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Review

Microbial metabolites and immune regulation: New targets for major depressive disorder

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A B S T R A C T

Treatments for depression and mood disorders have been singularly targeted at the brain without consideration for the context of the rest of the body. As evidence mounts for a role of autoimmunity and inflammation as risk factors and contributors to mood disorders, attention has shifted to one of the primary immunoregulatory organs in the body–the gut. Gut-brain interactions have been established and correlative links between the microbiome and mood have been examined, but with novel tools and a base of understanding, focus shifts to the mechanisms of these communications. In this review, we examine how the small molecules produced by metabolic processes of bacteria in the gut influence the host immune system. The gaps in knowledge discussed here include the under characterized diversity of small molecules crossing the gut walls, as well as the need to close the logical loop connecting the microbiome to the immune system, and the immune system to behavior and mood. As we move past the dawn of this field, more precise understanding using novel tools and techniques will help move toward a more informed and systematic process for clinically evaluating the efficacy of probiotics and bacterially derived compounds as antidepressants and mood regulators.

1. Introduction to depression

Mood disorders, which affect nearly 10% of the world population each year are undertreated and not well understood. Major depressive disorder (MDD) is the leading claim for disability aid in the United States, resulting in millions of dollars in federal unemployment costs (World Health Organization, 2018). Currently, most treatment plans include various types of counseling, but also rely heavily on pharmacological approaches, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), cyclic antidepressants, and less commonly monoamine oxidase inhibitors (MAOIs) (World Health Organization, 2018); however, due to the heterogenous nature of depression, many individuals are treatment-resistant or forgo drug therapy due to adverse side effects. For these reasons, there is continued interest in the identification of novel therapeutic targets that have improved efficacy and safety profiles. Evidence linking the gut microbiome and mood has opened new avenues for potential therapies.

A noteworthy indication that peripheral activity may be influencing the brain during stress and depression is that there is an increase in blood brain barrier (BBB) permeability in these patients. This increase in permeability allows for increased immune signals and other small molecules (some derived from the microbiome) to more easily cross into the brain. Some studies have shown that this effect is targeted to areas playing an important role in mood regulation like the nucleus accumbuns (Dudek et al., 2020) while others have shown a more ubiquitous effect (Menard et al., 2017).

The novel tools available to investigate the gut-brain axis have revolutionized how we understand the impact of diet and microbes on brain function. Current work has shown that diet and microbiome not only affect the function of the periphery, but are also crucial for central nervous system (CNS) development and health. The link between the gut and the brain was first proposed by anatomists in the 18th century, but was pioneered and popularized by John Abernethy and his 1829 book *The Abernethian Code of Health and Longevity,* in which he traces all mental disorders to their ultimate cause of "gastric derangement" (Abernethy, 1360). Since then, researchers have been able to use evidence-based, hypothesis-driven approaches to elucidate mechanistic links between the digestive and nervous systems for most known neurological and psychiatric disorders (Dinan and Cryan, 2017). In this review, we aim to describe the known function of small molecules produced by microbes in our gut in the context of their effect on the CNS, with a focus on stress, anxiety, and depression.

2. Microbiome changes in depression

About 90% of the bacterial species in the healthy, adult human gut fall within the *Bacteriodetes* and *Firmicutes* phyla (Qin et al., 2010). Phyla refers to the broadest classification in the kingdom of bacteria. More

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specific taxonomy then includes class, order, family, genus, and species. The microbiome is established in the first 3–5 years of life and remains relatively stable thereafter. The primary influencing factors that establish a healthy gut microbiome are seeding of the microbiome by early exposure to the vaginal and skin microbiota of the mother and the diet. This stable gut microbiota is crucial for health. A strong colonization by a healthy microbiota can outcompete pathogenic bacteria, protozoa, and fungi thus offering protection from the infiltration and compromise of the gut niche by pathogens. In addition, these bacteria are an important component in the proper digestion of food allowing efficient processing of essential nutrients and providing, through their metabolic processes, essential vitamins and nutrients.

Researchers have compared the bacterial families in the guts of patients with MDD to healthy controls. Fecal samples of patients suffering from depression, but not those whose depression was controlled by medication, had increased α-diversity, indicating increased number of bacterial families or genera able to inhabit a person's intestine (Jiang et al., 2015). Through fecal sequencing, increases have been observed in the proportion of *Coriobacteriaceae, Enterobacteriaceae, Rikenellaceae, Porphyromonadaceae, Thermoanaerobacteraceae, Acidaminococcaceae, and Fusobacterium.* There is evidence for decreases in the following bacterial families: *Bacteroidaceae, Ruminococcaceae, and Clostridiaceae.* Finally, there have been mixed findings when examining species of some families including *Prevotellaceae, Lachnospiraceae, Erysiopelotrichaceae, and Veillonellaceae* (Jiang et al., 2015; Kelly et al., 2016; Naseribafrouei et al., 2014).

Meta-analyses of probiotic studies as treatment for depression have not typically accounted for probiotic type. However, they are in agreement that the use of probiotics to improve mood, especially in patients with mild-to-moderate depression, is better than placebo and has fewer side effects than current treatment options (Huang et al., 2016; Ng et al., 2018). One of the current drawbacks of probiotic treatment is that the effect size of the treatment is often not as great as that of neuromodulator therapies and, therefore, its efficacy as a primary treatment has yet to be supported in clinical trials (Nadeem et al., 2019). At this time, it is primarily proposed for use in conjunction with current therapies, for use in patients with mild-to-moderate depression, or as an additional therapy option for those with treatment-resistant depression.

