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Review

Microbe-metabolite-host axis, two-way action in the pathogenesis and treatment of human autoimmunity

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ABSTRACT

The role of microorganism in human diseases cannot be ignored. These microorganisms have evolved together with humans and worked together with body's mechanism to maintain immune and metabolic function. Emerging evidence shows that gut microbe and their metabolites open up new doors for the study of human response mechanism. The complexity and interdependence of these microbe-metabolite-host interactions are rapidly being elucidated. There are various changes of microbial levels in models or in patients of various autoimmune diseases (AIDs). In addition, the relevant metabolites involved in mechanism mainly include short-chain fatty acids (SCFAs), bile acids (BAs), and polysaccharide A (PSA). Meanwhile, the interaction between microbes and host genes is also a factor that must be considered. It has been demonstrated that human microbes are involved in the development of a variety of AIDs, including organ-specific AIDs and systemic AIDs. At the same time, microbes or related products can be used to remodel body's response to alleviate or cure diseases. This review summarizes the latest research of microbes and their related metabolites in AIDs. More importantly, it highlights novel and potential therapeutics, including fecal microbial transplantation, probiotics, prebiotics, and synbiotics. Nonetheless, exact mechanisms still remain elusive, and future research will focus on finding a specific strain that can act as a biomarker of an autoimmune disease.

1. Introduction

Human health is significantly affected by commensal microbe. They normally colonize many sites of body, including respiratory tract, oral cavity, digestive tract, genitourinary tract, and skin. Especially in GI tract, approximately 100 trillion microorganisms are colonized here, containing > 1000 prevalent bacterial species [1–4].

Research of the interactions between gut microbiota and human health can be traced the 1900s. Scientific interest in microbiome entranced a recession with introduction of antibiotics, and antibiotics were thought to solve all bacterial infections. Nevertheless, conventional techniques of cultivating microbe can only detect 20% of microbe. They limited the range of detectable organisms [5,6]. DNA-based methods, simple and rapid, had been available since the 1970s [7,8].

Abbreviations: A-LPS, anionic lipopolysaccharide; AMP, anti-microbial peptide; AHR, aryl hydrocarbon receptor; AIDs, autoimmune diseases; BAs, bile acids; CYP7A1, cholesterol 7α-hydroxylase; DCs, dendritic cells; ERK, extracellular-signal-regulated kinase; FXR, Farnesoid X Receptor; FGF15, fibroblast growth factor 15; GPCRs, G protein-coupled receptors; HDACs, histone deacetylases; IAld, indole-3- aldehyde; IBD, inflammatory bowel disease; IL, interleukin; LP, lamina propria; Mfs, macrophages; mROS, mitochondrial reactive oxygen species; MS, multiple sclerosis; NF-κB, nuclear factor-κB; Nod2, oligomerization domain 2; OMVs, outer membrane vesicles; Pglyrp3, peptidoglycan recognition protein 3; PAD, peptidylarginine deiminase; PD, periodontal disease; PSA, polysaccharide A; P. gingivalis, porphyromonas gingivalis; Treg, regulatory T cell; RA, rheumatoid arthritis; rRNA, ribosomal RNA; SFB, segmented filamentous bacterium; SCFAs, short-chain fatty acids; Slc5a8, solute carrier gene family 5a, member 8; SLE, systemic lupus erythematosus; Th17, T helper cell 17; TLR 4, Toll-like receptor 4; TGF-β, transforming growth factor–β; T1D, Type 1 diabetes; ILC3s, type 3 innate lymphoid cells; ZO-1, zona occludens-1

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And the advent of DNA-based methods has made great progress in the 1980s. Thus high-throughput sequencing approaches have expanded scholars' horizon, by generating enormous new data sets that can be exploited for information on the composition and functional properties of tremendously greater numbers of microbial communities [9,10]. A recent research presents a new RNAseq-based metataxonomics protocol, dubbed IMSA + A, incorporates IMSA. This protocol can efficiently and firmly discern bacteria, fungi, and viruses in same sample and base on metatranscriptome data of any read length for accurate taxonomy classification [11]. Therefore, with the advance of sequencing and bioinformatics technologies, microbiome research has prompted a renewed focus on the contribution of microbiota to pathogenesis. Metagenomics tools analyzing sequencing data primarily include short marker sequencing such as 16S and 18S ribosomal RNA (rRNA) gene sequencing, and shotgun DNA sequencing [11–13]. 16S rRNA gene sequencing is extensively applied to phylogenetic reconstruction, nucleic acid-based detection, and quantification of microbial diversity [14]. And advances next-generation sequencing of 16S rRNA to enumerate microbiota have elucidated that humans are colonized with dozens of bacterial species within gut. Shotgun sequencing can explore profile taxonomic composition and functional potential of microbial communities and to recover whole genome sequences [10].

In the meantime, more studies show that microbes and metabolites play a key role in health and diseases. On the one hand, modifications in the composition of gut microbiota have been directly affected in a wide variety of human diseases [15,16]. On the other hand, the dysbiosis of host-associated microbiota has altered various metabolites [17]. Gut microbiota can produce myriad metabolites such as short-chain fatty acids (SCFAs), bile acids (BAs), polysaccharide A (PSA) [18]. In general, these microbe-related molecules can be broadly divided into three categories: 1) metabolites produced by microbial degradation diet, 2) microbial modifications of metabolites formed by host-generated precursors, 3) de novo synthesis of gut microbes' metabolites. One of the major products of intestinal microbial metabolites is SCFAs in which acetic acid, butyric acid, and propionic acid play an important role [19]. Studies indicate that gut microbiota and metabolites interact with many diseases. Examples of diseases include organ-specific autoimmune diseases (AIDs) and systemic AIDs [17,20]. And recent studies have revealed crucial effect of the microbe in host immune responses [21,22]. Microbial impact of immune response is mainly through regulatory T cell (Treg) and T helper cell 17 (Th17). Treg, playing an anti-inflammatory role in autoimmune disease, is activated by bacterial sets which include *Clostridium and Bacteroides species* in large intestine [23]. Treg activation can be mediated by a variety of signals, ranging from metabolites (SCFAs) [24–26] to bacterial structures (PSA) [27]. Th17 frequently occurs in intestine, attaching great importance to intestinal immune homeostasis by providing defense against extracellular bacteria and clearance of pathogens [28].

Furthermore, environmental factors are equally important and even more important than host genes' effects on gut microflora [29]. Fecal microbiota transplantation, probiotics, and prebiotics therapies provide new ideas for treatment [30]. Hence, this review mainly summarizes a vital role of microbiota and metabolites in pathogenesis of AIDs. In addition, related research status of AIDs and relevant therapeutic methods are introduced.

2. Microbiological related immune mechanism

2.1. Signal pathway of microbe

Gut microbiota as a signal molecule can directly regulate the symbiotic homeostasis of intestinal mucosa (Fig. 1). For instance, *segmented filamentous bacterium* (*SFB*) closely promotes differentiation of Th17. Th17 is induced by SFB via serum amyloid A expression, meanwhile intestinal CX3CR1 macrophages (Mfs) and MHCII expression on dendritic cells (DCs) are involved in Th17 induction [31–33]. Correspondingly, Interleukin (IL) -17R-dependent signaling regulates *SFB* colonization through α-defensins, polymeric immunoglobulin receptor, and Nox1 expression [34].

Through transforming growth factor–β (TGF-β) expression, Foxp3$^+$ Treg accumulation is mediated via colonization of *Clostridium* strains in gut lamina propria (LP), and this process can induce anti-inflammatory cytokine IL-10 production to maintain intestinal mucosal homeostasis [35].

A study finds that periodontal disease (PD) has a certain correlation with rheumatoid arthritis (RA) [36,37]. Between PD and RA, *Porphyromonas gingivalis* (*P. gingivalis*) may play a "bridge" role [38]. *P. gingivalis* is the major pathogen of PD and is the only gram-negative bacteria known to express peptidylarginine deiminase (PAD) [39]. Anionic lipopolysaccharide (A-LPS) promotes the formation of outer membrane vesicles (OMVs) via deacylation. The virulence factors (including PAD) of *P. gingivalis* can be transported to synovium joint via OMVs [40]. At the same time, OMVs also have immune escape and aggravate inflammatory status [41]. PAD being transported catalyzes the

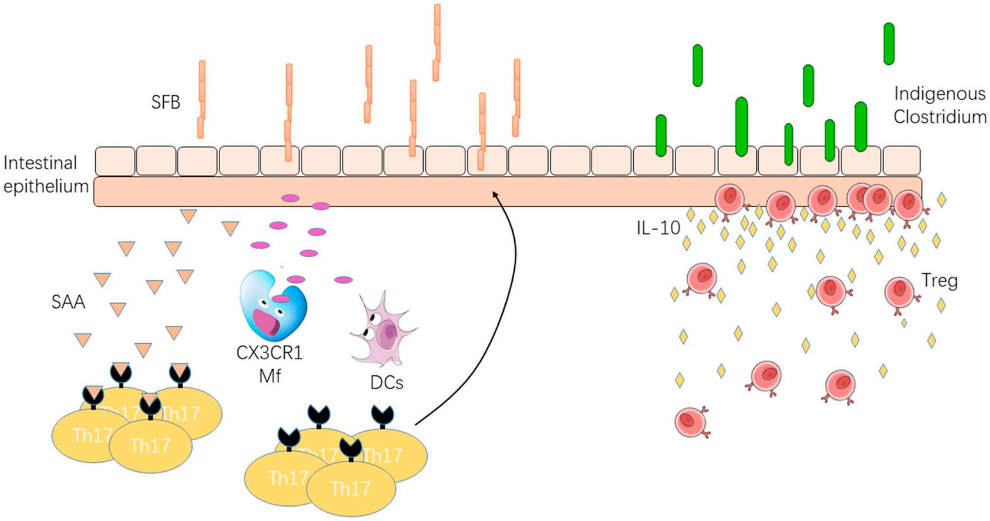

Fig. 1. Signal pathway of microorganism.

conversion of arginine residues to citrulline, leading to high-level citrullination in synovium [42,43]. Citrullinated proteins bind anti-cyclic citrullinated peptide antibody, one of specific indicators of RA [44,45], to produce immune complexes and bind Fc and C5a receptors of inflammatory cells, leading to inflammation in gums and synovium [46]. In addition, the peptide 19 from *P. gingivalis* heat shock protein 60 has also been found to drive epitope spreading in periodontitis-related AIDs [47,48], despite, the specific mechanism is unknown.

Other microbes may also have a direct immunomodulatory effect which is still undetermined and needs further study.

2.2. *Signal pathway of microbial dietary metabolites*

Microbial dietary metabolites can also participate in pathogenesis through related pathways, mainly including SCFAs and indole derivatives (Fig. 2). SCFAs, generated by anaerobic intestinal microflora fermentation of plant-derived polysaccharide, can maintain epithelial integrity as well as exert strong anti-inflammation by modulating immune response [49,50]. The concentrations of acetate, propionate, and butyrate, the most abundant SCFAs in intestinal lumen, have been found a significant decreasing trend from caecum to descending colon [51], suggesting differences in distribution and species of microbe in intestines.

