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Review Article

Research Progress on the Molecular Mechanisms of Immune and Inflammatory Pathways and Targeted Therapy in Acute Cerebral Infarction

Gaobin Liang[1], Chongdong Jian[2*]

[1] *Graduate School, Youjiang Medical University for Nationalities, Baise 533000, Guangxi Zhuang Autonomous Region, China.*

[2] *Department of Neurology, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise 533000, Guangxi Zhuang Autonomous Region, China.*

Abstract Neural injury in acute cerebral infarction (ACI) is not only caused by ischemia and hypoxia but is also closely associated with complex immune and inflammatory responses. Recent studies have revealed that key inflammatory pathways, including TLR4/NF-κB, the NLRP3 inflammasome/IL-1β, JAK/STAT, and the complement system, play central roles in the pathogenesis of ACI and have emerged as potential therapeutic targets. These pathways modulate inflammation in ACI; however, challenges remain in achieving precise spatiotemporal regulation. The application of multi-omics technologies and the development of precision drugs will promote the clinical translation of immune-targeted interventions for ACI.

Keywords: Acute cerebral infarction; neuroinflammation; TLR4/NF-κB; NLRP3 inflammasome; JAK/STAT; complement system; targeted therapy

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Cerebrovascular diseases are common and frequently occurring conditions in the nervous system, among which acute cerebral infarction (ACI) is the most prevalent, accounting for approximately 80% of all strokes [1]. ACI is characterized by high incidence, disability, and recurrence rates. Despite treatment, most patients still suffer from sequelae such as hemiplegia, imposing a significant economic and caregiving burden on both families and society. The pathogenesis of ACI is not only due to direct ischemic injury caused by the interruption of blood flow but also involves complex secondary inflammatory responses. Key inflammatory pathways—including TLR4/NF-κB, the NLRP3 inflammasome/IL-1β, JAK/STAT, and the complement system—play central roles in the progression of ACI and have thus garnered significant attention as potential therapeutic targets.

1. The Relationship Between TLR4/NF-κB and ACI

The Toll-like receptor 4 (TLR4)/nuclear factor κB (NF-κB) signaling pathway plays a crucial role in mediating early inflammatory responses. TLR4 is a pattern recognition receptor (PRR) of the innate immune system that recognizes endogenous danger signals (e.g., DAMPs), while NF-κB is a key transcription factor that regulates the

*Correspondence: Chongdong Jian, Department of Neurology, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise 533000, Guangxi Zhuang Autonomous Region, China. Email: 2515097438@qq.com

expression of pro-inflammatory cytokines. In the course of ACI, activation of the TLR4/NF-κB pathway occurs across multiple stages, exacerbating neuroinflammation and influencing disease progression and prognosis [2].

1.1Ischemia and hypoxia trigger activation of the TLR4/NF-κB pathway:

In the hyperacute phase of ACI (0–6 h), ischemic and hypoxic brain tissue releases large amounts of DAMPs such as high-mobility group box 1 (HMGB1), heat shock proteins (HSPs), and ATP. These molecules bind to TLR4 and activate NF-κB via the MyD88-dependent pathway, leading to upregulation of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) and chemokines (e.g., MCP-1, ICAM-1), promoting microglial activation and neutrophil recruitment. Studies have shown that elevated serum TLR4 and HMGB1 levels in ACI patients are significantly associated with increased infarct volume and worsening neurological function, suggesting that excessive pathway activation may aggravate brain injury.

1.2 NF-κB-driven inflammation exacerbates blood-brain barrier (BBB) disruption:

NF-κB activation induces expression of matrix metalloproteinase-9 (MMP-9), which degrades basement membrane proteins (e.g., occludin, claudin-5), compromising BBB integrity, increasing vascular permeability, and raising the risk of vasogenic cerebral edema and hemorrhagic transformation. Additionally, this pathway upregulates adhesion molecules (VCAM-1, ICAM-1), facilitating leukocyte adhesion and infiltration into ischemic brain tissue, further releasing reactive oxygen species (ROS) and pro-inflammatory mediators, forming a "vicious cycle" of inflammation.

1.3 Therapeutic targeting of TLR4/NF-κB in ACI:

Due to its pivotal role in ACI, the TLR4/NF-κB pathway has been investigated as a potential therapeutic target in recent years.

· TLR4 antagonist (TAK-242): Shown to reduce infarct volume and decrease pro-inflammatory cytokine release in mouse models [3].

· NF-κB inhibitors (e.g., Bay11-7082): Exhibit anti-inflammatory and neuroprotective effects in ischemia-reperfusion injury models [4].

