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Gut Microbiome-Mediated Regulation of Neuroinflammation

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Abstract

The intestinal microbiome influences neuroinflammatory disease in animal models, and recent studies have identified multiple pathways of communication between the gut and brain. Microbes are able to produce metabolites that enter circulation, can alter inflammatory tone in the intestines, periphery, and central nervous system (CNS), and affect trafficking of immune cells into the brain. Additionally, the vagus nerve that connects the enteric nervous system (ENS) to the CNS is implicated in modulation of brain immune responses. As preclinical research findings and concepts are applied to humans, the potential impacts of the gut microbiome-brain axis on neuroinflammation represent exciting frontiers for further investigation.

Introduction

Neuroinflammation in the central nervous system (CNS) in response to injury, infection, or disruption in neural tissue homeostasis is generally self-limiting and beneficial to the host, mediating both the defense and repair of tissue. However, in some conditions, inflammatory responses may become chronic or damaging and result in neuroinflammatory disease. Growing evidence has defined a role for the microbiome in the regulation of several acute and chronic diseases, including stroke [1–**4], multiple sclerosis [5–**9], Alzheimer's (AD) [10,11], and Parkinson's disease (PD) [12]. These conditions are characterized by neuronal damage, microglial activation, peripheral immune cell infiltration into the CNS, and interestingly, often co-occur with gastrointestinal (GI) dysfunction [10,13–16]. The fecal microbiome is altered compared to controls, showing enrichment of pro-inflammatory microbes and depletion of anti-inflammatory species [17]. Since human research has been largely observational and most mechanistic studies have been performed in animal models to date, it remains unknown what (if any) contributions the gut microbiome has on disease-associated pathology and symptoms. Translation of preclinical findings to interventional

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Declaration of interests

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clinical studies will be critical in appreciating the impact of the gut microbiome on human health.

The GI tract is home to commensal microbes and approximately 70% of the body's immune cells [18]. Immune development is intricately linked to the composition of the gut microbiome in mice. For example, the lack of a microbiome can stunt immune development, particularly T cell differentiation, whereas the presence of a complex microbiome induces immune responses that resemble those of humans [19]. Furthermore, microbes can produce signals affecting both the local enteric nervous system (ENS) and the more distal CNS [*20,21]. Gut dysbiosis and intestinal inflammation are consistent features of some CNS diseases in humans, ranging from acute conditions such as stroke [22], to chronic diseases such as neurodegeneration [7,8,10,23] and depression [24]. Microbiome-regulated connections between the gut and brain are important in health and disease and occur through several mechanisms, including transport of metabolites and other molecules to the brain through the circulation, activation of immune cells at peripheral sites (e.g., gut and lung) that migrate to the brain, and direct communication through the vagus nerve and connected efferent and afferent neurons that innervate the gastrointestinal tract (Figure 1) [17]. This Review will present and synthesize the state-of-the-art findings in gut microbiome influences on neuroinflammation.

Metabolites and Other Microbe-Derived Molecules

Metabolites and other molecules, sourced from the host, diet, and/or microbiome, can be transported from the gut to the brain through the circulation and have been shown to influence neuroinflammatory diseases. These molecules can originate from the microbiome or from host-microbial co-metabolism, and include microbial components and secreted factors (e.g., hormones), metabolites, and host-induced hormones, cytokines, neuropeptides, and neurotransmitters [25,26]. Altered metabolomes are implicated in numerous diseases of the CNS, including stroke [27,28], multiple sclerosis (MS) [29], Parkinson's disease [23], Alzheimer's disease [11], and depression [24]. Several microbiome-derived molecules have been identified as regulators of inflammation and disease symptoms in experimental autoimmune encephalomyelitis (EAE), including tryptophan metabolites signaling through the aryl hydrocarbon receptor (Ahr) [*30], capsular carbohydrates [31], and peptide mimics of myelin oligodendrocyte glycoprotein (MOG) [**9]. There is some overlap between the metabolome in MS and PD patients, with alterations in metabolites related to oxidative stress and mitochondrial function [32,33]. In PD, increased sulfur metabolism, p-cresol, and phenylacetylglutamine, and decreased carbohydrate fermentation are factors in disease [32,34,35]. Metabolite profiles can be drastically altered by dietary intake, and many of the currently studied microbial metabolites are produced from dietary compounds as precursors, highlighting the intertwined neuromodulatory potential of diet and gut metabolites. While these findings are intriguing, their mechanism of action and how they affect disease remains largely unknown. To date, most research has focused on short-chain fatty acids (SCFAs), microbial surface structures, secreted metabolites, and bacterial mimics of mammalian molecules.

