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Role of the intestinal microbiome in autoimmune diseases and its use in treatments

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ABSTRACT

The role of the intestinal microbiome in the pathogenesis of autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and type 1 diabetes is being increasingly appreciated. Many studies have reported that the compositions of the intestinal microbiomes of patients with these autoimmune diseases are different from those of healthy individuals. Analyses of the intestinal microbiome of humans suggest that various factors affect the composition of the intestinal microbiome, including, but not limited to: geographical location, diet, sex, and age. However, patients with rheumatoid arthritis and type 1 diabetes show unique intestinal microbiome profile even after considering these confounding factors. This review will describe the known differences in the microbial composition for each of the aforementioned autoimmune diseases, how it impacts the immune system, and how these compositions may potentially be modulated by treatments with probiotics, prebiotics, and other microbiome altering therapies.

1. Introduction

All surfaces of our body are lined with microbes, making up a majority of our own DNA [1]. Ninety five % of the microbes found in our intestinal tract live harmoniously together and make up a diverse community that helps us break down different types of insoluble foods and contributes towards synthesizing various vitamins such as vitamin K, Folate, and B12 [2,3]. In the intestinal lining of our gut, the mucosa acts as a barrier between the host's epithelial cells and the microbes that reside on top of them; however, the mucosal layer also serves as a region where a symbiotic state can occur between beneficial microbes (commensals) and intestinal tissue [4,5]. The gut microbial communities have co-evolved with the humans to maintain a symbiotic relation and are diversified by the hosts' dietary habits and genetic makeup [6]. In the event of a disruption to the gut microbial community, or dysbiosis, permeabilization of the mucosal/epithelial lining can occur, resulting in the migration of microbiota-derived byproducts into the systemic circulation, which may subsequently affect external organs, such as the central nervous system [7]. Gut-associated lymphoid tissue (GALT) is one of the main defense mechanisms that can protect against such potential gut derived pathogens. GALT is comprised of multiple immune cells that can detect pathogen derived molecules, such as lipopolysaccharide (LPS), flagellin, or microbial DNA within the gastrointestinal (GI) tract [8]. Recently, it has become-clear that microbes are able to produce metabolites, such as short chain fatty acids (SCFAs) that allow them to indirectly interact with the host. A normal and well balanced microbiome routinely stimulates the immune system via intestinal epithelial cells [9] in order to maintain a mature innate and adaptive response within the GI tract. Studies have shown that the colon has the most diverse microbial community which produces the majority of SCFAs. SCFAs are defined as free fatty acids with fewer than 6 carbons and having water soluble short aliphatic carbon-chains that are absorbed or transferred into cells [10]. The most studied SCFAs are butyrate, propionate, and acetate. Butyrate is known to inhibit pro-inflammatory NFkB pathway and stimulate T regulatory cell activity, which leads to the production of the anti-inflammatory cytokine IL-10 [10,11]. Propionate can be produced from various sugars such as pentose, hexose and rhamnose [12]. Bacteroidetes and some Firmicutes are known to produce propionate, mainly through the succinate pathway while Firmicutes produce high levels of butyrate [10]. Acetate is readily made by most enteric and acetogenic bacteria [13]. Bacteria of bacteroides phylum generally produce high levels of acetate. SCFAs suppress histone deacetylase (HDAC), an enzyme that removes acetyl groups form *N*-acetyl lysine amino acids on a histone; they can affect transcription and alter function of protein [14]. Studies have shown that the acetylation of the H3 histone could be a major regulator of the FoxP3 locus [15–17]. Thus, the secretion of SCFAs can result in the regulation of the immune response by increasing the activity of T regulatory cells. In addition, SCFA have also been shown to produce IFN-γ and IL-17 [14]. Autoimmune diseases like rheumatoid arthritis (RA), type 1 diabetes (T1D), and multiple sclerosis (MS) show dysbiosis of the intestinal microbiome as compared to healthy controls (Fig. 1). The review discusses the role of gut microbiome in these autoimmune diseases and how gut microbiome can be modulated via probiotics and

