

Neuroinflammation in Ischemic Stroke: Mechanisms, Therapeutic Targets, and Future Perspectives

Jia Wang¹, Jiaqian Liu^{1*}

¹ Shaanxi University of Chinese Medicine, Xianyang, China

*Correspondence: Jiaqian Liu

Received: 23 May 2026; Accepted: 18 June 2026; Published: 25 July 2026

Abstract:

Ischemic stroke remains one of the leading causes of mortality and long-term disability worldwide. Although timely reperfusion therapies, including intravenous thrombolysis and mechanical thrombectomy, have significantly improved clinical outcomes, many patients continue to experience poor neurological recovery due to secondary brain injury. Neuroinflammation is increasingly recognized as a critical contributor to both acute ischemic damage and post-stroke tissue repair. Following cerebral ischemia, the activation of resident glial cells, disruption of the blood–brain barrier, infiltration of peripheral immune cells, and release of inflammatory mediators collectively shape the dynamic inflammatory microenvironment. Emerging evidence indicates that neuroinflammation exerts both detrimental and protective effects depending on the cellular context and temporal stage of ischemic injury. Recent advances in single-cell sequencing, spatial transcriptomics, and multi-omics technologies have further refined our understanding of immune cell heterogeneity and intercellular communication after stroke, providing novel opportunities for precision immunotherapy. This review summarizes the current understanding of the cellular and molecular mechanisms underlying neuroinflammation in ischemic stroke, discusses emerging therapeutic strategies targeting inflammatory pathways, and highlights current challenges and future directions for translating experimental discoveries into effective clinical interventions.

Keywords:

Ischemic Stroke, Neuroinflammation, Microglia, Neurovascular Unit, Precision Immunotherapy

1. Introduction

Ischemic stroke (IS) is the most common subtype of stroke, accounting for approximately 80–85% of all stroke cases worldwide, and remains a leading cause of mortality and long-term disability[1]. Although significant advances in reperfusion therapies, including intravenous thrombolysis and mechanical thrombectomy, have improved clinical outcomes, many patients continue to experience poor neurological recovery due to secondary brain injury following cerebral ischemia. The pathophysiology of ischemic stroke involves a complex cascade of events, including excitotoxicity, oxidative stress, mitochondrial dysfunction, blood–brain barrier (BBB)

disruption, programmed cell death, and neuroinflammation[2]. Among these mechanisms, neuroinflammation has emerged as a critical contributor to both acute ischemic injury and post-stroke recovery. Following cerebral ischemia, damaged neurons release damage-associated molecular patterns (DAMPs), which activate resident immune cells such as microglia and astrocytes and promote the recruitment of peripheral immune cells into the ischemic brain. The subsequent release of inflammatory cytokines, chemokines, and reactive oxygen species amplifies local inflammatory responses and profoundly influences stroke progression. Importantly, accumulating evidence suggests that neuroinflammation is a double-edged sword. Excessive or prolonged inflammatory activation can exacerbate neuronal death, BBB disruption, cerebral edema, and hemorrhagic transformation during the acute phase of stroke, whereas appropriately regulated immune responses contribute to debris clearance, angiogenesis, neurogenesis, and tissue repair during later stages[3]. Therefore, understanding the temporal and spatial dynamics of neuroinflammation is essential for developing effective therapeutic strategies. Recent advances in single-cell RNA sequencing, spatial transcriptomics, and multi-omics technologies have substantially improved our understanding of immune cell heterogeneity and intercellular communication within the ischemic microenvironment, revealing previously unrecognized cellular subsets and signaling networks involved in stroke pathology[4]. In this review, we summarize current advances in the cellular and molecular mechanisms underlying neuroinflammation after ischemic stroke, discuss emerging therapeutic targets and anti-inflammatory strategies, and highlight future directions for translating mechanistic insights into effective clinical interventions.

2. Cellular Basis of Neuroinflammation After Ischemic Stroke

2.1. Microglial activation and functional heterogeneity

Microglia are the resident innate immune cells of the central nervous system (CNS) and serve as the first responders to cerebral ischemic injury. Within minutes after arterial occlusion, microglia rapidly detect danger-associated molecular patterns (DAMPs) released from injured neurons and undergo profound morphological and functional changes. Activated microglia migrate toward the ischemic core, where they initiate innate immune responses through phagocytosis, antigen presentation, and the secretion of inflammatory mediators[5].

