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REVIEW

NcRNA Regulated Pyroptosis in Liver Diseases and Traditional Chinese Medicine Intervention: A Narrative Review

Jiasheng Deng[1,*], Le Qin[2,*], Sulang Qin[3,*], Ruisheng Wu[1], Guidong Huang[1], Yibin Fang[4], Lanlan Huang[4], Zhipin Zhou[4]

[1]School of Pharmacy, Guangxi University of Chinese Medicine, Nanning, Guangxi, 530200, People's Republic of China; [2]Department of Pharmacy, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise, Guangxi, 533000, People's Republic of China; [3]School of Graduate Studies, Youjiang Medical University for Nationalities, Baise, Guangxi, 533000, People's Republic of China; [4]Department of Pharmacy, Liuzhou People's Hospital, Liuzhou, Guangxi, 545006, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zhipin Zhou, Department of Pharmacy, Liuzhou People's Hospital, 8 Wenchang Road, Cheng Zhong District, Liuzhou, Guangxi, People's Republic of China, Tel +86 −18776921947, Email gxzhouzhipin@126.com

Abstract: Pyroptosis is a novel pro-inflammatory mode of programmed cell death that differs from ferroptosis, necrosis, and apoptosis in terms of its onset and regulatory mechanisms. Pyroptosis is dependent on cysteine aspartate protein hydrolase (caspase)-mediated activation of GSDMD, NLRP3, and the release of pro-inflammatory cytokines, interleukin-1 (IL-1β), and interleukin-18 (IL-18), ultimately leading to cell death. Non-coding RNA (ncRNA) is a type of RNA that does not encode proteins in gene transcription but plays an important regulatory role in other post-transcriptional links. NcRNA mediates pyroptosis by regulating various related pyroptosis factors, which we termed the pyroptosis signaling pathway. Previous researches have manifested that pyroptosis is closely related to the development of liver diseases, and is essential for liver injury, alcoholic fatty liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), liver fibrosis, and liver cancer. In this review, we attempt to address the role of the ncRNA-mediated pyroptosis pathway in the above liver diseases and their pathogenesis in recent years, and briefly outline that TCM (Traditional Chinese Medicine) intervene in liver diseases by modulating ncRNA-mediated pyroptosis, which will provide a strategy to find new therapeutic targets for the prevention and treatment of liver diseases in the future.

Keywords: non-coding RNA, pyroptosis, liver diseases, inflammasomes, gasdermin, traditional Chinese medicine

Introduction

Data statistics indicate that approximately one in five people in China is affected by some form of liver disease, including viral hepatitis, non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), liver injury, liver fibrosis, liver cancer, etc.[1,2] Liver disease has gradually become a serious cause of death in China.[3] During the development of these diseases, a variety of infectious or non-infectious activators can stimulate liver cells to produce the corresponding immune response, which can lead to inflammatory changes in liver cells, thus causing liver inflammation.[4] In 2005, Fink et al first discovered and defined the phenomenon of cell pyroptosis, also known as cell inflammatory necrosis.[5] Acute/chronic hepatic inflammation is associated with pyroptosis in liver injury, NAFLD, ALD, liver fibrosis, and hepatocellular carcinoma. Therefore, pyroptosis may play a pivotal role in the development of liver disease.[6] Pyroptosis is a novel pro-inflammatory programmed cell death pathway that depends on the activation of Caspases, including Caspase-1, Caspase-4, Caspase-5 and Caspase-11. It then mediates the hydrolysis of gasdermin D (GSDMD) into GSDMD-N, which is embedded in the plasma membrane and forms soluble membrane pores, leading to ion decompensation, water influx, cell swelling and rupture, release of cell contents, and a large number of inflammatory mediators,[7,8] thereby initiating the inflammatory cascade.[9,10] Therefore, pyroptosis acts as a key adjustment factor in the immune defense mechanism, and pyroptosis

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mediated by Caspase-1 activation is an important mode of cell death in the clearance of pathogens and inhibition of pathogen infection.[11] Notably, hepatocytes are resistant to pyroptosis primarily with low expression levels of caspase-1 or −11, which are insufficient to cleave sufficient GSDMD to cause cell lysis through membrane pore formation. It is speculated that there are still sufficient activity in hepatocytes such as release of inflammasomes or HMGB1.[12] Inflammation caused by pyroptosis is the common basis for the development of liver diseases and is essentially accompanied by the development of malignant liver diseases, culminating in a full-cycle liver disease course.[13]

Non-coding RNA(ncRNAs) are a class of RNA without protein-coding functions, including microRNAs (miRNAs), long non-coding RNA (lncRNAs), and circular RNA (circRNA).[14] Although ncRNAs lack the potential to encode proteins, they can affect the expression of many molecular targets to drive specific cellular biological reactions and destinies.[15] Studies have indicated that ncRNAs regulate gene expression at multiple levels, including replication, transcription, and post-transcription,[16] and are involved in chromatin modification, cell differentiation, protein function regulation, and disease development.[17] An increasing number of studies have found that ncRNAs can mediate the transcriptional or post-transcriptional regulation of pyroptosis-related genes by participating in the regulatory network of pyroptosis, thereby affecting the pathogenesis of certain diseases such as diabetes and diabetic nephropathy,[18] cardiovascular disease,[19] atherosclerosis,[20] and cancer.[21] Consequently, pyroptosis regulated by ncRNAs is crucial for the occurrence of liver inflammation, and ncRNAs have become a key factor in liver diseases caused by pyroptosis. They are strongly associated with the occurrence and development of liver diseases, and can be used as biomarkers and potential targets for the diagnosis and treatment of liver diseases. In this study, we reviewed the effects of the ncRNA-mediated pyroptosis signaling pathway on liver diseases and the mechanism by which TCM regulates liver diseases through the ncRNA intervention pyroptosis signaling pathway. It aims to provide a new direction for the treatment of liver diseases.

Signaling Pathways of Pyroptosis

Pyroptosis is a novel pro-inflammatory programmed cell death, and it is accompanied by caspase activation, gasdermin cleavage, and release of the pro-inflammatory cytokines IL-1β and IL-18. Initially, it was suggested that pyroptosis is related to bacterial infection of immune cells. The morphological features and functions of pyroptosis were first observed in macrophages infected with the Gram-negative bacterium *Shigella fowleri*, but this was mistaken for apoptosis.[22] Comparable phenotypes were observed in Salmonella-infected macrophages, but it was found that caspase-1 was not involved in apoptosis,[23–25] this also signals the emergence of a new form of cell death. To date, pyroptosis is usually divided into two pathways based on the caspase-1-dependent pathway: canonical and non-canonical pyroptosis pathways. Moreover, Caspase-3 and Caspase-8, as apoptosis-related caspase proteins, can also trigger pyroptosis, which we refer to as other pyroptosis pathways. We summarize the mechanisms of these three pyroptosis pathways in Figure 1 according to the literatures.

