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Role of the Inflammasome in Liver Disease

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Abstract

The involvement of inflammasomes in the proinflammatory response observed in chronic liver diseases, such as alcohol-associated liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD), is widely recognized. Although there are different types of inflammasomes, most studies to date have given attention to NLRP3 (nucleotide-binding oligomerization domain-like receptor family, pyrin domain containing 3) in the pathogenesis of ALD, NAFLD/nonalcoholic steatohepatitis, and fibrosis. Canonical inflammasomes are intracellular multiprotein complexes that are assembled after the sensing of danger signals and activate caspase-1, which matures interleukin (IL)-1β, IL-18, and IL-37 and also induces a form of cell death called pyroptosis. Noncanonical inflammasomes activate caspase-11 to induce pyroptosis. We discuss the different types of inflammasomes involved in liver diseases with a focus on (*a*) signals and mechanisms of inflammasome activation, (*b*) the role of different types of inflammasomes and their products in the pathogenesis of liver diseases, and (*c*) potential therapeutic strategies targeting components of the inflammasomes or cytokines produced upon inflammasome activation.

Keywords

canonical inflammasomes; noncanonical inflammasomes; nonalcoholic steatohepatitis; alcohol-associated liver diseases; macrophage; hepatocyte; pyroptosis; IL-1β; IL-18; GSDMD

1. INTRODUCTION

Liver disease is a major global health concern and is responsible for 2 million deaths worldwide annually (1). Nonalcoholic fatty liver disease (NAFLD) and alcohol-associated liver disease (ALD) are the leading clinically diagnosed chronic liver diseases with mild clinical symptoms (2). However, in ALD, acute episodes driven by increased alcohol consumption can worsen disease pathogenesis with symptoms of an acute clinical syndrome called alcoholic hepatitis (AH) (3). Both ALD and NAFLD/nonalcoholic steatohepatitis

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(NASH) can lead to fibrosis and cirrhosis and increase the risk for hepatocellular carcinoma (1).

The pathogenesis of most chronic liver diseases involves a proinflammatory cascade activation in the liver and circulation driven by innate immune cells (4). Due to the close connection with the intestine via the portal circulation, the liver is constantly exposed to assorted gut-derived microbial particles identified as pathogen-associated molecular patterns (PAMPs), which activate resident immune cells. In addition to the intestinal- or virus-derived PAMPs, hepatic innate immune cells are also activated by damage-associated molecular patterns (DAMPs), which are released from injured parenchymal and nonparenchymal cells (5). Both PAMPs and DAMPs bind to pattern-recognition receptors, such as Toll-like receptors (TLRs), or intracellular receptors, such as inflammasome sensors [nucleotide-binding domain, leucine-rich repeat containing receptors (NLRs); absent in melanoma 2 (AIM2); and pyrin] for initiation of the inflammatory responses (6).

The role of TLRs in liver disease has been extensively described (7). In this review, we focus first on the circuitry of inflammasomes and then describe the role of inflammasomes in the pathogenesis of relevant liver diseases.

2. INFLAMMASOME COMPLEXES AND SIGNALS FOR ACTIVATION

The activation of inflammasome sensors by DAMPs and PAMPs gives rise to assembly of an intracellular multiprotein complex with the effector protein caspase-1 that leads to secretion of cytokines such as interleukin (IL)-1β and IL-18 and to the processing of the pyroptotic protein gasdermin D (GSDMD). In most cases, procaspase-1 binds to the inflammasome sensors through an adapter protein named apoptosis-associated speck-like protein containing a CARD (ASC) (8).

NLRs are the most described family of inflammasome sensor proteins. NLRs have three distinct domains: (*a*) the C-terminal domain, which contains a sequence of leucine-rich repeats (LRRs) important for ligand binding; (*b*) a central nucleotide-binding domain (NBD), also known as NACHT, which is crucial for sensor oligomerization; and (*c*) a variable N-terminal domain that contains a pyrin domain (PYD), a caspase recruitment domain (CARD), or a baculovirus inhibitory repeat domain, which interacts with downstream signaling proteins (6, 9). NLRs are distributed in two families according to their N-terminal domain: (*a*) a nucleotide-binding oligomerization domain (NOD)-like receptor family, pyrin domain (NLRP) if the N-terminal domain holds a PYD domain or (*b*) a NOD-like receptor family, CARD domain (NLRC) if the N-terminal domain holds a CARD domain (9). There are 22 genes in humans and 34 genes in mice that encode NLRPs, but only NLRP1, NLRP3, NLRP6, NLRP12, NLRP9b, and NLRC4 have been described to form inflammasome complexes (10, 11).

In addition to the NLRs, other inflammasome sensor proteins contain a PYD domain, such as AIM2, interferon-inducible protein 16 (IFI16), or pyrin (8, 12). In liver diseases, the canonical inflammasomes of the NLR family, NLRP1, NLRP3, NLRP6, and NLRC4, as well as AIM2 are well known to be involved in disease pathogenesis (6, 13).

Recently, the role of noncanonical inflammasomes, which culminate in caspase-11 activation, was also reported in liver diseases (14). The signal for activation of each of these inflammasomes and their role in different liver diseases is detailed in this review (Figure 1).

2.1. NLRP3

The NLRP3 inflammasome (also named cryopyrin) is the most described member of the NLR family and has been widely studied in liver disease (15). In the liver, NLRP3 is highly expressed in macrophages and monocytes, but hepatocytes and stellate cells express NLRP3 in lower levels (16–18). Usually, NLRP3 is activated in a two-step process by an extensive array of diverse stimuli. In the first step, also known as priming, PAMPs bind to TLR and activate the transcription factor nuclear factor κB (NF-κB), culminating in the transcription of NLRP3 and the precursors proIL-1β and pro-IL-18. In a second step, a diversity of stimuli including uric acid crystals, cholesterol crystals, and extracellular ATP induce an intracellular event [for example, increase of reactive oxygen species (ROS), lysosomal destabilization, calcium influx, potassium efflux, or oxidized mitochondrial DNA] for the activation and oligomerization of NLRP3 (6). Among the intracellular mechanisms that induce NLRP3 oligomerization, potassium efflux is considered the mechanism common to all NLRP3 ligands (8). After oligomerization, the adaptor protein ASC is recruited to NLRP3 through the interaction of their PYD domains. Thus, ASC starts its polymerization and further forms a macromolecular structure called ASC specks. Finally, procaspase-1 binds to the CARD domain of ASC and induces the proximity-induced autoprocessing that results in the formation of the catalytically active caspase-1 for IL-1β, IL-18, and GSDMD processing (19).

The serine/threonine kinase NIMA-related kinase 7 (NEK7) has recently been shown to be involved in NLRP3 inflammasome activation. The N-terminal (catalytic) domain of NEK7 directly interacts with the C-terminal (LRR) domain of NLRP3 and controls its oligomerization upon potassium efflux signaling (8, 20). Another protein related to interaction with NLRP3 is thioredoxin-interacting protein (TXNIP). TXNIP is an oxidative sensor that in homeostasis interacts with thioredoxin. Upon ROS stimulation, TXNIP is released and interacts with NLRP3 to promote its activation (6, 21).