Traditionally, activated microglia were classified into pro-inflammatory M1 and anti-inflammatory M2 phenotypes. However, recent advances in single-cell RNA sequencing have revealed that microglial activation is considerably more heterogeneous than previously recognized. Distinct microglial subpopulations emerge dynamically throughout different stages of ischemic stroke, exhibiting diverse transcriptional profiles and functional properties that cannot be adequately described by the classical M1/M2 paradigm[6]. This functional heterogeneity suggests that microglia continuously adapt to the evolving ischemic microenvironment and may simultaneously exert neurotoxic and neuroprotective effects.

Activated microglia produce numerous inflammatory mediators, including interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), nitric oxide, and reactive oxygen species, which amplify local inflammation and promote the recruitment of circulating immune cells. Conversely, microglia also release neurotrophic factors and anti-inflammatory cytokines that facilitate debris clearance, angiogenesis, synaptic remodeling, and neurological recovery during later stages of

stroke. Therefore, therapeutic strategies aimed at modulating microglial function should focus on restoring immune homeostasis rather than broadly suppressing microglial activation.

2.2. Astrocyte-mediated inflammatory responses

Astrocytes are another major glial population involved in post-stroke neuroinflammation. Following ischemic injury, astrocytes undergo reactive astrogliosis characterized by cellular hypertrophy, proliferation, and marked alterations in gene expression[7]. Although reactive astrocytes are often categorized into neurotoxic A1 and neuroprotective A2 phenotypes, recent studies suggest that astrocytic responses exist along a dynamic spectrum rather than as two discrete states.

Reactive astrocytes contribute to the maintenance of BBB integrity by regulating endothelial function and extracellular ion homeostasis. However, excessive astrocyte activation may enhance inflammatory signaling through the secretion of cytokines, chemokines, and matrix metalloproteinases, thereby aggravating leukocyte infiltration and BBB disruption. In contrast, astrocytes also support neuronal survival by producing neurotrophic factors, regulating glutamate metabolism, and promoting tissue repair during the recovery phase, highlighting their context-dependent roles in ischemic stroke.

2.3. Peripheral immune cell infiltration

Disruption of the BBB after ischemic stroke permits the infiltration of peripheral immune cells into the injured brain, further amplifying local inflammatory responses[8]. Neutrophils are among the earliest infiltrating leukocytes and contribute to ischemic injury through the release of proteases, reactive oxygen species, and neutrophil extracellular traps (NETs), which exacerbate endothelial damage and microvascular obstruction.

Circulating monocytes subsequently infiltrate the ischemic tissue and differentiate into macrophages that cooperate with resident microglia in phagocytosing cellular debris and orchestrating inflammatory resolution. In addition, T lymphocytes play complex immunomodulatory roles following stroke. While pro-inflammatory T helper cells may aggravate neuronal injury through cytokine production, regulatory T cells contribute to immune suppression, BBB stabilization, and tissue repair. These findings underscore the importance of coordinated interactions between central and peripheral immune systems in determining stroke outcomes.

2.4. Cellular crosstalk within the neurovascular unit

Neuroinflammation after ischemic stroke is not mediated by individual cell types but rather by coordinated interactions within the neurovascular unit (NVU), which comprises neurons, astrocytes, microglia, endothelial cells, pericytes, and extracellular matrix components[9]. Ischemic injury disrupts the structural and functional integrity of the NVU, resulting in BBB breakdown, vascular dysfunction, and extensive immune cell infiltration. Endothelial cells regulate leukocyte adhesion and transmigration, whereas pericytes contribute to microvascular stability and inflammatory signaling. Increasing evidence indicates that bidirectional communication among glial cells, vascular cells, and infiltrating immune cells orchestrates both injury progression and tissue repair. Therefore, understanding the

cellular crosstalk within the NVU provides an essential foundation for the development of targeted immunomodulatory therapies.