Canonical Pyroptosis Pathway

The canonical pyroptosis pathways is defined as pyroptosis mediated by Caspase-1-dependent. The activation of this pathway is mainly triggered by pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs). After receiving danger signal molecules through the pattern recognition receptor (PRR), apoptosis-associated spot protein (ASC) is recruited, and pro-caspase-1 is assembled to form an inflammasome.[26] These inflammasomes stimulate the activation of caspase-1, finally leads to pyroptosis. PRRs (also known as inflammasome sensors) are widely expressed in immune cells and are classified into four categories: Toll-like receptors (TLRs), C-type lectin receptors (CLRs), AIM2-like receptors (ALRs), RIG-I-like receptors (RLRs), and NOD-like receptors (NLRs), which are widely expressed in immune cells.[27] Among them, TLRs and NLRs both play direct or indirect roles in pyroptosis. Nuclear factor kappa-B (NF-κB) is an essential signaling molecule in the pyroptosis pathway. During the activation of inflammatory factors, endogenous cytokines or microbial components in the cell membrane stimulate other factors, such as TLRs or tumor necrosis factor (TNF), on the cell surface to activate NF-κB.[28] Further, NLRP3 protein synthesis and pro-IL-1βand pro-IL-18 expression were promoted. Currently, it has been found that inflammasome associated with pyroptosis include NLRP1, NLRP3, NLRC4, and AIM2 inflammasome,[29] of which the most classical and intensively investigated is the pyroptosis mediated by the NLRP3 inflammasome, such as depressive symptoms,[30] sepsis-associated encephalopathy[31] and myocardial injury.[32] NLRP3 protein

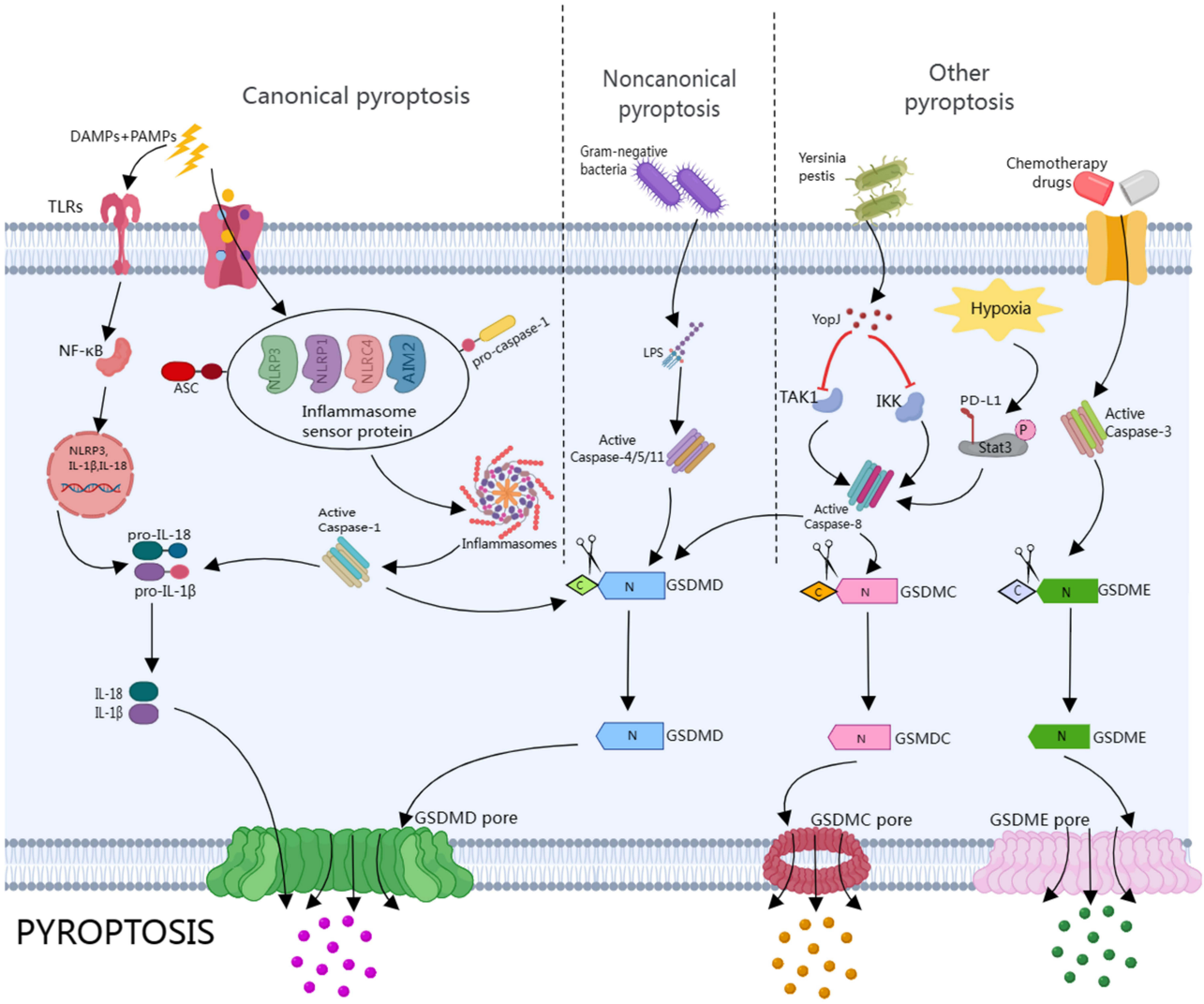

Figure 1 Overview of pyroptosis signaling pathways. In the canonical pyroptosis pathway, diverse inflammasomes are stimulated by PAMPs and DAMPs, assembly of the inflammasome sensor protein, the adapter protein ASC and pro-caspase-1 is complete, which activate the inflammasomes and caspase-1. The activated caspase-1 cleaves GSDMD and pro-IL-1β/pro-IL-18, and then mature IL-1βand IL-18 flow out of the GSDMD pore formed by the GSDMD-N oligomerization. Meanwhile, PAMPs /DAMPs can also stimulate TLRs to activate NK-κB, which induces the transcription of NLRP3, pro-IL-1b and pro-IL-18. In the non-canonical pyroptosis pathway, when stimulated by gram-negative bacteria, cytosolic LPS directly activates caspase-4/5/11, and the corresponding activated caspase will cleave GSDMD, ultimately triggering pyroptosis. In the other pyroptosis pathway, this pathway mainly depends on the activation of caspase-3 and caspase-8. In the response to Yersinia pestis, the inhibition of TAK1 or IκB kinase (IKK) activates caspase-8, and eventually triggers GSDMC-mediated pyroptosis. Additionally, under hypoxic conditions, PD-L1 binds to p-Stat3 in the nucleus, inducing caspase-8/GSDMC-mediated pyroptosis. Besides, chemotherapy drugs could directly activate caspase-3/GSDME-mediated pyroptosis.

