

Lymphocytes T Helper 17 in Multiple Sclerosis: Regulation by Intestinal Microbiota

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Received: May 30, 2018

Accepted: April 18, 2019

Published: April 22, 2019

Citation: de Souza Moreira BB, de Almeida Franzoi AE, Gonçalves MVM, do Nascimento OJM, Becker J, et al. 2019. Lymphocytes T Helper 17 in Multiple Sclerosis: Regulation by Intestinal Microbiota. *J Neurol Exp Neurosci* 5(1): 40-47

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Abstract

Multiple sclerosis (MS) is an autoimmune disease with significant damage to the central nervous system (CNS). Despite many studies, it is not clear what triggers the mechanism for the disease to manifest or to exacerbate itself. There is a central role of T helper 17 (Th17) lymphocytes in the proinflammatory cascade of MS. Recent scientific studies have been evaluating the influence of intestinal dysbiosis in MS. However, there are no studies that correlate the role of intestinal dysbiosis on Th17 lymphocytes in MS patients.

This review focused on understanding the role of these lymphocytes and their relationships with MS. For this, we need to understand the role of bacteria and their metabolites in the activation of Th17 lymphocytes. We hypothesize that there is a closed cycle of stimulation between intestinal dysbiosis and Th17 lymphocytes in MS patients. We believe that both Th17 lymphocytes influence intestinal dysbiosis, and intestinal dysbiosis increases the activity of these immune cells.

Keywords

Multiple sclerosis, Lymphocytes Th17, Intestinal microbiota, Dysbiosis

Introduction

MS is a common neuroinflammatory disease of the CNS. The disease is characterized by chronic leukocyte infiltration of the subpial spaces and brain parenchyma. Over time, histopathological changes become dominated by microglial and astrocytic activation associated with extensive and chronic demyelination followed by either focal and diffuse axonal damage, which correlates with a progressive accumulation of clinical disability with progression of time [1-5].

The T helper 1 (Th1) and Th17 lymphocytes and their pro-inflammatory products - tumor necrosis factor α (TNF- α), interferon γ (IFN- γ), interleukin 17 (IL-17) and interleukin 22 (IL-22) - initiate and perpetuate the tissue damage observed in MS patients. On the other hand, the T helper 2 lymphocytes (Th2) and T regulatory cells (Treg) secrete cytokines, such as interleukin 4 (IL-4), interleukin 10 (IL-10), and tumor growth factor β (TGF- β), which are importantly associated with inhibition and regulation of the aforementioned immune responses [6-8]. The development of Th1-Th17 or Th2-Treg responses is mainly orchestrated by the cytokines present during antigenic presentation,

but also by the type of stimulating antigen, costimulatory molecules and by the transcription factors involved, evidencing the importance of the microenvironment [6-12].

Th17 cells were first described as a resident population of the intestinal lamina propria, further highly involved on the pathogenesis of several autoimmune diseases, including MS. The orphan nuclear receptor ROR γ t directs the differentiation program of proinflammatory IL-17⁺ T helper cells [13], where the microbiota is an important player in modulating its biology. The collection of bacteria, archaea and eukarya colonizing the gastrointestinal (GI) tract is termed the gut microbiota. While the gut microbiota refers to the total number of microbes that inhabit the gut, the microbiome comprises the complete genetic makeup of the microbiota. Quantitative and qualitative changes of gut microbiota define dysbiosis. These changes may lead to altered host microbial interaction or homeostatic imbalance that can contribute to a disease state leading to inflammation [14].

However, there are few studies that correlate Th17 lymphocytes with intestinal dysbiosis in MS patients. In this review, we highlight the correlation between intestinal dysbiosis and the activation of the adaptive immune system, specifically Th17 lymphocytes, and its relevance on the pathogenesis of MS.

