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The Bidirectional Relationship of Depression and Inflammation: Double Trouble

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Abstract

Depression represents the number one cause of disability worldwide and is often fatal. Inflammatory processes have been implicated in the pathophysiology of depression. It is now well established that dysregulation of both the innate and adaptive immune systems occur in depressed patients and hinder favorable prognosis, including antidepressant responses. In this review, we describe how the immune system regulates mood and the potential causes of the dysregulated inflammatory responses in depressed patients. However, the proportion of never-treated major depressive disorder (MDD) patients who exhibit inflammation remains to be clarified, as the heterogeneity in inflammation findings may stem in part from examining MDD patients with varied interventions. Inflammation is likely a critical disease modifier, promoting susceptibility to depression. Controlling inflammation might provide an overall therapeutic benefit, regardless of whether it is secondary to early life trauma, a more acute stress response, microbiome alterations, a genetic diathesis, or a combination of these and other factors.

Major Depressive Disorder (MDD)

Mood disorders are the most common of the severe psychiatric illnesses. Episodes of major depression occur in both unipolar depression (in which mood varies between euthymia and

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depressed) and bipolar disorder (mood has pathological “highs,” termed hypomania and mania, as well as euthymia and depression). Major depressive episodes are defined in DSM-5 by a constellation of signs and symptoms (DSM-5, 2013). Patients with major depression exhibit alterations in a variety of critical functions including sleep, appetite, psychomotor activity, cognition, and, of course, mood.

Lifetime prevalence of major depression in the United States is 21% of women and 11%–13% of men (Belmaker and Agam, 2008; Kessler et al., 2003). It is the major cause of suicide, now in the top 10 cases of death in the United States, with almost 50,000 reported suicides per year (Mann et al., 2005). Indeed, major depression is associated with a significant reduction in lifespan, in part due to suicide and the remainder due to the marked increase in vulnerability to major medical disorders, including cardiovascular disease and stroke, autoimmune disease, diabetes, and cancer (Benros et al., 2013; Windle and Windle, 2013; Bortolato et al., 2017). Not only are depressed patients more vulnerable to these and other disorders, but their treatment outcomes for these medical disorders are poorer (Katon, 2011). The morbidity and mortality associated with major depression renders it the number one cause of disability worldwide and exerts an extraordinary economic burden on society in terms of lost productivity (Bloom et al., 2011).

Risk factors for depression include family history of depression (approximately 35% of the risk is hereditary), early life abuse and neglect, as well as female sex and recent life stressors. Medical illness also increases the risk of depression, with particularly high rates associated with metabolic (e.g., cardiovascular disease) and autoimmune disorders.

Treatment of depression includes three major modalities: (1) antidepressants and other medications that augment antidepressant action, (2) evidence-based psychotherapy such as cognitive-behavior therapy (CBT) and inter-personal psychotherapy (IPT), and (3) somatic non-pharmacological treatments including electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and vagus nerve stimulation (VNS) (Gartlehner et al., 2017). Monotherapy with either an antidepressant or evidence-based psychotherapy results in the virtual absence of any depressive symptoms and return to the premorbid state, termed remission, in approximately 50% of previously untreated depressed patients (Dunlop et al., 2017) and in 28% in a more heterogeneous mix of “real-world” patients in an effectiveness study (Trivedi et al., 2006). At the current time, there are no clinically useful predictors of response in a given individual to one antidepressant versus another (Zeier et al., 2018) in spite of claims to the contrary (Greden et al., 2019). Such biomarkers are of great interest, as ongoing depression is associated with increasing treatment resistance and increased risk for substance abuse and suicide. Depressed patients with increases in inflammatory markers may represent a relatively treatment-resistant population. In this regard, it is of interest to note that patients with autoimmune disorders have inordinately high prevalence rates of depression. This is discussed in further detail in subsequent sections.

Peripheral and Central Immunity

Mammals are protected by the immune system from infectious agents and many types of insults that cause injury. Immunity involves (1) recognition of infection or damage, (2) immune functions to contain the infection/damage, (3) regulation limiting the magnitude and duration of the immune response that can itself be damaging to tissues, and (4) memory to enhance the future response to the same infectious agent/damage if reencountered (Murphy, 2012). Inflammation or inflammatory response are the result of the activation of the immune system that often manifests as a localized reaction resulting from irritation, injury, or infections; are associated with warmth, redness, swelling and pain, and sometimes fever; and are necessary to eliminate the insult. Many types of immune cells and mechanisms are in place to maintain homeostasis, but dysregulation of their actions often contributes to diseases, with increasing evidence that this occurs in psychiatric disorders, including depression (Murphy, 2012).

The immune system is classically divided into innate and adaptive arms, though these two act cooperatively to ensure proper immune actions. The innate immune system is the first line of defense, because innate immune myeloid cells (e.g., macrophages/monocytes, dendritic cells) and lymphoid cells (e.g., natural killer [NK]) constantly patrol the circulation to provide rapid responses. Receptors on these cells are activated when they encounter damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs); DAMPs (also called alarmins) are host molecules that signal cellular damage (e.g., Heat shock proteins), whereas PAMPS are present on infectious pathogens (Gong et al., 2020). After activation, macrophages and dendritic cells produce cytokines (interleukins and/ or chemokines), which recruit other immune cells to the site of infection or insult. As part of the inflammatory activity, dendritic cells initiate the adaptive immune response by presenting antigens to cells of the adaptive immune system and are therefore also called antigen-presenting cells (APCs).

The adaptive immune system, composed of lymphocytes (T and B cells), is slower to respond, as it often requires recruitment, activation, and differentiation of the lymphocytes to exert effector functions. A key characteristic of adaptive immune cells is their capacity to clonally express a large repertoire of antigen-specific receptors, T cell receptors (TCR), and B cell receptors (BCR), which are produced by site-specific somatic recombination (Smith-Garvin et al., 2009). Each lymphocyte expresses one unique antigen receptor variant. This confers an antigen specificity to the adaptive immune system, which does not exist in the innate immune system, highlighting the specialization of the adaptive immune system in contrast to the innate immune system that respond to a wide variety of DAMPs and PAMPs. Until lymphocytes are activated by “their” antigen, they are considered naive and inactive cells. Upon antigen recognition, they are activated and undergo clonal differentiation to become fully functional effector lymphocytes. B cells clonally proliferate and differentiate into plasma cells, which produce antigen-specific antibodies. Activated T cells can become one of three broad types of effector T cells: cytotoxic, helper, and regulatory. Thus, cytotoxic T cells (CD8+ cells) kill infected cells. T helper (Th) cells influence the behavior and activity of other immune cells, and regulatory T cells (Tregs) suppress the activity of other lymphocytes that control or limit immune responses to prevent autoimmunity. Some

activated B and T cells differentiate into memory cells, which can mount a rapid immune response if the same antigen is encountered again by differentiating into a large pool of specific effector cells (Murphy, 2012).

Microglia—The CNS Immune System

The brain possesses specialized immune cells called microglia that comprise 5%–10% of total brain cells and carry out macrophage-like and other specialized functions (Kim and de Vellis, 2005). Microglia are maintained by self-renewal with minimal contribution from immune cells outside of the CNS, and their main functions are to maintain CNS homeostasis and to provide rapid responses to damage or infection. Microglia exhibit a broad spectrum of activation states upon receiving various stimuli. Recent findings have shown that microglia are important for synaptic modulation (e.g., synapse pruning and neurogenesis) and are activated in many neurodegenerative and neuropsychiatric diseases, where they contribute to pathology by promoting neuroinflammation (Yirmiya et al., 2015). The heterogeneity of microglia suggests that microglia subsets have distinct roles in the brain (Masuda et al., 2019), but a more complete understanding of the complex roles of microglia is necessary to provide further insights in understanding their role in brain function and pathology.

Interfaces between CNS and Peripheral Immunity

There is a role for non-microglial cells in CNS immunity with three other types of CNS macrophages: perivascular, meningeal, and choroid plexus macrophages (for review, see Li and Barres, 2018) as well as lymphoid cells (Beureland Lowell, 2018). These macrophages are localized at the interface of the parenchyma and blood vessels. Under physiological conditions, peripheral immune cells do not enter the brain parenchyma, though some are present in cerebrospinal fluid (CSF) and the meninges (Wilson et al., 2010). However, in certain conditions, macrophages, and T cells, can cross the blood-brain barrier (BBB) and enter the brain parenchyma, generally producing damage (Wilson et al., 2010). The BBB is composed of specialized endothelial cells linked by tight junctions, limiting the entry of immune cells, various blood constituents, and pathogens. Indeed, the BBB prevents >98% of antibodies and small molecules from entering the parenchyma, while assuring the efflux of other molecules. Various hypotheses have been proposed to explain how peripheral immune cells may cross the BBB under pathological conditions (for review, see Ousman and Kubes, 2012; Ransohoff and Engelhardt, 2012). In conditions that weaken the BBB or in regions where the BBB is more permissive, such as the circumventricular organs and choroid plexus, immune cells infiltrate the brain parenchyma via diapedesis. Because the choroid plexus has a secretory epithelium that produces CSF, it also allows the passage of lymphocytes to access and provide immune surveillance of the CSF (for review, see Ransohoff and Engelhardt, 2012). In physiological circumstances, few immune cells are present in the CSF, but a higher percentage of memory or CNS antigen experienced CD4+ T cells are found in the CSF compared to the circulation (Ransohoff and Engelhardt, 2012).

