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REVIEW

NLRP3 Inflammasome Activation in Liver Disorders: From Molecular Pathways to Therapeutic Strategies

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Abstract: The NOD-like receptor protein 3 (NLRP3) inflammasome, a cytosolic multi-protein complex, detects danger signals released by injured cells and pathogens. It plays a critical role in the pathogenesis of various acute and chronic liver diseases. NLRP3 activation triggers caspase-1-mediated processing and secretion of pro-inflammatory cytokines interleukin (IL)-1β and IL-18. Unlike other inflammatory pathways, NLRP3 activation requires two signals, ensuring a tight control over inflammation. Caspase-1 activation further amplifies the response by cleaving IL-1β, a potent pro-inflammatory mediator. Extensive research suggests the NLRP3 inflammasome contributes significantly to hepatocyte injury, immune cell activation, and the perpetuation of inflammatory responses in various human and experimental liver disease models. This review comprehensively examines NLRP3 inflammasome activation and its functional consequences in the context of liver injury and disease progression, including conditions such as alcoholic liver disease (ALD), metabolic dysfunction-associated fatty liver disease (MAFLD), viral hepatitis, hepatic fibrosis, and drug-induced liver injury (DILI). We specifically highlight emerging therapeutic strategies targeting NLRP3 inflammasome that show translational promise in attenuating liver inflammation and fibrosis. This review provides a theoretical framework and reference for the development of novel therapeutics targeting the NLRP3 inflammasome in liver injury and chronic liver diseases.

Keywords: NLRP3, liver injury, chronic liver diseases, inhibitors, pattern recognition receptors

Introduction

The mammalian immune system employs two fundamental mechanisms to combat threats: innate immunity and adaptive immunity. Innate immunity, a principle first proposed by Charles Janeway, provides a rapid, broad-spectrum defense against microbial pathogens. This response is initiated by pattern recognition receptors (PRRs) on antigen-presenting cells (APCs) that specifically recognize pathogen-associated molecular patterns (PAMPs).[1] Additionally, the "danger signal hypothesis" postulates that APCs can also be activated by endogenous danger-associated molecular patterns (DAMPs) released by injured or stressed cells, even in the absence of pathogens.[2] These two principles, innate immune recognition of PAMPs and DAMPs, collectively contribute to the initiation of inflammatory responses in various human diseases, including liver diseases.[3,4] The liver is the largest gland in the human body, and a variety of cells in the liver, including immune cells and hepatic parenchymal cells, are also central components in the initiation and regulation of bacterial or aseptic inflammatory responses in the liver through the innate immune system, which therefore plays an important role in the pathogenesis of inflammation-associated acute and chronic liver diseases.[5]

The NLRP3 inflammasome, one of the most studied inflammasomes, plays a dual role in the immune response. The NLRP3 inflammasome is a cytosolic multiprotein complex composed of a nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family member (NLRP3), the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD), and the effector protease pro-caspase-1.[6] Upon activation by diverse stimuli—including microbial

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components and danger signals—NLRP3 self-oligomerizes, recruiting ASC and pro-caspase-1 into a supramolecular "speck" that drives caspase-1 maturation. Mature caspase-1 then processes pro-IL-1β and pro-IL-18 into their active forms.[6] In infectious settings, NLRP3-derived IL-18 enhances interferon-γ production by natural killer cells, helping to control hepatitis C virus, while IL-1β promotes expression of additional immune mediators and lymphocyte recruitment to sites of hepatitis B and C infection.[7,8] However, excessive or sustained NLRP3 activation can trigger pathological inflammation and is now recognized as a key contributor to sterile inflammatory diseases.[9] Emerging studies link aberrant NLRP3 inflammasome activity to the initiation and progression of chronic liver injury and fibrosis.

Although several reviews have described NLRP3 inflammasome activation in broad inflammatory, neurodegenerative conditions and metabolic contexts,[10–12] few have provided a comprehensive overview focusing specifically on its role in liver disorders. While related reviews exist, there is currently no dedicated summary that integrates recent findings on NLRP3 inflammasome activity specifically in hepatic pathophysiology. This gap highlights the need for a detailed examination of NLRP3-driven mechanisms in hepatic injury and chronic liver diseases. This review will explore the recent advances in understanding the molecular pathways governing NLRP3 inflammasome regulation and its contribution to chronic liver disease and liver injury. This study elucidates the molecular regulatory mechanisms governing NLRP3 inflammasome activation and investigates its pathologically dysregulated signaling in the pathogenesis of chronic hepatic disorders and hepatocellular injury. Furthermore, we systematically explore the emerging therapeutic value of pharmacologically targeting NLRP3 through specific inhibitors as a potential strategy for mitigating liver inflammation and disease progression.

NLRP3 Inflammasome and Molecular Mechanisms

The NLRP3 inflammasome is a cytosolic multi-protein complex composed of three main domains: a leucine-rich repeat (LRR) domain that recognizes activation signals, a central nucleotide-binding domain (NACHT) domain responsible for oligomerization, and an N-terminal pyrin domain (PYD) that mediates apoptosis-associated speck-like protein (ASC) recruitment.[13] Upon exposure to PAMPs, DAMPs, or other stimuli, NLRP3 molecules undergo conformational changes and oligomerize through NACHT domain interactions. These NLRP3 oligomers then recruit the adaptor molecule ASC via PYD-PYD domain interactions, leading to ASC speckle formation. Subsequently, caspase-1, a pro-inflammatory cysteine protease, is recruited to the ASC speckles through interactions with the caspase-activating recruitment domains (CARDs) on ASC. This proximity-induced autocleavage of pro-caspase-1 leads to the generation of its active form. Activated caspase-1 then cleaves pro-interleukin (IL)-1β and IL-18 into their mature and biologically active forms, promoting their secretion.[13] Additionally, caspase-1 can cleave gasdermin D (GSDMD), which translocates to the plasma membrane and forms pores, facilitating the non-canonical release of mature IL-1β and IL-18. This massive release of pro-inflammatory cytokines and pyroptosis, a caspase-1-dependent programmed cell death, ultimately contributes to a potent inflammatory response.[14]

In addition to the classical NLRP3 inflammasome pathway dependent on caspase-1, recent studies have revealed a non-classical pathway relying on caspase-11 (homologous to caspase-4/5 in humans). Caspase-11 possesses a similar domain structure to caspase-1 but plays a distinct role in NLRP3 activation.[15] Unlike caspase-1, caspase-11 directly interacts with the lipid A moiety of lipopolysaccharide (LPS) upon its intracellular recognition. This interaction triggers caspase-11 oligomerization and activation, leading to the cleavage of GSDMD at Asp276. The cleaved GSDMD N-terminal fragment then translocates to the plasma membrane and forms pores, facilitating the non-canonical release of mature IL-1β and IL-18.[15] Interestingly, while non-classical caspase-11 activation can directly induce GSDMD-mediated pyroptosis, it can also indirectly activate the classical pathway by promoting caspase-1 cleavage and subsequent IL-1β/IL-18 maturation.[16] Furthermore, similar to most classical NLRP3 activators, non-classical caspase-11 activation appears to be partially dependent on K^+ efflux.[16]

