Journal of Clinical and Translational Hepatology **2024** vol. 12(2) | 191–200
DOI: 10.14218/JCTH.2023.00231

Review Article

Progress in the Correlation Between Inflammasome NLRP3 and Liver Fibrosis

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Received: 14 May 2023 | **Revised:** 2 September 2023 | **Accepted:** 13 September 2023 | **Published online:** 30 October 2023

Abstract

Liver fibrosis is a reversible condition that occurs in the early stages of chronic liver disease. To develop effective treatments for liver fibrosis, understanding the underlying mechanism is crucial. The NOD-like receptor protein 3 (NLRP3) inflammasome, which is a part of the innate immune system, plays a crucial role in the progression of various inflammatory diseases. NLRP3 activation is also important in the development of various liver diseases, including viral hepatitis, alcoholic or nonalcoholic liver disease, and autoimmune liver disease. This review discusses the role of NLRP3 and its associated molecules in the development of liver fibrosis. It also highlights the signal pathways involved in NLRP3 activation, their downstream effects on liver disease progression, and potential therapeutic targets in liver fibrosis. Further research is encouraged to develop effective treatments for liver fibrosis.

Citation of this article: Sun M, Zhang Y, Guo A, Xia Z, Peng L. Progress in the Correlation Between Inflammasome NLRP3 and Liver Fibrosis. J Clin Transl Hepatol 2024;12(2):191–200. doi: 10.14218/JCTH.2023.00231.

Introduction

Liver disease is a serious public health problem, accounting for about 2 million deaths worldwide each year.[1] Chronic liver injuries are caused by a range of stimuli including viral hepatitis, alcoholic and nonalcoholic liver disease, and autoimmune liver disease. These conditions lead to liver inflammation and fibrosis, ultimately progressing to cirrhosis. In China, liver cirrhosis accounts for 11% of all the deaths from liver diseases worldwide.[2] Constant or repeated inflammation and necrosis of liver cells lead to an enhanced repair response, triggering massive production of fibrous substances such as collagen, proteoglycans, etc. Insufficient degradation of fibrous substances results in the formation of liver fibrosis. If timely interventions are taken, the possibility of liver fibrosis evolving into cirrhosis, liver failure, and liver cancer can be reduced.

Inflammasomes comprise a variety of protein complexes assembled with the involvement of cytoplasmic pattern recognition receptors, and are a key component of the innate immune system.[3] Inflammasome components are found in various cells, including immune and nonimmune cells, such as macrophages, neutrophils, monocytes, hepatic stellate cells (HSCs), and fibroblasts/myofibroblasts. Those components are expressed in multiple intracellular locations including mitochondria, Golgi apparatus, and nucleus.[4,5] Inflammasomes recognize damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), and subsequently activate caspase-1. This triggers the release of interleukin (IL)-18 and IL-1β, which contributes to the progression of fibrosis. To date, several types of inflammasomes have been revealed, including NOD-like receptor protein 1 (NLRP1), NLRP3, and NOD-like receptor C4. Among them, NLRP3 has been studied extensively and is known to play a crucial role in antibacterial immunological responses.[6,7] Abnormal activation of NLRP3 has been linked to various diseases, including Alzheimer's disease, arthritis, atherosclerosis, and cancer.[8] Importantly, several studies have shown that NLRP3 participates in the development of liver fibrosis.[9–11] This review discusses current research on the role of NLRP3 in liver fibrosis.

Activation of NLRP3

NLRP3 is a typical NLR protein that contains the innate immune receptor NLRP3, caspase-1, and apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC). In the activation of NLRP3 (Fig. 1), the first step is the initiation of NLRP3, involving the upregulation of NLRP3, IL-18, and IL-1β. PAMPs bind to Toll-like receptors (TLRs) and activate the transcription factor nuclear factor-kappa B (NF-κB), which subsequently mediates the transcription of NLRP3, IL-1β precursor (pro-IL-1β) and IL-18 precursor (pro-IL-18). Meanwhile, damaged cell DAMP signals such as uric acid crystals, cholesterol crystals, reactive oxygen species

Keywords: NLRP3; Liver disease; Liver fibrosis; Hepatic stellate cells; Macrophages.

Abbreviations: AIH, autoimmune hepatitis; ALD, alcohol-related liver disease; ASC, apoptosis-associated speck-like protein containing a caspase-recruitment domain; Con A, concanavalin A; DAMPs, damage-associated molecular patterns; ECM, extracellular matrix; HBV, hepatitis B virus; HCV, hepatitis C virus; HSCs, hepatic stellate cells; IL, interleukin; KCs, Kupffer cells; LPS, lipopolysaccharide; Mt, mitochondrial; NAFLD, nonalcoholic liver disease; NASH, nonalcoholic steatohepatitis; NF-κB, transcription factor nuclear factor-kappa B; NLRP1, NOD-like receptor protein 1; NLRP3, NOD-like receptor protein 3; PAMPs, pathogen-associated molecular patterns; PBC, Primary biliary cholangitis; PKA, protein kinas A; pro-IL-1β, IL-1β precursor; pro-IL-18, IL-18 precursor; PSC, Primary sclerosing cholangitis; ROS, reactive oxygen species; TGF-β, transforming growth factor beta; TIMPs, tissue inhibitors of metalloproteinases; TLRs, Toll-like receptors; Th, T helper; *XBP1*, X-box binding protein-1; α-SMA, alpha smooth muscle actin.

