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REVIEW

Targeting the NLRP3-ROS Axis: Disrupting the Oxidative-Inflammatory Vicious Cycle in Intracerebral Hemorrhage

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Abstract: Intracerebral hemorrhage (ICH) is a highly fatal disease that currently lacks effective treatment options. However, secondary brain injury has become a key focus in translational research, with oxidative stress (OS) identified as a central factor in ICH pathophysiology. Following ICH, hematoma components and inflammatory factors overwhelm the antioxidant defense system, triggering OS. Concurrently, neuroinflammation arises, driven by activated microglia that adopt a pro-inflammatory phenotype and release cytokines and chemokines. While neuroinflammation may support repair, it can also cause harmful secondary damage. Recent evidence indicates that NLRP3 is an important inflammasome considered a key player in OS and neuroinflammation. OS can activate the NLRP3 inflammasome by producing reactive oxygen species (ROS), further exacerbating the inflammatory response. Additionally, NLRP3 also plays an important role in regulating neuroinflammation. The activation of the NLRP3 inflammasome promotes the release of pro-inflammatory cytokines, further intensifying the neuroinflammatory response. The activation of NLRP3 is closely related to the polarization of microglia, potentially driving microglia to polarize towards the M1 type (pro-inflammatory), thereby exacerbating neuroinflammation. Therefore, we hypothesize that NLRP3 plays a critical regulatory role in OS and neuroinflammation following ICH. This review summarizes the regulatory role of the NLRP3 inflammasome in the interplay between OS and neuroinflammation, as well as its potential therapeutic targets related to ICH.

Keywords: intracerebral hemorrhage, NLRP3 inflammasome, oxidative stress, neuroinflammation, brain injury

Introduction

Intracerebral hemorrhage (ICH) is a severe neurological disorder caused by the rupture of blood vessels within the brain parenchyma, characterized by high mortality rates and significant neurological dysfunction.[1] In the United States, Europe, and Australia, ICH accounts for approximately 10% to 15% of all strokes, while in Asia, it accounts for 20% to 30% of all stroke cases.[2] Although our understanding of its underlying pathological mechanisms has rapidly progressed over the past two decades, there are currently no pharmacological or surgical treatments that can significantly improve neurological function after ICH.[3] After ICH, brain tissue undergoes a series of pathophysiological changes, among which neuroinflammation is a significant process.[4] Following ICH, microglia are rapidly activated, exhibiting a pro-inflammatory phenotype and releasing cytokines and chemokines.[5] The neuroinflammation triggered by ICH may have beneficial reparative effects but can also lead to harmful secondary damage.[6] Oxidative stress (OS) plays an important role after ICH as well. Following ICH, brain tissue is affected by hematoma, components of red blood cells, and inflammatory factors, leading to an overload of the antioxidant defense system and subsequently triggering OS.[7] After OS, the blood-brain barrier (BBB) is compromised, inducing an inflammatory response and releasing inflammatory mediators, which exacerbates neuroinflammation.[8] OS is closely related to neuroinflammation following ICH.[9] NLRP3 is

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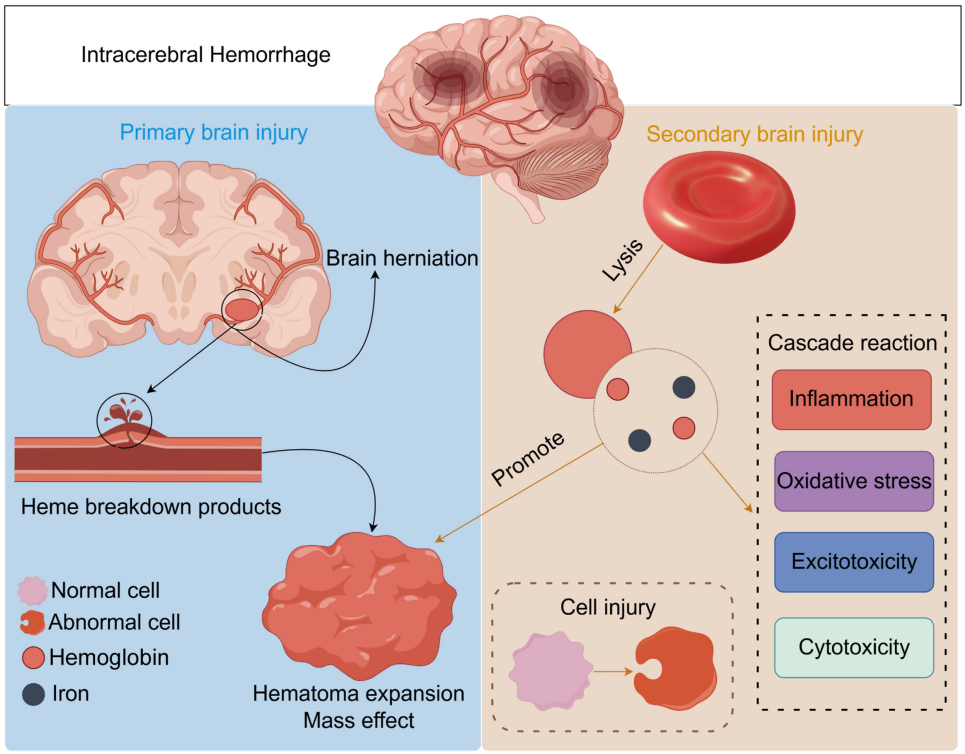

Figure 1 Mechanisms following ICH. Primary injury results from hematoma compression, elevating intracranial pressure and reducing cerebral blood flow. Secondary injury involves cytotoxicity, inflammation, and OS triggered by thrombin, hemoglobin/iron release, and complement activation. These processes disrupt BBB, induce edema, and promote neuronal death, persisting from minutes to weeks post-ICH.

a central mediator of OS and neuroinflammation, establishing a vicious cycle.[10–13] In this review, we summarize the mediating role of the NLRP3 inflammasome in OS and neuroinflammation following ICH, as well as its potential therapeutic targets.

Pathophysiological Mechanisms of ICH

Brain injury caused by ICH is generally believed to primarily include primary injury resulting from direct compression and stimulation by hematomas, and secondary brain injury induced by the pathophysiological reactions of hematomas (Figure 1).[14] The severity of primary injury is closely related to the volume of bleeding, the location and volume of the hematoma, and the degree of edema surrounding the hematoma.[15] After ICH, blood in the brain parenchyma compresses brain regions, leading to increased intracranial pressure, reduced cerebral blood flow, and potentially causing brain herniation.[16] The hematoma is composed of red blood cells, red blood cell lysis products, thrombin, complement, and immunoglobulins.[17] The release of these toxic substances triggers danger-associated molecular patterns, which not only initiate innate immune responses but also lead to neuronal death, necrosis surrounding the hematoma, and BBB disruption.[17] This results in cerebral edema, subsequently causing secondary brain injury and neurological dysfunction.[18] Secondary brain injury following ICH is the result of a series of complex reactions, including cytotoxicity, excitotoxicity, inflammation, and OS, which lead to BBB disruption, cerebral edema, and cell death.[19] These cascade reactions begin within minutes and may persist for days to weeks or even longer.[20] The coagulation cascade is rapidly activated following ICH and persists for 24 hours.[21] Insufficient thrombin activity in ICH may lead to hematoma expansion and persistent bleeding.[22] Conversely, high concentrations of thrombin can induce secondary injury through multiple kinases and their receptors, activate the complement cascade, participate in the formation of membrane attack complex, and recruit microglia.[23] These reactions lead to excitotoxicity and inflammation.[23] Moreover, hemoglobin and iron released from the hematoma, along with complement activation or energy depletion, are primary causes of subsequent brain injury, including oxidation, inflammation, BBB disruption, edema, and cell death.[14]

OS After ICH

OS refers to the excessive imbalance of reactive oxygen species (ROS) and/or a deficiency in the antioxidant system within cells. Reactive nitrogen species (RNS) are primarily composed of nitric oxide and its derivatives (Figure 2).[24] ROS are generated from oxygen radicals (such as superoxide anion radical and hydroxyl radical) and non-radical oxidants (such as hydrogen peroxide and singlet oxygen).[25] RNS include nitric oxide and nitrogen dioxide. The damage caused by OS in the body is primarily due to ROS, which arise from two different mechanisms: first, due to their unstable and highly reactive chemical nature, ROS react with lipids, proteins, and DNA, leading to cellular aging and death; second, ROS participate in cellular homeostasis functions through heat shock transcription factor 1, nuclear factor-kappa B (NF-κB), phosphoinositide 3-kinase, and mitogen-activated protein kinases.[24] OS is a condition in which the body responds to harmful stimuli by producing excessive amounts of ROS and RNS. Free radicals are characterized by their high reactivity and unstable chemical properties, which cause them to capture electrons from other molecules, stabilizing themselves. Free radicals can damage cell membranes, internal membranes, proteins, lipids, and DNA molecules, leading to cellular or tissue damage.[3] The brain has a high lipid content but low levels of antioxidants such as superoxide dismutase, making it particularly susceptible to OS damage.[3] Additionally, the oxygen consumption of human brain cells accounts for 20% of the total oxygen consumption of the body, while the brain only weighs 2% of the body, indicating that the free radicals produced in the brain are significantly greater than those produced in other

