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NLRP3 Inflammasome: Key Regulatory Molecules in Acute Liver Injury and Advances in Targeted Therapeutics

Yulei Gou[1], Jie Xiao[2], Yu Fan[1,2,*]

[1]College of Basic Medicine, Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]College of Clinical Medicine, Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
*Correspondence Author

Abstract: ***Acute liver injury refers to hepatocyte damage and abnormal liver function triggered by various factors such as infection, drugs, toxins, and immune abnormalities, with its pathological process closely associated with inflammatory responses. The NLRP3 inflammasome, as a crucial intracellular pattern recognition receptor complex, plays a central role in mediating inflammatory responses and regulating pyroptosis. Recent studies confirm that NLRP3 inflammasome activation serves as a pivotal link between liver injury triggers and the inflammatory cascade, with its activation level directly influencing injury severity and prognosis. This paper systematically reviews the structure, function, and activation mechanisms of the NLRP3 inflammasome. It focuses on elucidating the role and mechanism of the NLRP3 inflammasome in different types of acute liver injury and summarizes intervention strategies targeting the NLRP3 inflammasome, providing a theoretical basis for the clinical treatment of acute liver injury.***

Keywords: NLRP3 inflammasome; Acute liver injury; Inflammatory regulation; Targeted intervention.

1. Introduction

Acute liver injury is a common clinical emergency characterized by hepatocyte necrosis and rapid deterioration of liver function [1]. Without timely intervention, it can progress to acute liver failure with a mortality rate exceeding 50%. The etiology of acute liver injury is complex, encompassing viral infections, drug toxicity, alcohol abuse, immune attacks, and toxin exposure. Although the initial mechanisms of liver injury vary across different triggers, the inflammatory response remains the core pathological feature throughout disease progression.

The NLRP3 inflammasome is a member of the nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family and serves as a key molecule for intracellular recognition of "danger signals." Upon sensing pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), NLRP3 assembles with apoptosis-associated speck-like protein containing CARD (ASC) [2] and precursor caspase-1 to form an inflammasome. Activated caspase-1 cleaves precursor IL-1β and precursor IL-18 into mature cytokines while simultaneously mediating pyroptosis, triggering a robust inflammatory response [3]. In recent years, increasing evidence indicates that the NLRP3 inflammasome plays a pivotal role in the development of acute liver injury, with its activation level

directly influencing the severity and prognosis of liver damage.

This review summarizes the current research on the mechanism of NLRP3 inflammasome in acute liver injury and intervention strategies targeting NLRP3 inflammasome, providing a theoretical basis for studying the mechanisms of acute liver injury and developing targeted therapies.

2. NLRP3 Inflammasome

2.1 Structure of the NLRP3 Inflammasome

The NLRP3 inflammasome is a polymeric complex composed of multiple proteins, with NLRP3 protein, ASC protein, and precursor caspase-1 serving as its core components. The NLRP3 protein serves as the complex's "sensor," comprising three functional domains: the N-terminal pyrin domain (PYD), the central NOD-like domain (NOD-like domain, NACHT), and the C-terminal leucine-rich repeat domain (LRR) [5]. The LRR domains recognize external stimulus signals, the NACHT domain regulates NLRP3 oligomerization via ATPase activity, and the PYD domain mediates interaction with ASC [6]. The ASC protein acts as an "adapter," containing both PYD and CARD (caspase recruitment domain) domains. The PYD domain of ASC binds to the PYD domain of NLRP3 through homodimeric interaction, while the CARD domain binds to the CARD domain of precursor caspase-1, enabling signal transduction [7]. The precursor caspase-1, acting as an "effector," undergoes oligomerization and self-cleavage mediated by ASC, generating the active caspase-1 p20/p10 heterodimer, thereby initiating downstream inflammatory responses.