Activated T cells gain access to the brain by extravasation into the tissue, by upregulating many adhesion molecules and integrins, allowing them to roll and adhere to the vessel walls. Upregulation of very late antigen-4 (VLA-4) or lymphocyte function-associated-1 (LFA-1)

on T cells promotes the binding to vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) present on endothelial cells, and infiltration to the parenchyma. Furthermore, the gradient of chemokines produced by the choroid plexus (e.g., CCL9, CCL20) also attracts T cell subsets to the brain, which has particularly been demonstrated in studies of autoimmune diseases (Oukka and Bettelli, 2018; Reboldi et al., 2009). Finally, immune cells are present in the meninges, and the role of meningeal immune cells has been mainly studied in the context of viral, bacterial, or parasitic infections (for review, see Forrester et al., 2018). The recent (re) discovery of the lymphatic system within the meninges of the brain has revealed another pathway for immune cells to reach the meninges (Sandrone et al., 2019). Indeed, the lymphatic system is critical for the drainage of immune cells and soluble factors from the CNS into the deep cervical lymph nodes (Louveau et al., 2015). It has also been proposed that the lymphatic vessels maintain anergy of CNS-reactive T cells within the meningeal spaces promoting T cell tolerance, whereas infections may trigger CNS-reactive T cells to attack the CNS. The immune response within the CNS is not always detrimental, such as after CNS injury when the immune response limits secondary degeneration (for review, see Louveau et al., 2017). Similarly, although pathogenic T cells have been associated with autoimmune diseases and neuropsychiatric and neurodegenerative disease, not all T cells are detrimental to brain function. For example, T cells support cognition under physiological conditions (Kipnis, 2016). Clearly, the immune system in the CNS functions in a unique way compared to peripheral tissues.

Cytokine Production and Regulation

Cytokines are small proteins that affect cell functions and interactions and can have either pro-inflammatory or anti-inflammatory effects. There are many families of cytokines that provide specialized functions. Cytokines are predominantly produced by immune cells, including microglia in the CNS, but other CNS cells such as neurons and astrocytes also produce cytokines. Immune activity including cytokine production is influenced by a myriad of factors, including but not limited to genetics, and previous exposures to pathogens (MacGillivray and Kollmann, 2014). The most studied cytokines in the context of psychoneuroimmunology are interleukin (IL)-6, tumor necrosis factor (TNF), IL-1b, and interferons (IFNs) on the inflammatory side and IL-10 on the resolving side. Table 1 summarizes the cytokines and related molecules studied in the context of depression and lists their main functions.

In the brain, cytokines produced by microglia and other CNS cells are crucial positive modulators of several CNS functions, such as maintenance of neuroplasticity (Stellwagen and Malenka, 2006; Yirmiya and Goshen, 2011). However, excess or prolonged inflammatory cytokine activity perturbs multiple neuronal functions, including impairment of neurotransmitter signaling, disruption of the synthesis, reuptake, and release of neurotransmitters (Deverman and Patterson, 2009; Elmer and McAllister, 2012; Stephan et al., 2012). This, in turn, affects neurocircuit function, including that implicated in mood and cognition (Dantzer et al., 2008; Figure 1). The effects of cytokines on the dopaminergic system have been recently reviewed (Treadway et al., 2019; Felger and Treadway, 2017; Capuron et al., 2012). Relevant mechanisms that may increase cytokine activity in the brain to pathological levels include psychological and physical stressors. Nevertheless, it remains

unclear how the same cytokine exhibit opposite effects on neuronal function depending on the context. It has been proposed that the source and the combination of cytokines dictate the effects of cytokines on brain function. The field of neuroinflammation has been focusing on central cytokines, whereas peripheral cytokines certainly contribute to behavioral effects, as suggested by findings showing that blocking peripheral cytokines is sufficient to tighten the BBB and that blocking BBB disruption is sufficient to exhibit antidepressant actions (Cheng et al., 2018; Menard et al., 2017). There are several well-documented pathways by which peripheral cytokines reach the brain, similarly to the immune cells: (1) through “leaky” regions of the BBB, such as the circumventricular organs, or through disease-induced disruptions of the BBB (Quan and Banks, 2007; Vitkovic et al., 2000), (2) through a neural route via afferent nerve fiber cytokine receptors that relay the signal to the brain parenchyma (Watkins et al., 1995) and (3) through the infiltration of immune cells that produce cytokines after being attracted by a chemokine gradient to the meninges or brain parenchyma (Lewitus et al., 2008).

Cytokines are one of the most studied components of the immune system in depression (for review, Dantzer et al., 2008; Miller and Raison, 2016; Raison et al., 2006), but little is known about the source and the contribution of cytokines in MDD and their mechanisms of action in the brain.

Immune Findings in Depression

Over the past two decades, there has been growing evidence that MDD is associated with a systemic immune activation, comprising abnormality in inflammatory markers, immune cell numbers, and antibody titers (Gibney and Drexhage, 2013; Müller, 2014; Figure 2).

Immune Activation

Aberrant Cytokine Production

It is now well established in multiple meta-analyses (Dowlati et al., 2010; Howren et al., 2009; Liu et al., 2012b; Kö hler et al., 2017) that proinflammatory cytokines and acute phase proteins are increased in MDD patients, with a fairly unanimous consensus of increases in IL-6, TNF, and C-reactive protein (CRP) in the blood of MDD patients compared to healthy controls (Maes et al., 2009; Miller et al., 2009; Stewart et al., 2009). With the advances in the measurement of cytokines by multiplexing (Papakostas et al., 2013), many other cytokines are now evaluated (Kiraly et al., 2017; Syed et al., 2018). A relatively recent meta-analysis of 82 studies including 3,212 MDD patients and 2,798 healthy controls reveals increased levels of IL-6, TNF, IL-10, sIL-2, C-C motif ligand (CCL)2, IL-13, IL-18, IL-12, IL-1RA, and soluble TNF receptor (sTNFR)2 in MDD patients, whereas the level of interferon-γ (IFN-γ) is reduced (Köhler et al., 2017). Gene expression upregulation of inflammatory pathways have also been reported in peripheral blood mononuclear cells (PBMCs) of depressed patients. Similarly to the protein data, the expression of *Il-1β*, *Il-6*, *tnf*, *macrophage migration inhibiting factor* (*mif*), and *Ifnγ* genes are increased in PBMCs of MDD patients compared to healthy controls, whereas *Il-4* mRNA level is decreased (Hepgul et al., 2013). Overall, there is a large heterogeneity in the data, which depends on the cytokine component studied, and is at least partly due to the absence of consideration of the

clinical course and the illness duration, and the effects of potential confounding factors such as comorbidity, medications, fasting status, smoking, assay methodology, or body mass index (BMI) among others.

Are All MDD Patients Exhibiting Increased Cytokine Production?

Not all MDD patients exhibit increased inflammation. Increased inflammatory markers have been associated with atypical symptoms of depression (Lamers et al., 2018), and with suicidal MDD (Black and Miller, 2015), which contrasts with a recent study of measurement of cytokines in never-treated relatively homogeneous MDD patients, for which cytokine levels are elevated in the majority (Syed et al., 2018). This suggests that prior exposure to various regimens of antidepressants might affect the cytokine production in some MDD patients. Although most studies of cytokines in MDD include patients free of antidepressant, these patients have been previously exposed to antidepressants (Dowlati et al., 2010). Therefore, even though the study of Syed et al. reported a relatively small sample size of MDD patients, with an overrepresentation of females and high absolute levels of measured cytokines compared to many other studies, this type of study might provide benefit in understanding the impact of immune dysregulation in MDD independent of prior exposure to antidepressants. It is also plausible that different inflammatory profiles are associated with different subtypes of depression (Dunjic-Kostic et al., 2013; Kaestner et al., 2005; Karlović etal.,2012). Thus,non-melancholic patients exhibit proinflammatory states, whereas melancholic patients, in contrast, exhibit reduced proinflammatory cytokine production (for review, see Kronfol, 2002; Rothermundt et al., 2001a; Rothermundt et al., 2001b). In addition, TNF has been associated with atypical features and chronicity, while IL-6 might represent a “state indicator for acute exacerbation” in melancholic patients (Dunjic-Kostic et al., 2013). Furthermore, higher levels of IL-6 predicted over time the chronicity of depression, as well as higher severity of depression at follow-up (Lamers et al., 2019). CRP and TNF have also been associated with greater symptom severity in MDD (Haapakoski et al., 2015). This is consistent with the findings that low-grade inflammation is associated with treatment-resistant depression (Chamberlain et al., 2019; Strawbridge et al., 2015) and poor treatment response to antidepressants (Uher et al., 2014; Vogelzangs et al., 2014), which will be discussed later in this review. Although there is merit in subcategorizing MDD to fit the different cytokine profiles, the subcategorization should take into account all the disease modifiers to avoid bias in our understanding of the immune response in MDD.

Is Inflammation Unique to MDD?

It is important to note that aberrant blood levels of cytokines have been reported in other psychiatric disorders, such as bipolar disorder and schizophrenia, raising the possibility of common underlying immune pathways among MDD, schizophrenia, and bipolar disorder (Goldsmith et al., 2016). Thus, for example, IL-6, TNF, IL-1RA, and sIL2R are significantly elevated in all three of these disorders during acute illness episodes and reduced after treatment. This suggests that an acute inflammatory state might be present in acutely symptomatic psychiatric patients, which is consistent with findings that psychological stress, a prominent risk factor for depression, induces an inflammatory response, and elevation of inflammatory markers after stress in healthy volunteers, including these proinflammatory cytokines, is associated with the development of depressive symptoms (Maes et al., 1998;

Miller and Raison, 2015, 2016). In addition, ~40% of patients treated with IFN-α for hepatitis C infection or certain types of cancers develop depressive symptoms after starting treatment (Raison et al., 2005). This is reinforced by the notion that environmental factors also contribute to both depression and immune dysregulation. Thus, childhood trauma (e.g., maltreatment, sexual abuse, violence) has been shown to cause long-lasting effects on peripheral inflammation later in life (Baumeister et al., 2016; Coelho et al., 2014; Grosse et al., 2016a; Rasmussen et al., 2019) and is associated with increased risk of depression (Chapman et al., 2004). The co-occurrence of MDD and inflammation is present in individuals with a history of childhood adversity but not in those without the latter (Miller and Cole, 2012). This topic has been covered in great details in a recent review (Nemeroff, 2016). Altogether, although common causes (e.g., stress) are associated with similar outcomes (e.g., cytokine production), it is important to recognize that cytokine production is only one part of the story and a better understanding of the role of cytokines is necessary to move the field forward.