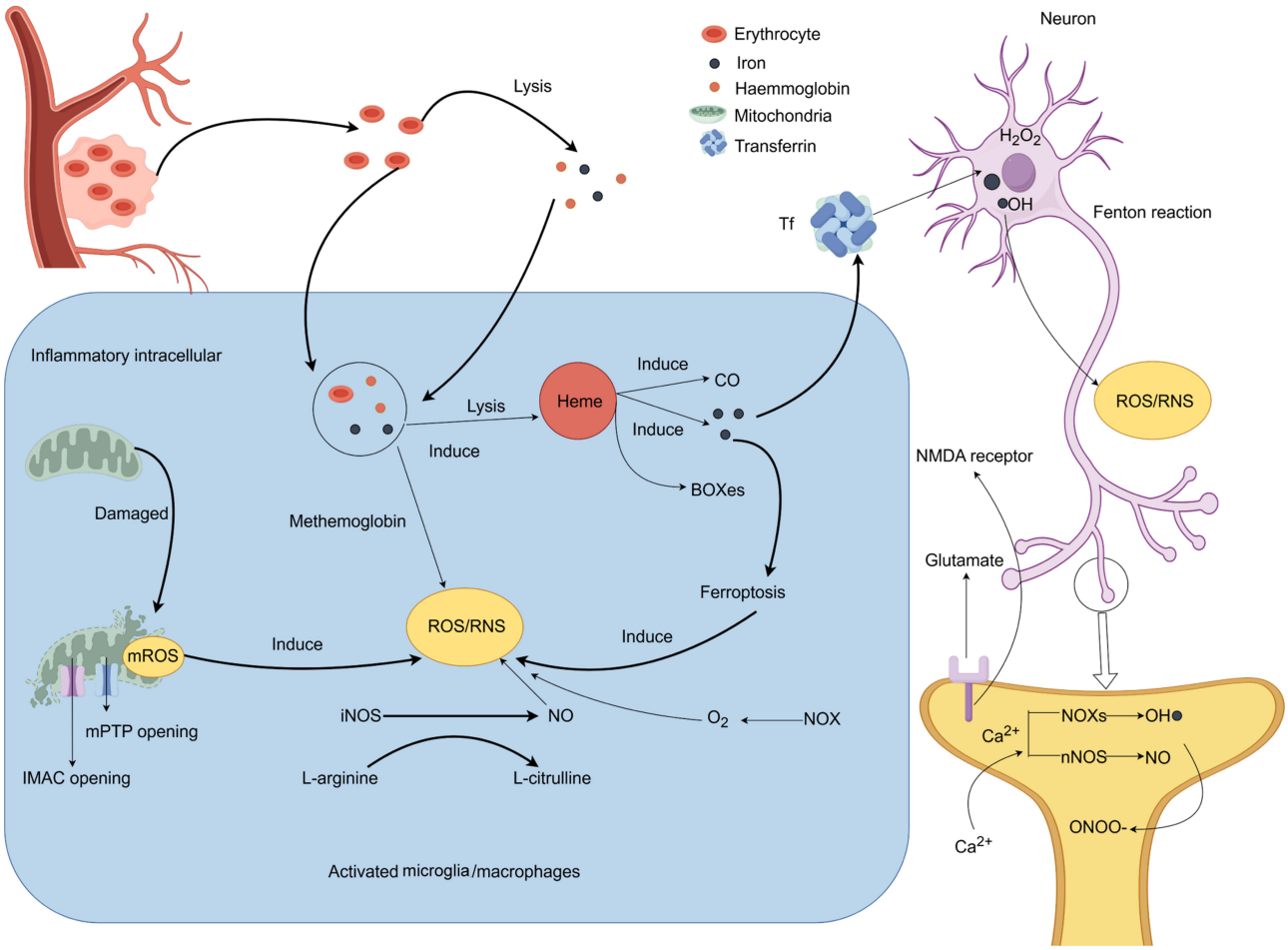

Figure 2 Major pathways of ROS/RNS generation after ICH. ICH induces erythrocyte lysis, releasing hemoglobin and heme engulfed by microglia/macrophages. Hemoglobin oxidation produces free radicals, while heme oxygenase (HO) degrades heme into iron, biliverdin, and carbon monoxide. Transferrin-mediated iron transport facilitates Fenton reactions with H2O2, generating cytotoxic hydroxyl radicals (•OH). Mitochondrial dysfunction (via IMAC/mPTP) and glutamate-triggered NMDA receptor activation promote calcium overload, stimulating neuronal nitric oxide synthase (NOS) and NADPH oxidases (NOXs) to synthesize nitric oxide (NO) and superoxide (O2•−), which combine into peroxynitrite (ONOO−). Microglial NOX/NOS systems further amplify OS, exacerbating neuronal injury.

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organs.[26] Compared to other organs, the brain contains a large amount of iron, which can catalyze the production of free radicals.[26] The brain is also rich in lipids containing unsaturated fatty acids, which are targets for lipid peroxidation, and it has a low to moderate protective antioxidant system.[26] Therefore, the brain is more vulnerable to damage caused by OS. Following ICH, the primary sources of ROS are the activated neutrophils, microglia, and macrophages. The most prominent source of these is microglia. In addition, OS plays a critical role in regulating the pathophysiology following ICH. After ICH, OS can promote the upregulation of autophagy to clear dysfunctional mitochondria, damaged intracellular proteins, and other impaired organelles, thereby maintaining intracellular homeostasis.[27] Moreover, molecular networks damaged by ROS, including toll-like receptor 4, PI3K-Akt-mTOR, and AMPK, are closely associated with the activation of autophagy-related genes.[27] OS also plays a significant role in apoptosis after ICH. Study have shown that OS can induce apoptosis by activating p53, which leads to DNA damage.[24] ROS and oxidative modifications of mitochondrial proteins result in the opening of the mitochondrial permeability transition pore, followed by the release of cytochrome c, which activates the intrinsic pathway of cell death.[24] In addition to these two forms of cell death, OS after ICH can also induce other types of cell death, such as necrosis, necroptosis, and ferroptosis.[24] Furthermore, OS increases the levels of NF-κB, which upregulates pro-inflammatory cytokines, inflammatory molecules, and matrix metalloproteinases (MMPs), thereby exacerbating inflammation.[24] MMPs degrade the basement membrane and tight junctions of cerebrovascular endothelial cells, increasing capillary permeability and leading to inflammation and BBB disruption.[28] Additionally, OS can directly damage endothelial cells and impair BBB integrity.[29] In conclusion, OS is crucial in secondary injury after ICH and is involved in all key stages of the pathophysiological response following ICH (Figure 3).

Neuroinflammation After ICH

Inflammation is an important host defense response to brain injury, particularly following ICH (Figure 4).[1] When ICH occurs, blood components, including red blood cells, white blood cells, macrophages, and plasma proteins (such as thrombin), immediately enter the brain parenchyma.[1] The inflammatory response begins immediately after the entry of blood components into the brain parenchyma, characterized by the accumulation and activation of inflammatory cells.[1] Resident microglia and astrocytes are considered early inflammatory cells responding to the extravascular blood components.[30] The subsequent inflammatory process involves the infiltration of various circulating inflammatory cells, including leukocytes, macrophages, and T cells.[1] Activated inflammatory cells then release a variety of cytokines, chemokines, free radicals, and other potentially toxic chemicals.[31] Approximately 24 hours after ICH occurs, red blood cells undergo lysis, releasing more cytotoxic substances such as hemoglobin, heme, and iron, which further exacerbate brain injury.[32] As ICH progresses, cell death occurs, leading to a new phase of the inflammatory response. Dead cells release various "danger" signals to activate the immune system.[33] These so-called damage-associated molecular patterns released from dead cells can induce leukocyte infiltration into the brain, further aggravating inflammatory damage.[34] The activation of innate immunity and the inflammatory response promotes the pathogenesis of inflammatory injury following ICH.[35] The activation of innate immunity after ICH leads to the activation of microglia, inflammatory responses around the hematoma, infiltration of blood-derived inflammatory cells, release of pro-inflammatory cytokines (such as TNF-α and IL-1β), and cerebral edema.[36] The inflammatory response following ICH exacerbates the brain injury caused by ICH, ultimately leading to tissue damage, disruption of the BBB, and extensive neuronal death.[28] In summary, inflammatory injury plays a critical role in the secondary brain injury caused by ICH.

NLRP3 Inflammasome After ICH

The inflammasome is an oligomeric protein complex distributed in the cytoplasm, playing a crucial role in the innate immune response in central nervous system (CNS) diseases.[37] Among the members of the inflammasome, the NLRP3 inflammasome is the most extensively studied, serving as the most characteristic pattern recognition receptor (PRR) that initiates the innate immune response.[2] The NLRP3 inflammasome has been extensively studied in the immune system of CNS, particularly playing a significant role in the inflammation response induced by ICH.[38] The NLRP3 inflammasome complex is composed of the NLRP3 scaffold, the apoptosis-associated speck-like protein adapter, and the caspase-1 effector.[39] The N-terminal of the NLRP3 protein contains a pyrin domain (PYD), while the C-terminal has a leucine-rich

