The microbiota-immune axis as a central mediator of gut-brain communication

Thomas C. Fung

Department of Integrative Biology and Physiology, University of California Los Angeles, 610 Charles E. Young Dr. East, Los Angeles, CA 90095, United States

ARTICLE INFO

Keywords:
- Gut microbiota
- Immune modulation
- Chronic intestinal inflammation
- Systemic inflammation
- Neuroinflammation
- Neurodegenerative disorders
- Microbial therapeutics

ABSTRACT

Intestinal inflammatory disorders are associated with neurophysiological and behavioral symptoms. Conversely, many disorders of the central nervous system (CNS) are accompanied by intestinal complications. These observations suggest that intestinal and nervous system physiologies are functionally linked. Indeed, a growing body of literature has revealed multiple pathways mediating bidirectional communication between the intestine and the CNS, collectively referred to as the gut-brain axis. In particular, microbes naturally colonizing the mammalian gastrointestinal (GI) tract, termed the gut microbiota, not only correlate with but also play a causative role in regulating CNS function, development and host behavior. Despite these findings, our understanding of the cellular and molecular mechanisms that mediate gut-brain communication remains in its infancy. However, members of the gut microbiota have been established as potent modulators of intestinal, systemic and CNS-resident immune cell function, suggesting that gut-brain interactions may involve the host immune system. Multiple CNS disorders with gut microbiota associations, including neuroinflammatory, neuropsychiatric and neurodegenerative disorders, also have significant inflammatory manifestations. In this review, I discuss recent advances exploring the role of microbiota-immune interactions as a critical regulator of the gut-brain axis in the context of CNS and related disorders.

1. Gut microbes are potent regulators of host immune responses

The mammalian gastrointestinal (GI) tract is colonized by trillions of microorganisms including bacteria, fungi and viruses, collectively termed the gut microbiota. These organisms serve diverse roles in promoting health in local and extra-intestinal tissue environments by limiting pathogen invasion, regulating host metabolism and priming host-protective immune responses (Belkaid and Harrison, 2017). The lamina propria and gut-associated lymphoid structures found along the GI tract are also home to the mucosal immune system, which provides protective immunity to a multitude of microbial threats. Early evidence that the microbiota is critically involved in intestinal immunity arose from studies using germ-free (GF) mice raised in a sterile environment and the CNS, collectively referred to as the gut-brain axis. In particular, microbes naturally colonizing the mammalian gastrointestinal (GI) tract, termed the gut microbiota, not only correlate with but also play a causative role in regulating CNS function, development and host behavior. Despite these findings, our understanding of the cellular and molecular mechanisms that mediate gut-brain communication remains in its infancy. However, members of the gut microbiota have been established as potent modulators of intestinal, systemic and CNS-resident immune cell function, suggesting that gut-brain interactions may involve the host immune system. Multiple CNS disorders with gut microbiota associations, including neuroinflammatory, neuropsychiatric and neurodegenerative disorders, also have significant inflammatory manifestations. In this review, I discuss recent advances exploring the role of microbiota-immune interactions as a critical regulator of the gut-brain axis in the context of CNS and related disorders.

https://doi.org/10.1016/j.nbd.2019.104714

Received 2 July 2019; Received in revised form 5 November 2019; Accepted 13 December 2019
Available online 14 December 2019

0969-9961/ © 2019 The Author. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/BY/4.0/).
subsequent release of intestinal and systemic immunoglobulins (Ig) that limit inflammatory responses towards gut microbes themselves. The specific cellular and molecular pathways by which gut microbes modulate innate and adaptive immune homeostasis have been extensively reviewed (Belkaid and Harrison, 2017; Britanova and Diefenbach, 2017; Thaiss et al., 2016).

GF and ABX animals have additionally proven to be invaluable tools for functional studies evaluating the immunological effects of various microbial species commonly found in a healthy gut microbiota. In mice, colonization of GF animals with segmented filamentous bacteria (SFB) promotes Th17s (Gaboriau-Routhiau et al., 2009) and IL-22-producing ILC3s in the terminal ileum (Atarashi et al., 2015), germinal center formation and IgA production (Lecuyer et al., 2014). In contrast, colonization of GF animals with Clostridia strains promotes Tregs (Atarashi et al., 2013), which suppress pro-inflammatory T cell responses triggered during inflammation. Further studies demonstrate that induction of intestinal Tregs is not restricted to Clostridia and can be driven by a diversity of Bacteroides and Parabacteroides species (Faith et al., 2014; Sefik et al., 2015). Helicobacter species, prevalent pathogens of the gut microbiota that have the potential to trigger intestinal inflammation (Xu et al., 2018), promote Treg responses during homeostasis but activate pathogenic T effector responses during colitis (Chai et al., 2017). Akkermansia muciniphila, a gut microbe negatively associated with obesity, promotes T follicular helper cell (Tfh) responses, which provide B cell-help to generate Akkermansia-specific systemic IgG1 responses (Ansaldo, 2019). A large in vivo screen measuring the immunomodulatory properties of common gut microbes reveals that specific members of the gut microbiota have distinct and overlapping immunomodulatory effects in the small intestine, colon, gut-associated and systemic lymphoid organs (Geva-Zatorsky et al., 2017). Taken together, these studies establish that the gut microbiota regulates the host immune system in a species-specific manner, and that alterations in gut microbiota composition lead to altered intestinal and systemic immune activation states (Fig. 1).

