Review

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Inflammasomes in liver diseases

Gyongyi Szabo*, Timea Csak

Department of Medicine, University of Massachusetts Medical School, Worcester, USA

Summary

Inflammation is a common element in the pathogenesis of most chronic liver diseases that lead to fibrosis and cirrhosis. Inflammation is characterized by activation of innate immune cells and production of pro-inflammatory cytokines IL-1α, IL-1β, and TNFα. Inflammasomes are intracellular multiprotein complexes expressed in both parenchymal and non-parenchymal cells of the liver that in response to cellular danger signals activate caspase-1, and release IL-1β and IL-18. The importance of inflammasome activation in various forms of liver diseases in relation to liver damage, steatosis, inflammation and fibrosis is discussed in this review.

Inflammasomes and their signal transduction pathways

The term "inflammasome", introduced by Tschopp and colleagues [1] refers to large multiprotein complexes that sense intracellular danger signals via NOD-like receptors (NLR) [2].

NOD-like receptors, members of the pattern recognition receptor family, contain a C-terminal leucin-rich-repeat (LRR) domain that plays a role in the recognition of ligands, a central NACHT domain that is responsible for the oligomerization and dNTPase activity, and an N-terminal CARD, pyrin (PYD), BIR (baculoviral inhibitory repeat), or acidic transactivation domain. Based on the NACHT domain, three subfamilies of proteins are defined: (a) NODs, (NOD1–5, CIITA), (b) NLRPs or NALPs (NLRP/NALP 1–14), and (c) IPAF (IPAF, NAIP) subfamily [2] (summarized in Fig. 1). Other classifications, based on the N-terminal effector domain, are also known [3]. Several, but not all, NLRs play a role in the formation of inflammasomes. With the exception of AIM2, which is a member of the HIN-200 family, the nomenclature of inflammasomes is based on the NOD-like receptor (NLR).

Key Points 1

Nod like receptors (NLRs) contain a C-terminal leucin-rich-repeat (LRR) domain that plays a role in the recognition of ligands, a central NACHT domain that is responsible for the oligomerization and dNTPase activity, and an N-terminal CARD, pyrin (PYD), BIR (baculoviral inhibitory repeat), or acidic transactivation domain. NLRs have been grouped into subfamilies by either the NACHT domain or the N-terminal domain. Several, but not all, NLRs play a role in the formation of a multiprotein complex called the inflammasome. In addition, non-NLR proteins, such as AIM2 can also form a complex with caspase-1

The sensor, NLR, forms a complex with the effector molecule, pro-caspase-1, with or without the contribution of an adapter molecule, such as the apoptosis-associated speck like CARD-domain containing protein (ASC) [1–4]. Inflammasome activation leads to auto-activation of the 45 kDa inactive pro-caspase-1 precursor into p20 and p10 subunits that form the active caspase-1 [1–4], resulting in the cleavage of pro-IL-1β and pro-IL-18 into mature forms, and inactivation of IL-33 [1–5]. IL-1β is a pro-inflammatory cytokine, a central regulator of inflammation that binds to the IL-1 receptor (IL-1R) to exert its broad biological effects. IL-1R also recognizes IL-1α and binds IL-1R antagonist (IL-1Ra), the latter inhibiting IL-1R activation [6]. IL-18 activates natural killer (NK) cells to produce IFNγ [6], while IL-33 is a chromatin-associated cytokine of the IL-1 family that drives Th2 responses [4,6]. The full-length active IL-33 is cleaved and inactivated by caspase-1 [5].

Inflammasome activation is thought to be a two-step process in which signal 1 (mostly from TLR activation) upregulates inflammasome expression and signal 2 triggers functional inflammasome activation by an inflammasome ligand [2,4]. A recent publication suggests that the priming step is required only for activation of NLRP3 and not other inflammasomes such as

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* Corresponding author. Address: University of Massachusetts Medical School, Department of Medicine, LRB215, 364 Plantation Street, Worcester, MA 01605, USA. Tel.: +1 508 856 5275; fax: +1 508 856 4770.
E-mail address: gyongyi.szabo@umassmed.edu (G. Szabo).

Abbreviations: NLR, NOD-like receptor; ASC, apoptosis-associated speck like CARD-domain containing protein; IL, interleukin; IL-1R, interleukin-1 receptor; IL-1Ra, interleukin-1 receptor antagonist; NK, natural killer; IFN, interferon; TLR, toll-like receptor; PAMP, pathogen associated molecular pattern; DAMP, damage associated molecular pattern; NALP1, NACHT, LRR, and PYD domains-containing protein 1; NALP3, NACHT, LRR, and PYD domains-containing protein 3/cryoporin; NLRC4, NLR-family CARD domain containing protein 4; AIM2, absent in melanoma 2; MDP, muramyl dipeptide; NFκB, Nuclear factor kB; MSU, monosodium urate; ROS, reactive oxygen species; NADPH, nicotinamide adenine dinucleotide phosphate oxidase; ATP, adenosine triphosphate; TXNIP, thioredoxin-interacting protein; RIG-I, retinoic acid-inducible gene-I; APAP, N-acetyl-p-aminophenol; I/R, ischaemia-reperfusion; LPS, lipopolysaccharide; ASH, alcoholic steatohepatitis; NASH, nonalcoholic steatohepatitis; MCD, methionine-choline deficient; HFD, high fat diet; CDAA, choline deficient amino acid defined; TNFα, tumor necrosis factor α; MyD88, myeloid differentiation factor 88; CCl4, carbon tetrachloride; HCV, hepatitis C virus; HBV, hepatitis B virus.

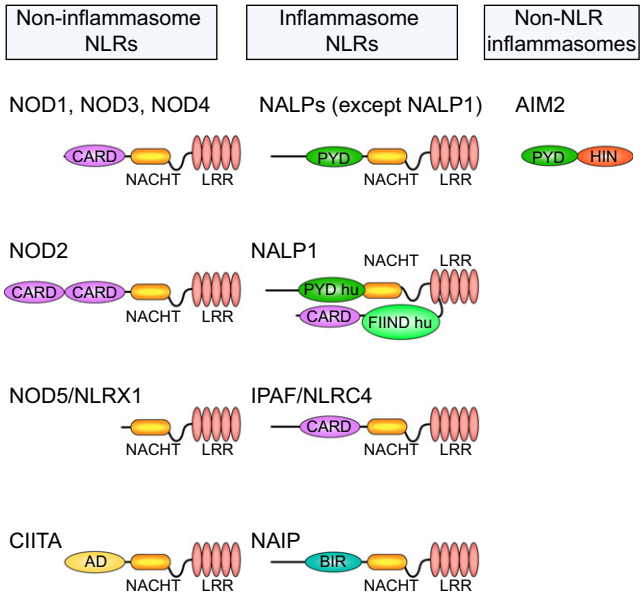

Fig. 1. Structure of inflammasome and non-inflammasome NLRs and non-NLR inflammasomes.

NLRC4 or AIM2 [7]. Inflammasome ligands include both pathogen-associated (PAMPs) and endogenous danger molecules (DAMPs) (summerized in Table 1) [1–4]. To date, four main prototypes of inflammasomes have been characterized: NLRP1 (NALP1); NLRP3 (NALP3, cryporin); NLRC4 (IPAF) and AIM2 [2,4]. They have different ligand recognition sites and utilization of adapter molecules but all culminate in caspase-1 activation.

NLRP1 inflammasome

NLRP1 (NACHT, LRR, and PYD domains-containing protein 1), the first inflammasome described, can directly interact with caspase-1 through its C-terminal CARD domain, and in humans, the presence of ASC enhances the activity of the complex [34]. Murine NLRP1 is unable to bind to ASC because it lacks a functional PYD domain [34]. Multiple alternatively spliced transcript variants of human NLRP1 exist [35].

NLRP1 is activated by the muramyl dipeptide (MDP) and the *Bacillus anthracis* lethal toxin [8–11]. An interaction was reported between NLRP1 and another NLR protein, NOD2, and Hsu *et al.* found that NLRP1 and NOD2 were both required for MDP or *B. anthracis* toxin-induced IL-1β secretion [11]. Potassium efflux plays a role in NLRP1 inflammasome activation [9] and NLRP1 can localize into the nucleus, and this feature is unique in

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Table 1. Known activators of inflammasome NLRs.

Inflammasome	Activator
NLRP1 (NALP1)	*Bacillus anthracis* lethal toxin [8-11] MDP [10,11]
NLRP3 (NALP3, cryoporin)	**Large particles via phagocytosis** Monosodium urate crystals (MSU) [12] CPPD (calcium pyrophosphate dehydrate) [12] Alum [13] Silica [14] Asbestos [15] Amyloid beta [16] Hyaluronan [17] Hemozoin [18] Vaccine adjuvants (poly lactide-co-glycolide and polystyrene microparticles) [19] Cholesterol crystals [20]
	Bacterial toxins (pore-forming) *Listeria monocytogene*s Lysteriolysin O [21,22] *Staphylococcus aureu*s alpha-toxin [21-23] *Aeromonas hydrophila* aerolysin [21,22] Streptolysin [24] Nigericin [21] Maitoxin (Dinoflagellates) [22]
	Ion channels and activators ATP(P2X7) [21] Influenza virus M2 channel protein [25]
	PAMPs (only if transferred to the cytoplasm by e.g. Streptolysin O pore-forming toxin) LPS, lipid A, PGN, MDP, LTA, Pam3, ssRNA, dsRNA, CpG DNA [26,27]
NLRC4 (IPAF)	**Gram - negative bacteria (flagellin-dependent and independent)** *Salmonella typhymurium* [28] *Shigella flexneri* [28,29] *Legionella pneumophila* [30] *Pseudomonas aeruginosa* [28]
AIM2	**dsDNA** bacterial [31,32] viral [31,32] mitochondrial [33] host [31]

comparison to the cytoplasmic distribution of other inflammasomes [36].

