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Microglia in depression: current perspectives

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Major depressive disorder (MDD) is a prevalent psychiatric disease that involves malfunctions of different cell types in the brain. Accumulating studies started to reveal that microglia, the primary resident immune cells, play an important role in the development and progression of depression. Microglia respond to stress-triggered neuroinflammation, and through the release of pro-inflammatory cytokines and their metabolic products, microglia may modulate the function of neurons and astrocytes to regulate depression. In this review, we focused on the role of microglia in the etiology of depression. We discussed the dynamic states of microglia; the correlative and causal evidence of microglial abnormalities in depression; possible mechanisms of how microglia sense depression-related stress and modulate depression state; and how antidepressive therapies affect microglia. Understanding the role of microglia in depression may shed light on developing new treatment strategies to fight against this devastating mental illness.

depression, microglia, microglial activation, pro-inflammatory cytokine, anti-inflammatory cytokine, antidepressant, ketamine

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Introduction

Major depressive disorder (MDD) is affecting more than 300 million people world-wide, and has become the world's leading cause of disability since 2017, according to World Health Organization. Unfortunately, due to its complexity and heterogeneity, the etiology and pathophysiology of depression are still not clearly understood. And there is a huge unmet clinical need for effective treatments for this prevalent and devastating disease.

Theories regarding the pathophysiological mechanism of depression have evolved over the last several decades. The once widely-adopted "monoamine deficiency hypothesis", attributing depression to a decreased level of brain monoamines (such as dopamine, serotonin and noradrenaline) (Schildkraut, 1965), cannot fully explain the much delayed onset and limited efficacy of classical antidepressants. In the last two decades, the neural plasticity hypothesis of depression has emerged, according to which depression may result

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from maladaptive plastic changes in the neural circuits involved in mood regulation (Vaidya and Duman, 2001). Along this direction, impaired neuroplasticity of the prefrontal-limbic neuronal circuits (Price and Duman, 2020) and abnormal activity of the lateral habenula (LHb) in depression patients and models (Hu et al., 2020a; Yang et al., 2018b) have been highlighted in recent studies.

Whereas previous models on depression mostly focus on neurons, much less attention has been paid to another type of "native resident" cells in the brain: glia. Unlike their Latin name "glue", glia do not simply hold neurons together, but rather, play important roles in modulating neuronal activities and maintaining brain homeostasis (Allen and Lyons, 2018). Glia mainly consist of astrocytes, oligodendrocytes, ependymal cells and microglia. Microglia, classified based on their unique origin and morphology (see next session), constantly survey the microenvironment with their highly motile and ramified processes (Kettenmann et al., 2011). As the primary resident immune cells acting at the first line of defense in the brain, microglia have attracted enormous attention during the past decades, due to their roles in mediating immunoresponses and neuroinflammation (Kettenmann et al., 2011; Wolf et al., 2017). Microglial abnormalities have been implicated in a wide range of brain diseases, including autism, neurodegenerative disorders (Alzheimer's disease and Parkinson's disease), neuropathic pain and depression (Bohlen et al., 2019; Salter and Stevens, 2017; Wolf et al., 2017). In particular, accumulating evidence suggests that inflammation or stress-triggered dysfunctions of microglia commonly occur in depression, and these dysfunctions may play a causal role in disrupting neural functions leading to depression (Yirmiya et al., 2015).

The topic of this review is on how microglia contribute to the pathophysiology of depression. We will first discuss the dynamic properties of microglia under homeostatic and pathological states. We will then review the correlative and causal evidence describing the relationship between microglial states and depression in both human patients and animal models. Possible mechanisms on how microglia sense stress and regulate depressive state will be summarized. Finally, we will describe the effects of antidepressants on microglia state, highlighting the effects of a new antidepressant ketamine. Understanding microglia-related mechanisms in MDD will shed light on developing new therapeutic strategies to treat this prevalent disease.

Ontogeny and development of microglia

Unlike neurons and other glial cell types derived from neuroectodermal lineage, microglia are derived from mesenchymal lineage. While earlier studies regarded peripheral monocytes as a source of microglia, recent fate mapping data clearly demonstrate that microglia originate from yolk sac-derived erythromyeloid progenitors (Ginhoux et al., 2013; Ginhoux and Prinz, 2015). They invade the brain rudiment at embryonic day 8.5–9 in mice using the vasculature before the formation of blood-brain barrier (Ginhoux et al., 2010; Gomez Perdiguero et al., 2015; Kierdorf et al., 2013).

Within the brain, microglia development progresses through proliferation, differentiation and maturation to acquire ramification morphology and homogeneous tiling throughout the brain (Matcovitch-Natan et al., 2016; Thion et al., 2018a). Microglia rapidly expand at perinatal and postnatal stages and fully colonize the brain by the end of the second week (Bennett et al., 2016; Nikodemova et al., 2015). In the adult, microglia population is maintained by self-renewal, with no replenishment of peripheral circulating monocytes under steady state condition (Hashimoto et al., 2013; Mildner et al., 2007). Microglia are emerging as important contributors to brain development by regulating neurogenesis, synapse formation and elimination, and neuronal circuit assembly (Kettenmann et al., 2011).

Characteristics and function of microglial dynamics

Without external stimulation, microglia adopt ramified morphology characterized by small stationery soma but motile processes that continuously monitor the brain parenchyma to maintain brain homeostasis (Kettenmann et al., 2013). In response to external stimuli, microglia undergo drastic morphological changes (Kettenmann et al., 2011). Upon injury or disease, ramified microglia rapidly convert into amoeboid morphology with swollen soma and shortened processes, accompanied by increased phagocytic activities and elevated cytokine production. This process is known as microglial activation. Activated microglia exhibit diverse responses to external stimuli and serve as a double-edged sword: acute microglial activation often facilitates tissue repair by clearing invading pathogens and cell debris; whereas sustained microglial activation evokes chronic neuroinflammation to deteriorate injury and promote disease progression (Kettenmann et al., 2011).

