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编者按 抑郁症是一种常见的精神疾病，全世界大约有2.8亿人患有抑郁症，约占总人口的3.8%，成年人中发病率为5.0%，60岁以上人群发病率为5.7%. 近年来，随着国民经济水平的提高，中国对国民的精神健康越来越重视，对精神类疾病如抑郁症的治疗花销投入也越来越多. 迄今为止，虽然抑郁症发生发展的分子机制尚不清楚，但已经发现，抑郁症的发生发展与脑内多种神经递质、细胞因子、神经炎症等相关. 抑郁症的干预和治疗方法也在探索中，已经采用的传统治疗抑郁症的手段包括药物、心理治疗和物理治疗等，同时，新的治疗方法也在不断涌现. 本期《生物化学与生物物理进展》刊出了5篇论文，从不同的角度探讨和研究了有关抑郁症的发病机制和潜在治疗方法，包括对抑郁症的易感性、小胶质细胞极化、转录激活因子的研究以及光疗对抑郁症的治疗作用及机制. 论文选题和内容属于当前抑郁症发病机制和潜在治疗方法的研究热点.

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Research Progress on The Relationship Between Microglia Polarization and Depression*

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Abstract Microglia mainly control the immune efficiency of the central nervous system and play an important role in various psychiatric diseases. Neuroinflammation triggered by the signaling pathway activation is related to the development of depression. Microglia are the main mediators of neuroinflammation. Different stimulations promote the polarization of microglia, which secrete inflammatory cytokines that affect the regulation of neuroinflammation. Clinical and experimental research *in vivo* and *in vitro* have demonstrated the relationship of depression with neuroinflammation mediated by microglial polarization. The possible mechanisms of polarization mediating depression involve NF-κB signaling pathway activation, respiratory bursts, complement receptor 3 (CR3) signaling pathway activation, NLRP3 inflammation activation, cannibalism receptor 1 (CB1) activation, Notch-1 signal pathway stimulation, and PPARγ receptor activation. This review discusses research progress on the relationship between microglial polarization and depression.

Key words depression, microglial polarization, neuroinflammation
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With improvements in social productivity, as well as lifestyle changes, stress caused by social competition, obesity due to poor nutrition, poor living habits, *etc*., humans are increasingly at risk for chronic inflammation resulting from the disruption of homeostasis. Moreover, depression is closely related to peripheral and center inflammation and has become a common disease in humans[1]. Depression is characterized by low emotion, slow thinking, and attenuation of consciousness, which significantly hinder daily life and impair human health. The World Health Organization (WHO) predicted that depression will become the second largest disease contributing to disability and death. Sex, age, family history, family type, orphan status, divorce, social support, *etc*. contribute to depression, which is difficult to cure.

Microglia are the resident immune cells of the central nervous system (CNS). Various inflammatory signals cause microglial polarization to modulate CNS inflammation. Microglial polarization usually occurs in patients with major depressive disorder (MDD)[2]. Thus, microglial polarization is of great concern, as it is closely related to depression. The competition between transcription factors and histone deacetylases against pro-inflammatory transcription factors to affect the transcription of inflammatory factors is tightly related to depression. This review provides an overview of the relationship between microglial polarization and neuroinflammation in depression.