NLRP3 inflammasome activation plays a critical role in various liver diseases.[17–19] NLRP3, a member of the Nod-like receptor (NLR) family, is a key sensor of danger signals within the cell. Inflammasome activation involves a priming step and an activation step.[20] During priming, PAMPs like LPS can upregulate NLRP3 expression through the NF-κB signaling pathway;[21] Additionally, endogenous DAMPs released by damaged cells can trigger NLRP3 inflammasome activation through several mechanisms. Furthermore, DAMPs released from damaged cells can activate the NLRP3

inflammasome through the following three main pathways: ① Extracellular ATP released from damaged cells can induce NLRP3 activation via potassium ion efflux through the P2X7 receptor;[22–24] ② Phagocytic uptake of cholesterol crystals, uric acid crystals, or misfolded proteins by macrophages can cause lysosome rupture, leading to the release of lysosomal cathepsin B. This alters intracellular pH and activates NLRP3;[25,26] ③ Production of reactive oxygen species (ROS) during cellular stress can directly activate NLRP3.[27] The NLRP3 inflammasome exhibits distinct activation mechanisms and pathophysiological roles in sterile versus infectious liver injury. In sterile models (eg, ALD, MAFLD and DILI), activation is primarily driven by endogenous DAMPs, such as mitochondrial reactive oxygen species (mtROS), extracellular ATP, cholesterol crystals, or saturated fatty acids.[25–27] These DAMPs trigger NLRP3 assembly via secondary signals, including lysosomal destabilization, K^+ efflux (eg, ATP-P2X7 axis), or calcium dysregulation.[28] Subsequent caspase-1 activation promotes pyroptosis and IL-1β/IL-18 release, perpetuating chronic inflammation and fibrosis through hepatic stellate cells (HSCs) activation.[29] In contrast, infectious models rely on PAMPs, such as viral RNA or bacterial LPS, which activate NLRP3 through direct pathogen-immune interactions or indirect mechanisms like lysosomal damage.[30] Here, inflammasome activation coexists with antiviral/antibacterial responses, where STAT1 may suppress NLRP3 to balance immune defense and tissue protection.[31] Therapeutically, sterile inflammation emphasizes targeting DAMPs,[32] NLRP3 assembly inhibitors,[33] or IL-1 blockade,[34] whereas infectious contexts require combined pathogen clearance and controlled anti-inflammatory interventions to avoid immunosuppression. These differences underscore the need for context-specific strategies to modulate NLRP3 in liver diseases.

During the activation phase of the NLRP3 inflammasome, recognition of agonists and subsequent assembly and activation of the complex take center stage. NLRP3 responds to a diverse range of stimuli, including both PAMPs and DAMPs. Recent research has shed light on several upstream signals that contribute to NLRP3 inflammasome assembly and activation, including alterations in ion homeostasis, lysosomal damage, and mitochondrial dysfunction.[35] Potassium (K^+) efflux is a critical upstream signal for NLRP3 activation. In macrophages, extracellular adenosine triphosphate (ATP) binding to the P2X7 receptor (P2X7R) mediates K^+ efflux, triggering NLRP3 inflammasome assembly.[36] Conversely, increased intracellular calcium ($Ca2^+$) flux can promote NLRP3 inflammasome assembly but also reduces cyclic AMP levels, which inhibits inflammasome activation.[28,37] This intricate interplay between K^+ and $Ca2^+$ fluxes highlight the dynamic nature of NLRP3 regulation. The intracellular engulfment of various substances, such as saturated fatty acids, cholesterol crystals, uric acid crystals, or foreign particles like alum and silica, can lead to lysosomal damage. This damage results in the release of lysosomal proteases that activate NLRP3. Interestingly, lysosomal damage triggered by these stimuli also induces K^+ efflux and $Ca2^+$ influx, suggesting potential convergence of these pathways during NLRP3 activation.[28] Drugs like fluoxetine and acetaminophen, along with chronic mitochondrial dysfunction caused by metabolic disorders, can activate NLRP3 via the production of excessive mtROS.[38,39] Additionally, translocation of mitochondrial DNA to the cytoplasm or the induction of α-microtubule acetylation can relocate mitochondria near NLRP3, promoting its activation.[40,41] Recent studies suggest that metabolic reprogramming and dysfunction in the trans-Golgi network may also act as upstream signals for NLRP3 inflammasome activation, highlighting the complex and multifaceted nature of NLRP3 regulation[42,43] (Figure 1).

Inflammasomes in immune cells play a critical role in liver diseases by promoting a potent inflammatory response mediated by IL-1β.[44,45] IL-1β, a pro-inflammatory cytokine, exerts its deleterious effects through multiple mechanisms, exacerbating liver pathology. IL-1β can synergize with Toll-like receptor (TLR) signaling, amplifying the inflammatory response triggered by bacterial LPS and other TLR ligands.[46,47] This synergistic action further potentiates the inflammatory cascade, leading to tissue damage and disease progression. Inflammasome-mediated IL-1β release creates a positive feedback loop, exacerbating the inflammatory response. IL-1β promotes the transcription of its own precursor (pro-IL-1β), the production of other inflammasome components, and the release of additional inflammatory factors and chemokines.[48] This autocrine and paracrine amplification fuels the inflammatory milieu, contributing to liver injury and disease pathogenesis. IL-1β plays a multifaceted role in liver disease pathogenesis, promoting various pathological processes. IL-1β promotes the recruitment of inflammatory cells, such as neutrophils and macrophages, to the liver, amplifying the inflammatory response.[49] In addition, IL-1β can induce hepatocyte apoptosis, a form of programmed cell death, by promoting triglyceride accumulation and oxidative stress.[50–52] Hepatocyte apoptosis

