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Multiple sclerosis: Possibility of a gut environment-induced disease

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ABSTRACT

Multiple sclerosis is a putative autoimmune disease of the central nervous system, a representative disease of 'neuroimmunology.' We now understand that gut microbiota constitutes an integral part of our body and play critical roles in various neurological diseases with which no intestinal pathology was previously associated. In fact, several reports from Japan, North America, and Europe confirmed dysbiosis of the gut microbiome in MS patients. Given the increase in the prevalence of MS worldwide, especially in Japan, some previously unknown causal environmental factors needed to be identified to inhibit the development of MS in future generations. In this review, we will introduce recent key topics related to MS pathogenesis and immune cells linking gut and brain, and then summarize studies on gut microbiome in MS and its mouse model. Lastly, we will discuss the potential role of diet in the development of MS and propose a hypothesis that could explain the dramatic increase in the number of patients suffering with MS in Japan in the past few decades.

1. Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease affecting various parts of the central nervous system (CNS) (Compston, 2006). Typically, patients experience repeated bouts of neurological deficits (called relapses), eventually leading to various disabilities, including lowered activity of daily living (ADL). MS usually affects at the age of 20–40 years, with predominance in females. The clinical course of MS has the following two components: relapse-remitting and progressive (Lublin et al., 2014). It is now widely accepted that autoimmune mechanisms play a pivotal role in MS. Genome-wide association studies have revealed more than 200 susceptibility loci, majority of which are related to cellular immune function and also include variants associated with other autoimmune diseases such as rheumatoid arthritis or type 1 diabetes (Patsopoulos et al., 2017);(International Multiple Sclerosis Genetics et al., 2011). Similar to that in the other autoimmune diseases, there is an imbalance between inflammatory versus regulatory components of the immune system in patients with MS. However, so far neither causative autoantibodies nor specific target antigens (presumably myelin components) have been confirmed to be associated with MS (Hohlfeld et al., 2015). A relapse, or worsening of certain neurological functions in a few days, is characterized by formation of a new inflammatory lesion (called plaque) in the CNS, usually detected in brain/spinal cord MRI scan (Steinman, 2014). Such lesions are caused by infiltrations by autoreactive oligoclonal T cells and macrophages from the periphery through blood brain barrier, and subsequently, lead to inflammatory responses in the CNS. Drugs targeting lymphocytes (depletion, blocking migration, etc.) significantly reduce the relapse of MS, which provides a proof-of-concept of the pivotal contributions of the adaptive immune system (Ransohoff et al., 2015). In progressive MS, which is characterized by progressive worsening of the symptoms accompanied by brain/spinal cord atrophy along with neuronal loss, different mechanisms (most probably including innate immunity) are thought to be participate in the process (Ontaneda et al., 2016), although recent clinical trials targeting lymphocytes showed some efficacy, indicating an important role of adaptive immunity in the disease process (Kappos et al., 2018; Montalban et al., 2017). Another important feature of MS is that it is a heterogeneous disease in many aspects. There are four major pathological patterns observed (Lucchinetti et al., 2000): distributions/shape of lesions vary among patients, efficacy of a certain disease-modifying drug varies among patients, there is a wide range of severity and prognosis, etc. Therefore, precision medicine for MS is an important challenge; prognostic and predictive biomarkers for efficient treatment are urgently needed.