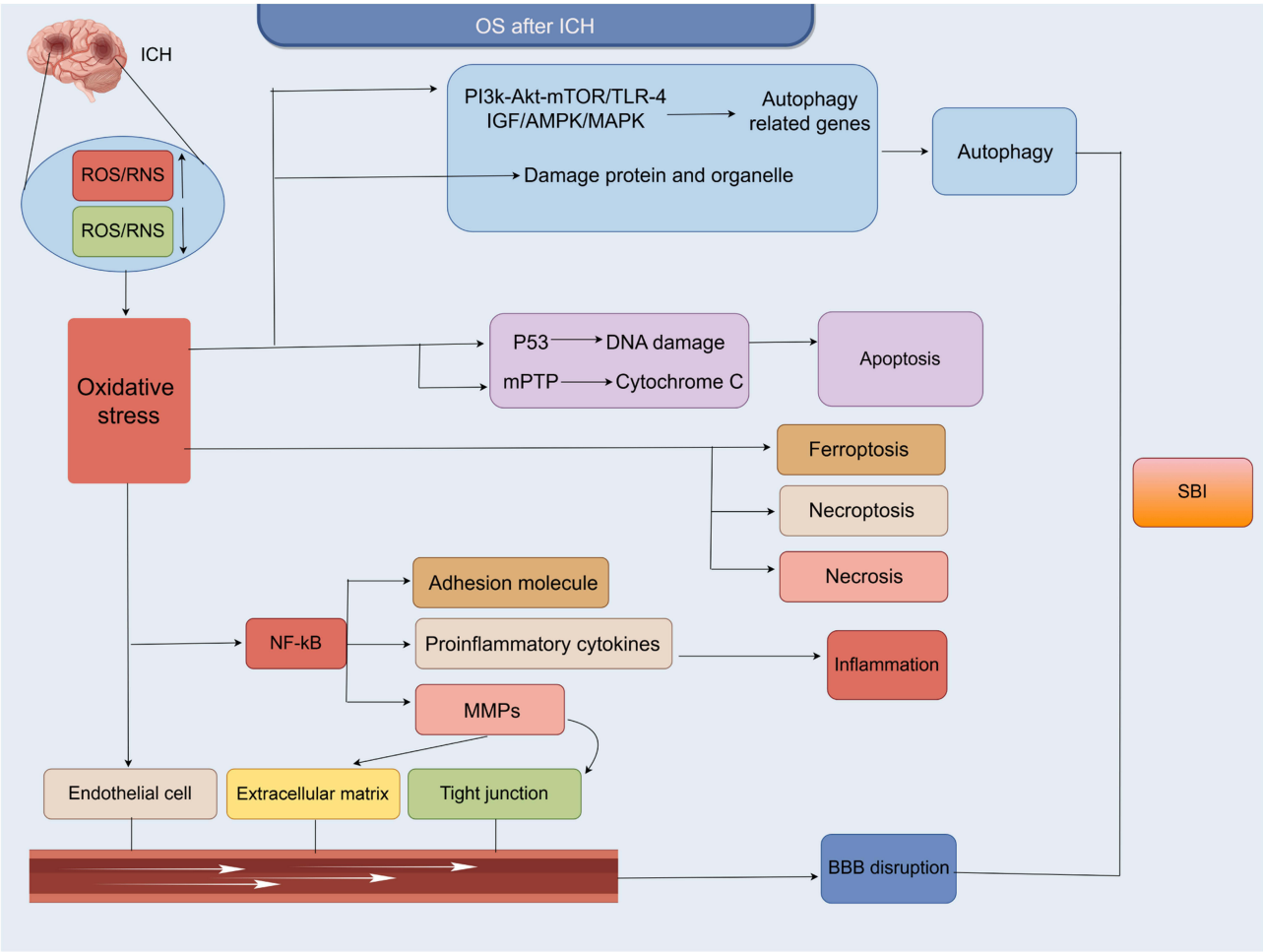

Figure 3 Oxidative stress-mediated brain injury mechanisms after ICH. Excessive ROS/RNS production overwhelms endogenous antioxidant defenses, causing oxidative damage to lipids, proteins, and DNA. This activates molecular pathways triggering apoptosis, necrosis, necroptosis, ferroptosis, and autophagy. Concurrently, OS stimulates NF-κB signaling, upregulating proinflammatory cytokines and matrix metalloproteinases (MMPs). MMPs degrade cerebrovascular basement membranes and tight junctions, increasing capillary permeability and exacerbating BBB disruption. Direct oxidative injury to endothelial cells further compromises BBB integrity, facilitating neuroinflammation and secondary brain injury.

repeat (LRR) domain; the central region consists of a nucleotide-binding and oligomerization domain (NACHT).[40] The LRR domain is believed to play a role in ligand sensing and self-regulation during NLRP3 activation.[2] Upon sensing danger signals, NLRP3 monomers can be activated and oligomerize to form distinct oligomers, which then combine to form a circular structure, recruiting ASC monomers through homologous PYD-PYD interactions to induce the formation of ASC filaments or specks.[41,42] Subsequently, ASC filaments or specks recruit the caspase-1 precursor pro-caspase-1, forming an activated inflammasome complex through the caspase activation and recruitment domain (CARD).[43] The activation of the NLRP3 inflammasome can then catalyze and cleave pro-caspase-1 into caspase-1, further promoting the conversion of pro-IL-1β and pro-IL-18 into active IL-1β and IL-18, thereby exacerbating the inflammatory response (Figure 5).[2]

Classical Activation Pathway

However, it is well known that the activation of the classical NLRP3 inflammasome requires two distinct steps: priming (signal 1) and activation (signal 2).[44] The priming signal is typically mediated by Toll-like receptors (TLRs) and tumor necrosis factor receptors (TNFRs), leading to the activation of NF-κB.[44] Subsequently, NF-κB translocates to the nucleus and binds to DNA, ensuring the adequate expression of the NLRP3, pro-IL-1β, and pro-IL-18 genes/proteins.[45] The activation signal is necessary for the assembly and activation of the NLRP3 inflammasome, transmitted through various

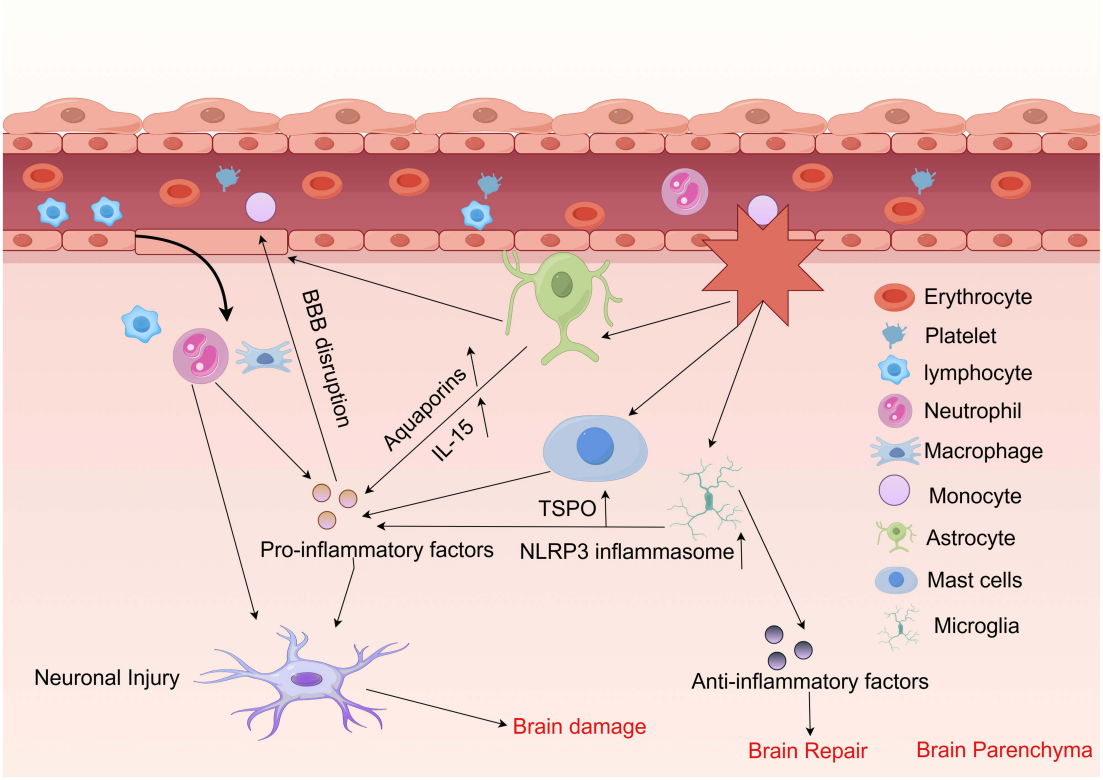

Figure 4 Inflammatory responses after ICH. After ICH, multiple blood components (eg erythrocytes, leukocytes, platelets) are released into the brain parenchyma where they can activate microglia, astrocytes, and mast cells by distinct pathways. After activation, microglia upregulate the expression of NLRP3 and TSPO and produce large amounts of pro-inflammatory factors. However, they also produce anti-inflammatory factors such as TGF-b which contributes to brain repair. Astrocytes contribute to the composition of the BBB and are destroyed directly after ICH, leading to BBB disruption. In addition, astrocytes secrete various pro-inflammatory factors that aggravate neuronal injury and brain damage. Pro-inflammatory factors from diverse cell types not only exacerbate BBB disruption and leukocyte infiltration, but also kill neurons directly.

stimuli, including pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).[46] Currently, widely accepted events that activate the NLRP3 inflammasome include K+ efflux through the purinergic 2×7 receptor (P2X7R), caspase B leakage due to lysosomal damage, the production of ROS, the release of mitochondrial DNA or mitochondrial phospholipid cardiolipin, Ca2+ influx, and changes in cell volume.[2] Importantly, components of blood that invade the brain, such as heme released from hemoglobin degradation, are also considered activators of NLRP3.[47] Previous studies have shown that the expression of NLRP3 signaling in the perihematomal tissue gradually increases within 1 to 5 days after ICH.[48] Following ICH, blood invades brain tissue, and the NLRP3 inflammasome is activated according to the aforementioned steps, thereby amplifying neuroinflammation, promoting neutrophil infiltration, exacerbating cerebral edema, and worsening neurological function.[49] Furthermore, substantial evidence suggests that the NLRP3 inflammasome plays a crucial role in regulating neuroinflammation following ICH. In summary, the NLRP3 inflammasome plays a significant role in regulating neuroinflammation following ICH (Figure 6).