2.2 Activation Mechanism of the NLRP3 Inflammasome

The activation of the NLRP3 inflammasome follows a "two-step activation model," involving the combined action of an "initiator signal" and an "activator signal." Priming signals are primarily triggered by inflammatory signals such as lipopolysaccharide (LPS) and tumor necrosis factor (TNF-α). These activate the NF-κB pathway, upregulating the gene expression of NLRP3, pro-IL-1β, and pro-IL-18 [8], thereby stockpiling "raw materials" for inflammasome assembly. This process is a prerequisite for inflammasome activation; without priming signals, subsequent stimuli alone cannot effectively induce an inflammatory response. Alarm signals encompass diverse stimuli, including abnormal ion distribution (e.g., K^+ efflux, Ca^{2+} influx), organelle damage (e.g., mitochondrial dysfunction, lysosomal rupture), and metabolic disorders (e.g., uric acid crystal or cholesterol crystal accumulation). These signals induce conformational changes in NLRP3, shifting it from an autoinhibited state to an activated state. This enables NLRP3 to assemble with ASC and precursor caspase-1 into a functional inflammasome. Recent studies have revealed that mitochondria play a pivotal role in NLRP3 activation. When cells are stimulated, increased mitochondrial reactive oxygen species (mtROS) production and the release of mitochondrial DNA (mtDNA) into the cytoplasm can both directly activate NLRP3 [9]. Furthermore, impaired autophagy clearance of damaged mitochondria further exacerbates NLRP3 inflammasome activation, forming a positive feedback loop of "mitochondrial damage-NLRP3 activation."

3. The Role of NLRP3 Inflammasome in Different Types of Acute Liver Injury

Acute liver injury arises from diverse triggers, each activating the NLRP3 inflammasome through specific mechanisms, ultimately leading to hepatocyte damage and hepatic dysfunction. This review summarizes the role and mechanisms of the NLRP3 inflammasome in clinically common types of acute liver injury—drug-induced, immune-mediated, viral, and alcoholic—based on recent research findings.

3.1 Relationship Between NLRP3 Inflammasome and Drug-Induced Acute Liver Injury

Drug-induced acute liver injury (DILI) is the leading cause of acute liver failure worldwide, with acetaminophen (APAP) overdose being the most common trigger [10], accounting for approximately 50% of all DILI cases in Western countries. APAP is metabolized within hepatocytes to produce the toxic intermediate N-acetyl-p-benzoquinone imide (NAPQI). NAPQI depletes glutathione (GSH) [11], triggering oxidative stress, mitochondrial damage, and hepatocyte necrosis. Concurrently, it releases large amounts of DAMPs, activating the NLRP3 inflammasome.

Yuan Xinying et al. [12] demonstrated in an APAP-induced acute liver injury mouse model that specific inhibition of the NLRP3 pathway attenuates liver damage. Compared to the control group, mice with hepatocyte-specific NLRP3 knockout or those treated with the NLRP3 inhibitor MCC950 or the GSDMD inhibitor disulfiram (DSF) showed marked improvements. These included decreased serum ALT and AST levels, reduced hepatic necrosis area, and downregulated expression of NLRP3, activated Caspase-1, and GSDMD-N in liver tissue. Furthermore, hepatocyte pyroptosis was inhibited, and the release of proinflammatory factors (IL-1β, IL-18, TNF-α, IL-6) and chemokines (MCP-1, CXCL1/2) was reduced. These findings indicate that targeted intervention in the NLRP3/Caspase-1/GSDMD signaling pathway and its downstream proinflammatory factor pathways can alleviate liver injury by suppressing pyroptosis and inflammatory responses.

In APAP-induced drug-induced liver injury, emodin methyl ether significantly suppresses the expression of the key injury factor HMGB1 and further downregulates the NLRP3 inflammasome and its downstream inflammatory mediators IL-1β and IL-18, thereby supporting the "HMGB1-NLRP3 axis" and exerting hepatoprotective effects [13]. Previously, Ulf Andersson et al. [14] demonstrated that HMGB1 activates the NF-κB signaling pathway by binding to the TLR4 receptor. Furthermore, Peter Lundbäck [15] found that neutralization of HMGB1 effectively alleviated liver injury. These findings collectively identify the HMGB1-TLR4-NF-κB-NLRP3 pathway as a potential therapeutic target for DILI.

