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Role of diet in regulating the gut microbiota and multiple sclerosis

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1. Introduction

Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system (CNS) that affects 2.5 million people worldwide [1], There is currently no cure for MS; however, recent studies demonstrating the influence of diet and the gut microbiota on disease suggest new therapeutic avenues. While nutrition and microorganisms have previously been associated with MS through epidemiological studies, several factors have contributed to the resurgence in attention towards the host-microbe axis. First is the recognition of the importance of the gut microbiota in the development of host immunity. Second is the establishment of gnotobiotic mouse models that allow for more precise investigation of the gut microbiota. Third is a greater appreciation for the role of metabolism, and, by extension, host dietary intake, in host immune function. While difficult to study, the multidirectional relationship between host diet, commensal gut microbiota, and host immunity will be important to understand in order to leverage diet and microbiota-based interventions for the benefit of MS patients.

In this review, we discuss major dietary components and diet regimens that have been associated with MS and the most commonly used preclinical model of MS, experimental autoimmune encephalomyelitis (EAE). We examine recent evidence supporting the role of commensal gut microbiota in the development and progression of disease. We further consider our current understanding of the relationship between host diet and commensal gut microbiota generally before highlighting studies addressing this relationship in the context of EAE and MS. Lastly, we close by posing critical questions related to the interactions between diet, gut microbiota, and MS that must be answered in order to translate diet- and microbiota-based therapies to MS patients.

2. Diet and multiple sclerosis

It is important to precede a review of the literature concerning diet and MS with a note that multiple systematic reviews of dietary intervention trials for MS find no strong evidence for the use of diet in treating MS due to the lack of robust clinical trial design [2,3]. These systematic reviews do not necessarily dismiss the potential benefit of nutritional

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intervention in MS, but they highlight the challenges of studying dietary interventions in disease. First, many dietary studies use self-reported diet data, which is limited in terms of accuracy. Second, many diet studies are observational/retrospective and do not randomize subjects to diet regimens, thus confounding the results. Third, studies are often limited in population size and duration and thus may miss subtle effects. While the utility of diet-based interventions to manage MS remains tentative, here we focus our review on dietary regimens and specific components that have been studied in MS patients and/or preclinical models of MS with special attention to underlying mechanism, when applicable. The following dietary regimens and components represent promising candidates for more robust follow-up clinical studies.

2.1. Dietary regimens

2.1.1. The Swank diet—The Swank Diet is a low-fat diet developed by Dr. R. L. Swank aimed to benefit patients with MS [4]. The diet was based on an early observation in 1950 that the incidence of MS appeared to correlate with fat consumption [5]. In a follow-up, 34-year-long, non-randomized study of low-fat diets in MS patients, it was found that MS patients that consumed more fat had higher rates of disability compared to MS patients that limited their fat intake; of the patients that began the study with minimum disability, patients that limited their fat intake to below 20 g of fat per day had a lower final mean neurological grade versus patients that consumed 20 g or more of fat per day [6].

2.1.2. Caloric restriction—Calorie restriction regimens that under nourish, but are not mal-nourishing, have been shown to extend the lifespan of model organisms [7], in part by reducing inflammation associated with aging [8,9]. Fasting has been demonstrated to suppress disease in a number of different EAE models [10–12]. In addition, intermittent fasting has also been shown to suppress EAE by suppressing the proinflammatory T helper 17 (Th17) response, inducing anti-inflammatory regulatory T cells (Tregs), and altering the microbiota (discussed in more detail below) [13]. Based on these results, a small, 15-day-long pilot study was performed in which patients with relapse-remitting MS (RRMS) on an intermittent energy restriction diet demonstrated a decrease in circulating lymphocytes, compared to patients who ate ad libitum, and changes were seen in the microbiota at the phylum level that resembled those seen in EAE [13]. More recently, a fasting mimicking diet has been shown to suppress EAE by inducing leukocyte apoptosis, and a 3-month-long trial of the diet improved self-reported quality of life in RRMS patients [14].

2.1.3. Ketogenic diet—A ketogenic diet is generally defined as a low-carbohydrate, high-fat diet that induces the production of ketone bodies as an energy source [15]. A ketogenic diet has been shown to suppress EAE by reducing proinflammatory T helper 1 (Th1) and Th17 responses, reducing reactive oxygen species production, and increasing the proportion of Tregs [14,16]. Pilot studies of the ketogenic diet in RRMS showed improvement in self-reported quality of life, fatigue, and depression over a 3- to 6-month period [14,17], though it will be interesting to perform more longitudinal studies with more objective measures including functional testing and magnetic resonance imaging (MRI).

2.1.4. Western diet and obesity—The rise in obesity in Western countries [18] and prevalence of MS in the Western world [19] has spurred recent investigations into the relationship between the Western diet, obesity, and MS. A Western diet is characterized by excess consumption of refined and processed food, red meat, fat, sugar, and salt as well as reduced consumption of fruits and vegetables [20]. In mice fed a high-fat, high-sugar diet mimicking the Western diet for 18 weeks, their gut microbiota were altered and the concentration of anti-inflammatory short chain fatty acids (SCFAs) were decreased. This supports work in EAE models demonstrating that mice fed a high-fat diet exhibit more severe disease [21]. Furthermore, long chain fatty acids, which are enriched in processed foods typical of the Western diet, have been shown to exacerbate EAE by promoting the differentiation of proinflammatory Th1 and Th17 cells [22]. In a small pilot study, MS patients on a Western diet were shown to have a significant increase in proinflammatory Th17 cells associated with an increase in their expanded disability status scale (EDSS) and a higher relapse rate compared to MS patients on a high-vegetable, low protein diet over a 12 month follow-up period [22].

Obesity, defined by excess body fat and weight for a given height, is intimately tied to the caloric excess associated with the Western diet [18]. In EAE models, obese mice exhibit more severe disease associated with an increase in proinflammatory Th17 cells and a differential gene expression signature in the brain [21,23,24]. This agrees with epidemiological studies that have associated high body mass index (BMI) early in life with a two-fold increased risk of MS [25,26]. This effect, however, was not seen in an Italian case-control population [27]. In pediatric patients with either clinically isolated syndrome (CIS), an initial neurological lesion that may progress to clinical definite MS (CDMS), or CDMS, obesity was associated with increased morbidity [28].

2.1.5. Plant-based diets—Plant-based diets, including vegetarian and vegan diets, have been shown to have anti-inflammatory effects mediated by plant-derived compounds. Such anti-inflammatory compounds include antioxidant polyphenols and carotenoids, as well as fiber, which is metabolized by gut microbiota to produce SCFAs with anti-inflammatory effects. Indeed, in a prospective, randomized trial of healthy male patients, increasing the consumption of carotenoid-rich fruits and vegetables over the course of four weeks resulted in a decrease in the inflammatory biomarker C-reactive protein [29]. In a study of a very low-fat, plant-based diet, MS patients that adhered to the diet for a year versus patients on the control diet had no difference in terms of EDSS, relapse rate, and MRI lesions; however, patients had improvements in BMI, metabolic biomarkers including insulin and cholesterol, and self-reported fatigue [30]. Interestingly, in a pilot study in which healthy omnivores switched to a lacto-ovo vegetarian diet (a plant-based diet that allows the consumption of eggs and dairy) for three months and were compared to long-term omnivores and long-term lacto-ovo vegetarians, there was a decrease in expression of genes related to pro-inflammatory lipopolysaccharide in the gut microbiome of long-term vegetarians that was not seen in either the long-term omnivores nor the short-term vegetarians [31]. These data suggest that while plant-based diets can modulate inflammatory processes, beneficial anti-inflammatory effects may require long-term adherence and warrant further study.

2.1.6. Mediterranean diet—The Mediterranean diet emphasizes fruits, vegetables, whole grains, and unsaturated fats; encourages intake of dairy, fish, and ethanol in moderation; and limits meat consumption [32]. The Mediterranean diet is proposed to influence inflammation by increased consumption of antioxidants including polyphenols [33]. In one prospective study, healthy patients on the Mediterranean diet exhibited a significant reduction in circulating leukocytes and platelets [34], however inflammatory markers C-reactive protein and interleukin (IL)-6 were not changed compared to patients on a control diet. A retrospective case-control study of patients with CIS suggests that adherence to a Mediterranean diet, with consumption of unprocessed red meat, is associated with a lower risk of CIS [35]. This result agreed with another case-control study of MS patients that correlated Mediterranean diet adherence with a reduced risk of MS [36]. However, another case control study of MS patients found no association between a Mediterranean diet and the risk of developing MS [37]. A pilot study randomizing female MS patients onto the Mediterranean diet or a control diet for six months demonstrated a reduction in EDSS and improved fatigue [38].