Role of Anti-inflammatory Cytokines

To contain the immune response and prevent harm to the host, there is also induction of anti-inflammatory cytokines, which presumably resolve the immune response. It is important to note that the levels of anti-inflammatory cytokines, including transforming growth factor (TGF)-β and IL-10, are also often elevated in MDD patients, raising the question of their role in depression (Dowlati et al., 2010; Howren et al., 2009; Köhler et al., 2017) and their potential impact on the cellular immune response. Defects in the anti-inflammatory response has indeed been recently associated with resistance to antidepressant treatment and the overall net effect of cytokines in MDD on the immune system seems to be anti-inflammatory (Syed et al., 2018). Therefore, although a wide variety of cytokines are upregulated in MDD patients, the role of these cytokines in depressed patients remains to be specified.

Immune Cells

PBMC Immunophenotypes

It has been speculated that, for example, elevations in IL-6 and Il-1β were associated with a possible activation of monocytes/ macrophages in MDD, whereas elevated levels of sIL-2R produced by activated T cells would serve to downregulate T cell activation. Furthermore, the number of leukocytes (Irwin et al., 1990; Kronfol and House, 1989), neutrophils (Irwin et al., 1990; Kronfol and House, 1989; Kronfol et al., 1983), and monocytes (Müller et al., 1989) are increased in depressed patients. Depressed patients also display increases in the ratio of CD4/ CD8 (T helper/T cytotoxic) cells (Darko et al., 1988; Müller et al., 1989; Tondo et al., 1988), and this increased CD4/CD8 ratio is associated with an increased percentage of CD4 cells and a decreased percentage of CD8 cells. However, evidence that “depression is accompanied by immunosuppression” also exists (Asnis and Miller, 1989; Maes, 1995) and has been exemplified by findings showing decreased lymphoproliferative responses of T cells (Kronfol et al., 1983; Schleifer et al., 1984)or NK cell activity (Irwin and Gillin, 1987; Kronfol et al., 1989; Maes et al., 1992) and decreased number of T helper cells (Schleifer et al., 1989). This raises the question as to whether these apparently

discordant observations are part of a single pathological pathway within the same individual (activation of the innate immune system, but reduction of the adaptive immune system) or whether they represent two independent processes that occur either in different individuals or at different stages of the disease. Recent studies have found that levels of IL-6 are elevated (1) in bipolar patients while cytotoxic T cells are decreased (Wu et al., 2017), and (2) in MDD patients, NK cells and T helper cell maturation are deficient (Grosse et al., 2016b; Syed et al., 2018), suggesting that increased cytokine production and cell immunosuppression can occur in the same individual. It has been proposed that these observations are disease stage and age dependent, speculating that abnormality in the T cells response during aging or a depressive episode (e.g., reduced T regulatory function) would unleash the inflammatory capacity of the monocytes/macrophages to produce cytokines (Grosse et al., 2016b). Consistent with this notion, antidepressant free MDD patients exhibit a less diverse TCR repertoire expressed on T cells than matched non-depressed patients (Patas et al., 2018), resembling symptoms of chronic viral infections, in which T cell often acquire tolerance mechanisms, reducing their activity (Li et al., 2008). However, further studies are warranted to immunophenotype MDD cells and to identify which cell(s) are responsible for the cytokine production. Rather than inhibiting cytokine(s) to improve MDD, it might be more beneficial to eliminate particular immune cell(s).

PBMC Gene Networks

Some transcriptomics analyses have started to identify networks of expression of inflammatory genes in subsets of PBMCs in depressed patients. Thus, the gene expression of the *ApoE receptor ApoER2* decreases in lymphocytes (Suzuki et al., 2010), whereas the gene expression of *triggering receptor expressed on myeloid cells 1* (*trem-1*), *DNAX-activation protein of 12 kDa* (*Dap12*), and *purine-rich Box-1* (*pu.1*) increases in monocytes of depressed patients (Weigelt et al., 2011). Furthermore, various immune-inflammatory processes, such as the nuclear factor kB (NF-κB) pathway, which is important for cytokine production as discussed later in the review, IL-1β, IL-6, and TNF signaling pathways, toll-like receptor pathway, NK cell activation pathway, IFN-α/β signaling pathway, oxidative stress pathways are affected in MDD patients' PBMCs (Beech et al., 2010; Elovainio et al., 2015; Galecki et al., 2012; Jansen et al., 2016; Leday et al., 2018; Mostafavi et al., 2014; Yi et al., 2012), reinforcing the idea that immune pathways contribute to MDD.

Th Cell Differentiation

Cytokines are required for the differentiation of T helper (Th) subsets, suggesting that the chronic production of cytokines found in MDD patients might influence Th cell fate. There is limited information available about the roles of the T helper CD4+ cells: Th1, Th2, Th17, and Treg cells in depression, which includes the findings that depressed patients have elevated levels of Th1 and Th2 cytokines (Myint et al., 2005), and the Th1/Th2 (IFN-α/IL-4) ratio is increased in depressed patients (Maes et al., 1992). In contrast, antidepressants reduce the Th1/Th2 ratio (Kubera et al., 2001a). MDD patients also have elevated blood levels of Th17 cells (Chen et al., 2011), and the levels of Th17 cells were highest in patients with high risk of suicide (Schiweck et al., 2020). *In vitro* activation of CD4 cells isolated from patients with generalized anxiety disorder induces them to acquire a Th17 phenotype (Ferreira et al., 2011; Vieira et al., 2010), and patients with autoimmune diseases with

elevated Th17 cells often exhibit comorbid depression (Kurd et al., 2010; Patten et al., 2017). Consistent with these findings, IL-17A was found to be elevated in some (Chen et al., 2011; Davami et al., 2016), but not all (Kim et al., 2013; Liu et al., 2012a), MDD patients, IL-17A predicts treatment response to certain antidepressants (Jha et al., 2017). Anti-IL-17A (Ixekizumab) treatment reduces depressive symptoms in 40% of psoriasis patients experiencing MDD (Griffiths et al., 2017), whereas blocking the downstream effects of IL-17A by blocking its receptor using anti-IL-17RA (Brodalumab therapy) has been associated with increased suicidality risk and psychiatric disorders in psoriasis patients (Lebwohl et al., 2018). Studies in rodents provides corroborative evidence of these detrimental links to Th17/IL-17A, such as administration of IL-17A in rodents promotes depressive-like behaviors (Nadeem et al., 2017), stress increases IL-17A levels (Cheng et al., 2018; Gu et al., 2018; Lu et al., 2017; Zhang et al., 2019), brain accumulation of Th17 cells (Beurel et al., 2013, 2018), and increased splenic Th17 cells after stress induced by social defeat (Ambrée et al., 2019). This suggests that Th1 and Th17 cells also participate to the production of proinflammatory cytokines, and targeting these cells might provide antidepressant actions.

Antibody Production

Antibodies have also been implicated in the physiopathology of depression (Denburg et al., 1988). Thus, a high titer of anti-phospholipid antibodies was found in 63 depressed patients compared to healthy controls (Gorman and Cummings, 1993; Maes et al., 1993). In addition, the presence of anti-ribosomal-P antibodies has been associated with depression and psychosis in patients with lupus erythematosus (Nojima et al., 1992; Schneebaum et al., 1991; Tzioufas et al., 2000; Watanabe et al., 1996). Furthermore, CSF anti-N-methyl-D-aspartate receptor NR2 antibodies are elevated in systemic lupus erythematosus patients with active neuropsychiatric manifestations, and these are associated with BBB damage (Hirohata et al., 2014), whereas only the serum level of anti-Sm antibodies but not serum levels of anti-NR2, anti-P, or anti-phospholipid antibodies contributes to the BBB disruption in these patients (Hirohata et al., 2018). Nevertheless, a better understanding of the role of antibodies in MDD is necessary.

Potential Causes of Immune Activation in MDD Patients

Genetic Contribution to Cytokine Production

Because of the sizeable contributions of heredity in depression vulnerability, it has been proposed that the physiology of immune function in depression may be, in part, predicted by genetic mechanisms. Over the past few years, the number of samples in genome-wide association studies (GWASs) has grown into the hundreds of thousands, with a number of gene variants contributing very small effects to depression vulnerability (Border et al., 2019; Howard et al., 2019). Among the 44 risks variants identified in MDD, 4 risk variants relate to immune responses: *LACC1*, *OLFM4*, *TIAF1*, and *NR4A2* (Wray et al., 2018). With the advance of RNA sequencing, networks of genes with association to inflammation in depression pathogenesis have been identified. In addition, polymorphisms in the genes encoding IL-1β, IL-6, IL-10, TNF, MCP1/CCL2, CRP, and phospholipase-A2 (PLA2) have

been the most replicated findings in MDD (Barnes et al., 2017). However, the contribution of these polymorphisms to MDD remains difficult to determine, as, for example, a polymorphism in the IL-1β promoter at position 511, has been associated with higher depressive symptoms severity whether the polymorphism is associated with increased IL-1β production (allele 511T) or low IL-1β production (allele 511C) (Fertuzinhos et al., 2004; Hwang et al., 2009; McCulley et al., 2004; Rosa et al., 2004; Yu et al., 2003). Similar results were found with polymorphisms in the TNF, CRP, and CCL2 promoters (Bufalino et al., 2013). This discrepancy might be due to the facts that not all depressed patients exhibit inflammation, and the environmental factors and gene-environment interactions are likely more important than pure genetic factors to account for depression. Furthermore, the same genetic variants also increase the risks for inflammation-associated metabolic diseases. Finally, genome-wide methylation profiles in whole blood showed that IL-6 methylation is decreased in depressed patients with increased levels of IL-6 and CRP (Crawford et al., 2018; Uddin et al., 2011). Altogether these findings support the notion that epigenetics profiles of inflammatory genes in MDD might provide information on the immune biology of MDD.