· Natural anti-inflammatory compounds (e.g., curcumin, resveratrol): Partially inhibit NF-κB-mediated inflammation, reducing neuronal injury [5, 6].

However, most current studies are preclinical, and further clinical trials are needed to validate safety and efficacy. Future strategies may involve multi-omics approaches to identify key regulatory molecules in the TLR4/NF-κB pathway for optimized precision anti-inflammatory treatment of ACI.

2. The Relationship Between the NLRP3 Inflammasome/IL-1β Signaling Pathway and ACI

The NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome is a multiprotein complex composed of NLRP3, the adaptor protein ASC, and pro-caspase-1. It plays a central role in the innate immune response by regulating the maturation and release of interleukin-1β (IL-1β) and interleukin-18 (IL-18). In ACI, ischemic injury, oxidative stress, mitochondrial damage, and ion flux disturbances activate the NLRP3 inflammasome, triggering a cascade of inflammatory responses.

2.1 NLRP3 activation exacerbates neuronal injury and brain edema:

Following ischemia-reperfusion, large amounts of DAMPs (e.g., ATP, ROS, mitochondrial DNA) activate the NLRP3 inflammasome via P2X7 receptor and ROS-NLRP3 pathways. This leads to the cleavage of pro-caspase-1 into active caspase-1, promoting the conversion of pro-IL-1β and pro-IL-18 into their mature forms. IL-1β, as a potent pro-inflammatory cytokine, enhances endothelial permeability and leukocyte infiltration, further damaging the blood-brain barrier and increasing cerebral edema and infarct volume.

2.2 NLRP3-mediated pyroptosis aggravates tissue damage:

Recent studies have found that NLRP3 activation not only promotes inflammatory cytokine release but also induces pyroptosis—a form of inflammatory programmed cell death. Activated caspase-1 cleaves gasdermin D (GSDMD), forming pores in the plasma membrane, resulting in cell swelling, rupture, and the release of large amounts of pro-inflammatory mediators, thus amplifying the local inflammatory response. Pyroptosis occurs in microglia, neurons, and endothelial cells in ischemic brain tissue, worsening neurological damage.

2.3 Targeting the NLRP3 inflammasome as a therapeutic strategy:

- MCC950, a specific NLRP3 inhibitor, has been shown in multiple experimental ACI models to significantly reduce infarct size, brain edema, and improve neurological scores [7].
- IL-1β antagonists, such as anakinra, have demonstrated neuroprotective effects in ischemic brain injury models, suggesting that blocking downstream cytokines can also effectively alleviate inflammation [8].
- Natural compounds like baicalin, luteolin, and ginsenoside Rg1 have been reported to inhibit NLRP3 activation and exert anti-inflammatory effects.

Taken together, the NLRP3 inflammasome is not only a key component of ACI-related inflammation but also a promising target for intervention. Future research may focus on exploring upstream regulatory mechanisms and clinical translation of NLRP3-targeted therapies.

3. The Relationship Between the JAK/STAT Signaling Pathway and ACI

In recent years, studies have revealed that the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway plays a critical role in the pathogenesis of acute cerebral infarction (ACI), influencing the progression and prognosis of ischemic brain injury by regulating inflammation, apoptosis, and oxidative stress.

3.1 Activation of the JAK/STAT pathway and ischemic brain injury:

After cerebral ischemia, damaged neurons and glial cells release cytokines (e.g., IL-6, IL-10, IFN-γ) and growth factors (e.g., EGF, PDGF), which bind to their respective receptors and activate members of the JAK kinase family (JAK1, JAK2, JAK3, TYK2). These kinases then phosphorylate STAT proteins—especially STAT1, STAT3, and STAT5. The phosphorylated STATs dimerize and translocate to the nucleus, where they regulate the transcription of inflammatory cytokines (e.g., TNF-α, IL-1β), anti-apoptotic proteins (e.g., Bcl-2), and oxidative stress-related genes. Experimental studies have shown significantly increased phosphorylation levels of JAK2 and STAT3 in the serum and ischemic brain tissues of ACI

patients, which are positively correlated with infarct size and neurological deficits, indicating that aberrant activation of this pathway exacerbates post-ischemic inflammation and neuronal injury.

3.2 Dual role of STAT3: pro-inflammatory and neuroprotective [15]:

STAT3 is a core molecule in the JAK/STAT pathway and exerts both pro-inflammatory and neuroprotective effects in ACI.