2.2. Dietary components

2.2.1. Vitamin D—Vitamin D is a fat-soluble vitamin, best characterized for its role in calcium homeostasis that can be taken in via diet or synthesized upon sun exposure [39]. Epidemiological studies of MS patients have shown an increase in MS prevalence in areas farther from the equator, suggesting that sun exposure, and by extension, vitamin D, may be protective against MS [40–42]. Such epidemiological evidence is also supported by genome wide association studies of MS patients that have identified vitamin D related genes (CYP27B1, encodes for 1-alpha-hydroxylase that is required to activate vitamin D; CYP24A1, encodes for 24-hydroxylase that metabolizes active vitamin D to an inactive form) as MS risk alleles (CYP27B1: odds ratio [OR] 1.11, 95% confidence interval [Cl] 1.06–1.15; CYP24A1: OR 1.12, 95% Cl 1.08–1.16) [43], In vivo, Vitamin D has been shown to suppress EAE prophylactically and therapeutically [44–46]. In vitro, vitamin D has been shown to suppress antigen-stimulated proliferation of lymphocytes and limit antibody production [47–49]. Studies investigating the effect of vitamin D on T cell differentiation have shown that vitamin D can suppress pathogenic Th1 [50] and Th17 [51] differentiation and induce protective Tregs [52]. The effects of vitamin D on the adaptive immune system are, in part, due to the tolerogenic effects of vitamin D on dendritic cells [53–55]. Surprisingly, mice that lack the vitamin D receptor or are fed a vitamin D-deficient diet exhibit less severe EAE [56]. In addition, mice that lack either of the hydrolase enzymes that are required to convert vitamin D to its biologically active form exhibit the same severity of EAE as wild-type mice, despite CYP27B1 being identified as a risk allele for MS [56]. This discrepancy underscores the importance of a minimum level of vitamin D signaling required to stimulate an immune response, as vitamin D signaling can potentiate canonical T cell receptor signaling in naïve T cells [57], but leaves open the possibility of a higher, therapeutic dose of vitamin D that may benefit MS patients.

Clinical trials of vitamin D in the context of MS have produced mixed results. There is evidence to suggest that prophylactic vitamin D supplementation can reduce the risk of developing MS: dietary intake of vitamin D during pregnancy was found to reduce the

risk of developing MS in offspring (relative risk [RR] 0.57, 95% Cl 0.35–0.91, comparing offspring from mothers in the highest quartile of dietary vitamin D consumption to those in the lowest) [58], and vitamin D levels in patients with CIS are inversely correlated with progression to CDMS (hazard ratio [HR] 0.48, 95% Cl 0.25–0.91, for a 50 nmol/L increase in vitamin D) [59]. Additionally, vitamin D administration may benefit patients with established MS. Vitamin D levels are inversely associated with the appearance of new MS lesions, as detected by MRI (RR 0.53, 95% Cl 0.37–0.78, comparing RRMS patients with vitamin D levels greater than 100 nmol/L to RRMS patients with vitamin D levels between 50.0 and 74.9 nmol/L) [60], and high-dose vitamin D administration (ranging from 10,000 to 40,000 IU/day) was sufficient to decrease the production of proinflammatory IL-17 in peripheral blood $CD4^+$ T cells and suppress proliferation of peripheral blood T cells in MS patients [61,62]. Still, confounding trials suggest that there is no relationship between serum vitamin D levels at birth and development of MS (OR 1.0, 95% Cl 0.68–1.44, comparing the highest quintile of vitamin D to the lowest) [63], nor between high-dose vitamin D (approximately 6000 IU/day to maintain target serum vitamin D concentration of 130–175 nmol/L) and MS progression [64]. A meta-analysis of studies investigating vitamin D in RRMS patients found no association with vitamin D and the risk of relapse (OR 0.98, 95% Cl 0.45–2.16) [65]. Of the specific dietary components associated with MS, vitamin D is among the earliest described and most studied, but more robust studies are needed to investigate and elucidate the potential benefit of vitamin D in MS.

2.2.2. Vitamin A—Like vitamin D, vitamin A is a fat-soluble vitamin with immunomodulatory effects. While vitamin A-deficient mice have blunted regulatory T helper 2 (Th2) responses [66], supplementation with retinoic acid, the active metabolite of vitamin A, potentiates Treg induction [67,68]. Interestingly, retinoic acid also limits the expression of retinoic-acid-receptor-related orphan receptor-γt, the master transcription factor for proinflammatory Th17 cells [67], but is required, at a lower level, for Th17 differentiation [69]. Thus, vitamin A is able to fine tune the immune response based on its local concentration. Work in EAE supports a predominantly beneficial effect of vitamin A and its derivatives to suppress neuroinflammation: 13-cis-retinoic acid, a retinoid related to vitamin A, was found to limit EAE by limiting leukocyte proliferation associated with decreased IL-2 production [70], and all-trans retinoic acid was also found to suppress leukocyte proliferation and skew the immune response to a regulatory Th2 response in EAE [71]. All-trans retinoic acid has also been shown to limit antigen presentation in dendritic cells and was associated with a decrease in proinflammatory Th1 and Th17 polarization in EAE [72]. The pleiotropic effects of vitamin A on both the innate and adaptive arms of the immune system make it a promising candidate for translation to MS patients.

Vitamin A and related retinoids are already used clinically to treat acne and psoriasis [73], however the clinical utility of vitamin A/retinoid supplementation in MS is not clear. MS patients are reported to have lower levels of retinol (mean 2.07 μmol/L, standard deviation 0.21 versus mean 2.53 μmol/L, standard deviation 0.26) and beta carotene (mean 0.41 μmol/L, standard deviation 0.13 versus mean 0.63 μmol/L, standard deviation 0.08), indicators of vitamin A status, compared to matched, healthy controls [74]. This observation also holds true comparing MS patients to patients with noninflammatory neurological

disease (mean 46.56 μg/dL, standard deviation 15.45 versus mean 61.50 μg/dL, standard deviation 17.35) [75]. Serum retinol has also been inversely associated with MRI lesions in RRMS patients (OR 0.54, 95% CI 0.32–0.97, for every 1 μmol/L increase in serum retinol) [76]. Promisingly, combining all-trans retinoic acid with interferon β (IFNβ), a disease modifying therapy for MS, has an additive effect in restoring suppressor T cell function in peripheral blood mononuclear cells (PBMCs) from MS patients [77]. However, in a prospective study of RRMS patients, vitamin A was not associated with relapse rates (RR 1.2, 95% Cl 0.8–1.8, comparing RRMS patients with serum levels of all-trans retinoic acid less than 2.9 μmol/L to patients with greater than 3.7 μmol/L) [78]. Given the amount of evidence supporting the immunomodulatory role of vitamin A in preclinical models and the growing literature suggesting a possible benefit of vitamin A supplementation in MS patients, further clinical investigation of vitamin A is warranted.