Multiple Sclerosis and Th17 Helper Lymphocytes

In 2006, it was first demonstrated that “naive” Th cells could functionally differentiate into a new lineage, called Th17, because of their ability to secrete significant amounts of cytokines of the IL-17 family, as IL-17A and IL-17F. Th17 differentiation depends on the presence of transforming growth factor beta (TGF- β) + IL-6 during antigen presentation, and is highly inhibited by interferon gamma (IFN- γ) and IL-4. Another important Th17-driving cytokine is IL-23 [15]. Th17 cells express chemokine receptor 6 (CCR6). With secretion of chemokine receptor 20 (CCL20) by choroid plexus cells, it indicates the preference of these lymphocytes to migrate to the CNS, justifying its importance in MS. This phenomenon favors the transposition of the blood-brain barrier (BBB) by the lymphocytes, allowing access to the brain parenchyma. The increase in the frequency of Th17 cells as well as in IL-17A levels were observed in the brain tissue of MS during acute and chronic lesions, when compared to healthy controls, evidencing the importance of Th17 cells in the pathogenesis and progression of MS [15].

In 2010, authors elucidated several important functions for the IL-17 in the inflamed CNS. Using conditional knockouts mice that lack the adaptor molecule Act1, pivotal for the IL-17 signaling pathway, Kang Z and colleagues showed that this cytokine acts mainly on astrocytes. In response, these cells are activated and secrete significant amounts of chemokines and matrix metalloproteinases, thus promoting the cellular infiltrate and activating resident cells. In the absence of Act1 on astrocytes by conditional knockout, fewer inflammatory cells were found in the CNS of the animals, resulting in reduced

demyelination and axonal damage [16]. Th17 committed lymphocytes start to express high levels of the IL-23 receptor chains. IL-23 is a pro-inflammatory cytokine of the IL-12 family composed of the p19 and p40 subunits. It greatly favors the viability and the pathogenicity of the Th17 cells. In fact, Th17 cells generated in the absence of IL-23 display reduced viability as well as reduced pathogenicity, with a differential transcriptional profile [17]. There are current researches aiming to target IL-23, thereby possibly decreasing the inflammation and overall degeneration [18].

However, are there specific pharmacological alternatives to target IL-17 lymphocytes and partially block their activity? Currently, there are three anti-IL-17 antibodies released: secukinumab [19], ixekizumab [20], and brodalumab [21]. These drugs were first used to treat psoriasis, then rheumatoid arthritis and ankylosing spondylitis. With the importance of Th17 cells in MS, the use of such drugs could also be debated for MS patients [19-21]. By analyzing the response of MS patients to each of these drugs, we can also evaluate the changes in the intestinal microbiota of each patient against MS.

Microbiota and Gut Dysbiosis in Healthy Humans

The adult human intestine contains over 70% of the body's microbes, up to 100 trillion, and the microbiome number is 10 times larger than that of somatic and germ cells [14]. Recent studies have shown that the placenta, amniotic fluid and meconium are not sterile, but instead, possess a wide range of resident bacteria [22]. Researchers have suggested that the placenta harbors its own microbiome. According to Parnell LA and colleagues, the altered placental microbiome is correlated significantly with pre-term births [23]. Moreover, the gut microbiota composition depends on the delivery mode. It reflects maternal gut microbiota composition in case of vaginal delivery and the maternal skin microbiota in case of Cesarean Section. Another hypothesis is that the placental microbiome, which will further compose the intestinal microbiota of the fetus, may be derived from maternal oral microbiome. This factor may explain why women with periodontitis are more prone to abortion [23, 24].

Studies suggest that placental bacteria may alter methylation of CpG sites of the placental cells, rendering several responsive elements of inflammatory genes to be targeted by transcription factors. For instance, nuclear factor kappa B (NF- κ B) signaling and its pro-inflammatory activity that may further influence fetal immune response [25, 26]. It is possible that the deregulation of Th17 lymphocytes already begins since the intrauterine life of patients who will present the MS phenotype [27]. Researchers suggest the division of the intestinal microbiota into three main groups: the health benefits group (*Bacteroidetes*), the opportunistic group (*Firmicutes*) and the bacteria of the genus *Lactobacillus* and *Bifidobacterium* [28].