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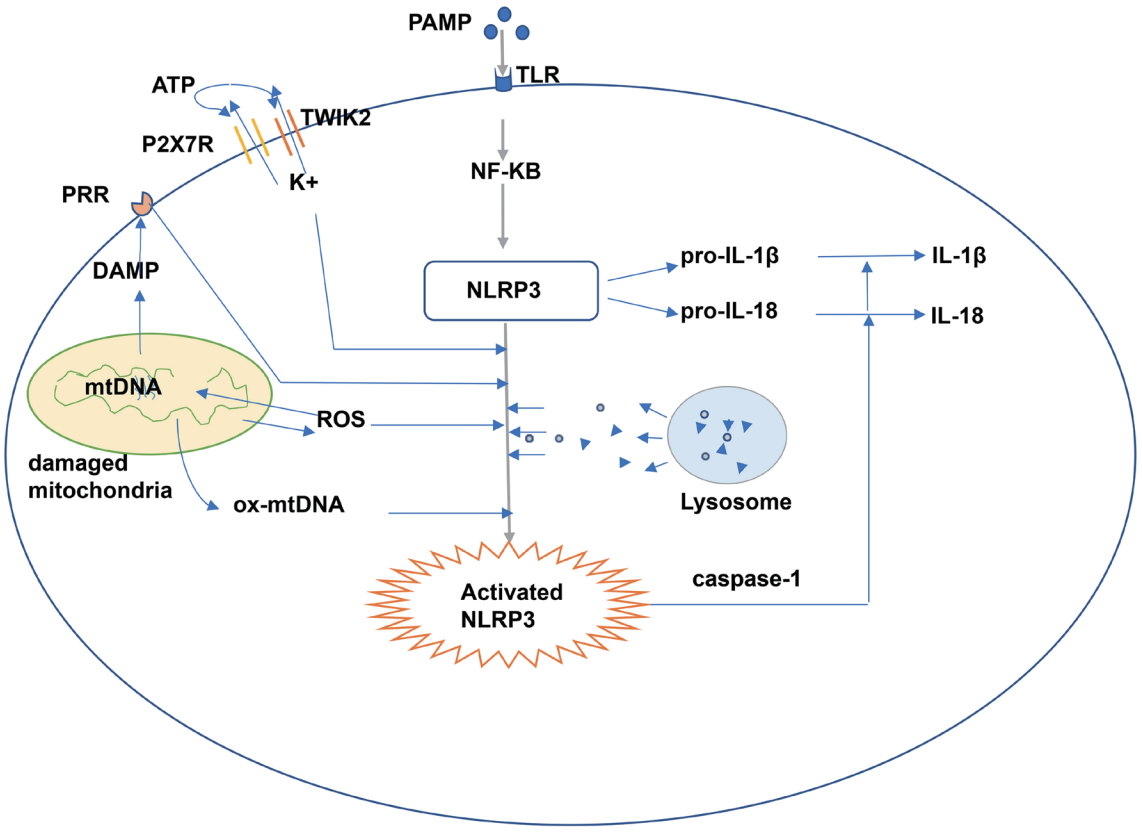

Fig. 1. Classical activation of NLRP3. PAMPs bind to TLR and activate NF-κB, participating in NLRP3 activation. DAMPs, K^+ efflux, and the contents released from damaged lysosomes activate and oligomerize NLRP3. The activated NLRP3 releases caspase-1, which promotes the maturation of pro-IL-1β and pro-IL-18. ATP, adenosine triphosphate; DAMP, damage-associated molecular pattern; IL-1β, interleukin-1β; IL-18, interleukin-18; NF-κB, transcription factor nuclear factor-kappa B; NLRP3, NOD-like receptor protein 3; ox-mtDNA, oxidized mitochondrial DNA; PAMP, pathogen-associated molecular pattern; pro-IL-1β, IL-1β precursor; pro-IL-18, IL-18 precursor; PRR, pattern recognition receptor; P2X7R, P2X purine receptor 7 channel; ROS, reactive oxygen species; TWIK2, two-pore domain weakly inward rectifying potassium channel 2; TLR, Toll-like receptor.

(ROS), and oxidized mitochondrial (mt)DNA activate and oligomerize NLRP3.[12,13]

After NLRP3 inflammasomes are triggered, the components are recruited and assembled, promoting the cleavage of procaspase-1 into active caspase-1. This process facilitates the maturation of IL-18 and IL-1β. Additionally, activated caspase-1 cleaves gasdermin D and release its N-terminal domain, which induces pyroptosis and the subsequent release of cellular contents.[8] Caspase-11 activates NLRP3 inflammasomes through pyroptosis.[14] In addition, NLRP3 can be activated by a noncanonical activation pathway that involves the activation of caspase-4 and caspase-5 in humans or caspase-11 in mice. The interaction between caspase-4/5/11 and lipopolysaccharide (LPS) along with lipid A results in their transformation into an active form. Activated caspase-4/5/11 further triggers the activation of NLRP3 by K^+ efflux and pyroptosis.[14–16] Recent research suggests that the orphan receptor Nur77 combines with mtDNA and LPS to mediate nontypical activation of NLRP3. However, Nur77 association with intracellular LPS does not depend on caspase-11 or gasdermin D.[16]

Activation mechanism of NLRP3

K^+ outflow

K^+ efflux is one of the upstream signals that activates NLRP3. For example, extracellular ATP triggers K^+ efflux through the ATP-gated P2X purinoceptor 7 channel and the two-pore domain weakly inward rectifying potassium channel 2, which then triggers the activation of NLRP3.[17,18] Moreover, particles like calcium pyrophosphate crystals, cholesterol crystals, and silica can also induce potassium efflux, activating NLRP3.[19] A study has shown that NLRP3 is activated when the K^+ content of cells drops below 80%.[20] Moreover, caspase-11 triggers the noncanonical inflammasome pathway and involves the activation of the pannexin-1 channel and leads to K^+ efflux and NLRP3 activation.[21]

Lysosome rupture

Under some pathological conditions, such as the phagocytosis of particulate matter, lysosome damage can activate the NLRP3 inflammasome. Phagocytosed crystals lead to lysosome acidification, swelling, and loss of lysosomal membrane integrity over time. Upon damage, lysosomal contents leak into the cytoplasm and trigger NLRP3.[19,22] Release of lysosome contents into the cytoplasm is also related to the activation of caspase-1.[23]