Is There an Infectious Contribution to Immune Alterations in MDD?

The fact that MDD is associated with a dysregulation of the immune response raises the question as to whether MDD patients are more affected by infections than the general population. A past history of MDD has been associated with an increased risk of infections (Andersson et al., 2016; Irwin et al., 2011; Seminog and Goldacre, 2013; Troidle et al., 2003). A large retrospective study of ~50,000 US college students found increased odds of ear infection, bronchitis, sinus infection and streptococcal throat infection in students reporting depression (Adams et al., 2008). Furthermore, depression increases the risk of infections after coronary artery bypass grafting (Doering et al., 2008), for herpes zoster in older adults (Irwin et al., 2011, 2013), predicts the immune system rate decay in HIV patients (Cruess et al., 2005), and prolongs increased proinflammatory cytokines levels after influenza vaccination (Glaser et al., 2003). An increased risk of infection after the onset of depression remaining relatively stable over time, and a relationship between the risk of infections and the number of depressive episodes, with a relative risk of infections of 64% with one depressive episode increasing to 84% with ≥4 depressive episodes, were found in a Danish population-based prospective study including 976,398 individuals of whom 142,169 had an history of depression between 1995 and 2012 (Andersson et al., 2016). The interpretation of the study should be, however, taken with caution as socioeconomic status was not controlled for but could account for the differences observed. There is also evidence that various viral and bacterial infections (e.g., gastroenteritis-related virus, influenza virus, herpes virus, Epstein-Barr virus, cytomegalovirus, and Borna disease virus) are associated with depressive symptoms and are known to induce the production of cytokines (Yirmiya et al., 2015), suggesting a bidirectional communication between cytokines and mood. All these studies suggest that immune responses in MDD patients are altered in a way that MDD patients are more prone to infections, which is consistent with the observation of immunosuppression in MDD patients. This also reinforces the idea that, although there is an increased production of cytokines in MDD, other parts of the immune response such as the

adaptive immune system might participate in increased susceptibility to infections that in turn might impact the long-term immune characteristics.

Autoimmune Diseases and MDD

The epidemiological link between psychiatric and autoimmune diseases has been observed for almost a century (Nissen, 1936). Thus, there is an increased risk of developing subsequent autoimmune diseases (rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, systemic lupus erythematosus) in depressed patients (Andersson et al., 2015; Dickens et al., 2002; Euesden et al., 2017; Kurina et al., 2001; Patten et al., 2017). Reciprocally, patients with autoimmune diseases have some of the highest rates of comorbid depression. Thus, for example, MDD is less common early in multiple sclerosis than in its later stages (Feinstein et al., 1992) and more prevalent in relapsing-remitting than progressive multiple sclerosis (Zabad et al., 2005) and might correlate with relapses (Mooreet al., 2012). Cytokines and T cells have been proposed to contribute to both multiple sclerosis and depression pathologies (Feinstein et al., 2014). Th17 cells in particular have attracted attention as they are pathogenic in many autoimmune diseases, and anti-IL-17A therapy induces remission of depression in 40% of psoriasis patients experiencing moderately severe depression (Griffiths et al., 2017), whereas blocking the downstream effects of IL-17A by blocking its receptor using anti-IL-17RA therapy has been associated with increased suicidality risk and psychiatric disorders in psoriasis patients (Lebwohl et al., 2018), suggesting that Th17 cells could be a potential therapeutic target in populations of MDD patients with autoimmune diseases with elevated levels of Th17 cells.

Other Co-morbidities Associated with MDD and Linked to Inflammation

It has been estimated that more than half of MDD patients have associated comorbidities, and more than a third of MDD patients exhibit drug and alcohol dependence (Hasin et al., 2018; Kessler et al., 1996), which are often associate with microglial inflammation (He and Crews, 2008). Depression also increases disease rate progression and death in cancer (Bortolato et al., 2017), cardiovascular diseases (Rudisch and Nemeroff, 2003), diabetes, renal diseases (Hedayati et al., 2009), and obesity (Hasler et al., 2004), all diseases associated with increased inflammation. In the case of diabetes, anti-diabetic drugs such as the thiazolidinediones or pioglitazone, which are peroxisome proliferators activated receptor (PPAR) agonists, increase insulin sensitivity and normalize glycemia, affecting also cytokine production (Nanjan et al., 2018), have been shown to improve depressive symptoms in diabetic patients (Moulton et al., 2018) or as add-on or monotherapy in MDD or bipolar patients (Colle et al., 2017). However, this was not confirmed in a recent study with bipolar depressed patients (Aftab et al., 2019). A large cohort study found that newly diagnosed type 2 diabetic patients treated for a year with glucagon-peptide-1 agonists and dipeptidyl peptidase-IV inhibitors therapy, which increase insulin secretion, exhibited a reduction in depression symptoms, which was correlated with reduced CRP levels, suggesting that reduction of inflammation might provide an antidepressant effect (Moulton et al., 2016). It remains, however, to be determined whether, the observed antidepressant effect resulted from improvement of the diabetic pathology, and if MDD patients without diabetes would benefit from such agents. The same precautious can be applied to other co-morbidities associated with inflammation and depression.

Peripheral versus Central Inflammation

Besides systemic inflammation, many studies are now focusing on CNS inflammation. In MDD patients, central immune dysregulation, also called neuroinflammation, has been analyzed at the level of cytokines in CSF or post-mortem tissue, and at the level of the cells involved in the immune response (e.g., microglia, astrocytes, or infiltrating immune cells) using both post-mortem tissue and positron emission tomography (PET) imaging. Indeed, expression level of the translocator protein (TSPO), analyzed by PET scans using TSPO ligands, is low in the healthy brain and is upregulated locally during neuropathological conditions, and has been therefore used to measure neuroinflammation (Rupprecht et al., 2010). It is, however, important to note that the expression of TSPO initially thought to represent microglia activation, has been recently proposed to also measure local myeloid cell proliferation, or monocytes infiltration (Owen et al., 2017). Using the [^{18}F]FEPPATSPO ligand, elevations of TSPO volume in prefrontal cortex, insula, and anterior cingulate cortex that correlated with depression severity (Setiawan et al., 2015) and duration (Setiawanet al., 2018) have been reported, whereas no correlation was found with other ligands (Hannestad et al., 2013). A recent study found that the serum level of products synthetized by activated microglia and actively removed from the brain (e.g., TNF and prostaglandin E2), normalized to peripheral CRP level predicts TSPO volume in depressed patients, reinforcing the role of gliosis in depression (Attwells et al., 2019). Microglial activation is also found in the hippocampus of multiple sclerosis patients and correlates with depressive symptomatology (Colasanti et al., 2014). Increased Toll-like receptor (TLR)3 and TLR4 mRNA in post-mortem tissue also correlate with increased microglial activation, as TLR3 and TLR4, which recognize DAMPs and PAMPS, are critical in the induction of cytokine production (Pandey et al., 2014). Cytokine concentrations are also elevated in post-mortem brain tissue (Shelton et al., 2011). Furthermore, a recent meta-analysis suggests increased microglial activity is associated with increased IL-6, IL-8, and TNF levels in CSF and brain parenchyma of MDD patients (Wang and Miller, 2018) and reduced astrocytes and oligodendrocytes numbers in MDD patients (Enache et al., 2019). It has been speculated that the reduction of the astrocytic population is associated with a more permeable BBB, allowing the recruitment and infiltration of monocytes to the brain parenchyma (Enache et al., 2019). It is important to note that suicidal patients exhibit increased recruitment of monocytes (Torres-Platas et al., 2014), as well as increased microglial priming and activation (Steiner et al., 2008), whether or not they exhibit psychiatric symptoms. Microglial activation has also been reported in illness-associated depression. Indeed, many of the bacterial and viral infections we discussed previously associated with depression, induce microglia activation (Rock et al., 2004). Similarly, immune challenges in humans (e.g., endotoxin [LPS] or *Salmonella typhi* administrations) are known to activate microglia and induce depressive symptoms; the severity of the symptoms directly correlates with high blood levels of proinflammatory cytokines (Grigoleit et al., 2011; Harrison et al., 2009; Reichenberg et al., 2001). Consistent with this, neuroinflammation induced by microglia has been thought to be responsible for the high prevalence of depression in HIV-infected patients (Del Guerra et al., 2013; Kaul et al., 2001). However, data also suggest that microglia are suppressed during depression, as, for example, results of PET studies demonstrating reductions in glial cells, but not neurons, in the subgenual anterior cingulate (Cotter et al., 2001a, 2001b; Ongür et al., 1998) or in

many brain regions (Hannestad et al., 2013) of depressed patients compared to healthy controls. This might explain some of the discordant results found with NSAIDs on depressive symptoms (discussed later in the review). Indeed, cyclooxygenase-1 (COX-1) inhibitors, are associated with increased depressive symptoms (as opposed to COX-2 inhibitors that are antidepressant), and COX-1 is predominantly active in microglia, whereas COX-2 is active in neurons and astrocytes (Choi et al., 2009) reinforcing the notion that suppression of certain microglial activity is associated with depressive symptoms. With the recent findings on the various phenotypes of microglia in healthy brain, it is plausible that certain populations of microglia have beneficial roles, whereas others, in contrast, are detrimental in depression. Loss of beneficial microglia or enrichment of detrimental microglia may enhance depression, but such a hypothesis will need further testing experimentally.