Stress is one of the highest risk factors for depression and so most models of depression focus on different life stressors. Some of the strongest evidence for the role of the microbiome in regulating stress and mood responses comes from studies using animal models. The germ-free animal model lacks a microbiome, not only in the gut, but the skin and mouth as well. These mice have a striking increased response to a mild restraint stressor, a model where the mice are physically restrained for one hour. The increase in adrenocorticotropic hormone (ACTH) and corticosterone in response to the stressor are two-fold higher levels than those of a regularly colonized mouse undergoing the same procedure. This effect can be ameliorated by recolonizing germ free mice during development indicating that the microbiome is vital to regulating the stress response (Sudo et al., 2004). The necessity of bacterial colonization for proper regulation of stress response has been supported in several other reports and has been expanded upon to show that anxiety- and depressive-like behavior are markedly decreased in response to stress in germ-free mice, which can be reversed by colonization (Clarke et al., 2013). Germ-free mouse models have also led to the discovery of many microbially-derived metabolites that are only present in the CNS after recolonization with gut bacteria (Matsumoto et al., 2013).

Early work in animal models has shown that stressors can change the gut microbiota composition in animals. For example in an early study of rhesus monkeys, the number of fecal *Lactobacilli* correlated with signs of behavioral stress in a maternal separation early life stress model (Bailey and Coe, 1999). Remarkably, depressive symptoms, including increased anxiety-like behavior and anhedonia, can also be transferred to rats using fecal transplants from severely depressed patients (Kelly et al., 2016). Numerous studies have pointed to specific bacterial strains as being beneficial in reversing depressive- and anxiety-like behaviors in models of stress. For example, in the unpredictable chronic mild stress model of depression, *Lactobacillus reuteri* (Marin et al., 2017), *Lactobacillus rhamnosus* (Bravo et al., 2011) and *Clostridium butyricum* (Sun et al., 2018) have shown antidepressant effects. *Lactobacillus* is commonly used as "antidepressant" bacteria, which is likely effective as it reverses the reduction of *Lactobacillus* that is seen in stress-induced depression (Marin et al., 2017). While mechanisms mediating behavioral changes have been suggested in many of these studies and reviews have presented a wide variety of hypotheses based on decades of work, bacterial interaction with the host remains a complex, only partially understood, system . Here we examine the different modes of communication with the CNS involving some of the small molecules that are produced by the commensal bacteria in the gut (Fig. 1).

3. Indirect effects on the central nervous system

Indirect effects of the microbiome on the central nervous system range from peripheral metabolism control to activity in the vagus nerve. The most studied method of indirect communication between the gut and the brain is along the immune axis. The bidirectional communication between the microflora of the gut and the immune system of the host, both locally and systemically, is highly conserved and well-established. The nature of communication between the CNS and the immune system is less understood, but has been a focus of scientific study in recent decades. One of the most direct connections lies in the immune cells' recognition of stress signals as they express both adrenergic and glucocorticoid receptors (Cho et al., 2019). Of primary importance, glucocorticoid receptors, which bind the stress hormones, are found on all circulating leukocytes including monocytes, neutrophils, T cells, eosinophils, and basophils. There have been noted sex differences in expression which may be a contributing factor to the increased prevalence of MDD in females compared to males (Cho et al., 2019; Rainville et al., 2018).

The immune system affects the CNS by 1) direct attack and autoimmunity, as in multiple sclerosis, 2) developmentally, as in autism spectrum disorder, and 3) in more nuanced and less well described ways for other conditions including mood disorders. There is higher incidence of depression in people diagnosed with autoimmune disorders than with other disorders that have comparable quality of life changes (Pryce et al., 2017). Meta-analysis of immune cell populations of patients diagnosed with depression has shown that there are changes in the number of circulating immune cells of both the innate and adaptive immune systems, as well as a decrease in the proliferative potential of lymphocytes (Herbert and Cohen, 1993). Here, we will give a brief overview of how major immune compartments are affected during MDD; a topic which has been reviewed in depth elsewhere (Miller and Raison, 2016).

3.1. Innate immune system

R. S. Smith first proposed that the patterns of MDD reflected an increase in immune cell activation, specifically, macrophage activation. He cited the *in vitro* activation of rat monocytes by estradiol as an explanation for observed sex differences in MDD incidence (HuMitcho and Rath, 1988). He also cited the increased rates of depression in patients with coronary heart disease, rheumatoid arthritis, and stroke, all conditions with high macrophage activity as support for this hypothesis (Smith, 1991). Some mechanistic approaches of antidepressant therapy have been proposed to work through macrophage activation. Splenic macrophages have decreased cytotoxicity in response to antidepressants (desipramine, fluvoxamine, and fluoxetine) (Belowski et al., 2004). In addition, a non-pharmacological treatment of mindfulness can decrease the macrophage migration inhibitory factor back to normal levels (Wang et al., 2018). Finally, circulating natural killer (NK) cells, another subset of the classical innate immune cells are reduced in patients with MDD (Suzuki et al., 2017).

