Proceedings of the 6th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/2026.33680

Research Progress on NLRP3 Inflammasome in the Pathogenesis of Depression and Its Comorbidities

Ying Tao

Medical College, Shantou University, Shantou, China
23ytao@stu.edu.cn

Abstract. Prolonged low mood and anhedonia are the main characteristics of depression, which has become a prevalent mental disorder nowadays. The monoamine hypothesis has guided relevant research for a long time, but this theory has many limitations, such as delayed onset of action and limited efficacy of antidepressants, indicating that the pathophysiological mechanism of depression is complex and the existing problems cannot be explained by the monoamine hypothesis alone. Recently, the neuroinflammation hypothesis has become a research hotspot in depression, and NLRP3 is considered a key factor in the development of neuroinflammation, attracting extensive attention. This paper systematically reviews the process by which the NLRP3 inflammasome participates in the pathogenesis of depression. Starting from the epidemiology of depression and the pathophysiological functions of NLRP3, it presents relevant clinical and preclinical evidence showing that NLRP3 activation is positively correlated with depression-like behaviors. Then, it discusses the potential mechanisms of the NLRP3 inflammasome in the pathogenesis of depression from the perspectives of microglial activation, pyroptosis, ATP-P2X7R axis and gut microbiota dysbiosis. This paper also elaborates on the association between NLRP3 activation and stress susceptibility and stress resistance, and clarifies the key role of NLRP3 in the comorbidity of depression with diabetes mellitus, cardiovascular diseases, neurodegenerative diseases and intestinal inflammation. Most studies suggest that the NLRP3 inflammasome is a key molecular bridge connecting neuroinflammation and depression. Therefore, NLRP3 and its downstream pathways may serve as new targets for antidepressant therapy, providing new directions for exploring the treatment of depression.

Keywords: NLRP3 inflammasome, Depression, Neuroinflammation, Stress susceptibility and stress resistance, Comorbidity mechanism

1. Introduction

In 2021, there were approximately 357.44 million new cases of depression worldwide and about 332.41 million prevalent cases [1]. From 1990 to 2021, the number of depression cases increased by 54% from 34.4 million to 53.1 million [2]. Patients with depression are particularly prone to suicidal ideation and suicidal behaviors. Studies have found that the suicide attempt rate of people with depression is five times that of the general population [3]. The currently recognized pathogenesis of depression includes the inflammatory response hypothesis, the monoamine neurotransmitter and

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2026.33680

receptor hypothesis (the main neurotransmitters are dopamine, serotonin and norepinephrine), the hypothalamic-pituitary-adrenal axis dysfunction hypothesis and the neurotrophic factor hypothesis [4]. In recent years, the treatment of depression has attracted increasing attention. Antidepressants can be divided into several categories: monoamine oxidase inhibitors represented by moclobemide; bicyclic compounds represented by sertraline and venlafaxine; tricyclic antidepressants represented by amitriptyline; tetracyclic antidepressants represented by maprotiline; selective serotonin reuptake inhibitors with fluoxetine as the early representative; serotonin-norepinephrine reuptake inhibitors represented by duloxetine; and dual-channel antidepressants such as mirtazapine, which enhances norepinephrine neurotransmission by blocking central α_2-adrenergic and 5-HT_2 receptors and promotes serotonin release simultaneously, showing high efficacy and safety in the treatment of depression; as well as other treatments including ketamine and its isomers, and probiotic adjuvant therapy [4-7]. Nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 is an important member of the nucleotide-binding oligomerization domain-like receptor family. Its inflammasome complex is composed of NLRP3 receptor protein, apoptosis-associated speck-like protein and cysteine-aspartic acid specific protease-1 [8]. Among them, the NLRP3 receptor protein contains an N-terminal PYD domain, a NACHT domain and a C-terminal leucine-rich repeat domain [9-13].

At present, NLRP3 is considered a key factor in the development of neuroinflammation, and inhibition of the NLRP3 inflammasome is regarded as an effective method to alleviate depression-like behaviors [11]. However, the pathological mechanism of depression is complex, the potential mechanisms of NLRP3 inflammasome activation have not been fully elucidated, and there is still a lack of comprehensive understanding of the pathophysiology and pathogenesis of depression. This paper reviews the process of the NLRP3 inflammasome participating in the pathogenesis of depression, and proposes the feasibility of targeting NLRP3 inflammasome-driven pathways to produce antidepressant effects, providing a new research direction for exploring the treatment of depression.

2. Pathophysiological functions of NLRP3

The core structure of the NLR family consists of a central nucleotide-binding oligomerization domain flanked by a C-terminal leucine-rich repeat and an N-terminal caspase recruitment or pyrin domain. According to the phylogenetic analysis of the NACHT domain in the NLR family, the NLR family can be divided into three distinct subfamilies: NODs, IPAF and NLRP. The NLRP subfamily consists of 14 proteins, named NLRP1 to NLRP14, and the corresponding NLRP inflammasomes are named accordingly [14]. Although various inflammasomes have been described, the best-characterized inflammasome associated with depression is the NLRP3 inflammasome. It has a pyrin domain of the NLR family [15].

