Neuropsychiatric Disease and Treatment

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REVIEW

The Fractalkine (FKN/CX3CL1) Pathway in Depression: A Critical Review of Its Role in Neuroinflammation and Therapeutic Potential

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Abstract: Major Depressive Disorder (MDD), a global psychiatric disorder, involves complex pathogenesis in which neuroinflammation is considered one of the core pathophysiological processes. The fractalkine (FKN, CX3CL1)/CX3CR1 signaling pathway, a critical mediator of neuron-microglia communication, has been implicated in neuroinflammation and comorbid models depression, yet its precise and dynamic role in MDD remains controversial and insufficiently understood. This review aims to critically synthesize the existing literature to address these gaps. We first analyze the evidence for neuroinflammation in MDD, involving glial cells and pro-inflammatory cytokines. We then focus on the dual and context-dependent roles of the FKN/CX3CR1 pathway in regulating microglial function, synaptic plasticity, and inflammatory responses. Through a comparative analysis of existing literature, we suggest that neuroinflammation is a significant driver in the onset and progression of MDD, potentially engaging immune cells like microglia and astrocytes, and triggering the discharge of pro-inflammatory factors. The FKN/CX3CR1 pathway may play a dual role in regulating microglial function, maintaining synaptic homeostasis, and mediating inflammatory responses. Its dysregulation is potentially closely associated with inflammatory responses and synaptic damage in comorbid models, such as depression with diabetes and depression with rheumatoid arthritis. However, its specific role in MDD has not been fully elucidated, and direct evidence linking this pathway to major depressive disorder remains limited, as most current findings are derived from comorbid models or preclinical studies rather than clinical investigations. This review will systematically explore the general role of neuroinflammation in MDD, dissect the mechanisms of the FKN/CX3CR1 pathway in neuroinflammation and existing depression models, and prospectively potential therapeutic strategies and future research directions based on this pathway, thereby attempting to provide a new theoretical basis for the precision diagnosis and treatment of MDD.

Keywords: major depressive disorder, neuroinflammation, FKN/CX3CR1, microglia

Introduction

MDD is a psychiatric disorder with extremely high rates of prevalence and disability, severely impacting the quality of life for hundreds of millions of people worldwide.[1,2] Despite continuous advancements in treatment, a substantial number of patients respond poorly to existing therapies or face the risk of relapse.[3] As traditional theories such as the monoamine hypothesis, Hypothalamic-Pituitary-Adrenal (HPA) axis dysfunction, and neurotrophic factor deficiency fail to fully explain the heterogeneity of MDD,[4,5] research has shifted towards broader biological mechanisms, among which the neuroinflammation hypothesis has emerged as a prominent and cutting-edge area of research.[1,6,7]

Neuroinflammation, an aberrant immune response within the central nervous system (CNS), is considered a key driving factor in the onset and development of MDD.[1,6] When this inflammatory process kicks off, it triggers the

https://doi.org/10.2147/NDT.S607481
Received: 6 March 2026
Accepted: 30 April 2026
Published: 17 May 2026

mobilization of the body's built-in immune defense system, particularly microglia and astrocytes, while simultaneously setting off a cascade of pro-inflammatory cytokines and chemokines that flood the affected area. These mediators not only directly damage neurons but also affect neuroplasticity, neurogenesis, and synaptic function, thereby leading to mood dysregulation and cognitive impairment.[1,8] As key molecules that mediate the directed migration of immune cells and regulate immune responses, chemokines play a central role in CNS inflammation.[9,10] Among them, the FKN and its sole receptor CX3CR1 signaling pathway has garnered significant attention due to its unique position in neuron-microglia interactions.[11] The FKN/CX3CR1 pathway plays a crucial role in maintaining synaptic homeostasis, regulating microglial activity, and mediating neuroinflammation.

Given the prominent role of neuroinflammation in MDD and the importance of the FKN/CX3CR1 pathway in neuroimmune regulation, this review aims to systematically explore the association between the FKN/CX3CR1 signaling pathway and depression from an inflammatory perspective (Figure 1).

This review will comprehensively analyze the general role of neuroinflammation in MDD, dissect the specific mechanisms of the FKN/CX3CR1 pathway in regulating microglial function, neuron-glia interactions, and inflammatory responses, and, by integrating existing research, explore its potential role in MDD. Furthermore, it will prospect its potential as a novel therapeutic target and outline future research directions. Despite the growing interest, several critical gaps remain in our understanding. Currently, direct evidence is mainly derived from preclinical studies, yet it must be acknowledged that this may lead to biased inferences regarding the role of this pathway in "uncomplicated" MDD. Second, the dual role of the FKN/CX3CR1 pathway—acting as either neuroprotective or pro-inflammatory depending on the context—has not been sufficiently synthesized. Finally, its interaction with other key inflammatory networks (eg, NF-κB, NLRP3) in the context of depression requires further clarification. This review aims to address these gaps by critically synthesizing the existing literature, highlighting the current limitations, and proposing future research directions.

Biological Basis of FKN/CX3CR1 Signaling Pathway

Molecular Structure and Expression Characteristics of Fractalkine (FKN)

FKN, also known as CX3CL1, is a unique chemokine that plays a significant role in neuroinflammation and is primarily expressed in neurons. Its molecular structure is characterized by a distinctive CX3C chemokine domain, which is critical