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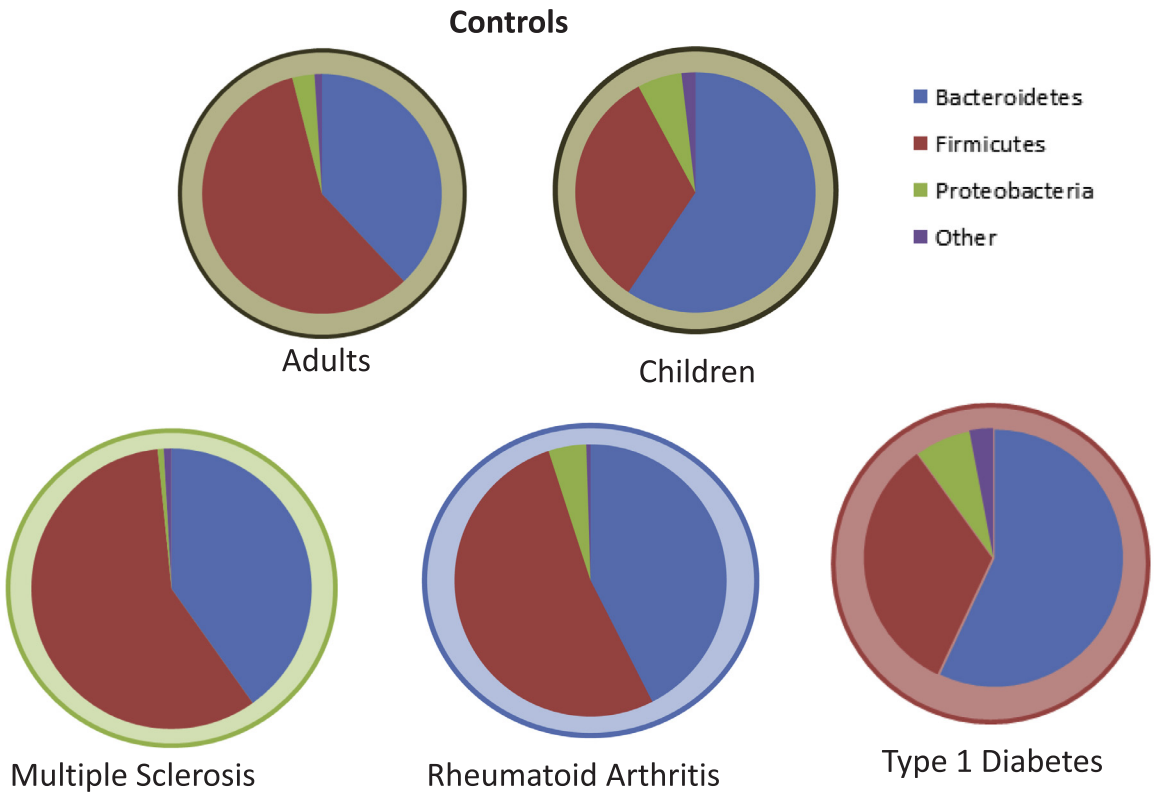

Fig. 1. Distribution of Phyla observed in the three autoimmune diseases, T1D, MS, and RA. For the T1D pie chart, data from 16s rRNA gene evaluations of stool from children were used, and should be compared to the Children Control profile. For the multiple sclerosis and rheumatoid arthritis, stool samples from adults were evaluated by 16s rRNA gene analysis, and should be compared to the adult controls. All data presented are from analyses of individuals on a Western diet. Data for each disease was obtained from: T1D-[30], RA-[68], MS-[53], Controls Children [30], Controls Adults [68].

gut-derived commensals for suppressing autoimmunity.

1.1. Type 1 diabetes

Type 1 diabetes (T1D) is an autoimmune disease wherein an autoreactive response occurs against the pancreatic beta cells. Like most of the autoimmune diseases, it has a strong genetic predisposition, although a number of environmental factors have been implicated, including diet [18]. Since diet has a big impact on microbiome, many studies have studied the link between T1D and microbial composition. The initial work done with non-obese diabetes (NOD) mice showed that interaction of intestinal microbiota with immune system regulates diabetes in mice [19]. The observations in NOD mice led to an interest in patients with T1D. A number of studies done in different countries have determined that patients with T1D do have dysbiosis [20–32]. Each of these studies demonstrated that the composition of the intestinal microbiome of patients with T1D is different from age and sex matched controls.

In one of the early studies by Giongo et al., in which fecal samples from pediatric T1D patients from Finland were evaluated, the authors observed an increase in levels of Bacteroidetes in the four children that went onto develop T1D [32]. On the other hand, Firmicutes decreased in the four diabetic patients' over time, but increased in the control children. In addition, the alpha diversity increased in the controls with age, but not in the diabetics. Thus, this study indicated that infants at risk of developing T1D have dysbiosis at a young age which is characterized by an increase in Bacteroidetes and a decrease in Firmicutes.

A metagenomics study of the same stool samples from the 8 T1D children from Finland revealed a decrease in the genes that contribute to the production of butyrate as well as degradation of mucin in the intestinal microbiomes of these T1D children [31]. The stool samples that were used in the metagenomic analysis were collected after the patients were positive for at least two antibodies associated with T1D. Shotgun sequencing confirmed the 16s analysis showing higher Bacteroidetes than *Firmicutes* in the T1D fecal samples. In addition, T1D patients had higher levels of Bacteroides with a decrease in Prevotella, a mucin degrader, in the T1D patients. With the use of the KEGG (Kyoto Encyclopedia of Genes and Genomes) database and the SEED (a comparative genomics environment found at http://www.theseed.org/wiki/Home_of_the_SEED), the authors determined that the T1D patients did have a decreased ability to produce butyrate as compared to the healthy controls which was due mainly to the observed decrease in the T1D patients of the some butyrate producers including the most common genus in humans, *Faecalibacterium*.