1 Microglial polarization and neuroinflammation

Microglia, the resident immune cells of the central nervous system (CNS), mainly monitor for foreign pathogens and tissue debris. They can be rapidly activated to perform phagocytosis and secrete a variety of pro-inflammatory factors, which have significant effects on inflammatory regulation. Microglia are derived from primitive hematopoietic stem cells from the embryonic yolk sac, are transferred to the brain during the embryonic period, and maintain proliferation capacity during all developmental periods[3]. Microglia possess several polarization states. Under stimulation by pathogen-associated and damage-associated molecular pattern molecules, microglia are activated from their resting state to the classical or selectively activated states. M1-phenotype microglia are classically activated microglia that result from pattern recognition receptor (PRR) stimulation by membrane components of viruses and bacteria, alcohol, long-chain saturated lipid acids, *etc*[4]. M1 microglia mediate the inflammatory reaction by causing the secretion of multiple inflammatory cytokines, including interleukin-1β (IL-1β), IL-6, tumor necrosis factor (TNF)-α, chemokine C-C motif ligand 2, and nitric oxide (NO). M2 microglia are selectively activated with three subtypes (M2a, M2b, and M2c). Both IL-4 and IL-13 induce the M2a phenotype[5]. In particular, IL-4 induces the expression of arginase 1 (Arg1) and the M2a phenotype to promote nerve tissue repair. A previous study provided the first direct evidence that IL-4-induced microglia are critical for hippocampal neurogenesis and the ability to recover from chronic stress[6]. Microglia are triggered to the M2b phenotype by Toll-like receptor 4 (TLR4) agonists and immune complexes that kill pathogens[7-8]. Furthermore, the anti-inflammatory IL-10 and corticosteroids induce the M2c phenotype[9]. Both M2a and M2c microglia remove debris and promote tissue repair[4]. M1 and M2 microglia play an inverse role in neuroinflammation modulation and, therefore, may be important for microglial polarization control to modulate the diseases associated with neuroinflammation, especially depression.

2 Neuroinflammation and depression

Neuroinflammation is defined as a reaction to injury, infection, or disease in the brain. Neuroinflammation usually aims to clear or inactivate the potential damaging factors or injured tissues and is mainly conducted by two cell systems, including microglia and astrocytes in the CNS and lymphocytes, monocytes, and macrophages in the blood system[10]. Immune markers are changed in patients with depression, including increased activity of pro-inflammatory cytokines and inflammatory reaction[11]. Neurodegeneration and reduction of hippocampal neurogenesis induce depression[12-13]. Changes in brain construct and synaptic plasticity due to inflammation may trigger neurodegeneration[14] and both neurodegeneration and increased glucocorticoid levels in inflammation may contribute to decreased neuronal repair and neurogenesis, which characterize depression[15]. Simultaneously, the inflammation and neurodegeneration disease hypothesis proposes that cell-mediated immune activation and inflammatory pathways cause neurodegeneration, and that pro-

inflammatory cytokines secreted during this period, such as TNF-α, IL-1β, and, to a small extent, IL-6, in addition to oxidative and nitrosative stress may cause neurodegeneration and decreased neurogenesis[16]. Depression and pro-inflammatory cytokines activate the hypothalamic-pituitary-adrenal and pituitary-adrenal axes to facilitate glucocorticoids synthesis, potentially contributing to increased glucocorticoid levels in depression[17-19].

In summary, inflammatory cytokines in neuroinflammation can induce depression. Microglia, the resident immune cells of the CNS, play key roles in the transformation of neuroinflammation by modulating neuroinflammation and normal neuron construction and function. Microglial polarization is an important manifestation of neuroinflammation[20]. Trial results have suggested that depression is closely related to microglial polarization and underscored the need for deeper research on depressant disorders[21]. Microglia regulate neurogenesis by secreting various factors that modulate the neurogenic microenvironment[22]. Under stressful or pathological conditions, microglia secrete inflammatory mediators that disrupt neuronal function, impair neurogenesis, increase vulnerability to stress, and promote depression onset and progression[23]. The following text summarizes the research related to the relationship between microglial polarization and depression.

