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Review Article

Microglia Involves in the Immune Inflammatory Response of Poststroke Depression: A Review of Evidence

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Poststroke depression (PSD) does not exist before and occurs after the stroke. PSD can appear shortly after the onset of stroke or be observed in the weeks and months after the acute or subacute phase of stroke. The pathogenesis of PSD is unclear, resulting in poor treatment effects. With research advancement, immunoactive cells in the central nervous system, particularly microglia, play a role in the occurrence and development of PSD. Microglia affects the homeostasis of the central nervous system through various factors, leading to the occurrence of depression. The research progress of microglia in PSD has been summarized to review the evidence regarding the pathogenesis and treatment target of PSD in the future.

1. Microglia

Microglia can be transformed into activated microglia post-brain trauma, infection, or other central nervous system diseases. Rapid proliferation and activation of microglia can have various forms and move to the lesion area. Its activation process includes proliferation, chemotaxis, and cytokine secretion. Microglia can secrete many inflammatory cytokines and molecules, inducing immune-inflammatory reactions and increasing the blood-brain barrier (BBB) permeability. On the other hand, activated microglia promote the regeneration of the nerve cells, facilitating nerve repair after acute cerebral stroke [1–3]. When the external stimulus is eliminated, activated microglia gradually return to the resting state. Microglia can be divided into two polarized phenotypes based on their secreted cytokines, namely, M1 and M2 types [4]. M1 microglia account for most activated microglia, mainly expressing surface antigens such as CD16, CD32, and CD86 [5]. M1-type microglia can exert a phagocytic effect through contact with nerve cells or activating the colony-stimulating factor (CSF) and tumor necrosis factor-α (TNF-α). Moreover, it promotes the synthesis and secretion of interleukin-1 (IL-1), IL-4, and other inflammatory factors, thereby triggering the immune-inflammatory cascade reaction [6–8]. M2 microglia can be divided into M2a, M2b, and M2c subtypes based on different stimuli. M2a microglia can be generated by IL-4, IL-13, and other stimuli and release IL-10 and other anti-inflammatory factors, thus achieving inflammatory response inhibition and neuroprotection [9–11]. In general, cytokines secreted by activated M1-type microglia have proinflammatory effects, while activated M2-type microglia are essential in nerve repair and plasticity.

2. Microglia and Stroke

Different stimuli and pathological environments determine the phenotypes of microglia. Several studies have demonstrated that nerve cells can release cytokines to promote the transformation of M2 to M1. When a stroke occurs, microglia exhibits the characteristics of dynamic change. The early stage of stroke is dominated by the M2 type, which appears 1~3 days after stroke, peaking at 3~5 days, and is sustainable for 14 days. M1-type microglia appeared on

day three and peaked on day 14, revealing the dynamic process of microglia from neuronal protection to nerve injury after stroke [12]. Based on physiological conditions, M1 and M2 microglia maintain a dynamic balance. However, this balance will be disrupted when stimulated with stroke, trauma, inflammation, and other stimuli. Ultimately, the different substances induced by stimulation directly affect whether microglia could protect or damage the nervous system [13].

Microglia can exert a neuroprotective effect by releasing factors such as glial cell-derived neurotrophic factor (GDNF), transforming growth factor-β (TGF-β), and P2X7 receptor, involved in Ca^{2+} overload inhibition, angiogenesis, and remodeling of the cytoskeleton. On the other hand, microglia can promote the induction of matrix metalloproteinases (MMPs), nitric oxides (NOS), TNF-α, and other inflammatory factors involved in BBB disruption, vasospasm, cellular death, and thrombosis, aggravating the brain injury poststroke [14, 15].

The activation of microglia in the inflammatory response is a "double-edged sword" which plays a dual role in the occurrence and development of ischemic stroke as the first line of defense for central nervous system injury [16, 17]. M1-type microglia mainly produces proinflammatory mediators and additionally plays a cytotoxic role in damaging the nervous system. In contrast, M2-type microglia has protective factors supporting neuronal repair and regeneration. Due to the pleiotropy of microglia during ischemic stroke, its clinical significance deserves further study. Therefore, regulating the activation of microglia and exploring the dynamic changes of microglia after stroke is crucial in the prognosis of ischemic stroke. Future studies will continue to explore how to promote the M2-type polarization of microglia, thus enabling brain injury repair. Moreover, methods to inhibit the M1-type differentiation of microglia need to be explored to reduce the secretion of inflammatory factors, attenuate the brain damage, and ultimately reduce the degree of cerebral ischemia injury and promote functional recovery of the brain tissue [18].

3. Ischemic Stroke and Depression

Stroke is the leading cause of death, disability, and reduced life span worldwide, and its incidence and prevalence are increasing with age [19, 20]. According to the World Health Organization (WHO) report, 15 million people suffer from stroke yearly, which significantly burdens society [20, 21]. Poststroke depression (PSD) is the most common noncognitive neuropsychiatric complication, and about 30% of patients after stroke have depression [22]. The major clinical manifestations are depressed mood, significant changes in appetite or body mass, low self-worth, sleep disorders, fatigue, inattention, and suicidal tendencies [23]. PSD harms physical, cognitive, and functional rehabilitation, reduces the survival rate, and delays the recovery among stroke patients, thereby becoming a severe social and public health problem [24–27].

The prevalence of PSD is associated with the time point of stroke onset, and about 30% of stroke survivors are affected within five years after stroke [28]. Previous studies have shown that the cumulative incidence of depression after stroke is 39%-52%, usually occurring in the first month after stroke, then gradually increasing and reaching its peak around six months [29]. Another study assessed the occurrence of PSD at three and 12 months after stroke, with a rate of 27.6% at three months and 24.8% at 12 months [30]. Based on the severity of PSD, it is divided into mild, moderate, and severe types. A previous study revealed that 57% of patients after stroke have PSD, 33% with mild depression, 20% with moderate depression, and 4% with severe depression [31]. The prevalence of PSD varies among different studies. In the investigation of outpatients after stroke, it was observed that the prevalence of mild PSD was about 23.9%, and that of severe PSD was approximately 24.0%. Community patients had the lowest prevalence, 14% with severe depression and 9% with low depression. In hospitals, including emergency and convalescent patients, the prevalence of major depression was 21.6%. However, among the discharged patients after stroke, the prevalence rate of major depression was 24.0% [32].

The etiology of PSD includes psychosocial and biological factors. In the first year after stroke, patients with PSD depicted more neurological dysfunction, poorer recovery outcomes, and higher morbidity and mortality. Therefore, it is vital to identify the risk factors for PSD at an early stage. PSD risk factors include smoking, mild global cognitive impairment, female gender, less education, exposure to stressful life events in the months leading up to stroke, and comorbidities like diabetes and hypertension [33, 34]. Gender is the most frequently studied risk factor in PSD with controversial results [35, 36]. Other risk factors of PSD include stroke severity and lesion location [37–41].

The pathogenesis of PSD is complex, with many processes. The widely studied mechanism is the neurotransmitter imbalance, a popular theory for the pathogenesis of PSD [42–45]. Neurons can secrete a variety of monoamine neurotransmitters, such as 5-hydroxytryptamine (5-HT) and norepinephrine (NE). 5-HT exists in mammalian brain tissues, especially in the cortex and synapses. 5-HT is catalyzed by monoamine oxidase into 5-hydroxytryptophan and 5-hydroxyindoleacetic acid, excreted through the urine. Decreasing 5-HT concentration can lead to depressive symptoms, including low mood and lack of confidence. In contrast, the reduction of NE concentration causes the decline of emotion, cognitive function, and activity regulation ability [46–48]. A decrease in monoamine transmitters is inversely related to the severity of depression. The possible explanation for this may be because, among the brain regions involved in emotion regulation, the amygdala, prefrontal lobe, and hypothalamus are dominant, which play a transmitter regulation role by influencing the release of NE and 5-HT [49–51]. Stroke lesions interrupt the neural pathways of NE and 5-HT release, reducing monoamine neurotransmitters in the brain, which contribute to depression [52–54]. Previous studies depicted that the increased activity of monoamine oxidase in PSD patients increases 5-HT catabolism and decreases its function, causing neurological dysfunction of the limbic system, reticulate structure, and midline region of the brain stem, thereby aggravating depressive symptoms [55–57].