Short-chain fatty acids

SCFAs are metabolites produced by the microbiome from dietary fiber, the most abundant of which include acetate, butyrate, and propionate [36]. Studies have revealed altered levels of SCFAs, closely associated with microbial dysbiosis, in certain neuroinflammatory diseases [11,23,28,29,32,35,37], though cause and effect have not been established.

In animals, SCFA treatments modulate immune responses in multiple disease models but with differing outcomes. In the context of Alzheimer's disease, mixed SCFA supplementation in the 5xFAD mouse model attenuates the development of brain Aβ pathology and memory deficits, increases brain interleukin (IL)-10, and decreases brain IL-6 levels [38]. However, in the APPPS1 mouse model of AD, SCFA supplementation increases brain Aβ pathology [*39]. Other studies have found that decreased levels of SCFAs in the circulation are associated with increased severity of stroke [27,28]. In these studies, young mouse microbiomes produced higher levels of SCFAs and lower levels of intestinal and circulating pro-inflammatory cytokines (e.g., IL-17A, IL-6, Eotaxin, RANTES, and tumor necrosis factor (TNF) compared to aged mouse microbiomes [27,28]. Furthermore, fecal microbiome transfer (FMT) from young to aged mice decreased stroke severity whereas FMT from aged to young mice resulted in worse outcomes [27,28]. However, a causal role for SCFAs was not identified. Rather, these studies found that the microbiome influenced inflammatory tone. In MS, compositional changes in the microbiome are correlated with reduced propionic acid (PA) in humans, and supplementation with PA changes inflammatory tone by modifying the microbiome and increasing the number and suppressive capacity of regulatory T cells (Tregs) [40]. In an alpha-synuclein-overexpressing (ASO) mouse model of Parkinson's disease, feeding a mix of SCFAs to antibiotic-treated mice induces alpha-synuclein (αSyn) aggregation, neuroinflammation, and motor deficits [12]. However, in human PD, a meta-analysis of microbiome changes in PD across multiple studies consistently find decreased abundance of the SCFA-producing bacterial family Lachnospiraceae and genus *Faecalibacterium* [23]. These findings paint a complex picture in which SCFA effects are disease dependent.

In particular, butyrate and acetate may have opposite effects on inflammatory processes and disease pathology. Butyrate in the gut can induce Tregs and may be protective in neuroinflammation [41]. Feeding sodium butyrate to 5xFAD mice decreases brain Aβ deposition and improves memory function [42]. In another model of AD, FMT from butyrate-rich WT mice to butyrate-deficient APP/PS1 mice increases butyrate to WT levels, improves memory function, and decreases both Aβ and tau pathology [43]. Restoration of microbiota in antibiotic-treated APP/PS1 mice restores high levels of Aβ deposition and microglial activation [44], suggesting that butyrate may promote anti-inflammatory responses in the context of this AD model. Immune regulation may also be relevant in humans, as higher Aβ reactivity on positron emission tomography (PET) scans negatively correlates with levels of butyrate and anti-inflammatory cytokines [45]. Additionally, an *in vitro* rotenone-based model of PD also demonstrated a protective effect of sodium butyrate treatment [46]. However, in multiple sclerosis, butyrate is increased and positively correlates with levels of pro-inflammatory cytokines interferon γ (IFNγ) and TNF [29].

In contrast to butyrate, acetate supplementation of 5xFAD mice increased Aβ pathology, decreased microglial uptake of Aβ, decreased mitochondrial ROS production, and led to expression of disease-associated microglial genes such as *Trem2, Apoe,* and *Ldl* [**47], although as a caveat, these experiments were performed in the artificial situation of a germ-free mouse. In humans, higher Aβ reactivity on PET scans positively correlates with levels of acetate, as well as lipopolysaccharide (LPS), and circulating pro-inflammatory cytokines [45]. However, in multiple sclerosis patients, acetate negatively correlate with IFNγ levels [29]. It is likely that the effects are disease and SCFA-specific, potentially acting through modulation of microglial states. SCFAs that increase microglial activation and phagocytosis may be helpful in clearing Aβ plaques, but harmful in promoting further inflammation in PD or MS. Results obtained from SCFA studies in mice are varied in their manifestations and interpretations, and more work is needed to confidently assign SCFA levels and profiles in humans. Further, SCFAs have functions outside the immune system, such as an energy source of intestinal epithelial cells that interact with immune cells and possible enteric neurons [48]. The ease and safety of a potential diet-based intervention is offset by the widespread and context-dependent effects of SCFA, currently limiting their development as treatments for human disease.

