid hormones (hyperthyroidism). The circulating autoantibodies known as thyroid-stimulating immunoglobulins played a role in binding to and activating thyrotropin receptors, resulting in enlargement of the thyroid gland and increased synthesis of thyroid hormones by the thyroid follicles. The exact cause is unknown; however, it is believed that genetic and environmental factors are responsible for it. Physical or emotional stress and infection have been considered the triggering factors. Individuals having other autoimmune diseases are more likely to be affected. Women are more frequently affected than men [116].

Hashimoto's thyroiditis (HT) is an autoimmune disease characterized by lymphocytic infiltration of the thyroid gland along with generation of autoantibodies against thyroglobulin and thyroid peroxidase, which causes gradual destruction of the thyroid gland and results in subclinical or overt hypothyroidism [117]. Genetic (family history), hormonal (women more likely affected than men), and environmental (diet rich in iodine) factors, and exposure to radiation are thought to contribute to HT [118]. Shor, *et al.* reported the occurrence of gastrointestinal autoantibodies such as anti-gliadin antibodies (AGA), tissue transglutaminase (tTG) and anti-saccharomyces cerevisiae antibodies (ASCA) in patients with HT and GD, of which ASCA were found to be highly prevalent in patients with GD [119]. This finding was confirmed by Covelli and Ludgate who showed presence of increased yeast in fecal samples ofpatients with GD [120]. The first report of association of gut microbiota in GD showed a major reduction of the *Bacteroides* genus in small number of patients [121]. More work is required to determine the role of gut microbiota in the development of GD. Penhale and Young reported increased susceptibility of specific pathogen free rats to experimental autoimmune thyroiditis after transfer of microbiota from conventional rats, which supports the

role of microbiota in HT pathogenesis [122].

Role of Gut Microbiota in Skin Related Autoimmune Diseases

Psoriasis is an autoimmune disease of skin, which is noncontagious and chronic, characterized by red or purple, dry, itchy, and scaly raised areas of abnormal skin. The suggested causative factors are infections, genetic, psychological stress and environmental. Oliveira Mde, *et al.* showed a relation between CD and psoriasis. The study reported CD as a comorbidity of psoriasis. Furthermore, the risk of development of CD in patients with psoriasis was 2.9 times higher, and risk of development psoriasis in CD patients was 7 times higher compared to general population [123]. The role of intestinal dysbiosis in CD has also been suggested for psoriasis. Psoriatic arthritis, a comorbidity of psoriasis is a chronic spondyloarthritis of unknown etiology. The gut microbiota of patients with psoriatic arthritis and psoriasis showed reduced bacterial diversity and abundance of *Akkermansia*, *Ruminococcus*, and *Pseudobutyrivibrio* compared to healthy controls. In addition, the gut microbiota profile of psoriatic arthritis patients resembled that of IBD patients, which supports a possible role for the gut microbiota in this skin disease [124].

Scleroderma and vitiligo are other skin diseases related to intestinal dysbiosis. Scleroderma or systemic sclerosis is an autoimmune disease characterized by changes in the texture and appearance of skin. GI tract dysfunction has been observed in the majority of scleroderma patients, which might be associated with changes in the gut microbiota composition. In two different cohort studies, Volkmann, *et al.* reported an increase in Firmicutes in patients with systemic sclerosis (63.5 and 42.8%) as compared to healthy controls (33%) and a decrease in *Bacteroidetes* in one of the cohort (21.3%) as compared to healthy controls (63.2%). The study also observed an increase in *Clostridium*, *Lactobacillus* and *Prevotella spp*. in patients with low GI symptom severity, mild constipation and in those with moderate to severe gastrointestinal symptom severity, respectively in both cohorts [125].

Role of Gut Microbiota in Psychiatric Disorders

Psychiatric disorders or mental disorders include depression, bipolar disorder, schizophrenia, dementia, and autism, among others., characterized by combination of abnormal thoughts, perceptions, emotions, behavior and relationships with others. In mice experiments, Bercik, *et al.* and Guida, *et al.* reported that different strains of mice or different antibiotic treatments differently affected the gut microbiota composition and behavior, which was associated with Brain Derived Neurotrophic Factor (BDNF), an important growth factor for neuronal survival and synaptic plasticity. An explorative behavior was associated with an enhanced level of BNDF, while depression behavior and altered social interaction was associated with reduced level of BNDF [126,127]. Similarly, decreased BDNF levels were observed in the serum of patients with major depressive disorders and treatment to improve BNDF level was found to be effective in these patients [128,129]. Schwarz, *et al.* in a small cohort study reported an increase in *Lactobacillus* and *Bifidobacterium* in fecal samples of patients with First-Episode Psychosis (FEP) [130]. Adams, *et al.* and Schwarz, *et al.* showed increased amounts of *Lactobacillus* in gut microbiota of autistic children [130,131]. A decrease in Veillonellaceae family was observed in depressive patients [132]. It has been observed that increased intestinal permeability and dysbiosis were strongly associated with psychiatric disorders and impairment of immune function [133-135].