The microbiome differs among individuals. Factors that contribute to the formation and stable establishment of the

normal human gut microbiota include mode of delivery in parturition, type of infant feeding (breast vs bottle), pharmacological treatments and diet. Going into adulthood, diet is arguably the primary determinant of gut microbial composition and shapes the prospective interactions between the host and microbiota [29]. Diets rich in fruits, vegetables, and fibers promote gut bacterial diversity and enrich for genus *Bacteroidetes*. These diets with low-levels of *Firmicutes*, results in an increase in the production of butyrate. This cascade increases the digestion of complex carbohydrates. It decreases the activation of the NF- κ B responsive genes, decreasing overall intestinal inflammation. When the *Bacteroidetes*/*Firmicutes* ratio is low (as on a diet rich with animal fat, red meat, fried food, high salted food) there will be more activation of this proinflammatory factor [29].

Both exogenous (like stress and fatty diet) or endogenous (like genetics) can break the symbiotic reaction in the microbiota, leading to dysbiosis, which is characterized by changes in the composition of resident commensal communities [28]. A dysbiotic microbiota enhances the activity of NF- κ B and AP-1 which are pro-inflammatory transcription factors, impairing the suppressive intestinal microenvironment, as well as favoring the translocation of lipopolysaccharide (LPS) to the circulation [29]. The dysbiosis culminates in T cell activation, further promoting a pro-inflammatory process. The Th17 cells are potent immunological inflammatory mediators of the mucosa. Th17 cells produces IL-17 proinflammatory cytokines, promoting IgA secretion (which are the main immunoglobulins of the mucosa) [30].

Experimental Autoimmune Encephalomyelitis and Gut Dysbiosis

The experimental approaches using experimental autoimmune encephalomyelitis (EAE), a rodent MS model, have successfully proven that alterations of the gut microbiota are a potential risk factor for developing autoimmune diseases such as MS. Gut bacteria are required for induction of EAE. Mice under germ free (GF) conditions, that is, when the gut is devoid of bacterial pathogens, have developed a significantly less severe course of EAE compared to those in specific pathogen free (SPF) conditions [31]. This was supported by a decrease in the proinflammatory cytokines interferon gamma (IFN- γ) and IL-17A and a concomitant increase in the abundance of immunosuppressive Foxp3⁺ regulatory T cells (Tregs) [32].

A study performed in 1994 demonstrated that when segmented filamentous bacteria (SFB) was introduced, it was possible to colonize the intestines of GF mice. With the induction of proinflammatory T cells, there was maintenance of the EAE model [33]. The Clostridium-related bacterium promotes IL-17A producing Th17 differentiation [33, 34]. Another study, in a transgenic mouse model of spontaneous EAE, GF mice maintained an extremely low disease incidence compared with SPF counterparts throughout rearing [35]. This evidences the importance of gut microbiota in inducing pathogenic Th17 cells.

Berger K and researchers found a marked deficit of Th17-

like cells in GF mice. The deficit was most pronounced in T cells intimately connected to the intestinal wall, lamina propria and in Peyer's patches, but not in mesenteric lymph node populations. There were no notable changes in remote organs such as spleen or inguinal and axillary lymph nodes [35]. Kadowaki A et al. demonstrated that gut bacterial presence leads to gut Th17 induction and cooperation with myelin-reactive B cells to initiate autoimmune demyelination and disease. There is a regulatory population of gut intraepithelial auto antigen-specific CD4⁺ T cells in mice transgenic for a myelin-specific CD4⁺ T cell clone. These cells were induced by nonselfantigens derived from gut microbiota and suppressed proinflammatory T cell responses via their expression of the immune-suppressive molecule Lag-3 [36].