In addition, PSD is associated with dysregulation of BDNF, an essential neurotrophic factor in the hippocampus, cerebral cortex, and cerebellum. It binds to tyrosine kinase receptor B (TrkB) and plays a crucial neurotrophic role [58–61]. Its functions include nourishing damaged neurons, regulating neural plasticity, depicting a vital role in the survival, differentiation, growth, and postinjury repair of neurons, and participating in the initiation and development of depression, regarded as a landmark indicator for the diagnosis of depression [62, 63]. Many studies have revealed that the expression of BDNF and its high-affinity receptor TrkB protein in the thalamus decrease after PSD, indicating PSD occurrence is tightly associated with BDNF level, and the lesser the production of BDNF, the more likely PSD will occur [64, 65]. Infantino et al. found that the MED1/BDNF/TrkB pathway is involved in thalamic hemorrhage-induced pain and depression by regulating the activation of microglia [66]. A recently published prospective multicenter cohort study that enrolled 530 patients with minor stroke indicates that the important markers affecting PSD at three months are BDNF in females [67].

Moreover, inflammation is also involved in PSD development [68, 69]. Considerable evidence indicates that inflammation is involved in the occurrence and development of PSD through related inflammatory pathways by producing inflammatory mediators [70, 71]. Studies have suggested that brain injury during stroke stimulates the body to produce a rapid immune regulatory response. The peripheral immune system recruits inflammation-related cells and develops inflammation-related factors, which migrate to the brain injury area through the damaged blood-brain barrier for immune regulation [72–75]. The imbalance of homeostasis in the inflammatory state alters the endocrine function of nerve cells. It influences the balance of neurotransmitter secretion in the brain, reducing the synthesis and secretion of monoamine neurotransmitters, causing PSD [76–78]. P2X4 receptors on the immune cells modulate the inflammatory response, and receptor deletion protects against stroke acutely. However, it predisposes depression-like behavior chronically after stroke, associated with the P2X4 receptors-induced regulation of BDNF release [79]. Kozak et al. reported no significant relationship between major depression and basal proinflammatory cytokines such as TNF-α, IL-1 β, IL-18, and BDNF expression in patients who have experienced an acute ischemic stroke [80]. Other researchers have proposed that stroke causes neurological deficits and loss of daily living and social functions, putting patients in a slow and long-term stress response that activates the hypothalamic-pituitary-adrenal (HPA) axis. Moreover, it causes excessive corticosteroid releasing hormone and sympathetic nerve activity [81–83]. Excessive hormones have toxic effects on nerve cells and affect the production of neurotransmitters; overactivated sympathetic nerve activity causes mood changes in patients leading to corresponding mood and behavior changes. In addition, the activation of the HPA axis can stimulate the upregulation of the expression of inflammatory factors, further promoting the activity of the HPA axis and forming a vicious cycle leading to the onset and persistence of PSD [84]. Presently, there are various studies on inflammatory factors involved in PSD occurrence. Studies have shown that elevated levels of cytokines such as IL-1β, IL-6, and TNF-α in serum are related to the incidence of depression [85, 86]. Effective antidepressant therapy reduces serum levels of inflammatory cytokines, including IL-1β, TNF-α, and IL-6, in depressed patients [87]. Neutrophil-to-lymphocyte (NLRs) and platelet-to-lymphocyte ratios (PLRs) are also associated with depression. Higher NLRs and PLRs are associated with depression six months after stroke, and the combined index is more meaningful than being alone in the early clinical detection of PSD [88]. A clinical study that enrolled 299 ischemic stroke patients showed that increased NLRs at admission are associated with PSD and could add prognostic information for the early discovery of PSD [89].

There is no clear consensus on the pathogenesis of PSD. Both depression and stroke should be considered to study the pathogenesis of PSD comprehensively. The biological abnormalities and the interrelation between neurotransmitters involve multiple systems and signaling pathways. One single pathogenesis of a specific system or a particular aspect cannot provide a perfect explanation. Although detailed research progress has been made in the neurobiology of PSD, its pathogenesis's etiology has not been fully clarified. Fragmented studies are not linked together. Therefore, exploring the influence of neural cellular signaling pathways on the regulation of neurotransmitters and then revealing their role in the pathogenesis of PSD could become a hotspot of future research.

4. Microglia and PSD

The imbalance of the neuroimmune system could be an essential factor in the pathophysiology of depression [90]. Compared with the control group, mice exposed to chronic unpredicted stress depict significant depressed-like behaviors and increased corticosterone levels. Moreover, the number of microglia in the hippocampus of stressed mice decreases, while certain microglia present malnutrition forms [91, 92]. Chronic stress may contribute to differences in the clinical presentation of stress-induced depression under the control of sex-specific mechanisms by differentially affecting neurons and microglia [93]. A systematic review and meta-analysis, including 69 studies, examined the cerebrospinal fluid, positron emission tomography, and postmortem brain tissue and observed that increased microglia activity and reduction of astrocytes were associated with major depressive disorder [94]. Another systematic review analyzed 51 articles evaluating inflammatory markers in postmortem bipolar disorder brain samples. Fifteen studies evaluated microglial cell markers, indicating a potential link between microglia activation and the occurrence and outcome of bipolar disorder [95]. Animal experiments and autopsy results suggested that microglia could be involved in the onset and progression of depression (Table 1). Activation of microglia has a vital role in the pathogenesis of major psychiatric disorders associated with hippocampal atrophy and disconnection of cognitive structures [96, 97].

Table 1: Summary of researches regarding the effect of microglia in poststroke depression.