Role of Gut Microbiota in Autoimmune Liver Disease

The autoimmune liver disease consists of Primary Biliary Cholangitis (PBC) and Autoimmune Hepatitis (AIH). The triggering factors for AILD are environmental, genetic, abnormal bile acid homeostasis, augmented intestinal permeability, inability to inactivate endotoxins, and activated innate immunity. All these factors contribute to bacterial translocation. Autoimmune Hepatitis (AIH) or lupoid hepatitis is a chronic, severe, inflammatory autoimmune disease of liver characterized by presence of autoantibodies and hypergammaglobulinemia. AIH has two types - type 1 and type 2 characterized by different autoimmune serology. Patients with type 1 AIH have autoantibodies for anti-smooth muscle and/or anti-nuclear, whereas those with type 2 AIH have anti-liver kidney microsomal type 1 and/or anti-liver cytosol type 1 autoantibodies. The immune system attacks the liver cells causing inflammation of the liver, which results in cirrhosis and liver failure. The aetiology of AIH is unknown; however, genetic factors, history of certain infections (measles, herpes simplex or Epstein-Barr virus, hepatitis A, B or C infection), presence of other autoimmune diseases and environmental factors are suggested to trigger the disease. Muhammed Yuksel, *et al.* investigated the gut microbiota in fecal samples of HLA-DR3 AIH mice and WT NOD mice six months after autoantigen (CYP2D6/FTCD) immunization. The study reported strikingly different gut microbiota in HLA-DR3 mice than that of the WT NOD mice in terms of phylogenic diversity (PD, or alpha diversity), beta diversity, as well as taxonomic classification levels [136]. Nahla M. Elsherbiny, *et al*. studied stool samples from AIH patients and healthy controls and reported reduced gut bacterial diversity in AIH patients compared to healthy controls. In addition, augmentation of Firmicutes, Bacteroides, and Proteobacteria phyla, and at genus level augmentation of *Faecalibacterium*, *Blautia*, *Streptococcus*, *Haemophilus*, *Bacteroides*, *Veillonella*, *Eubacterium*, *Lachnospiraceae* and *Butyricicoccus* was reported in contrast to *Prevotella*, *Parabacteroides* and *Dilaster*, which were significantly reduced in such patients [137]. In a cross sectional study of AIH patients, Yiran Wei, *et al*. showed a lower alpha-diversity and distinct overall gut microbial composition in steroid treatment-naïve AIH patients compared with healthy controls. They also reported a reduction in obligate anaerobes

and augmentation of potential pathobionts including *Veillonella dispar* in these patients [138]. Rui Lin, *et al.* reported an increase in intestinal permeability (leaky gut), derangement of the gut microbiome and bacterial translocation in AIH patients, which correlated with the severity of the disease. AIH patients showed a decrease in *Bifidobacterium* and *Lactobacillus* and no change in the quantitiy of *Escherichia coli* and *Enterococcus*. Furthermore, the balance of intestinal flora (*Bifidobacteria*/*Escherichia coli* (B/E)) was found to be decreased. The study concluded that leaky gut and gut microbial dysbiosis played an important role in the pathogenesis of AIH [139].

Primary biliary cholangitis or primary biliary cirrhosis is a chronic, slow, progressive autoimmune disease of liver characterized by injured and inflamed small bile ducts, immune-mediated destruction of the intrahepatic bile ducts resulting in liver damage, and the presence of highly specific anti-mitochondrial antibodies in serum.

Tang R, *et al.* investigated the alterations in specific gut microbiota composition in naive PBC patients and reported an increase in eight bacteria namely *Haemophilus*, *Veillonella*, *Clostridium*, *Lactobacillus*, *Streptococcus*, *Pseudomonas*, *Klebsiella*, and Enterobacteriaceae, and decrease in four bacteria namely *Sutterella*, *1 Faecalibacterium*, and *Bacteroides* [140]. Kazumichi Abe, *et al*. reported an increase in *Veillonella* and *Eubacterium* genus and decrease in *Fusobacterium* genus in the PBC patients than in the healthy controls. In addition, alteration in gut microbiota was noted by an increase in Lactobacillales order and decrease in genus *Clostridium subcluster XIVa.* The study also noted an increase in *Sutterella*, *Oscillospira*, and *Bacteroides,* and a decrease in *Haemophilus*, *Veillonella*, *Streptococcus*, and *Pseudomonas* in UDCA treated PBC patients [141].