The decrease in Firmicutes was confirmed in another study of Spanish children with T1D [25]. *Bacteroidetes* was significantly increased with respect to healthy children, resulting in the *Firmicutes* to *Bacteroidetes* ratio being significantly decreased in the T1D patients. Of great interest was the observation that within the Bacteroidetes phylum, the quantity of Bacteroides was significantly higher and the level of *Prevotella* was significantly lower. Within the *Firmicutes, Lactobacillus and Bifidobacterium* were significantly decreased in T1D subjects as compared to the control subjects. With this significant decrease in *Lactobacillus* and *Bifidobacterium*, it would be expected that lactate production would be significantly decreased in these patients as well. This is important as many bacteria break down lactate to generate butyrate [31].

More recent studies have confirmed that T1D patients have increased levels of species of the Bacteroidetes phylum. Recently a study from China investigating T1D patients that ranged in age from 12 to 33 years old [20], observed *Porphyromonadaceae*, belonging to the phylum *Bacteroidetes*, was significantly increased in patients as compared to matched healthy controls. Similarly, analysis of 18 T1D children and 18 healthy control children from two studies done in Finland

(TRIGR- Trial to Reduce IDDM in the Genetically at Risk and FINDIA-Finnish Dietary Intervention Trial for Prevention of Type 1 Diabetes), showed an increase in *Bacteroides* from the *Bacteroidetes* phylum, in T1D subjects and the *Firmicutes* phylum in controls [28]. In addition, the most common *Bifidobacteria, B. adolescentis and B. pseudocatenulatum*, both of which produce lactate, from which butyrate can be produced, were decreased in the children with β-cell autoimmunity.

Thus, many studies from different countries performed in the last 10 years point to butyrate deficiency as being a trigger for the onset of type 1 diabetes in patients. To prove this point, an animal model of type 1 diabetes, the non-obese diabetic (NOD) mouse was used. In this study, diabetes incidence was compared between butyrate supplemented chows and a control chow in NOD mice [33]. Diabetes was significantly inhibited with the butyrate enriched chow, although addition of acetate to the butyrate chow inhibited diabetes further, resulting in almost 90% of the NOD mice being diabetes free at 30 weeks of age, whereas mice only 30% of mice on the control chow that was supplemented with propionate only were diabetes free at 30 weeks of age. The authors observed a significant increase in the number of regulatory T cells (CD4 + FoxP3 +) in the spleens and pancreatic lymph node cells of the mice that were given the butyrate supplemented chow, suggesting that one way in which the butyrate contributes to the inhibition of pancreatic inflammation was through the generation of regulatory T cells and their recruitment to the pancreas.

Another approach to increasing butyrate levels, and which may prove to be more practical for patients, is the administration of butyrate producing bacteria to patients. One study evaluated this using the prospective cohort study called TEDDY (The Environmental Determinants of Diabetes in the Young) [34]. In this study, six sites (Institute of Diabetes Research at the Turku University Hospital, Lund University, Pacific Northwest Diabetes Research Institute, University of Colorado Health Science Center, and Georgia Regents University) contributed data for an evaluation of the impact of probiotic use upon the development of autoimmunity in children who later developed T1D. The authors showed that if probiotics were taken by children, positive for the HLA-*DR3/4,* within 0–27 days after birth, there was a decreased risk of islet autoimmunity when compared with probiotic supplementation after 27 days or no probiotic supplementation. It should be noted though, that this only evaluated probiotic use in general and did not evaluate a specific probiotic mix or strain, such as butyrate producers.

Currently, at the time of this publication, there is an ongoing clinical trial (NCT03423589) to evaluate the efficacy of a specific probiotic mix called VSL#3. In this trial, the mix of *Bifidobacterium* (*B. breve*, *B. infantis*, and *B. longum*), *Lactobacilli* (*L. acidophilus*, *L. casei, L. delbrueckii* subsp. *L. bulgaricus* and *L. plantarum*) and *Streptococcus salivarius* subsp. *thermophilus* is being administered to infants at risk of developing T1D. This mix has previously been proven to be effective in inhibiting the development of T1D in the NOD mouse [35–37]. Two other clinical trials (NCT03032354 and NCT03556631) have been designed to administer *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* BB12 (NCT03032354) and of Live Combined *Bifidobacterium* and *Lactobacillus* (NCT03556631) to T1D patients in order to determine the impact on the development of T1D. These two clinical trials are also supported by previous studies with NOD mice and BioBreeding rats, another well-established model of T1D [38,39]. It should be noted though, that no clinical trial exists to determine if butyrate and butyrate producers can also inhibit the development of T1D in human patients.