Ref	Model	Animals	Main findings
92	MCAO/R+CUMS	Sprague-Dawley rats	Foraging exercise improves the behavioral scores, reduces the number of microglia in the frontal lobe and striatum, and downregulates serum levels of IL-6 and the IL-6/IL-10 ratio.
90	MCAO/R+CUMS	Wistar rats	LCN2 may affect PSD by regulating microglial activation in the hippocampus, with the involvement of the P38 MAPK pathway.
134	tMCAO+CUMS	Sprague-Dawley rats	Morinda officinalis oligosaccharides attenuate depressive-like behaviors after stroke by inhibiting hippocampal inflammation through modulating microglial NLRP3 inflammasome.
11	MCAO/R+CUMS	Wistar rats	The mRNA expression of proinflammatory markers (IL-1, TNF-α, iNOS, and IL-1β), anti-inflammatory markers (CD206), and the M2 microglia marker Arg1 upregulate in the hippocampal region in the PSD group.
61	MCAO+CUMS	Sprague-Dawley rats	Amygdala microglia contribute to PSD pathogenesis and depression-like behaviors by reducing the level of BDNF and TrkB.
25	BCCAO	ICR mice	Inhibition of the fractalkine/CX3CR1 signaling pathway improves depression and cognition via inhibiting microglia activation, promoting OPC maturation and remyelination after cerebral ischemia.
13	MCAO/O+SIR	ICR mice	Neurons and microglia-released IN-18 contribute to depression-like behavior poststroke through activating the IL-18 receptor/NKCC1 signaling pathway.
18	MCAO/R+CUMS	Sprague-Dawley rats	Xingnao Jieyu alleviates PSD by attenuating neuroinflammation, including reduction of Iba1-positive cells, and downregulation of the TNF-α, IL-6, and IL-1β expressions.
129	MCAO/R+CUMS	Sprague-Dawley rats	Curcumin improves PSD by inhibiting neuroinflammation via diminishing the P2X7R-mediated Ca^{2+} accumulation in microglia.
96	BCCAO	C57BL/6 mice	Minocycline administration exerts antidepressant and anxiolytic effects by inhibiting microglial activation.
97	BCCAO	ICR mice	Minocycline exerts an antidepressant effect by inhibiting microglia activation, promoting OPC maturation and remyelination.
45	MCAO/R+SIR	C57BL/6 mice	Microglia function-induced IDO1-dependent neurotoxic kynurenine metabolism contributes to the PSD pathogenesis. Aripiprazole reduces depressive-like behavior and cognitive impairment by inhibiting IDO1, HAAO, QUIN, and ROS.
79	MCAO/R	Global or myeloid-specific P2X4R KO and wild-type mice	Global and myeloid-specific P2X4R KO mice show intermediate microglia activation after stroke, with shorter processes, less arborization, and larger soma. Myeloid-specific P2X4R KO mice show increased mRNA levels of proinflammatory cytokines, decreased depression-related gene expression, and reduced proinflammatory cytokine IL-1β in plasma after stroke.
68	Social defeat+4-VO	Sprague-Dawley rats	Progesterone attenuates stress-induced microglia activation by regulating polarized microglia and the inflammatory environment in the hippocampus after ischemic injury.
69	Transient BCCAO	Gerbils	DXT is widely used for the treatment of major depressive disorders. Pretreated DXT exerts neuroprotective effect by attenuating microglia and astrocyte activation and decreasing oxidative stress.
26	MCAO/R	Young and aged Sprague-Dawley rats	HTR2B expression in the infarcted territory may render degenerating neurons susceptible to attack by activated microglia and thus aggravate the consequences of stroke, including anhedonic behavior.
27	Microsphere embolism model	Wistar rats	Anxiety-like behavior is increased in males despite a significant increase in microglial activation following microembolic stroke in both males and females.
14	MCAO/R	C57Bl/6 male	Pair housing enhances sociability and reduces avolitional and anhedonic behavior, which is associated with reducing serum IL-6 and enhancing peri-infarct microglia arginase-1 expression. Social interaction reduces PSD and improves functional recovery.

Table 1: Continued.

Ref	Model	Animals	Main findings
15	Microembolism model	Wistar rats	Microembolism infarcts are sufficient to lead to an increase in anxiety- and depressive-like behaviors followed by spatial memory impairment, with no trigger response of microglia, macrophages, or astrocyte.
135	MCAO/R	Sprague-Dawley rats	Fluoxetine is a selective serotonin reuptake inhibitor that is widely used in the treatment of major depression including after stroke. Fluoxetine exerts neuroprotective effects associated with marked repressions of microglia activation, neutrophil infiltration, and proinflammatory marker expressions.

CUMS: chronic unpredictable mild stress; BCCAO: bilateral common carotid artery occlusion; SIR: spatial restraint stress; 4-VO: four-vessel occlusion; PSD: poststroke depression; DXT: duloxetine; LCN2: lipocalin-2; IDO-1: indoleamine 2,3-dioxygenase 1; HAAO: hydroxyanthranilate 3,4-dioxygenase; QUIN: quinolinic acid (QUIN); ROS: reactive oxygen species; KO: knock-out; HTR2B: serotonin receptor 2B.

Various bacterial and viral infections could induce depression [98–101]. These infectious pathogens have a particular affinity for the brain and can induce microglial activation [102, 103]. These pathogens can also induce microglia to secrete proinflammatory cytokines, whose concentration levels have been associated with depression-like symptoms [104–106]. Lipopolysaccharide (LPS) can activate microglia to cause depressive symptoms, whose severity is connected with the level of inflammatory cytokines [107, 108]. LPS also induces depression by activating microglia, and many drugs have exerted an antidepression effect by inhibiting the activation of LPS-induced microglia [109–111]. O'Connor et al. revealed a pivotal role for interferon-γ and tumor necrosis factor-α in inducing indoleamine 2,3-dioxygenase and depressive-like symptoms in response to bacillus Calmette-Guerin [112]. A previous study showed that activation of peripheral blood mononuclear cells correlated with depression in patients with chronic hepatitis C. This suggests a pivotal role of immune cell activation in depression and neurocognitive dysfunction among chronic hepatitis C patients [113]. In addition, the injection of interferon-γ and poly(I:C), a Toll-like receptor-3 (TLR3) agonist mimicking the effect of HCV double-strand RNA, caused depression-like symptoms, and the proinflammatory genes were synergistically induced in the hippocampus and prefrontal cortex [105]. The tight association between HCV infection and depression suggests that optimal care for the overall well-being of patients with HCV infection needs adequate knowledge of their psychological status [114]. Infection with human immunodeficiency virus (HIV) has been associated with an increase in the prevalence of depression [115, 116]. HIV infection is associated with neuroinflammation and more significant psychopathological symptoms, which imbalances may mediate in the kynurenic pathway [117]. As the critical kynurenic pathway enzymes that catabolize kynurenine, kynurenine-3-monooxygenase produces neurotoxic metabolites in microglia [118], while kynurenine-aminotransferase II synthesizes kynurenine acid in astrocytes [119]. Targeted intervention that reduces neuroinflammation and increases kynurenine acid in at-risk kynurenine-aminotransferase II-TT-carriers may lessen the depressive symptoms of HIV [120].

The inflammasome is a cytoplasmic protein complex, an essential immune system component [121–123]. Microglia play an important role in activating inflammasome as they carry pattern recognition receptors (PRR) such as the Toll-like receptor, triggering receptor expressed in myeloid cells 2 (TREM2). It recognizes pathogen-associated molecular patterns (PAMP) and damage-associated molecular patterns (DAMP) [124–126]. The microglia membrane is rich in P2X7, activating the NLRP3 inflammasome in the microglia under chronic stress, thus mediating depression-like behavior [127–129]. Therapy such as electroacupuncture, curcumin, and simvastatin exhibit the antidepressant effect and alleviate neuroinflammation by inhibiting the NLRP3 inflammasome and inflammatory mediators [130–135]. Selective serotonin reuptake inhibitors (SSRI) are the first-line treatment for depression. Its representative drug fluoxetine significantly inhibits the NLRP3 inflammasome activation in microglia and relieves depression-like behavior by downregulating NLRP3 [136]. In addition, fluoxetine prevents the exacerbation of cardiovascular dysfunction due to socially isolated depression by activating Nrf2/HO-1 and inhibiting the TLR4/NLRP3 inflammasome signaling pathway [137]. Moreover, clomipramine, perilla aldehyde, cholecalciferol, geraniol, and silymarin also attenuate depressive symptoms by the NLRP3-relative inflammatory response [138–142].

5. Conclusion

PSD is common among stroke patients and has a high recurrence rate. Its risk factors and pathophysiological mechanism are still unclear, so it is significant for preventing and treating PSD. Microglia are a vital part of maintaining mental health and a key mediator in managing stress and lifestyle. In the pathophysiological mechanism of depression, microglia could be involved in many processes and play a regulatory role in neuroinflammation, nerve growth, and neuroplasticity. The function of microglia in depression and the sequence of various mechanisms and their interrelation are not clarified. Therefore, understanding the role of microglia in the pathogenesis of depression is of great significance for developing treatment strategies against depression.

Data Availability

The availability of data and materials is not applicable.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

GCY and TGY conceptualized the research project. WLX, YX, and YDG drafted the manuscript. GCY, TGY, and XJC reviewed and modified the manuscript. GCY and TGY supervised the research and led the discussion. All authors approved the final version of the manuscript.