binds to ASC through the PYD-PYD interactions, and ASC connects NLRP3 to Pro-caspase1 via the caspase activation and recruitment domains (CARD), and the three together form the NLRP3 inflammasome.[33] Next, the NLRP3 inflammasome activates caspase-1 to cleave GSDMD proteins into GSDMD-N and GSDMD-C, from which GSDMD-N forms membrane pores and releases contents, such as interleukin-1 alpha (IL-1α) and HMGB1, inducing pyroptosis. Simultaneously, activated caspase-1 cleaves pro-IL-1β and pro-IL-18 to form active IL-1β and IL-18, which are released into the extracellular space, inducing pyroptosis and causing inflammation.[34,35]

Non-Canonical Pyroptosis Pathway

Unlike canonical pyroptosis, which relies on caspase-1, the non-canonical pyroptosis process refers to pyroptosis that is dependent on the activation of caspase-4/5 or caspase-11. Amusingly, caspase4/5 can only mediate pyroptosis in human cells, whereas caspase-11 can only mediate pyroptosis in mice, indicating that there are species differences in non-

canonical pyroptosis pathways.[36] In contrast to canonical pyroptosis, caspase-4/5/11 can directly bind bacterial lipopolysaccharide (LPS) through its CARD domain to promote oligomerization and activation. Activated caspase-4/5/11 cleave GSDMD to produce GSDMD-N, leading to pore formation in the cell membrane. It induces the release of cellular contents and a large number of pro-inflammatory factors, IL-18, and IL-1β, thereby inducing pyroptosis.[37,38] With the further research, it was found that activated caspase-4/5/11 could not only directly induce pyroptosis, but also indirectly causes K^+ efflux / pannexin-1 cleavage /ATP release or P2X7 release through the pore previously formed by GSDMD-N, which in turn mediates NLRP3 inflammasome activation.[39,40] Whether it's the canonical or the non-canonical pyroptosis pathways, it can be seen that GSDMD proteins play crucial roles in both of the above.

Other Pyroptosis Pathways

In addition, evidence demonstrated that gasdermin family protein E (GSDME) also mediates pyroptosis,[41,42] chemotherapy drugs activate caspase-3 in tumor cells, then caspase-3 cleave GSDME to form GSDME-N active fragment. Since GSDME-N is similar to GSDMD-N, both can perforate the cell membrane, leading to cell swelling and rupture, ultimately promoting tumor cell pyroptosis.[43] Meanwhile, NLRP3 inflammasome can also be activated by caspase-8, suggesting that caspase-8 may induce pyroptosis.[44] Further exploration revealed that extrinsic and intrinsic apoptosis both activate pannexin-1 to drive NLRP3 inflammasome assembly, and caspase-1 and caspase-8 cleave GSDMD to trigger pyroptosis.[45] Among several caspase families, caspase-1 appears to be the strongest driver of GSDMD cleavage and caspase-8 is the weakest, it is probable that caspase-8 act as a fallback measure when other members of the caspase family are damaged.[46] Excitingly, researchers have found that PD-L1 transforms TNFα-induced apoptosis into pyroptosis in cancer cells, leading to tumor necrosis. Under hypoxia, p-Stat3 physically interacts with PD-L1 and promotes its nuclear translocation, thereby enhancing the transcription of the GSDMC gene. GSDMC is specifically cleaved by caspase-8, generating the GSDMC N-terminal structural domain, which forms a pore in the cell membrane and induces pyroptosis.[47] Of interest, Orning et al found that the activity of TGF-β activated kinase-1 (TAK1) and IκB kinase (IKK) was blocked in the immune response to Yersinia infection, which activated the caspase-8 pathway, leading to cleavage and activation of the GSDMD at the same location, ultimately causing pyroptosis.[48] Hence, these results indicate that the Caspase-8/GSDMD/GSDMC and Caspase-3/GSDME pathways may be other mechanisms causing pyroptosis. These results provide new directions for the study of pyroptosis. Importantly, clarifying the changes in these mechanisms may be a key point for understanding the different pyroptosis pathways.

Nc-RNA Mediated Pyroptosis Pathway in Liver Injury

Liver injury was defined as the onset of all chronic liver diseases. There are many causes of liver injury, including viral infections, drug abuse, long-term alcoholism, and liver surgery. Serious liver injury may develop into liver fibrosis, cirrhosis, or even liver cancer if no intervention is made.[49] Pyroptosis-related proteins and pro-inflammatory factors are secreted in the process of pyroptosis, which can induce an inflammatory response and aggravate liver injury. An in-depth study of the mechanism revealed that ncRNAs affect hepatic inflammation through the regulation of the pyroptosis signaling pathway, thereby affecting the occurrence and development of liver injury.

Several miRNAs can cause pyroptosis in the liver by regulating the abnormal expression of pyroptotic factors such as NLRP3, GSDMD, and caspase-1, which trigger an inflammatory response and worsen the liver. The expression level of miR-494 in hepatocytes gradually increased with alleviation of liver injury. In vivo experiments have shown that upregulation of miR-494 expression in hepatocytes can activate the PI3K/AKT/Nrf2 pathway to inhibit the expression of the NLRP3 inflammasome, reduce pyroptosis and inflammation, and alleviate liver injury.[50] MiR-4057 is up-regulated in acute liver injury induced by LPS and galactoside (D-GalN), and miR-4057 targets to inhibit the activation of the NLRP3 inflammasome and the release of pro-inflammatory factors IL-1β and IL-18.[51] Similarly, compared to normal mice, the expression of XBP1, NLRP3, caspase-1, and other pyroptotic proteins was increased in mice with liver injury, indicating that pyroptosis aggravated liver injury in mice. Further exploration determined that raising miR-182 expression suppression XBP1 / NLRP3 pathways activated, which in turn alleviated the occurrence of pyroptosis and attenuated liver injury in mice.[52] Interestingly, miR-182-5p plays a bidirectional regulatory role in pyroptosis-induced liver injury. FoxO3a, a miR-182-5p target involved in hepatocyte pyroptosis, reduces FoxO3a expression and can increase the

expression of the pro-inflammatory factors caspase-1, IL-1, and IL-18. Overexpression of miR-182-5p reduced the expression of FoxO3a; conversely, it increases the expression of FoxO3a, and miR-182-5p interfered with hepatocyte pyroptosis by directly targeting FoxO3a. Therefore, upregulation of miR-182-5p exacerbates liver injury, whereas downregulation of miR-182-5p could mitigate liver injury.[53] Another study indicated that upregulation of miR-330-3p reduces cleaved caspase-1 and GSDMD protein expression in mouse hepatic tissues by targeting phosphoglycerate mutase 5(PGAM5)-mediated caspase-1 and GSDMD expression,[54] leading to ameliorat the extent of liver injury in mice. Moreover, Yang et al demonstrated that overexpression of miR-30b-5p could target cannabinoid receptor 1 (CB1) to indirectly inhibit NLRP3 mRNA expression, thereby reducing NLRP3 inflammasome activation and pyroptosis.[55] Similarly, miR-23a-3p downregulation attenuated NLRP3 inflammasome-induced pyroptosis, mechanistically, miR-23a-3p targeted NIMA associated kinase 7 (NEK7) to inhibit NLRP3 inflammasome activation.[56] In the LPS- and ATP-induced hepatocyte injury models, exosomes containing miR-233 were found to significantly reverse liver injury and downregulate the expression of NLRP3 and caspase-1 at both the protein and mRNA levels in hepatocytes, resulting in protection against liver injury.[57] According to research, the expression of miR-297 is significantly upregulated in vitro cell model of liver injury. In vitro transfection of miR-297 antagonist targeting SIRT3 inhibited activation of the NLRP3 inflammasome and alleviated hepatic ischemia/reperfusion injury.[58]

