The impact of the gut microbiome on extra-intestinal autoimmune diseases

Eiji Miyauchi[1,7,8], *Chikako Shimokawa*[1,2,8], *Alex Steimle*[3], *Mahesh S. Desai*[3,4]✉ *and Hiroshi Ohno*[1,5,6]✉

Abstract | The prevalence of autoimmune diseases (ADs) worldwide has rapidly increased over the past few decades. Thus, in addition to the classical risk factors for ADs, such as genetic polymorphisms, infections and smoking, environmental triggers have been considered. Recent sequencing-based approaches have revealed that patients with extra-intestinal ADs, such as multiple sclerosis, rheumatoid arthritis, type 1 diabetes and systemic lupus erythematosus, have distinct gut microbiota compositions compared to healthy controls. Faecal microbiota transplantation or inoculation with specific microbes in animal models of ADs support the hypothesis that alterations of gut microbiota influence autoimmune responses and disease outcome. Here, we describe the compositional and functional changes in the gut microbiota in patients with extra-intestinal AD and discuss how the gut microbiota affects immunity. Moreover, we examine how the gut microbiota might be modulated in patients with ADs as a potential preventive or therapeutic approach.

Autoimmune diseases (ADs) are characterized by dysregulated immune responses to self-antigens, resulting in chronic inflammation. Although both genetic and environmental risk factors (such as smoking, toxic chemicals, or infections and molecular mimicry (BOX 1)) have been implicated in the development of ADs, over the past decade, it has been postulated that modifications in the composition of the gut microbiota, which are closely associated with lifestyle changes[1–3], may underlie the rapid increase in ADs. The human gastrointestinal tract harbours a diverse population of organisms, including bacteria, fungi, viruses and sometimes parasites, which interact with each other and with the immune system. Next-generation sequencing (NGS) techniques have revealed that the genes of gut microbes outnumber human genes by ~150-fold[4], and that the gut microbiota displays unique metabolic activities. Recent studies using NGS and related omics approaches examined the composition of the gut microbiota and microbial metabolites in several extra-intestinal ADs, including multiple sclerosis (MS), rheumatoid arthritis (RA), type 1 diabetes (T1D) and systemic lupus erythematosus (SLE) (TABLE 1). These studies found that not only an altered composition of the gut microbiota but also some specific bacterial taxa and their metabolites show associations with clinical indices in patients with extra-intestinal ADs. Here, we highlight recent progress in our understanding of how the gut microbiome is altered in these ADs and how these alterations may affect immune cells. We also discuss potential therapeutic strategies to modulate the gut microbiome in order to treat extra-intestinal ADs, mainly focusing on studies conducted in experimental models of MS and in patients with MS.

✉*e-mail: mahesh.desai@lih.lu; hiroshi.ohno@riken.jp*

https://doi.org/10.1038/s41577-022-00727-y

Alterations in the gut microbiome in ADs

The gut microbiota contribute to the maturation and activation of the mucosal and systemic immune system. Alterations in the bacterial composition of the gut microbiota (with regards to both richness and structure) and their association with dysregulated immune responses have been discussed in many diseases, and sequencing-based analyses have revealed distinct compositions of gut microbiota in patients with various extra-intestinal ADs (TABLE 1).

Multiple sclerosis. MS is characterized by chronic inflammation and demyelination in the central nervous system (CNS). In addition to genetic factors[5], environmental factors, including diet and viral infections, contribute to the risk for MS development[6,7]. Pro-inflammatory autoreactive T cells, especially T helper 17 (T_H17) cells, play a key role in CNS inflammation[8,9]. Impairment in immunosuppressive cells, such as FOXP3$^+$ regulatory CD4$^+$ T cells (T_{reg} cells), are also a feature of this disease[10]. The pivotal role of the microbiota in the development of MS was discovered a decade ago in mice with experimental autoimmune encephalomyelitis (EAE), a model of MS[11,12]. Thereafter, NGS studies focused on the gut microbiota in patients with MS. In 2015, Miyake et al. first reported dysbiosis in patients with MS[13], with

a significant reduction of spore-forming clostridial species that can induce colonic T_{reg} cells[14,15]. Subsequently, dysbiosis in patients with MS was also shown by other groups[16–21] (TABLE 1). Although the disease-associated bacteria are distinct among studies, likely owing to differences in sample preparation methods[22] and the ethnicity of patients, some common features were identified. For example, the genera *Prevotella* and *Parabacteroides* were decreased in faeces of patients with MS[13,18,20,21]. *Prevotella histicola* has been shown to suppress inflammatory responses in the spinal cord of EAE mice by inducing T_{reg} cells[23]. *Parabacteroides distasonis* were also shown to induce T_{reg} cells upon mono-colonization in EAE mice[24].

By contrast, *Akkermansia muciniphila*, a well-known mucin degrader[25,26], is commonly increased in patients with MS[17,20,21]. Although a number of studies have demonstrated an association of *A. muciniphila* with obesity, colitis and the antitumour efficacy of anti-PD1 immunotherapy[27–29], its role in ADs remains elusive. One possibility is that *A. muciniphila* promotes the differentiation of T_H1 and/or T_H17 cells, which may participate in the inflammatory processes of MS[30], as shown in vitro using human peripheral blood mononuclear cells[20] (FIG. 1). However, faecal microbiota transplantation (FMT) from patients with MS does not lead to increases in T_H1 cells in recipient EAE mice. Further studies are needed to determine whether the increased populations of *A. muciniphila* in patients with MS have a pathogenic role.

All reports discussed above investigated faecal microbiota, which are considered representative of colonic microbiota (BOX 2). So far, only one study has investigated the microbiota of the small intestine in patients with MS. Cosorich et al.[19] analysed duodenum tissue biopsy samples and showed that a prominent feature of small intestine microbiota of patients with MS was a decreased abundance of *Prevotella* spp. Of note, the relative abundance of *Prevotella* spp. negatively correlated with the abundance of T_H17 cells, which are increased in small intestine tissue biopsies of patients with MS. In addition, *Streptococcus* spp. that were shown to induce T_H17 cells in humans[31] were increased in the small intestine tissue of patients with MS, and the abundance of *Streptococcus* spp. showed a positive correlation with the number of T_H17 cells (FIG. 1). These data indicate that altered gut microbiota in patients with MS might modulate the balance of T_{reg} cells and pro-inflammatory T_H1 and T_H17 cells. It is also noteworthy that, following treatment with immunomodulatory therapy, the composition of the microbiota of patients with MS changes and becomes more like the microbiota of healthy individuals, including a decrease in *A. muciniphila* and an increase in *Prevotella* spp.[16]. These results suggest the possibility that microbiome modulation might enhance the efficacy of MS treatment. Further studies are needed to confirm the causal relationship between treatment and changes in the composition of the gut microbiota and to elucidate the underlying mechanisms (BOX 2).

Rheumatoid arthritis. RA is characterized by inflammation and tissue destruction in the synovial joints; however, autoimmune responses are thought to be initiated in mucosal surfaces[32]. Both the oral and the gut microbiota are implicated in dysregulated immune responses in individuals with RA[33,34]. Research into the gut microbiota in RA dates back to the 1960s, when a high frequency of faecal *Clostridium perfringens* was observed in patients with RA[35]. In contrast to patients with MS and T1D (discussed below), recent NGS-based studies highlight a higher abundance of faecal *Prevotella* spp., especially *Prevotella copri*, in patients with new-onset RA (NORA)[36–38]. This *Prevotella* species was shown to induce pro-inflammatory responses[37]; on the contrary, *P. histicola* has anti-inflammatory capacity[23]. Moreover, these two *Prevotella* species exert opposite effects on disease severity in mouse models of RA[37,39]. Intriguingly, antibodies against *P. copri* can be detected in patients with NORA but not in healthy individuals[40]. The authors identified the HLA-DR-presented peptide Pc-P27, which is derived from *P. copri*, as the peptide that stimulates T_H1 responses in patients with NORA[40]. Additionally, *P. copri*-specific IgA responses positively correlated with serum concentrations of T_H1-related and T_H17-related cytokines[40], indicating that the immune response against increased *P. copri* in the patient gut may play a role in the onset of RA. A comprehensive analysis using shotgun metagenome sequencing also revealed the detailed taxonomic and functional differences of the gut microbiota between healthy controls and patients with chronic RA[33,41] (TABLE 1). Certain gut bacteria in patients with RA associate with clinical and pathogenic indices. For example, a decrease of the relative abundance of genus *Haemophilus* in patients with RA correlates with lower titres of the RA-specific autoantibodies (anti-cyclic citrullinated peptides) and rheumatoid factors[33].