2. Epidemiology of MS

The prevalence of MS is strikingly diverse around the world: high in Europe, North America, and Australia, but low in Asia, South America, and Africa (Browne et al., 2014). Immigration studies have revealed

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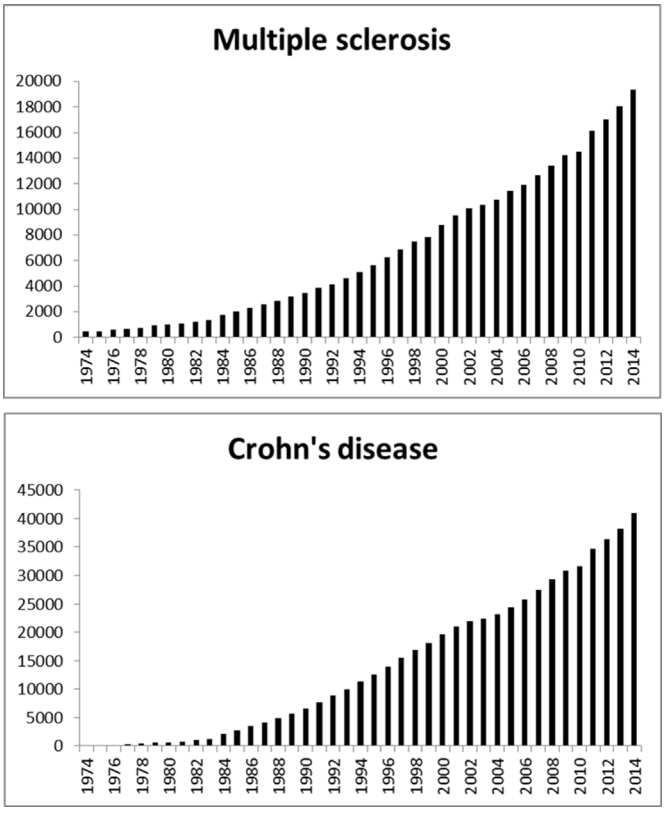

Fig. 1. Increase of multiple sclerosis (MS) and Crohn's disease in Japan. Data obtained from Ministry of Health, Labor and Welfare (Japan). The number of recipient certificates issued for specific disease treatment of each year was shown as bar graph.

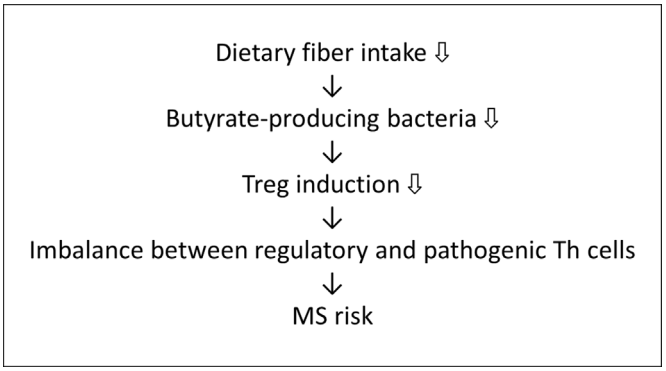

Fig. 2. Our hypothesis indicating how change of eating habit could contribute to increased risk of MS for Japanese population.

that the place of residence of an individual at his/her young age affects the future risk of MS (Milo and Kahana, 2010). As discussed by Milo et al., MS prevalence depends on the age of immigration, implicating environmental factor(s) encountered before adolescence. The overall incidence of MS has been gradually increasing in Western countries (Koch-Henriksen and Sørensen, 2010). In Japan, the number of officially registered MS patients increased almost 20-fold between 1980 and 2014 (from 1040 in 1980–19389 in 2014; Fig. 1). There is a longitudinal regional epidemiological study performed in Tokachi area in Hokkaido, Northern part of Japan (Houzen et al., 2012). In this restricted area with around 360,000 population (unchanged for a half century), the prevalence of MS was 8.6/100,000 in 2001 but 10 years later, it was 16.2/100,000. Interestingly, in both Western countries and in Japan, the female/male ratio has significantly increased. In 1970s, Japanese neurologists performed a national survey compiling 1084 MS cases (Kuroiwa et al., 1975). They classified each case into either optico-spinal type of MS (OSMS), characteristic of no brain lesion, or Western type MS, with disease-specific brain lesions. They concluded that optico-spinal MS were common in Japan. A recent national survey on Japanese MS held in the early 21st century revealed that the incidence of Western type of MS, but not OSMS, is rapidly increasing in Japan (Osoegawa et al., 2009). Studies in Northern part of Japan also observed an increase in the incidence of Western type MS. It was speculated that OSMS cases mostly corresponds to neuromyelitis optica spectrum disorder (NMOSD), characterized by anti-AQP4 autoantibody, which was discovered in 2004. Interestingly, the prevalence of NMOSD was reported to be not significantly different among other parts of the world, suggesting that different environmental factors contributed to NMOSD (Pandit et al., 2015) (Miyamoto et al., 2018). It should be noted that the number of immigrants in Japan is very limited and would not play a major role in the incidence and prevalence of MS. Moreover, such rapid increase in prevalence in such a short period should be attributed to environmental factors and not genetic factors. Before we discuss on the MS risk factors, let us introduce our clinical experience and our working hypothesis built around the turn of the 21st century (see Fig. 2).