Key Points 2

Inflammasomes, the members of PRR family, are large intracellular, multiprotein complexes that sense danger signals via NOD-like receptors. Inflammasome priming and activation lead to autoactivation of caspase-1 that in turn cleaves pro-IL-1β, pro-IL-18 into their mature form, inactivates IL-33 and regulates cell death and survival. The four main prototypes of inflammasomes are NLRP1, NLRP3, NLRC4 and AIM2. They have different recognition sites and ligand specificity and all culminate in caspase-1 activation. The activation of the inflammasomes by either PAMPs or DAMPs is usually a 2-step process

NLRP3 inflammasome

NLRP3 (NACHT, LRR, and PYD domains-containing protein 3, cryoporin) was first described by Hoffman *et al.* who discovered four single mutations in the *NLRP3* gene, in families with familial cold autoinflammatory syndrome and Muckle–Wells syndrome, which lead to increased IL-1β production [37]. Later, Agostini *et al.* reported that NLRP3 forms an IL-1β-processing inflammasome complex [38]. To date, NLRP3 is the most fully characterized member of the inflammasome family. It consists of the NOD-like receptor NLRP3, the adaptor molecule ASC, and the effector molecule pro-caspase-1. Since NLRP3 does not contain a CARD domain, the presence of the adaptor molecule is necessary for the complex formation [34].

The expression of NLRP3 is tightly regulated at the transcriptional level via NFκB [39]. NLRP3 activation requires two signals. Cell priming with an NFκB activator, such as the TLR4-ligand LPS, is the first step of NLRP3 inflammasome activation [39] leading to up regulation of NLRP3 expression [39] while the second signal includes a broad variety of activators.

Three major pathways have been implicated in NLRP3 inflammasome activation (Fig. 2) induced by a wide variety of activators [12–27]. First, extracellular ATP sensed by the P2X7 purinergic receptor results in potassium efflux and recruitment of pannexin that induces NLRP3 activation [21,26,40]. Pannexin is a membrane pore that allows the delivery of extracellular PAMPs and DAMPs into the cytosol [26].

Second, NLRP3 activation is induced by crystals or large particles such as silica, asbestos, aluminium, amyloid, monosodium urate, and cholesterol [12–20]. It has been shown that disruption of lysosomes by chemical damage [41] or lysosomal damage after phagocytosis of these large particles induces NLRP3 inflammasome activation [14,16,20]. Consistent with the role of lysosomal damage in inflammasome activation, the role of a lysosomal protease, cathepsin B, has been implicated in certain forms of NLRP3 activation [4,18,42].

Third, some studies suggest that reactive oxygen species (ROS) contribute to inflammasome activation. This is based on the observation that inhibitors or scavengers that block mitochondrial ROS or NADPH oxidase suppress inflammasome activation [4,15,43–45]. ROS induction may represent a common pathway from different cellular insults. For example, large particles [43] and ATP [44], that are known "inflammasome-activators", induce ROS production. ROS-dependent release of thioredoxin-interacting protein (TXNIP) from thioredoxin and direct interaction between TXNIP and NLRP3 have been described [45]. However, ROS production does not always result in inflammasome activation [4,7,14,34] and NLRP3 activation is not impaired in macrophages deficient in NADPH oxidase subunits [46,47]. In addition Bauernfeind *et al.* showed that ROS inhibitors blocked priming and not activation of the NLRP3 inflammasome [7].

NLRC4 inflammasome

NLRC4/IPAF (NLR-family CARD domain containing protein 4) inflammasome is activated by the flagellin of Gram-negative and Gram-positive bacteria [28–30] or the type III secretion system (T3SS) of Gram-negative bacteria [28–30]. The steps of NRLC4 inflammasome activation are not yet fully explored. Zhao *et al.* have reported that other NLR proteins, such as murine NAIP5 and NAIP2, interact with the bacterial flagellin or type III secretion system (T3SS) rod components, respectively, and promote the assembly and activation of NLRC4 inflammasome [48]. Human NAIP recognizes the T3SS needle subunit [48].

AIM 2 inflammasome

AIM 2 (absent in melanoma 2) is a cytosolic dsDNA sensing inflammasome [31–33] activated by bacterial, viral, and mammalian host DNA to trigger caspase-1 activation [31–33]. AIM2 can directly bind to its ligand [32] and may contribute to the pathogenesis of autoimmune diseases by recognizing the mammalian DNA [49]. Caspase-1 activation can also occur as a result of inflammasome activation by dsRNA via the helicase receptor RIG-I, after association with the inflammasome adaptor molecule ASC [50].

Secretion of interleukin-1β

Activation of inflammasomes culminates in caspase-1 activation and IL-1β secretion. Early observations suggested that IL-1β was secreted independently of the "classical" endoplasmatic reticulum-Golgi route [51]. The molecular mechanisms of IL-1β secretion are yet to be clarified. Some studies suggested that caspase-1 was present in secretory lysosomes together with other lysosomal proteins and pro-IL-1β [52]. Andrei *et al.* reported that ATP-triggered potassium efflux led to calcium-dependent phospholipase C activation, followed by activation of phospholipase A2 and eventually exocytosis and IL-1β release [52]. Recently, pyroptosis has been suggested as an alternative mechanism for IL-1β release [53].

Importantly, IL-1 production has an auto-regulatory loop. The secreted active IL-1β or IL-1α can activate the IL-1 receptor complex and increase the transcription of its own precursor as well as the synthesis of the inflammasome components [53–55,39]. This amplification loop suggests that small amounts of IL-1β could have a significant biological effect.

Inflammasomes regulate cell fate

Increasing evidence suggests important, IL-1β- and IL-18-independent, "non-canonical" roles of inflammasomes that have been recently reviewed by Lamkanfi [56]. In addition to inflammation, inflammasome activation regulates cell death [56,57]. NLRP1, NLRC4 (IPAF), and NAIP activate pyroptosis, while NLRP3 activa-

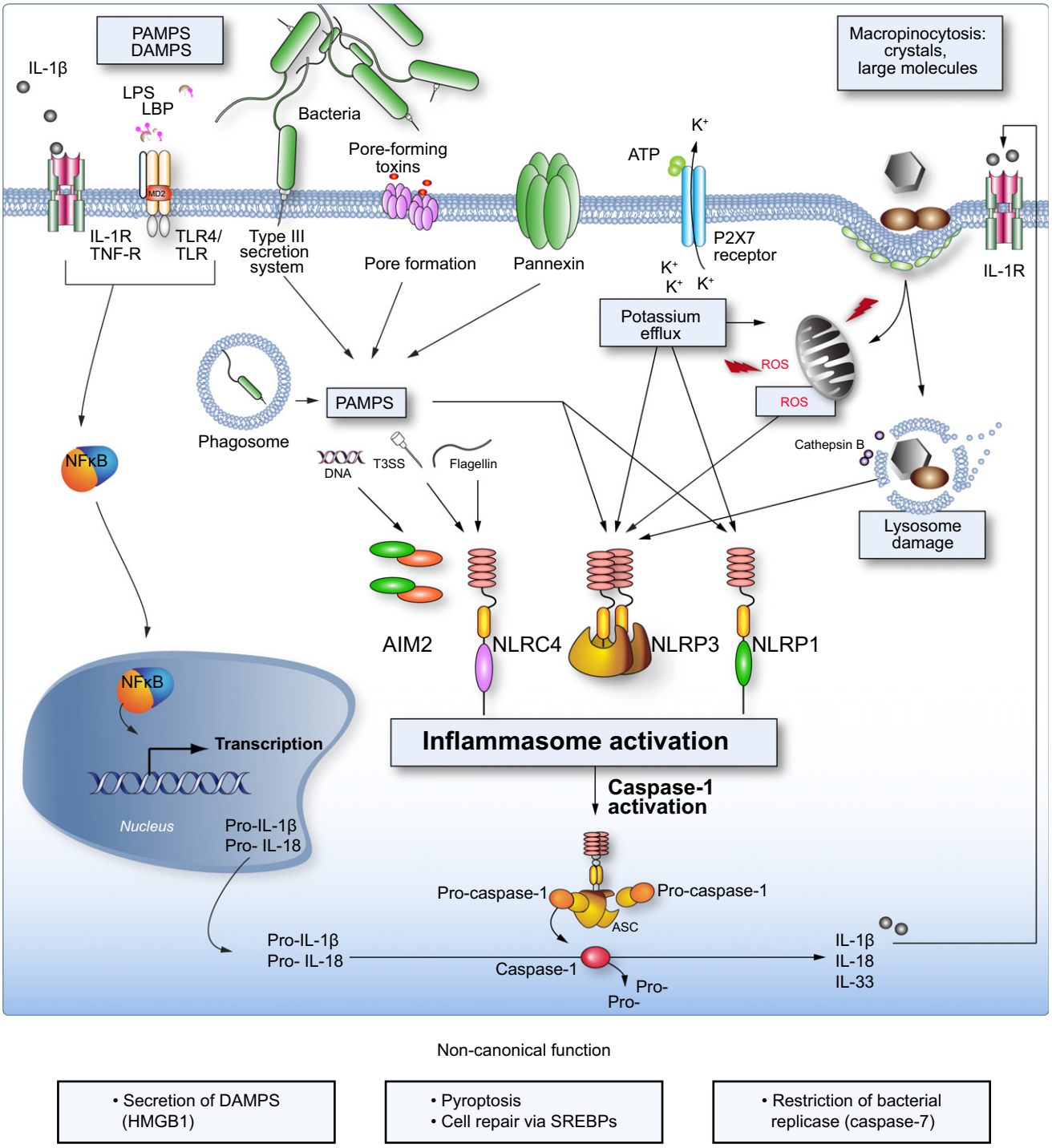

Fig. 2. Inflammasome activating pathways.

tion contributes to pyronecrosis [57]. Pyroptosis is a caspase-1-dependent cell death showing similarities to apoptosis and DNA damage. Unlike apoptosis, pyroptosis does not depend on apoptotic caspases and it is accompanied by loss of plasma membrane integrity and lack of chromatin condensation [57]. Pyronecrosis shows similarities to necrosis since it is not caspase dependent and leads to breakdown of the plasma membrane without chromatin condensation. NLRP3-induced pyronecrosis utilizes the adaptor molecule ASC, and involves the lysosomal enzyme cathepsin B [57]. The loss of plasma membrane integrity might lead to the secretion of various dangerous molecules. Both pyroptosis and pyronecrosis elicit inflammation thereby linking various forms of cell death to innate immune activation. Most recently, Motani *et al.* have described an ASC-dependent necrosis that is independent of the catalytic activity of caspase-1, but is still inhibited by long-term caspase-1 knockdown [58]. Interestingly,

a study in HeLa and Chinese hamster ovary (CHO) cells suggests that inflammasome activation and caspase-1 may promote cell survival via sterol regulatory element binding proteins (SREBPs) and lead to membrane repair and healing [22].

