NEUROPSYCHIATRICSCIENCES
AND MOLECULAR BIOLOGY

Journalnsmb.com Vol.02,N0.04,July 2025

NSMB
www.journalnsmb.com

| Original study

Research progress of Cross-talk between Microglia and Astrocyte in the Comorbidity of Neuropathic Pain and Depression

Xiaolina Zhang[1 2],Haoran Xing[2], Yingying Zhang[2],
Mier Li[2], Luanmei Ding[2], Haiqiang Zhao[2], Tianhao Bao[2]*

1.Department of Pain Management, The First Affiliated Hospital of Kunming Medical University, Kunming 650032,
2. Department of Science and Education, Kunming Medical University Affiliated Mental Health Center, Yunnan Province Mental Hospital, Kunming, 650224,
*Corrseponding author:Tianhao Bao, doctor@kmmu.edu.cn

Abstract

Neuropathic pain (NP) is a prevalent, chronic, and refractory condition that frequently co-occurs with depression and other negative affective states. The reciprocal relationship between NP and depression contributes to a self-perpetuating vicious cycle. Although the mechanisms underlying this comorbidity are complex and not yet fully elucidated, recent evidence highlights the pivotal roles of glial cells—particularly microglia and astrocytes—and their bidirectional interactions in the onset and progression of NP and depression comorbidity. This review systematically summarizes recent advances regarding microglia-astrocyte interactions in NP and depression comorbidity, aiming to provide a theoretical foundation for a deeper understanding of pathogenesis and the development of novel therapeutic strategies.

Keywords: Neuropathic pain; Depression; Comorbidity; Cross-talk; Glial cell

Neuropathic pain (NP) is a form of chronic pain characterized by spontaneous pain, hyperalgesia, or allodynia.This clinically refractory condition not only causes unbearable physical discomfort but also results in severe physiological and psychological impairments, potentially triggering psychiatric symptoms such as depression [1,2]. Substantial evidence indicates a high rate of comorbidity between NP and depressive disorder (DD). Negative mood states related to depression and pain perception interact to form a vicious cycle, which contributes significantly to the persistence of NP. The comorbidity of NP and DD significantly complicates clinical management and is associated with a poorer prognosis compared to either condition alone [3].The management of patients with neuropathic pain and depression comorbidity (NPDC) is considerably more complex than treatment for either condition in isolation [4]. Currently, clinical management of NPDC primarily involves the combined use of anticonvulsants and antidepressants. However, patients with comorbid NPDC often demonstrate increased resistance to pharmacotherapy and higher rates of treatment discontinuation due to adverse drug effects.To date, there is a lack of safe and effective alternative pharmacological interventions.Therefore, elucidating the mechanisms underlying the comorbidity of NP and DD and identifying novel therapeutic targets are of paramount importance.

Emerging evidence indicates that glial cell-mediated pathophysiological processes in the central nervous system (CNS)-particularly those involving microglia and astrocytes, such as neuroinflammation, neurotransmitter imbalance, and disturbances in neural network plasticity-play critical roles in the comorbidity of neuropathic pain (NP) and depressive disorder (DD), although the precise underlying mechanisms remain unclear. This review focuses on the activation of astrocytes and microglia in both the spinal cord and supraspinal regions, as well as their bidirectional interactions. By systematically summarizing relevant signaling pathways, cellular polarization mechanisms, and therapeutic interventions, we aim to elucidate the specific roles of these factors in NP-DD comorbidity. This approach is intended to provide novel insights and potential strategies for clinical management and future basic research

targeting NP and DD comorbidity.

1.Clinical and Fundamental Characteristics of the Comorbidity Between Neuropathic Pain and Depression

Neuropathic pain (NP) is a complex and refractory pain syndrome resulting from lesions or diseases of the nervous system. It is frequently encountered in clinical practice and severely compromises patients' quality of life[5]. The typical clinical manifestations of NP include hyperalgesia (increased pain response to noxious stimuli), allodynia (pain induced by normally non-noxious stimuli), and spontaneous pain (persistent pain in the absence of external stimuli). Patients frequently report sensations such as stabbing, electric shock-like, pricking, or persistent burning pain [6]. NP is notable for its refractory nature, with symptoms that may persist long after the initial noxious stimulus has been removed and, in some cases, may last for a lifetime. Individuals with NP commonly experience comorbidities such as memory impairment, attentional deficits, and sleep disturbances, and are at increased risk for psychiatric disorders, including anxiety, depression, and even suicidal ideation.