3. Bedside observation in MS clinic in Japan

One of the authors (Yamamura) has encountered a series of clinical cases that developed MS during their stay (for more than one year) in Europe or North America (MS high prevalence regions) for study or job. On the other hand, there were no cases where MS developed during their stay in Asian countries. We performed a questionnaire survey asking about a patient's habits on diet. We found, at the time of onset of the disease, many patients had irregular eating habits and constipation (unpublished data). Conversely, we encountered cases where a patient's disease activity was controlled by changing the diet habit from Western type of meal to traditional Japanese diet. Epidemiological studies have revealed that the prevalence of inflammatory bowel disease (Crohn's disease and ulcerative colitis) have also dramatically increased recently in Japan (Asakura et al., 2009). Various dietary risk factors such as high fat diets have been reported in Japanese inflammatory bowel disease (IBD) patients (Sakamoto et al., 2005). With these facts, we built a hypothesis that change of diet at the population level induces susceptibility to both MS and IBD, presumably mediated through the gut immune system, as already described, by citing this Yamamura's hypothesis, in a book written by Howard Weiner (2005). Then, what, in fact, are the environmental factors triggering MS?

4. Environmental risk factors of MS

There are several established environmental risk factors in MS (McKay et al., 2017), such as insufficient vitamin D level, smoking, and Epstein-Barr Virus (EBV) infection (especially infectious mononucleosis), among others. It must be noted that epidemiological studies supporting these risk factors have been conducted in MS high-prevalence areas, such as Europe. In fact, relatively few epidemiological studies support that these factors contributed to the onset of MS in Japan (Funatogawa et al., 2013); (Takeuchi et al., 2006), although reports indicating the relation between vitamin D or EBV infection and Japanese MS are to be noted (Yoshimura et al., 2012);(Niino et al., 2015). Recently, obesity (especially in adolescents) is emerging as a new risk factor for MS (McKay et al., 2017). Increase in the prevalence of obesity is a global phenomenon, but in Japan it is still quite low (Collaborators, 2017). Another new candidate risk factor for MS is high salt intake (Farez et al., 2014), based on the findings that pathogenic Th17 cells are induced *in vitro* with high salt concentration (Wu et al., 2013). However, salt intake by Japanese is in fact decreasing (Wakita et al., 2013). Now, we can consider changing diet along with changing

gut microbiota as a new candidate risk factor for the surge in MS prevalence in Japan for the past few decades. Before introducing microbiota study of MS, we will look at how the concept of the gut-brain axis has evolved recently.