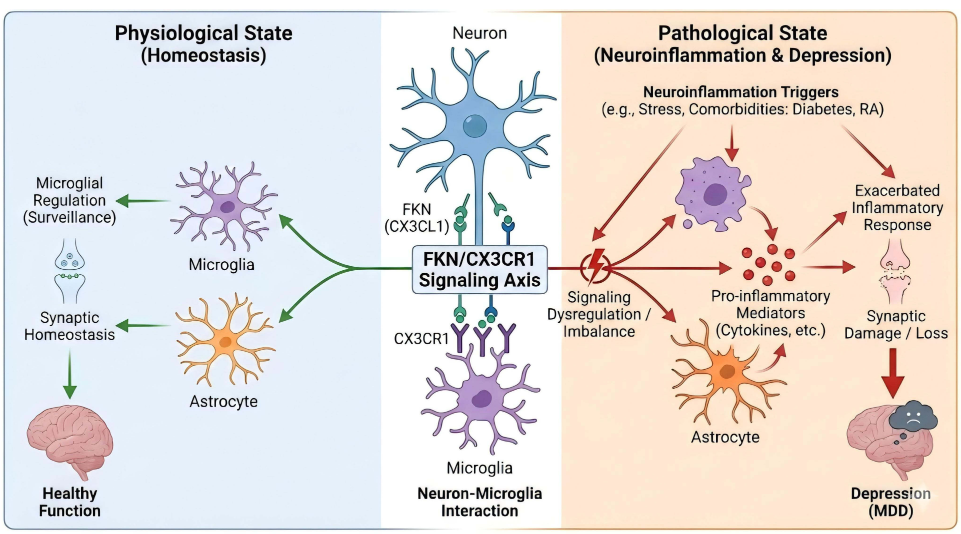

Figure 1 The dual role of the FKN/CX3CR1 signaling axis in physiological homeostasis and pathological neuroinflammation in major depressive disorder. Under normal conditions, the FKN/CX3CR1 signaling pathway facilitates communication between neurons and microglia, supporting brain health by maintaining microglial function, astrocyte balance, and synaptic integrity. However, in pathological states, stress and conditions like diabetes and rheumatoid arthritis disrupt this signaling, triggering neuroinflammation. This results in overactive microglia and astrocytes, increased pro-inflammatory mediators, and synaptic damage, contributing to major depressive disorder (MDD). Green arrows represent physiological homeostatic processes; red arrows represent pathological neuroinflammatory processes; the lightning bolt symbol indicates signaling dysregulation/imbalance.

Abbreviations: FKN (CX3CL1), Fractalkine (CX3C chemokine ligand 1); CX3CR1, CX3C chemokine receptor 1; MDD, Major Depressive Disorder; RA, Rheumatoid Arthritis.

 https://doi.org/10.2147/NDT.S607481

for its interaction with the sole receptor CX3CR1. This structural feature not only defines the binding affinity of FKN to CX3CR1 but also determines the functional outcomes of this signaling pathway. The presence of both membrane-bound and soluble forms of FKN allows for versatile roles in cellular communication. The membrane-bound form facilitates adhesion between neurons and microglia, while the soluble form serves as a chemotactic agent, attracting immune cells to sites of injury or inflammation. This dual functionality underscores the importance of FKN in preserving neural equilibrium and countering disease states. Moreover, FKN expression is dynamically regulated by various stimuli associated with neuroinflammatory processes, such as cytokines and stress signals. For instance, studies have shown that inflammatory factors can significantly upregulate FKN expression in neurons, which in turn can enhance microglial activation and promote neuroinflammatory responses.[12] This dynamic regulation highlights the potential of FKN as a biomarker for neuroinflammatory conditions and its relevance in the pathophysiology of diseases such as major depressive disorder and neurodegenerative disorders. Understanding the molecular structure and expression characteristics of FKN is crucial for elucidating its role in neuroinflammation and developing targeted therapeutic strategies that modulate this signaling pathway for neuroprotection and recovery from neurological injuries.

Distribution and Function of the CX3CR1 Receptor

The CX3CR1 receptor is predominantly expressed in microglial cells, serving as the sole known receptor for FKN, a CNS-associated chemomodulator controlling neuroimmunological reactions. The brain's immune cells, microglia, are essential for maintaining equilibrium and addressing pathological conditions or tissue damage. The expression of CX3CR1 on microglia is essential for mediating the signaling pathways activated by FKN, which facilitates the migration, activation, and inflammatory responses of these cells. Under pathological conditions, FKN plays a key role in maintaining microglial phenotype and neuroprotective functions.[13–15] Specifically, the interaction between FKN and CX3CR1 promotes microglial survival and proliferation, as well as their ability to migrate towards sites of neuronal damage or inflammation. This receptor-ligand interaction is crucial in modulating the immune landscape of the CNS, particularly during neuroinflammatory processes associated with various neurological disorders, including MDD, where neuroinflammation is a significant contributing factor.[16]

The functional status and expression levels of CX3CR1 have profound implications for the progression of neuroinflammation. For instance, studies have demonstrated that alterations in CX3CR1 expression can influence the behavior of microglia, either promoting a protective phenotype or exacerbating inflammatory responses depending on the context of the CNS environment. In conditions such as chronic neuroinflammation or neurodegenerative diseases, dysregulation of CX3CR1 signaling can lead to maladaptive microglial activation, resulting in increased production of pro-inflammatory cytokines and chemokines that further propagate neuroinflammation and neuronal damage.[17]

Moreover, the distribution of CX3CR1 is not uniform across different brain regions, which may contribute to the regional variability in microglial function and response to injury. For example, in the context of traumatic brain injury (TBI), CX3CR1 expression levels can significantly impact the extent of neuroinflammation and subsequent neuronal recovery. High levels of CX3CR1 expression have been associated with enhanced microglial activation and a more robust inflammatory response, while lower levels may correlate with a protective, anti-inflammatory microglial phenotype.[18]

The implications of CX3CR1 expression extend beyond mere localization and functional mediation; they also encompass the receptor's role in the interplay among microglial and alternative cellular elements within the CNS. For instance, the CX3CR1-FKN axis has been shown to facilitate communication between neurons and microglia, allowing for a coordinated response to neuronal activity and injury. This communication is vital for maintaining synaptic health and plasticity, as well as for the effective clearance of cellular debris following neuronal death or damage.[19]

In summary, the distribution and functional dynamics of the CX3CR1 receptor are pivotal in shaping the microglial response to neuroinflammation and injury. Its role as a mediator of FKN signaling underscores the importance of microglial activation in both protective and pathological processes within the CNS. Understanding the nuances of CX3CR1 expression and function may provide critical insights into therapeutic strategies aimed at modulating microglial activity in various neuroinflammatory and neurodegenerative conditions, including major depressive disorder and other related disorders.[20]

https://doi.org/10.2147/NDT.S607481

Signaling Mechanism of the FKN/CX3CR1 Pathway

The interaction between FKN and its receptor CX3CR1 initiates a cascade of intracellular signaling pathways, prominently including the phosphoinositide 3-kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK) pathways. Upon binding of FKN to CX3CR1, these pathways are activated, leading to various cellular responses that regulate cell survival and inflammatory reactions. For instance, the activation of the PI3K/Akt pathway is crucial for promoting cell survival and inhibiting apoptosis, while the MAPK pathway is involved in the regulation of gene expression associated with inflammatory responses.[21] This dual activation not only enhances the survival of microglial cells but also modulates their functional state, determining whether they adopt a pro-inflammatory or anti-inflammatory phenotype. The balance between these phenotypes is pivotal in the context of neuroinflammation and neurodegenerative diseases, such as major depressive disorder, where an overactive pro-inflammatory response can exacerbate neuronal damage. Although no studies on this mechanism have been conducted in the field of depression to date, investigations of the same mechanism in cardiology provide evidence for the relationship between this mechanism and the signaling pathway.[22]