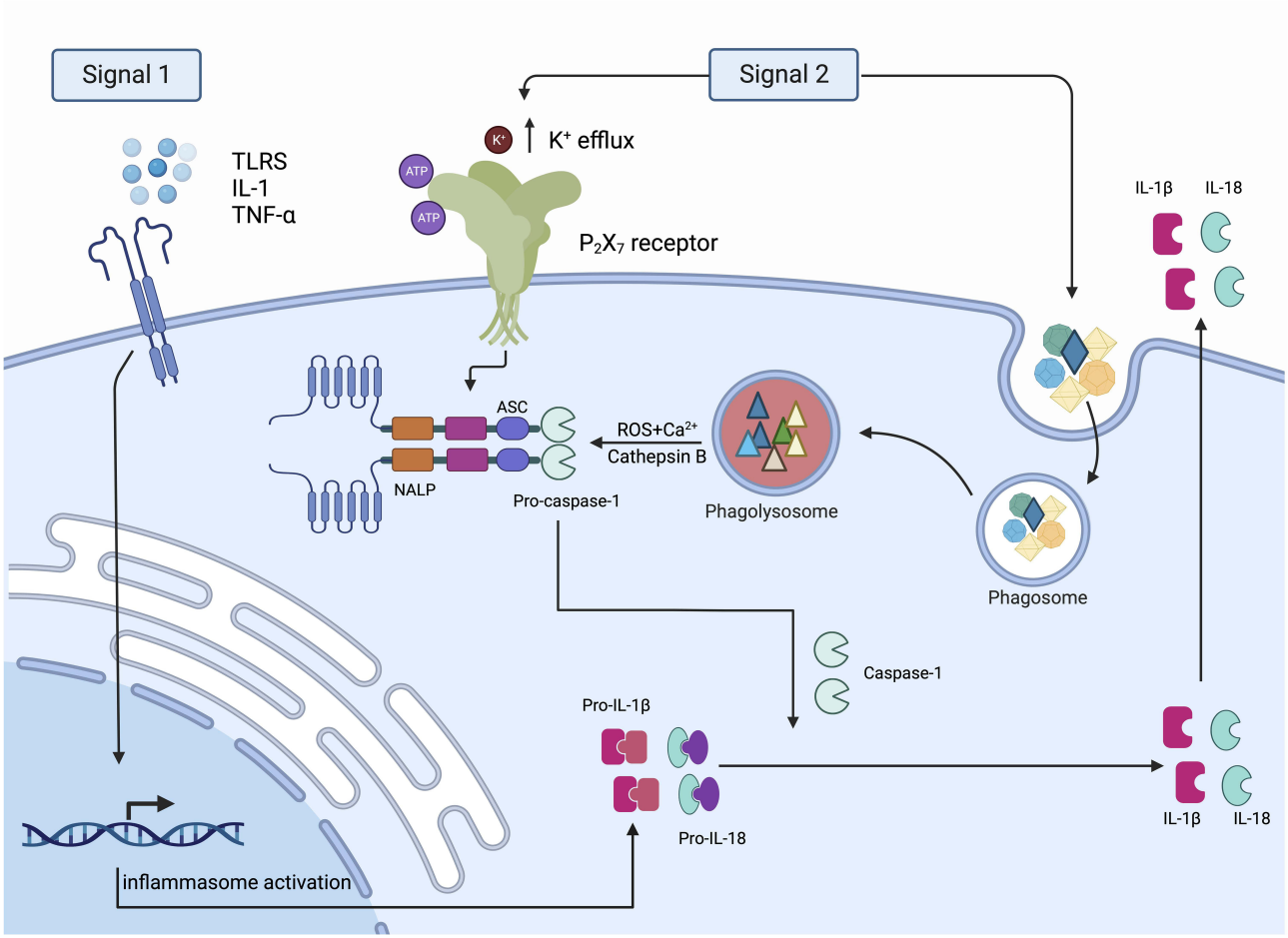

Figure 1 Mechanisms of inflammasome activation. Two types of signals are required for inflammasome activation and the production of mature IL-1β and IL-18. Signal-1: This results in the production of pro-IL-1β and pro-IL-18 through the interaction of various DAMPs/PAMPs and cytokines like TNF-a with TLRs and TNFR. Signal-2: This leads to inflammasome activation through multiple signaling pathways. MSU and other crystals form phagolysosomes. Another pathway of inflammasome activation is via the P2X7 receptor. The inflammasome activation causes cleavage and activation of caspase-1, which subsequently cleaves pro-IL-1β and pro-IL-18 to mature IL-1β and IL-18 that are secreted out of the cell.

contributes to liver injury and dysfunction. The IL-1 receptor antagonist (IL-1RA) acts as a natural inhibitor of IL-1β signaling by competitively binding to the IL-1 receptor, thereby blocking its activation by both IL-1α and IL-1β.[51,53] IL-1RA plays a crucial role in regulating IL-1β signaling and preventing excessive inflammation.[54] While caspase-1 is the primary enzyme responsible for IL-1β maturation, as demonstrated in caspase-1 knockout mice.[55–57] While caspase-1 is the primary enzyme responsible for IL-1β maturation, as demonstrated in caspase-1 knockout mice.[58,59] The role of these alternative pathways in IL-1β maturation during liver disease remains to be elucidated.

While IL-1β is a key player in inflammasome-mediated liver inflammation, recent research suggests that other inflammasome-derived cytokines, IL-18 and IL-33, may also play complex roles in this process.[60] While IL-1β is a key player in inflammasome-mediated liver inflammation, recent research suggests that other inflammasome-derived cytokines, IL-18 and IL-33, may also play complex roles in this process.[29] Interestingly, IL-18 deficiency also altered the gut microbiota composition, promoting the growth of colitis-associated bacteria. This shift in gut flora composition led to the transfer of bacterial metabolites to the liver, further fueling inflammation.[29] These findings highlight the potential importance of the gut-liver axis in inflammasome-mediated liver disease and the unique role of IL-18 in regulating this interaction. The function of IL-33 in liver disease remains less well-defined. Current research suggests that IL-33 acts as an alarmin, a danger signal released by damaged or dying cells in the liver.[61] Studies in mouse models of ALD, liver fibrosis, and ischemia-reperfusion injury have shown a significant increase in IL-33 expression.[34,62,63] However, the therapeutic implications of targeting IL-33 signaling appear to be context-dependent. While inhibiting IL-33 signaling

can suppress liver macrophage activation, thereby reducing ischemia-reperfusion injury, it can also accelerate CCl_4-induced liver fibrosis.[64,65] Additionally, no significant effects were observed in canavalin-A-induced acute liver injury models. These findings suggest that the role of IL-33 may vary depending on the specific type of liver disease.[66] Further research is needed to elucidate the precise functions of IL-33 in different liver pathologies, such as ALD, non-alcoholic steatohepatitis (NASH), and hepatitis C infection.

IL-1β and IL-18, released by inflammasome activation, can induce tissue and cell damage through pyroptosis.[67,68] Therefore, effective control of injury occurrence requires rapid and efficient inflammasome action followed by immediate control. Additionally, existing stimuli should be converted to prevent inflammasome overactivation and unnecessary immune damage. Thus, effective control of inflammasome-triggering factors is essential. Various pathogenic and injury-related proteins have been experimentally studied. Autophagy, a cellular self-protection process mediated by lysosomes, can indirectly inhibit inflammasome activation by suppressing endogenous activation factors or directly degrading inflammasome components.[69–71] Interferons (IFNs) can reduce IL-1β production by inhibiting the transcription factor STAT1-dependent NLRP1 and NLRP3 inflammasome activation.[72] Moreover, acquired immunity strongly inhibits innate immunity. Effector and memory T cells can suppress inflammation-mediated caspase-1 activation and IL-1β release in mononuclear macrophages and APCs.[73,74] Additionally, numerous activated molecules, including those inhibiting the inflammasome, require further study to elucidate their mechanisms of action and provide evidence for clinical application.

Mechanisms of NLRP3 in Different Liver Diseases

ALD

Acute alcohol consumption may trigger fatty liver disease, while chronic alcoholism can lead to a more serious cascade of steatohepatitis, liver fibrosis, and potentially even cirrhosis. In advanced stages, ALD becomes largely irreversible, and liver failure can cause fatal outcomes. Recent research highlights the critical role of the innate immune system, specifically the NLRP3 inflammasome, in the pathogenesis of ALD.[17,75,76] Studies reveal a significant rise in various inflammatory markers in patients with acute ALD. This includes increased levels of serum TNF, IL-1, and IL-8, alongside elevated liver caspase-1 and NLRP3 expression.[77,78] Furthermore, a substantial rise in neutrophil count and activated mononuclear macrophages has been observed. Notably, patients with severe ALD exhibit significantly higher levels of serum IL-1β compared to healthy individuals.[79] The increased IL-1β levels, coupled with a rise in neutrophil numbers and the presence of aseptic inflammation, strongly suggest that NLRP3 inflammasome activation plays a key role in the development of ALD.[80]

The crucial role of NLRP3 inflammasome activation in ALD has been demonstrated in a murine experimental model. Prolonged alcohol administration induced fatty liver injury and upregulated the expression of IL-1β, pro-caspase-1, ASC, and NLRP3 in the liver.[34]

Similarly, exposure of mouse livers to alcohol increased caspase-1 activation, indicating inflammasome activation.[34] Furthermore, in IL-1R1, caspase-1, or ASC knockout mice, NLRP3 inflammasome activation was not observed, and IL-1β release occurred after long-term alcohol administration. Remarkably, alcohol-induced fatty liver disease and liver injury were ameliorated in these mice.[34] Inhibition of NLRP3 inflammasome activation also reduced inflammatory cell accumulation in the liver and decreased the production of TNF, IL-6, and other inflammatory factors. IL-1 receptor antagonists dose-dependently reduced liver inflammation in fatty liver and liver injury.[34] Notably, symptoms of fatty liver and liver damage were significantly relieved in mice treated with an IL-1 receptor antagonist for 2 weeks.[34] Therefore, inhibiting IL-1 signaling can impede the progression of ALD and promote liver recovery after alcohol withdrawal. Analysis of primary mouse cells revealed that the expression of caspase-1, ASC, and NLRP3 in liver immune cells was 20 times higher than in primary liver cells.[34] Further experiments showed that alcohol induced caspase-1 activation in liver immune cells in mice but had no effect on liver cells.[34] In a mouse model of ALD, liver macrophages were the primary cells dependent on the NLRP3 inflammasome for disease progression.[34] A 2014 study reported that the NLRP3 inflammasome was involved in alcohol-induced liver cell death.[81] However, their conclusions were based on liver cell lines treated with 10 times the alcohol concentration used by other researchers, limiting the generalizability of these

findings.[81,82] In summary, the pathological role of the NLRP3 inflammasome in alcoholic hepatitis is mediated by its activation in liver macrophages.