Effects of Antidepressants on Inflammation

The role of inflammation in treatment response is of paramount importance. There are two major questions that have been addressed. The first is whether successful treatment of depression is associated with a reduction in inflammation. The second is whether anti-inflammatory treatments are effective antidepressants, especially in depressed patients with evidence of increased inflammation. Although no currently approved treatments for depression were developed with the intent of modulating the immune response, there is evidence that conventional antidepressants have an anti-inflammatory effect and that response may depend partially on immune phenotype. The largest meta-analysis of 45 studies representing 1,517 MDD patients revealed that antidepressant treatment significantly decreases peripheral levels of IL-6, TNF, IL-10, and CCL2, but these are not associated with treatment response (Köhler et al., 2018). Reduction of IL-6 by antidepressants has been reported in various meta-analyses (Hannestad et al., 2011; Hiles et al., 2012; Strawbridge et al., 2015; Wang et al., 2019; Wie dłocha et al., 2018), although they are very heterogeneous. Sources of heterogeneity include baseline inflammation, BMI, smoking, methodology/standardization, type of depression (melancholic versus atypical depression), and class of antidepressants. These factors were not always taken into account due to lack of data availability. For example, the selective serotonin reuptake inhibitors (SSRIs) reduce IL-1β, IL-6, and TNF (Wang et al., 2019). CBT also exhibits anti-inflammatory actions in responders (Syed et al., 2018). In other studies, in contrast, antidepressants such as serotonin and norepinephrine reuptake inhibitors (SNRIs) induce IL-6 and TNF production (Hannestad et al., 2011; Warner-Schmidt et al., 2011; Piletz et al., 2009). Treatment with ECT also induces transient elevation of plasma proinflammatory cytokine levels (Hestad et al., 2003; Lehtimäki et al., 2008), and increases the numbers of monocytes, NK cells and granulocytes. In rodents, ECT has been associated with microglial activation (Wennström et al., 2006). Altogether, these findings suggest that the effects of antidepressants on cytokines remain unclear, though it is generally thought that antidepressants shift the balance toward an anti-inflammatory response (Kubera et al., 2001b; Lanquillon et al., 2000; Maes et al., 1999; Sluzewska et al., 1997). Conversely, proinflammatory cytokine levels, especially TNF, have been shown to be elevated in treatment-resistant depressed patients, suggesting a negative correlation between treatment response and proinflammatory cytokine levels

(Kubera et al., 2001b; Lanquillon et al., 2000). In contrast, elevated levels of IL-17A at baseline is associated with greater reduction of depression severity after treatment with two antidepressants in combination therapy, buproprion-SSRI, (Jha et al., 2017), whereas higher CRP levels at baseline were reported to predict better treatment outcomes with either an SSRI or SNRI (Uher et al., 2014).

Impact of Anti-inflammatory Approaches on MDD Symptoms

There is a comparatively larger body of literature examining depression response following treatment that modulates the immune system. Patients with inflammatory illnesses, especially autoimmune diseases, treated with immune suppressive drugs often experience improvement in depression symptoms. Trials in this area have focused on two drug classes, non-steroidal anti-inflammatory drugs (NSAIDs), and cytokine inhibitors. Most of the studies have used NSAIDs as add-ons to conventional antidepressants, though data also exist on monotherapy with NSAIDs. A recent meta-analysis comprised of 36 RCTs including data from 10,000 patients found that both monotherapy and add-on NSAID therapy, cytokine-inhibitor monotherapy, statin add-on therapy, glucocorticoid add-on therapy, and minocycline (microglia inhibitor) add-on and monotherapy possess antidepressant efficacy (Köhler-Forsberg et al., 2019). However, previous studies concluded that the efficacy of NSAIDs on depressive symptoms is negligible (Eyre et al., 2015), possibly due to the inclusion of studies using aspirin that has no effect on depression. Cytokine inhibitor monotherapies are promising as 4 out of 6 anti-inflammatory drugs ameliorate depression (Kappelmann et al., 2018; Köhler-Forsberg et al., 2019). However, it is important to note that these studies were conducted in patients with comorbid inflammatory diseases (e.g., psoriasis, rheumatoid arthritis), which may have a distinct pathophysiology. Furthermore, TNF inhibitors such as etanercept (Tyring et al., 2013; Tyring et al., 2006), adalimumab (Loftus et al., 2008; Menter et al., 2010), IL-4Ra antagonists (Simpson et al., 2015) or IL-12/IL-23 antagonists (Langley et al., 2010), anti-IL-17A antibody (Ixekizumab [Griffiths et al., 2017]) or anti-IL-6 antibody (Sirukumab [Sun et al., 2017]) have all been shown to be more efficacious than placebo in the treatment of MDD symptoms. In non-randomized and/or non-placebo controlled trials that targeted TNF or IL-6, similar effects have been observed (Kappelmann et al., 2018), indicating an improvement of depressive symptoms with cytokine inhibitor treatments. Infliximab, a TNF-neutralizing antibody, only benefits a sub-population of treatment-resistant MDD patients with elevated levels of inflammation (CRP >5 mg/ L) (Miller and Raison, 2015; Raison et al., 2013) or patients with a history of childhood trauma (McIntyre et al., 2019). In a recent multisite study, infliximab did not significantly reduce depressive-symptoms in bipolar depressed patients (McIntyre et al., 2019). All these anti-inflammatory treatments show relatively goodsafety profiles, without major side effects noted, but caution should be taken as the trials were of short duration (Köhler-Forsberg et al., 2019). Overall, these findings suggest that cytokine inhibitor approaches provide benefit in depressed patients with prominent inflammation, but it remains to be determined whether the improvement is due, at least in part, to their effects on somatic diseases. Although all these drugs aim at reducing inflammation, they all target different mechanisms involved in the inflammatory process. NSAIDs inhibit COX-2, which is involved in the induction of inflammation. Cytokine inhibitors selectively inhibit

cytokines. Glucocorticoids act upon a myriad of targets. Statins decrease CRP levels and inhibit lymphocytes. In contrast, drugs targeting circulating monocytes to prevent their infiltration in the brain, such as the C-C chemokine receptor (CCR)2 inhibitor (pioglitazone) have no effect on depressive symptoms (Dean et al., 2017; Rasgon et al., 2016; Sepanjnia et al., 2012). Anti-inflammatory drug adjunctive treatment of antidepressants seems also to improve efficacy of the antidepressant, and treatment-resistant depressed patients may also benefit from anti-inflammatory drugs (Raison et al., 2013). Mesenchymal stem cell therapy, which has been studied fairly extensively in rodent models of a variety of neuroinflammatory conditions (Regmi et al., 2019) and in humans, produces a pan-inhibition of inflammation after intravenous administration characterized by long-lasting (>6 months) reductions in TNF and CRP (Tompkins et al., 2017). There is currently an ongoing NIH-funded clinical trial in patients with comorbid MDD and alcohol-use disorder.

Overall, there is a large body of evidence that immune responses are dysregulated in MDD patients (Figure 3). Most of these findings have been replicated and expanded in rodent and non-human primate models to identify the mechanisms of action and the cause of the dysregulated immune responses in order to develop new treatments targeting the immune system that may benefit MDD patients.

Possible Molecular Basis of Inflammation in MDD

As discussed in the previous section, there are likely several “sources” of immune dysfunction that contribute to the pathogenesis of depression: infection, microbiome alterations, medical illness, stress, and other factors (Figure 4).

HPA Axis and SNS

From Stress to Inflammation—The HPA axis and the sympathetic nervous system (SNS) are activated in response to various types of stress and are known to be immunoregulatory (for review, see Sternberg, 2006). The HPA axis consists of hypothalamic corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which release adrenocorticotropic hormone (ACTH) from the anterior pituitary gland, which, in turn, releases cortisol (corticosterone in rodents) from the adrenal cortex, whereas the SNS promotes the secretion of catecholamines, norepinephrine, and epinephrine, from the adrenal medulla and sympathetic nerve endings. Both cortisol and catecholamines regulate inflammation, acting as immunosuppressants, inhibiting leukocyte trafficking and activation, as well as inflammatory cytokine production (for review, see Dhabhar, 2009). Some subsets of T cells even undergo apoptosis upon receiving a glucocorticoid signal (Pariante and Lightman, 2008).

These relationships are also bidirectional in that inflammatory cytokines also activate the HPA axis and the SNS, similarly to what occurs in infection and injury (for review, see Kenney and Ganta, 2014). Depression is often associated with hypercortisolemia and glucocorticoid resistance (Raison and Miller, 2003). Stress, particularly in early life, including maternal stress during the intrauterine period, affects glucocorticoid sensitivity via epigenetic mechanisms, turning down the sensitivity of the immune system to cortisol (for review, see Wadhwa et al., 2011). These changes in the communication between the HPA

axis and immune system lead to increased rates of inflammatory and metabolic diseases in survivors of childhood abuse and neglect, as well as increased depression (Heim et al., 2008).

The autonomic nervous system is also altered in depression, with increased sympathetic activity (Murphy, 1991) and lower parasympathetic tone. The parasympathetic nervous system has also been implicated in immune function. Sickness behavior, a physiological and behavioral response associated with increased immune response activity, is, in part, mediated by the vagus nerve, through immune cells (e.g., macrophages and dendritic cells) present in the perineural sheath (Dantzer, 2009) that relay the signals from proinflammatory cytokines (IL-6, TNF, IL-1β) to the brain (Dantzeret al., 2008). Stimulation of the vagus nerve through cholinergic signaling, in contrast, exerts anti-inflammatory properties, reducing proinflammatory cytokine production.