2.2. NLRP6

The NLRP6 inflammasome sensor protein is highly expressed by cells of the immune system, such as neutrophils and T cells. In addition, NLRP6 is detected in tissues such as lung and liver and is abundantly expressed in intestines (6, 22).

The mechanism of NLRP6 activation depends on two steps, as observed for the NLRP3 inflammasome. The first step that induces NLRP6 transcription is mediated mainly by peroxisome proliferator-activated receptor-gamma (PPARγ) (23). In addition, tumor necrosis factor alpha (TNF-α) has also been shown to induce NLRP6 transcription via PPARγ (24). The second step involves NLRP6 assembly; ASC recruitment for caspase-1 activation, depending on the stimulus, also can induce caspase-11 activation (22, 25).

Besides activating caspase-1 and caspase-11, numerous reports demonstrate that the NLRP6 inflammasome can activate NF-κB signaling to promote inflammation. However,

other reports demonstrate that the NLRP6 inflammasome inhibits NF-κB, exerting anti-inflammatory functions (22). The role of NLRP6 in the liver is yet to be fully explored.

2.3. NAIP–NLRC4

The NLRC4 inflammasome sensor contains a C-terminal (LRR) domain, a central nucleotide-binding domain, and a CARD domain at its N terminus that interacts directly with the CARD domain of procaspase-1, giving rise to an NLRC4 inflammasome complex independent of the adaptor protein ASC. In normal conditions, NLRC4 is in its inactive conformation by stereo-chemical blocking of the NBD by the LRR domain (11).

The mouse NLRC4 inflammasome detects multiple ligands and requires different NLR family apoptosis inhibitory proteins (NAIPs) for this recognition (8). Upon ligand stimulation [for example, the type three secretion system (T3SS) needle protein to NAIP1, T3SS rod protein to NAIP2, and flagellin to NAIP5 and NAIP6], NAIPs bind to NLRC4, favoring its oligomerization for caspase-1 activation and further IL-1β, IL-18, and GSDMD processing (8, 26).

2.4. AIM2

AIM2 is the most described member of the absent in melanoma-like receptor (ALR) family of proteins. It encompasses a C-terminal hematopoietic, interferon-inducible, and nuclear localization (HIN) domain for ligand binding and an N-terminal PYD domain that interacts with the adaptor molecule ASC to activate caspase-1 (27).

AIM2 differs from NLRPs in terms of interaction with the ligand. AIM2 directly recognizes its ligand, double-stranded DNA (dsDNA), derived from a bacterial, viral, or mammalian host, to induce its oligomerization. The dsDNA sequence seems not to influence ligand binding; however, AIM2 recognizes only dsDNA of a minimum length of 80 bp (11). The HIN domain of AIM2 is composed of two folds of oligonucleotide/oligosaccharide binding, specifying its recognition of dsDNA instead of single-stranded DNA (27).

The mechanism of AIM2 activation has been described as involving a single step. In normal conditions, AIM2 is in an inactive conformation with its HIN-200 domain interacting with its PYD domain in a self-inhibited manner. Upon ligand binding, the PYD domain is released, which allows AIM2 to oligomerize and to recruit ASC through interaction with the PYD domains, for caspase-1 activation (11).

2.5. Other Inflammasome Complexes

NLRP1 was the first member of the NLR family described to form inflammasomes. Different from all NLR proteins, the NLRP1 sensor contains a function-to-find domain (FIIND) and a CARD in addition to a PYD, an NBD, and an LRR domain. Murine NLRPs lack the PYD domain, enabling the induction of inflammasome formation in the absence of ASC. Murine NLRP1 also has various paralogues (Nlrp1a, -b, and -c), and NLRP1b has been described as activated by lethal toxin derived from *Bacillus anthracis* and by *Toxoplasma gondii* (10, 11). Upon ligand binding, the FIIND domain of NLRP1 undergoes autoproteolysis and results in procaspase-1 recruitment (11).

NLRP12 was the first described member of the NLR protein family and is highly expressed by macrophages and neutrophils (28). The role of NLRP12 in inflammasome formation and IL-1β and IL-18 release was described in infections caused by *Yersinia pestis* and *Plasmodium chabaudi* (29, 30). However, NLRP12 can also negatively regulate the NF-κB signaling pathway by interacting with NF-κB inducing kinase, promoting its degradation (31).

2.6. Noncanonical Inflammasome Complexes

The noncanonical inflammasome pathway has been recently demonstrated and involves caspase-4 and caspase-5 (humans) and caspase-11 (mice) as sensor and effector proteins (32). Caspase-11 directly recognizes intracellular lipopolysaccharide (LPS) through its CARD domain, eliciting its dimerization and activation, which culminates in the cleavage of GSDMD (33).

The noncanonical inflammasome (caspase-11) cannot cleave pro-IL-1β and IL-18 directly, but through pyroptosis it can activate the NLRP3 inflammasome, in a process termed noncanonical NLRP3 inflammasome activation, inducing the cleavage and release of IL-1β and IL-18 (32). One possible mechanism by which caspase-11 induces NLRP3 activation is that caspase-11 cleaves pannexin-1, which leads to potassium efflux and subsequent NLRP3 activation (34).

Recently, it has been shown that ligands other than those derived from gram-negative bacteria bind to caspase-11 as well, such as endogenous oxidized phospholipids and *Aspergillus fumigatus* (35).

3. THE INFLAMMASOME IN LIVER DISEASES

3.1. NAFLD/NASH

NAFLD is the most common chronic liver disease, affecting approximately 20–30% of the world population. NAFLD is usually associated with metabolic syndrome, which includes obesity, type 2 diabetes mellitus (T2DM), and hyperlipidemia (36). The clinical spectrum of NAFLD ranges from steatosis to NASH with or without fibrosis and, over time, progresses to cirrhosis. NASH also increases the risk of hepatocellular carcinoma even in the absence of cirrhosis (37). NASH is characterized by hepatocellular damage in addition to liver and systemic inflammation (38). Several reports point to the multiple-hit hypothesis for the development of NAFLD. The first hit is caused by exacerbated fat intake, increased influx of free fatty acids in the liver, and insulin resistance that leads to excessive saturated fatty acid (ceramide and palmitate) and triglyceride (TG) accumulation in hepatocytes. This event predisposes the liver to hepatocellular damage caused by a second hit, which includes dysfunction of mitochondria that leads to excess production of ROS (36). In animal models, the most common ways to induce NASH are through a prolonged high-fat diet (HFD), a high-fat/high-cholesterol/high-sugar diet, or a methionine/choline-deficient (MCD) diet (39, 40).

The association between NLRP3 inflammasome activation, metabolic syndrome, and insulin resistance has been observed in patients with T2DM who expressed elevated levels of

NLRP3, *IL-1β*, and *ASC* mRNA in peripheral blood monocytes as well as increased levels of IL-1β and IL-18 in serum compared with healthy controls (6, 41). In addition, an increase in mRNA levels of NLRP3 inflammasome components was also observed in the livers and abdominal fat of obese humans and mice. This increase was ameliorated after weight loss (42).