SCFAs, especially butyrate, might inhibit inflammatory cytokines secretion, Mfs activation, and Toll-like receptor 4 (TLR 4) expression by reversing the aberrant expression of *zona occludens-1* (ZO-1) and reducing LPS translocation [52–54]. The development of LPS-stimulated DCs is blocked by butyrate. Moreover, Th1 development is blocked by butyrate through suppressing IL-12 production [55]. At present, the pathway of SCFAs regulating immune response is mainly divided into intracellular and extracellular pathways: extracellular and intracellular signaling pathways, including G protein-coupled receptors (GPCRs) and histone deacetylases (HDACs) [56].

Extracellular pathways are demonstrated to involve the epithelial cells surface ligands for SCFAs, including GPR41 (also known as free fatty acid receptor 3, FFA3), GPR43 (also known as FFA2) and GPR109A (also known as hydroxycarboxylic acid receptor 2, HCA2) [57]. GPR43 recognizes all three SCFAs, GPR41 recognizes propionate and butyrate, and GPR109A only recognizes butyrate [57,58].

A similar inflammation dysregulation has been observed in GPR43-deficient (Gpr43$^{-/-}$) and germ-free (GF) mice, and this status suggests that the binding of GPR43 with SCFAs is vital biological behavior in immunomodulatory properties [59]. The recognition of SCFAs and GPR43, including GPR109A, initiates the mechanism that involve membrane hyperpolarization resulting from K^{+} efflux and Ca^{2+} mobilization, triggering NLRP3 inflammasome activation. Meanwhile, caspase 1 is activated and then modify pro-IL-18 into IL-18 [60,61]. IL-18 might regulate goblet cell deletion and block the gene expression of goblet cell to prevent goblet cell maturation [62].

Moreover, several studies have found that GPR43$^{-/-}$ and GPR41$^{-/-}$ mice show lower inflammatory response and slower bacterial clearance, and indicate that GPR43 and GPR41 induce production of

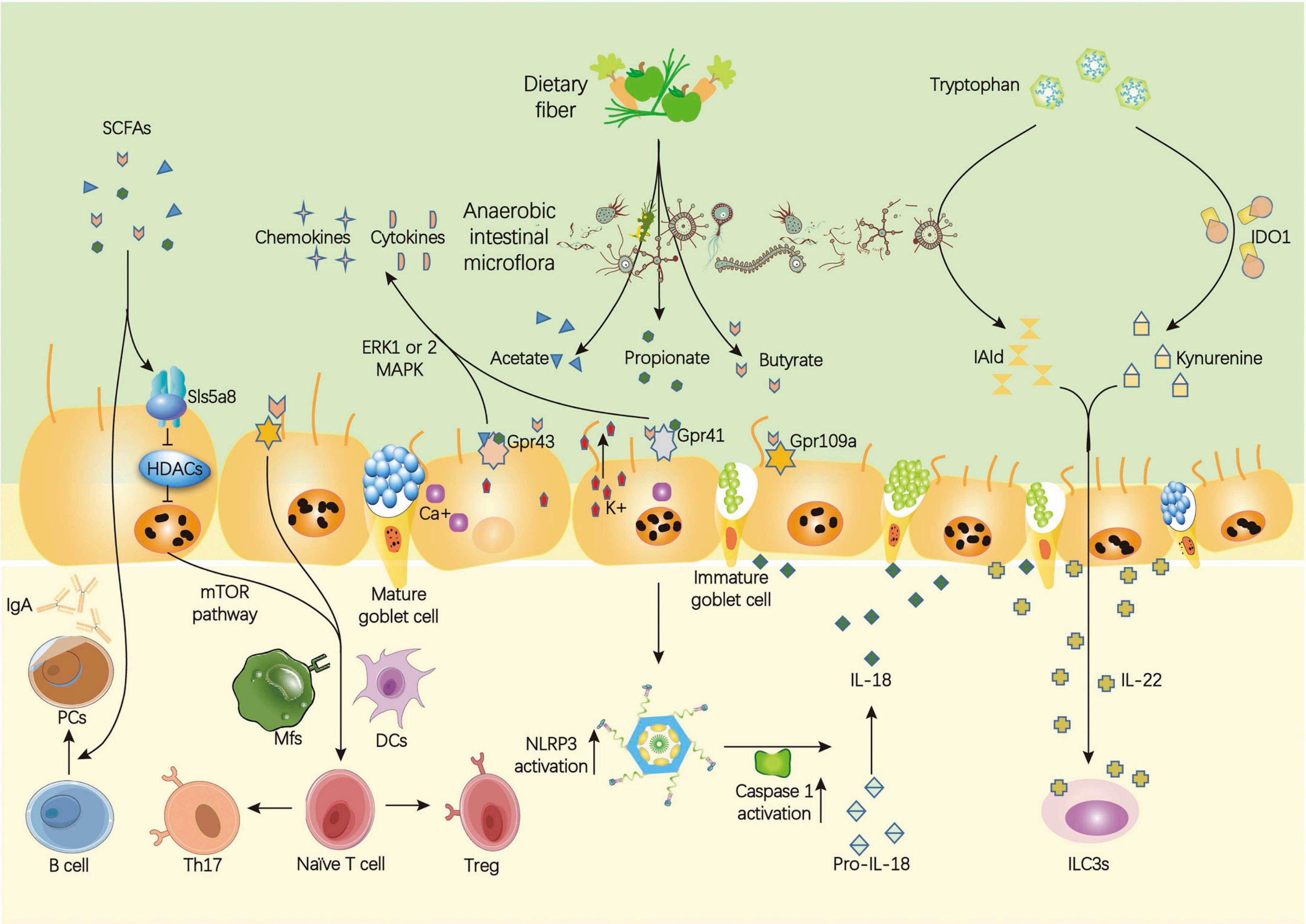

Fig. 2. Signal pathway of microbial dietary metabolites.

chemokines and cytokines by activating extracellular-signal-regulated kinase (ERK) 1 and 2 and p38 mitogen-activated protein kinases (MAPKs) signaling pathways in epithelial cells [63–65].

In addition to activating inflammation, GPR109A (encoded by Niacr1) exerts an epithelial barrier function by maintaining the balance between Treg and Th17. It has been reported that buryrate-GPR109A signaling induces the secretion of anti-inflammatory cytokine, such as IL-10, Aldh1a1, and IL-18 in colonic DCs and Mfs [58]. Niacr1$^{-/-}$-mice expresses an increased level of the pro-inflammatory cytokine IL-6 that induces the differentiation of naïve CD4^{+} T cell into pro-inflammatory Th17, as well as others, including Il1a, CCL2, CCL3, CXCL1, CXCL9, and IL-1b, whereas IL-10, IL-18, and tight junction protein claudin-3 decrease [58,66].

Concomitantly, SCFAs are transported by solute carrier gene family 5a, member 8 (Slc5a8), a Na^{+} – coupled high-affinity transporter in colon, into cell in the form of sodium salt [67–69]. Additionally, based on consistency of the concentration of SCFAs to the number of Treg, it is found that HDACs play a crucial role in intracellular transcriptional regulation [70,71].

Propionate and butyrate, but acetate, inhibit HDACs and promote histone crotonylation and thus reduce PU.1 and RelB promoter expression, causing that DCs development is blocked [25,69,72]. Accordingly, pro-inflammatory cytokines expressed by DCs are reduced and differentiation of Tregs are promoted [26,73]. This process involves that SCFAs increase acetylation of p70 S6 kinase and phosphorylation of ribosomal protein S6. These are a major target of mTOR pathway [74]. Furthermore, SCFAs can also be transported into B cell and play a HDACs inhibitory role. SCFAs produce energy through metabolic pathways to sustain antibody production and regulate plasma cell differentiation in B cell [75,76].

Despite these mechanisms, an increase in acetate inhibits the transport of *Bacterium coli O157: H7 Shiga* toxin from intestinal lumen to bloodstream [77]. Furthermore, goblet cell and mucin glycosylation are also involved in modulating intestinal barrier through *Bacteroides thetaiotaomicron* and *Faecalibacterium prausnitzii* [78]. Moreover, decreased diversity of microbiota is an obstruction to induce microglia maturation that is necessary to exert the innate immune response in brain [79,80]. These mechanisms remain to be clarified.

Beyond SCFAs, indole derivatives, degraded by gut microbiota, are also important metabolites from dietary components. Tryptophan is degraded by *Lactobacilli* into indole-3- aldehyde (IAld) that could bind aryl hydrocarbon receptor (AHR) expressed on type 3 innate lymphoid cells (ILC3s) to induce IL-22 expression, and then intestinal mucosal homeostasis is maintained [81–83]. In parallel, tryptophan is catabolized to kynurenine through enzymes indoleamine 2,3-dioxygenase 1 (IDO1) [84]. Kynurenine is another AHR agonist and exerts a similar regulation.

Recent years, arginine-related metabolites, such as spermine, participate in shaping intestinal mucosal homeostasis [85]. The process is elucidated that spermine and other metabolites eventually activate anti-microbial peptide (AMP) program through co-modulating NLRP6 signaling to secrete IL-18 in colon [85]. Yet, the effect of arginine-related metabolites has not been investigated thoroughly.

2.3. Signal pathway of co-metabolites of microbe and host

Over and above, microbe is also involved in processing of BAs (Fig. 3). Primary BAs, such as cholic acid and chenodeoxycholic acid, are synthesized in liver from cholesterol. Subsequently, primary BAs could be translated into secondary BAs, such as deoxycholic acid and lithocholic acid, by gut microbe [86]. Whether primary BAs or secondary BAs, they both maintain intestinal mucosal homeostasis through their binding and activation of nuclear receptor, Farnesoid X Receptor (FXR), and plasma membrane BAs receptor TGR5 [86,87]. The colonic mRNA expression of pro-inflammatory genes IL-1b, IL-6 is significantly inhibited by INT-747, the FXR agonist, by suppressing nuclear factor-κB (NF-κB) transcriptional activity [88]. Moreover, fibroblast growth factor 15 (FGF15) will inhibit the production of cholesterol 7α-hydroxylase (CYP7A1) which is a rate-limiting enzyme in BAs synthesis [84,89]. Liu et al. [90] observed that TGR5$^{-/-}$ mouse stomach exhibited an increased pro-inflammatory cytokines expression and elucidated TGR5 activation inhibited NF-κB transcription to suppress inflammation. In addition, CD4^{+} T effector (Teff) cells are induced by CD103^{+} DCs to express and upregulate the xenobiotic transporter Md1 in intestinal lumen. Correspondingly, Mdr1 maintains Teff homeostasis by averting conjugated BAs-driven oxidative stress [91]. Nevertheless, finer mechanism is not yet explicit. Similar with spermine, taurine also induces IL-18 secretion through NLRP6 activation and upregulates AMPs to maintain intestinal mucosal homeostasis [85].

