



# Microbiome, Immunomodulation, and the Neuronal System

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## Abstract

Vertebrates harbor both symbiotic and pathogenic bacteria on the body and various mucosal surfaces. Of these surfaces, the intestine has the most diverse composition. This composition is dependent upon various environmental and genetic factors, with diet exerting the maximum influence. Significant roles of the intestinal bacteria are to stimulate the development of a competent mucosal immune system and to maintain tolerance within the intestine. One manner in which this is achieved is by the establishment of epithelial integrity by microbiota found in healthy individuals (healthy microbiota); however, in the case of a disrupted intestinal microbiome (dysbiosis), which can be caused by various conditions, the epithelial integrity is compromised. This decreased epithelial integrity can then lead to luminal products crossing the barrier, generating a systemic proinflammatory response. In addition to epithelial integrity, healthy intestinal commensals metabolize indigestible dietary substrates and produce short-chain fatty acids, which are bacterial metabolites that are essential for colonic health and regulating the function of the intestinal immune system. Intestinal commensals are also capable of producing neuroactive molecules and neurotransmitters that can affect the function of the vagus nerve. The observations that intestinal dysbiosis is associated with different diseases of the nervous system, suggests that cross-talk occurs amongst the gut, the nervous system, and the immune system.

**Keywords** Immunomodulation · Neuronal · Dysbiosis · Intestinal · Microbiome

## Introduction

The human intestine is colonized by a large number of microorganisms, including around  $10^{14}$  types of bacteria that are involved in various functions. The colonization of the gut begins at birth and continues throughout the teenage years, forming a unique intestinal microbiome signature for each individual. The composition of an individual's gut microbiota is influenced by many factors, including diet, geographical location, genetics, age, and sex [1]. Recent studies have provided evidence that the intestinal microbiome has a mutualistic relationship with the host and helps regulate the host's innate and adaptive immune systems.

In this mutualistic relationship, the human body acts as a host providing gut microbes with the nutrients that they need.

In return, the microbes help with the catabolism of indigestible carbohydrates and fatty-acid chains leading to the production of short-chain fatty acids (SCFAs) [2]. The SCFAs produced by gut microbes are essential for many physiological pathways, as well as for regulating immune responses. For example, butyrate, a SCFA, is required for colonic health and epithelial integrity. Other benefits that the gut microbiota provide to the host include the production of vitamins, such as vitamin B, as well as the secretion of hormones that signal the body to store fat [3]. Along with aiding in nutrient uptake, hormone signaling, and vitamin production, some of these bacteria also help to shape and to regulate the immune system.

However, the above-described beneficial effects come from beneficial commensals. In order to remove deleterious and pathogenic bacteria, the host has a significant amount of lymphoid tissue called mucosa-associated lymphoid tissue (MALT), which consists of 70% of the body's lymphoid tissue. Immunologically active T and B lymphocytes are found in the MALT, which routinely samples the microbes that enter the gut in order to detect and eliminate pathogenic bacteria. This regulation of the gut microbiota can be achieved in many ways, as various bacterial species express different cell surface receptors, as well as different metabolites. Intestinal epithelial

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and immune cells will recognize conserved microbial sequences called microbe-associated molecular patterns, using receptors called pattern recognition receptors [4]. Detection of microbe-associated molecular patterns by the MALT will lead to epithelial cells producing regenerating Protein-III gamma (Reg III gamma), which is an antibacterial lectin that targets Gram-positive bacteria [5]. This is, therefore, one example of how intestinal microbiota, through the release of natural antigens, can stimulate and modulate our mucosal immune system. In fact, analysis of the transcriptomes of healthy adult C3H/HeN mice raised in germ-free conditions (no fecal microbiota), conventional housing, and mice colonized with fecal microbiota showed that 45% of genes induced by the fecal microbiota were assigned to immune response pathways [6].

Pathogenic bacteria and in some cases, symbiotic-turned-pathogenic bacteria, will certainly stimulate the immune response. Another way that intestinal microbiota can affect the immune response is through the alteration of the overall composition of the intestinal microbiota. Altered gut microbial composition has been associated with obesity and inflammatory bowel disease [6], and as well as with systemic diseases like multiple sclerosis (MS) and rheumatoid arthritis [1, 7]. Examples of environmental factors that may alter a patient's microbiome include noncommensal bacteria, antibiotics, diet, lifestyle, and exercise. Such shifts in the intestinal microbiome would affect health by: changing nutrient uptake by the host, altering the host's ability to mount appropriate immune responses, and disrupting the host's ability to tolerate their own intestinal commensal bacteria.

