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EDITORIAL

The Microbiome and Neurologic Disease: Past and Future of a 2-Way Interaction

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Ilya Metchnikoff, the renowned microbiologist who was awarded the Nobel Prize in 1908 for his discovery of phagocytic cells and their activity in human immunity, made a unique and novel discovery while investigating cholera. He observed that the growth of cholera could be reduced by some microbes and enhanced by others. On the basis of these observations, he proposed that commensal bacteria within the intestine could contribute to protection against this pathogen and alteration of the gut bacteria could prevent disease. This hypothesis ran contrary to medical dogma at the time that conceived of the gut bacteria as a reservoir of toxins and other noxious products being produced by the microflora. While working at the Pasteur Institute he suggested that lactic acid-producing bacilli that cause milk to thicken as yogurt could be administered to prevent infection with known orally transmitted pathogens such as cholera. In the early 1900s, the approach to treating human gastrointestinal (GI) infections began to focus on using yogurt as a therapeutic, the first being a Catalan company named Danone. In the 1930s, the trend for using yogurt as a therapeutic began to lose favor with the advent of antibiotics, although the potential complications associated with antibiotic overuse were first noted in the 1950s. However, following World War II the importance of gut microflora in the production of a wide range of nutrients and vitamins necessary for human health became increasingly apparent. In 2001, Joshua Lederberg, who won the Nobel Prize 23 years earlier for his work in bacterial translocation, is credited with coining the term microbiome, expanding upon this as previously defined by others. It is now accepted that the microbiome can be defined as the "ecological community of commensal, symbiotic, and pathogenic microorganisms" that inhabit the various mucosal surfaces of our body including the lungs, surface of the eye, mouth, and gut, the latter being the largest and perhaps most critical to the homeostatic balance of our immune system. It is the bidirectional interaction of the genome of the colonized microbial flora of the host mucosal surface with the genome of the host that is responsible for the dynamic and important function of this organ.

Microbial colonization of our body begins at birth, although the colonization of the fetus through the mother has also been proposed. Recent research on this topic suggests that the early establishment of the microbiome is dependent upon the delivery method (vaginal *vs* cesarean section), which may have relevant implications in the context of human diseases. Nevertheless, recent advances in molecular techniques and bioinformatics have allowed the exploration of complex multifactorial interactions that occur between the microbiota and the host. In this special issue of *Neurotherapeutics*, the most recent findings on the association between the intestinal microbiota and central nervous system (CNS) diseases are reviewed. The review articles published in this issue explore the early establishment of the intestinal microbiota and its effect on neurodevelopment and the endocrine system, the potential effects of dysbiosis on CNS diseases, the bidirectional association of the gut/brain axis, and the potential of gut microbiota and its metabolic products as a unique and novel source for neurotherapeutic intervention.

The microbiota and CNS interactions may occur at interconnected pathways that include the immune, neural, and endocrine systems. In the first review, Farzi et al. [1] cover the most recent findings on the bidirectional association that exists between the microbiota and the brain in the context of the hypothalamic–pituitary–adrenal system. They discuss the effects of early life events on intestinal permeability and gut microbiota composition, as well as the potential impact of microbiota changes on hypothalamic–pituitary–adrenal function. Some microbial metabolites may directly regulate the endocrine

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system as well as immune function. As reviewed by Marietta et al. [2], the mucosal-associated lymphoid tissues constitute 70% of the body's immune reservoir. Because of the microbial load present, the gut-associated lymphoid tissue is of particular importance in immune surveillance. Immunomodulation mediated by gut microbes and microbial metabolites is discussed in other diseases such as autism spectrum disorder and amyotrophic lateral sclerosis based on results obtained from studies using a transgenic murine model, as well as results from a pilot experiment using six patients with amyotrophic lateral sclerosis. In their review, Marrietta et al. [2] also summarize the most relevant findings observed in studies that compared the gut microbiota, gut permeability, cytokines used as systemic inflammation markers, levels of short-chain fatty acids (SCFAs), and levels of the presynaptic protein α-synuclein aggregates in intestines in patients with Parkinson's disease with the microbiota of healthy controls.

The importance of the gut microbiome in neurodevelopment, myelination, and social–behavioral responses is reviewed by Ntranos and Casaccia [3]. In this review, gut microbes and their multifactorial association with the brain is proposed as a relevant regulator of CNS function in different aspects, such as microglial activation, the process of myelination, neurogenesis, and neuroendocrine effects. Because of the broad effects proposed, the gut microbiota might be a relevant regulator of behavior and social–behavioral diseases, as the most recent animal studies suggest. These authors review the relevance of myelination as a mechanism of control of gut microbes in the gut–behavior axis. This interaction is associated with metabolites produced by gut microbes, particularly p-cresol, that are able to promote oligodendrocyte differentiation. Among the broad effects of SCFAs, it has been proposed that butyrate promotes remyelination, microglia function, and also oligodendrocyte differentiation. Intestinal peptides and their importance in regulating social behavior are reviewed by Lach et al. [4]. Peptides produced by GI-specialized enteroendocrine cells play a significant role regulating neuroendocrine pathways that could be associated with metabolic, inflammatory, and autoimmune diseases, and their synthesis is modulated by the gut microbiota. The bidirectional nature of the gut/brain axis is covered in the context of peptides produced in the intestine and their effects on stress, anxiety, and depression, as well as intestinal barrier permeability changes and alterations of the microbiota.