3. Molecular Mechanisms of Neuroinflammation After Ischemic Stroke

Neuroinflammation after ischemic stroke is regulated by a complex network of intracellular signaling pathways that integrate danger signals, immune activation, oxidative stress, and cell death responses. Following cerebral ischemia, energy depletion and cellular injury lead to the release of damage-associated molecular patterns (DAMPs), including high mobility group box 1 (HMGB1), extracellular ATP, mitochondrial DNA, and heat shock proteins. These endogenous danger signals activate pattern recognition receptors (PRRs) expressed by microglia, astrocytes, endothelial cells, and infiltrating immune cells, subsequently triggering multiple inflammatory cascades[10]. Among these pathways, Toll-like receptor (TLR)-mediated NF- κ B activation, NLRP3 inflammasome signaling, JAK/STAT pathway, cGAS-STING activation, oxidative stress-related mechanisms, and ferroptosis have emerged as important regulators of post-stroke neuroinflammation.

3.1. TLR4/NF- κ B signaling pathway

The Toll-like receptor 4 (TLR4)/nuclear factor- κ B (NF- κ B) pathway represents one of the best-characterized inflammatory signaling cascades involved in ischemic stroke. Following cerebral ischemia, DAMPs released from damaged neurons activate TLR4 on microglia and other CNS-resident cells[11]. Activated TLR4 initiates downstream signaling through adaptor proteins such as MyD88 and TRIF, resulting in the phosphorylation and degradation of I κ B α and subsequent nuclear translocation of NF- κ B.

Once activated, NF- κ B regulates the transcription of numerous pro-inflammatory genes, including interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2). Excessive activation of this pathway promotes microglial inflammatory polarization, endothelial dysfunction, BBB disruption, and neuronal apoptosis. However, NF- κ B signaling is not exclusively detrimental, as transient activation may participate in tissue repair and immune regulation during later phases of stroke. Therefore, therapeutic strategies targeting TLR4/NF- κ B require precise temporal modulation rather than complete inhibition.

3.2. NLRP3 inflammasome activation

The nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome is a critical intracellular inflammatory platform that regulates innate immune responses after ischemic injury. NLRP3 activation requires two sequential signals: a priming signal mediated mainly by NF- κ B-dependent transcription of NLRP3 and pro-IL-1 β , followed by an activation signal induced by cellular stress factors such as mitochondrial dysfunction, reactive oxygen species (ROS), potassium efflux, and extracellular ATP.

Following activation, the NLRP3 inflammasome recruits apoptosis-associated speck-like protein containing a CARD (ASC) and activates caspase-1, leading to the maturation and release of IL-1 β and IL-18. In addition, inflammasome activation can induce pyroptotic cell death through gasdermin D cleavage, further amplifying

inflammatory responses[12]. Increasing evidence indicates that excessive NLRP3 activation contributes to neuronal injury, BBB impairment, and neurovascular inflammation after ischemic stroke. Consequently, targeting NLRP3 inflammasome activation has become an attractive therapeutic strategy for limiting secondary brain injury.

3.3. JAK/STAT signaling pathway

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway plays a dual role in regulating inflammatory responses after ischemic stroke. Cytokines such as IL-6, interferons, and other inflammatory mediators activate membrane-associated receptors, leading to JAK phosphorylation and subsequent STAT activation. Activated STAT proteins translocate into the nucleus and regulate the expression of genes involved in immune responses, inflammation, and cell survival[13].

Among STAT family members, STAT3 has received considerable attention in stroke research. Excessive STAT3 activation in microglia and astrocytes promotes the production of inflammatory mediators and contributes to glial activation. Conversely, controlled STAT3 signaling may support neuronal survival, angiogenesis, and recovery processes. The context-dependent effects of JAK/STAT signaling highlight the complexity of inflammatory regulation and suggest that selective modulation of specific STAT pathways may provide greater therapeutic benefits than broad pathway inhibition.

3.4. cGAS-STING pathway

The cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway has recently emerged as an important regulator of sterile inflammation after ischemic stroke. Under ischemic conditions, mitochondrial damage and nuclear injury result in the accumulation of cytosolic DNA, which is recognized by cGAS. Activated cGAS generates cyclic GMP-AMP (cGAMP), which binds to STING and induces downstream activation of interferon regulatory factors (IRFs) and NF- κ B.