Depressive disorder (DD) is a psychiatric condition characterized by persistent low mood and loss of interest, and has become a major public health issue worldwide.DD is highly heterogeneous, involving not only affective symptoms but also significant impairments in cognitive, somatic, and social functioning, and it is recognized as a leading cause of long-term disability.According to the World Health Organization (WHO), by 2030, depression is projected to surpass cancers and cardiovascular or metabolic diseases to become the leading cause of global disease burden[7]. Depression represents the most common psychiatric comorbidity among patients with NP, with a prevalence of approximately 60%, —about five times higher than in the general population[8]. Studies have shown that 42% of patients with NP exhibit depressive symptoms, while about 37% of individuals with depression report pain symptoms. Depression lowers pain thresholds and enhances pain sensitivity, creating a vicious cycle in which negative emotions and pain mutually reinforce each other.This reciprocal relationship substantially increases the risk of comorbidity, complicates clinical management, and results in a poorer prognosis compared to patients with either NP or DD alone[3].At present, there is a lack of safe and effective alternative pharmacological interventions to address this clinical challenge.

Although the pathophysiological mechanisms underlying NP and DD have not been fully elucidated, extensive evidence indicates that immune dysregulation and glial cell-mediated neuroinflammation are key pathogenic factors. These processes contribute not only to the comorbidity of NP and DD but also to treatment resistance, thereby influencing disease onset, progression, and prognosis.Numerous studies have confirmed that aberrant activation of glial cells induces neuroinflammation, leading to both peripheral and central sensitization and resulting in persistent neuropathic pain[9–11]. Moreover, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and neurotransmitter imbalance have been identified as critical molecular mechanisms driving depression within the context of comorbidity[12].Following nerve injury, both microglia and astrocytes become activated, releasing a variety of endogenous algesic factors, including pro-inflammatory cytokines, matrix metalloproteinases (MMPs), and chemokines. These mediators induce inflammatory responses that play pivotal roles in the initiation of pain and acute negative affective states[13,14]. With persistent glial activation, the continued release of bioactive factors further amplifies excitatory synaptic transmission (facilitation) while diminishing inhibitory synaptic activity (disinhibition), resulting in central sensitization. This process also involves modulation of neuronal membrane ion channels-such as sodium, calcium, and potassium channels-and activation of intracellular pain signaling pathways, ultimately leading to sustained neuronal hyperexcitability that maintains both neuropathic pain[14–16] and depressive states[17].

2.The Role of Microglia in the Comorbidity of Neuropathic Pain and Depression

2.1The Role of Microglial Activation in

Neuropathic Pain

Microglia are the principal immune surveillance cells of the central nervous system (CNS) and serve as its "sentinels," responding rapidly to nervous system injury. Upon activation, microglia secrete a variety of bioactive molecules that enhance the sensitization of interneurons. Aberrant activation of microglia in both the spinal cord and brain is critically involved in the initiation and maintenance of neuropathic pain[18].Studies have demonstrated that, following nerve injury, spinal microglia are the first to become activated, subsequently releasing pro-inflammatory cytokines (e.g., IL-35, IL-1β), excitatory molecules such as colony-stimulating factor 1, (CSF1), and ion channel modulators (such as transient receptor potential vanilloid 4, TRPV4). These mediators act directly on pain-transmitting neurons and surrounding cells, thereby triggering acute pain responses[19].Sustained and aberrant microglial activation exacerbates the inflammatory response and increases neuronal excitability, ultimately resulting in central sensitization and the persistence of chronic NP [20].Additionally, peripheral nerve injury induce spinal microglia to increase IL-1β secretion and suppress IL-35 release[21]. These cytokines interact with IL-1 receptors (IL-1Rs) expressed by surrounding astrocytes and dorsal horn neurons, thereby facilitating the development of pain.Activated microglia upregulate CSF1 expression, and CSF1 binding to its own receptor (CSF1R) promotes microglial proliferation, further aggravating neuroinflammation and pain induction[22]. Moreover, TRPV4 expression isupregulated in activated microglia, contributing to the hyperexcitability of spinal dorsal horn neurons and the manifestation of neuropathic pain-like behaviors.Changes in the expression of P2X7R on activated microglia have also been shown to induce NP behaviors, and P2X7R antagonists can alleviate pain in animal models[23,24].Recent animal studies indicate that microglial pyroptosis regulates NLRP3 inflammasome activation, which acts as a key driver in the progression of neuropathic pain. Conversely, inhibition of microglial pyroptosis can relieve mechanical allodynia[25].