The NLRP3 inflammasome is highly expressed in human cells related to the pathogenesis of immune defense and non-immune cells [15]. Under normal conditions, the NLRP3 inflammasome is activated during microbial infection, participates in host defense, and helps eliminate pathogens through a programmed cell death mechanism called pyroptosis. Activation of the NLRP3 inflammasome induces the release of mature IL-18 and IL-1β cytokines and triggers inflammatory cell death. In addition, the NLRP3 inflammasome can sense a wide range of activators and stimuli, including pathogens, tumor necrosis factor and other intracellular components. Abnormal or inappropriate activation, inactivation or dysfunction during infection, and failure to properly terminate activation after infection are harmful to health. Mutations in the components of the NLRP3 inflammasome are the main cause of its dysregulated activation and can trigger

DOI: 10.54254/2753-8818/2026.33680

inflammatory diseases such as cryopyrin-associated periodic syndromes. Activation of the NLRP3 inflammasome leads to hyperphosphorylation of tau protein and amyloid-β, thereby exacerbating Alzheimer's disease. In addition, dysregulation of the NLRP3 inflammasome activation process, especially chronic activation, has been proven to be related to the pathogenesis of two types of inflammatory arthritis (rheumatoid and gouty), diabetes mellitus and disease progression [15]. Relevant clinical studies on patients with depression have shown that the mRNA levels of NLRP3 and caspase-1 are significantly increased in people with major depressive disorder, indicating upregulated expression of the NLRP3 inflammasome in these individuals [9, 16]. Another clinical study showed that the levels of NLRP3 inflammasome, IL-18 and NF-κB were significantly higher in patients with major depressive disorder than in the control group [17]. Therefore, these findings suggest a link between NLRP3 inflammasome activation and chronic stress as well as major depressive disorder [9].

3. Preclinical and clinical manifestations of depression

3.1. Clinical manifestations of depression

3.1.1. Hippocampus

Studies have shown that significant structural and functional changes occur in multiple brain regions of people with depression [17]. The hippocampus is rich in glucocorticoid receptors and glutamate, and participates in the regulation of the hypothalamic-pituitary-adrenal axis through a negative feedback mechanism, making it extremely vulnerable to stress. Chronic stress can induce dendritic spine atrophy, neuronal loss and inflammatory cell infiltration in the hippocampus, thereby directly or indirectly promoting the pathogenesis of depression. Multiple magnetic resonance imaging studies have shown that the hippocampal volume of untreated depressed patients is significantly reduced compared with healthy controls, and the greater the reduction in hippocampal volume, the longer the duration or the higher the severity of depressive episodes. Among them, the gray matter volume of the left hippocampus is significantly reduced in patients with major depressive disorder, and the degree of gray matter loss is closely related to the disease course [18-20]. In conclusion, structural damage to the hippocampus is an important neurobiological basis for the occurrence and development of depression.

3.1.2. Prefrontal cortex

The human prefrontal cortex is mainly divided into three subregions: dorsolateral, ventromedial and orbitofrontal cortices [21]. In patients with major depressive disorder, the most obvious areas of reduced frontal lobe volume are the anterior cingulate cortex and bilateral orbitofrontal cortices [22]. A large-scale structural MRI study further revealed that adult patients with major depressive disorder showed significant cortical gray matter thinning involving the subgenual region, perisylvian region and dorsal region, accompanied by obvious gray matter atrophy in the ventromedial and orbitofrontal cortices compared with healthy controls [22]. In conclusion, structural damage to the prefrontal cortex and its subregions is an important neuropathological feature of major depressive disorder.

DOI: 10.54254/2753-8818/2026.33680

3.1.3. Amygdala

As the center of emotion processing, the amygdala is crucial for the generation or regulation of emotions, especially the processing of negative emotions, and the regulation of emotions such as fear and anxiety [23]. In patients with major depressive disorder, the higher the embedding degree of the central nucleus of the right amygdala, the more severe the depressive symptoms; the functional changes of these limbic subregions in the whole-brain connectome are closely related to the diagnosis and severity of depression [24]. Studies have shown that patients with major depressive disorder exhibit increased amygdala volume compared with healthy individuals [23], accompanied by enhanced amygdala activity or enlarged volume. Compared with the healthy control group, the major depressive disorder group had longer planning time, enhanced amygdala activity, hyperactivity of the rostral lateral prefrontal cortex, and strengthened negative connectivity between the amygdala and dorsolateral prefrontal cortex under the condition of comparable planning accuracy [25]. In conclusion, the amygdala plays a key role in regulating the progression of depression.

3.1.4. Locus coeruleus

The brain's norepinephrine is mainly derived from the locus coeruleus, a structure located in the dorsal pons of the brainstem, composed of dense noradrenergic neurons. This neuromodulatory system plays a central role in regulating arousal, attention, stress response, sleep-wake cycle and emotional behavior [26]. In depressed patients, pathological changes occur in the locus coeruleus at multiple levels, including changes in volume, cell number and receptor expression [26]. In the pathogenesis of stress-induced neuropsychiatric disorders, the input of corticotropin-releasing factor to the locus coeruleus-norepinephrine system is activated and recruited [27].