Other Microbial Products

Structural components and metabolites of microbes are also able to stimulate immune responses and influence disease-related pathways. One such metabolite, trimethylamine N-oxide (TMAO), is generated by metabolism and oxidation of dietary amines by microbes in the gut and further processed by enzymatic reactions in the liver [1,49]. Several studies have demonstrated an increased risk for thrombotic events (e.g., stroke and myocardial infarction) correlated with higher circulating TMAO levels [1,50]. Mechanistically, TMAO can enhance platelet activation and clot formation, among other features [51]. Indeed, in a mouse model of ischemic stroke, animals with TMAO-high microbiomes were at greater risk of poor outcomes than those with TMAO-low microbiomes [**4]. This effect was mediated by the activity of the bacterial enzyme cutC [**4]. These findings suggest that neutralizing microbial production of TMAO or limiting colonization of TMAO producers may be a therapeutic avenue for stroke or other thrombotic events.

Lipopolysaccharide (LPS) is a well-known bacteria-derived immune activator, and systemic levels can influence disease processes. Genes involved in LPS biosynthesis are increased in the fecal metagenome of PD patients [35] and expression of its receptor toll-like receptor 4 (TLR4) is increased in PD colon samples [37]. TLR4 knock-out mice have less intestinal inflammation, decreased microglial activation, less neurodegeneration in the substantia nigra par compacta (SNpc), and less severe motor dysfunction upon administration of the neurotoxin rotenone [37]. These findings directly connect gut-derived products to neurodegenerative disease processes in mice through activation of the immune system. LPS and other bacterial carbohydrates may play an opposite role in EAE, as increased LPS levels in the lung microbiome can shift the inflammatory state of microglia and decrease EAE severity [*52]. Additionally, polysaccharide A (PSA) from the capsule of *Bacteroides fragilis* has been shown to reduce the severity of EAE after oral treatment by enhancing Treg induction and suppressing T helper 17 cell (Th17) response [31]. These findings suggest

the broader concept that disease context or nature of the bacterial molecule can determine whether microbial components are positive or negative regulators of disease.

The microbiome can also produce molecules that mimic host proteins. Molecular mimicry occurs when foreign (in this case, microbial) antigens share enough sequence similarity to self-antigens to trigger adaptive immune activation. A study by Miyauchi and colleagues identified a peptide produced by the *Lactobaccilus reuteri* gene *UvrA* that can stimulate MOG-specific T cells in EAE [**9]. The presence of two ampicillin-sensitive bacteria, *L. reuteri* and *Allobaculum sp.*, is sufficient to induce IL-17A-producing CD4+ T cells in the intestine and worsen EAE, whereas bacterial knockout of *UvrA* reduces T cell proliferation [**9]. Intestinal T cells are thought to migrate to the CNS and contribute to neuroinflammation [**2,*53,**54], providing a link between bacterial products, auto-reactive T cell activation, and CNS disease. Alternative hypotheses describe T cells with dual T cell receptors responsive to both self and bacterial antigens, as demonstrated by segmented filamentous bacteria induction of pathogenic Th17 cells [55].

Other bacterial products may also induce pathology. Curli are functional bacterial amyloid proteins that can induce aggregation of αSyn in a prion-like manner. Production of curli increases gut and brain synuclein pathology and enhances neuroinflammation in a mouse model of PD [56]. It has been shown that curli can interact with αSyn *in vitro* and promote its aggregation in biochemical reactions [12,57,58], suggesting a direct effect on neuroinflammation mediated by αSyn aggregates that can travel from the gut to the brain. This view has been supported by a recent study in nematodes that shows bacterial curli can enhance aggregation of αSyn and other mammalian amyloids such as Aβ and huntingtin [59]. It appears that several different classes of microbial molecules produced in the gut can directly or indirectly lead to or modulate neuroinflammation in preclinical models. Caution must be taken to not extrapolate these findings to humans without further research, though intriguing associations appear to be emerging.