Activation of the cGAS-STING pathway promotes the production of type I interferons and pro-inflammatory cytokines, contributing to microglial activation and inflammatory amplification. Recent studies suggest that excessive STING activation may aggravate ischemic brain injury, whereas pharmacological inhibition of this pathway can reduce inflammatory responses and improve neurological outcomes[14]. Given its role in linking cellular damage signals with immune activation, cGAS-STING represents a promising emerging target in stroke immunotherapy.

3.5. Oxidative stress and ROS-mediated inflammation

Oxidative stress is a major contributor to neuroinflammation following ischemic stroke. During ischemia and subsequent reperfusion, mitochondrial dysfunction, NADPH oxidase activation, and inflammatory responses lead to excessive production of reactive oxygen species (ROS). Elevated ROS levels directly damage lipids, proteins, and nucleic acids while simultaneously activating inflammatory signaling pathways, including NF- κ B and NLRP3 inflammasome signaling.

Furthermore, oxidative stress disrupts BBB integrity by impairing endothelial cells and increasing matrix metalloproteinase activity, thereby facilitating immune cell infiltration. Although endogenous antioxidant systems, particularly the nuclear factor

erythroid 2-related factor 2 (Nrf2) pathway, counteract oxidative injury, their protective capacity may become insufficient during severe ischemic stress[15]. Therefore, restoring redox balance represents a potential strategy for controlling neuroinflammation.

3.6. Ferroptosis and inflammatory regulation

Ferroptosis is a newly recognized form of regulated cell death characterized by iron accumulation and lipid peroxidation. Unlike apoptosis, ferroptosis is primarily driven by disturbances in iron metabolism and antioxidant defense systems, particularly the glutathione (GSH)-glutathione peroxidase 4 (GPX4) pathway[16]. Increasing evidence indicates that ferroptosis contributes to neuronal damage after ischemic stroke and interacts closely with inflammatory responses.

Ferroptotic cells release intracellular danger signals that activate immune responses, while inflammatory cytokines can further enhance oxidative stress and ferroptotic susceptibility. The interaction between ferroptosis, microglial activation, and inflammatory signaling represents an emerging area of stroke research. Targeting ferroptosis-related pathways may provide new opportunities for reducing inflammation-associated neuronal injury and improving functional recovery after ischemic stroke.

4. Therapeutic Strategies Targeting Neuroinflammation After Ischemic Stroke

Given the pivotal role of neuroinflammation in the progression and recovery of ischemic stroke, targeting inflammatory responses has emerged as an attractive therapeutic strategy[17]. However, unlike conventional neuroprotective approaches aimed at suppressing injury pathways, successful modulation of neuroinflammation requires maintaining a balance between inhibiting excessive inflammatory activation and preserving immune functions necessary for tissue repair. Recent therapeutic strategies have therefore shifted from broad immunosuppression toward selective regulation of inflammatory pathways, cellular responses, and immune microenvironments.

4.1. Pharmacological approaches targeting neuroinflammatory pathways

A variety of pharmacological agents have been investigated to modulate neuroinflammation after ischemic stroke. Several compounds targeting inflammatory mediators, immune signaling pathways, and oxidative stress responses have demonstrated neuroprotective effects in experimental models[18].

Minocycline, a tetracycline derivative with anti-inflammatory properties, has been extensively studied because of its ability to inhibit microglial activation, reduce inflammatory cytokine production, and suppress matrix metalloproteinase activity. Preclinical studies have demonstrated that minocycline can decrease infarct volume and improve neurological outcomes; however, clinical evidence remains inconclusive, highlighting the challenges of translating anti-inflammatory therapies into human stroke treatment.

Inflammasome-related therapies have also attracted increasing attention. Because excessive NLRP3 inflammasome activation contributes to IL-1 β maturation, pyroptosis, and BBB disruption, pharmacological inhibition of NLRP3 or downstream inflammatory mediators represents a promising strategy[19]. In addition, IL-1

receptor antagonists and agents targeting inflammatory cytokines have shown potential in reducing ischemic injury by limiting excessive immune activation.

