



Microbiota-immune interactions: from gut to brain

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ABSTRACT

The vast diversity of bacteria that inhabit the gastrointestinal tract strongly influence host physiology, not only nutrient metabolism but also immune system development and function. The complexity of the microbiota is matched by the complexity of the host immune system, where they have coevolved to maintain homeostasis ensuring the mutualistic host-microbial relationship. Numerous studies in recent years investigating the gut-brain axis have demonstrated an important role for the gut microbiota in modulating brain development and function, with the immune system serving as an important coordinator of these interactions. Gut bacteria can modulate not only gut-resident immune cells but also brain-resident immune cells. Activation of the immune system in the gut and in the brain are implicated in responses to neuroinflammation, brain injury, as well as changes in neurogenesis and plasticity. Impairments in this bidirectional communication are implicated in the etiopathogenesis of psychiatric and neurodevelopmental diseases and disorders, including autism spectrum disorders, or comorbidities associated with Gastrointestinal diseases, including inflammatory bowel diseases, where dysbiosis is commonly seen. Consequently, probiotics, or beneficial microbes, are being recognized as promising therapeutic targets to modulate behavior and brain development by modulating the gut microbiota. Here we review the role of microbiota-immune interactions in the gut and the brain during homeostasis and disease and their impact on gut-brain communication, brain function, and behavior as well as the use of probiotics in central nervous system alterations.

Statement of novelty: The microbiota-gut-brain axis is increasingly recognized as an important physiological pathway for maintaining health and impacting the brain and central nervous system. Increasing evidence suggests that the immune system is crucial for gut-brain signaling. In this review, we highlight the critical studies in the literature that identify the key immune pathways involved.

Introduction

The intestine is the largest surface of the body and is constantly exposed to dietary and bacterial antigens as well as potentially noxious substances and infectious agents, which threaten the balance between health and disease (Salvo Romero et al. 2015). In mammals, the gastrointestinal (GI) tract harbors a complex microbial community, known as the intestinal microbiota, composed of thousands of different species of bacteria, viruses, fungi, archaea, and protists (Parfrey et al. 2011; Hillman et al. 2017). This complex community plays a critical role in the digestive process, protection

against colonization with pathogens (Sonnenburg et al. 2004), as well as influencing the maturation and function of the intestinal immune system (Caricilli et al. 2014). In addition, there is increasing evidence that these microbial communities can regulate brain development, mood, and cognitive function through the bidirectional signaling between the gut and the brain (Deverman and Patterson 2009; Lakhan and Kirchgessner 2010). The complexity of the microbiota is matched by the complexity of the host immune system to ensure the maintenance of this balance and for preventing access of organisms to the host inner milieu. Chronic inflammation not only changes the microbiota

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composition, but it can also trigger significant and long-lasting behavioral changes, such as the development of cognitive impairment and depression, in a bottom-up manner (Lakhan and Kirchgessner 2010). Taken together, this suggests a critical role for the gut microbiota in regulating brain development and behavior, with the immune system emerging as an important coordinator of these interactions.

Despite the recent discovery of meningeal lymphatics reshaping our understanding of immunity within the central nervous system (CNS) (Louveau et al. 2015), the brain parenchyma is still considered “immune privileged” compared to peripheral tissues. The brain contains numerous resident immune cells that play a role in the defense against infection and injury, critically supporting neurons, and in maintaining and remodeling circuit connectivity, and regulating plasticity (Tremblay et al. 2011). Pathways that have been traditionally recognized for their functions in maintaining peripheral immunity are now known to be important in regulating neurodevelopment, including cytokines present in the developing brain, which can regulate neuronal differentiation, axonal growing, and synaptic plasticity (Deverman and Patterson 2009). In addition, expression of neuroendocrine receptors and factors on immune cells, such as neuropeptide receptors [i.e., calcitonin gene-related peptide (CGRP), substance (SP), adrenomedullin, neurokinins A and B, vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), and gastrin releasing peptide (GRP), etc.], glucocorticoids, or adrenoceptors can lead to the release of immune-derived mediators and are increasingly recognized for their role in the immune system (Hadden et al. 1970; Pert et al. 1985; Procaccini et al. 2014).

Microbial colonization of the GI tract has a significant impact on neurophysiology and behavior (Sampson and Mazmanian 2015). Given the immunomodulatory properties of the gut microbiota, peripheral immune cell pathways have been implicated as important mechanisms mediating microbial modulation of brain function and behavior (Rook et al. 2014; Rea et al. 2016), including neurodevelopmental disorders, such as autism spectrum disorder (ASD), and GI disease, such as inflammatory bowel disease (IBD), where psychosocial deficits commonly occur in patients. In this review, we discuss the roles for the gut microbiota as an integral mediator of neuroimmune interactions, examining how microbiota interacts between gut and brain-resident immune cells,

and how they can impact the etiopathogenesis or manifestation of symptoms relevant to neurobehavioral and neurodegenerative disorders. Finally, we summarize effective probiotic interventions on the function of the CNS and discuss how probiotics can modulate this interaction.

The gut-brain axis

The gut-brain axis plays an important role not only in the proper maintenance of the GI tract but also brain function and behavior. This bidirectional signaling pathway is important in maintaining homeostasis and is regulated at different levels by the CNS, the enteric nervous system (ENS), the hypothalamic pituitary adrenal (HPA) axis, and immune system through complex communication by endocrine, immune, and neuronal factors (Figure 1) (Romijn et al. 2008; Weltens et al. 2018). CNS-mediated regulation of intestinal function and immune responses occurs through systemic, regional, and local pathways. The autonomic nervous system (ANS; sympathetic and parasympathetic branches; drives both afferent and efferent signals), the peripheral nervous system (through the release of neuropeptides), and the HPA axis (through the systemic release of glucocorticoids) are all involved. Moreover, neurally-mediated responses triggered by the activation of sensory afferents in response to changes in luminal content or pressure, muscle distention, and inflammation can be transmitted to target cells through reflexes of local enteric nerves, independent of the CNS (Carabotti et al. 2015).

In the GI tract, in addition to the well-characterized intestinal epithelial cells (Sharkey and Mawe 2002) and resident immune cells (Dantzer 2018), the microbiota also critically contributes to brain-gut communication. This microbiota-gut-brain axis ensures not only the proper maintenance of GI function, but also maintains cognition and emotional behaviors (Martin and Mayer 2017). Moreover, disturbances of this system have been implicated in a wide range of disorders, including functional and inflammatory GI disorders such as irritable bowel syndrome (IBS) and IBD (Rhee et al. 2009; Mayer et al. 2014) as well as neurodevelopmental disorders, such as ASD (van De Sande et al. 2014).