ROS and mitochondria

Cells under harmful stimuli produce ROS and reactive nitrogen species that cause physiological and pathological responses in cells and tissues. Excess ROS can result in oxida-

tive stress. Oxidative stress can increase liver inflammation and activate HSC, thereby enhancing the production of extracellular matrix (ECM), ultimately leading to fibrosis.[24] Damaged hepatocytes caused by various factors such as alcohol abuse, hepatitis virus infection, and chronic cholestasis may generate ROS and participate in the assembly and activation of NLRP3. ROS is one of many important NLRP3 inflammasome activators.[25] Conversely, ROS inhibitors (e.g., diphenyl iodine, and n-acetyl-l-cysteine) can suppress NLRP3 transcription.[5] In the early stage of an inflammatory response, ROS activate the NF-κB pathway. ROS causes conformational change and activation of NLRP3 by promoting the transcription of NF-κB.[26–28] A study reported that the activation of NLRP3 occurred via the ROS-TXNIP axis.[29] Furthermore, both O^{2-} and H_2O_2 in some cells have been shown to participate in NLRP3 activation.[29,30]

Mitochondria are the main source of ROS. Therefore, mitochondrial dysfunction can trigger inflammatory responses through the inflammasome signaling pathway. The production of mtROS during mitochondrial injury is a known activator of NLRP3.[31] A study showed that excessive free fatty acids in the livers of high-fat/calorie diet mice led to mitochondrial damage, leading to ROS generation and NLRP3 activation.[32] Under long-term ethanol stimulation, mouse macrophages, or human peripheral blood mononuclear cells were shown to induce the release of mtROS, activating NLRP3.[33] The 66 kDa isoform of Shc, a redox enzyme can mediate the generation of mitochondrial ROS and activate NLRP3 inflammasome, hence promoting HSC activation. ROS can also induce the oxidation of mtDNA.[34] Oxidized mtDNA is capable of binding and directly activating NLRP3, which triggers caspase-1 activation, and promotes the release of IL-18 and IL-1β. In addition, mtDNA amplifies the activation of NLRP3.[35] Notably, most NLRP3 agonists lead to mitochondrial malfunction, ROS generation, and mtDNA oxidation, all of which encourage NLRP3 activation.[36] Similarly, the activation of NLRP3 also leads to mitochondrial damage and mtROS production. Recent evidence suggests that mitochondrial homeostasis largely depends on the removal of damaged mitochondria.[37] Inhibition of mitochondrial autophagy can increase the accumulation of ROS, thus activating NLRP3 inflammasomes.[38]

Activation of NLRP3 involves complex and diverse mechanisms, such as K^+ efflux, lysosome rupture, oxidative stress, etc. K^+ efflux functions with many NLRP3 activators but is not necessary for NLRP3 inflammasome activation. For instance, CL097 and imiquimod directly target mitochondria without involving K^+ efflux to induce NLRP3 inflammasome activation.[39] An ethanolic extract of *Artemisia anomala* has a lysosome protective function by inhibiting the TAK1-JNK pathway, thus preventing activation of NLRP3.[40] However, it neither inhibits mitochondrial damage nor affects the efflux of K^+ and chloride ions.[40] In addition, multiple cell signaling events sometimes overlap and function with each other. For instance, lysosome damage and K^+ efflux together participate in NLRP3 inflammasome activation driven by polybrominated diphenyl ethers.[41] Similarly, K^+ efflux-induced mtDNA release activates NLRP3 inflammasomes.[42] Apilimod relies on lysosomal mediated mitochondrial damage and ROS production to activate NLRP3.[43] Overall, the activation signals can act independently or in together. Such complexities make the activation mechanism of NLRP3 inflammasome more multifaceted and diversified. Therefore, a precise NLRP3 activation mechanism under specific conditions remains unknown.

Fibrosis of liver

Under various chronic stimuli, chronic inflammation, and necrosis of hepatocytes trigger an enhanced repair response, resulting in massive proliferation and insufficient degradation of fibers. This causes a massive deposition of fibrous materials in the liver tissue, i.e. liver fibrosis. Numerous cellular pathways participate in fibrosis, and HSCs play a significant role. Many stimuli act on HSCs to promote their activation, resulting in a significant buildup of ECM progressing to fibrous scar tissue. Systemic inflammation driven by immune cells is another key factor in the progression of cirrhosis. Macrophages ensure immune balance in the liver and also participate in inflammation. Inflammatory responses in the liver mediate hepatocyte damage, cause cell differentiation and proliferation, perpetuate chronic liver inflammation, promote fibrous tissue growth, and worsen liver fibrosis. Both Kupffer cells (KCs) and HSCs have high levels of NLRP3 inflammasome activation, which is critical in the development of liver fibrosis.[44]

HSCs and NLRP3

In healthy livers, about 15% of resident cells are HSCs, which is about one-third of the population of nonparenchymal cells. After activation, HSCs can transform into myofibroblasts, which secrete ECM, generate fibrous scars, and participate in the process of liver fibrosis. HSC is the main source of myofibroblasts, but other sources include resident liver cells, portal vein fibroblasts, and bone marrow-derived cells.[45,46] Under normal conditions, HSCs are quiescent. When the liver is damaged, HSCs are activated by inflammatory mediators or other stimulatory factors. Activated HSCs proliferate and move toward the injured liver tissue. Apart from producing alpha smooth muscle actin (α-SMA), activated HSCs produce tissue inhibitors of metalloproteinases (TIMPs) that inhibit the activity of matrix metalloproteinases. This reduces ECM degradation, causing excessive deposition of ECM and thereby the formation of fibrotic scars.[45,47]

A wide range of factors are involved in HSC activation, such as platelet-derived growth factor, transforming growth factor beta (TGF-β), IL6, IL8, and inflammasomes (NLRP1, NLRP3, etc.). NLRP3 is closely related to hepatic fibrosis and acts on HSC to promote liver fibrosis. NLRP3 along with the main proinflammatory factor NF-κB promotes profibrosis molecules (IL-1β and IL-18) to activate HSCs.[26] However, NLRP3 can be directly expressed and triggered in HSCs, causing hepatic fibrosis (Fig. 2).[4] All components of NLRP3 exist in HSCs and regulate their various functions, including the transition of quiescent HSCs to a collagen-producing myoblast state.[48–50] The NLRP3 inflammasome is a downstream effect factor of DAMPs, and it has been reported that DAMPs released from dead hepatocytes may directly or indirectly promote HSC activation and fibrosis (Fig. 2).[51,52] Notably, NLRP3 mutant mice had significantly higher expression of connective tissue growth factor and TIMP 1 than wild-type mice. That implies that NLRP3 inflammation can induce HSC activation and collagen deposition.[51]