## Interactions Amongst the Intestinal Microbiome and the Neuronal and Immune Systems

Germ-free (GF) mice have been crucial in our understanding of the complex interactions that occur amongst the intestinal microbiome and the neuronal and immune systems. For example, GF mice have a poorly developed mucosal immune system characterized by reduced IgA production, smaller Peyer's patches, and altered expression of Toll-like receptors (TLRs) [8, 9]. GF mice also have lower levels of serotonin [10]. In addition, GF mice have reduced numbers of enteric neurons, which is associated with decreased gut motility and lower excitability of neurons, suggesting a role of the microbiota in the development of the enteric nervous system [11].

The decreased levels of TLRs in GF mice suggest that the expression of TLRs is influenced by the presence of intestinal microbiota. Two lines of mice, the TLR2<sup>-/-</sup> and TLR4<sup>-/-</sup> mice, have also been used to show the interaction between the intestinal microbiome and the nervous system. Both TLR2 and TLR4 are TLRs, which are pattern recognition receptors that can detect antigens from gut microbes. Mice that have TLR2

and TLR4 knocked out (TLR2<sup>-/-</sup> and TLR4<sup>-/-</sup>) have reduced gut motility and enteric neurons [12], similar to GF mice. In addition, TLR2<sup>-/-</sup> mice also have an altered neurochemical profile and reduced expression of glial fibrillary acidic protein (GFAP) in the myenteric plexus. As TLR2 expression on enteric glial cells is enhanced by certain microbes, the microbiota/TLR pathways may be involved in the development of diseases associated with the enteric nervous system.

It should also be noted that pathways between the nervous and immune system also exist, in which stimuli from the nervous system leads to changes in the immune system. For example, neurotransmitters like norepinephrine can bind to the  $\beta$ 2 adrenergic receptor expressed by T helper 1 cells. This will then lead to a change in the production of cytokines by the T helper 1 cells, such as a reduction in interleukin (IL)-2 production [13].

The above-described studies in total demonstrate that communication does occur amongst the immune system, the nervous system, and the intestinal microbiome. In order to describe how these communication pathways are disrupted in neuronal diseases, this review will first discuss the communication pathways that are normally present and functioning, such as the microbiota–gut–brain axis, and then a review of those immune-associated neurological disorders that have also been associated with changes in the intestinal microbiome (dysbiosis).

The microbiota–gut–brain axis is essentially an extension of the gut–brain axis, which is a bidirectional communication pathway between the gut and the brain. The communication along the gut–brain pathway is achieved primarily by the vagal nerve, and the [hypothalamic–pituitary–adrenal axis](#) [14]. The term microbiota was added (microbiota–gut–brain axis) because studies have shown that the intestinal microbiota can communicate with the gut–brain axis. For example, some bacteria have evolved to produce hormone-like chemicals and monoamine neurotransmitters in the intestine, which can then directly stimulate the intestinal immune and nervous systems [15–17]. The sympathetic nervous system also serves as a conduit between the brain and the immune system, and many immune cells produce neuroactive products. These neuroactive products include: vasoactive intestinal peptide (mast cells and neutrophils), somatostatin (delta cells), adrenocorticotrophic hormone, endorphins, and substance P (latter three by macrophages). Specific mechanisms have been identified by which intestinal microbiota can affect the enteric nervous system. For example, intestinal microbiota can induce the production of neurotransmitters. Spore-forming bacteria have been shown to augment the production of serotonin by enterochromaffin cells of the intestinal epithelium via the upregulation of the enzyme tryptophan-hydroxylase-1. Serotonin in the gut is regulated by serotonin-selective reuptake transporter, which is expressed by the intestinal epithelium and controlled by TLRs [10]. G protein-coupled receptors, GPR41 and GPR43, are expressed by epithelial cells and enteric neurons. Both can be activated by SCFAs [18]. SCFA-induced

activation of GPR43 promotes the secretion of hormone glucagon-like peptide-1, which is involved in gastrointestinal transit [19]. Another mechanism by which SCFAs affect enteric neurogenesis is by inhibition of histone deacetylase activity. Treatment of cultured enteric neurons with butyrate has been shown to enhance the expression of excitatory choline acetyltransferase and enhance the acetylation of H3K9 [20]. SCFAs in conjunction with other dietary factors and bile acids can also regulate gut motility [12]. Thus, there are ample pathways in which each system, nervous, immune, and intestinal microbiome, can all communicate with each other.

