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REVIEWS

Microglia Sing the Prelude of Neuroinflammation-Associated Depression

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Abstract

Major depressive disorder (MDD) is a psychiatric condition characterized by sadness and anhedonia and is closely linked to chronic low-grade neuroinflammation, which is primarily induced by microglia. Nonetheless, the mechanisms by which microglia elicit depressive symptoms remain uncertain. This review focuses on the mechanism linking microglia and depression encompassing the breakdown of the blood–brain barrier, the hypothalamic–pituitary–adrenal axis, the gut-brain axis, the vagus and sympathetic nervous systems, and the susceptibility influenced by epigenetic modifications on microglia. These pathways may lead to the alterations of microglia in cytokine levels, as well as increased oxidative stress. Simultaneously, many antidepressant treatments can alter the immune phenotype of microglia, while anti-inflammatory treatments can also have antidepressant effects. This framework linking microglia, neuroinflammation, and depression could serve as a reference for targeting microglia to treat depression.

Keywords Major depressive disorder · Microglia · Neuroinflammation · Immunity

Abbreviations

5-HT	5-Hydroxy tryptamine
ACC	Anterior cingulate cortex
Ach	Acetylcholine
ACTH	Adrenocor ticotropic hormone
AG	Adrenal gland
Akt1/Akt2	AKT serine/threonine kinase 1/2
Amy	Amygdala
Arg1	Arginase-1
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
cAMP	Cyclic adenosine monophosphate
CCL2	C-C motif chemokine ligand 2
CCL5	C-C motif chemokine ligand 5
CCL9	C-C motif chemokine ligand 9
CCR10	C-C motif chemokine receptor 10
CD	Cluster of differentiation
CNS	Central nervous system
COX2	Cyclooxygenase-2
CPA	Conditioned place aversion
CRH	Corticotropin-releasing hormone
CRP	C-reaction protein
CSDS	Chronic social defeat stress
CSF	Cerebrospinal fluid
CUMS	Chronic unpredictable mild stress
CUS	Chronic unpredictable stress
CX1CR1	C-X-C chemokine receptor 1
CX3CR1	C-X3-C chemokine receptor 1
DBS	Deep brain stimulation
DHEA	Dehydroepiandrosterone
DNMT	DNA methyltransferase
DNMT3B	DNA methyltransferase 3 beta
IL-1R1	IL-1 receptor type I
IL-6	Interleukin-6
iNOS	Inducible nitric oxide synthase
JMJD3	Jumonji domain protein 3
JSE	Juvenile social exploration
KYN	Kynurenine
LAG3	Lymphocyte-activating gene-3

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LC	Locus coeruleus
LDT	Light/dark box test
Lgals3	Advanced glycation end-product receptor 3
LHb	Lateral habenula
LPS	Lipopolysaccharide
MAOI	Monoamine oxidase inhibitor
MBT	Marble burying test
MDD	Major depressive disorder
MHC	Major histocompatibility complex
mPFC	Medial prefrontal cortex
NE	Norepinephrine
NF-κB	Nuclear factor-kappa B
NLRP3	NOD-, LRR-, and pyrin domain-containing protein 3
NO	Nitrogen monoxide
Nrf2	Nuclear factor erythroid 2-related factor 2
NSAIDs	Nonsteroidal anti-inflammatory drugs
OFT	Open field test
P2RY12	Purinergic receptor P2Y12
PET	Positron emission computed tomography
PFC	Prefrontal cortex
PGE2	Prostaglandin E2
PKA	Protein kinase A
PKB	Protein kinase B
PVN	Paraventricular nucleus of the hypothalamus

Introduction

Major depressive disorder (MDD) is a complicated condition that manifests as a combination of various signs and symptoms, mainly characterized by sadness and anhedonia. The impact of depression on individuals can lead to significant health loss [1, 2]. According to the World Health Organization, depression will be the primary cause of the worldwide disease burden by 2030 [3]. Due to the diverse symptoms and pathophysiology of the condition, various biological mechanisms are involved in its etiology. These mechanisms include dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, maladjustment of monoamine neurotransmitters, abnormal neuroplasticity and neurogenesis, and inflammatory imbalance [4]. Previous studies on depression have primarily focused on neuronal changes in the brains of both depressed patients and animal models. As a result, many antidepressants have been developed to modulate the level of 5-HT, dopamine, norepinephrine, and their receptors. However, despite following correct medical advice, approximately two-thirds of diagnosed patients still fail to see improvement or even experience relapse [4].

Microglia, which are the primary immune cells of the central nervous system (CNS), have a crucial role in monitoring and modulating the immune system as neurons undergo maturation, damage, aging, etc. [5, 6]. Accumulating evidence suggests that chronic low-grade neuroinflammation significantly contributes to the pathogenesis of mental health disorders [7, 8]. Chronic low-grade neuroinflammation is also described as "para-inflammation", which means the adaptive response that is intermediate between basal and inflammatory states. Para-inflammation represents an adaptive response intermediate between basal and inflammatory states, with graded levels ranging from near-basal to more inflammatory responses triggered by infection or tissue damage. This adaptive process helps tissues adapt to adverse conditions and promotes functional tissue restoration [7, 8]. Under normal conditions, short-term inflammation acts as a guardian to prevent the spread of pathogenic microorganisms, remove necrotic tissue, and promote tissue repair [9]. However, prolonged tissue dysfunction can perpetuate low-grade inflammation, potentially leading to a chronic state where inflammation can be the real culprit in triggering mood disorders [10]. As the major locus of neuroinflammation response, microglia are possibly involved in modulating neurobiochemistry, neuroendocrine, and behavioral alterations associated with depressive symptoms [11, 12]. Clinical evidence also demonstrates microglial dynamics in the brains of patients with depression, supporting the idea that depression may be a microglial disease [13]. Nevertheless, the underlying mechanism concerning the relationship between microglia-induced neuroinflammation and MDD remains uncertain, and the understanding of the intersection of immunology and neuroscience remains pending, which is the subject of a current review.

The Immunomodulation of Microglia with Depression

Immune Disorders in MDD

Factors such as environment, genetics, stress, and infection can affect individual immunity to varying degrees, and eventually trigger the remodeling of the inflammatory phenotype in MDD patients, manifested by the elevated inflammation scores in both pro-inflammatory and anti-inflammatory cytokines. The pro-inflammatory markers interleukin (IL)-6 (IL-6), tumor necrosis factor (TNF)-α (TNF-α), IL-1β, and C-reaction protein (CRP, a biomarker of systemic inflammation) are reliable biomarkers of immune disorders occurring in MDD [14–16]. A clinical study of 89 MDD patients showed that cerebrospinal fluid (CSF) IL-6, TNF-α, and IL-1β were associated with high plasma CRP (> 3 mg/L), as well as the severity of depressive symptoms [17]. It has been found that peripheral monocytes in MDD were less responsive to lipopolysaccharide (LPS) [18]. Similarly, MDD plasma also has an immunosuppressive effect on peripheral blood mononuclear cells from healthy donors, resulting in

reduced activation of monocyte/dendritic cells and B cells and reduced T cell memory [19]. The aforementioned evidence strongly indicates the potential existence of immune tolerance among individuals experiencing depression. Furthermore, high levels of cytokines alone can also lead to depressive symptoms. Striking examples are two reports of depression in 45% of patients with malignant melanoma and 35% of patients with hepatitis C virus after treatment with high doses of the pro-inflammatory cytokine interferon (IFN)-α (IFN-α) [20, 21]. These human data are consistent with the literature in many experimental animals, such as the LPS-induced depression model, suggesting that cytokines can induce a range of behavioral changes that overlap with those observed in depression, including anhedonia, cognitive dysfunction, and reduced activity [22–24].