In addition to bacteria, the intestine is also colonized with diverse fungal species, collectively referred to as the gut mycobiota (Paterson et al., 2017; Richard and Sokol, 2019). Although found in much lower abundance compared to bacteria, these organisms are emerging as...
critical players in the pathogenesis of inflammatory bowel disease (IBD) through modulation of antigen-presenting, T helper 1 (Th1) and Th17 cell function. (Jiang et al., 2017; Leonardi et al., 2018; Limon et al., 2019). The GI tract is also colonized by endogenous viruses known as the gut virome (Neil and Cadwell, 2018). In mice, mouse norovirus (MNV) is a viral pathogen that infects intestinal myeloid cells but can remain dormant following resolution of infection, thereby establishing persistence alongside the GI tract. Colonization of GF or ABX mice with MNV induces type 1 interferon responses that protect the host from enteric pathogen infection and chemical-induced intestinal injury (Kernbauer et al., 2014), suggesting that similar to gut bacteria, intestinal viral colonization can serve host protective functions. Consistent with this, a recent study demonstrates that SPF mice depleted of endogenous intestinal viruses with a cocktail of anti-viral compounds (ribavirin, lamivudine and acyclovir) have reduced levels of intraepithelial lymphocytes (IELs). These mice are more susceptible to chemical-induced intestinal inflammation, which is rescued by IL-15 administration to restore IEL homeostasis (Liu, 2019). Altogether, these findings support the hypothesis that the gut mycobiome and virome are emerging as critical immunomodulators with host physiological consequences (Fig. 1).

2. Gut microbes promote peripheral immune responses associated with CNS disorders

2.1. IL-17A in multiple sclerosis and autism

The immunomodulatory effects of the gut microbiota are becoming increasingly appreciated in tissues beyond the GI tract, as gut microbe-immune interactions play an important role in the etiology of neuroinflammatory and neuropsychiatric disorders. Early studies in microbiota-depleted animals have shown that CNS development, function, as well as mood and behavior (Lu et al., 2018; Vuong et al., 2017) are significantly impaired compared to microbiota-replete controls, suggesting that the gut microbiota plays a critical role in neurological function throughout life. Initial support for this hypothesis came from studies examining the role of the mouse indigenous gut bacteria, SFB, on susceptibility to experimental autoimmune encephalomyelitis (EAE), a rodent model for multiple sclerosis (MS). GF mice are highly resistant to EAE compared to SPF mice (Lee et al., 2011). However, SFB colonization alone in GF mice is sufficient to induce extra-intestinal Th17 cells and EAE symptoms. Furthermore, loss of homeostatic control of the SFB-Th17 axis in intestinal-specific IL-17R-deficient animals results in exacerbated EAE severity (Kumar et al., 2016). Conversely, Bacteroides fragilis and Prevotella histicola colonization suppresses disease in EAE by promoting Treg function (Mangalam et al., 2017; Ochoa-Reparaz et al., 2010). In humans, intestinal Th17 cell responses positively correlate with MS disease and negatively correlate with the relative abundance of Prevotella in the human small intestine (Cosorich et al., 2017), suggesting that Prevotella is an important modulator of neuroinflammation in both EAE and MS. Transplantation of human MS fecal samples to GF mice induces a less potent anti-inflammatory Treg response compared to healthy fecal samples and facilitates the development of both spontaneous and induced models of EAE (Berer et al., 2017; Gekanovicu et al., 2017). Altogether, these findings illustrate that T cell responses during CNS inflammation can be modulated by gut microbes (Table 1).

Studies using maternal immune activation (MIA) as a rodent model of autism identify a similar gut microbe-immune axis whereby SFB colonization is sufficient to promote autism spectrum disorder (ASD)-like symptoms through Th17 cells (Choi et al., 2016; Kim et al., 2017; Lammert et al., 2018; Shin Yim et al., 2017) (Table 1). MIA-induced systemic release of IL-17A in pregnant dams contributes to abnormal patch development in the dysgranular zone of the primary somatosensory cortex (S1DZ) in the offspring brain (Choi et al., 2016; Shin Yim et al., 2017). Later studies identify intestinal Th17 cells as the source of IL-17A, which are significantly elevated in mice harboring SFB (Kim et al., 2017; Lammert et al., 2018). Treatment of dams with anti-IL-17A neutralizing antibody limited cortical patch development and behavioral abnormalities (Choi et al., 2016; Lammert et al., 2018). These findings are consistent with clinical reports identifying significant microbiota associations in human ASD and suggest a causative role for gut microbes in regulating a subset of ASD symptoms (Kang et al., 2019; Sharon et al., 2019; Wang et al., 2019) (Table 1).

Under homeostatic conditions, intestinal Th17 cell responses driven by gut microbes are non-inflammatory and host tissue-protective (Omenetti, 2019). However, in the context of immune challenge or loss of immunological tolerance, gut microbes can drive inflammatory Th17 cell responses that can contribute to inflammatory disease (Omenetti, 2019; Xu et al., 2018). Recent studies highlight differential functions of IL-17A and IL-17F, both produced by Th17 cells, in microbe-mediated intestinal inflammation (Tang et al., 2018). While many studies on Th17 cells focus on the functions of IL-17A, investigating the mechanisms that balance protective versus pathogenic microbiota-dependent Th17 cell responses will be necessary to determine the role of microbiota-immune crosstalk in neuroinflammatory disease.