In addition to APAP, other drugs such as the anti-tuberculosis agents isoniazid (INH) and rifampicin (RIF) also induce acute liver injury closely associated with NLRP3 inflammasome activation. In an acute liver injury mouse model induced by isoniazid (INH) combined with rifampicin (RIF), significantly elevated ROS levels were observed in liver tissue following INH+RIF treatment, accompanied by marked upregulation of mRNA and protein expression for NLRP3, Caspase-1, and GSDMD. Following intervention with Andrographis paniculata (SYX), serum ALT and AST levels decreased in mice, along with reduced hepatic necrosis area and inflammatory cell infiltration. Concurrently, ROS levels in liver tissue and secretion of downstream inflammatory mediators IL-1β and IL-18 significantly declined. This indicates that inhibiting the ROS/GSDMD signaling pathway mitigates inflammation and pyroptosis, thereby alleviating INH+RIF-induced drug-induced liver injury [16].

3.2 The Role of NLRP3 Inflammasome in Immune-Mediated Acute Liver Injury

Immune-mediated acute liver injury primarily encompasses autoimmune hepatitis (AIH) and graft-versus-host disease (GVHD), with the core mechanism involving abnormal activation of immune cells that subsequently attack hepatocytes. The NLRP3 inflammasome plays a pivotal role in regulating immune cell function and mediating inflammatory responses. The Concanavalin A (ConA)- induced liver injury model is a classic model for studying immune-mediated liver injury. By activating T lymphocytes and macrophages, it simulates the pathological process of AIH and is widely used.

Luan et al. [17] found that in a ConA-induced autoimmune hepatitis model, expression of NLRP3,

cleaved caspase-1, and mature IL-1β proteins was significantly elevated in mouse liver tissue, accompanied by substantial infiltration of $CD68^+$ macrophages and $CD11b^+$ myeloid cells. Following NLRP3 gene knockout, hepatic pathological damage was mitigated, and serum ALT and AST activity, along with caspase-1 and IL-1β expression, decreased, indicating that the NLRP3 inflammasome plays a critical role in this liver injury process. Mechanistically, ConA induces elevated hepatic ROS levels. Treatment with IL-1 receptor antagonists or the ROS scavenger NAC suppressed NLRP3 activation, caspase-1 cleavage, and IL-1β secretion, thereby alleviating hepatic inflammation and pyroptosis. This study suggests the ROS-NLRP3-IL-1β axis is a core pathway driving hepatic inflammation and pyroptosis in ConA-induced hepatitis.

Research by Hao et al. [18] revealed that Gentiopicroside significantly reduced serum ALT and AST levels in Con A-induced immune-mediated liver injury in mice, improved hepatic histopathological changes, alleviated hepatosplenomegaly, and suppressed the expression of NLRP3 inflammasome, TLR4, and phosphorylated p65 protein in liver tissue. The results indicate that Gentiopicroside exerts hepatoprotective effects by regulating the NLRP3/TLR4/NF-κB signaling pathway to suppress inflammatory responses.

Additionally, Lewis lung carcinoma (LLC) and PD-1 monoclonal antibodies exacerbate ConA-induced immune-mediated liver injury through distinct mechanisms. LLC promotes cGAS activation by enhancing neutrophil extracellular trap (NET) formation and infiltrating hepatic macrophages, while PD-1 monoclonal antibodies activate cGAS by boosting macrophage phagocytosis of NETs. Both ultimately converge on the cGAS/STING/NLRP3 axis to activate NLRP3 inflammasomes, prompting caspase-1 to cleave IL-1β and IL-18 precursors, thereby amplifying hepatic inflammation. Clearing NETs, depleting macrophages, or knocking down cGAS effectively mitigates liver injury. Ginsenoside Rd can inhibit cGAS, thereby blocking excessive activation of this pathway [19].