Similar to peripheral macrophages, two main polarization states are defined in activated microglia: M1 (classical activation) and M2 (alternative activation) phenotypes (Boche et al., 2013; Saijo and Glass, 2011; Tang and Le, 2016). M1 polarized microglia are usually induced by pro-inflammatory stimuli (for example, Toll-like receptor (TLR) agonists related to infection), and adopt the pro-inflammatory state that produces pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, nitric oxide (NO) and reactive oxygen species (ROS) etc. By contrast,

M2 polarization is mainly induced by IL-4 and IL-13, and is associated with the production of anti-inflammatory cytokines such as IL-4, IL-13, IL-10 and TGF-β. M2 microglia are also involved in phagocytosis of cell debris, neuron protection and tissue repair (Boche et al., 2013; Saijo and Glass, 2011; Tang and Le, 2016).

Of note, the M1/M2 categorization of microglia is not universally accepted (Ransohoff, 2016), as the binary division of microglial activation states may not represent the heterogeneous microglial molecular profiles in the complicated homeostatic or diseased environment *in vivo* (Ransohoff, 2016; Wes et al., 2016; Yamasaki et al., 2014). Below, we will use "pro-inflammatory" or "anti-inflammatory" microglia instead to highlight microglial contributions to depression.

The opposite state of microglia activation, microglia decline (also sometimes referred to as dystrophy or senescence) has also been documented (Saijo and Glass, 2011; Streit, 2006; Yirmiya et al., 2015). It refers to a state of decreased mitotic activity or number of microglia, with swelling and de-ramified morphology. This state has been observed in aging, Alzheimer's disease, and depressive-like state (Kreisel et al., 2014; Streit et al., 2020; Streit et al., 2004). The decline state is hypothesized to arise from over-activation of microglia, which disrupts the balance between the microglial anabolism and catabolism. Microglia may be unable to tolerate a high metabolic load and are susceptible to death after a limited period of activation (Streit, 2006).

In this review, we will discuss the connections between depression and these three states of microglia: pro-inflammatory, anti-inflammatory, and declined state (Figure 1). To be consistent with most published works, we will refer to the pro-inflammatory state as the main microglia activation state. The anti-inflammatory responses will be separately described whenever appropriate.

Inflammation, microglial abnormalities and depression

Depression and inflammation

Clinical data on depression suggest a strong link between the disease etiology and inflammation. Inflammation-related features have been strongly implicated in depression patients (Miller et al., 2009; Miller and Raison, 2016). In meta-analysis of depression studies, patients with depression showed consistently upregulated levels of pro-inflammatory cytokines such as TNF-α and IL-6 (Dowlati et al., 2010; Enache et al., 2019). In addition to these correlative analysis, there is also evidence that inflammation may causally contribute to depressive illness. Pro-inflammatory cytokines, vaccines and endotoxins, are the three main types of immune stimuli that have been reported to induce transient depressive mood in human volunteers. For example, treatment of the pro-inflammatory cytokine interferon-α (IFN-α) in healthy volunteers causes anxiety and depressive mood, with comparable

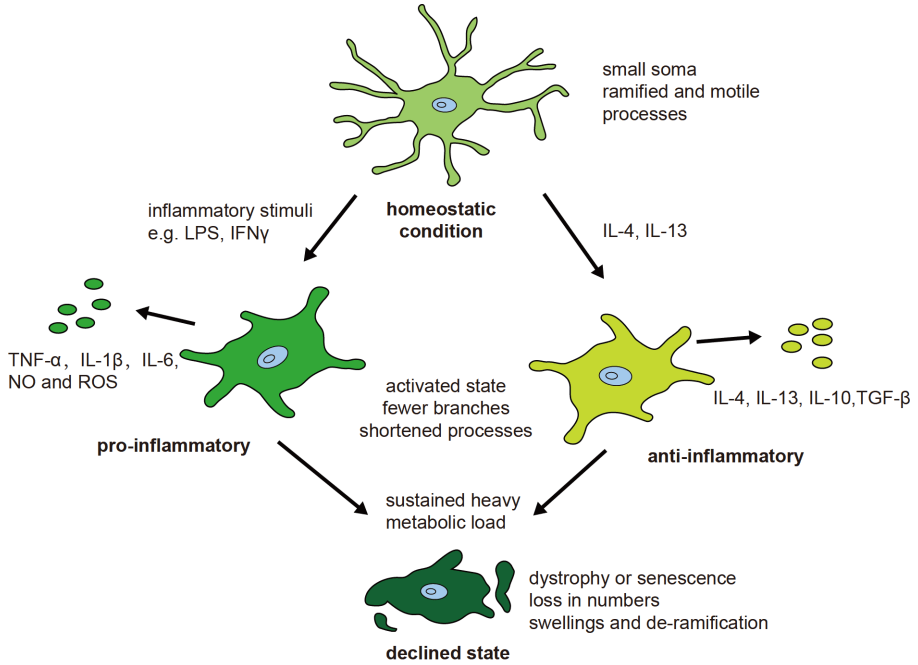

Figure 1 Dynamic properties of microglia. Under the homeostatic condition, microglia exhibit small soma and thin, ramified and motile processes. Upon stimuli, microglia switch to de-ramified morphology with swollen soma and shortened processes. Two major phenotypes of activated microglia have been identified: proinflammatory microglia (induced by LPS, IFN-γ, etc.) that produce pro-inflammatory cytokines (TNF-α, IL-1β and IL-6), NO and ROS to promote neuroinflammation and the anti-inflammatory microglia (induced by IL-4 and IL-13) that secrete anti-inflammatory cytokines (IL-4, IL-13, IL-10 and TGF-β). Microglial overactivation may lead to the declined state with microglial apoptosis and loss of microglial number.

severity to those of depression patients (Capuron et al., 2009). Similarly, typhoid vaccination also induces depressed mood in healthy volunteers who show mild acute inflammatory responses to the vaccination (Strike et al., 2004). Injection of the bacterial endotoxin and lipopolysaccharide in humans leads to elevated levels of plasmal pro-inflammatory cytokines and dose-dependent depressed mood (Grigoleit et al., 2011). These results suggest that immunoresponses may play a causal role in the depression etiology.