The species *Bacteroides fragilis* produces the capsular molecule polysaccharide A (PSA). This molecule reduces EAE severity by reducing IL-17A and IFN- γ expression in T cells and inducing an IL-10-producing Foxp3⁺ Treg population [37, 38]. According Takata K et al., the oral treatment of mice with the lactic acid bacterial species *Pediococcus acidilactici* ameliorated clinical EAE [39]. There is a lower expression of IFN- γ and IL-17A but a significant increase in the number of IL-10-producing Treg cells. Lavasani S et al. speculate that this bacterial infection could induce a population of IL-10-producing Foxp3-T regulatory cells (Tr1). Furthermore, a combination of lactobacilli strains reduced CNS inflammation and MOG-reactive T cell responses in EAE [40].

According to Bettelli E and colleagues, the strain *L. plantarum* DSM 15313 increased serum IL-27 levels. The cytokine IL-27 can suppress Th1 and Th17 responses but enhance Tr1 expression of IL-10 [41]. A probiotic combination of 5 strains - *L. casei*, *L. acidophilus*, *L. reuteri*, *Bifidobacterium bifidum*, and *Streptococcus thermophilus* - known as IRT5, also ameliorated EAE prophylactically and therapeutically decreased Th1 and Th17 but increased IL-4 and IL-10 from CD4⁺ T cells [42]. Another study demonstrated that the Bacteroidetes members, including *Bacteroides*, *Butyrivimonas*, and *Prevotella* are involved in metabolism of large, complex polysaccharides otherwise indigestible, into short-chain fatty acids (SCFAs), including butyrate. Fatty acid chain length is known to greatly influence immune responses. Long-chain fatty acids (LCFAs) promote CD4⁺ T cell differentiation toward Th1 and Th17, worsen EAE and decrease Treg differentiation. The SCFAs promote Treg differentiation and ameliorate EAE. PSA from *B. fragilis* should also be kept in mind for its immunosuppressive properties mainly through enhancing Treg differentiation [43].

Some endogenous ligands such as 6-formylindole [3,2-b] carbazole (FICZ) have also been shown to induce Th17 cells. Quintana FJ et al. report that the aryl hydrocarbon receptor (AHR) regulates the generation of Treg and Th17 cells in mice. AHR activation by 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD) induces Treg cells. These cells are suppressed in EAE by a TGF- β 1-dependent mechanism, whereas AHR activation by FICZ interfered with Treg cell differentiation, boosted Th17 cell differentiation and worsened EAE. Thus, AHR regulates Treg and Th17 cell differentiation in a ligand-specific manner. These ligands may have a link with the

microbiota and the dysbiosis in EAE model [44, 45].

The ability of AHR ligands to induce Tregs versus Th17 cells may depend on their capacity to cause epigenetic changes and microRNA modulation [46], and clearly more research is needed to understand the complexity of the receptor. Hwang SJ et al. focused on AHR activation and inhibition in EAE. The experiments have resulted in polarized effects of either amelioration or perpetuation of symptoms, through induction of Treg and Th17 cells, respectively [47].

In supplementation with long chain saturated fatty acids, lauric acid, there was upregulation of Th17 cells and Th1 cells and downregulation of regulatory T cells [43]. In depth analysis of the transcriptome from these experiments showed an increase in pro inflammatory markers (TNF- α , IFN- γ and Csf2). There was a decrease in the anti-inflammatory marker Foxp3. These differential cytokine levels coincided with an upregulation of the AHR, which shows a potential increased susceptibility to both endogenous and microbiota-produced compounds to compete as antagonists/agonists to drive further T cell proliferation towards either an inflammatory or anti-inflammatory phenotype [43, 48].