TLR4-Mediated Inflammation

It has become clear that immune activity in the brain itself is important. Thus, brain-induced immune activation has been partially illuminated by the discovery of alarmins produced in the brain in response to stress that trigger toll-like receptor pathway-dependent cytokine production. Toll-like receptors are a major class of receptors that detect DAMPs and PAMPs and are critical for the innate immune response. Although the prototypic pathway involving lipopolysaccharide (LPS)-induced sickness behavior has pointed toward the role of TLR4 in regulating cytokine-dependent induction of depressive-like behavior, the finding that TLR4 knockout mice are resistant to depressive-like behavior (Cheng et al., 2016) confirmed its importance. Upon ligand recognition, TLR4 activates glycogen synthase kinase-3 (GSK3) that activates NF-κB to promote proinflammatory cytokine production (Martin et al., 2005). However, only recently have some additional ligands responsible for the activation of TLR4 in depressive-like behaviors been discovered. These include the alarmins: high-mobility group box 1 protein (HMGB1), adenosine triphosphate (ATP), or Myeloid-related protein 8/14 (Mrp8/14, also called S100A8/9) (Cao et al., 2013; Cheng et al., 2016; Gong et al., 2018; Wang et al., 2018; Wu et al., 2015). Psychological stressors increase TLR4-induced inflammation (Jope et al., 2017). TLR4 activation promotes upregulation of its own expression, and TLR4 mRNA and protein have been found elevated in both the periphery and CNS of MDD patients (Hung et al., 2014). Furthermore, TLR4 levels are restored after successful treatment of MDD, confirming a role for TLR4 in MDD patients (Raison and Miller, 2017).

Inflammasome

Activation of the TLR4 pathway is also associated with activation of the inflammasome pathway (Fleshner et al., 2017), though it is not required. The inflammasome pathway is part of the innate immune response and is responsible for the production of IL-1b and IL-18 (for review, see Guo et al., 2015). Nod-like receptor (NLR), caspase-1, and apoptosis-associated speck-like protein containing C-terminal caspase recruitment domain (ASC)-1 comprise the inflammasome complex. Once activated, pro-IL-1b and pro-IL-18 are cleaved by caspase-1 to produce active IL-1b and IL-18. NLRP3 induces CNS inflammation and increases susceptibility to depressive-like behaviors, and NLRP3- and caspase-1-deficient mice are

resilient to depressive-like behaviors (Alcocer-Gómez et al., 2014; Iwata et al., 2016; Wong et al., 2016). In contrast, inflammasome activation is prevented by antidepressants (Alcocer-Gómez et al., 2017). In addition, expression of NLRP3 and caspase-1 in circulating immune cells of MDD patients is increased, suggesting that MDD patients have an activated NLRP3 inflammasome, which correlated with increased blood IL-1β and IL-18 (Alcocer-Gó mez et al., 2014; Syed et al., 2018). Interestingly, caspase-1 cleavage of glucocorticoid receptors induces glucocorticoid resistance in leukemia cells (Paugh et al., 2015), and glucocorticoid resistance has been associated with MDD (Raison and Miller, 2003), suggesting a potential pathway whereby glucocorticoid resistance might originate.

IDO/Kynurenine Pathway

Stress has also been shown to induce the indoleamine 2,3-dioxygenase (IDO)/kynurenine pathway through cytokine production. IDO is responsible for the first step of tryptophan catabolism. It reduces tryptophan levels so less tryptophan is available for the synthesis of serotonin, which is important because serotonin depletion has been hypothesized to promote depression. IDO is activated in macrophages, dendritic cells, endothelial cells, and brain glial cells comprising microglia (Dantzer, 2009) by signaling from proinflammatory cytokines, such as IL-1β, TNF, and IFN-γ, as well as psychological stress or glucocorticoids (Kiank et al., 2010) and IDO is inhibited by anti-inflammatory cytokines (Cervenka et al., 2017). IFN-α-induced depression development and severity in hepatitic C patients is directly associated with an increase in CSF and peripheral tryptophan metabolism through the kynurenine pathway (Capuron et al., 2002, 2003; Raison et al., 2010). When tryptophan is catabolized, intermediates collectively known as kynurenines are produced (Cervenka et al., 2017). Consistent with this, in rodents, administration of L-kynurenine induced depressive-like behaviors, whereas LPS-induced depressive-like behaviors are blocked by an IDO competitive inhibitor (O'Connor et al., 2009a, 2009b).

BBB Disruption

It is only recently that researchers are starting to tease apart the contribution of peripheral and central inflammation in depression with the discovery of the disruption of the BBB in depressive-like behaviors allowing peripheral signals to reach the brain, reinforcing the importance of the findings in MDD patients of a dysregulated peripheral immune response. A compromised BBB was described 40 years ago in MDD patients (Niklasson and Agren, 1984) but only recently in mice exhibiting depressive-like behaviors, independently of the stressor (Cheng et al., 2018; Menard et al., 2017). Both IL-6 and TNF have been shown to increase BBB permeability, and blocking IL-6 or TNF actions decreases stress-induced BBB opening (Cheng et al., 2018; Menard et al., 2017). Furthermore, closing of the BBB, using the sphingosine-1 phosphate receptor inhibitor, fingolimod, is sufficient to rescue learned helplessness in mice (Cheng et al., 2018). One question remaining regarding the opening of the BBB after stress is the biological consequence for the brain, and whether immune cells infiltrating the brain take advantage of this mechanism. It has been shown that both T cells and monocytes infiltrate the brain after stress. Thus, Th17 cells are able to accumulate in the hippocampus and prefrontal cortex of mice exhibiting depressive-like behavior and Th17 cells are sufficient to promote depressive-like behaviors (Beurel et al., 2013; Beurel et al., 2018). Whether these brain Th17 cells are required to induce depressive-like behavior

remains to be determined. Similarly, peripheral monocytes infiltrate the brain and promote anxiety-like behaviors (McKim et al., 2018; Wohleb et al., 2013, 2014). These findings provide new avenues to identify potential relevant peripheral biomarkers associated with MDD and selective target(s) to induce antidepressant effects.

Microbiome

The dysregulated peripheral immune response in MDD patients might also result from changes at the microbiome level. The microbiome has increasingly been implicated in shaping the immune response and brain functions (gut-brain axis) (for review, see Foster et al., 2017). Recent evidence indicates the presence of microbiome alterations in depressed patients (Rogers et al., 2016), which therefore might contribute to dysregulated inflammatory responses. MDD patients exhibit significant changes in the relative abundance of *Firmicutes*, *Actinobacteria*, and *Bacteroidetes* compared to healthy individuals (Zheng et al., 2016; for review, see Cheung et al., 2019). A recent study with two large cohorts of Europeans reported that patients with depression are deficient in several species of gut bacteria (*Coprococcus* and *Dialister)* (Valles-Colomer et al., 2019). *Coprococcus* in particular has been associated with activity of the dopamine pathway, which is affected in depressed patients, and also leads to the production of butyrate, an anti-inflammatory signal, yet, depressed patients are inflamed. In addition, *Coprococcus* is positively associated with measures of quality of life (Valles-Colomer et al., 2019). A recent meta-analysis of 10 studies reported that the findings were inconsistent at the phylum level, whereas at the family level, *Veillonellaceae*, *Prevotellaceae*, and *Sutterellaceae* were less abundant and *Actinomycetaceae* more abundant in MDD patients than healthy controls (Sanada et al., 2020). At the genus level, *Coprococcus*, *Faecalibacterium*, *Ruminococcus*, *Bifidobacterium*, and *Escherichia* were reduced in MDD patients compared to healthy controls (Sanada et al., 2020). Nevertheless, it remains to be determined how microbial compounds produced in the gut influence mood. In mice, the use of germ-free mice has allowed the study of the role of the microbiome in cognition and mood (Cruz-Pereira et al., 2020). Similarly, antibiotic treatments alter multiple behaviors of mice, suggesting that bacteria influence neurobehavioral outcomes (Desbonnet et al., 2015; Hao et al., 2013; Hoban et al., 2016; Majidi et al., 2016; O'Mahony et al., 2014; Wang et al., 2017). Also, the development of fecal transfer approaches has opened new pathways to understand microbiome alteration effects on behaviors (Zheng et al., 2016). In addition, there is evidence for the role of probiotics in regulating behaviors, although the efficacy of probiotics in humans remains questionable (Suez et al., 2019). Nonetheless, meta-analysis of 6 studies using probiotics in MDD patients shows a positive effect of the probiotics in combination with antidepressant treatments (Sanada et al., 2020). Probiotics act by a variety of mechanisms of action, which include (1) increasing the biosynthesis of GABA, which may be reduced in MDD patients (Dhakal et al., 2012), (2) downregulating the HPA axis, which is often overactive in MDD patients (Ait-Belgnaoui et al., 2014), and (3) upregulating the production of tryptophan and therefore serotonin availability (Desbonnet et al., 2008). As for the studies of the role of inflammatory markers in depression, there are limitations in the studies of the microbiome in MDD patients, comprising the small size of most studies, the fact that the different populations in the studies have different ages, and age affect the microbiota composition (Chen et al., 2020), the absence of consideration of the diet, or of the effects of the

antidepressant treatment, the regional variations (most studies are from Asia), and the methodology to sequence the microbiome, which might affect the results. In a more controlled environment, where a large population of psychiatric inpatients (comprising 74% MDD patients with or without other comorbidities) remain in the hospital for an 50 days, where diet was controlled for as patients received the same meals, remission was associated with an increased richness of the microbiome (Madan et al., 2020). Altogether, this suggests that the microbiota remains an interesting avenue to understand the dysregulation of the immune system in depression.