Pro-inflammatory microglia in depression

Both microglia and peripheral immune cells have been implicated in depression-related inflammation (Hodes et al., 2015; Miller and Raison, 2016; Wohleb et al., 2016). The peripheral immune cells, in brief, respond to stress-induced hormone regulations and the innervation of immune organs by the continuously activated sympathetic neurons in depression (Won and Kim, 2016). The peripheral myeloid cells are the main source of pro-inflammatory cytokines, which circulate in the blood and cross the blood brain barrier to affect microglia (Miller and Raison, 2016). A subpopulation of myeloid cells, monocytes, can even infiltrate into the brain under exposure to depression-related chronic stress (Wohleb et al., 2013).

As the native mediator of inflammatory responses in the brain, microglia may play more direct roles than peripheral immune cells in depression. Post-mortem brain studies have found that the percentage of activated microglia is increased in the dorsal anterior cingulate cortex of depressed suicides, compared to those without psychiatric or inflammatory illness (Torres-Platas et al., 2014). Moreover, positron emission tomography (PET) examining the levels of translocator protein 18 kD (TSPO), which correlate with activated microglia-related neuroinflammation, has been used to monitor the microglial activation state *in vivo* in human (Banati, 2002; Rupprecht et al., 2010), yet with mixed results. The earliest study using [^{11}C] PBR28 as the ligand did not observe elevation of TSPO in mild-to-moderate depression patients (Hannestad et al., 2013). However, two studies applying the ligand [^{11}C]-(*R*)-PK11195 discovered significantly increased TSPO in the right hippocampus of bipolar patients (Haarman et al., 2014) and in the anterior cingulate cortex of patients in a major depressive episode (MDE) (Holmes et al., 2018). Another study using the [^{18}F] FEPPA ligand also observed significant increase of TSPO levels in the prefrontal cortex, anterior cingulate cortex and insula in patients with MDE (Setiawan et al., 2015). While the inconsistencies may arise from differences in the therapeutic progress of patients, the severity of the cohorts, the chemical property of ligands, and TSPO elevation are no longer evident after antidepressant treatment. Together, these studies demonstrate a close relationship between microglia activation and depression (Setiawan et al., 2018).

Growing evidence also suggests increased microglial activation in inflammatory and non-inflammatory animal models of depression. Taking the LPS model, the most commonly used inflammation-induced depression animal model as an example (Yirmiya, 1996), systematic LPS challenge not only prominently triggers peripheral immune responses but also activates microglia in the brain. Upregulated pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) are observed in multiple brain areas (Hoogland et al., 2015). Animals (rats and mice) stimulated by LPS exhibited decreased preference of sucrose to water and increased immobility in forced swim tests, indicating anhedonia and behavior despair respectively (Adzic et al., 2015; Guan et al., 2020). In addition, animals that receive depression-related stress also exhibit microglial activation along with morphological changes, increased level of pro-inflammatory but not anti-inflammatory cytokines. For example, acute stress induces microglial activation in multiple brain regions including the hippocampus (Frank et al., 2007; Sugama et al., 2007), thalamus, hypothalamus (Sugama et al., 2007) and periaqueductal gray (PAG) (Sugama et al., 2009), whereas different chronic stresses induce microglial activation in the medial prefrontal cortex, nucleus accumbens, hippocampus, PAG and LHb (Brevet et al., 2010; Guan et al., 2020; Hinwood et al., 2013; Tynan et al., 2010; Wohleb et al., 2012). Therefore, pro-inflammatory microglia activation is engaged in both inflammatory and non-inflammatory animal models of depression.

Despite of a strong correlation between microglial activation and depression in both patients and animal models, it remains challenging to determine whether microglial abnormities play a causal role in depression. Using PLX5622, a colony-stimulating factor 1 receptor (CSF1R) antagonist, to deplete microglia *in vivo*, a recent study observed that microglia-depleted mice are protected from chronic social defeat (CSD) stress-induced anxiety and anti-social behaviors (Lehmann et al., 2019). However, two weeks after the removal of PLX5562 when microglia repopulate to the normal states, the mice exhibited CSD-related behavioral defects. Considering that CSD mice have been well-established as a depression model, this study suggests that microglia may play a causal role in stress-induced depression.

Additional evidence demonstrating a causal role for microglial activation in depression comes from minocycline treatment. Minocycline is an anti-inflammatory tetracycline that suppresses microglial activation and neuroinflammation (Maes et al., 2008). Although minocycline treatment does not induce anti-depressive behavioral effects in naïve mice (Vogt et al., 2016), it exhibits robust anti-depressive effects in the rat depression model of chronic unpredictable mild stress (Zhang et al., 2019). Encouragingly, in an open-label

study, combinatorial application of minocycline with traditional antidepressants provide significantly better mood improvement in unipolar depression patients, compared with patients merely taking antidepressants (Miyaoka et al., 2012), suggesting the contribution of microglial activation to depression.

Anti-inflammatory microglia in anti-depression

Based on molecular markers, stress seems to predominantly induce the pro-inflammatory responses in microglia. That's why most studies have mainly focused on the role of pro-inflammatory microglia in depression. Recent studies suggest that anti-inflammatory microglia may play an anti-depressive role (Zhang et al., 2018). Microglia-derived anti-inflammatory cytokines can oppose the actions of pro-inflammatory cytokines, thus reverse depression. For example, intracerebroventricular infusion of IL-4 antagonizes IL-1β-induced depressive behaviors in rats via increased noradrenergic and serotonergic neurotransmission (Park et al., 2015). Moreover, drug-induced shift from pro- to anti-inflammatory state in hippocampal microglia produces anti-depressive effects (Duan et al., 2020; Zhang et al., 2017). For example, salvianolic acid B inhibits LPS-induced pro-inflammatory microglia and promotes the anti-inflammatory phenotypes *in vitro* (Zhang et al., 2017). When used *in vivo*, it decreases the pro-inflammatory cytokines but increases anti-inflammatory cytokines in the hippocampus and cortex of CMS-induced depression mouse models. As a result, it restores the hippocampal neurogenesis and produces anti-depressive effects (Zhang et al., 2017). Additional drug-induced shift from pro- to anti-inflammatory microglial phenotype also exhibits similar anti-depressive effects in chronic unpredictable mild stress mice (Duan et al., 2020), demonstrating a beneficial role for anti-inflammatory microglia in depression.