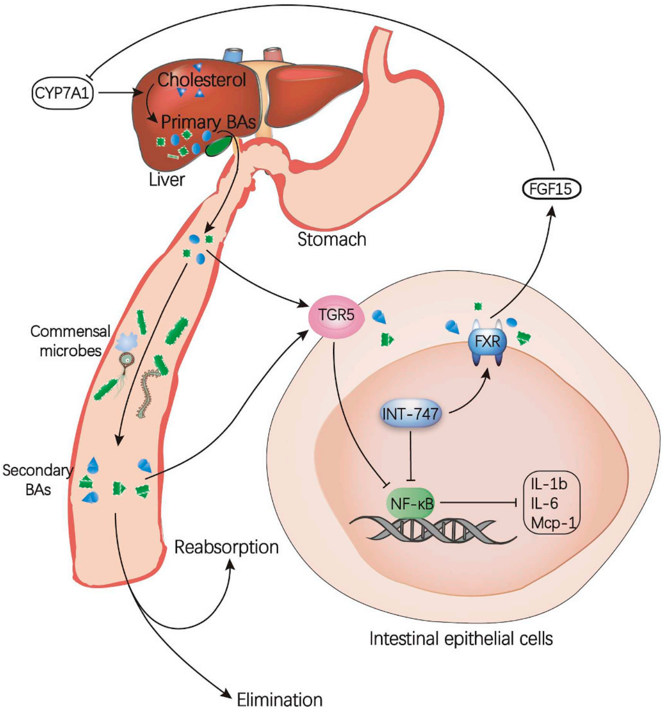

Fig. 3. Pathway of co-metabolites of microorganism and host.

2.4. Signal pathway of microbial synthesis products

In addition to related metabolites, microbes can also synthesize modulating molecules to maintain intestinal mucosal homeostasis (Fig. 4). For example, polysaccharide A (PSA), originated from *Bacteroides fragilis*, is also described as an immunomodulatory molecule. PSA activates the TLR 2 expressed on plasmacytoid DCs and induces CD4+ T cell to secrete IL-10, causing naïve CD4^{+} T cell differentiate into Th1 and restraining Th17 activity [92,93]. Via TLR 2 signaling, intestinal barrier could be retained by commensal microbiota colonization [94]. In addition, PSA also mediates CD4^{+} T cell into Foxp3^{+} Treg that exerts Th17 suppressive effect [27]. Also, PSA could promote CD39 expression, suggesting might have a common regulatory pathway with ATP [95].

In immune response, purinergic receptors, such as P2X7, recognize ATP to activate NLRP3 via K^{+} efflux and Ca^{+2} influx, contributing to IL-18 secretion. Similarly, mitochondrial reactive oxygen species (mROS) signaling also triggers NLRP3 activation [96]. Perruzza et al. [97] showed an altered microbiota composition in P2X7$^{-/-}$ mice and suggested ATP produced by intestinal microbiota inhibited IgA

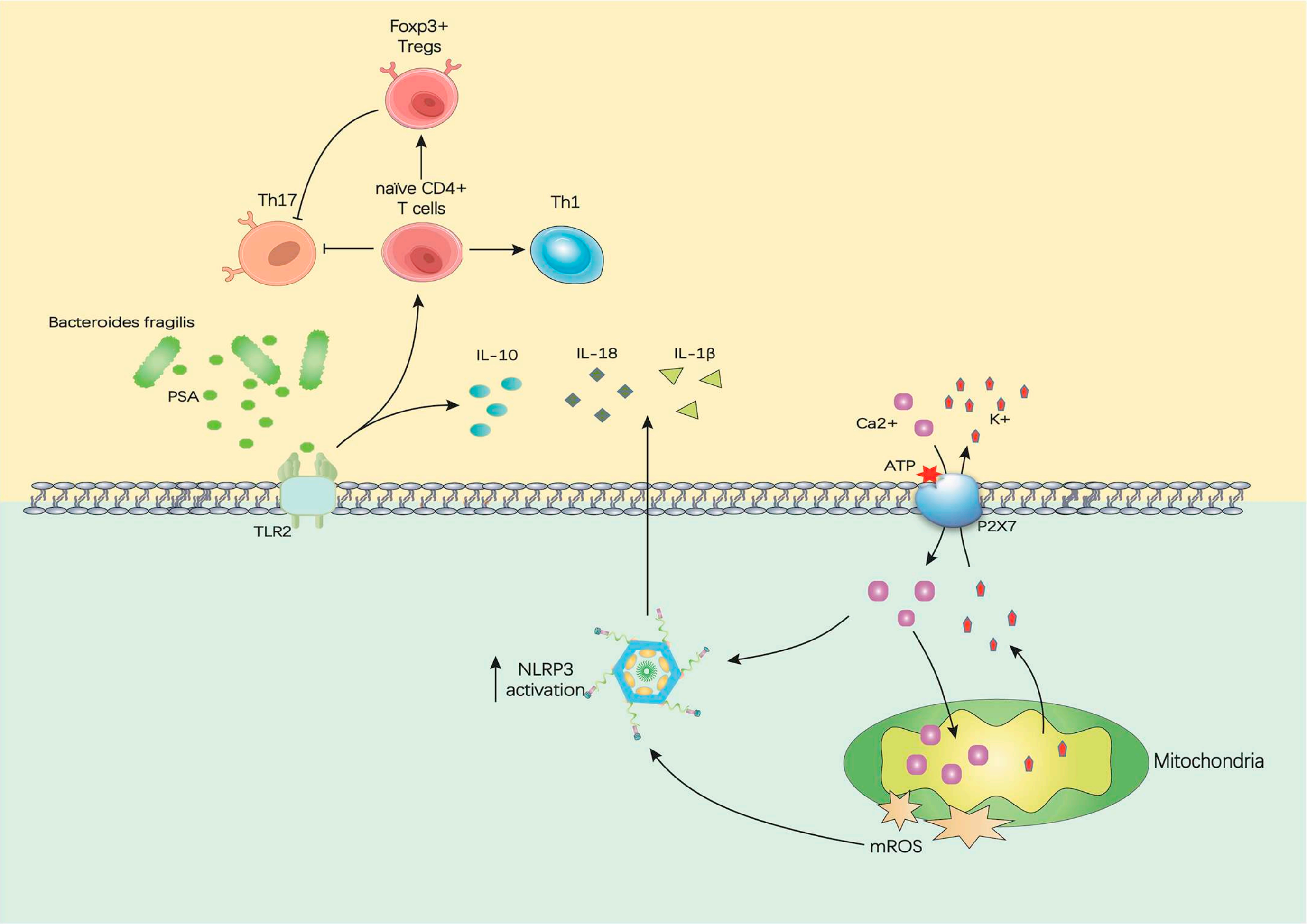

Fig. 4. Signal pathway of microbial synthesis products.

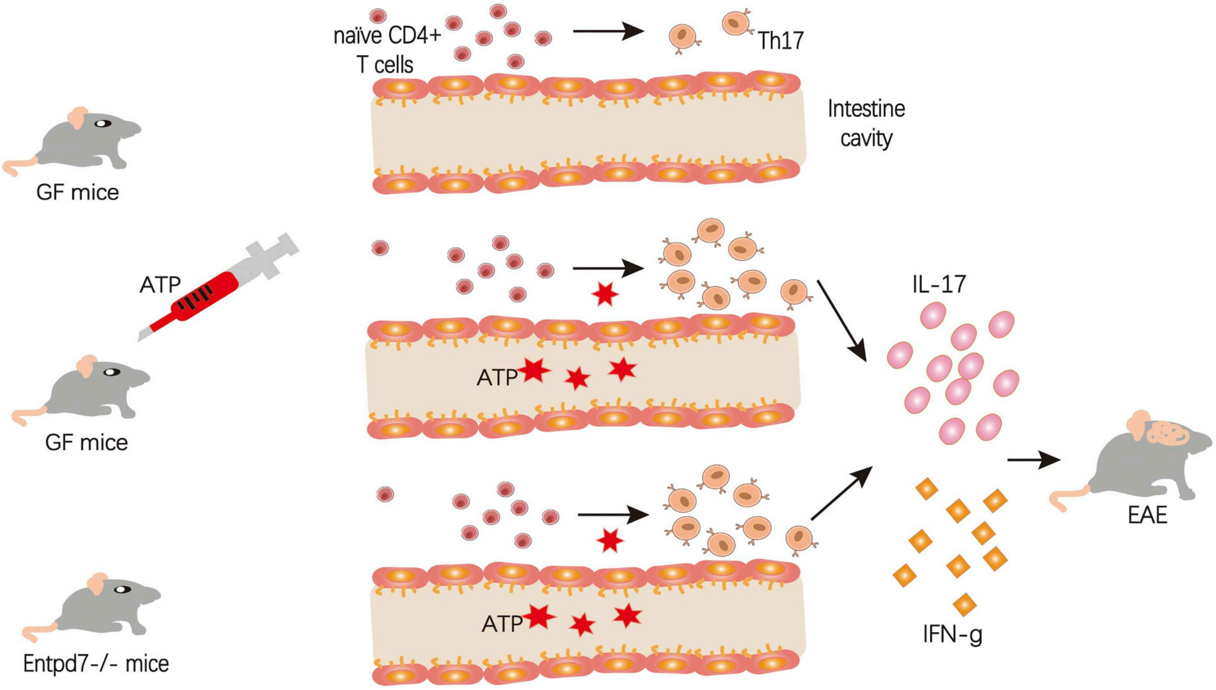

Fig. 5. Pathway of ATP and T cell differentiation.

response. At the same time, extracellular ATP is an essential regulator which depends on the balance between ATP and adenosine as a bidirectional regulation of anti-inflammatory and pro-inflammatory [98]. First, after adding ATP to GF mice, Th17 increases significantly, demonstrating ATP plays a role in differentiation of naïve CD4$^+$ T cell into Th17 [99]. ATP could be degraded into adenosine via Ecto-nucleoside triphosphate diphosphohydrolases (ENTPDases). Second, increased levels of IL-17 and interferon-γ (IFN-γ) are detected in Entpd7$^{-/-}$ mice that cannot encode ENTPDase7 and more susceptible to experimental autoimmune encephalomyelitis (EAE) [100] (Fig. 5).

3. Autoimmune diseases (AIDs)

The immune system is one of the most complex systems. The pathogenesis and related factors of diseases caused by immune system are still uncertain. It has been determined that the colonization of microbe in the intestinal tract of infants affects the development of AIDs in adulthood [101]. Recently, there have been a large number of reports that microbe may be involved in AIDs. For example, in AIDs, microbe can cause gender bias [102], and this situation may partly explain why some AIDs are responsible for a certain sex. Here, this article reviews AIDs that are mainly divided into organ-specific AIDs and extra-intestinal AIDs. Still, some of concrete results are diverse and different. These may be partly due to some factors, such as individual, race, and geography.