5. Evolution of the gut-brain axis: focus on lymphocytes linking the gut and brain

Even before modern medicine revealed various levels (anatomical, physiological, cellular, molecular, and now microbiota levels) of intricate connections between the gut and CNS, we understood its significance, as shown in our common words. For example, 'Hara' in Japanese literally means belly, but it implies more than just an anatomy. This word is often used to refer to one's mind or heart. The important role of crosstalk between the brain and gut were extensively reviewed in other literature (Fleck et al., 2017; Miyake, 2012; Tremlett et al., 2017), and we would not go into the details here. Gut is the largest immune organ and a vast number and a variety of immune cells, such as innate lymphoid cells (ILCs), populate and function in it. Moreover, we now comprehend that these gut-residing cells could translocate from the intestine to the CNS and affect neurological diseases, including MS. Invariant natural killer T (iNKT) cells and Mucosal associated invariant T (MAIT) cells are unique in that, unlike conventional T cells, they lack T cell receptor diversity and express single α-chain; iNKT cells express Vα34-Jα18 in humans, whereas MAIT cells express Vα7.2-Jα33 in humans. iNKT cells are a unique subset of lymphocytes that recognize glycolipid antigens such as α-galactoceramide (α-GalCer) presented by MHC like molecule CD1d (Bendelac et al., 2007). iNKT cells have been detected in the brain lesion of MS affected individuals (Illés et al., 2000) and they have been demonstrated to decrease in number in the blood of MS patients (Araki et al., 2003). A possible regulatory role of iNKT cells via IL-5 has been reported (Sakuishi et al., 2007). Although α-GalCer recognition activates iNKT cells to produce various cytokines, both proinflammatory (such as IFN-γ) and regulatory (such as IL-4), an analogue named OCH (shorter sphingosine chain) selectively stimulates IL-4 production from iNKT cells in ameliorating experimental autoimmune encephalomyelitis (EAE) and other autoimmune disease models. Interestingly, recent findings have revealed that these glycolipids were produced by *Bacteroides fragilis*, commensal bacteria in humans. OCH is under development as a new disease-modifying drug for MS and Crohn's disease. MAIT cells were discovered in 2004, enriched in the gut (mucosal-associated) (Treiner et al., 2003), and relatively abundant in human blood. Similar to iNKT cells, MAIT cells have been detected in MS lesions (Illés et al., 2004), their number has been found to decrease in the blood of MS patients (Miyazaki et al., 2011), and they have been suggested to play a regulatory role (Croxford et al., 2006). Antigens of MAIT cells were vitamin B2 derivatives that are presumably derived from bacterial metabolites (Kjer-Nielsen et al., 2012) (Lopez-Sagaseta et al., 2013), which explained why no MAIT cells were observed in germ-free mice. More recently, using genetically engineered mice, we found that myelin reactive T cell clones derived from intraepithelial lymphoid cells (IEL) had suppressive activity when they were transferred to mice and induced EAE (Kadowaki et al., 2016). Interestingly, aryl hydrocarbon receptor (AhR) ligand influenced the generation of this population of cells. Because AhR ligand is contained in vegetables of the family Brassicaceae (such as cabbage and broccoli), the CNS inflammation could be influenced by diet through IEL $CD4^+$ T cells in mice model (Kadowaki et al., 2016). These findings clearly show the importance of lymphocytes in the gut: 1) they are influenced by the gut environment (which is influenced by diet, antibiotics, etc.), and 2) they migrate into the CNS and influence CNS diseases.