Declined microglia in depression

In contrast to microglial activation, microglial decline, first identified in depressive-like animals by Kreisel et al. (2014), received much less attention. Studies have observed that microglia in the hippocampal dentate gyrus (DG) undergo dynamic changes in the progression of chronic unpredictable stress (CUS)-induced depression-like behaviors (Kreisel et al., 2014). At the first several (2–3) days, stress exposure induces microglial activation and proliferation. At this stage, blocking microglia activation by minocycline can effectively rescue the depressive behavior, consistent with discussions above. However, after weeks of chronic unpredictable stress stimulation, hippocampal microglia turn into a dystrophic morphology, with smaller soma and shorter processes. By then, minocycline cannot rescue the depressive-like behaviors anymore. Instead, activating microglia using microglial activators such as LPS or colony stimulating factors (CSF) can rescue the depressive phenotypes (Kreisel et al., 2014). Additional studies also observed microglial loss or dystrophy in the hippocampal DG region at later stages of three commonly used chronic-stress mouse depression models of CUS, CRS and CSDS (Tong et al., 2017) or microglial decline in the orbitofrontal cortex of female rats suffering from chronic restraint stress (Bollinger et al., 2017). Accordingly, activating microglia or restoring declined microglial number by LPS (even with the dose that is sufficient to cause depression symptoms in naïve animals) or CSF stimulation after weeks of stress exposure reverses depressive behavior (Kreisel et al., 2014; Tong et al., 2017). A recent study further characterized the time window for LPS-stimulated microglia activation in anti-depressive effects (Cai et al., 2020). After 35 days of CUS stimulation, a single dose of LPS can reverse the depressive phenotypes in 5 hours and the effects remain for at least ten days in mice. A parallel study using the adolescent intermittent alcohol exposure (AIE) also observed similar hippocampal microglial decline at late phases of alcohol exposure, and antidepressive effects of early-stage minocycline application and late-stage LPS stimulation (Hu et al., 2020b). Collectively, these studies demonstrate that preventing hippocampal microglial decline at late phase elicits anti-depressive effects.

In summary, pro-inflammatory microglia may directly contribute to depression; and anti-inflammatory microglia may antagonize the pro-inflammatory responses to produce anti-depressive effects. Microglia declination may occur at later stage of depression due to sustained over-activation of microglia after chronic stress.

Mechanisms of how stress/depression alters microglial state

Efforts have been made in the past decades to figure out how stresses alter microglia activity (Frank et al., 2019). While it remains unclear which signaling cascade initiates stress-triggered microglial changes (Wohleb et al., 2016), increasing evidence suggests that several factors, including pattern recognition receptor (PPR) agonists, neurotransmitters and neuron-derived cytokines, the endocrine system and the gut-brain-axis may be involved (Figure 2).

First, exposure to stressors can lead to a pro-inflammatory environment in the brain that contributes to depression. Stressors can induce specific molecular patterns of threat including pathogen-associated molecular patterns (PAMPs, such as LPS from bacteria and RNA from viruses) and danger-associated molecular patterns (DAMPs, such as ATP, heat shock proteins, high mobility group box-1 and etc.)-mediated signaling to prime microglia and amplify the

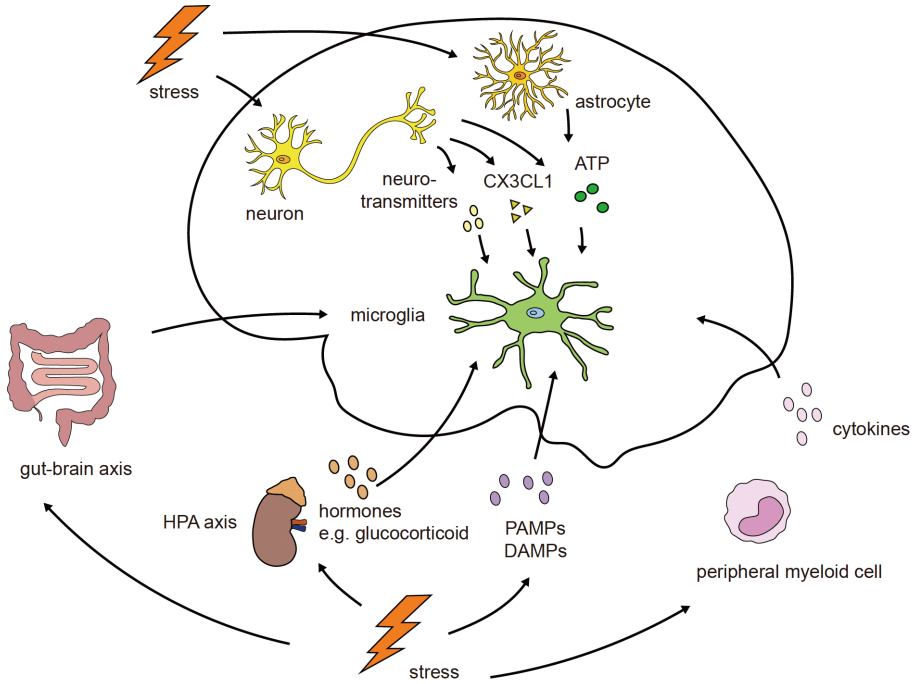

Figure 2 Possible mechanisms for microglia to sense the stress or the depressive state. Microglia sense molecular changes in the local brain environment, such as ATP, neurotransmitters or CX3CL1 derived from neurons or astrocytes. Microglia receive stress-related information from the molecular patterns (PAMPs and DAMPs) through surface pattern recognition receptors, the endocrine system (the hypothalamic-pituitary-adrenal axis), the gut-brain axis, or the peripheral immune cells, which release inflammatory cytokines that may enter the brain to disrupt the brain homeostasis under stress.

neuroinflammatory responses (Fleshner, 2013). For example, repeated electric tail shocks increase the hippocampal release of high mobility group box-1 (HMGB1), a DAMP known to induce microglial activation (Weber et al., 2015). Pharmacological blockade of HMGB1 signaling prevents stress-induced sensitization of microglial pro-inflammatory responses (Weber et al., 2015). Moreover, chronic stresses can induce the expression of PAMP receptors, TLR, on microglia, thereby augmenting PAMPs mediated pro-inflammatory effects (Wohleb et al., 2011). Genetic ablation of TLR2/4 in mice abolishes repeated social defeat (RSD) stress-induced social avoidance and anxiety. Selective depletion of TLR2/4 in medial PFC microglial cells mitigates stress-induced microglial activation and social avoidance (Nie et al., 2018). These studies suggest that upregulated PAMPs or DAMPs signaling after stress exposure augments the inflammatory responses and contributes to depressive-like behaviors.