2.2. Low-grade systemic inflammation in neuropsychiatric disorders

Elevated levels of circulating pro-inflammatory cytokines IL-1β, IL-6 and TNFα are associated with neuropsychiatric disorders in humans (Chu et al., 2019; Khandaker et al., 2018; Kohler et al., 2017; Treadway et al., 2019). However, the cellular sources of these cytokines and the pathways by which they are induced are not well understood. Moreover, whether these responses are a cause or consequence of neuropsychiatric symptoms requires further investigation. Low grade systemic inflammation is observed in rodent models of anxiety and depression (Hodes et al., 2014; Zhang et al., 2017), and is associated with impaired intestinal barrier function (de Punder and Pruimboom, 2015) (Table 1). One consequence of a disrupted GI barrier is the translocation of gut microbes, leading to impaired intestinal immune homeostasis and systemic immune activation (de Punder and Pruimboom, 2015). The inflammasomes, a class of cytosolic innate immune receptors that recognizes intracellular microbe- and damage-associated molecular patterns (MAMPs, DAMPs), has emerged as a critical pathway involved in regulating microbiota-immune interactions (Man, 2018). Activation of the inflammasome pathway results in caspase 1- or 11-mediated cleavage and release of the pro-inflammatory cytokines IL-1β and IL-18 (Yang et al., 2019). Classically known to respond to intracellular bacterial pathogens such as Shigella, Salmonella and Legionella, recent studies suggest that inflammasomes play an important role in coordinating interactions between the healthy gut microbiota and host immune system (Levy et al., 2015; Man, 2018). Loss of the NLRP3- and NLRP6-inflammasomes is associated with altered microbiota composition and increased susceptibility to colitis (Henao-Mejia et al., 2012; Wlodarska et al., 2014; Yao et al., 2017), a condition often linked to systemic inflammation observed in neuropsychiatric disorders. Interestingly, caspase-1-deficient mice, which lack inflammasome signaling and are protected from chemical-induced intestinal inflammation (Blazejewski et al., 2017), have reduced anxiety- and depressive-like behaviors following chronic restraint stress (Wong et al., 2016). However, whether these behavioral changes are a result of impaired microbiota-inflammasome interactions requires further investigation.

Functional associations between gut microbiota composition and stress-induced depressive-like behaviors are beginning to be elucidated. Animal models of physiological and psychological stress lead to altered gut microbiota composition (McGaughy et al., 2019; Werbner et al., 2019; Wong et al., 2016) and fecal transplantation regulates depressive-like symptoms through metabolic and inflammatory pathways (Kelly et al., 2016; Pearson-Leary, 2019; Zheng et al., 2016), suggesting that the gut microbiota contributes to stress-induced depressive-like behaviors (Table 1). One study, which profiled the gut microbiota of over
### Table 1
The role of microbiota-immune interactions in CNS disorders.

| Neurophysiologically or psychiatric disorder | Microbiota-immune interaction | Disease outcome | References |
|---------------------------------------------|--------------------------------|----------------|------------|
| **Experimental autoimmune encephalomyelitis (EAE)** | - SFB colonization induces Th1 and Th17 responses in small intestine and spinal cord <br> - Prevotella histicola oral gavage limits Th1 and Th17 responses in the CNS and promotes Tregs and tolerogenic DCs in spleen <br> - PSA-expressing Bacteroides fragilis colonization promotes IL-10 production by Tregs in cervical lymph node | - Promotes EAE <br> - Suppresses EAE <br> - Suppresses EAE | (Lee et al., 2011) <br> (Mangalam et al., 2017) <br> (Ochoa-Reparaz et al., 2010) |
| **Multiple sclerosis** | - High frequencies of small intestinal Th17 cells in relapsing-remitting MS positively associated with Streptococcus and negatively associated with Prevotella <br> - MS twins have increased abundance of Akkermansia <br> - Mice colonized with MS microbiota have reduced IL-10 production from splenocytes <br> - MS patients have increased abundances of Akkermansia, Acinetobacter, which induces inflammatory Th1 responses <br> - MS patients have reduced abundance of Parabacteroides, which induces anti-inflammatory Treg responses | - Relapsing-remitting MS patients with active disease have increased and decreased abundance of Streptococcus and Prevotella, respectively, compared to healthy controls <br> - Mice colonized with gut microbiota from twins discordant for MS enhances susceptibility to spontaneous EAE | (Cosorich et al., 2017) <br> (Bierer et al., 2017) |
| **Maternal immune activation (MIA)** | - SFB colonization in pregnant dams is required and sufficient to promote serum IL-17A during MIA | - SFB and Th17-inducing human-derived gut microbes promote abnormal cortical development in fetal brain and behavioral abnormalities in MIA | (Choi et al., 2016; Kim et al., 2017; Lammert et al., 2018; Shin Yim et al., 2017) |
| **Autism spectrum disorder (ASD)** | - FMT of healthy human microbiota elevated abundances of Bifidobacteria and Prevotella; immune consequences unknown | - FMT of healthy human microbiota into ASD patients improved behavioral symptoms compared to pre-transplant condition | (Sharon et al., 2019) |
| **Anxiety and depression** | - Chronic social defeat stress increased frequencies of Th17 and Tregs in mesenteric lymph node in microbiota-dependent manner <br> - Pharmacological inhibition of inflammasome function increases abundances of Akkermansia and Blautia <br> - FMT from social defeat stress mice, which have increased abundance of Clostridia, enhances microglial activation, IL-1β, IL-10 in the ventral hippocampus <br> - Butyrate-producing bacteria Faecalibacterium and Coprococcus are depleted in human depression; butyrate promotes anti-inflammatory immune responses <br> - Amyloid-positive AD has elevated Escherichia coli and Shigella, which correlates with systemic expression of Il1b, Nlrp3 and Cxcl2; amyloid-positive AD has reduced abundance of Eubacterium rectale, which is negatively associated with Il1b, Nlrp3, Cxcl2 and positively associated with Il10 | - Depressive-like behavior is negatively associated with Akkermansia, Ruminococcus, Dorea <br> - Reduction in stress-induced depressive-like behavior <br> - Increase in depressive-like behavior | (McGaughy et al., 2019; Werber et al., 2019) <br> (Wong et al., 2016) <br> (Pearson-Leary, 2019) |
| **Alzheimer’s disease** | - Helicobacter pylori intestinal infection promotes proinflammatory innate and adaptive immune responses <br> - Intestinal infection with enterobacteria in Drusophilus promotes hemocyte recruitment and immune activation in the brain | - Reduced and increased abundance of Firmicutes and Bacteroidetes, respectively, in AD, correlate with CSF biomarkers <br> - Positively associated with AD <br> - Enhances AD neurodegeneration | (Kountouras et al., 2006) <br> (Wu et al., 2017) |
| **Parkinson’s disease (PD)** | - Anti-TNFα is used to suppress intestinal and systemic inflammation in IBD | - Anti-TNFα in IBD patients is associated with 78% reduction in incidence of PD <br> - IBD patients have 22% increased risk of PD, with UC patients slightly higher risk compared to CD | (Peter et al., 2018) <br> (Villansen et al., 2019) <br> (Peter-Pardo et al., 2019) |
| Abbreviations - Th1, T helper 1 cell; Th17, T helper 17 cell; Treg, regulatory T cell; SFB, segmented filamentous bacteria; PSA, polysaccharide A; FMT, fecal microbiota transplant; CSF, cerebrospinal fluid; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn’s disease; TLR4, Toll-like receptor 4. |
1000 individuals, demonstrates that butyrate-producing bacteria *Fae-
collibacterium* and *Coprococcus* are associated with increased quality of
life (Valles-Colomer et al., 2019). Given the effects of butyrate and
other short chain fatty acids (SCFAs) on generating Treg responses
(Arpaia et al., 2013; Furusawa et al., 2013; Smith et al., 2013), future
studies investigating whether these taxa are causally related to de-
pression are warranted.