The NLRP3 inflammasome plays a pivotal role in ALD, but the exact signaling pathway for its activation remains incompletely understood. Gut-derived LPS likely serves as the first signal, inducing IL-1β release via the TLR4 pathway.[83,84] However, the second activation signal remains elusive. Changes in uric acid and ATP metabolism due to alcohol-induced mitochondrial dysfunction may act as potential candidates.[85–87] Increased serum uric acid levels in alcohol-treated mice and the efficacy of uric acid synthesis inhibitors in reducing liver inflammation, fatty liver, and damage support this hypothesis.[88] The role of sterile inflammatory signals, including PAMPs from the gut and DAMPs from liver cells, in ALD pathogenesis is still being explored. Targeting DAMPs, NLRP3 inflammasome, and IL-1β signaling holds promise as potential therapeutic approaches for ALD. Further research is crucial to identify the second inflammasome activation signal and fully elucidate the role of sterile danger signals. Understanding these pathways will pave the way for developing novel therapies to combat ALD.

MAFLD

The activation of the NLRP3 inflammasome in MAFLD has garnered the attention of several researchers.[89,90] Inflammasome activation occurs during metabolic syndrome and insulin resistance, which can predispose the body to MAFLD and hepatitis.[91]

Studying the mechanisms underlying specific inflammasome activation in non-alcoholic hepatitis within the complex cellular environment of the liver is of utmost importance. In ALD, the activation of the NLRP3 inflammasome in liver macrophages is known to play a crucial role in the development of alcoholic hepatitis.[81] However, the role of the NLRP3 inflammasome in MAFLD and hepatitis is more complex than initially anticipated. In MAFLD, the signals and corresponding ligands that activate inflammasomes have only been partially identified. Deletion of Myd88, Tlr4, and Tlr9 reduced the symptoms of MAFLD in mice.[50,92,93] Toll-like receptor (TLR)-activated ligands may derive from LPS secreted by gut bacteria or other potential pathogen-associated molecular pattern signals, such as HMGB1 (a TLR-activated aseptic inflammatory signal).[50,92,93] The second signal for inflammasome activation may be related to hepatocyte injury induced by saturated fatty acids, reactive oxygen species (ROS), and cholesterol esters.[94,95] These signaling molecules accumulate during the course of the disease and eventually induce sustained inflammasome activation through TLRs, inflammasomes, and cytokine receptors.

In non-alcoholic hepatitis, aside from liver immune cells, liver parenchymal cells also participate in NLRP3 inflammasome activation.[29,92,96] Macrophages from bone marrow and parenchymal cells of the liver contribute to NLRP3 inflammasome activation in mice with methionine-choline-deficient (MCD)-induced non-alcoholic hepatitis.[92] Moreover, unsaturated fat can activate and upregulate the NLRP3 inflammasome in hepatocytes, leading to IL-1β production.[96] To elucidate the role of NLRP3 inflammasome activation in hepatocytes, we employed a mouse model with overexpressed NLRP3.[97] Although the study did not specifically investigate the pathological process of non-alcoholic hepatitis, activation of the NLRP3 inflammasome throughout the mouse body resulted in hepatocyte pyroptosis (inflammasome-mediated cell death).[98] Conversely, NLRP3 inflammasome activation in bone marrow-derived cells did not induce pathological liver damage.[97] Replicating these findings in a non-alcoholic hepatitis model could help determine whether NLRP3 activation in liver parenchymal cells significantly contributes to its pathogenesis. Additionally, other studies have suggested the essential role of the NLRP3 inflammasome in non-alcoholic hepatitis. For instance, one study demonstrated that choline-deficient diets induce hepatocyte death, inflammasome activation, and hepatic fibrosis; however, these symptoms were significantly reduced after NLRP3 knockout.[97]

The gut-liver axis (GLA) plays a central role in the pathogenesis and progression of MAFLD through bidirectional interactions involving gut microbiota, microbial metabolites, intestinal barrier integrity, and systemic inflammation.[99] Dysbiosis and impaired intestinal barrier integrity in the GLA lead to increased translocation of PAMPs and DAMPs into the liver via the portal circulation. These stimuli activate hepatic toll-like receptors (TLRs), particularly TLR4, initiating a priming phase that upregulates NLRP3 inflammasome components via NF-κB signaling. Subsequent DAMPs, such as saturated fatty acids or oxidative stress, trigger NLRP3 inflammasome oligomerization, activating caspase-1.[100] This process cleaves pro-inflammatory cytokines IL-1β and IL-18 into their active forms and induces pyroptosis via

gasdermin-D (GSDMD) pore formation, amplifying hepatic inflammation, hepatocyte death, and fibrogenesis.[101] Dietary factors like fructose and high-fat diets exacerbate intestinal permeability and dysbiosis, further promoting endotoxemia and NLRP3 activation.[102] Experimental models demonstrate that NLRP3 deficiency or pharmacological inhibition (eg, MCC950) reduces steatosis, inflammation, and fibrosis, highlighting NLRP3 as a therapeutic target in MAFLD.[103] Thus, the NLRP3 inflammasome serves as a critical mediator linking gut-derived inflammatory signals to hepatic injury in MAFLD progression.

Viral Hepatitis

HBV viral infection can mediate the activation of NLRP3 inflammasome,[104] and the X protein encoded by the HBV X gene plays a role in the chronicity of HBV infection by promoting the level of expression of ROS in the hepatocytes and activating the NLRP3 inflammasome.[105] Biopsies from patients with chronic hepatitis B also show high levels of IL-1β and caspase1 mRNA, and IL-1β mRNA levels correlate closely with the degree of inflammation.[106] In the treatment of hepatitis B, several advances have been made in controlling the disease by negatively regulating NLRP3 inflammasome. Yu et al found that HBeAg inhibits the NLRP3 inflammasome in two ways: by inhibiting the NF-κB signaling pathway to inhibit the expression of NLRP3 and pro-IL-1β, and by inhibiting the activation of caspase-1 and IL-1β through the inhibition of ROS.[8] In HBV-associated liver disease, hepatic farnesoid X receptor (FXR) levels are negatively correlated with the degree of NLRP3 inflammasome activation, and FXR offers new therapeutic perspectives by inhibiting endoplasmic reticulum stress-mediated activation of the protein kinase RNA-like endoplasmic reticulum kinase (PERK), and thus inhibiting CCAAT-enhanced binding protein homologous protein (CHOP)-dependent NLRP3 overexpression.[104]