In the past decade, several reports demonstrated an association between the NLRP3 inflammasome and NAFLD pathogenesis. In livers of NAFLD patients, mRNA levels of *NLRP3*, *IL-1*β, *IL-18*, and procaspase-1 are remarkably increased compared with those of healthy controls (43). In addition, in livers of NASH patients, an increase in mRNA levels of inflammasome components (NLRP3, ASC, caspase-1, and pannexin) as well as IL-1β and IL-18 protein was observed (17, 44). Furthermore, elevated activity of caspase-1 and high levels of IL-1β were detected in the liver and serum of NASH patients compared with those of healthy controls (17, 45).

Experimentally, our group showed that in animals with only steatosis (early NAFLD), increases in NLRP3 inflammasome components in the liver were observed only at mRNA levels and not at protein levels. However, after NASH establishment as characterized by an increase of immune cell infiltrates in the hepatic tissue, increased mRNA and protein levels of NLRP3 inflammasome components (caspase-1 activity and IL-1β protein) were observed in the liver and serum compared with those of the control mice (17). The role of the NLRP3 inflammasome in NASH pathogenesis was further demonstrated in mice lacking NLRP3, ASC, and caspase 1–inflammasome components. HFD-induced hepatocyte death, inflammation, and liver fibrosis were attenuated in these inflammasome-component-deficient mice (44, 46, 47).

In NASH, it has been demonstrated that both liver immune cells and parenchymal cells participate in the NLRP3 inflammasome activation. Pan and colleagues (48) demonstrated that Kupffer cells from mice fed an MCD diet produce high amounts of IL-1β, which is dependent on NLRP3 activation by mitochondrial DNA released after stimulation with palmitic acid. Palmitic acid also binds to TLR2, and TLR2-deficient mice fed a choline-deficient amino-acid-defined diet showed decreased hepatic caspase-1 activation and lower serum levels of IL-1α and IL-1β (49). Furthermore, Csak et al. (17) demonstrated that palmitic acid augmented caspase-1 activation and IL-1β release induced by LPS in hepatocytes.

Although the molecules involved in the activation of inflammation in NASH are not well established, a few ligands other than palmitic acid through TLR2 have been described to be involved in this process (Figure 2). The participation of extracellular ATP in inflammasome activation in NASH was demonstrated in mice deficient in its cell membrane receptor, the purinergic 2X7 receptor (P2X7R). The deficiency of P2X7R protects mice from MCD- or HFD-induced liver damage that was linked to a decrease in NLRP3 inflammasome activation in liver sinusoidal endothelial cells (50, 51). Furthermore, P2X7 protein levels were increased in liver biopsies from patients with NASH, mainly detected in infiltrated macrophages and Kupffer cells, compared with those of the healthy controls. The high levels of P2X7 detected in NASH livers correlated with an increase in inflammation and

inflammasome activation (52). In addition, bile acids were also demonstrated to modulate inflammasome signaling through interaction with their surface receptor, TGR5, or their nuclear receptor, farnesoid X receptor (FXR). In livers of NASH mice and humans, the expression of TGR5 was diminished compared with that in controls and correlated to increased NLRP3 inflammasome activation, contributing to NASH progression (39). In accordance with this work, the deficiency of the bile acids nuclear receptor, FXR, in diet-induced NASH mice increased NLRP3 activation in livers (53).

In addition to the ligands responsible for inflammasome activation in NASH, the molecular mechanisms and intracellular processes that contribute to or interfere in the activation of NLRP3 have also received considerable attention in liver disease research. In the livers of NASH mice, the expression of the transcription factor hypoxia-inducible factor 1-alpha (HIF-1α) is elevated, and it has been demonstrated that HIF-1α induces inflammasome activation by increasing *pro-Il-1*β mRNA in diverse cell types (54, 55). Indeed, in NASH, HIF-1α is increased in macrophages induced by palmitic acid, which impairs autophagic flux and increases IL-1β production. The stabilization of HIF-1α in macrophages in vivo using $LysM^{Cre}$-$HIFdPA^{fl/fl}$ mice worsened the liver damage induced by an MCD diet compared with $HIFdPA^{fl/fl}$ mice (56). Autophagic flux impairment also increases ROS production by mitochondrial dysfunction, which is a trigger for NLRP3 inflammasome activation (57). In addition, the pharmacological increase of the autophagic flux by ezetimibe in MCD-fed mice attenuates steatosis and NLRP3 inflammasome activation in the liver (58, 59). Recently, the role of mitophagy, a physiological process in which defective mitochondria are degraded by autophagy, in NLRP3 inflammasome activation in NASH has been reported. In this work, the authors demonstrated that excessive accumulation of free fatty acids in the livers of mice fed a high-fat/calorie diet (HFCD) induced mitochondrial damage and impairment mitophagy that led to ROS production and NLRP3 activation (60). In addition, the role of endoplasmic reticulum stress in NLRP3 inflammasome activation has been demonstrated in NASH, correlated with nuclear receptor FXR deficiency (53).

Cathepsin B has been reported to activate NLRP3, and the suppression of cathepsin B activity by the cathepsin inhibitor CA-074 in a mouse model of NASH induced by an MCD diet decreased liver damage and hepatic caspase-1 activity and reduced serum levels of IL-1β and IL-18 (61). In Kupffer cells from NASH mice, the interaction of the TXNIP protein with the NLRP3 inflammasome was increased. In addition, mice deficient in TXNIP developed more steatosis and liver inflammation on an MCD diet, demonstrating a protective role for TXNIP in NASH (62).

Contrary to the proinflammatory effect shown for NLRP3 in NASH, Henao-Mejia et al. (63) demonstrated that feeding mice deficient in NLRP3 an HFD intensified the pathogenesis of NASH due to amplified bacteremia. In the liver of NASH mice, the NLRP3 inflammasome is activated, in contrast to activation in the gut, and the expression of NLRP3 inflammasome components is attenuated, demonstrating a protective role for NLRP3 in gut dysbiosis in NASH (13).

The highest levels of NLRP6 are expressed in the intestinal cells. Similar to what was observed in NLRP3-deficient mice, mice lacking NLRP6 also present with worse features of

NASH when administered an MCD diet, compared with wild-type (WT) mice. This result is due to alteration of the intestinal microbiota and an increase in microbial transport to the liver, advancing steatohepatitis (63). In vitro, the treatment of hepatocytes with palmitic acid or LPS increases the mRNA levels of *Nlrp6* as well as *Nlrp10*. However, the hepatic-specific role of NLRP6 in NAFLD/NASH deserves more attention (33, 64).

The role of NLRP1 in metabolic syndrome has been shown to be protective. NLRP1-deficient mice have increased amounts of adipose tissue under a normal diet, and the amount of adipose tissue was intensified by administration of an HFD. This effect on adiposity correlated with low levels of IL-18 (65). In a model of NASH in which mice were fed an HFCD together with drinking water containing high fructose and glucose, NLRP1 levels were elevated in hepatocytes, stellate cells, and Kupffer cells, together with increases in IL-1β and IL-18 protein levels, compared with control mice (60, 66). Whether NLRP1 has a protective or detrimental role in NASH itself is yet to be determined.

The role of the NLRC4 inflammasome in NAFLD has been indicated in vitro using hepatocytes treated with palmitic acid. It was observed that palmitic acid increased the secretion of IL-18, IL-1β, and TNF-α dependent on NLRC4, a mechanism regulated by TNF-α (67). In addition, the pathogenic role of NLRC4 in NAFLD was confirmed in vivo in mice lacking NLRC4, in which the M2 polarization of tumor-associated macrophages and IL-1β production was attenuated in NLRC4-deficient mice after 6 weeks of an HFD followed by an injection of MC38 cancer cells to form a tumor (68).