Although these mechanisms appear disjointed, they have the common theme of regulating the cytokine production, which seems central to MDD symptomatology.

Future Directions

Although substantial progress has been made in understanding immune system dysregulation in depression, many questions remain (Table 2). Thus, clinical studies have provided mixed results concerning the potential efficacy of anti-inflammatory agents in depression. Whether this is the result of a poor understanding of the immune system defect, the presence of comorbidity that complicates the clinical picture or a narrow focus on targeting a single cytokine to improve mood symptoms remains to be determined. We also lack a clear understanding of how signals from the environment (such as childhood maltreatment or stress in adulthood) initiate changes in neuroinflammation, or peripheral inflammation, and whether one precedes the other. For example, although rodent studies suggest DAMP production is important in initiating the immune response to stress, leading to the production of cytokines, we do not yet understand how stress causes DAMP production and where the production is initiated or how it is regulated. Similarly, factors that may determine the magnitude of the immune response, whether it includes downstream effector pathways such as kynurenine metabolism and/or excess of neuroinflammation are still unanswered and will have a major impact on the field.

From a clinical perspective, it is also poorly understood whether the role of the immune system in depression is of clinical importance in most patients or only in a subset of cases (Figure 5). For example, an immune index analogous to the polygenic risk factor score in genomics, may more effectively classify the immune state in depressed patients compared with the use of a single marker such as CRP. Such an index or signature might help define composite criteria for clinical trials addressing the contribution of the immune system to MDD pathogenesis. Such criteria may also include imaging approaches to assess inflammation both peripherally and centrally, which are currently lacking, and/or algorithms taking into account multiple cytokines, immune cell subset prevalence or function, and microbiota species to predict the probability of developing MDD, or responding to particular treatment modalities or drugs (Figure 5).

New paths have been taken to target inflammation to obtain antidepressant effects, such as mesenchymal stem cell therapy, which has been proposed to induce a global anti-inflammatory response and putative antidepressant effects, which are currently being tested in clinical trials. In addition, treatment of microbiota alterations might also help improve

responses to antidepressant therapy similarly to exercise, providing among other, anti-inflammatory actions. There continues to be much interest in future treatment approaches using existing or novel pharmacotherapies to control inflammation and promote or potentiate antidepressant responses. A successful immunotherapy must improve MDD symptoms without excess immunosuppression, which can occur with multiple cytokine inhibition therapy. Thus, disease modifier therapy such as modulation of the gut microbiota via diet or probiotics regime might help control the unwanted immune responses of MDD in a more physiological, and safe manner. However, the contribution of the microbiota to MDD will have to be clarified first, as well as the action of probiotics, for which a great deal of debate has been generated (Suez et al., 2019). Similarly, exercise, which provides anti-inflammatory effects, besides its other known beneficial effects, is also an option to enhance healthy diet habits and antidepressant effects in MDD patients. In addition, initiating studies to determine whether non-pharmacological treatments for depression, including evidence-based psychotherapies, transcranial magnetic stimulation, or electroconvulsive therapies modulate inflammation and immune function might provide valuable new insights. Due to the major contribution of early life trauma in the development and maintenance of chronic inflammation in adults, early intervention after trauma, especially in childhood, might prevent inflammation-associated depression. Consistent with this idea, determining whether methods to reverse the consequences of trauma, for example, via epigenetic mechanisms, prevent the inflammatory response and associated depression, might also open new therapeutic avenues.

Finally, and of considerable importance, is an important fundamental philosophical difference that has plagued this field. We are referring to some who simply believe that peripheral measures of immune dysfunction or inflammation are, at best, epiphenomena and are in no way related to the pathophysiology of depression. They dismiss the evidence of increased inflammatory markers in depressed patients and of CNS effects of induced inflammation as interesting, but certainly not causal. This in spite of overwhelming evidence that increases in peripheral inflammation produces in humans and laboratory animals CNS changes as assessed by brain imaging, neurochemistry, and behavioral changes, and moreover they minimize the now well-documented pathways reviewed above by which inflammatory cytokines can indeed act upon the CNS. Believing that the only evidence worth considering are measures of increased inflammation in the brain, which, although documented in some CNS studies and PET studies, are relatively meager at the current time might be reductionist and lead to missed therapeutic opportunity. In spite of a myriad of examples of peripheral mechanisms affecting psychiatric state, e.g., hypothyroidism and hypoglycaemia, to name only two, the argument continues to plague the field. As more research is conducted, the role of inflammation and cognate immune function dysregulation in depression will become clear.

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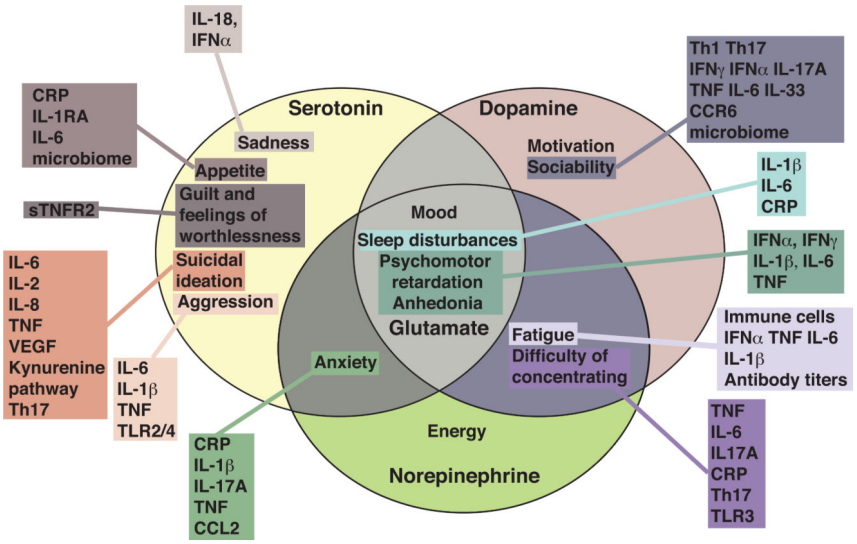

Figure 1. Symptoms of Depression Associated with Different Immunological Changes

Monoamine neurotransmitters have been associated with various symptoms of depression as depicted in each oval. Some symptoms are dependent on multiple neurotransmitters, such as psychomotor retardation that is regulated by serotonin, dopamine, norepinephrine, and glutamate. Each box represents the different immunological changes (e.g., cytokines, immune cell, and others) associated with each symptom.

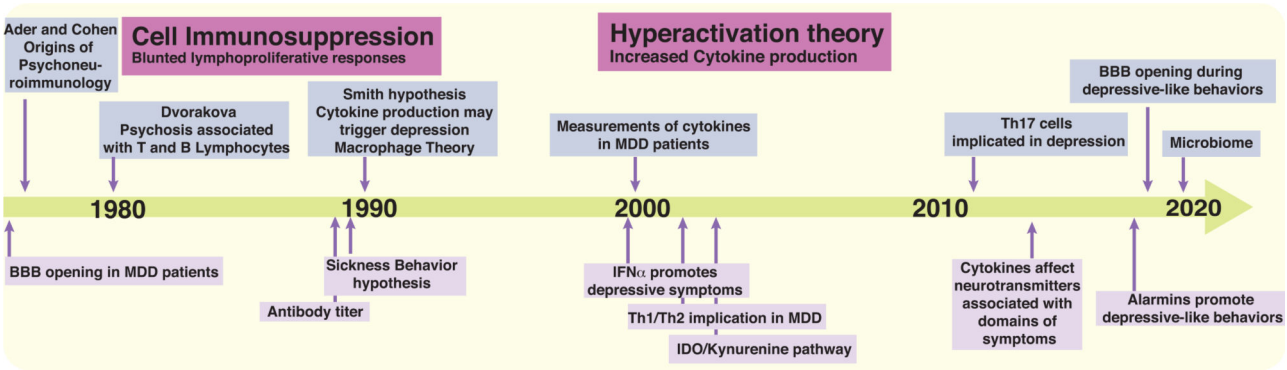

Figure 2. Timeline of Discoveries Associating Depression with Immunological and Inflammatory Changes

This timeline depicts the origins of psychoneuroimmunology (Ader and Cohen, 1975), and several prominent inflammatory theories related to depression, starting with the cell immunosuppression theory initiated by Dvorakova et al., 1980, followed by the sickness behavior hypothesis (reviewed in Dantzer et al., 2008) and the theory of hyperactivation of the immune system (initiated by Smith, 1991, and reviewed by Raison et al., 2006) and ending with more recent findings, such as possible effects of changes in the microbiome in MDD patients.

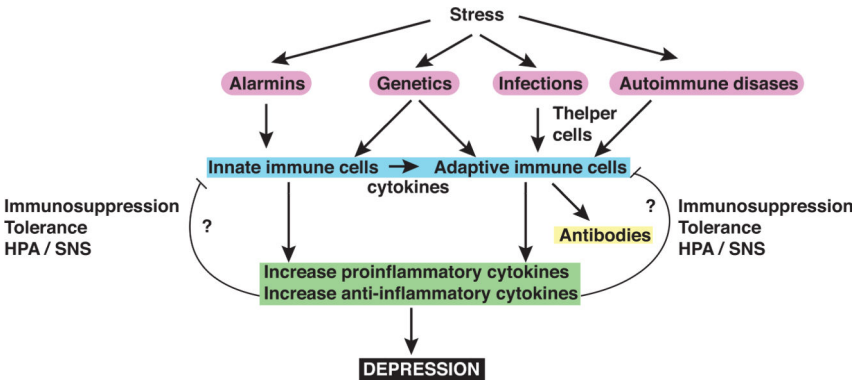

Figure 3. Diagram of Potential Immune Response Dysregulations in MDD Patients

Stress induces the production of alarmins, molecules that trigger the production of proinflammatory cytokines by innate immune cells that promotes depressive-like behaviors in rodents. Genetically mediated susceptibility, a history of infection, and autoimmune diseases also can prime the immune system's response to stress, through both the innate and adaptive immune systems. Infection and autoimmune diseases, for example, may act on T helper cells and affect cytokine production and antibody production. The proinflammatory cytokines are thought to promote depression, whereas the role of anti-inflammatory cytokines is less understood, and it remains to be determined whether anti-inflammatory cytokines induce cell immunosuppression or tolerance, and whether the hypothalamic-pituitary-adrenal axis (HPA) and/or the sympathetic nervous system (SNS) axis are implicated in this phenomena.