Haghikia A and researchers included fecal filtrates from saturated long-chain fatty acids (LCFA) fed mice to cell cultures in Th17 cell polarizing conditions, which resulted in higher proportions of activated Th17 cells than control groups, when compared to media that was supplemented with the fecal filtrates of normal diet fed mice [43]. Researchers demonstrated that Clostridia clusters XIVa and IV are formed by highly diverse bacterial species, many of which are characterized by the ability to produce SCFAs [49]. Second Furusawa Y et al. butyrate is implicated in colonic epithelium homeostasis, stimulation of anti-inflammatory responses for inflammatory bowel diseases (IBD), and the induction of colonic Tregs [50]. It is conceivable that a depletion of a large subset of clostridial butyrate producers is associated with MS pathogenesis [49]. Miyake S and colleagues suggest that species from Clostridia clusters XIVa and IV that are associated with MS might be distinct from those associated with IBD [51].

The activated encephalitogenic cells tend to migrate towards GALT and that interrupt balance between regulatory and inflammatory immunity, the GALT might have decisive role in the initiation and propagation of the CNS autoimmunity. Gut microbiota composition has the major impact on the balance in the GALT. Stanisavljević S and colleagues compared two different species of rats with the EAE model. Albino Oxford (AO) rats that are highly resistant to EAE induction and Dark Agouti (DA) rats that develop EAE after mild immunization were compared to gut microbiota composition in different phases after EAE induction. Microbial analyzes of the genus *Lactobacillus* and related lactic acid bacteria showed higher diversity of *Lactobacillus* spp. in EAE-resistant AO rats. Some members of *Firmicutes* and *Proteobacteria* were detected only in faeces of DA rats at the peak of disease (between 13 and 16 days after induction). The data of this research contribute to the idea that gut microbiota and GALT considerably influence multiple sclerosis pathogenesis [27].

Some studies started to inquire about salt intake through the induction of salt-sensitive kinase receptor (SGK1), which could lead to the pathological induction of Th17 lymphocytes [52-54]. Several intestinal bacteria were affected by high salt. Particularly the genus *Lactobacillus* spp. were suppressed. Faecal metabolites levels, particularly bacterial tryptophan metabolites, responded to high salt diet in mice. Such effects may contribute to salt-induced Th17 cell responses and salt-sensitive conditions. Because *L. murinus* produces indole-3-lactic Acid (ILA), Wilck N and researchers speculate that its salt-induced decrease with reduced ILA generation could be responsible for an increased Th17 cell response [54].

Researchers have shown that such Th17 modulation occurs and is responsive to salt contact in the intestinal mucosa, leading to exacerbation of autoimmune disease that has Th17 in its pathophysiology, such as MS [55]. Although in 2018, researchers have found that when a pathobiont, *Enterococcus gallinarum*, translocated to the liver and others tissues, it triggers inflammation autoimmune responses induced by Th17 at mice and humans. According to Vieira SM et al. the intestinal pathobionts may translocate and promote autoimmunity at predisposed hosts genetically [55].

We summarize the scientific results of the EAE model and the gut dysbiosis in figure 1.

Gut Dysbiosis in MS Patients

There is scientific evidence that exists dysbiosis in MS patients [56]. The MS patients displayed a reduction in the frequency of bacteria of the genus *Bacteroidetes*, including the species *B. stercoris*, *B. coprophilus* and *B. coprola* [51]. Chen J et al. reported no overall difference in gut bacterial species richness between healthy controls and patients with relapsing-remitting MS (RRMS). However, there was a trend toward decreased richness in active versus inactive RRMS disease. This study did observe a difference in microbiota structure between RRMS patients and Non-MS Persons. They identified differential abundance in 35 taxa in the 4 most abundant phyla. The genera *Adlercreutzia* and *Collinsella* of *Actinobacteria* were decreased in those with MS [57].