HCV infection is a global health concern, with an estimated 1.8 billion individuals infected worldwide in 2010.[107] Viral hepatitis is a group of infectious diseases dominated by inflammatory and necrotic lesions of the liver, where both viral virulence and host immune response determine the replication and clearance of hepatitis viruses. Dylan et al[108] reported for the first time the presence of NLRP3 inflammasome assembly in Kupffer cells of patients with chronic HCV infection-associated liver injury and found that their IL-1β levels were significantly higher than those of patients with other forms of liver injury and that, after effective anti-HCV drug treatment, IL-1β and Caspase-1 levels were significantly reduced. Csak et al[96] found that hepatic NLRP3 inflammasome mRNA levels were elevated in chronic HCV-infected individuals, suggesting that NLRP3 inflammasome expression is upregulated, and this study also demonstrated that ROS play an important role in HCV infection-mediated IL-1β secretion. Negash et al[109] found that HCV induces activation of NLRP3 inflammasome, releases caspase-1, and stimulates IL-1β production by macrophages through a partial study of human hepatocellular carcinoma cells, and hypothesized that when antiviral therapy fails, chronic HCV infection-associated liver injury could be treated with inhibitors targeting IL-1β or NLRP3 inflammasome. HCV interacts with various intracellular PRRs on immune cells, including TLR2, 3, 4, 7, 8, and 9. This interaction stimulates IFNs production.[110,111] Macrophage activation and subsequent release of pro-inflammatory factors upon HCV infection contribute to both hepatitis and liver fibrosis.[112] Recent research has revealed a novel role for inflammasome activation and IL-1β production in HCV pathogenesis. Studies have demonstrated that HCV infection induces inflammasome activation and IL-1β production in macrophages.[113] Notably, blocking TLR7 using small interfering RNA (siRNA) significantly inhibited HCV-induced inflammasome activation, suggesting TLR7 as a critical signaling pathway in this process.[113] Furthermore, inflammasome activation in monocytes isolated from HCV-infected patients leads to IL-18 production, which in turn activates natural killer T cells. Additionally, in vitro studies have shown that HCV can directly trigger NLRP3 inflammasome activation.[113] Collectively, these findings indicate that inflammasome activation and IL-1β production occur in diverse liver immune cell populations during HCV infection.

Hepatic Fibrosis

Hepatic fibrosis is a pathological change in liver structure and/or function caused by abnormal deposition of extracellular matrix (ECM) in the liver due to increased synthesis and relatively insufficient degradation of ECM in liver tissues, and it is a common pathological feature in the progression of various chronic liver diseases to cirrhosis. The activation and proliferation of HSCs, as a central part of the development of liver fibrosis, promotes the release of various inflammatory

factors, leading to excessive deposition of various ECMs, including collagen, proteoglycans and glycoconjugate proteins in the liver, which exacerbates the parenchymal injury of the liver.[114] Inflammasomes, cytosolic protein complexes, play a multifaceted role in regulating this process, acting both directly and indirectly on HSCs, the primary drivers of fibrosis.[115,116] Direct regulation involves inflammasome expression within HSCs themselves. Studies have shown that DAMPs released by injured hepatocytes and PAMPs of intestinal origin can trigger HSC activation through inflammasome activation mediated by TLRs. TLRs are a pattern recognition receptor mainly involved in the natural immune response, activated HSCs express TLR-4 and TLR-2 and upon stimulation by their ligands (eg endotoxin is a TLR4 ligand), promote fibrogenesis through activation of NF-κB signaling pathway and JNK signaling production of chemokines and inflammatory cytokines that have the ability to recruit and activate macrophages and downregulate the TGF-β pseudo-receptor BAMBI, thereby promoting fibrogenesis.[117] Classical inflammasome activators, such as uric acid crystals, can directly stimulate human and mouse primary HSCs.[118] This stimulation upregulates TGF-β expression, promoting HSC activation and subsequent ECM production.[115] The inflammasome indirectly regulates liver in HSCs abolishes this effect.[115] Indirect regulation of fibrosis progression by secretion from Kupffer cells (KCs), liver-resident macrophages. Similar to HSC activation, enteric-derived PAMPs and DAMPs from hepatocyte injury can activate the inflammasome in KCs via TLRs, leading to IL-1β release and subsequent HSC activation[119](Figure 2). In a mouse model of liver fibrosis, researchers observed significantly increased IL-1β levels and fibrosis attenuation upon IL-1R deficiency, highlighting the critical role of this pathway.[120] Furthermore, blocking IL-1β signaling inhibited liver fibrosis in rat models induced by CCl_4 and thioacetamide.[120] Notably, IL-1β also regulates the expression of matrix metalloproteinases and their inhibitors, enzymes involved in ECM remodeling.[120] Additionally, studies using CCl_4- and thioacetamide-induced liver fibrosis models have demonstrated that knocking down NLRP3 or ASC significantly reduces TGF-β and type I collagen expression, further supporting the role of inflammasomes in this process.[120] While the general mechanism of fibrosis formation appears applicable to many chronic liver diseases, direct evidence specifically implicating inflammasomes in diseases beyond alcoholic and non-alcoholic fatty liver disease is lacking. For instance, although alcohol is a known causative factor in human liver fibrosis and cirrhosis, mice fed an alcohol diet develop only moderate disease. Moreover, studies suggest that the pathogenic effects of IL-1β in ALD depend on inflammasome activation in liver macrophages rather than parenchymal cells, highlighting the potential for an indirect role of inflammasomes.[34] Future research should aim to elucidate the precise mechanisms by which NLRP3 inflammasome contribute to hepatic fibrosis. Key areas of investigation include determining whether inflammasome directly activate HSCs via DAMPs or indirectly induce IL-1β and IL-18 secretion from liver macrophages through DAMP stimulation.

DILI

DILI is a significant safety concern in clinical pharmacology, frequently leading to drug development termination and market withdrawal. Growing evidence suggests a role for inflammasome activation, particularly NLRP3, in the hepatotoxic effects of various medications, including psychotropic drugs. Fluoxetine, a widely used antidepressant, has been shown to directly trigger NLRP3 inflammasome activation, potentially linked to mitochondrial damage and mtROS accumulation induced by the drug. In a mouse model of fluoxetine-induced hepatotoxicity, elevated serum aminotransferase levels, hepatic inflammatory injury, and cell death were observed, all dependent on the NLRP3 pathway. Notably, pretreatment with MCC950, an NLRP3 inflammasome inhibitor, effectively reversed these effects.[39] Similar NLRP3-dependent effects on liver inflammation have been documented for other antidepressants (eg, amitriptyline, paroxetine, promethazine) and antipsychotics (eg, asenapine).[39] Acetaminophen (APAP), a common analgesic and antipyretic drug, can cause hepatotoxicity and acute liver failure when taken in excessive doses.[121] APAP-induced liver injury (AILI) progresses through two distinct pathological stages. Initially, APAP directly causes cellular damage and sterile inflammation. Metabolic conversion of APAP by cytochrome P450 enzymes (primarily CYP2E1) generates the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI). Intrahepatic accumulation of NAPQI depletes glutathione stores, disrupts mitochondrial function, and leads to ATP depletion, DNA breaks, and ultimately, cell necrosis. Necrotic hepatocytes release DAMPs, triggering innate immune system activation and further promoting AILI development.[122–124] Studies in mice have shown that APAP administration significantly increases serum lactate dehydrogenase (LDH) levels and pyroptosis-related protein expression, indicating disruption of the liver cell membrane and release of cellular contents. Furthermore, APAP-mediated liver injury appears to be closely linked to