The state of activation of these signaling pathways is crucial for the phenotypic transition of microglia, which can shift between a neuroprotective M2 phenotype and a neurotoxic M1 phenotype. For example, when the FKN/CX3CR1 axis is activated, it can lead to a predominance of M2 microglial activation, which is associated with tissue repair and anti-inflammatory actions. Conversely, dysregulation of this signaling can result in M1 activation, characterized by the production of pro-inflammatory cytokines and neurotoxic factors, contributing to the pathogenesis of various neurological disorders, including depression and neurodegeneration.[23] This mechanistic understanding underscores the potential therapeutic implications of targeting the FKN/CX3CR1 pathway to modulate microglial responses and mitigate neuroinflammation, offering a molecular basis for intervention strategies aimed at controlling neuroinflammatory processes in diseases like major depressive disorder.[24]

In summary, the signaling mechanisms activated by the FKN/CX3CR1 interaction provide a molecular foundation for understanding how microglial cells respond to inflammatory stimuli and transition between different functional states (Figure 2). This knowledge not only elucidates the role of neuroinflammation in the context of major depressive disorder but also highlights the potential of the FKN/CX3CR1 axis as a therapeutic target for modulating neuroinflammatory responses and improving clinical outcomes in related neuropsychiatric conditions. Further research into this pathway could yield novel strategies for the treatment of depression and other neuroinflammatory diseases, emphasizing the importance of maintaining a balanced microglial activation state for neural health.[25]

Neuroinflammatory Pathophysiological Basis of Depression

The pathophysiology of depression is a multifactorial and multi-layered complex process, and the neuroinflammation hypothesis has become one of the key theories explaining its core mechanisms.[1,6,26] Substantial research suggests that inflammatory responses within the central nervous system, whether acute or chronic, contribute significantly to development and advancement of depression, affecting neurotransmitter balance, neuroplasticity, neurogenesis, and synaptic function.

The Core Role and Cellular Mechanisms of Neuroinflammation in Depression

Depression is widely considered a neuroimmune disorder, and its onset involves adaptive changes in neurotransmission, neurogenesis, and circuit connectivity, which are driven by the immune and endocrine systems.[6] MDD is closely associated with an abnormal cerebral immune response—neuroinflammation—which has a particularly significant impact on hippocampal neurogenesis, especially in the dentate gyrus (DG) region, leading to depressive-like behaviors and cognitive dysfunction.[1] In various types of depression, such as post-stroke depression (PSD), neuroinflammation also plays a central role, where both astrocytes and microglia undergo morphological and functional changes, exerting dual pro-inflammatory or anti-inflammatory roles.[27]

The complexity of neuroinflammation lies in its involvement of multiple cell types and molecular mechanisms. As the CNS's main immunocompetent cells, microglia become activated under pathological conditions, triggering neuroinflammation, while excessive inflammation leads to neuronal damage.[28,29] Astrocytes also play a critical role; they not only support neuronal function but also release cytokines, chemokines, and neurotrophic factors, influencing neuronal