In addition to elevated cytokines in peripheral blood and CSF, there is also direct evidence of inflammation in depressed patients' brains by imaging. Translocator protein (TSPO) is highly expressed in activated microglia during neuroinflammation, making it a biomarker of brain inflammation [25], which also supports the neuroinflammatory hypothesis of depression [26, 27]. However, using TSPO binding as an indicator of activated microglia is still controversial. Using the positron emission computed tomography (PET) ligand [^{18}F], FEPPA found that the TSPO distribution volume in MDD was increased in the anterior cingulate cortex (ACC), prefrontal cortex (PFC), and insula [28]. Using the ligand [^{11}C]PK-11195 exhibited that there is a raised TSPO distribution volume in the ACC of MDD and a substantial increase in depression with suicidal tendencies [29]. Although there is no direct evidence that TSPO represents pro-inflammatory or anti-inflammatory microglia activation, several animal and human studies have shown that elevated TSPO correlates with behavioral manifestations of upward pro-inflammatory cytokines in depression. Nonetheless, several PET analyses have examined the microglial status of postmortem whole-brain samples in individuals with depression, yielding negative results, which is likely because depression is predominantly linked to microglial activation or reduction in particular brain regions, rendering the overall status of microglia in the entire brain sample unreliable [13]. In conclusion, because of limited ethical and inadequate post-mortem brain samples, as well as many confounding variables including medication, age, and severity, the TSPO results should be taken with care. Thus, either central or peripheral immune system dysregulation can mediate depressive-like symptoms.

Microglia in CNS

Microglia are resident innate immune cells that serve as the first line of immune janitors, constituting 5 to 10% of the CNS population [30]. They are derived from immature yolk sac progenitor cells during early embryogenesis and persist throughout life [31]. In adults, regeneration occurs solely on residual microglia without the presence of de novo progenitors [32]. As the neurons' inseparable partners, microglia are involved in adjusting neuronal activity through various mechanisms [33], covering neurogenesis, synaptic and neuronal plasticity [34], phagocytosis, antigen-presentation, cytokines release, metabolic support, neurotransmitter release and uptake, extracellular matrix reconstruction [35], and signal feedback [36]. According to the morphology, function, and specific position, microglia can be classified into the following forms: ramified microglia, amoeboid microglia, hypertrophic microglia, rod microglia, dystrophic microglia, and satellite microglia [37]. Under normal circumstances, microglia are in a "resting" state, with a ramified morphology. In response to tissue injury or pathogen invasion, ramified microglia proliferate and transform into activated "brain macrophages," also known as "reactive microglia," or hypertrophic microglia, eventually obtaining an amoeboid shape with enlarged somas and sprout, an excess of short and thick protrusions [37, 38].

Referencing the dichotomy of macrophage activation, microglia are classified into M1 and M2 types based on distinct stimulatory factors, although their transcriptional adaptations differ from those of peripheral macrophages [39]. M1 phenotype is induced by LPS and/or IFN-γ stimulation, which activates toll-like receptor 4 (TLR4) or IFN-γ receptors 1 and 2, respectively, followed by activation of transcription factors the nuclear factor-kappa B (NF-κB) and signal transducer and activator of transcription (STAT) 1 and raised levels of CD86 and MHC II, at which point M1 phenotype markers include CD16, CD32, CD86, inducible nitric oxide synthase (iNOS), and MHCII. M1 secrete pro-inflammatory cytokines (IL-1α, IL-1β, TNF-α, IL-6, IL-12, IL-23), chemokines (CCL2, CCL9, CCR10), cyclooxygenase-2 (COX2), reactive oxygen species (ROS), etc. M2 phenotype is induced by IL-4/IL-13 stimulation, in which IL-4 binding to its receptor triggers activation of STAT6, which lets microglia shift toward anti-inflammatory phenotype with increased expression of arginase-1 (Arg1), CD206, mannose receptor, and release of anti-inflammatory factors (IL-4, IL-10, IL-13, IL-1RA) [40]. During the progression of the disease, activated microglia can switch from M2 to M1 phenotype. A transient neuroinflammatory response is protective during stress and tissue damage under normal conditions, as M1 microglia release chemokines to move rapidly and purposefully to the site of damage, while M2 microglia release trophic factors such as brain-derived neurotrophic factor (BDNF) to promote neuronal microenvironmental homeostasis. In abnormal contexts, microglia become dysfunctional (e.g., suppressed microglia function, reduced numbers, senescence) and are unable to "put out the fire" after inflammation, leading to a constant and chronic

CNS inflammatory state, causing neuronal excitotoxicity, excessive synapse pruning, demyelination, and death, which disrupts mood and cognition and causes various behaviors associated with depression [41].

Two-photon microscopy techniques have directly revealed the activity state of microglia that always performs to have highly motile protrusions, even in the absence of conventional stimulus signals [22]. Since there is no absolute concept of the "resting" state of microglia, the classification of these cells into M1 and M2 subtypes is no longer applicable. Theoretically, the distinction between M1 and M2 serves to facilitate the description of microglial inflammatory features and to investigate the mechanisms of microglial dual regulation, and microglia are always in kinetic equilibrium to accomplish their mission due to their high susceptibility to the fluctuating microenvironment [42]. Hence, microglia are morphologically and phenotypically distinct at various phases of life and in various brain regions [43]. For example, the aging brain contains a specific subset of dysfunctional lipid-droplet-accumulating microglia that exhibit pro-inflammatory effects and weak phagocytosis [44].

Immunological Alterations of Microglia in Different Brain Regions

The brain regions linked to depression can be broadly categorized as the PFC, which governs cognition, and the limbic system, which controls emotional responses [45–47]. The medial prefrontal cortex (mPFC) has been linked to affective experiences such as anxiety, guilt, and humiliation in individuals with MDD [48]. In the depression model, there is an elevation in pro-inflammatory markers on microglia, commonly observed cytokines comprise IL-1α, TNF-α, IL-1β, and IL-6, while anti-inflammatory markers such as Arg1, IL-4, and IL-10 experience a decrease [49–54]. Exposure to an inflammatory environment has been observed to lead to a decrease in BDNF, as well as a reduction in neuronal response, dendritic atrophy, synapse loss, and an imbalance in local excitatory and inhibitory transmission. These changes can ultimately contribute to the development of depressive symptoms [49–54]. The ACC is linked to the cognitive respects of emotions, while activated microglia in the ACC are known to have a significant impact on mood disorders [55]. The occurrence of an inflammatory response in the ACC during the early stages of childhood boosts the likelihood of an individual developing depression in adulthood. This is because early inflammation triggers excessive phagocytosis of the glutamatergic neuronal spines by microglia, subsequently enduring maladaptation of neurons to stress, thereby facilitating the emergence of symptoms resembling depression during adolescence [22].