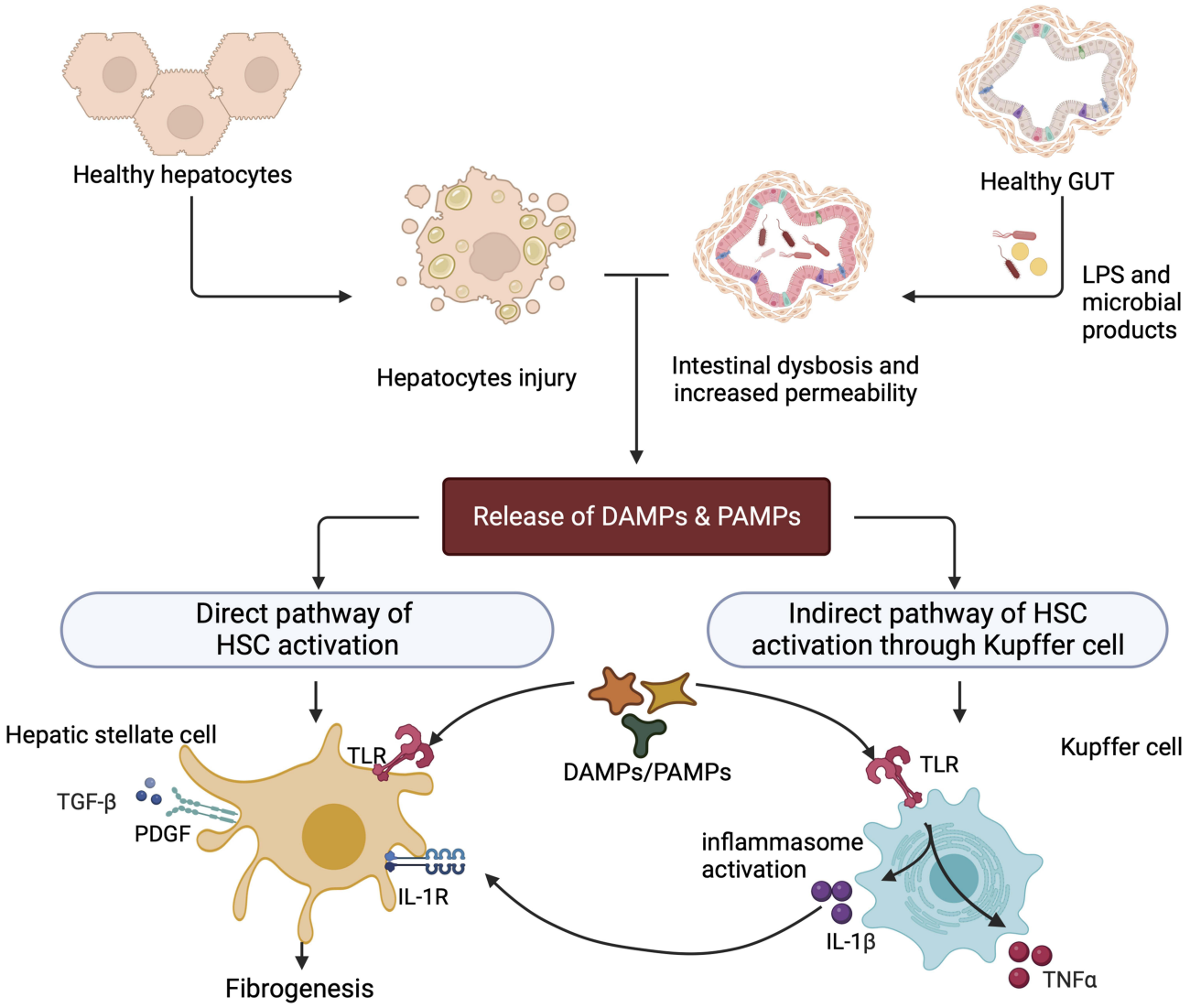

Figure 2 Mechanism of inflammasome activation in hepatic fibrosis. Most signals are produced by hepatocytes (DAMPs) and intestinal luminal contents (PAMPs). Various stresses, including metabolic stress, cause hepatocyte damage and the release of DAMPs, which then induce the activation of KCs and HSCs. In addition, the release of LPS and other microbial products from the lumen to the portal circulation can activate KCs and HSCs. KC activation induces IL-1β and TNF-α production, which can activate HSCs and induce hepatocyte death.

pyroptosis of hepatocytes. Co-culturing hepatocytes with KCs, liver-resident macrophages, upon APAP treatment resulted in increased LDH release and pyroptosis protein expression compared to hepatocytes treated with APAP alone. Additionally, caspase-1 activation and GSDMD-N fragment levels were significantly higher, and IL-1β and IL-18 expression were markedly upregulated in hepatocytes co-cultured with KCs. These findings suggest that KCs may promote hepatocyte death during APAP treatment.[38] N-dimethylformamide (DMF), a widely used industrial solvent, can cause multi-organ damage, with the liver being particularly susceptible.[125] However, DMF exposure can cause multiorgan damage, with the liver being particularly susceptible.[126] To investigate the mechanisms underlying DMF-induced hepatotoxicity, a mouse model was employed. The model exhibited significant oxidative stress, as evidenced by elevated hepatic malondialdehyde and 4-hydroxydialdehyde adduct levels and reduced glutathione stores. Interestingly, treatment with well-established antioxidants, N-acetylcysteine (NAC) and radicicol thiols, failed to protect against DMF-induced liver injury. Further investigation revealed infiltration of hepatic macrophages and their polarization towards the M1 phenotype upon DMF exposure. This correlated with NLRP3 inflammasome activation and focal hepatocellular necrosis, suggesting a potential role for inflammasomes in the pathogenesis. Notably, tail vein injection of gadolinium trichloride, which inactivates

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macrophages, significantly ameliorated abnormal serum aminotransferase activity, neutrophil infiltration, and NLRP3 inflammasome activation in the livers of DMF-treated mice. These findings suggest that DMF-induced acute liver injury is primarily associated with NLRP3 inflammasome activation in hepatic macrophages, rather than being directly mediated by oxidative stress.[126] However, oxidative stress does play a role in NLRP3 inflammasome activation in other DILI models. For instance, imatinib (IM), used to treat certain cancers, induces NLRP3 inflammasome activation via the ROS/NF-κB pathway. Treatment with the antioxidant NAC or the NF-κB inhibitor PDTC significantly abrogated the effects of IM on the NLRP3 inflammasome in HepG2 cells.[127] Similarly, andrographis, an herbal supplement, triggered NLRP3 inflammasome activation in mouse liver, which was closely linked to ROS accumulation. Importantly, scavenging excess ROS with the autophagy inducer rapamycin effectively inhibited NF-κB nuclear translocation and downregulated the TXNIP/NLRP3 pathway, thereby preventing ROS-mediated NLRP3 inflammasome activation.[128]

Inhibitors of NLRP3 Inflammasome-Associated Targets

As deeper insights are gained into the mechanisms of the NLRP3 inflammasome in chronic liver disease and injury, this pathway is increasingly recognized as a prime target for therapeutic intervention. Drug development strategies are now focusing on the NLRP3 inflammasome signaling cascade, aiming to block upstream signals that trigger inflammasome activation, inhibit inflammasome assembly and subsequent caspase-1 activation, and suppress the production of inflammatory factors downstream of caspase-1 activation (Figure 3).