Regarding gray matter volume, patients with major depressive disorder show higher gray matter volume in the middle occipital gyrus and precuneus, and the structural covariance between these regions is increased [28]. In addition, patients with major depressive disorder mainly exhibit elevated MSE/ReHo ratios in the orbitofrontal cortex, sensorimotor cortex and visual cortex, and these MSE/ReHo ratios are significantly correlated with clinical indicators (including depression severity and cognitive function tests) [29]. Patients with major depressive disorder show higher interindividual structural covariance values in the anterior occipital lobe and lingual gyrus, but lower values in the medial frontal gyrus, putamen, cuneus and anterior cerebellum [27]. In contrast, they exhibit overall enhanced interindividual functional connectivity in almost the entire brain, including the middle frontal gyrus, anterior cingulate cortex, hippocampus, insula, striatum and prefrontal region [30].

3.2. Preclinical manifestations of depression

To understand the pathophysiology of depression, invasive interventions on brain tissue are usually required. However, such procedures cannot be performed on the human brain due to legal and ethical restrictions. Therefore, experimental depression studies usually use laboratory animals such as mice and rats. The ability to establish animal models is crucial to simulate human diseases in experimental animals. Long-term stress, such as social defeat, restraint stress and unpredictable mild stress, can induce a series of depression-related symptoms within days to weeks, including behavioral despair, anhedonia, negative bias and cognitive dysfunction. Specifically, reduced swimming time in the forced swimming test or reduced struggling time in the tail suspension test

DOI: 10.54254/2753-8818/2026.33680

reflect helplessness and despair in escape or self-defense responses. Decreased sucrose preference or intake and reduced social interaction reflect anhedonia, one of the most important symptoms of depressed patients, namely the inability to enjoy daily activities or behaviors. Spatial working memory deficits and inability to remember maze tasks reflect decreased cognitive ability in animals. Anxiety-like behaviors, negative judgment bias in ambiguous cue tests and impaired cognitive control are also common [31-33].

4. NLRP3 and depression

4.1. NLRP3 affects depressive behaviors

Studies have shown that knockout, knockdown and overexpression of NLRP3 significantly affect the occurrence and development of depression. In the chronic unpredictable mild stress model, after 4 weeks of stress exposure, both NLRP3 knockout and wild-type mice showed lower body weight gain compared with the control group. However, typical depression-like behaviors, such as reduced sucrose preference and increased immobility time, were observed in wild-type mice, while NLRP3 knockout mice did not show these behavioral changes [34]. In addition, in a mouse model of postpartum depression, reducing the expression level of NLRP3 in the hippocampus alleviated depression-like behaviors. In contrast, overexpression of NLRP3 in the hippocampal dentate gyrus induced depression-like behaviors in non-stressed female mice [35]. Further studies showed that CUMS exposure significantly increased the expression of NLRP3 in the dorsal raphe nucleus of male C57BL/6J mice, especially in neurons. Specific knockdown of NLRP3 in the dorsal raphe nucleus or treatment with NLRP3 inhibitors produced significant antidepressant effects [36]. In addition, fluoxetine partially inhibits the activated NLRP3 inflammasome in the peripheral and central nervous systems, thereby exerting its therapeutic effect [37]. NLRP3 plays a key role in the progression of depression, and its knockout or knockdown produces significant antidepressant effects, while its overexpression may induce depression-like behaviors, indicating that NLRP3 is a very promising therapeutic target for depression.

4.2. Abnormalities and dysfunction in depression

The NLRP3 inflammasome is activated in blood cells of patients with major depressive disorder, accompanied by elevated serum IL-1β and IL-18 levels [38]. As a key component of the microbiota-gut-brain axis, gut microbiota dysbiosis is considered a contributing factor to major depressive disorder. Transplanting fecal microbiota from postpartum depression mice into antibiotic-treated mice induced depression and anxiety-like behaviors as well as hippocampal neuropathological changes in recipient mice. In contrast, transplanting fecal microbiota from healthy mice into postpartum depression mice alleviated these depression and anxiety-like behaviors [36]. Long-term high-fat diet induced significant depression-like behaviors in Zucker diabetic fatty rats and increased the expression of P2X7R, NLRP3 and IL-1β in the prefrontal cortex [39]. Studies explored the effects of small-molecule NLRP3 inhibitors on inflammatory activity and depression-like behaviors induced by chronic unpredictable mild stress in mice. The results showed that CUMS led to reduced sucrose preference and increased immobility time, while treatment with the NLRP3 inhibitor MCC950 reversed these effects. In addition, inhibition of NLRP3 reduced the number of microglia, decreased the expression of NLRP3 and IL-1β in the prefrontal cortex, and inactivated the NLRP3/caspase-1/IL-1β signaling pathway [40].