3.3 Relationship Between NLRP3 Inflammasome and Viral Acute Liver Injury

Viral hepatitis is a major cause of acute liver injury. Among these, hepatitis B virus (HBV), as a hepatotropic DNA virus, not only leads to acute, chronic, and even fulminant hepatitis but also serves as a key pathogenic factor driving liver fibrosis, cirrhosis, and hepatocellular carcinoma [20]. HBV is considered a "stealth virus" capable of evading immune surveillance during early infection. It produces multiple viral-associated proteins that suppress innate and adaptive antiviral immune responses, enabling persistent viral carriage. Viral nucleic acids and proteins act as pathogen-associated molecular patterns (PAMPs), recognized by intracellular pattern recognition receptors (e.g., NLRP3) to activate the inflammasome pathway. Hepatocyte damage caused by viral replication releases damage-associated molecular patterns (DAMPs), which synergize with PAMPs to dramatically amplify the i

Zhang et al. [21] found that hepatitis B virus (HBV) induces apoptosis in M1 macrophages and downregulates their surface marker molecules CD68 and CD86, and HLA-DR. Concurrently, HBV suppressed the expression of Toll-like receptor 4 (TLR4) and NLRP3 inflammasome pathway-associated proteins NLRP3 and caspase-1 p20 in M1 macrophages, while reducing the production of downstream inflammatory cytokines IL-1β and IL-18. HBV hijacks hepatocyte-derived exosomes to deliver HBV-DNA to M1 macrophages. The highly expressed miR-146a and FEN-1 within these exosomes further suppress the activity of the TLR4–NLRP3–caspase-1 signaling axis in M1 macrophages and reduce IL-1β and IL-18 expression. These findings indicate that suppressing NLRP3 inflammasome function represents a key mechanism by which HBV evades antiviral immunity mediated by M1 macrophages.

Injection of a recombinant adenovirus vector to establish an AAV8-1.3HBV-infected mouse model revealed elevated protein expression levels of NLRP3, GSDMD, and NF-κB in the liver tissue of HBV-infected mice, along with enhanced caspase-1 activity and increased secretion of downstream inflammatory cytokines IL-1β and IL-18. Following intervention with paeoniflorin, the expression of NLRP3, GSDMD, and NF-κB expression in the liver tissue of infected mice was significantly suppressed, with reduced inflammatory infiltration and fibrosis in the liver tissue, decreased serum ALT and AST levels, and reduced HBeAg and HBsAg expression. This suggests that paeoniflorin may alleviate HBV-induced liver tissue damage by inhibiting the NF-κB/NLRP3/GSDMD signaling axis, thereby blocking inflammasome activation and the pyroptosis process [22].

Xie et al. [23] found in a hydrogen peroxide (H_2O_2) induced oxidative stress HL7702 hepatocyte model that HBx significantly upregulates NLRP3, ASC, caspase-1, and proinflammatory factors IL-1β, IL-18, HMGB1 expression in a hydrogen peroxide (H_2O_2)-induced oxidative stress model of HL7702 hepatocytes. Concurrently, it increased hepatocyte PI positivity rates and lactate dehydrogenase (LDH) release, suggesting HBx activates the NLRP3 inflammasome and induces hepatocyte pyroptosis. HBx provides a critical "activation signal" for NLRP3 inflammasome assembly by inducing mitochondrial swelling and elevating mitochondrial reactive oxygen species (mitoROS). Intervention with the ROS scavenger N-acetyl-L-cysteine (NAC) downregulated caspase-1 p10 and IL-1β expression while significantly attenuating hepatocyte pyroptosis. Clinical sample analysis further confirmed that NLRP3, ASC, and IL-1β expression levels in HBV-positive patients' liver tissues positively correlated with HBV DNA load. Collectively, these findings indicate that under oxidative stress conditions, HBx drives hepatocyte inflammation and pyroptosis via the mitoROS-NLRP3 signaling axis, representing a key mechanism of HBV-associated liver injury.