1.2. Multiple sclerosis

Multiple sclerosis (MS) is a *T*-helper cell mediated autoimmune disease which targets myelin and proteins produced by neurons [40]. MS is characterized by an increase of proinflammatory T cells, such as CD4+ T cells with a Th1 or Th17 phenotype [40]. Individuals with MS develop life-long disabilities, including muscle atrophy, blurry vision and difficulties in coordination. Furthermore, there are genetic risk factors, including specific HLA class II genes that are associated with a predisposition to develop MS [41]. Among the various mouse models of MS, a model called experimental autoimmune encephalomyelitis (EAE) has been studied extensively. In both the EAE model and in MS patients, the inflammatory cytokines IL-17 and IL-23 are produced and contribute to the generation of Th1 and Th17 cells [42]. Studies using MS patients and the EAE model have characterized the immune-pathogenic process extensively; however, only recent studies have revealed the role of the intestinal microbiota in the immune-pathogenesis of MS and EAE.

An early study done with the EAE model suggested that the gut microbiome may play a significant role in the pathogenesis of MS [43]. In that study, antibiotics were given either orally or intra-peritoneally to the mice before inducing EAE. The oral administration of antibiotics ablated the intestinal microbiota and inhibited EAE development, whereas the intraperitoneal administration did change the microbiome or disease incidence, suggesting that the intestinal microbiome was required in order for EAE to develop. In contrast, another study demonstrated that elements of the microbiome could also be protective for EAE [44]. In that study, the authors administered a mix of *Lactobacillus* species and showed that, when administered, this Lacto-mix not only inhibited the progression of EAE but also established EAE was significantly reversed. In another model of EAE, a relapsing remitting disease in SJL/J mice was abolished when mice were in a germ free condition [45]. Conversely, colonization of C57/BL6 mice with segmented filamentous bacteria (SFB), which are IL-17 producers, induced EAE [46]. These studies demonstrated that the intestinal microbiome has a significant impact upon the development of EAE and that, while some microbiota could exacerbate disease development, others could protect/inhibit the development of disease [45].

A number of studies published in 2015 and 2016 revealed that MS patients indeed have dysbiosis, confirming the observations in the mouse model. Using stool samples, elevated levels of *Methanobrevibacter and Akkermansia*, along with a corresponding reduction in *Butyric monas* were associated with the MS microbiome [47]. Another study observed reduced numbers of *Faecalibacterium* in MS patients [48]. However, observations in MS patients have not been consistent as another study reported a decrease in the numbers of *Prevotella* and *Adelcreutzia* along with an increase in the Psuedomonas*, Mycoplana, Haemophilus, Blautia,* and *Dorea* genera in patients [49]. An absence of *Fusobacteria* was associated with a relapse risk in MS patients [50]. Thus, the human studies demonstrate that the development of MS and the onset of relapses are associated with both deleterious bacteria and beneficial bacteria, but there isn't one unique bacterial group that defines all MS patients.

This lack of a unique MS microbiome profile was further confirmed in a recent study in which the intestinal microbiomes of monozygotic twins discordant for MS were evaluated [51]. Surprisingly the microbiomes of each twin pair clustered together, demonstrating that diet and genetics had a greater effect on beta diversity than the disease. However, the authors did report an increase in several taxa (most notably *Akkermansia muciniphila*) in the untreated MS twin siblings. In order to prove the role of microbiome in MS, the authors did transfer experiments of the stool from each twin of a pair to mice with Relapsing Remitting EAE. Mice transplanted with microbiota from the MS twin developed EAE at a higher frequency than those mice given the microbiota from the healthy twins. This indicates that there is something present in the MS microbiome that can transfer disease.

Taken individually, each study evaluating the intestinal microbiome of MS patients demonstrates that MS patients have dysbiosis. However, due to confounding factors, no unique MS signature was identified. One factor that may be confounding in these studies is the treatment that MS patients receive. Indeed, one study found that immunomodulatory treatment of the MS patients resulted in increased abundances of Prevotella and *Sutterella*, and a decreased level of *Sarcina* [47]. In another study, an increase in *Akkermansia*, *Faecalibacterium*, and

Coprococcus genera [48] was observed after vitamin D supplementation. Thus, the type of treatments that MS patients receive will significantly impact the composition of the intestinal microbiome.