Although the levels of short-chain fatty acids (SCFA) have not yet been studied in patients with RA (BOX 2), in a mouse model of arthritis, the concentration of caecal butyrate drops before disease onset, an observation associated with dysbiosis[42]. Conversely, supplementation with butyrate attenuates arthritis in mice[42]. Studies in patients with RA also show a decrease in SCFA-producing bacteria such as the genera *Faecalibacterium* and *Bacteroides*[36,37,43,44], whereas *Collinsella*, known to expand under low SCFA conditions, are increased[43].

Type 1 diabetes. T1D, an AD with frequent childhood onset that triggers hyperglycaemia owing to insulin insufficiency, is caused by the destruction

Author addresses

[1]RIKEN Center for Integrative Medical Sciences, Yokohama, Kanagawa, Japan.
[2]Department of Parasitology, National Institute of Infectious Disease, Tokyo, Japan.
[3]Department of Infection and Immunity, Luxembourg Institute of Health, Esch-sur-Alzette, Luxembourg.
[4]Odense Research Center for Anaphylaxis, Department of Dermatology and Allergy Center, Odense University Hospital, University of Southern Denmark, Odense, Denmark.
[5]Immunobiology Laboratory, Graduate School of Medical Life Science, Yokohama City University, Yokohama, Kanagawa, Japan.
[6]Laboratory for Immune Regulation, Graduate School of Medicine, Chiba University, Chiba, Chiba, Japan.
[7]Present address: Institute for Molecular and Cellular Regulation, Gunma University, Haebashi, Gunma, Japan.
[8]These authors contributed equally: Eiji Miyauchi, Chikako Shimokawa.

Box 1 | **Molecular mimicry**

One of the leading hypotheses for the development of autoimmune diseases is that structural similarities between infectious agents or commensals and host proteins lead to the activation of adaptive immune cells that cross-react with host proteins, a phenomenon termed 'molecular mimicry'[202–204]. Even at steady state, a vast range of diverse antigens from gut commensals are continuously presented to T cells and B cells, and recent studies have revealed the identity of particular commensals and pathogens that can induce cross-reactive T cells.

For example, it was shown that the Pc-P27 peptide derived from *Prevotella copri* stimulates T cells and B cells in a subset of patients with rheumatoid arthritis but not in healthy individuals[40]. The authors also identified two autoantigens specific for rheumatoid arthritis[205] that are highly expressed in inflamed synovial tissue and share T cell epitopes with microbial peptides from *Prevotella* sp. and *Parabacteroides* sp.

Ro60, a highly evolutionally conserved RNA-binding protein, is considered a primordial autoantigen in systemic lupus erythematosus, and anti-Ro60 autoantibodies have been detected in individuals years before disease onset[206]. Bacterial orthologues of Ro60 are expressed in human commensals, such as *Propionibacterium propionicum* and *Bacteroides thetaiotaomicron*, and $CD4^+$ T cells from patients with anti-Ro60-positive systemic lupus erythematosus can cross-react with bacterial Ro60 orthologues. Germ-free mice monocolonized with *B. thetaiotaomicron* develop anti-human Ro60 antibodies and lupus nephritis-like disease.

Molecular mimicry has also been proposed as a possible aetiology in multiple sclerosis (MS)[207,208]. Although there is no direct evidence that autoreactive T cells are activated in the gut of patients with MS, it has been shown that autoreactive $CD4^+$ T cells in the cerebrospinal fluid of patients with MS can cross-react with bacterial antigen expressed in gut commensals[193].

The studies described above demonstrate the cross-reactivity of bacterial antigens using synthetic peptides; however, they do not demonstrate that cross-reactive peptides expressed in microbes are properly processed and presented to autoreactive immune cells. Several groups have sought to validate the cross-reactivity and pathogenic roles of gut microbes that express potential mimicry peptides using gnotobiotic mice[67,78]. A study by our group revealed that a peptide from the UvrA protein of *Lactobacillus reuteri* induces the proliferation of myelin oligodendrocyte glycoprotein (MOG)-specific $CD4^+$ T cells in the small intestine and facilitates central nervous system inflammation in the experimental autoimmune encephalomyelitis mouse model of MS (FIG. 1). Of note, the cross-activation of MOG-specific $CD4^+$ cells was abrogated by the deletion of the gene encoding UvrA protein in *L. reuteri*[78]. Further validation studies using gnotobiotic mice and genetically manipulated microbes are required to confirm the molecular mimicry theory.

of insulin-producing pancreatic β-cells and is characterized by the presence of autoantibodies against β-cells[45]. Despite intensive research, the precise mechanisms of the destruction of pancreatic β-cells remain unknown. There is mounting evidence for an association between susceptibility to T1D and specific HLA alleles. Nevertheless, only 20% of children with high-risk HLA alleles produce autoantibodies against β-cells[46], suggesting that environmental factors are of importance.

Like for other conditions that develop in childhood, such as food allergy, an association of T1D with breast-feeding or Caesarean birth has been reported[47,48]. Breast-feeding for 12 months or longer decreased the incidence of T1D among children with the high-risk HLA genotype[47]. A meta-analysis showed that the risk of developing T1D was increased by about 20% in children born by aseptic Caesarean compared to those born by natural transvaginal birth[48]. This suggests the involvement of commensal microbiota in the pathogenesis of T1D as it is well-known that birth modes affect the diversity and colonization pattern of the gut microbiota[49]. In this regard, a report that investigated the relationship between the usage of antibiotics in childhood and T1D in Denmark showed that treatment with broad-spectrum antibiotics in the first years of life significantly increased the risk of developing T1D among children who were delivered by Caesarean birth[50].

In contrast to what is observed in other ADs, some studies have shown a reduced richness of bacterial species in children with T1D[51,52]. Disease-associated changes in bacterial composition in children with T1D have some common features such as a decrease in *Prevotella* spp. and an increase in *Bacteroides* spp.[51–57] (TABLE 1). Of note, a longitudinal study of children with high-risk HLA alleles revealed an expansion of *Bacteroides dorei* before seroconversion, implying a pathogenic role of this bacterium in the development of T1D[56]. Metagenomic analyses have also demonstrated that the pathways involved in SCFA production are decreased in children with T1D compared to healthy controls. This functional change (in addition to a reduction of genera *Akkermansia*[57,58], which are involved in the regulation of the intestinal barrier) might contribute to the increased intestinal permeability observed in children with T1D[59] (FIG. 2).

Systemic lupus erythematosus. SLE is characterized by autoantibodies and immune-mediated tissue damage[60], and the gut microbiota has been implicated in the pathogenesis of the disease. The composition of the gut microbiota has a major effect on antibody production by shaping the human B cell repertoire, and it affects the balance between different populations of T helper cells and T_{reg} cells[61,62]. Despite a multitude of studies exploring the mechanism by which the intestinal microbiota affect the development of SLE, little is known regarding the causal relationship or the underlying mechanisms[63,64].

In patients with SLE, the relative abundance of *Firmicutes* is decreased whereas *Bacteroidetes* are increased compared with healthy controls[65–68] (TABLE 1). An expansion of *Ruminococcus gnavus* in patients with SLE was shown to correlate with an increase in disease activity and the incidence of lupus nephritis[69]. It has also been shown that antibodies against the *R. gnavus* strain can cross-react with native DNA, triggering an anti-double-stranded DNA antibody response[70].

Immune modulation in extra-intestinal ADs

A variety of immune cells, both innate and adaptive, participate in the autoimmune inflammatory responses in ADs. In addition, increases in intestinal permeability, which might allow abnormal passage of luminal antigens and bacterial products into the lamina propria, also play a pathogenic role in both intestinal and extra-intestinal ADs[71–73]. The link between innate and adaptive immune cells at the intestinal barrier of the host and the gut microbiota has been well summarized in other reviews[74,75]. Here, we focus on the functional and systemic effects of compositional changes of the gut microbiota on adaptive immune cells.

Induction of inflammatory and anti-inflammatory T cells in MS. Patients with MS have an increase in T_H17 cells in the blood and cerebrospinal fluid[76,77], and their T_{reg} cells have a decreased anti-inflammatory capacity[10]. The role of gut microbiota in shaping T cell subsets has been investigated intensely in mouse models (FIG. 1).