3.1. Organ-specific AIDs

3.1.1. Inflammatory bowel disease (IBD)

IBD, including ulcerative colitis (UC) and Crohn's disease (CD), has been reported an increasing prevalence trend around the world, especially in Europe and North America [103]. Similarly, the situation in China is not optimistic [104]. IBD is often associated with extra-intestinal complications, including liver damage [105]. The precise etiology and pathogenesis remain to be elucidated. On the one hand, it has identified > 200 IBD associated-susceptible genes and 163 loci associated with development of IBD [106,107]. On the other hand, the rapid increase in incidence of IBD in recent decades indicates that other factors besides genes are also involved. Among them, intestinal microbe plays an essential role [108,109].

The adhesion of pathogenic bacteria changes the diversity of intestinal microflora and further leads to IBD by activating inflammatory responses [110]. In addition, at phylum level, *Firmicutes* and *Actinobacteria* are more abundant in small intestine of IBD patients when compared with that in colon, whereas, *Bacteroidetes* are less abundant [111–113]. Collectively, it has been confirmed that a reduced microbial diversity in intestine of IBD patients. Further subgroup analysis demonstrates that IBD patients have fewer microbiota with anti-inflammatory properties (predominantly *F. prausnitzii*, *B. adolescentis*, *D. invisus*) and/or more microbiota with pro-inflammatory properties (predominantly *R. gnavus*) [114–117]. Specifically, it has been observed that abundance of *Prevotella*, *Eubacterium*, *Faealibacterium*, *Ruminococcus*, *Odoribacter*, *Akkermansia*, *Roseburia*, *Parabacteroides*, *Alistipes*, *Coprococcus*, *Dorea*, and *Ruminococcus* decrease, and abundance of *Escherichia*, *Klebsiella*, *Enterococcus*, *Bifidobacterium*, *Lactovacillus*, and *Veillonella* increase in IBD patients [109,118]. Moreover, it has been detected a decreased level of SCFAs in UC patients ($p = .014$) [119]. Studies also found that butyrate-producing bacterial species (including *Blautia faecis*, *Roseburia inulinivorans*, *Coprococcus*, *Ruminococcus torques*, *Clostridium lavalense*, *Bacteroides uniformis*, *Fecalibacterium prausnitzii*, and *Lactobacillus lavlense*) decreased in CD patients as compared with healthy individuals ($p < .05$) [113,120]. A study revealed that the levels of tumor necrosis factor-α (TNF-α) and IL-6 decreased and colitis was ameliorated in IL-10$^{-/-}$- mice after treatment with sodium butyrate [121]. These may suggest that SCFAs have a definite relationship with disease activity of IBD, but its specific causality is still unclear. Meanwhile, BAs level also changed. Compared with conventional mice, a GF mice model experiment showed a higher level of conjugated BAs and 3-OH-sulphated BA. Interestingly, IBD patients also had an increased conjugated BAs when compared with healthy individuals [122]. BAs have antibacterial effects. After the change in homeostasis of intestinal microbe, synthesis and metabolism of BAs are affected and then affect the homeostasis of intestinal mucosa [123,124]. ATP is also involved in pathogenesis of IBD. Peptidoglycan recognition protein 3 (Pglyrp3) and Nucleotide-binding oligomerization domain 2 (Nod2) are associated with IBD. A study demonstrated that Pglyrp3($^{-/-}$)Nod2($^{-/-}$) mice exhibited altered gut microflora and elevated ATP, resulting in higher sensitivity to DSS-colitis [125]. Altogether, microbes and their related metabolites play non-negligible roles in pathogenesis of IBD.

Meanwhile, changes in composition of microbe coincide with severity of the disease over time which is more conducive to understanding the dynamic changes in intestinal microbe in IBD development [126]. Additionally, 17 strains of *Clostridia* have been revealed to enhance Treg differentiation and induce IL-10, maintaining intestinal mucosal homeostasis [23]. Moreover, microbiota in intestine of mice exposed to dexamethasone have dramatically changed, indicting commensal microbiota may be a pivotal mediator of anti-inflammatory effects [127]. The anti-inflammatory and pro-inflammatory microbiota are not completely determined and additional, and in-depth analyses are remained to address these mechanisms.

3.1.2. Rheumatoid arthritis (RA)

RA is a chronic systemic inflammatory disease affecting over 20 to 30 million people worldwide [128]. The etiology of RA is multi-factorial. There have identified over thirty genes that are associated with RA in genome-wide association studies [129–132]. Besides, smoking, food intake, and other environmental factors may also participate in the onset of RA. Recently, more and more studies have shown that intestinal microbe plays important roles in etiology of RA [133].

A study showed that patients with RA revealed a significant decrease in intestinal microbial diversity when compared with controls [134]. Increased abundance of the phylum *Actinobacteria* and *Bacteroidetes* was identified in RA patients [134]. At genera level, studies showed that the abundance of some genera like *Bacteroides* and *Bifidobacteria*, decreased significantly in newly diagnosed RA patients, while *Lachnospiraceae bacterium*, *Actinomyces*, and *Lactobacillus* were enrichment [135–137].

In a classical RA model with collagen-induced arthritis (CIA), comparison of bacterial families over time revealed that family *Lactobacillaceae* significantly increased while *S24–7* decreased significantly at days 14 and 21, and family *Lachnospiraceae* increased significantly at day 35 when compared with baseline. Autoreactive B cell that develops at mucosal surfaces expands, circulates, and results in systemic autoimmunity [138]. Species *Prevotella copri* (*P. copri*) is also found more abundant in new-onset RA patients than in HCs. Moreover, it can reduce abundance of beneficial microbe. The SKG mice colonized with a P. copri-dominated microbiota from RA patients show increased numbers of Th17 in large intestine. In chronic RA patients with treatment and less disease severity, however, *P. copri* seems to be normal. One possible hypothesis is that this kind of species cannot thrive when less inflammation exists [137].

Recently, genes are verified to cooperate with gut microbiota to play roles in human health. DRB1*0401 gene in association with gut microbiome is proved to determine immune environment and susceptibility to arthritis. The DRB1*0401 gene may lead to a lower gut *Bacteroidetes/Firmicutes* (B/F) ratio. *Clostridia-like bacterium* (*Firmicutes* phylum) is dominated in susceptible individuals. Then gut immune system is prone to induce pro-inflammatory (Th1/Th17) responses [139].

A metagenomic study indicates that in newly diagnosed RA patients, dysbiosis of oral microbiota are related with gut microbiota. Further in RA patients the most association between disease and microbiota relate to the oral dysbiosis that is observed in patients with periodontitis [140]. RA and PD are chronic inflammatory diseases that share similar osteoclasia, HLA-DR4 allelic genes and immunological profile, and characteristic cytokines [141]. *P. gingivalis*, a usually mentioned bacteria in PD, has been found to increase significantly in RA patients when compared with control group [142].

To gain an insight into the causal mechanism of RA via periodontal infection, administered *P. gingivalis* W83 aggravated CIA in DBA/1 mice. A study demonstrated a significantly higher level of serum IL-17 in *P. gingivalis*-administered mice when compared with that in *P. intermedia*-, and sham-administered mice. The results demonstrated that the serum IL-17 level in *P. gingivalis*-administered mice was significantly higher than that in *P. intermedia*-, and sham-administered mice [143].

Especially, *P. gingivalis* increases serum Th17 response by increasing IL-17 level and decreasing serum level of IFN-γ [144–146]. Therefore, subgingival scaling can reduce the level of *P. gingivalis* to alleviate RA symptoms [147]. Considering smoking can contribute to more severe RA. Smoking can also increase the abundance of pathogenic bacterium like *P. gingivalis*. Whether smoking impact on RA by interrupting the balance of gut microbiota or by interacting with gut microbiota may become an interesting question needs to be solved.

Besides, metabolites of microbiota like SCFAs can also affect onset of RA. In K/BxN mouse model under GF conditions, serum autoantibody titers, splenic autoantibody-secreting cells, germinal centers and splenic Th17 population are reduced, followed by autoimmune arthritis also eased [148]. However, recent studies have concluded that gut microbiota regulated arthritis through T follicular helper cell but not Th17 through K/BxN autoimmune arthritis model [149,150].

3.2. Systemic AIDs

3.2.1. Systemic lupus erythematosus (SLE)

SLE is a chronic autoimmune disease affecting multiple tissues and organs, with a female to male ration of 9:1 [151–153]. Previous studies have proved that SLE is affected by genetic and external environmental factors [154]. With deepening of research in recent years, imbalance of intestinal flora, as an important internal environmental factor, is also proved to be related with SLE.

Selecting lupus-prone MRL/lpr mice as study objects, Zhang et al. [155] revealed that the abundance of phylum *Firmicutes* was disrupted. A significant reduction in the family *Lactobacillaceae* (under clsss "*Firmicutes_Bacilli*") and an increase in the family *Lachnospiraceae* (under class "*Firmicutes_Clostridia*") were found. Taking gender into consideration, situations were different. Higher family *Lachnospiraceae* and genus *Bacteroidetes S24–7*, and lower family *Erysipelotrichaceae* and genus *Bifidobacterium* were found in female than male MRL/lpr mice. Genus *Bifidobacterium* has anti-inflammatory functions. Therefore, sex-specific differences in gut microbiota may be partly explain in the onset and severity of SLE between males and females. In another SLE mice model of B6/lpr mice, the family *Clostridiaceae* and *Lachnospiraceae* were more abundant than controls [155]. Furthermore, in female NZB/W F1 lupus-prone mice, genera *Clostridium*, *Dehalobacerium*, *Lactobacillus* (family *Lactobacillaceae*), *Oscillospira*, *Dorea* (family *Lachnospiraceae*), *Bilophila* (family *Desulfovibrionaceae*), *AF12* (family *Rikenellaceae*), and an unnamed genus within the family *Ruminococcaceae* increased significantly from pre-onset to onset stages [156]. Results of the changes in *Lactobacillaceae* are inconsistent. These differences may be partly due to the following reasons: 1) types of mice are different. 2) The ages of two groups of mice are different 3) sample sizes are small, ranges from 3 to 5 in each strain/cage. 4) controls are different. 5) The times for collecting fecal samples are different. 6) The stages of disease are different. In addition, it was found that the intestinal microbial community of mice decreased variability and increased diversity after dexamethasone (Dex) treatment [156,157]. This suggests that one of the pathways of Dex treatment of SLE may be to relieve the imbalance of gut microbe.

Taking population as studies' objects, Hevia et al. [158] found a significantly higher B/F ratio in SLE patients in remission than in HCs. Another study from China also found a higher B/F ratio in SLE patients. Specifically, in phylum *Firmicutes*, genera *Pseudobutyrivibrio* and *Dialister* decreased in SLE patients, while *Eubacterium*, *Flavonifractor*, and *Incertae sedis* increased. But still, only the levels of the genera *Prevotella* in phylum *Bacteroidetes* were higher in SLE patients than in HCs. Phylum *Actinobacteria* and *Proteobacteria* were also more abundant in SLE individuals, which were represented by more genera *Rhodococcus* and *Eggerthella* in phylum *Actinobacteria* and genera *Klebsiella* in phylum *Proteobacteria* [159]. Different sample sizes, ethnicity, and Body Mass Index could partly explain the differences of these two studies. Among active SLE patients taking systematic SLE treatments, more Gram-negative bacteria and less diversity of microbiota were found. Genera *Odoribacter*, *Blautia*, and unnamed genus under the family *43 Rikenellaceae* decreased [156]. This suggested that SLEDAI (systemic lupus erythematosus disease activity index) and medication might be related with intestinal flora. More importantly, it should be emphasized that few researches take new-onset patients as objects. New-onset patients are less affected by medication and duration of disease. Therefore, the relationship between SLE and intestinal flora can be studied with less biases caused by factors listed above. Apart from the change of intestinal flora, the fecal metabolites in SLE individuals are significantly different from that of HCs, such as decreased levels of homoserine lactone and N-acetylmuramic acid and increased levels of ribose-1,5-bisphosphate [160].