The role of AIM2 in NAFLD/NASH has also been addressed. MCD-diet-induced steatohepatitis increased the hepatic expression of AIM2 dependent on TLR/MyD88 signaling both in hepatocytes and macrophages (69, 70). In accordance with this work, increased levels of hepatic AIM2 were also observed in a NASH model induced by prolonged feeding of an HFD (70, 71). However, AIM2-deficient mice fed a chow diet presented with increased body weight, insulin resistance, and increased inflammation in adipose tissue in comparison with WT mice (72).

3.2. Alcohol-Associated Liver Disease

Excessive alcohol consumption (heavy alcohol intake and binge drinking) represents a risk for developing ALD (73). ALD is characterized by a spectrum of conditions quite similar to NAFLD, ranging from steatosis to steatohepatitis/fibrosis and, over time, cirrhosis that could progress to hepatocellular carcinoma. However, as opposed to patients with NAFLD, in patients with ALD, AH can arise at any stage of the disease (3). The ALD pathogenesis involves the activation of a proinflammatory cascade both in the liver and systemically. In the liver, PAMPs derived from the intestine and DAMPs derived from damaged hepatocytes induce a proinflammatory cascade that involves activation of inflammasomes (74) (Figure 3). Increased levels of IL-1β, IL-18, and caspase-1 were found in the livers of patients with ALD, compared with those of healthy individuals (75). In addition, severe AH patients have significantly elevated levels of serum IL-1β, demonstrating a role for inflammasomes in ALD (76). Protein levels of NLRP3 and IL-1β as well as caspase-1 activity were significantly enhanced in livers of alcohol-fed mice, in accordance with those of human ALD patients (16). Mice deficient in the inflammasome components NLRP3, caspase-1,

or ASC presented less steatosis and liver damage (hepatic inflammation) compared with WT mice on an alcohol diet (16, 77). In addition, IL-1R1-knockout mice were protected from ALD (16). In chronic alcohol–fed mice, liver macrophages (Kupffer cells) play the major role in the activation of the NLRP3 inflammasome in ALD, demonstrated by the high expression of inflammasome components in immune cells compared with parenchymal cells and also by the deficiency of caspase-1 in immune cells that decreased inflammasome activation in alcohol-fed mice (16). Likewise, Cui et al. (78) demonstrated an upregulation of inflammasome components (ASC and NLRP3) as well as IL-1β protein in Kupffer cells of ethanol-fed mice.

Our group demonstrated that signals for NLRP3 inflammasome activation in ALD involve a well-known priming signal in the form of gut-derived LPS translocated to liver as a result of leaky gut and a second signal for inflammasome assembly in the form of extracellular ATP and uric acid, released by the ethanol-damaged hepatocytes (16, 77). Mice deficient in the ATP receptor P2X7R had abolished alcohol-induced inflammasome activation in the livers compared with those of control mice (79). High circulating levels of uric acid have been detected in individuals exposed to alcohol (77, 80).

Furthermore, few studies have addressed an intracellular mechanism involved in the activation of the NLRP3 inflammasome in ALD. In a mouse model of ALD, the mRNA and protein levels of the NLRP3 binding protein TXNIP were elevated in the livers compared with those of controls. The elevated levels of TXNIP observed in mice were linked to a decrease in the expression of microRNA 148a (miR-148a) mediated by FoxO1, as demonstrated in ethanol-fed mice. The treatment of ethanol-fed mice with a liver-specific miR-148a lentivirus decreased TXNIP and IL-1β protein levels as well as steatosis and liver damage (81). The exposure of human peripheral blood mononuclear cells or mouse macrophages to chronic ethanol induced a mitochondrial ROS release, which resulted in NLRP3 inflammasome activation (82).

The spleen tyrosine kinase (SYK) regulates inflammasome activation through phosphorylation of ASC (8). Levels of activated SYK were elevated in the livers of alcohol-fed mice and in liver biopsies of ALD/AH patients compared with those of controls. The inhibition of SYK in alcohol-fed mice remarkably decreased the serum levels of IL-1β and caspase-1 activation in the liver (83).

A protective role for NLRP6 in ALD was recently revealed. The expression of the NLRP6 protein was downregulated in livers of alcohol-fed mice and correlated with increased activation of NF-κB. The overexpression of NLRP6 in alcohol-fed mice decreased the expression of CCL20 induced by alcohol and decreased the activation of hepatic stellate cells (HSCs) (84). Besides NLRP6, the mRNA levels of *Naip1*, *Nlrc3*, *Nlrp10*, and *Nlrp14* were reduced in the livers of alcohol-fed mice (84). A protective role for NLRP12 has been reported in ALD. High levels of NLRP12 were found in liver tissues of ethanol-fed mice, ethanol-stimulated RAW264.7 cells, and primary Kupffer cells. Overexpression of NLRP12 in alcohol-fed mice reduced steatosis and liver inflammation (85).

3.3. Liver Fibrosis

Fibrosis is associated with most chronic liver diseases and is characterized by the accumulation of extracellular matrix proteins. Fibrosis in its advanced form contributes to organ failure (86). The inflammasomes contribute to fibrosis in a direct manner, by the presence of inflammasome components in the major cells responsible for liver fibrosis (i.e., HSCs) or in an indirect manner, induced by inflammasome activation in other cells.

Human and mouse-derived HSCs can be activated by uric acid crystals, increasing the expression of transforming growth factor (TGF)-β1 for collagen production dependent on the ASC adaptor protein (87). In addition, the role of extracellular ATP through P2X7R in HSC activation has been reported (88).

In mouse models of liver fibrosis, Kupffer cells highly express NLRP3, NLRP1, and AIM2 compared with HSCs (18). In addition, in a fibrosis model induced by carbon tetrachloride, the hepatic expression of TGF-β1 and collagen-1α1 was significantly attenuated in mice deficient in the inflammasome proteins NLRP3 or ASC (89). Recently, the expression of constitutively active NLRP3 in HSCs in vivo revealed that mice on a normal chow diet spontaneously developed liver fibrosis, as observed by an increase in the fibrotic marker αSMA in the liver (90).

Several reports also showed the role of the NLRP3 inflammasome in fibrosis induced by NASH. In NLRP3 knock-in mice, HSCs are activated (44) and the inhibition of the NLRP3 inflammasome in NASH also significantly reduced fibrosis and reduced liver inflammation (91). Furthermore, NLRP3 inflammasome components derived from pyroptotic hepatocytes induced HSC activation, advancing fibrosis in NASH (45).

Other inflammasome sensors have been reported in liver fibrosis. In fibrotic and cirrhotic livers, NLRP6 expression was diminished compared with healthy controls. In addition, NLRP6 overexpression in an HSC cell line, LX-2, decreased the accumulation of collagen and αSMA, and the opposite effects were observed in LX-2 cells deficient in NLRP6 (92). An increase in AIM2 protein expression, as well as IL-1β, IL-18, and active caspase-1, has been observed in ascitic fluid macrophages of cirrhotic patients in comparison with blood monocytes (93).