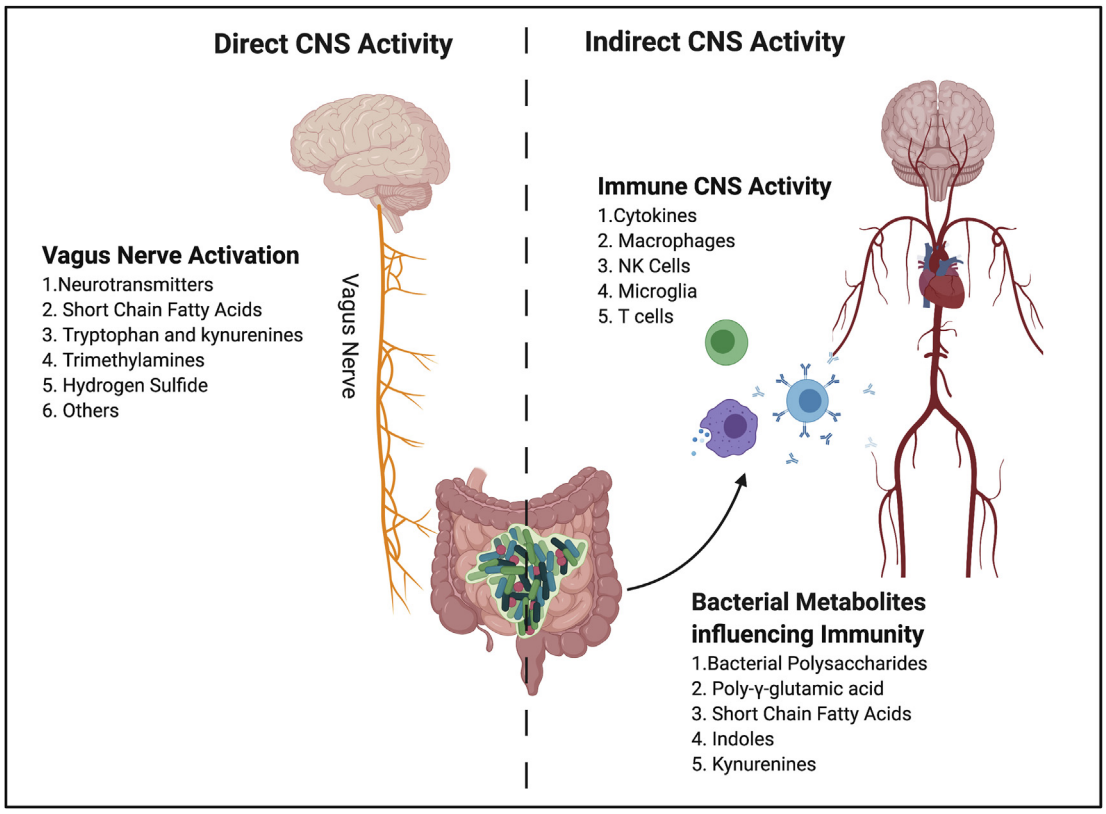

Fig. 1. The gut microbiota produces diverse small molecules which can impact the central nervous system. Several act through neuromodulation directly on the vagus nerve which innervates the viscera, or by entering circulation and crossing the blood-brain barrier to interact directly with the brain. While there are several modes of indirect communication with the central nervous system, modulation of the immune system has the greatest evidence for modulation of mood in stress and depression.

Cytokine profiling can give a snapshot of the cumulative immune response in the body. It is most often measured from the serum as it is easy to sample and analyze. Some of the most studied cytokines in the context of depression are the pro-inflammatory cytokines TNFα and IL-6, as well as one of their downstream targets C-reactive protein (CRP), all of which are risk factors for depression when upregulated (Gimeno et al., 2009). Another family of cytokines likely to have a role in perpetuating depressive symptoms are the IL-1 family of cytokines which are primarily produced by peripheral mononuclear cells (Jamilian et al., 2018). Polymorphisms in the genes encoding IL-1β, TNF and CRP have been found in patients with depression and are correlated with therapy outcomes (Bufalino et al., 2013). Notably, there is a functional variant of the IL-6 receptor (IL-6R), that reduces the sensitivity to IL-6 in immune cells leading to increased levels circulating IL-6 but a decrease in circulating CRP. These patients have a decreased likelihood of having an episode of major depression or psychosis (Khandaker et al., 2018).

Toll-like receptors (TLRs) are immune receptors that bind pathogen associated molecular patterns (PAMPs), danger signals that are often the first to trigger the inflammatory cascade. They are of primary importance for initiating the innate immune system, which is fast acting and initiates a strong inflammatory response. Depressed patients have increased TLR3, 4, 5, and 7 expression and decreased TLR1 and 6 mRNA expression levels. However, increased TLR4 expression, which is critical to the immune response to bacterial polysaccharides, seems to be the most important risk factor of developing MDD (Hung et al., 2014).

3.2. Adaptive immune system

By far, the most studied population of adaptive immune cells in MDD are T cells. There is an increase in total number of peripheral T cells with a higher inflammatory T helper (Th) to regulatory T cell (Treg) ratio in patients with MDD (Maes et al., 1992). Specifically, there is an increase of circulating Th17 cells and their principle proinflammatory cytokine, IL-17, in patients with depression (Rainville et al., 2018). Medicated MDD patients have lower levels of Tregs as well as impaired Th2 cell and Th17 cell maturation when compared to age matched controls (Grosse et al., 2016). Other cell types of the adaptive immune system also appear to play a role in depression, however, there is not consensus on their roles. A metanalysis by Eyre et al. examined multiple cell types that were changing at different stages of clinical depression from sub-syndrome phase, through the acute clinical phase, and to the post-acute phase. They found that while many immune cell types have certain levels of dysfunction, the T cells are the most variable (Eyre et al., 2014).