2.2 The Role of Microglial Activation in Depression

Numerous studies indicate that microglial activation in various brain regions, through the release of pro-inflammatory cytokines, induce excitotoxicity, excessive or aberrant synaptic pruning, demyelination, and neuronal death, all of which contribute to a range of depression-related behavioral abnormalities.Activation of microglia in the prefrontal cortex and hippocampus elevates pro-inflammatory cytokine levels, disrupts the homeostasis of the hypothalamic-pituitary-adrenal (HPA) axis, and promotes the onset and progression of depression[26].In the anterior cingulate cortex (ACC) of lipopolysaccharide (LPS)-treated mice, microglial activation leads to abnormal phagocytic activity, resulting in excessive engulfment of neuronal dendritic spines and subsequent neuronal damage, thereby facilitating the development of adolescent depression[27,28]. Non-pharmacological interventions, such as electroacupuncture, exercise, and transcranial magnetic stimulation, have been shown to suppress hippocampal microglial activation and associated inflammation, thus exerting antidepressant effects[29].In summary, dysfunction of activated microglia exacerbates neuroinflammation and, through multiple pathways, promotes the onset and progression of depression.

2.3 The Role of Microglia in the Comorbidity of Neuropathic Pain and Depression

Neuroinflammation is recognized as a fundamental mechanism underlying the comorbidity of NP and DD. Microglia play a pivotal immunomodulatory role in maintaining CNS homeostasis. Upon activation, microglia release multiple cytokines, exacerbate neuroinflammation, and induce abnormalities in pain signaling, synaptic plasticity impairment, and dysregulate neurotransmitter systems, ultimately resulting in both neuropathic pain and depression.Clinical studies have confirmed that glial activation and a surge of pro-inflammatory cytokine release in the brains of NP patients can trigger neuroinflammatory responses and promote depressive behaviors[12].In chronic constriction injury (CCI) models, activation of NLRP3 inflammasomes in hippocampal neurons has been closely associated with the comorbidity of NP, anxiety, and depression; inhibition of

NLRP3 can effectively alleviate chronic pain and negative emotional states[23].Accumulating evidence indicates that neuroimmune interactions mediate the causal link between chronic pain and depression. The expression of inflammatory factors such as interleukin-1β (IL-1β), IL-6, and TNF-α is upregulated in brain regions associated with pain and emotional regulation. Notably, TNF-α can activate the HPA axis, leading to enhanced pro-inflammatory cytokine release and the establishment of a pathological feedback loop[24]. Furthermore, animal experiments using the microglial inhibitor minocycline have demonstrated that, in the spared nerve ligation (SNL) model, there is a reduction in M1-type microglia and an increase in M2-type microglia in the prefrontal cortex (PFC), accompanied by decreased IL-1β and increased IL-10 expression, resulting in reduced pain sensitivity and amelioration of depressive behaviors[26].

3.The Role of Astrocytes in the Mechanisms of Comorbidity

3.1The Role of Reactive Astrocytes in Neuropathic Pain

Astrocytes are the most abundant cells in the central nervous system (CNS), and astrocyte-mediated neuroinflammation is considered a key mechanism in the maintenance of chronic pain.Under physiological conditions, astrocytes provide metabolic support to neurons, maintain the extracellular balance of potassium ions and glutamate, and play vital roles in synaptic development, maturation, clearance, and function[30]. Upon external stimulation, astrocytes become reactive and release pro-inflammatory mediators. This reactive transformation results in the activation of various intracellular protein kinases, alters the expression of receptors and channel proteins, disrupts neurotransmitter homeostasis, and causes synaptic dysregulation, thereby inducing and sustaining neuropathic pain[20].Following nerve injury, reactive astrocytes upregulate the expression of complement component C3, leading to allodynia and abnormal mechanical pain behaviors[31].In partial sciatic nerve ligation (PNL) rat models, spinal dorsal horn astrocytes are activated and release pro-inflammatory factors, while downregulating glutamate transporters GLAST and GLT-1, thereby reducing glutamate uptake and inducing pain behaviors[32].Studies have demonstrated that spinal astrocytes contribute to neuropathic pain by upregulating the expression of chemokines CCL2 and CXCL1, which enhance excitatory synaptic transmission and increase the frequency of excitatory postsynaptic currents in neurons[33].