4. OUTCOMES (EFFECTS) OF INFLAMMASOME ACTIVATIONIN LIVER DISEASES

The activation of caspase-1 by the canonical inflammasomes elicits the cleavage of the immature proteins pro-IL-1β and pro-IL-18 into their active forms as well as the cleavage of GSDMD for pyroptosis initiation (33). Activation of noncanonical inflammasomes (caspase-11) culminate in a direct activation of GSDMD and a secondary activation of the canonical inflammasome (32).

4.1. IL-1β Effects

The major effects of inflammasome activation in liver diseases are related to the role of IL-1β in inducing and contributing to liver disease progression (94). IL-1β binds

to its receptor IL-1R1, and the receptor undergoes a structural modification, allowing an interaction with the coreceptor IL-1R3. This interaction triggers NF-κB and mitogen-activated protein kinase signaling pathways, culminating in the production of inflammatory cytokines (TNF-α), chemokines (CCL2), and inflammasome components, such as pro-IL-1β and NLRP3 (95, 96). The IL-1 receptor antagonist protein (IL-1RA) is an endogenous regulator of IL-1β effects that competes for the same receptor (IL-1R1) by blocking its signaling (6, 96).

In the liver, pro-IL-1β mRNA and protein are highly expressed in immune cells compared with the parenchymal cells. After an alcohol challenge, the liver's immune cells increase the expression of IL-1β. In addition, IL-1R1-deficient mice fed an ethanol diet had reduced accumulation of liver TGs, inflammation, and fibrosis in comparison with WT mice (16, 17). In ALD, the effect of macrophage-derived IL-1β has been demonstrated to induce liver damage and increases recruitment of neutrophils (78). In mice with AH, IL-1β also inhibits liver regeneration driven by cessation of alcohol consumption (97). In ALD patients, the hepatic and circulating levels of IL-1β are augmented compared with healthy controls (75) (Figure 3).

In the context of NASH, in a mouse model induced by an atherogenic diet, IL-1β-deficient mice showed reduced liver inflammation and fibrosis compared with WT mice (98). Recently, it has been demonstrated that the release of mitochondrial DNA activates NLRP3 and induces IL-1β released by Kupffer cells in NASH (48). In addition, IL-1R1-knockout mice had attenuated HFD-induced steatosis, inflammation, and fibrosis (99). In hepatocytes, IL-1β also promotes cholesterol and TG accumulation (94) (Figure 2).

In vitro experiments showed that IL-1β can directly activate HSCs, inducing their proliferation and transdifferentiation into myofibroblasts, with an increase in fibrotic markers such as collagen and TGF-β (100). The constitutive activation of NLRP3 in myeloid-derived cells induces IL-1β, which increases hepatic levels of IL-17 and TNF-α, liver injury, and fibrosis. In addition, the absence of TNF-α reduced fibrosis in these mice, which was observed as less deposition of collagen in the liver (101). IL-1 also inhibits liver regeneration.

4.2. IL-18 Effects

The effects described for IL-18 in liver diseases were anti-inflammatory or proinflammatory, depending on the stimulus. IL-18 binds to its receptor IL-18Rα (IL-1R5) with low affinity. However, when the coreceptor IL-18Rβ (IL-1R7) is expressed on cells, a high-affinity complex is formed, triggering downstream signaling similar to IL-1R1. IL-18-binding protein (IL-18BP) is a soluble protein that binds to IL-18 and prevents its interaction with IL-18Rα (96). IL-18 is expressed in its immature form (pro-IL-18) and requires proteolytic cleavage by caspase-1 to be activated. In addition, in a different manner than IL-1β, the IL-18 precursor is constitutively expressed by myeloid cells (blood monocytes and peritoneal macrophages) and epithelial cells (for example, the keratinocytes and Paneth cells) (102).

The circulating levels of IL-18 are increased extensively in T2DM patients and in children with high body mass index (BMI), compared with healthy controls with low BMI, and positively correlate with steatosis (103). In addition, in patients with AH, the circulating levels of IL-18 are increased and correlate with liver damage (104).

In experimental NAFLD induced by an HFD, mice deficient in IL-18 showed increased body weight and altered glucose and lipid metabolism, resulting in insulin resistance and steatosis compared with their WT littermates. The metabolic alterations observed in IL-18-knockout mice under an HFD were reverted by administration of IL-18 recombinant protein, demonstrating a protective role for IL-18 in NAFLD (105) (Figure 2).

In the context of ALD, the circulating levels of IL-18 are increased in mice exposed to intragastric administration of alcohol plus an HFD (14). The effects described for IL-18 in mice exposed to alcohol were anti-inflammatory or proinflammatory, depending on the affected organ. Similarly, as observed in NAFLD, IL-18-deficient mice fed an alcohol diet presented with worse liver outcomes compared with WT controls, as observed by augmented hepatocyte damage and hepatic neutrophil recruitment (14). In contrast, in the small intestine of WT mice exposed to an alcohol diet, the amplified production of IL-18 led to increased gut permeability (106) (Figure 3).

4.3. IL-37 Effects

IL-37 is another cytokine that is cleaved by caspase-1 to increase its biological activity. IL-37 is present only in human cells, and its overexpression in mice was paramount to understanding its function as an anti-inflammatory cytokine (107). The precursor of IL-37 is induced by triggering of the NF-κB signaling pathway by an inflammatory stimulus. IL-37 is secreted from cells in its immature and mature forms and exerts its extracellular effect by signaling through a complex formed by the IL-18Rα receptor and the IL-1R8 coreceptor. IL-37 can also exert anti-inflammatory functions intracellularly after its translocation to the nucleus, to decrease the expression of proinflammatory cytokines and chemokines. High amounts of extracellular IL-37 homodimerize and interact with IL-18BP, blocking the anti-inflammatory activity of both molecules (108).

In patients with alcoholic steatohepatitis (ASH), the detected levels of hepatic *IL-37* mRNA were lower compared with those of patients with NAFLD (109). In addition, the levels of *IL-37* mRNA in the adipose tissue of healthy individuals were higher compared with the *IL-1β* levels, which correlated with a less inflammatory adipose tissue environment under normal conditions (110). Transgenic mice overexpressing human IL-37 (IL-37tg) were used to address the role of IL-37 in ALD, obesity, and fibrosis. IL-37tg mice exposed to 16 weeks of an HFD exhibited less weight gain, lower hepatic TG levels, and less adipose tissue inflammation compared with WT mice (110). However, IL-37tg mice exposed to a chronic ethanol diet showed similar hepatic injury in comparison with ethanol-fed WT mice. In an acute model of ALD, induced by one dose of an alcohol binge, the administration of human IL-37 recombinant protein to WT mice decreased liver inflammation (109) (Figures 2 and 3).

In a fibrotic model induced by CCl4, IL-37tg mice exhibited lower hepatic levels of TGF-β and IL-6 compared with WT mice (111).

4.4. Pyroptosis

Pyroptosis is a programmed type of cell death induced by canonical or noncanonical inflammasomes, morphologically represented by cell swelling and subsequent lysis that culminate in the release of intracellular content (8, 10). Pyroptosis is activated by proinflammatory caspase-1 and caspase-11 through GSDMD cleavage. GSDMD contains a pyroptotic N-terminal domain (GSDMD-N) associated to a C-terminal regulatory domain (GSDMD-C) by a linker domain. Inflammatory caspases (caspase-1, caspase-4, and caspase-5) cleave the linker domain of GSDMD, liberating the GSDMD-N from its autoinhibitory GSDMD-C. While GSDMD-C remains in the cytosol, GSDMD-N has a high affinity to membrane lipids, in which it oligomerizes to form pores of approximately 20 nm, thereby promoting cell swelling and lysis (112).