3.4 Relationship Between NLRP3 Inflammasome and Alcoholic Acute Liver Injury

Alcoholic acute liver injury represents an acute inflammatory response in the liver caused by chronic or excessive alcohol consumption. Its pathological mechanisms involve the toxicity of alcohol metabolites, oxidative stress, and gut microbiota dysbiosis. The NLRP3 inflammasome plays a central regulatory role in alcohol-induced inflammatory responses. Acetaldehyde and reactive oxygen species (ROS) produced during alcohol metabolism directly damage hepatocytes and release damage-associated molecular patterns (DAMPs). Additionally, alcohol impairs intestinal barrier function, allowing endotoxin (LPS) to enter the bloodstream and further activate the NLRP3 inflammasome.

In an acute alcohol-induced liver injury mouse model established by intragastric alcohol administration, Shen et al. [24] made several key observations. They found that MLKL knockout ($Mlkl^{-/-}$) mice exhibited improved hepatic histopathological damage after alcohol challenge. Specifically, these mice showed decreased serum concentrations of pro-inflammatory factors such as IL-1β and IL-18, downregulated mRNA and protein expression of NLRP3, ASC, and caspase-1 in the liver, and inhibited generation of activated caspase-1. These results indicate that Mlkl knockout alleviates AALI by suppressing NLRP3 inflammasome activation. Furthermore, the study revealed that acute alcohol exposure promotes the translocation of MLKL into the nucleus. Once in the nucleus, MLKL reduces the nuclear translocation of the p65 protein, a key component of the NF-κB signaling pathway, thereby inhibiting Nlrp3 gene transcription and subsequent NLRP3 protein expression.
Feng et al. [25] found in a mouse model of alcoholic liver injury that alcohol induces oxidative stress, leading to excessive ROS accumulation that activates the NLRP3/caspase-1 inflammatory pathway. This pathway upregulates NLRP3 and caspase-1 protein expression, promotes the release of proinflammatory factors IL-1β and IL-18, and mediates pyroptosis. Inhibition of the Keap1-Nrf2/ARE pathway reduces the expression of antioxidant proteins such as HO-1, NQO1, and GCLM, and

decreases the activity of antioxidant factors like SOD. Natural medicines like Ficus lyrata activate the Keap1-Nrf2/ARE antioxidant pathway, upregulating antioxidant proteins like HO-1, NQO1, and GCLM. This reduces ROS production, inhibits NLRP3 inflammasome activation, and alleviates hepatocyte pyroptosis and inflammatory injury. These studies indicate that oxidative stress induced by alcoholic liver injury also participates in the development of liver damage by regulating NLRP3 activation.

Additionally, in an alcohol-induced acute liver injury mouse model, PTH upregulates the ratio of autophagy marker proteins LC3-II/LC3-I and the expression level of Beclin1, indicating its ability to enhance hepatic autophagy activity. Concurrently, PTH significantly inhibits NLRP3 inflammasome activation, manifested by downregulation of key proteins including NLRP3, Caspase-1 p20, and IL-18. At the level of inflammatory mediators, PTH also reduced the expression levels of pro-inflammatory factors such as IL-6, IL-1β, and TNF-α in liver tissue. These findings suggest that PTH may mitigate alcohol-induced inflammatory responses and liver tissue damage by inducing cellular autophagy, inhibiting NLRP3 inflammasome activation, and suppressing the production and release of downstream inflammatory mediators [26].

4. Intervention Strategies Targeting NLRP3 Inflammasome in Acute Liver Injury

Given the pivotal role of NLRP3 inflammasome in acute liver injury, intervention strategies targeting NLRP3 inflammasome have emerged as a research hotspot.