2.2.3. Other vitamins—While vitamins D and A have been studied extensively in the context of MS, relatively less is known regarding the effect of other vitamins [79,80]. Vitamin B1 (thiamine) is an important cofactor for metabolic enzymes. Deficiency of thiamine in EAE results in exacerbated disease associated with an increase in chemokine production, T cell infiltration, and proinflammatory Th1 and Th17 cells. There is a case report of a small cohort of MS patients treated with high-dose thiamine that observed improvements in self-reported fatigue, however there was no placebo-control in this study [81]. Vitamin B2 (riboflavin) is an antioxidant and important for the process of myelination [82]. Supplementation of riboflavin has a modest effect on suppressing EAE associated with an increase in the expression of brain-derived neurotrophic factor in the CNS [83]. Studies of riboflavin in MS patients are equivocal. A case-control study identified a significant negative linear correlation between the level of riboflavin intake and the risk of developing MS [84]. In contrast, a randomized clinical trial of riboflavin supplementation in MS for six months found no difference in EDSS compared to MS patients given placebo [85]. Vitamin B3 (niacin) is used to make the cofactors nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate that are used in metabolic processes, cell signaling, and DNA repair [86]. Supplementation with niacin in EAE results in less severe disease associated with reduced immune cell infiltration into the CNS, increased neurogenesis, and increased proliferation of oligodendrocytes in vitro [87]. However, no clinical trial has been performed to investigate the effect of niacin supplementation in MS patients. Vitamin B6 (pyridoxine) can be interconverted into a number of forms, of which pyridoxal 5’-phosphate is the active form that can act as a cofactor for metabolic reactions [88]. Supplementation with pyridoxamine, another form of vitamin B6, has no effect on the severity of EAE [89] and no trials of vitamin B6 supplementation in MS have been reported. Vitamin B7 (biotin) is an important cofactor for enzymes related to metabolism and cell growth and is proposed to have neuroprotective effects through supporting the metabolism of neurons and glial cells in the CNS [90]. In a progressive EAE model, biotin supplementation had no effect on disease progression [91]. However, an uncontrolled pilot study of high-dose biotin supplementation in secondary progressive MS (SPMS) and primary progressive MS (PPMS) patients demonstrated evidence of clinical improvement as measured by clinical, electrophysiological, and nuclear magnetic resonance spectroscopic assessments [92]. This was followed up with a randomized clinical trial that demonstrated that 12.6% of SPMS or

PPMS patients had reduced MS-associated disability after high-dose biotin supplementation at 12 months with significant overall improvement compared to placebo [93]. Vitamins B9 (folate) and B12 (cobalamin) are important cofactors in metabolism and nucleic acid synthesis [94]. Cobalamin is needed to regenerate active folate, thus deficiency in cobalamin can precipitate folate deficiency. Cobalamin supplementation plus IFNβ treatment in EAE was superior to IFNβ treatment alone [95]. In a number of retrospective studies of MS patients, cobalamin was found to be reduced in the serum [96] and cerebrospinal fluid [97]. These reports were supported by a randomized, placebo-controlled trial in which Vitamin B12 and folate supplementation resulted in improvements in self-reported physical and mental quality of life measures in RRMS patients [98]. Of note, certain constituents of the gut microbiota have the ability to synthesize B vitamins [99].

Beyond the B vitamins, vitamin C (ascorbic acid) is an antioxidant that is important for collagen synthesis, wound healing, and the production of neurotransmitters [100]. Therapeutic treatment with ascorbic acid failed to suppress established EAE [101], however L-as-corbyl-2-phosphate, a form of vitamin C, enhanced remyelination in response to cuprizone-induced demyelination [102]. A case-control study reported an inverse correlation with serum vitamin C and MS risk [74]. Vitamin E is an antioxidant that include tocopherols and tocotrienols [103]. Supplementing vitamin E [104] or a vitamin E derivative [105] in EAE results in less severe disease associated with decreased T cell proliferation, muted Th1 response, and reduced demyelination. In chemically-induced demyelination models, vitamin E and a vitamin E derivative have also been shown to enhance remyelination [105,106]. A case-control study of SPMS patients reported decreased serum α-tocopherol in patients compared to controls [74]. This agrees with a prospective cohort study of RRMS patients treated with IFNβ, in which increased serum α-tocopherol was associated with a reduced risk of MRI disease activity [107]. Vitamin K is important for blood coagulation and includes vitamin K1 (phylloquinone), which is derived from plants, and vitamin K2 (menaquinone), which is derived from the metabolism of vitamin K1 by gut microbiota [108]. Prophylactic vitamin K2 supplementation suppressed EAE associated with decreased immune cell infiltration into the CNS and decreased expression of major histocompatibility complex class II and inducible nitric oxide synthase [109]. In contrast, a vitamin K-deficient diet does not affect remyelination in a cuprizone-induced demyelination model [110]. In a case-control study of MS patients, vitamin K2 was found to be decreased compared to controls [111].

2.2.4. Salt—Recent attention has been given to the effect of dietary salt intake on MS given the excessive salt consumption characteristic of the Western diet [112]. Fundamental work investigating the effects of hypertonic saline has shown that the resulting osmotic stress can activate immune cells [113] and stimulate proinflammatory cytokine production [114]. This observation is in agreement with studies in EAE in which a high salt diet induces proinflammatory Th17 cells and exacerbates disease through both a direct [115,116] and gut microbiota-mediated mechanism (discussed in more detail below) [117]. In the direct mechanism, an increase in salt concentration upregulates the expression of serum glucocorticoid kinase 1 (SGK1), which is downstream of p38/mitogen-activated protein kinase [116] and IL-23 signaling [115]. While SGK1 is reported to regulate sodium intake

via phosphorylation of epithelial sodium channels, SGK1 can also phosphorylate Foxo1, which deactivates Foxo1, promotes IL-23 signaling, and drives Th17 effector function [115]. Interestingly, a high salt diet induces Th17 differentiation most strongly in the gut lamina propria [115], suggesting that gut-resident immune cells are especially sensitive to the proinflammatory effects of dietary salt.

Clinical investigation into the immunomodulatory effects of a high salt diet are just beginning. Supplementing sodium chloride in healthy patients (additional 6 g of sodium chloride per day above baseline salt intake) for 14 days was sufficient to observe a modest increase in proinflammatory IL-17^{+} tumor necrosis factor (TNF)$^{+}$ CD4^{+} T cells [117]. Indeed, high salt intake (greater than 4.8 g of sodium per day) in MS patients was found to increase disease activity compared to patients with low salt intake (less than 2 g of sodium per day) (exacerbation rate 3.95, 95% Cl 1.4–11.2) [118]. However, other studies in adult patients with CIS (HR of converting to CDMS per 1 g increase in sodium intake 0.91, 95% Cl 0.67–1.24) [119], adult patients with MS (HR of developing MS 0.98, 95% Cl 0.74–1.30, comparing highest and lowest quintiles) [120], and pediatric MS patients (OR of excess sodium intake 1.05, 95% CI 0.67–1.64, comparing pediatric MS cases to controls; HR of relapse 1.37, 95% Cl 0.74–2.51, comparing the high tertile of sodium intake to the low tertile) [121,122] have not shown an association between salt and the development of MS or the progression of disease. Further work, with an emphasis on randomized clinical trials, will be needed to resolve conflicting data regarding the influence of salt on MS.

2.2.5. Polyphenols—Dietary polyphenols are derived from fruits, vegetables, cereals, legumes, herbs, spices, wine, fruit juices, tea, and coffee [4]. This family of compounds can be structurally categorized into flavonoids, such as quercetin, and non-flavonoids, such as resveratrol. Polyphenols have been shown to influence the immune response through direct antioxidant effects [123] and by suppressing the activity of the pro-inflammatory nuclear transcription factor κB (NF-κB) [124]. To date there has been no study of the effect of polyphenol supplementation in MS patients and results in preclinical MS models have been mixed. Green tea polyphenol epigalloatechin 3 gallate was sufficient to ameliorate EAE and was associated with lower pro-inflammatory cytokine production and reduced T cell proliferation to myelin peptide [125]. Natural flavonoids, including apigenin, hesperidin, luteolin, and quercetin, have also been shown to protect against EAE by modulating the immune response [126–128]. Resveratrol has been reported to support remyelination in a chemically-induced preclinical model of MS [129]. However, resveratrol has also been shown to exacerbate disease in EAE and virus-induced preclinical MS models [130]. In addition, quercetin was also found to mildly ameliorate EAE in one study [128] and exacerbate EAE in another [131].

2.2.6. Thiolic compounds—Thiolic compounds contain a thiol (-SH) functional group and include α-lipoic acid, glutathione, and *N*-acetylcysteine [4]. In EAE, α-lipoic acid has been shown to suppress disease by limiting T cell infiltration into the CNS [132,133]. In a double-blind, randomized, placebo-controlled trial, lipoic acid supplementation over two years resulted in a reduction in percent change brain volume in SPMS patients, but no significant change in EDSS and a trending increase in T2 lesion volume [134].