Non-Canonical Activation Pathway

Unlike the canonical caspase-1-dependent mechanism, the alternative activation pathway of the NLRP3 inflammasome operates via caspase-4/5/11. When Gram-negative bacteria are phagocytosed by immune cells, their membrane components are degraded, releasing lipopolysaccharide (LPS). LPS directly binds to and activates mouse caspase-11 or human caspase-4/5, leading to the oligomerization and auto-cleavage of these caspases, which subsequently triggers the non-canonical activation of the NLRP3 inflammasome.[50] Distinct from caspase-1, activated mouse caspase-11 or human caspase-4/5 cannot directly cleave pro-IL-1β or pro-IL-18. However, these caspases are capable of hydrolyzing GSDMD, generating the GSDMD-N fragment. GSDMD-N binds to phospholipids, such as cardiolipin and phosphatidylinositol-4-phosphate kinase 1 (PIPK1), forming pores and leading to

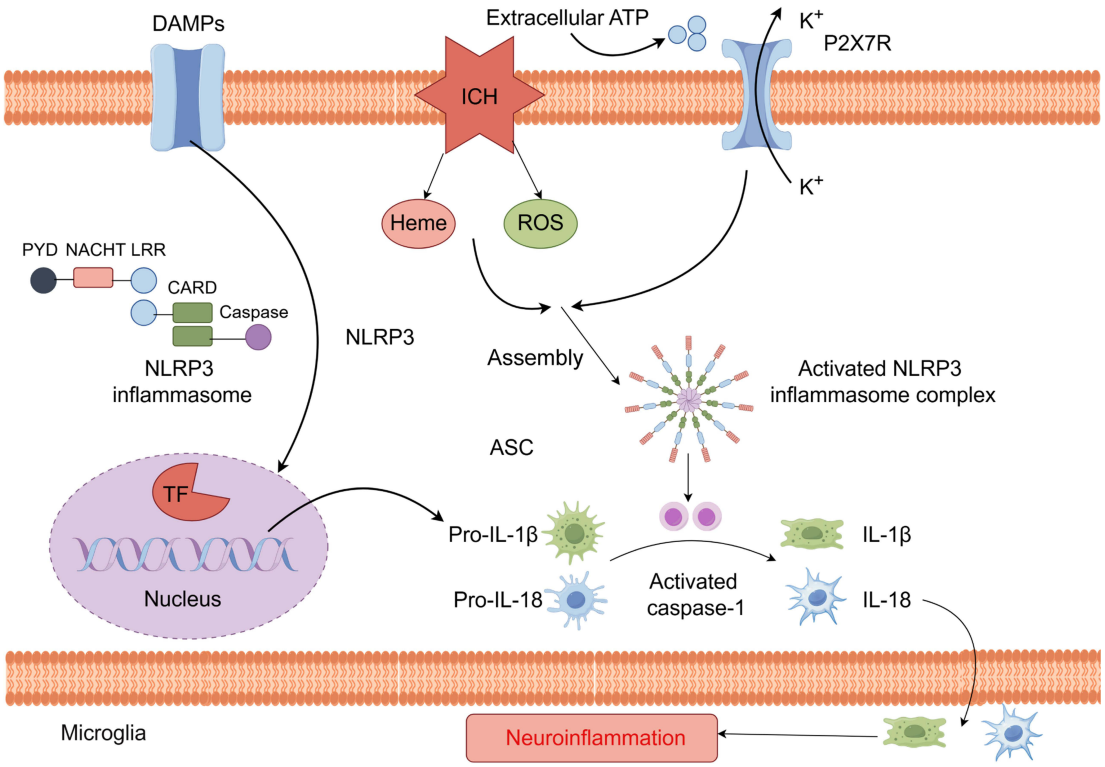

Figure 5 Schematic representation of the components of the NLRP3 inflammasome and its simple activation process in ICH. The NLRP3 inflammasome comprises three core components: NLRP3 scaffold (containing N-terminal pyrin/PYD, central NACHT, and C-terminal LRR domains), ASC adaptor, and caspase-1 effector. Danger signal recognition induces NLRP3 oligomerization through NACHT domain interactions. These oligomers recruit ASC via PYD domain binding, triggering ASC speck formation. ASC specks subsequently engage pro-caspase-1 through CARD-CARD interactions, enabling its autocatalytic cleavage into active caspase-1. Mature caspase-1 processes pro-inflammatory cytokines IL-1β/IL-18 into biologically active forms, driving post-ICH neuroinflammation.

potassium ion efflux.[51] This process subsequently activates the NLRP3 inflammasome, ultimately triggering caspase-1-dependent pyroptosis, thereby effectively linking the non-canonical and canonical pyroptosis pathways.[52] Therefore, the NLRP3 inflammasome, as a key mediator of pyroptosis, both amplifies inflammatory responses and participates in immune regulation.

Alternative Activation Pathway

The alternative activation pathway of the NLRP3 inflammasome operates via a single-signal mechanism and has only been identified in human monocytes. In this pathway, TLR4 recognizes extracellular LPS and triggers NLRP3 activation through the caspase-8/FADD/receptor-interacting protein kinase 3 (RIPK3) signaling pathway, thereby promoting NLRP3 activation and the production of pro-inflammatory cytokines. However, this process does not lead to ASC speck formation nor does it induce pyroptosis.[51] Furthermore, apolipoprotein C3 (ApoC3) can activate the caspase-8-mediated alternative NLRP3 inflammasome pathway in human monocytes. ApoC3 binds to TLR2 and TLR4 to form a heterodimer, subsequently activating a signaling cascade via SCIMP (SLP65/SLP76, csk-interacting membrane protein), tyrosine-protein kinase (Lyn), spleen tyrosine kinase (Syk), and transient receptor potential melastatin 2 (TRPM2). This cascade promotes calcium ion (Ca^{2+}) influx, ROS production, NADPH oxidase activation, and ultimately activates caspase-8.[53] Although caspase-8 plays a crucial role in NLRP3 inflammasome activation, the precise molecular mechanisms of this pathway remain unclear and warrant further investigation.

Comparison of the NLRP3 Inflammasome with NLRC4 and AIM2 Inflammasomes

NLRP3 inflammasomes, along with NLRC4 and AIM2 inflammasomes, are all composed of pattern recognition receptor/sensor proteins, adaptor proteins, and effector enzymes.[54] Although their upstream activation pathways may differ, once

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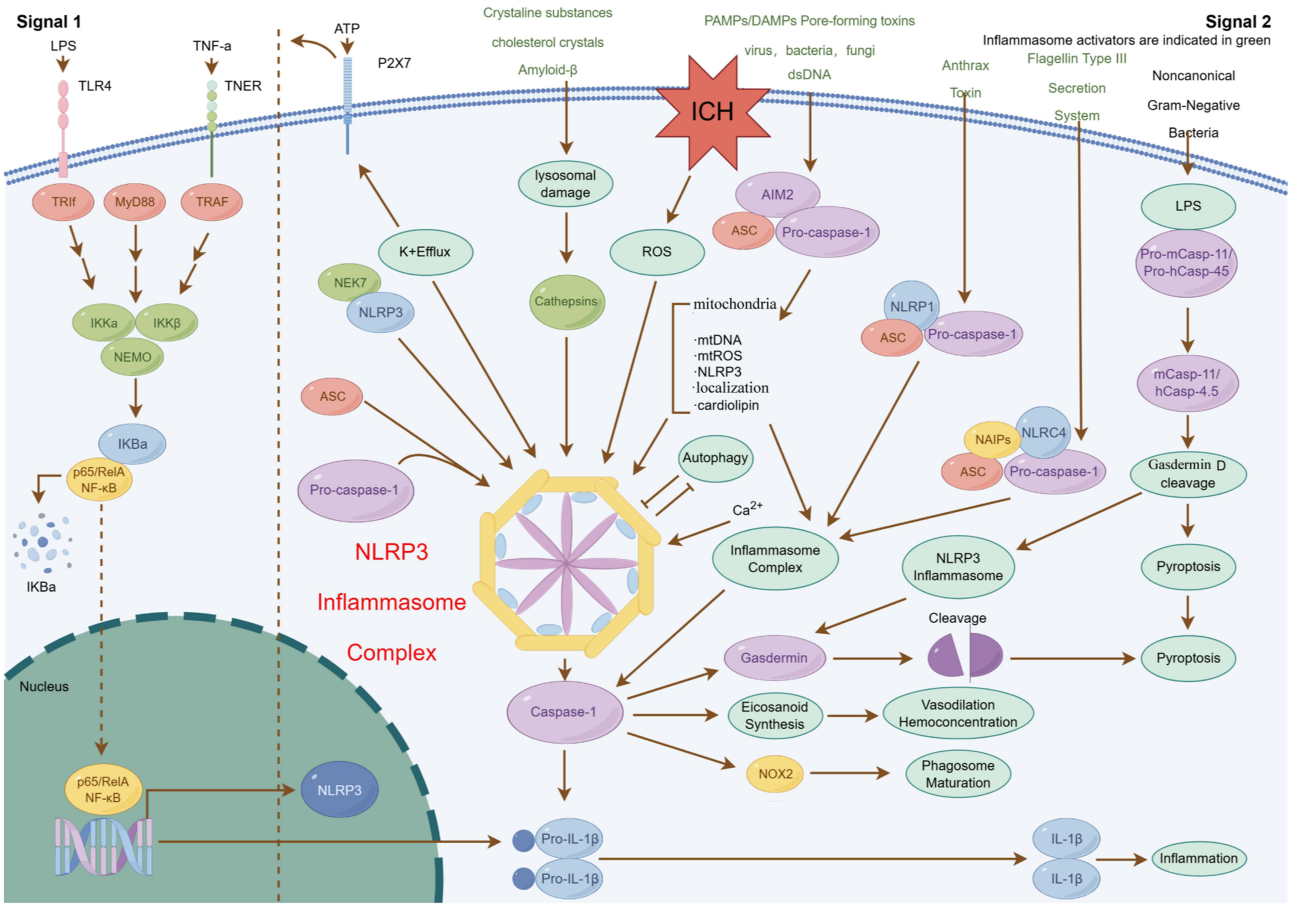