Recently, the role of GSDMD-mediated pyroptosis has been demonstrated in NASH pathogenesis. In a mouse model of NASH induced by an MCD diet, steatosis, inflammation, and fibrosis were significantly ameliorated in GSDMD-knockout mice compared with WT controls. Furthermore, high protein levels of total and cleaved GSDMD protein were detected in livers of NASH patients, compared with those of NAFLD patients and healthy controls (113) (Figure 2).

In a study of ALD, Khanova et al. (14) demonstrated that cleaved GSDMD is present in hepatic macrophages and hepatocytes of ethanol-fed mice. The expression of cleaved GSDMD in hepatocytes in naive mice promotes steatohepatitis and hepatic damage. In this work, the authors correlated GSDMD activation and pyroptosis with the noncanonical inflammasome by the activation of caspase-11. However, pyroptosis in hepatocytes in another ALD mouse model has been linked to NLRP3 inflammasome activation (81) (Figure 3).

5. THE INFLAMMASOME AS A THERAPEUTIC TARGET

Due to the lack of therapy recognized by the US Food and Drug Administration (FDA) for chronic liver diseases such as NASH and ASH and the low effectiveness of the few treatments to avoid the risk factors, there is a great demand for the effective treatment of these chronic diseases. The growing evidence for the role of the inflammasome, in particular NLRP3, in the pathogenesis of ASH and NASH suggests the relevance of therapies that target inflammasome complex activation as well as signaling involved in the effects of IL-1β and/or IL-18.

FDA-approved therapies that target IL-1R signaling, such as anakinra (an IL-1R antagonist) and canakinumab (an IL-1β-targeting monoclonal antibody), have been described to be effective in the treatment of autoinflammatory diseases such as Muckle-Wells syndrome and adult-onset Still’s disease.

Anakinra showed beneficial effects when tested in experimental ALD. Treatment of ethanol-fed mice with anakinra for 2 weeks, after 2 weeks of established ALD, remarkably attenuated liver injury, inflammation, and steatosis, in addition to reducing neutrophil hepatic infiltration, compared with the vehicle-treated ethanol-fed mice (77). In order to address whether anakinra promotes hepatocyte regeneration in AH, the IL-1R antagonist was given to mice after an acute-on-chronic established liver injury, when the alcohol diet was replaced with a control diet. In this model, anakinra successfully decreased liver inflammation and neutrophil infiltration and also increased hepatocyte regeneration (97). Due to the effectiveness of anakinra in the treatment of experimental ALD, a phase 2 clinical trial using anakinra in combination with zinc and pentoxifylline compared with the standard methylprednisolone therapy is in progress (ClinicalTrials.gov, AH/NCT01809132). In this clinical trial, anakinra did not improve the 30-day survival rates. Nevertheless, a tendency toward improved survival was observed at 3 and 6 months (74). Anakinra was also clinically tested in T2DM patients, and the treatment improved insulin sensitivity and overall inflammation as compared with placebo-treated patients (114).

In an experimental model of liver fibrosis, anakinra administration in mice subjected to CCl4 injections also attenuated liver damage and fibrosis, as observed by a decrease in the activation of HSCs and a lowering of the circulating levels of procollagen III (115).

In another study targeting IL-1R signaling, patients with T2DM were tested for canakinumab. This antibody-based intervention decreased the glycosylated hemoglobin (HbA1c) levels over the first year of treatment compared with placebo-treated patients (116). In addition, a clinical trial using an IL-1β antibody as a therapy for severe AH is in progress (ClinicalTrials.gov, AH/NCT03775109).

Targeting inflammasome components is another therapeutic approach, and some inhibitors have been developed to target the sensor NLRP3. The drug MCC950, an NLRP3 inhibitor, has been studied experimentally in different inflammatory disease models. MCC950 has been reported to effectively attenuate inflammation in autoimmune encephalomyelitis and spontaneous colitis. In NASH, the treatment of MCD-diet-fed mice with MCC950 attenuated hepatic inflammation, steatosis, and fibrosis yet decreased circulating and hepatic levels of IL-1β (91). In an ALD context, MCC950 has been administered to female and male mice to analyze voluntary alcohol consumption. It was reported that only female mice treated with MCC950 decreased alcohol intake compared with vehicle-treated mice, an effect not observed with male mice (117). The inhibition of caspase-1 using AC-YVAD-cmk in NASH pathogenesis was another approach targeting inflammasome components. Administration of AC-YVAD-cmk in obese mice deficient in the low-density lipoprotein receptor attenuated liver and adipose tissue inflammation (118).

The targeting of inflammation upstream from inflammasome complexes was reported for extracellular ATP and uric acid. The role of P2X7 in liver fibrosis has been reported in monkeys treated with the P2X7R pharmacological inhibitor SGM-1019 and submitted to CCl4 injections to induce liver fibrosis. The inhibition of P2X7 decreased the liver damage and fibrotic markers as well as collagen deposition in the liver of these nonhuman primates (52). In addition, rats treated with a uric acid synthesis inhibitor had decreased liver damage

and inflammation induced by an ethanol diet (119). Treatment of alcohol-fed mice with alopurinol, an inhibitor of an enzyme that synthesizes uric acid, or probenecid, which depletes uric acid, decreases alcohol-induced steatohepatitis and inflammasome activation in the liver (79). In addition, the treatment of MCD-diet-induced NASH mice with a bile acid synthetic variant, obeticholic acid, inhibited the NLRP3 inflammasome, leading to amelioration of liver inflammation and steatosis (120).

6. CONCLUSIONS

In conclusion, inflammasomes are essential components of the innate immune response that promote or protect the development of chronic liver diseases. Studies over the past decade have demonstrated that inflammasome activation is present in different types of acute and chronic liver diseases and have shown detailed roles for NLRP3 in the induction of proinflammatory (IL-1β and GSDMD-N) and anti-inflammatory (IL-18 and IL-37) effects in NASH and ALD. Furthermore, upstream triggers, activating mechanisms and cell-specific roles in inflammasome activation, have been extensively demonstrated for the NLRP3 inflammasome. Further exploration of other types of inflammasomes in acute and chronic liver diseases is keenly awaited. Given the central role of NLRP3 in steatohepatitis, its therapeutic targeting deserves attention.