2.1 Clinical research

Zhong *et al*.[24] reported neuron hyperactivity in the amygdala and hippocampus in functional magnetic resonance imaging scans of patients with depression. The severity of depression is negatively related to neuronal synaptic density in the dorsal lateral prefrontal cortex (DLPFC), hippocampus, and anterior cingulum gyrus[25]. Depressed patients show altered hippocampal morphology and function. High-resolution *in vivo* magnetic resonance imaging studies have also consistently documented reduced hippocampal volume in patients with depression. Hippocampal neurogenesis is regulated by various factors, including stress and inflammation. Functional abnormalities of the potassium ion channel and aquaporin 4 expressed on astrocytes of patients with depression lead to mood circuit hyperactivity and M1 microglial polarization[26]. Stimulation of M1 microglia and excitatory glutamate generated by astrocytes causes dysfunction of neuron transmission between the prefrontal cortex (PFC) and mood circuit and simultaneous PFC hyperactivity[27]. Moreover, IL-1β and IL-6 enhance the metabolic pathway from tryptophan (TRP) to kynurenine (KYN) and quinolinic acid[28], which suggests the inhibitory efficacy of M1 microglial polarization in the synthesis of 5-hydroxytryptamine (5-HT). The monoamine hypothesis of depression suggests that depressed mood mainly results from decreased projection activity of surrounding neurons projecting to the cortex, in which M1 microglia trigger depressed mood by affecting 5-HT transfer and synthesis. Masahiro *et al*.[29] reported decreased levels of the M2 microglia marker CD206 in bipolar disorder by gene sequencing. Several clinical double-blind studies have revealed that celecoxib in combination with antidepressant drugs improved the Hamilton Depression Scale (HDS) score of patients with depression[30]. This suggests that the anti-inflammatory reaction of M2 microglia is probably related to the improvement of depressed mood.

Microglial polarization usually occurs in patients with MDD and plays a key role in brain inflammation in these patients. During severe episodes of MDD, significant microglial activation was observed in brain regions associated with depression, such as the prefrontal and anterior cingulum cortexes. Moreover, microglial M1 polarization in the anterior cingulum was positively correlated with the severity of depressive episodes[31]. In a cadaveric study of patients with MDD, suicidal patients with MDD showed increased densities of quinolinic acid-producing M1 microglia in the subcortical anterior cingulum and anterior middle cingulate cortex, indicating an enhanced microglial cell response to cytokine signals[32]. These clinical studies confirm that the development of depression is closely associated with increased microglial polarization-mediated inflammation.

The reciprocal transformation of microglia M1 and M2 phenotypes affects depression. However, clinical research is still needed to clarify the relationship between the specific morphology and function of microglia by establishing an animal model of depression.

2.2 Experimental research *in vivo* and *in vitro*

2.2.1 Whole-animal research *in vivo*

Depression mainly results from neuroinflammation mediated by M1 microglia, which

synthesize and secrete various pro-inflammatory cytokines. Many antidepressant drugs have efficacy by reversing M1 polarization or potentiating M2 polarization. Zhao *et al*. [33] explored the antidepressant-like effect of pioglitazone in a chronic mild stimulation (CMS) mouse model by separately injecting pioglitazone and vehicle. Compared to the vehicle group, the pioglitazone groups showed lower expression levels of M1 phenotype markers such as IL-1β, IL-6, TNF-α, inducible nitric oxide synthase (iNOS), and CCL-2. In contrast, the expression levels of M2 phenotype markers such as Ym1, Arg1, IL-4, IL-10, and transforming growth factor β (TGF-β) were increased. Varona *et al*.[34] found that activation of liver X receptors prevented emotional and cognitive dysfunction by suppressing microglial M1-polarization and restoring synaptic plasticity in the hippocampus of mice. These results show that some antidepressant drugs lead to reduced levels of M1 phenotypes and increased levels of M2 phenotypes, which play an antidepressant role in animal models of depression.

Bupropion inhibited the release of pro-inflammatory cytokines and NO induced by lipopolysaccharide (LPS) and increased the secretion of the anti-inflammatory cytokine IL-10 in an animal model of depression[35]. Bellerophon also repressed the uptake of dopamine (DA) to activate the G protein-coupled receptor and increase cAMP levels[4], which may result in M2 polarization in an animal model of depression. Classical antidepressant drugs such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) increase norepinephrine and serotonin levels in the brain in an animal model of depression. Norepinephrine activates the β-receptor to stimulate adenylyl cyclases (ACs) that eventually increase cellular cAMP levels[36]. The efficacy of serotonin was similar to that of norepinephrine. The antidepressant drugs mentioned above increase intracellular cAMP levels to activate cAMP, protein kinase A (PKA), and the CREB signaling pathway[37]. Finally, Ser133-activated CREB competitively binds to CREB-binding protein (CBP), thereby repressing inflammatory transcription factors including NF-κB subunit RelA/P65, STAT1/STAT2, and interferon regulatory factor 5 (IRF5) [38]. In summary, these antidepressant drugs are dependent on intracellular cAMP concentration and not only inhibit M1 polarization but also promote microglial M2 polarization, which contributes to the downregulation of inflammatory cytokines and upregulation of anti-inflammatory cytokines. Based on these results, we modulated intracellular cAMP concentration to control microglial polarization and subsequently maintain the dynamic balance between neuron impairment and repair, which may be a novel idea for preventing and treating depression.