6. Gut commensal bacteria in animal models of MS

To investigate the mechanistic role of gut microbiota in the CNS pathology, an animal model of MS, experimental autoimmune encephalomyelitis (EAE), has been applied. The injection of a defined protein of the myelin sheath (e.g., myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), or proteolipid protein (PLP)) combined with an adjuvant causes either acute or chronic EAE (active EAE) in recipient animals. EAE can be induced by the adoptive transfer of *in vitro* activated $CD4^+$ Th cells that are specifically reactive to myelin antigens (passive EAE). The following three experimental findings argue the critical role of microbiome in the induction of EAE: 1) antibiotic-treated mice study, 2) germ-free mice study, and 3) gnotobiote mice study. We investigated whether antibiotics altering gut microbiota affected EAE development (Yokote et al., 2008). We introduced MOG 35–55 peptide into B6 mice to induce EAE. Non-absorbing antibiotics (kanamycin, colistin, and vancomycin) were given to mice via drinking water before and during the induction phase. The antibiotic treatment not only significantly altered the composition of the intestinal microbiota (but without any pathological change in the gut), but also reduced the clinical and pathological signs of EAE. T cells isolated from the gut-associated lymph nodes showed suppressed IL-17 production. Intriguingly, the effect of antibiotics was suppressed in mice in which invariant NKT (iNKT) cells were genetically depleted, suggesting a critical role of iNKT cells in this model. Similar antibiotic treatment effect on EAE was also reported by another group of researchers (Ochoa-Reparaz et al., 2009). Thereafter, using germ-free mice, Lee et al. showed that commensal bacteria are required to induce EAE (Lee et al., 2011). Without intestinal bacteria, the simulation of pathogenic Th17 cells was significantly diminished. Another evidence showing the critical role of gut microbiota came from spontaneous RRMS disease model named RR mice (Berer et al., 2011). In germ-free condition, they did not develop disease. However, as soon as microbiome was transferred from SPF mice, they developed CNS inflammation. Finally, recent studies from Germany and North America showed that when microbiome from an MS patient was administered to germ-free mice and EAE was induced, the mice developed more severe symptoms and pathology compared to that when microbiome from a healthy subject was given (Berer et al., 2017; Cekanaviciute et al., 2017). Collectively, these animal studies implicate that changes in gut microbiota play a *causative* role in the inflammation of CNS.

7. Analyses of microbiome of MS patients

16S ribosomal RNA sequencing is generally used for unbiased, comprehensive analyses of microbiota of fecal samples. Several studies using this method have been published so far from Japan, North America, and Europe (Berer et al., 2017; Cantarel et al., 2015; Cekanaviciute et al., 2017; Chen et al., 2016; Jangi et al., 2016; Miyake et al., 2015; Tremlett et al., 2016). The highlights of each study are summarized in Table 1. One important conclusion is that while the diversity and richness of microbiota was generally preserved, there was dysbiosis in the microbiome of MS patients. Although the abundance of several microbe species was commonly increased or decreased across different studies, many disease-specific species have been reported in just a single study. Such inconsistency in the results is relatively common in such analyses of human fecal samples, even though each study employed sound methodology. Following are some of the limitations explaining this discrepancy. First, control 'healthy' samples are different among different populations (countries). For example, gut microbiota of healthy Japanese is significantly different from that from other countries (Nishijima et al., 2016). In addition, sample handling methods, sequencing methods, and reference database vary among studies. Other factors that potentially influence the analyses of human gut microbiota include body mass index (BMI), treatment including MS disease-modifying drugs or antacids like proton pump inhibitors, food habits (yogurt, supplements, etc.), and physical activity. They basically differ among different cohorts. In general, BMI in Western cohort is higher than that in Japanese cohort, which might affect the results.

Table 1
Summary of the 16S ribosomal RNA study on multiple sclerosis microbiota (case-control study).