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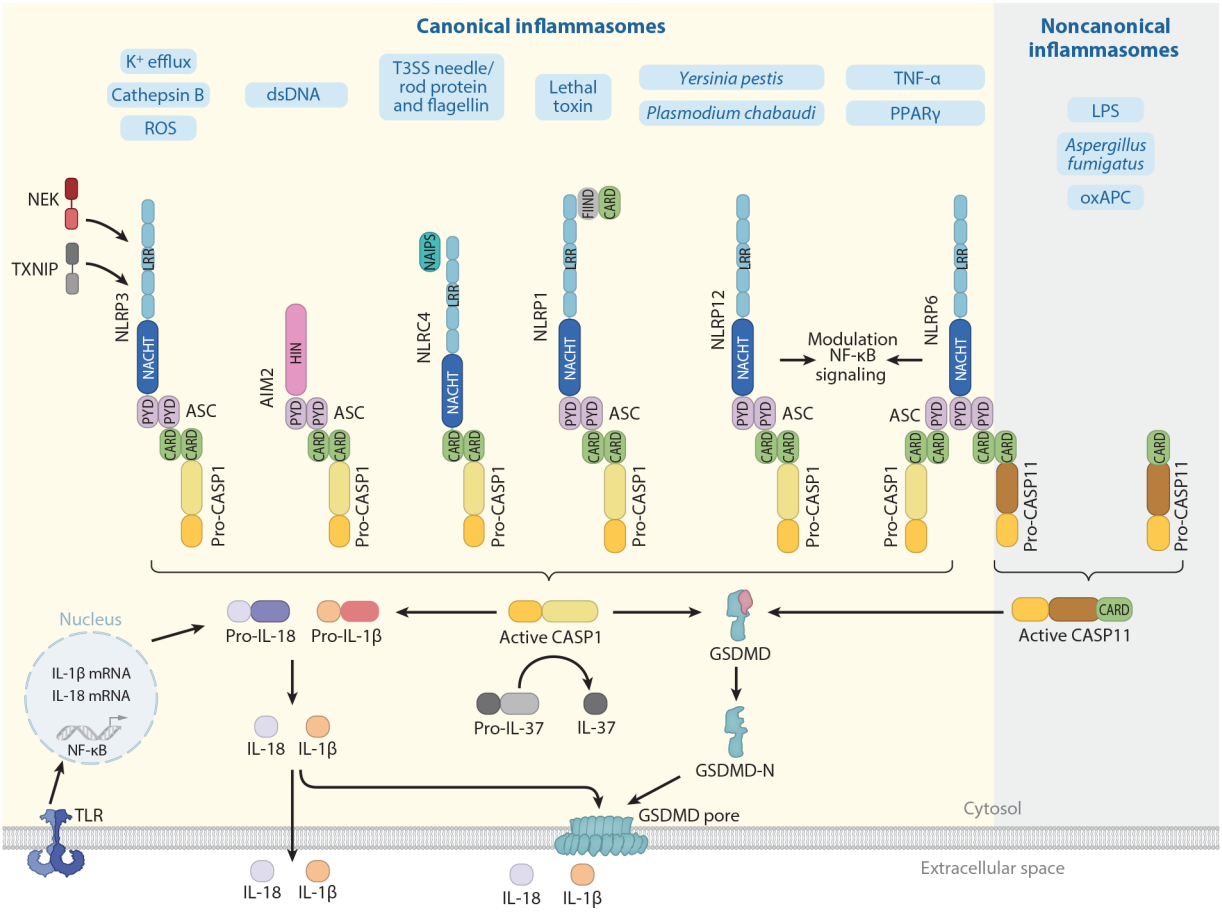

Figure 1.

Roles of the canonical and noncanonical inflammasomes. Activation of the canonical inflammasomes results in CASP1 activation. Members of the NLR family of receptors including NLRP3, NLRP1, NLRP6, and NLRP12 and the ALR family member AIM2, activate CASP1 in the presence of the adaptor protein ASC. NLRC4 activates CASP1 in the absence of ASC. The activation of CASP1 culminates in the cleavage of cytokine precursors pro-IL-1β, pro-IL-18, and pro-IL-37 into their mature forms IL-1β, IL-18, and IL-37. The noncanonical pathway culminates in CASP11 activation. NLRP6 also activates CASP11. CASP1 and CASP11 cleave the inactive protein GSDMD into the pyroptotic membrane pore protein GSDMD-N. Abbreviations: AIM2, absent in melanoma 2; ALR, absent in melanoma-like receptor; ASC, apoptosis-associated speck-like protein containing a CARD; CARD, caspase recruitment domain; CASP1, caspase-1; CASP11, caspase-11; dsDNA, double-stranded DNA; FIIND, function-to-find domain; GSDMD, gasdermin D; HIN, hematopoietic, interferon-inducible, and nuclear localization; IL, interleukin; LPS, lipopolysaccharide; LRR, leucine-rich repeats; NAIP, NLR family apoptosis inhibitory protein; NEK, NIMA-related kinase; NF-κB, nuclear factor κB; NLR, nucleotide-binding domain, leucine-rich repeat containing receptor; NLRC, NOD-like receptor family, CARD domain; NLRP, NOD-like receptor family, pyrin domain; oxAPC, oxidized phospholipid; PPARγ, peroxisome proliferator-activated receptor-gamma; PYD, pyrin domain; ROS, reactive oxygen species; T3SS, type three secretion system; TNF-α, tumor necrosis

factor alpha; TLR, Toll-like receptor; TXNIP, thioredoxin-interacting protein. Data from References 121, 122, and 123.

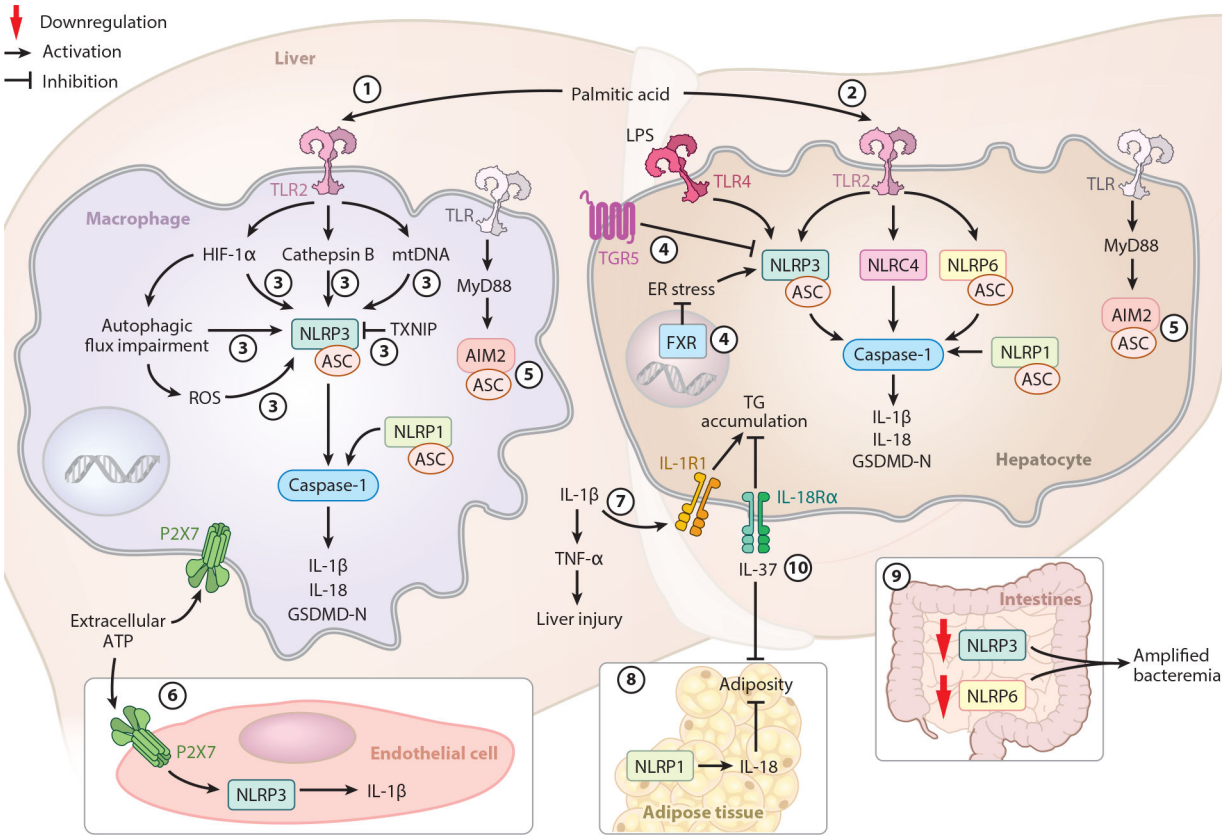

Figure 2.