3.2 The Role of Reactive Astrocytes in Depression

The proliferation of reactive astrocytes is closely associated with the release of multiple inflammatory mediators, regulation of neuronal survival, synaptic plasticity, and neurotransmitter levels, which can induce excitotoxicity and neuronal injury, thereby contributing to the development of depression.Activated astrocytes promote the release of inflammatory cytokines, disrupt regional energy metabolism in the brain, and exacerbate depressive symptoms[34].In addition, studies have shown that following nerve injury, reactive astrocytes mediate neuroinflammatory responses and induce disturbances in glutamate cycling, ultimately leading to the onset of depression[35].Moreover, under depressive conditions, reactive astrocytes exhibit impaired abilities to secrete neurotrophic factors, resulting in reduced neuroplasticity and the emergence of depressive and other negative emotional states. Conversely, drugs that enhance the synthesis and release of neurotrophic factors from astrocytes may alleviate depressive symptoms[36].

3.3 The Role of Astrocytes in the Comorbidity of Neuropathic Pain and Depression

Activated astrocytes play a crucial role in the comorbidity of NP and DD. Reactive astrocytes can upregulate the expression of P2X7 receptors, resulting in neuronal injury and promoting both neuropathic pain and depression. Dihydromyricetin has been shown to reverse astrocyte activation, exerting both analgesic and antidepressant effects[37].In mouse models of chronic constriction injury (CCI) and spared nerve injury (SNI), astrocytes in the hippocampus and anterior cingulate cortex are activated and undergo

functional changes, releasing inflammatory mediators that induce neuropathic pain and depression-related behaviors[10].Furthermore, following nerve injury, activation of astrocytes in the locus coeruleus leads to neurotransmitter imbalance and impaired glutamate uptake, further contributing to the development of NP and depression-like behaviors[38].

4.Cross talk between Microglia and Astrocytes

4.1 Interactions between Microglia and Astrocytes

Current research indicates that following CNS injury, both microglia and astrocytes become activated, and the inflammatory responses mediated by both glial cells represent key mechanisms underlying neuronal injury[39]. Our findings demonstrate that, in rat models of middle cerebral artery occlusion (MCAO) and neonatal hypoxic-ischemic brain damage (HIBD), extensive activation of both microglia and reactive astrocytes is observed in ischemic or injured brain regions. These two types of glial cells are closely associated and interspersed within the affected areas, suggesting direct interactions.Subsequent studies have confirmed that activated microglia can directly promote astrocyte activation[40,41], and ongoing “cross-talk” between the two contributes to neuronal injury.Increasing evidence suggests that cellular interactions within the brain are essential in both physiological and pathological processes, particularly “cross-talk” between distinct types of glial cells, which plays a pivotal role in the regulation of neuroinflammatory responses[42]. These interactions occur through microglia directly contacting with astrocytes via cellular processes[43] or through secretion of bioactive mediators and cytokines that modulate astrocytic functions and phenotypes[44]. Such intercellular communications are multi-phasic, bidirectional, and highly complex, thereby forming an intricate regulatory network. This network enables the precise transfer of complex biological information, ultimately influencing neuronal apoptosis or repair, synaptogenesis or aberrant synaptic pruning, and the maintenance or disruption of CNS homeostasis.