The imbalance of Th17/Treg was confirmed to play important roles in the onset of SLE. Lopez et al. [161] found microbiota isolated from SLE patient fecal samples could promote lymphocyte activation and Th17 differentiation from naïve CD4$^+$ lymphocytes. This result discovered the mechanism of microbiota's impact on SLE. In contrast, *Bifidobacterium* supplementation could prevent over-activation of CD4$^+$ lymphocyte [161], thus providing a therapy to restore Th17/Treg balance to treat SLE. Meanwhile, *Lactobacillus* can reduce IL-6 and increase IL-10, so as to reverse Th17/Treg imbalance and to form an anti-inflammatory environment in MRL/lpr model of lupus nephritis [22]. Furthermore, in two spontaneous mice models of lupus (B6Sle.123 and NZBxNZW F1), *Lactobacillus reuteri* has also been shown to increase level of Treg [162]. Johnson et al. [163] found that (SWR 3 NZB) F1 (SNF1) mice receiving acidic pH water (AW) developed slower lupus nephritis than mice receiving neutral pH water (NW). At the same time, AW mice had higher levels of *Lactobacillus reuteri* and *Turicibacter spp.* (both belong to phylum *Firmicutes*) than NW mice. Furthermore, lower levels of IL-23, IL-21, IL-22, IL-17, IL-9 were found in AW mice than NW mice. This suggests that NW may be one of the risk factors of intestinal microbial imbalance, while AW can improve intestinal microbial environment and thus alleviate disease progression.

3.2.2. Type 1 diabetes (T1D)

T1D is a systemic AIDs characterized by T lymphocytes-mediated progressive damage of islet β cell. The pathogenesis of T1D involves genetic factors, environmental factors, and autoimmune factors [164–170]. As one of environmental factors, intestinal flora has a direct association with the occurrence and development of T1D, by changing intestinal permeability and host immune system [171–174].

Present literatures have indicated that specific gut microbiota may play a protective role in T1D [175]. At the same time, gut microbiota can interact with host gene. For example, TIR-domain-containing adapter-inducing interferon-β (TRIF)-deficient (TRIF$^{-/-}$) non-obese diabetic (NOD) mice showed significant changes in *Sutterella*, *Rikenella*, and *Turicibacter species*, compared with WT NOD mice. The inflammatory immune responses of WT NOD mice were more intense, while the proliferation of T cell in TRIF$^{-/-}$NOD mice were reduced. This suggested that TRIF deficiency can induce intestinal microbial changes and reduce immune cell activation, thereby inhibiting the development of diabetes in NOD mice [176]. Diabetes in NOD/Jax mice were higher rate than in NOD/MrkTac mice. It was further found that *Mucispirillum, genus AF12* of *Rikenellaceae*, *Odoribacter*, *SFB*, and *Akkermansia* in NOD/Jax mice were lower than those in NOD/MrkTac mice [177]. In a NOD mice model treated by vancomycin experiment, the incidence of diabetes was lower in neonatally treated group than in untreated group, and further gut microbiota composition analysis showed that vancomycin depleted most of the major genera of Gram-positive and Gram-positive bacteria. Among them, *Akkermansia (A.) muciniphila* dominated [178]. One study found that pH of drinking water may affect incidence of T1D in NOD mice. Compared with mice receiving neutral pH water (NW), the microflora diversity of mice receiving AW was restricted, accompanied increased in inflammatory cytokines and transcription factors and showed severe insulitis and differences in gut immune response [179]. When NOD mice were placed on NW, it was shown that there was an increased development of diabetes, exhibiting a decrease in Firmicutes (including *Lactobacillus sp*. and *Clostridia sp*.) and an increase in *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria* from as early as two weeks of age [180]. In the light of the role of *Firmicutes* and *Bacteroidetes* in AIDs, Giongo et al. [181] observed a temporal decline in *Firmicutes* and an increase in *Bacteroidetes* in individuals who were at risk for developing T1D, compared with healthy subjects. Similarly, individuals with T1D displayed lower abundances of *Firmicutes* and higher *Bacteroides* in their GI tract when compared with HCs [182]. After antibiotic treatment, overall microbial diversity in offspring of gestational NOD mice decreased when compared with untreated controls [183].

The specific mechanism of intestinal flora participation in T1D is not clear. It is believed that intestinal flora may be involved in the pathogenesis of T1D by changing the barrier function of intestinal tract and intestinal immune system. Gut microbiota promotes the expression of cathelicidin-related antimicrobial peptide (CRAMP) in pancreatic α- and β-cells through SCFAs and further prevents the development of T1D in NOD mice [184]. Moreover, acetate reduces the number of marginal zone B (MZB) cells which promote the proliferation of islet-autoantigen-reactive T cells, whereas butyrate enhances the function of Treg and further attenuates insulitis and diabetes in NOD mice [185]. And, SCFAs can enhance intestinal integrity and reduce the serum concentration of a diabetic risk factor such as IL-21 [186]. As we know, Bacteroides can not only enhance Treg and anti-inflammatory cytokine production [187], but also inhibit the activation of the NF-κB pathway which is involved in the induction of proinflammatory gene expression [187,188]. Moreover, Li et al. [189] found that myeloid differentiation factor-88 (MyD88) deficiency changed the composition of distal gut microbiota, and suggested that exposure to the microbiota of specific pathogen-free MyD88-negative NOD donors attenuated T1D in GF NOD recipients, and indicated that microbe was involved in the pathogenesis of T1D through natural immune antigen. In addition, TLR-3, MyD88, and gut bacteria were involved in the mechanism of polyinosinic: polycytidylic acid-induced diabetes in RIP-B7.1 model [190]. Besides, detection of mucosal-associated invariant T (MAIT) cells may be a new biomarker of T1D, providing a novel method for predicting T1D [191]. Overall, the relationship between gut microbiota and T1D is very complex, thus there is still room for future research.

Recently, prevention of T1D with intestinal flora as intervention target is gradually emerging. *SFB* induces production of Th17 in LP of NOD female mice [192], Meanwhile, *SFB* colonization also delays T1D in NOD mice when drinking AW, but not NW [179]. Furthermore, by providing specific probiotics, one can affect the colonization of intestinal tract in newborn infant or strengthen immune education in early life [193]. A multicenter longitudinal cohort study from TEDDY shows that SCFAs have a potential preventive effect on T1D [194]. It is expected that more effective treatments can be applied to clinic in the future.

3.2.3. Multiple sclerosis (MS)

MS is a chronic, demyelinating and degenerative disease characterized by repeated remission and relapse [195]. Regarded as an organ-specific autoimmune disease, the vast majority of MS studies base on EAE models [196]. It refers to a broad variety of experimental brain inflammation models which are distinguished by the genetics of experimental animal, target autoantigen, and the method of induction [197]. EAE models have provided evidence to suggest that intestinal microbiota significantly influence brain autoimmunity, such as MS [198]. Mechanistically, MS is driven by both genetic factors and environmental exposures [199–201], and gut microbiome as major environmental risk factor could lead to Treg deficiency and an activation of proinflammatory Th17 [202–204]. It has been shown that many gastrointestinal disorders with impaired intestinal barrier are associated with MS.MRI findings in patients with IBD show a marked increase in the severity of white matter (WM)and gray matter. It potentially indicates that central nervous system (CNS) demyelination is associated with intestinal barrier breakdown in gastrointestinal disorders [205]. The presence of gut-brain axis explains that imbalance of intestinal microbiome can affect function of CNS [206].

There were few studies on changes of bacterial flora in MS patients, but they reflected uniqueness of microbial changes [207]. Comparing microflora of untreated MS patients and HCs, intestinal mucosa in MS patients had higher levels of *Clostridium perfringens*, *Methanobrevibacter*, *A. muciniphila*, and *Acinetobacter calcoaceticus* and lower levels of *Butyricimonas* and *Parabacteroides distasonis* [208–211]. In comparison between patients, some patients with MS who have ameliorated disease had higher abundances of *Prevotella* and *Sutterella* and a lower abundance of *Sarcina* than untreated MS patients [211]. A study in pediatric patients with relapsing-remitting (RR) MS was found that a level of *Desulfovibionaceae* increased significantly, and levels of *Lachnospiraceae* and *Ruminococcaceae* decreased [212]. Branton et al. [213] also found a significant increase of *Proteobacteria* in progressive MS patients' cerebral WM, which was associated with increased inflammatory gene expression and related to a broader range of bacterial phyla in RR MS patients' WM. When comparing fecal samples from RR MS individuals and HCs, in MS patients, abundances of *Psuedomonas*, *Mycoplana*, *Haemophilus*, *Blautia*, and *Dorea genera* increased [214]. The changes in the composition of these gut microbes may be related to MS through different mechanisms.

Surely, some microbial metabolites have also been shown to be involved in MS. It has been shown that SCFAs in EAE model revealed an increase of Treg and suppressed Th17 differentiation [54], thus leading to inflammation. *Lactobacillus reuteri* is capable of metabolizing dietary Trp into an AHR agonist, such as IPA and IAld, and regulating astrocytes to relieve EAE [215]. Using RR mouse model of spontaneously developing EAE, Berer et al. [216] proposed that commensal gut flora was essential in triggering immune processes when pathogenic agents were absent, leading to MS driven by myelin-specific CD4^{+} T cells. Also, *SFB* significantly affected severity of EAE mainly via activation of gut-induced Th17 [217]. Moreover, Berer et al. [209] transferred human-derived microbiota into transgenic mice expressing a myelin autoantigen-specific T cell receptor, and found that gut microbiota from MS-affected twins induced CNS-specific autoimmunity at a higher incidence than microbiota from healthy co-twins.

Table 1
Related studies using FMT for different autoimmune disease subtypes.