Beyond direct inflammatory inhibition, modulation of endogenous protective pathways has emerged as another therapeutic approach. Activation of antioxidant pathways, particularly the Nrf2 pathway, can reduce oxidative stress and indirectly suppress inflammatory signaling. Similarly, regulation of NF- κ B, JAK/STAT, and other immune-related pathways may provide opportunities for controlling post-stroke inflammation. Nevertheless, because these pathways also participate in physiological immune regulation and tissue repair, future therapies require precise control of timing, dosage, and target specificity[20].

4.2. Mesenchymal stem cell-based therapy

Mesenchymal stem cell (MSC)-based therapy represents one of the most promising regenerative approaches for ischemic stroke. MSCs derived from bone marrow, adipose tissue, and other sources possess immunomodulatory, neuroprotective, and angiogenic properties. Rather than replacing damaged neurons directly, MSCs primarily exert therapeutic effects through paracrine mechanisms, including the secretion of growth factors, cytokines, and extracellular vesicles.

Following transplantation, MSCs can regulate immune responses by suppressing pro-inflammatory macrophage activation, reducing microglial inflammatory responses, and promoting anti-inflammatory immune phenotypes[21]. Furthermore, MSCs enhance angiogenesis, neurogenesis, and synaptic remodeling, thereby contributing to functional recovery after stroke.

Despite encouraging results from preclinical studies, several challenges limit clinical application. These include variability among different MSC sources, optimal administration routes, cell survival after transplantation, and potential immune-related complications[22]. Therefore, further optimization of MSC-based therapies and standardized clinical protocols are required before widespread clinical implementation.

4.3. Extracellular vesicles as cell-free therapeutic platforms

Extracellular vesicles (EVs), particularly exosomes, have recently emerged as promising alternatives to cell transplantation[23]. EVs are nano-sized membrane-bound vesicles released by various cell types and contain bioactive molecules, including microRNAs, proteins, lipids, and messenger RNAs. These cargos enable EVs to regulate recipient cell function and modulate inflammatory responses.

In ischemic stroke, MSC-derived extracellular vesicles have demonstrated significant neuroprotective effects by reducing microglial activation, suppressing inflammatory cytokine production, enhancing angiogenesis, and promoting neuronal survival. Compared with direct cell transplantation, EV-based therapies offer several advantages, including lower immunogenicity, improved safety profiles, and easier storage and delivery[24].

However, challenges remain regarding EV isolation methods, characterization standards, optimal dosage, and large-scale production. Future studies should focus on improving EV engineering approaches to enhance targeting efficiency and therapeutic potency.

4.4. Nanomedicine-based strategies for targeted immunomodulation

Nanomedicine provides a novel platform for improving the delivery of anti-inflammatory agents after ischemic stroke. Due to the complex inflammatory microenvironment and limited drug penetration into the ischemic brain, conventional systemic administration often results in insufficient therapeutic concentrations and unwanted adverse effects[25].

Nanoparticle-based delivery systems can enhance drug stability, improve BBB penetration, and provide targeted delivery to inflammatory cells such as activated microglia and macrophages. Various nanomaterials, including lipid nanoparticles, polymeric nanoparticles, and biomimetic nanoparticles, have been developed to deliver anti-inflammatory drugs, nucleic acids, and antioxidant molecules.

For example, nanoparticles designed to target inflammatory macrophages or reactive oxygen species-rich environments may selectively regulate pathological immune responses while preserving beneficial repair processes[26]. Although nanomedicine remains largely at the preclinical stage, its ability to achieve spatial and temporal control of drug delivery makes it a promising direction for future stroke immunotherapy.

4.5. Clinical translation and current challenges

Despite substantial progress in experimental studies, clinical translation of neuroinflammation-targeted therapies remains challenging. Several factors contribute to this gap. First, immune responses after stroke are highly dynamic, and therapeutic interventions may have different effects depending on the disease stage. Early suppression of inflammation may reduce tissue damage, whereas excessive inhibition during later stages may interfere with repair processes[27].