Inflammasomes and interleukin-1β in autoinflammatory diseases

The pathogenic role of IL-1β and inflammasomes has been implicated in several autoinflammatory diseases [53]. Furthermore, the role of inflammasome activation and IL-1 is becoming a focus of investigation in chronic inflammatory conditions including metabolic, neurological, and gastrointestinal disorders. Various pharmacologic agents are available to inhibit IL-1β (or IL-1α) activity: IL-1 receptor antagonist (anakinra); soluble IL-1 receptor (rilonacept); IgG1 type anti-IL-1β (canakinumab); IgG2 type anti-IL-1β (Xoma 052) and anti-IL-1R MoAb IgG1 (AMG108). Dinarello has recently reviewed the available anti-inflammatory agents [53,59]. Beyond the anti-IL-1β therapies, there are ongoing clinical trials with caspase-1 inhibitors and P2X7R blockers [60,61]; of these, the latter failed to improve the symptoms of rheumatoid arthritis [61].

Key Points 3

The role of IL-1β has been implicated in several auto-inflammatory diseases, that were recently reviewed by Dinarello. He summarized the auto-inflammatory diseases that respond to anti-IL-1β therapy, grouping them as classic auto-inflammatory diseases (Familial Mediterranean Fever, CAPS, Hyper IgD syndrome, Still's disease, Behçet's diseases, Schnitzler's syndrome, TNF-receptor-associated periodic syndrome), probable auto-inflammatory diseases (macrophage activation syndrome, urticarial vasculitis, anti-synthetase syndrome, relapsing chondritis, PAPA syndrome, Blau's syndrome, Sweet's syndrome) and common, IL-1β-mediated diseases (gout, rheumatoid arthritis, osteoarthritis, type 2 diabetes, smoldering multiple myeloma, post-myocardial infarction heart failure and PFAPA) [53]

Cell-specific expression of inflammasomes in the liver

While marked constitutive expression of caspase-1 has been reported in the liver [62], the expression of inflammasomes and the subcellular localization of the different NLRs vary between tissues [36]. Early studies showed the highest expression of NLRP3 (CIAS1) and NLRP1 (NAC) in peripheral blood leukocytes, while the liver showed relatively low levels [63,64]. Recent studies have suggested that the liver expresses NLRP1, 2, 3, 6, 10, 12, and NLRC4 at the mRNA level [65]. Compared to the spleen, human livers express higher levels of NLRP10 [65], while murine livers express higher levels of NLRP6 [65].

Key Points 4

Inflammasomes are expressed and likely functionally active in the liver in hepatocytes, liver sinusoidal endothelial cells, hepatic stellate cells and macrophages

The liver is comprised of both parenchymal (hepatocytes) and immune cells (macrophages, neutrophil leukocytes, dendritic cells, T cells, NK/NKT cells, B lymphocytes), where hepatocytes represent the majority of the cell populations. Innate immune cells, including monocytes, macrophages, neutrophils, and dendritic cells, express inflammasomes and there is increasing evidence that inflammasomes exist and are functionally active in non-immune cells, including hepatocytes [66–68], stellate cells [69], endothelial cells [70,71], and myofibroblasts [72]. Hepatocytes, bile duct epithelial cells and stellate cells express ASC protein [36,69,73]. The liver resident macrophages, Kupffer cells, produce significant amounts of IL-1β [74] and express most of the NLRs (Petrasek and Szabo, unpublished data), although NLRP1 expression was absent in one study [36]. The presence of NLRP3 inflammasome and/or inflammasome activation has been shown in sinusoidal endothelial cells [71], stellate cells [69], and hepatocytes [66–68,75]. The cell-specific expression of the inflammasome components in the liver is summarized in Fig. 3.

The role of inflammasomes in liver diseases

The below detailed potential triggers of inflammasomes in liver diseases are summarized in Fig. 4.

Drug-induced liver injury (DILI)

Acetaminophen (APAP)-induced liver injury remains the leading cause of DILI. In APAP-induced liver damage, release of DAMPs from necrotic hepatocytes and sinusoidal endothelial cells [76] triggers sterile inflammation via pattern recognition receptors including TLRs (e.g. apoptotic DNA) and NLRs/inflammasomes (e.g. ATP, MSU) [77]. However, reports are controversial on the role of inflammasomes and IL-1β in the pathogenesis of APAP-induced liver injury. In a small study in children and adolescents, APAP overdose was not associated with increased serum IL-1β levels [78], while the majority of reports found increased IL-1β mRNA and protein levels in the liver and serum of animal models [71,79–85]. The question of whether the relatively low increases in IL-1β levels could explain APAP-induced liver damage remains under debate. Several studies examined the functional role of IL-1β and IL-18, another inflammasome-dependent cytokine, in APAP-induced liver failure. Chen *et al.* found that IL-1R deficiency resulted in attenuation of APAP-induced liver injury indicated by the lower ALT levels and reduced neutrophil recruitment [82]. Blocking antibodies against IL-1α, IL-1β, and IL-1R also lead to attenuation of the APAP-induced liver failure, however, the extent of protection was milder than in the IL-1R deficient mice [82]. Consistent with this observation, administration of IL-1β neutralizing antibodies and use of *IL-18* KO mice also increased survival after a lethal dose of APAP administration [71]. It has been proposed that apoptotic DNA from damaged cells results in pro-*IL-1β* mRNA production via TLR9, and that together with other DAMPs induce inflammasome activation [71,77]. Imaeda *et al.* found that APAP liver injury was attenuated in mice lacking components of NLRP3 inflammasome (ASC, NLRP3, caspase-1), but not NLRC4 (IPAF), suggesting a role for NLRP3 inflammasome in APAP-induced liver injury [71]. In contrast, Williams *et al.* reported that *IL-1R* KO mice, or mice lacking inflammasome components (caspase-1, ASC, NLRP3) showed no protection, and administration of a pan-caspase inhibitor also failed to prevent

APAP-liver injury while it blocked IL-1β increase [81,83]. These contradictory observations may be related to the complex role of inflammasome and IL-1β signaling that extends beyond inflammation to cell death. Another consideration is the timing of the interventions in relation to the APAP injury, and age and gender differences between animal models. Beyond IL-1β, the role of IL-1α should also be considered in APAP toxicity as IL-1α levels are also increased [79]. To further complicate the picture, IL-1R antagonist-deficient mice showed reduced liver injury in response to APAP overdose. This might be explained by the observation that *IL-1Ra* KO mice generated less toxic metabolites (NAPQI) than wild type mice [85]. Finally, the cell specificity of inflammasome activation and IL-1β production is only partially understood. Inflammasome activation was shown to result in IL-1β production in sinusoidal endothelial cells after APAP exposure [71] and in RAW264.7 macrophages, suggesting that multiple cell types are affected [86].

Key Points 5

The role of IL-1 signaling and inflammasomes has been implicated in the pathogenesis of acute liver injury induced by acetaminophen, ischemia/reperfusion or endotoxin, as well as in chronic liver diseases with increased gut permeability, including alcoholic and non-alcoholic steatohepatitis. Inflammasomes also play a role in the pathogenesis of infectious diseases of the liver, including hepatitis C virus infection and Schistosomiasis. In addition, inflammasome activation and/or IL-1 signaling may contribute to the progression of the liver diseases regulating fibrosis. The potential triggers of inflammasome in liver diseases are summerized in Figure 4

Ischemia–reperfusion

Ischemia–reperfusion (I/R) has clinical relevance to liver transplantation, partial hepatectomy, and hypovolemic shock [87]. The characteristics of I/R are hepatocyte death, release of DAMPs, inflammatory cell infiltration, Kupffer cell activation, ROS production, and disruption of liver sinusoidal endothelial cells (LSEC) that can all lead to inflammasome activation [88]. Silencing *NLRP3* ameliorated I/R-induced hepatocellular injury and reduced IL-1β, IL-18, HMGB1, IL-6, and TNFα release via inhibition of caspase-1 and NFκB activity [89]. Consistent with this, decreased caspase-1 activation was found in the presence of the antioxidant N-acetylcysteine, in I/R injury [75].

Involvement of caspase-1 (ICE) and apoptosis were observed during the re-oxygenation phase in contrast to the predominantly necrotic features in the hypoxic phase [75]. Caspase-1 activation was present during hypoxia and during the re-oxygenation phase, and a specific caspase-1 inhibitor (YVAD) prevented I/R-induced cell death [75]. The role of the inflammasome/caspase-1 system in I/R injury is further supported by observations where IL-1R antagonist pretreatment, delivery of an IL-1 receptor antagonist (IL-1Ra) cDNA into the liver, or IL-18 neutralizing antibodies significantly reduced liver damage, inflammation, and mortality in animal models [90–92]. Notably, TLR4 and TLR9, both of which control IL-1β and NLRP transcription, play a role in I/R liver injury [93,94].

Recent findings suggested that caspase-1 was hepatoprotective in a trauma model [95]; however, NLRP3-independent caspase-1 activation was found in hemorrhagic shock and trauma in I/R injury.

Endotoxin-induced liver injury and cholestasis

Endotoxin (lipopolysaccharide (LPS)), a cell wall component of Gram-negative bacteria, is a major mediator of sepsis-induced liver damage, multi-organ failure, and chronic liver disease. Owing to the portal blood supply arriving from the intestines and its unique microcirculation, the liver is exposed to high concentrations of nutrients and gut-derived substances including LPS. The role of the gut microbiota, increased intestinal permeability and portal endotoxinaemia has been described in several liver diseases [96].

LPS, a ligand of TLR4, is a potent inducer of mRNA expression of all inflammasome components (NLRP3, ASC, caspase-1 and pannexin-1), pro-IL-1β and pro-IL-18 via NFκB activation [39,97], although TLR-independent, LPS-induced upregulation of inflammasome has also been described [26]. In mice, *in vivo* LPS administration increased the mRNA expression of the components of the inflammasome as well as serum and liver mature IL-1β levels, indicating caspase-1/inflammasome activation [97].