Glutathione is a major antioxidant in the CNS [135] and level of glutathione is decreased in the spinal cord of EAE-induced mice [136]. *N*-acetylcysteine administration has been shown to suppress EAE by increasing glutathione production as well as acting as a reactive oxygen species scavenger itself [137,138]. Oral glutathione supplementation has low bioavailability [139] and limited penetration of the blood-brain barrier [135]. While no trial of glutathione in MS patients has been performed, there is a randomized prospective trial of *N*-acetylcysteine currently under way (NCT0303601).

2.2.7. Fibers—Fibers, such as inulin and galacto-oligosaccharides, are composed of resistant starch and oligosaccharides that are not digested by the human host, but instead metabolized by colonic bacteria [140]. Fruits, vegetables, whole grains, and legumes are rich in fiber whereas the typical Western diet is low in fiber [141]. As a substrate for bacteria, the abundance of fiber can alter the gut microbiota and is suggested to promote the growth of tolerogenic commensal bacteria. Fibers can also be fermented to SCFAs by bacteria, which themselves have anti-inflammatory properties [142]. Indeed, fiber supplementation has been shown to ameliorate EAE and is associated with an increase in intestinal SCFAs and an altered gut microbiota [143,144]. While no study has been conducted to examine the effects of dietary fiber supplementation specifically in MS patients, there is evidence to suggest that the consumption of fiber-rich foods can benefit MS patients (see plant-based diets).

2.2.8. Short chain fatty acids (SCFAs)—SCFAs include acetic acid, butyric acid, propionic acid, and pentanoic acid and are largely derived from the fermentation of dietary fiber by commensal gut microbiota [145]. SCFAs have been shown to promote tolerogenic responses, via signaling through G-protein coupled receptors and inhibition of histone deacetylases that can inactivate NF-κB, and suppress the expression of proinflammatory cytokines as well as induce anti-inflammatory macrophages, dendritic cells, and regulatory T cells [146–151]. SCFAs also have been shown to affect the maturation and function of microglia, the resident myeloid cell population in the CNS, and support the integrity of the blood-brain barrier [152,153]. The SCFA propionic acid has been shown to ameliorate EAE through the induction of Tregs and a decrease in proinflammatory IL-17 [22]. Additionally, pentanoic acid, butyric acid, and acetic acid have also been shown to ameliorate EAE [144,154] and butyric acid, in particular, has been shown to ameliorate chemically-induced demyelination [155]. A case-control study of SPMS patients found decreased blood concentrations of acetic acid, butyric acid, and propionic acid, but pentanoic acid was unchanged compared to healthy controls [156]. A pre-print suggests that supplementation of propionic acid in healthy volunteers and MS patients can increase Tregs and decrease Th17 with reduced relapse rate and disease progression after one year of supplementation [157].

2.2.9. Long chain polyunsaturated fatty acids (LC-PUFAs)—LC-PUFAs are defined by having more than one double bond in their structure and include omega-3 (n-3) and omega-6 (n-6) fatty acids [158]. Nuts, seeds, fish oil, and fish such as salmon, tuna, mackerel, herring, and sardines are major sources of n-3 LC-PUFAs [159]. In contrast, n-6 LC-PUFAs are derived predominantly from vegetable oils such as soybean and corn oil [160]. Linoleic acid, a major dietary n-6 LC-PUFA, can be converted to arachidonic acid and further metabolized to eicosanoids such as prostaglandins and leukotrienes

that have pleotropic effects on the production of pro- and anti-inflammatory cytokines, reactive oxygen species, immunoglobulins, and the proliferation of lymphocytes [161,162]. α-linolenic acid, a major dietary n-3 LC-PUFA, can be converted to eiosapentaeoic acid (EPA) and docosahexanoic acid (DHA) that compete with the same enzymes that metabolize arachidonic acid in order to form alternative eicosanoids that have less biological activity than eicosanoids derived from arachidonic acid [163]. Thus, the Western diet is thought to promote inflammation, in part due to a relative increase in the ratio of n-6 to n-3 LC-PUFAs [164]. In a randomized, placebo-controlled trial, MS patients that were supplemented with high-dose n-3 LC-PUFAs and vitamin D had improvements in EDSS and inflammatory biomarkers over a 12-week period, though their experimental design does not isolate the effect of n-3 LC-PUFAs alone [165]. In a retrospective case-control study, it was found that high fish consumption reduced the risk of developing MS or CIS (OR 0.55, 95% Cl 0.4–0.75) independent of serum vitamin D concentration, and single nucleotide polymorphisms in fatty acid desaturase 2, an enzyme involved in fatty acid biosynthesis, were also found to decrease MS risk [166]. However, in a randomized, double-blind, placebo-controlled trial, MS patients supplemented with n-3 LC-PUFAs EPA and DHA for six months exhibited no difference in relapse rate, quality of life, nor MRI lesion activity [167].

3. Gut microbiota and multiple sclerosis

Closely tied to diet is the role of the commensal gut microbiota in MS. This is unique from the role of infection in MS, which has been associated with an increased risk of developing MS and exacerbation of MS symptoms [168–172]. In contrast to these more transient host-pathogen interactions, host-commensal interactions have effects on physiology throughout the host's lifespan. In the context of demyelinating disease, this is most evident in germ-free mice that lack an endogenous microbiota and develop less severe EAE compared to conventionally colonized animals [173,174]. This effect can be recapitulated in conventionally colonized mice treated with antibiotics [175,176]. Indeed, specific commensal microorganisms, such as segmented filamentous bacteria [173], have been shown to exacerbate EAE, whereas other commensals such as *Bacteroides fragilis* [177], *Lactobacillus* species [117,178–182], and *Prevotella histolitica* [183] have been shown to ameliorate disease. These results in EAE have been supported by studies in MS patients demonstrating that patients with MS have distinct bacterial taxa that are differentially abundant compared to healthy controls [184–186]. Subsequent studies have demonstrated that colonization of germ-free mice with microbiota derived from MS patients results in more severe EAE than germ-free mice colonized with microbiota from healthy controls [187,188], suggesting that the gut microbiota plays a functional role in disease.

3.1. Identifying an MS-associated microbiota

There is a growing body of literature investigating gut microbial communities in MS patients. While the broad gut bacterial community composition of MS patients is not different from healthy controls, there are strains of bacteria that have been reproducibly found to be altered in MS patients. Among the first studies to examine the gut microbiota in MS, Yamamura and colleagues performed 16S ribosomal RNA (rRNA) sequencing on fecal samples from 20 Japanese RRMS patients and 40 Japanese healthy patients and

found that the gut microbiota of MS patients was less similar than the gut microbiota of healthy patients compared to the inter-individual variation in gut microbiota between healthy patients [184]. However, the inter-individual variation in gut microbiota between MS patients was greater than the difference in gut microbiota between MS patients and healthy patients, which may be due to the relatively small cohort size in the MS population and the variability in disease modifying therapies being used in the MS cohort. Still, at the genus level, *Faecalibacterium, Prevotella*, and *Anerostipes* were found to be significantly decreased in MS patients compared to healthy patients.

Mangalam and colleagues published a subsequent study examining the gut microbiome of 31 American RRMS patients and 36 age- and sex-matched healthy controls [185]. Gut community analysis revealed that RRMS patients had a distinct gut microbiota from healthy controls, and of note, the gut microbial community of RRMS patients in remission was more similar to healthy controls than the gut microbiota of RRMS patients with active disease. At the genus level, *Adlercrutzia, Collinsella, Parabacteroides, Coprobacillus, Lactobacillus*, and *Haemophilus* were found to be significantly decreased in MS patients. Conversely, *Flavo-bacterium, Pedobacter, Blautia, Dorea, Mycoplana*, and *Pseudomonas* were found to be significantly increased in MS patients.