In addition, a few lncRNAs have also been found to affect the development of liver injury by regulating the pyroptosis pathway, which are directly or indirectly involved in the process of pyroptosis by participating in mRNA degradation, competitive binding of mi-RNA, or regulating the translation of mRNA.[59] It has been shown that lncRNA-KCNQ1OT1 participates in liver injury pyroptosis signaling through the miR-142a-3p/HMGB1 axis, competitively binds to miR-142a-3p, upregulates the expression of the downstream target gene High Mobility Group Protein B1 (HMGB1), and activates the downstream TLR4/NF-κB pyroptosis pathway. Therefore, the miR-142a-3p/HMGB1 axis is regulated by silencing lncRNA-KCNQ1OT1 to reduce pyroptosis to improve liver injury.[60] Furthermore, knockdown of lncRNA-AK139328 inhibited macrophage infiltration and caspase-3 activation in the liver. Silencing of lncRNA-AK139328 improved liver injury by inhibiting NF-κB activity and inflammatory cytokine expression. These results suggest that lncRNA-AK139328 inhibits the production of downstream pyroptotic proteins and pro-inflammatory factors via the NF-κB pathway to repair liver injury.[61] Meanwhile, LncRNA-Gm15441 was abnormally upregulated in mice, and lncRNA-Gm15441 overexpression inhibited its antisense transcription encoding thioredoxin interacting protein (TXNIP), which in turn reduced TXNIP-induced NLRP3 inflammasome activation, caspase-1 cleavage, and pro-IL-1β maturation, ultimately reducing the inflammatory response and the level of damage in the liver.[62] Therefore, by targeting and regulating lncRNA-Gm15441, new insights into the treatment of metabolic stress-induced liver inflammation and injury can be obtained. The pharmacological mechanisms of ncRNA-mediated pyroptosis signaling against liver injury are summarized in Table 1.

Nc-RNA Mediated Pyroptosis Pathway in Liver Fibrosis

Liver fibrosis is a wound-healing response caused by various chronic liver injury factors, including inflammation, viral infection, bacterial infection, and alcohol abuse. It is characterized by necrosis of liver parenchyma cells and abnormal deposition of collagen fibers, which mainly manifests as an imbalance in extracellular matrix (ECM) degradation and production, leading to abnormal proliferation of connective tissue in the liver and subsequent development of liver fibrosis.[63] Without timely intervention in the evolutionary process, liver fibrosis may develop into liver failure, cirrhosis, and even liver cancer at the end stage of liver disease. Activated hepatic stellate cells (HSC) are the main source of ECM production, and α-smooth muscle actin (α-SMA) and collagen secreted by HSC are the major components of ECM.[64,65] In recent years, increasing evidences have show that ncRNAs not only bind to specific mRNA targets to affect HSC activation but also participate in liver fibrosis by regulating pyroptosis signaling pathways.

Jimenez et al reported that in mice with liver fibrosis, miR-223 3p disrupted the activation of the NLRP3 inflammasome and inhibited pyroptosis by impairing the mature IL-1β and, NLRP3 proteins, and the activation of caspase-1 p10. Engagingly, miR-223 3p can also inhibit the release of IL-1β from liver macrophages, thereby inhibiting the activation of HSCs.[66] Furthermore, another exploration suggested that early fibrosis occurred in the livers of knockout miR-223 mice, and the degree of injury correlated with the expression level of NLRP3, whereas restoration of miR-223 levels by

Table 1 NcRNA Regulated Pyroptosis to Attenuate Liver Injury

NcRNAs	Regulation	Target Genes	Mechanisms	References
miR-494	Up	PI3K/AKT/Nrf2	Inhibit NLRP3 inflammasome activation, reduce pyroptosis and inflammatory	[50]
miR-4057	Up	NLRP3	Inhibit NLRP3 inflammasome, IL-1β and IL-18 activation and attenuated pyroptosis	[51]
miR-182	Up	NLRP3/XBP1	Suppress NLRP3/XBP1 pathway, decrease the expression of NLRP3 and caspase-1	[52]
miR-182-5p	Down	FoxO3a	Negatively regulate the release of caspase-1, IL-1β and IL-18, reduce pyroptosis	[53]
miR-330-3p	Up	PGAM5	Inhibition of capase-1 and GSDMD expression inhibited pyroptosis	[54]
miR-30b-5p	Up	CB1	Attenuating NLRP3 mRNA and NLRP3 inflammasome expression	[55]
miR-23a-3p	Up	NEK7	Inhibition of NLRP3 inflammasome	[56]
miR-223	Up	NLRP3, caspase-1	Inhibit NLRP3 and caspase-1 mRNA expression	[57]
miR-297	Down	SIRT3	Reduce NLRP3 inflammasome activation and reduce pyroptosis	[58]
LncRNA-KCNQ1OT1	Down	miR-142a-3p	Inhibition of TLR4/NF-κB pathway and the release of proinflammatory cytokine	[60]
LncRNA-AK13932	Down	NF-κB	Inhibition of NF-κB pathway	[61]
LncRNA-Gm15441	Up	TXNIP	Inhibition of NLRP3 activation, caspase-1 cleavage and IL-1β maturation	[62]

injection of miR-223 mimics into neutrophils reversed fibrosis, implying that miR-223 is a key negative regulator of the inflammasome of NLRP3.[67] Therefore, the upregulation of miR-223 could be used as a novel anti-hepatic fibrosis treatment. Besides, miR-379-5p regulates arsenate-induced HSC activation by targeting GSDMD. Transfection of miR-379-5p in vitro blocked the increase in GSDMD levels and the release of IL-1β, thereby reducing the secretion of collagen type I protein and α-SMA and inhibiting HSC activation. These results indicate that miR-379-5p inhibits pyroptosis by reducing GSDMD expression and inhibiting liver fibrosis.[68] Researchers on liver fibrosis demonstrated that miR-21 expression was significantly increased in patients with liver fibrosis and in animal models, indicating that miR-21 overexpression promoted the activation of the NLRP3 inflammasome in HSCs. The above phenomenon was found to be induced by two pathways: miR-21 activates the NLRP3 inflammasome and releases IL-1βby targeting the Spry1-ERK-NF-κB pathway, and miR-21 activates the NLRP3 inflammasome and releases IL-1β in HSCs. Both pathways result in enhanced NLRP3 expression, which promotes HSC activation and collagen synthesis, leading to the exacerbation of hepatic fibrosis.[69]