Priming with heat-killed *Proprionibacterium acnes* induced liver inflammatory cell aggregates and rendered mice susceptible to LPS-induced liver injury [98,99]. IL-18 and IL-1β played a role in this process [100–107] and Kupffer cell depletion could attenuate the *P. acnes*/LPS-induced liver injury [102,106]. In this model, LPS challenge resulted in NLRP3-mediated caspase-1 activation in Kupffer cells in a TRIF-dependent manner without affecting the ATP/P2X7R pathway [106]. In *TRIF* KO mice, hepatic granulomas, but no IL-18 release or liver injury, were present. MyD88, the common TLR adaptor, was crucial for the transcriptional regulation of IL-18 and IL-1β, but not for their maturation and release [106]. NLRP3- and ASC-deficient mice were also resistant to *P. acnes* and LPS-induced liver injury and failed to secrete IL-18 [106]. The effector role of IL-1/IL-1R signaling in LPS-induced liver injury was suggested by the observation that IL-1Ra pretreatment attenuated the liver injury [107].

Kupffer cells were identified as the main source of LPS-induced IL-1β and IL-18 [102,106], and caspase-1-deficient Kupffer cells were not able to secrete mature IL-1β or IL-18 upon LPS stimulation [105]. A potential role for other cell types cannot be excluded because in one study depletion of macrophages resulted in only moderate amelioration of the liver injury and it did not influence IL-18 levels [108].

Alcoholic and non-alcoholic fatty liver diseases

There is increasing evidence that gut microbiota, increased gut permeability and endotoxin contribute to the pathogenesis of both alcoholic (ASH) and non-alcoholic steatohepatitis (NASH) [96]. In alcoholics with liver disease, as well as in animal models of alcohol-induced liver disease, serum levels of IL-1β were increased [109,110]. Hsiang *et al.* showed IL-1β and TNFα secretion from HepG2 hepatocytes treated with acetaldehyde, a metabolic product of alcohol [111]. In a mouse model of chronic alcohol feeding, we found increased serum and liver mature IL-1β (17 kDa) levels, increased caspase-1 activation and upregulation of the inflammasome components, NLRP3, ASC, and

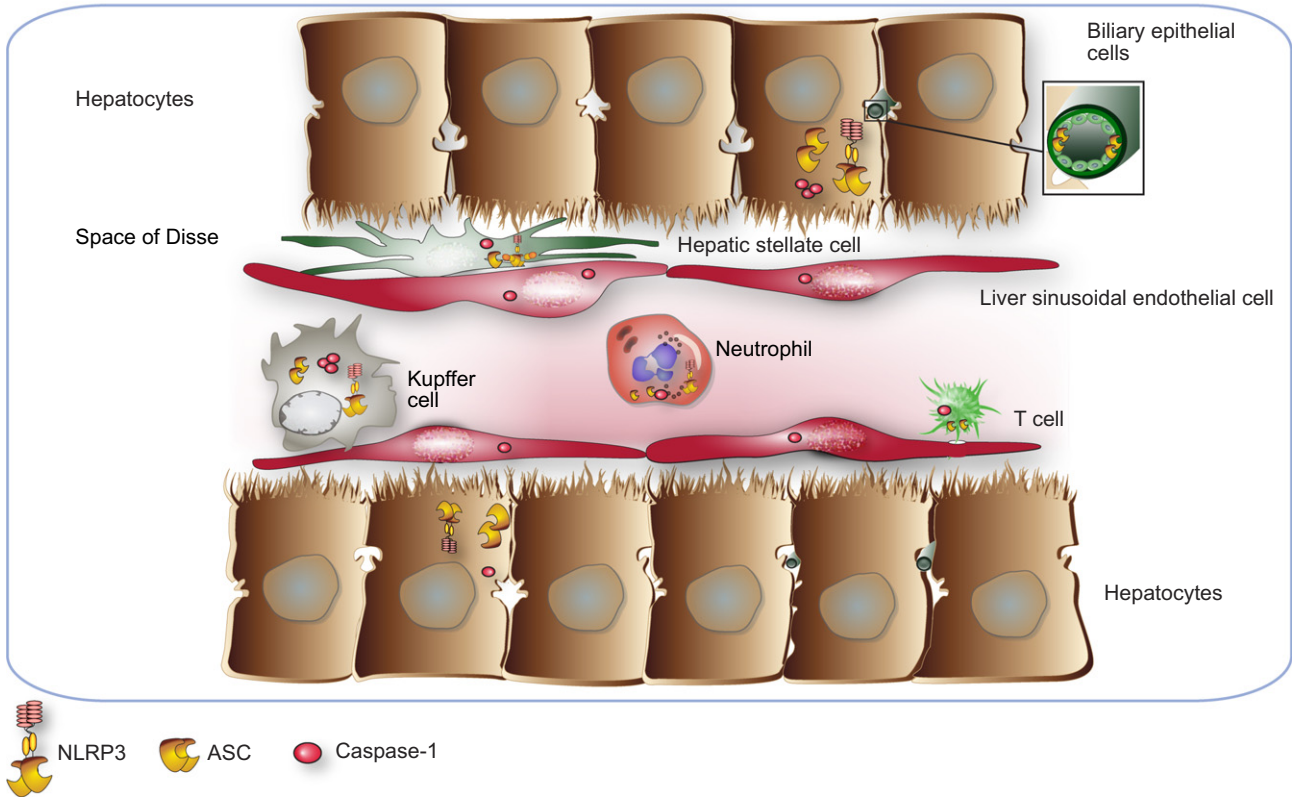

Fig. 3. Cell-specific inflammasome expression in the liver.

pro-caspase-1 in the liver (Petrasek and Szabo, manuscript under review) suggesting that inflammasome activation is a component of the liver pathophysiology in ALD.

The role of inflammasomes and IL-1β in the metabolic syndrome and NASH is receiving increasing attention [66,74,112–118]. IL-1β protein and mRNA levels are increased in various diet-induced NASH models in mice, including methionine–choline-deficient (MCD), high fat (HF) and choline-deficient amino acid-defined (CDAA) diets [66,74,112–118]. Inflammasome activation was associated with steatohepatitis (NASH) [66,113] but not with steatosis alone as it occurs in leptin-deficient mice or after short-term high fat diet feeding [66]. *IL-1R* KO mice showed attenuated liver injury, steatosis, and fibrosis in the CDAA and HF diet-models [74,117]. *IL-1β* KO mice also had attenuated hepatocellular damage, steatosis, and fibrosis in atherogenic diet-induced steatohepatitis [114]. IL-1α may also contribute to the pathogenesis of NASH as *IL-1α* KO mice also showed attenuated liver damage and fibrosis in a HF diet-induced steatohepatitis model [114]. IL-1R antagonist (IL-1Ra)-deficient mice showed severe hepatic fat accumulation and fibrosis when kept on an atherogenic diet as compared to wild type controls [118]. Consistent with inflammasome involvement, long-term high fat diet administration resulted in reduced hepatic steatosis in *NLRP3* KO mice [113]. In *db/db* mice fed an MCD diet, administration of a pan-caspase inhibitor, VX-166, prevented mature IL-1β production and reduced steatosis and fibrosis without preventing liver injury [112].

Potential molecular triggers for inflammasome activation in NASH include DAMPs such as DNA, saturated fatty acids, and PAMPs (LPS). In primary hepatocytes, saturated, but not unsaturated fatty acids induce caspase-1 activation and IL-1β release in the presence of LPS [66]. Furthermore, we have recently demonstrated that danger signals from fatty acid-treated hepatocytes can induce inflammasome activation in liver mononuclear cells [66], suggesting a crosstalk between liver parenchymal cells and immune cells in NASH (Fig. 4) This intercellular crosstalk provides potential amplification of inflammasome activation and inflammatory pathways in NASH. Observations from *MyD88* KO and *TLR9* KO mice, where steatohepatitis was attenuated in a CDAA-diet model, lead to the hypothesis that apoptotic DNA from damaged cells is sensed by TLR9 that triggers *IL-1β* mRNA transcription, while other DAMPs activate the inflammasome [74]. Fatty acid-induced inflammasome activation in macrophages was NLRP3-dependent and involved increased mitochondrial ROS production and decreased autophagy due to reduced AMPK activity [115]. The role of ceramide was also reported in fatty acid-induced inflammasome activation [113].

IL-1β promoted the development of hepatic steatosis via suppression of peroxisome proliferator-activated receptor α (PPARα) activity [116] but it also increased cell death in lipid-loaded hepatocytes [74]. Petrasek *et al.* found that IL-1β increased the hepatotoxic effect of TNFα [119]. Thus, the crosstalk between TLR and inflammasome activation is another important determinant of steatohepatitis and the inflammatory response in the liver.

Understanding the cell-specificity of inflammasome activation in fatty liver disease has implications for future potential therapeutic approaches. An important role for Kupffer cells is sup-