Applications of Prebiotics, Probiotics And Fmd in Autoimmune Diseases

Dietary interventions may be effective in order to maintain gut homeostasis in patients with autoimmune diseases. Prebiotics are the types of fibers that are present in many vegetables, fruits and legumes. Although humans cannot digest them, gut microbiota can do so and thus support healthy digestive and immune function. Probiotics are live beneficial bacteria found in certain foods or supplements and provide numerous health benefits to the host. Probiotics play a role in influencing systemic immune responses, ensuring homeostasis of the gut microbiota and therefore, can be used as an adjuvant therapy to treat autoimmune diseases [142]. Oral treatment of NOD mice with Lactobacillaceae-enriched probiotic resulted in suppression of IL-1β expression, release of immunomodulatory indoleamine 2,3-dioxygenase, promoting the differentiation of $CD103^{+}$tolerogenic dendritic cells in the gut, and also protected mice from T1D [143].

In children between 4 and 10 years of age, early probiotic treatment was well correlated with reduced risk of islet autoimmunity compared to controls. Several studies in EAE mice model showed that probiotics induce Treg cells in the gut mucosa by secretion of IL-10 and TGF-β, decreasing Th1/Th17 inflammatory subsets, thereby ameliorating CNS inflammation. Beneficial effects of probiotic treatment were also reported in autoimmune diseases like MS, RA, and SLE etc. The Fasting-mimicking Diet (FMD) is made from specific healthy plant-based ingredients that are scientifically tested and contains low carbohydrates and proteins and good fatty acids that keeps body in fasting state. This triggers the body to develop a set of protective measures by rejuvenating its cells and optimizing performance. In autoimmune diseases such as IBD, the 4 days FMD cycle intervention in a chronic Dextran Sodium Sulfate (DSS)-induced murine model resulted in decreased intestinal inflammation, increased numbers of stem cells, stimulation of protective gut microbiota, and reversal of intestinal pathology, while water-only fasting intervention increased regenerative mechanisms and decreased inflammatory markers without reversing intestinal pathology. Furthermore, reversal of DSS-induced colon shortening, reduction in inflammation, and increase in colonic stem cells has been observed after transfer of *Lactobacillus* or fecal microbiota from FMD-treated mice [144].

Conclusion

In summary, the gut microbiota has tremendous potential in health and in disease, particularly autoimmune diseases. The recent advancement of whole-genome shotgun metagenomics opens the doors of research to study the human microbiota. Most of the studies focused on comparative analysis of fecal microbiota composition in patients with autoimmune conditions and healthy controls. Several autoimmune animal models have been developed and used to study the interaction between gut microbiota and autoimmune disease. An alteration in the gut microbiota has been observed in various autoimmune diseases as compared with healthy controls. Similar findings were also observed in various animal studies (autoimmune models). The gut microbiota related therapeutic approaches in health and in diseased states need to be increased in future so as to prevent or repair perturbations in host autoimmune diseases and thus may be effective in the prevention or treatment of autoimmune diseases. It has been observed that changes in gut microbiota can affect the Th17 and Tregs cell balance, which influences the pro-/ anti-inflammatory cytokine levels and thus the autoimmune disease state. Additonally, other factors such as altered TLR expression, molecular mimicry, bystander T-cell activation, defective post-translational modification of luminal proteins etc. have been implicated in the development of autoimmune diseases. However, detailed studies are warranted on role of gut microbiota in influencing the immune system, which can lead to autoimmune diseases. The current approaches such as use

of prebiotics, probiotics, and FMD therapies have demonstrated a beneficial effect on autoimmune diseases. Nonetheless, more studies are required to elucidate the mechanisms of their interaction with the host. The other influencing factors such as age, sex, and geographical location are also crucial and should be taken into account while considering gut microbiota-related therapeutic approaches. In this review, we have summarized the role of gut microbiota in various autoimmune diseases to improve the understanding of the association of gut microbiota in these diseases, which will help to discover new biotherapies targeting gut microbiota and in establishing highly personalized treatments for patients with autoimmune diseases.

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