Second, neurotransmitters released from aberrant neuronal activities in depressive states can affect microglial states. Microglia express a wide range of neurotransmitter receptors (Pocock and Kettenmann, 2007), including glutamate receptors, GABA receptors and etc. As demonstrated in cultured microglia, the process morphology and motility are positively regulated by ionotropic glutamatergic transmission showing larger dendritic covered area, increased dendrite length and more dendritic branches, but negatively regulated by GABAergic transmission with the opposite changes (Fontainhas et al., 2011). Microglial activation is found in close proximity to activated neurons (labeled by c-Fos staining) in PAG of rats suffering from instant stress (Sugama et al., 2009). Moreover, neuronal hyperactivity can recruit microglial processes via NMDAR receptor activation-triggered ATP release and microglia ATP receptors (Dissing-Olesen et al., 2014; Eyo et al., 2014). Interestingly, genetic ablation of P2X7, a microglial ATP ionotropic receptor, results in anti-depressive effects in mice (Basso et al., 2009). Consistently, chronic treatment of P2X7 antagonist reverses anhedonia phenotype in chronic unpredictable stress mouse models (Iwata et al., 2016b).

Third, a prominent neuron-microglia regulatory pathway in stress and depression is fractalkine signaling. Fractalkine (also known as CX3C-ligand 1 or CX3CL1) is a chemokine mainly expressed by neurons, and its receptor, CX3CR1, is exclusively expressed in microglia in the brain (Lyons et al., 2009). Fractalkine attenuates microglial activation and maintains microglia in a homeostatic state both *in vivo* and *in vitro* (Lyons et al., 2009). Both CX3CL1 and CX3CR1 are found decreased in the brains of mice after repeated social defeat (Wohleb et al., 2014; Wohleb et al., 2013). Genetic ablation of CX3CR1 in mice causes mixed consequences when mice face different depression-related stresses. In response to LPS injection, which activates microglia in the hippocampus and prefrontal cortex, CX3CR1-deficient mice, but not the control, show behavioral despair in the tail suspension test (TST) (Corona et al., 2010). However, in

response to instant non-inflammatory stresses, CX3CR1-deficient mice are more resilient than the control mice (Hellwig et al., 2016; Liu et al., 2020; Rimmerman et al., 2017; Winkler et al., 2017). Moreover, Venlafaxine, a traditional antidepressant, is able to alleviate depressive behaviors in wild-type but not CX3CR1-deficient mice in chronic despair models (Hellwig et al., 2016), suggesting a significant role of fractalkine signaling in microglia-mediated stress response.

Fourth, the hypothalamus-pituitary-adrenal gland (HPA) axis may be involved in stress-induced microglial activation (Sorrells and Sapolsky, 2007). Stress is known to activate the HPA axis and increase the release of corticotrophin-releasing hormone (CRH) from the hypothalamus and glucocorticoids (GC) from the adrenal glands. Elevated levels of stress hormones have been observed in the serum of depressed patients (Dinan, 1994). Both CRH and GC can prime the pro-inflammatory responses in cultured microglia (Wang et al., 2002). GC-activated NF-κB-Nod-like receptor protein 3 (NLRP3) pathway in hippocampal microglia has been reported to contribute to chronic stress-induced hippocampal neuroinflammation and depressive-like behaviors (Feng et al., 2019). Either pharmacological antagonism of GC receptors or adrenal ectomization blocks stress-induced microglia priming and decreases the LPS-induced microglial pro-inflammatory responses (Frank et al., 2012), suggesting that GC may play a critical role in stress-triggered microglia alteration.

Finally, the gut microbiome may play an important role in stress-related microglia activation. Microbiota has close connection to depression in both patients and experimental models (Cruz-Pereira et al., 2020). The composition of microbe species is greatly altered in patients with depression symptoms (Jiang et al., 2015). Alterations in gut microbiome can directly regulate depressive-like behaviors in mice and the pathogenesis of MDD (Zheng et al., 2016). Normal gut microbiota is important for microglial maturation and homeostasis (Gilbert et al., 2018). Stress-induced gut microbiota changes can activate microglia. When exposed to social stressors, such as aggressive conspecifics, the bacteria species in mouse gut undergoes significant change (Bailey et al., 2011). Depletion of microbiota or reduced microbiota complexity changes microglial morphology, with increased process length, segments and branches, and reduced innate immunoresponses upon LPS challenge (Erny et al., 2015). Also, the impact of microbiome on microglia appears to be sexually-dimorphic, and microglia in male embryos or female adults are more affected than male adults (Thion et al., 2018b). In germ-free mice, LPS injection fails to induce upregulation of TNF-α and Iba1 as well as depression-like behavior in TST, suggesting that microbiota serves as an important bridge for LPS to induce microglia changes and depressive behaviors (Campos et al., 2016). How microbiome-induced microglial changes contribute to depression remains to be further clarified in the future.

Mechanisms of how microglia contribute to depression

Microglia are important neuro-immune sensors of stress, and stress-elicited microglial alterations can contribute to depression state through various mechanisms, including microglia-derived cytokines, non-cytokine metabolites and other possible mechanisms (Figure 3).

Pro-inflammatory cytokines

Multiple pro-inflammatory cytokines, such as TNF-α, IL-6 and IL-1β, derived from both peripheral immune cells and microglia, can modulate neuronal functions contributing to the depressive illness.