Country	Cohort	Control samples	Amplified 16rRNA sequences	increased species/genera	Decreased species/genera	Year	Reference
Japan	RRMS in remission (n = 20)	healthy controls (n = 40) and longitudinal 158 samples from 18 controls	Roche 454, V1-V2 regions	Streptococcus thermophilus. Eggerthella lenta (species)	19 species including 14 f clostridial species belonging to Clostridia clusters XIVa and IV and Bacteroidetes	2015	Miyake et al.
North America	RRMS female with vitamin D insufficiency (n = 7; 5 with Gratilamer acetate-treated)	healthy controls with vitamin D insufficiency (n = 8)	forward primer: 27F.1 5'-AGRGTTTGATCMTGGCTCAG -3' and a non-degenerate reverse primer: 1492R.jgi 5'-GGTTACCTTGTTACGACTT- 3'	Ruminococcusa (genus)	Bacteroidaceae, Faecalibacterium (genus)	2015	Cantarel et al.
North America	Children < 18 years old within 2 years of MS onset (n = 18, 12.5 years old (417)	healthy children (n = 17, 13.5 years old (9-18))	Illumina MiSeq, V4 region	Desulfovibrionaceae, Methanobrevibacter, Enterobacteriaceae (genus)	Lachnospiraceaea, Ruminococcaceaea (genus); Faecalibacterium prausnitziid, Butyricimonasa fragilisc (species)	2016	Tremlett et al.
North America	RRMS in remission (n = 60, 22 untreated),	healthy controls (n = 43)	Roche 454, V3-V5 regions; Illumina MiSeq, V4	Methanobrevibacter, Akkermansia. (untreated patients: Sarcina) (genus)	Butyricimonasa (genus): Untreated patients: Prevotella, Sutterella (genus)	2016	Jangi et al.
North America	RRMS (n = 31; active n = 12, remission n = 19)	healthy controls (n = 36)	Illumina MiSeq, V3-V5 regions	Psuedomonas,Mycoplana, Haemophilus, Blautia,and Dorea (genus)	Parabacteroides, Adlercreutzia and Prevotella (genus)	2016	Chen et al.
North America	untreated RRMS (n = 71)	healthy controls (n = 71)	Earth Microbiome Project standard protocol (V4 region)	Akkermansia muciniphila and Acinetobacter calcoaceticus (species)	Parabacteroides distasonis (species)	2017	Cekanaviciute et al.
Germany	monozygotic twin with RRMS (n = 34; 15 untreated)	monozygotic twin with no disease (n = 34)	Roche 454, V3-V5 regions	Akkermansia muciniphila (species) in co-twins with untreated MS	Sutterella (genus)	2017	Berer at al.

Here, we introduce our results of analysis of Japanese MS microbiota and discuss the implications of our study (Miyake et al., 2015). Twenty RRMS (mostly typical Western type but not all) fecal samples during remission were compared with samples from 40 healthy subjects. We used additional 158 samples from 18 healthy controls that repeatedly provided fecal samples. Bacterial 16S ribosomal RNA (V1–V2 region) sequencing revealed that species diversity and richness were not altered by MS. UniFrac analysis revealed that overall structure of MS fecal samples is significantly different from that of samples obtained from healthy controls, evaluated as moderate dysbiosis. We detected significant difference in the abundance of 21 species, out of which two increased and 19 decreased in MS affected subjects. The differences were confirmed when MS samples were compared to the 158 longitudinal healthy samples. Intriguingly, the bacterial taxa reduced in MS comprised primarily of clostridial species belonging to Clostridia clusters XIVa and IV and *Bacteroidetes*. Abundance of one of the reduced clostridial strains, *Faecalibacterium prausnitzii*, was also reported to be decreased in fecal samples obtained from pediatric MS cases of North America, but this observation was not confirmed by other studies. Of note, *Faecalibacterium prausnitzii* abundance was reduced in fecal samples and mucosa-associated microbiota obtained from Crohn's disease patients and linked to a higher risk of post-operative recurrence (Sokol et al., 2008). Another clostridial strain whose abundance was reduced, *Eubacterium rectale*, was not reported to be altered in other MS studies, but its abundance was reduced in Crohn's disease (Mondot et al., 2011). *Faecalibacterium prausnitzii* and *Eubacterium rectale* constitute two of the major species in microbiome of Japanese population (Nishijima et al., 2016), which may explain the discrepancy between our study and those of Western countries.