Recent research has shown that some neurological conditions are associated with perturbations of the intestinal microbiota. However, it has been difficult to determine whether or not these changes in the intestinal microbiota are causative of disease, an exacerbating factor for disease, or a consequence of disease. MS is the neurological condition that has been best characterized with regard to the role of dysbiosis. This has been achieved by studying both patients and using an animal model of MS called experimental autoimmune encephalomyelitis (EAE). Intestinal dysbiosis has also been found in other neurological diseases, and the role of the dysbiosis in the pathogenesis of these neurological diseases is even less clear. These diseases include autism spectrum disorder (ASD), amyotrophic lateral sclerosis (ALS), and Parkinson's disease (PD). That which follows then, will be a series of descriptions and discussions of these neurological diseases and the current understanding of the role of the intestinal microbiome in each disease (Table 1).

## Microbiome and MS

The role of the intestinal microbiome in the development of MS has recently become an area of intense research. One recent paper showed that the species richness (alpha diversity)

was lower in patients with active MS than in healthy controls [21]. In addition, a Bray–Curtis distance-based community analysis (beta diversity) demonstrated that the microbiomes of patients with relapsing-remitting MS (RRMS) were significantly different than healthy controls. Taxonomic analysis found that *Parabacteroides*, *Prevotella* (*Bacteroidetes*), *Adlercreutzia*, *Collinsella* (*Actinobacteria*), and *Erysipelotrichaceae* (*Firmicutes*) were decreased in the fecal microbiota of patients with RRMS as compared with healthy controls [21]. Another publication found MS associated with increases in *Methanobrevibacter* and *Akkermansia* and decreases in *Butyricimonas* [22].

Studies with animal models of MS, EAE, have provided insight into the role of intestinal microbiota in the development of MS. In one study, the authors induced EAE in GF mice and found that the clinical severity was decreased *versus* EAE induced in specific-pathogen-free conditions [30]. This would indicate that the presence of intestinal microbiota makes the symptoms of EAE more severe. When the GF mice were colonized with segmented filamentous bacteria, mice developed much more severe EAE after induction [30]. How MS-associated gut microbiome influences disease was studied by transferring the microbiomes of patients with MS into GF mice [23]. In this study, the recipient mice retained the signature of the microbiome of the patient with MS, which was characterized by significant increases in *Akkermansia* and *Acinetobacter*, with a significant decrease in *Parabacteroides*. The GF mice induced for EAE that received the MS stool samples had more severe disease than the mice that received stool samples from healthy controls and GF mice that did not receive human stool samples. This increased severity was associated with a decreased number of regulatory T cells in the GF MS mice. Thus, this model proves that the MS microbiome can modulate the immune response and lead to severe disease.

**Table 1** Microbial changes in human diseases

Neuronal disease	Affected neuronal system	Examples of microbiota changes in humans	Mouse models	Mouse models indicate modulatory properties of disease-associated microbiome
MS	CNS	Increased <i>Haemophilus</i> , <i>Blautia</i> , and <i>Dorea</i> genera, and decreased <i>Parabacteroides</i> , <i>Adlercreutzia</i> , and <i>Prevotella</i> [21] Increased <i>Methanobrevibacter</i> and <i>Akkermansia</i> , and decreased <i>Butyricimonas</i> [22]	Yes	Yes [23]
ASD	CNS	Decreased in <i>Prevotella</i> [24] Increased <i>Erysipelotrichaceae</i> , <i>Clostridium lituseburense</i> , and <i>Terrisporobacter</i> with low tryptophan; increased <i>Lachnospiraceae</i> , <i>Lachnospiraceae</i> , and <i>Flavonifractor plautii</i> with high serotonin [25]	Yes	Not tested
ALS	CNS, PNS	Reduced <i>Oscillibacter</i> , <i>Anaerostipes</i> , and <i>Lachnospiraceae</i> , and increased <i>Dorea</i> [26]	Yes	Not tested
PD	CNS, PNS	Reduction of <i>Prevotellaceae</i> and <i>Lactobacillaceae</i> [27, 28]	Yes	Yes [29]

MS = multiple sclerosis; CNS = central nervous system; ASD = autism spectrum disorder; ALS = amyotrophic lateral sclerosis; PNS = peripheral nervous system; PD = Parkinson's disease



in these patients with ALS *versus* healthy controls. To determine if the microbiomes of patients with ALS truly are producing significantly lower levels of butyrate as the mouse model and microbiome analysis of patients with ALS would suggest, more studies need to be done on larger numbers of patients with ALS.