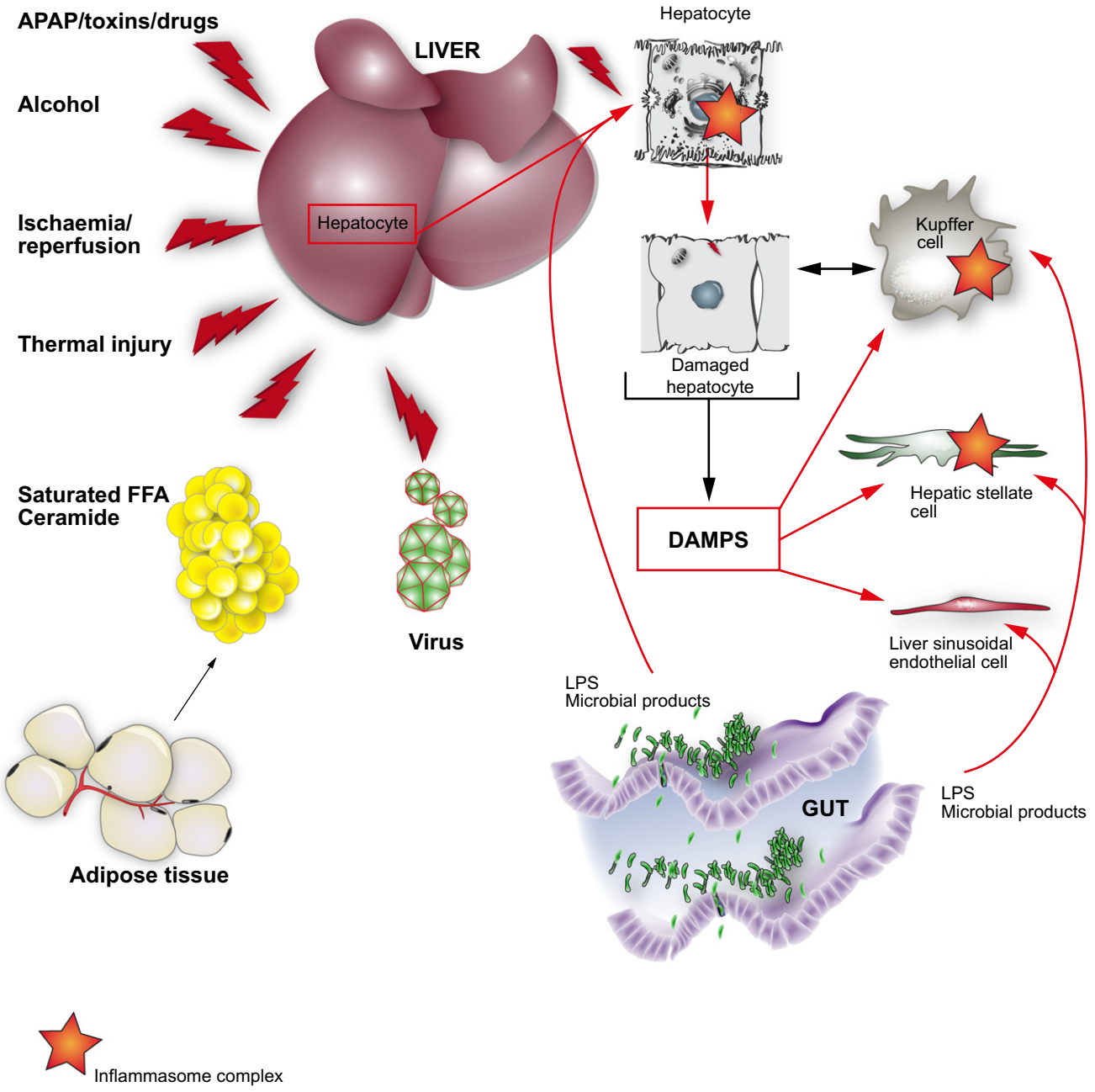

Fig. 4. Triggers of inflammasome activation in liver diseases.

ported by the fact that these cells exhibited the highest levels of *IL-1β* mRNA among liver cell types, and depletion of Kupffer cells markedly decreased liver mRNA and serum IL-1β levels [74,116]. Selective deficiency in IL-1β or IL-1α in liver parenchymal cells, but not in bone-marrow-derived cells, protected mice from diet-induced steatohepatitis and fibrosis [114]. These observations suggest that inflammasome and IL-1β production by different cell types contribute to different aspects of steatohepatitis.

Translation of findings from animal models to human NASH has limitations. Increased mRNA expression of NLRP3 inflammasome components was found in human livers of NASH patients [66] as well as in abdominal fat of obese patients with type 2 diabetes [117] where NLRP3 levels were decreased after weight loss [117]. Interestingly, others found that while weight loss did not influence liver and adipose tissue NLRP3 expression, the hepatic IL-1β, IL-18, and IL-Ra levels were significantly reduced [120]. The lack of an animal model that mimics all features of human NASH challenges translation of specific findings from animals to humans. For example, MyD88 deficiency prevented CDAA-induced NASH in one study and [74] it worsened the HF diet-induced steatohepatitis in another study [121]. Further studies are needed to provide clarifications.

Viral hepatitis

IL-1β levels are increased in patients with chronic HCV infection and these levels are even higher in those with cryoglobulinaemia [122–124]. Serum IL-1β and caspase-1 levels are decreased in those individuals who respond to anti-HCV therapy [122]. The cellular source of IL-1β in HCV infection is yet to be determined. Kupffer cells have been described as a source of IL-1β because HCV proteins induced IL-1β, TNFα, and IL-10 production from KCs [124,125]. Recently, Burdette *et al.* have reported NLRP3 inflammasome activation and IL-1β production from HCV infected human hepatoma cells (JFH1) [67]. Notably, HCV core protein downregulated caspase-1 and caspase-4 in human B lymphocytes [126]. We found increased expression of NLRP3 inflammasome at the mRNA level in livers of patients with chronic hepatitis C infection suggesting that inflammasome upregulation may be a component of HCV immunopathology [66].

Hepatitis B virus (HBV) core antigen induced caspase-1-dependent IL-18 secretion from human PBMCs and IL-18 levels were increased in PBMCs from HBeAg negative patients, suggesting the possibility of inflammasome activation in chronic HBV infection [127]. Inflammasome involvement in other viral diseases [128] and involvement of the RIG-I pathway in IL-1β production [50] suggest that inflammasomes may play role in HCV and other forms of viral hepatitis.

Liver fibrosis

Chronic liver inflammation, that is amplified by IL-1, leads to fibrosis and cirrhosis. In rats, IL-1Ra administration attenuated dimethylnitrosamin (DMN)-induced liver cirrhosis [129] and IL-1R-deficient mice were protected from thioacetamide (TAA)-induced fibrogenesis [130]. The expression of MMP9, MMP13, and TIMP, regulators of fibrosis and tissue remodeling, is IL-1-dependent [130]; however, the exact mechanisms by which IL-1R signaling promotes fibrosis and the cell type(s) that produce(s) IL-1β are yet to be fully defined. Hepatic stellate cells expressed components of the inflammasome and activation of primary mouse stellate cells or LX-2 HSC cells with MSU resulted in increased TGFβ and collagen-1 expression, actin reorganization, and inhibition of HSC chemotaxis in an NLRP3-dependent manner [69]. In a carbon-tetrachloride (CCl_4) and TAA-induced *in vivo* liver fibrosis model, expression of TGFβ and collagen-1 was significantly reduced in mice lacking either NLRP3 or the adaptor molecule ASC [69]. Additional data from the CCl_4-induced fibrosis model indicated that IL-1Ra protected mice from acute hepatocyte damage and promoted hepatocyte proliferation [131]. In an animal model of NASH, inhibition of hepatic cell death with a pan-caspase inhibitor suppressed fibrosis [112]. The specific role of caspase-1 versus other caspases is yet to be fully understood in liver fibrosis.

Other liver diseases

While the characterization of the role of inflammasomes in autoimmune hepatitis is still under investigation, increased serum IL-1β levels were found in patients with primary biliary cirrhosis (PBC) [132].

Although parasitic schistosomiasis is rare in the Western world, it is common in Africa, Asia, and South America. *Schistosoma mansoni* egg antigens were shown to induce NLRP3 inflammasome activation and IL-1β secretion from macrophages via Dectin-2, ROS production and potassium efflux [133], and NLRP3-deficient mice exhibited decreased immunopathology and smaller granulomas following *S. mansoni* infection [133].

IL-1β gene polymorphisms were found to influence the susceptibility of developing HCC in chronic liver diseases [134]. Another study found that caspase-1 expression was downregulated in hepatocellular carcinoma [135]. However, Yan *et al.* found higher caspase-1 activity both in human HCC and in hepatoma cell lines exposed to hypoxia [68]. In addition, IL-18 has been reported to promote hepatic metastases of melanoma via the adhesion molecule VCAM-1 [136].

IL-1 and inflammasome activation may be related to complications of liver diseases. For example, in addition to contributing to the development of liver injury, inflammation and fibrosis, IL-1β, IL-18, and the inflammasomes may also mediate encephalopathy. Caspase-1 and IL-18 levels were higher in patients with acute or acute-on-chronic liver failure compared to controls or patients with stable chronic liver diseases [137]. Furthermore, the onset of hepatic encephalopathy in toxic liver injury was delayed in *IL-1R* KO mice [138]. The role of local inflammasome activation and IL-1β in the brain was demonstrated in various forms of cognitive and brain diseases, such as Alzheimer's disease, and in alcohol-related behavioral changes [16,139].

Finally, in auto-inflammatory syndromes, such as the macrophage activation syndrome (MAS), hepato-splenomegaly and abnormal liver function tests can occur and some of these auto-inflammatory diseases improve with anti-IL-1 therapy [53]. Case reports documented successful treatment of MAS with anakinra [140], however, in some rare cases, the onset of MAS [141] or acute hepatitis has also been reported after anakinra therapy [142].

Caveats in the evaluation of inflammasome activation in liver diseases

While the involvement of NLRs, inflammasome activation and IL-1β is increasingly evident in various forms of liver diseases, several additional concepts deserve consideration.

Key Points 6

There are caveats in the evaluation of the role of inflammasomes in liver diseases which include the alternative cleavage of IL-1β, the tissue-/cell-specific distribution and role of inflammasomes and the inflammasome-independent role of the adaptor molecule ASC

Alternative pathways of IL-1β cleavage

While caspase-1 is the most important enzyme involved in the cleavage of pro-IL-1β into its mature form, other enzymes such as caspase-8 [143] and neutrophil- and macrophage-derived serine proteases [144,53] cleave pro-IL-1β. This may explain that while IL-1β deficiency prevented inflammation in some sterile

inflammation models, the lack of caspase-1 was not protective [144]. In addition, the functional importance of IL-1β and IL-18 may be distinct in different tissues and cell types. This notion is supported by recent data suggesting a prominent role for IL-18 in intestinal homeostasis, while IL-1β seems to play a bigger role in liver diseases.

Tissue- and cell-specific expression and role of inflammasomes

Given the multiple functions and distinct tissue and cell distribution [36] of the inflammasomes, they may have different roles in different tissues. For example, while inflammasomes and caspase-1 induced cell death, pyroptosis, and pyronecrosis in macrophages, caspase-1 was found to promote cell survival in HeLa and CHO cell lines [22]. Moreover, even though the NLRP3 inflammasome is important for the maintenance of the intestinal barrier and protection against colitis [145], it can still contribute to inflammation in gut immune cells. Cell specificity of inflammasomes has particular relevance to liver diseases where increased gut permeability contributes to the pathogenesis.

ASC is not just a passive adaptor

ASC is necessary for the formation of many (but not all) inflammasome complexes. There is increasing evidence that ASC has inflammasome-independent functions, for example in lymphocyte migration and antigen presentation of dendritic cells [146] as well as in regulation of MAPK activity and chemokine expression [147].