Inflammasomes involved in NASH. Inflammasomes are activated in NASH in different organs. In the liver, palmitic acid triggers (①) the activation of NLRP3 in macrophages and (②) the activation of NLRP3, NLRC4, and NLRP6 in hepatocytes. (③) The intracellular mechanisms of NLRP3 activation in macrophages involve HIF-1α, cathepsin B, mtDNA, ROS, and impaired autophagic flux, and the NLRP3 negative regulator is TXNIP. (④) In hepatocytes, the bile acid receptors TGR5 and FXR inhibit NLRP3 activation. (⑤) AIM2 is activated in both macrophages and hepatocytes in a TLR/MyD88-dependent manner. The mechanism of NLRP1 activation in the liver is not well described. (⑥) Extracellular ATP contributes to IL-1β production by endothelial cells in an NLRP3-dependent manner. (⑦) IL-1β induces TG accumulation in hepatocytes and induces liver injury through TNF-α activation. (⑧) In adipocytes, NLRP1–mediated IL-18 production inhibits adiposity. (⑨) In intestines, downregulation of NLRP3 and NLRP6 amplifies bacteremia. (⑩) IL-37 decreases steatosis and adiposity. Abbreviations: AIM2, absent in melanoma 2; ASC, apoptosis-associated speck-like protein containing a CARD; CARD, caspase recruitment domain; ER, endoplasmic reticulum; FXR, farnesoid X receptor; GSDMD, gasdermin D; HIF-1α, hypoxia-inducible factor 1-alpha; IL, interleukin; LPS, lipopolysaccharide; mtDNA, mitochondrial DNA; NASH, nonalcoholic steatohepatitis; NLRC, NOD-like receptor family, CARD domain; NLRP, NOD-like receptor family, pyrin domain; ROS, reactive oxygen species; TG, triglyceride; TLR, Toll-like receptor; TNF-α, tumor necrosis factor alpha; TXNIP, thioredoxin-interacting protein.

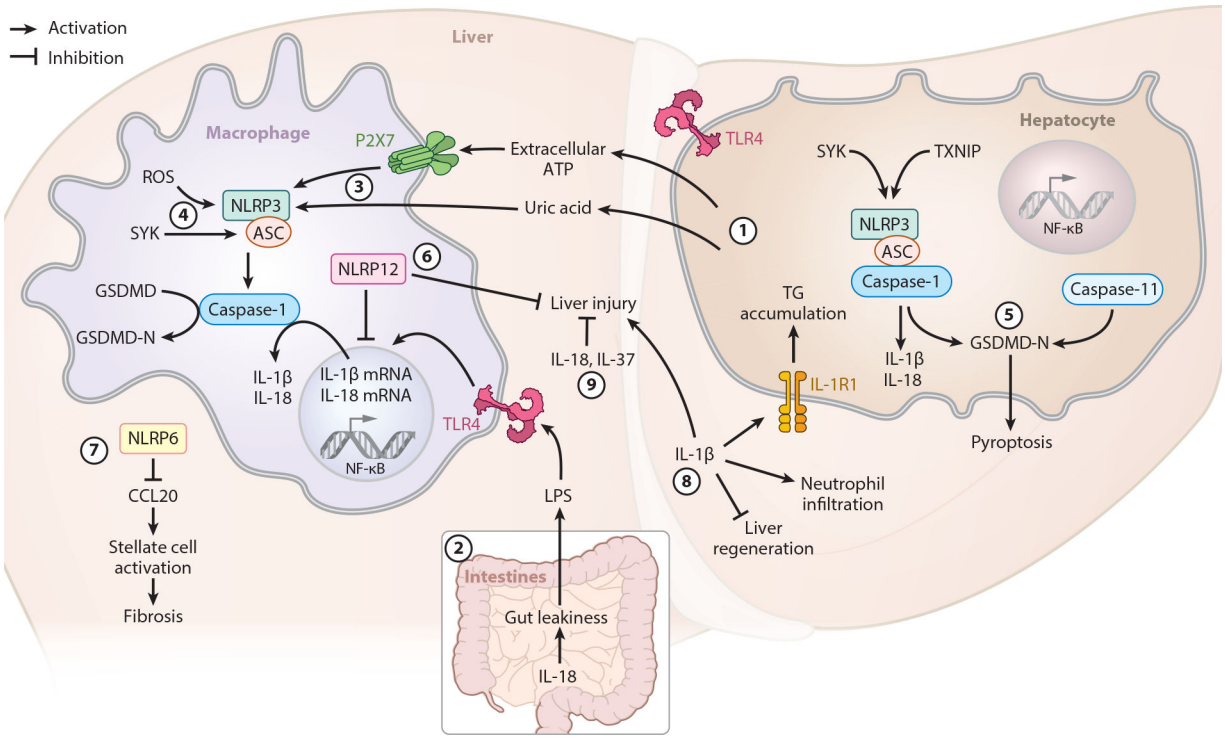

Figure 3.

Inflammasomes involved in ALD. Alcohol consumption (①) induces the release of extracellular ATP and uric acid from damaged hepatocytes and (②) increases the transport of gut-derived LPS to the liver due to increased gut permeability partially mediated by IL-18. (③) Extracellular ATP and uric acid induce NLRP3 activation in macrophages. (④) The intracellular mechanisms of NLRP3 activation in macrophages involve ROS and SYK. (⑤) Pyroptosis is induced in hepatocytes by caspase-1 and caspase-11. (⑥) NLRP12 activation in macrophages inhibits NF-κB signaling and decreases liver injury. (⑦) Liver activation of NLRP6 inhibits CCL20 and stellate cell activation. (⑧) IL-1β induces TG accumulation in hepatocytes, leading to liver injury and neutrophil infiltration and inhibiting liver regeneration. (⑨) IL-18 and IL-37 inhibit liver injury. Abbreviations: ALD, alcohol-associated liver disease; ASC, apoptosis-associated speck-like protein containing a CARD; CARD, caspase recruitment domain; GSDMD, gasdermin D; IL, interleukin; LPS, lipopolysaccharide; NF-κB, nuclear factor κB; NLRP, NOD-like receptor family, pyrin domain; ROS, reactive oxygen species; SYK, spleen tyrosine kinase; TG, triglyceride; TLR, Toll-like receptor; TXNIP, thioredoxin-interacting protein.