Moreover, dysregulation of lncRNAs is an important trigger of hepatic fibrosis, and some lncRNAs can influence the development of hepatic fibrosis by regulating the pyroptosis signaling pathway. Current study found that interfering with macrophage pyroptosis can also affect liver fibrosis, and silencing lncRNA-Lfar1 attenuated M1 macrophage pro-inflammatory activation and inhibited NLRP3 inflammasome-mediated pyroptosis in vivo. Simultaneously, knockdown of lncRNA-Lfar1 could block the activation of the NLRP3 inflammasome and thus reduce the release of pro-inflammatory factors IL-1β and IL-18 to inhibit pyroptosis and liver fibrosis.[70] Early research suggested that the positive regulation of lncRNA-p21 could promote liver fibrosis and increases the levels of fibrosis-related proteins (collagen I, α-SMA, and TIMP-1). In vitro, lncRNA-p21 was significantly upregulated in HSCs, which further activated the PI3K-AKT -NF-κB pathway and induced pyroptotic factors, thereby promoting HSC activation and α-SMA secretion.[71] More attractively, Wang et al examined that salvianolic acid B (Sal B) could improve liver fibrosis by regulating the NF-κB signaling pathway. Further mechanism found that Sal B can downregulate lncRNA-ROR by targeting the NF-κB signaling pathway to downregulate the expression of inflammatory factors, thereby inhibiting the proliferation and activation of HSCS. Not only that, Sal B can also upregulate miR-6499-3p to competitively target and degrade lncRNA-ROR, which can also play a role in downregulating lncRNA-ROR, and finally play a key in anti-liver fibrosis.[72] It is interesting to note that lncRNA-GAS5 also plays an important role in the regulation of liver fibrosis, lncRNA-GAS5 was revealed to be significantly downregulated in induced activated HSC, whereas in vitro experiments transfected with

upregulated lncRNA-GAS5 inhibited the downstream NF-κB pyroptosis signaling pathway by binding to the 3'-UTR of TLR10, which in turn hindered HSC activation.[73] In general, these studies revealed that ncRNAs regulate pyroptosis and expanded the research field of pyroptosis in liver fibrosis. The association between ncRNAs and pyroptosis is summarized in Table 2.

Nc-RNA Mediated Pyroptosis Pathway in ALD and NAFLD

ALD is characterized by liver tissue damage and inflammation caused by excessive alcohol consumption. It is mainly characterized by structural changes and dysfunction of hepatocytes.[74] The initial clinical manifestation is steatosis, which then develops into liver fibrosis, alcoholic hepatitis (AH), cirrhosis and liver cancer.[75] NAFLD is characterized by the accumulation of lipids in the liver caused by factors other than high alcohol intake, drug use, or other factors that contribute to hepatic steatosis,[76] which can be classified pathologically as varying in severity, ranging from simple steatosis to NASH and liver fibrosis.[77,78] Increasing number of studies have found that pyroptosis is the inflammatory link between simple steatosis and NASH.[79,80] Specifically, pyroptosis is rarely observed in animal models of simple steatosis without inflammation, and pyroptosis has been suggested to occur in NASH in humans and animal models, implying that the pro-inflammatory factors released by pyroptosis process are key molecules in the development of NAFLD.[81] Similarly, pyroptosis is a key driver of ALD in patients and animal models, and inhibition of pyroptosis prevents ALD progression and has beneficial effects on liver injury and steatosis.[82]

Recently, growing works have suggested that ncRNAs are involved in the development of ALD and NAFLD by regulating the pyroptosis signaling pathways. Bala et al reported that miR-155 knockout NASH mice exhibited less liver injury, steatosis, and fibrosis than normal NASH mice. In miR-155 knockout mice, pyroptotic proteins such as NLRP3, ASC, and caspase-1 were downregulated, and collagen deposition was also indirectly attenuated.[83] Therefore, miR-155 knockout could alleviated steatosis and liver fibrosis in NASH mice, thereby mitigating the development of NAFLD. Similarly, another finding suggested that the overexpression of ATG2B (an autophagy-related protein) was shown to attenuates lipid droplet accumulation and reduces ALT, AST, inflammatory cytokines, and pyroptosis in established mouse and cellular models of NASH. Thus, by knocking down miR-375-3p, its specific binding to ATG2B is reduced, thereby promoting autophagy, inhibiting pyroptosis, and improving the occurrence and development of NASH.[84] Pan et al applied that liver Kupffer cells are activated in ASH mice with alcoholic steatohepatitis, contributing to alcoholic liver injury. miR-34a-5p can target and inhibit the expression of SIRT1 to promote Kupffer cells pyroptosis. When SIRT1 was knocked down, the protein expression of NLRP3, GSDMD, IL-1β, and IL-18 was significantly increased.[85] In addition, miR-148a levels were significantly reduced in patients with ALD and mouse models. Forkhead box protein O1 (FoxO1), as a transcription factor for miR-148a transcription activation, inhibits the expression of FoxO1 with alcohol and then reduces the expression of miR-148a. Reduction in miR-148a expression induced upregulation of TXNIP

Table 2 NcRNA Regulated Pyroptosis to Attenuate Liver Fibrosis

NcRNAs	Regulation	Target Genes	Mechanisms	References
miR-223-3p	Up	NLRP3/caspase-1	Inhibit the activation of NLRP3 inflammasome, reduce pyroptosis, and then inhibit the activation of HSC	[66]
miR-223	Up	NLRP3	Inhibition of NLRP3 inflammasome, IL-1β and IL-18 release	[67]
miR-379-5p	Up	GSDMD/IL-1β	Inhibit pyroptosis, thereby reducing collagen type I protein deposition, α-SMA, and inhibiting HSC activation	[68]
miR-21	Down	Smad7/Smad2/NOX4/ Spry1-ERK-NF-κB	Block NLRP3 activation, inhibit HSC activation as well as collagen synthesis	[69]
miR-6499-3p	Up	NF-κB	Inhibition of pyroptosis and HSC activation	[72]
LncRNA-Lfar1	Down	NLRP3	Suppress NLRP3 inflammasome activation, reduced the release of proinflammatory factors IL-1β and IL-18	[70]
LncRNA-p21	Down	PI3K-AKT-NF-κB	Inhibits pyroptosis and hinder HSC activation and α-SMA increase	[71]
LncRNA-ROR	Down	NF-κB	Inhibition of pyroptosis and HSC activation	[72]
LncRNA-GAS5	Up	TLR10/NF-κB	Inhibit the activation of HSC	[73]