In addition, diet-induced changes in microbial composition may lead to differences in microbiomes of MS patients as well. A study comparing subjects on Western diet or Japanese diet showed differences in the microbiome [47,52,53]. This diet induced difference was directly evaluated in one study wherein MS patients were on a high fiber/high-vegetable/low-protein diet or a typical low fiber Western diet (low vegetables/high protein) for 12 months [54]. The HV/LP diet was characterized as high intake of legumes, whole grains, fresh fruits, vegetables, nuts, and olive oil along with a low intake of salt, sugar, animal proteins, refined cereals, fried food, red meat, saturated fats, and *trans*-fats. Alcohol was completely avoided/ excluded. The most remarkable result from this study was that the group of MS patients on the HV/LP diet had significantly fewer relapses than the MS patients on the Western diet. The *Lachnospiraceae* family was significantly more abundant in the HV/LP group and the Expanded Disability Status Scale score was significantly decreased compared to the subjects on Western diet. The lower levels of *Lachnospiraceae* may indicate an overall lower production of butyrate, since *Lachnospiraceae* produces butyrate, which is known to stimulate regulatory T cell activity.

Despite this lack of a unique signature for an MS microbiome and the many confounding factors that can affect microbiome analysis of MS patients, studies with both MS patients and EAE mice have been done with probiotics in order to determine if such treatment can normalize the MS microbiome. A number of mouse studies have been proven that this approach can be successful. Using an HLA transgenic mouse model of EAE, one study showed that the administration of Prevotella histicola reduced the incidence of disease from 100% to 25% with a delayed onset from10.6 ± 0.2 days to 17.5 ± 0.3 days [49]. At least two studies have demonstrated that inflammatory immune responses in MS patients can be reduced with mixes of different species and strains of *Lactobacillus* [44,55]. Thus, while studies indicate that MS is associated with dysbiosis which may contribute to the severity of disease, a direct causative role of microbiota is yet to be proven.

Based on the available data, dietary changes may in fact be the most effective. In addition, an individualized approach to correct the dysbiotic microbiome may be helpful to alleviate disease severity.

1.3. Rheumatoid arthritis

Rheumatoid arthritis (RA) has a strong genetic predisposition though increasing evidence shows that environmental factors like smoking, infections and the microbiome play a role in the onset and severity of disease. RA is strongly associated with the presence of HLA-DRB1*0401 in most of the ethnic populations while *0402 is associated with resistance. Smoking is suggested to enhance the expression of an enzyme, peptidyl arginine deiminase (PAD), required for citrullination of proteins. There has been some evidence that mucosal surfaces like lungs may the site of origin for the autoreactive responses in RA. This is supported by the presence of anti-citrullinated peptide antibodies (ACPA) from 1 to 10 years prior to the onset of clinical symptoms of RA in smokers [56,57]. Smoking is associated with seropositive erosive arthritis in DRB1*0401 positive individuals [58]. Smoking is also linked to periodontitis caused by an oral commensal, *Porphyromonas gingivalis* [59]. Patients with RA have higher occurrence of periodontitis as well as *P gingivalis* [60]. An infectious etiology of RA has been suggested, although a specific infectious pathogen has not been implicated. Epidemiological studies have shown the presence of antibodies to *P. gingivalis* in RA patients. *P. gingivalis* is the only known commensal that expresses the PAD enzyme and has been shown to citrullinate human proteins, which can then lead to the loss of tolerance to self-proteins. Recent studies have shown a change in gut microbiota in smokers suggesting a link between mucosal surfaces and immunity in RA. This is supported by recent studies on the role of the lung microbiome in early onset patients of RA [61].

However, the notion that the pathogen may be an opportunistic commensal in the gut has gained attention from the role of intestinal microbiome in autoimmunity. Significant progress has been made in understanding the intestinal microbial composition and their role in regulating immunity. While genetic factors, smoking, as well as infections, can impact the gut microbiome, the role of the intestinal microbiome in RA has not been studied as extensively as other autoimmune diseases. The support for the role of gut microbiome was first realized when germ free mice were protected from developing arthritis [62]. A direct role of a commensal in causing arthritis came from a study showing TH17 dependent onset of arthritis in germ free mice colonized with a bacterium, segmented filamentous bacteria (SFB). A comparison of intestinal microbiota in DRB1*0401 and *0402 mice suggested that a loss of a dynamic shift of the microbiome with chronological aging in the mice with RA-susceptibility gene was associated with an increased gut permeability, suggesting its role in the predisposition to arthritis [63]. The observations in mice suggest that a host with susceptible genetic factors may have dysbiotic microbiota, which can trigger systemic inflammation.

The concept that gut commensals may be involved in RA was supported by studies showing the presence of microbial DNA in the synovial fluids of patients [64,65]. The first study to show dysbiosis of the intestinal microbiome in RA patients used older technology [66]. In that study, a decrease in *Bacteroidetes-Prevotella* group was observed in patients with RA as compared to osteoarthritis patients. With the advent of 16S next generation sequencing, a study of new onset untreated RA (NORA) patients showed *Prevotella copri* was found in 75% of patients and only 25% of controls, suggesting that P. *copri* may play a pathogenic role in the development of RA [67]. To prove that *P. copri* could be inflammatory in some circumstances, the authors used the dextran sulfate sodium (DSS) induced model of colitis in C57BL/6 mice. The observations suggested a role of *P. copri* in exacerbation of intestinal inflammation with worse disease score as compared to medium only treated mice.