3.3. Evolutionary hypothesis

A working hypothesis to describe the relationship between inflammation and depression derives from an evolutionary advantage of stress-induced inflammation. The theory posits that in times of stress, including social stress, stress due to injury, or stress caused by harsh environment, it was advantageous to have a primed and ready immune attack. This would allow the immune system to be better equipped to handle injury and sickness (Miller and Raison, 2016). In addition, the sickness behavior that mirrors chronic depression was advantageous in that it results in resting the body, preventing spread of infectious pathogens, and preventing the of consumption of contaminated food. All of this is supported by a wealth of data supporting interconnected inflammatory, behavioral, and genetic changes in mammals that have yet to be fully understood (Barnes et al., 2017).

3.4. Impact of bacteria on immunity

The balance between autoimmunity in the gut and prevention of pathogenic infection of one of the largest and most regulated tissue

barriers requires constant cross talk between the immune system and gut microbiota. Oral probiotics given therapeutically have the capacity to change the immune activity of peripheral blood lymphocytes, including mediating changes in cytokines associated with depression, like IL-1, IL-8, and TNF-α (Borzabadi et al., 2018). The distal physiological effects non-pathogenic bacteria can have on inflammatory markers shows their therapeutic potential. Here we examine a range of small molecules produced by non-pathogenic bacteria and their effects on the immune system. As the connection between the immune system and mood has been well established, here, we will examine the other end of the microbiome-immune-brain axis-the impact of bacterial metabolites on the immune system (Fig. 2).

4. Bacterial polysaccharides

Bacterial lipopolysaccharide (LPS) is a commonly used model of inflammation that causes an innate immune response and subsequent cytokine storm. Injection of LPS also has been used as a model of sickness behavior and depression because the resulting behaviors during the immune event closely resemble those of depression and anxiety, even after vagotomy (Gaykema et al., 2000). LPS, as well as other molecules that cause TLR activation, lead to a strong cytokine release both peripherally and by the epithelial cells of the blood-brain barrier directly exposing brain resident cells to inflammatory cytokines (Quan and Banks, 2007). While the validity of i. p. injection of PAMPs as a model for major depressive disorder is questionable, it can lead to clues to the milder inflammatory events observed in patients with MDD.

There is an increase in gut permeability in response to stress which seems to be the result of a decreased number of tight junctions as well as a weakened mucosal barrier due to high levels of circulating cortisol (Zong et al., 2019). Recent speculation has suggested that this observed decrease in gut barrier function leads to an increase in bacteria crossing the intestinal barrier. This would lead to higher exposure of the immune system to bacterial polysaccharides and other PAMPs, increasing TLR4 signaling and thus monocyte activation.

While in animal models, evidence for this theory is strong, there is limited clinical evidence. In a study of naturalistic stress using a public speaking paradigm, stress leads to a leakier gut in humans. When these same subjects were exposed to an infusion of corticotropin-releasing hormone, a stress induced hormone, the same patterns of gut leakiness persisted (Vanuytsel et al., 2014). There are also increases in the antibodies IgA and IgM against LPS in patients with MDD supporting the hypothesis that stress leads to increased gut permeability, and thus higher immune activation. Unfortunately, this study is limited by the low number of healthy control patients used and a high variability within patients (Maes et al., 2012). While these piecemeal studies have provided foundational data, it is important that we gather more clinical evidence to support the theory that PAMPs are a contributing factor to the development of depressive episodes.

5. Poly-γ-glutamic acid

Poly-γ-glutamic acid (γ-PGA) is produced primarily through fermentation of soy and other legumes by *Bacillus* spp. (Lee et al., 2010). A γ-PGA supplemented diet increases GABA and glutamate in the brain, both neurotransmitters associated with mood (Lee et al., 2010). γ-PGA also has the capacity to decrease Th17 migration and induce an anti-inflammatory phenotype by increasing differentiation of Tregs in a partially TLR4 dependent manner (Lee et al., 2012). As TLR4, Tregs, and Th17s are all mediating factors of depression, γ-PGA most likely plays a role in mood disorders, and may have the potential to treat depression via TLR4 inhibition.

6. Short chain fatty acids

The primary metabolic output of microbial fermentation of dietary fibers are 1–6 carbon chain saturated fatty acids, commonly known as short chain fatty acids (SCFAs). The bacterial genera that produce them

Bacterial Metabolites that Regulate Mood

Metabolite Family	Bacterial Polysaccharides	Short Chain Fatty Acids	Indoles	Kynurenines
Examples	Lipopolysaccharide (LPS)	Acetate Proprionate Iso Butyrate Butyrate	1-methyl-3-(phenylselanyl) -1H-indole Indole-3-aldehyde	Kynurenine Kynurenic Acid Xanthurenic Acid Quinolinic Acid
Select Bacterial Producers	Gram Negative Bacteria	*Bacteroides* *Bifidobacterium* *Propionibacterium* *Eubacterium* *Lactobacillus* *Clostridium* *Roseburia* *Prevotella*	*Bacteroides* *Lactobacillus* *Fusobacterium* *Kleibsella*	*Clostridium* *Streptomyces* *Pseutodmonas* *Bacillus* *Burkholderia*
Receptor Activation	TLR4, Caspase 11	FFAR2, FFAR3, HDAC inhibition	AHR	NMDA, AMPA, GCPR35, AHR
Resulting Immune Changes	Innate immune response and cytokine cascade (IL-1β and IL-18) [40, 41]	Increase in neutrohpil chemoattractants [60], decrease of proinflammatory cytokines (TNFa, IL-17, IL-12), Treg increase [62, 67]	Ligand-dependent shift in inflamatory T cell population and cytotoxicity [89, 90], ILC3 cytokine release [85]	Increased macrophage activation and migration [92], modulation of oxidative stress [95], shift in inflamatory T cell population and cytotoxicity [89, 90]
Effects on Mood	Depressant [40, 43, 44]	Antidepressant [8, 53-54]	Antdepressant [69-71]	Antidepressant [8, 93, 96, 97]