Figure 6 Dual-Signal activation mechanism of NLRP3 inflammasome and pathological effects in ICH. NLRP3 inflammasome activation requires sequential priming (Signal 1) and triggering (Signal 2). Priming involves TLRs/TNFRs-mediated NF-κB activation, upregulating NLRP3 and cytokine precursors (pro-IL-1β/IL-18). Triggering occurs through heme/P2X7R/K^+ efflux/ROS, inducing inflammasome oligomerization. Activated caspase-1 converts precursors into mature IL-1β/IL-18, amplifying neuroinflammation. Post-ICH, this cascade drives neutrophil infiltration, exacerbates cerebral edema via MMPs, and aggravates neurological deficits through sustained cytokine release.

activated, they all initiate a common downstream pathway leading to the secretion of IL-1β and IL-18, as well as a form of inflammatory cell death known as pyroptosis.[55] However, their activation mechanisms differ. In contrast to NLRP3, AIM2 specifically recognizes cytoplasmic double-stranded DNA (dsDNA).[56] Upon dsDNA recognition, AIM2 oligomerizes and assembles with ASC and pro-Caspase-1.[56] Bacterial infections often activate AIM2 by exposing bacterial DNA through bacterial lysis. NLRC4 primarily responds to pathogen-specific structures of Gram-negative bacteria.[56] Upon recognizing bacterial ligands, it induces the recruitment of more NLRC4 monomers and oligomerizes in a self-propagating manner. NLRC4 inflammasome assembly can directly recruit pro-Caspase-1 via the CARD domain of NLRC4, and certain functions may not require ASC involvement, though ASC can facilitate more efficient activation.[57] Furthermore, NLRC4 inflammasomes selectively promote IL-1β maturation in neutrophils without inducing pyroptosis. In contrast, AIM2 inflammasomes can simultaneously trigger pyroptosis, apoptosis, and necroptosis as part of the host defense mechanism.[57] Current reports indicate that NLRP3 is widely involved in both infectious and sterile inflammatory diseases, and may play a dual role in cancer. AIM2's role is primarily focused on viral infections, autoimmune diseases, as well as radiation-induced lung injury and ischemic brain injury. NLRC4 mainly functions in the immune response to Gram-negative bacterial infections.[58] Therapeutically, due to its broad activation spectrum and extensive disease associations, NLRP3 is currently a major target for developing specific small-molecule inhibitors and downstream cytokine blockers. AIM2 therapeutic strategies primarily focus on blocking the interaction between dsDNA and AIM2. Specific small-molecule inhibitors for NLRC4 still require further research in the future.[57] In summary, the NLRP3 inflammasome has been the most thoroughly studied due to its broad activator recognition capabilities and

extensive involvement in various diseases. In contrast, NLRC4 and AIM2 are notable for their specific recognition of particular pathogens or molecular patterns.

OS and NLRP3

After ICH, brain tissue is affected by hematoma, components of red blood cells, and inflammatory factors, leading to an overload of the antioxidant defense system and subsequently triggering OS.[7] Following OS, BBB is compromised, inducing an inflammatory response and releasing inflammatory mediators, which exacerbates neuroinflammation.[8] OS is closely associated with neuroinflammation following ICH.[9] NLRP3 is an important inflammasome that is considered a key player in neuroinflammation.[10] Study has shown that NLRP3 is activated following ICH, leading to an inflammatory cascade that further exacerbates brain injury.[2] OS and NLRP3 play significant roles in ICH, and they are closely related. Studies have shown that OS activates the NLRP3 inflammasome by producing ROS, further exacerbating the inflammatory response.[11,59,60] The activation of NLRP3 not only results in the release of cytokines but also further increases OS through pro-inflammatory responses, creating a vicious cycle.[12,61,62] In addition, OS plays an important role in regulating NLRP3. Research has also shown that inhibiting the activity of transforming growth factor-β-activated kinase 1 reduces the production of ROS and further activates nuclear factor erythroid 2-related factor 2, which helps to suppress the activation of the NLRP3 inflammasome and reduce the occurrence of pyroptosis, thereby alleviating neuronal injury caused by ICH.[63] Sirtuin 3 maintains the homeostasis of ROS by deacetylating superoxide dismutase 2, thereby inhibiting the activation of the NLRP3 inflammasome.[64] Research has also shown that baicalein can further inhibit the activation of the NLRP3 inflammasome by suppressing the production of ROS, thereby alleviating neuronal injury following ICH.[65] Isoliquiritigenin inhibits OS by activating the nuclear factor erythroid 2-related factor 2 pathway, thereby suppressing the activation of the NLRP3 inflammasome and reducing brain injury following ICH.[66] Melatonin reduces the generation of ROS, lowering the activity of the NLRP3 inflammasome, thereby alleviating the inflammatory response and apoptosis of neuronal cells caused by ICH.[67] In summary, this section provides a detailed review of the relationship between OS and NLRP3 in ICH, as well as how OS regulates NLRP3, offering new insights for future research on the regulation of NLRP3 by OS (Table 1).

Table 1 Interactions Between OS and NLRP3 Inflammasome in ICH: Key Mechanisms and Therapeutic Interventions

Category	Key Mechanisms/Findings	References
OS Production & Role	Post-ICH, antioxidant system overload leads to OS, triggering inflammatory responses.	[7]
	OS disrupts the BBB, releasing inflammatory mediators and exacerbating neuroinflammation.	[8, 9]
NLRP3 Activation & Impact	NLRP3 is activated post-ICH, inducing inflammatory cascades and aggravating brain injury.	[2, 10]
OS-NLRP3 Interaction	ROS activates NLRP3, amplifying inflammatory responses.	[11, 48, 49]
	NLRP3 activation releases pro-inflammatory factors, further increasing OS and forming a vicious cycle.	[12, 59, 60]
Regulatory Mechanisms	Inhibiting TAK1 reduces ROS production and activates Nrf2, suppressing NLRP3.	[61]
	Sirtuin 3 maintains ROS homeostasis via SOD2 deacetylation, inhibiting NLRP3 activation.	[62]
Therapeutic Strategies	Baicalein suppresses ROS generation, reduces NLRP3 activity, and mitigates post-ICH neuronal injury.	[63]
	Melatonin decreases ROS levels and NLRP3 activity, reducing neuronal inflammation/apoptosis.	[65]

NLRP3 and Neuroinflammation

After ICH, brain tissue undergoes a series of pathophysiological changes, among which neuroinflammation is an important process.[4] Following ICH, microglia are rapidly activated, exhibiting a pro-inflammatory phenotype and releasing cytokines and chemokines.[5] The neuroinflammation triggered by ICH can have beneficial repair effects, but it may also lead to harmful secondary damage.[6] The functions and polarization states of microglia and macrophages vary at different time points; in the early stages, they may promote inflammation and damage, while in the later stages, they contribute to the clearance of debris and facilitate recovery.[6] NLRP3 is an important inflammasome that is considered a key player in neuroinflammation.[10] Study has shown that NLRP3 is activated following ICH, leading to an inflammatory cascade that further exacerbates brain injury.[2] NLRP3 and neuroinflammation both play important roles in ICH, and they are closely related to each other. Research has shown that the activation of the NLRP3 inflammasome promotes the release of pro-inflammatory cytokines, which further exacerbates the neuroinflammatory response.[2] The activation of NLRP3 is closely related to the polarization of microglia, potentially driving microglia to polarize towards the M1 type (pro-inflammatory), thereby intensifying neuroinflammation.[2] Study have also demonstrated that neuroinflammation induced by ICH further activates the NLRP3 inflammasome, forming a vicious cycle that leads to more extensive cellular damage and inflammatory responses.[13] Here, we provide a detailed summary of the important role of the NLRP3 inflammasome in regulating neuroinflammation following ICH (Table 2).

Activation of the NLRP3 Inflammasome

Following ICH, the activation of the NLRP3 inflammasome can exacerbate neuroinflammation. The reduction of endogenous hydrogen sulfide, combined with P2X7 receptor activation, jointly promotes the recruitment and activation of the NLRP3 inflammasome, further triggering neuroinflammation in ICH.[38,68] Research has also reported that factors such as potassium ion efflux from cells, mitochondrial dysfunction, and ROS can induce NLRP3 inflammasome activation, further exacerbating neuroinflammation in ICH.[44] After ICH, high mobility group box 1 transfers from the cell nucleus to the cytoplasm, and by binding to Toll-like receptor 4 (TLR4), activates downstream NLRP3 inflammasome, ultimately leading to neuroinflammation and further exacerbating.[69] Furthermore, when the activation of the

Table 2 NLRP3 Inflammasome-Mediated Neuroinflammation in ICH: Cellular Mechanisms and Feedback Loops

Category	Key Mechanisms/Findings	References
Neuroinflammatory Initiation	Post-ICH pathophysiological changes (eg, hematoma, inflammatory factors) trigger neuroinflammation.	[66]
Microglial Activation	Microglia rapidly activate post-ICH, adopt a pro-inflammatory phenotype, and release cytokines (eg, IL-1β, TNF-α) and chemokines.	[5]
Dual Role of Neuroinflammation	ICH-induced neuroinflammation may promote repair or cause secondary damage, depending on the phase and microenvironment.	[6]
Microglial Polarization Dynamics	Early phase (M1 pro-inflammatory phenotype): exacerbates injury; Late phase (M2 anti-inflammatory phenotype): facilitates hematoma clearance and tissue repair.	[6]
Core Role of NLRP3	NLRP3 inflammasome is a key driver of neuroinflammation; its activation triggers inflammatory cascades that worsen brain injury.	[2, 10]
NLRP3 and Pro-Inflammatory Cytokines	NLRP3 activation promotes the release of IL-1β, IL-18, and other pro-inflammatory cytokines, amplifying neuroinflammation.	[2]
NLRP3 and Microglial Polarization	NLRP3 may drive microglial polarization toward the M1 phenotype (via pathways like NF-κB), creating a pro-inflammatory microenvironment.	[2]
NLRP3-Inflammation Cycle	Cycle neuroinflammation further activates NLRP3 through signals like ROS and ATP, forming an "injury-inflammation" vicious cycle.	[13]