The effects of the gut microbiota in the recovery from spinal cord injury (SCI) is discussed by Kigerl et al. [5]. In this review, the role of the gut microbiota in murine models of SCI are associated with long-term shifts in major microbial taxa, including increases in Clostridiales and reductions in Bacteroidales, when compared with control mice. The authors summarize the results describing that the alterations in the relative abundance of the gut microbiota were accompanied by effects on immune cell frequencies of Peyer's patches and mesenteric lymph nodes. Furthermore, SCI induced increases in the intestinal barrier permeability. As discussed by Marietta et al. [2], and more specifically by Buscarini et al. [6] in the context of multiple sclerosis (MS), disruption of intestinal permeability is associated with neurologic diseases. Bacterial translocation, defined as the movement of bacteria or bacterial products across the intestinal epithelium, also characterizes SCI effects on the intestinal environment, as gut microbes were isolated from mesenteric lymph nodes. Furthermore, the analysis of the gut microbiota of a small cohort of patients suffering from SCI (n = 30) suggests that, when compared with healthy controls (n = 10), disease is associated with dysbiosis characterized by a reduction in the abundances of butyrate-producing bacteria in patients with SCI. Owing to the proposed neuromodulatory and immunomodulatory effects of the SCFA butyrate, the results summarized by Kigerl et al. [5] suggest a potential mechanism by which probiotic intervention of the gut microbiome may be considered a possible neurotherapeutic approach.

As a major modulator of the gut microbiota, diet and dietary habits could play a significant role on the effects mediated by gut peptides within the CNS. Riccio and Rossamo [7] review the extensive literature that exists on diet and the microbiota, and postulate its importance in regulating inflammation and autoimmune diseases such as MS. However, owing to the rapid effects caused by diet and other factors on the microbiota, it is difficult to define what we would consider to be a healthy microbiota. The effects of dietary factors, supplements, and lifestyle on MS are extensively reviewed. As an immunomodulatory factor, the importance of vitamin D in association with autoimmunity has been evaluated. Low sunlight exposure and linked vitamin D deficiency are considered as an environmental risk factor for MS. Riccio and Rossamo [7] highlight findings suggesting that regardless of sun exposure and geographical latitude, patients with MS, in general, are vitamin D deficient. In their review, the association of vitamin D and diet with the gut microbiota is explored in the context of MS.

The association between autoimmune diseases of the CNS and the gut microbiota is of increasing interest from both a disease pathogenesis and therapeutic approach. In patients with neuromyelitis optica (NMO), IgG autoantibodies to aquaporin-4 (AQP4) expressed in astrocytes attack myelin in axons of the spinal cord, brainstem and optic nerve. Demyelination and optic neuritis cause paralysis and loss of vision. The mechanism behind the disease is based on the action of the AQP4-specific antibodies and the complement system against astrocytes. Zamvil et al. [8] review the importance of the gut microbiota eliciting T-cell-dependent responses in the pathogenesis of NMO. The role of T cells in the pathogenesis of NMO has been associated with their requirement in the production of AQP4-specific IgG1 antibodies by plasma cells, and the potential role of follicular helper T cells in class switching and plasma cell maturation. Moreover, T cells appear to play a pathogenic role

in NMO as interferon-γ and interleukin (IL)-17 producers. Polymorphisms in major histocompatibility complex class II genes have been identified in patients with NMO, and 1 specific AQP4 determinant of 20 peptides identified most frequently in NMO induces polarization of T helper (Th)17 cells *in vitro*. The epitope identified within this determinant has a 90% homology with a sequence of an adenosine triphosphate binding cassette transporter permease expressed by *Clostridium perfringens. In vitro*, adenosine triphosphate binding cassette transporter permease promoted the differentiation of naïve T cells into proinfammatory IL-17-producing Th17 cells, associated with the immunopathogenesis of NMO and MS, that responded specifically to AQP4 leading toward a proposed hypothesis of molecular mimicry in NMO. Zamvil et al. [8] review their recent findings showing that in patients with NMO the microbiota harbored several bacterial taxa that differed significantly in relative abundances from the abundances found in healthy individuals, with a highly significant overabundance of *C. perfringens*. The association between the bacterium and the disease is based on the induction of Th17 cells and a mechanism of cross-reaction between AQP4 and the determinant present on the surface of *C. perfringens.*