In a multi-tiered approach, Weiner and colleagues combined 16S rRNA sequencing with blood and breath analysis of RRMS and healthy controls [186]. For 16S rRNA sequencing, fecal samples were collected from 60 American RRMS patients and 43 American healthy controls and sequenced on two different sequencing platforms that differed in sequencing read length and sequencing depth. While no significant difference was found between broad gut microbial community structure between RRMS patients and healthy controls, *Butyricimonas, Paraprevotella*, and *Slackia* were genera identified to be decreased in RRMS patients regardless of sequencing platform. In contrast, *Methanobrevibacter* and *Akkermansia* were significantly upregulated in RRMS patients. Interestingly, *Haemophilus* was found to be both significantly upregulated or downregulated in RRMS patients depending on the sequencing platform used, however *Haemophilus* was consistently increased when comparing only untreated RRMS patients to healthy controls. *Collinsella* was not significantly changed between RRMS patients and healthy controls, though it was decreased when comparing only untreated RRMS patients and healthy controls. *Cloacibacillus, Prevotella*, and *Sutterella* are significantly decreased in untreated RRMS patients compared to healthy controls, whereas treated RRMS patients have significantly higher relative abundance of these genera. The opposite trend is observed for *Megasphaera. Sarcina* is significantly decreased only in treated MS patients compared to untreated MS patients. Additionally, *Holdemania, Desulfovibrio, Barnesiella, Megamonas, Guggenheimella, Buttiauxella*, and *Sporanaerobacter* were also identified as being differentially abundant between study groups, though significance of these differences and even detection of these genera was dependent on the sequencing platform. Transcriptomic analysis of blood $CD4^+$ T cells and monocytes showed that the abundance of *Methanobrevibacter* and *Akkermansia* had a positive correlation with the expression of proinflammatory genes in line with their enrichment in RRMS patients. In contrast, the abundance of *Butyricimonas* had a negative correlation with proinflammatory genes parsimonious with its depletion in RRMS patients. Additionally, breath methane was

measured in a second, independent cohort of RRMS patients and healthy controls as *Methanobrevibacter* is the dominant methane-producing commensal bacteria in the gut. Breath methane was demonstrably higher in RRMS patients, providing in vivo support for one of their metagenomic results.

Wekerle and colleagues sought to better isolate the effect of the gut microbiota and minimize the effect of host genetic variability by examining the gut microbiota of German monozygotic twin pairs in which one twin had MS (ranging from CIS, RRMS, SPMS, and PPMS) and the other twin was unaffected [188]. Microbiomes were characterized using both 16S rRNA sequencing and metagenomics shotgun sequencing and found no significant differences in overall microbial community structure. Interestingly, when MS patients were subdivided into treated and untreated groups, *Akkermansia* was significantly increased in untreated MS twins. To functionally test the contribution of the gut microbiota in disease, the fecal microbial communities from five RRMS discordant monozygotic twin pairs were transferred to germ-free transgenic mice that develop spontaneous relapse-remitting EAE. While there was a significant reduction in number of bacterial taxa retrieved from colonized mouse feces compared to their human donor, suggesting an inability of certain human gut commensals to colonize the mouse, mice that received microbiota from the MS-affected twin had a higher incidence of spontaneous EAE compared to mice that received microbiota from the unaffected twin. The genus *Ruminococcus* was found to be enriched in mice colonized with microbiota from the MS-affected twin while the genera *Adlercreuzia, Tannerella*, and *Sutterella* were found to be decreased. Functionally, splenic T cells derived from MS microbiota-colonized mice as well as blood $CD4^+$ T cells of MS-affected twins produced less IL-10 when stimulated.

In a larger scale study, Baranzini and colleagues performed 16S rRNA sequencing on fecal samples from 71 American untreated RRMS patients and 71 American healthy patients [187]. While there were no significant differences in microbial community structure, there were significant differences at a number of taxonomic levels. At the genus level, *Prevotella, Serratia, Bacillus, Acidaminococcus, Clostridium, Aquamonas, Parabacteroides*, and *Phascolarctobacterium* were found to be significantly decreased in RRMS patients whereas *Acinetobacter, Varibaculum, Corynebacterium, Bifidobacterium, Megamonas, Megasphaera, Klebsiella, ph2, Actinomyces, Mogibacterium, Akkermansia, SMB53*, and *Bulleidia* were found to be significantly increased. At the operational taxonomic unit (OTU) level, in which sequencing reads are clustered based on sequence similarity and assigned an OTU that refers to a bacterial sequence reference database [189], an additional 247 OTUs were differentially abundant in RRMS patients. A number of these OTUs refer to genera identified in their previous analysis (e.g. *Acinetobacter, Akkermansia, Parabacteroides*, etc.) and others refer to new genera (e.g. *Lactobacillus, Suttera*, etc.) not identified in their previous analysis. Based on their metagenomic analysis, the strains *Acinetobacter calcoeticus, Akkermansia muciniphila*, and *Parabacteroides distasonis* were further validated in in vitro and in vivo systems to test their immunomodulatory properties. *A. calcoeticus* was found to inhibit the differentiation of Tregs and both *A. calcoeticus* and *A. muciniphila* were found to induce the differentiation of Th1 cells in healthy human PBMCs, consistent with their enrichment in RRMS patients. In contrast, *P. distasonis* was found to induce anti-inflammatory, IL-10-producing Tregs in healthy human PBMCs, in line with its depletion in

RRMS patients. These results were largely recapitulated by monocolonization of germ-free or antibiotic-treated mice with these strains, however *A. mucinophila* was unable to induce Th1 cells in the mouse, possibly due to differences in mouse and human interaction with *A. mucinophila.* To more broadly investigate the role of the gut microbiota in MS, three fecal donor pairs, each consisting of one RRMS patients and a household control, were randomly chosen to transfer fecal microbiota to germ-free mice. While overall gut microbial community structure was altered in recipient mice compared to their corresponding human donors, suggesting a difference in the ability of bacteria to colonize the mouse gut versus the human gut, the mice that received MS-associated microbiota had distinct community structure from mice that received control-associated microbiota. Furthermore, mice that received MS-associated microbiota exhibited more severe EAE associated with reduced proportions of Tregs.

These studies of the MS-associated microbiome have failed to find a distinct change in broad gut community structure, however changes in certain bacterial taxa have been reproduced. Table 1 lists the various microbial genera identified in gut microbiota studies of MS patients with potential mechanistic links, where available. Table 2 provides the demographics of the patient populations studied in the context of MS-associated gut microbiota. Variability in the results of these and other studies of the MS-associated microbiome raise important methodological and conceptual considerations. In terms of study design, the recruitment of patients from multiple study sites is important for the external validity of the study as it has previously been shown that the microbiota can vary by geographic region [190]. In addition, special considerations should be made when enrolling untreated patients versus patients on various disease modifying therapies (DMTs) as DMTs also have varying effects on the gut microbiota [191]. The protocol for DNA extraction, sequencing, and metagenomic analysis also affects results and adds to the difficulty of comparing studies using different pipelines [192,193]. Inconsistencies apparent in the MS gut microbiota literature may also reflect the inherent difficulty in resolving species-and strain-level taxa through 16S rRNA sequencing, leading to different OTUs defined as the same genera being both increased and decreased in MS patients even within the same study (e.g. *Prevotella* in Table 1). Fundamentally, these types of case-control metagenomic studies are correlative and act as a starting point for further investigation into mechanistic understanding of the influence of the microbiota on MS. Critically, while differentially abundant microbial strains provide promising targets for investigation, the contribution of non-differentially abundant strains, which may function differently in MS patients compared to healthy controls, should also be considered.

3.2. Clinical trials of microbiota-based interventions

Clinical trials have been and are currently being performed to investigate the potential benefit of probiotic administration in MS patients. In a small, randomized, placebo-controlled trial, MS patients were given either a probiotic supplement containing *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus fermentum*, and *Bifidobacterium bifidum* or placebo for 12 weeks [194]. PBMCs from probiotic-supplemented MS patients had decreased expression of proinflammatory cytokines IL-8 and TNFα, but no difference was observed in the expression of proinflammatory cytokine IL-1.

A follow up study by the same group demonstrated improvement in EDSS, self-reported quality of life measures, and biomarkers of inflammation with probiotic supplementation [195]. Another pilot study of VSL3, a probiotic cocktail of *Lactobacillus, Bifidobacterium, and Streptococcus* species, in MS patients demonstrated that probiotic administration can transiently alter the gut microbiota in MS patients and decrease antigen presentation in peripheral dendritic cells [196]. Further studies are needed to determine whether probiotic regimens can benefit MS progression with long term administration.

3.3. How diet influences the gut microbiota

While it has been appreciated that diet is able to shape gut commensal microorganisms [197,198], our understanding of the interactions that drive diet-based modulation of gut commensal organisms is still expanding [199,200].