Two other studies used RA patients classified according to the criteria established by American Rheumatology Association (ACR) to define the gut microbial composition in patients with established disease undergoing treatment. In a study by Chen et al, the authors showed perturbations in the intestinal microbiome with decreased microbial diversity in RA patients, which correlated with the presence of antibodies and disease duration [68]. Patients with RA showed an expansion of rare lineage commensals that occurs with low abundance in healthy individuals. Using a predictive model, a microbial profile for association with RA was generated which showed an increase in species from the genera, *Eggerthella* and *Collinsella*, with a concomitant decrease in *Faecalibacterium*. Interestingly, the cohort of healthy controls included first degree relatives of the RA patients. The relative controls were closer to random controls suggesting that the microbial profile associated with RA patients was due to the disease status and not due to any confounding factors such as diet, genetics, and geographical location. A role of *Collinsella aerofaciens* in arthritis was confirmed by an exacerbation of CIA in DQ8 mice gavaged with it. *Collinsella* gavaged mice showed an increase in gut permeability and an enhanced expression of Th17 cytokines. *Faecalibacterium* is one of the most predominant commensal in human gut and is a known butyrate producer. Butyrate is used by epithelial cells for proliferation and repair to maintain integrity of the gut epithelial layer. This data suggested that the microbial composition of an individual determines the microbial-derived metabolic profile in the gut which may determine the immune status. The observations in this study were supported by another study which compared the oral and intestinal microbiomes of RA patients [69]. They showed dysbiosis in oral and intestinal microbiota of RA patients. In addition, the study suggested that *Collinsella* may be involved in RA due to molecular mimicry with the RA-susceptible DRB1*0401 molecule.

These studies suggest that alterations of the intestinal microbiome in RA contribute to the severity of disease. One can envisage that genetic factors determine the host immune system and interaction between the immune system and ecology determine the microbes that can live in a symbiotic relationship with the host. The bacterial communities determine the overall microbial metabolites. Any alterations or perturbations caused due to external sources via smoking or infections can change the homeostasis leading to an expansion of opportunistic pathogens. This can lead to an increase in byproducts produced by specific expanded microbes changing the microbial derived metabolic profile and also lead to the activation of T follicular helper (Tfh) cells and generation of germinal centers as shown in mouse models [70]. Mouse models using SFB showed a significant role of gut-derived bacteria in the onset of systemic inflammation, which was attributed to Tfh and B cells that migrate from the gut to the peripheral circulation and produce antibodies. However, since SFB is not a human pathogen, the observations are not applicable to human disease. A recent study tested the relevance of the association of *P copri* by measuring antibodies in a cohort of RA patients. The study showed the presence of IgA or IgG antibodies to a peptide or whole organism of *P copri*. The subgroup with IgG antibodies also showed Prevotella DNA in synovial fluid [71]. However, P *copri* has not been tested in an arthritis model. These studies suggest that one way by which pathogens can cause systemic immune response could be via modulating gut epithelial permeability. Some of the commensals shown to be associated with RA were used in CIA model to confirm their pathogenicity. Two studies (Jung et al and Sato et al) observed that *P. gingivalis* exacerbated the development of CIA in DBA/1 mice [72,73]. Of interest was the fact that the aggravating effect of *P. gingivalis* was not due to a heightened response to collagen II, which was used to induce CIA in the mice. Interestingly, *Prevotella intermedia*, which were used as a control, did not exacerbate the development of CIA. This is in contrast to a recent study showing antibodies to *P. intermedia* in a subset of patients with RA [74]. The presence of systemically distributed antibodies to gut commensals could be explained due to migration of antibody producing B cells from the gut; however, their pathogenicity has not yet been defined. These studies suggest that: 1) expansion of various microbes in different cohorts could be due to the heterogeneity of disease, 2) presence of antibodies to a commensal may be a way to remove the pathogen and 3) the impact of the associated microbes may be indirect through metabolites rather than direct on the immune system. Since many microbes may be involved in producing same metabolites, the overall metabolic profile may provide a better biomarker for disease status. These studies therefore suggest that, while some bacterial components are associated with the exacerbation of RA, others may be associated with the suppression of disease. Studies in mice using the CIA model support this theory. Kato et al showed that oral administration of *Lactobacillus casei* resulted in a significant decrease in the incidence and severity of arthritis in the CIA-susceptible DBA/1 mice [75]. The reduced disease was with a decrease in the levels of anti-collagen antibodies in the *L. casei* treated mice, suggesting that the oral administration of L. *casei* can modulate the immune system. In a recent study, oral administration of a human-gut derived strain of *Prevotella histicola* to DQ8 mice showed a modulatory effect on the immune system. DQ8 mice induced for arthritis and treated with *P histicola* in a prophylactic and therapeutic protocol showed a decreased incidence and severity of CIA as compared to medium treated mice [76]. The reduced disease incidence and severity after administration of P. histicola was associated with a decrease in the antigen-specific cellular and humoral responses, the generation of T regulatory cells, and an increase in myeloid suppressors. The change in immune profile in the gut shifted the cytokine profile from Th17 to regulatory. Most of the studies have used species of *lactobacillus* for treating CIA in mice; however, treatment of RA patients with *Lactobacilli* has not shown consistent results.