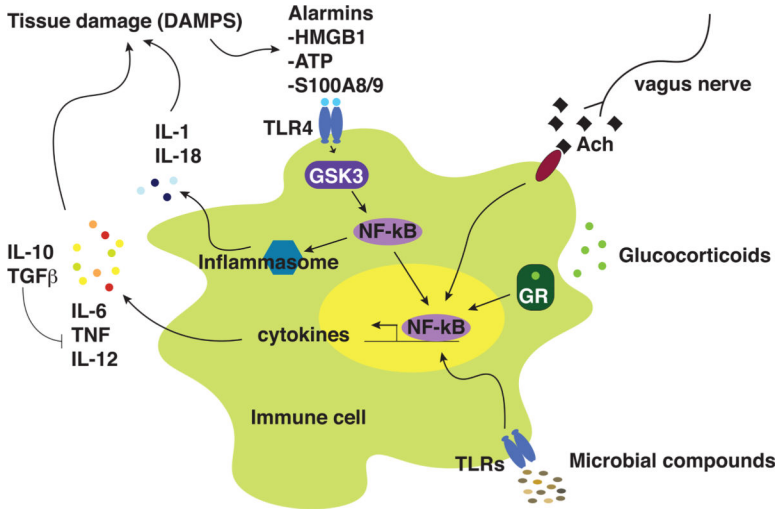

Figure 4. Multiple Mechanisms May Contribute to the Dysregulation of Cytokines in MDD

Immune cell production of cytokines is regulated by multiple mechanisms, including anti-inflammatory actions by glucocorticoids, and vagus nerve pathways, and proinflammatory actions influenced by the microbial composition and stress-induced DAMPs involving both the inflammasome and the NF-κB pathways. Ach, acetylcholine; ATP, adenosine triphosphate; DAMP, danger-associated molecular pattern; GR, glucocorticoid receptor; GSK3, glycogen synthase kinase-3; HMGB1, high-mobility group binding protein-1; IL, interleukin; NF-κB, nuclear factor-kappa B; TLR, Toll-like receptor; TGF, transforming growth factor; TNF, tumor necrosis factor

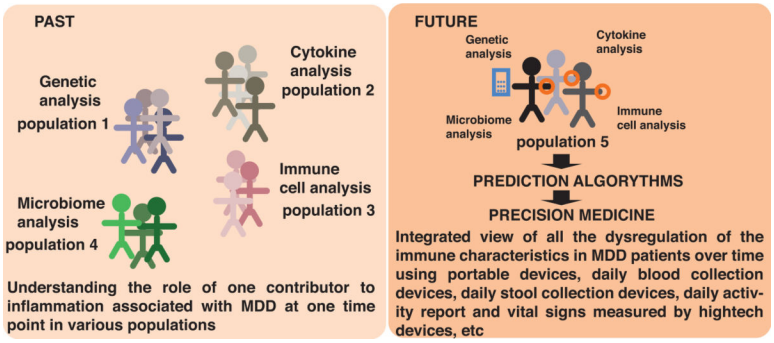

Figure 5. Where the Field Is Going

Historically many studies of immunological factors that may affect MDD focused on a single component, such as genetic variables, cytokines, immune cell types or actions, and the microbiome composition. With technological advances that have recently become available, or are under development, we envision that researchers will be able to apply a more integrated approach to analyze multiple parameters in each individual subject to obtain a more complete and integrated picture of genetic, microbial, and immunological factors that influence the onset, course, and treatment response of MDD patients.

Table 1.

Cytokines and Their Peripheral Immune Functions and Blood Levels in MDD Patients Compared to Healthy Control Subjects

Cytokines	Function	Role in MDD	References
CCL2	attracts to site of inflammation: T cells (Th2 > Th1), monocytes, basophils, immature dendritic cells, NK cells	varies	Köhler et al., 2017; Leighton et al., 2018
CCL3	attracts to site of inflammation: T cells (Th1 > Th2), monocytes/macrophages, NK cells, basophils, immature dendritic cells, eosinophils, fibroblasts, neutrophils, astrocytes, osteoclasts	↑	Syed et al., 2018; Leighton et al., 2018
CCL4	targets T cells (Th1 > Th2), NK cells, monocytes/macrophages, basophils, immature dendritic cells, eosinophils, B cells	↓	Syed et al., 2018; Leighton et al., 2018
CCL5	targets T cell (memory cell > T cell, Th1 > Th2), NK cells, eosinophils, neutrophils, immature dendritic cells, monocytes/ macrophages	↑	Syed et al., 2018
CCL11	recruits eosinophils, implicated in allergic response	↑	Leighton et al., 2018
CXCL4	released from platelets, attracts neutrophils, fibroblasts, and monocytes, arrests monocytes on the endothelium, important in wound healing and in promoting coagulation and artherogenesis	↑	Leighton et al., 2018
CXCL7	released from platelets, attracts neutrophilsangionenic, first chemokine to arrive at the site of injury	↑	Leighton et al., 2018
CXCL10	targets NKcells, B cells, activated Tcells (Th1 > Th2), endothelial cells	↓	Syed et al., 2018
G-CSF	stimulates neutrophil development and differentiation	↑	Kirali et al., 2017; Syed et al., 2018
GM-CSF	promotes granulocyte maturation and proliferation, monocyte development	↑	Kirali et al., 2017
IFN-γ	induces macrophage activation, increased expression of MHC molecules and antigen processing components, Immunoglobulin class switching, suppresses Th2 cells	varies	Köhler et al., 2017
IL-1β	induces fever, T cell activation, macrophage activation	varies	Köhler et al., 2017
IL-1RA	antagonizes IL-1 function	varies	Köhler et al., 2017
IL-2	promotes T cell proliferation	↑	Köhler et al., 2017
IL-4	induces B cell activation, IgE switch, and differentiation toward Th2 cells	↓	Köhler et al., 2017
IL-5	promotes eosinophil growth, differentiation	↑	Köhler et al., 2017
IL-6	induces T and B cell growth and differentiation, acute phase production, fever	↑	Köhler et al., 2017
IL-7	induces growth of preB-cells and preT-cells	↑	Syed et al., 2018
IL-8 /CXCL8	targets neutrophils, basophils, CD8 cell subsets, endothelial cells	varies	Köhler et al., 2017; Leighton et al., 2018
IL-9	induces mast cell activity, stimulates Th cells	↑	Syed et al., 2018
IL-10	potent suppressant of macrophage functions, anti-inflammatory	↑	Köhler et al., 2017
IL-12	activates NK cells, induces CD4 T cell differentiation into Th1-like cells	↑	Köhler et al., 2017
IL-13	induces B cell growth and differentiation, inhibits macrophage inflammatory cytokine production and Th1 cells, induces allergy/ asthma	↑	Köhler et al., 2017

Cytokines	Function	Role in MDD	References
IL-15	IL-2 like cytokine, stimulates growth of intestinal epithelium, T cells and NK cells, enhances memory CD8 T cell survival	↑	Syed et al., 2018
IL-17A	pro-inflammatory, induces cytokine production by epithelia, endothelia, astrocytes, and fibroblasts	↑	Köhler et al., 2017
IL-18	induces IFN-γ production by T cells and NK cells, promotes Th1 induction	↑	Köhler et al., 2017
sIL-2 receptor	increased in autoimmune disease	↑	Köhler et al., 2017
sIL-6 receptor	promotes IL-6 signal	no change	Köhler et al., 2017
TGFβ1	anti-inflammatory	no change	Köhler et al., 2017
sTNFR2	activated by TNF	↑	Köhler et al., 2017
TNF	promotes inflammation, endothelial activation	↑	Köhler et al., 2017

Table 2.

Open Research Questions

Questions
1. Does dysregulation of the immune system contribute to MDD pathology?
If so:
What are the important immune system components that contribute to MDD?
Do these act independently or in synergy to promote MDD?
Is central or peripheral immune system dysregulation mediating the effects?
What are the CNS systems that are altered by the immune system dysregulation that promote MDD?
Are there different immune system alterations that promote MDD in different individuals, or are specific changes common to many MDD patients?
2. What causes immune system dysregulation linked to MDD?
To what extent do genetic influences determine these immune system characteristics?
Does stress (and is it acute or chronic) contribute to immune dysregulation linked to MDD?
How does the environment modulate the immune system dysregulation linked to MDD?
Do repeated episodes of depression cause long-lasting changes in immune characteristics?
Does the microbiome contribute to immune system dysregulation in MDD?
3. Can treating immune system dysregulation facilitate recovery from MDD and/or promote resilience to MDD onset?
What are the immune system targets that are effective interventions for MDD?
Can controlling the stress response normalize immune system characteristics?
Is controlling peripheral immune system characteristics sufficient to counteract MDD or does the central immune system need to be targeted?
Do non-invasive interventions (therapy, nutrition, exercise) normalize immune system alterations associated with MDD?
Are microbiome interventions that alter the immune system effective in MDD?