Authors	Year	Country	Type of Study	Subjects enrolled	Gender	Age (y)	Disease type and duration	Pre-FMT medication
Angelberger *et al.* [139]	2013	Austria	Clinical trial	5 pts (FMT)	3 M + 2 F	22–51	UC/1.3–9.7 y	5-ASA, metronidazole
Kump *et al.* [140]	2013	Austria	Clinical trial	6 pts (FMT)	3 M + 3 F	17–52	UC/2-12 y	5-ASA, Adalimumab, Prednisolone, anti-TNF-a antibodies
Rossen *et al.* [141]	2015	Netherlands	Clinical Trial, Phase II/RCT	23 pts (FMT) and 25 pts (Autologous stool)	NM	NM	UC/NM	Thiopurines, Mesalamine
Moayyedi *et al.* [142]	2015	Canada	RCT	38 pts (FMT) and 37 pts (Water)	18 M + 20 M	42.2 ± 15.0	UC/NM	5-ASA, Glucocorticoids, Immunosuppressants, Anti-TNF therapy
Nishida *et al.* [143]	2017	Japan	Clinical Trial	41 pts (FMT)	28 M + 13 F	39.6 ± 16.9	UC/91.2 ± 103.3 m	5-ASA, glucocorticoids, immunomodulator, anti-TNF drugs
Paramsothy *et al.* [144]	2017	Australia	RCT	41 pts (FMT) and 40 pts (Discoloured and odoured water)	22 M + 19 F and 25 M + 15 F	35.6 (27.8–48.9) and 35.4 (27.7–45.6)	UC/5.8 y (3.4 – 9.0 y) and 5·8 y (2·7 – 9·4 y)	5-ASA, thiopurine, and MTX, Pred, ABX or probiotics, calcineurin inhibitors
Cui *et al.* [145]	2015	China	Clinical trial	30 pts (FMT)	19 M + 11 F	38.0 ± 13.83 (15–71)	CD/7.4 ± 5.3 y	Immunomodulator, Pred, anti-TNF,
Vaughn *et al.* [146]	2016	USA	Clinical trial	19 pts (FMT)	12 M + 7 F	36 ± 12.3	CD/12.5 ± 10.6 y	Mesalamines, steroids, Immunomodulators,

Authors	Stool dosage and dilutant	Severity of Disease	FMT delivery	Fecal stage (fresh/ frozen)	Follow-up (w) and frequency	Donor	Remission induction donor FMT vs control	Adverse events
Angelberger *et al.* [139]	60 g of stool + 250 mL of 0.9% sterile saline	Mayo score ≥ 6	NJT and Enema	Fresh	12 w/3	Unrelated Screened Donor	NM	Flatulence (2), Fever (1) Vomiting (1), Itchiness (1), Erythema (1), Paresthesia of the hip (1)
Kump *et al.* [140]	100–150 g + 200 ml–350 ml of sterile saline	Mayo 8–11	Colonoscopy	Frozen	90 d/1	Unrelated Screened Donor	0	Fever (1),
Rossen *et al.* [141]	60 g + 500 ml saline	SCCAI ≥4, Endoscopic Mayo Score ≥ 1	Nasoduodenal tube	Fresh	12 w/2	Unrelated Screened Donor or Patient-Selected Screened Donor	7/23 (30%) vs 5/25 (20%) $p = .51$	Fever (2), Nausea (2), diarrhea (5), Headache (1), Vomiting (1), Abdominal pain (1), Mild constipation (1)
Moayyedi *et al.* [142]	50 ml + 300 ml water	UC Mayo Score ≥ 4; UC Endoscopic Mayo Score ≥ 1	Enema	Fresh + Frozen	7 w/6	Unrelated Screened Donor or Patient-Selected Screened Donor	9/38 (24%) vs 2/37(5%) $p = .03$	worsening colitis (1), Patchy inflammation of the colon and also rectal Abscess formation (3),
Nishida *et al.* [143]	150–200 g + 500 ml of physiological saline	Mayo 3–9 with a Mayo endoscopic score of 1or greater	Colonoscopy	Fresh	8 w/1	Healthy adult relatives	0(11 of 41 pts. (26.8%) showed clinical Response)	No

(continued on next page)

Table 1 (*continued*)

Authors	Stool dosage and dilutant	Severity of Disease	FMT delivery	Fecal stage (fresh/frozen)	Follow-up (w) and frequency	Donor	Remission induction donor FMT vs control	Adverse events
Paramsothy *et al.* [144]	37.5 g + 97.5 ml saline (65%)	UC Mayo Score: 4–10	Colonoscopy and Enema	Frozen	8 w/40	Unrelated Screened Donor	11/41 (27%) vs 3/40 (8%) $p = .02$	Abdominal pain (12), Colitis (10), Flatulence (10), et al.
Cui *et al.* [145]	NM + NM	HBI ≥ 7 (m ± SD) 11.7 ± 4.5)	EGD	Fresh or Frozen	15 m/1	Unrelated screened donor or patient selected screened donor	76.7% (23/30) at first month	Fever (2), Diarrhea (7)
Vaughn *et al.* [146]	50 g of stool + 250 ml of sterile normal saline	Harvey Bradshaw Index (HBI) of ≥5	colonoscopy	Frozen	26 w/1	Unrelated screened donor	NM	Mild abdominal cramping or constipation, Fever' Hives (1)

5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine; ABX, antibiotics; AFM, amoxicillin, fosfomycin, and metronidazole; anti-TNF-α, antitumor necrosis factor-α; AZA, azathioprine; CD, Crohn's disease; CDAI, CD Activity Index; d, day; EGD, esophagogastroduodenoscopy; F, female; FMT, fecal microbiota transplantation; HBI, Harvey-Bradshaw Index; IBD, Inflammatory bowel disease; IFX, infliximab; m, month; M, male; MP, mercaptopurine; MTX, methotrexate; NJT, nasojejunal tube; NM, not mentioned; Pred, prednisone; PCDAI, Pediatric CD Activity Index; pts., patients; PUCAI, Pediatric UC Activity Index; SASP, salicylazosulfapyridine; SCCAI, Simple Clinical Colitis Activity Index; UC, ulcerative colitis; w, week; y, year.

Further, some targeted treatments have also been proposed. Fasting mimicking diet is considered a clinically feasible treatment for reducing the levels of pro-inflammatory cytokines and inducing lymphocyte apoptosis to improve disease severity in EAE models [218]. Recent studies have also found that the use of somatic cell-derived neural stem cells can effectively relieve the neurological inflammation in MS model mice and indicated that inflammatory metabolite succinate can activate the anti-inflammatory effect of neural stem cells [219]. Other treatments are still under exploration.

4. Therapeutic strategies

Therapies to relieve AIDs by regulating and restoring microbial homeostasis are diverse and have generality and particularity. This section briefly summarizes some of the treatment that improve AIDs symptoms by balancing microbe, mainly fecal microbiota transplantation (FMT), probiotics, prebiotics, and synbiotics. The main findings from the treatment in AIDs are presented in tables.

4.1. Fecal microbiota transplantation (FMT)

FMT for treatment of diseases has a long history. As early as the fourth century, Ge Hong, a Chinese physician, proposed using a fecal suspension to treat food poisoning and severe diarrhea. For now, FMT is most widely used to treat antibiotic refractory or recurrent *Clostridium difficile* infections (CDI) and has been reported to have a secondary cure rate of up to 98% [220].

For intestinal AIDs, there are also reports of FMT. In 1989, the first report of FMT for IBD was published. Bennet JD, who was suffered from continuously active, severe UC for many years, used himself as a subject to replace his own colonic flora with that of a disease-free donor. Six months later, his UC symptom was remitted without any medication [221]. Since then, FMT has drawn increasing attention for the treatment of IBD [222].

Many case series and clinical trials with large sample size were performed. These results were inconsistent. Detailed information is listed in Table 1 [90,223–238]. In 2015, RCTs related to FMT on UC were reported. Rossen et al. [230] conducted a single-center, double-blind, placebo RCT. There were only small differences in treatment effect between mild-moderately active UC patients who received FMT from healthy donors and those who received their own fecal microbiota. This might be partly due to small sample sizes and suboptimal mode of administration they applied. Moayyedi et al. [231] also evaluated the efficacy of FMT in active UC. They suggested that FMT induced remission in a statistically significant proportion of cases when compared with placebo. Besides, efficacy of FMT may be donor dependent. Paramsothy et al. [235] conducted a multicenter, double-blind, randomized, placebo-controlled trial at three hospitals in Australia. They found that intensive-dosing, multi-donor FMT induced clinical remission and endoscopic improvement in active UC patients. Patients achieving clinical remission had higher baseline microbial diversity and a greater increase in α-diversity with FMT (detailed information is listed in Table 1). To integrate clinical results, a systematic review and meta-analysis was performed. A total of fourteen clinical trials and four RCTs on FMT were included. This study found that FMT was more effective than placebo (OR = 3.67, 95% CI = 1.82–7.39) and had a lower rate of adverse events [239]; However, another systematic review and meta-analysis found that IBD still had an overall risk of deterioration of 14.3% (95%CI = 11%–19%) [240]. Zhang et al. [241] conducted a cost-effectiveness analysis using a Chinese cohort and found FMT was superior especially on improving the life quality and decreasing the medical and societal cost, for the moderate to severe IBD. From these studies, we can reach a conclusion that FMT is not "one size fits all". Individual baseline characters, FMT donors' number and features, disease severity, infusion doses, therapeutic methods used in control groups etc. need to be accounted before larger RCTs were conducted. Until now, the therapeutic effect of FMT on CDI has been confirmed, and holds promise in UC, but has not been fully studied in CD individuals [242]. And, the clinical remission rate of IBD is 22% [243].

There are not many studies of FMT in T1D. Feces from diabetes-protected MyD88-deficient NOD mice reduce insulitis and delay the onset of diabetes in NOD mice and result in a long-term change of host intestinal microbiota [244]. It is reported that FMT could regulate insulin signal transduction in MS patients [208,209]. Problem to be solved at present is to figure out which gut flora participated in development of MS, as well as promote the use of FMT and probiotics into clinical treatment. In general, clinical trials of FMT are still problematic in many processes [245].

In addition to viable bacteria, the composition of fecal includes colonocytes, archaea, viruses, fungi, protists, and metabolites [246]. Although this treatment has a promising application prospects, it can also increase the risk of pathogenic microbe infection for receptors [247]. In a randomized double-blind trial of 232 patients with CDI, 114 patients were given frozen FMT, 118 patients were given fresh FMT, and they all were analyzed at the 13th week, in per-protocol population, frozen FMT remission rate was 83.5%, and fresh FMT was 85.1%; in modified intention-to-treat (mITT) population, frozen FMT remission rate was 75%, and fresh FMT was 70.3%. There were no significant differences between two effects. It also pointed out that fecal preparation can be completed by disposable equipment, enema administration is less invasive than colonoscopy or nasal jejunal administration, and frozen FMT can reduce costs by reducing the number and rate of donor screening [248]. Therefore, setting the standard of donor bacteria screening applied in clinical treatment, and making use of its regulation function on the premise of safety is still in exploration [249].

Therefore, FMT therapy can be optimized through the following three points: 1) solve the problem of donor fecal heterogeneity via adaptive tests, 2) collect as much information as possible about the donor in trial to better assess donor heterogeneity, 3) use local or national stool banks to apply uniform standards [250]. In the future, we also need to understand FMT more accurately and make full use of its beneficial side.

4.2. Probiotics

Probiotics are considered to be live microorganisms that are administered in appropriate amounts to promote the health of host [251]. Probiotic treatment (mainly divided into single probiotics and various probiotics) is mainly used for intestinal diseases. The therapeutic effects of probiotics on some diseases are presented in Table 2 [252–278].