Fig. 2. Neuroactive small molecules produced by the bacteria of the gut fall into several families. Summary of their origins as well as their effects on the immune system are listed here. Also included are citations for studies that examine their ability to modulate depression and anxiety in humans and animal models.

include *Bacteroides, Bifidobacterium, Propionibacterium, Eubacterium, Lactobacillus, Clostridium, Roseburia,* and *Prevotella* (Macfarlane and Macfarlane, 2012). This group of small molecules has a high absorption rate in the host body (up to 95%) (Rechkemmer et al., 1988) and are prime candidates for bioactive molecules that can affect host physiology. SCFAs can act on the immune, endocrine, and nervous systems showing their diverse neuroactive potential (Zeng et al., 2019).

There are differences in fecal SCFA levels in patients with disparate CNS disorders including Parkinson's disease (Unger et al., 2016), multiple sclerosis (Zeng et al., 2019), and autism spectrum disorder (Caspani and Swann, 2019). Many studies have reported differences between fecal SCFA in patients with symptoms of stress or depression to healthy controls, for example, one study found increases in fecal sodium butyrate (Wang et al., 2012). However, this remains controversial as another study found no differences in fecal acetate, proprionate, isobutyrate, or butyrate in depressed patients when compared to controls (Kelly et al., 2016). It is important to recognize, however, that the fecal levels of SCFAs are not necessarily reflective of the levels that are present in the intestinal lumen or that are being absorbed by the body.

In a wide range of animal models of stress and depression, including chronic mild stress, early-life stress, and fear conditioning, sodium butyrate was shown to reduce anxiety and depression-like phenotypes (Dalile et al., 2019a). One study examined the interaction of sodium butyrate with SSRIs. When the SCFA was administered in conjunction with fluoxetine, an SSRI, in a mouse model of depression, the mice treated with both the drug and SCFA displayed less despair behavior measured through the tail suspension test than either group receiving fluoxetine or SCFAs alone (Schroeder et al., 2007). While these preclinical experiments are promising, there is a lack of clinical trials examining the safety and efficacy of sodium butyrate and other SCFAs as a primary or supplemental therapy for depression.

The most common SCFAs in the body are acetate (two carbon chain), propionate (three carbon chain), and butyrate (four carbon chain) which are found primarily in the colon (Macfarlane and Macfarlane, 2003). Free Fatty Acid Receptor 2 (FFAR2) is the most abundant SCFA receptor in the gut and is present predominantly on immune cells. It is also present in high levels on enteroendocrine cells expressing PYY and on gut associated mast cells that contain serotonin, and it is thought to promote serotonin release in the colon (Karaki et al., 2006). FFAR2 is crucial to regulating the immune response, specifically neutrophil activation and recruitment in the gut. *Ffar* knockout mice were found to have exacerbated and extended colitis, arthritis, and asthma and increased levels of ROS in the colon (Maslowski et al., 2009). FFAR3 is much less abundant, but is also found on small intestine and colonic enteroendocrine cells. No cells have yet been found to express both receptors. FFAR3 seems to have different responses to different SCFAs and to mediate contractility of the smooth muscle of the colon (Tazoe et al., 2009). FFAR3 is found on the afferent nerve fibers on the portal vein and are necessary for proprionate-induced glycogenesis in the intestines. FFAR2 and 3 are the most well described receptors, but there are a variety of other SCFA receptors that are located on different organs with different specificities (Dalile et al., 2019b). Most of the receptors, including FFAR2 and FFAR3, have a primary role in regulating metabolic output and glycogenesis with secondary roles modulating the immune system. Evidence of SCFAs affecting the immune system is extensive and well documented (Corrêa-Oliveira et al., 2016). Here we will present a brief overview of SCFA immunomodulatory mechanisms and review the literature linking SCFAs to changes in the CNS via the immune system.

Luminal-derived butyrate is a primary form of energy for the epithelial cells of the colon. As such, presence of butyrate is vital to maintaining a strong barrier in the gut (Corrêa-Oliveira et al., 2016). This barrier strength has a substantial impact on the circulating cytokine levels as well as immune cell activation as any bacteria that can cross into the host tissue will initiate a strong innate immune response. SCFAs are able to locally regulate the chemoattractants CXCL1 and CXCL8, both important for neutrophil recruitment. Neutrophils are the first responders to an inflammatory event whether that be injury or infection. They proliferate dramatically in response to cytokines and then just as quickly undergo controlled cell death as other immune cells take over. Neutrophils express FFAR2, which, when activated, decreases chemotaxis. In addition to neutrophil trafficking, SCFAs cause neutrophils to have a decrease in the proinflammatory cytokine TNF (Corrêa-Oliveira et al., 2016). These data indicate that neutrophil inflammatory response seen in patients with depression can be tempered by SCFAs, which will have downstream immune effects. This regulation of the immune response may be another checkpoint for mediating mood.

High concentrations of SCFAs cause histone deacetylase (HDAC) inhibition in innate immune cells including monocytes, dendritic cells (DCs), and macrophages. When these cells are exposed to SCFAs, they do not differentiate as readily and decrease the production of pro-inflammatory cytokines IL-12 and TNF (Corrêa-Oliveira et al., 2016; Chang et al., 2014). The decrease of TNFα and the anti-inflammatory changes evident in macrophage activity indicate that SCFAs tend to reverse the patterns that are evident in patients with MDD. This supports the theory that SCFA antidepressive-like effects may operate, in part, through innate immune regulation.