The limbic system is accountable for the regulation of emotional responses and is linked to states of physiological and psychological activity, such as excitement, fear, anxiety, and emotional memories [56, 57]. Specifically, the amygdala dominates anxiety, fear, and other negative emotions. In models of depression induced by acute or chronic stress, microglia located in the amygdala demonstrate an activated state characterized by an increase in numbers, enlarged cytosomes, and a reduction in total protrusion length, with inflammation-related markers including CD14, CD86, and TLR4 on their surface [58, 59]. The depressive symptoms may be attributed to the dysregulation of synaptic and non-synaptic transmission through inflammation in the amygdala [58, 59]. The hippocampus preserves emotional memory. The activation of microglia in the hippocampus shows a notable increase of several pro-inflammatory markers, including NLRP3 inflammasome, IL-1β, IL-6, and IL-18, which have been observed to impact neurogenesis in the hippocampus within a depression model [60]. The striatum has been linked to impulsivity, fatigue, and negative affect in the context of depression [58, 61]. The induction of aversion in mice can be achieved through the targeted activation of striatal microglia. This process relies on the critical involvement of IL-6 signaling and COX-1-mediated prostaglandin synthesis within the microglia [62]. Studies have indicated a correlation between depression and activated insula, showing atypical somatic sensitivity. Furthermore, it has been observed that individuals suffering from depression exhibit a reduction in connectivity between the insula and ACC, which is concomitant with an increase in microglia activation [63]. The lateral habenula (LHb) has been connected to feelings of helplessness, anhedonia, and excessive concern with negative stimuli [64]. The activation of microglia in the LHb can be also found in repetitive social defeat stress and LPS-induced depression models [65] (Table 1).

Microglia Link Bidirectional Immune Communication in Depression

Activated microglia are considered the manifestation of neuroinflammation, the pivotal convergence of various stimulation-induced neuroinflammatory responses, and an important source of pro-inflammatory factors and oxidative stress [73]. There are multiple pathways to activate microglia.

BBB

As a highly selective and dynamic interface between blood and brain tissue with monitoring brain immune dynamics [74], the blood–brain barrier (BBB) is a territorial boundary between the brain and inflammatory signals in the circulating blood [75] and is mainly composed of vascular endotheliocytes with tight junctions [76]. The dramatically increased microglia and macrophage recruitment observed in the dorsal ACC of depressed suicidal individuals may be linked

Table 1 Immunological alterations of microglia in different depressed brain regions

Brain region	Model of depression	Depressive-like behavior	State of microglia	Alteration relating to neuron	Alteration relating to immunity	Reference
ACC	Early-life inflammation induced by LPS	Anhedonia (SPT); Despair (FST, TST)	IF: Iba1↑ (number↑, soma size↑, total process length↓, branch points↓), CD68↑, MHCII↑; Protein: TLR4↑	LPS increases the extent of microglial engulfment around neuronal spines in adolescence	Protein: p-NF-κB p65↑, CX3CR1↑; mRNA and protein: IL-1β↑, IL-6↑, TNF-α↑	[22]
ACC	Chronic LPS stress	Anhedonia (SPT); Anxiety (OFT, EPM); Despair (FST, TST); Body weight loss	IF: Iba1↑ (number↑, soma size↑, total process length↓, branch points↓); mRNA: Iba1↑, CD68↑	Dendritic spines↓	mRNA: CX3CR↑, caspase4↑, CCL5↑, TLR1↑, TLR9↑, TLR13↑	[66]
ACC	MDD with suicidal ideation	Suicidal ideation	TSPO: volume↑	-	-	[29]
Amy	LPS stress	Anhedonia (SPT); Anxiety (EPM, OFT); Despair (FST, TST)	IF: Iba-1 (number↑, soma size↑, total process length↓)	Presynaptic glutamate↑; Intrinsic neuronal excitability↑	ELISA: IL-1β↑, TNF-α↑; Protein: IL-1β↑, TNF-α↑, TNF-α receptor↑	[59]
Amy PFC Hip	Social disruption stress	Anxiety (LDT)	IH/IF: Iba-1 (number↑); Flow cytometry: CD14↑, CD86↑, TLR4↑	-	mRNA: IL-1β↑, GC responsive genes↓; ELISA: IL-6↑	[58]
Hip	Chronic mild stress	Anxiety (EPM, OFT); Despair (FST)	IF: Iba-1 (number↑), TSPO↑	-	Protein: NLRP3 inflammasome↑; mRNA: IL-1β↑, IL-6↑, IL-18↑, IL-4↑, IL-10↑	[67]
Hip	Chronic social defeat	Aberrant socialization (SIT); Anxiety (LDT)	IF: Iba-1 (number↑)	-	ROS activity↑	[68]
Hip	Chronic social defeat stress	Social avoidance (SAT); Body weight loss	IH: Iba-1 (number↑)	Neurogenesis↓	IF: NLRP3↑, CX1CR1↓; ELISA: IL-6↑	[69]
Hip	Chronic jetlag with a chronic phase advance model	Anhedonia (SPT); Anxiety (OFT, EPM, JSE); Despair (FST); Sleep disturbance	mRNA: CD68↑	BDNF↓	ELISA: GC↑; mRNA: IL-1β↓, Arg1↑	[70]
Hip	An experimental model of shift-work	Anhedonia (SPT); Anxiety (OFT); Hypoactivity (24-h activity)	IH: Iba-1 (number↑)	-	-	[71]
Hip	LPS stress	Anxiety (OFT); Despair (FST)	IH: Iba-1 (number↑); mRNA: Iba1↑	-	mRNA: IL-1β↑, IL-6↑, TNF-α↑	[72]
LH	Repeated social defeat stress/ LPS stress	Anhedonia (SPT); Despair (FST, TST); Social avoidance (SIT)	IF: Iba1↑ (soma size↑, total process length↓)	Neuronal excitability↑	mRNA: TNF-α↑, IL-1β↑, IL-6↑; Protein: iNOS↑	[65]
mPFC	IL-10 knockout mice	Anhedonia (SPT); Anxiety (MBT); Despair (FST, TST)	IF: Iba-1 (number↑)	Protein: GAD67↓, parvalbumin↓;	Protein: IL-1β↑, IL-6↑, IL-10↓	[51]
mPFC	Chronic mild stress	Anhedonia (SPT); Despair (FST); Anxiety (OFT)	IF: Iba-1 (number↑), CD68↑	Synapse loss↑; Dendritic spine density↓; Neuronal activity↓	ELISA: TNF-α↑, IL-1β↑	[49]
PFC	Chronic stress	Anhedonia (SPT); Anxiety (FST, OFT); Body weight loss	IH: Iba-1 (number↑)	5-HT_{2A}↑	mRNA: TNF-α↑, COX-1↑	[53]

Table 1 (continued)

Brain region	Model of depression	Depressive-like behavior	State of microglia	Alteration relating to neuron	Alteration relating to immunity	Reference
mPFC	Chronic social defeat stress	Anhedonia (SPT); Despair (FST); Social avoidance (SIT)	IF: Iba-1 (number↑), Arg1↓, TREM2; Protein: Arg1↓, TREM2↓	Protein: BDNF↓, PSD95↓	mRNA: IL-4↓, IL-10↓; IF: Nrf2↓; Protein: Nrf2↓	[50]
mPFC	Repeated social defeat stress	Anxiety (EPM); Social avoidance (SIT)	IF: CD68↑, Iba-1 (number↑), CD11b↑; mRNA: CD11b↑, TLR2↑, TLR4↑	Neuronal response attenuation; Dendritic atrophy	mRNA:IL-1α↑, TNF-α↑, IL-1R1↑	[52]
mPFC	Repeated social defeat stress	Anxiety (EPM); Social avoidance (SIT, submissive posture)	IF: Iba-1 (number↑)	Attenuation of the mesocortical dopaminergic pathway	ELISA: corticosterone↑; ELISA: PGE2↑	[54]
PFC ACC Insula	MDD episodes	Anhedonia; Anorexia; Low mood; Body weight loss	TSPO: volume↑	-	-	[28]
Striatum	LPS stress/ Chemogenetic activation	Aversion (CPA); Anhedonia (SPT); Anxiety (OFT); Despair (FST)	IF: Iba-1 (number↑)	Excitability of striatal medium spiny neurons↓	mRNA:IL-1↑, IL-6↑, TNF-α↑, CD14↑	[62]