Both M1- and M2-type polarized microglia are involved in the pathogenesis of depression. M1-type microglia promoted depression occurrence and development, while M2-type microglia inhibit depression. Microglial polarization and its effects are important mechanisms that promote depression. Stress activates microglia and induces depressive symptoms by changing microglial polarization. Inhibition of M1 microglia and promotion of M2 microglia effectively prevent depressive behaviors in animals.

2.2.2 Isolated brain slice research *in vitro*

Pusic *et al*.[39] studied cultures of hippocampal slices *in vitro*. They treated the slice culture with alendronate liposomes to selectively delete the microglia, as identified by Iba-1 staining. Compared to the control group, the application of clodronate liposomes in the experimental groups increased the threshold of trans-synaptically induced spreading depression (SD). However, the current did not evoke SD in any microglia-depleted cultures at a maximum stimulus of 10 000 nC. Moreover, potassium chloride (KCl) applied to agar to cultivate the hippocampal slice also did not induce SD. The next operation restored the microglia deleted before in the hippocampal slice, consequently establishing susceptibility to SD. These findings indicated that microglia are necessary for trans-synaptic and KCl-induced SD, suggesting that microglial dysfunction may be a risk factor for depression initiation. Inhibition of the M1 signal with minocycline resulted in increased SD threshold. In addition, the SD threshold of rats exposed to an enriched environment and the IL-11 level in the neocortex was increased, which decreased TNF-α signaling and polarized microglia to an M2a-dominant phenotype. M2a microglia inhibit SD by reducing pro-inflammatory signals and increasing anti-inflammatory cytokine production. Intranasal administration of IL-11 to simulate the effect of environmental enrichment also increased M2a polarization and SD threshold. Similarly, the application of conditioned medium

from M2a polarized primary microglia to slice culture also increased the SD threshold. Therefore, microglia and their polarization play an important role in SD initiation[39].

2.2.3 Cell-based research *in vitro*

Zhao *et al*. [33] observed amoeboid LPS-stimulated M1 microglial morphology, with an inflated cell body and short neuronal processes. Enzyme-linked immunosorbent assays (ELISAs) showed increased levels of IL-1β, IL-6, TNF-α, and other pro-inflammatory cytokines. Furthermore, the administration of pioglitazone suppressed M1 microglia activation in the dentate gyrus of the hippocampus and facilitated M2 polarization in mice. Under the microscope, the numbers of "amoeboid-like" and Iba1-positive microglia decreased and M2 microglia with thin cell bodies, fewer synapses, and long neuronal processes increased. ELISA showed increased levels of IL-10, which promotes tissue repair[33]. Blocking the activation of the N-type voltage-dependent calcium channel (VDCC) (Cav2.2) of microglia enhances microglial replacement activation (transformation to neuroprotective M2 microglia) without changing the transformation to neuroinflammatory M1 microglia. The depression-like behavior of microglia-specific Cav2.2-deficient mice was also quickly suppressed[40].

3 Possible mechanisms of microglia polarization mediating depression

3.1 Activation of the NF−κB signal pathway

Nuclear factor-κB (NF-κB) activation plays an important role in pro-inflammatory gene expression. Cytoplasmic NF-κB is not generally expressed but promotes inflammatory gene expression when its inhibitors are blocked[41]. Zhao *et al*. [33] reported reduced IκB expression and NF-κB activation by LPS in N9 microglia, which are changed to M1-type, resulting in neuroinflammation.

