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Review Article

Gut environmental factors and multiple sclerosis

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ABSTRACT

Commensal bacteria have maintained a symbolic relationship with the human body including the immune system and central nervous systems by co-evolving with humans for more than five million years. Recently, however, dysbiosis has emerged as a risk factor for various disorders including immune-mediated diseases. In this review, we discuss the interactions between commensal microbiota and the immune system and the association of immune-mediated diseases such as multiple sclerosis with microbial components and metabolic products as well as the presence of dysbiosis recently reported in multiple sclerosis patients.

1. Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) characterized by white matter lesions containing activated immune cells and resident CNS cells such as astrocytes and microglia. In the later stages of disease, irreversible damage and neurological symptoms occur caused by the chronic demyelination of axons and neuro-axonal injury. Based on pathological findings of MS lesions and studies using animal models of MS such as experimental autoimmune encephalomyelitis (EAE), it has been suggested that MS is an immune-mediated disease. Current evidence from genetic studies linking MS susceptibility genes to cellular immune responses and the efficacy of immune-targeted therapies in MS have indicated MS is a T cell-mediated disease (International Multiple Sclerosis Genetics Consortium;Wellcome Trust Case Control Consortium 2, 2011; Wingerchuk and Carter, 2014). Although genetic susceptibility is thought to be a relevant risk factor for MS, recent epidemiological studies have reported an increased incidence of allergies such as asthma and autoimmune diseases such as MS, type-1 diabetes (T1D), and inflammatory bowel diseases (IBDs) during the past two centuries (Cosnes et al., 2011, Eder et al., 2006, Patterson et al., 2009a, 2009b, World Health Organization, 2008). This increased incidence over a short period suggests the development of these disorders might be influenced by environmental factors in addition to genetic factors. Epstein-Barr virus infection, smoking low vitamin D and lack of sun exposure as well as adolescent obesity have been recognized as risk factor of multiple sclerosis (Ascherio et al., 2012, Olsson et al., 2017). Among other relevant environmental factors, interactions with the microbiome are considered important for the development of autoimmune diseases including MS via molecular mimicry and/or bystander immune activation (Croxford and Miyake, 2015). However, these mechanisms have not been conclusively demonstrated in human autoimmune diseases. Strachan proposed the “hygiene hypothesis”, which suggested the recent increased incidence of chronic inflammatory diseases in developed countries was associated with a decrease in infectious diseases (Strachan, 1989). Subsequently, Rook hypothesized that exposure to microbes had a protective effect on inflammatory disorders by modulating the immune system (Rook, 2012). The hygiene hypothesis suggests that a modern lifestyle and environment have affected the composition of gut microbiota and altered the immune system causing individuals to become more susceptible to allergy or autoimmune disease. Recently, accumulating evidence from animal experiments has revealed that the microbiome, existing symbiotically in the gut, affects the development and regulation of the immune system. Furthermore, commensal microbiota are implicated in immune-mediated disorders including rheumatoid arthritis, inflammatory bowel disease and MS. This review article provides an overview of the recent advances in our understanding of interactions between the gut microbiota and autoimmune diseases such as MS.

2. Gut microbiota and immunoregulation

More than 100 trillion organisms, most of which are bacteria, exist in our intestinal tract, providing essential non-nutrient factors such as vitamins and various metabolites as well as nutrients. Commensal bacteria both limit the outgrowth of pathogenic bacteria and maintain a symbiotic relationship with our immune system resulting from co-evolution for nearly half a billion years. The intestine is the largest barrier tissue in the human body, and is also an immune tissue and interactions with microbiota are important for intestinal development and function (Maynard et al., 2012). The gut immune system is composed of several lymphoid tissues in the intestinal mucosa including