4.2 The Role of Microglia-Astrocyte Interactions in the Comorbidity of Neuropathic Pain and Depression

Under nociceptive stimulation, glial cells are activated and secrete a range of bioactive molecular mediators. Through mechanisms such as ligand-receptor interactions and phenotypic modulation, they further release pro-inflammatory cytokines and neuroactive substances to modulate inflammatory responses, playing important roles in the manifestation of both NP and depressive behaviors[45].Research has demonstrated that, in the hippocampus, co-activation and interaction between microglia and astrocytes regulate levels of molecules such as adenosine, which influence the excitability of ventral hippocampal pyramidal neurons and mediate both chronic pain and depression-like behaviors[46].Furthermore, inflammatory soup (IS) can induce microglial activation, which subsequently regulates astrocyte activation via the IL-18/IL-18R pathway and upregulates the nuclear factor-κB (NF-κB) signaling pathway, contributing to migraine-associated hyperalgesia and abnormal pain[47].Studies have shown that the NLRP3 inflammasome in microglia can induce neurotoxic A1-type astrocytes via the NF-κB/caspase-1 pathway, leading to neuronal dysfunction and playing a key role in major depressive disorder[48].In mouse models of chronic constriction injury (CCI), activated hippocampal astrocytes release CCL2, which interacts with CXCL10 expressed by activated microglia, leading to the downregulation of the protective protein S100B and the induction of pain and depressive behaviors[10].Additionally, pro-inflammatory M1-type microglia secrete inflammatory mediators that induce phenotypic transformation of astrocytes into neurotoxic A1-type cells, thereby aggravating inflammatory responses, enhancing glutamatergic neuronal sensitivity and excitotoxicity, and ultimately contributing to the symptoms associated with depression-pain comorbidity syndrome[3].

5.Future Perspectives

In summary, interactions among the components of the neuroimmune system are exceedingly complex. Activated glial cells not only undergo functional changes but also interact dynamically with other

types of glial cells, collectively regulating the cytokine network and cellular signaling pathways. These integrated processes lead to the release of pro-inflammatory factors, neurotransmitter dysregulation, impaired synaptic plasticity, and destabilization of neural networks, all of which play critical roles in the pathogenesis and progression of comorbid neuropathic pain and depression. Understanding these mechanisms provide valuable insights into the pathological basis of NP and DD comorbidity, and aids in identifying potential therapeutic strategies.Nevertheless, our comprehensive understanding of the specific roles and regulatory networks of glial cells in comorbid mechanisms remains incomplete, and the precise molecular mechanisms involved in disease progression warrant further investigation. Future research is expected to further delineate the pathological processes underlying NP and DD comorbidity, providing a foundation for developing more effective interventions and therapeutic approaches.

Acknowledgements

1.Fund name: Yunnan Fundamental Research Projects Basic Research Special Project; Fund No. 202401AT070067.
2.Fund name:Yunnan health training project of high level talents; Fund No.H-2024014.
3.Fund name:Science and Technology Plan Project of Baoshan-Medical research joint project in 2024; Fund No.2024bskjylzd008

References

[1]Corrigendum to: A Comprehensive Algorithm for Management of Neuropathic Pain [J]. Pain Med, 2023, 24(2): 219.

[2]MITSIKOSTAS D D, MOKA E, ORRILLO E, et al. Neuropathic Pain in Neurologic Disorders: A Narrative Review [J]. Cureus, 2022, 14(2): e22419.

[3]CAMPOS A C P, ANTUNES G F, MATSUMOTO M, et al. Neuroinflammation, Pain and Depression: An Overview of the Main Findings [J]. Front Psychol, 2020, 11: 1825.

[4]ZHA T, FANG X, WAN J, et al. Preclinical Insights into the Role of Kir4.1 in Chronic Pain and Depression: Mechanisms and Therapeutic Potential [J]. Biomolecules, 2025, 15(2).

[5]SCHOLZ J, FINNERUP N B, ATTAL N, et al. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain [J]. Pain, 2019, 160(1): 53-9.

[6]FINNERUP N B, KUNER R, JENSEN T S. Neuropathic Pain: From Mechanisms to Treatment [J]. Physiol Rev, 2021, 101(1): 259-301.

[7]SINGH P, VASUNDHARA B, DAS N, et al. Metabolomics in Depression: What We Learn from Preclinical and Clinical Evidences [J]. Mol Neurobiol, 2025, 62(1): 718-41.

[8]CHEN J, GAO Y, BAO S T, et al. Insula-->Amygdala and Insula-->Thalamus Pathways Are Involved in Comorbid Chronic Pain and Depression-Like Behavior in Mice [J]. J Neurosci, 2024, 44(15).

[9]ROBINSON R R, DIETZ A K, MAROOF A M, et al. The role of glial-neuronal metabolic cooperation in modulating progression of multiple sclerosis and neuropathic pain [J]. Immunotherapy, 2019, 11(2): 129-47.