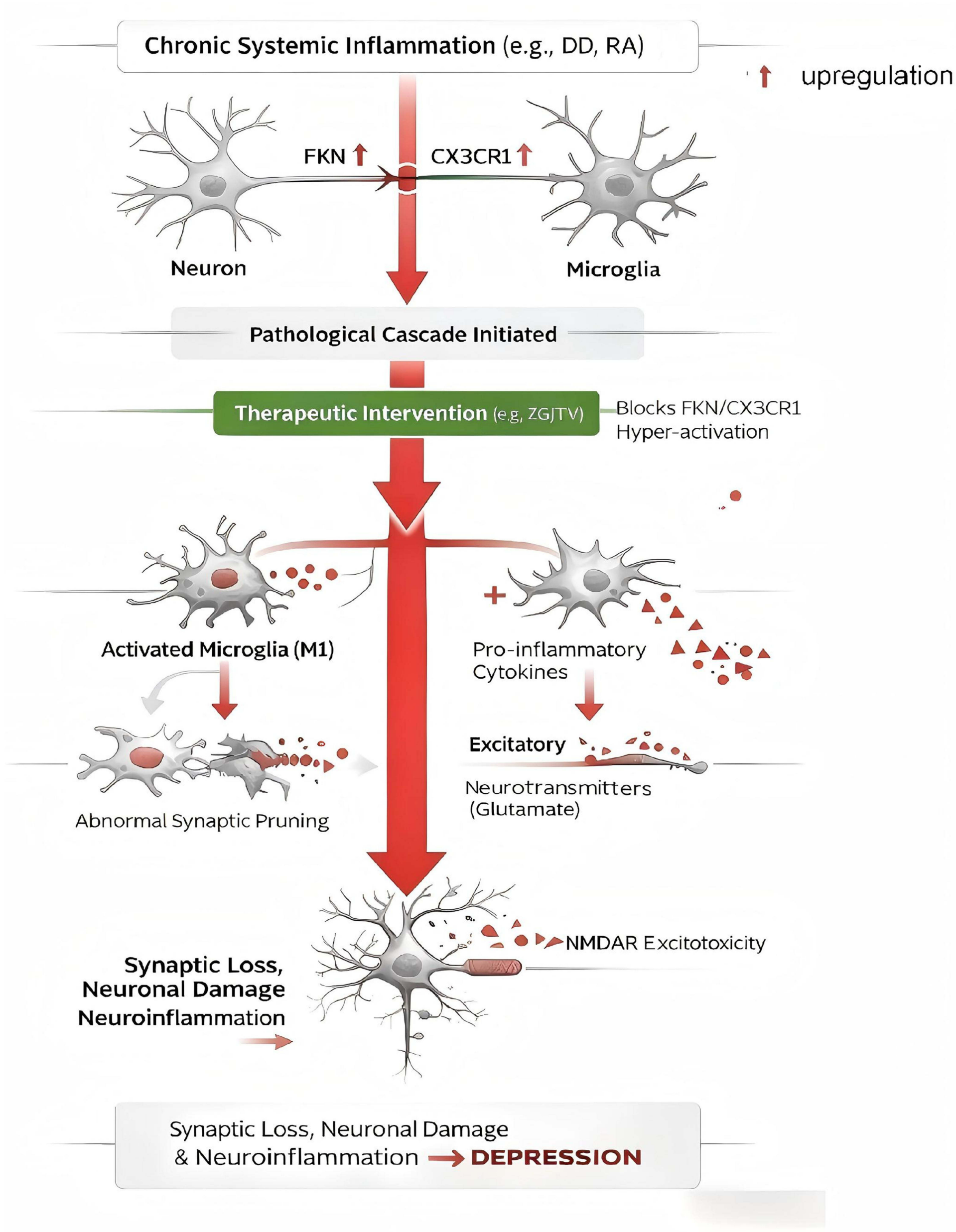

Figure 2 Schematic diagram of the pathological cascade of FKN/CX3CR1 pathway and traditional Chinese medicine intervention mechanism in depression. Chronic systemic inflammation, such as in DD and RA, increases FKN in neurons and CX3CR1 in microglia, causing harmful activation of the FKN/CX3CR1 axis. This leads to microglial M1 polarization, excessive pro-inflammatory cytokine release, abnormal synaptic pruning, and astrocyte-driven glutamate excitotoxicity, resulting in synaptic loss, neuronal damage, and ongoing neuroinflammation, which ultimately causes depression. ZGJTJY serves as a therapeutic intervention by blocking FKN/CX3CR1 hyperactivation, thereby halting the pathological process and providing antidepressant effects. Upward arrows indicate upregulation; red signals indicate pathological processes; green signals indicate therapeutic intervention.

Abbreviations: FKN, Fractalkine; CX3CR1, CX3C chemokine receptor 1; ZGJTJY, Zuogui Jieyu Tongluo Recipe; TNF-α, Tumor necrosis factor-α; IL-1β, Interleukin-1β; NMDAR, N-methyl-D-aspartate receptor; Cx43, Connexin 43; DD, Periodontal disease; RA, Rheumatoid arthritis.

survival and neural circuit function, and exhibit complex responses in neuroinflammation.[30,31] Patani emphasized the importance of reactive astrocytes in the progression of neuroinflammation and neurodegenerative diseases.[31]

Mechanisms of Inflammatory Mediators and Signaling Pathways in Depression

Neuroinflammation relies on multiple inflammatory mediators and signaling pathways. Gut microbiota dysbiosis promotes depressive-like behaviors through aberrant synaptic pruning, in which complement C3 activation and C3/CR3-mediated microglial phagocytosis serve as key steps.[32] In CUMS mouse models, gut dysbiosis (elevated Proteobacteria

https://doi.org/10.2147/NDT.S607481

and LPS) is closely associated with peripheral and central C3 activation and C3/CR3-mediated synaptic pruning; these changes can be alleviated by antidepressants or fecal microbiota transplantation, supporting the complement system's role in depression.

The NLRP3 inflammasome is a vital inflammatory complex involved in neuroinflammation across neurological diseases. In a postpartum depression-like mouse model, gut microbial imbalance induces depressive-like behaviors by activating hippocampal neuroinflammation via the NLRP3 pathway, highlighting its role in gut-brain crosstalk.[33] Nano-oligomers targeting NF-κB and NLRP3 reduce neuroinflammatory cytokines, improve cognition in aging and tauopathy mice, suppress glial activation, and promote favorable transcriptomic alterations.[34] Hartmann reported that SKA2-mediated excessive autophagic secretion leads to inflammatory neural damage, marked by increased IL-1β release and activation of NLRP3 inflammasome and Gasdermin D.[35] Together, these studies confirm the critical role of NLRP3 inflammasome in depression-related neuroinflammation, with its inhibitors representing potential therapeutic candidates.[36,37]

Pro-inflammatory cytokines including IL-6, TNF-α, and IL-1β are commonly elevated in depressed patients. Kerkis indicated that dysregulated IL-6 contributes to neuroinflammation in neurodegenerative disorders and aggravates neuronal injury.[38] MSCs modulate neuroinflammation by regulating IL-6 levels, inhibiting pro-inflammatory factors and enhancing anti-inflammatory mediators, suggesting cytokine modulation (especially IL-6) as a viable strategy against depression-related neuroinflammation.[39] Lang and Kang also observed elevated acute-phase proteins in MDD patients and proposed cytokine inhibitors such as anti-TNF-α antibodies as therapeutic approaches.[40]

The Nuclear Factor-kappa B (NF-κB) pathway, a master regulator of neuroinflammation, is fundamentally linked to the FKN/CX3CR1 axis as it directly controls the transcription of the chemokine FKN/CX3CL1.[41] This direct regulatory relationship is critical, as it situates the FKN/CX3CR1 axis downstream of numerous pro-inflammatory stimuli that converge on NF-κB activation. Consequently, this axis is influenced by broader regulatory networks: it is indirectly suppressed by master anti-inflammatory regulators like Sirtuin 1 (SIRT1) and Nrf2, which are known to inhibit NF-κB activity. Conversely, stimuli that activate NF-κB will not only upregulate FKN/CX3CL1 but will also co-activate other pro-inflammatory effectors such as Cyclooxygenase-2 (COX-2) and inducible Nitric Oxide Synthase (iNOS).[42,43] Therefore, the activation state of NF-κB serves as a central switch, orchestrating an inflammatory cascade in which FKN/CX3CR1-mediated neuron-microglia signaling is a key downstream component.

Crosstalk Between Neuroinflammation and Other Depression-Related Mechanisms

Neuroinflammation does not exist in isolation; it has complex crosstalk and interactions with other pathological mechanisms of depression, such as oxidative stress, gut microbiota dysbiosis, and epigenetic alterations. Correia explored the connection between oxidative stress and depression,[8] highlighting how an overabundance of free radicals coupled with an inadequate antioxidant defense system can set off inflammatory processes in the body, neurodegeneration, and neuronal death, and are closely linked to stress responses, neuroinflammation, the serotonergic pathway, neurogenesis, and synaptic plasticity imbalance. Zha also identified ferroptosis as a key mechanism in both atherosclerosis (AS) and depression,[44] with iron and lipid metabolism disorders being important pathogenic factors.

Gut microbiota dysbiosis affects the onset and development of neuroinflammation and depression through the gut-brain axis. The studies by Hao and Xu clearly indicated the role of gut microbiota dysbiosis in depressive-like behaviors and neuroinflammation.[32,33] The review by Liu detailed the association between gut microbiota dysbiosis and depression and explored the potential health benefits of microbiota-targeted therapies for depression.[45] Qian found that Bifidobacterium with indole-3-lactic acid production capacity exhibits psychobiotic potential by reducing neuroinflammation,[46] offering insights for microbial therapies targeting mood disorders. These studies collectively construct a complex network of the "microbiota-gut-brain axis-neuroinflammation-depression."