Physical and biochemical barriers in the GI tract anatomically prevent the microbiota from entering the body and the underlying tissues, restricting it to the

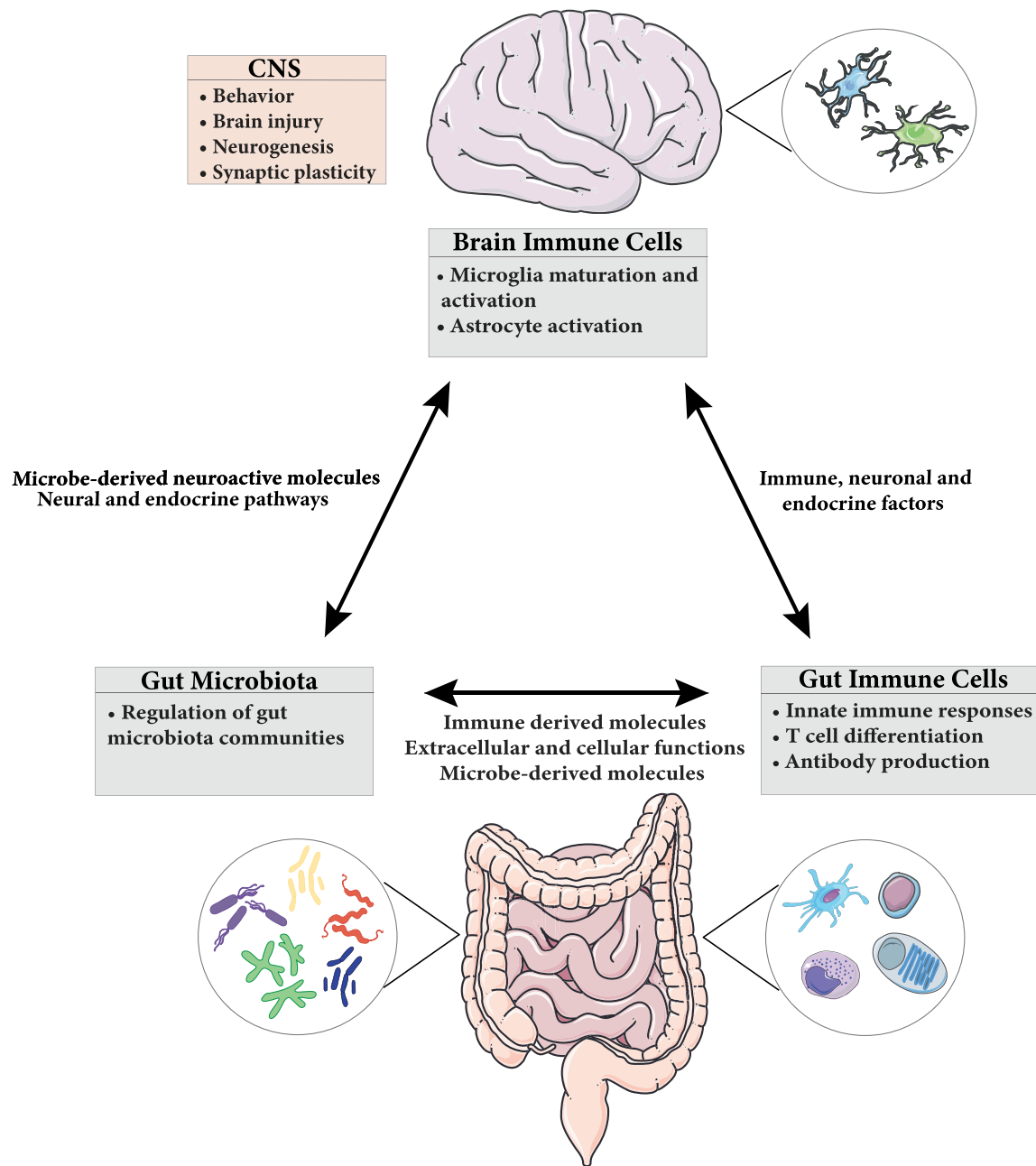


Figure 1: Pathways of immune signaling regulating the microbiota-gut-brain axis. The gut microbiota influences the maturation and function of both innate and adaptive immune responses, which can subsequently alter the brain and behavior. The mucosal immune response contributes to the establishment of the gut microbiota by mediating host-microbe symbiosis and influencing antibody production and T cell populations. These host-microbe interactions can alter immunity in the brain, impacting the maturation and activation of both microglia and astrocytes. Altogether, these communication pathways have important consequences in the central nervous system (CNS) impacting neurogenesis and synaptic plasticity leading to changes in behavior.

lumen. In case of a breach in barriers, immune cells in the GI tract are present to contain and restrict the passage of microbial components, while limiting inappropriate immune activation and overt inflammation (Hooper et al. 2012), which can impact the microbiota-gut-brain axis.

Microbiota-immune interactions in the gut

Impact of microbiota on immune system

The immune system is composed of a complex network of innate and adaptive cells and components

endowed with an extraordinary capacity to respond to highly diverse challenges. Collectively, this cellular network acts as a regulator of host homeostasis to sustain and restore tissue function in the context of microbial and environmental encounters in the body. This homeostasis is crucial, with commensal microorganisms being required for the proper maturation of the immune system (Chung et al. 2012). This fundamental role of the microbiota has been derived from studies on germ-free (GF) mice or antibiotic-treated animals, supporting the concept that the development of the immune system coincides with the acquisition of a complex microbiota (Sharkey and Mawe 2002). GF mice exhibit immature gut-associated lymphoid tissues (GALT), decreased number of intestinal lymphocytes, decreased Immunoglobulin (Ig) A production and impaired antimicrobial peptides compared to colonized controls (Bauer et al. 1963; Hamada et al. 2002; Mazmanian et al. 2005; Smith et al. 2007). Many of these impairments can be restored by colonization of the microbiota, however some of these components can only be restored if colonization is performed early in development (Hansen et al. 2012).