Macrophages and NLRP3

Hepatic macrophages mainly include resident macrophages (KCs) and monocyte-derived macrophages, all of which ensure immunological homeostasis in the liver. In the steady state, resident macrophages derived from the yolk sac predominate. Under injury stimulation, monocyte-derived macrophages are recruited, which differentiate from circulating monocytes in the liver.[53] Macrophages can be grouped into M1 macrophages and M2 macrophages. M1 macrophages produce inflammatory cytokines with a proinflammatory role. M2 macrophages have healing and anti-inflammatory functions that regulate inflammation. The balance of M1 and

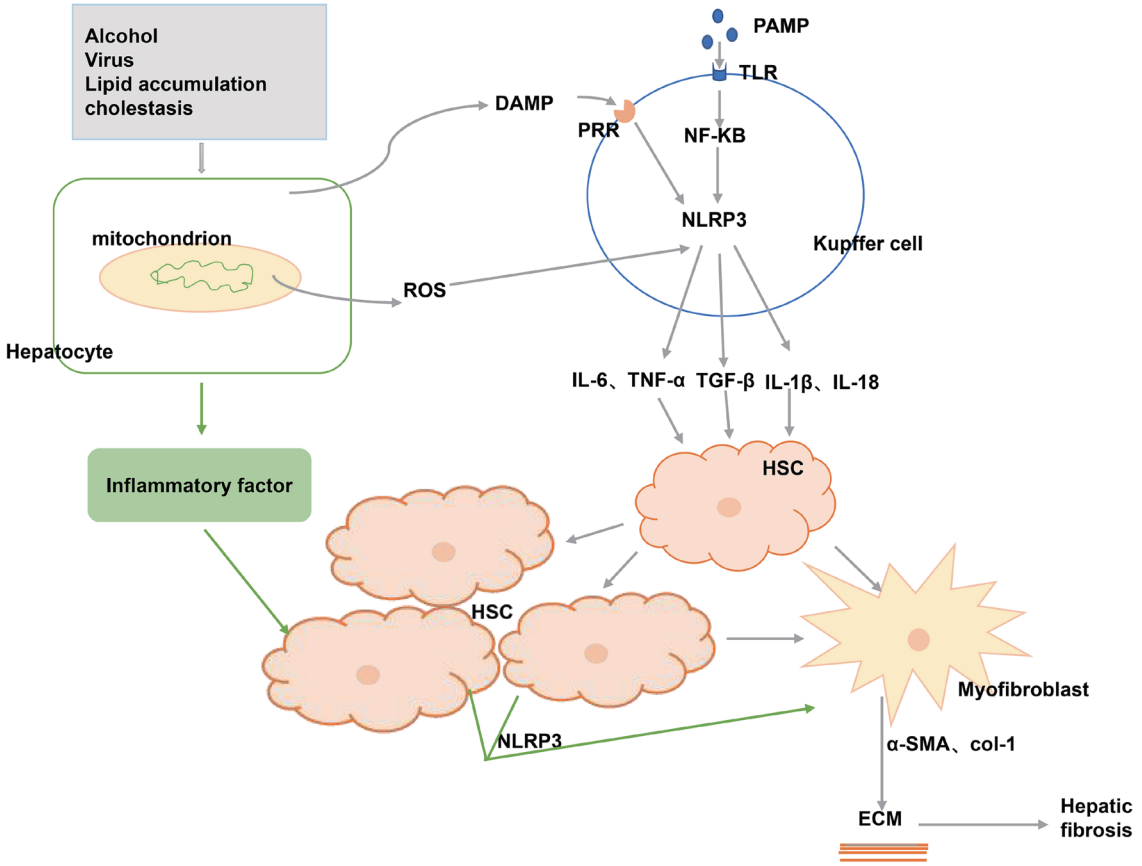

Fig. 2. Hepatic macrophages, HSCs, and NLRP3. Chronic stimuli such as alcohol, viruses, cholestasis, and lipid accumulation damage hepatocytes. PAMPs and DAMPs activate NLRP3 in macrophages. This activation triggers the release of proinflammatory factors (IL-1β, IL-18, IL-6, TNF-α) and TGF-β. Proinflammatory factors and TGF-β then promote the proliferation and differentiation of HSCs into myofibroblasts. Furthermore, HSCs can also directly express and activate NLRP3. α-SMA, alpha smooth muscle actin; col-1, type I collagen; DAMP, damage-associated molecular pattern; ECM, extracellular matrix; HSC, human hepatic stellate cell; IL-1β, interleukin 1β; IL-18, interleukin 18; IL-6, interleukin 6; NLRP3, NOD-like receptor protein 3; NF-κB, transcription factor nuclear factor-kappa B; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor; ROS, reactive oxygen species; TGF-β, transforming growth factor beta; TLR, Toll-like receptor; TNF-α, tumor necrosis factor alpha.

M2 macrophages may mediate the advancement and regression of liver fibrosis.[47,54] Upon liver damage, a large number of bone marrow-derived monocytes aggregate in the liver and differentiate into macrophages to produce proinflammatory and profibrotic cytokines that promote inflammatory responses and HSC activation. Activated HSCs express α-SMA and collagen I, which promotes ECM deposition and progression of liver fibrosis.[47,52] Studies have shown that when HSCs are cocultured with KCs, KCs promote the proliferation and activation of HSCs. Furthermore, HSCs cocultured with KCs secrete more intracellular and extracellular collagen I, as well as TIMP 1.[55]