3.2 Respiratory bursts

Tetrahydrobiopterin (BH4), which is metabolically unstable and easily oxidized, is a necessary cofactor for neurons to synthesize DA[42]. Under the stimulation of TLRs and non-like receptors, M1 microglia take in large amounts of oxygen and subsequently release peroxide anions disproportionate to hydrogen peroxide and react to generate stronger oxides[43]. Oxides not only cause neuronal tissue or cell damage but also oxidize BH4 to neopterin. BH4 deficiency hinders the functions of BH4-dependent enzymes, which decreases DA and serotonin levels and ultimately leads to depression[44].

3.3 CR3 signal pathway activation

A recent study showed that microglia shape neuronal synapses *via* synaptic pruning, which requires the activation of complement receptor 3 (CR3) [45]. CR3 can also directly recognize various types of neuroinflammatory stimulus factors, such as LPS and filamentous hemagglutinin. Zhang *et al*. [46] found that LPS and hypoxic conditions didnot trigger long-term synaptic depression (LTD) in microglia after CR3 knockout of hippocampal microglia, indicating the pivotal role of CR3 for the regulation of synaptic plasticity. However, LPS + hypoxia-induced LTD was still observed after TLR4 deletion, suggesting that TLR4 is not necessary for LTD induction by LPS + hypoxia. NADPH generated under hypoxic conditions by glycolysis reacts with NADPH oxidase and produces a large amount of peroxide, which activates phosphatase 2A (PP2A) to induce post-synaptic terminal endocytosis. This may be the reason for LTD and synaptic functional disorders and may also trigger neurodegeneration. Although it has not been proven that patients with depression are characterized by hypoxia, the postulation mentioned above may explain depression in brain hypoxia. This also indicates that CR3 signaling pathway activation in LPS-stimulated microglia may be another significant reason for depression.

3.4 Activation of NLRP3 inflammation

NLRP3 inflammation, a multiple protein complex, leads to serious inflammatory reactions[47]. The prion domain of NLRP3 interacts with that of ASC to initiate inflammation assembly, which promotes the transformation of procaspase-1 to caspase-1 and pro-IL-1β into IL-1β[48]. Three models of NLRP3 have been proposed, one of which is involved in facilitating ROS synthesis, consistent with the findings that a large amount of NLPR3 inflammation agonists increases ROS levels[49]. Levels of caspase-1 and NLRP3 mRNA are higher in patients with depression[50]. Zhu *et al*. [51] administered Ac-YVAD-CMK, an NLRP3 inhibitor, in LPS-induced murine models of depression, demonstrating improve behavioral alterations by contributing to lower IL-1β, IL-18, and TNF-α levels but higher IL-10 levels compared to those in the LPS group. Thus, NLPR3

inflammation may participate in LPS-induced depression-like pathological alterations and promote IL-1β secretion and synthesis. ROS and IL-1β are pivotal in depressed mood[52]. Although there is no strong evidence that microglial polarization is directly connected with NLRP3 inflammation, LPS triggers microglial polarization and increases IL-1β and ROS levels. Thus, M1 microglia likely release ROS and IL-1β through intracellular NLRP3 inflammation activation. Therefore, NLRP3 inflammation may be a mechanism of depression.

3.5 CB1 receptor activation

Cannabinoid receptor type 1 (CB1) is one of the richest neuronal regulatory receptors and is mainly expressed in the brain cortex, hippocampus, cerebellum, and basal ganglion. While CB1 receptors are mainly located in neuronal tissue, CB2 receptors are mainly found in the immune system[53]. The activation of CB1 receptors contributes to microglial M1 polarization and the secretion of pro-inflammatory cytokines[54], whose agonists induce the synthesis of ceramide catalyzed by neurophospholipase[55]. Thus, CB1 receptors promote and maintain microglial M1 polarization and are correlated with multiple neuroinflammation-associated diseases. CB1 is a G protein-coupled receptor that modulates several ion channels and secondary messenger activity[56].