The initial exposure of the immune system to commensal microbes occurs during birth via passage through the birth canal, and subsequently by maternal milk. Controversial evidence has suggested the potential for *in utero* exposure to microbes, however, this is likely limited to microbial metabolites or bacterial DNA, given the absence of viable microbes and the likelihood of contamination of placental samples during birth (Perez-Muñoz et al. 2017; Martinez et al. 2018; Theis et al. 2019). These early interactions are important to set the tone of the mucosal and systemic immune system into adulthood (Hooper et al. 2012). This capacity to establish tolerance of the immune system at an early age could be explained by the immaturity of the neonatal immune system, and the tolerogenic environment during development. For example, early in life the immune system has blunted inflammatory cytokine production, skewing T and B cell development to a more regulatory phenotype (Siegrist 2001; PrabhuDas et al. 2011). Toll-like receptors (TLRs), innate immune pattern recognition receptors, are involved in this differential recognition, being responsible for the normal development of the intestinal mucosal immune system which recognize microbial pathogens relevant to infants, such as group B *Streptococcus*, *Listeria monocytogenes*, and Respiratory Syncytial Virus (RSV)

(Levy 2007). TLR-mediated cytokine production by mononuclear cells *in vitro* demonstrated less interferon (IFN)- α , IFN- γ , and interleukin (IL)-12 subunit p70 (IL-12-p70) expression from cells obtained from infants versus cells obtained from adults, which increases between birth and 1–2 years of age (PrabhuDas et al. 2011). Furthermore, TLR activation by antigens belonging to the normal intestinal microbiota signal the inhibition of inflammatory reactions and maintain epithelial barrier and protection from direct epithelial injury, suggesting an essential role of maintaining intestinal homeostasis (Rakoff-Nahoum et al. 2004). Complementarily, nucleotide-oligomerization-domain (Nod)-like receptors (NLRs) recognize various microbial specific molecules and trigger the assembly of inflammasomes, which can act as sensors of microbial-associated molecular patterns (MAMPs), with NLR deficiency associated with an altered immune response (Elinav et al. 2011) and impairments in behavior (Pusceddu et al. 2019). Microbiota colonization in the GI tract during early life affects the development of T cell populations into different types of T helper cells (Th) including: Th1, Th2, and Th17 or into regulatory T cells (Tregs) (Mazmanian et al. 2005; Gaboriau-Routhiau et al. 2009; Atarashi et al. 2011). For example, GF mice show reduced Treg cell induction, absence of Th17 cells, and an imbalance of Th1/Th2 ratio exhibiting a bias toward Th2 responses (Ivanov et al. 2009; Belkaid and Hand 2014). Colonization with *Bacteroides fragilis* recovered the development of the Th1-associated immune response through the bacterial product polysaccharide A-dependent pathway (Mazmanian et al. 2005). Moreover, *B. fragilis* also induced Treg accumulation through TLR-2 and inhibition of Th17 development (Round et al. 2011).

Antibody responses, while highly influenced by the microbiota, can still occur in GF animals (Zeng et al. 2018). Production of IgA by intestinal plasma cells is rapidly induced following microbial colonization and can occur through both T-dependent and T-independent pathways (Benckert et al. 2011; Bunker et al. 2015), which generates polyreactive IgA with low affinity to commensal bacteria, providing beneficial effects on surface-coated microbes. IgA is transcytosed and secreted through the epithelial layer into the lumen, and it has been shown that IgA coating can promote intestinal colonization of some commensals (Donaldson et al. 2018). Microbiota can modulate antibody production by generation of ATP through a mechanism that includes P2X7-mediated signaling of T follicular helper

cells, which also limits the generation of protective IgA against enteropathogens (Proietti et al. 2014, 2019).

Impact of innate immune system on microbiota

In addition to the important role for rapid elimination of pathogens, innate immune responses also contribute to the establishment of the symbiotic relationship of the host with the microbiota. The intestinal innate immune system can also help define the overall niche of gut microbial communities by regulating secretion of defense mechanisms including mucus, antimicrobial peptides, and antibodies along the intestinal epithelial barrier (Kinnebrew and Pamer 2012).

The relationship between host immunity and the microbiota has been extensively explored using loss-of-function animal models (i.e., knockout [KO] mice). By using a simple model organism with an extremely simple gut commensal microbiota, Ryu et al. (2008) demonstrated that the immune status of the host can influence the composition of the microbiota, which can consequently dramatically impact the host. Using *Drosophila melanogaster*, defective regulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) signaling in the intestinal epithelium caused the overgrowth of a pathogenic commensal microbial community, leading to the death of the host (Ryu et al. 2008). However, in mammals, the enormous diversity of the resident microbiota community and the genetic complexity of the host immune system make it difficult to clearly establish the molecular links that would identify the unique interactions between immune genotype and commensal microbiota structure.

Several studies in mice also highlight the importance of innate immune responses for maintaining the mutualism for host-microbe interactions. In MyD88-deficient mice, defective in TLR signaling, intestinal dysbiosis was identified, predisposing mice to intestinal inflammation (Araki et al. 2005). Moreover, similar effects were shown in TLR-5 and NOD1/NOD2-double deficient mice, where alterations in microbiota composition were identified compared to WT mice (Kobayashi et al. 2005; Bouskra et al. 2008; Vijay-Kumar et al. 2010). Similarly, MyD88-mediated signaling in non-hematopoietic cells is required for clearance of the Gram positive intracellular pathogen *L. monocytogenes* from the GI tract by the antimicrobial C-type lectin Regenerating islet-derived protein 3 gamma (RegIIIγ)

(Brandl et al. 2007). Humans and mice deficient in TLR/MyD88 signaling pathways also have diminished antimicrobial protein and mucus production (Vaishnava et al. 2008; Slack et al. 2009), however, translocation of bacteria into the blood stream is minimized by the compensation of high antibody titers. These antibody responses represent an important interaction between the 2 systems to regulate microbial-host responses in response to innate immune deficiency. Despite these initial studies, the lack of adequate littermate controls to standardize the microbiota of WT and KO groups largely prevented the ability to identify clear mechanistic insight into genetic regulation of the microbiota (Robertson et al. 2018). In this regard, other studies showed a little influence on the microbiota composition structure at homeostasis in KO mice defective in innate immune receptors (Robertson et al. 2018). For example, in *Nod2*^{-/-} animals, where an impaired antibacterial response may influence the microbiota, genotype-dependent influences on the microbiota or differences in α-defensin secretions compared to wild-type (WT) controls were not observed (Robertson et al. 2013; Shanahan et al. 2014; Goethel et al. 2019). In addition, inflammasome-deficient mice, including *Nlrp6*-deficient mice and ASC-deficient mice which were initially thought to influence microbiota composition, showed no impact when the appropriate littermate controls were employed, highlighting the necessity of adequate littermate controls (Mamantopoulos et al. 2017). In this study, gut microbiota phylogenetic analyses were performed on ex-GF and littermate-controlled mice that were all allowed to shape their gut microbiota under physiological conditions after birth, minimizing non-genetic confounders (Mamantopoulos et al. 2017).