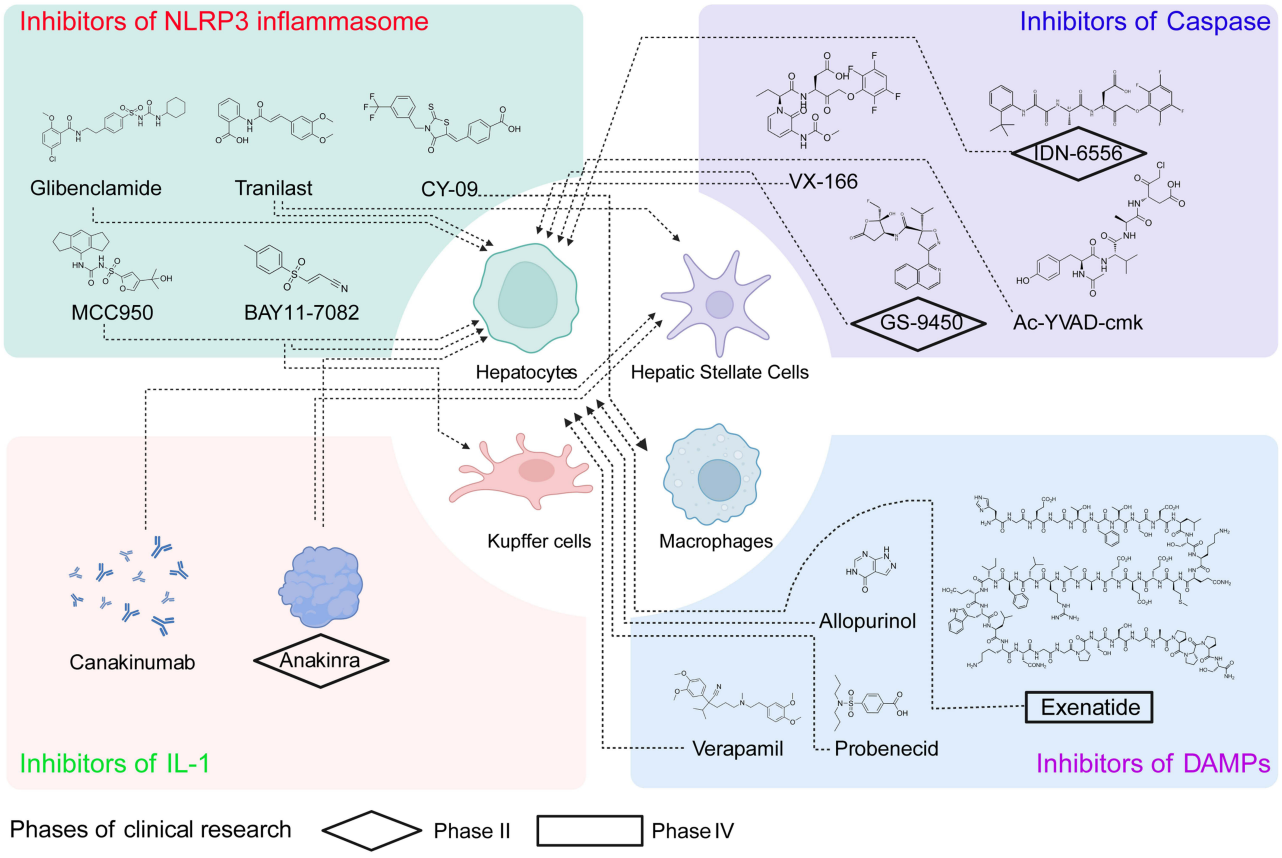

Figure 3 Schematic overview of therapeutic targets and agents for NLRP3 inflammasome. Inhibitors of the NLRP3 inflammasome, Caspases, IL-1 and DAMPs, as well as the main hepatocyte cell types involved in the inflammatory response (hepatocytes, hepatic stellate cells, Kupffer cells, macrophages) were classified. Clinical research phases are highlighted to indicate developmental progress of these therapies.

NLRP3 Inflammasome Inhibitors

With the NLRP3 inflammasome emerging as a key therapeutic target in chronic liver diseases, drug development efforts are focusing on inhibitors that target different stages of the pathway. MCC950, the first identified NLRP3 inhibitor, exhibits efficacy in reducing inflammation and liver fibrosis in MAFLD and DILI models.[103,127,129] More recently, CY-09 emerged as a direct NLRP3 inhibitor, blocking ATP binding and consequently caspase-1 activation and IL-1β release in macrophages. In a high-fat diet MAFLD model, CY-09 significantly reduced hepatic steatosis. Additionally, glibenclamide, by inhibiting K^+ channels, suppresses NLRP3 inflammasome activation and reduces steatosis, inflammation, and apoptosis in a rat MAFLD model, while improving blood lipid profiles and reducing hepatic DNA damage.[130] Similarly, BAY11-7082 targets both the NF-κB pathway and NLRP3 ATPase activity by inhibiting K^+ channels. This dual action directly inhibits NLRP3 inflammasome assembly and activation, reducing mtDNA release from hepatocytes and pro-inflammatory cytokine expression in Kupffer cells in high-fat diet mice.[131] In vivo studies demonstrated that BAY11-7082 treatment significantly reduced mtDNA release from hepatocytes and TNF-α/IL-6 expression in KCs of high-fat diet mice.[132] These advancements highlight the potential of NLRP3 inflammasome inhibitors for treating chronic liver diseases. Caspase inhibitors are also emerging as a therapeutic strategy for NLRP3 inflammasome-associated liver diseases.

Caspase Inhibitors

The pan-caspase inhibitor IDN-6556 significantly ameliorated inflammation, hepatic injury, and apoptosis in a high-fat diet-induced mouse model of MAFLD.[133] Similarly, caspase-1 specific inhibitor Ac-YVAD-cmk treatment attenuated insulin resistance and reduced fibrosis markers in a NASH mouse model.[134] VX-166, another pan-caspase inhibitor, exhibited efficacy in reducing oxidative stress, inflammation, and serum alanine aminotransferase (ALT) levels in mice with MCD diet-induced steatohepatitis.[135] In a clinical setting, GS-9450, a selective caspase-1 inhibitor, demonstrated promising results in a Phase II MAFLD trial. Treatment with GS-9450 led to a significant improvement in NASH-related clinical parameters, including dose-dependent reductions in ALT levels and some improvement in cytokeratin-18 fragment and AST levels.[136] These findings suggest that caspase inhibition holds promise as a therapeutic approach for NLRP3 inflammasome-linked liver diseases.

IL-1 Inhibitors

Beyond direct NLRP3 and caspase-1 inhibition, therapeutic strategies targeting downstream signaling molecules are being explored. Blocking IL-1β, a key effector cytokine of the NLRP3 inflammasome pathway, demonstrates promise in slowing disease progression. In vivo studies by Petrasek et al showed that anabolic acid, an IL-1 receptor inhibitor, significantly ameliorated ethanol-induced hepatic steatosis, inflammation, and the onset of liver injury.[34] Similarly, canakinumab, a human monoclonal antibody targeting IL-1β, effectively inhibited the expression of fibrosis-related proteins (α-SMA, fibronectin, and poikilocyte) in LX-2 cells stimulated by TGF-β or IL-1β.[137] The integration of clinical evidence, such as the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), significantly strengthens the translational relevance of NLRP3 inflammasome-targeted therapies. In CANTOS, a randomized, placebo-controlled trial involving 10,061 patients with prior myocardial infarction and elevated high-sensitivity C-reactive protein (hsCRP), canakinumab—a human monoclonal antibody neutralizing IL-1β—demonstrated a 15% reduction in recurrent cardiovascular events, independent of lipid-lowering effects. Mechanistically, canakinumab suppressed systemic inflammation (hsCRP reduction by 30–40%) and IL-6 levels, underscoring the pivotal role of IL-1β in perpetuating chronic inflammatory cascades.[138] While CANTOS focused on cardiovascular outcomes, its findings directly inform NLRP3-driven pathologies in liver diseases, such MASH and ALD, where IL-1β exacerbates hepatocyte pyroptosis, macrophage activation, and HSCs-mediated fibrosis. Preclinical parallels include studies showing that IL-1 receptor antagonists (eg, anakinra) ameliorate alcohol-induced liver injury in murine models by attenuating NLRP3 inflammasome activity.[34] However, liver-specific clinical trials remain sparse, with challenges including infection risks from systemic IL-1β blockade and the need for tissue-selective delivery systems. Future efforts should prioritize trials evaluating NLRP3 inhibitors (eg, MCC950) or IL-1β-neutralizing agents in well-defined liver disease cohorts, leveraging biomarkers like