Peripheral Immunity

Immune cells rely on microbial signals for proper development, particularly the development and differentiation of pathogenic and regulatory T cells, key adaptive immune subsets implicated in CNS disease [60]. Recent findings have described direct trafficking of immune cells between the gut and CNS [**2,*53,**54]. Acute (e.g., infection) and chronic (e.g., autoimmune disease, diabetes, atherosclerosis) inflammation play roles in disease etiology and progression, suggesting an intimate connection between the microbiome and the immune system in the progression of CNS inflammation. Here we discuss how peripheral immune activation may impact neuroinflammation.

Role of acute and chronic inflammatory conditions

Acute infection can affect the risk and development of CNS disease. Stroke is associated with acute immune responses to infection and individuals with signatures of chronic inflammation display elevated risk [61]. A recent study determined that the risk for MS is greatly increased by a previous infection with peripheral Epstein-Barr virus (EBV), and

antibodies that cross-react with an EBV transcription factor and CNS proteins have recently been identified in patient cerebrospinal fluid (CSF) [62,63], supporting the role of viral infections in the development of neuroinflammatory disease. Alzheimer's disease has also recently been linked to EBV, as Gate et al. (2020) identified clonally expanded CD8+ T cells in the CSF of AD patients specific to EBV antigens [**64]. Although a direct link between viral infections and PD has not been established, increased risk has been associated with viral infections and viral pandemics [65,66]. It will be interesting to see how the current coronavirus disease 2019 (COVID-19) pandemic affects rates of neuroinflammatory disease in the future, as future increases in diagnoses of parkinsonian disorders similar to that which occurred after the 1918 influenza pandemic have been hypothesized [66,67].

A chronic inflammatory state, whether induced by comorbid disease or altered baseline inflammatory tone, can also influence CNS disease, and the microbiome can regulate systemic inflammatory profiles. Circulating factors like C-reactive protein (CRP), IL-6, TNF and IL-1β are signatures of systemic inflammation and are also elevated in neuroinflammatory disease [68]. In mice, DSS colitis in an αSyn-overexpressing model worsens motor symptoms [69]. In humans, chronic intestinal inflammation appears to be associated with PD [16]. Inflammatory bowel disease (IBD), such as Crohn's disease or ulcerative colitis (UC), increases the risk of PD, and IBD patients that receive systemic anti-TNFα therapy have a decreased risk for neurodegeneration [70]. Recurring gut infections also increase the risk of developing dementia [71], indicating that gut inflammation may trigger neurodegenerative processes, both in AD and PD. Mood disorders have also recently been linked to inflammation and the gut. IBD patients are more likely to develop depression or anxiety, and IBD patients with depression are at a higher risk for flare ups and hospitalization [72]. Patients with UC and anxiety/depression have a less diverse gut microbiome [24,*73] and FMT from IBD patients with depression to mice enhances features of colitis, increases circulating inflammatory cytokines, increases hippocampal IL-1β and IBA1, and correlates with the appearance of depressive behaviors [*73]. These data indicate a potential contribution by the microbiome and inflammation to depression.

Immune cell activation and trafficking

Immune cells can traffic from the periphery to the brain and meninges in health and disease, and studies suggest that the gut may act as a reservoir for CNS-trafficking immune cells in neuroinflammation [**2,*53,**54,**74]. Seminal work demonstrated that, in an experimental stroke model, the recruitment of IL-17A-producing γδ T cells from the small intestine to the meninges is regulated by the microbiome and positively correlates with the severity of disease [**2]. In other neuroinflammatory conditions, Schnell and colleagues demonstrated that a pathogenic clonotype of Th17 cells in EAE can derive from a pool of homeostatic cells in the small intestine and traffic to the CNS [**54]. Mice treated with antibiotics have fewer Th17 cells in the spleen and intestines, and increased resistance to EAE induction, linking microbial regulation of Th17 cell development and/or function in peripheral locations to disease outcomes [**54]. Other work has highlighted the importance of the cytokine IL-17A in the recruitment of inflammatory neutrophils and monocytes in early stages of EAE [75]. These findings suggest that the recruitment of microbially-regulated IL-17A-producing cells from the gut may be a key event in either the

initiation or development of several neuroinflammatory diseases, providing a clear paradigm for gut-brain interactions that warrant further investigation.