2.3. Chronic intestinal inflammation and neurodegenerative disorders

IBD is a chronic inflammatory condition that affects the mammalian
GI tract. The etiology of IBD is multifactorial with genetic and en-
vironmental contributions. Among the many diseases associated with
the microbiota, the causal role of the microbiota in IBD has been the
most extensively explored (Britton et al., 2019). In IBD, gut microbes
are potent drivers of pathologic intestinal inflammation, in part due to
breakdown of physical and immune mechanisms that maintain se-
paration between gut microbes and the host immune system
(Ananthakrishnan et al., 2018). Epidemiological data have linked IBD
with various neuropsychiatric and neurodegenerative disorders
(Villumsen et al., 2019). For example, patients with IBD are 22% more
likely to develop Parkinson’s disease (PD) than healthy controls. In fact,
there is considerable overlap between genetic susceptibility loci in IBD
and PD. These associations suggest that chronic inflammation in the
intestine, which is significantly affected by the gut microbiota, mod-
ulate susceptibility to neurodegeneration. Despite these observations,
the pathways by which chronic intestinal inflammation affects neuro-
pathophysiology is not well understood. Immune dysregulation in
neurodegenerative diseases share common signatures with IBD in-
cluding elevated T helper 1 (Th1), Th17 and reduced Treg cell re-

sponses, (Ananthakrishnan et al., 2018; Chitnis and Weiner, 2017). In addition, IBD is associated with loss of intestinal barrier function, mi-
crobial translocation and systemic immune activation (Sartor, 2008).
Consistent with this, PD patients exhibit increased intestinal perme-
ability (Perez-Pardo et al., 2019), disrupting homeostatic interactions
between gut microbes and the host immune system (Table 1). Multiple
hypotheses have been proposed to explain the functional link between
chronic intestinal inflammation and neurodegeneration: 1) imbalance of pro-
versus anti-inflammatory gut microbes (Ho et al., 2018; Wu et al.,
2017), 2) systemic inflammation due to loss of intestinal barrier function and microbial translocation (Perez-Pardo et al., 2019) and 3)
influence of microbial amyloids on host amyloidosis (Friedland and
Chapman, 2017). One intriguing hypothesis that has not been explored
is the role of aging in mediating microbiota effects on neurodegenera-
tion. Age-related deficits in immune function such as germinal center
formation in gut-associated lymphoid tissues can be corrected by fecal
microbiota transplantation in mice (Stebegg et al., 2019). Additional
studies are necessary to determine the functional role of age-related
microbiota variation and immune dysfunction in PD and Alzheimer’s
disease (AD).

Alterations in gut microbial taxa with pro-inflammatory and anti-
inflammatory properties have been observed in AD (Table 1). The gut
microbiota of AD patients with brain amyloidosis are enriched for *Es-
cherichia coli* and *Shigella* (Cattaneo et al., 2017), which are potent pro-
inflammatory drivers of chronic IBD (Palmela et al., 2018) and acute
intestinal inflammation (Sansone, 2001). The abundance of *E. coli*
and *Shigella* correlates with expression of the inflammatory genes *Il1b,*
*Nlrp3* and *Cxc12* in peripheral blood. These findings are consistent with
*Helicobacter* intestinal infection in humans (Kountouras et al., 2006)
and enteric bacterial infection in *Drosophila* (Wu et al., 2017) positively

converging with the pathogenesis and progression of AD. In the latter
study, neuroinflammation and AD neuropathology triggered by oral
infection with an enteric pathogen are dependent on immune hemocyte
recruitment to the brain. Reduced abundance of *Clostridium* in the gut
microbiota of AD patients diagnosed with dementia correlates with
increased CSF levels of Aβ42/Aβ40 ratio, phosphorylated tau and
phosphorylated tau/Aβ42 ratio (Vogt et al., 2017). However, the con-
tribution of the immune system was not explored.