4.1 Small-Molecule Inhibitors Targeting the NLRP3 Inflammasome

MCC950 directly binds to specific domains of NLRP3, inhibiting its oligomerization or interaction with ASC to block inflammasome activation. This represents the most thoroughly studied intervention strategy to date. MU et al. [27] established a drug-induced liver injury model in female C57BL/6 mice and found that MCC950 effectively suppressed NLRP3 inflammasome activation, significantly reducing serum ALT and AST elevation, hepatic inflammation, and cell death induced by the combination of fluoxetine and LPS. These findings indicate that the NLRP3 inflammasome plays a central role in psychotropic drug-induced specific liver injury. As a specific inhibitor, MCC950 holds potential clinical intervention value, offering a novel strategy for the prevention and treatment of drug-induced liver injury. In a non-alcoholic steatohepatitis (NASH) model established in C57BL/6 mice [28], methionine-choline deficiency (MCD) induces NLRP3 inflammasome activation in mouse hepatic Kupffer cells (KCs), promoting downstream IL-1β and IL-18 expression. This triggers hepatocyte ballooning degeneration, inflammatory infiltration, and fibrosis, elevating serum IL-1β and TNF-α levels. Intraperitoneal injection of MCC950 specifically inhibits NLRP3 activation and downstream cytokine expression in KCs without affecting upstream TLR4 expression, significantly attenuating hepatic pathological damage.

CY-09 directly targets NLRP3 by inhibiting its activation through blocking ATP binding to NLRP3. Wang et al. [29] elucidated that hyperglycemia promotes NLRP3 inflammasome activation by suppressing AMPK/mTOR - mediated autophagy in hepatic Kupffer cells, thereby exacerbating TAA-induced acute liver injury. The use of the NLRP3-specific inhibitor CY-09 confirmed that NLRP3 activation is a key step in hyperglycemia-mediated liver injury progression. Conversely, restoring autophagy function by activating AMPK with an AMPK agonist (AICAR) or knocking down mTOR with siRNA effectively suppressed NLRP3 inflammasome activation and ultimately mitigated liver injury.

OLT1177 is an orally active β-sulfonyl nitrile compound that acts as a specific inhibitor of the NLRP3 inflammasome. By directly binding to the NLRP3 protein and inhibiting its ATPase activity, it effectively blocks inflammasome assembly, thereby suppressing the maturation and release of IL-1β and IL-18, while showing no effect on the NLRC4/AIM2 inflammasome. In animal models, OLT1177 not only alleviates LPS-induced systemic inflammation but also reverses inflammation-induced metabolic exhaustion, ameliorates oxidative stress, and enhances mitochondrial function. [30] Key Phase I clinical trials demonstrated OLT1177's favorable safety profile and excellent pharmacokinetic characteristics in healthy human subjects. These findings establish OLT1177 as a highly promising NLRP3-targeting oral therapeutic strategy applicable to multiple IL-1-driven inflammatory diseases.

4.2 IL-1 Receptor Antagonists

Beyond directly inhibiting NLRP3, blocking the signaling of IL-1β—a downstream effector molecule of the NLRP3 activation pathway—can also significantly slow the progression of related liver diseases. Ghulam Ilyas[31] established a myeloid-specific Atg5 autophagy gene knockout mouse model, revealing that impaired macrophage autophagy exacerbates alcohol-induced and alcohol-LPS-induced liver injury and inflammatory responses. Autophagy defects led to elevated expression of proinflammatory cytokines (such as IL-1β) in the liver, enhanced inflammasome activation, and promoted hepatocyte apoptosis and systemic inflammation. Treatment with IL-1 receptor antagonists mitigated liver injury, indicating a critical role for IL-1β in this process.

4.3 Caspase Inhibitors

Caspase inhibitors effectively block the production of inflammatory mediators downstream of NLRP3 and the pyroptosis process, offering a potential therapeutic strategy for alleviating NLRP3-associated diseases. Investigating how caspase inhibitors regulate the NLRP3 pathway is crucial for understanding inflammatory mechanisms and developing novel anti-inflammatory drugs. Ac-YVAD-cmk is a highly specific peptide inhibitor primarily targeting caspase-1. In a Phase II clinical trial of GS-9450 for non-alcoholic steatohepatitis (NASH), Vlad Ratziu[32] observed significant reductions in patients' ALT and AST levels, alongside decreased levels of caspase-3-cleaved cytokeratin 18 (CK-18) fragments. The study demonstrated that the selective caspase inhibitor GS-9450 improves liver injury in NASH patients.