NLRP3 inflammasome is inhibited, neuroinflammation following ICH is significantly alleviated. Didymin alleviates neuroinflammation and brain injury caused by ICH by inhibiting the formation of the NLRP3 inflammasome.[70] Study has also shown that oxytocin can improve neurological function after ICH by inhibiting the activation of the NLRP3 inflammasome, reducing neuroinflammation.[62] Neuroinflammation induced by ICH (ICH) is closely associated with the activation of the NLRP3 inflammasome, while V-set and immunoglobulin domain containing 4 alleviates neuroinflammation and improves neurological function by suppressing NLRP3 expression.[71] BRD3308 improves neurological function after ICH by inhibiting histone deacetylase 3, enhancing peroxisome proliferator-activated receptor gamma activity, and subsequently suppressing NLRP3 activation, thereby alleviating neuroinflammation.[72] Study has found that low-dose fimasartan can inhibit the activation of the NLRP3 inflammasome, reduce neuroinflammatory responses induced by ICH, improve neurological function, and alleviate brain edema.[73] Activation of dopamine D1 receptor and increased expression of IFN-β can effectively inhibit NLRP3-mediated inflammatory responses, thereby improving neurological function and reducing brain injury after ICH.[74] Epigallocatechin gallate alleviates neuroinflammation in ICH by inhibiting NLRP3 inflammasome activation.[75] Nuclear factor erythroid 2-related factor 2 can negatively regulate NLRP3 inflammasome activity by inhibiting ROS production, thereby further alleviating inflammation after ICH.[66] Cordycepin can inhibit NLRP3 inflammasome activation, alleviate neuroinflammation after ICH, improve neurological function, and reduce brain tissue damage.[76] Ghrelin can alleviate neuroinflammation caused by ICH by inhibiting NLRP3 inflammasome activation.[77]

Release of Inflammatory Factors

After ICH, in addition to directly activating the NLRP3 inflammasome to exacerbate neuroinflammation, the NLRP3 inflammasome can further aggravate neuroinflammation by releasing inflammatory factors upon activation. Research has indicated that the activation of the NLRP3 inflammasome after ICH promotes the polarization of microglia toward the M1 phenotype, leading to the release of pro-inflammatory cytokines and exacerbating neuroinflammation.[37] Activation of the p2Y purinoreceptor 6 receptor promotes the activation of the NLRP3 inflammasome, leading to the release of pro-inflammatory cytokines and exacerbating the inflammatory response of microglia.[78] Following ICH, heme activates the NLRP3 inflammasome and promotes IL-1β production and activation, triggering neuroinflammatory responses that lead to neurological deficits.[79] Complement activation enhances the function of the NLRP3 inflammasome, further promoting the maturation and release of IL-1β, thereby exacerbating neuroinflammation after ICH.[48] Furthermore, after inhibiting the activation of the NLRP3 inflammasome, neuroinflammation following ICH can also be alleviated by further suppressing inflammatory factors. Study has shown that Febuxostat, as a xanthine oxidase inhibitor, exhibits significant anti-inflammatory effects.[80] By inhibiting NLRP3 inflammasome activation, it reduces inflammatory factor levels, thereby alleviating neuroinflammation and cell apoptosis after ICH, and improving neurological function.[80] MitoQ, a selective mitochondrial antioxidant, can inhibit ROS generated by mitochondria, thereby preventing NLRP3 inflammasome activation.[81] This inhibitory effect helps reduce M1 microglia polarization, promote M2 microglia transformation, alleviate inflammatory responses and cerebral edema, ultimately improving neurological function after ICH.[81] OLT1177 alleviates neuroinflammation, protects the integrity of the BBB, and reduces neuronal cell death by inhibiting NLRP3 activation and lowering caspase-1 and IL-1β levels.[82] MCC950 is a selective small-molecule NLRP3 inhibitor. Studies have shown that it can effectively inhibit NLRP3 activation, reduce IL-1β production, thereby alleviating neuronal damage and inflammatory responses after ICH.[83]

Inhibition of the NLRP3 Inflammasome by microRNAs and Other Compounds Targeting Specific Signaling Pathways

MicroRNAs are a class of small RNA molecules that play a role in post-transcriptional gene regulation. They can form ribonucleoprotein complexes and inhibit the translation of specific mRNAs.[2] Research has shown that MicroRNA-152 alleviates neuroinflammation and brain injury by inhibiting thioredoxin interacting protein-mediated activation of the NLRP3 inflammasome.[84] In addition, MicroNAR-194-5p targets tumor necrosis factor receptor-associated factor 6, reducing its interaction with NLRP3, thereby inhibiting the activation of the NLRP3

inflammasome, lowering IL-1β and IL-18 levels, and ultimately alleviating neuroinflammation in ICH.[85] MicroNAR-183-5p alleviates neuroinflammation following diabetic ICH by targeting programmed cell death 4 and inhibiting NLRP3 activation.[86] MicroNAR-23b regulates the nuclear factor erythroid 2-related factor 2 signaling pathway by inhibiting phosphatase and tensin homolog, enhancing antioxidant capacity, reducing OS levels, thereby suppressing NLRP3 inflammasome activation, and ultimately alleviating neuroinflammation and promoting neurological function recovery.[11] Additionally, compounds targeting specific signaling pathways can also inhibit the NLRP3 inflammasome. Research has shown that ursolic acid inhibits the M1 polarization and pyroptosis of microglia by regulating the NF-κB/NLRP3 pathway, thereby alleviating the neuroinflammatory response induced by ICH.[10] Stellate ganglion block can alleviate neuroinflammation caused by ICH by inhibiting the hypoxia-inducible factor 1 alpha/NLRP3 signaling pathway.[61]

Role of NLRP3 Inflammasome in BBB Disruption and Apoptosis

The BBB is crucial for maintaining CNS homeostasis, serving as the first line of defense by preventing the entry of foreign pathogens, toxins, and drugs from the bloodstream into the CNS.[87] Consequently, BBB disruption is considered a key mechanism in various forms of ICH.[88] Furthermore, apoptosis is a caspase-dependent programmed cell death.[24] Accumulating evidence suggests that the NLRP3 inflammasome is activated following ICH, leading to the release of pro-inflammatory cytokines. These cytokines elicit an exaggerated inflammatory response and increase vascular permeability, contributing to BBB disruption and neuronal cell death.[89]

The Bridging Role of NLRP3 in OS and Neuroinflammation

Research has shown that OS activates the NLRP3 inflammasome through the production of ROS, further exacerbating the inflammatory response.[11] The activation of NLRP3 not only leads to the release of cytokines but also further increases OS through pro-inflammatory responses, creating a vicious cycle.[12] Additionally, study have indicated that the activation of the NLRP3 inflammasome can further intensify the neuroinflammatory response.[2] Research has also demonstrated that ICH-induced neuroinflammation further activates the NLRP3 inflammasome, forming a vicious cycle that results in more extensive cellular damage and inflammatory responses.[13] Here, we provide a detailed summary of how the NLRP3 inflammasome regulates the interplay between OS and neuroinflammation. Research has indicated that the activation of transforming growth factor-β-activated kinase 1 promotes the generation of ROS, thereby exacerbating the activation of NLRP3 and ultimately intensifying neuroinflammation following ICH.[63] MicroRNA-23b inhibits the activation of NLRP3 and alleviates neuroinflammation following ICH by enhancing antioxidant capacity through the regulation of the phosphatase and tensin homolog deleted on chromosome/nuclear factor erythroid 2-related factor 2 signaling pathway.[11] Peroxiredoxin II inhibits the activation of NLRP3 and ultimately reduces pyroptosis of neuronal cells following ICH by alleviating endoplasmic reticulum stress, reducing intracellular calcium release, protecting mitochondrial function, and decreasing the generation of ROS.[12] Activation of nuclear factor erythroid 2-related factor 2 can reduce ROS levels and inhibit the activity of NF-κB, further decreasing the assembly and activation of NLRP3, ultimately alleviating neuroinflammation following ICH.[66] In summary, intervention strategies targeting the NLRP3 inflammasome may provide new therapeutic approaches for neuroprotection following ICH (Table 3).

Research Progress on Drugs Targeting NLRP3

The NLRP3 inflammasome is closely associated with secondary injury following ICH and plays a crucial regulatory role between OS and neuroinflammation. Many molecules targeting the NLRP3 inflammasome have been reported so far. Here, we provide a detailed summary of various potential molecules targeting the NLRP3 inflammasome for the treatment of secondary injury after ICH, offering new ideas and insights for future approaches to NLRP3 following ICH (Table 4 and Table 5).