The effect of SCFAs on the adaptive immune system is complex as there are numerous contributing factors. Exposure of dendritic cells (DCs) to butyrate causes an increase in the expression of enzymes indolamine 2,3-dioxygenase (IDO1) and aldehyde dehydrogenase 1A2 which, in turn, push T cells to a more regulatory phenotype (Gurav et al., 2015). In addition, SFCAs affect the differentiation of T cells by inhibiting the maturation of DCs, causing impaired IL-12 and TNF production in T cells (Kim et al., 2014). T cell differentiation can also be mediated directly by activity of SCFAs. They do not have the FFAR2 and FFAR3 receptors (Park et al., 2015); however, SCFAs can modulate mTOR activity in CD4 helper cells which promotes differentiation into Th1, Th17 or IL-10 producing Tregs (Delgoffe et al., 2009). mTOR modulation can occur through two different SCFA-dependent pathways. First, mTOR activation can be mediated through HDAC inhibition, and second, the SCFAs can be converted into acetyl-coA which increases the metabolic activity of the CD4 T cells and increases mTOR activity (Chen et al., 2014). Changes in systemic immunity are also seen with oral administration of SCFAs. With mice fed butyrate, there was a measurable increase in circulating T regulatory cells (Arpaia et al., 2013). Together these studies show that signaling by SCFAs can modulate gut homeostasis through diverse immune signaling mechanisms. As such, they can be seen as a sort of master regulator, impacting diverse swaths of immune activity. SCFAs have robust therapeutic potential for mediating mood through a variety of mechanisms both direct and indirect.

7. Indoles

Indoles are small molecules derived from tryptophan whose synthesis in mammals is rare. As such, most of the indoles in the body are a result of gut bacteria metabolism through the shikimate pathway (Paley et al., 2018). One of the direct downstream metabolites of indoles is the uremic toxin indoxyl sulfate which is low in animal models of depression (Zheng et al., 2010) and MDD patients (Chen et al., 2017). Indoles are just beginning to be studied in the context of depression, but one of the first promising studies shows that 1-methyl-3-(phenylselanyl)-1*H*-indole reverses stress induced depressive-like behavior in mice (Bampi et al., 2020). Indoles derived from bacteria and plants are potential novel targets for antidepressant therapy and are in need of further investigation (Hamid et al., 2017).

Like SCFAs, indoles can act on the first line of defense from pathogens by increasing the mucus production of endothelial cells as well as strengthening tight junctions (Bansal et al., 2010). Tryptophan catabolites, including kynurenine, kynurenic acid, indoles, and others are principle ligands for the aryl hydrocarbon receptor (AHR) (Fig. 3). The AHR, also known as the dioxin receptor, binds planar exogenous small molecules in the barrier tissues as well as endogenous ligands (Denison

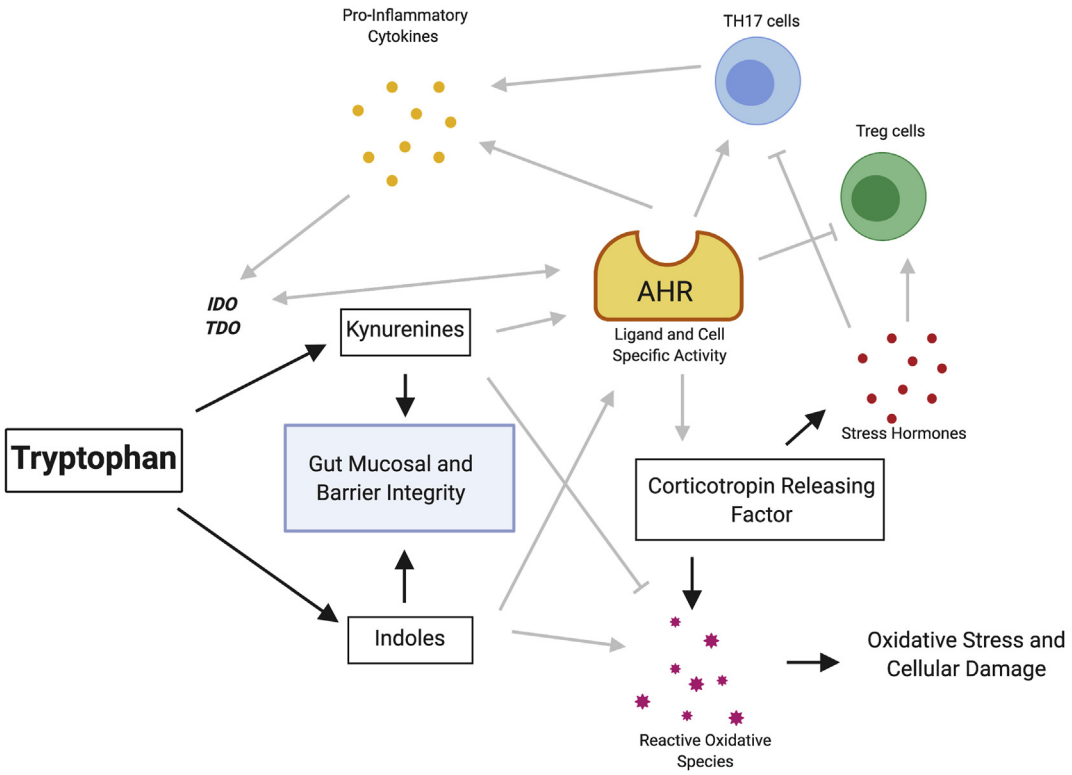

Fig. 3. The aryl hydrocarbon receptor (AHR) has a complex ligand and cell specific repertoire of activity. The nuance of its function depends on the affinity of the ligands available as well as the presence of antagonists (not pictured). Most members of the kynurenine metabolic pathway act as AHR agonists leading to changes in the T cell compartment as well as stress hormone release.