Epigenetic alterations are also closely linked to neuroinflammation and depression. Bi hypothesized that epigenetic alterations induced by early-life stress may serve as biomarkers for the diagnosis of MDD.[47] The reviews by Chen and Yuan examined the functions of epigenetic processes like Deoxyribonucleic Acid (DNA) methylation, histone alterations, and non-coding Ribonucleic Acid (RNAs),[48,49] and RNA modifications in depression, which affect neuroendocrine responses, neuroplasticity, neurotransmission, and glial function. Xian described the molecular mechanisms of N6-methyladenosine (m6A) modification in the pathogenesis of depression,[50] including its interactions with inflammation, stress, and neuroplasticity. These studies suggest that epigenetic modifications may influence the onset and progression of depression by regulating the expression of neuroinflammation-related genes.

In summary, neuroinflammation is a common and central link in the pathogenesis of depression (Table 1). It leads to neuronal damage, synaptic dysfunction, and impaired neuroplasticity by activating microglia and astrocytes, releasing various pro-inflammatory mediators, and interacting with other pathological mechanisms (such as oxidative stress, gut microbiota dysbiosis, and epigenetic alterations), ultimately manifesting as depressive symptoms.

Association of FKN/CX3CR1 in the Pathogenesis of Depression

As a key mediator of neuron-microglia interactions, the role of the FKN/CX3CR1 signaling pathway in neuroinflammation has been widely recognized. Recently, increasing attention has been paid to its potential involvement in the pathogenesis of depression. Although direct evidence specifically linking this pathway to the pathological process of depression remains limited, considerable indirect evidence supports its possible role from the perspectives of neuroinflammation, microglial function, and synaptic plasticity (Figure 3).

The Role of FKN/CX3CR1 in Comorbid Models of Depression

Currently, research directly linking the FKN/CX3CR1 signaling pathway to depression is primarily concentrated in comorbid models of depression, particularly in depression with diabetes (DD) and depression with rheumatoid arthritis. These studies provide preliminary yet important evidence for the role of FKN/CX3CR1 in the pathophysiology of depression.

The study by Liu Zhuo explicitly investigated the mechanism by which the Zuogui Jiangtang Jieyu (ZGJTJY) formula regulates a quadruple synapse in vitro model of depression with DD.[51] They found that in the DD in vitro cell model, there was elevated expression of glial fibrillary acidic protein (GFAP) and Iba-1 (glial cell activation), decreased levels of SYN and PSD-95 (synaptic damage), along with increased expression of FKN, CX3CR1, Glutamate Ionotropic Receptor NMDA Type Subunit 2A (NR2A), and Glutamate Ionotropic Receptor NMDA Type Subunit 2B (NR2B), and elevated levels of the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6. These results clearly indicate that in the DD model, the activation of the FKN/CX3CR1 signaling pathway occurs concurrently with neuroinflammation and synaptic damage. Following intervention with ZGJTJY, all the aforementioned indicators improved, including the downregulation of FKN and CX3CR1 expression, and the alleviation of the inflammatory response and synaptic damage. This directly suggests that ZGJTJY may ameliorate the inflammatory response and synaptic pathology in the DD quadruple synapse in vitro model by modulating the FKN/CX3CR1 signaling pathway. Another similar study by Liu Jian,[52] while primarily

Table 1 Key Cellular and Molecular Mechanisms in the Neuroinflammation of Depression

Mechanism Type	Key Cells	Major Mediators/ Pathways	Depression-Related Effects	Representative References
Cellular Activation	Microglia	Activation, polarization (M1/M2)	Neuronal damage, aberrant synaptic pruning	[25,26]
	Astrocytes	Reactive astrocytes	Support of neuronal function, release of inflammatory mediators	[27,28]
Inflammatory Mediators	Complement System	C3/CR3	Aberrant synaptic pruning, depressive-like behaviors	[29]
	Inflammasome	NLRP3	Neuroinflammation, depressive-like behaviors	[30,33]
	Cytokines	IL-6, TNF-α, IL-1β	Neuronal damage, mood disorders	[35,37]
Signaling Pathways	NF-κB	Inflammatory gene expression	Neuroinflammation, cytokine release	[38,39]
Crosstalk Mechanisms	Oxidative Stress	ROS accumulation	Inflammation, neurodegeneration	[8]
	Gut Microbiota	Metabolites, LPS	Gut-brain axis inflammation, depressive behaviors	[29,42]
	Epigenetics	DNA methylation, histone modifications	Gene expression regulation, neuroplasticity	[44,47]

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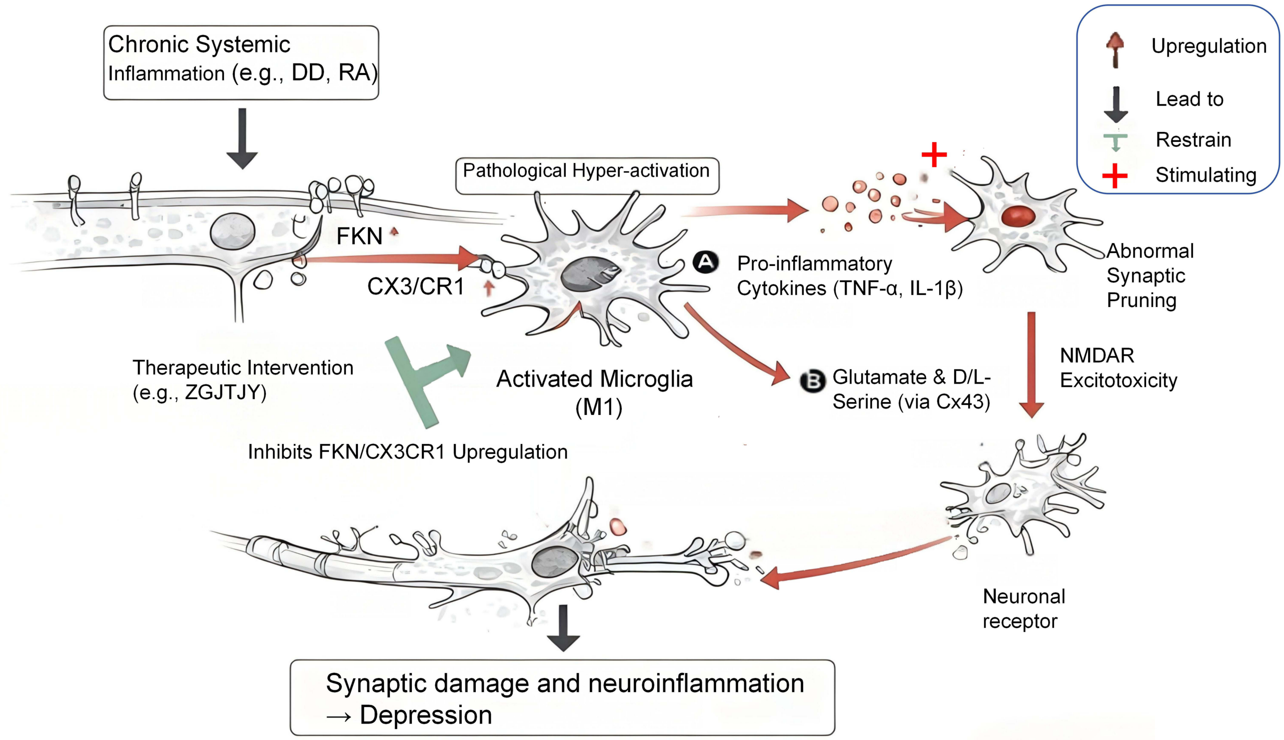

