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Review

The Role of NLRP3 Inflammatory Bodies in Cerebral Hemorrhage and Progress in Targeted Therapy

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Abstract

The review aims to provide the basis for clinical treatment and prognosis improvement of cerebral hemorrhage. NLRP3 inflammatory bodies are localized to multiple fine cell organelles and transition to different intracellular sites during activation, The mechanism of NLRP3 activation in cerebral hemorrhage is becoming more and more clear. More and more studies tend to selectively inhibit NLRP3 inflammasome pathway to improve the prognosis of cerebral hemorrhage. Cerebral hemorrhage is a kind of devastating illness and a common form of cerebral apoplexy, which has a high disability and fatality rate. In this review, the role of NLRP3 inflammatory corpuscle in cerebral hemorrhage and the progress of targeted therapy are summarized.

Keywords: cerebral hemorrhage, NLRP3 inflammasome, inflammatory response, target

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1 INTRODUCTION

Intracerebral hemorrhage (ICH) is a devastating neurological disease caused by rupture of blood vessels in the brain parenchyma, characterized by high mortality, disability, and recurrence rates, with no effective treatments currently available. ICH accounts for approximately 10-15% of stroke cases in the United States, Europe, and Australia, and 20-30% of all stroke cases in Asia[1]. Primary brain injury from ICH typically occurs within the first few hours of onset, resulting from rapid accumulation of hematoma that tears and directly compresses brain tissue, disrupting the normal anatomical structures of the brain[2]. Although surgical hematoma evacuation can alleviate mass effect and reduce intracranial pressure, previous clinical trials have shown no positive results[3-7]. This may be because surgical removal of the hematoma does not address secondary brain injury following ICH. Recent studies indicate that activation of the nucleotide-binding oligomerization domain (NOD)-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome is associated with secondary brain injury, such as neuroinflammation, oxidative stress, pyroptosis, and apoptosis following ICH[8,9], which is crucial for determining ICH prognosis. Increasing experimental studies

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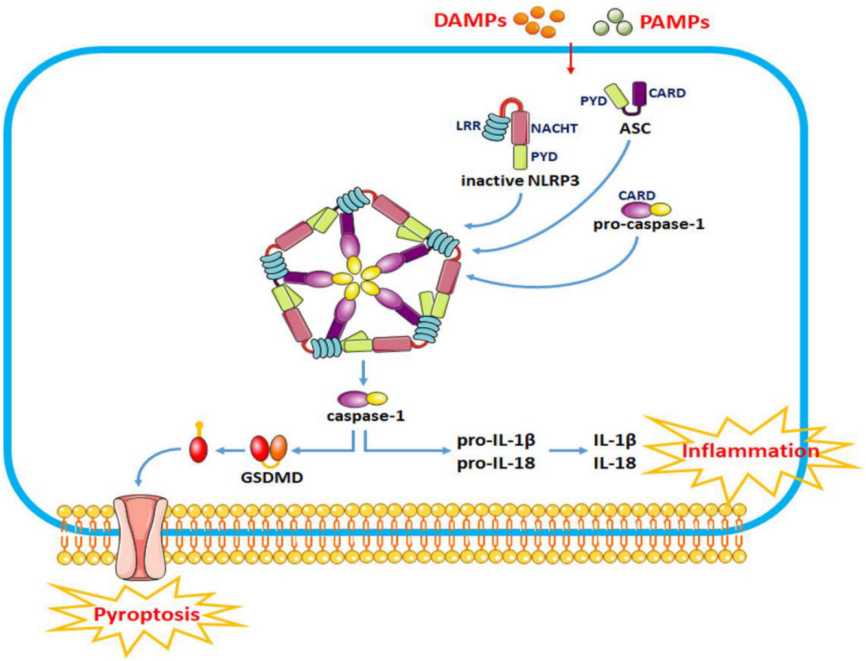

Figure 1. Schematic of NLRP3 inflammasome composition and activation.

on targeting NLRP3 inflammasome in ICH are emerging. Therefore, this review summarizes the mechanisms by which the NLRP3 inflammasome acts in ICH and reviews drugs targeting NLRP3 over the past decade, providing a reference for effective clinical treatment of ICH.

1.1 The Relationship Between Inflammation and ICH

Inflammation is the body's first immune defense response to harmful stimuli, induced by exogenous infections and endogenous tissue injury. The pathophysiological process of ICH is complex, involving apoptosis, oxidative stress, inflammation, and more. Inflammatory responses are a key factor in acute brain injury and are closely related to patient prognosis. Abnormal or dysregulated inflammation exacerbates damage to brain tissues[10,11]. Post-ICH, both the central nervous system (CNS) and systemic immune responses are activated, characterized by microglial activation and neutrophil infiltration, leading to the release of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), myeloperoxidase, and other toxic chemicals[12-14]. These inflammatory mediators, along with degradation products from cell death, damage the blood-brain barrier and exacerbate edema surrounding the hematoma.

2 NLRP3 INFLAMMASOME

The NLRP3 inflammasome is a multiprotein complex and an essential component of the innate immune system, primarily existing in immune and inflammatory cells activated by inflammation, such as macrophages, monocytes, dendritic cells, and neutrophils[15,16]. The NLRP3 inflammasome comprises three main components: sensor molecules (PRRs), adapter molecules (apoptosis-associated speck-like protein containing a caspase activation and recruitment domain, ASC), and effector components (caspase-1)[17]. These components form a large complex through interactions. The NLRP3 protein, containing NOD and leucine-rich repeat regions, acts as a sensor capable of recognizing various pathogen-associated molecular patterns and danger-associated molecular patterns, thereby activating the inflammasome. ASC, containing pyrin domains and CARD domains, serves as a bridging protein, linking NLRP3 and caspase-1. Activated caspase-1 cleaves and activates pro-inflammatory mediators, including IL-1β and IL-18, triggering inflammation (Figure 1). While these mediators play key roles in immune responses, overactivation of NLRP3 inflammasome can contribute to diseases like systemic lupus erythematosus (SLE)[18], type 1 diabetes (T1D)[19], multiple sclerosis[20], atherosclerosis[21,22], and gout[23].