and Nagy, 2003). The characterized list of bacteria that produce these and other AHR ligands is extensive and includes several species of *Lactobacillus, Bacteroides, Fusobacterium, Kleibsella,* among others (Lamas et al., 2018). It is a cytoplasmic receptor and transcription factor that exists in complex with the proto-oncogene c-SRC and heat shock protein 90 (HSP90) which stabilize it in a conformation that increases the affinity of its ligand binding domain. Once a ligand binds, part of the AHR complex translocates to the nucleus and then becomes associated with the AHR nuclear translocator (ARNT) and promotes transcriptional control of a variety of genes with disparate functions (Rothhammer and Quintana, 2019).

Transcriptional patterns can be further modified by interaction with other nuclear proteins, for example, RORgt (Quintana et al., 2008) and c-Maf (Rutz et al., 2011), which differentiate $CD4^+$ cells to become Th17 or induced Tregs respectively. Several other transcription partners that lead to a variety of cell-type-specific transcriptional activities. In all cell types, the activation of AHR leads to the transcription of cytochrome p450 enzymes. These include Cyp1A1 and Cyp1B1 which both degrade small molecules that activate AHR (Schmidt and Bradfield, 1996). In this way, there is consistent negative feedback with AHR activation. AHR interaction with nuclear factor-κB (NF-κB) leads to increased transcription of inflammatory regulators CCL1, interferon responsive factor and B cell-activating factor (BAFF) (Vogel et al., 2007). The interaction of AHR with other transcription factors has been documented but the downstream effects have not yet been thoroughly described.

In addition to these modulatory elements, AHR activity can also be mediated by microbially derived antagonistic ligands, thereby preventing homeostatic cell responses, such as cell cycle regulation and migration (Dietrich and Kaina, 2010). Another mechanism of AHR suppression is through the binding of certain ligands that can change the conformation of the cytoplasmic complex. This allows for the ubiquitination and subsequent proteasome-mediated degradation of AHR (Xing et al., 2012). A final regulatory mechanism is the AHR repressor (AHRR) that binds to the downstream elements of AHR signaling, including ARNT, and suppresses the ability of AHR to conduct transcriptional activity in a ligand-dependent manner (Hahn et al., 2009). Because of the promiscuous nature of the AHR and the diversity of its ligands, it is difficult to predict the transcriptional readout of any single AHR-ligand interaction, especially in the context of the complex metabolism of the microbiome.

In Th17 cells, the interaction between AHR and RORgt in the nucleus leads to an increase in production of IL-22. In addition, in Th17 cells, AHR inhibits STAT1 and STAT5 transcriptional activity. However, the c-Maf/AHR interaction in Tregs leads to increased production of IL-10, IL-21, and AHR leading to positive feedback loop. The role in AHR mediating the balance between Th17 cells and Treg cells is important for homeostasis as lack of Th17s causes an increase in microbial translocation across the epithelial barrier of the intestine (Ouyang et al., 2008). This can then lead to the presence of immunogenic material that can induce a strong immune response which can then influence mood and other CNS functions. Type 3 innate lymphoid cells (ILC3s) are a group of innate immune cells crucial for barrier function which have similar immune activity to Th17 cells. They are also highly influenced by AHR and can change the inflammatory state of the lamina propria of the small intestine via local cytokine release (Qiu et al., 2013). These effects also seem to have a light-dependent circadian component showing the integration between the CNS and gut immune system (Godinho-Silva et al., 2019). These studies emphasize that Th17 and ILC3s are regulated and highly responsive to changes in the bacterial microenvironment through AHR.

Corticotropin-releasing factor (CRF) regulates the stress response and it appears that AHR can upregulate the transcription of *Crf* in a ligand-dependent manner. In this way AHR activation by exogenous ligands can directly impact the stress hormone response (Aguiniga et al., 2019). Most of the current literature, however, is focused on how it impacts the immune system.

In humans, a mutation that decreases the transcription of AHR mRNA

is associated with MDD (Liu et al., 2018). This mutation leads to a decrease in mRNA levels in the cerebellum, colon, and esophagus, but it likely affects most tissues. This decrease in AHR expression is associated with an increase in expression of many enzymes that are critical for the kynurenine pathway including TDO2. These genetic changes in patients with MDD strengthens the argument that dysregulation of this immune-metabolic connection-genetically or through changes in the AHR ligands in the gut lumen-may contribute to mood dysregulation in some patients.

Indole induced activation of AHR regulates the adaptive immune system by mediating maturation and differentiation of T helper cells and T regulatory cells (Mezrich et al., 2010) and their cytokine release (Zelante et al., 2013). Recently, it has also been shown to regulate the cross talk between astrocytes and microglia in the brain (Rothhammer et al., 2018). This indicates that AHR regulates homeostatic immune function in the brain itself as a response to exogenous ligands.