ACC, anterior cingulate cortex; *Amy*, amygdala; *Arg1*, arginase-1; *BDNF*, brain-derived neurotrophic factor; *CPA*, conditioned place aversion; *CX1CR1*, C-X-C chemokine receptor 1; *ELISA*, enzyme-linked immunosorbent assay; *EPM*, elevated plus maze; *FST*, forced swimming test; *GAD67*, glutamate decarboxylase 67; *GC*, glucocorticoid; *Hip*, hippocampus; *IL-1R1*, IL-1 receptor type I; *iNOS*, inducible nitric oxide synthase; *IF*, immunofluorescence staining; *IH*, immunohistochemistry staining; *JSE*, juvenile social exploration; *LDT*, light/dark box test; *LH*, lateral habenula; *MBT*, marble burying test; *mPFC*, medial prefrontal cortex; *NLRP3*, NOD-, LRR- and pyrin domain-containing protein 3; *Nrf2*, nuclear factor erythroid-2-related factor 2; *OFT*, open field test; *PFC*, prefrontal cortex; *SAT*, social avoidance test; *SPT*, sucrose preference test; *SIT*, social interaction test; *TREM2*, triggering receptor expressed on myeloid cells-2; *TSPO*, translocator protein; *TST*, tail suspension test

to BBB disruption [77]. When the BBB compromised, periphery immune cells and cytokines entered the brain parenchyma and modulated the inflammatory response from within [78], producing much more inflammatory cytokines through mutual action with microglia and astrocytes during the process [79], and elevated levels of inflammatory cytokines such as TNF-α and IL-1β in the brain able to cause prolonged mouse depression-like behavior [80–82]. Changes in the BBB's tight junctions allow the entry of monocytes/macrophages and circulating inflammatory cytokines into the brain, while endothelial cell dysfunction increases the adherence of leukocytes and yields conditions that induce inflammation [83]. Meanwhile, endothelial cells can transmit peripheral inflammatory signals directly to astrocytes and microglia, while activated microglia can recruit more monocytes for transport to the brain by releasing CCL2 [84], without BBB destruction [85]. For instance, under conditions of chronic stress, microglia can selectively increase CCL2 expression, thereby attracting monocytes that subsequently express IL-1β to bind to IL-1R1 in brain endothelial cells [86]. Systemic inflammation can also induce microglia migration to the vasculature via the chemokine CCL5, while early inflammation promotes microglia expression of the tight junction protein cldn5 to preserve BBB integrity and physical contact with endothelial cells, which may refer to the P2RY12 receptor of microglia [87]. However, persistent inflammation leads to enhanced microglia phagocytosis of astrocyte end-foot and destructed BBB function, instead of limiting microglia activation [88].

Neuroimmune Interactions

Microglia are in a unique position as immune sensors of the stress response [89, 90], able to rapidly sense and respond to changes, which in turn adjust the CNS to respond to acute or chronic stress [91]. The stress involved in the mechanism of depression acts mainly through the HPA axis, which is consistent with the clinical finding of abnormalities in the HPA axis in depressed patients who manifested by elevated plasma cortisol levels. Two hypotheses could explain the paradox of both high GC levels and high levels of pro-inflammatory factors in depressed patients: GC resistance and GC synergy with pro-inflammatory cytokines. In the model of depression induced by LPS, GC combined with its receptor (GR) to inhibit the activity of NF-κB in the early phase of the NF-κB activity, but had no inhibitory effect in the late phase. The lack of inhibitory effect could be explained by the GC resistance which is probably mediated by selective accumulation of GRβ protein [92]. Meanwhile, in the late phase of NF-κB activity when depression-like behavior was evident, microglia in the infralimbic PFC significantly increased, emphasizing the key role of microglia immunity in the process of acute stress [93]. In addition, the time effect of GC application modulates the cellular state to produce anti-inflammatory, pro-inflammatory, or combined effects. Short-term pre-exposure to GC inhibits pro-inflammatory responses, whereas long-term pre-exposure to GC induces increased NLRP3 expression, sensitizes microglia to extracellular ATP signaling molecules, and increases the release of ATP-mediated pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 [94, 95], or increases microglia proliferation through NMDA receptor activation [96]. Both the in vivo and ex vivo studies suggest that GC treatment sensitizes the TNF-α and IL-1β response to LPS, and upregulates the expression of microglia activation markers [97] and receptors including MHCII, TLR2, and TLR4 in the hippocampal microglia [98]. The bidirectional regulation of inflammation by GC complicates its role in depression, and addressing the question of how to reconcile the time-dependency response of GC may help to normalize the immune system characteristics by modulating abnormally elevated GC in response to stress, thereby ameliorating MDD. The other way to regulate neuroimmune interactions is through sympathetic and parasympathetic systems. Chronic stress also affects peripheral immune cells by activating the sympathetic nervous system. Under stressful conditions, sympathetic nerves bias hematopoietic stem cells toward differentiation into GC-resistant myeloid immune cells, which can then be recruited to the CNS by chemokines secreted by microglia to participate in the inflammatory response [99]. Stress can also induce microglia activation via β-adrenergic receptors [100]. The vagus nerve suppresses inflammation by activating the HPA axis [101] and binding to the α7 nicotinic acetylcholine receptor (α7nAChR) of microglia through the cholinergic anti-inflammatory pathway [102]. The activation of α7nAChR increases Ser3-phosphorylation of GSK9, which in turn activates PKB, and GSK3β, inhibiting NF-κB transcriptional activity and exerting anti-inflammatory effects [103].

Gut-Brain Axis

In the absence of a microbiome, microglia in the male embryonic stage showed substantial downregulation of gene expression associated with metabolic processes, cell and protein organization, and adaptive immune responses, while microglia in adult female mice exhibited dysregulation of genes associated with regulation of transcription, adaptive immune responses, cell migration, and chemotaxis, suggesting that microglia respond to the absence of a microbiome at the prenatal stage in a sex and time specific manner [104], and from this perspective, the increased baseline microglia activation status in adult females may partially explain why they show greater susceptibility to depression than adult males [105]. Microbiomes generate a variety of neuromodulators (e.g., catecholamine, aminobutyric acid,

5-HT), immune modulators (e.g., quinolinic acid (QUIN)), and short-chain fatty acids (SCFAs) (e.g., acetate, propionate, butyrate) that cross the BBB and exhibit immunomodulatory effects on microglia [106, 107]. Among them, SCFAs facilitate the maturation of microglia and possess properties that mitigate inflammation [108], resulting in a decrease in the levels of pro-inflammatory IL-1β, CCL2, TNF-α, and an increase in the levels of anti-inflammatory TGF-β and IL-4 [109, 110]. Studies on adult mouse models of depression have found that depression-like behavior can be improved in mice by remodeling the microbiota [111], and its antidepressant effects are possibly related to promoting microglia to an anti-inflammatory phenotype [112]. However, it remains to be determined whether the effect of the microbiome on the immune system can ameliorate MDD. A meta-analysis of the use of probiotics in alleviating depressive symptoms showed that probiotic supplementation had an overall insignificant effect on mood, possibly limited by the discrepancies concerning probiotic dosing, bacterial strains, and strain combinations [113]. The antidepressant effect of minocycline, a microglia inhibitor, is associated with a reduction in the number of microglia in the PFC and changes in microbial composition and metabolites [114]. However, changes in the microbial composition may also be due to the direct inhibition of intestinal inflammation by minocycline as an antibiotic, rather than modulation by direct inhibition of microglia activation. Similarly, mice showed abnormal gut microbiota composition and SCFAs after repeated administration of colony-stimulating factor 1 receptor inhibitor PLX5622 to clear microglia [115]. These results mirror each other and suggest there is a tight immunomodulation between microglia and microbiota. In addition to interacting with microglia during development and adulthood, intestinal flora also triggers microglia mitochondrial dysfunction by increasing the microglial accumulation of N^6-carboxymethyllysine in the aging brain's microglia [116]. In addition, there is an interaction between enteroendocrine cells and vagal afferent neuron function. Vagal afferent neurons expressing TLR4 can directly sense bacterial products such as LPS [117], and convey changes in intestinal inflammatory status to microglia, thereby inhibiting microglia proliferation and expression of pro-inflammatory cytokines [118], and restoring microglia to a resting state [119] (Fig. 1).