Table 1 | **Altered gut microbiota in patients with autoimmune diseases**

Sample source	Application	Bacterial richness	Decrease in patients	Increase in patients	Country (Ref.)
Multiple sclerosis					
Faeces	16S	Comparable	Genera *Faecalibacterium*, *Prevotella*, *Anaerostipes*, Clostridia cluster IV and XIVa spp.	*Streptococcus* sp., *Eggerthella* sp.	Japan[13]
Faeces	16S	Comparable	Genera Parabacteroides, *Adlercreutzia*, *Prevotella*	Genera *Pseudomonas*, *Mycoplana*, *Haemophilus*, *Blautia*, *Dorea*	US[18]
Faeces	16S	Comparable	Genera *Butyricimonas*, *Collinsella*, *Slackia*, *Prevotella*	Genera *Methanobrevibacter*, *Akkermansia*	US[16]
Faeces	16S	Comparable	–	*Akkermansia* spp.	Germany[17]
Faeces	16S	Comparable	Genera *Parabacteroides*, *Prevotella*, *Serratia*, *Clostridium*, *Aquamonas*, *Bacillus*, *Acidaminococcus*	Genera *Akkermansia*, *Bifidobacterium*, *Acinetobacter*, *Corynebacterium*, *Megamonas*, *Actinomyces*, *Mogibacterium*, *Bulleidia*	US[20]
Small intestine biopsy	16S	Comparable	Genus *Prevotella*	Genus *Streptococcus*	Italy[19]
Faeces	16S	Comparable	Genera *Prevotella*, *Slackia*	Genera *Akkermansia*, *Clostridium*, *Blautia*, *Dorea*, *Adlercreutzia*	US[21]
Faeces	16S, metagenome LC-MS/MS	Comparable	*Ruminococcus* sp., *Eubacterium* spp., genus *Roseburia*, [butyrate metabolism, propionate metabolism, carbohydrate metabolism], (acetate, butyrate, propionate)	*Streptococcus* spp., *Akkermansia* sp., genus *Bifidobacterium*, [mismatch repair], (oxidized forms of cysteine and glutathione)	Japan[96]
Faeces	16S LC-MS/MS	ND	Genera *Bacteroides*, *Parabacteroides*, *Butyricimonas*, *Romboutsia*, (propionate)	Genera *Oscillibacter*, *Ruminiclostridium*, *Anaerostipes*, *Erysipelatoclostridium*, *Blautia*, *Collinsella*, *Anaerofilum*, *Flavonifractor*, *Dorea*, *Akkermansia*, *Marvinbryantia*	Germany[94]
Rheumatoid arthritis					
Faeces	16S, metagenome	Comparable	Genus *Bacteroides*, [vitamin E metabolism, pentose phosphate pathway]	*Prevotella* spp., [cysteine biosynthesis]	US[36]
Faeces (saliva)	Metagenome	Comparable	*Klebsiella pneumoniae*, *Haemophilus* sp., *Veillonella* sp., *Coprococcus catus*, *Dialister invisus*, *Sutterella wadsworthensis*, *Megamonas hypermegale*, *Lactobacillus sanfranciscensis*, *Bifidobacterium bifidum*, [lipopolysaccharide biosynthesis, lipopolysaccharide transport, secretion systems (type II, type IV and type VI)]	*Bacteroides* sp., *Clostridium asparagiforme*, *Lactobacillus* sp., *Holdemania filiformis*, *Bifidobacterium dentium*, *Coprobacillus* sp., *Eggerthella lenta*, *Gordonibacter pamelaeae*, *Ruminococcus lactaris*, [reductive acetyl-CoA]	China[33]
Faeces	16S	Comparable	ND	*Prevotella* spp.	Japan[37]
Faeces	Metagenome	Comparable	ND	*Prevotella* spp., *Bacteroides sartorii*, *Gardnerella* spp., *Porphyromonas somerae*, [fatty acid biosynthesis, ubiquinone and terpenoid-quinone biosynthesis, adipocytokine signalling pathway]	Japan[41]
Type 1 diabetes					
Faeces	Metagenome	ND	Genera *Prevotella*, *Lactobacillus*, *Lactococcus*, *Bifidobacterium*, *Streptococcus*, *Akkermansia*, *Faecalibacterium*, *Subdoligranulum*, [protein metabolism, aerobic respiration, amino acid synthesis]	Genera *Bacteroides*, *Veillonella*, *Alistipes*, [carbohydrate metabolism, adhesions, motility, phages, prophages, sulfur metabolism, stress responses]	Finland[53]
Faeces	16S	Comparable	Genera *Prevotella*, *Acidaminococcus*, *Megamonas*	Genus *Bacteroides*	Mexico[54]
Faeces	16S, metagenome	ND	Phylum *Firmicutes*	*Bacteroides dorei*	Finland[55]
Faeces	16S	Decrease in patients	Genera unclassified *Bacteroidetes*, *Alistipes*	Genera *Catenibacterium*, unclassified Prevotellaceae, RC9 gut group, *Lactobacillus*, *Succiniclasticum*	US[51]
Faeces	16S, metagenome LC-MS	Decrease in patients	*Coprococcus eutactus*, *Dialister invisus*, [tyrosine biosynthesis, phenylalanine biosynthesis]	*Ruminococcus gnavus*, *Streptococcus infantarius*, [multiple sugar transport system]	Finland[52]

Table 1 (cont.) | **Altered gut microbiota in patients with autoimmune diseases**

Sample source	Application	Bacterial richness	Decrease in patients	Increase in patients	Country (Ref.)
Type 1 diabetes (cont.)					
Faeces	Metagenome	ND	*Streptococcus thermophilus*, *Lactococcus lactis*, [superpathway of fermentation, superpathway of L-arginine, putrescine and 4-aminobutanoate degradation, acetyl-CoA fermentation to butanoate II, acetylene degradation, (*S*)-propane-1,2-diol degradation]	*Bifidobacterium pseudocatenulatum*, *Roseburia hominis*, *Alistipes shahii*	Finland, Germany, Sweden and US[56]
Faeces	16S metagenome	Comparable	Genera unclassified Ruminococcaceae, *Enterobacter*, *Hungatella*, *Lactococcus*, *Streptococcus*, *Dialister*, *Enterococcus*, *Akkermansia*	Genera *Parabacteroides*, *Veillonella*, unclassified Prevotellaceae, *Collinsella*	Finland, Germany, Sweden and US[57]
Systemic lupus erythematosus					
Faeces	16S	Comparable	*Firmicutes* to *Bacteroidetes* ratio	ND	Spain[65]
Faeces	16S	Comparable	Genera *Eubacterium*, *Dialister*, *Pseudobutyrivibrio*	Genera *Rhodococcus*, *Eggerthella*, *Klebsiella*, *Prevotella*, *Eubacterium*, *Flavonifractor*	China[66]
Faeces (saliva, skin)	16S	Comparable	*Firmicutes* to *Bacteroidetes* ratio	ND	US[67]

Altered pathways and metabolites are shown in square brackets and parentheses, respectively. LC-MS, liquid chromatography–mass spectrometry; LC-MS/MS, liquid chromatography with tandem mass spectrometry; ND, not determined or not described bacteria, pathways, metabolites.

Using EAE mice, we and others observed autoreactive myelin oligodendrocyte glycoprotein (MOG)-specific T cells in the intestine during EAE development[78,79], indicating that these T cells might interact with resident bacteria in the intestine before migrating into the CNS. Segmented filamentous bacteria (SFB; formerly known as *Candidatus* Arthromitus and recently renamed to *Candidatus* Savagella[80]) are among the most intensively investigated commensals. These attach tightly to epithelial cells and induce T_H17 responses in the small intestine[81,82]. Mono-colonization of germ-free mice with SFB results in increased levels of T_H17 cells in the intestine and exacerbates EAE[83], arthritis[84] and SLE[85]. Other bacteria, such as an unclassified Erysipelotrichaceae species, also activate intestinal T_H17 cells and promote inflammation in the spinal cords of EAE mice[78]. In accordance with previous reports[82,86,87], this Erysipelotrichaceae sp. also seems to attach to epithelial cells, specifically in the small intestine, and induce T_H17-related factors such as IL-23 and serum amyloid A (SAA). These factors push T_H17 cells towards a more pathogenic phenotype by inducing the expression of the transcriptional factor BLIMP1 and its target genes, including *Il17a*, *Csf2* (encoding GM-CSF) and *Il23r*. As described above, T_H17 cell-inducing mucosa-associated bacteria are also increased in the small intestine of patients with MS[19]. It is possible that some gut microbes that activate T_H17 responses might increase the pathogenicity of CNS-autoreactive T cells in the intestine. However, FMT experiments demonstrated that faecal microbiota from patients with MS do not induce T_H1 and T_H17 cells in EAE mice[17]. However, it might be possible that the investigation of faecal microbiota cannot capture the pro-inflammatory bacteria for the following reasons: (1) the microbial composition of the small intestine and faeces (colon) are quite different, especially in humans; and (2) faecal samples mainly contain luminal bacteria but few mucosa-associated bacteria that are involved in T_H17 responses[68,71].