A case report stated that *Bifidobacterium* (six mg/day) were administrated on the 86th day when the drug (including salazosulfapyridine, prednisolone, oral mesalazine, ciclosporin, ganciclovir, vancomycin) was ineffective for a man with active UC, and colonoscopy was improved one week later [257]. Moreover, *bifidobacteria* administrated to UC also was applied. In 2004, Kato et al. [258] divided twenty mild to moderate, active UC patients into bifidobacterial-fermented milk group (BFM group, n = 10) and placebo group (n = 10). After twelve weeks, CAI, endoscopic activity index, and histological score of BFM group were significantly lower than those of placebo group, while SCFA concentration increased in BFM group. The limitations of this study were mainly short duration and small sample size. Furthermore, Ishikawa et al. [279] used a similar method to observe for one year, further confirmed that BFM supplementation had the effect of maintaining UC remission and preventing relapse. It has been indicated that *Bifidobacterium breve* prevented the recurrence of UC through an extracellular polysaccharide- and MyD88-dependent manner [280].

In treatment of UC, *E. coli Nissle 1917* (EcN) also entered the field of vision earlier. In 1997, Kruis et al. [267] enrolled 120 patients with inactive UC and conducted a double-bind, double-dummy study. EcN 1917 group and mesalazine group had similar relapse rates (16.0% vs 11.3%) and no serious adverse events at the twelfth week. Therefore, EcN 1917 could be proposed as an alternative to mesalazine. Similar results were also verified in 120 active UC patients [253]. A single-center, randomized, double-dummy study was conducted by Rembacken et al. [253]. After twelve months of follow-up, EcN 1917 was still found to have a same effect as mesalazine. Later, Kruis et al. [254] conducted a double-blind, double-dummy trial of 327 UC patients. The relapse rates were also similar (36.4% in EcN 1917 group vs 33.9% in mesalazine group, significant equivalence $p = .003$). EcN 1917 showed similar efficacy and safety as mesalazine in treatment of UC. Probiotic EcN 1917 is one of few probiotics that can effectively treat UC. This may be due to its ability to induce the production of human β-defensin 2 (HBD2) in intestinal epithelial cells [281]. Meanwhile, EcN-expressed TcpC protein upregulates claudin-14 through PKCζ and ERK1/2 signaling, thereby enhancing intestinal barrier function [282].

Two RCTs also showed that *Lactobacillus* was effective and safe for maintaining UC remission [260,261]. After enema with *Lactobacillus reuteri*, levels of IL-1β, TNF-α, and IL-8 in patients with UC were significantly reduced [262], suggesting that it may be used as a treatment for UC. Heat-killed Lactobacillus brevis K65 could reduce levels of TNF-α, IL-6, and IL-1β, and inhibit myeloperoxidase activity, further improve UC symptoms [283].

In order to reduce the incidence of adverse events, some scholars have also used a variety of probiotics to treat UC. As a mixture of various probiotics, VSL#3, a highly concentrated probiotic preparation consisting of eight kinds of human gastrointestinal microbiota, including *Lactobacilli* (*Lactobacillus casei*, *L. plantarum*, *L. acidophilus*, and *L. delbrueckii subsp. bulgaricus*), *Bifidobacteria* (*Bifidobacterium longum*, *B. breve*, and *B. infantis*) and *Streptococcus salivarius subsp. thermophilus* [284], is mainly used for UC. Sood et al. [275] conducted a multicenter, randomized, double-blind, placebo-controlled trial in UC patients. Both groups were given 3.6×10^{12} colony forming units (CFU) VSL#3 and placebo for twelve weeks. At the sixth week of observation, the UCDAI score of VSL#3 group was better than that of placebo group ($p = .001$). Meanwhile, in the twelfth week, 33 patients (42.9%) in VSL#3 group achieved remission when compared with 11 (15.7%) in placebo group ($p < .001$). Individual symptoms in VSL#3 group improved better and no major adverse event was reported [275]. In 2010, Tursi et al. [277] conducted a similar RCT and obtained consistent results with Sood et al., but there were minor side effects.

Guslandi et al. [285] initially demonstrated in 32 quiescent CD patients that *Saccharomyces boulardii* (*S boulardii*) could reduce the recurrence rate of patients ($p = .04$). However, an RCT enrolling 165 patients lasting 52 weeks found no significant difference in the relapse rate between *S boulardii* group and placebo group [267]. The factors that cause difference may be mainly sample size and others. But not all results were significant (detailed information is listed in Table 2).

A systematic review showed that the remission rate of probiotics to UC was higher than placebo ($p < .0001$, RR = 1.80), and there were no significant different adverse events between UC ($p = .94$, RR = 0.99) and CD ($p = .33$, RR = 0.87) [286]. Nevertheless, another systematic review showed that probiotics had a good effect on UC ($p = .007$), but no significant effect on CD ($p = .07$) [287], unlike the results of Derwa et al. [288]. Derwa et al. [288] found that probiotics had no effect on relieving active UC when compared with placebo (RR of failure to achieve remission = 0.86; 95% CI = 0.68–1.08). However, VSL#3 showed an effect [289]. The reasons for these differences may be the choice of database, search terms, and retrieval time. Therefore, in order to obtain more accurate results, a more comprehensive and large-scale RCTs are still needed.

Studies have shown that probiotic supplements can relieve experimental arthritis in rats. A systematic review and meta-analysis of 249 participants from six RCTs found a significant reduction in laboratory index C-reactive protein (CRP) (mg·L-1) and decreased inflammatory

Table 2
Related studies using probiotics for different autoimmune disease subtypes.

Authors	Year	Country	Type of Study	Subjects enrolled (Treatment/ Control)	Gender	Age (y)	Disease type and duration	Treatment method (treatment vs control)	Treatment medication	Severity of Disease	Follow-up	Remission induction treatment vs control	Adverse events
Rembacken *et al.* [159]	1999	UK	RCT	116 (57/59)	29 M + 28 F vs 32 M + 27 F	39(30– 60) vs 41(30– 49)	Active UC/5 y (2 - 12 y) vs 3 y (1 - 8 y)	Two capsules containing *EcN* 1917 vs Mesalazine	Oral gentamicin, Steroids, Aminosalicylates, AZA, Prednisolone	Activity index: 9 vs 11; Sigmoidoscopy score: 4 vs 4	12 m	Remission rate: 68%(39) vs 75%(44)	Similar relapse rate: 67%(26) vs 73%(32) Abdominal pain or bloating (8 vs 6); Headache (1 vs 1); Nausea (1 vs 1); Mouth ulcer (1 vs 0);
Kruis *et al.* [160]	2004	10 European countries/ Germany	RCT	327 (162/ 165)	ITT population: 56.8% M vs 52.7% M;	43 (19 – 69) vs 41 (19 – 82)	Quiescent UC/≤ 5 y: 71 (43.8%) vs 84 (50.9%), > 5 y: 91 (56.2%) vs 81 (49.1%)	200 mg of *EcN* 1917 vs Mesalazine 500 mg	Oral salicylates, Salofalk 500 mg, Mutaflor 100 mg,	CAI ≤ 4, EI ≤ 4	12 m	NM	Bloody stools, nausea, diarrhoea, mucous secretion (*EcN* 4.3%, mesalazine 4.2%), abdominal pain (*EcN* 0.6%, mesalazine 2.4%).
Nagasaki *et al.* [161]	2010	Japan	Case report	1	M	71	UC/NM	Bifidobacterium 6 mg/ day	Prednisolone, oral mesalazine, ganciclovir, vancomycin	Active	1 w	physical condition and colonoscopic findings were improved	NM
Kato *et al.* [162]	2004	Japan	RCT	20 (10/10)	5 M + 5 F vs 5 M + 5 F	Mean age: 30.2 vs 33.7	Active UC/3.4 y (0.3 - 12 y) vs 3.8 y(0.3 - 12 y)	100 mL/day of bifidobacteria-fermented milk vs PL	5-ASA (250 mg tablet, 2250–3000 mg/day) or SASP (500 mg tablet, 3–4 g/day)	Mean CAI score: 7.9 ± 0.8 vs 7.9 ± 0.6	12 w	Remission rate: 40%(4/10) vs 33%(3/9); The CAI score: 3.7 ± 0.4 vs 5.8 ± 0.8 ($p < .05$)	No
Zocco *et al.* [163]	2006	Italy	RCT	187 (65/60/ 62)	36 M + 29 F vs 34 M + 26 F vs 34 M + 28 F	34 ± 6 vs 33 ± 4 vs 33 ± 7	Quiescent UC/ 8 ± 5 vs 8 ± 4 vs 8 ± 7	Lactobacillus GG 18×10^9 viable bacteria/day vs mesalazine 2400 mg/ day vs Lactobacillus GG + mesalazine	5-ASA	0.86 ± 0.92 vs 0.91 ± 0.84 vs 0.92 ± 0.82	12 m	maintaining clinical remission: 85% vs 80% vs 84%	NM
Wildt et al. [164]	2011	Denmark	RCT	32 (20/12)	6 M + 14 F vs 4 M + 8 F	40.5 (23 – 68) vs 35.5 (25 – 67)	Quiescent UC/ 51.5 m (3 – 288 m) vs 33.5 m (2 – 194 m)	1.25 × 1010 CFU Lactobacillus acidophilus La-5 and Bifidobacterium animalis subsp. lactis BB-12 (Probio-Tec AB-25) vs identical appearing PL	5-ASA orally and rectally, prednisolone	SCCAI: 0.5 (0 – 2) vs 0.5 (0 – 1)	52 w	Remission: 25% (5/20) vs 8% (1/ 12) (ITT $p = .37$)	Flatulence, abdominal bloating and pain (4 vs 2), Arthralgia, sacroilitis (2 vs 0), Tiredness, incontinence, stress, oral blisters, eye dryness (6 vs 2), Headache, dizziness (2 vs 2), Influenza, gastroenteritis, cystitis and pneumonia (3 vs 2)

(*continued on next page*)

Table 2 (*continued*)