TNF-α has been reported to modulate synaptic efficacy by up-regulating the expression of surface α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (AMPA receptors, AMPAR), as reflected in the increased ratio of AMPAR/NMDAR (N-methyl-d-aspartic acid receptor) currents (A/N ratio) in acute hippocampal slices (Beattie et al., 2002; Stellwagen and Malenka, 2006). Consistently, genetic ablation of TNF-α receptor subtype 1 decreases the levels of synaptic AMPAR and the frequency of miniature excitatory postsynaptic currents in the hippocampus (He et al., 2012). Intriguingly, cocaine administration increases TNF-α expression in the striatum, and incubation of TNF-α on striatum acute slices reduces A/N ratio of corticostriatal synapse by decreasing membrane AMPAR expression (Lewitus et al., 2016; Lewitus et al., 2014). TNF-α-mediated synaptic modulation may occur in depression-related circuits, since microglial activation and the up-regulation of TNF-α have been observed in medial prefrontal cortex, nucleus accumbens and hippocampus that participate in depression or stress coping behaviors (Hinwood et al., 2013; Tynan et al., 2010; Wohleb et al., 2012). A recent study found that TNF-α is up-regulated in the LHb, a brain region critically involved in depression, in a mouse model of morphine withdrawal (Valentinova et al., 2019). Upregulated TNF-α is sufficient to decrease the A/N ratio of LHb neurons projecting to the raphe nuclei and account for depression-like social avoidance behavior (Valentinova et al., 2019).

Increased levels of IL-6 are frequently seen in depression patients and associated psychiatric disorders (Dowlati et al., 2010; Enache et al., 2019). IL-6 also plays a role in the central nervous system of depression individuals (Hodes et al., 2016). When overexpressed or directly injected into the brain, IL-6 is sufficient to induce depression-like phenotypes in mice (Sukoff Rizzo et al., 2012). Using antibodies to block IL-6 signaling in the brain effectively reverses depression-

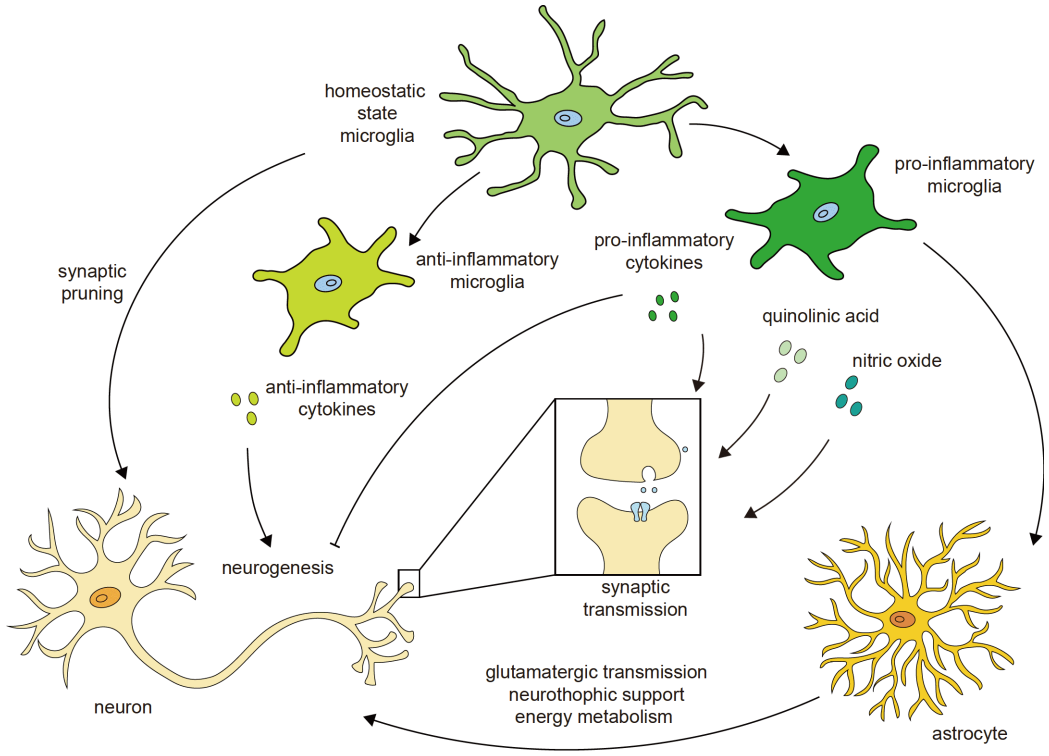

Figure 3 Possible mechanisms underlying microglial contribution to depression. Pro-inflammatory microglia contribute to the development of depression by releasing pro-inflammatory cytokines and increasing the production of quinolinic acid and nitric oxide to inhibit neurogenesis and modify neuronal transmission. Anti-inflammatory microglia may participate in neuroprotection via secreting anti-inflammatory cytokines to promote neurogenesis. Microglia may also contribute to depression through synaptic pruning and interacting with astrocytes.

like behaviors in these mice. Interestingly, in the presence of exogenous IL-6, the antidepressant fluoxetine failed to elicit its anti-depressive effects (Sukoff Rizzo et al., 2012). IL-6 promotes the depression state in the brain mainly through three pathways below. First, it may regulate monoamine metabolism. Systematic injection of IL-6 down-regulates dopamine level in the nucleus accumbens. Second, it alters synaptic transmission in the prefrontal cortex. IL-6 decreases synaptic inhibition and excitation ratio in the prefrontal cortex, which is blocked in the presence of soluble version of gp130, an IL-6 antagonist (Garcia-Oscos et al., 2015). Third, IL-6 may modulate synaptic plasticity at the transcriptional level. For example, the classical IL-6 signaling triggers the activation of downstream IκB kinase (IKK) signaling cascade, leading to increased spine densities and synapses in the NAc in susceptible CSDS mice (Christoffel et al., 2011; Hodes et al., 2016).