The altered composition of the gut microbiota also appears to impair regulatory immune responses in ADs. T_{reg} cells play a major role in the suppression of autoreactive T cells and the transfer of T_{reg} cells into mouse models of ADs, including MS, RA, T1D and SLE, attenuates disease symptoms and delays disease onset[88–91]. Indeed, T_{reg} cells from patients with MS were shown to have a reduced immunosuppressive function[92–95]. Recent studies using metabolomic and metagenomic approaches have demonstrated that altered gut microbiota in patients with MS can be attributed to the dysfunction of T_{reg} cells[94,96]. Moreover, faecal and serum propionate was found to be decreased in patients with MS[94], and supplementation with propionate in patients with MS and in EAE mice improved the suppressive effects of T_{reg} cells and correlated with an alleviation of clinical symptoms[94,97]. Shotgun metagenome analyses suggest a reduced biosynthesis of SCFAs by the gut microbiota in patients with MS[96].

The administration of a single strain of microbes also appears to be effective in inducing T_{reg} cells and suppressing CNS inflammation in EAE mice[23,98]. For example, *P. histicola* induces T_{reg} cells in mesenteric lymph nodes, cervical lymph nodes, and the spleen and suppresses autoreactive T_H1 and T_H17 cells in EAE mice[23]. Moreover, *Bacteroides fragilis* is also well studied as a microorganism with immunosuppressive properties[99]. Polysaccharide A (PSA) derived from *B. fragilis* can modulate both the abundance and function of T_{reg} cells in EAE mice and, by promoting the accumulation of gut-derived T_{reg} cells in cervical lymph nodes, it can attenuate EAE[98]. More importantly, PSA induces an expansion of $CD39^+$ $CD4^+$ T_{reg} cells, which migrate more efficiently to the CNS than $CD39^-$ $CD4^+$ T_{reg} cells[100,101]. It is unclear whether these functions are specific to

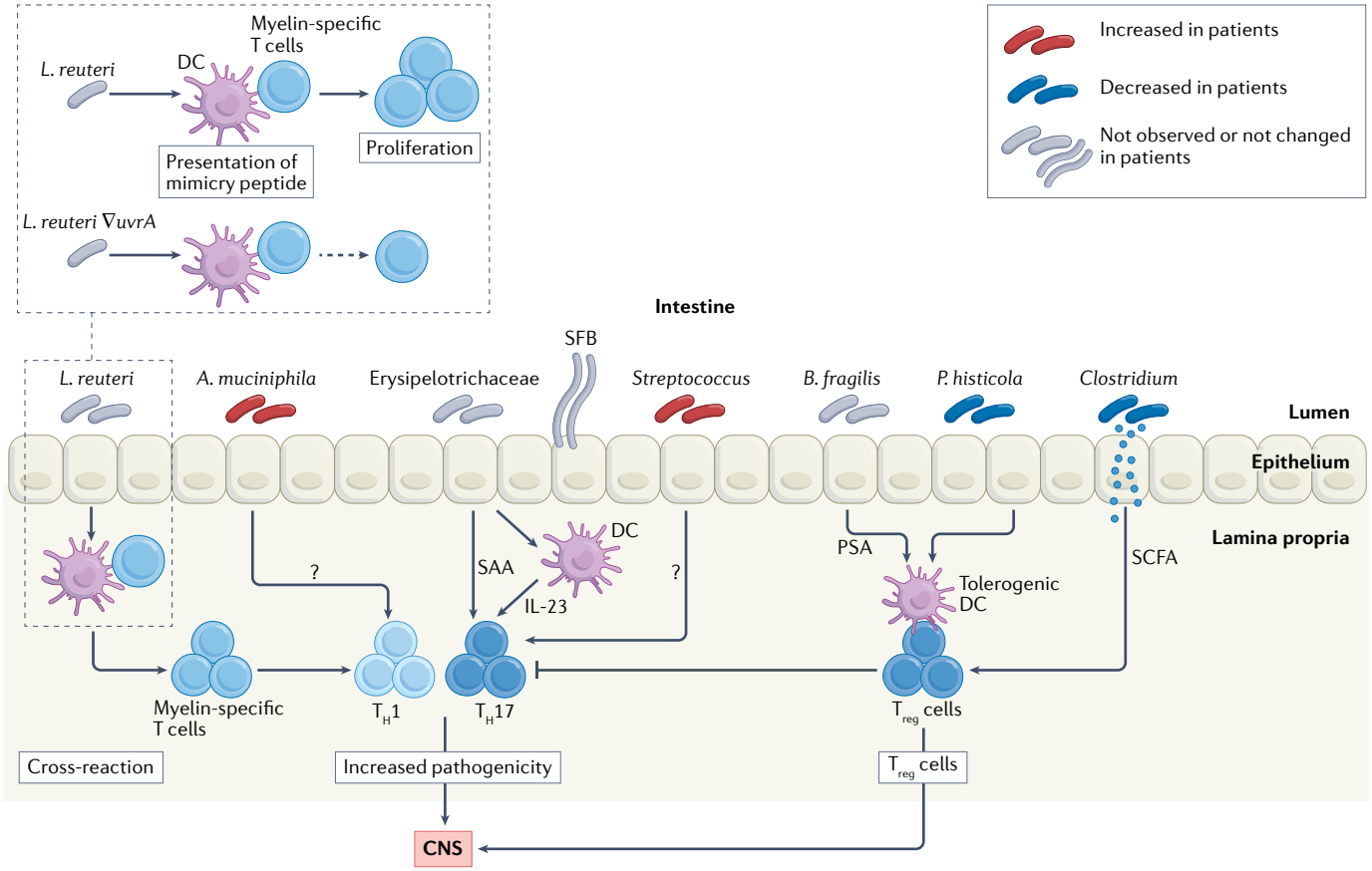


Fig. 1 | **Intestinal commensal bacteria can modulate autoreactive T cells and inflammation in the CNS.** Peripherally induced autoreactive myelin-specific T cells migrate to the gut, where *Lactobacillus reuteri* but not its myelin-mimicry antigen-deficient mutant (*L. reuteri* ∇*uvrA*) cross-reacts and activates them in experimental autoimmune encephalomyelitis mice[78]. Other commensals, such as Erysipelotrichaceae species, act like an adjuvant for the generation of pathogenic T helper 17 (T_H17) cells by inducing serum amyloid A (SAA) and IL-23 (REF.[78]), probably by a similar mechanism to segmented filamentous bacteria (SFB), which adhere to the epithelium and trigger SAA production[82,87]. As a result, an increased number of autoreactive T_H17 cells with high pathogenicity migrate to the central nervous system (CNS) and induce severe demyelination. Other intestinal bacteria, such as *Akkermansia muciniphila* and genus *Streptococcus*, are increased in patients with multiple sclerosis and may contribute to the differentiation of autoreactive T cells into T_H1 and T_H17 cells, respectively, by unknown mechanisms[19,20]. On the other hand, other bacterial species, such as *Bacteroides fragilis*, *Prevotella histicola* and genus *Clostridium*, induce regulatory T (T_{reg}) cells via the production of polysaccharide A (PSA) or short-chain fatty acids (SCFA), and these cells might suppress inflammatory responses in the intestine and the CNS. DC, dendritic cell.

B. fragilis. Nevertheless, symbiotic factors might support suppressive immune responses in ADs via their effects on T_{reg} cells. Interestingly, reduced or defective expression of CD39 in T cells is globally observed in patients with ADs, including MS, RA, T1D and SLE[102–105].

In addition to the critical role of $CD4^+$ T_{reg} cells, an essential role of $CD8^+$ T_{reg} cells has also been described in EAE mice. Here, depletion of $CD8^+$ T_{reg} cells resulted in persistent EAE symptoms whereas transfer of pre-activated $CD8^+$ T_{reg} cells improved EAE symptoms, especially during the recovery phase[106,107].

In addition to bacteria, parasites and fungi (BOX 3) can also affect the development of ADs. A prospective cohort study indicated that patients with MS who are also infected by parasites, such as *Trichuris trichiura*, have significantly less disease exacerbations and a minimal variation in disability scores and signs of disease compared with patients with MS who are not infected by parasites[108]. These patients have elevated levels of IL-10 and/or TGFβ as well as an increased number of $CD4^+$ T_{reg} cells, suggesting that T_{reg} cells induced by parasite infection can alter the course of MS[108]. Thus, parasites or parasite-derived molecules may be used as potential therapeutic agents for MS (BOX 2) although there is a clear need for careful risk–benefit assessment.