· Pro-inflammatory effect: Activated STAT3 upregulates the expression of COX-2, iNOS, and MCP-1, promotes microglia/macrophage polarization toward the M1 phenotype, and releases large quantities of pro-inflammatory cytokines, aggravating neuroinflammation.

· Neuroprotective effect: STAT3 also promotes the expression of Bcl-2 and HIF-1α, enhances neuronal anti-apoptotic capacity, and plays a positive role in angiogenesis following ischemia. Studies suggest that transient activation of STAT3 may protect neurons, whereas sustained activation exacerbates inflammation, highlighting the importance of precise spatiotemporal regulation of STAT3 activity.

3.3 JAK/STAT pathway as a therapeutic target for ACI [17]:

Given its pivotal role in ACI, several therapeutic strategies have been explored:

· JAK inhibitors (e.g., tofacitinib, baricitinib): Preclinical studies have shown that they can reduce STAT3 phosphorylation, attenuate neuroinflammation, and decrease infarct size.

· STAT3-specific siRNA or inhibitors (e.g., Stattic): In animal models, these have improved neurological outcomes after ischemia, though excessive inhibition may compromise STAT3's protective functions.

· Combined anti-inflammatory therapy: Co-administration with IL-1β or NF-κB inhibitors may synergistically suppress inflammatory cascades.

The JAK/STAT signaling pathway plays a complex role in ACI by modulating inflammation, oxidative stress, and apoptosis. Future studies should further clarify the spatiotemporal dynamics of STAT3 regulation and optimize targeted therapies to improve safety and efficacy, offering new strategies for precise intervention in ACI.

4. The Relationship Between the Complement System and AIS

Excessive activation of the complement system has been confirmed as a key mechanism promoting neuroinflammation and ischemic brain injury. As a crucial component of innate immunity [18], the complement system can be activated via the classical, lectin, and alternative pathways, generating various effector molecules (e.g., C3a, C5a, and the membrane attack complex [MAC]). These molecules aggravate post-ischemic inflammatory responses, disrupt the blood-brain barrier (BBB), and contribute to neuronal death [19, 20].

4.1 Mechanisms of complement system activation in AIS:

In the early stage of AIS, ischemia and hypoxia cause neurons and vascular endothelial cells to release damage-associated molecular patterns (DAMPs), such as mitochondrial DNA and heat shock proteins. These molecules activate the complement cascade through the classical pathway (C1q-mediated) or the lectin pathway

(via MBL-MASP complexes). Additionally, oxidative stress products generated during ischemia-reperfusion can activate the alternative pathway, amplifying complement activation. Clinical studies have demonstrated significantly elevated levels of C3a, C5a, and MAC in the serum and cerebrospinal fluid of AIS patients, which are closely associated with infarct volume and the severity of neurological deficits [21].

4.2 Roles of complement effector molecules in ischemic brain injury:

· Pro-inflammatory effects [22]: The complement activation product C5a binds to its receptor (C5aR1), promoting infiltration of microglia and neutrophils and stimulating the release of pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β), thereby exacerbating neuroinflammation.

· Blood-brain barrier disruption: C3a and C5a increase vascular permeability and upregulate matrix metalloproteinase-9 (MMP-9), which degrades tight junction proteins, leading to cerebral edema and increased risk of hemorrhagic transformation.

· Direct cytotoxicity: MAC (C5b-9) deposits on neuronal and glial cell membranes, triggering calcium influx and cell lysis, further aggravating apoptosis in the ischemic penumbra. Additionally, the complement system interacts with the coagulation system and may promote microthrombus formation, further impairing cerebral perfusion.

4.3 Therapeutic potential of targeting the complement system:

Given its detrimental effects in AIS, multiple intervention strategies are under exploration:

· C5a receptor antagonists (e.g., PMX53): Shown in animal models to reduce neutrophil infiltration and infarct size.

· C3 inhibitors (e.g., Compstatin analogs): Inhibit upstream complement activation and block the generation of C3a, C5a, and MAC.

· Anti-MAC antibodies: Protect cells from lytic injury caused by membrane attack complexes.

However, since the complement system also plays a role in tissue repair, complete inhibition may impair neuroregeneration. Therefore, development of spatiotemporally specific regulatory strategies is essential.

Excessive complement activation exacerbates post-AIS neurological injury through pro-inflammatory actions, BBB disruption, and direct cytotoxicity. Future research should delve into the molecular mechanisms underlying complement regulation and optimize targeted therapeutic strategies to balance its detrimental and protective effects, offering new directions for immune interventions in AIS.

Conflict of Interests statement

None.

Conflict of funding statement

None.

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