In support of the theory that it is the decreased levels of butyrate that contribute to the pathogenesis of ALS, a study utilizing the G93A ALS mice demonstrated that the administration of sodium phenylbutyrate (PBA) significantly ameliorated gross spinal cord atrophy in the ALS mice [36]. In addition, reactive astrogliosis was also significantly reduced in the PBA-treated mice. However, it should be mentioned that animal models such as this one use high doses of PBA (100–900 mg/kg mouse) [37]. This assessment is based on the fact that the concentration of butyrate is approximately 1 to 32.6 g/kg of stool [37, 38]. If the concentration of butyrate in the stool is used as a guide for biologically relevant concentrations, then the typical amount of butyrate (PBA) injected into mice is much higher than we would expect to be in the gut. More studies need to be done to determine what exactly the concentrations of butyrate within the intestine are and whether or not this concentration is variable within a day.

Sodium butyrate has also been shown to act as an anti-inflammatory agent for LPS-induced responses in primary microglia but not for proliferating microglial cells isolated from rats [39]. Butyrate can signal through GPR109a, which is not only expressed in T cells, but has also been found in microglia [40]. While the beneficial effects of butyrate have been shown in the colon, very few studies have probed its beneficial neurological effects. Restoration of the blood–brain barrier in GF mice was achieved when colonized with *Clostridium tyrobutyricum*. This restoration was due to an increase in the expression of the tight junction proteins, occludin, and claudin-5, suggesting a crosstalk amongst the intestinal metabolites, the brain, and the immune system [41]. Thus, observations from mouse models and human studies suggest that the decreased levels of butyrate-producing bacteria contribute to or are a factor of disease pathogenesis in ALS.

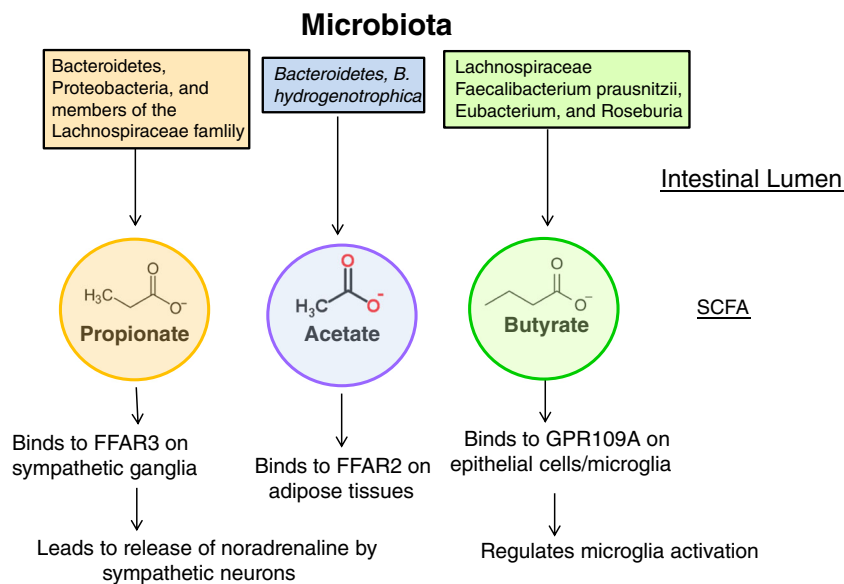
## PD

A reduced abundance of *Prevotellaceae* and *Lactobacillaceae* was observed in patients with PD *versus* healthy controls [27, 28]. This reduction of *Prevotellaceae* and *Lactobacillaceae*, both anti-inflammatory in nature, could result in inflammatory conditions in PD. In another study, 19 patients with PD and 14 age-matched healthy controls were evaluated for colonic inflammation [42]. Transcript levels of proinflammatory cytokines, tumor necrosis factor- $\alpha$ , interferon- $\gamma$ , and IL-6, measured from colonic biopsies were significantly increased in the colons of patients with PD. A correlated increase in glial markers, GFAP and Sox-10 mRNA, was also observed in

the colon biopsies of patients with PD. Additionally, the pro-inflammatory cytokine mRNA levels and GFAP and Sox-10 mRNA levels were correlated with disease duration.