hsCRP or caspase-1 activation to stratify patients and monitor therapeutic efficacy. These findings suggest that targeting IL-1β signaling may be a viable therapeutic approach for NLRP3 inflammasome-associated liver diseases.

DAMP-Related Inhibitors

Since DAMPs are critical triggers of NLRP3 activation, inhibiting their production offers a strategy to block early inflammasome activation. Allopurinol, a medication used to lower uric acid levels, effectively reduces hepatic steatosis and inflammation in mouse models of ethanol and high-fructose-induced fatty liver disease by inhibiting uric acid synthesis.[139] Probenecid, another drug that promotes uric acid excretion, additionally inhibits NLRP3 activation by suppressing the ATP-mediated P2X7 signaling pathway.[140] Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, protects against liver injury in diabetic mice with MAFLD by modulating hepatic cell proliferation and autophagy pathways while reducing ROS production and NLRP3 inflammasome activation.[141] Verapamil, a calcium channel blocker, also exerts protective effects in high-fat diet-induced MAFLD by inhibiting the TXNIP/NLRP3 pathway.[142] These findings highlight the potential for targeting DAMP production and NLRP3 inflammasome regulatory pathways in the treatment of liver diseases.

Discussion

Inflammasomes are essential components of the natural immune system, protecting the liver from pathogenic infections, metabolic imbalances, cellular stress, and tumor cells. However, in pathological states, overactivation of inflammasomes leads to uncontrolled inflammatory responses, promoting the development and progression of liver-related diseases. Overactivation of the NLRP3 inflammasome is closely associated with the development of aseptic inflammation-associated liver conditions such as ALD, NASH, hepatic fibrosis, and DILI. Danger signals generated during metabolic disturbances in the body, such as ATP, uric acid, cholesterol crystals, and mitochondrial damage, can activate the NLRP3 inflammasome in hepatic parenchymal and non-parenchymal cells, triggering severe hepatic inflammation or even hepatic cell death.

Continuous stimulation of HSCs by inflammatory mediators secreted by damaged or dead hepatocytes, bone marrow-derived macrophages, and Kupffer cells can further induce liver fibrosis. Therefore, targeting the NLRP3 inflammasome is crucial for treating aseptic inflammation-associated liver diseases. Inhibitors targeting NLRP3 inflammasome-activated pathway-related targets have been developed and entered clinical trials to treat liver diseases (Table 1). The study of NLRP3 inflammasome regulation mechanisms can help understand the pathogenesis of chronic liver disease and liver injury and provide a theoretical basis and reference for the development of new clinical drugs based on NLRP3 inflammasome

Table 1 Inhibitors of NLRP3 Inflammasome Activation-Related Targets in Related Liver Diseases

Style	Name	Indications	Clinical advance	Ref.
Inhibitors of NLRP3 inflammasome	Glibenclamide	MAFLD, Liver fibrosis	–	[130,143]
	BAY11-7082	MAFLD	-	[132]
	MCC950	MAFLD, DILI	-	[39,103]
	CY-09	MAFLD	-	[144]
	Tranilast	Liver injury, MAFLD	-	[145,146]
Inhibitors of Caspase	GS-9450	NASH	Phase II	[136]
	IDN-6556	NASH	Phase II	[133]
	VX-166	NASH	-	[135]
	Ac-YVAD-cmk	NASH, Liver fibrosis	-	[134,143]
Inhibitors of IL-1	Anakinra	ALD, Liver fibrosis	Phase II	[34,143]
	Canakinumab	Liver fibrosis	-	[137]
Inhibitors of DAMPs	Exenatide	MAFLD	Phase IV	[141]
	Allopurinol	ALD, MAFLD	-	[139,140]
	Probenecid	ALD	-	[139]
	Verapamil	MAFLD	-	[142]

inhibition to prevent and treat chronic liver disease and liver injury. Nevertheless, several issues remain to be resolved in studying NLRP3 inflammasome in chronic liver disease and liver injury. Firstly, besides known liver disease-associated inflammasome activation signaling molecules, the role of other DAMPs in NLRP3 inflammasome hyperactivation-associated liver disease remains unclear. Additionally, the cell specificity of NLRP3 inflammasome activation in hepatic parenchymal and non-parenchymal cells during the pathogenesis of different types of liver diseases and its crosstalk between different cells in the development of hepatic inflammatory injury need further investigation. Secondly, while current small-molecule inhibitors targeting NLRP3, caspase-1, and IL-1 have shown promising effects in basic and clinical trials, the NLRP3 inflammasome serves as an essential immune defense mechanism against pathogenic infections. Non-targeted systemic blockade of the NLRP3 inflammasome pathway may increase the risk of infection and impair the normal immune defense system. Therefore, in-depth studies on the mechanism of NLRP3 inflammasome regulation, especially in different types and stages of chronic liver disease and liver injury, are necessary. Further screening and optimization of the structure of relevant inhibitors from chemical synthesis or natural products, combined with nanomaterials and other drug-targeted transporter systems, can provide cell-specific NLRP3 inhibitors with clear, safe, and controllable effects for the prevention and treatment of chronic liver disease and liver injury in the clinic. Continued investigation into its mechanisms of action and therapeutic targets will facilitate the development of effective anti-hepatitis drugs, offering new hope for the treatment of hepatic disorders. Nevertheless, critical gaps remain in translating preclinical successes to clinical practice. While emerging NLRP3 inhibitors show promise in early trials, comprehensive studies on their long-term safety profiles—particularly regarding immunosuppression, metabolic disturbances, and off-target effects—are imperative. Furthermore, the efficacy and tolerability of these therapies must be validated across diverse patient populations, accounting for variables such as genetic polymorphisms, comorbidities (eg, diabetes, obesity), and stages of liver disease. Addressing these challenges through multicenter, longitudinal studies will be essential to optimize personalized therapeutic strategies and ensure equitable clinical benefits.

Despite the challenges in NLRP3-targeted therapies, emerging innovations hold promise for overcoming current limitations. Advances in structural biology (eg, cryo-EM) and computational drug design may enable the development of next-generation NLRP3 inhibitors with enhanced specificity, minimizing off-target effects. Novel delivery systems, such as nanoparticle-based platforms or conditional activation strategies, might enhance tissue selectivity and reduce systemic toxicity. In conclusion, the NLRP3 inflammasome demonstrates promising therapeutic potential for liver diseases. Continued investigation into its mechanisms of action and therapeutic targets will facilitate the development of effective anti-hepatitis drugs, offering new hope for the treatment of hepatic disorders.

Data Sharing Statement

No data was used for the research described in the article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare in this work.

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