DOI: 10.54254/2753-8818/2026.33680

4.3. Effects of antidepressants

Traditional Chinese medicine treatment can reduce the assembly and activation of the NLRP3 inflammasome by affecting oxidative stress response, initiating signaling pathways, activating cell membrane receptors and other mechanisms, thereby inhibiting neuroimmunological inflammation, reducing neurotoxicity related to inflammatory cytokines, and further alleviating depression [41]. For example, in a study on the antidepressant effect of icariin, treatment with different doses of ICA inhibited the production of serum pro-inflammatory cytokines and alleviated CUMS-induced depression-like behaviors, as evidenced by a significant increase in sucrose preference. In addition, ICA alleviated inflammatory damage to hippocampal neurons, downregulated the expression level of related proteins, reduced the positive signal intensity of NLRP3, and inhibited the activity of the NLRP3 inflammasome [42]. Studies have shown that natural compounds also have significant therapeutic effects. Curcumin, derived from turmeric, is a natural polyphenol. Curcumin has anti-inflammatory and antioxidant effects, can effectively inhibit the NLRP3 inflammasome, and exerts a certain antidepressant effect [12].

Fluoxetine, a commonly used clinical antidepressant, may exert an antidepressant effect by inhibiting the inflammasome signaling pathway, resulting in decreased levels of inflammatory factors in the brain [43]. Ketamine can also inhibit the NLRP3 inflammasome, leading to reduced assembly and expression of the NLRP3-ASC-CASP1 complex and decreased IL-1β levels in cerebrospinal fluid and serum, which contributes to its antidepressant effect [44].

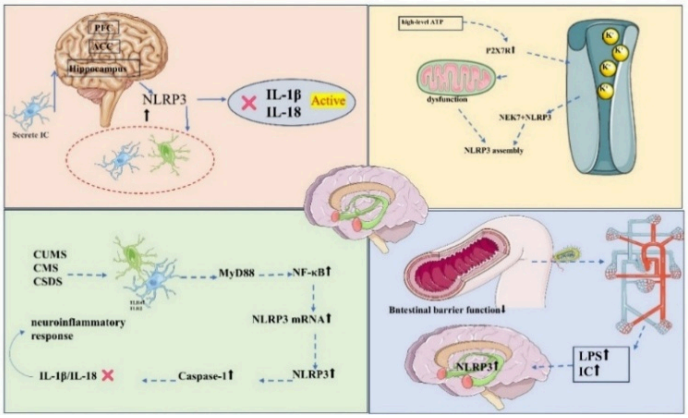

Figure 1. The role of NLRP3 in depression

5. Pathogenesis of NLRP3 in depression

5.1. Glial cells and inflammatory pathways

Maintaining central nervous system homeostasis is the main function of microglia [12, 45]. It is also the first cellular population discovered to respond to the disruption of central nervous system homeostasis, and plays a role by secreting inflammatory cytokines and chemokines when the central nervous system is injured [46]. In Figure 1, the NLRP3 inflammasome converts pro-IL-1β and pro-IL-18 into their active forms. These cytokines activate microglia and astrocytes, maintain a neuroinflammatory state, damage neurons and glial cells, impair neurotransmitter metabolism and synaptic plasticity, thereby promoting the occurrence of depression [12]. A large body of evidence indicates that neuroinflammation caused by excessive microglial activation in emotion-related brain regions (such as the anterior cingulate cortex and hippocampus) promotes the development of

DOI: 10.54254/2753-8818/2026.33680

anxiety and depression [45]. Other studies have shown that activation of the NLRP3 inflammasome occurs in neurons, astrocytes and microglia, promotes the release of neurotoxic astrocytes and triggers neurotoxic responses, which are of great significance for the pathogenesis and progression of depression [47]. Studies have also shown that mice exhibiting significant anxiety and depression-like behaviors show obvious microglial activation in the prefrontal cortex after ovarian exposure, accompanied by increased expression of NLRP3 and IL-1β [45, 48].

5.2. ATP dysregulation

High concentrations of ATP can activate the P2X7 receptor, especially under neuroinflammatory conditions. After binding to P2X7R, ATP opens cation channels, leading to potassium ion efflux. This K^+ efflux is a prerequisite for the binding of NIMA-related kinase 7 to NLRP3, a key step in the assembly of the NLRP3 inflammasome. In addition, activation of P2X7R may further promote the activation of the NLRP3 inflammasome by inducing mitochondrial dysfunction and reactive oxygen species production [49]. Prolonged exposure to high concentrations of ATP can induce depression-like behaviors in animals. Existing studies have shown that the P2X7R/NLRP3/IL-1β cascade plays an important role in mediating depression-like behaviors [8]. Therefore, ATP acts as a key regulatory factor in the neuroinflammatory mechanism by activating the P2X7R-NLRP3-IL-1β signaling axis, and targeting this pathway may represent a novel intervention strategy for depression.