8. Kynurenines

Tryptophan metabolism is completed by both the cells of the gut as well as the microbiota. Kynurenines are the most commonly investigated tryptophan-derived metabolites in the context of the peripheral immune system. Examples include kynurenic acid, quinolinic acid, and 3-hydroxykynurenine to name a few. While the majority of the kynurenic acid used by the body is produced in the gut (with highest concentrations near the colon), it is also found in food products and some traditional medicines at high concentrations (Turski et al., 2009). Patients with disparate etiologies of depression have shown increases of kynurenines in the peripheral blood (Achtyes et al., 2020), especially with respect to circulating tryptophan (Kelly et al., 2016). In a clinical trial using *Lactobacillus* as a probiotic therapy for depression, those treated with the probiotic had an increased 3-Hydroxykynurenine to Kynurenine ratio compared to those who received placebo (Rudzki et al., 2019). 3-Hydroxykynurenine, another member of the kynurenine family of metabolites, acts much like quinolinic acid. As it crosses the blood-brain barrier, it increases the oxidative stress and contributes to apoptosis in the brain (Heyes et al., 1997). Kynurenine can also contribute to macrophage activation through an increase CCL2-mediated migration by monocytes which can target most tissues including the brain (Zang et al., 2017).

Kynurenine activates AHR in CNS cells like astrocytes and peripheral cells including monocytes. In fact, kynurenine AHR activation can mediate monocyte trafficking to the brain as well as rescue depressive-like behavior in the mice (Zang et al., 2017). The aryl hydrocarbon receptor also exhibits bidirectional communication with IDO, the primary initiator of the kynurenine pathway outside of the liver. IDO is highly regulated by the inflammatory state of the environment. Normal basal activity of T regulatory cells (the primary producers of IL-10) plays a critical role in regulating both IDO1 and mood (Laumet et al., 2018). IDO1 is highly upregulated by cytokines including TNFα and IFNγ (Hassanain et al., 1993) and is downregulated by IL-4 and IL-13 (Chaves et al., 2001). It is also regulated by SCFAs, specifically butyrate (Martin-Gallausiaux et al., 2018). The interplay between IDO and AHR further emphasizes the role of kynurenines in tightly modulating both the immune response and metabolic activity.

9. Challenges and new frontiers

9.1. Mapping the metabolic output of microbial communities

The metabolic web of a healthy microbiome has not been fully mapped, but efforts using computer modeling are getting closer to understanding what small molecules are being produced and how they are being used within the gut. The availability of the small molecules not only depends on how much is being produced by each species but, in addition, what is being used by other bacteria in the same niche (Nussinov and Papin, 2017). The bacteria have a codependent metabolic pattern in which metabolites produced by some are used by others.

The challenges facing researchers aiming to understand the metabolic interactions of the microorganisms and the host require the collaboration between several fields, ranging from microbiology to endocrinology. The complexity of this system requires that researchers continue to develop new methods of mapping and experimenting. While experimental work has focused in on the neuroactivity of a select few metabolites, hundreds of unique molecules are crossing our gut walls every day (Kunzelmann and Mall, 2002). It is crucial that we continue to work to identify molecules that could be modulating our health. This will give us a better understanding for therapeutics and novel medications that will supplement the production of our microbiota.

9.2. Understanding how population-level changes influence the immune system

In addition, emphasis should be placed on understanding how these molecules work in concert. Some integral receptors, like AHR, have such a diverse range of specificity and nuanced effects, that in order to understand homeostatic immune states, we must examine how small molecules compete and interact mediating AHR function.

While there may be bioactive effects that mediate the gut-immune system, there is also a high probability that the molecules are able to cross the blood-brain barrier and maybe, like in the case of SCFAs, directly influence the cells in the brain. A starting point of this complex work is to determine the biological effects of the metabolites and small molecules released by a single commensal, non-pathogenic microbe in health and disease.

9.3. Understanding the impact on mood and mental health

Finally, it is important as a field that we begin to segregate the different etiologies of major depressive disorder. Psychologists have separated them based on surrounding life events and presentations. However, this remains difficult as the physiological changes seen in depression vary dramatically form patient to patient. Metanalysis of immunophenotyping data of patients with similar depressive symptoms, may allow for better physiological characterization of this complex disorder.

Clinical trials using probiotics to treat mood disorders and, specifically, depression have generally improved mood scores in patients; however, there are some drawbacks to current approaches. The effect sizes are relatively small and so combined therapies may be necessary. In addition, there is no specific guidance for probiotic selection in clinical trials; thus, most trials use different bacterial strains and even bacterial families, making it difficult to draw direct comparisons. In addition, many studies do not sequence the microbiome before and after treatment to determine the consequences of that particular supplement. Overall, the translational work examining neuromodulatory microbiota-derived metabolites is just beginning. While SCFAs and some tryptophan-derived metabolites have strong translational evidence for clinical promise for the treatment of depression, there are several unexplored molecular targets that present immense opportunity for new scientific discovery and therapeutics.

The link between the gut microbiota, as described in the first part of this review is well established. In addition, the link between immune activation and mood has been revisited for decades with a strong consensus that immunity is linked to mood. Where most work is needed is understanding how immune dysregulation occurs in depression. We propose that direct communication via small molecules is important for mediating the feedback loop between the immune system and the gut microbiota. Of particular interest is the complex, ubiquitous activity of the aryl hydrocarbon receptor as a homeostatic immune regulator. It allows for proper function in a variety of tissues and its activity is so tightly regulated and nuanced that it is the next frontier for study in autoimmunity and depression.

Declaration of competing interest

The authors have no conflicts of interest to report.

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