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References

[1] X. Hu, R. K. Leak, Y. Shi et al., "Microglial and macrophage polarization–new prospects for brain repair," *Nature Reviews Neurology*, vol. 11, no. 1, pp. 56–64, 2015.

[2] C. Rawlinson, S. Jenkins, L. Thei, M. L. Dallas, and R. Chen, "Post-ischaemic immunological response in the brain: targeting microglia in ischaemic stroke therapy," *Brain Sciences*, vol. 10, no. 3, p. 159, 2020.

[3] F. Yu, T. Huang, Y. Ran et al., "New insights into the roles of microglial regulation in brain plasticity-dependent stroke recovery," *Frontiers in Cellular Neuroscience*, vol. 15, article 727899, 2021.

[4] R. Zhao, M. Ying, S. Gu et al., "Cysteinyl leukotriene receptor 2 is involved in inflammation and neuronal damage by mediating microglia M1/M2 polarization through NF-κB pathway," *Neuroscience*, vol. 422, pp. 99–118, 2019.

[5] S. Monga, N. Denora, V. Laquintana et al., "The protective effect of the TSPO ligands 2,4-Di-Cl-MGV-1, CB86, and CB204 against LPS-induced M1 pro-inflammatory activation of microglia," *Brain, Behavior, & Immunity-Health*, vol. 5, article 100083, 2020.

[6] S. Kim and Y. Son, "Astrocytes stimulate microglial proliferation and M2 polarization in vitro through crosstalk between astrocytes and microglia," *International Journal of Molecular Sciences*, vol. 22, no. 16, p. 8800, 2021.

[7] A. Suzumura, T. Tamaru, M. Yoshikawa, and T. Takayanagi, "Multinucleated giant cell formation by microglia: induction by interleukin (IL)-4 and IL-13," *Brain Research*, vol. 849, no. 1-2, pp. 239–243, 1999.

[8] A. Quarta, Z. Berneman, and P. Ponsaerts, "Neuroprotective modulation of microglia effector functions following priming with interleukin 4 and 13: current limitations in understanding their mode-of-action," *Brain, Behavior, and Immunity*, vol. 88, pp. 856–866, 2020.

[9] L. Wei, J. Guo, X. Yu et al., "Role and characteristics of hippocampal region microglial activation in poststroke depression," *Journal of Affective Disorders*, vol. 291, pp. 270–278, 2021.

[10] X. Hu, P. Li, Y. Guo et al., "Microglia/macrophage polarization dynamics reveal novel mechanism of injury expansion after focal cerebral ischemia," *Stroke*, vol. 43, no. 11, pp. 3063–3070, 2012.

[11] D. Wu, G. Zhang, C. Zhao, Y. Yang, Z. Miao, and X. Xu, "Interleukin-18 from neurons and microglia mediates depressive behaviors in mice with post-stroke depression," *Brain, Behavior, and Immunity*, vol. 88, pp. 411–420, 2020.

[12] R. Verma, B. D. Friedler, N. M. Harris, and L. D. McCullough, "Pair housing reverses post-stroke depressive behavior in mice," *Behavioural Brain Research*, vol. 269, pp. 155–163, 2014.

[13] C. L. Nemeth, M. S. Shurte, D. M. McTigue, C. B. Nemeroff, and G. N. Neigh, "Microembolism infarcts lead to delayed changes in affective-like behaviors followed by spatial memory impairment," *Behavioural Brain Research*, vol. 234, no. 2, pp. 259–266, 2012.

[14] N. Dudvarski Stankovic, M. Teodorczyk, R. Ploen, F. Zipp, and M. H. H. Schmidt, "Microglia-blood vessel interactions: a double-edged sword in brain pathologies," *Acta Neuropathologica*, vol. 131, no. 3, pp. 347–363, 2016.

[15] H. Takeda, T. Yamaguchi, H. Yano, and J. Tanaka, "Microglial metabolic disturbances and neuroinflammation in cerebral infarction," *Journal of Pharmacological Sciences*, vol. 145, no. 1, pp. 130–139, 2021.

[16] Y. Yan, T. Li, D. Wang, B. Zhao, and Q. Zhou, "Antidepressant effect of Xingnao Jieyu decoction mediated by alleviating neuroinflammation in a rat model of post-stroke depression," *Journal of Traditional Chinese Medicine*, vol. 39, no. 5, pp. 658–666, 2019.

[17] I. Turnbull, R. Clarke, N. Wright et al., "Diagnostic accuracy of major stroke types in Chinese adults: a clinical adjudication study involving 40,000 stroke cases," *The Lancet Regional Health-Western Pacific*, vol. 21, article 100415, 2022.

[18] Q. Ma, R. Li, L. Wang et al., "Temporal trend and attributable risk factors of stroke burden in China, 1990-2019: an analysis for the Global Burden of Disease Study 2019," *The Lancet Public Health*, vol. 6, no. 12, pp. e897–e906, 2021.

[19] T. Cumming and A. Brodtmann, "Dementia and stroke: the present and future epidemic," *International Journal of Stroke*, vol. 5, no. 6, pp. 453-454, 2010.

[20] J. Das and G. K. Rajanikant, "Post stroke depression: the sequelae of cerebral stroke," *Neuroscience and Biobehavioral Reviews*, vol. 90, pp. 104–114, 2018.

[21] G. L. Lenzi, M. Altieri, and I. Maestrini, "Post-stroke depression," *Revue Neurologique (Paris)*, vol. 164, no. 10, pp. 837–840, 2008.

[22] L. Gabaldón, B. Fuentes, A. Frank-García, and E. Díez-Tejedor, "Poststroke depression: importance of its detection and treatment," *Cerebrovascular Diseases*, vol. 24, pp. 181–188, 2007.

[23] B. Du, M. Liang, H. Zheng et al., "Anti-mouse CX3CR1 antibody alleviates cognitive impairment, neuronal loss and myelin deficits in an animal model of brain ischemia," *Neuroscience*, vol. 438, pp. 169–181, 2020.

[24] A. M. Buga, O. Ciobanu, G. M. Bădescu et al., "Up-regulation of serotonin receptor 2B mRNA and protein in the peri-

infarcted area of aged rats and stroke patients," *Oncotarget*, vol. 7, no. 14, pp. 17415–17430, 2016.

[25] C. L. Nemeth, R. Reddy, M. Bekhbat, J. Bailey, and G. N. Neigh, "Microglial activation occurs in the absence of anxiety-like behavior following microembolic stroke in female, but not male, rats," *Journal of Neuroinflammation*, vol. 11, no. 1, p. 174, 2014.

[26] J. M. Gaete and J. Bogousslavsky, "Post-stroke depression," *Expert Review of Neurotherapeutics*, vol. 8, no. 1, pp. 75–92, 2008.

[27] M. Volz, S. Ladwig, and K. Werheid, "Gender differences in post-stroke depression: a longitudinal analysis of prevalence, persistence and predictive value of known risk factors," *Neuropsychological Rehabilitation*, vol. 31, no. 1, pp. 1–17, 2021.

[28] B. Grabowska-Fudala, K. Jaracz, K. Górna et al., "Depressive symptoms in stroke patients treated and non-treated with intravenous thrombolytic therapy: a 1-year follow-up study," *Journal of Neurology*, vol. 265, no. 8, pp. 1891–1899, 2018.

[29] A. Saxena and A. Suman, "Magnitude and determinants of depression in acute stroke patients admitted in a rural tertiary care hospital," *Journal of Neurosciences in Rural Practice*, vol. 6, no. 2, pp. 202–207, 2015.