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Peyer's patches and isolated lymphoid follicles (ILFs) in the lamina propria, mesenteric lymph nodes (MLNs) and intraepithelial lymphocytes, which provide protection against pathogenic organisms. In addition, the lamina propria contains innate type lymphocytes such as innate lymphoid cells (ILCs), γδT cells, invariant natural killer cells, and mucosal associated invariant T cells. Of note, interactions with commensal microbiota are important for the development and regulation of these gut innate cell functions (Maynard et al., 2012; Levy et al., 2017). Indeed, many gut innate cells have been shown to be implicated in the regulation of autoimmune diseases (Araki et al., 2003, Chiba et al., 2005, 2012, 2017, Croxford et al., 2006, Miyake and Yamamura, 2007, Miyazaki et al., 2011, Haga et al., 2016, Hayashi et al., 2016.). Macrophages in the lamina propria have a unique phenotype— they express lower levels of Toll-like receptors (TLR), and TLR signaling is suppressed to avoid inflammatory responses to commensal microbiota (Smythies et al., 2005). Peyer's patches and MLNs develop prenatally in contrast to ILFs that develop after the postnatal colonization of microbiota (Cherrier and Eberl, 2012). ILFs exist in non-mammalian vertebrates and class-switching of IgA occurs both T-cell independently and dependently in ILFs (Tsuji et al., 2008). Intestinal epithelial cells (IECs) closely interact with microbiota and modulate the immune system through the secretion of cytokines and chemokines. IECs produce thymic stromal lymphopoietin IL-25, IL-33 and TGF-β, which induce dendritic cells to become tolerogenic and promote the generation of FoxP3 $^{+}$ regulatory T (T_{reg}) cells and IgA producing plasma cells (Hill and Artis, 2010). T_{reg} cells affect the structure of microbiota and are crucial for maintaining immune homeostasis to the commensal microbiota and systemic immune functions (Izcue et al., 2009). More recently, specific commensals contributing to the induction of T_{reg} cells have been reported. *Bacteroides fragilis* induces T_{reg} cells through the activation of TLR-2 by polysaccharide-A, although not all TLR-2 ligands promote T_{reg} cells (Ochoa-Repáraz et al., 2010a, 2010b). *Clostridium clusters IV and XIVa* also induce T_{reg} cells in the intestine partly through the production of short chain fatty acids (SCFAs) (Atarashi et al., 2011; Furusawa et al., 2013). Effector T cells in the intestine of individuals from countries where helminth infections are not common are mainly Th17 or Th1 cells rather than Th2 cells observed in areas of helminth infection (Maynard et al., 2012). Th17 cells expressing transcription factor RORγt and producing effector cytokines such as IL-17A, IL-17F and IL-22 contribute to maintenance of the mucosal barrier and host defense against pathogenic bacteria together with ILCs, which share similar effector cytokines and transcriptional factors. In particular, the development of IL-17, which is dependent on TGF-β, also contributes to the generation of T_{reg} cells and is affected by the balance of anti- and pro-inflammatory cytokines including IL-1β, IL-6 and IL-23. Segmented filamentous bacteria (SFB) in mice and epithelial cell adhesive bacteria in humans have been linked to the induction of Th17 cells (Ivanov et al., 2009; Gaboriau-Routhiau et al., 2009; Atarashi et al., 2015). Intriguingly, Th17 cells can acquire a regulatory phenotype as demonstrated in anti-CD3 antibody treated mice or oligodendrocyte glycoprotein-specific T cell receptor transgenic 2D2 mice (Esplugues et al., 2011, Kadowaki et al., 2016).

3. Gut microbiota and EAE

Experimental approaches using EAE have proven the association of gut microbes and CNS inflammation. EAE disease severity was reduced in germ-free or antibiotic-treated mice (Yokote et al., 2008; Ochoa-Repáraz et al., 2009; Lee et al., 2011). A spontaneous model of relapsing-remitting EAE in T-cell receptor transgenic mice did not develop disease when raised in germ-free conditions. However, the recolonization of indigenous commensal bacteria restored the susceptibility of mice to EAE (Berer et al., 2011). Studies investigating specific members of the microbiome have increased our understanding of the interactions between microbiota and CNS inflammation. The colonization of SFB restored susceptibility to EAE associated with the induction of enteric Th17 cells (Lee et al., 2011). In addition to disease-promoting bacteria, the influence of intestinal commensal bacteria on immune-suppressive functions in EAE were investigated. The oral administration of *Bacteroides fragilis* ameliorated EAE and was mediated by the induction of IL-10 producing T_{reg} cells via TLR-2 stimulation with polysaccharide A (Ochoa-Repáraz et al., 2010a, 2010b; Wang et al., 2014).

4. Analysis of MS patient microbiota

Given the importance of the gut microbiome in animal models of various diseases including EAE, the analysis of human samples has gathered much attention. The advance of high-throughput DNA sequencing technology allows the direct analysis of microbiota without culturing. A reduced diversity of microbiota was reported in dysbiosis observed in IBD, T1D and other conditions (Otto et al., 2004; Manichanh et al., 2006; Kostic et al., 2015; Mosca et al., 2016). Chen et al. also reported that microbiota species richness was reduced in MS patients with active disease (Chen et al., 2016). However, Miyake et al. did not observe the reduced richness of intestinal microbiota in MS patients in remission. Dysbiosis features either a reduction or a loss of normally residing bacteria or the bloom of pathobionts. Differences in the composition of fecal microbiota at the genus level were reported in four independent investigations. An analysis of MS patients in Japan identified 21 species whose relative abundance was significantly changed when patients were compared with controls (Miyake et al., 2015). Among these species, 19 were reduced in MS samples and fourteen belonged to *Clostridium XIVa and IV clusters* and three belonged to *Bacteroides*. These clostridial clusters are composed of highly diverse bacterial species, and many of them possess the ability to produce SCFAs leading to the expansion of T_{reg} cells. Intriguingly, 14 clostridial species did not overlap between 17 T_{reg}-inducing strains described previously, probably because the analysis of Japanese MS samples only included bacteria with an average relative abundance of more than 0.1% in either MS patients or controls (Miyake et al., 2015, Atarashi et al., 2013). A reduction in OTU belonging to *Feacalibacterium* and *Bacteroidacea* was also reported by Cantarel et al. in the USA (Cantarel et al., 2015). Although the decreased bacteria belonged to a different genus, Jangi et al., reported a reduction in *Butyricimonas*, a butyrate-producing genus (Jangi et al., 2016). Taken together, the reduction of SCFA producing bacteria may be a common feature of MS patients. In addition, they observed the decrease tendency of *Prevotella* and *Sutterella* which were also found as reduced bacteria in Japanese MS patients (Jangi et al., 2016; Miyake et al., 2015). Furthermore, the *Methanobrevibacter* and *Akkermansia* species were increased also in MS patients. Because *Methanobrevibacter* is the dominant methane-producing microbe, it can be detected in the breath. Jangi et al., reported elevated levels of breath methane in MS patients compared with healthy controls (Jangi et al., 2016). In addition, Chen et al. observed an increased abundance of *Pseudomonas, Mycoplana, Haemophilus, Blautia* and *Dorea* genera and a decreased abundance of *Parabacteroides, Adlercreutzia* and *Prevotella* genera in MS patients (Chen et al., 2016).