"Non-canonical" functions of caspase-1 [56]

Beyond its role in IL-1β, IL-18, IL-33 cleavage, regulation of caspase-7, and cell death, caspase-1 was shown to be necessary for release of HMGB1, a major DAMP [148].

Caspase-11 in non-canonical inflammasome activation

Recently, Kayagaki *et al.* have reported that caspase-11 (human caspase-4 and -5) triggers caspase-1-independent macrophage death and caspase-1-dependent IL-1β and IL-18 production in response to certain inflammasome activators, including CTB, *Escherichia coli*, *Citrobacter rodentium*, *Vibrio cholera* [149].

NLRP6: a "new" inflammasome

To date, mostly four main prototypes of inflammasomes have been characterized, but there are other NLRs, such as the recently discovered NLRP6, that have uniquely increased levels in the liver compared to the spleen [65]. Recent evidence suggests that NLRP6 is a key component in the maintenance of epithelial cell integrity [150] and its role in liver diseases associated with increased gut permeability deserves investigations.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of pro-IL-beta. Mol Cell 2002;10:417–426.
[2] Martinon F, Mayor A, Tschopp J. The inflammasomes: guardians of the body. Annu Rev Immunol 2009;27:229–265.
[3] Ye Z, Ting JP. NLR, the nucleotide-binding domain leucine-rich repeat containing gene family. Curr Opin Immunol 2008;20:3–9.
[4] Bauernfeind F, Ablasser A, Bartok E, Kim S, Schmid-Burgk J, Cavlar T, et al. Inflammasomes: current understanding and open questions. Cell Mol Life Sci 2011;68:765–783.
[5] Cayrol C, Girard JP. The IL-1-like cytokine IL-33 is inactivated after maturation by caspase-1. Proc Natl Acad Sci USA 2009;106:9021–9026.
[6] Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. Annu Rev Immunol 2009;27:519–550.
[7] Bauernfeind F, Bartok E, Rieger A, Franchi L, Nunez G, Hornung V. Cutting edge: reactive oxygen species inhibitors block priming, but not activation, of the NLRP3 inflammasome. J Immunol 2011;187:613–617.
[8] Boyden ED, Dietrich WF. Nalp1b controls mouse macrophage susceptibility to anthrax lethal toxin. Nat Genet 2006;38:240–244.
[9] Wickliffe KE, Leppla SH, Moayeri M. Anthrax lethal toxin-induced inflammasome formation and caspase-1 activation are late events dependent on ion fluxes and the proteasome. Cell Microbiol 2008;10:332–343.
[10] Bruey JM, Bruey-Sedano M, Luciano F, Zhai D, Balpai R, Xu C, et al. Bcl-2 and Bcl-XL regulate proinflammatory caspase-1 activation by interaction with Nalp1. Cell 2007;129:45–46.
[11] Hsu LC et al. A NOD2-NALP1 complex mediates caspase-1-dependent IL-1β secretion in response to *Bacillus anthracis* infection and muramyl dipeptide. Proc Natl Acad Sci USA 2008;105:7803–7808.
[12] Martinon F, Petrilli V, Mayor A, Tardivel A, Tshopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 2006;440:237–241.
[13] Eisenbarth SC, Colegio OR, O'Connor W, Sutterwala FS, Flavell RA. Crucial role for the Nalp3 inflammasome in the immunstimulatory properties of aluminium adjuvants. Nature 2008;453:1122–1126.
[14] Hornung V, Bauernfeind F, Halle A, Samstad EO, Kono H, Rock KL, et al. Silica crystals and aluminium salts activate the NALP3 inflammasome through phagosomal destabilization. Nat Immunol 2008;9:847–856.
[15] Dostert C, Petrilli V, Van Bruggen R, Steele C, Mossman BT, Tschopp J. Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. Science 2008;320:674–677.
[16] Halle A, Hornung V, Petzold GC, Stewart CR, Monks BG, Reinheckel T, et al. The Nalp3 inflammasome is involved in the innate immune response to amyloid-beta. Nat Immunol 2008;9:857–865.
[17] Yamasaki K, Muto J, Taylor KR, Cogen AL, Audish D, Bertin J, et al. NLRP3/cryoporin is necessary for interleukin-1beta (IL-1beta) release in response to hyaluronan, an endogenous trigger of inflammation in response to injury. J Biol Chem 2009;284:12762–12771.
[18] Dostert C, Guarda G, Romero JF, Menu P, Gross O, Tardivel A, et al. Malarial hemozoin is a Nalp3 inflammasome activating danger signal. PloS One 2009;4:e6510.
[19] Sharp FA, Ruane D, Claass B, Creaqh E, Harris J, Malyala P, et al. Uptake of particulate vaccine adjuvants by dendritic cells activate the NALP3 inflammasome. Proc Natl Acad Sci USA 2009;106:870–875.
[20] Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, et al. NLRP3 inflammasome are required for atherogenesis and activated by cholesterol crystals. Nature 2010;464:1357–1361.
[21] Mariathasan S, Weiss DS, Newton K, McBride J, O'Rourke K, Roose-Girma M, et al. Cryopyrin activates the inflammasome in response to toxins and ATP. Nature 2006;440:228–232.
[22] Gurcel L, Abrami L, Girardin S, Tschopp J, van der Goot FG. Caspase-1 activation of lipid metabolic pathways in response to bacterial pore-forming toxins promotes cell survival. Cell 2006;126:1135–1145.
[23] Munoz-Planillo R, Franchi L, Miller LS, Nunez G. A critical role for hemolysins and bacterial lipoproteins in *Staphylococcus aureus*-induced activation of the Nlrp3 inflammasome. J Immunol 2009;183:3942–3948.
[24] Harder J, Franchi L, Munoz-Planillo R, Park JH, Reiner T, Nunez G. Activation of Nlrp3 inflammasome by *Streptococcus pyogenes* requires streptolysin O and NFkappa B activation but proceeds independently of TLR signaling and P2X7 receptor. J Immunol 2009;183:5823–5829.
[25] Ichinohe T, Pang IK, Iwasaki A. Influenza virus activates inflammasomes via its intracellular M2 ion channel. Nat Immunol 2010;11:404–410.
[26] Kanneganti TD, Lamkanfi M, Kim YG, Chen G, Park JH, Franchi L, et al. Pannexin-1 mediated recognition of bacterial molecules activates the