Induction of inflammatory and anti-inflammatory T cells in T1D. The detection of autoantibodies against β-cells is critical for the diagnosis of T1D[109]. In pathological examinations, infiltrations of T cells into the pancreatic islets are observed[110]. Previous studies on mouse models of T1D have demonstrated that autoantibodies against β-cells fail to induce the destruction of pancreatic β-cells, suggesting that pancreatic β-cell-specific autoreactive T cells are crucial for T1D pathogenesis[45]. Indeed, non-obese diabetic (NOD) mice develop T1D spontaneously but NOD mice that lack MHC class I molecules, and therefore cannot present antigens to $CD8^+$ T cells, do not develop insulitis[111]. Furthermore, the depletion of $CD4^+$ T cells in NOD mice suppresses T1D development[112]. Autoreactive T cells are normally removed via negative selection in thymus. However, in

individuals genetically predisposed to T1D, autoreactive T cells that are specific for β-cell autoantigens, such as (prepro)insulin, are thought to be incompletely removed and thus able to attack pancreatic β-cells[45]. It is known that $CD4^+$ T cells that bind B:9-23, a peptide from the insulin β-chain, are present in NOD mice[113]. These T cells produce IFNγ in response to binding the B:9-23 peptide and attack pancreatic β-cells[114]. Moreover, the B:9-23 peptide can also act as autoantigen for cytotoxic T cells[115]. Thus, a number of studies have demonstrated the pivotal role of both $CD4^+$ and $CD8^+$ T cells recognizing autoantigens derived from pancreatic islets in the development of T1D[111,113–115].

A recent study showed that inoculation of NOD mice with SCFAs increases the number of T_{reg} cells in the pancreas, which results in suppression of disease onset[116]. Interestingly, a higher incidence rate of diabetes in female compared to male NOD mice[117] correlated with a lower expression of cathelicidin-related antimicrobial peptide (CRAMP) in female NOD mice[118]. It was shown that CRAMP protects pancreatic β-cells by suppressing the induction of inflammatory cytokines in macrophages and dendritic cells[117]. In addition, a recent study has shown that butyrate induces the expression of CRAMP through the SCFA receptors GPR41 and GPR43, which are expressed on pancreatic β-cells[119]. The depletion of intestinal bacteria by administration of antibiotics in NOD mice decreased the expression of CRAMP in the pancreas[120], demonstrating that the development of T1D is intimately associated with intestinal microbiota.

NOD mice with a deletion of *MyD88*, a Toll-like receptor signalling adaptor protein, do not develop T1D under SPF conditions[121]. The concentration of SCFAs in blood and faeces is higher in these mice compared to that in normal NOD mice[122]. In addition, the resistance of $MyD88^{-/-}$ NOD mice to T1D is lost under germ-free conditions[123].

We have recently shown that the helminth *Heligmosomoides polygyrus* suppresses the development of T1D in NOD mice as well as in streptozotocin-treated mice[124]. Here, trehalose secreted by *H. polygyrus* increases the frequency of *Ruminococcus gnavus* in the gut, which suppresses disease onset via the induction of $CD8^+$ T_{reg} cells (FIG. 2). Consistent with this, the levels of genus *Ruminococcus* in faeces and the number $CD8^+$ T_{reg} cells in peripheral blood mononuclear cells were lower in patients with T1D than in healthy volunteers[124].

These findings imply that the gut microbiota play a suppressive role in T1D (FIG. 2). So far, pathogenic microbes have not been elucidated in T1D. SFB, which accelerate disease progression in mouse models of MS and RA, also show a protective effect in T1D by promoting barrier integrity[125] (FIG. 2). Thus, further studies are needed for a better understanding of the disease-specific roles of particular gut microbes.

Helminth-mediated immune modulation in RA and SLE. In addition to the involvement of the gut microorganism *P. copri* and microbial butyrate in RA pathogenesis as described above, helminth infection can also contribute to alleviating RA in animal models. In mice with collagen-induced arthritis, infection with *Schistosoma mansoni* downregulated T_H1 responses, TNF, and IL-17 and upregulated T_H2 responses and IL-10 (REF.[126]). A similar type of immunomodulation has been observed in other animal models of RA when these were infected with the tapeworms *Hymenolepis diminuta* or *Schistosoma japonicum*[127]. Some compounds derived from helminths also regulate host immune responses in RA[128]. One of the most well-studied helminth compounds is ES-62, which is produced by the nematode *Acanthocheilonema viteae*. A segment of ES-6S, which contains phosphorylcholine, is responsible for modulating macrophage and dendritic cell cytokine production[129]. ES-62 has a protective role in a mouse model and in patients with collagen-induced arthritis through its normalizing effect on the gut microbiome and by preventing the loss of intestinal barrier integrity[130].

Infection with helminths is also suggested to be involved in SLE pathogenesis. For example, *Hymenolepis microstoma* can improve all symptoms and signs of disease and prevent death in mouse models of SLE[131]. It also suppresses the generation of circulating autoantibodies, the main aetiology of SLE, probably by inducing T_{reg} cells, especially $CD8^+$ T_{reg} cells, which prevent T follicular helper cell and B cell activation[131]. It is possible that *H. microstoma* affects host immunity by modulating the gut microbiota. Indeed, interactions between intestinal helminths and the microbiota are well documented[132] and, for example, the tapeworm *H. diminuta* was reported to alter the composition of the gut microbiota[133]. Further studies to unveil the underlying mechanisms will provide new insights into the development of SLE and may guide therapeutic strategies.

Effects of the gut microbiota on immune cell migration. Memory T cells that recognize antigens derived from gut commensals circulate in the blood and these T cells can respond to pathogens[134,135]. The emigration and immigration of intestinal T cells has been studied in transgenic mice, where it was shown that colonic T_H17 cells can migrate and traffic to the small intestine, spleen and lymph nodes[136]. In a mouse model of RA (using K/BxN mice), α4β7 integrin-expressing intestinal T_H17 cells were observed in the spleen, where they interact

Box 2 | **Open questions regarding the treatment of extra-intestinal ADs with microbes**

1. Faecal dysbiosis is partially resolved after therapeutic treatment in some cases[16,33,54]; however, the mechanism of its resolution and the relation to clinical outcomes are still unknown.
2. There is limited information in patients with extra-intestinal autoimmune diseases (ADs) regarding:
   a. microbiota of the upper gastrointestinal tract (for example, stomach and ileum)
   b. mycobiome and virome
   c. metabolic changes in the gut including short-chain fatty acids and other bacterial metabolites
3. Considering the heterogeneity with regards to genetic background and gut microbiota in humans, is there a bacterial species or strains with a general impact on the pathogenesis of each AD or different species or strains for each patient suffering from the same AD?
4. Although the relationship between parasites, infections and ADs has been suggested (hygiene hypothesis[3,108]), how do intestinal parasites affect ADs?