Within *Proteobacteria*, RRMS patients had higher *Pseudomonas* and *Mycoplana* levels but less *Haemophilus* compared with healthy controls. In RRMS *Bacteroidetes* phylum, *Pedobacter* and *Flavobacterium* were lower and *Parabacteroides* was at higher abundance than healthy controls. Finally in *Firmicutes*, the genera *Blautia* and *Dorea* were both decreased, while some members of the genera *Lactobacillus* and *Coprobacillus* were decreased in RRMS relative to their healthy controls. Families of *Erysipelotrichaceae*, *Lachnospiraceae*, *Veillonellaceae* in *Firmicutes* were also lower in RRMS persons [57].

Researchers demonstrated potential differences in gut bacteria between early onset pediatric MS and control children. There was a difference with exposure to the drugs within the patient population. Patients exposed to immunomodulatory drug (IMD) had alpha diversity higher richness and gut microbiota that were more similar to controls in comparison

to IMD-naive MS patients [58]. They noted a relative increase in abundance of *Desulfovibrio*, *Bifidobacterium*, and *Christensenellaceae* family, with relative decrease in *Clostridiales* order members such as *Lachnospiraceae* and *Ruminiococcaceae* in MS versus Non-MS. Functional pathway analyses showed enrichment of those involved in glutathione metabolism and LPS biosynthesis in MS patients. Tremlett H discovered that *Bacteroidetes* were inversely associated with Th17 only in MS and *Fusobacteria* correlated with Tregs only in controls [58].

According to Ghoreschi K and colleagues, the increased Th17 cell frequency is present in the small intestinal mucosa but not in peripheral blood of RRMS patients further underlies the similarities between pathogenic Th17 cell differentiations in MS patients. The acquisition of an IL-22⁺ phenotype by Th17 cells increased their effector function and proinflammatory properties [59]. The Th17 cells residing in the small intestine of RRMS patients are myelin-specific. The selective Th17 cell expansion in RRMS patients with disease activity suggests that, similar to what is observed in EAE model, the gut environment enhances pathogenicity of self-reactive T cells by driving them toward a Th17 cell phenotype. The expansion of myelin reactive Th17 cells is detected in T cells residing in the intestinal wall [60].

Researchers found that increased frequency of Th17 cells correlates with high disease activity and with specific alterations of the gut mucosa-associated microbiota in MS patients. By using 16S ribosomal RNA sequencing, they analyzed the microbiota isolated from small intestinal tissues and found that MS patients with high disease activity and increased intestinal Th17 cell frequency showed a higher *Firmicutes/Bacteroidetes* ratio, increased relative abundance of *Streptococcus*, and decreased *Prevotella* strains compared to healthy controls and MS patients with no disease activity. They demonstrated that the intestinal Th17 frequency is inversely related to the relative abundance of *Prevotella* strains in the human small intestine [60].

We suggest that both lymphocyte dysregulation in the CNS and intestinal dysbiosis contribute together to degrade the clinical state of the MS patient, as depicted in figure 1. The activation of the p19 and p40 subunit generates increased transcription and translation of IL-23. With higher concentration of IL-23, there is more stimulation for the release of IL-17. In turn, IL-17 differentiates more T-CD4 lymphocytes in T Helper 17. This pathway increases inflammation in the gut-associated lymphoid tissue (GALT system). With excess inflammation, dysregulation of intestinal bacterial equilibrium occurs, characterizing dysbiosis. Dysbiosis in MS patients is markedly characterized by an increase in populations of the genus *Firmicutes*. Meanwhile, bacterial populations of the genus *Bacteroidetes* decay (as described in figure 2).

Permeability of Body Barriers and Gut Dysbiosis

In the intestinal lamina propria, there are many immune cells, such as macrophages, dendritic cells, and T and B cells,