On the contrary, some species whose abundance is reported to be altered in Western MS patients were not significantly different between MS cases and healthy subjects of Japan. One such representative was *Akkermansia muciniphila*, which was reported to be upregulated in three studies from Western countries (Berer et al., 2017; Cekanaviciute et al., 2017; Jangi et al., 2016) and the pathogenic role of T helper 1 (Th1) cells was discussed (Berer et al., 2017; Cekanaviciute et al., 2017). Another example, *Methanobrevibacter*, an archaea, was reported to be increased in abundance in both adult and pediatric MS patients in North America (Jangi et al., 2016; Tremlett et al., 2016), but not in our Japanese cohort. *Methanobrevibacter* has been reported to be related to constipation owing to its methane-producing capacity (Kim et al., 2012), as well as its immunostimulatory function through its adjuvant properties (Krishnan and Sprott, 2008). However, most Japanese people do not harbor *Methanobrevibacter* (Nishijima et al., 2016), and our MS cohort rarely possessed this archaea either (unpublished data). By increasing the number of samples and/or by comparing between patients affected by similar type of MS (by strictly distinguishing between typical Western type of MS and atypical MS in Japan for example), we could elucidate the reason for such discrepancies across different populations.

8. Change of diet might contribute to the surge of Western type MS prevalence in Japan

In the past several decades, the dietary habit of the Japanese population has significantly changed. Traditionally they took a lot of rice and fish, but now they take more meat and less rice. In fact, an epidemiological study demonstrated that dietary fiber intake in Japanese population has significantly reduced in around past 50 years, especially in younger generation (Nakaji et al., 2002). The decreased intake of rice, which was the main source of dietary fiber for the Japanese population, is pointed out as a reason (Nakaji et al., 2002).

Dietary change from vegetarian to meat or vice versa rapidly affects the composition of the microbiota in human (David et al., 2014) and in rodents (Desai et al., 2016; Faith et al., 2011; Rey et al., 2013). Dietary fibers have diverse physiological functions in human health. *Clostridial*

species including *Eubacterium rectale* and *Faecalibacterium prausnitzii* are involved in fermenting of dietary fiber, which leads to production of short chain fatty acids (SCFA), including acetate, propionate, and butyrate. In fact, these bacteria act as major sources of gut-microbiota derived butyrate production, because these bacteria contain abundant butyryl-CoA:acetate, which is a key enzyme during production of butyrate (Louis et al., 2010). Butyrate exhibits anti-inflammatory properties via inhibition of NK-κB activation and via stimulating differentiation of colonic Foxp3 + Treg cells. (Furusawa et al., 2013; Segain et al., 2000). Moreover, the ameliorating effects of SCFA in EAE have been reported (Haghikia et al., 2015; Mizuno et al., 2017). Although there are no epidemiological studies of dietary fiber intake in MS patients, we could speculate that the decreased dietary fiber intake in the Japanese population significantly contributed to the surge in the incidence of MS in Japan for the past few decades.

9. Perspective

Although great advances have been achieved with respect to understanding MS pathogenesis and developing disease-modifying drugs, there are many problems yet to be solved. What triggered MS and what determined the variety of MS (such as disease course, prognosis, and treatment effect)? We anticipate that gut microbiome studies could contribute a lot in answering these fundamental questions. In fact, animal studies have already shown that the gut microbiome critically determines the onset of the disease and affects the disease course. However, the situation is different in humans; it is quite difficult to obtain and analyze fecal samples before the onset of the disease. So far, no studies have been reported with respect to the progressive MS-specific change in gut microbiota. No studies so far have succeeded in predicting a patient's prognosis from the patient's fecal sample. No studies could foresee the treatment responder or non-responder. By increasing the number of samples to be analyzed and by performing comparison between different types of MS, future studies might answer these questions. We also need to establish effective strategies for modulating the gut microbiota. These may include probiotics and prebiotics (augmentation specific species); symbiotic (a mixture of these two); antibiotics (depleting specific bacteria); fecal microbiome transplantation (changing the composition of microbiota). Importantly, these interventions need to be specifically tailored for each patient. Despite all these challenges, microbiome study in MS will open new avenues to develop strategies to treat, cure and prevent the intractable disease.

Conflicts of interests statement

The authors declare no conflict of interests.

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