cryoporin inflammasome independent of toll-like receptor signaling. Immunity 2007;26:433–443.
[27] Kanneganti TD, Ozören N, Body-Malapel M, Amer A, Park JH, Franchi L, et al. Bacterial RNA and small antiviral compounds activate caspase-1 through cryoporin/Nalp3. Nature 2006;440:233–236.
[28] Miao EA, Mao DP, Yudkosky N, Bonneau R, Loranq CG, Warren SE, et al. Innate immune detection of the type III secretion apparatus through the NLRC4 inflammasome. Proc Natl Acad Sci USA 2010;107:3076–3080.
[29] Mariathasan S, Newton K, Monack DM, Vucic D, French DM, Lee WP, et al. Differential activation of the inflammasome by caspase-1 adaptors ASC and Ipaf. Nature 2004;430:213–218.
[30] Vinzing M, Eitel J, Lippmann J, Hocke AC, Zahlten J, Slevogt H, et al. NAIP and Ipaf control *Legionella pneumophila* replication in human cells. J Immunol 2008;180:6808–6815.
[31] Muruve DA, Pétrilli V, Zaiss AK, White LR, Clark SA, Ross PJ, et al. The inflammasome recognizes cytosolic microbial and host DNA and triggers innate immune response. Nature 2008;452:103–108.
[32] Hornung V, Ablasser A, Charrel-Dennis M, Bauernfeind F, Horvath G, Cafrey DR, et al. AIM2 recognizes cytosolic dsDNA and forms a caspase-1 activating inflammasome with ASC. Nature 2009;26:514–518.
[33] Nakahira K, Haspel JA, Rathinam VA, Lee SJ, Dolinay T, Lam HC, et al. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nat Immunol 2011;12:222–230.
[34] Schroder K, Tschopp J. The inflammasomes. Cell 2010;140:821–832.
[35] Pontillo A, Catamo E, Arosio B, Mari D, Crovella S. NALP1/NLRP1 genetic variants are associated with Alzheimer disease. Alzheimer Dis Assoc Discord 2011, Dec. 6 [Epub ahead of print].
[36] Kummer JA, Broekhuizen R, Everett H, Agostini L, Kuijk L, Martinon F, et al. Inflammasome components NALP1 and 3 show distinct but separate expression profiles in human tissues suggesting a site-specific role in the inflammatory response. J Histochem Cytochem 2007;55:443–452.
[37] Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle–Wells syndrome. Nat Genet 2001;29:301–305.
[38] Agostini L, Martinon F, Burns K, McDermott MF, Hawkins PN, Tschopp J. NALP3 forms an IL-1β processing inflammasome with increased activity in Muckle–Wells auto-inflammatory disorder. Immunity 2004;20:319–325.
[39] Bauernfeind FG, Horvath G, Stutz A, Alnemri ES, MacDonald K, Speert D, et al. Cutting edge: NF-kappaB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. J Immunol 2009;183:787–791.
[40] Petrilli V, Papin S, Dostert C, Mayor A, Martinon F, Tschopp J. Activation of the NALP3 inflammasome is triggered by low intracellular potassium concentration. Cell Death Differ 2007;14:1583–1589.
[41] Gong YN, Wang X, Wang J, Yang Z, Li S, Yang J, et al. Chemical probing reveals insights into the signaling mechanism of inflammasome activation. Cell Res 2010;20:1289–1305.
[42] Tschopp J, Schroder K. NLRP3 inflammasome activation: the convergence of multiple signaling pathways on ROS production? Nat Rev Immunol 2010;10:210–215.
[43] Fubini B, Hubbard A. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) generation by silica in inflammation and fibrosis. Free Radic Biol Med 2003;34:1507–1516.
[44] Cruz CM, Rinna A, Forman HJ, Ventura AL, Persechini PM, Ojcius DM. ATP activates a reactive oxygen species-dependent oxidative stress response and secretion of proinflammatory cytokines in macrophages. J Biol Chem 2007;282:2871–2879.
[45] Zhou R, Tardivel A, Thorens B, Choi I, Tschopp J. Thioredoxin-interacting protein links oxidative stress to inflammasome activation. Nat Immunol 2010;11:136–140.
[46] van Bruggen R, Köker MY, Jansen M, van Houdt M, Roos D, Kuijpers TW, et al. Human NLRP3 inflammasome activation is NO1–4 independent. Blood 2010;115:5398–5400.
[47] van de Veerdonk FL, Smeekens SP, Joosten LA, Kullberg BJ, Dinarello CA, van der Meer JW, et al. Reactive oxygen species-independent activation of the IL-1beta inflammasome in cells from patients with chronic granulomatous disease. PNAS 2010;107:3030–3033.
[48] Zhao Y, Yang J, Shi J, Gong YN, Lu Q, Xu H, et al. The NLRC4 inflammasome receptors for bacterial flagellin and type III secretion apparatus. Nature 2011;477:596–600.
[49] Rathinam VAK, Jiang Z, Waggoner SN, Sharma S, Cole LE, Waggoner L, et al. The AIM2 inflammasome is essential for host defense against cytosolic bacteria and DNA viruses. Nat Immunol 2010;11:395–402.
[50] Poeck H, Bscheider M, Gross O, Finger K, Roth S, Rebsamen M, et al. Recognition of RNA virus by RIG-I results in activation of CARD9 and inflammasome signaling for interleukin-1β production. Nature Immunol 2009;11:63–69.
[51] Rubartelli A, Cozzolino F, Talio M, Sitia R. A novel secretory pathway for interleukin-1β, a protein lacking a signal sequence. Embo J 1990;9:1503–1510.
[52] Andrei C, Margiocco P, Poggi A, Lotti LV, Torrisi MR, Rubartelli A. Phospholipases C and A2 control lysosome-mediated IL-1 beta secretion: implications for inflammatory processes. Proc Natl Acad Sci 2004;101:9745–9750.
[53] Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. Blood 2011;117:3720–3732.
[54] Dinarello CA, Ikejima T, Warner SJ, et al. Interleukin 1 induces interleukin 1. Induction of circulating interleukin 1 in rabbits in vivo and in human mononuclear cells in vitro. J Immunol 1987;139:1902–1910.
[55] Goldbach-Mansky R, Dailey NJ, Cann SW, Gelabert A, Jones J, Rubin BI, et al. Neonatal-onset multisystem inflammatory disease responsive to interleukin-1β inhibition. N Engl J Med 2006;355:581–591.
[56] Lamkanfi M. Emerging inflammasome effector mechanisms. Nat Rev Immunol 2011;11:213–220.
[57] Ting JPY, Willingham SB, Bergstralh DT. NLRs at the intersection of cell death and immunity. Nat Rev Immunol 2008;8:372–379.
[58] Motani K, Kushiyama H, Imamura R, Kinoshita T, Nishiuchi T, Suda T. Caspase-1 protein induces apoptosis-associated speck-like protein caspase-recruitment domain (ASC)-mediated necrosis independently of its catalytic activity. J Biol Chem 2011;286:33963–33972.
[59] Dinarello CA. Anti-inflammatory agents: present and future. Cell 2010;140:935–950.
[60] Cornelis S, Kersse K, Festjens N, Lamkanfi M, Vandenabeele P. Inflammatory caspases: targets for novel therapies. Curr Pharm Des 2007;13:367–385.
[61] Keystone EC, Wang MM, Layton M, Hollis S, McInnes IBOn behalf of the D1520C00001 Study Team. Clinical evaluation of the efficacy of the P2X7 purinergic receptor antagonist AZD9056 on the signs and symptoms of rheumatoid arthritis in patients with active disease despite treatment with methotrexate or sulphasalazine. Ann Rheum Dis 2011. http://dx.doi.org/10.1136/ard.2010.143578, Mar 15 [Epub ahead of print].
[62] Paszkowski AS, Rau B, Mayer JM, Moller P, Berger HG. Therapeutic application of caspase 1/IL-1β converting enzyme inhibitor decreases the death rate in severe acute experimental pancreatitis. Ann Surg 2002;235:68–76.
[63] Anderson JP, Mueller JL, Rosengren S, Boyle DL, Schaer P, Cannon SB, et al. Structural, expression, and evolutionary analysis of mouse CIAS1. Gene 2004;338:25–34.
[64] Chu ZL, Pio F, Xie Z, Welsh K, Krajewska M, Krajewski S, et al. A novel enhancer of the Apaf1 apoptosome involved in cytochrome c-dependent caspase activation and apoptosis. J Biol Chem 2001;276:9239–9245.
[65] Lech M, Avila-Ferrufino A, Skuginna V, Susanti HE, Anders HJ. Quantitative expression of RIG-like helicase, NOD-like receptor and inflammasome-related mRNAs in humans and mice. Int Immunol 2010;9:717–728.
[66] Csak T, Ganz M, Pespisa J, Kodys K, Dolganiuc A, Szabo G. Fatty acid and endotoxin activate inflammasomes in mouse hepatocytes that release danger signals to stimulate immune cells. Hepatology 2011;54:133–144.
[67] Burdette D, Haskett A, Presser L, McRae S, Iqbal J, Waris G. Hepatitis C virus activates interleukin-1 {beta} via caspase-1-inflammasome complex. J Gen Virol 2012;93 (Pt2):235–246.
[68] Yan W, Chang Y, Liang X, Cardinal JS, Huang H, Thorne SH, et al. High mobility group box 1 activates caspase-1 and promotes hepatocellular carcinoma invasiveness and metastases. Hepatology 2012;55:1863–1875.
[69] Watanabe A, Sohail MA, Gomes DA, Hashmi A, Nagata J, Sutterwala FS, et al. Inflammasome-mediated regulation of hepatic stellate cells. Am J Physiol Gastrointest Liver Physiol 2009;296:G1248–G1257.
[70] Kolly L, Busso N, Palmer G, Talabot-Ayer D, Chobaz V, So A. Expression and function of NALP3 inflammasome in rheumatoid synovium. Immunology 2010;129:175–185.
[71] Imaeda AB, Watanabe A, Sohail MA, Mahmood S, Mohamadnejad M, Sutterwala FS, et al. Acetaminophen-induced hepatotoxicity in mice is dependent on Tlr9 and the Nalp3 inflammasome. J Clin Invest 2009;119:305–314.
[72] Rawat R, Cohen TV, Ampong B, Francia D, Henriques-Pons A, Hoffman EP, et al. Inflammasome up-regulation and activation in dysferlin-deficient skeletal muscle. Am J Pathol 2010;176:2891–2900.
[73] Masumoto J, Taniguchi S, Nakayama J, Shihara M, Hidaka E, Katsuyama T, et al. Expression of apoptosis associated speck-like protein containing a caspase-recruitment domain, a pyrin N-terminal homology domain-con-