NLRP3 is mainly expressed in macrophages.[56] In contrast to HSCs, KCs were shown to express higher levels of NLRP3, NLRP1, and Absent In Melanoma 2 in a mouse model of hepatic fibrosis.[13] After binding to the membrane receptors on KCs, PAMP activated NLRP3 in KCs through the NF-κB signaling pathway (Fig. 2), causing the production of its related components (NLRP3, caspase-1, and IL-1β).[4] In addition, the macrophage X-box binding protein-1 (*XBP1*) gene can induce M1 macrophage polarization and activate macrophage NLRP3.[57] Activation of macrophage NLRP3 has a significant impact on liver fibrosis. A study suggested that the activation of macrophage NLRP3 can promote disease progression in cholestasis causing liver damage.[58] Zhang *et al*.[44] reported that NLRP3 inflammasomes play a vital role in S. japonicum-induced liver fibrosis through the NF-κB signaling pathway. They also revealed that NLRP3 inflammasomes in both KCs and HSCs contributed to the development of liver fibrosis in S. japonicum-infected mice, and NLRP3 activation was mainly caused by KCs. In addition, s100a8-mediated NLRP3-dependent macrophage pyroptosis was shown to promote the activation of human HSCs.[59] NLRP3 in mouse macrophages participated in ECM deposition by activating HSCs (Fig. 2).[60]

Gut microflora and NLRP3

Due to the existence of the gut-liver axis, risk factors originating from the intestine have become one of the contributing factors in the development of liver diseases. The gut microbiota is a group of microorganisms that are present in the human intestine and affect health. In addition to participating in digestion and absorption, it also has a role in immune regulation. NLRP3 is widely distributed in epithelial cells and immune cells. In the intestine, PAMPs bind to pattern recognition receptors to activate NLRP3, triggering an inflammatory response to maintain intestinal immune homeostasis.[61] External stimuli such as infection, trauma, drugs, poor diet, etc., can disrupt the gut microbiota, increasing the propor-

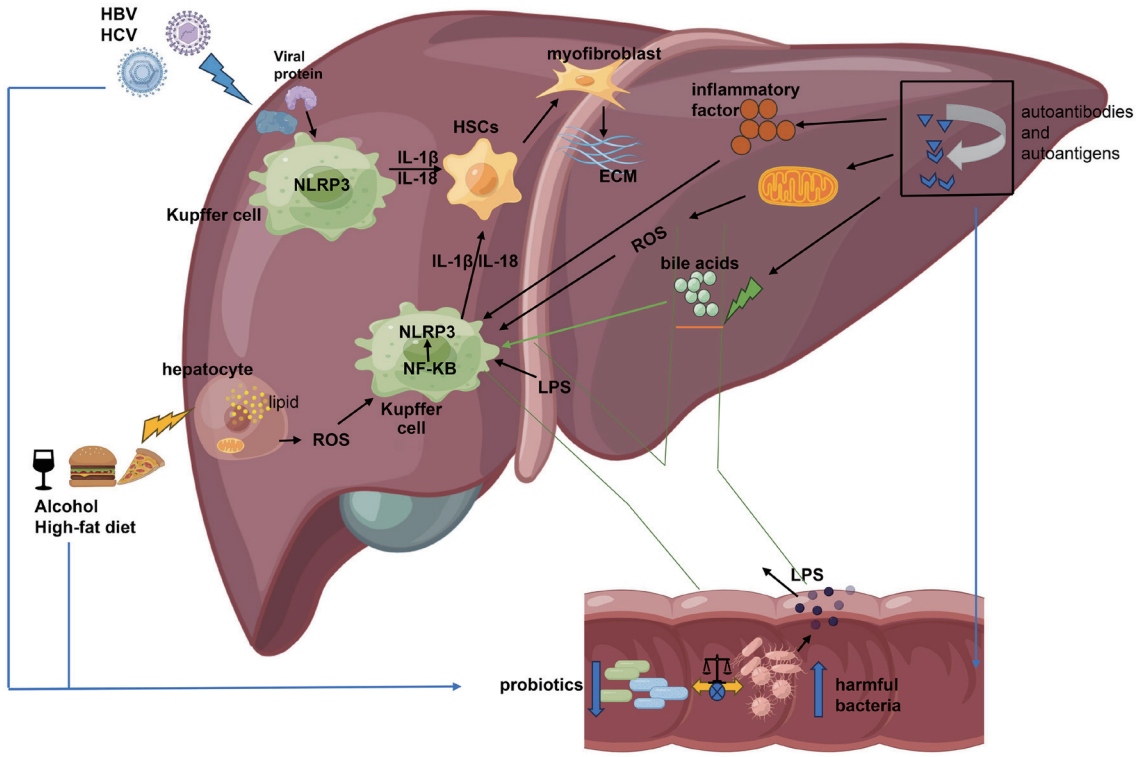

Fig. 3. Activation of NLRP3 inflammasome in chronic liver disease. High-fat diet and long-term alcohol consumption damage hepatocytes, leading to the accumulation of lipid in hepatocytes and causing an inflammatory response. Lipid-accumulated liver cells are prone to lipid peroxidation and oxidative damage, activating NLRP3. Viral proteins activate NLRP3, resulting in inflammatory reactions and activating HSCs. Abnormal expression of autoantigens may lead to an abnormal immune response in the liver, causing the activation of NLRP3. Immune-mediated bile duct injury results in intrahepatic bile duct narrowing and bile stasis. Bile stasis, in turn, activates NLRP3 through the NF-κB pathway. High-fat diet, alcohol, virus infection, and cholestasis lead to dysbiosis of the gut microbiota and increase intestinal permeability. Gut-derived PAMPs enter the liver and then activate NLRP3. ECM, extracellular matrix; HSCs, human hepatic stellate cells; HBV, hepatitis B virus; HCV, hepatitis C virus; IL-1β, interleukin 1β; IL-18, interleukin 18; LPS, lipopolysaccharide; NLRP3, NOD-like receptor protein 3; NF-κB, transcription factor nuclear factor-kappa B; ROS, reactive oxygen species.