5.3. Gut microbiota

At present, relevant studies indicate that the main source of inflammation in patients with major depressive disorder is the gut microbiota. Its interaction with the intestinal mucosa regulates pro-inflammatory cytokines or chemokines including IL-8, IL-10 and TGF-β [38]. Changes in the gut microbiota may also further activate the peripheral immune system by stimulating immune cells to release pro-inflammatory cytokines. In addition, studies have found that metabolites of the gut microbiota damage the function of the intestinal barrier. Increased intestinal permeability allows bacterial components and inflammatory cytokines to enter the circulation, elevating the levels of lipopolysaccharide and inflammatory cytokines entering the blood circulation, thereby activating the NLRP3 inflammasome in the hippocampus, leading to neuroinflammation and depression-like behaviors [50].

6. Role of NLRP3 in stress susceptibility and stress resistance

There are differences in the activation level of the NLRP3 inflammasome in hippocampal microglia between stress-susceptible mice and stress-resistant mice. Relevant studies have shown that pattern recognition receptor-related signaling pathways are significantly enriched in stress-susceptible mice, and NLRP3 activation-related pathways mediating neuroinflammation are significantly enhanced, indicating that microglia in stress-susceptible mice have enhanced responsiveness to pro-inflammatory stimuli. Therefore, activation of the NLRP3 inflammasome plays an important role in stress-susceptible mice [51]. Increased activation of the NLRP3 inflammasome in the hippocampus is closely related to behavioral changes in stress-susceptible mice. MCC950 is an NLRP3 inflammasome inhibitor. Researchers used MCC950 to analyze the effect of NLRP3 on stress susceptibility in mice. The results showed that the MCC950-treated group significantly reversed depression-like behaviors in mice. Specifically, MCC950 treatment improved the grooming score of stressed mice, alleviated abnormal behaviors in the forced swimming test, partially improved

DOI: 10.54254/2753-8818/2026.33680

abnormal behaviors in the tail suspension test, and alleviated anxiety-like behaviors in stressed mice. Activation of the NLRP3 inflammasome leads to massive maturation and release of functional IL-1β. Existing experiments have shown that compared with the control group, the levels of pro-IL-1β and mature IL-1β are increased in stress-susceptible mice, and MCC950 treatment significantly reduces stress-induced elevation of IL-1β [40, 52]. NU9056 also inhibits the activity of the NLRP3 inflammasome to a certain extent, reduces LPS-induced microglial apoptosis, mean fluorescence intensity of reactive oxygen species, and the release of IL-1β and IL-18, thereby effectively alleviating LPS-induced cognitive and emotional disorders [52]. Therefore, inhibiting the activation of the NLRP3 inflammasome can reduce stress susceptibility and stress resistance in experimental animals, and decrease depression and anxiety-like behaviors.

7. Comorbid relationships

7.1. Diabetes mellitus

The NLRP3 inflammasome is highly expressed in innate immune cells and non-immune cells. A large number of studies have shown that the NLRP3 inflammasome plays a key role in the pathogenesis of chronic inflammatory diseases and metabolic diseases [53]. The NLRP3 inflammasome is an important pathogenic mechanism for the comorbidity of diabetes mellitus with other diseases [8]. As an endogenous sensor of stress and metabolic disorders, the NLRP3 inflammasome may be located at the intersection of metabolism and inflammation, as well as the crossroad of diabetes mellitus and depression [54]. Interleukin-1β is one of the most important inflammatory mediators in the development of diabetes mellitus and depression. IL-1β may damage pancreatic β cells by inducing endoplasmic reticulum and mitochondrial stress, leading to insufficient insulin secretion. It can also promote serine phosphorylation of IRS-1, leading to insulin resistance in the liver and adipose tissue, and participate in the pathogenesis of type 1 and type 2 diabetes mellitus [54]. In addition, cytokine-mediated inflammatory responses induced by excessive activation of innate immunity may be the biological source of diabetes comorbidity [8]. Local inflammatory responses in peripheral organs may trigger neuroinflammation, which in turn leads to depression-like behaviors. Activation of the NLRP3 inflammasome is involved in peripheral inflammation-induced neuroinflammation. Hyperglycemia increases the production of reactive oxygen species in hippocampal neurons, thereby activating the NLRP3 inflammasome [8]. NLRP3 deficiency alleviates depression-like behaviors in diabetic mice (modeled by streptozotocin). Gastrodin inhibits the activation of the NLRP3 inflammasome and alleviates depression-like behaviors [8]. In a mouse model of chronic unpredictable mild stress, the antidiabetic drug glibenclamide improved depression-like behaviors associated with insulin resistance, which may be due to the inhibitory effect of this hypoglycemic drug on the NLRP3 inflammasome [54].