Despite growing interest in intestinal fungal and viral communities
on chronic immune activation and IBD (Wheeler et al., 2017), their role
in CNS disorders is not well characterized. However, links between
fungal infections and associated immune responses have been reported
primarily in MS, but also in AD and amyotrophic lateral sclerosis (ALS)
(Forbes et al., 2018). One recent report demonstrates that Crohn’s dis-
ease (CD) patients are more likely to be colonized with the common
skin yeast, *Malassezia restricta*, in the intestinal mucosa (Limón et al.,
2019). Colonization of mice with *M. restricta*, but not the fungal mi-
crobe *Candida albicans*, increases susceptible to chemical-induced co-
litis, suggesting that the gut mycobacteria affects host immunity in a
species-specific manner. Additional studies are required to determine
the role of fungal-mediated intestinal inflammation on the develop-
ment and pathogenesis of neurodegenerative disorders.

3. Gut microbes have long-range effects on CNS-resident immune
cell function

3.1. Microglia

The CNS is densely populated with tissue-resident myeloid cells
known as microglia, which play important functions in regulating and
fine-tuning neuronal circuitry during development and throughout
adulthood. Similar to tissue-resident macrophages in other organs,
microglia exert their neuronal functions through cytokine release,
complement activation and phagocytosis (Salter and Stevens, 2017).
Neurodevelopmental, neuropsychiatric and neurodegenerative dis-
orders have all been associated with impaired microglia function.
Although several genetic factors regulating microglia activity have been
characterized, the influence of environmental factors such as the gut
microbiota is beginning to be elucidated. Microglia in microbiota-de-
pleted animals have altered inflammatory gene expression profiles
and adopt an immature state (Erny et al., 2015). More recent studies have
shown that the role of the microbiota on microglia function is devel-

opment- and sex-dependent (Thion et al., 2018). Despite these findings,
the precise mechanisms by which microbes from the gut can affect
brain-resident microglia remain unclear. The microbe-derived fer-
mentation product of dietary fiber, SCFAs, can restore microglia dysfunction
in GF and AXB animals (Erny et al., 2015), suggesting that microbial
metabolites may be a general mechanism for gut-brain interactions.
Consistent with this, dietary metabolites of tryptophan produced by the
gut microbiota are involved in regulating microglial production of
TGFα and VEGF-B, which limit CNS inflammation during EAE and
human MS (Rothhammer et al., 2018). Taken together, these studies
demonstrate that microbial signals originating from the intestine have
long-range effects in modulating microglia function.

3.2. Astrocytes

In addition to microglia, astrocytes are major cellular players among
the glia that participate in the maintenance of CNS health and disease
(Valori, 2019). Astrocytes provide support to endothelial cells that form
the blood brain barrier and also play immune regulatory roles in CNS
development and inflammation through antigen presentation, and cy-
kotine and chemokine production. Astrocyte function can be modulated
by dietary metabolites of tryptophan produced by the gut microbiota
(Rothhammer et al., 2016). During EAE, type 1 interferons activate an
anti-inflammatory pathway in astrocytes through the cytosolic tran-
scription factor, aryl hydrocarbon receptor (AHR). AHR activation is
dependent on indoles produced by ampicillin-sensitive gut microbes as
by-products of dietary tryptophan metabolism. Bacterial tryptoph-
ases, which catalyze tryptophan to indoles and related compounds, are
highly expressed by specific members of gut microbes including *Lac-
tobacilli* (Zelante et al., 2013), *Escherichia coli* (Li and Young, 2013) and
**Bacteroides** (Devlin et al., 2016), suggesting that metabolic activities of these microbes are involved in regulating AHR-expressing astrocytes. Astrocytes release the IL-1 family cytokine IL-33 to activate microglial synapse engulfment (Vainchtein et al., 2018). This highlights a cytokine-mediated pathway by which astrocytes regulate neuronal circuitry remodeling, although a role for the gut microbiota has not been explored. Altogether, these findings illustrate that gut microbial metabolism regulates immune-related functions in astrocytes.

### 3.3. CNS-resident innate and adaptive immune cells

Previous work has linked AHR signaling regulated by microbial metabolites of tryptophan to IL-22 production at mucosal tissues (Zelante et al., 2013). More recent studies illustrate that cell-intrinsic AHR activation in ILCs (Li et al., 2018), B cells (Villa et al., 2017) and intestinal epithelial cells (Metidji et al., 2018) modulate specific functions in anti-helminth immunity and anti-tumor responses. Given the effect of AHR ligands on astrocytes, this raises the possibility that the function of other AHR-expressing innate (ILCs) and adaptive immune cells (T cells) resident in the CNS can be similarly modulated. CNS-resident plasma cells and IgA of intestinal origin are also implicated in the pathogenesis of EAE (Rojas et al., 2019). Tissue-resident plasma cells and plasmablasts produce the immunoregulatory cytokine IL-10 to suppress neuroinflammation. Collectively, these findings suggest that gut microbes can affect CNS-resident innate and adaptive immune cell functions with neuropathological consequences.