A third pro-inflammatory cytokine implicated in depression is IL-1β, which is involved in both monoamine metabolism and neurogenesis. The receptor of IL-1β is necessary for the enhanced serotonin transporter (SERT) activity in response to LPS stimuli both in cultured cells and in mice (Zhu et al., 2006; Zhu et al., 2010). The elevated SERT activity increased uptake of serotonin in the synapse cleft, thus down-regulating serotoninergic transmission, which may contribute to depression. In addition, IL-1β can modulate neurogenesis to affect the development of depression (Koo and Duman, 2008). Cannula injection of IL-1β into the lateral ventricle of the brain produces depressive-like behaviors in rats (Koo and Duman, 2008). As hippocampal atrophy is associated with depression symptoms (Belleau et al., 2019), increased IL-1β in the hippocampus has been found to be both necessary and sufficient to suppress hippocampal neurogenesis and induce depressive behaviors when animals are exposed to acute and chronic stressors (Goshen et al., 2008). Such effects may be mediated by IL-1β-regulated transcription through NF-κB pathway (Goshen et al., 2008).

Upregulated microglial IDO pathway

Indoleamine 2,3-dioxygenase (IDO) is a key enzyme that catalyzes tryptophan to kynurenine in multiple cell types. Exogenous inflammatory stimuli including LPS and vaccine, as well as repeated stress can robustly elevate the level of IDO in the brain (Corona et al., 2013; Kiank et al., 2010; O'Connor et al., 2009a; O'Connor et al., 2009b). Induction of IDO relies on microglia-derived pro-inflammatory cytokines since blocking cytokine such as IFN-γ or TNF-α-mediated signaling suppresses the up-regulation of IDO in depression-like animals (O'Connor et al., 2009a). Upregulated IDO and affected tryptophan metabolism have been implicated in inflammation or stress-induced depressive

behaviors (Parrott et al., 2016a; Parrott et al., 2016b; Verdonk et al., 2019).

By converting tryptophan to kynurenine, upregulated IDO increases the kynurenine/tryptophan ratio and skews the kynurenine metabolism towards production of quinolinic acid, an NMDA receptor agonist (Lugo-Huitron et al., 2013). Increased activity of IDO and levels of quinolinic acid has been observed in rodent models of depression, especially in those induced by overt inflammation (Parrott et al., 2016a; Parrott et al., 2016b; Verdonk et al., 2019). Upregulated quinolinic acid may lead to a modified NMDAR-dependent synaptic transmission in neuronal circuits involved in the development of depression. Interestingly, lower level of plasma quinolinic acid has been shown to be a predictor of better mood improvement after ketamine application in treating resistant depression patients (Verdonk et al., 2019). In addition, enhanced IDO consumes more tryptophan and reduces substrates for tryptophan hydroxylase to produce serotonin (Dantzer, 2017). By increasing kynurenine and quinolinic acid production but decreasing serotonin synthesis, IDO upregulation promotes NMDA neurotransmission but suppresses serotoninergic neurotransmission. IDO inhibition can abrogates LPS-induced depressive-like behaviors in LPS depression mice model (Dobos et al., 2012), suggesting that IDO-mediated tryptophan metabolism plays a pivotal in inflammation-induced depression.

Microglia-derived NO and ROS

NO is a neurotoxic metabolite produced through the NO synthase (NOS) pathway in activated microglia, neuron and endothelial cells (McLeod et al., 2001; Wolf et al., 2017). By propagating the production of ROS, NO can further enhance microglial activation and production of pro-inflammatory cytokines (Kudlow et al., 2016). NO can also modulate monoaminergic and glutamatergic transmission (Dhir and Kulkarni, 2011). Therefore, NO may be implicated in depression pathophysiology by affecting both pro-inflammatory cytokines production and neuronal transmissions. Further studies are worth carrying out to elucidate more detailed mechanisms on specific circuits and evaluate the anti-depressive effects of inhibiting NO and ROS signaling.

Other microglial mechanisms

Other than the immune-related functions, microglia also have non-immune functions such as synaptic pruning, limiting the number of neural precursor cells (NPCs), or removing debris after cell death (Cunningham et al., 2013; Neniskyte and Gross, 2017; Wang et al., 2020; Wilton et al., 2019; Wolf et al., 2017). Some of these non-immune functions may contribute to depression pathophysiology. For example, given that synaptic plasticity and change of spine numbers occur in multiple brain regions in depression-like animals (Duman and Duman, 2015; Sheline et al., 2019), it is likely that microglia-mediated synaptic elimination may be involved in these processes. In addition, it has been shown that microglia limit the number of NPC by phagocytosis to keep neurogenesis in order during development (Cunningham et al., 2013). In adult animals, quiescent microglia tend to protect NPCs whereas pro-inflammatory activated microglia damage NPCs in numbers and functions (Su et al., 2014). Considering that hippocampal neurogenesis is critical for antidepressant response (David et al., 2009; Hill et al., 2015), it may also be relevant to examine whether microglia interaction with NPCs may impact antidepressant response.

Activated pro-inflammatory microglia have been shown to induce neurotoxic reactive astrocytes (A1) (Liddelow et al., 2017), therefore microglia may also contribute to depression via interaction with astrocytes. Astrocytes can participate in depression pathophysiology through decreased glutamate up-take, impaired neurotrophic support, and disrupted glucose energy metabolism (Wang et al., 2017). Recent researches also point out novel mechanisms, involving either menin-related astrocyte-mediated neuroinflammation (Leng et al., 2018), or astroglial-Kir4.1-mediated potassium buffering and regulation of neuronal burst firing in the LHb (Cui et al., 2018). It would be interestingly to investigate whether stress-induced pro-inflammatory microglia contribute to depression by inducing astrocyte dysfunctions.

In addition, a molecule exclusively expressed in microglia in the brain and has been closely associated with Alzheimer's disease (Ulland and Colonna, 2018), the triggering receptor expressed on myeloid cells-2 (TREM2), has recently been found to regulate microglia activation and the development of depression. In LPS or CSDS induced depression models, M1 microglia activation is accompanied by significantly decreased TREM2 in the LHb; and region-specific knockdown of TREM2 in the LHb induces local microglial M1 phenotypes and depressive-like behaviors (Guan et al., 2020). Since Trem2 deficiency causes increased microglial autophagy vesicles by inhibition of mTOR signaling (Ulland et al., 2017), its decrease in the LHb may affect local microglial metabolism and lead to microglial misregulation.