4.4 GSDMD Inhibitors

Gasdermin D (GSDMD) is a key effector molecule in the NLRP3 inflammasome pathway that mediates pyroptosis. Upon NLRP3 inflammasome activation, activated caspase-1 specifically cleaves GSDMD, releasing its N-terminal domain. This domain subsequently oligomerizes to form pores in the cell membrane, leading to cell swelling, lysis (i.e., pyroptosis), and the release of mature proinflammatory cytokines such as IL-1β and IL-18, thereby driving intense inflammatory responses. Consequently, direct targeting of GSDMD has emerged as a novel strategy for regulating NLRP3-associated diseases. GSDMD inhibitors can directly and effectively suppress pyroptosis and subsequent inflammatory mediator release by blocking GSDMD cleavage or the pore-forming activity of its N-terminal domain, thereby downstream-blocking the destructive effects of the NLRP3 pathway. Wu et al. [33] demonstrated that in LPS/D- GalN-induced mouse acute liver failure (ALF) models, both classical and non-classical pyroptosis pathways were activated, with significant increases in expression of the key executor protein GSDMD and its active form GSDMD-NT. The GSDMD-specific inhibitor Necrosulfonamide (NSA) exerts hepatoprotective effects by inhibiting the pyroptotic pathway through suppression of caspase-1/11 activation and GSDMD cleavage, thereby blocking NLRP3 inflammasome activation.

4.5 Natural Products

Natural products have garnered significant attention as targets for NLRP3 inflammasome modulation due to their wide availability, low toxicity, and multi-target effects. Multiple active components from traditional Chinese medicine have been demonstrated to exert therapeutic effects.

Zhang et al. [34] demonstrated that ginsenoside Rc exerts dual benefits in suppressing hepatic inflammation and improving lipid metabolism disorders by targeting the P2X7R-NLRP3 axis. Song et al. [35] found that curcumin exerts hepatoprotective effects by synergistically regulating oxidative stress and NLRP3 inflammasome activation. Zhou et al. [36] discovered that resveratrol may alleviate hepatocyte pyroptosis and inflammation by targeting the NLRP3 inflammasome pathway.

5. Summary

In summary, with the deepening research on the NLRP3 inflammasome, it has become clear that the NLRP3 inflammasome plays a crucial role in the development and progression of acute liver injury. Substantial evidence indicates that regardless of whether acute liver injury is triggered by drugs, viruses, alcohol, or immune factors, the pathological process ultimately converges on NLRP3 inflammasome activation. This inflammasome dramatically amplifies hepatic inflammatory responses through caspase-1-mediated pyroptosis and the release of proinflammatory cytokines such as IL-1β and IL-18, leading to massive hepatocyte necrosis and liver failure. Currently, multiple small-molecule inhibitors, natural products, and biologics targeting NLRP3 and its downstream signaling molecules (such as caspase-1 and GSDMD) have demonstrated promising hepatoprotective potential in preclinical studies, offering new therapeutic directions for acute liver injury. However, research in this field still faces several limitations and challenges. First, although NLRP3 inflammasome inhibitors demonstrate significant therapeutic potential in animal models of acute liver injury, their mechanisms of action in clinical settings require further validation due to the greater complexity of the human immune microenvironment and inflammatory regulatory networks. Drugs like OLT1177 have entered early clinical trials, but clinical data specifically addressing acute liver injury remain limited. Second, as a crucial component of the innate immune system, the physiological activation of NLRP3 inflammasomes is vital for host defense against infection. While existing inhibitors (e.g., MCC950) effectively suppress pathological excessive inflammatory responses, long-term or systemic administration may compromise immune surveillance capabilities, thereby increasing infection risks. Furthermore, the NLRP3 inflammasome exhibits complex functions in extrahepatic organs such as the central nervous system and gut. Systemic administration may induce off-target effects or unforeseen side effects. Consequently, future research must delve deeper into the mechanisms of NLRP3 inflammasome involvement across different types of acute liver injury. This will facilitate the discovery and development of safe, potent, and highly specific NLRP3 inhibitors for the prevention and treatment of acute liver injury in clinical settings.

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