[30] J. P. Chau, D. R. Thompson, A. M. Chang et al., "Depression among Chinese stroke survivors six months after discharge from a rehabilitation hospital," *Journal of Clinical Nursing*, vol. 19, no. 21-22, pp. 3042–3050, 2010.

[31] M. Altieri, I. Maestrini, A. Mercurio et al., "Depression after minor stroke: prevalence and predictors," *European Journal of Neurology*, vol. 19, no. 3, pp. 517–521, 2012.

[32] Y. Shi, Y. Xiang, Y. Yang et al., "Depression after minor stroke: prevalence and predictors," *Journal of Psychosomatic Research*, vol. 79, no. 2, pp. 143–147, 2015.

[33] F. Acciai and M. Hardy, "Depression in later life: a closer look at the gender gap," *Social Science Research*, vol. 68, pp. 163–175, 2017.

[34] S. E. Kim, H. N. Kim, J. Cho et al., "Direct and indirect effects of five factor personality and gender on depressive symptoms mediated by perceived stress," *PLoS One*, vol. 11, no. 4, article e0154140, 2016.

[35] J. Guo, J. Wang, W. Sun, and X. Liu, "The advances of post-stroke depression: 2021 update," *Journal of Neurology*, vol. 269, no. 3, pp. 1236–1249, 2022.

[36] C. Wei, F. Zhang, L. Chen, X. Ma, N. Zhang, and J. Hao, "Retraction note to: factors associated with post-stroke depression and fatigue: lesion location and coping styles," *Journal of Neurology*, vol. 265, no. 2, p. 451, 2018.

[37] R. Perrain, D. Calvet, V. Guiraud, L. Mekaoui, J. L. Mas, and P. Gorwood, "Depressive-, cognitive- or stroke-related risk factors of post-stroke depression: which one could better help clinicians and patients?," *Neuropsychiatric Disease and Treatment*, vol. Volume 17, pp. 1243–1251, 2021.

[38] Y. Shi, D. Yang, Y. Zeng, and W. Wu, "Risk factors for post-stroke depression: a meta-analysis," *Frontiers in Aging Neuroscience*, vol. 9, p. 218, 2017.

[39] E. Zhang and P. Liao, "Brain-derived neurotrophic factor and post-stroke depression," *Journal of Neuroscience Research*, vol. 98, no. 3, pp. 537–548, 2020.

[40] X. E. Zhao, Y. He, S. Zhu et al., "Stable isotope labeling derivatization and magnetic dispersive solid phase extraction coupled with UHPLC-MS/MS for the measurement of brain neurotransmitters in post-stroke depression rats administrated with gastrodin," *Analytica Chimica Acta*, vol. 1051, pp. 73–81, 2019.

[41] S. F. Nabavi, O. M. Dean, A. Turner, A. Sureda, M. Daglia, and S. M. Nabavi, "Oxidative stress and post-stroke depression: possible therapeutic role of polyphenols?," *Current Medicinal Chemistry*, vol. 22, no. 3, pp. 343–351, 2015.

[42] X. W. Ji, C. L. Wu, X. C. Wang, J. Liu, J. Z. Bi, and D. Y. Wang, "Monoamine neurotransmitters and fibroblast growth factor-2 in the brains of rats with post-stroke depression," *Experimental and Therapeutic Medicine*, vol. 8, no. 1, pp. 159–164, 2014.

[43] Y. S. Koo, H. Kim, J. H. Park et al., "Indoleamine 2,3-dioxygenase-dependent neurotoxic kynurenine metabolism contributes to poststroke depression induced in mice by ischemic stroke along with spatial restraint stress," *Oxidative Medicine and Cellular Longevity*, vol. 2018, Article ID 2413841, 15 pages, 2018.

[44] D. Grinchii and E. Dremencov, "Mechanism of action of atypical antipsychotic drugs in mood disorders," *International Journal of Molecular Sciences*, vol. 21, no. 24, p. 9532, 2020.

[45] I. O. Blokhin, O. Khorkova, R. V. Saveanu, and C. Wahlestedt, "Molecular mechanisms of psychiatric diseases," *Neurobiology of Disease*, vol. 146, article 105136, 2020.

[46] K. Seki, S. Yoshida, and M. K. Jaiswal, "Molecular mechanism of noradrenaline during the stress-induced major depressive disorder," *Neural Regeneration Research*, vol. 13, no. 7, pp. 1159–1169, 2018.

[47] P. Licznerski and R. S. Duman, "Remodeling of axo-spinous synapses in the pathophysiology and treatment of depression," *Neuroscience*, vol. 251, pp. 33–50, 2013.

[48] M. R. Bennett, "The prefrontal-limbic network in depression: modulation by hypothalamus, basal ganglia and midbrain," *Progress in Neurobiology*, vol. 93, no. 4, pp. 468–487, 2011.

[49] A. T. Beck, "The evolution of the cognitive model of depression and its neurobiological correlates," *The American Journal of Psychiatry*, vol. 165, no. 8, pp. 969–977, 2008.

[50] A. Zahrai, F. Vahid-Ansari, M. Daigle, and P. R. Albert, "Fluoxetine-induced recovery of serotonin and norepinephrine projections in a mouse model of post-stroke depression," *Translational Psychiatry*, vol. 10, no. 1, p. 334, 2020.

[51] I. Loubinoux, G. Kronenberg, M. Endres et al., "Post-stroke depression: mechanisms, translation and therapy," *Journal of Cellular and Molecular Medicine*, vol. 16, no. 9, pp. 1961–1969, 2012.

[52] J. Weinberger, G. Cohen, and J. Nieves-Rosa, "Nerve terminal damage in cerebral ischemia: greater susceptibility of catecholamine nerve terminals relative to serotonin nerve terminals," *Stroke*, vol. 14, no. 6, pp. 986–989, 1983.

[53] L. Turner-Stokes and N. Hassan, "Depression after stroke: a review of the evidence base to inform the development of an integrated care pathway. Part 2: treatment alternatives," *Clinical Rehabilitation*, vol. 16, no. 3, pp. 248–260, 2002.

[54] G. Li, Y. Ma, J. Ji, X. Si, and Q. Fan, "Effects of gastrodin on 5-HT and neurotrophic factor in the treatment of patients with post-stroke depression," *Experimental and Therapeutic Medicine*, vol. 16, no. 6, pp. 4493–4498, 2018.

[55] C. Wang, C. Wu, Z. Yan, and X. Cheng, "Ameliorative effect of Xiaoyao-jieyu-san on post-stroke depression and its potential mechanisms," *Journal of Natural Medicines*, vol. 73, no. 1, pp. 76–84, 2019.

[56] N. Prowse and S. Hayley, "Microglia and BDNF at the crossroads of stressor related disorders: towards a unique trophic phenotype," *Neuroscience and Biobehavioral Reviews*, vol. 131, pp. 135–163, 2021.

[57] B. Podyma, K. Parekh, A. D. Güler, and C. D. Deppmann, "Metabolic homeostasis via BDNF and its receptors," *Trends in Endocrinology and Metabolism*, vol. 32, no. 7, pp. 488–499, 2021.

[58] A. Berretta, Y. C. Tzeng, and A. N. Clarkson, "Post-stroke recovery: the role of activity-dependent release of brain-derived neurotrophic factor," *Expert Review of Neurotherapeutics*, vol. 14, no. 11, pp. 1335–1344, 2014.

[59] H. X. Zhu, L. J. Cheng, R. W. Ou Yang et al., "Reduced amygdala microglial expression of brain-derived neurotrophic factor and tyrosine kinase receptor B (TrkB) in a rat model of poststroke depression," *Medical Science Monitor*, vol. 26, article e926323, 2020.

[60] E. Castrén and L. M. Monteggia, "Brain-derived neurotrophic factor signaling in depression and antidepressant action," *Biological Psychiatry*, vol. 90, no. 2, pp. 128–136, 2021.