Despite the lack of an effect of innate immune impairment on the microbiota at homeostasis in *Nod2*^{-/-} mice (Goethel et al. 2019), induction of inflammation and dysbiosis using antibiotics impaired microbial resilience in these mice. Similarly, neonatal antibiotic administration in *Nod2*^{-/-} mice resulted in increased severity of colitis after administration of dextran sodium sulfate (DSS) to induce colitis (Goethel et al. 2019). During this acute inflammation in mice, the gut microbiota community shifts to resemble IBD-associated dysbiosis (Robertson et al. 2013), specifically with depletion of the beneficial short chain fatty acid (SCFA) butyrate-producing members of the microbiota reported (Rivera-Chavez et al. 2016). Taken together gene-deficiency in innate immune receptors appears to have little influence

on microbiota structure in homeostasis, suggesting a redundancy in these gene functions and compensation of the adaptive system with respect to colonization of the microbiota. Conversely, their ability to influence bacterial structure occurs after the establishment of inflammation following an insult has been clearly established (Schwab et al. 2014).

Impact of adaptative immune system on the microbiota

Efficient immune responses in the GI tract are generated in highly organized structures, namely gut-associated lymphoid tissues (GALT). These secondary immune structures are only found in birds and mammals, not only for protection against infectious insults but also to allow and maintain complex bacterial communities in the gut. In addition, the microbiota of mammals appears to display evidence of coevolution, independently of the geographical location or diet (Ley et al. 2008a, 2008b). In mice, defects in the acquired immune system appear to have considerable effects on the microbiota. For example, Rag1^{-/-} mice, which lack both T and B cells, have significantly decreased bacterial diversity than their littermate controls (Kwon et al. 2015). Similarly, mice lacking T-bet (T-box transcription factor family that regulates the development of the immune system) have severe intestinal inflammation and the promotion of an outgrowth of colitogenic bacteria (Garrett et al. 2007).

B cells are key players in mucosal immunity, with impairments in their function significantly impacting the intestinal microbiota. B-cell deficient mice have higher lipopolysaccharide (LPS) concentrations compared to WT control mice, coupled with colonization of fewer *Clostridiaceae* and increased *Paracoccus* and *Lactococcus* genus, suggesting that antibody deficiency might change the species distribution within the microbial community (Shulzhenko et al. 2011). In the gut, most B cells differentiate into plasma cells, specifically IgA producing cells. The absence of IgA, or the impaired IgA selection in germinal centers due to deregulated T cell control, results in massive activation of the whole body immune system (Kawamoto et al. 2012; Nakajima et al. 2018). Interestingly, IgA promotes homeostatic bacterial composition by altering the expression of polysaccharide utilization loci (PUL), including a functionally uncharacterized molecular family provisionally named Mucus-Associated Functional Factor (MAFF), found in mice and humans, detected in mucus-resident bacteria, with expression requiring the presence of a complex microbiota (Nakajima et al. 2018).

T cells are also important in maintaining mucosal and systemic immunity. Tregs contribute to diversification of the gut microbiota, particularly by promoting species belonging to the Firmicutes phylum, by suppressing inflammation and regulation of IgA selection in Peyer's patches (Kawamoto et al. 2014). Other adaptive immune cells such as IL-17 and IL-22-producing Th17 cells, can directly shape the microbial composition by promoting colonization of certain microbes and neutralization of invasive pathogens (Dubin and Kolls 2008; Bunker and Bendelac 2018). IL-22 deficiency or disruption of IL-17R signaling can severely affect the balance of gut bacterial communities, resulting in dysbiosis and increased susceptibility to intestinal inflammation (Ni et al. 2017).

Thus, the adaptive immune system, through cellular and molecular components that are required for immune tolerance and selection of antibody repertoire, help mediate host-microbial symbiosis, controlling the richness and balance of bacterial structures. Taken together, the immune system clearly exerts a central role in shaping the composition of the microbiota, while conversely, resident microbes provide signals that promote normal immune system development and influence immune responses. Disruption of these complex and dynamic interactions can have profound consequences for host health.

Microbiota-immune interactions in the brain

The maturation and development of the CNS is regulated by both intrinsic and extrinsic factors. Studies from GF mice, or those treated with broad-spectrum antibiotics, show that specific microbiota can impact CNS physiology and neurochemistry (Smith 2015), as they exhibit both neurological and cognitive deficits (Gareau et al. 2011), and neurotransmitter alterations compared to colonized controls (Strandwitz 2018). This communication between gut microbiota and the CNS is thought to be mediated by a combination of immune, enteric, and neural pathways providing a physical and chemical connection through the functional lymphatic vasculature and the blood-brain barrier (BBB). This suggests an important role for immune cells in CNS homeostasis as well as during microbial and environmental challenges (Louveau et al. 2015; Yoo and Mazmanian 2017).

Immune regulation within the CNS is mediated by microglia, astrocytes, and oligodendrocytes, given that the BBB limits access of circulating T and B cells to the underlying parenchyma. It has been demonstrated that the gut microbiota can influence and modulate microglial maturation and function (Erny et al. 2015), highlighting its critical role within the CNS (Braniste et al. 2014).

Microglia

Microglia are the tissue resident macrophages of the brain responsible for maintaining homeostasis, regulating synaptic transmission, synaptic pruning, and neuronal circuit formation (Schafer and Stevens 2015; Hong et al. 2016). Microglia work to protect the brain against various pathological conditions through immune activation, phagocytosis, and cytokine production (Nayak et al. 2014; Prinz et al. 2017). In GF mice, increased numbers of immature microglia across multiple brain areas such as the hippocampus, cerebellum, and cortex, are found compared to specific pathogen free (SPF)-colonized controls (Bercik et al. 2011a). These microglia show a more branching phenotype and downregulation in expression of genes that are associated with maturation to an active phenotype, highlighting their immaturity. Similarly, antibiotic treatment in colonized WT mice is associated with increased immature microglia, though total microglia numbers remain unchanged, with a normal phenotype restored following reintroduction of a complex microbiota (Erny et al. 2015). This suggests a role for the microbiota in microglia development that depends on developmental timing and (or) duration of microbial colonization. While the mechanisms of gut microbes influence on brain microglia remain unclear, they appear to be regulated by a great diversity and complexity of bacterial load more than by specific bacterial taxa. For example, GF mice colonized with a minimal community of bacterial species (*Bacteroides distasonis*, *Lactobacillus salivarius* and a member of Clostridium cluster XIV) maintained abnormalities in microglia (Schafer and Stevens 2015). However, the oral application of a mixture of the 3 major SCFAs acetate, propionate, and butyrate, was sufficient to drive maturation of microglia. It is known that SCFAs are able to cross the BBB and may therefore affect microglia directly (Huuskonen et al. 2004; Frost et al. 2014). While the mechanism of action is not well understood, SCFAs can act as signaling molecules by binding to G protein-coupled receptors, Gpr41 and Gpr43, which are highly expressed on intestinal epithelial and immune cells