Microglia in Antidepressant Treatment

The Immunomodulatory Effects of Antidepressants

In the 1950s, it was discovered that iproniazid, an anti-tuberculosis drug, could increase 5-HT, dopamine, and norepinephrine levels in the brain by inhibiting monoamine oxidase, thereby improving mood, increasing appetite, making sleep better, becoming energetic, and increasing social willingness, thus establishing the classic monoamine hypothesis of depression [120, 121]. Classical antidepressants modify neurotransmitters and directly eliminate the symptoms of "low monoamine neurotransmitter levels" in the brain, which seems to bypass the underlying cause of depression [122]. A major argument against the monoamine hypothesis is that although these antidepressants rapidly elevate inter-synaptic monoamine neurotransmitter concentrations, the antidepressants require 2–4 weeks to take effect, leading to the speculation that there may be downstream signaling molecules may be responsible for the therapeutic effects of antidepressants [123]. In light of pharmacogenomic approaches, most of the antidepressants' effects can be divided into two categories: reinforcing the process of neuroplasticity and neurotrophy, and accommodating the inflammation, immunity, and redox reactions [124]. Numerous in vivo and in vitro studies on the effects of antidepressants on microglia have revealed that different classes of antidepressants have significant effects on alleviating depressive behaviors and the inflammatory environment of the brain, as well as on the immune and oxidative stress signaling of microglia [125]. Tricyclic antidepressants are thought to work through G_S-coupled microglial receptor activation, increase intracellular cAMP levels, and activate the cAMP-dependent protein kinase A (PKA), which blocks GSK3 enzyme function [103], while the blocked GSK3β inhibits the subsequent transcriptional activity of NF-κB, reducing the production of pro-inflammatory cytokines including IL-1β, TNF-α, and IL-6 [126]. In particular, imipramine also prevents stress-related anxiety and depressive-like behaviors by preventing the accumulation of macrophages in the brain [127]. Selective serotonin reuptake inhibitors (SSRIs), similar to tricyclic antidepressants (TCA), demonstrate anti-inflammatory properties via PKA inhibition in microglia [128]. For instance, the administration of fluoxetine, paroxetine, sertraline, and citalopram has been observed to impede the production of nitrogen monoxide (NO) and TNF-α by microglia, as well as diminish the release of glutamate. These effects have been shown to facilitate the survival of neurons [129–131]. Tranylcypromine, a monoamine oxidase inhibitor, has been observed to hamper the synthesis of pro-inflammatory cytokines, including but not limited to IL-1β, and IL-6[132]. Additional classes of antidepressants can also regulate the inflammatory responses of microglia. Melatonin relieves LPS-induced depression by blocking the microglial NLRP3 inflammasome [133]. Ketamine, a blocker of NMDA receptors at glutamate receptors in the brain, can rapidly improve depressive symptoms and suicidal ideation within hours after a single dose, and its antidepressant action may be mediated by microglial production of QUIN [128, 134], the BDNF pathway [135], and TGF-β1 [136].