In addition to colonic inflammation, patients with PD have higher permeability of their gut than controls [15], and this permeability may arise as a result of a dysbiosis of the intestinal microbiota and/or other factors. Patients with PD also had significantly decreased levels of the SCFAs acetate, propionate, and butyrate in their feces [28]. These particular SCFAs are recognized by the intestinal immune system and promote the production of IgA, much of which is specific for microbiota [43]. The importance of the intestinal microbiota in stimulating the production of intestinal IgA is demonstrated in GF mice, as they produce almost no intestinal IgA [44]. Because patients with PD develop colitis and have a decreased production of SCFAs, it is possible that their production of intestinal IgA may also be decreased.

Also of interest are the studies that suggest that dysbiosis in PD could be modulating the nervous system.  $\alpha$ -Synuclein is a highly conserved presynaptic protein that was originally associated with PD in 1997 [45], owing to the identification of a mutation in the  $\alpha$ -synuclein gene in patients with PD who had a familial history of PD. This mutation leads to abnormal aggregation in both the brain (substantia nigra) and the gut of patients with PD [15, 46], with the level of  $\alpha$ -synuclein aggregates in the intestine correlating with intestinal permeability [15]. Also of great interest is another study that was able to demonstrate that the  $\alpha$ -synuclein aggregates in the gut appear years (as many as 8) before the development of motor symptoms [47]. This would suggest that the inflammation in the gut, possibly due to aggregation of  $\alpha$ -synuclein, precedes the inflammation in the brain. If the inflammation of the gut does precede the inflammation in the brain, it would be of interest to determine if the dysbiosis of the gut precedes the aggregation of the  $\alpha$ -synuclein in the gut or vice versa. A recent study showed that fecal microbes from patients with PD, when transplanted into mice that overexpress  $\alpha$ -synuclein, can further impair motor function [29], which was associated with an increase in *Proteus* spp., *Bilophila* spp., and *Roseburia* sp., and reduced species of *Lachnospiraceae*, *Rikenellaceae*, and *Peptostreptococcaceae*. Further, the authors showed that gut microbiota is required for microglia activation via  $\alpha$ -synuclein. The mouse model of PD upon treatment with a mixture of SCFAs showed microglia morphology similar to specific-pathogen-free mice. It should also be noted that patients with PD have increased levels of constipation and irritable bowel syndrome-like symptoms, both of which are associated with alterations in the intestinal microbiome [48–50]. However, the previously described fecal transfer mouse model would suggest that the PD microbiome enhances motor dysfunction (brain), as well as affects the enteric nervous system [29].



**Fig. 1** Effect of bacterial metabolites upon the host. The intestinal lumen is depicted at the top of the diagram, along with some of the taxa that produce the 3 main bacterial metabolites. These metabolites directly stimulate cells of the host via binding to receptors on epithelial cells and immune cells. Depicted at the bottom are some examples of

receptors that the metabolites can bind to, as well as examples of cells/tissue that express these receptors. Dysbiosis causing alterations in the metabolites can impact immune system and neurotransmitters produced by the microbes. SCFA = short-chain fatty acid; FFAR = free fatty acid receptor; GPR = G protein-coupled

## Therapies For Neurological Disorders Based on Targeting Microbiota

For those neurological disorders in which bacterial species clearly cause or exacerbate the neurological damage, such as Guillain-Barré syndrome and neuromyelitis optica, treatment with antibiotics could be used. However, as the numbers of antibiotic-resistant bacteria increase, this may not be a feasible solution in the future. Hence, research is currently being done on developing bacteriophages that can be used for eradicating pathogenic bacteria [51]. For those neurological disorders in which complex changes of the composition of the intestinal/oral microbiome occur, a more nuanced and complex approach will be necessary. This could be achieved by changing the diet, supplementing the microbiome with commensals of which the individual has low levels, and/or the use of generalized prebiotics and probiotics. Changing the diet of the individual and the use of prebiotics are essentially altering the composition by expanding certain groups of microbiota. Unfortunately, this is not a targeted approach, and there has been limited success with these types of approaches. A much more individualized and targeted approach would be to determine, through next-generation sequencing, which bacterial groups the individual is replete in and then providing a supplement to expand that beneficial bacterial group. Examples of this include the use of *P. histicola* to treat those patients that have low levels of *Prevotella* species that are beneficial for the health of patients [52]. Administration of *P. histicola* to a mouse model of autoimmune disease has demonstrated that this course of treatment can be successful [53]. In addition, the

administration of SCFAs has also been successful in mouse models of neurological disorders (Fig. 1). In conclusion, research on how the microbiome interacts with both the brain and the immune system is revealing the complexities of neurological disorders, and research on the use of individualized microbiome targeted therapies for neurological diseases holds great promise.

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