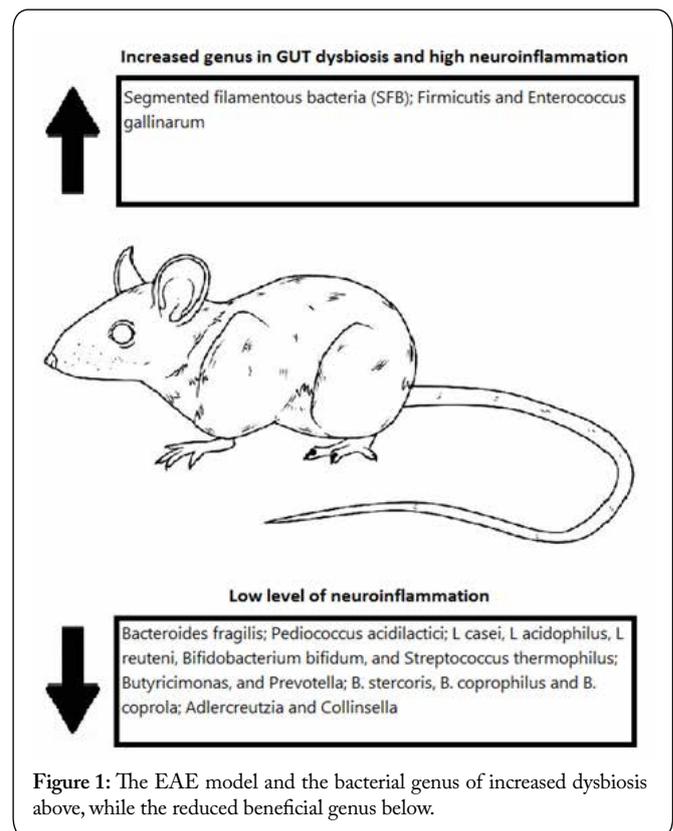


Figure 1: The EAE model and the bacterial genus of increased dysbiosis above, while the reduced beneficial genus below.

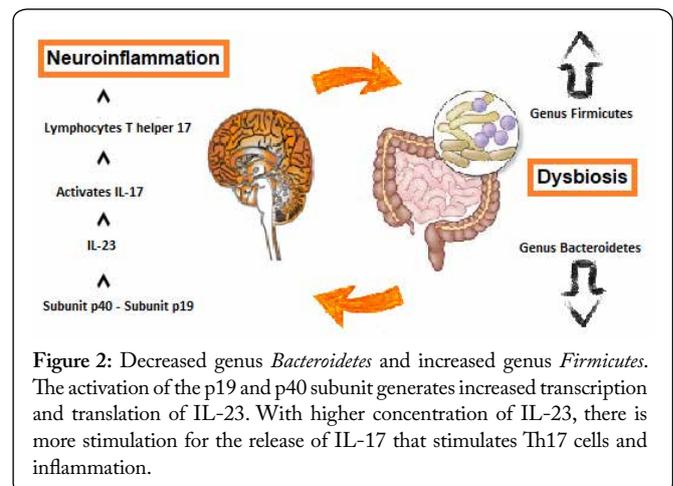


Figure 2: Decreased genus *Bacteroidetes* and increased genus *Firmicutes*. The activation of the p19 and p40 subunit generates increased transcription and translation of IL-23. With higher concentration of IL-23, there is more stimulation for the release of IL-17 that stimulates Th17 cells and inflammation.

and more recently, innate lymphoid cells (ILCs), forming the GALT system [28]. Normally, the intestinal microbiota and the GALT system have an intimately orchestrated relationship. The microbiota contributes to the defense against colonization by pathogenic bacteria, as well as promoting the repair of the intestinal epithelial barrier through TLRs, and the induction of secretory IgA. This barrier limits the penetration of pathogenic bacteria in the tissues, facilitating the absorption of nutrients [30].

Further studies have also linked the clinical course of EAE to intestinal barrier dysfunction. Increased intestinal permeability and altered intestinal morphology were observed as early as seven days after immunization. Both factors were maintained as constant features in the clinical course of EAE compared with control mice [61, 62]. A study suggested

that intestinal barrier dysfunction in EAE could expose gut microbiota antigens to local lymph nodes (LNs) and trigger not only a local pro-inflammatory response but also a systemic and chronic reaction. The gut microbiota has been associated with increased blood-brain barrier (BBB) permeability and altered expression of tight junction (TJ) proteins. GF mice had increased BBB permeability, and their TJs appeared as diffuse, disorganized structures compared with SPF mice. However, when GF mice were colonized with a SPF microbiota or Clostridium strains or treated with SCFAs, the mice exhibited decreased BBB permeability, which returned to near-normal levels [62].