(Brown et al. 2003). Their activation can provoke a pro-inflammatory immune response, increase GI permeability, and increase absorption of neuro-active metabolites (Milo et al. 2002; Kim et al. 2013). SCFAs can also directly activate the sympathetic nervous system through Gpr41 that are found on sympathetic ganglionic neurons (Kimura et al. 2011), which can modulate catecholaminergic systems by affecting tyrosine hydroxylase gene transcription (DeCastro et al. 2005).

Immature microglia from GF mice are also impaired in their ability to respond to a stimulus. Microglia from GF mice display functionally impaired responses following challenge with LPS or lymphocytic choriomeningitis virus (LCMV), exhibiting altered morphology and attenuation of several genes relevant to interferon responses, pro-inflammatory cytokines, and effector processes. This suggests that gut immune-stimulatory products can influence microglia function to prevent CNS damage following viral or bacterial infection (Matcovitch-Natan et al. 2016).

Astrocytes

Astrocytes are the most abundant glial cell population in the brain and, similarly to microglia, have multiple functions in CNS integrity and homeostasis, including BBB integrity, ion gradient balance, neurotransmitter turnover and nutrient transport. They can also integrate information from adjacent glial, neuronal, vascular and immune cells to regulate neural excitability and synapse formation (Jensen et al. 2013; Khakh and Sofroniew 2015). Although they are not classically considered to be a CNS-resident immune cell, they (i) express MAMPs and major histocompatibility complex (MHC) class II antigen presenting receptor, (ii) are able to detect danger signals and respond via secretion of cytokines and chemokines, and (iii) activate adaptive immune defenses (Dong and Benveniste 2001; Farina et al. 2007).

The gut microbiota modulates astrocyte activity via microbial metabolites that activate aryl hydrocarbon receptors (AHR) (Rothhammer et al. 2016), a ligand-activated transcription factor that integrates environmental, dietary, microbial and metabolic cues to control complex transcriptional programs (Rothhammer and Quintana 2019). Gut microbiota-derived metabolites can bind to AHR and induce anti-inflammatory activity by restricting the recruitment of neurotoxic immune cells though type 1 IFN signaling. Studies with mice

treated with the antibiotic ampicillin exhibit reduced AHR activation and decreased adverse disease symptoms. Ampicillin-sensitive bacteria can catalyze the conversion of dietary tryptophan to AHR agonists, and mice treated with ampicillin have decreased levels of AHR activation and worse disease scores in an experimental autoimmune encephalomyelitis (EAE) model, which is a commonly used mouse model of multiple sclerosis (MS). EAE mice supplemented with tryptophan have a reduction in pro-inflammatory molecules expressed in astrocytes and a reduction in symptom severity (Gareau et al. 2011; Strandwitz 2018). Microbial-derived tryptophan metabolites can also modulate astrocyte activation via microglia. Microglia activation by dietary tryptophan metabolites, through a mechanism also mediated by the AHR, modulate pro-inflammatory and neurotoxic activities in astrocytes in the EAE mouse model via production of TGF α and VEGF-B. Microglia-derived TGF α limit pathogenic activation via the ErbB1 receptor. Conversely, microglial VEGF-B triggers FLT-1 signaling in astrocytes and worsens EAE, including increasing demyelination and CNS monocyte recruitment (Rothhammer et al. 2018).

In human studies, astrocytes treated with tryptophan metabolites, including indole-3-propionic acid and indole-3-aldehyde, have reduced expression of pro-inflammatory factors such as IL-6, IL-12, IL-23a, nitric oxide synthase 2 (Nos2) and CC chemokine family 2 (Ccl2), markers associated with MS in humans (Rothhammer et al. 2016). Taken together, these findings suggest that microbial metabolites of dietary tryptophan can modulate the inflammatory status of astrocytes thus contributing to neuroinflammation.

Microbiota-immune interactions and CNS alterations

Brain injury

Accumulating evidence indicates that brain-resident and peripheral immune cells are critically involved in MGB axis communication, with deficits in signaling contributing to inflammatory disorders and impaired neurogenesis in the CNS (Fung et al. 2017). Studies investigating the contributions of specific species of the microbiota to neuroinflammation have revealed complex interactions between intestinal bacteria, immune system activation, and neuroinflammation.

For example, segmented filamentous bacteria (SFB) are epithelial-associated bacteria that promote the development of IL-17A-producing Th17 cells in the mouse small intestine (Gaboriau-Routhiau et al. 2009). Colonization of GF mice with SFB promotes the development of EAE symptoms via induction of Th17 cells (Lee et al. 2011). In EAE, brain autoimmunity is driven by a pro-inflammatory T cell response that promotes infiltration of immune cells in the CNS, with effector Th17 cells representing the first wave of pathogenic T cells (Korn et al. 2007) because of their ability to efficiently breach the blood-brain barrier (Kebir et al. 2007). On the other hand, colonization of mice with *B. fragilis*, which induces IL-10-producing regulatory Tregs, can reduce EAE severity. Additionally, metabolites produced by the gut microbiota, such as SCFAs, can also reduce EAE and axonal damage promoting Treg differentiation (Haghikia et al. 2015). In humans, excessive Th17 cell expansion in the intestine is associated with intestinal dysbiosis and brain autoimmunity. A higher *Firmicutes/Bacteroidetes* ratio, increased relative abundance of *Streptococcus*, and decreased *Prevotella* strains were observed in MS patients compared to healthy controls and with MS patients with no disease activity (Cosorich et al. 2017).