Diet can directly affect the gut microbiota by providing substrates to support the growth of gut community members. This is predominantly in the form of indigestible carbohydrates such as resistant starch, inulin, and cellulose that can be degraded by bacteria expressing carbohydrate-active enzymes. Sugars released by such bacteria can further feed subsequent bacteria forming a complex metabolic network whose metabolites include SCFAs, hydrogen gas, lactate, and succinate [201]. Diet can also directly affect the gut microbiota by inhibiting the growth of gut community members as seen with salt [117] and plant-derived compounds including tannins, terpinoids, alkaloids, and flavonoids [202]. In addition, diet can indirectly influence the gut microbiota by influencing host immunity, intestinal barrier function, and production of host-derived secondary products. Intraepithelial lymphocytes in the gut rely on signaling through the aryl hydrocarbon receptor (AhR), the ligands of which can be plant-derived, in order to be maintained, and without AhR ligands bacterial outgrowth of the phylum *Bacteroidetes* was observed in mice [203]. Vitamin D signaling appears to be critical for the development of tolerogenic dendritic cells in the lamina propria as mice that cannot product the active form of vitamin D have fewer dendritic cells and are associated with increases in *Desulfoibrionceae, Bacteroidaceae*, and *Bacteroidales* and decreases in *Ruminococcaceae, Lachnospiraceae, Lactobacillceae*, and *Streptococcaceae* [204]. Supplementation of n-3 LC-PUFAs increases intestinal alkaline phosphatase, which can directly act on gut microbes to shift composition by decreasing *Escherichia coli* and increasing *Bifidobacterium* [205]. Vitamin D signaling is also critical for the expression of antimicrobial defensins by Paneth cells that can directly inhibit bacteria [206]. Vitamin A deficiency results in increased bile acid that can directly inhibit the growth of bacteria such as *Bacteroides vulgatus* [207]. Even dietary emulsifiers, which are common additives in processed food, have been shown in mice to disrupt the protective mucus coating of the intestine and alter the mucosa-associated bacterial consortia [208].

The change in gut microbiota occurs rapidly in response to diet, as four days on an animal-based diet in healthy human subjects is sufficient to increase β diversity, enrich bile-resistant bacteria including *Bilophila, Alistipes*, and *Bacteroides*, and deplete bacteria able to metabolize plant polysaccharides including *Roseburia, Eubacterium*, and *Ruminococcus* [209]. However, the gut microbiota is relatively resilient to dietary perturbation, as returning to a baseline diet after four days on an animal-based diet resulted in a return of β diversity

back down to baseline levels [209]. In addition, six weeks of psyllium supplementation in children with irritable bowel syndrome did not result in significant changes in the gut microbiota [210]. Furthermore, two weeks of either white bread or sourdough bread supplementation in healthy human subjects did not result in significant changes in overall community structure compared to each individual's baseline, however, *Anerostipes* and *Eubacterium* were enriched in subjects supplemented with white bread versus sourdough bread [211]. Alterations in gut microbiota have been observed within 24 h of starting a high-fiber/low-fat or low-fiber/high-fat diet [212]. Specific diet-microbiota interactions that have been reported, with special consideration towards diet regimens and dietary components associated with MS, are listed in Table 3. There is notable variation in the response of the gut microbiota to host diet and a relative lack of understanding regarding the mechanisms by which diet alters the gut microbiota. Still, associations between Table 1 and Table 3 suggest relevant crosstalk between diet and gut microbiota in MS. For example, *Bacteroides*, which has been reproducibly shown to be decreased in MS patients (Table 1), is also enriched with vitamin D in two separate reports (Table 3). Thus vitamin D, beyond its direct immunomodulatory effects, may also act through *Bacteroides* and other vitamin D-sensitive microbial strains to decrease the risk of MS. Future studies of dietary intervention in MS would benefit greatly by including changes in the gut microbiota as relevant read-out to parse out direct diet-mediated effects versus microbiota-dependent effects.

3.4. Strategies to study interplay between diet, gut microbiota, and MS

While diet and the gut microbiota have been investigated in isolation in the context of demyelinating disease, less well studied is the relationship between diet, gut microbiota, and disease. One approach to study this more complicated system is a top-down approach: to examine identified dietary risk factors for developing MS and test whether the effects of such a diet are mediated by the gut microbiota. This is the strategy employed by Wilck and colleagues [117] in which they examine a high salt diet and identify *Lactobacillus murinis*, a salt-sensitive gut microorganism that 1) was significantly depleted by a high salt diet, and 2) was found to suppress the Th17 response when used as a treatment in mice with EAE. Importantly, germ-free mice were utilized to isolate the effect of diet from the effect on the gut microbiota. Germ-free mice were fed a high salt diet, however this resulted in no change in Th17 frequency, compared to germ-free mice fed a normal salt diet, suggesting that gut microbiota are necessary for a high salt diet to induce Th17 cells [117]. Interestingly, this is seemingly at odds with previous studies indicating that salt can induce Th17 cells in vitro [115,116]. This strategy has also been used by Cignarella and colleagues [13] in which intermittent fasting was found to ameliorate EAE. They demonstrated that intermittent fasting changed the gut microbiota in mice and were able to recapitulate the benefit of intermittent fasting by colonizing germ-free mice with microbiota from intermittent fasting mice. Promisingly, in a pilot study in MS patients, they demonstrated that intermittent fasting also changed the gut microbiota of human patients comparable to mice at the phylum level [13].

Another approach to studying the relationship between diet, gut microbiota, and demyelinating disease is a bottom-up approach: starting with a microbial metabolite with known beneficial effects in EAE and determining whether supplementing the

dietary precursor for the metabolite can ameliorate disease. This is the approach taken by Rothhammer and colleagues in which they identified gut microbiota-derived indole metabolites as a major beneficial microbial metabolite in EAE, previous work having identified tryptophan as the precursor for such indole metabolites [213], and then went on to demonstrate that mice with a tryptophan-deficient diet exhibited exacerbated EAE [214]. Critically, they show that antibiotic treatment reduced the level of indole-derived metabolites, suggesting that the gut microbiota contributes to the production of such metabolites [214]. However, it is unclear whether dietary tryptophan supplementation requires the gut microbiota to have a beneficial effect. In a prospective study of patients with pediatric-onset MS and CIS, higher levels of tryptophan and indole lactate were associated with a lower risk of MS [215]. Interestingly, a lower relative abundance of gut microbial genes involved in tryptophan catabolism was associated with increased relapse risk and a higher abundance of gut-microbe derived tryptophan metabolites was associated with lower disability [215]. It will be interesting to see whether supplementation with tryptophan or indole would be beneficial for patients with MS.

Another approach to studying diet, gut microbiota, and demyelinating disease is an unbiased approach: screening diets, using the EAE model, that modulate disease regardless of prior association with MS, sequencing the gut microbiota of mice on different diets, and subsequently validating the functional impact of the gut microbiota. This is the approach we took when we observed that mice on different diets exhibited different disease [216]. While the two diets were considered standard rodent diets, they differed in macro-and micro-nutrient composition (specific nutritional information can be found in [216]) with the beneficial diet supplemented with vitamins to accommodate autoclave sterilization and the detrimental diet formulated to exclude soybean protein. Mice on the beneficial diet had lower clinical scores, lower incidence of disease, less weight loss, and lower mortality compared to mice on the alternative diet. Spinal cord pathology also showed that mice on the detrimental diet had higher pathology scores for demyelination, perivascular cuffing, meningitis, and overall pathology. Importantly, the severity of disease did not cluster in individual cages of a particular diet, making the possibility of cage-specific effects less likely. To determine the microbiota changes due to diet and disease, we performed 16S rRNA sequencing on mice grouped by clinical score and diet. We also analyzed the microbial composition of naive mice and mice administered complete Freund's adjuvant and *Bordetella pertussis* toxin without myelin peptide to control for changes in microbiota due to the injection adjuvant. Sequencing the gut microbiota of mice on these different diets and accounting for the severity of disease exhibited by individual mice, we identified *Lactobacillus* species as being depleted in mice induced with EAE compared to naive and adjuvant injected control animals, inversely correlated in terms of relative abundance and EAE severity, and enriched in EAE-induced animals on the beneficial diet compared to EAE-induced animals on the detrimental diet [181]. The *Lactobacillus* genus was unique in exhibiting these three features. Finally, we were able to recapitulate the effects of the beneficial diet by supplementing a human gut-derived commensal strain of *Lactobacillus* [181]. In our experimental paradigm, mice on the beneficial diet were fed L. *paracasei* daily via oral gavage starting two weeks prior to EAE induction. *L. paracasei*-treated mice exhibited lower clinical scores, lower EAE incidence, and less weight loss compared to

vehicle-treated animals. While this approach has the ability to uncover novel relationships between diet, gut microbiota, and disease, the complex relationship between these factors makes untangling the mechanisms of the system difficult.