### 4. Therapeutic implications targeting the microbiota-immune axis

The gut microbiota plays a critical role in modulating the development and pathogenesis of neuroinflammation in EAE, which is supported by clinical associations between gut microbiota composition and human MS (Berer et al., 2017; Cekanaviciute et al., 2017; Chen et al., 2016; Jang et al., 2016). Existing immune-based therapeutics, such as IFN-β, have been effective at limiting neuroinflammation in MS. Despite a large body of evidence supporting a pathogenic role for IL-17A in MS, antibody-based therapeutics targeting this pathway have produced mixed results (Steinman, 2010), potentially due to neutralization of tissue-protective functions of IL-17A (McGeachy et al., 2019). Therefore, approaches to target the microbiota through probiotic administration, dietary intervention and fecal microbiota transplantation (FMT) are being explored as alternative strategies.

Clinical trials have tested probiotic administration alone or in combination with existing MS medications with promising outcomes (Tankou et al., 2018a; Tankou et al., 2018b). VSL3, a probiotic cocktail of 8 bacteria strains, administered to MS patients and healthy controls twice daily for 2 months, transiently elevates the relative abundance of VSL3-derived strains in the gut microbiota and decreases frequencies of circulating inflammatory monocytes and expression of activation markers CD80 and HLA-DR on blood monocytes and dendritic cells, respectively (Tankou et al., 2018a; Tankou et al., 2018b). Administration of a similar probiotic cocktail of *Lactobacillus* spp. and *Bifidobacterium* once daily for 3 months results in improvements in mental health and reductions in circulating inflammatory markers (Kouchaki et al., 2017) in MS patients. Clinical studies evaluating the use of FMT in large cohorts of individuals with CNS disorders are limited. One case report in a secondary progressive MS patient demonstrates beneficial outcomes following FMT (Makkawi et al., 2018). In ASD, an open-label FMT trial reveals long-term GI and autism-related health benefits in 18 pediatric patients (Kang et al., 2019). Based on these preliminary findings, additional randomized, double-blinded trials employing targeted probiotics or FMTs to treat various neurophysiological and behavioral disorders are necessary and currently in progress.

Mood disorders including major depressive disorder, mild chronic depression, and bipolar disorder affect 9.7% of adults in the United States each year with a lifetime prevalence of 21.4% (Kessler et al., 2009; Kessler et al., 2005). Similarly, anxiety disorders, which include generalized anxiety, panic disorder, social anxiety and obsessive-compulsive disorders, affect 19% of the US adult population each year with a lifetime prevalence of 31% (Kessler et al., 2009; Kessler et al., 2005). These statistics coincide with a 65% increase in use of anti-depressant medications from 1999 to 2004 (Pratt et al., 2017). Use of anti-
depressants and anti-psychotics modulates the inflammatory environment (Hou, 2019; Szalach et al., 2019) and are linked to changes in the human gut microbiota (Jackson et al., 2018; Lukic et al., 2019; Maier et al., 2018). These data suggest that modulation of systemic immune activation by these medications may partially occur through changes to the gut microbiota. A growing body of animal and clinical findings illustrating causal relationships between the gut microbiota and symptoms of mood disorders strongly indicates that modulating the composition and function of the gut microbiota may be an effective therapeutic approach and alternative to anti-depressants and anti-psychotics. Clinical studies to test microbial-based therapies, however, have been met with mixed results. Meta-analyses of clinical probiotic use in depression and schizophrenia only found a modest beneficial effect in a subset of studies (Ng et al., 2018; Ng et al., 2019), while several newer studies demonstrate improvement in depression symptoms (Chahwan et al., 2019; Wallace et al., 2019). Lack of reproducible efficacy using commercially available probiotics may be due to poor mucosal colonization and persistence of ingested strains (Suez et al., 2018; Zmora et al., 2018). These findings warrant additional clinical investigation to measure host determinants of probiotic colonization, such as endogenous gut microbiota composition, host metabolism and immune status, between probiotic-responsive and non-responsive patient cohorts. More importantly, rational design of specific bacterial strains with immunological potential, especially those that are depleted in the diseased gut microbiota, should be considered in future trials.

Adherence to a Mediterranean diet, which provides a rich source of dietary fiber for gut microbial fermentation and generation of anti-inflammatory SCFAs, is negatively associated with depressive symptoms (Gialluisi, 2019). However, meta-analysis of clinical prebiotic use indicates a lack of improvement in depression and anxiety compared to probiotic use (Liu et al., 2019b). Since dietary tryptophan can modulate susceptibility to MS (Nourbaksh et al., 2018) potentially through the microbiota (Rothhammer et al., 2016; Sonner et al., 2019), a prebiotic therapy that modulates microbial tryptophan metabolism and downstream AHR-immune responses to treat neuroinflammation is worth exploration. More importantly, future trials should evaluate the specific prebiotic components tailored to enrich gut bacterial species with anti-inflammatory and neuroprotective potential in a disease-specific manner.

5. Concluding remarks
The GI tract is colonized with trillions of indigenous microorganisms that shape local and extra-intestinal host immune function. Dysregulated immune responses are increasingly appreciated as drivers of not only neuroinflammatory, but also neuropsychiatric and neurodegenerative diseases. New findings in animal and human studies implicate the gut microbiota as a significant contributor of immune dysregulation in various CNS disorders. Gut microbes directly modulate intestinal and systemic immune homeostasis to affect neuroinflammation and may contribute to low grade systemic inflammation in neuropsychiatric disorders. Pathological immune activation towards gut microbes, a feature of chronic intestinal inflammation, is also a significant risk factor for neurodegeneration. Furthermore, the gut microbiota regulates the function of CNS-resident immune cells with potential consequences for neurodevelopmental and neuroinflammatory conditions. Therefore, targeting the microbiota-immune axis is a promising therapeutic approach for treating CNS and related disorders.