Vagus nerve

The gut microbiome can also communicate with the brain through direct neuronal signaling pathways. The vagus nerve connects the enteric and the central nervous systems, among other organs in the periphery, and this direct connection may transmit a variety of signals from the gut to the brain [76]. It was reported in humans that vagotomy, the surgical cutting of one or more branches of the vagus nerve, reduces the risk for developing PD later in life [77]. Additionally, appendectomy in early adulthood decreases risk of later developing PD [78]. The mechanism proposed was prevention of the spread of αSyn from the appendix to the brain via the vagus, which requires further validation [78]. Although these studies have not been directly connected to microbes, studies have shown that multiple genera of microbes can produce neurotransmitters such as γ-aminobutyric acid (GABA) [79], indicating neuromodulatory potential by the human microbiome.

Research in mice has made progress in identifying mechanisms of vagal contributions to disease, particularly in models of PD, AD, and depression. In the inducible 6-hydroxydopamine (6-OHDA) lesion model of PD, vagotomy blocks disease-related increases of IL-1β and markers of oxidative stress in the SNpc [80]. Alternatively, acute and chronic intestinal inflammation via DSS administration leads to increases in nigral IL-1β and loss of TH+ neurons, which can be prevented by vagotomy [80]. Injection of αSyn fibrils into the aged mouse duodenum, which is heavily innervated by the vagus nerve, increases αSyn pathology in the brain, slows gut motility, and increases duodenal cytokine release [**81,82]. Vagotomy can prevent αSyn propagation to brain and the development of motor symptoms [82]. Injecting either recombinant Aβ and tau or extracts from AD patient brains into the colon in the 3xTg mouse model of AD led to increased pathology in the vagus and brain, which was prevented with vagotomy [83]. It has also been reported that non-invasive stimulation of the vagus nerve in aged APP/PS1 mice can decrease microglial reactivity in the cortex [84]. In a corticosterone-based model of anxiety and depression in mice, feeding *Lactobacillus rhamnosus*, a species that produces high amounts of GABA, can increase brain GABA levels and reduced depressive behaviors [21]. Vagotomy prevented these effects [21], providing striking evidence for microbial regulation of the brain via the vagus nerve. Together, these studies implicate the vagus nerve as a bidirectional highway for the brain and gut to affect immune responses related to neuroinflammation and neurodegeneration, in addition to the many homeostatic functions of the vagus nerve.

Conclusions

The studies highlighted in this Review provide evidence that gut-immune-brain communications appear to regulate CNS disease in animal models and correlate with outcomes in humans. Acute and chronic inflammation in the GI tract and/or periphery can change the risk of CNS inflammatory disease, affecting the baseline state of immune cells or stimulating immune cell trafficking from the gut to the CNS [**2,*53,**54]. Peripheral immune cell infiltration into the CNS can have direct effects on brain pathology and

behavior [14,85,86]. Finally, the nature of microbial molecules, their biodistribution, and mechanisms-of-action in modulating neuroinflammation have received increasing attention in recent years [25,26].

How, and in what contexts, metabolites and bacterial components directly affect neurons is less well explored compared to the role of infiltrating or brain-resident immune cells. Furthermore, the ways in which acute and chronic inflammation can influence CNS disease requires further investigation, but could act through changes in the baseline state of immune cells or stimulation of immune trafficking from the gut to the CNS. With a growing knowledge base and new tools being developed or repurposed for gut-brain studies, research in coming years will clarify the role of the microbiome in CNS inflammation and may provide new insights into the treatment of diseases related to neuroinflammation.

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Highlights

- Microbe-derived molecules influence disease outcomes through diverse mechanisms
- Short chain fatty acid (SCFA) production in the gut can alter microglial reactivity
- Intestinal microbes regulate immune cell activation and trafficking from the gut to the brain
- Microbe regulation of gut-brain signaling via the vagus nerve remains understudied
- To date, most mechanistic and interventional insights come from animal models