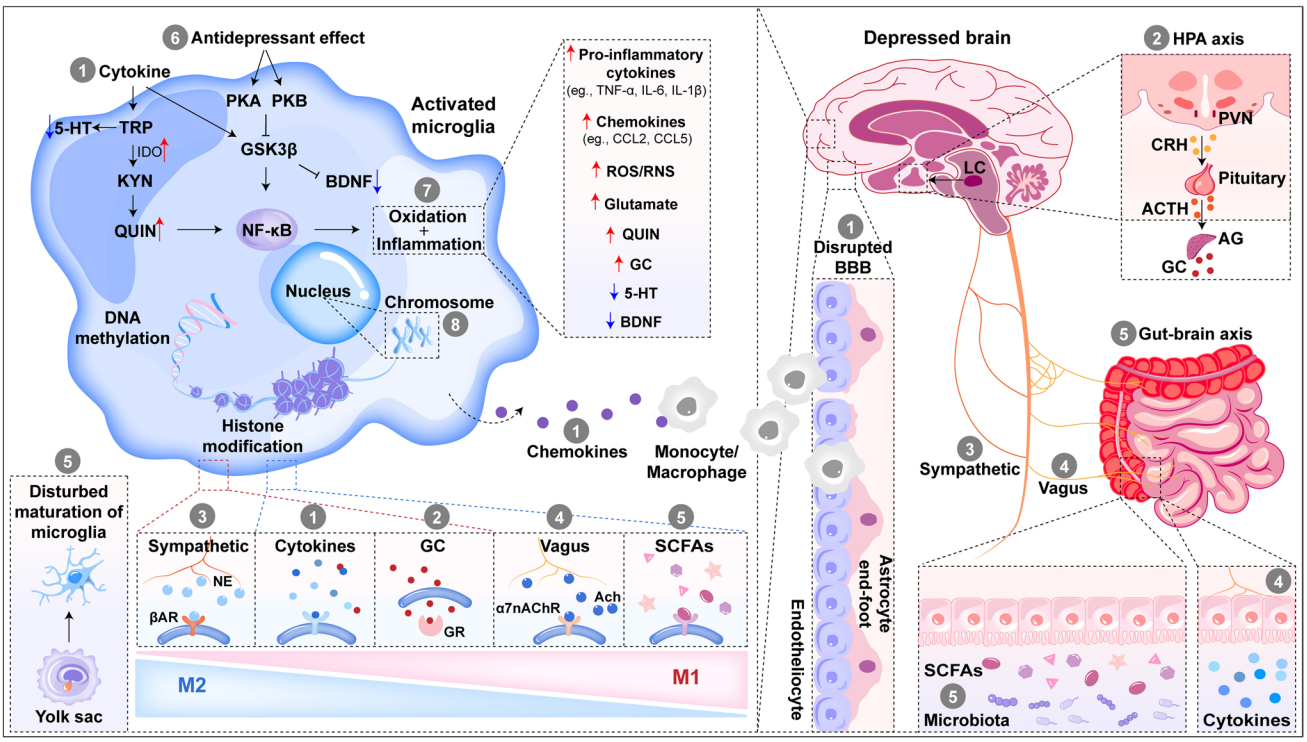

Fig. 1 Microglia link bidirectional immune communication via multiple direct and indirect pathways in depression. (1) Impairment of the BBB leads to the infiltration of peripheral monocytes/macrophages and circulating inflammatory cytokines into the brain, resulting in the activation of microglia. The increased activity of IDO in microglia drives tryptophan metabolism toward the kynurenine pathway, which produces the neurotoxic QUIN and reduces the synthesis of 5-HT. Simultaneously, the dysfunction of endothelial cells results in heightened leukocyte adhesion, thereby creating an environment that triggers inflammation. Furthermore, the activation of microglia can attract a greater number of monocytes for transportation to the brain through the discharge of chemokines. (2) Microglia act as immune sensors of stress responses primarily through the HPA axis. The binding of GC to its receptors can result in anti-inflammatory, pro-inflammatory, or combined effects, which are dependent upon the duration of GC exposure. (3) An alternative approach to regulating neuroimmune interactions involves the sympathetic and parasympathetic nervous systems. The activation of microglia can be induced by sympathetic through the β-adrenergic receptors. (4) The inhibition of inflammation is facilitated by the binding of the vagus to the α7nAChR of microglia through the cholinergic anti-inflammatory pathways. (5) The microbiota generates a diverse range of SCFAs, which traverse the BBB and demonstrate immunomodulatory properties on microglia. Additionally, they contribute to the maturation of microglia. (6) The activation of microglial PKA and PKB to block GSK3β, which subsequently inhibits the transcriptional activity of NF-κB and ultimately reduces oxidation and inflammation, may account for the antidepressant effect of multiple drugs or pathways. (7) The oxidation and inflammation afterward stimulate additional pro-inflammatory cytokines, chemokines, ROS, and RNS. The cascade of events ultimately causes elevated levels of glutamate, QUIN, and GC, as well as decreased levels of 5-HT and BDNF, culminating in depressive symptoms. (8) Moreover, the susceptibility to depression is closely linked with epigenetic alterations in microglia. The aforementioned pathways represent three distinct modes of bidirectional immune communication between the peripheral and central systems. These include the humoral pathway, which is linked to the BBB, the neural pathway, which is associated with the vagus and sympathetic nerves, and the cellular pathway, which is connected to microglia. BDNF, brain-derived neurotrophic factor; TRP, tryptophan; IDO, indoleamine 2,3-dioxygenase; KYN, kynurenine; QUIN, quinolinic acid; LC, locus coeruleus; PVN, paraventricular nucleus of the hypothalamus; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; AG, adrenal gland; GC, glucocorticoid; GR, glucocorticoid receptor; βAR, β-adrenergic receptor; NE, norepinephrine; α7nAChR, α7 nicotinic acetylcholine receptor; Ach, acetylcholine; SCFAs, short-chain fatty acids; PKA, protein kinase A; PKB, protein kinase B; GSK3β, glycogen synthase kinase 3β; NF-κB, nuclear factor-kappa B; TNF-α, tumor necrosis factor; IL, interleukin; CCL2, C–C motif chemokine ligand 2; ROS, reactive oxygen species; RNS, reactive nitrogen species; 5-HT, 5-hydroxy tryptamine

The Antidepressant Effects of Anti-inflammatory Drugs

Numerous clinical studies find that inflammation-related diseases have a higher incidence of depression, such as chronic hepatitis [137] and autoimmune diseases [138]. An increase in inflammatory biomarkers may predict a lack of response to antidepressants, one reason for which may be the presence of a defect in the anti-inflammatory response, which may also be a reason why traditional antidepressants do not work [19]. Therefore, anti-inflammatory treatments may be beneficial for depressed patients with increased immune baselines. Given the wide range of biological functions involved in inflammatory pathways, several clinical studies suggested

the possible clinical antidepressant benefit of targeting specific inflammatory cytokines [139]. A clinical trial targeting seven mechanisms of action (TNF-α, IL-12/23, IL-6, CD20, COX2, BLγS, and P38/MAPK14) in depressed patients, who are diagnosed with one of nine inflammation-related diseases (ulcerative colitis, rheumatoid arthritis, psoriasis, asthma, ankylosing spondylitis, multicentric Castleman disease, osteoarthritis-knee, systemic lupus erythematosus, neuropathic pain), and the conclusion was that anti-inflammatory drugs significantly improved two core symptoms of depression: anhedonia and depressed mood, and these effects were not exclusively attributable to the therapeutic effect on physical health [140]. A systematic review and meta-analysis of clinical trials of chronic inflammatory conditions revealed that monoclonal antibodies against the IL-6 receptor and TNF-α ameliorated depressive symptoms in a statistically significant manner [139]. Despite there being controversial results [141], ineffective results obtained by targeting only a single cytokine and ignoring the complexity of inflammatory factor types and functions are not sufficient to negate the effectiveness of anti-inflammatory treatment, since cytokines do not act independently, but rather cause MDD synergistically. Although there is a wealth of clinical data suggesting that the treatment of depression with nonsteroidal anti-inflammatory drugs (NSAIDs) alone or in addition may have side effects such as gastrointestinal bleeding, studying the mechanisms of its antidepressant effects may be useful in elucidating the etiology of depression. The antibiotic minocycline is often tested as an antidepressant in animals [142, 143], and its antidepressant effects have been confirmed in clinical trials as an adjunctive therapy [144–146], and even in treatment-resistant depression [147–149]. Minocycline treats depression mainly through its immunomodulatory effects, including inhibition of microglia signaling in microglia such as MAPK, the release of cytokines such as TNF-α and IL-6 [150], and reduction of IDO activity, and impact on QUIN production. QUIN can interact with Fe^{2+} to increase ROS and RNS, limit SOD activity and GSH levels [151], impact 5-HT synthesis [152], and activate the HPA axis [153].

Microglia in Non-pharmacological Antidepressant Treatment

Electro-acupuncture treatment exhibited antidepressant effects associated with microglia, significantly reversed chronic unpredictable stress (CUS)-induced increases in IL-1β, IL-18, TNF-α, and IL-6 expression, and alleviated neuroinflammation in the hippocampus [154, 155], while microglia-derived LAG3 may be involved in it [156]. In addition, repetitive transcranial magnetic stimulation functions as an antidepressant by switching the microglial phenotype from M1 to M2 without reducing the number of microglia in the hippocampal and cortical regions [157]. Running exercise reduces the amount and activity of hippocampus microglia, which improves depressive-like behaviors caused by CUS [158]. Some articles suggest that the activation of microglia has antidepressant effects. For example, before starting the deep brain stimulation (DBS) treatment, the operation of electrode implantation already has an antidepressant effect by activated microglia, and the effect can be blocked by treatment with NSAIDs [159]. However, DBS is often used to treat treatment-resistant depression, where the microglia in the brain may have become senescent or even reduced in number due to the severity of the illness or the prolonged inflammation in the brain, so that external stimulation may alleviate depression by activating microglia or stimulating microglia proliferation [38]. Treating immune system dysregulation aids in the recovery of MDD, and both activating and inhibiting microglia have antidepressant effects, possibly because of differences in microglia status in MDD (Table 2).

Genetic and Epigenetic Regulations of Microglia in Depression

Neuroimmune and neuroendocrine responses elicited by prolonged stress are diverse due to individual differences, and early-life stress is associated with overt inflammation before the development of neuropsychiatric diseases, which presumably leads to behavioral vulnerability and resilience [164, 165]. Most people can adapt to the blow of stress by increasing their resilience, but some will collapse under similar circumstances and ultimately get depressed [166]. Whether the source of individual differences in depression susceptibility is related to gene and epigenetics alterations has been a hot issue in related research. In MDD, the most replicated and relevant genetic variants include polymorphisms in the genes for IL-1β, IL-6, IL-10, CCL2, TNF-α, and CRP [167], and the best replication risk alleles for depression have pro-inflammatory or protective effects against pathogens [168]. Nevertheless, these genes do not show a substantial contribution to the occurrence of depression [169, 170].