Since the BBB matures progressively during both the intrauterine and postnatal stages, higher BBB permeability (partially related to disorganized TJ structures) has also been described in fetuses from GF mothers [62, 63]. According Saraiva C et al. the microbiota has not only been linked to intestinal barrier dysfunction but also affects the function of peripheral tissues such as the BBB. In fact, changes in BBB integrity might alter the selective permeability of the CNS to external molecules and allow them to promote CNS inflammatory responses and neuronal damage. The altered BBB permeability could also have consequences in perivascular cells such as astrocytes, neurons and microglia, which are important mediators of BBB integrity in physiological conditions [64].

Researchers investigated the possible association between intestinal permeability (IP) changes and MS. They studied 22 patients with RRMS and 18 age- and sex-matched healthy donors (HDs), including five twin pairs (one concordant, and four discordant for disease). Measurement of lactulose (L) and mannitol (M; two non-metabolized sugars) levels in urine samples, after an oral load, allowed to quantify gut dysfunction. The proportion of participants with increased IP was significantly higher in patients than in HDs (16/22 (73%) versus 5/18 (28%); $p=0.001$). The L/M urinary ratio showed significantly higher values in MS patients than in controls ($p=0.0284$). Urinary mannitol concentration was significantly lower in patients than in controls ($p=0.022$), suggesting a deficit of absorption from intestinal lumen [65].

Conclusions

Environmental risk factors largely contribute to MS development. The commensal microbiota has emerged as an environmental risk factor due to insights from EAE studies. The gut microbiota is essential to triggering autoimmune demyelination. The dysbiosis can modulate the host immune system, alters the integrity and function of biological barriers, and has effect on several types of CNS-resident cells. A characteristic gut dysbiosis has been recognized as a consistent feature during the clinical course of MS, and the MS-related microbiota is being progressively elucidated. Microbial taxa associated with and decreased in MS have a proinflammatory and regulatory effect in human T lymphocytes, respectively. The analysis of microbial abundance and immune genes implicated in MS pathogenesis found a positive correlation between over-represented genera and the expression of innate and activating adaptive immune genes. By contrast, under-

represented microorganisms were negatively correlated with MS inflammatory genes.

Although much progress has been made in understanding Th17 lymphocytes and their proinflammatory action in several experimental models, we have only recently recognized the Th17 response amplification link with intestinal dysbiosis. We also need to better understand the clinical relevance of dysbiosis in MS. It seems to be an endless cycle, with dysbiosis as a trigger for Th17 response amplification as well as a secondary complication in MS.

The authors suggest that anti-IL-17 drugs (like secukinumab, ixekizumab, and brodalumab), could be useful to attenuate diseases that have Th17 lymphocytes playing a role on the physiopathology, like MS. Considering the large number of genetic variants and environmental factors associated with MS, more precise, future individualized testing may aid to tailor a specific bacterial concoction per MS subject for better disease prognosis. More research will determine if there is an association of abundance of certain gut bacterial strains in the MS gut with specific sets of MS genetic variants and lifestyle habits within the MS pool.

The understanding of which bacteria are most striking in the dysbiosis that occurs in MS patients is a topic of great interest to stimulate new diagnostic and therapeutic approaches in MS. Finally, further studies are needed to better understand the relation between intestinal dysbiosis, Th17 response and clinical relevance in MS, and later to recognize possible therapeutic targets.

Disclosure Statement

The authors declare no conflicts of interest.

Statement of Funding

The authors state that there was no financial support. JPSP is funded by FAPESP (2017/22504-1).

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