Inhibition of the NLRP3 Inflammasome by microRNAs

MicroRNA is a kind of small RNA molecules in volved in post-transcriptional gene expression.[2] It can form ribonucleoprotein complex and suppress the translation of the specific mRNA.[2] The research has reported MicroRNA-7 alleviates secondary brain injury after ICH by inhibiting NLRP3.[90] MicroNAR-194-5p inhibits the activation of the

Table 3 NLRP3 Inflammasome as a Signaling Hub Linking OS and Neuroinflammation in ICH: Molecular Crosstalk and Therapeutic Implications

Category	Key Mechanisms/Findings	References
OS-NLRP3 Vicious Cycle	OS activates the NLRP3 inflammasome via ROS, releasing cytokines (eg, IL-1β), while NLRP3 activation further amplifies OS through pro-inflammatory responses, forming an "OS-inflammation" loop.	[11, 12]
Neuroinflammation-NLRP3 Interaction	ICH-induced neuroinflammation (eg, microglial activation) reactivates NLRP3 via ROS/ATP signaling, exacerbating cellular damage and inflammatory spread.	[13]
TAK1 Regulatory Role	TAK1 activation promotes ROS production, enhances NLRP3 inflammasome assembly, and aggravates post-ICH neuroinflammation.	[61]
MicroRNA-23b Intervention	miR-23b suppresses NLRP3 activation and mitigates neuroinflammation by enhancing antioxidant capacity via the PTEN/Nrf2 signaling pathway.	[11]
Peroxiredoxin II Protection	Prx II inhibits NLRP3 activation by alleviating ER stress, reducing Ca^{2+} influx, preserving mitochondrial function, and lowering ROS levels, thereby reducing neuronal pyroptosis.	[12]
Nrf2 Regulatory Mechanism	Nrf2 activation reduces ROS levels and inhibits NF-κB activity, suppressing NLRP3 inflammasome assembly/activation and alleviating neuroinflammation.	[64]
Therapeutic Strategies	Targeting the NLRP3 inflammasome (eg, TAK1 inhibition, Nrf2 activation) may offer novel neuroprotective approaches for ICH.	[11, 12, 61, 64]

Table 4 Pharmacological Targeting of the NLRP3 Inflammasome in ICH: A Systematic Review of MicroRNAs and Upstream Pathway Targeting

Category	Agent/Molecule	Mechanism of Action	References
MicroRNA Interventions	MicroRNA-7, MicroRNA-194-5p, MicroRNA-152, MicroRNA-124-3p	Inhibits NLRP3 activity.	[82, 83, 85, 90]
	MicroRNA-223, MicroRNA-23b	Downregulates NLRP3 expression.	[11, 86]
Upstream Pathway Targets	Ursolic Acid	Inhibits NF-κB/NLRP3/GSDMD pathway.	[10]
	Isoquercitrin	Blocks Piezo1/NLRP3 pathway.	[10]
	Atorvastatin	Suppresses NLRP3 via TLR4/MyD88 pathway.	[91]
	P2Y6 Receptor Inhibitor	Upregulates PI3K/AKT pathway, inhibiting NLRP3-dependent pyroptosis.	[76]
	Cystatin C	Inhibits cathepsin B/NLRP3 pathway.	[92]
	VSIG4	Alleviates NLRP3-driven neuroinflammation via JAK2-STAT3 -A20 axis.	[69]
	Baicalin	Targets ROS/NLRP3 pathway.	[63]
	HDAC10	Reduces inflammation through PTPN22/NLRP3 pathway.	[93]
	MSC-derived EVs	Alleviates neuroinflammation via miR-183-5p/PDCD4/ NLRP3.	[84]
	HDAC3 Inhibitor (BRD3308)	Modulates pyroptosis and neuroinflammation via PPARγ/ NLRP3/GSDMD.	[70]
	Isoliquiritigenin (ILG)	Activates Nrf2 to regulate ROS/NF-κB-NLRP3 axis.	[64]
	Epigallocatechin Gallate (EGCG)	Suppress Caspase-1/GSDMD/NLRP3-mediated pyroptosis.	[73]
	Sirtuin 3	Reduces NLRP3/IL-1βpathway.	[62]

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Table 5 Pharmacological Targeting of the NLRP3 Inflammasome in ICH: a Systematic Review of Small-Molecule Inhibitors and Molecular Mechanisms

Category	Agent/Molecule	Mechanism of Action	References
Small-Molecule Inhibitors	OLT1177, MCC950	NLRP3-specific inhibitor, reduces edema and neurological deficits.	[80, 81, 94]
	Didymin, Wogonin	Downregulates NLRP3 expression, inhibits pyroptosis.	[68, 95]
	Verapamil, 5Z-7-Oxozeaenol (OZ), Silybin, Edaravone, Fimasartan, Ghrelin, Memantine, Cordycepin, Glibenclamide, Andrographolide, Febuxostat, Melatonin, MitoQ	Inhibits NLRP3 activation.	[61, 65, 71, 74, 75, 78, 79, 96–101]
	Verbascoside	Alleviates acute inflammatory damage by targeting NLRP3.	[102]
	Pioglitazone	PPAR-γ agonist decreases NLRP3-related edema.	[90]
	Astragaloside IV	Suppresses NLRP3-mediated pyroptosis via KLF2 upregulation.	[89]
	Ethyl Pyruvate	Downregulates NLRP3 in diabetic ICH, mitigating inflammation.	[103]
Gene Knockdown/ Inhibition	FUN14 Domain-Containing 1 Knockdown	Promotes NLRP3-mediated inflammation by suppressing mitophagy.	[104]
	Dectin-1 Blockade, Lipocalin-2 (LCN2) Inhibition, TRAF6 Inhibition, P2X7R Gene Silencing, Kindlin-1 Knockout	Inhibits NLRP3 activation.	[36, 67, 105–108]
Other Molecules	Oxytocin (OXT), Adiponectin	Reduces NLRP3 expression.	[60, 109]
	MST4	Alleviates inflammation and injury by inhibiting NLRP3 activation.	[110]
	Dopamine D1 Receptor Activation	Reduces NLRP3-mediated inflammation.	[72]

NLRP3 inflammasome and alleviates neuroinflammation during ICH by blocking the interaction between TRAF6 and NLRP3.[85] MicroRNA-152 alleviates neuroinflammation in ICH by inhibiting the activation of the NLRP3 inflammasome mediated by thioredoxin-interacting protein.[84] MicroRNA-223 can inhibit inflammation, reduce brain edema, and improve neurological function by downregulating NLRP3.[91] MicroRNA-23b exhibits antioxidant effects by alleviating NLRP3 inflammasome-mediated pyroptosis, thereby promoting neurological recovery after ICH.[11] MicroRNA-124-3p inhibits the activation of the NLRP3 inflammasome by targeting tumor necrosis factor receptor-associated factor 6, thereby suppressing secondary inflammation in microglia after ICH in the basal ganglia.[92] In summary, microRNAs are potential targets for NLPR3 after ICH in the future.

Molecules and Drugs Targeting the Upstream Signaling Pathways of the NLRP3 Inflammasome

Ursolic acid is a pentacyclic triterpene found in various plants and is widely used to treat a range of diseases.[10] After ICH, ursolic acid inhibits microglial pyroptosis through the NF-κB/NLRP3/GSDMD pathway, thereby alleviating the neuroinflammatory response.[10] Isoquercitrin is the main glycoside form of the flavonoid quercetin, known for its anti-inflammatory effects by attenuating pro-inflammatory/inflammatory cytokines. Studies have shown that isoquercitrin can block the Piezos/NLRP3 pathway to mitigate neurological damage following ICH. As a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor, atorvastatin possesses anti-inflammatory properties.[93] Atorvastatin inhibits the activation of the NLRP3 inflammasome in ICH through the TLR4/MyD88 pathway.[93] P2Y purinergic receptor 6 plays an important role in regulating the inflammatory response in CNS diseases.[78] Inhibiting P2Y purinergic receptor 6 activation alleviates NLRP3-dependent microglial pyroptosis in ICH by upregulating the PI3K/AKT pathway.[78] Cystatin C alleviates secondary brain injury around the hematoma in ICH by inhibiting the cathepsin B/NLRP3 signaling pathway.[95] The V-set and immunoglobulin domain containing 4 is specifically expressed in resting tissue-resident macrophages and can transmit anti-inflammatory signals in various inflammatory diseases. After ICH, VSIG4 alleviates NLRP3 and improves neuroinflammation through the JAK2-STAT3-A20 pathway.[71] Baicalin exhibits strong anti-inflammatory activity and can inhibit the ROS/NLRP3 inflammasome pathway to treat brain injury following ICH.[65] Histone deacetylase 10 (HDAC10) is a newly discovered class II histone deacetylase involved in immune responses.[96] HDAC10 can alleviate inflammation following ICH through the PTPN22/NLRP3 pathway.[96] Extracellular vesicles derived from bone marrow mesenchymal stem cells alleviate neuroinflammation following diabetic ICH through the miR-183-5p/PDCD4/NLRP3 pathway.[86] HDAC3 inhibitor (BRD3308) modulates microglial pyroptosis and neuroinflammation through PPARγ/NLRP3/GSDMD to improve neurological function after ICH.[72] Isoliquiritigenin (ILG) is a flavonoid with a chalcone structure. Following ICH, ILG reduces early brain injury and neurological deficits by modulating the activation of the NLRP3 inflammasome pathway through the triggering of Nrf2 activity and the Nrf2-induced antioxidant system, regulating ROS and/or NF-κB.[66] Epigallocatechin gallate pretreatment alleviated microglial pyroptosis and neuroinflammation, at least partially through the Caspase-1/GSDMD/NLRP3 pathway, by upregulating HO-1 expression after ICH.[75] Sirtuin 3 plays a crucial role in improving OS and mitochondrial dysfunction.[64] In diabetic rats with ICH, activation of Sirtuin 3 can reduce levels of NLRP3 and interleukin-1β by deacetylating SOD2 and clearing ROS.[64]