In recent years, a growing body of research has demonstrated that distinct stress elicits unique epigenetic modifications in both brain neurons and the immune system. Notably, alterations in microglial epigenetics have been identified as a significant contributor to the preservation of brain health [171]. Under conditions of early-life stress, a significant reduction in DNA methylation occurs in microglia, which is linked to altered microglial activity [171]. The process of DNA demethylation increases the transcription of IL-1β in microglia and regulates type I IFN responses induced by TLR-4 [172]. The in vivo

Table 2 Alterations of microglia in different types of antidepressant therapies

Treatment	Subject	Effect on microglia	Pro-inflammation	Anti-inflammation	Reference
Fluoxetine/norfluoxetine (SSRI)	Primary microglia with LPS	Inhibition	Gas chromatography: NO↓, TNF↓	-	[130]
Fluoxetine (SSRI)	BV2 with LPS	Inhibition	ELISA: TNF-α↓, IL-6↓; Griess reagent: NO↓; mRNA: TNF-α↓, IL-6↓, iNOS↓; Protein: iNOS↓; NF-κB↓	-	[160]
Vortioxetine (SSRI)	Rats with LPS	Inhibition	ELISA:IL-1β↓, IL-6↓, TNF-α↓	ELISA:IL-4↑	[161]
Escitalopram (SSRI)				-	
Amitriptyline (TCA)					
Tranylcypromine (MAOI)					
Paroxetine (SSRI)	BV2/primary microglia with LPS	Inhibition	ELISA: TNF-α↓, IL-1β↓; mRNA: TNF-α↓, IL-1β↓; Measurement of nitrite: NO↓; Protein: iNOS↓, TNF-α↓, IL-1β↓	-	[131]
Sertraline (SSRI)	Mice with CUMS	Inhibition	ELISA: NO↓, IL-1β↓, TNF-α↓; mRNA: Iba1↓; Protein: IL-1β↓, TNF-α↓, iNOS↓	-	[129]
Tranylcypromine (MAOI)	BV2 with LPS	Inhibition	mRNA: IL-1β↓, TNF-α↓, iNOS↓	-	[132]
Melatonin	Mice with LPS	Inhibition	IF: Iba-1↑; Protein: pro-IL-1β↓, IL-1β↓, NLRP3↓, cleaved caspase-1↓	-	[133]
Ketamine	Mice with LPS	Inhibition	Luminex assays:IL-1α↓, IL-6↓, Eotaxin↓, G-CSF↓, MIP1b↓, TNF-α↓; mRNA: Ptgs2↓	mRNA: Lgals3↓, IL-1RA↓	[134]
(R)-ketamine	Mice with CSDS	Inhibition	mRNA: Tgfb1↑, Tgfbr1↑, Tgfbr2↑	-	[136]
Lithium	HM/primary microglia/ hiPSC-derived microglia with IFN-γ/LPS	Inhibition	-	Multi-Spot Assay System: IL-10↑	[162]
taVNS	Rats with CUMS	Inhibition	Protein:IL-1β↓, NF-κB p65↓, p-NF-κB p65↓	Protein: α7nAChR↑	[163]
Running exercise	Rats with CUS	Inhibition	ELISA: IL-1β↓, iNOS↓, IL-6↓, TNF-α↓; mRNA: IL-1β↓, iNOS↓, IL-6↓, TNF-α↓	-	[158]
Imipramine (TCA)	Mice with RSD	Inhibition	ELISA: IL-6↓; mRNA: IL1-β↓, IL-6↓, TNF-α↓, TLR-4↓, CCL2↓, CX3CR1↓	-	[127]
EA	Rats with CUS	Inhibition	mRNA: IL-1β↓, IL-18↓, TNF-α↓; Protein: IL-1β, pro-IL-1β↓, NLRP3 inflammasome↓	-	[155]
ECS	Mice with CUS/BV2 with Poly I:C	Inhibition	Protein: TNF-α↓	-	[156]
rTMS	Mice with CUMS	Inhibition	ELISA: IL-6↓, IL-1β↓, TNF-α↓; mRNA: IL-6↓, IL-1β↓, TNF-α↓	-	[157]

α7nAChR, α7 nicotinic acetylcholine receptor; *CCL2*, C–C motif chemokine ligand 2; *CUMS*, chronic unpredictable mild stress; *CUS*, chronic unpredictable stress; *CSDS*, chronic social defeat stress; *CX3CR1*, C-X3-C chemokine receptor 1; *EA*, electro-acupuncture; *ECS*, electroconvulsive stimulation; *ELISA*, enzyme-linked immunosorbent assay; *hiPSC*, human-induced pluripotent stem cells; *HM*, immortalized human microglia; *IL*, interleukin; *iNOS*, inducible nitric oxide synthase; *Lgals3*, advanced glycation end-product receptor 3; *LPS*, lipopolysaccharide; *MAOI*, monoamine oxidase inhibitor; *NO*, nitrogen monoxide; *RSD*, repeated social defeat; *rTMS*, repetitive transcranial magnetic stimulation; *SSRIs*, selective serotonin reuptake inhibitors; *taVNS*, transcutaneous auricular vagus nerve stimulation; *TCA*, tricyclic antidepressants

experiments have also confirmed that the use of DNA demethylation drugs promotes LPS-induced pro-inflammatory responses in microglia [173]. Apart from DNA methylation, histone post-translational modifications also have a regulatory function in the immune function of microglia. The histone methyltransferase EZH2 has been implicated in susceptibility to neuroinflammation and depressive-like behaviors. Its upregulation of H3K27me3 exacerbates depression and neuroinflammation by inducing microglia M1-type polarization [174, 175]. While the utilization of the EZH2 inhibitor EPZ-6438 or methylation-reducing medications can impede the activation of M1 microglia, diminish the levels of pro-inflammatory cytokines, and augment the levels of anti-inflammatory cytokines in the brain. This, in turn, can alleviate depression-like behaviors and spatial memory impairment [176, 177]. The activation of microglia and expression of pro-inflammatory cytokines induced by LPS can be reduced by the SCFAs acetate and butyrate through increasing histone acetylation [110]. The deacetylase SIRT1 has been observed to induce a shift in microglial polarization toward the M2 phenotype through a decrease in the expression of IL-6, IL-1β, and iNOS, as well as an increase in the expression of IL-10, TGF-β, and Arg1, and mitigate depressive-like behaviors [178]. Research has demonstrated that the administration of LPS in vivo can result in microglia retaining alterations in epigenetic modifications for an extended duration. Upon subsequent immune stimulation, microglia exhibit immune memory, which triggers the secretion of a greater quantity of pro-inflammatory cytokines [179]. Therefore, early life adversity may cause prolonged epigenetic modifications of microglia that consistently and profoundly alter individual stress susceptibility and stress resilience [180], which was consistent with the finding that childhood trauma increased immune activation in MDD [181]. However, it was also discovered that microglia, upon receiving secondary immune stimulation, exhibited a sluggish proinflammatory response. This could be attributed to the fact that the initial immune stimulation caused a decrease in active histone modifications in the promoters of the IL-1β and TNF-α genes, while there was an increase in the amount of repressive histone modification in the IL-1β promoter. This mechanism could be interpreted as a protective measure to prevent excessive damage to the CNS during recurrent peripheral inflammation [182]. In human studies, alterations in DNA methylation in the peripheral monocyte were associated with MDD, and the methylation status of peripheral macrophages may be a potential biomarker for detecting indicators of depression, and given the similarity of monocytes, macrophages, and microglia, brain microglia may also have similar methylation alterations [183] (Table 3).

Conclusion

Since microglia may be involved in many biological processes simultaneously, external determinants (stress), internal factors (gene, BBB, sympathetic and parasympathetic nervous systems, microbiota, and microglia), and the body's coping mechanisms (GC and cytokines) collectively influence the interaction between depression and immunity, playing different roles in the development of depression depending on a certain context, to varying degrees [185].