expression. TXNIP overexpression activates NLRP3 inflammasome, caspase-1 and promoted pyroptosis.[86] Therefore, upregulation of miR-148a levels by hepatocyte-specific transfection can inhibit TXNIP overexpression and inflammasome activation, which can be used as a new research direction for the treatment of ALD. Furthermore, lncRNA-Platr4 is an lncRNA associated with steatohepatitis, whose expression is driven by NF-κB, and upregulation of lncRNA-Platr4 repairs NASH in mice. Mechanistically, lncRNA-Platr4 prevents the NF-κB/Rxrα complex from binding to the κB site through physical interactions, which inhibits the transcriptional activation of NLRP3 and ASC, which in turn inactivates the NLRP3 inflammasome, reduces pyroptosis, and improves NASH.[87] Another outcome in NAFLD indicated that lncRNA-GAS5 as a sponge, can bind to miR-28a-5p, and miR-28a-5p enhanced pyroptosis by targeting the 3'-untranslated region (UTR) of the E3 ligase MARCH7 during NAFLD development. With the negative regulation of miR-28a-5p, MARCH7 overexpression could cause NLRP3 proteasomal degradation, thereby inhibiting pyroptosis.[88] Above all, these studies not only further determine the vital role of ncRNAs in pyroptosis but also provide a new direction for the identification of fatty liver markers. (Table 3)

Nc-RNA Mediated Pyroptosis Pathway in Liver Cancer

Liver cancer is one of the most common malignant tumors worldwide, and hepatic malignancies originates from the epithelial or mesenchymal tissues of the liver. Its pathogenesis of hepatocellular carcinoma has been reported to be related to pyroptosis.[89] In particular, it has been reported that the expression level of the NLRP3 inflammasome is significantly reduced in hepatocellular carcinoma (HCC) compared to normal liver tissues, and the levels of pyroptosis-related proteins are also decreased.[90] Additionally, berberine activated caspase-1 and triggered pyroptosis, showing a strong inhibitory effect on the proliferation and metastasis of HCC cells in vitro. Interestingly, similar results were observed for 17βestradiol-induced NLRP3 inflammasome activation and caspase-1-dependent pyroptosis, which suppressed HCC progression by inhibition autophagy.[91] In Recent years, certain ncRNAs have been detected to influence the pathological process of liver cancer through mediating the pyroptosis pathway. However, the mechanisms underlying ncRNA-mediated pyroptosis in HCC remain unclear.

Du et al investigated that miRNA-30a-3p mediates pyroptosis by targeting caspase-1. Upregulation of miRNA-30a-3p could reduce the expression level of caspase-1, thereby inhibiting the release of the pro-inflammatory cytokines IL-18, IL-1β, and pyroptosis, implying that the reduction of pyroptosis in HCC cells can inhibit the proliferation, invasion, and metastasis of HCC cells.[92] Dramatically, lncRNA-SNHG7 expression was upregulated in liver cancer tissues and HCC cells, which inhibited NLRP3, caspase-1, and IL-1β, suggesting that lncRNA-SNHG7 may play an oncogenic role in liver cancer by inhibiting pyroptosis.[93] Vitro experiments showed that lncRNA-SNHG7 knockdown increased the expression levels of NLRP3, caspase-1, and IL-1β, caused caspase-1-dependent pyroptosis in liver cancer cells, and then inhibited the proliferation and metastasis of cancer cells. It has been demonstrated that the inhibition of lncRNA-SNHG7 may promote pyroptosis to aggravate the death of HCC cells and inhibit the growth of liver tumors.[93] In summary, these studies illustrate that pyroptosis plays a dual regulatory role in liver cancer development. Pyroptosis may promote the proliferation and metastasis of liver cancer tissues and aggravate liver cancer, which must be reduced to play

Table 3 NcRNA Regulated Pyroptosis to Attenuate ALD and NAFLD

NcRNAs	Regulation	Target Genes	Mechanisms	References
miR-155	Down	NLRP3	Inhibit pyroptosis-related proteins such as NLRP3, ASC, and caspase-1 expression	[83]
miR-375-3p	Down	ATG2B/PTEN-AKT	Negatively regulate the release of pro-inflammatory cytokines	[84]
miR-34a-5p	Down	SIRT1	Inhibiting expression of NLRP3 and GSDMD	[85]
miR-148a	Up	TXNIP	Repress TXNIP and NLRP3 inflammasome	[86]
LncRNA-Platr4	Up	NF-κB/Rxrα1	Block the transcriptional activation of NLRP3 and ASC and then inactivate NLRP3 inflammasome	[87]
LncRNA-GAS5	Up	miR-28a-5p/MARCH7/NLRP3 axis	Inhibition of NLRP3 protein synthesis	[88]

an anti-liver cancer role. In contrast, pyroptosis may also inhibit the proliferation and invasion of liver cancer tissues through a certain mechanism, and by promoting pyroptosis, it may play a direct role in the anti-liver cancer effect. Until now, researches that investigate the role of pyroptosis in liver cancer are very rare, but pyroptosis seems to be crucial for liver cancer development and therapeutic treatment. Extensive studies have shown that HCC is still more related to apoptosis,[94,95] and the pyroptosis pathway can provide a new approach to treat HCC. (Table 4)

Traditional Chinese Medicine and Its Active Ingredients Influence ncRNA-Mediated Pyroptosis Pathway in Liver Disease

Increasing reports denoted that traditional Chinese medicine (TCM) in the clinical treatment of liver disease plays a unique efficacy in the treatment of multiple targets, multiple components, and multi-level outstanding advantages because it contains many bioactive components, such as alkaloids, flavonoids, steroids, glycosides and phenylpropanoids.[96–100] Previous studies have found that *Isodon ternifolius* can reduce the release of fibrotic and inflammatory cytokines by inhibiting the activation of the TLR4/NF-κB/NLRP3 pathway, which downregulates the expression of NF-κB p65, NLRP3, GSDMD, ASC proteins, and mRNAs. This leads to the attenuation of hepatocyte inflammation, inhibition of HSC activation, and have the effect of anti fibrosis.[101,102] In the aspect of experiment reveals that TCM via signaling pathways and more targets way to explore new strategies for the treatment of liver disease. With the in-depth exploration of TCM, it can be observed that Chinese herbal compounds and their active ingredients regulate pyroptosis at the ncRNA level, impacting the development process of liver diseases. Although many researches have reported that Chinese medicines and their active ingredients are involved in pyroptosis to influence liver disease, there are very few studies on the role of ncRNAs in the regulation of pyroptosis to influence liver disease. Therefore, we have summarized this information as follows.