IL-17 and $\gamma\delta$ T cells have also been implicated in ischemic stroke, a highly prevalent disease with limited therapeutic options, where inflammation is a key component in the pathophysiology (Iadecola and Anrather 2011). In a recent study, antibiotic-induced alterations in the intestinal microbiota were found to reduce ischemic brain injury in mice. This dysbiosis alters immune homeostasis through bacterial priming of intestinal dendritic cells, leading to an expansion of local Treg and a suppression of effector IL-17 and $\gamma\delta$ T cells, thus improving outcome after brain ischemia (Benakis et al. 2016), and revealing an impact of the intestinal microbiota and meningeal IL-17 $\gamma\delta$ T cells on ischemic injury.

Neurogenesis

Neurogenesis is an important physiological process that occurs throughout life and is critical for maintaining cognitive function (Aimone et al. 2014). Intestinal bacteria have recently been demonstrated to regulate both fetal and adult neurogenesis. For example, bacterial cell wall peptidoglycan (PGN), a universal MAMP for TLR2, traverses the maternal-fetal interface during maternal infection, leading to an altered neuroproliferative response and abnormal cognitive behavior during

adulthood (Humann et al. 2016). In GF mice, studies assessing hippocampal neurogenesis reveal increased proliferation relative to conventional mice (Ogbonnaya et al. 2015). However, post-weaning exposure of GF mice to microbes could not influence neurogenesis, suggesting a critical time period where neuronal growth is stimulated by the microbiota during early post-natal development. In studies using antibiotic administration in adult animals for 7 weeks to reduce the microbiota abundance and diversity, decreases in hippocampal neurogenesis and spatial and object recognition were observed (Mohle et al. 2016). Reconstitution with normal SPF gut microbiota by fecal microbiota transplantation did not completely reverse the deficits in neurogenesis, unless the mice were supplemented with probiotics or exercise. Cells of the innate immune system, in particular Ly6C^{hi} monocytes, were critical for the restorative effect (Mohle et al. 2016). This suggests that modification of the microbiota coupled with environmental enrichment (Noack et al. 2014) could help to restore monocyte homeostasis and brain plasticity and may help to counteract side effects of prolonged antibiotic treatment.

Synaptic plasticity and memory

Brain plasticity, a critical process involving change in structure and function of neurons following stimulation, is crucial for learning and memory. Brain plasticity results in multiple, dissociable changes including increases in dendritic length, alterations in spine density, synapse formation, increased glial activity, and altered metabolic activity (Kolb and Whishaw 1998). Cytokines, together with neurotransmitters and hormones, are signaling molecules playing a key role in the maintenance of neuro-immune-endocrine system homeostasis in the brain from early development until aging (Alboni and Maggi 2015). Early exposure to infectious agents or environmental stressors can influence reactivity to stress, immune regulation, and susceptibility to disease later in life. For instance, neonatal exposure to bacterial products (e.g., LPS) increases HPA responses to stress, decreases susceptibility to inflammation, and attenuates fever in response to a subsequent challenge in adult rats (Shanks et al. 2000; Boissé et al. 2004). Pro-inflammatory cytokines are important mediators of abnormal brain development during perinatal infection, and behavioral alterations following infection may occur as a result of an increase in pro-inflammatory cytokines, particularly in the hippocampus, where cytokine receptors are widely

expressed (Cunningham and De Souza 1993; Cai et al. 2000; Urakubo et al. 2001). Immune cells are increasingly implicated for their role in synaptic plasticity mechanisms within the brain, including memory, particularly during early life.

Neonatal systemic exposure to non-pathogenic *E. coli* in rats causes memory impairments. This impairment, however, was only observed following a secondary peripheral immune challenge with LPS following contextual fear conditioning exposure, where increased astrocyte reactivity in the hippocampus was shown. The pro-inflammatory cytokine IL-1 β is induced within the hippocampus in response to normal learning and is critical for maintaining long-term-potential (LTP) (Cunningham and De Souza 1993; Ross et al. 2003). Mice lacking IL-1 β , or its type 1 receptor, exhibit markedly impaired hippocampal-dependent learning and memory (Goshen et al. 2007; Spulber et al. 2009). High levels of IL-1 β can profoundly impair memory (Barrientos et al. 2002, 2009), with increased levels observed in patients with Alzheimer's disease (AD) and other neurodegenerative disorders such as Parkinson's disease and amyotrophic lateral sclerosis (Griffin et al. 1989; Stanley et al. 1994). In fact, peripherally-induced neuroinflammation modeling neurodegenerative disease are driven by LPS administration, which has become an important tool for deciphering pathological mechanisms involved in neurodegeneration (Catorce and Gevorkian 2016). In neonatally infected rats, a marked deficit in hippocampal-dependent memory in adulthood was observed, but similar to the previously mentioned studies, only after a subsequent immune challenge with LPS at the time of learning. Cluster of differentiation molecule 11b (CD11b)-enriched cells, a marker for microglia, produced exaggerated IL-1 β *ex vivo* and after LPS exposure prior to learning *in vivo*, implicating the necessity of a second hit to impact memory dysfunction once a long-term change within the immune system has been established in early life. Prevention of microglial activation during learning prevents memory impairment in infected rats (Williamson et al. 2011). Taken together, these studies highlight a critical role for the immune system in mediating learning and memory.

Behavior

The host immune system is also critical in the development of behavioral and cognitive function. Consequently, long-term peripheral illnesses and

chronic intestinal inflammation are associated with behavioral disturbances such as cognitive impairment, deficits in learning, impaired memory, depression and anxiety, which is linked to disrupted adult hippocampal neurogenesis in animal models (Zonis et al. 2015; Chesnokova et al. 2016).

ASD

ASD is a neurodevelopmental disorder characterized by stereotypic behavior, language deficits, and impaired social interaction. A high proportion of patients also suffer from GI disturbances (Hsiao 2014), including altered bowel habits in the context of intestinal dysbiosis, suggesting it represents a gut-brain disorder. In fact, GI disturbances have been specifically associated with changes in microbial communities in ASD patients (Brandl et al. 2007; Vuong and Hsiao 2017). In a pilot study, children diagnosed with ASD showed an improvement in both GI symptoms and aberrant behaviors following 5 weeks of administration of *B. infantis* (Sanctuary et al. 2019). Similarly in a mouse model, probiotic administration of *Bacteroides fragilis* resulted in restoration of gut permeability and improvement in some behavioral abnormalities (Hsiao et al. 2013). Social behavior, another common behavioral alteration in ASD, was detrimentally impacted in offspring following exposure to maternal high fat diet, and associated with a shift in intestinal microbial ecology (Buffington et al. 2016). Social deficits in offspring can also be rescued by administration of the probiotic *L. reuteri* (Buffington et al. 2016), which was found to act via the vagus nerve (Sgritta et al. 2019).