Second, substantial heterogeneity exists among patients due to differences in age, sex, stroke severity, comorbidities, and immune status. Therefore, identifying reliable biomarkers for patient stratification will be essential for implementing personalized immunomodulatory therapies.

Currently, several anti-inflammatory approaches have entered clinical evaluation, including cytokine-targeted therapies, stem cell-based interventions, and immune-modulating agents. However, consistent evidence supporting their efficacy remains limited. Future clinical trials should incorporate advanced imaging, immune profiling, and molecular biomarkers to identify appropriate patient populations and optimize therapeutic timing[28].

Overall, the future of neuroinflammation-based therapy for ischemic stroke is likely to shift from nonspecific immune suppression toward precision immunomodulation[29]. Combining molecular targets, advanced delivery systems, and individualized patient characteristics may provide new opportunities to improve neurological outcomes after stroke.

5. Future Perspectives

Although substantial progress has been made in understanding neuroinflammation after ischemic stroke, several critical challenges remain before effective immunomodulatory therapies can be successfully translated into clinical practice[30]. Future research should focus on developing more precise approaches that account for the complexity, heterogeneity, and temporal dynamics of post-stroke immune responses.

Single-cell sequencing technologies have revolutionized the investigation of cellular heterogeneity within the ischemic brain. Unlike traditional bulk sequencing approaches, single-cell RNA sequencing (scRNA-seq) enables the identification of distinct immune and glial cell populations and reveals their unique transcriptional signatures during different stages of stroke[31]. Integration of single-cell sequencing with spatial transcriptomics may further provide detailed information regarding the spatial distribution and functional interactions of immune cells within the neurovascular unit. These approaches are expected to facilitate the discovery of novel therapeutic targets and biomarkers for patient stratification[32].

Artificial intelligence (AI) and machine learning approaches represent another promising direction for advancing stroke immunotherapy. By integrating multi-omics data, imaging information, and clinical parameters, AI-based models may help predict inflammatory trajectories, identify patients who are most likely to benefit from specific interventions, and optimize treatment timing[33]. Furthermore, AI-driven drug discovery may accelerate the development of novel compounds targeting inflammatory pathways.

The future of neuroinflammation-based therapy will likely shift toward precision immunotherapy rather than generalized immune suppression. Because inflammatory responses after stroke involve both detrimental and protective mechanisms, future interventions should aim to selectively inhibit harmful immune activation while preserving endogenous repair processes. Strategies combining immune profiling, targeted drug delivery systems, extracellular vesicle engineering, and biomarker-guided treatment may provide more effective therapeutic solutions[34].

Nevertheless, several obstacles remain, including the lack of standardized biomarkers, insufficient understanding of long-term immune remodeling after stroke, and limited clinical validation of experimental findings. Addressing these challenges will require multidisciplinary collaboration among neuroscientists, immunologists, bioengineers, and clinicians. Ultimately, integrating advanced technologies with individualized therapeutic approaches may transform the management of ischemic stroke from broad neuroprotection toward precise immune-based intervention[35].

6. Conclusions

Neuroinflammation represents a central component of ischemic stroke pathology and plays a dual role in both brain injury and repair[4]. Following ischemic insult, coordinated interactions among microglia, astrocytes, peripheral immune cells, and the neurovascular unit determine the progression of inflammatory responses and neurological outcomes[36]. Multiple molecular pathways, including TLR4/NF- κ B, NLRP3 inflammasome, JAK/STAT, cGAS-STING, oxidative stress-related signaling, and ferroptosis, contribute to the regulation of post-stroke inflammation[37].

Although numerous therapeutic strategies targeting neuroinflammation have shown promising results, successful clinical translation remains challenging due to immune complexity and patient heterogeneity[38]. Future advances in single-cell technologies, spatial transcriptomics, artificial intelligence, and precision immunotherapy may provide new opportunities for developing individualized treatments[39]. A deeper understanding of immune regulation after stroke will be essential for transforming neuroinflammation from a therapeutic obstacle into a target for improving neurological recovery[40].