7.2. Cardiovascular diseases

The prevalence of depression is significantly higher in patients with cardiovascular diseases, while depression increases the risk of cardiovascular diseases and is a key risk factor for disease progression. Epidemiological studies have shown that the risk of cardiovascular diseases in people with depression can be three times that of the general population [55]. Oxidative stress, mitochondrial dysfunction and immune activation may also trigger common signaling pathways leading to NLRP3 inflammasome activation, thereby exacerbating endothelial dysfunction [53]. The NLRP3 inflammasome is a key inflammatory signaling platform in the innate immune system,

DOI: 10.54254/2753-8818/2026.33680

playing a crucial role in cardiovascular diseases and depression, mediating the maturation and release of IL-1β and IL-18, and inducing pyroptosis. In addition, studies have found that the NLRP3 inflammasome is continuously activated in patients with depression and cardiovascular diseases, and this activation is related to disease severity [55]. NLRP3-dependent pathways and endothelial dysfunction may be the common mechanisms of comorbidity between cardiovascular diseases and depression. The NLRP3 inflammasome plays a key role in the progression of atherosclerosis, coronary artery disease and myocardial ischemia-reperfusion injury [53]. Fluoxetine, one of the most widely used antidepressants, exerts neuroprotective effects, mainly antioxidant and anti-inflammatory properties. It also shows cardioprotective effects, improves blood lipid profile, and significantly reduces the levels of myocardial enzymes CK-MB, troponin and MEF2 [56].

7.3. Alzheimer's disease

Alzheimer's disease is a chronic neurodegenerative disease characterized by cognitive dysfunction and memory loss. Depression is a risk factor for this disease, and there is a comorbid relationship between them [56]. This disease is closely related to major depressive disorder and schizophrenia [57]. Fluoxetine, one of the most widely used antidepressants, mainly exerts neuroprotective effects through antioxidant and anti-inflammatory effects. Experimental studies have shown that fluoxetine treatment shows positive responses to social isolation and Alzheimer's disease. Fluoxetine improves animal behaviors, increases the levels of monoamines and brain-derived neurotrophic factor in the brain, and enhances antioxidant defense mechanisms including superoxide dismutase [57]. It also increases the expression and protein levels of Nrf2/HO-1, and reduces the levels of amyloid-β, tau protein, malondialdehyde and TNF-α. It significantly inhibits acetylcholinesterase activity, while reducing the expression of related proteins such as TLR4, NLRP3 and caspase-1. Neurological diseases such as depression and dementia share common pathological mechanisms involving upregulated oxidative stress and inflammatory signaling [56].

8. Conclusion

The NLRP3 inflammasome plays a core role in the pathogenesis of depression and its comorbidity with a variety of chronic diseases. Animal and clinical studies have shown abnormal activation of NLRP3 in stressed animals and depressed patients, and its knockout or inhibition can significantly alleviate depression-like behaviors. NLRP3 mediates neuroinflammation through multiple mechanisms, including microglial activation, induction of pyroptosis, regulation of the TLR4/NF-κB signaling pathway, participation in the ATP-P2X7R axis, and regulation of the gut microbiota-gut-brain axis. It is also a key molecular bridge connecting depression with comorbidities such as metabolic diseases and neurodegenerative diseases. Traditional antidepressants, natural compounds and active ingredients of traditional Chinese medicine have been proven to exert certain antidepressant effects by inhibiting the activity of the NLRP3 inflammasome, highlighting this pathway as an important target for antidepressant drug development.

References

[1] Rong, J., et al., Global, regional and national burden of depressive disorders and attributable risk factors, from 1990 to 2021: results from the 2021 Global Burden of Disease study. Br J Psychiatry, 2025. 227(4): p. 688-697.
[2] Tian, W., et al., Burden of depressive and anxiety disorders in China and its provinces, 1990-2021: findings from the Global Burden of Disease Study 2021. Br J Psychiatry, 2026. 228(1): p. 18-28.