Theaflavin is a compound derived from black tea and has a variety of pharmacological effects, including hypolipidemic, hypotensive, antioxidant, antiradical, antibacterial, and anti-cancer.[103–106] A study demonstrated that theaflavin-3,3 '-digallate (TFDG) in this group of compounds showed stronger biological activity. TFDG not only ameliorated learning and memory dysfunction,[107] but also effectively diminished high-fat diet-induced liver injury and inflammatory response by inhibiting the NLRP3/IL-1β pathway through upregulation of miR-223, which reduced the excessive activation of the NLRP3 inflammasome as well as the release of large amounts of cytokines, such as IL-1βand IL-18, and alleviated high-fat diet-induced liver injury.[108] Zhao et al examined that polydatin inhibited ROS-driven TXNIP activation of the NLRP3 inflammasome by upregulating miR-200a, decrease pyroptosis, and improving fructose-induced liver inflammation and lipid deposition.[109] Similarly, curcumin, a polyphenolic compound extracted and isolated from turmeric, exhibits strong biological activity and alleviates fructose-induced liver inflammation. It also works through the miR-200a-mediated TXNIP/NLRP3 pathway, directly targeting the inhibition of TXNIP and reducing the activation of NLRP3 inflammasome, which ultimately plays a role in liver protection.[110] Ginseng saponin Rg1 (Rg1) is separated from the TCM-ginseng, which possesses a variety of biological activities such as anti-inflammatory and anti-cancer properties.[111–113] In another probe on NASH, researchers discovered that Rg1 participates in autophagy and pyroptosis through the miR-375-3p/ATG2B/PTEN-AKT axis, which mainly manifests as knocking down miR-375-3p, reducing ALT, AST, IL-1β, IL-18, and pyroptosis protein NLRP3 and caspase 1 expression, promoting autophagy, and inhibiting pyroptosis, thus attenuating NASH.[84]

Table 4 NcRNA Regulated Pyroptosis to Attenuate Liver Cancer

NcRNAs	Regulation	Target Genes	Mechanisms	References
miRNA-30a-3p	Up	Caspase-1	Down-regulate caspase-1 could inhibit the release of pro-inflammatory factors IL-18 and IL-1β, and inhibit the metastasis and invasion of cancer cells.	[92]
LncRNA-SNHG7	Down	NLRP3	Raise the expression levels of NLRP3, caspase-1 and IL-1β, and promote pyroptosis of liver cancer cells	[93]

According to previous research, Atractylodes macrocephala Koidz (AMK) has plentiful pharmacological effects, including anti-tumor, anti-inflammatory, anti-oxidation, and hypoglycemic.[114] The polysaccharide components of AMK play a crucial role in immune regulation of the body.[115] Experimental studies have demonstrated that AMK polysaccharides alleviate LPS-induced inflammatory liver tissue injury and act as anti-hepatic injury agents by regulating the miR-223/NLRP3 axis, thus significantly reducing the expression levels of IL-1β and IL-18.[116] Additionally, Silibinin is an effective component of traditional Chinese medicine, used as a hepatoprotective agent in clinical therapy, and its phospholipid complex has been used in the clinical treatment of acute liver injury.[117] Further finding found that the Silibinin-phospholipid complex significantly diminished d-GalN/LPS-induced liver injury by enhancing the expression of miR-223-3p, and miR-223-3p directly targeted the 3' UTR of NLRP3, thereby inhibiting the activation of the NLRP3 inflammasome and the expression of pyroptotic proteins to achieve hepatoprotective effects.[118] Curcumol is an effective active ingredient extracted from the genuine medicinal herb Curcuma kwangsiensis S. G. Lee et C. F. Liang in Guangxi, China, which is known for its ability to invigorate blood circulation and remove blood stasis, protect the liver, and have anti-inflammatory, cholagogic and antioxidant effects.[119,120] Curcumol inhibits miR-125b/NLRP3 pathway to prevent liver fibrosis. Mechanistically, it can upregulate the expression of miR-125b, which decreases the downstream NLRP3 inflammasome and the expression of Caspase-1, GSDMD, IL-1β, and IL-18, reduces the onset of pyroptosis, and inhibits the activation of HSC to prevent liver fibrosis.[121] Evidences have implied that Salvianolic acid B (Sal B), an active ingredient in Salvia miltiorrhiza extract, blocks the NF-κB signaling pathway by downregulating lnc-ROR and inhibiting the expression of pyroptotic proteins and inflammatory cytokines, which in turn hinders the proliferation and activation of HSC. Meanwhile, Sal B could also target the degradation of lnc-ROR through the regulation of miR-6499-3P, which can also play an anti- hepatic fibrosis effect.[72] As a Chinese medicine compound formula, the main effects of Shugan Jianpi formula are to relieve liver and depression, nourish blood and strengthen spleen.[122] Studies on liver fibrosis have demonstrated that this formula reduces pyroptosis and inhibits HSC activation by regulating the lnc-ECONEXIN/miR-26b-5p/TLR4 signaling axis. Mechanistically, it can downregulate lncECONEXIN, which acts as a ceRNA to competitively bind to miR-26b-5p. MiR-26b-5p is indirectly upregulated, which reduces hepatocyte pyroptosis and inhibits HSC activation to achieve anti-hepatic fibrosis effects.[123] Analogously, Chaihu Shugan powder is also a liver protection formula in TCM, which has the effect of soothing the liver, regulating qi, promoting blood circulation and relieving pain. It is mainly used for the treatment of chronic hepatitis, chronic gastritis, intercostal neuralgia, and liver qi depression.[124] Further studies indicated that the formula increased miR-155 expression, inhibiting the TLR4 /NF-κB signaling pathway, activated the NLRP3 inflammasome, and reduced TLR4, NF-κB, NLRP3, Caspase-1, ASC and IL - 1β expression.[125] Amusingly, researchers have also presented new insights into TCM-ncRNA-pyroptosis in liver diseases. Although there have been few reports in this area, the role of TCM in pyroptosis is worthy of further investigation. These results indicate that the active ingredients and compounds of TCM can against liver disease by regulating the pyroptosis signaling pathway through ncRNA. Therefore, it is necessary to explore key ncRNAs that could provide potential targets for the future treatment of liver diseases. The pharmacological mechanisms of TCM against liver disease are summarized in Table 5.

Conclusion and Future Perspectives

Liver diseases appear in an increasing proportion of current clinical diseases, including liver injury, ALD, NAFLD, liver fibrosis, and liver cancer. During the process of liver lesions, the pyroptosis associated protein abnormal expression, such as NLRP3, caspase-1, and GSDMD, which subsequently causes the release of the downstream proinflammatory factor IL-1βand IL - 18. These findings suggest that pyroptosis plays a key role in hepatocyte inflammation, lipid accumulation, fibropathy, and carcinogenesis. Accordingly, the pyroptosis signaling pathway is closely related to the pathological process of liver disease and is emerging as one of the most important avenues for the treatment and prevention of liver disease. Obviously, the final manifestation of pyroptosis in the liver is the cascade response of inflammation, generating a massive storm of inflammatory factors that exacerbate hepatocyte inflammation, and ncRNAs are involved in the progression of these liver diseases through the regulation of the pyroptosis signaling pathway. Furthermore, this review summarizes the available evidence on the mechanism of ncRNA-mediated pyroptosis in liver disease (Figure 2). In liver injury, ALD, and NAFLD, ncRNAs mediate the pyroptosis pathway by regulating the expression of pyroptotic factors, such as NLRP3, GSDMD, caspase-1, and thus inhibiting the release of pro-inflammatory factors IL-1β and IL-18. It is