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

References

- [1] Arslan, E.; O. Cetinkaya. Analysis of the demographic characteristics and clinical profile of acute ischemic strokes admitted to the emergency centre in the Somalia population. *Afr J Emerg Med*, 2022. 12(3), 216-224.
- [2] Liu, X.W, et al. Photo-thermo-induced room-temperature phosphorescence through solid-state molecular motion. *Nat Commun*, 2022. 13(1), 3887.
- [3] Jurcau, A.; A. Simion Neuroinflammation in Cerebral Ischemia and Ischemia/Reperfusion Injuries: From Pathophysiology to Therapeutic Strategies. *Int J Mol Sci*, 2021. 23(1).
- [4] Lombardozi, G., et al. Neuroinflammation strokes the brain: A double-edged sword in ischemic stroke. *Neural Regen Res*, 2026. 21(5), 1715-1722.
- [5] Zhang, Y., et al. Microglia: The Hub of Intercellular Communication in Ischemic Stroke. *Front Cell Neurosci*, 2022. 16, 889442.
- [6] Ma, H., et al. Microglia Exhibit Distinct Heterogeneity Rather than M1/M2 Polarization within the Early Stage of Acute Ischemic Stroke. *Aging Dis*, 2023. 14(6), 2284-2302.
- [7] He, T.; G.Y. Yang.; Z. Zhang. Crosstalk of Astrocytes and Other Cells during Ischemic Stroke. *Life (Basel)*, 2022. 12(6).
- [8] Vandenbark, A.A., et al. Microglia and astrocyte involvement in neurodegeneration and brain cancer. *J Neuroinflammation*, 2021. 18(1), 298.
- [9] Wang, L. et al. Neurovascular Unit: A critical role in ischemic stroke. *CNS Neurosci Ther*, 2021. 27(1), 7-16.
- [10] Kursun, O., et al. Migraine and neuroinflammation: the inflammasome perspective. *J Headache Pain*, 2021. 22(1), 55.
- [11] Wang, H., et al. Regulation of microglia polarization after cerebral ischemia. *Front Cell Neurosci*, 2023. 17, 1182621.
- [12] Moltrasio, C.; M. Romagnuolo.; A.V. Marzano. NLRP3 inflammasome and NLRP3-related autoinflammatory diseases: From cryopyrin function to targeted therapies. *Front Immunol*, 2022. 13, 1007705.
- [13] Fornari Laurindo, L., et al. Immunological dimensions of neuroinflammation and microglial activation: exploring innovative immunomodulatory approaches to mitigate neuroinflammatory progression. *Front Immunol*, 2023, 14, 1305933.
- [14] Kong, L., et al. mtDNA-STING Axis Mediates Microglial Polarization via IRF3/NF- κ B Signaling After Ischemic Stroke. *Front Immunol*, 2022. 13, 860977.