[61] E. Castrén and M. Kojima, "Brain-derived neurotrophic factor in mood disorders and antidepressant treatments," *Neurobiology of Disease*, vol. 97, pp. 119–126, 2017.

[62] D. Shan, Y. Zheng, and K. Froud, "Brain-derived neurotrophic factor as a clinical biomarker in predicting the development of post-stroke depression: a review of evidence," *Cureus*, vol. 13, no. 6, article e15662, 2021.

[63] D. Kotlęga, B. Peda, A. Zembroń-Łacny, M. Gołąb-Janowska, and P. Nowacki, "The role of brain-derived neurotrophic factor and its single nucleotide polymorphisms in stroke patients," *Neurologia i Neurochirurgia Polska*, vol. 51, no. 3, pp. 240–246, 2017.

[64] R. Infantino, C. Schiano, L. Luongo et al., "MED1/BDNF/TrkB pathway is involved in thalamic hemorrhage-induced pain and depression by regulating microglia," *Neurobiology of Disease*, vol. 164, p. 105611, 2022.

[65] X. Qiu, H. Wang, Y. Lan et al., "Blood biomarkers of post-stroke depression after minor stroke at three months in males and females," *BMC Psychiatry*, vol. 22, no. 1, p. 162, 2022.

[66] C. Espinosa-Garcia, I. Sayeed, S. Yousuf et al., "Stress primes microglial polarization after global ischemia: therapeutic potential of progesterone," *Brain, Behavior, and Immunity*, vol. 66, pp. 177–192, 2017.

[67] T. K. Lee, J. H. Park, J. H. Ahn et al., "Pretreated duloxetine protects hippocampal CA1 pyramidal neurons from ischemia-reperfusion injury through decreases of glial activation and oxidative stress," *Journal of the Neurological Sciences*, vol. 370, pp. 229–236, 2016.

[68] J. Hu, L. Wang, K. Fan et al., "The association between systemic inflammatory markers and post-stroke depression: a prospective stroke cohort," *Clinical Interventions in Aging*, vol. Volume 16, pp. 1231–1239, 2021.

[69] L. Zhang, L. Zhang, and R. Sui, "Ganoderic acid A-mediated modulation of microglial polarization is involved in depressive-like behaviors and neuroinflammation in a rat model of post-stroke depression," *Neuropsychiatric Disease and Treatment*, vol. 17, pp. 2671–2681, 2021.

[70] Y. Wang, J. H. Zhang, J. Sheng, and A. Shao, "Immunoreactive cells after cerebral ischemia," *Frontiers in Immunology*, vol. 10, p. 2781, 2019.

[71] D. Zhang, J. Ren, Y. Luo et al., "T cell response in ischemic stroke: from mechanisms to translational insights," *Frontiers in Immunology*, vol. 12, p. 707972, 2021.

[72] C. Couch, K. Mallah, D. M. Borucki, H. S. Bonilha, and S. Tomlinson, "State of the science in inflammation and stroke recovery: a systematic review," *Annals of Physical and Rehabilitation Medicine*, vol. 65, no. 2, article 101546, 2022.

[73] A. Shao, Z. Zhu, L. Li, S. Zhang, and J. Zhang, "Emerging therapeutic targets associated with the immune system in patients with intracerebral haemorrhage (ICH): from mechanisms to translation," *eBioMedicine*, vol. 45, pp. 615–623, 2019.

[74] M. S. Abdallah, A. N. Ramadan, H. Omara-Reda et al., "Double-blind, randomized, placebo-controlled pilot study of the phosphodiesterase-3 inhibitor cilostazol as an adjunctive to antidepressants in patients with major depressive disorder," *CNS Neuroscience & Therapeutics*, vol. 27, no. 12, pp. 1540–1548, 2021.

[75] O. A. Levada and A. S. Troyan, "Poststroke depression biomarkers: a narrative review," *Frontiers in Neurology*, vol. 9, p. 577, 2018.

[76] R. F. Villa, F. Ferrari, and A. Moretti, "Post-stroke depression: mechanisms and pharmacological treatment," *Pharmacology & Therapeutics*, vol. 184, pp. 131–144, 2018.

[77] R. Verma, C. G. Cronin, J. Hudobenko, V. R. Venna, L. D. McCullough, and B. T. Liang, "Deletion of the P2X4 receptor is neuroprotective acutely, but induces a depressive phenotype during recovery from ischemic stroke," *Brain, Behavior, and Immunity*, vol. 66, pp. 302–312, 2017.

[78] H. H. Kozak, F. Uğuz, İ. Kılınç et al., "A cross-sectional study to assess the association between major depression and inflammatory markers in patients with acute ischemic stroke," *Indian Journal of Psychiatry*, vol. 61, no. 3, pp. 283–289, 2019.

[79] P. B. de la Tremblaye and H. Plamondon, "Alterations in the corticotropin-releasing hormone (CRH) neurocircuitry: insights into post stroke functional impairments," *Frontiers in Neuroendocrinology*, vol. 42, pp. 53–75, 2016.

[80] D. Radak, I. Resanovic, and E. R. Isenovic, "Changes in hypothalamus-pituitary-adrenal axis following transient ischemic attack," *Angiology*, vol. 65, no. 8, pp. 723–732, 2014.

[81] T. K. Craft and A. C. Devries, "Vulnerability to stroke: implications of perinatal programming of the hypothalamic-pituitary-adrenal axis," *Frontiers in Behavioral Neuroscience*, vol. 3, p. 54, 2009.

[82] G. C. Medeiros, D. Roy, N. Kontos, and S. R. Beach, "Post-stroke depression: a 2020 updated review," *General Hospital Psychiatry*, vol. 66, pp. 70–80, 2020.

[83] S. Kitaoka, "Inflammation in the brain and periphery found in animal models of depression and its behavioral relevance," *Journal of Pharmacological Sciences*, vol. 148, no. 2, pp. 262–266, 2022.

[84] M. Gałecka, K. Bliźniewska-Kowalska, M. Maes, K. P. Su, and P. Gałecki, "Update on the neurodevelopmental theory of depression: is there any 'unconscious code'?," *Pharmacological Reports*, vol. 73, no. 2, pp. 346–356, 2021.

[85] P. Kopschina Feltes, J. Doorduin, H. C. Klein et al., "Anti-inflammatory treatment for major depressive disorder: implications for patients with an elevated immune profile and non-responders to standard antidepressant therapy," *Journal of Psychopharmacology*, vol. 31, no. 9, pp. 1149–1165, 2017.

[86] J. Hu, W. Zhou, Z. Zhou, J. Han, and W. Dong, "Elevated neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios predict post-stroke depression with acute ischemic stroke," *Experimental and Therapeutic Medicine*, vol. 19, no. 4, pp. 2497–2504, 2020.

[87] H. Chen, X. Luan, K. Zhao et al., "The association between neutrophil-to-lymphocyte ratio and post-stroke depression," *Clinica Chimica Acta*, vol. 486, pp. 298–302, 2018.

[88] L. Wei, Y. Du, Y. Xie, X. Yu, H. Chen, and Y. Qiu, "Lipocalin-2 regulates hippocampal microglial activation in poststroke depression," *Frontiers in Aging Neuroscience*, vol. 13, article 798335, 2021.

[89] T. Kreisel, M. G. Frank, T. Licht et al., "Dynamic microglial alterations underlie stress-induced depressive-like behavior and suppressed neurogenesis," *Molecular Psychiatry*, vol. 19, no. 6, pp. 699–709, 2014.

[90] X. Tao, S. Wu, W. Tang et al., "Alleviative effects of foraging exercise on depressive-like behaviors in chronic mild stress-induced ischemic rat model," *Brain Injury*, vol. 36, no. 1, pp. 127–136, 2022.