There are several possible mechanisms by which CB1 causes depression. CB1 receptor activation inhibits presynaptic N-type calcium channels but activates inwardly rectifying potassium channels[57], which reduces the release of neuronal transmitters by decreasing exocytosis of calcium-dependent presynaptic vesicles. The binding of guanosine 5'-O-[gamma-thio] triphosphate due to stimulation of the CB1 receptor and the density of CB1 receptors were increased in depressed suicides (DS). A weaker cAMP signal was also reported in victims with depression[53]. These results suggest that endogenous CB1 has an important function in the etiology of depression and DS through its combination with CB1 receptors. Depression is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5-HT2) antagonism[58]. Soriano *et al*. [59] reported a lower density of 5-HT1A, 5-HT2C, and 5-HTT receptors in mice after CB1 gene knockout, which resulted in increased extracellular 5-HT levels. Thus, the CB1 receptor affects 5-HT release through negative feedback regulation. Although the mechanism by which CB1 receptors cause depression remains to be clarified, recent studies have shown that the activation of CB1 receptors is related to neuroinflammatory reactions and decreased intracellular cAMP and 5-HT secretion, which are the key components of depression. We speculate that microglial M1 polarization and subsequent activation of multiple signaling pathways caused by the CB1 receptor may be a novel mechanism of depression.

3.6 Notch−1 signal pathway stimulation

The Notch signaling pathway is mainly responsible for cell differentiation, reproduction, and apoptosis. Cao *et al*. [60] showed that Notch-1 synergistically regulated the production of proinflammatory mediators such as IL-1, IL-6, TNF-α, and iNOS in microglia activated by LPS. In addition, the Notch signaling pathway modulated microglial function and controlled pro-inflammatory cytokine release[61]. The Notch signal was enhanced in M1 microglia, whose function of pro-inflammatory cytokine secretion can be effectively curbed by utilizing the γ-secretase inhibitor DAPT to block this signal. This mechanism is probably correlated to cross-signal pathway activation such as NF-κB[62]. Moreover, the Notch signal facilitated the differentiation of multiple gliacytes including radial glial cell astrocytes[63]. These results suggest that activation of the Notch-1 signaling pathway results in M1 polarization and neuroinflammation, which trigger depression.

3.7 PPARγ receptor activation

The peroxisome proliferator-activated receptor (PPAR) is divided into three subtypes: PPARα, PPARβ/δ, and PPARγ. PPAR is an important nuclear transcription factor involved in inflammation regulation. PPARγ attenuated the inflammatory response in the CNS[64]. Our experiments in mice showed that CMS decreased mRNA and protein levels of PPARγ, but not PPARα or PPARβ/δ, in the hippocampus and cortex. The activated form of PPARγ binds to DNA-specific PPAR response elements and regulates the transcription of its target genes. Thus, the activation of PPARγ regulated the expression of inflammatory cytokines and microglial cell phenotypes. Recent studies have shown that signal transducer and activator of transcription 6 (STAT6) regulates PPARγ activity and inhibits NF-κB and STAT3 activity in M2 phenotype microglia[65]. We

also found that inhibition of PPARγ activation produced significant deregulation in microglia-mediated neurogenesis, highlighting the functional role of microglia as components of the neurogenic ecotone in the brain. These experiments and research advances have demonstrated that PPARγ activation shifts microglia toward an anti-inflammatory phenotype with antidepressant effects.

4 Conclusion and prospects

This review indicates that neuroinflammation, which impairs neuron construction and function, is a major reason for depression (Figure 1). Microglia, the resident immune cells in the CNS, release pro- or anti-inflammatory cytokines under different polarized conditions. Thus, they play an important role in inflammation regulation of the CNS. Neuroinflammatory processes are the main cause of depression. Therefore, microglia M1 and M2 polarization are closely related to depression, which suggests that targeting molecules that promote alterations of microglial polarization may be a practical and valid approach to prevent and treat depression. Some current antidepressant drugs are involved in M1/M2 polarization and inflammation-resolving treatment. However, additional research on the molecular mechanism of microglial M1 and M2 polarization is needed to identify more accurate and effective molecular targets to overcome the side effects and drug resistance. Future studies will not only increase our knowledge of the relationship between microglial polarization and depression but will also provide novel thoughts and methods for depression prevention and treatment.