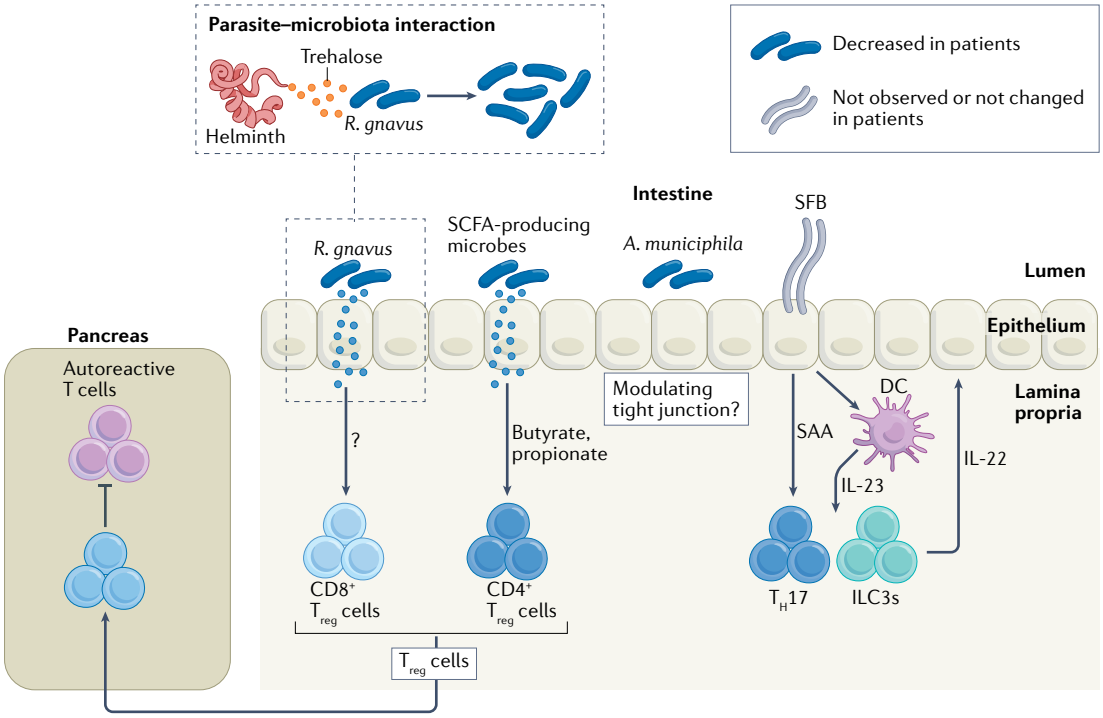


Fig. 2 | **Regulatory function of helminths and intestinal commensal bacteria in autoimmune-mediated diabetes.** The helminth *Heligmosomoides polygyrus* can suppress the development of type 1diabetes (T1D) in non-obese diabetic mice and in streptozotocin-treated mice by secreting trehalose in the intestine of infected mice[124]. Trehalose increases the frequency of the commensal *Ruminococcus gnavus*, which induces the differentiation of $CD8^+$ regulatory T (T_{reg}) cells in pancreatic lymph nodes via undefined mechanisms, and these cells suppress the development of T1D by inhibiting autoreactive T cells in the pancreas[124]. Patients with T1D generally have lower numbers of $CD8^+$ T_{reg} cells in the blood and the level of genus *Ruminococcus* in faeces is lower than in healthy individuals[124]. Intestinal microbes also produce short-chain fatty acids (SCFA) that cross the epithelial barrier of the gut and reach the lamina propria, where they promote the induction of $CD4^+$ T_{reg} cells that can suppress autoreactive T cells. Conversely, a decrease in *Akkermansia muciniphila* can exacerbate disease by increasing gut permeability[58]. In animal models, segmented filamentous bacteria (SFB) colonization induces serum amyloid A (SAA) and IL-23 and activates T helper 17 (T_H17) cells and group 3 innate lymphoid cells (ILC3s) that produce IL-22 (REFS[87,125]). This cytokine promotes epithelial barrier integrity and might prevent the leaky gut that is observed in non-obese diabetic mice. The effect of bacteria that are found to be decreased in patients with T1D, with regards to their impact on disease development, has been investigated extensively in animal models; however, less is known about the role of bacteria that are increased in patients with T1D. DC, dendritic cell.

with B cells and support the production of autoreactive antibodies[84]. In this model, both intestinal T_H17 and T follicular helper cells were shown to traffic into the spleen[136,137]. Other studies in models of AD also demonstrated that microorganism-stimulated intestinal T cells directly migrate into inflammatory sites[79,138]. Pro-inflammatory T cells were shown to migrate towards pre-existing inflammatory sites or cause de novo inflammation. For example, in a mouse model of EAE that is induced by transfer of MOG-specific T cells, the transferred T cells were shown to migrate into the intestine, where they were activated by gut microbes before inducing inflammation in the CNS[75]. It was also shown that $CD4^+$ memory T cells that express the gut-homing chemokine receptor CCR9 can infiltrate the inflamed CNS of patients with MS[139].

Colonic T_{reg} cells also circulate to other tissues or lymph nodes[136], although the trafficking of colonic T_{reg} cells in autoimmune conditions has not been studied. Indirect evidence from cell transfer experiments suggests that intestinal T_{reg} cells and type 1 T_{reg} ($CD4^+Foxp3^-IL\text{-}10^+$) cells migrate to the periphery and attenuate the development of diabetes in NOD mice[140,141]. Butyrate-treated NOD mice showed an increased frequency of gut-imprinted (positive for CCR9, GPR15 or α4β7 integrin) T_{reg} cells in the pancreas, implying that butyrate may facilitate the migration of T_{reg} cells to the target sites[141]. Another bacterial factor, *B. fragilis* PSA, has also been shown to modulate the migratory capacity of T_{reg} cells in EAE mice[100,101]. PSA was shown to induce $CD39^+$ $CD4^+$ T_{reg} cells and attenuate EAE[100]. Collectively, these studies imply that intestinal immune cells, especially T cells stimulated by bacteria, play a role in the progression and remission of extra-intestinal autoimmune conditions by migrating into the target sites.

Microbiome-focused therapeutic approaches

Given the impact of the gut microbiome on the susceptibility to extra-intestinal ADs, microbiota manipulation (BOX 4) for therapeutic purposes may hold promise. However, two main unresolved questions pose a barrier to this approach. The first is the question of the nature of the 'targeted manipulation' that would be the best option for the benefit of a given patient; the second question is

whether and how such manipulations could or should be personalized with respect to their design and execution. Most research in this regard has so far focused on the treatment of MS. Owing to the shared underlying molecular mechanisms with other ADs in the context of the gut microbiome as described above, general conclusions from MS-focused research can likely be translated to other ADs.

Therapeutic approaches in MS. Before microbiota manipulation is considered for the treatment of MS, a desired specific therapeutic outcome of such a modulation needs to be defined in the patient setting. Depending on the goal of the outcome, the microbiota modulation might be used: (1) as an intervening approach to halt already established neurodegenerative symptoms; (2) for disease prevention before the appearance of clinical signs in patients at risk; or (3) to reverse pathology-inducing events through active remyelination. As the key molecular factors behind the aetiology of MS remain, for a considerable part, elusive[5–7], the question of how to prevent the onset of clinical manifestation is largely underexplored. Currently available interventional therapies for MS and other ADs are summarized under the umbrella term 'disease-modifying therapies' (DMTs). Popular DMTs for MS comprise treatment with dimethyl fumarate[142], fingolimod[143], natalizumab[144] or ocrelizumab[145], which are designed to reduce the frequency and severity of relapses, and need to be taken indefinitely, raising concerns regarding their cost and effectiveness (reviewed in REFS[146,147]). Furthermore, there is no established therapy that induces active remyelination[148]. Thus, there is an unmet need to improve the therapeutic options for patients with MS. Ideally, any therapy should be cost-effective and should provide significant benefit over long periods of time with minimal risk. As established MS therapies mostly target the adaptive immune system and given the interplay between the intestinal microbiome and host immunity, manipulation of the host immune system through modulation of the microbiota may be feasible. The targeted manipulation of the microbiota could potentially be used to either completely replace DMT or to supplement it. Ideally, it should also activate remyelination, which would not only re-establish conduction and subsequent neurological function, but likely also protect axons from further degeneration[149]. Despite doubts that the microbiome is able to actively promote remyelination in the CNS[148,150], it was demonstrated that butyrate, a crucial microbial metabolite[151], enhanced remyelination in mice with cuprizone-induced MS-like demyelination[152]. Although this is an exciting observation, prospective induction of neuronal remyelination through the manipulation of the microbiota in humans will require further supporting studies.

Direct modulation of an indigenous gut microbiome. Data on the direct modulation (BOX 4) of the microbiota in patients with MS and their effect on MS-related neurological conditions are scarce. Although studies in mice report striking beneficial effects of various probiotics in the EAE model[153–156], there are no corresponding reliable data in humans owing to the lack of well-controlled large-scale human trials addressing this question. However, two pioneering studies involving small cohorts of patients with MS were recently performed. One study involving patients with relapsing-remitting MS (RRMS) and healthy control volunteers demonstrated that the administration of a probiotic cocktail twice daily, for 2 months, was associated with an anti-inflammatory peripheral immune response[157]. However, no long-term observation of the clinical outcome of this intervention was performed. A randomized, double-blind, placebo-controlled trial involving patients with RRMS treated with probiotics indicated a general decrease in inflammatory markers[158]. However, it seems that such effects do not persist when interventions are discontinued, which may be due to strain-specific and host-specific resistance to colonization by the administered probiotic strains[159]. Given the considerable influence of antibiotics on the composition of the intestinal microbiota, the impact of antibiotic treatment on the course of disease in EAE mice and in patients with MS was investigated. Several studies reported a reduced susceptibility to EAE in mice that were treated with antibiotics either before disease induction[160] or after disease induction but before the onset of symptoms[161]. However, a beneficial impact on EAE progression through antibiotic treatment was not observed in mice that had already developed symptoms[160]. On the contrary, a different study reported more severe disease in antibiotic-treated EAE mice[162]. Although a large-scale case control study in humans reported a decreased risk of MS in response to antibiotic intake[163], other studies revealed a positive correlation between antibiotic intake and MS prevalence[164,165].