Figure 3 Schematic diagram of pathological hyperactivation of FKN/CX3CR1 signaling and ZGJTV intervention in depression. Chronic systemic inflammation triggers the excessive activation of FKN/CX3CR1 signaling, which activates microglia. Activated M1 microglia then mediate two key pathological pathways: (**A**) the release of pro-inflammatory cytokines that drive abnormal synaptic pruning and (**B**) the release of glutamate and D/L-serine, which leads to NMDAR excitotoxicity. These combined effects cause synaptic damage and neuroinflammation, contributing to depression. ZGJTV can inhibit FKN/CX3CR1 upregulation and block harmful signaling, providing neuroprotective and antidepressant benefits. Red arrows represent pathological processes; green T-shaped symbol represents therapeutic inhibition.

Abbreviations: FKN, Fractalkine; CX3CR1, CX3C chemokine receptor 1; ZGJTV, Zuogui Jieyu Tongluo Recipe; TNF-α, Tumor necrosis factor-α; IL-1β, Interleukin-1β; NMDAR, N-methyl-D-aspartate receptor; Cx43, Connexin 43; DD, Periodontal disease; RA, Rheumatoid arthritis.

focusing on CD300 Antigen Family Member f (CD300f)/Glucose Transporter 1 (GLUT1), further explored the mechanism by which ZGJTJY improves hippocampal synaptic microenvironment damage in DD by regulating microglial glucose metabolism. Its background and objectives are highly relevant to the former study, both pointing towards microglial dysfunction and synaptic microenvironment damage in depression with diabetes. These two studies collectively emphasize that in depression with diabetes, neuroinflammation and synaptic damage are core pathological links, and the FKN/CX3CR1 signaling pathway, as a key regulator of microglial function and inflammatory responses, may play an important role.

The research by Liu Jian focused on the mechanism of action of the Zhuanggu Zhitong Jieyu formula against depression with rheumatoid arthritis,[53] which also involves the FKN/CX3CR1 signaling pathway. By inducing an inflammatory model in synovial cells and establishing a cell co-culture system, they found that the Zhuanggu Zhitong Jieyu formula could counteract depression with rheumatoid arthritis via the FKN/CX3CR1 signaling pathway. This study explicitly indicates the involvement of the FKN/CX3CR1 signaling pathway in depression with rheumatoid arthritis, further supporting the universal role of FKN/CX3CR1 in inflammation-related depression. As a chronic inflammatory disease, the depression that accompanies rheumatoid arthritis is often considered to be inflammation-mediated. Therefore, the role of FKN/CX3CR1 in this comorbid model further strengthens its status as a bridge between inflammation and depression.

These comorbid models suggest that FKN/CX3CR1 may have a universal role in inflammation-driven subtypes of depression. The comorbid and in vitro cell models indicate a key role for the FKN/CX3CR1 signaling pathway in mediating neuroinflammation, synaptic damage, and ultimately leading to depressive-like symptoms. The value of these studies lies in the fact that they not only provide direct experimental evidence for the association between FKN/CX3CR1 and depression but also offer a preliminary theoretical basis for developing therapeutic strategies targeting FKN/CX3CR1.

The Role of Neuroinflammation, Microglia, and Synaptic Plasticity in Depression

A large body of research on the roles of neuroinflammation, microglial function, and synaptic plasticity in depression also provides strong indirect support for the potential role of FKN/CX3CR1 in depression.

Neuroinflammation is a core component of the pathogenesis of depression.[1,6,26] As an important neuroimmune regulatory pathway, the role of FKN/CX3CR1 in neuroinflammation is widely recognized.[11] Therefore, if neuroinflammation is a driving factor for depression, it is highly likely that FKN/CX3CR1, as a key regulator of inflammation, plays a role. Corrigan emphasized that depression is a disease of neuroimmune origin,[6] involving immune mediators in the nervous system. As a chemokine, FKN is precisely one of these immune mediators, regulating the function of immune cells (mainly microglia) through CX3CR1.

The aberrant activation and dysfunction of microglia are key features of neuroinflammation in depression.[28,29] The FKN/CX3CR1 signaling pathway plays a central role in regulating the activation state, migration, phagocytosis, and cytokine release of microglia. When FKN/CX3CR1 signaling is imbalanced, it may lead to the polarization of microglia towards a pro-inflammatory phenotype, releasing excessive pro-inflammatory cytokines and thereby damaging neurons. The study by Hao,[32] which revealed that gut microbiota dysbiosis induces depressive-like behaviors through complement Complement Component 3 (C3)-mediated aberrant synaptic pruning by microglia, highlights the critical role of microglia-mediated synaptic pruning in depression. The FKN/CX3CR1 pathway is believed to maintain the "resting" state of microglia under physiological conditions and regulate their interactions with neurons, including synaptic pruning. Therefore, abnormalities in FKN/CX3CR1 signaling could lead to dysfunctional synaptic pruning by microglia, thereby indirectly promoting the onset of depression. Cai found that circ-Ubiquitin-Conjugating Enzyme E2 K (UBE2K) in microglia exacerbates neuroinflammation and depression by upregulating UBE2K expression,[26] further confirming the pathogenic role of microglial activation in depression. As an important regulator of microglial function, abnormalities in FKN/CX3CR1 could lead to the upregulation of inflammation-related molecules like circ-UBE2K, thus exacerbating depressive symptoms.