Table 5 TCM Regulated Pyroptosis by ncRNA to Treat Liver Diseases

TCM	NcRNA	Mechanisms	Liver Diseases	References
Theaflavin	miR-223	Suppress the NLRP3/IL-1β inflammatory pathway and reduce the maturation of NLRP3, IL-1β, and IL-18	Liver injury	[108]
Polydatin	miR-200a	Inhibition of NLRP3 inflammasome activation and reduction of pyroptosis	NAFLD	[109]
Curcumin	miR-200a	Blocking the TXNIP/NLRP3 pathway	NAFLD	[110]
Ginseng saponin Rg1	miR-375-3p	Control the expression of IL-1β, IL-18, NLRP3 and caspase 1	NAFLD	[84]
Atractylodes macrocephala Koidz	miR-223	Negatively regulate the miR-223/NLRP3 axis and decrease the levels of IL-1β and IL-18	Liver injury	[116]
Silibinin	miR-223-3p	Targeting the 3' UTR of NLRP3 and inhibiting NLRP3 inflammasome activation	Liver injury	[118]
Curcumol	miR-125b	Inhibition of miR-125b/NLRP3 pathway	Liver fibrosis	[121]
Salvianolic acid B	Lnc-ROR/miR-6499-3P	Regulation of the Lnc-ROR/NF-κB/miR-6499-3P axis inhibits pyroptosis and HSC activation	Liver fibrosis	[72]
Shugan Jianpi formula	Lnc- ECONEXIN/ miR-26b-5p	Regulation of lncECONEXIN/miR-26b-5p/TLR4 signaling axis suppresses pyroptosis and HSC activation	Liver fibrosis	[123]
Chaihu Shugan powder	miR-155	Blocking the TLR4 / NF-κB pathway and inhibiting NLRP3 activation	Liver injury	[125]

well known that IL-1β, IL-18 are pivotal molecules in the inflammatory response, steatosis, and fibrosis that occur in the liver, and play an important role in the pathogenesis of above three of these liver diseases.

Amusingly, for ncRNA anti-liver fibrosis via pyroptosis signaling pathway, although pyroptosis does not play a direct regulatory role in it, the inflammatory factor storm caused by pyroptosis can indirectly promote the activation of HSCs, thereby aggravating liver fibrosis. Moreover, the NLRP3 inflammasome, a crucial key in the development of pyroptosis,

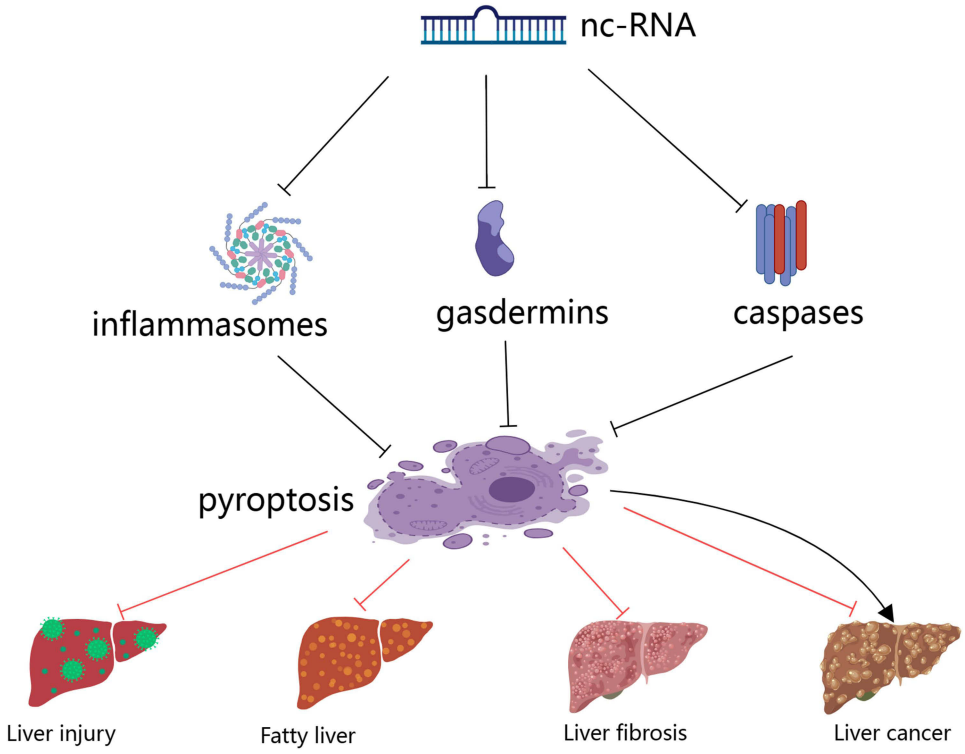

Figure 2 NcRNA regulates major pyroptosis signaling molecules to influence liver disease.

was found to be persistently activated, causing an increase in the expression of the HSC activation markers α-SMA and type I collagen in mice,[126] which implies that the NLRP3 inflammasome may play a straightforward role in HSC activation. Overall, the ncRNA-regulated pyroptosis signaling pathway mediates the inflammasome that induces HSC activation and exacerbates liver fibrosis. To date, a few ncRNAs have been found to mediate the pyroptosis signaling pathway in HCC, but it is not difficult to conclude that pyroptosis is also closely related to the development of HCC. What is remarkable is that pyroptosis plays a dual regulatory role in the development of liver cancer. First, pyroptosis may promote the proliferation and metastasis of liver tumor tissues and aggravate liver cancer. Second, pyroptosis may also inhibit the proliferation and metastasis of liver tumor tissues, and by promoting pyroptosis, it may also play a role in anti-hepatocellular carcinoma. Unfortunately, there are no in-depth studies on this two-sided regulatory mechanism for the time being. Furthermore, how to trigger pyroptosis in tumor cells by regulating ncRNAs is still facing a huge challenge.

Notably, TCM has shown great advantages in the prevention and treatment of chronic liver diseases[127,128] because it contains a large number of effective active ingredients to protect the liver. In recent years, ncRNAs regulation of post-transcriptional gene expression has become a hot topic in the field of biomedical research. Concurrently, with the in-depth exploration of TCM-target-disease mechanisms based on the regulation of ncRNAs, the multi-level and multi-target therapeutic characteristics of TCM have been scientifically expounded. Such qualities broaden the way and provide new research strategies for the molecular mechanisms of TCM anti-liver diseases. However, due to few studies have been conducted on Chinese medicines against liver disease by modulating the ncRNA-mediated pyroptosis signaling pathway, it can be used as a breakthrough point to continue intensive research to provide new ideas for the treatment of liver disease with TCM. In the future, with the development of bioinformatics, high-throughput sequencing, and metabolomics, it will be possible to screen and predict ncRNAs for disease-drug-target associations, which will further clarify the molecular mechanisms of ncRNAs and active ingredients of TCM against liver disease.

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Disclosure

The authors report no conflicts of interest in this work.

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