tion of harmful bacteria. Metabolites and toxins secreted by harmful bacteria can cause intestinal inflammation and intestinal barrier damage. Damage of the intestinal barrier allows intestinal LPS entry into the liver through the portal vein, where LPS binds to TLR and activates NLRP3, causing liver inflammation (Fig. 3).[62] This contributes to the progression of various chronic liver diseases such as nonalcoholic liver disease (NAFLD), alcohol-related liver disease (ALD), viral hepatitis, and autoimmune liver diseases (Table 1).[63–66] Recently, it was shown that ursolic acid inhibited the NOX4/NLRP3 inflammasome signaling pathway, reduced the abundance of harmful gut bacteria, and increased the abundance of beneficial gut bacteria, all of which helped to reverse liver fibrosis.[67] *Tylophora yunnanensis* Schltr can regulate the gut microbiota by inhibiting the activation of NLRP3 to improve nonalcoholic steatohepatitis (NASH).[68] Astragaloside IV can regulate gut microbiota imbalance, improve intestinal barrier function, inhibit the NLRP3/Caspase-1 inflammatory signaling pathway, and alleviate alcohol-induced liver inflammation.[69] Additionally, probiotics can enhance the intestinal mucus barrier by increasing the secretion of specific mucins. Probiotic intervention can help rebalance the gut microbiota and regulate intestinal barrier, thereby alleviating the liver damage.[64,70,71]

NLRP3 downstream molecules

IL-1β is a key inflammatory cell factor. It is an active version of IL-1 that is mainly produced by macrophages.[72] PAMPs and DAMPs participate in the release of mature IL-1β and IL-18 by triggering NLRP3. IL-1β and IL-18 have biological activity and participate in fibrosis.[4,72] IL-1β can regulate the expression of TIMPs and matrix metalloproteinases, which have an impact on fibrosis and tissue regeneration.[73] The NLRP3/IL-1β secretory axis is also present in the HSCs.[72] *In vitro* studies have demonstrated that IL-1β can directly activate HSCs, promoting their proliferation and differentiation into myofibroblasts. The myofibroblasts increase the release of fibrosis markers such as collagen and TGF-β.[13] IL-1β promotes fibrous tissue development by binding to cell surface IL-1β receptors.[74] Endogenous inhibitors of IL-1β receptors were shown to improve liver fibrosis in a mouse model of alcoholic hepatitis.[75]

Multifunctional cytokine IL-18 has proinflammatory and fibrosis-promoting activity. IL-18 has previously been linked to the progression of fibrosis in the lungs, heart, and kidneys.[76] It also has a key role in the progression of liver injury and liver fibrosis. Significant increase of IL-18 plasma level has been observed in chronic liver disease and hepatosclerosis.[77] Increased IL-18 expression was found in the livers of NASH patients, and involvement in liver fibrosis.[78] IL-18 can activate HSCs promoting their differentiation into myofibroblasts, upregulating the expression of collagen genes, and the production of connective tissue growth factor and α-SMA.[76] As liver cells do not have IL-18 receptors, IL-18 cannot directly act on the hepatic cells. However, IL-18 can activate $CD4^+$ T cells. The $CD4^+$ T cells secrete various cell

Table 1. Summary and comparison of NLRP3 activation in chronic liver disease

Liver disease	Etiology	Activation of NLRP3	
NAFLD	Lipid toxicity; chronic inflammation; oxidative stress; insulin resistance	Lipid toxicity, mitochondrial dysfunction, and excessive ROS are involved in the activation of NLRP3; Activation of NLRP3 by regulating the NF-κB pathway	High-fat diet, alcohol, virus infection, and cholestasis lead to dysbiosis of the gut microbiota, increasing intestinal permeability. Gut-derived PAMPs enter the liver and then activate NLRP3.
ALD	Long-term ethanol toxicity (damage to intestinal mucosa, direct damage to liver)	Ethanol exposure increases recruitment of inflammatory cells and activates NLRP3 by regulating the NF-κB pathway; Alcohol metabolism exacerbates oxidative stress and induces the production of ROS to activate NLRP3	
Viral hepatitis	Virus infection; immune response caused by virus-related components	HBV and HCV infection activate NLRP3 by promoting the production of ROS and the oxidative stress response; HBV and HCV infection activate NLRP3 by regulating the NF-κB pathway	
Autoimmune liver disease (AIH,PBC,PSC)	Autoimmune reaction; immune-mediated bile duct injury; cholestasis	Abnormal expression of autoantigens may lead to an abnormal immune response in the liver, activating NLRP3; Oxidative stress and mitochondrial damage are involved in the activation of NLRP3; Cholestasis triggers TLR/NF-κB signaling and activates NLRP3	

ALD, alcohol-related liver disease; AIH, autoimmune hepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; NLRP3, NOD-like receptor protein 3; NF-κB, transcription factor nuclear factor-kappa B; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PAMPs, pathogen-associated molecular patterns; ROS, reactive oxygen species; TLR, Toll-like receptor.

factors that exacerbate liver inflammation, progressing to liver fibrosis. In conjunction with this, anti-IL-18 therapy can reduce liver inflammation and noticeably delay liver fibrosis.[79]

Chronic liver disease and NLRP3

NAFLD

NAFLD includes a range of liver changes, starting with nonalcoholic fatty liver potentially progressing to NASH. In advanced cases, NASH can lead to cirrhosis, liver failure, and liver cancer.[80] The occurrence and progression of NAFLD supposedly involve multiple parallel attacks involving different events such as lipid toxicity, chronic inflammation, and oxidative stress that simultaneously participate in the development of NAFLD (Table 1).[81] Abnormal activation of NLRP3 is a major driver of liver injury, steatosis, inflammation, and fibrosis (Fig. 3).[82,83] The role of abnormal activation of NLRP3 in NALFD has been extensively studied (Table 1). In NAFLD patients and NASH mouse models, activation of NLRP3 exacerbates liver inflammation and progression of liver fibrosis.[9,82] In NASH patients, XBP1 promotes lipid accumulation and expression of proinflammatory factors in hepatocytes by activating NLRP3 in macrophages, thereby exacerbating the progression of steatohepatitis. On the contrary, XBP1 knockout in macrophages inhibited the expression of TGF-β and HSCs activation.[57] Mitochondria-derived risk signals (ROS and mitochondrial dysfunction) promote expression of inflammatory factors and activate HSCs (Fig. 3), driving liver fibrosis in mice and NASH patients.[84,85] Disturbed mitophagy was shown to activate NLRP3 inflammasomes, which was associated with the progression of nonalcoholic steatosis to nonalcoholic steatohepatitis.[32] The above examples demonstrate the close relationship of NLRP3 with NAFLD. Many studies have suggested that inhibiting NLRP3 reduced liver inflammation and fibrosis. For instance, blocking NLRP3 inflammasome activation with echinatin can improve NASH and lessen liver inflammation and fibrosis.[86] The NLRP3 inhibitor MCC950 was shown to reduce the severity of liver inflammation.[9] Although MCC950 is an effective inhibitor of NLRP3, it was found to be hepatotoxic in phase II clinical trials of rheumatoid arthritis, which prevented further evaluation.[87] Some traditional Chinese medicines and extracts, such as rhubarb-free anthraquinones, danshen, cryptotanshinone, etc., regulate the activation of NLRP3, thereby improving liver inflammation in NAFLD and NASH.[88–91] Although targeting the inflammasome pathway can inhibit the development of NAFLD, the studies are still at an early stage, which limits clinical application.