Differing results have been reported among studies of intestinal microbes in MS patients. The gut microbiome is affected by various endogenous and exogenous factors including genetic background, age, gender, body mass index, location of living and dietary habit, and therefore further studies with large cohorts and longitudinal collection of samples would aid our understanding of the relationship between gut microbiota and MS.

5. The effect of bacterial-derived metabolites on the immune system

Microbiota influence the host immune system via microbiota components and metabolites (Thorburn et al., 2014; Rooks and Garrett, 2016). Among diverse metabolites produced by the anaerobic fermentation of dietary components by gut microbiota, SCFAs, aryl

hydrocarbon receptor (AHR) ligands and polyamines have immunomodulatory functions. Studies of the microbiome in MS patients as well as IBD and T1D patients demonstrated a reduction of bacteria producing SCFAs suggesting SCFAs might be involved in the pathogenesis of immune-mediated diseases (Sokol et al., 2008; Mondot et al., 2011; Joossens et al., 2011; De Goffau et al., 2014; Miyake et al., 2015). SCFAs such as acetic acid, butyric acid and propionic acid, are abundant products of the bacterial fermentation of undigested carbohydrates and have diverse functions on host immune systems and the CNS in addition to being an energy source for both gut microbiota and intestinal epithelial cells. SCFAs stimulate G protein-coupled receptors (GPCRs), inhibit histone deacetylases (HDACs) and suppress inflammatory responses by peripheral blood mononuclear cells, neutrophils, macrophages and dendritic cells via the inactivation of nuclear factor-κB similar to that of HDAC inhibitors (Usami et al., 2008; Vinolo et al., 2011; Kendrick et al., 2010; Chang et al., 2014; Singh et al., 2010; Trompette et al., 2014). SCFAs were shown to increase the frequency and enhance the suppressive function of T_{reg} cells via the induction of FoxP3 by DHAC inhibition (Arpaia et al., 2013; Smith et al., 2013; Furusawa et al., 2013; Tao et al., 2007). Furthermore, the administration of SCFAs was reported to inhibit colonic inflammation, allergic airway diseases and collagen-induced arthritis (Arpaia et al., 2013; Furusawa et al., 2013; Mizuno et al., 2017). In addition, high-fiber diet or SCFA-supplementation was also shown to ameliorate the development of EAE associated with an increased number of T_{reg} cells (Mizuno et al., 2017; Haghikia et al., 2015). Circulating microbiota metabolites also directly influence CNS and immune cell functions (Fung et al., 2017) including microglial development and function (Erny et al., 2015). Microglia from GF mice or antibiotic-treated mice exhibited an immature phenotype with impaired functions. However, the abnormal microglial phenotype was restored by supplementation with SCFAs.

In contrast, several other studies have reported that SCFAs exacerbate inflammation. Antibody-induced arthritis, a murine model of arthritis dependent on innate immune cells but independent of lymphocytes, was augmented by feeding with SCFAs or a high-fiber diet in contrast to T cell-mediated arthritis model (Mizuno et al., 2017). In humans, high concentrations of SCFAs in the sputum of patients with cystic fibrosis were associated with enhanced inflammatory responses by the recruitment and persistence of neutrophils (Ghorbani et al., 2015). SCFAs produced by *Porphyromonas gingivalis*, one of the major microbes associated with periodontal diseases, was suspected to be involved in the pathogenesis of periodontitis by inducing reactive oxygen species (Chang et al., 2012). Thus, the effect of SCFAs are dependent on cell type and the local environment probably based on cell specific GPCRs and their varied metabolite sensing capacity.

6. Conclusions

In summary, many animal studies and several human studies have suggested the importance of the gut microbiota in immune-regulation and autoimmune disease including MS. Maintaining the correct balance of certain strains of gut microbiota appears to be crucial for homeostasis between pathogenic T cells such as Th1 and Th17 cells and regulatory cell types. The reconstitution of diminished microbiota or probiotics might be an effective way to treat or prevent dysbiosis-associated diseases. Furthermore, targeted microbe-derived metabolites could be an alternative method to modulate disease. For the future, it will be important to determine the symbiotic mechanisms used by commensal bacteria and to identify what microbiota-derived factors and molecular pathways contribute to the protective effect for autoimmune diseases.

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