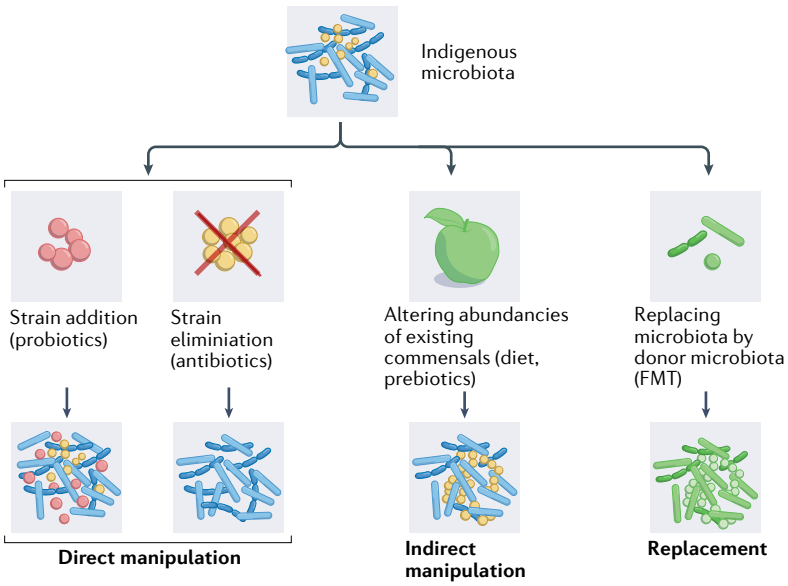
Indirect modulation of the indigenous microbiome. As the prevalence of MS is up to 80 times higher in industrialized regions such as North America or Europe compared with developing countries in sub-Saharan Africa[166], society-specific environmental factors, including the consumption of Western-style diets that are high in fats and low in dietary fibres[167–169], might contribute to MS pathogenesis[170]. Indeed, different dietary components appear to significantly impact the progress of autoimmune neuro-inflammation in humans[171–173] and mice[174,175]. Thus, changing nutritional habits back to 'pre-industrial' diets might reduce the overall presence of MS. Considering the effects of diet on neuro-inflammation, one has to distinguish between dietary

Box 3 | **Fungi and extra-intestinal ADs**

High-throughput DNA sequencing technologies have also been applied to the mycobiome[209]. Although it is known that commensal fungal species in the gut play a role in inflammatory bowel disease[210] and cancer[211], knowledge of their functions in autoimmune diseases (ADs) is still limited. Autoantibodies against *Saccharomyces cerevisiae* have been detected in patients with several ADs, including type 1 diabetes and systemic lupus erythematosus[212], and the gut commensal *Candida albicans* is thought to be an immunogen for autoantibodies against *S. cerevisiae*[213]. Further studies may reveal a pathogenic function for these fugal members in ADs because *C. albicans* is one of the potent inducers of T helper 17 cells in the gut[82,214].

Box 4 | **Approaches to indigenous microbiome manipulation**

In general, there are three different potential approaches to manipulate the microbiota: (1) direct modulation by adding or eliminating specific bacterial strains or communities, that is, by administration of certain bacteria, or certain antibiotics or bacteriophages, respectively; (2) indirect modulation through diet, medication or other environmental factors; or (3) a more or less complete replacement of the indigenous microbiota through faecal microbiota transplantation (FMT) from a suitable donor. Although all these approaches have been shown to have beneficial effects on the susceptibility or progress of autoimmune neuro-inflammation in experimental autoimmune encephalomyelitis mice, corresponding trials in humans are largely inconclusive and display a considerable variety.



metabolites that directly affect inflammation and indirect effects caused by altering the composition of the microbiota, which, in turn, affect host immunity. Such indirect modulation (BOX 4) of the microbiome can either be achieved through a broad-scale change of dietary habits[176] or through oral administration of dietary supplements (prebiotics)[177,178]. Importantly, some of the most potent immunomodulatory dietary metabolites, such as SCFAs and secondary bile acids, are exclusively produced by intestinal microbes[179]. Given the promising outcome of oral propionate supplementation in patients with MS[94], using a dietary intervention to boost propionate production by the indigenous gut microbiota appears to be a feasible mid-term strategy. Furthermore, a comparative study revealed that children in industrialized countries have a lower relative abundance of known butyrate-producing bacteria[180], which is potentially due to the reduced fibre content of contemporary Western-style diets as outlined above. This observation further highlights the impact of lifestyle on microbiome composition and the possibility of diet-mediated microbiome modulation. However, to achieve the goal of personalized dietary recommendations, it is necessary to not only understand how therapy alters the gut microbiota between MS patient cohorts but also within a given individual patient over time.

Replacement of the indigenous microbiome. An alternative strategy to diet-mediated microbiome modulation is the replacement of pre-existing indigenous microbiota by FMT (BOX 4), an approach that was proven to be highly efficient for the treatment of complicated *Clostridioides difficile* infections[181,182]. Owing to the convincing success in restoring gut microbiota barrier properties and treating microbial dysbiosis in patients with *C. difficile* infections, FMT emerged as an interesting therapeutic approach for the treatment of ADs. As the aetiopathology of ADs is much more complex than that of *C. difficile* infections, the aim of FMT-based therapy in patients with ADs is not only to restore microbial homeostasis and to outcompete a single pathogenic strain but also to normalize a disturbed host–microorganism communication. There are no double-blind, placebo-controlled human trials on the effects of FMT in patients with ADs. However, some case–control studies have reported encouraging outcomes as demonstrated by the improvement of neurological symptoms for 10 to 15 years in patients with MS after FMT[183,184]. Whereas the selection of a specific donor seems to be irrelevant for FMT-mediated treatment success in *C. difficile* infections, it appears to be a decisive criterion for therapeutic outcome in ADs such as ulcerative colitis[185]. Although this aspect has not yet been investigated in patients with MS, the observation in patients with ulcerative colitis suggests that FMT-mediated effects on the intestinal immune system and its extra-intestinal manifestation are highly dependent on the composition of the donor microbiota.

Combinations of microbiome manipulation and DMTs. As using microbiome manipulation as a therapeutic option still faces considerable challenges[186], it seems reasonable that such an approach would be first introduced as a supporting strategy to boost or improve the efficacy of established DMTs instead of replacing them. However, robust data on the impact of microbiome manipulation on DMTs, and vice versa, are still scarce. Small trials in specific human cohorts indicate that certain dietary interventions, which are almost inevitably associated with compositional changes of the intestinal microbiome, provide beneficial outcomes for patients with MS who are treated with DMTs[187,188]. Furthermore, a study focused on probiotics reported beneficial effects in patients with RRMS who were treated with copaxone and received the probiotic cocktail VSL#3 (REF.[189]). Nevertheless, such results should be interpreted with caution considering that participants within a given study may be receiving different DMT treatments as well as the small number of participants, lack of detailed microbiome analyses and the generally inconclusive outcomes in terms of clinical parameters.

Bacterial surface structures in a therapeutic context. Besides mechanisms mediated by viable bacteria, host responses to conserved bacterial structures are pivotal for maintenance of the intestinal homeostasis, for example, by contributing to the preservation of the mucosal barrier integrity[190]. Thus, it is possible to modulate the immune responses in ways that are beneficial to the host by utilizing the capacity of the host immune system to directly sense such bacterial structures. For example, oral administration of commensal-derived

cell wall components was shown to mediate immune tolerance in mouse models of MS[98] and inflammatory bowel disease[191,192] via specific interactions with host Toll-like receptors (TLRs). These findings suggest that manipulating host cell signalling pathways by administration of either artificial ligands that mimic bacterial structures or the associated signalling responses or by administering isolated cell wall components of beneficial gut microbes might be a feasible strategy to support microbiome manipulation for therapeutic purposes. However, therapeutic approaches based on the delivery of bacterial cell wall structures depend on the delivery of the therapeutic to the right place. For example, it was shown that the translocation of lipopolysaccharide (LPS; a hallmark surface molecule of Gram-negative bacteria) across the intestinal barrier can result in their release into the systemic circulation and in aberrant immune responses, which can potentially promote the onset or progression of ADs[193]. In patients with ankylosing spondylitis or autoimmune hepatitis, increased levels of LPS were detected in the plasma[194,195]. Additionally, increased serum concentrations of CD14, which are used as a proxy for detecting blood LPS levels, were detected in patients suffering from SLE[196]. Nevertheless, it remains unclear whether changes in microbiome composition are causally driving the translocation of LPS and whether this is a source or a consequence of the autoimmune responses.