ALD

ALD, which ranges from early steatosis to alcoholic fatty liver, cirrhosis, and liver cancer, is the result of liver damage brought on by long-term ethanol toxicity and a complex immunological reaction.[23] Long-term ethanol consumption activates the innate immune system, producing proinflammatory and anti-inflammatory cytokines. It induces an inflammatory cascade in the liver and in the whole body.[23] Long-term exposure to ethanol increases neutrophil and macrophage recruitment, which promotes the activation of NLRP3/caspase-1/ASC inflammasome and the release of pro-inflammatory cytokines (Table 1, Fig. 3). Mice lacking caspase-1, ASC, and IL-1 receptors had a reduction in ethanol-induced hepatic steatosis and inflammation.[75,92] This suggests that NLRP3 activation in ALD is closely related to inflammatory response and liver injury. Correspondingly, inhibiting the activation of NLRP3 can improve the prognosis of alcoholic liver disease. For instance, diallyl disulfide was shown to inhibit the activation of ethanol-induced mouse liver NF-κB signals and NLRP3, slowing disease progression.[93] Zeaxanthin dipalmitate inhibited hepatic inflammatory infiltration and fat droplet accumulation in a rat ALD model by restoring mitophagy that was impaired due to ethanol poisoning and suppressed NLRP3.[94] A traditional Chinese medicine magnolol extract can inhibit NLRP3 preventing alcohol-induced liver injury.[95]

Ethanol inhibits the breakdown of fatty acids, which promotes fat accumulation in liver cells, which makes them prone

to lipid peroxidation and oxidative damage (Fig. 3). ROS production by dysfunctional mitochondrial and oxidative stress are key causes of ALD. Oxidative metabolism of alcohol damages mitochondria, which produce ROS and activate NLRP3, causing inflammatory responses in the liver (Table 1).[80] Ginsenoside Rg1 was shown to suppress NLRP3 activation by preventing oxidative stress, which alleviated pathological changes in the liver tissue of mice and rats on alcohol.[96] Oroxylin A can reduce the accumulation of mitochondrial superoxide and intracellular ROS in hepatocytes induced by ethanol, thus mediating the inactivation of NLRP3.[97] The inhibition of NLRP3 signaling can restrain the oxidative stress response in ALD, thus improving ALD. Traditional Chinese medicine extracts astragaloside IV was shown to inhibit the NLRP3/Caspase-1 inflammatory signaling pathway, alleviating alcohol-induced liver inflammation and oxidative stress in the liver.[69] Moreover, hepatocytic pyroptosis is closely associated with NLRP3 activation in the pathogenesis of ALD. Diallyl trisulfide alleviates alcohol-induced hepatocyte apoptosis by downregulating the accumulation of intracellular ROS and inhibiting NLRP3.[98] In conclusion, NLRP3 plays a pivotal role in the pathogenesis and progression of ALD, and suppression of NLRP3 activation can ameliorate the prognosis of alcoholic liver disease.

Viral hepatitis

Viral hepatitis is an infectious disease mainly caused by multiple hepatitis viruses (hepatitis A, B, C, D, and E viruses). The most common are hepatitis B and C. Viral infection activates the host immune response system, causing inflammatory responses activating NLRP3 (Table 1, Fig. 3). An excessive and ongoing inflammatory response causes chronic inflammatory disorders that lead to liver fibrosis. The expression levels of NLRP3, ASC, and IL-1β in the cytoplasm of hepatitis B virus (HBV)-negative patients are lower, while the same increase in HBV-positive patients.[99] The severity of HBV-induced liver inflammation is proportional to the expression levels of NLRP3, gastric dermal protein D, caspase-1, IL-1β, and IL-18.[100] Therefore, therapeutic targeting of NLRP3 can potentially suppress excessive inflammatory responses and alleviate inflammatory damage caused by viral hepatitis. HBV infection induces hepatic injury through the actions of HBV-associated proteins. Hepatitis B core antigen upregulates NLRP3 by promoting the phosphorylation of NF-κB thereby promoting liver injury.[101] Hepatitis B virus X protein activates NLRP3 under oxidative stress, enhancing NLRP3 inflammasome-mediated inflammation and pyroptosis by enhancing the generation of mtROS in liver cells.[99] Investigating the activation mechanisms of NLRP3 in hepatitis B virus infection can aid the development of NLRP3-directed antiviral therapies.