Small Molecule Inhibitors Targeting the NLRP3 Inflammasome

OLT1177 is a novel NLRP3 inflammasome inhibitor that significantly reduces brain edema following ICH and effectively alleviates neurological deficits.[82] Didymin is a dietary citrus flavonoid with anticancer, antioxidant, anti-inflammatory, neuroprotective, hepatoprotective, and cardiovascular activities.[70] Administration of Didymin downregulates the expression of NLRP3 following ICH and can inhibit microglial pyroptosis and neuroinflammation.[70] Treatment of ICH with traditional wogonin by modifying NLRP3 with METTL14 to inhibit neuronal cell pyroptosis.[94] Verapamil can inhibit the activation of the NLRP3 inflammasome and has neuroprotective effects following ICH.[102] MCC950 is a selective inhibitor of the NLRP3 inflammasome that effectively suppresses NLRP3 inflammasome activation and blocks the subsequent release of inflammatory factors.[83] It has been shown that MCC950 can alleviate neuroinflammation and reduce neurological deficits and brain edema following ICH.[97] 5Z-7-Oxozeaenol (OZ) is a small molecule compound that can inhibit the activation of the NLRP3 inflammasome following ICH.[63] Additionally, OZ alleviates OS by reducing the generation of ROS, thereby indirectly suppressing the activation of NLRP3.[63] Verbascoside is an active component found in herbal medicine, possessing antioxidant, anti-inflammatory, and neuroprotective properties.[98] Verbascoside alleviates acute inflammatory damage caused by ICH by inhibiting the NLRP3 inflammasome.[98] Plant-derived silybin exhibits potent antioxidant activity and can prevent the activation of the NLRP3 inflammasome, thereby protecting against ICH.[99] Edaravone reduces the expression of NLRP3 and significantly alleviates brain edema following ICH, providing neuroprotection.[100] Low-dose fimasartan pretreatment alleviates brain injury following acute ICH by inhibiting the NLRP3 inflammasome.[73] Ghrelin, a gut-brain peptide, has been shown to exert neuroprotective effects in various neurological disorders. It alleviates secondary brain injury following ICH by inhibiting the activation of the

NLRP3 inflammasome.[77] Pioglitazone, a peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist, has been shown to play a role in regulating CNS inflammation.[101] Treatment with pioglitazone reduces NLRP3-related brain edema following ICH.[101] Memantine reduces the expression of NLRP3 and improves BBB disruption and neurological dysfunction in ICH.[111] Cordycepin exerts neuroprotective effects in ICH by inhibiting the activation of the NLRP3 inflammasome.[76] Glibenclamide is a widely used sulfonylurea drug, and study has shown that it improves the disrupted BBB in ICH by inhibiting the activation of the NLRP3 inflammasome.[89] Andrographolide improved ICH-induced secondary injury by inhibiting the assembly of the NLRP3 inflammasome, reducing IL-1β and LDH levels, and alleviating microglial pyroptosis.[103] Astragaloside IV inhibited NLRP3-mediated pyroptosis and alleviated inflammatory damage after ICH by promoting the expression of Kruppel-like factor 2.[104] Ethyl pyruvate can downregulate the expression of the NLRP3 inflammasome and reduce the inflammatory response in diabetic ICH.[105] Febuxostat is a xanthine oxidase inhibitor with potent anti-inflammatory effects.[80] Febuxostat pretreatment alleviated inflammatory damage after ICH by inhibiting the NLRP3 inflammasome.[80] Melatonin is an antioxidant and free radical scavenger. Melatonin treatment reduced the expression of NLRP3 and decreased the production of ROS, revealing its inhibitory effect on ROS-NLRP3 inflammasome activation ICH.[67] MitoQ is a selective mitochondrial ROS antioxidant.[81] After ICH, MitoQ alleviates brain injury by polarizing microglia to the M2 phenotype through the inhibition of the NLRP3 inflammasome.[81]

Knockdown and Inhibition of Certain Genes Regulate the NLRP3 Inflammasome

FUN14 domain containing 1 is a mitochondrial autophagy receptor that can eliminate mitochondrial dysfunction following hypoxia and mitochondrial stress.[106] Study has shown that silencing FUN14 domain containing 1 can inhibit mitochondrial autophagy, promote NLRP3-mediated inflammation, and exacerbate injury after ICH.[106] Blocking dendritic cell-associated C-type lectin-1 inhibits the activation of the NLRP3 inflammasome, thereby alleviating neuroinflammatory damage after ICH by reducing NLRP3 inflammasome-mediated pyroptosis.[107] LCN2, also known as neutrophil gelatinase-associated lipocalin, is a glycoprotein that transports small and hydrophobic molecules.[108] Inhibition of Lipocalin-2 leads to downregulation of NLRP3 expression and alleviates brain injury following ICH.[108] Inhibiting TRAF6 can reduce the expression of NLRP3, thereby decreasing neuronal pyroptosis and secondary brain injury following ICH.[109] Gene silencing of P2X7R inhibited the activation of the NLRP3 inflammasome and the release of IL-1β/IL-18, significantly improving brain edema and neurological deficits.[38,68] FERM domain containing kindlin 1, which contains kindlin-1, is an integrin-binding protein involved in microglial-related inflammation.[110] Knockout of FERM domain containing kindlin 1 inhibited the activity of the NLRP3 inflammasome, alleviating microglial inflammation and brain injury induced by ICH.[110]

Other Molecules That Inhibit the NLRP3 Inflammasome

Oxytocin, as a multifunctional neuropeptide, possesses various functions, including anti-inflammatory and antioxidant properties.[62] OXT can reduce the expression of NLRP3 and improve outcomes following ICH by inhibiting neuronal pyroptosis and mitochondrial fission.[62] Adiponectin is strongly expressed in human brain tissue and cerebrospinal fluid, and it reduces brain injury after ICH by decreasing the expression of the NLRP3 inflammasome.[112] MST4 may alleviate the progression of inflammation and brain injury in mice with ICH by inhibiting the activation of the NLRP3 inflammasome.[113] Activation of the dopamine D1 receptor reduces NLRP3-mediated inflammation following ICH.[74]

Discussion

ICH, a severe neurological disorder characterized by high mortality and morbidity rates, has seen significant advancements in understanding its complex and dynamic pathophysiology over the past two decades. Unfortunately, effective pharmacological or surgical interventions that significantly improve neurological outcomes for patients remain lacking. This review systematically dissects the intricate and destructive interplay between OS and neuroinflammation in

secondary brain injury following ICH. For the first time, it places the NLRP3 inflammasome, a pivotal mediator, at the center, highlighting its critical role in orchestrating this detrimental "oxidation-inflammation vicious cycle."

This review thoroughly elucidates the pathological processes of OS and neuroinflammation after ICH. We emphasize that OS rapidly develops after ICH, particularly under the influence of hematoma components (eg, erythrocyte lysis products, hemoglobin, iron) and inflammatory factors. The overwhelmed antioxidant defense system leads to the massive production of ROS and RNS, which not only directly damages cells and disrupts the BBB but, more importantly, creates favorable conditions for the initiation and progression of inflammatory responses. Concurrently, neuroinflammation ensues, primarily characterized by the rapid activation of microglia and their polarization towards a pro-inflammatory M1 phenotype, alongside the copious release of pro-inflammatory cytokines and chemokines. Notably, neuroinflammation is not entirely detrimental; its early or moderate responses may contribute to hematoma clearance and tissue repair. However, uncontrolled or excessively sustained inflammatory responses trigger harmful secondary injury, exacerbating BBB disruption, brain edema, and neuronal death, ultimately leading to neurological dysfunction. A core finding of this review is its clear delineation of the NLRP3 inflammasome as a crucial nexus and amplifier in the "vicious cycle" between OS and neuroinflammation. Extensive evidence indicates that ROS generation is a key signal for activating the NLRP3 inflammasome, thereby initiating subsequent inflammatory cascades. Once activated, NLRP3 not only promotes the maturation and release of potent pro-inflammatory cytokines such as IL-1β and IL-18, but critically, these pro-inflammatory factors, in turn, further augment OS production and drive sustained microglial polarization towards a pro-inflammatory M1 phenotype. This establishes a self-sustaining, escalating pathological cycle that continuously exacerbates neuronal damage, brain edema, and BBB disruption. This "pathological triad" of OS-NLRP3-neuroinflammation constitutes a core driving force of ICH secondary brain injury.

Given the pivotal mediating role of the NLRP3 inflammasome in ICH pathophysiology, strategically disrupting this NLRP3-ROS-neuroinflammation axis undoubtedly presents a highly attractive therapeutic target for mitigating ICH secondary injury. Diverse and promising intervention strategies currently exist, including indirect inhibition of NLRP3 inflammasome activation by modulating miRNA expression, which offers new avenues for gene-level therapies. Intervening with signaling pathways such as TLR4/MyD88, PI3K/AKT, and Nrf2 to inhibit NLRP3 activation at its source holds broader regulatory potential. Directly targeting NLRP3 with specific small molecule inhibitors like MCC950 and OLT1177 has demonstrated significant neuroprotective effects. However, despite these encouraging findings, translating these research outcomes into clinical practice still faces numerous challenges. Future research should focus on drug specificity and systemic safety, optimal timing of intervention, translation from models to clinics, and a deeper understanding of the "double-edged sword" role of NLRP3 in inflammatory responses, which are crucial for future precision therapies. In summary, this review not only systematically summarizes the pivotal role played by the NLRP3 inflammasome in ICH secondary brain injury, particularly through mediating the vicious cycle between OS and neuroinflammation, but also provides a solid theoretical foundation and abundant target information for preclinical research and future translational medicine. We firmly believe that a deeper understanding and targeted intervention of the NLRP3 pathway, particularly by overcoming current research limitations, will bring new hope for improved outcomes for ICH patients.

Conclusion

The extensive evidence presented in this review unequivocally points to NLRP3's central role in the pathological process of ICH, particularly as a critical nexus in the vicious cycle between OS and neuroinflammation. Therefore, early and precise targeted inhibition of NLRP3 holds promise as a highly effective neuroprotective strategy, capable of interrupting ICH-induced oxidative damage and neuroinflammatory cascades, and thereby significantly improving patients' neurological functional outcomes. However, successfully translating these encouraging preclinical findings into safe and effective clinical interventions still necessitates continuous and rigorous translational research to fully unlock the immense potential of NLRP3 in ICH treatment.

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