Authors	Year	Country	Type of Study	Subjects enrolled (Treatment/ Control)	Gender	Age (y)	Disease type and duration	Treatment method (treatment vs control)	Treatment medication	Severity of Disease	Follow-up	Remission induction treatment vs control	Adverse events
Oliba *et al.* [165]	2011	Italy	RCT	30 (16/14)	9 M + 7 F vs 8 M + 6 F	12.5 (7– 18) vs 13 (7– 18)	Children with UC/2 y (0.6–4.5 y) vs 2 y (0.5–4.4 y)	10^{10} CFU of *L. reuteri* ATCC 55730 vs PL	Anti-inflammatory drugs, oral mesalazine, Immunomodulators, Biologics	Mayo score: 8.6 ± 0.8 vs 8.7 ± 0.7	8 w	Clinical remission: 31% of L. reuteri group and in no patient on PL ($p < .05$);	No
Bourreille *et al.*	2013	France	RCT	165 (84/81)	22 M + 58 F vs 23 M + 56 F	37.9 ± 14.2 vs 35.9 ± 13.2	CD/1.2 y vs 3.2 y	1 g/d of *Saccharomyces boulardii* vs PL	Prednisone, AZA/6-MP, MTX	CDAI: 71.4 ± 44.6 vs 61.3 ± 45.5	52 w	NM	diarrhea, arthralgia, constipation, and abdominal pain
Sood *et al.* [167]	2009	India	RCT	147 (77/70)	43 M + 3 M vs 45 M + 25 F	39.8 ± 13 vs 38.3 ± 12.5	Active UC/NM	3.6 × 10^{12} CFU VSL#3 vs PL	Mesalamine (2400 mg vs 2400 mg), AZA, corticosteroids	UCDAI: 6(4–8) vs 6(3–9)	12 w	Remission: 42.9% (33/77) vs 15.7% (11/70) ($p < .001$) UCDAI: 51.9%(40/77) vs 18.6%(13/70) ($p < .001$)	Abdominal bloating and discomfort (14/77), Unpleasant taste (7/77)
Tursi *et al.* [168]	2010	Italy	RCT	144 (71/73)	49 M + 22 F vs 44 M + 29 F	47.7 ± 14.1 vs 46.4 ± 14.4	Active UC/NM	3600 billion CFU/day VSL#3 vs PL	oral 5-ASA and/or AZA or 6-mercapropurine, mesalamine, balsalazide, MTX.	UCDAI: 5.52 ± 1.33 vs 5.42 ± 1.43	8 w	Remission rates 47.7%(31/71) vs 32.4%(23/73) (PP $p = .069$; ITT $p = .132$);	VSL # 3 group: Dizziness (1), Flu-like syndrome (1), Abdominal bloating and discomfort (6) PL group: Fever (1), Cystitis (1), Abdominal bloating (3), Unpleasant taste (4)

5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine; AZA, azathioprine; CAI, clinical activity index; CD, Crohn's disease; CDAI, CD Activity Index; CFU, colony-forming units; Cipro, Ciprofloxacin; d, day; DAI, Disease Activity Index; *EcN*, *Escherichia coli* Nissle; EI, endoscopic index; F, female; ITT, intention-to-treat analysis; m, month; M, male; MP, mercaptopurine; MTX, methotrexate; NM, not mentioned; PDAI, pouchitis disease activity index; PL, placebo; PP, per protocol analysis; pts., patients; SASP, salicylazosulfapyridine; SCCAI, Simple Clinical Colitis Activity Index; UC, ulcerative colitis; UCDAI, UC disease activity index; w, week; y, year.

Table 3
Related studies using prebiotics and synbiotics for different autoimmune disease subtypes.

Authors	Year	Country	Type of Study	Subjects enrolled (Treatment/ Control)	Gender	Age (y)	Disease type and duration	Treatment method (treatment vs control)	Treatment medication	Severity of Disease	Follow-up	Remission induction treatment vs control	Adverse events
Hafer *et al.* [296]	2007	Germany	RCT	31 (UC: 7 vs 7/ CD: 9 vs 8)	UC: 4 M + 3 F vs 3 M + 4 F CD: 4 M + 5 F vs 4 M + 4 F	UC: 38.8 ± 12.4 vs 38.1 ± 8.8 CD: 30.7 ± 7.0 vs 33.5 ± 11.7	14 UC + 17 CD/UC: 8.3 y ± 12.2 vs 9.3 y ± 5.0; CD: 5.0y ± 5.4 vs 6.7y ± 9.8	10 g lactulose daily vs drug	Prednisolone, 5-ASA, Immunosuppressive drugs	NM	4 m	Remission: UC: 4 vs 0 CD: No	Lactulose group: minor side effects (4), UC: increased defecation frequency and slight flatulence (1), abdominal pain (1) CD: abdominal pain (1), decreased stool consistency (1)
Ishikawa *et al.* [297]	2010	Japan	RCT	41 (21/20)	15 M + 6 F vs 11 M + 9 F	43.6 ± 13.2 vs 47.4 ± 12.0	UC/NM	5.5 g of GOS once a day vs 1 g of the probiotic powder (10^9 CFU/g) three times a day	salazosulfapyridine, mesalazine, steroids	NM	1 y	NM	NM
Benjamin *et al.* [298]	2011	UK	RCT	103 (54/49)	18 M + 36 F vs 22 M + 27 F	40 ± 14.8 vs 39 ± 13.7	CD/11 ± 7.7 vs 10 ± 7.6	Prebiotic: Fructo-oligosaccharides	Immunosuppression, AZA, MTX, 5-Aminosalicylates, Prednisolone	CDAI: 283 ± 61 vs 286 ± 62	12 w	NM	FOS group: Disease deterioration (3), acute asthma attack (1) PL group: disease deterioration (1), car accident (1)
Furrie *et al.* [299]	2005	UK	RCT	18 (9/9)	3 M + 5 F 5 M + 3 F	45 (24–6) vs 38 (26–59)	Active UC/10 y (1–23 y) vs 7 y (1–15 y)	2×10^{11} Bifidobacterium longum in a gelatin capsule and a sachet containing 6 g of prebiotic fructo-oligosaccharide/ inulin mix (Synergy 1) vs PL	Steroids, Immunosupressants, 5-ASA	CAI: 5.6 (2–13) vs 4.7 (1–8)	1 m	NM	No
Chermesh *et al.* [300]	2007	Israel	RCT	30 (20/10)	15 M + 5 F vs 8 M + 2 F	Age at diagnosis: 25.4 ± 7.6 vs 27.4 ± 11.5	CD	Symbiotic 2000 vs PL	5-ASA, steroids	NM	24 m	NM	NM

5-ASA, 5-aminosalicylic acid; CAI, clinical activity index; CD, Crohn's disease; CDAI, Crohn's disease activity index; d, day; F, female; GOS, galacto-oligosaccharide; m, month; M, male; NM, not mentioned; PL, placebo; pts., patients; UC, ulcerative colitis; w, week; y, year.

cytokines TNF-α and IL-1β but increased IL-10 expression in intervention group, but patients' DAIs have not yet been significantly improved [290]. The potential benefits of such an approach remain to be defined. Increasing studies have proved that probiotics, especially *Lactobacillus* and *Bifidobacterium*, can alleviate most symptoms of MS, such as improving the level of glucose tolerance, down regulation of intestinal inflammation etc. [291,292]. Results were confirmed in the MS animal models induced by high-fat feed. In particular, *Bifidobacterium* increases expression of closely linked protein, thereby enhancing the function of intestinal epithelial barrier in MS patients. Lactic acid bacteria (LAB) can stimulate the oxidation of fatty acids and regulate serum lipid metabolism by producing conjugated linoleic acid. Probiotics are a peptic polysaccharide, and it can adjust intestinal probiotics in proportion, can increase glucagon-like peptide (GLP)-1, reduce cheese casein peptide express and the accumulation of fatty acids, thus relieving a series of MS symptoms [293,294].

Recently, prebiotics and synbiotics can also be used as new treatments. Prebiotics, "foods" for probiotics, are defined as a substrate that is selectively utilizable by the host microorganisms conferring a health benefit [295]. These substances mainly include oligosaccharides and can further degrade fructo-oligosaccharides (FOS) (oligofructose and inulin), galacto-oligosaccharides (lactulose), and gluco- and xylo-oligosaccharides. Related detailed information is listed in Table 3 [296–300]. As early as twenty years ago, Gibson et al. [301] found that FOS significantly increased the level of *Bifidobacteria* in feces of healthy subjects, while levels of *Bacteroides*, *Fusobacteria*, *Clostridium*, and *gram-positive cocci* decreased. There were few clinical trials of probiotics. It may be for the relationship between the use of prebiotics and human health remains unclear [302]. In order to combine the advantages of probiotics (mainly *Lactobacillus* and *Bifidobacterium*) and prebiotics (mainly inulin and psyllium), the concept of "synbiotics" was proposed. The combination of prebiotics and probiotics is called a synbiotic and acts synergistically. Some studies on synbiotics are also being carried out hotly (detailed information is listed in Table 3). In 2008, Fujimori et al. [303] randomly divided 120 UC patients into three groups and treated them with probiotics (*Bifidobacterium longum* 2×10^9 CFU), prebiotics (daily 8.0 g doses of psyllium) and synbiotics (including both). Among them, at the end of observation, the IBDQ score of synbiotic treatment group was higher than that of probiotic group and prebiotic group, and CRP was also significantly reduced.

Due to limitations of FMT, probiotics, prebiotics, and synbiotics, a new therapy based on the metabolite from secretion, regulation or degradation of microorganisms has been proposed. Guanylate cyclase-C (GC-C) has been proposed as a new target for gastrointestinal diseases, including IBD. GC-C receptor is activated by uroguanylin and guanylin, resulting in the formation of cyclic GMP, maintaining intestinal barrier function and exerting anti-inflammatory effects [304]. However, more large-scale RCTs are still needed to correct them.

5. Conclusion and future perspectives

Overwhelming literature reported that the imbalance of gut microbe was associated with AIDs. It should be pointed out that relevance is not equal to causality. This article describes mechanisms by which microorganisms and their associated metabolites are involved in disease development, and details their association with several AIDs. The association between gut microbiota and health is very complicated, with no definition of good or bad bacteria [305]. First, there is no specific authoritative report on how to allocate the proportion of normal microbiota or pathogenic microbiota. Because of factors such as individual, race, and geography, gut microbiota is affected. Second, differences of research methods will lead to differences in sequencing results of a disease group. At present, enlarging sample size is an ideal way to increase statistical significance, so as to determine differences that are caused by intervention as much as possible. Meanwhile, abuse of antibiotics and microbial resistance also add to this complexity and become a global problem. Jacinta et al. [306] introduced in detail the two-way effects of drugs and gut microbes, including the effects of drugs on intestinal microbial function and composition and the metabolic changes of drugs produced by microorganisms. Twenty-seven percent of non-antibiotics inhibited the growth of at least one species, while some species had a tolerant effect on one or more drugs. Understanding the interaction mechanisms between gut microbes and drugs can take new ways to reduce drug side effects, improve drug efficacy, and alleviate antibiotic resistance [307]. More efforts are needed to solve these problems. Microorganisms and related products have also been used to treat some AIDs, and some good on-the-spot effects have been achieved, but problems still exist. The mechanism of treatment remains unclear and controversial. Future has great research value.

Take-home messages

- Autoimmune diseases are universal diseases in the world. There is no exact cause, but only multiple factors are involved in their pathogenesis.
- At present, the effects of gut microbes on human health have been gradually amplified, and it has been shown that gut microbes have a negligible relationship with autoimmune diseases.
- Gut microbes participate in the pathogenesis of autoimmune diseases in different structural forms (mainly includes short-chain fatty acids, bile acids and polysaccharide A).
- Patients with various autoimmune diseases (IBD, RA, SLE, T1D and MS) exhibit different levels of intestinal microbial composition and changes in their bodies.
- The use of microorganisms or related preparations can effectively alleviate symptoms of patients with autoimmune diseases clinically, but there are still some problems.

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Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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