Outlook

Our current understanding of extra-intestinal ADs emphasizes gut symbionts as potential preventive and therapeutic targets; however, there are challenges and limitations to this approach as summarized in BOX 2. Although accumulating data have allowed identification of gut microbes that are correlated or associated with extra-intestinal ADs (TABLE 1), the functional impact of these microbes on disease development and progression remains to be elucidated. Proof-of-concept studies using gnotobiotic mice colonized with a defined composition of microbes will overcome the limitations of this field. As discussed above, studies using animal models of extra-intestinal ADs demonstrate that some gut microbes alter the disease phenotypes by modulating barrier function or immune responses in the gut. However, only limited information is available on the state of intestinal tissues of patients with extra-intestinal ADs, and it is important to examine both the resident

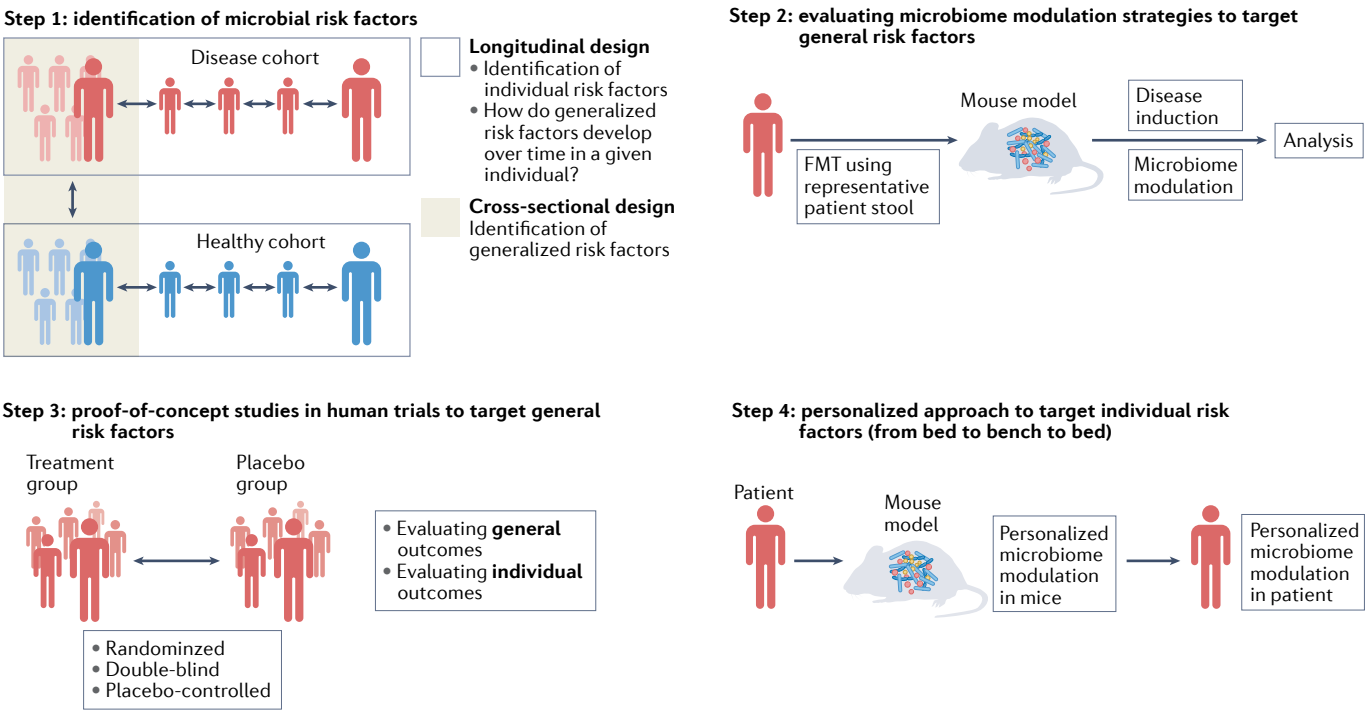


Fig. 3 | **Proposed study design to develop microbiome modulation strategies.** Step 1: a cross-sectional comparison of read-outs of interest between a cohort of patients and healthy individuals allows for identification of potential general risk factors (differences between the two groups). A longitudinal observation of certain individuals allows for the identification of potential individual (observed only in a given individual or subset of individuals) risk factors. Step 2: according to data obtained from Step 1, the general risk factors can be verified by faecal microbiota transplantation (FMT) using representative or pooled stool samples from patients into germ-free mice. Strategies can be developed to modulate the microbiome (and the corresponding general risk factors), for example, via dietary modulation either as an intervention during disease or as a preventative step before disease onset. Step 3: placebo-controlled, randomized, double-blind human cohorts can allow assessment of the potential of the developed microbiome modulation strategy (from Step 2) to benefit patients of a given disease (general outcomes). Larger cohort numbers will also help to elucidate whether predicted general risk factors (Step 1) might exhibit significant variations between individuals within a given treatment group (individual outcomes), thus requiring further refinement of modulation strategies. Step 4: based on the identification of individual risk factors from Steps 1 and 3, FMT is performed into germ-free mice using stool from a specific patient followed by disease induction in mice. Subsequent microbiome modulation is carried out in mice to evaluate the outcome of the chosen modulation strategy. In case of success, the patient can be treated with the same microbiome modulation strategy.

microbiota and host tissues in the gut of patients to confirm that observations from mouse models are of relevance to human disease.

Clinical trials of FMT in patients with extra-intestinal ADs are currently under way[197]. These microbiota-focused trials will aid the quest for efficient microbiome modulation. Such trials should always be conducted as randomized, double-blind, placebo-controlled studies whenever possible. The specific research question should be focused, and confounding variables need to be eliminated where possible. Aside from gathering averaged responses across a large cohort of volunteers to elucidate general effects in cross-sectional studies, it might be of specific interest to instead focus on individual responses of a given patient within the framework of a longitudinal study. Such longitudinal cohorts would aid in identifying microbiome-based disease risk factors such as microbial or metabolic biomarkers (FIG. 3). Why does a certain intervention or manipulation work in one individual and not in another? What are the shared taxonomic or functional characteristics of the microbiome to a given manipulation, and how do these differ between responders versus non-responders? Being able to adequately answer these questions might help to improve approaches for the treatment of extra-intestinal ADs. In this context, a 'from-bed-to-bench-to-bed' approach might be a promising (yet cost-intensive at present) way to optimize personalized microbiota manipulation in a given patient (FIG. 3). This could be done by assessing the disease-promoting potential of microbiota from the stool of individual patients under different conditions, for example, in gnotobiotic mice after transplantation of these samples, which would allow for individualized screening of treatments. It is likely that no single method for the therapeutic manipulation of the microbiota will evolve as a gold standard, but combining different strategies, ideally tailored to individual needs and pre-existing conditions, might be most successful. To achieve this, the molecular mechanisms underlying microbiome-mediated modulation of the immune system in various ADs need to be further investigated. A better understanding of such mechanisms would allow, for example, the therapeutic manipulation of molecular signalling cascades that are altered by the microbiome. The mechanisms by which the microbiome affects signalling cascades in host cells are so far not understood in great detail; however, a few promising examples offer hope. For example, TLR-mediated pathways in various host cells have emerged as interesting targets as they represent key microbiome-activated pathways, which are involved in balancing pro-inflammatory and anti-inflammatory responses in autoimmunity[198–201]. Nevertheless, it remains unclear how such interventions would alter the composition of the endogenous microbiome, individually and across larger cohorts, and whether it would boost or counteract the potential beneficial effects of targeted microbiome manipulation.

Published online 9 May 2022

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Acknowledgements
Work in the authors' laboratory was supported by the following grants: the research grant of Astellas Foundation for Research on Metabolic Disorders and JSPS KAKENHI Grant Number 19K05907 to E.M.; JSPS KAKENHI Grant Number 19K16682, Naito foundation, Yakult Bio-Science Foundation, Shiseido Female Researcher Science Grant, The Nakajima Foundation, Uehara Memorial Foundation, and Mochida Memorial Foundation for Medical and Pharmaceutical Research to C.S.; Luxembourg National Research Fund (FNR) CORE grant (C18/BM/12585940) and FNR INTER Mobility grant (16/11455695) to M.S.D.; and AMED-CREST (19gm0710009h0006), JSPS KAKENHI Grant Number 19H01030, and the Food Science Institute Foundation to H.O.

Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
M.S.D. works as a consultant and advisory board member at Theralution GmbH, Germany. The other authors declare no other competing interests.

Peer review information
Nature Reviews Immunology thanks Alexander Chervonsky and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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