[91] R. Gaspar, C. Soares-Cunha, A. V. Domingues et al., "The duration of stress determines sex specificities in the vulnerability to depression and in the morphologic remodeling of neurons and microglia," *Frontiers in Behavioral Neuroscience*, vol. 16, article 834821, 2022.

[92] D. Enache, C. M. Pariante, and V. Mondelli, "Markers of central inflammation in major depressive disorder: a systematic review and meta-analysis of studies examining cerebrospinal fluid, positron emission tomography and post-mortem brain tissue," *Brain, Behavior, and Immunity*, vol. 81, pp. 24–40, 2019.

[93] V. V. Giridharan, P. Sayana, O. F. Pinjari et al., "Postmortem evidence of brain inflammatory markers in bipolar disorder: a systematic review," *Molecular Psychiatry*, vol. 25, no. 1, pp. 94–113, 2020.

[94] Q. Camargos, B. C. Silva, D. G. Silva et al., "Minocycline treatment prevents depression and anxiety-like behaviors and promotes neuroprotection after experimental ischemic stroke," *Brain Research Bulletin*, vol. 155, pp. 1–10, 2020.

[95] B. Du, H. Li, H. Zheng et al., "Minocycline ameliorates depressive-like behavior and demyelination induced by transient global cerebral ischemia by inhibiting microglial activation," *Frontiers in Pharmacology*, vol. 10, p. 1247, 2019.

[96] Z. Karimi, M. Chenari, F. Rezaie, S. Karimi, N. Parhizgari, and T. Mokhtari-Azad, "Proposed pathway linking respiratory infections with depression," *Clinical Psychopharmacology and Neuroscience*, vol. 20, no. 2, pp. 199–210, 2022.

[97] S. El-Halabi, D. H. Cooper, D. S. Cha et al., "The effects of antidepressant medications on antiretroviral treatment adherence in HIV-positive individuals with depression," *Journal of Affective Disorders*, vol. 300, pp. 219–225, 2022.

[98] A. Mohammadkhanizadeh and F. Nikbakht, "Investigating the potential mechanisms of depression induced-by COVID-19 infection in patients," *Journal of Clinical Neuroscience*, vol. 91, pp. 283–287, 2021.

[99] K. Zhang, X. Wang, J. Tu, H. Rong, O. Werz, and X. Chen, "The interplay between depression and tuberculosis," *Journal of Leukocyte Biology*, vol. 106, no. 3, pp. 749–757, 2019.

[100] N. Cattane, A. C. Vernon, A. Borsini et al., "Preclinical animal models of mental illnesses to translate findings from the bench to the bedside: molecular brain mechanisms and peripheral biomarkers associated to early life stress or immune challenges," *European Neuropsychopharmacology*, vol. 58, pp. 55–79, 2022.

[101] F. B. Del Guerra, J. L. Fonseca, V. M. Figueiredo, E. B. Ziff, and E. C. Konkiewitz, "Human immunodeficiency virus-associated depression: contributions of immuno-inflammatory, monoaminergic, neurodegenerative, and neurotrophic pathways," *Journal of Neurovirology*, vol. 19, no. 4, pp. 314–327, 2013.

[102] L. Yarlott, E. Heald, and D. Forton, "Hepatitis C virus infection, and neurological and psychiatric disorders - a review," *Journal of Advanced Research*, vol. 8, no. 2, pp. 139–148, 2017.

[103] C. Hoyo-Becerra, Z. Liu, J. Yao et al., "Rapid regulation of depression-associated genes in a new mouse model mimicking interferon-α-related depression in hepatitis C virus infection," *Molecular Neurobiology*, vol. 52, no. 1, pp. 318–329, 2015.

[104] M. G. Frank, K. H. Nguyen, J. B. Ball et al., "SARS-CoV-2 spike S1 subunit induces neuroinflammatory, microglial and behavioral sickness responses: evidence of PAMP-like properties," *Brain, Behavior, and Immunity*, vol. 100, pp. 267–277, 2022.

[105] C. J. Henry, Y. Huang, A. M. Wynne, and J. P. Godbout, "Peripheral lipopolysaccharide (LPS) challenge promotes microglial hyperactivity in aged mice that is associated with exaggerated induction of both pro-inflammatory IL-1β and anti-inflammatory IL-10 cytokines," *Brain, Behavior, and Immunity*, vol. 23, no. 3, pp. 309–317, 2009.

[106] T. E. Nicholson and K. W. Renton, "Role of cytokines in the lipopolysaccharide-evoked depression of cytochrome P450 in the brain and liver," *Biochemical Pharmacology*, vol. 62, no. 12, pp. 1709–1717, 2001.

[107] B. Tastan, B. I. Arioz, K. U. Tufekci et al., "Dimethyl fumarate alleviates NLRP3 inflammasome activation in microglia and sickness behavior in LPS-challenged mice," *Frontiers in Immunology*, vol. 12, p. 737065, 2021.

[108] H. T. Bian, L. Xiao, L. Liang, Y. P. Xie, H. L. Wang, and G. H. Wang, "RGFP966 is protective against lipopolysaccharide-induced depressive-like behaviors in mice by inhibiting neuroinflammation and microglial activation," *International Immunopharmacology*, vol. 101, article 108259, 2021.

[109] W. Li, Y. Xu, Z. Liu et al., "TRPV4 inhibitor HC067047 produces antidepressant-like effect in LPS-induced depression mouse model," *Neuropharmacology*, vol. 201, p. 108834, 2021.

[110] J. C. O'Connor, C. André, Y. Wang et al., "Interferon-gamma and tumor necrosis factor-alpha mediate the upregulation of indoleamine 2,3-dioxygenase and the induction of depressive-like behavior in mice in response to bacillus Calmette-Guerin," *The Journal of Neuroscience*, vol. 29, no. 13, pp. 4200–4209, 2009.

[111] T. Pawlowski, M. Radkowski, K. Małyszczak et al., "Depression and neuroticism in patients with chronic hepatitis C: correlation with peripheral blood mononuclear cells activation," *Journal of Clinical Virology*, vol. 60, no. 2, pp. 105–111, 2014.

[112] P. Amodio, L. Salari, S. Montagnese et al., "Hepatitis C virus infection and health-related quality of life," *World Journal of Gastroenterology*, vol. 18, no. 19, pp. 2295–2299, 2012.

[113] L. M. Filiatreau, P. V. Ebasone, A. Dzudie et al., "Prevalence of stressful life events and associations with symptoms of

depression, anxiety, and post-traumatic stress disorder among people entering care for HIV in Cameroon," *Journal of Affective Disorders*, vol. 308, pp. 421–431, 2022.

[114] V. Hémar, M. Hessamfar, D. Neau et al., "A comprehensive analysis of excess depressive disorder in women and men living with HIV in France compared to the general population," *Scientific Reports*, vol. 12, no. 1, p. 6364, 2022.

[115] N. Drivsholm, A. D. Knudsen, M. Faurholt-Jepsen et al., "Alterations in the kynurenine pathway of tryptophan metabolism are associated with depression in people living with HIV," *Journal of Acquired Immune Deficiency Syndromes*, vol. 87, no. 2, pp. e177–e181, 2021.

[116] S. L. Rodriguez-Zas, C. Wu, B. R. Southey et al., "Disruption of microglia histone acetylation and protein pathways in mice exhibiting inflammation-associated depression-like symptoms," *Psychoneuroendocrinology*, vol. 97, pp. 47–58, 2018.

[117] P. Guidetti, G. E. Hoffman, M. Melendez-Ferro, E. X. Albuquerque, and R. Schwarcz, "Astrocytic localization of kynurenine aminotransferase II in the rat brain visualized by immunocytochemistry," *Glia*, vol. 55, no. 1, pp. 78–92, 2007.