[10] LIU Q, LI R, YANG W, et al. Role of neuroglia in neuropathic pain and depression [J]. Pharmacol Res, 2021, 174: 105957.

[11] LI L, LI T, QU X, et al. Stress/cell death pathways, neuroinflammation, and neuropathic pain [J]. Immunol Rev, 2024, 321(1): 33-51.

[12] TROUBAT R, BARONE P, LEMAN S, et al. Neuroinflammation and depression: A review [J]. Eur J Neurosci, 2021, 53(1): 151-71.

[13] LEE J H, KIM W. The Role of Satellite Glial Cells, Astrocytes, and Microglia in Oxaliplatin-Induced Neuropathic Pain [J]. Biomedicines, 2020, 8(9).

[14]KONG E, LI Y, DENG M, et al. Glycometabolism Reprogramming of Glial Cells in Central Nervous System: Novel Target for Neuropathic Pain [J]. Front Immunol, 2022, 13: 861290.

[15]YAN B, TANG S, ZHANG Y, et al. The Role of Glia Underlying Acupuncture Analgesia in Animal Pain Models: A Systematic Review and Meta-Analysis [J]. Pain Med, 2023, 24(1): 11-24.

[16]LI J, WEI Y, ZHOU J, et al. Activation of locus coeruleus-spinal cord noradrenergic neurons alleviates neuropathic pain in mice via reducing neuroinflammation from astrocytes and microglia in spinal dorsal horn [J]. J Neuroinflammation, 2022, 19(1): 123.

[17]YANG X Y, WANG H Q, WANG Z Z, et al. Linking depression and neuroinflammation: Crosstalk between glial cells [J]. Eur J Pharmacol, 2025, 995: 177408.

[18]ATTAL N, BOUHASSIRA D, COLVIN L. Advances and challenges in neuropathic pain: a narrative review and future directions [J]. Br J Anaesth, 2023, 131(1): 79-92.

[19]POTTORF T S, ROTTERMAN T M, MCCALLUM W M, et al. The Role of Microglia in Neuroinflammation of the Spinal Cord after Peripheral Nerve Injury [J]. Cells, 2022, 11(13).

[20]JI R R, NACKLEY A, HUH Y, et al. Neuroinflammation and Central Sensitization in Chronic and Widespread Pain [J]. Anesthesiology, 2018, 129(2): 343-66.

[21]FIORE N T, HAYES J P, WILLIAMS S I, et al. Interleukin-35 alleviates neuropathic pain and induces an anti-inflammatory shift in spinal microglia in nerve-injured male mice [J]. Brain Behav Immun, 2024, 122: 287-300.

[22]TANSLEY S, GU N, GUZMAN A U, et al. Microglia-mediated

degradation of perineuronal nets promotes pain [J]. Science, 2022, 377(6601): 80-6.

[23]ZOU H, PU W, ZHOU J, et al. Noradrenergic Locus Coeruleus-CA3 Activation Alleviates Neuropathic Pain and Anxiety- and Depression-Like Behaviors by Suppressing Microglial Neuroinflammation in SNI Mice [J]. CNS Neurosci Ther, 2025, 31(3): e70360.

[24]ZHANG K, RAN R, ZHANG C J, et al. Focus on P2X7R in microglia: its mechanism of action and therapeutic prospects in various neuropathic pain models [J]. Front Pharmacol, 2025, 16: 1555732.

[25]SHIN J, WU J, PARK H, et al. Microglial pyroptosis drives neuropathic pain and targeting NLRP3 alleviates pain and neuroinflammation [J]. Biochim Biophys Acta Mol Basis Dis, 2025, 1871(4): 167737.

[26]LI Q, XIE Y, LIN J, et al. Microglia Sing the Prelude of Neuroinflammation-Associated Depression [J]. Mol Neurobiol, 2025, 62(4): 5311-32.

[27]CAO P, CHEN C, LIU A, et al. Early-life inflammation promotes depressive symptoms in adolescence via microglial engulfment of dendritic spines [J]. Neuron, 2021, 109(16): 2573-89 e9.

[28]ZHENG Z H, TU J L, LI X H, et al. Neuroinflammation induces anxiety- and depressive-like behavior by modulating neuronal plasticity in the basolateral amygdala [J]. Brain Behav Immun, 2021, 91: 505-18.