Effects of antidepressants on microglia

Traditional antidepressants, including the selective serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), have been shown to have an impact on microglial activation and neuroinflammation (Kopschina Feltes et al., 2017).

Clinical studies on inflammatory level of antidepressant

treated patients and animal models found a significant alternation of inflammation after the treatment, as SSRI treatment attenuates the serum levels of multiple inflammatory cytokines including TNF-α, IL-6 and IL-1β in depression patients (Hannestad et al., 2011), suggesting the anti-inflammatory properties of traditional antidepressants. Studies on animal models of depression also found that antidepressant treatment alleviates microglia-mediated neuroinflammation: in rat models of learned helpless, the SSRI imipramine was found to decrease the number of stress-induced microglia activation in the hippocampal hilus (Iwata et al., 2016a). While these microglial changes may be secondary to antidepressant-induced modification of neuronal circuits, some *ex vivo* studies showed more direct evidence that SSRIs and tricyclics suppress LPS-induced production of TNF-α in cultured BV-2 murine microglia (Hwang et al., 2008; Tynan et al., 2012). Since the cytokine levels have been correlated with the efficacy of the antidepressant treatment in patients such that higher levels of IL-6 and TNF-α are more frequently seen in SSRI-resistant patients than SSRI-responders (Lanquillon, 2000), anti-inflammation may be an essential aspect for SSRI's function (O'Brien et al., 2007).

However, several studies have reported conflicting results that traditional antidepressants may actually increase inflammatory load in the brain. For instance, administration of an SSRI citalopram into mice elevates the levels of TNF-α in the prefrontal cortex, and the anti-inflammatory agent ibuprofen can inhibit its antidepressant effects (Warner-Schmidt et al., 2011). The MAOI phenelzine also enhances microglia-mediated immunoresponses (Chung et al., 2012). Studies need to be carried out to further clarify those conflicting results. Brain-region specificity and the heterogeneity of depression models and patients need to be taken into account.

In recent decades, a new antidepressant drug, ketamine, has revolutionized the field of antidepressant research owing to its rapid action and strong efficacy on treatment-resistant depression (Krystal et al., 2019). Ketamine's antidepressant mechanisms may involve disinhibition of glutamatergic neuronal activity in the mPFC (Homayoun and Moghaddam, 2007), elevated brain-derived neurotropic factor (BDNF) (Autry et al., 2011) and protein synthesis (Li et al., 2010), increased AMPAR-mediated synaptic transmission and synapse formation (Moda-Sava et al., 2019), and disinhibition of the reward center by blocking NMDAR-dependent neuronal burst firing in the LHb (Cui et al., 2019; Yang et al., 2018a). Several studies also suggest a role of ketamine in suppressing microglia-mediated neuroinflammation. In a mouse chronic restraint stress model, ketamine administration inhibited microglial activation in the hippocampus and reduced the plasma levels of pro-inflammatory cytokine levels (Tan et al., 2017). In addition, ketamine treatment significantly reduced LPS-induced production of TNF-α, NO and IL-1β in cultured microglia (Chang et al., 2009; Shibakawa et al., 2005). A recent study found that partial depletion of microglia by a CSF1R antagonist PLX3397 blocked both the rapid (within 3 hours) and sustained (up to 2 days) antidepressant effects of (R)-ketamine, an isomer of ketamine with potent antidepressant effects, suggesting that the antidepressant effects of ketamine may be partly attributed to microglia-related mechanisms (Zhang et al., 2020).

The anti-inflammatory effects of ketamine may be related to the inhibition of extracellular signal-regulated kinase (ERK1/2) and toll-like receptor that promote the synthesis of pro-inflammatory cytokines (Chang et al., 2009; Mei et al., 2011). Molecular profiling of human-derived microglial culture shows that STAT3, a member of major immune-related STAT protein factors, is significantly enriched after the treatment of ketamine or its metabolite hydroxynorketamine (HNK) (Ho et al., 2019). The increased STAT3 protein is then translocated into the nucleus to modulate downstream transcriptions and triggers the up-regulation of BDNF, postsynaptic density protein 95 (PSD95) and synapsin I (SYN1) to alter neuronal plasticity. Those synaptic modifications can be hypothesized as key antidepressive mechanisms in hippocampus and PFC, although corresponding ketamine-microglia interaction researches with region specificity have not been performed yet.

Concluding remarks

Microglia are key immune sensors in the brain. Accumulating evidence demonstrate that microglia sense depression-related stressors and elicit immunoresponses and neuroinflammation that contribute to the development of depression. While progresses have been made in understanding the role of microglia in depression, several concepts still remain elusive. First, it remains critical to determine, in a specific region or circuit, whether microglia are the primary responders to stresses, or the secondary effectors after stress-induced neuronal changes. Second, it is essential to track microglial dynamics at different stages in different brain regions to acquire a solid spatiotemporal profile of microglial phenotypes along the development of depression. Third, more mechanistic understandings are needed on how stress-induced changes in microglial cellular pathways lead to development of depression. Although the concept of microglial heterogeneity in different brain regions has been discussed (Kettenmann et al., 2011; Olah et al., 2011), it has not been incorporated in latest studies to reveal the differences of microglial contribution to depression targeting various neuronal circuits or brain regions. For this purpose, region-specific manipulations of microglia are needed to understand its role in depression. While viral tools have been widely

applied to studies on neurons and astrocytes, they work poorly on microglia, which are refractiled to recombinant adeno-associated virus (Balcaitis et al., 2005; Rosario et al., 2016). Some microglia-compatible viral tools such as lentivirus and adeno-associated virus have been recently attempted and achieved some success (Guan et al., 2020; Maes et al., 2019; Nie et al., 2018). Overall, new tools or drugs that enable microglia-specific manipulation in a brain-region-specific manner *in vivo* are in high demand. Further understanding of the interplay between microglia, neuroinflammation and depression will help to develop new therapeutics to mitigate depression.

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