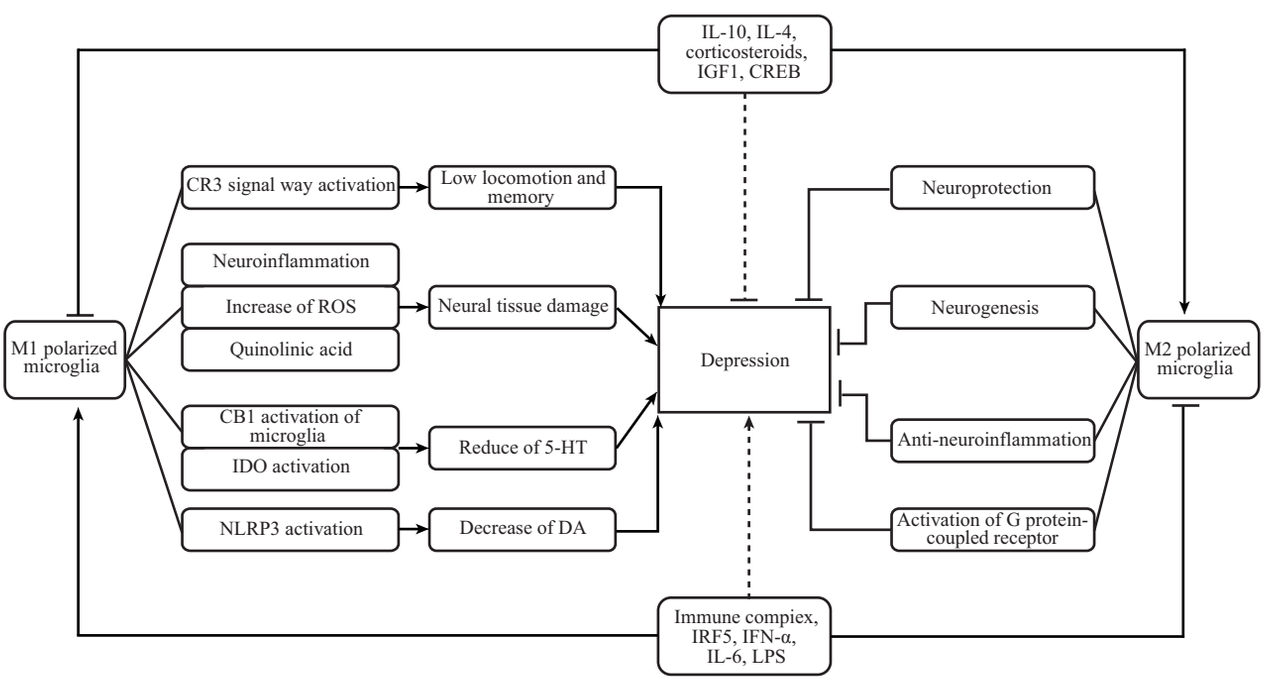

Fig. 1 A summary of the relationships between microglia polarization and depression based on a literature review

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小胶质细胞极化与抑郁症关系的研究进展*

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摘要　小胶质细胞控制着中枢神经系统主要的免疫功能，在各种精神疾病中发挥重要作用. 某些信号通路的激活引发的神经炎症与抑郁症的发生有着密切的关系. 小胶质细胞是神经炎症的主要介导者，不同的刺激促进小胶质细胞极化，不同极化类型的小胶质细胞能分泌多种炎性细胞因子，在神经炎症调节中具有重要的作用. 临床研究和体内外实验研究表明，抑郁症与小胶质细胞极化介导的神经炎症有关. 小胶质细胞极化参与抑郁症发生发展的可能机制包括NF-κB信号通路激活、呼吸爆发、补体受体3信号通路、NLRP3炎症激活、cannibalism受体1、Notch-1信号通路和过氧化物酶体增殖物激活受体γ的激活. 本文就小胶质细胞极化与抑郁关系的研究进展作一综述.

关键词　抑郁症，小胶质细胞极化，神经炎症

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