- [15] Wang, L. et al. Nrf2 Regulates Oxidative Stress and Its Role in Cerebral Ischemic Stroke. *Antioxidants (Basel)*, 2022. 11(12).
- [16] Stockwell, B.R. Ferroptosis turns 10: Emerging mechanisms, physiological functions, and therapeutic applications. *Cell*, 2022. 185(14), 2401-2421.
- [17] Candelario-Jalil, E.; R.M. Dijkhuizen.; T. Magnus. Neuroinflammation, Stroke, Blood-Brain Barrier Dysfunction, and Imaging Modalities. *Stroke*, 2022. 53(5), 1473-1486.
- [18] Yang, Q., et al. Potential Neuroprotective Treatment of Stroke: Targeting Excitotoxicity, Oxidative Stress, and Inflammation. *Front Neurosci*, 2019, 13, 1036.
- [19] Bellut, M., et al. NLPR3 inflammasome inhibition alleviates hypoxic endothelial cell death in vitro and protects blood-brain barrier integrity in murine stroke. *Cell Death Dis*, 2021, 13(1), 20.
- [20] Peng, L. et al., Microglia autophagy in ischemic stroke: A double-edged sword. *Front Immunol*, 2022. 13, 1013311.
- [21] Miclau, K., et al. Cellular expansion of MSCs: Shifting the regenerative potential. *Aging Cell*, 2023, 22(1), e13759.
- [22] Shan, Y. et al. Pharmacokinetic characteristics of mesenchymal stem cells in translational challenges. *Signal Transduct Target Ther*, 2024. 9(1), 242.
- [23] Wang, D.R.; J. Pan. Extracellular vesicles: Emerged as a promising strategy for regenerative medicine. *World J Stem Cells*, 2023. 15(4), 165-181.
- [24] Lui, P.P.Y.; Y.T. Leung. Practical Considerations for Translating Mesenchymal Stromal Cell-Derived Extracellular Vesicles from Bench to Bed. *Pharmaceutics*, 2022. 14(8).
- [25] Liu, W., et al. Targeted pathophysiological treatment of ischemic stroke using nanoparticle-based drug delivery system. *J Nanobiotechnology*, 2024, 22(1), 499.
- [26] Mata, R., et al. The Dynamic Inflammatory Tissue Microenvironment: Signaling and Disease Therapy by Biomaterials. *Research (Wash D C)*, 2021, 2021, 4189516.
- [27] Iadecola, C.; M.S. Buckwalter.; J. Anrather. Immune responses to stroke: mechanisms, modulation, and therapeutic potential. *J Clin Invest*, 2020, 130(6), 2777-2788.
- [28] Cera, J.; W. Krzyściak. Targeting Neuroinflammation in Adult Ischemic Stroke: Direct Immunotherapy, Regenerative Cell-Based Strategies, and Translational Challenges-A Systematic Review with Exploratory Meta-analysis. *Mol Neurobiol*, 2026, 63(1).
- [29] Saceleanu, V.M., et al. Integrative Approaches in Acute Ischemic Stroke: From Symptom Recognition to Future Innovations. *Biomedicines*, 2023. 11(10).
- [30] Alsbrook, D.L. et al. Neuroinflammation in Acute Ischemic and Hemorrhagic Stroke. *Curr Neurol Neurosci Rep*, 2023, 23(8), 407-431.
- [31] Qiu, M., et al. Cell Heterogeneity Uncovered by Single-Cell RNA Sequencing Offers Potential Therapeutic Targets for Ischemic Stroke. *Aging Dis*, 2022. 13(5), 1436-1454.

- [32] Liu, J., et al. Transcriptomics, single-cell sequencing and spatial sequencing-based studies of cerebral ischemia. *Eur J Med Res*, 2025. 30(1), 326.
- [33] Wenner, A.K.; L. Anderegggen.; M.M. Luedi. Molecular Mechanisms Driving Precision Medicine in Perioperative Care: Integrating Inflammation, Metabolism, and Neuroimmunomodulation for Personalized Outcomes. *Int J Mol Sci*, 2025. 26(24).
- [34] Qiu, C.; A. Lindley.; X. Jia. Stem Cell-Derived Extracellular Vesicle Therapy in Ischemic Brain Injuries. *J Stroke*, 2025. 27(3), 313-328.
- [35] Levinson, S.; B. Pulli.; J.J. Heit. Neuroinflammation and acute ischemic stroke: impact on translational research and clinical care. *Front Surg*, 2025. 12, 1501359.
- [36] Ma, F., et al. Cellular Communication Networks Mediated by Microglia in Ischemic Stroke. *CNS Neurosci Ther*, 2025, 31(12), e70687.
- [37] Tian, X. et al. Progress of Ferroptosis in Ischemic Stroke and Therapeutic Targets. *Cell Mol Neurobiol*, 2024. 44(1), 25.
- [38] Gowtham, A., et al. An update on the role of ferroptosis in ischemic stroke: from molecular pathways to Neuroprotection. *Expert Opin Ther Targets*, 2024. 28(12), 1149-1175.
- [39] Li, T. et al. Artificial intelligence in cancer immunotherapy: Applications in neoantigen recognition, antibody design and immunotherapy response prediction. *Semin Cancer Biol*, 2023. 91, 50-69.
- [40] Magnus, T.; A. Liesz. Unveiling the immunopathology of stroke: a comprehensive view on brain-immune interaction. *Semin Immunopathol*, 2023. 45(3), 279-280.



© 2026 by the author(s); licensee International Technology and Science Publications (ITS), this work for open access publication is under the Creative Commons Attribution International License (CC BY 4.0). (<http://creativecommons.org/licenses/by/4.0/>)