One of the characteristics of depression is impaired synaptic plasticity and neuronal damage, especially in key mood-controlling neural structures, including the hippocampus.[1,8] The FKN/CX3CR1 signaling pathway plays a role in maintaining synaptic integrity and regulating neuronal survival. For instance, FKN is thought to protect neurons from excitotoxicity and inflammatory damage. When the function of the FKN/CX3CR1 signaling pathway is impaired, neurons may become more vulnerable to attack by inflammatory mediators, leading to synaptic dysfunction and neuronal death, which in turn can trigger depressive symptoms. The study by Duarte showed that astrocytes drive depressive-like behaviors by releasing glutamate and D/L-serine through Connexin (Cx) 43 hemichannels,[54] leading to N-Methyl-D-Aspartate Receptor (NMDAR) over-activation. This suggests that glia-mediated neuronal excitotoxicity is an important mechanism in depression. By regulating the interaction between microglia and neurons, the FKN/CX3CR1 pathway may indirectly affect neuronal excitability, thus participating in the pathological process of depression.

In addition to FKN/CX3CR1, other chemokines and their receptors also play a role in depression. Yao found that astrocyte-derived C-C Motif Chemokine Ligand 5(CCL5)-mediated infiltration of C-C Chemokine Receptor Type 5 Positive (CCR5+) neutrophils drives the pathogenesis of depression.[55] This indicates that different chemokine-receptor axes may act synergistically to jointly promote neuroinflammation in depression. FKN/CX3CR1 may interact with other chemokine pathways (such as CCL5-CCR5), forming a complex network that collectively regulates immune responses and neural function in the central nervous system.

Limitations of Current Evidence and the Need for Primary MDD Models

While studies from comorbid models are informative, their generalizability to idiopathic MDD must be approached with caution. Conditions like diabetes and rheumatoid arthritis involve systemic inflammation, which may activate the FKN/CX3CR1 pathway in a manner not representative of all depression subtypes. Therefore, future research must prioritize the use of primary, non-comorbid animal models of depression (eg, chronic unpredictable mild stress, social defeat stress) to validate these findings and dissect the pathway's role in the absence of confounding systemic diseases.

https://doi.org/10.2147/NDT.S607481

Therapeutic Strategies and Future Perspectives

The treatment of depression continues to face numerous challenges, as traditional antidepressants have limited efficacy and considerable side effects. This reality prompts researchers to actively explore new therapeutic targets and intervention strategies.[2,3] Given the evidence linking the FKN/CX3CR1 signaling pathway to neuroinflammation, it has been proposed as a potential target for depression. However, its translation from a molecule of interest to a viable therapeutic strategy warrants a highly cautious approach.

A central challenge is the pathway's dual, context-dependent function, which can be either neuroprotective or pro-inflammatory. This complexity means that simply targeting the pathway without a deeper understanding could lead to unpredictable outcomes. Therefore, before this pathway can be considered for precision treatment, several fundamental questions must be addressed: Is pathway activity universally detrimental in MDD, or only in specific subtypes? Would inhibition disrupt essential homeostatic functions?

While preliminary studies suggest that modulators, including compounds from Traditional Chinese Medicine, might regulate this pathway in certain models, these findings need rigorous validation. Future research should prioritize clarifying the pathway's specific role in primary MDD models and identifying biomarkers to stratify patients. Only by addressing these foundational issues can we determine if targeting the FKN/CX3CR1 axis, perhaps in combination with other immunomodulatory strategies, represents a truly safe and effective therapeutic avenue for depression.

Potential Therapeutic Strategies Targeting the FKN/CX3CR1 Signaling Pathway

The role of the FKN/CX3CR1 signaling pathway in depression-related neuroinflammation and synaptic damage makes it an attractive therapeutic target. Directly modulating the activity of FKN or CX3CR1 may exert antidepressant effects by either inhibiting its over-activation or restoring its physiological function. For instance, if FKN/CX3CR1 signaling is over-activated in depression and leads to a pro-inflammatory response, then developing CX3CR1 antagonists or FKN expression inhibitors may help alleviate neuroinflammation and depressive symptoms. Conversely, if insufficient FKN/CX3CR1 signaling function leads to a weakened protective role of microglia, then enhancing the activity of this pathway may have therapeutic potential. However, the FKN/CX3CR1 signaling pathway has a dual role, and its effects may depend on the specific pathological context and degree of activation; therefore, more in-depth research is needed to determine the optimal direction for intervention.

Traditional Chinese medicine (TCM) offers unique advantages in modulating the FKN/CX3CR1 pathway. Studies by Liu Zhuo and Liu Jian have shown that Chinese herbal formulas such as Zuogui Jiangtang Jieyu (ZGJTJY) formula can improve inflammatory responses and synaptic damage in models of depression with diabetes and depression with rheumatoid arthritis by regulating the FKN/CX3CR1 signaling pathway.[51,53] Future research could further isolate the active ingredients in ZGJTJY and deeply investigate their specific mechanisms of action on the FKN/CX3CR1 signaling pathway, with the aim of developing more targeted TCM monomers or compound preparations. In addition to ZGJTJY, other Chinese herbs and their active components have also been confirmed to have anti-inflammatory and antidepressant effects and may act by indirectly regulating the FKN/CX3CR1 pathway, such as Saikosaponin D,[56] curcuminoids,[57] Curcuma wenyujin,[58] rhubarb (Rheum officinale),[59] and Gan-Mai-Da-Zao decoction.[60] The anti-inflammatory effects of these herbs may have potential cross-regulation with the FKN/CX3CR1 signaling pathway, providing a molecular pharmacological basis for the integrated treatment of depression with traditional and Western medicine, which merits further investigation.

Other Immunomodulatory and Neuroprotective Strategies and Future Research Directions

In addition to FKN/CX3CR1, other immunomodulatory strategies also offer new ideas for depression treatment. The research by Yao suggests that inhibiting CCL5/CCR5-mediated neutrophil infiltration is a potential strategy for treating depression.[55] Inhibiting the NLRP3 inflammasome and the NF-κB pathway are also important directions; the study by Wahl showed that nano-oligomers targeting NF-κB and NLRP3 can reduce neuroinflammatory cytokines and improve cognitive function.[34] Luo also reviewed the research progress on the NLRP3 inflammasome and its inhibitors in central nervous system diseases.[36] Modulating microglial polarization, for example, by activating the adiponectin/AdipoR1 pathway through running exercise,[61] or regulating alveolar macrophage polarization via electroacupuncture,[49] may become effective strategies for treating depression. Targeting astrocytes, such as the small molecule inhibitors of Cx43 hemichannels discovered by Duarte,[54] also provides new avenues for depression treatment. Gut microbiota intervention, by regulating the gut microbiota through diet, probiotics, or fecal microbiota transplantation, can indirectly improve neuroinflammation and depressive symptoms.[32,33,46,62]

Despite notable progress in elucidating the association between FKN/CX3CR1 signaling and depression, substantial research gaps and challenges remain. Future investigations should aim to clarify the precise role of FKN/CX3CR1 in distinct depression subtypes and pathological stages, along with its fine-tuned regulatory mechanisms. Advanced methodologies such as single-cell analysis and spatial RNA profiling should be employed to accurately map the expression patterns and functional states of FKN/CX3CR1 across diverse brain regions and cell types. These approaches will also facilitate an in-depth exploration of its crosstalk with other inflammatory signaling pathways, including NF-κB, MAPK, and the inflammasome, as well as its specific influence on neurotransmitter systems, neurogenesis, and synaptic plasticity.