Several clinical trials have shown that probiotics can suppress inflammation in arthritis [77–79]. Treating RA patients with stable disease and chronic synovitis with a mix of *Lactobacillus rhamnosus* and *Lactobacillus reuteri resulted* in a decrease of inflammatory cytokines, such as TNF-α; however, the decrease was not significant. In another study, female RA patients with inactive to moderate levels of disease taking disease-modifying anti-rheumatic drugs were given *Lactobacillus casei (L. casei)* [77]. The inflammatory cytokines, IL-12 and TNFα, were significantly decreased in the *L. casei* treated group. In addition, the *L .casei* – treated RA patients had decreased high sensitivity C-reactive protein (hsCRP) levels with reduced swollen joint counts. Administration of this probiotic mix (*Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum*) to RA patients led to decreased disease activity scores (DAS) and hsCRP levels [78]. Simultaneously, expanding the treatments to include more beneficial commensals (probiotics) while at the same time removing arthritis aggravating/inducing bacteria, such as *Porphyromonas gingivalis and Prevotella copri* may prove to be a more effective microbiome based treatment for rheumatoid arthritis patients.

2. Probiotics in autoimmune diseases

Probiotics are live microbes; mostly bacterial species, that upon consumption can improve the gut health of an individual. Probiotics perform many functions, such as providing nutrients to the host, reducing pathogenic bacteria, enhancing the growth of beneficial commensals, and improving the overall health of the host [80,81]. Probiotics are also involved in maintaining a healthy mucus layer, which preserves a properly functioning barrier between the lumen of the gut and the lamina propria [81]. Metabolic products derived from probiotics, such as short-chain fatty acids (SCFA) and vitamins, not only nourish the host, but are also involved in the modulation of the gut microbiome and the regulation of the intestinal immune system in order to maintain intestinal homeostasis [81–83]. Recent studies have focused on the therapeutic aspects of probiotics, especially the use of probiotics to treat autoimmune conditions. Treating EAE, a model of MS, showed that probiotics inhibited pro-inflammatory polarization of Th1/Th17 and enhanced the production of $IL10^+$ producing regulatory T cells [84,85]. Another study, using an EAE model, determined that a mix of *L. paracasei* DSM 13434, *L. plantarum* DSM 15312 and *L. plantarum* DSM 15313 efficiently inhibited the development of disease as well as treated established EAE in mice. One recent study of adult MS patients determined that a mix of *Lactobacillus* species (*L. acidophilus, L. casei,* and *L. fermentum*) along with a species of *Bifidobacterium* (*B. bifidum*) was able to significantly improve different clinical parameters of MS patients [55]. These parameters included EDSS (expanded disability status scale), C-reactive protein, plasma nitric oxide metabolites, malondialdehyde, serum insulin, Beta cell function, and HDL-cholesterol levels. However, currently no probiotic mix seems to have such a potent response in MS patients as was observed with some of the EAE mouse models.

Similarly, Abhari and colleagues, [86] showed that treatment with probiotic *Bacillus coagulans* in a rat model of rheumatoid arthritis (RA) suppressed pro-inflammatory cytokines such as TNF-α, thereby significantly reducing pathology in the treated rats. These studies demonstrate that probiotic treatment can result in compositional changes of the intestinal microbiome that favor immune regulation, and consequently, modulate the host immune system and severity of developing and/or established disease. Treating NOD mice with a probiotic mixture called VSL#3 (a mixture of *Bifidobacterium longum, B. infantis, B. breve, Lactobacillus acidophilus, L. paracasei, L. delbrueckii* subsp. *Bulgaricus* and *L. plantarum*) prevented autoimmune diabetes by modulating gut microbial communities and promoting the differentiation of CD103+ DCs and reducing the expansion of Th1 and Th17 cells [36]. The authors further showed that the immunological changes were associated with the modulation of intestinal microbiota, where the VSL#3 treatment increased the abundance of *Clostridia, known to* have tolerogenic properties. Clostridia were shown to induce immune tolerance in

the gut [87,88].

However, probiotics that are currently approved for clinical use are non-specific and improve the overall gut health in a general and non-specific fashion to maintain gut homeostasis. In order to introduce specificity, novel technology is being used to genetically modify probiotic organisms to express antigens to which tolerance is desired or with which tolerance is improved. For example, Steidler and coworkers genetically engineered *L. lactis* to secrete IL-10 and tested its efficacy in treating a dextran sulfate sodium (DSS) induced mouse model of inflammatory bowel disease (IBD) [89]. Treatment of the DSS model with the IL-10 secreting L. lactis reduced colitis by 50%.