It is reasonable to speculate on the role of microglia-associated neuroinflammation in depression: Early-life stress induces long-term epigenetic changes in immune-related genes of microglia (e.g., DNA demethylation processes increase IL-1β transcription in microglia [172]), profoundly altering an individual's stress susceptibility and resilience. Subsequently, when individuals face significant stress in adulthood, abnormal immune regulation fails to timely control immune responses, resulting in chronic low-grade neuroinflammation. In this state, the body's production of anti-inflammatory, pro-inflammatory, or combined effects through GC production regulated by the HPA axis may vary over time. Concurrently, pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β), chemokines (e.g., CCL2, CCL5), ROS/RNS, etc., perpetuate a vicious cycle of oxidative stress and inflammation. This cascade leads to the production of excitotoxic substances such as QUIN, excessive glutamate causing excitotoxicity, and reduced release of 5-HT and BDNF, potentially accompanied by dysregulation of sympathetic and vagal function and imbalance of the microbiota. Ultimately, these mechanisms contribute to aberrant neuron-microglia interactions (e.g., maladjustment of neurotransmitters, abnormal neuroplasticity and neurogenesis, neuronal excitotoxicity), culminating in depressive symptoms in individuals. Therefore, the relationship between depression and inflammation likely involves multifaceted interplays among these factors rather than a simple one-way causative relationship.

Controlling neuroinflammation favors depression treatment for long-term benefits, although it is unclear whether inflammation in depression is only a consequence rather than a cause, the pro-inflammatory environment does have an exacerbating effect on the conditions, and chronic inflammation in the CNS drives disease progression, not just a secondary event [186, 187]. Interpreting depression from a microglial perspective, we are forced to face the thorny question of how abnormalities in microglia contribute to depression rather than other psychoneurological disorders. Indeed, as microglia are increasingly explored, there are many studies analyzing the role of microglia in

Table 3 Epigenetic regulations of microglia in depression

Epigenetic modification	Gene	Definition	Drug	Mechanism on microglia	Phenotype	Reference
DNA methylation	TET2	DNA demethylase	-	TET2 is upregulated in microglia and regulates the proinflammatory response induced by LPS in vitro and in vivo, and regulates TLR-4-induced type I IFN response and LPS-induced aerobic glycolysis	TET2 regulates the proinflammatory response in microglia of mice intraperitoneally injected with LPS	[172]
	-	-	5-azacytidine (a demethylating drug)	5-azacytidine decreases IL-1β promoter DNA methylation and promotes the transcription of IL-1β in microglia	Aged mice have decreased methylation of the IL-1β gene promoter in primary microglia basally or following systemic LPS that is associated with increased IL-1β mRNA, intracellular IL-1β production, as well as prolonged sickness behavior	[173]
Histone modification	EZH2	Histone methyltransferase	EPZ-6438 (an inhibitor of EZH2)	EPZ-6438 inhibits M1 microglia activation, decreases levels of proinflammatory cytokines and P-p65 in the PFC and hippocampus in young and aged mice	EPZ-6438 relieves depression-like behaviors and spatial memory impairment in CUMS	[177]
			-	EZH2 inhibits miR-29b-3p expression by combining with miR-29b-3p promoter and H3K27me3 upregulation, and then elevates MMP2 transcription and triggers microglia M1-type polarization	EZH2 exacerbates depression-like behaviors and neuroinflammation of depression by modulating microglia polarization	[174]

Table 3 (continued)

Epigenetic modification	Gene	Definition	Drug	Mechanism on microglia	Phenotype	Reference
Histone modification	H3K9me3	Methylation	FA	FA promotes the expression of IL-13 by reducing the promoter binding of H3K9me3 in microglia	FA improves depressive- and anxiety-like behaviors in adults, accompanied by a decrease in the number of activated microglia, as well as a reduction in the inflammatory response in the cortex and hippocampus of neonatal mice	[176]
	H3K4me3	Methylation	-	LPS preconditioning is accompanied by a reduction in H3K4me3 in the promoters of the IL-1β and TNF-α genes, and results in an increase in the amount of repressive histone modification H3K9me2 in the IL-1β promoter	-	[182]
	JMJD3	Histone demethylase	DHEA (a steroid hormone that increases the expression of JMJD3)	DHEA regulates microglial inflammatory responses through phosphorylation of TrkA and subsequent activation of a pathway involving Akt1/Akt2 and cAMP response element-binding protein. The latter induces the expression of JMJD3, which thereby controls the expression of inflammation-related genes and microglial polarization	-	[175]
	H3K9ac	Acetylation	Acetate (a HDAC inhibitor)	Acetate increases histone acetylation and reduces LPS-induced microglial activation and IL-1β expression	-	[110]

Table 3 (continued)

Epigenetic modification	Gene	Definition	Drug	Mechanism on microglia	Phenotype	Reference
Histone modification	SIRT1	Class III deacetylase	SRT2104 (a selective agonist of SIRT1)	SRT2104 abrogates the increased expression of M1 markers (IL-6, IL-1β, and iNOS) and the decreased expression of M2 markers (IL-10, TGF-β, and Arignase1) induced by CUMS, shifting microglial polarization toward the M2 phenotype	SRT2104 ameliorates CUMS-induced depressive-like behaviors, as indicated by SPT, TST, and FST	[178]
	H3 or H4	Histone	SB (a histone deacetylase inhibitor)	SB suppresses the LPS-induced release of pro-inflammatory factors from microglia in vitro and increases histone acetylation in the hippocampus	SB abolishes LPS-induced depression-like behaviors and hippocampal microglial activation in mice	[72]
	H3S10phK14ac	Phosphorylation	-	H3S10phK14ac promotes inflammatory cytokines releases by driving the transcription of some of the principal genes mediating LPS response, such as c-Fos, IL-6, and iNOS	-	[184]

Akt1/Akt2, AKT serine/threonine kinase 1/2; *cAMP*, cyclic adenosine monophosphate; *CUMS*, chronic unpredictable mild stress; *DHEA*, dehydroepiandrosterone; *DNMT*, DNA methyltransferase; *DNMT3B*, DNA methyltransferase 3 beta; *EZH2*, enhancer of zeste 2 polycomb repressive complex 2 subunit; *FA*, folic acid; *HDAC*, histone deacetylase; *H3K4me1*, histone 3 lysine 4 monomethylation; *H3K4me3*, histone 3 lysine 4 trimethylation; *H3K9ac*, acetyl-histone H3 (Lys9); *H3K9me2*, histone 3 lysine 9 dimethylation; *H3K9me3*, histone 3 lysine 9 trimethylation; *H3K27me3*, trimethylation of histone H3 lysine 27 trimethylation; *H3S10phK14ac*, histone H3 phospho(Ser10)-acetylation(Lys14); *ICV*, intracerebroventricular; *IL*, interleukin; *JMJD3*, jumonji domain protein 3; *LPS*, lipopolysaccharide; *NF-κB*, nuclear factor-kappa B; *SB*, sodium butyrate; *SIRT1*, sirtuin 1; *TET2*, tet methylcytosine dioxygenase 2; *TLR-4*, toll-like receptor 4; *TrkA*, tyrosine kinase receptor A

various CNS disorders, such as Alzheimer's disease, but whether there is a uniform paradigm for the microglia state in a particular brain region leading to depression remains unknown. At present, we are still facing some urgent questions. Firstly, are microglia initiators or passive receivers of signals in response to neuronal changes? Secondly, as epigenetic alterations in microglia can be triggered by stress or immune stimulation, whether there exist typical epigenetic modifications in MDD that are shared among the pathologies of this disorder, and what is the extent of microglia epigenetic involvement in each stage of depression? Finally, due to the dynamic and region-specific nature of microglia, how to track the dynamic changes of microglia in emotion-related brain regions in real-time, is the most important for further in-depth research. This framework linking microglia, neuroinflammation, and depression could serve as a reference for targeting microglia to treat depression.

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