Hepatitis C virus (HCV) infection can activate NLRP3 inflammasomes, thus increasing the expression of NLRP3-related components in HCV-infected liver cells.[12,102] NLRP3 can influence macrophage activation and promote the regulation of the immune response. HCV activates NLRP3 in liver macrophages or KCs, driving liver inflammation. HCV core protein activates NLRP3, promoting the production and release of IL-1β by macrophages.[103] HCV infection activates NLRP3 in KCs by inducing potassium efflux, resulting in production of IL-1β. The secretion of IL-1β drives chemokines, proinflammatory cytokines, and immunoregulatory genes that are associated with the severity of HCV disease.[104] NLRP3 is activated in HCV infection through the NF-κB signaling pathway. In addition, HCV infection can induce endoplasmic reticulum stress that increases the release of intracellular ROS and subsequently activates NLRP3.[102] Although the aberrant activation of NLRP3 is important in viral hepatitis pathogenesis, the specific regulatory mechanism remains needs to be further explored.[105]

Autoimmune liver disease

Autoimmune hepatitis

Autoimmune hepatitis (AIH) is an autoimmune inflammation reaction in liver tissue, involving the action of innate immune cells, such as macrophages, T cells, and natural killer T cells (Fig. 3).[106,107] NLRP3 is a component of the innate immune system that the occurrence and development of AIH. In the pathogenesis of AIH, T helper (Th)0 lymphocytes differentiate into Th1 and Th2 cells. Th1 can activate macrophages by secreting IL2 and interferon gamma, thereby releasing IL-1.[106] TLRs 2, 4, and 9 can mediate the activation of inflammasomes in AIH and *de novo* autoimmune hepatitis, suggesting that the inflammasome activation has a role in the pathogenesis of AIH.[108] NLRP3 inflammasomes are known to contribute to concanavalin A (Con A)-induced hepatitis (AIH model). NLRP3 and ASC expression levels are upregulated in Con A-induced hepatitis. NLRP3 inflammasome activation, IL-1β production, and pyroptosis were significantly increased in Con A-induced AIH mice.[10] Recombinant human IL-1 receptor antagonists can inhibit NLRP3 in AIH by inhibiting ROS production and mitochondrial dysfunction in liver tissue.[10] The activation of NLRP3 may involve the NF-κB (Table 1) and the protein kinase A (PKA) signaling pathways. Formononetin inhibits NLRP3 activation by inhibiting the NF-κB pathway and protects the liver against Con A-induced liver injury in mice.[109] Dimethyl fumarate can inhibit the activation of the NLRP3 inflammasome by regulating the PKA signaling pathway, and prevent Con A-induced hepatitis.[110] The regulatory mechanism of NLRP3 is extensive, and its relationship with the PKA and NF-κB signaling pathways in the pathogenesis of AIH should be intensely studied.

Primary biliary cholangitis

Primary biliary cholangitis (PBC) is a chronic inflammatory autoimmune cholestasis liver disease that is characterized by immune-mediated bile duct injury and is accompanied by chronic cholestasis.[111,112] However, the specific pathogenesis of PBC is still unclear. Bile stasis can trigger TLR 4 signaling and enhance NF-κB activation, activating NLRP3 and thereby aggravating liver fibrosis (Table 1, Fig. 3).[113] NLRP3 is involved in liver inflammation and fibrosis. It is not only expressed in immune cells but also in liver cells and bile duct cells.[114] NLRP3 expression is significantly increased in the livers of PBC patients and mice, as shown by studies.[115] Moreover, in a mouse PBC model, galectin-3 directly stimulated the activation of NLRP3, causing autoimmune cholangitis and fibrosis.[116] MCC950, an NLRP3 inhibitor, can dramatically lessen bile duct ligation-induced liver injury by inhibiting the activation of NLRP3.[117] Paeoniflorin can reduce the degree of liver injury and liver fibrosis in PBC mice by inhibiting NLRP3 and related cascade inflammatory pathways.[115] Therefore, inhibiting NLRP3 and related cascading inflammatory pathways may be a new approach to the prevention and treatment of PBC.

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is also a chronic cholestatic liver disease. Inflammation and fibrosis result in multifocal biliary strictures and end-stage liver disease. The etiology of PSC is not clear, and so far, there is no specific and effective treatment. Elevated markers of NLRP3 inflamma-

some activation have been detected in liver biopsies of PSC patients.[118] NLRP3 immunostaining had positive expression of reactive bile duct cells in the livers of PSC patients and mouse PSC models, suggesting that activation of NLRP3 may have a role.[119] Although NLRP3 does not affect the proliferation of bile duct cells, it can destroy the integrity of bile duct epithelium, increasing epithelial permeability.[114,120] It has been established that primary pathogenesis of PSC in Mdr2$^{-/-}$ mice (a common PSC mouse model) includes loss of the integrity of the bile duct epithelial cell layer.[120] Furthermore, NLRP3 was found significantly activated in human PSC and Mdr2$^{-/-}$ livers. The extent of liver fibrosis in PSC patients positively correlates with the levels of NLRP3 and IL-1β.[65] Therefore, targeting NLRP3 is a new direction in the treatment of PSC.

Conclusion

This article provides a comprehensive review of the relationship between NLRP3 and liver fibrosis. The process of liver fibrosis involves the interaction of multiple cells and molecules. The mechanisms of these interactions need to be further studied in the future. Several NLRP3 inflammasome-related molecular inhibitors have been studied in liver diseases and have shown good results in reducing inflammation, fibrosis, and other tissue damage. Many traditional Chinese medicines have lipid-metabolism regulating, anti-inflammatory, and antioxidant effects, and alleviate hepatitis and liver fibrosis by inhibiting the NLRP3 inflammatory pathway. Furthermore, traditional Chinese medicines can slow down the progression of chronic liver disease by regulating the gut microbiome.[68,69] These experimental studies provide a preliminary foundation for clinical practice and new strategies for the development of drugs or treatments targeting NLRP3. In the future, the pharmacological effects of NLRP3-related molecular inhibitors and the synergistic effects of other drugs, especially traditional Chinese medicine preparations, are worthy of further exploration. Although some preliminary clinical trials and animal studies have shown the potential efficacy of targeted NLRP3 therapy, it has not yet been widely applied in clinical practice. The activation mechanism of the NLRP3 pathway is not fully understood and therefore targeted NLRP3 therapy needs deeper evaluations.

Funding

The work was supported in part by Shandong Provincial Natural Science Foundation (ZR2023MH295, LJP) and Linyi People's Hospital Postgraduate Fund Project (YJS2023002, MHS).

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Literature review and manuscript writing (MS), giving suggestions and revising the manuscript (YZ, AG), drafting figures (ZX), and topic conception and critical revision (LP). All authors made significant contributions to this study and have approved the final manuscript.

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