Polymorphisms in major histocompatibility complex class II genes, among other genes associated with immune responses, have been associated with the risk of developing MS. Although genetic susceptibility is a factor that may determine disease, other risk factors are also necessary, in particular, environmental triggers such as those associated with known risk factors. We, among other investigators, explored the effects of the gut microbiota in experimental autoimmune encephalomyelitis (EAE) models of MS and proposed the idea that the composition of the gut microbiota is relevant for the balance of the proinflammatory and anti-inflammatory cell subpopulations that result in disease induction or protection [9–17]. This special issue covers the most recent literature on the experimental models and the clinical evidence for changes in the gut microbiota observed in patients with MS. Tremlett and Waubant [18] explore the microbiota of pediatric MS cases. Their studies performed in children with MS indicate that the changes observed in the microbiota in adult MS are already observed in pediatric MS, which provides preliminary evidence for the presence of a gut signature of MS. Remarkably, their study also suggests that the treatment with immunomodulatory drugs shape the microbiota strongly, promoting differences that are higher than those found in patients with MS. The adult MS microbiota complexity is covered by the reviews of Freedman et al. [19], Pröbstel and Baranzini [20], and Cox and Weiner [21]. These studies highlight the current limitations of microbiota studies in disease populations, owing to interindividual variability, the effects of multiple possible environmental factors that could affect the composition of the microbiota, and also the relevant role of immunomodulatory drugs in shaping the microbiota. Despite the limitations, the findings shown in this special issue provide mounting evidence for changes in the gut microbiota of patients with MS. The discussion of whether a gut microbial signature for MS can be established is covered in the 3 works cited above. In this regard, Freedman et al. [19] hypothesize that in MS an overall increase in the abundance of proinflammatory microbes is observed with no specific taxa associated. Despite a discrepancy in the changes observed in the abundances of specific microbial taxa, certain species such as *Akkermansia muciniphila* are observed in several recent studies. Are these changes relevant? Two recent studies evaluated whether the changes in the specific taxa observed in patients with MS had functional effects on disease [22, 23]. The results obtained in the studies of transplantation of fecal content of patients with MS to germ-free mice that suffer from a less severe form of EAE suggest that changes in the microbiota of individuals with MS could be functionally relevant by enhancing experimental disease. Pröbstel and Baranzini [20] review their own [22] and findings by Berer et al. [23], providing evidence for the importance of alterations of the microbiota in the severity and progression of the disease. Fecal transplantations of MS samples were able to restore EAE susceptibility in 2 different models of germ-free mice. Mechanistically, dysfunctional IL-10-producing T cells were associated with the role of the MS microbiota regulating disease. The gut–brain axis in MS is evaluated by Cox and Weiner [21] from neuronal, neuroendocrine, and immunological perspectives. The association between the microbiota and other neurological diseases such as Parkinson's disease, mood disorders such as anxiety, aggressive behavior, and autism are also covered.

The bidirectional nature of the gut–brain axis is also proposed by Cox and Weiner [21]. We recently proposed that in CNS inflammatory diseases the association with the gut microbiota is bidirectional [24]. In nonobese diabetic mice, the induction of EAE promoted a significant change in the overall structure of the gut microbiota, which was more significant in mice that developed severe disease compared with mice that did not develop or developed a milder form of disease. In this context, the disease promoted changes in the microbiota. Similarly, treatment with antibiotics at early stages of disease (from day 0 to 14) resulted in reduced severity of disease, indicating the bidirectional association between disease and the microbiota [24]. The induction of EAE in mice has remarkable cellular and molecular effects on the intestinal barrier by promoting the induction of a "leaky gut" and accumulation of proinflammatory Th17 and Th1 cells, concomitant with reductions in regulatory T cells in the intestinal mucosa [25]. The effects of MS in intestinal barrier disruption are reviewed by Buscarini et al. [6]. These authors discuss the relatively high frequency of intestinal barrier dysfunction in patients with MS, perhaps inherited genetically. The comorbidities of MS and other diseases associated with the intestine, such as Crohn's disease and other inflammatory diseases, are nicely covered in this review.

Collectively, the discussions presented in this special issue indicate that interindividual variability caused by genetic and environmental factors constitutes a limitation that affects the interpretation of studies, particularly when sample sizes are small. The question of whether we can identify a specific microbial signature for a specific disease remains unanswered. Moreover, we are unable to determine whether the changes observed in the composition and structure of the microbiota are a cause or consequence of disease. However, it is now increasingly understood that the gut microbiota is an organ to consider when exploring the pathogenesis of CNS diseases. Perhaps most importantly, the articles in this special issue of *Neurotherapeutics* suggest that the gut microbiome is the new frontier of human biology. This newly appreciated organ represents a treasure trove of possible therapeutic interventions for neurologic disease as well as a wide range of other human diseases. Enjoy and savor reading about the cutting-edge of human biology.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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