4. Discussion

Whether using the top-down, bottom-up, or unbiased approach to dissect diet, microbiota, and disease relationships, it is clear that such networks are complex. The difficulty in understanding the interplay between these factors is magnified by tentative results of diet and probiotic treatments in MS patients that require validation in larger, longer clinical trials. Outstanding questions in this area are: Does the benefit of vitamin D supplementation, the most studied dietary intervention in MS, work through a microbiota-based mechanism? How stable are diet-induced changes in gut microbiota? How are diet-based and gut microbiota-based interventions affected by current MS disease modifying therapies? Addressing these questions will require the use of 16S rRNA sequencing and bioinformatics tools to assess changes in the gut microbiota, germ-free animal systems to isolate the effects of diet versus the gut microbiota, and the commitment of clinician scientists to pursue well-powered and longitudinal clinical trials of these interventions.

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Table 1.

Bacterial genera significantly altered in MS

Genera	Abundance MS: controls	Reference(s) in which difference identified	Reference(s) in which opposite difference identified	Mechanistic understanding
Acidaminococcus	increased	[217]	[187]	
Acinetobacter	increased	[187]		*A. calcoaceticus* reduced $CD25^+$ $FoxP3^+$ Tregs in human PBMCs [187] *A. calcoaceticus* increased differentiation of human peripheral blood $CD4^+$ T cells to IFNγ-producing Th1 cells [187] Antibody cross-reactivity between *Acinetobacter* and myelin peptides [218]
Actinomyces	increased	[187]		
Adlercreutzia	decreased	[185]		
Akkermansia	increased	[217] [186] [187] [188]		*A. muciniphila* increased differentiation of human peripheral blood $CD4^+$ T cells to IFNγ-producing Th1 cells [187]
Anaerococcus	increased	[187]		
Anaerostipes	increased	[217]	[184]	
Aquamonas	decreased	[187]		
Atopobium	increased	[217]		
Bacillus	decreased	[187]		
Bacteroides	decreased	[217] [184] [187]	[217]	Decreased EAE severity via *B. fragilis* polysaccharide A-mediated induction of regulatory dendritic cells and Tregs and suppression of Th17s [177,219] *B. fragilis* expands of regulatory $CD39^+CD4^+$ T cells [220]
Barnesiella	decreased	[186]		
Bifidobacterium	increased	[217] [187]	[187]	Supplementation of *Bifidobacterium* ameliorates EAE in Lewis rats [221] Supplementation of *Bifidobacterium* ameliorates EAE in C57BL/6 mice [182]
Bilophila	increased	[217]	[187]	
Blautia	increased	[217] [185] [187]	[217] [187]	
Bulleidia	increased	[187]		
Buttiauxella	decreased	[186]		
Butyricimonas	decreased	[217] [186] [187]		
Catenibacterium	increased	[217]	[217]	

Genera	Abundance MS: controls	Reference(s) in which difference identified	Reference(s) in which opposite difference identified	Mechanistic understanding
Citrobacter	increased	[217] [187]		*C. rodentium* induces inflammatory Th17 cells [222]
Cloacibacillus	increased	[186]		
Clostridium	decreased	[184] [187]	[187]	*C. butyricum* suppresses EAE associated with decreased Th17 and increased Treg [223] Clostridia consortia induces colonic Treg [224]
Collinsella	decreased	[185] [186] [187]		
Coprobacillus	decreased	[185] [187]		
Coprococcus	decreased	[217] [184] [187]	[217] [187]	
Corynebacterium	increased	[187]		
Dehalobacterium	increased	[217]		
Desulfotomaculum	decreased	[184]		
Desulfovibrio	increased	[217] [184] [186] [187]	[187]	
Dialister	increased	[217] [187]	[217]	
Dorea	decreased	[217] [187]	[185]	
Eggerthella	increased	[184]		
Enterobacter	increased	[187]		*E. lenta* does not affect human PBMC differentiation towards Th1 or Treg [187]
Eubacterium	increased	[217] [187]	[184] [187]	
Faecalibacterium	decreased	[217] [187]	[187]	*F. prausnitzii* decreases Th17 differentiation and increases Treg differentiation in mouse CD4 + T cells va production of butyrate [225]
Flavobacterium	increased	[185]		
Fusobacterium	decreased	[187]		
Guggenheimella	decreased	[186]		
Haemophilus	decreased	[185] [186]	[186]	

Genera	Abundance MS: controls	Reference(s) in which difference identified	Reference(s) in which opposite difference identified	Mechanistic understanding
Klebsiella	increased	[187]		Intratracheal infection with *K. pneumoniae* induces Th17 cells [226]
Lachnospira	decreased	[217] [184] [187]		
Lactobacillus	decreased	[217] [185] [187]	[217]	*L. reuteri* ameliorates EAE with reduced Th1 and Th17 cells [178] *L. paracasei* DSM 13434, *L. plantarum* DSM 15312, and L. *plantarum* DSM 15313 ameliorate EAE via IL-10 producing Tregs and suppression of IFNy and IL-17 production [179] *L. helviticus* SBT2171 attenuates EAE by reducing IL-6 production, T cell infiltration into the spinal cord, and Th17 proportions [227] *L. murinis* ameliorates EAE by reducing Th17 cells through indole metabolites [117] *L. paracasei* ATCC27092 ameliorates EAE [181] *L. plantarum* A7 ameliorates EAE via induction of Tregs [182]
Megamonas	increased	[217] [186] [187]	[184]	
Megasphaera	increased	[217] [186] [187]		
Methanobrevibacter	increased	[217] [186]		
Mitsuokella	decreased	[217]		
Mogibacterium	increased	[187]		
Mycoplana	increased	[185]		
Odoribacter	increased	[187]	[187]	
Oscillospira	decreased	[217] [187]	[217]	
Oxalobacter	decreased	[187]		
Parabacteroides	decreased	[185] [187]	[217]	*P. distasonis* increased differentiation of human peripheral blood $CD4^+$ T cells to $CD25^+$ $IL\text{-}10^+$ T cells [187]
Paraprevotella	decreased	[217] [186] [187]	[217]	
Pedobacter	increased	[185]		
Peptostreptococcus	decreased	[217]		
ph2	increased	[187]		
Phascolarctobacterium	increased	[217]	[187]	

Genera	Abundance MS: controls	Reference(s) in which difference identified	Reference(s) in which opposite difference identified	Mechanistic understanding
Porphyromonas	increased	[217] [187]		Subcutaneous application of *P. gingivalis* A7436 five days after EAE induction exacerbates disease associated with increased nitric oxide and prostaglandin E2 production from glial cells [228]
Prevotella	decreased	[217] [184] [186] [187]	[217] [187]	Human gut-derived *P. histolitica* induced tolerogenic dendritic cells and Tregs and suppressed Th1 and Th1 7 response [183,229]
Providencia	increased	[217]		
Pseudomonas	increased	[185] [187]	[187]	
rc4–4	increased	[217] [187]		
Ruminococcus	increased	[217] [187]	[217] [187]	*R. gnavus* produces a polysaccharide that induces TNFα production [230]
Sarcina	decreased	[186]		
Serratia	decreased	[187]		
Slackia	decreased	[186]		
SMB53	increased	[187]		
Sporanaerobacter	decreased	[186]		
Streptococcus	increased	[217] [184]	[187]	*S. pneumoniae* infection seven days after EAE induction increases severity of EAE via a Toll-like receptor 2-dependent mechanism with increased serum TNFα and IL-6 and increased expression of MHC-II, CD80, and CD86 in splenic dendritic cells [231]
Succiniclastum	increased	[217]		
Sutterella	decreased	[217] [184] [186] [187]	[217]	
Trabulsiella	decreased	[217]		
Varibaculum	increased	[187]		
Veillonela	increased	[187]		
WAL_855D	increased	[217] [187]		

Table 2.