Declaration of Competing Interest
T.C.F. became an employee of Federation Bio during peer review and revision of this manuscript.

Acknowledgements
I thank Elaine Y. Hsiao (University of California, Los Angeles), members of the Hsiao Lab and Connie W. Y. Ha ( Cedars-Sinai Medical Center) for critical feedback of the manuscript.

References

Acknowledgements
I thank Elaine Y. Hsiao (University of California, Los Angeles), members of the Hsiao Lab and Connie W. Y. Ha (Cedars-Sinai Medical Center) for critical feedback of the manuscript.
Hou, B., et al., 2019. Effects of SSRI on peripheral inflammatory cytokines in patients with generalized anxiety disorder. Brain Behav. Immun. 81, 105–110.

Jackson, M.A., et al., 2018. Gut microbiota associations with common diseases and prescription medications in a population-based cohort. Nat. Commun. 9, 2655.

Jiang, S., et al., 2017. Altered gut microbiota of the human endometrium in multiple sclerosis. Nat. Commun. 7, 12015.

Jiang, T.T., et al., 2017. Commensal fungus recapitulate the protective benefits of intestinal bacteria. Cell Host Microbe 22, 809–816 (e4).

Kang, D.W., et al., 2019. Long-term benefit of microbiota transfer therapy on autism symptoms and gut microbiota. Sci. Rep. 9, 5821.

Kelly, J.R., et al., 2016. Transferring the blues: depression-associated gut microbiota induces neurobehavioural changes in the rat. J. Psychiatr. Res. 82, 109–118.

Kernbauer, E., et al., 2014. An enteric virus can replace the beneficial function of commensal bacteria. Nature 516, 94–98.

Kessler, R.C., et al., 2009. The global burden of mental disorders: an update from the World Health Organization. World Psychiatry 8, 41–55.

Khosravi, A., et al., 2014. Gut microbiota promote hematopoiesis to control bacterial infection. Cell Host Microbe 20, 1269–1277.

Lammert, C.R., et al., 2018. Cutting edge: critical roles for microbiota-mediated regulation of the immune system in a prenatal immune activation model of autism. J. Immunol. 201, 845–850.

Lecuyer, E., et al., 2014. Segmented filamentous bacterium uses secondary and tertiary lymphoid tissues to induce IgA and specific T helper 17 cell responses. Immunity 40, 608–620.

Lee, Y.K., et al., 2011. Proinflammatory T-cell responses to gut microbiota promote experimental autoimmune encephalomyelitis. Proc. Natl. Acad. Sci. U. S. A. 108 (Suppl 1), 6461–6462.

Leonardi, I., et al., 2018. CXCR1(+) mononuclear phagocytes control immunity to enteric fungal. Science 359, 232–236.

Levy, M., et al., 2018. Cutting edge: critical roles for microbiota-mediated regulation of the immune system in a prenatal immune activation model of autism. J. Immunol. 201, 845–850.

Liu, R.T., et al., 2019b. Prebiotics and probiotics for depression and anxiety: a systematic review and meta-analysis of controlled clinical trials. Neurosci. Biobehav. Rev. 102, 13–23.

Lu, J., et al., 2018. Effects of enteric microbiota on brain development in humanized Gnotobiotic mice. Sci. Rep. 8, 5444.

Lucie, L., et al., 2019. Antidepressants affect gut microbiota and Ruminococcus flavefaciens is able to abolish their effects on depressive-like behavior. Transl. Psychiatry 9, 1615–1624.

Ng, Q.X., et al., 2018. A meta-analysis of the use of probiotics to alleviate depressive symptoms. J. Affect. Disord. 228, 13–19.

Ng, Q.X., et al., 2019. A systematic review of the effect of probiotic supplementation on schizophrenia symptoms. Neuropsychopharmacology 78, 1–6.

Nourbash, B., et al., 2018. Altered tryptophan metabolism is associated with pediatric multiple sclerosis risk and course. Ann. Clin. Transl. Neurol. 5, 1211–1221.

Ochoa-Reparaz, J., et al., 2010. Central nervous system demyelinating disease protection by the human commensal Bacteroides fragilis depends on poly(ADPribose) polymerase 1 expression. J. Immunol. 185, 4101–4108.

Omenetti, S., et al., 2019. The intestine Harbors functionally distinct homing tissue resident and inflammatory Th17 cells. Immunity 51 (1), 77–89.e6.

Palma, C., et al., 2018. Adherent-invasive Escherichia coli in inflammatory bowel disease. Gut. 67, 574–587.

Paterson, M.J., et al., 2017. Host-microbe interactions: commensal fungi in the gut. Curr. Opin. Microbiol. 40, 13–23.

Pearson-Leary, J., et al., 2019. The gut microbiome regulates the increases in depressive-type behaviors and in inflammatory processes in the ventral hippocampus of stress vulnerable rats. Mol. Psychiatry 30833676. https://doi.org/10.1038/s41380-019-0112-6.

Perez-Pardo, P., et al., 2019. Role of TLR4 in the gut-brain axis in Parkinson’s disease: a translational study from men to mice. Gut. 68, 829–843.

Peter, I., et al., 2018. Anti-tumor necrosis factor therapy and incidence of Parkinson disease among patients with inflammatory bowel disease. JAMA Neurol. 75, 939–946.

Pratt, L.A., et al., 2017. Antidepressant Use Among Persons Aged 12 and Over: United States,2011–2014. NCHS Data Brief. pp. 1–8.

Richard, M.L., Sokol, H., 2015. Aryl hydrocarbon receptor: insights into analysis, environmental interactions and role in gastrointestinal diseases. Nat. Rev. Gastroenterol. Hepatol. 16, 331–345.