In maternal immune activation (MIA), a well-established animal model of ASD consisting of administration of the TLR3 agonist poly(I:C) in pregnant mice, offspring develop behavioral phenotypes similar to those observed in ASD, including anxiety, repetitive behavior and altered sociability (Hsiao et al. 2013). MIA offspring also exhibit GI mucosal barrier defects and intestinal dysbiosis compared to sham controls (Hsiao et al. 2013). Oral treatment with the human commensal *B. fragilis* restored intestinal permeability defects, as well as microbiota dysbiosis, and significantly improved behavioral abnormalities (Hsiao et al. 2013). IL-17A was implicated as a critical mediator inducing behavioral and cortical abnormalities in offspring in response to maternal intestinal bacteria that promotes Th17 differentiation. Pregnant mice colonized with the commensal SFB, or human commensal bacteria that

induce intestinal Th17 cells, were more susceptible to having offspring with MIA-associated abnormalities (Kim et al. 2017), linking MIA-induced immune dysregulation to intestinal dysbiosis. Finally, in a genetic model of ASD using inbred BTBR T+Itpr3tf/J mouse (BTBR) mice, authors showed a reduction in the relative abundance of a bile-metabolizing *Bifidobacterium* and *Blautia* species, a particular bacterial taxa, associated with impaired social interactions as well as GI dysfunction and bile acid and altered tryptophan metabolism in the intestine (Golubeva et al. 2017). Together these studies support the concept of microbiota-based interventions on ASD behavior.

IBD

GI diseases are associated with a high risk for extra-intestinal manifestations, particularly psychiatric disturbance, which significantly impact patient quality of life. IBDs, consisting of Crohn's disease (CD) and ulcerative colitis (UC), have a strong association with behavioral abnormalities in patients suffering from both active or resolved GI inflammation (van Langenberg et al. 2017). Adolescent IBD patients are particularly vulnerable to behavioral comorbidities and have been demonstrated to display mild cognitive problems, particularly with verbal memory (Filipovic and Filipovic 2014; van Langenberg et al. 2017), thought to be related to the significant brain development occurring during this critical developmental period. Stress significantly contributes to the development and (or) exacerbation of IBD (de Punder and Pruimboom 2015). Few clinical studies have also revealed that stress is associated with digestive problems and poor GI health (Walker et al. 2001). For instance, maternal prenatal stress was strongly and persistently associated with aberrant microbial colonization patterns in pediatric patients and associated with increased infant GI symptoms and allergic reactions (Zijlmans et al. 2015). Additionally, stress-related disorders such as depression are also associated with increased bacterial translocation and increased immune responses against commensal microbiota (Maes et al. 2012).

The effect of the MGB axis and its implication in behavior in IBD has increasingly been studied using mouse models. In a chronic murine DSS model, anxiety-like behavior was demonstrated after 3 cycles of DSS-induced colonic inflammation, which could be ameliorated by administration of a *Bifidobacterium*-containing probiotic via a vagally mediated pathway

(Bercik et al. 2011b). In acute inflammation, changes in mood and behavior, including anxiety-like behavior, were observed following DSS-induced colitis, which were associated with a shift in the composition of the gut microbiota due to colonic inflammation (Emge et al. 2016). Similarly to the chronic DSS study, administration of probiotics could normalize changes in behavior, which widely correlated with restoration of the microbiota (Emge et al. 2016).

Probiotics on central nervous system functions

Probiotics are defined as “live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host” (Morelli and Capurso 2012). While their exact mechanisms of action remain to be completely elucidated, probiotics are considered a novel and relatively safe way (Yelin et al. 2019) to beneficially modulate the gut microbiota for many GI and extra-intestinal diseases.

Multiple studies have used probiotics to modify the MGB axis, with improvements in behaviors associated with stress-related psychiatric conditions, improved memory abilities, and induction of neuronal plasticity. For instance, probiotic-induced promotion of neurogenesis by increasing hippocampal brain derived neurotrophic factor (BDNF) expression normalizes the abnormal response of the HPA axis in mice (Ait-Belgnaoui et al. 2014). *B. longum*, *B. breve*, *B. infantis*, *L. helveticus*, *L. rhamnosus*, *L. plantarum*, and *L. casei* were the most commonly used probiotics for beneficially impacting behaviors, as either single- or multi-strain preparations, all of which were able to improve anxiety, depression, and memory related behaviors, based on multiple animal models (Wang et al. 2016). For example in depression, each of the single strains of *B. longum*, *B. breve*, *L. rhamnosus*, and *L. helveticus* all showed antidepressant effects (Desbonnet et al. 2008; Bravo et al. 2011; Singh et al. 2012; Ohland et al. 2013). In another study in both rats and mice, these same strains also improved spatial and non-spatial memory abilities (Luo et al. 2014; Liang et al. 2015; Savignac et al. 2015).

In humans, many studies demonstrated a beneficial effect of probiotics on psychiatric conditions in both patients and healthy individuals, although not all studies found a benefit. With respect to anxiety and

depression, a probiotic formulation of *B. longum* and *L. helveticus* could improve anxiety and depression in all participants (Messaoudi et al. 2011a, 2011b). Other probiotic strains also have effects on anxiety and depression. A probiotic yogurt containing *B. lactis* and *L. acidophilus* improved general health questionnaire (GHQ) and depression anxiety and stress scale (DASS) scores on petrochemical workers (Mohammadi et al. 2016) and a recent study using multi-strain probiotics found improvement in the Leiden index of depression sensitivity scale (LEIDS-r score) in healthy participants, demonstrated by a significantly reduced overall cognitive reactivity to sad mood, which is predictive of depression (Steenbergen et al. 2015).

Similarly, in a study in chronic fatigue syndrome patients, *L. casei* Shirota administration decreased anxiety levels following treatment (Rao et al. 2009; Ait-Belgnaoui et al. 2014). In contrast, patients with schizophrenia showed no changes in the Positive and Negative Symptom Scale Score (PANSS) after 14 weeks following *L. rhamnosus* administration (Dickerson et al. 2014). Similarly, patients with rheumatoid arthritis showed no change in anxiety levels after intervention with *L. casei* for 8 weeks (Vaghef-Mehrabany et al. 2014). A recent study in healthy volunteers using the Paired Associate Learning test from the Cambridge Neuropsychological Test showed improvements of visuospatial memory performance following intake of *B. longum* 1714 (Allen et al. 2016). Finally, human immunodeficiency virus patients treated with a multi-strain probiotic supplementation (Vivomixx®; Visbiome®) also demonstrated improved neurocognitive functions including verbal and visual memory related to memory improvement (Ceccarelli et al. 2017). Currently, only animal studies have provided strong evidence for a beneficial effect of probiotics on cognition and memory, therefore additional clinical studies are needed to adequately test these effects. The effect of probiotics on the CNS in humans is reviewed extensively elsewhere (Wang et al. 2016; Cryan et al. 2019).