[118] V. Douet, N. Tanizaki, A. Franke, X. Li, and L. Chang, "Polymorphism of kynurenine pathway-related genes, kynurenic acid, and psychopathological symptoms in HIV," *Journal of Neuroimmune Pharmacology*, vol. 11, no. 3, pp. 549–561, 2016.

[119] W. Xu, T. Li, L. Gao et al., "Apelin-13/APJ system attenuates early brain injury via suppression of endoplasmic reticulum stress-associated TXNIP/NLRP3 inflammasome activation and oxidative stress in a AMPK-dependent manner after subarachnoid hemorrhage in rats," *Journal of Neuroinflammation*, vol. 16, no. 1, p. 247, 2019.

[120] S. M. Man, R. Karki, and T. D. Kanneganti, "Molecular mechanisms and functions of pyroptosis, inflammatory caspases and inflammasomes in infectious diseases," *Immunological Reviews*, vol. 277, no. 1, pp. 61–75, 2017.

[121] A. Thapa, M. Adamiak, K. Bujko et al., "Danger-associated molecular pattern molecules take unexpectedly a central stage in Nlrp3 inflammasome-caspase-1-mediated trafficking of hematopoietic stem/progenitor cells," *Leukemia*, vol. 35, no. 9, pp. 2658–2671, 2021.

[122] H. Scheiblich, L. Bousset, S. Schwartz et al., "Microglial NLRP3 inflammasome activation upon TLR2 and TLR5 ligation by distinct α-synuclein assemblies," *Journal of Immunology*, vol. 207, no. 8, pp. 2143–2154, 2021.

[123] X. Fu, H. Zeng, J. Zhao et al., "Inhibition of dectin-1 ameliorates neuroinflammation by regulating microglia/macrophage phenotype after intracerebral hemorrhage in mice," *Translational Stroke Research*, vol. 12, no. 6, pp. 1018–1034, 2021.

[124] M. Gallizioli, F. Miró-Mur, A. Otxoa-de-Amezaga et al., "Dendritic cells and microglia have non-redundant functions in the inflamed brain with protective effects of type 1 cDCs," *Cell Reports*, vol. 33, no. 3, p. 108291, 2020.

[125] I. A. von Muecke-Heim, C. Ries, L. Urbina, and J. M. Deussing, "P2X7R antagonists in chronic stress-based depression models: a review," *European Archives of Psychiatry and Clinical Neuroscience*, vol. 271, no. 7, pp. 1343–1358, 2021.

[126] C. Ren, L. X. Li, A. Q. Dong et al., "Depression induced by chronic unpredictable mild stress increases susceptibility to Parkinson's disease in mice via neuroinflammation mediated by P2X7 receptor," *ACS Chemical Neuroscience*, vol. 12, no. 7, pp. 1262–1272, 2021.

[127] Z. Wang, W. Ren, F. Zhao, Y. Han, C. Liu, and K. Jia, "Curcumin amends Ca(2+) dysregulation in microglia by suppressing the activation of P2X7 receptor," *Molecular and Cellular Biochemistry*, vol. 465, no. 1-2, pp. 65–73, 2020.

[128] W. Y. Zhang, Y. J. Guo, W. X. Han et al., "Curcumin relieves depressive-like behaviors via inhibition of the NLRP3 inflammasome and kynurenine pathway in rats suffering from chronic unpredictable mild stress," *International Immunopharmacology*, vol. 67, pp. 138–144, 2019.

[129] N. Yue, H. Huang, X. Zhu et al., "Activation of P2X7 receptor and NLRP3 inflammasome assembly in hippocampal glial cells mediates chronic stress-induced depressive-like behaviors," *Journal of Neuroinflammation*, vol. 14, no. 1, p. 102, 2017.

[130] E. T. Menze, H. Ezzat, S. Shawky et al., "Simvastatin mitigates depressive-like behavior in ovariectomized rats: possible role of NLRP3 inflammasome and estrogen receptors' modulation," *International Immunopharmacology*, vol. 95, p. 107582, 2021.

[131] N. Yue, B. Li, L. Yang et al., "Electro-acupuncture alleviates chronic unpredictable stress-induced depressive- and anxiety-like behavior and hippocampal neuroinflammation in rat model of depression," *Frontiers in Molecular Neuroscience*, vol. 11, p. 149, 2018.

[132] Z. Li, H. Xu, Y. Xu et al., "Morinda officinalis oligosaccharides alleviate depressive-like behaviors in post-stroke rats via suppressing NLRP3 inflammasome to inhibit hippocampal inflammation," *CNS Neuroscience & Therapeutics*, vol. 27, no. 12, pp. 1570–1586, 2021.

[133] C. M. Lim, S. W. Kim, J. Y. Park, C. Kim, S. H. Yoon, and J. K. Lee, "Fluoxetine affords robust neuroprotection in the postischemic brain via its anti-inflammatory effect," *Journal of Neuroscience Research*, vol. 87, no. 4, pp. 1037–1045, 2009.

[134] R. H. Du, J. Tan, X. Y. Sun, M. Lu, J. H. Ding, and G. Hu, "Fluoxetine inhibits NLRP3 inflammasome activation: implication in depression," *Neuropsychopharmacology*, vol. 19, no. 9, article pyw037, 2016.

[135] K. Abu-Elfotuh, A. H. Al-Najjar, A. A. Mohammed, A. S. Aboutaleb, and G. A. Badawi, "Fluoxetine ameliorates Alzheimer's disease progression and prevents the exacerbation of cardiovascular dysfunction of socially isolated depressed rats through activation of Nrf2/HO-1 and hindering TLR4/NLRP3 inflammasome signaling pathway," *International Immunopharmacology*, vol. 104, p. 108488, 2022.

[136] W. Gong, S. Zhang, Y. Zong et al., "Involvement of the microglial NLRP3 inflammasome in the anti-inflammatory effect of the antidepressant clomipramine," *Journal of Affective Disorders*, vol. 254, pp. 15–25, 2019.

[137] A. Camargo, A. P. Dalmagro, N. Platt et al., "Cholecalciferol abolishes depressive-like behavior and hippocampal glucocorticoid receptor impairment induced by chronic corticosterone administration in mice," *Pharmacology, Biochemistry, and Behavior*, vol. 196, article 172971, 2020.

[138] A. Ashraf, P. A. Mahmoud, H. Reda et al., "Silymarin and silymarin nanoparticles guard against chronic unpredictable mild stress induced depressive-like behavior in mice: involvement of neurogenesis and NLRP3 inflammasome," *Journal of Psychopharmacology*, vol. 33, no. 5, pp. 615–631, 2019.

[139] X. Y. Deng, J. S. Xue, H. Y. Li et al., "Geraniol produces antidepressant-like effects in a chronic unpredictable mild stress mice model," *Physiology & Behavior*, vol. 152, pp. 264–271, 2015.

[140] Y. Song, R. Sun, Z. Ji, X. Li, Q. Fu, and S. Ma, "Perilla aldehyde attenuates CUMS-induced depressive-like behaviors via regulating TXNIP/TRX/NLRP3 pathway in rats," *Life Sciences*, vol. 206, pp. 117–124, 2018.

[141] S. A. Amici, J. Dong, and M. Guerau-de-Arellano, "Molecular mechanisms modulating the phenotype of macrophages and microglia," *Frontiers in Immunology*, vol. 8, p. 1520, 2017.

[142] J. Tang, W. Yu, S. Chen, Z. Gao, and B. Xiao, "Microglia polarization and endoplasmic reticulum stress in chronic social defeat stress induced depression mouse," *Neurochemical Research*, vol. 43, no. 5, pp. 985–994, 2018.