3 NLRP3 INFLAMMASOME EXPRESSION AND REGULATION IN ICH

NLRP3 inflammasome expression in normal brain tissue involves complex regulation, mainly in neurons and glial cells. After ICH, NLRP3 activation occurs, with studies reporting its upregulation around the hematoma within 1-5 days post-ICH[24]. Activated NLRP3 promotes pro-inflammatory cytokines like IL-1β and IL-18, further exacerbating neuroinflammation, brain edema, and tissue damage. Persistent neuroinflammation negatively affects neurons by inducing oxidative stress and excitotoxicity. Therefore, targeting inflammation is a critical therapeutic direction[25].

4 POTENTIAL MECHANISMS OF NLRP3 AS A THERAPEUTIC TARGET

4.1 NLRP3-Related Diseases

Excessive activation is implicated in familial cold autoinflammatory syndrome[26], metabolic diseases

Table 1. Drugs Targeting NLRP3 Inflammasome for ICH Treatment

Drug	Experimental Model	Mechanism of Action	Experimental Conclusion	Reference
Isoliquiritigenin	ICH Rat Model	Inhibits ROS/NF-κB/NLRP3 Pathway	Promotes antioxidant system to alleviate brain injury and neurological function deficits	[46]
Artemisinin	ICH Mouse Model	Blocks NLRP3/ASC/Caspase-1 Signaling Pathway	Reduces activation of local inflammatory cells, decreases neuronal apoptosis and brain edema	[47]
Isoquercetin	ICH Rat Model	Blocks Piezo Ion Channels (Piezos)/ NLRP3 Pathway	Inhibits upregulation of inflammatory factors, alleviates neuronal damage	[48]
Dapansutrile (OLT1177)	ICH Mouse Model	Specifically Inhibits NLRP3 Inflammasome	Reduces brain edema and relieves neurological deficits after ICH	[49]
Dioscin	ICH Rat Model	Regulates ROS and Nrf2/NLRP3 Inflammasome Pathway	Alleviates early brain injury and neurological function deficits	[50]
Silymarin	ICH Mouse Model	Downregulates NLRP3 Inflammasome Proteins	Reduces oxidative stress and inflammatory injury	[51]
Oxytocin	ICH Mouse Model	Downregulates NLRP3 Inflammasome Proteins	Inhibits apoptosis and pro-inflammatory factor expression	[52]
MicroRNA-152 (miR-152)	ICH Rat Model	Inhibits Thioredoxin Interacting Protein (TXNIP)/NLRP3 Pathway	Reduces inflammation and ROS production induced by hemin, protecting neurons	[53]
Adiponectin	ICH Rat Model	Downregulates NLRP3 Inflammasome Proteins	Reduces TLR4/NF-κB signaling, lowering brain edema and blood-brain barrier dysfunction	[54]
Verbascoside	ICH Mouse Model	Downregulates NLRP3 Inflammasome Proteins	Reduces microglial activation and increases neuron survival; inhibits inflammatory response	[55]
Febuxostat	ICH Mouse Model	Downregulates NLRP3 Inflammasome Proteins	Alleviates inflammation, reduces neuronal degeneration and apoptosis	[56]
Edaravone	ICH Rat Model	Inhibits NF-κB/NLRP3	Inhibits inflammation, protects neurons	[57]
Cordycepin	ICH Mouse Model	Inhibits NLRP3 Inflammasome Activation	Reduces inflammation, provides neuroprotection	[58]
Andrographolide	ICH Rat Model	Inhibits NLRP3 Inflammasome Activation	Reduces IL-1β and LDH levels, inhibits microglial apoptosis, improves secondary brain injury	[59]

(e.g., type 2 diabetes)[27], neurodegenerative diseases (e.g., Alzheimer's)[28], cardiovascular diseases (e.g., atherosclerosis)[29,30], liver diseases (e.g., NASH)[31,32], and inflammatory bowel diseases[33].

4.2 Therapeutic Strategies

Targeting NLRP3 involves small-molecule inhibitors and antibodies[34-37]. Current inhibitors show promise but require further development and optimization.

5 NLRP3-TARGETED THERAPIES FOR ICH

Inhibitors like melatonin, ursolic acid, VSIG4, and MCC950 show potential in animal models[38-45]. Further clinical trials and studies are necessary to confirm their efficacy and safety for human use. (Table 1)

6 CONCLUSION AND OUTLOOK

Future research directions include drug optimization, clinical trials, mechanism exploration, timing strategies, and combination therapies to maximize therapeutic efficacy. NLRP3 inhibitors hold promise but require comprehensive validation.

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Conflicts of Interest

The authors declared no conflict of interest.

Data Availability

Data sharing is not applicable to this review as no datasets were generated or analyzed during the current study.

Author Contribution

The authors contributed to the manuscript and approved the final version.

Abbreviation List

CNS, central nervous system

ICH, Intracerebral hemorrhage
IL-1β, interleukin-1β
NLRP3, NOD-like receptor thermal protein domain associated protein 3
NOD, nucleotide-binding oligomerization domain
SLE, systemic lupus erythematosus
T1D, type 1 diabetes
TNF-α, tumor necrosis factor-α

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