Many of these probiotics presumably act beneficially in part by inhibiting the growth of other harmful bacteria or pathogens and (or) improving the immune system (Luo et al. 2014; Liang et al. 2015). The proposed mechanisms of actions by which probiotics have a beneficial effect are diverse and comprise endocrine, immune, neural, and metabolic pathways. Many probiotics have shown a reduction in HPA axis activity by

decreasing corticosteroid and (or) adrenocorticotrophic hormone (ACTH) levels. Our laboratory identified changes in neurogenesis and synaptic plasticity with effects on memory by modulating HPA axis activity. Using a combination of *L. rhamnosus* + *L. helveticus*, improved memory and cFOS expression, an immediate early gene serving as a neuronal activation marker, was found in mice infected with *C. rodentium* following exposure to an acute psychological stress (Gareau et al. 2011).

Probiotics can also influence the CNS directly via the vagus nerve and by modulating neurotransmitter levels. Treatments that target the vagus nerve increase the vagal tone and inhibit cytokine production. The stimulation of vagal afferent fibers in the gut influences monoaminergic brain systems within the brain stem that play crucial roles in major psychiatric conditions, such as mood and anxiety disorders. For example, behavioral changes following *L. rhamnosus* and *B. longum* administration, were not seen in vagotomized animals (Bercik et al. 2011b). Furthermore, *B. fragilis* could enhance serum tryptophan levels, a precursor of 5-hydroxytryptamine (5-HT) or serotonin synthesis (Emge et al. 2016). Serotonin is an important neurotransmitter in the gut that can stimulate peristalsis and induce nausea and vomiting by activating the vagus nerve. Interactions between the vagus nerve and serotonin systems, with the gut microbiota controlling tryptophan catabolism, appear to play an important role in the treatment of psychiatric conditions (Breit et al. 2018).

Finally, another mechanism of action of probiotics altering CNS function is thought to be by decreasing pro-inflammatory cytokines and increasing anti-inflammatory cytokines. Cultured intestinal mucosal tissues of CD patients with *L. casei*, *L. bulgaricus*, *L. crispatus* and *E. coli* showed an interaction with immunocompetent cells and modulation of the production of pro-inflammatory cytokines, resulting in a significant reduction in the pro-inflammatory cytokine TNF- α (Borrue et al. 2002). In IL-10-deficient mice, which spontaneously develop colitis, significant reductions of INF- γ and TNF- α by Peyer's patch lymphocytes and pro-inflammatory cytokine production by splenocytes were found in probiotic-treated mice (McCarthy et al. 2003). In healthy rats, the administration of a mixture of Lactobacillus and Bifidobacterium upregulated IL-10 and downregulated TNF- α and IL-6 (Karamese et al. 2016). Moreover, probiotics can ameliorate

inflammatory immune responses through modulation of the intestinal barrier permeability (Llopis et al. 2005, 2009; Rao and Samak 2013). Increased intestinal barrier permeability is associated with psychiatric disorders, such as depression and ASD, while it can be restored by probiotic formulations of *B. longum* and *L. helveticus*, along with improved CNS function (Arseneault-Breard et al. 2012; Hsiao et al. 2013).

It is important to highlight the limitations of probiotics studies in both animals and in humans. With respect to the translation of behavioral models in animals to human health, it is important to note that the tests used to measure behavior in animals have no direct equivalents in humans. These behavioral tests are designed to reflect the presumed CNS dysfunction in humans, based on specific animal behaviors. The common use of questionnaires in humans to assess behaviors could result in subjective biases. In the future, use of neuroimaging techniques may provide a better, more accurate, alternative way to assess changes in brain function (McFarland et al. 2018). Several studies have found that in contrast to inbred mice, humans present individual, regional, and strain-specific mucosal bacterial colonization patterns. In some individuals, these unique features prevent standard probiotics from transiently colonizing the gut, as determined by indistinguishable probiotic presence in the stool (Zmora et al. 2018). In the absence of individual-specific mucosal colonization to probiotics, lack of beneficial effects could be misunderstood (Llopis et al. 2009). Of importance for future studies will be the development of personalized medicine using strain-specific and individual-specific based probiotic therapy based on next-generation sequencing, to enable persistent live-bacteria colonization to beneficially impact the host.

Conclusions

Accumulating evidence indicates that brain-resident and gut-resident immune cells are critically involved in orchestrating MGB axis communication. The gut microbiota can influence the development and function of the intestinal immune system and conversely, the innate and adaptive immune system influence microbiota composition. This reciprocal relationship contributes to establishment of symbiosis with the gut microbiota, preventing potentially harmful bacteria and pathogens from breaching the host defenses. The microbiota can also modulate brain microglia and

astrocytes, which mediate neurophysiological processes including neural development, neurotransmission, and CNS immune activation. These microbial influences on immune responses have important consequences for brain inflammation, injury, behavior and brain plasticity and are increasingly associated with symptoms of various neuroinflammatory and psychiatric disorders. This relationship establishes a tight communication with the CNS and immune system as important cellular mediators across the gut-brain axis. Disruption of these complex and dynamic interactions can have profound consequences for host health.

Studies of probiotics in animal models, and a few studies in humans, have identified their effective application in the prevention and treatment of various health conditions and diseases such as GI infections but also in improving CNS function, including psychiatric disorders such as anxiety and depression, and cognition.

Finally, as the specific pathways of the MGB axis signaling are still incompletely characterized, it is critical for future studies to clarify these pathways to define specific microbe-derived factors, immune effector functions, and microbiota-immune pathways for modulating brain function and behavior. Also, it is crucial for future microbiota studies that appropriate controls be used to compare baseline variation in experimental groups. Likewise, it is important to note that laboratory mice have distinct immunological profiles from humans, limiting the ability to directly extrapolate conclusions to human diseases. Future mechanistic insights into how the immune system and microbiota interact will require development of novel approaches with high throughput analysis of metabolites as well as gene and protein expression, to move towards a personalized-based therapy.

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