DOI: 10.54254/2753-8818/2026.33680

[3] Riera-Serra, P., et al., Clinical predictors of suicidal ideation, suicide attempts and suicide death in depressive disorder: a systematic review and meta-analysis. Eur Arch Psychiatry Clin Neurosci, 2024. 274(7): p. 1543-1563.
[4] Marwaha, S., et al., Novel and emerging treatments for major depression. Lancet, 2023. 401(10371): p. 141-153.
[5] Wang, H., et al., Microglia in depression: an overview of microglia in the pathogenesis and treatment of depression. J Neuroinflammation, 2022. 19(1): p. 132.
[6] Huang, Y.Y., et al., Depression in Alzheimer's Disease: Epidemiology, Mechanisms, and Treatment. Biol Psychiatry, 2024. 95(11): p. 992-1005.
[7] Kandola, A., et al., Physical activity and depression: Towards understanding the antidepressant mechanisms of physical activity. Neurosci Biobehav Rev, 2019. 107: p. 525-539.
[8] Xia, C.Y., et al., The NLRP3 inflammasome in depression: Potential mechanisms and therapies. Pharmacol Res, 2023. 187: p. 106625.
[9] Kaufmann, F.N., et al., NLRP3 inflammasome-driven pathways in depression: Clinical and preclinical findings. Brain Behav Immun, 2017. 64: p. 367-383.
[10] Wang, D., et al., P2X7 receptor mediates NLRP3 inflammasome activation in depression and diabetes. Cell Biosci, 2020. 10: p. 28.
[11] Roy, S., et al., NLRP3 inflammasome in depression: A review. Int Immunopharmacol, 2023. 117: p. 109916.
[12] Ding, L., et al., The NLRP3 inflammasome in depression: A narrative review from neuroinflammation to novel therapeutic approaches. Brain Res Bull, 2025. 232: p. 111592.
[13] Ghaffaripour Jahromi, G., S. Razi, and N. Rezaei, NLRP3 inflammatory pathway. Can we unlock depression? Brain Res, 2024. 1822: p. 148644.
[14] Xu, Z., et al., NLRP inflammasomes in health and disease. Mol Biomed, 2024. 5(1): p. 14.
[15] Mokhtari, T. and K. Uludag, Role of NLRP3 Inflammasome in Post-Spinal-Cord-Injury Anxiety and Depression: Molecular Mechanisms and Therapeutic Implications. ACS Chem Neurosci, 2024. 15(1): p. 56-70.
[16] Taene, A., et al., The Association of Major Depressive Disorder with Activation of NLRP3 Inflammasome, Lipid Peroxidation, and Total Antioxidant Capacity. J Mol Neurosci, 2020. 70(1): p. 65-70.
[17] Tian, H., et al., Inflammatory cytokines derived from peripheral blood contribute to the modified electroconvulsive therapy-induced cognitive deficits in major depressive disorder. Eur Arch Psychiatry Clin Neurosci, 2021. 271(3): p. 475-485.
[18] Ye, T., et al., Mechanisms of NLRP3 inflammasome activation and the development of peptide inhibitors. Cytokine Growth Factor Rev, 2023. 74: p. 1-13.
[19] Chen, H., et al., Involvement of the SIRT1-NLRP3 pathway in the inflammatory response. Cell Commun Signal, 2023. 21(1): p. 185.
[20] Ma, J., et al., Mechanisms of acupuncture in treating depression: a review. Chin Med, 2025. 20(1): p. 29.
[21] Dion-Albert, L., et al., Vascular and blood-brain barrier-related changes underlie stress responses and resilience in female mice and depression in human tissue. Nat Commun, 2022. 13(1): p. 164.
[22] Chi, D., et al., Astrocytic pleiotrophin deficiency in the prefrontal cortex contributes to stress-induced depressive-like responses in male mice. Nat Commun, 2025. 16(1): p. 2528.
[23] Li, B., et al., Amygdala volume abnormalities and cognitive impairment in major depressive disorder and bipolar disorder II. BMC Psychiatry, 2025. 25(1): p. 839.
[24] Jacob, Y., et al., Altered hippocampus and amygdala subregion connectome hierarchy in major depressive disorder. Transl Psychiatry, 2022. 12(1): p. 209.
[25] Jones, N.P., H.W. Chase, and J.C. Fournier, Brain mechanisms of anxiety's effects on cognitive control in major depressive disorder. Psychol Med, 2016. 46(11): p. 2397-409.
[26] Mir, F.A., S.K. Jha, and C.J. Nehs, Noradrenergic dysregulation in the locus coeruleus: Implications for neuropsychiatric disease pathophysiology- A systematic review. Neurosci Biobehav Rev, 2025. 179: p. 106442.
[27] Reyes, B.A.S., The Locus Coeruleus: Anatomy, Physiology, and Stress-Related Neuropsychiatric Disorders. Eur J Neurosci, 2025. 61(7): p. e70111.
[28] Hu, X., et al., Gray matter volume and corresponding covariance connectivity are biomarkers for major depressive disorder. Brain Res, 2024. 1837: p. 148986.
[29] Hou, X.F., et al., Abnormal regional spontaneous brain activity in major depressive disorder with obesity comorbidity: A resting-state functional magnetic resonance imaging study. World J Psychiatry, 2026. 16(1): p. 113064.
[30] Fang, K., et al., Disrupted intersubject variability architecture in structural and functional brain connectomes in major depressive disorder. Psychol Med, 2025. 55: p. e56.
[31] Yao, C., et al., Increased individual variability in functional connectivity of the default mode network and its genetic correlates in major depressive disorder. Sci Rep, 2025. 15(1): p. 8853.