Parallel efforts are warranted to identify FKN/CX3CR1-associated biomarkers through large-scale clinical cohort studies, examining changes in relevant indicators within plasma, cerebrospinal fluid, and brain tissue of depression patients, thereby assessing their potential as diagnostic and prognostic tools. In addition, targeted therapeutic development should be prioritized, encompassing small-molecule inhibitors, monoclonal antibodies, and gene therapy strategies, while capitalizing on the pharmacological potential of traditional Chinese medicine to screen and optimize natural compounds capable of modulating FKN/CX3CR1 activity.

Moreover, integrating FKN/CX3CR1 research with other pathological mechanisms—such as gut microbiota imbalance, oxidative stress, epigenetic regulation of circadian clock genes,[63] mitochondrial dysfunction,[51,64] blood–brain barrier impairment,[65] and neurovascular unit abnormalities—will help construct a more comprehensive framework of depression pathogenesis, thereby fostering the design of multi-target, multi-pathway therapeutic strategies. Concurrently, the integration of genomics, proteomics, metabolomics, and neuroimaging will facilitate patient stratification, enable the identification of subgroups exhibiting FKN/CX3CR1 pathway dysregulation, and promote precision medicine approaches tailored to individual profiles.[66]

Finally, although accumulating evidence suggests that microRNAs (miRNAs) may function as molecular bridges linking neuroinflammation and depression,[67] there is still a lack of direct evidence demonstrating that they can be activated by upstream alterations in FKN/CX3CR1 and subsequently initiate downstream pathway activation.

Conclusion

This review has critically examined the role of the FKN/CX3CR1 signaling pathway in the nexus of neuroinflammation and depression. The available evidence indicates that this pathway is a compelling molecular link, particularly within depression subtypes characterized by a strong inflammatory component. By mediating neuron-microglia communication, it plays an undeniable role in regulating microglial homeostasis and synaptic health.

However, a sober assessment of the literature reveals that its specific role in primary MDD remains an open and critical question. Much of the enthusiasm for this pathway is extrapolated from comorbid disease models, where systemic inflammation provides a clear trigger for its dysregulation. The dual, context-dependent nature of FKN/CX3CR1 signaling—capable of both protective and pathogenic actions—further complicates its narrative as a straightforward therapeutic target.

Therefore, rather than being classified as a confirmed "pivotal node" in depression, the FKN/CX3CR1 pathway should be viewed more accurately as a promising but complex and potentially controversial player. Unlocking its true therapeutic potential is contingent upon future research that rigorously investigates its function in primary MDD models and elucidates the precise conditions that dictate its protective versus detrimental effects. Such work is essential to move beyond preliminary associations and pave the way for genuinely innovative and precise therapeutic strategies for depression.

Abbreviations

MDD, Major Depressive Disorder; FKN (CX3CL1), Fractalkine (CX3C chemokine ligand 1); HPA, Hypothalamic-Pituitary-Adrenal; CNS, central nervous system; TBI, traumatic brain injury; PI3K/Akt, phosphoinositide 3-kinase;

MAPK, mitogen-activated protein kinase; DG, dentate gyrus; PSD, post-stroke depression; CUMS, chronic unpredictable mild stress; NLRP3, NOD-like receptor family, pyrin domain-containing 3; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; IL-1β, Interleukin-1 beta; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-alpha; MSCs, Mesenchymal stem cells; SIRT1, Sirtuin 1; Nrf2, Nuclear Factor Erythroid 2-Related Factor 2; Cox-2, Cyclooxygenase-2; iNOS, inducible Nitric Oxide Synthase; LPS, inflammatory stimulus; PRMT2, Protein Arginine Methyltransferase 2; AS, atherosclerosis; DNA, Deoxyribonucleic Acid; RNAs, Ribonucleic Acid; m6A, N6-methyladenosine; DD, diabetes; ZGJTJY, Zuogui Jiangtang Jieyu; GFAP, glial fibrillary acidic protein; NR2A, Glutamate Ionotropic Receptor NMDA Type Subunit 2A; NR2B, Glutamate Ionotropic Receptor NMDA Type Subunit 2B; CD300f, CD300 Antigen Family Member f; GLUT1, Glucose Transporter 1; C3, Complement Component 3; UBE2K, Ubiquitin-Conjugating Enzyme E2 K; Cx, Connexin; NMDAR, N-Methyl-D-Aspartate Receptor; CCL5, C-C Motif Chemokine Ligand 5; CCR5+, C-C Chemokine Receptor Type 5 Positive; TCM, Traditional Chinese medicine; miRNAs, microRNAs.

Acknowledgments

The authors would like to thank Top Talent Program for the YingCai XingMeng.

Author Contributions

ZhiLi YanLuan: investigation, writing – original draft, visualization; Rula Sa: visualization; Yanting Fan: visualization; Jianmiao Ge: visualization; Huan Jia and Shuying Bai: writing – review and editing. Lijun Tong: funding acquisition. Ruiting Ma: writing – review and editing, conceptualization, funding acquisition.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Science and Technology Program Project of the Health Commission of Inner Mongolia Autonomous Region (2025WSJK076), Science and Technology Program Project of the Health Commission of Inner Mongolia Autonomous Region (2025WSJK066), The Clinical medicine research and clinical new technology promotion project of Inner Mongolia Medical Doctor Association (YSXH2024KYF015); The project of building high-level clinical specialties in public hospitals in the capital region (2023SGGZ045); The Clinical Need Oriented Basic Research Project of Inner Mongolia Academy of Medical Sciences (2023GLLH0149); Science and Technology Program of Inner Mongolia Autonomous Region (2025YFSH0066); College students entrepreneurship training program (101322025061).

Disclosure

The authors report no conflicts of interest in this work.

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