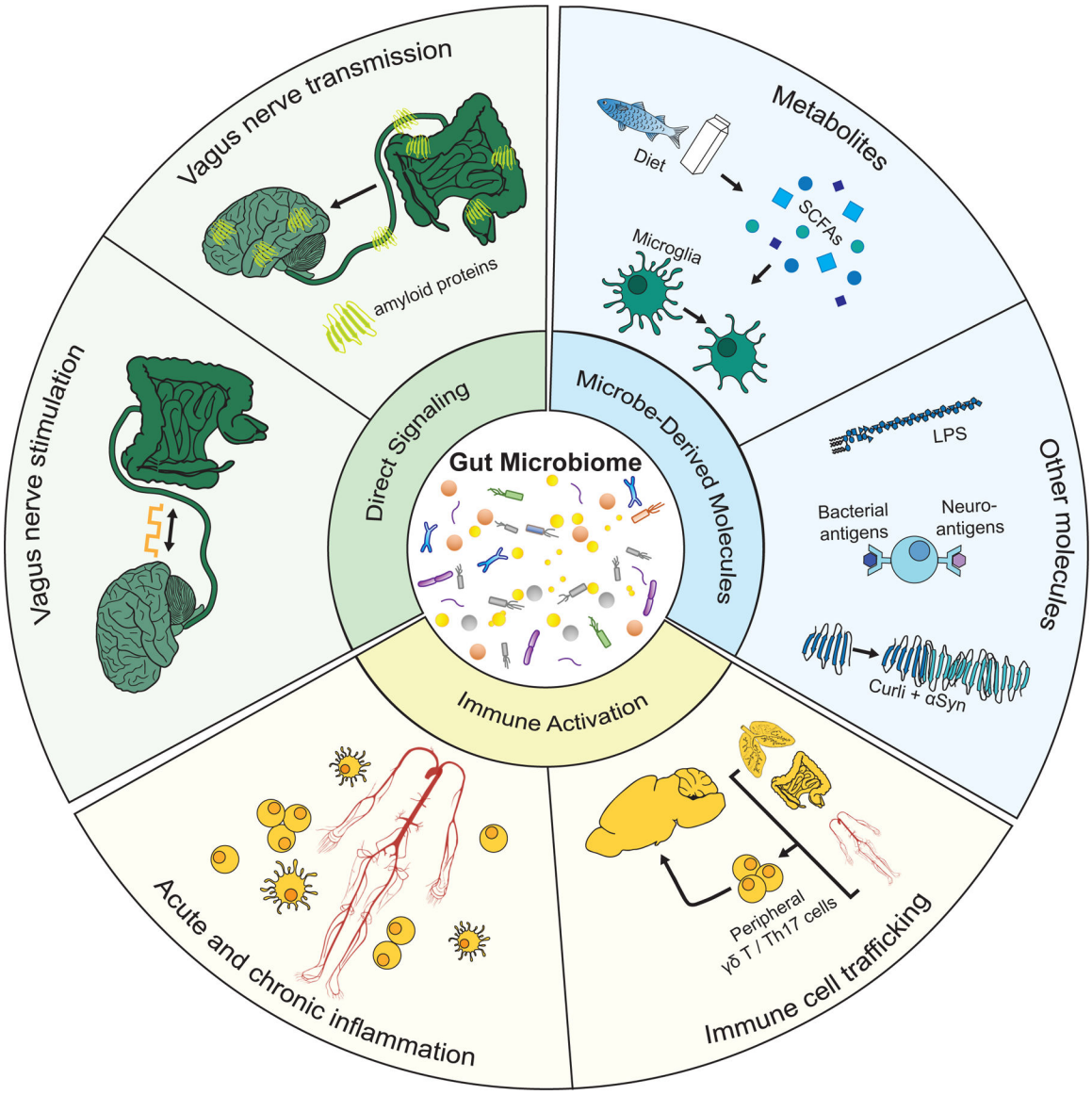

Figure 1. The gut microbiome influences neuroinflammatory disease through diverse pathways.

Microbes can affect distal systems, such as the central nervous system, through many routes, including microbe-derived molecules, immune activation, and direct signaling. Metabolites and other microbial-derived molecules alter microglial inflammatory tone, can act as molecular mimics of neural antigens, and can directly interact with host proteins to exacerbate neuropathology. Intestinal and systemic inflammation can affect risk for neuroinflammatory disease, and signals from microbes stimulate peripheral γδ T and Th17 cells to traffic to the brain. Direct connections exist between the gut and the brain via the vagus nerve, and stimulating or severing this connection impacts neuroinflammation, neurological symptoms, and brain pathology. The gut-immune-brain communication may be important to consider when developing therapeutics for certain human CNS disorders.