Demographics of patients in microbiome-wide association studies of MS.

Reference	Demographics
Miyake et al. [184]	20 Japanese RRMS cases vs 40 healthy controls
Tremlett et al. [217]	18 American pediatric MS cases vs 17 healthy age- and sex-matched controls
Chen et al. [185]	31 American RRMS cases vs 36 age- and sex-matched controls
Jangi et al. [186]	60 American RRMS cases vs 43 healthy controls and 28 untreated American RRMS cases vs 43 healthy controls
Berer et al. [188]	17 untreated American discordant twin MS cases vs 34 healthy discordant twin controls
Cekanaviciute et al. [187]	71 American RRMS cases vs 71 non-autoimmune controls

Table 3.

Dietary regimens and components associated with MS and their effects on the gut microbiota.

Diet and associated effects on the gut microbiota	Genera enriched	Genera depleted
Caloric restriction	Bacteroides [232] Blautia [13] Faecalibacterium [13] Lactobacillus [232]	Bifidobacterium [232] Clostridium [232,233] Eubacterium [233]
Ketogenic diet	Bacteroides [234–236] Desulfovibrio [237] Dorea [234] Escherichia [238] Prevotella [236]	Acinetobacter [235] Alistipes [236] Barnesiella [236] Bifidobacterium [238] Coprobacter [235] Cronobacter [236] Dialister [238] Enterococcus [236] Erysipelatoclostridium [236] Eubacterium [238] Faecalibacterium [234,235] Lachnospiraceae incertae sedis [235] Leucobacter [235] Pseudomonas [235] Ruminiclostridium [236] Streptococcus [236]
Western diet	Akkermansia [239] Bacteroides [240,241] Escherichia [242] Faecalibacterium [240] Shigella [242]	Butyrivibrio [240,242] Prevotella [241,242] Treponema [242] Xylanibacter [242]
Obesity	Akkermansia [243] Alistipes [243] Bacteroides [243,244] Clostridium [243,245,246] Desulfovibrio [243] Eggerthella [243] Escherichia [243] Parabacteroides [243] Ruminococcus [245] Streptococcus [246] Subdoligranulum [243]	Bacteroides [245,246] Eubacterium [243] Faecalibacterium [243,246] Haemophilus [243] Lachnospira [244] Oscillospira [244] Prevotella [246] Roseburia [243,246] Ruminococcus [246] Sporobacter [245]
Plant-based diet	Actinobacillus [31,209] Actinoplanes [31] Aggregatibacter [31] Atopobium [31] Bacteroides [247] Blautia [31] Capnocytophaga [31] Clostridium [209,247,248] Cryptobacterium [31] Faecalibacterium [247]	Aceto bacterium [31] Akkermansia [249] Alistipes [249] Bacteroides [31,249,251] Bifidobacterium [247,251] Bilophila [31,209] Blautia [209] Bulleidia [31] Caldanaerobacter [31] Campylobacter [31]

Diet and associated effects on the gut microbiota	Genera enriched	Genera depleted
	Haemophilus [31]	Clostridium [31,209]
	Holdemania [248]	Collinsella [247,248]
	Klebsiella [249]	Dehalogenimonas [31]
	Lachnospira [250]	Desulfitobaeterium [31]
	Micrococcus [31]	Desulfovibrio [31]
	Neisseria [31]	Dialister [31]
	Porphyromonas [31]	Dorea [31]
	Prevotella [249,250]	Eggerthella [31]
	Roseburia [248,250]	Escherichia [251]
	Staphylococcus [31]	Eubacterium [248]
	Subdoligranulum [247	Holdemania [31]
	Veillonella [31]	Methanosphaera [31]
		Oscillospira [209]
		Oxalobacter [31]
		Parabacteroides [249]
		Phascolarctobacterium [31]
		Prevotella [31]
		Ralstonia [31]
		Ruegeria [31]
		Ruminococcus [209]
		Streptobacillus [31]
		Streptococcus [247]
		Syntrophobacter [31]
		Taylorella [31]
		Thermoanaerobacter [31]
Animal-based diet	Alistipes [209]	Butyricimonas [252]
	Bacteroides [209]	Eubacterium [209]
	Bilophila [209]	Parabacteroides [252]
	Roseburia [252]	Phaseolaretobaeterium [252]
		Roseburia [209]
		Ruminoeoeeus [209]
Mediterranean diet	Bacteroides [246]	Clostridium [252]
	Catenibacterium [252]	Collinsella [250]
	Citrobacter [250]	Coprobaeillus [250]
	Enterorhabdus [253]	Enterococcus [250]
	Eubacterium [254]	Escherichia [256]
	Faecalibacterium [246]	Parabacteroides [253]
	Lachnoclostridium [253]	Prevotella [255]
	Lachnospira [250]	
	Oseillospira [255]	
	Parabacteroides [246,255]	
	Prevotella [246,250,254]	
	Roseburia [246,255]	
	Ruminococcus [246]	
Vitamin A	Butyricimonas [212]	Actinomyces [212]
	Coprococcus [212]	Dialister [212]
	Roseburia [212]	Parabacteroides [212]
Vitamin B2	Alistipes [212]	
	Blautia [212]	
	Coprococcus [212]	
Vitamin B9	Butyricicoccus [212]	Alistipes [212]
	Roseburia [212]	Anaerovorax [212]

Diet and associated effects on the gut microbiota	Genera enriched	Genera depleted
		Megasphaera [212]
		Odoribacter [212]
		Parabacteroides [212]
Vitamin C	Butyricicoccus [212]	Alistipes [212]
		Anaerovorax [212]
		Odoribacter [212]
		Parabacteroides [212]
Vitamin D	Bacteroides [212,257]	Bifidobacterium [257,261]
	Clostridium [258]	Clostridium [257]
	Lachnobacterum [259]	Coprococcus [261]
	Lactococcus [260]	Dialister [212]
	Prevotella [261]	Escherichia [262]
		Haemophilus [261]
		Lactococcus [259]
		Pseudomonas [262]
		Shigella [262]
		Veillonella [260,261]
Vitamin E	Roseburia [212]	Acidaminococcus [212]
		Anaerotruncus [212]
		Odoribacter [212]
Vitamin K	Butyricimonas [212]	Alistipes [212]
	Coprococcus [212]	Anaerotruncus [212]
		Fusobacteria [212]
		Parabacteroides [212]
		Ruminococcus [212]
		Streptococcus [212]
Salt	Collinsella [212]	Faecalibacterium [212]
	Megamonas [212]	Lactobacillus [117]
	Parabacteroides [212]	
Polyphenols	Bacteroides [263,264]	Blautia [268]
	Bifidobacterum [263,265–267]	Clostridium [266,268]
	Blautia [263]	
	Clostridium [264]	
	Eggerthella [263]	
	Enterococcus [263]	
	Eubacterium [263]	
	Lactobacillus [264,266]	
	Prevotella [263]	
	Lactococcus [264]	
Fibers	Akkermansia [268]	Acidaminococcus [212]
	Bacteroides [268]	Actinomyces [212]
	Clostridium [248]	Anaerotruncus [212]
	Coprococcus [248]	Anaerovorax [212]
	Dorea [252]	Holdemania [212]
	Haemophilus [248]	Odoribacter [212]
	Holdemania [248]	Parabacteroides [212]
	Lactobacillus [268]	
	Methanobrevibacter [252]	
	Phascolarctobacterium [212]	
	Roseburia [212,252]	

Diet and associated effects on the gut microbiota	Genera enriched	Genera depleted
Short chain fatty acids	Barnesiella [212] Coprobacillus [212] Odoribacter [212] Parabacteroides [212]	Prevotella [212]
Long chain polyunsaturated fatty acids	Bacteroides [244] Bilophila [248] Coprococcus [244] Dorea [252] Holdemania [248] Lachnospira [244] Lactobacillus [252] Oscillospira [244] Roseburia [244,248] Ruminococcus [248]	Butyricimonas [252] Collinsella [248] Slackia [252] Streptococcus [248]