Rojas, O.L., et al., 2019. Recirculating intestinal IgA-producing cells regulate dendritic cell migration and coordinate cytokine release. Cell Rep. 29, 1287–1299.

Rothhammer, V., et al., 2016. Type 1 interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor. Nat. Med. 22, 566–575.

Rothhammer, V., et al., 2018. Microbial control of astrocytes in response to microbial metabolites. Nature 557, 724–728.

Salter, M.W., Stevens, B., 2017. Microglia emerge as central players in brain disease. Nat. Med. 23, 1018–1027.

Sanz-Monterrubio, P.J., 2001. Rupture, invasion and inflammatory destruction of the intestinal barrier by Shigella, making sense of prokaryote-eukaryote cross-talks. FEMS Microbiol. Rev. 25, 3–14.

Sattar, R.B., 2008. Microbial influences in inflammatory bowel diseases. Gastroenterology 134, 577–594.

Sefik, E., et al., 2015. MUCOSAL IMMUNOLOGY. Individual intestinal symbionts induce a distinct population of ROR(+) regulatory T cells. Science 349, 993–997.

Sharon, G., et al., 2019. Human gut microbiota from autism Spectrum disorder promote Behavioral behavioral changes in mice. Cell 177, 1600–1618 (e17).

Shin Yim, Y., et al., 2017. Reversing behavioural abnormalities in mice exposed to maternal inflammation. Nature 549, 482–487.

Shi, P.M., et al., 2013. The microbial metabolites, short-chain fatty acids, regulate colonoscopic T cell homeostasis. Science 341, 569–573.

Sonner, J.K., et al., 2019. Dietary tryptophan links encephalopathy of autoreactive T cells with gut microbial ecology. Nat. Commun. 10, 4877.

Sprengers, M., et al., 2019. Heterochronic fascial transplantation boosts gut microbial cens in aged mice. Nat. Commun. 10, 2443.

Steinman, L., 2010. Mixed results with modulating of TH17 cells in human autoimmune diseases. Nat. Immunol. 11, 41–44.

Suez, Y., et al., 2014. Postsynaptic gut mucosal microbe reconstitution is impaired by probiotics and improved by autologous FMT. Cell 174, 1406–1423 (e16).

Szalach, L.P., et al., 2019. The influence of antidepressants on the immune system. Arch. Immunol. Ther. Exp. 67, 143–151.

Tang, C., et al., 2018. Suppression of IL-17F, but not of IL-17A, provides protection by probiotics and improved by autologous FMT. Cell 174, 1406–1423 (e16).

Thannickal, J.P., et al., 2018. Suppression of IL-17F, but not of IL-17A, provides protection by probiotics and improved by autologous FMT. Cell 174, 1406–1423 (e16).

Vazquez, T.E., et al., 2018. Astrocyte-derived interleukin-33 promotes microglial sy- napsis in the entanglement and neural circuit development. Science 359, 1269–1273.

Valles-Colomer, M., et al., 2019. The neuroprotective potential of the human gut microbiota in quality of life and depression. Nat. Microbiol. 4, 623–632.

Vogt, N.M., et al., 2017. Gut microbiome alterations in Alzheimer’s disease. Sci. Rep. 7, 13537.

Vuong, H.E., et al., 2017. The microbiome and host behavior. Annu. Rev. Neurosci. 40,
Wallace, C.J.K., et al., 2019. The effects of probiotics on symptoms of depression: protocol for a double-blind randomized placebo-controlled trial. Neuropsychobiology 1–9.

Wang, M., et al., 2019. Alterations in Gut glutamate metabolism associated with changes in Gut microbiota composition in children with autism spectrum disorder. mSystems 4.

Werbner, M., et al., 2019. Social-stress-responsive microbiota induces stimulation of self-reactive effector T helper cells. mSystems 4.

Wheeler, M.L., et al., 2017. Immunity to commensal Fungi: detente and disease. Annu. Rev. Pathol. 12, 359–385.

Wlodarska, M., et al., 2014. NLRP6 inflammasome orchestrates the colonic host-microbial interface by regulating goblet cell mucus secretion. Cell 156, 1045–1059.

Wong, M.L., et al., 2016. Inflammasome signaling affects anxiety- and depressive-like behavior and gut microbiome composition. Mol. Psychiatry 21, 797–805.

Xu, M., et al., 2018. C-MAF-dependent regulatory T cells mediate immunological tolerance to a gut pathobiont. Nature 554, 373–377.

Yang, Y., et al., 2019. Recent advances in the mechanisms of NLRP3 inflammasome activation and its inhibitors. Cell Death Dis. 10, 128.

Yao, X., et al., 2017. Remodelling of the gut microbiota by hyperactive NLRP3 induces regulatory T cells to maintain homeostasis. Nat. Commun. 8, 1896.

Zelante, T., et al., 2013. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. Immunity 39, 372–385.

Zhang, J.C., et al., 2017. Blockade of interleukin-6 receptor in the periphery promotes rapid and sustained antidepressant actions: a possible role of gut-microbiota-brain axis. Transl. Psychiatry 7, e1138.

Zheng, P., et al., 2016. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host’s metabolism. Mol. Psychiatry 21, 786–796.

Zhou, L., et al., 2019. Innate lymphoid cells support regulatory T cells in the intestine through interleukin-2. Nature 568, 405–409.

Zmora, N., et al., 2018. Personalized gut mucosal colonization resistance to empiric probiotics is associated with unique host and microbiome features. Cell 174, 1388–1405 (e21).