DOI: 10.54254/2753-8818/2026.33680

[32] Sahin, Z., Assessment of commonly used tests in experimental depression studies according to behavioral patterns of rodents. Med Rev (2021), 2023. 3(6): p. 526-531.
[33] Maitra, M., et al., Cell type specific transcriptomic differences in depression show similar patterns between males and females but implicate distinct cell types and genes. Nat Commun, 2023. 14(1): p. 2912.
[34] Su, W.J., et al., NLRP3 gene knockout blocks NF-κB and MAPK signaling pathway in CUMS-induced depression mouse model. Behav Brain Res, 2017. 322(Pt A): p. 1-8.
[35] Xu, Q., et al., Gut microbiota dysbiosis contributes to depression-like behaviors via hippocampal NLRP3-mediated neuroinflammation in a postpartum depression mouse model. Brain Behav Immun, 2024. 119: p. 220-235.
[36] Cai, J., et al., NLRP3 in the dorsal raphe nucleus manipulates the depressive-like behaviors. Brain Res Bull, 2025. 227: p. 111405.
[37] Du, R.H., et al., Fluoxetine Inhibits NLRP3 Inflammasome Activation: Implication in Depression. Int J Neuropsychopharmacol, 2016. 19(9).
[38] Li, S., et al., Transcutaneous vagus nerve stimulation modulates depression-like phenotype induced by high-fat diet via P2X7R/NLRP3/IL-1β in the prefrontal cortex. CNS Neurosci Ther, 2024. 30(5): p. e14755.
[39] Sah, A. and N. Singewald, The (neuro)inflammatory system in anxiety disorders and PTSD: Potential treatment targets. Pharmacol Ther, 2025. 269: p. 108825.
[40] Liu, Q., et al., Inhibition of Microglial NLRP3 with MCC950 Attenuates Microglial Morphology and NLRP3/Caspase-1/IL-1β Signaling In Stress-induced Mice. J Neuroimmune Pharmacol, 2022. 17(3-4): p. 503-514.
[41] Xu, X., et al., Selective NLRP3 inflammasome inhibitor reduces neuroinflammation and improves long-term neurological outcomes in a murine model of traumatic brain injury. Neurobiol Dis, 2018. 117: p. 15-27.
[42] Matsuoka, T., et al., Inhibition of NLRP3 inflammasome by MCC950 improves the metabolic outcome of islet transplantation by suppressing IL-1β and islet cellular death. Sci Rep, 2020. 10(1): p. 17920.
[43] Han, M., et al., Modulation of gut microbiota by Gardeniae Fructus oil exerts TLR4/NF-κB/NLRP3 pathway-mediated antidepressant effects based on transcriptomics and fecal transplantation. Front Pharmacol, 2025. 16: p. 1635897.
[44] Lyu, D., et al., Ketamine induces rapid antidepressant effects via the autophagy-NLRP3 inflammasome pathway. Psychopharmacology (Berl), 2022. 239(10): p. 3201-3212.
[45] Gao, Z., et al., TET2 deficiency promotes anxiety and depression-like behaviors by activating NLRP3/IL-1β pathway in microglia of allergic rhinitis mice. Mol Med, 2023. 29(1): p. 160.
[46] Fang, Y., et al., The role and mechanism of NLRP3 inflammasome-mediated astrocyte activation in dehydrocorydaline against CUMS-induced depression. Front Pharmacol, 2022. 13: p. 1008249.
[47] Wang, Y.P. and C. Gorenstein, Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. Braz J Psychiatry, 2013. 35(4): p. 416-31.
[48] Li, S., Fang, Y., Zhang, Y., et al., Microglial NLRP3 inflammasome activates neurotoxic astrocytes in depression-like mice. Cell Rep, 2022. 41(4): p. 111532.
[49] Xia, J., et al., Inflammation and Late-Life Depression: Unraveling the Complex Relationship and Potential Therapeutic Strategies. Front Biosci (Landmark Ed), 2023. 28(12): p. 356.
[50] Yao, H., et al., Gut microbiota regulates chronic ethanol exposure-induced depressive-like behavior through hippocampal NLRP3-mediated neuroinflammation. Mol Psychiatry, 2023. 28(2): p. 919-930.
[51] Rao, J., et al., Fecal microbiota transplantation ameliorates stress-induced depression-like behaviors associated with the inhibition of glial and NLRP3 inflammasome in rat brain. J Psychiatr Res, 2021. 137: p. 147-157.
[52] Chen, L., et al., NU9056, a KAT 5 Inhibitor, Treatment Alleviates Brain Dysfunction by Inhibiting NLRP3 Inflammasome Activation, Affecting Gut Microbiota, and Derived Metabolites in LPS-Treated Mice. Front Nutr, 2021. 8: p. 701760.
[53] Baysak, E., et al., The Possible Role of NLRP3 Inflammasome in Depression and Myocardial Infarction Comorbidity. J Pers Med, 2023. 13(9).
[54] Su, W.J., et al., Microglial NLRP3 inflammasome activation mediates diabetes-induced depression-like behavior via triggering neuroinflammation. Prog Neuropsychopharmacol Biol Psychiatry, 2023. 126: p. 110796.
[55] Chen, C., et al., NLRP3 Inflammasome: A New Target for the Treatment of CVD and Depression Comorbidity. Mediators Inflamm, 2025. 2025: p. 4330574.
[56] Abu-Elfotuh, K., et al., 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. Int Immunopharmacol, 2022. 104: p. 108488.
[57] Xia, N., et al., Neuroprotective effect of emodin on Aβ(25-35)-induced cytotoxicity in PC12 cells involves Nrf2/GPX4 and TLR4/p-NF-κB/NLRP3 pathways. Brain Res, 2024. 1841: p. 149019.