Another approach in improving probiotic treatments is to administer anaerobic strains that previously could not be cultured. Most of the commercially available probiotics are facultative anaerobic in nature and fail to colonize the lower gut. However, most of the gut microbiome is dominated with anaerobic gut bacteria that are involved in gut metabolism and homeostasis of the colon. Recent advances in the ability to culture anaerobic gut bacteria have advanced the field of probiotic treatment for various autoimmune conditions. These anaerobic probiotic-like bacteria can then colonize the gut epithelium, impact the adjacent microbial communities, and in doing so, interact with the intestinal and systemic immune systems either directly or indirectly. Anaerobic bacteria such as *Akkermansia muciniphila*, *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Faecalibacterium prausnitzii* and *Prevotella histicola* are some of the promising candidates that have shown efficacy in treating autoimmune diseases. There are various studies demonstrating that these anaerobes are abundantly present in the healthy human gut but are reduced in diseased individuals [53,68,90–92]. Collectively these bacteria are named as next-generation probiotics (NGP). *A. muciniphila* produces a high amount of SCFA in the gut and also has a high mucin degrading activity level; both of these functions help to maintain a healthy gut barrier [93,94]. *A. muciniphila* has been proven to modulate the immune system along with the intestinal microbiome when orally administered [95,96]. Similarly, *B. fragilis* was also shown to modulate gut microbiota in the context of disease. Specifically, when rats with antibiotic-associated diarrhea were treated with *B. fragilis*, the facultative anaerobic pathogenic bacteria of *Enterobacteriaceae* were eliminated and the abundance of beneficial bacteria such as *A. muciniphila* was increased [97]. *B. thetaiotaomicron* is able to modulate the gut microbiome by inducing the production of an antimicrobial peptide called angiogenin by Paneth cells and this peptide reduces the abundance of gram-positive pathogens such as *Listeria monocytogenes*, which in turn, increases the abundance of beneficial bacteria [98,99]. *F. prausnitzii* is the most widely reported human gut bacteria and its abundance represents a healthy gut [100,101]. *F. prausnitzii* is one of the main butyrate producers; butyrate can influence the growth of good commensal bacteria and also induces the production of IL-10 [100,102–104]. Recently a novel human gut-derived anaerobe, *P. histicola,* was shown to suppress autoimmune conditions using two autoimmune mouse models, EAE and CIA [49,76]. The effect was mediated by increasing the differentiation of T cells into Tregs and increasing the number of regulatory CD103 + DCs, thereby increasing the production of IL-10 [49,76]. Also, *P. histicola* treatment modulated the gut microbiome by increasing the abundance of beneficial bacteria such as *Prevotella* and *Sutterella* to that of a healthy condition [49]. In addition, treatment with *P histicola* did not alter the response to bacterial lipopolysaccharide, suggesting that it is not immunosuppressive

3. Conclusions/discussion

Of the three autoimmune diseases discussed in this review, only type 1 diabetes had a microbial profile that was common amongst all T1D patients, that of a low level of butyrate production and numbers of butyrate producers, albeit not a specific group of butyrate producers. Surprisingly, neither of the other two autoimmune diseases, MS and RA had a clear microbial signature that was disease specific (Fig. 1). Rather, these studies all suggest that any treatments that are probiotic based should be focused on the individual's microbial profile. Once the individualized profile is determined, then specific deficiencies or aberrations may be corrected by a carefully managed individualized treatment that would also include prebiotics and changes in diet in order for the probiotics to colonize and thrive in the gut of the patient. Colonization and long lasting effects of the administration of probiotics can be achieved as shown before [105]. This study demonstrated that the administration of an 11 strain probiotic mix comprising of 5 different *Lactobacillus* species and subspecies, four different *Bifidobacterium* species and subspecies, and *Lactococcus Lactis*, and *Streptococcus thermophilus,* after treatment with ciprofloxacin and metronidazole, delayed the restoration of the intestinal microbial composition to its previous state both in mice and humans. The study emphasizes the importance to proceed with caution when administering probiotics as a treatment to patients. Indeed, probiotic therapies that have significantly beneficial outcomes in mouse models of autoimmune disease do not always translate well to humans. This may be, in part, due to the constantly changing confounders of: geographical location, diet, genetics, disease- modulating drugs, antibiotics, and age on the microbial composition. In the future, it may be necessary to understand that there are many different states of normality that exist for the human intestinal microbiome, and that improving the health of an individual's intestinal microbiome should be tailored towards achieving a composition that is similar to that of the individual's healthy peers and relatives and not to a uniform and worldwide concept of what is a normal composition of the human intestinal microbiome.

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Appendix A. Supplementary data

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