[29]ZUO C, CAO H, FENG F, et al. Repetitive transcranial magnetic stimulation exerts anti-inflammatory effects via modulating glial activation in mice with chronic unpredictable mild stress-induced depression [J]. Int Immunopharmacol, 2022, 109: 108788.

[30]JI R R, DONNELLY C R, NEDERGAARD M. Astrocytes in chronic pain and itch [J]. Nat Rev Neurosci, 2019, 20(11): 667-85.

[31]VYGONSKAYA M, WU Y, PRICE T J, et al. The role and treatment potential of the complement pathway in chronic pain [J]. J Pain, 2025, 27: 104689.

[32]DE CEGLIA R, LEDONNE A, LITVIN D G, et al. Specialized astrocytes mediate glutamatergic gliotransmission in the CNS [J]. Nature, 2023, 622(7981): 120-9.

[33]ZHU C C, ZHENG Y L, GONG C, et al. Role of Exercise on Neuropathic Pain in Preclinical Models: Perspectives for Neuroglia [J]. Mol Neurobiol, 2025, 62(3): 3684-96.

[34]ZHANG Y M, QI Y B, GAO Y N, et al. Astrocyte metabolism and signaling pathways in the CNS [J]. Front Neurosci, 2023, 17: 1217451.

[35]VERKHRATSKY A, LI B, NIU J, et al. Neuroglial Advances: New Roles for Established Players [J]. J Neurochem, 2025, 169(5): e70080.

[36]JING D, HOU X, GUO X, et al. Astrocytes in Post-Stroke Depression: Roles in Inflammation, Neurotransmission, and Neurotrophin Signaling [J]. Cell Mol Neurobiol, 2023, 43(7): 3301-13.

[37]GE H, SUN M, WEI X, et al. Protective effects of dihydromyricetin on primary hippocampal astrocytes from cytotoxicity induced by comorbid diabetic neuropathic pain and depression [J]. Purinergic Signal, 2020, 16(4): 585-99.

[38]ZHAO Q, KONG Y, WAN L. Editorial: Pain and Depression [J]. Front Psychol, 2022, 13: 865071.

[39]LIDDELOW S A, GUTTENPLAN K A, CLARKE L E, et al. Neurotoxic reactive astrocytes are induced by activated microglia [J]. Nature, 2017, 541(7638): 481-7.

[40]GUTTENPLAN K A, LIDDELOW S A. Astrocytes and microglia: Models and tools [J]. J Exp Med, 2019, 216(1): 71-83.

[41]FANG M, YUAN Y, LU J, et al. Scutellarin promotes microglia-mediated astrogliosis coupled with improved behavioral function in cerebral ischemia [J]. Neurochem Int, 2016, 97: 154-71.

[42]JHA M K, JO M, KIM J-H, et al. Microglia-Astrocyte Crosstalk: An Intimate Molecular Conversation [J]. The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry, 2019, 25(3).

[43]LANA D, UGOLINI F, WENK G L, et al. Microglial distribution, branching, and clearance activity in aged rat hippocampus are affected by astrocyte meshwork integrity: evidence of a novel cell-cell interglial interaction [J]. FASEB journal : official publication of the Federation of American Societies for Experimental Biology, 2019, 33(3): 4007-20.

[44]CSERéP C, PóSFAI B, DéNES Á. Shaping Neuronal Fate: Functional Heterogeneity of Direct Microglia-Neuron Interactions [J]. Neuron, 2021, 109(2): 222-40.

[45]LIDDELOW S A, BARRES B A. Reactive Astrocytes: Production, Function, and Therapeutic Potential [J]. Immunity, 2017, 46(6): 957-67.

[46]LV X J, LV S S, WANG G H, et al. Glia-derived adenosine in the ventral hippocampus drives pain-related anxiodepression in a mouse model resembling trigeminal neuralgia [J]. Brain Behav Immun, 2024, 117: 224-41.

[47]GONG Q, LIN Y, LU Z, et al. Microglia-Astrocyte Cross Talk through IL-18/IL-18R Signaling Modulates Migraine-like Behavior in Experimental Models of Migraine [J]. Neuroscience, 2020, 451: 207-15.

[48]LI S, FANG Y, ZHANG Y, et al. Microglial NLRP3 inflammasome activates neurotoxic astrocytes in depression-like mice [J]. Cell Rep, 2022, 41(4): 111532.