taining protein, in normal human tissues. J Histochem Cytochem 2001;49:1269–1275.
[74] Miura K, Kodama Y, Inokuchi S, Schnabl B, Aoyama T, Ohnishi H, et al. Toll-like receptor 9 promotes steatohepatitis by induction of interleukin-1beta in mice. Gastroenterology 2010;139:e7.
[75] Shimizu S, Eguchi Y, Kamiike W, Akao Y, Kosaka H, Hasegawa J, et al. Involvement of ICE family proteases in apoptosis induced by reoxygenation of hypoxic hepatocytes. Am J Physiol 1996;271:G949–G958.
[76] Martin-Murphy BV, Holt MP, Ju C. The role of damage associated molecular pattern molecules in acetaminophen-induced liver injury in mice. Toxicol Lett 2010;192:387–394.
[77] Maher JJ. DAMPs ramp up drug toxicity. J Clin Invest 2009;119: 246–248.
[78] James LP, Farrar HC, Darville TL, Sullivan JE, Givens TG, Kearns GL, et al. Elevation of serum interleukin 8 levels in acetaminophen overdose in children and adolescents. Clin Pharmacol Ther 2001;70:280–286.
[79] Blazka ML, Wilmer JL, Holladay SD, Wilson RE, Luster MI. Role of pro-inflammatory cytokines in acetaminophen hepatotoxicity. Toxicol Appl Pharmacol 1995;133:43–52.
[80] Dambach DM, Watson LM, Gray KR, Durham SK, Laskin DL. Role of CCR2 in macrophage migration into the liver during acetaminophen-induced hepatotoxicity in the mouse. Hepatology 2002;35:1093–1103.
[81] Williams CD, Farhood A, Jaeschke H. Role of caspase-1 and interleukin-1beta in acetaminophen-induced hepatic inflammation and liver injury. Toxicol Appl Pharmacol 2010;247:169–178.
[82] Chen CJ, Kono H, Golenbock D, Reed G, Akira S, Rock KL. Identification of a key pathway required for the sterile inflammatory response triggered by dying cells. Nat Med 2007;13:851–856.
[83] Williams CD, Antoine DJ, Shaw PJ, Benson C, Farhood A, Williams DP, et al. Role of the Nalp3 inflammasome in acetaminophen-induced sterile inflammation and liver injury. Toxicol Appl Pharmacol 2011;252: 289–297.
[84] Jaeschke H, Cover C, Bajt ML. Role of caspases in acetaminophen-induced liver injury. Life Sci 2006;78:1670–1676.
[85] Ishibe T, Kimura A, Ishida Y, Takayasu T, Hayashi T, Tsuneyama K, et al. Reduced acetaminophen-induced liver injury in mice by genetic disruption of IL-1 receptor antagonist. Lab Invest 2009;89:68–79.
[86] Lacour S, Antonios D, Gautieer JC, Pallardy M. Acetaminophen and lipopolysaccharide act in synergy for the production of pro-inflammatory cytokines in murine RAW264.7 macrophages. J Immunotoxicol 2009;6: 84–93.
[87] Abu-Amara M, Yang SY, Tapuira N, Fuller B, Davidson B, Seifalian A. Liver ischemia/reperfusion injury: processes in inflammatory networks—review. Liver Transpl 2010;16:1016–1032.
[88] Jaeschke H. Reactive oxygen and mechanisms of inflammatory liver injury: present concepts. J Gastroenterol Hepatol 2011;26:173–179.
[89] Zhu P, Duan L, Chen J, Xiong A, Xu Q, Zhang H, et al. Gene silencing of NALP3 protects against liver ishaemia-reperfusion injury in mice. Hum Gene Ther 2011;22:853–864.
[90] Shito M, Wakabayashi G, Masakazu U, Motohide S, Nozomu S, Masao E, et al. Interleukin 1 receptor blockade reduces tumor necrosis factor production, tissue injury, and mortality after hepatic ishaemia-reperfusion in the rat. Transplantation 1997;63:143–148.
[91] Harada H, Wakabayashi G, Takayanagi A, Shimazu M, Matsumotot K, Obara H, et al. Transfer of the interleukin-1 receptor antagonist gene into rat liver abrogates hepatic ischemia-reperfusion injury. Transplantation 2002;74: 1434–1441.
[92] Takeuchi D, Yoshidome H, Kato A, Ito H, Kimura F, Shimizu H, et al. Interleukin 18 causes hepatic ischamia/reperfusion injury by suppressing anti-inflammatory cytokine expression in mice. Hepatology 2004;39:699–710.
[93] Tsung A, Hoffman RA, Izuishi K, Critchlow ND, Nakao A, Chan MH, et al. Hepatic ischemia/reperfusion injury involves functional TLR4 signaling in nonparenchymal cells. J Immunol 2005;175:7661–7668.
[94] Bamboat ZM, Balachandran VP, Ocuin LM, Obaid H, Plitas G, DeMatteo RP. Toll-like receptor 9 inhibition confers protection from liver ischemia-reperfusion injury. Hepatology 2010;51:621–632.
[95] Menzel CL, Sun Q, Loughran PA, Pape HC, Billiar TR, Scott MJ. Caspase-1 is hepatoprotective during trauma and hemorrhagic shock by reducing liver injury and inflammation. Mol Med 2011;17:1031–1038.
[96] Szabo G, Bala S, Petrasek J, Gattu A. Gut-liver axis and sensing microbes. Dig Dis 2010;28:737–744.
[97] Ganz M, Csak T, Nath B, Szabo G. LPS stimulation induces and activates the Nalp3 inflammasome in the liver. World J Gastroenterol 2011;17: 4772–4778.
[98] Mizoguchi Y, Tsutsui H, Miyajima K, Sakagami Y, Seki S, Kobayashi K, et al. The protective effects of prostaglandin E1 in an experimental massive hepatic cell necrosis model. Hepatology 1987;7:1184–1188.
[99] Romics Jr L, Dolganiuc A, Kodys K, Drechsler Y, Oak A, Velayudham A, et al. Selective priming to Toll-like receptor 4 (TLR4), not TLR2, ligands by *P. acnes* involves up-regulation of MD-2 in mice. Hepatology 2004;40:555–564.
[100] Okamura H, Tsutsi H, Komatsu T, Yutsudo M, Hakura A, Tanimoto T, et al. Cloning of a new cytokine that induces IFN-gamma production by T cells. Nature 1995;378:88–91.
[101] Gu Y, Kuida K, Tsutsui H, Ku G, Hsiao K, Fleming MA, et al. Activation of interferon-gamma inducing factor mediated by interleukin-1beta converting enzyme. Science 1997;275:206–209.
[102] Matsui K, Yoshimoto T, Tsutsui H, Hyodo Y, Hayashi N, Hiroishi K, et al. Propionibacterium acnes treatment diminishes CD4+ NK1.1+ T cells but induces type I T cells in the liver by induction of IL-12 and IL-18 production from Kupffer cells. J Immunol 1997;159:97–106.
[103] Sakao Y, Takeda K, Tsutsui H, Kaisho T, Nomura F, Okamura H, et al. IL-18-deficient mice are resistant to endotoxin-induced liver injury but highly susceptible to endotoxin shock. Int Immunol 1999;11:471–480.
[104] Nishioji K, Okanoue T, Mori T, Sakamoto S, Itoh Y. Experimental liver injury induced by propionibacterium acnes and lipopolysaccharide in macrophage colony stimulating factor-deficient osteopetrotic (op/op) mice. Dig Dis Sci 1999;44:1975–1984.
[105] Seki E, Tsutsui H, Nakano H, Tsuji N, Hoshino K, Adachi O, et al. Lipopolysaccharide-induced IL-18 secretion from murine Kupffer cells independently of myeloid differentiation factor 88 that is critically involved in induction of production of IL-12 and IL-1beta. J Immunol 2001;166:2651–2657.
[106] Imamura M, Tsutsui H, Yasuda K, Uchiyama R, Yumikura-Futatsugi S, Mitani K, et al. Contribution of TIR domain-containing adapter inducing IFN-beta-mediated IL-18 release to LPS-induced liver injury in mice. J Hepatol 2009;51:333–341.
[107] Calkins CM, Bensard DD, Shames BD, Pulido EJ, Abraham E, Fernandez N, et al. IL-1 regulates in vivo C-X-C chemokine induction and neutrophil sequestration following endotoxemia. J Endotoxin Res 2002;8:59–67.
[108] Nishioka T, Kuroishi T, Sugawara Y, Yu Z, Sasano T, Endo Y, et al. Induction of serum IL-18 with propionibacterium acnes and lipopolysaccharide in phagocytic macrophage-inactivated mice. J Leuk Biol 2007;82:327–334.
[109] McClain CJ, Cohen DA, Dinarello CA, Cannon JG, Shedlofsky SI, Kaplan AM. Serum interleukin-1 (IL-1) activity in alcoholic hepatitis. Life Sci 1986;39:1479–1485.
[110] Valles SL, Blanco AM, Azorin I, Guasch R, Pascual M, Gomez-Lechon MJ, et al. Chronic ethanol consumption enhances interleukin-1-mediated signal transduction in rat liver and in cultured hepatocytes. Alcohol Clin Exp Res 2003;27:1979–1986.
[111] Hsiang CY, Wu SL, Cheng SE, Ho Ty. Acetaldehyde-induced interleukin-1beta and tumor necrosis factor-alpha production is inhibited by berberine through nuclear factor-kappaB signaling pathway in HepG2 cells. J Biomed Sci 2005;12:791–801.
[112] Witek RP, Stone WC, Karaca FG, Syn WK, Pereirea TA, Agboola KM, et al. Pan-Caspase inhibitor VX-166 reduces firbosis in an animal model of nonalcoholic steatoehaptitis. Hepatology 2009;50:1421–1430.
[113] Vandanmagsar B, Youm YH, Ravussin A, Galgani JE, Stadler K, Mynatt RL, et al. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. Nat Med 2011;17:179–188.
[114] Kamari Y, Shaish A, Vax E, Shemesh S, Kandel-Kfir M, Arbel Y, et al. Lack of interleukin-1α or interleukin-1β inhibits transformation of steatosis to steatohepatitis and liver fibrosis in hypercholesterolemic mice. J Hepatol 2011;55:1086–1094.
[115] Wen H, Gris D, Lei Y, Jha S, Zhang L, Huang MT, et al. Fatty acid-induced NLRP3-ASC inflammasome activation interferes with insulin signaling. Nat Immunol 2011;12:408–415.
[116] Stienstra R, Saudale F, Duval C, Keshtkar S, Groener JE, van Rooijen N, et al. Kupffer cells promote hepatic steatosis via interleukin-1beta-dependent suppression of peroxisome proliferator-activated receptor alpha activity. Hepatology 2010;51:511–522.
[117] deRoos B, Rungapamestry V, Ross K, Rucklidge R, Reid M, Duncan G, et al. Attenuation of inflammation and cellular-stress related pathways maintains insulin sensitivity in obese type I interleukin-1 receptor knock-out mice on a high fat diet. Proteomics 2009:3244–3256.
[118] Isoda K, Sawada S, Ayaori M, Matsuki T, Horai R, Kagata Y, et al. Deficiency of interleukin-1 receptor antagonist deteriorates fatty liver and cholesterol metabolism in hypercholesterolemic mice. J Biol Chem 2005;280: 7005–7009.

[119] Petrasek J, Dolganiuc A, Csak T, Kurt-Jones EA, Szabo G. Type I interferons protect from Toll-like receptor 9-associated liver injury and regulate IL-1 receptor antagonist in mice. Gastroenterology 2011;140:e4.
[120] Moschen AR, Molnar C, Enrich B, Geiger S, Ebenbichler CF, Tilg H. Adipose and liver expression of interleukin (IL)-1 family members in morbid obesity and effects of weight loss. Mol Med 2011;17:840–845.
[121] Hosoi T, Yokoyama S, Matsuo S, Akira S, Ozawa K. Myeloid differentiation factor 88 (MyD88)-deficiency increases risk of diabetes in mice. PloS One 2010;5:e12537.
[122] Lapinski TW. The concentration of sFasL, ICE and IL-1beta in the serum and the liver tissue of chronic HCV infected patients. Hepatogastroenterology 2005;52:1479–1483.
[123] Antonelli A, Ferri C, Ferrari SM, Ghiri E, Goglia F, Pampana A, et al. Serum levels of proinflammatory cytokines interleukin-1beta, interleukin-6, and tumor necrosis factor alpha in mixed cryoglobulinemia. Arthritis Rheum 2009;60:3841–3847.
[124] Antonelli A, Ferri C, Ferrari SM, DeMarco S, Di Domenicantonio A, Centanni M, et al. Interleukin-1β, C-x-C motif ligand 10, and interferon-gamma serum levels in mixed cryoglobulinemia with or without autoimmune thyroiditis. J Interferon Cytokine Res 2010;30:835–842.
[125] Tu Z, Pierce RH, Kurtis J, Kuroki Y, Crispe IN, Orloff MS. Hepatitis C virus core protein subverts the antiviral activities of human Kupffer cells. Gastroenterology 2010:305–314.
[126] Wu CG, Budhu A, Chen S, Zhou X, Popescu NC, Valerie K, et al. Effect of hepatitis C virus core protein on the molecular profiling of human B lymphocytes. Mol Med 2006:47–53.
[127] Manigold T, Böcker U, Chen J, Gundt J, Traber P, Singer MV, et al. Hepatitis B core antigen is a potent inductor of interleukin-18 in peripheral blood mononuclear cells of healthy controls and patients with hepatitis B infection. J Med Virol 2003;71:31–40.
[128] Kanneganti TD. Central roles of NLRs and inflammasomes in viral infection. Nat Rev Immunol 2010;10:688–698.
[129] Mancini R, Benedetti A, Jezequel AM. An interleukin-1 receptor antagonist decreases fibrosis induced by dimethylnitrosamine in rat liver. Virchows Arch 1994;424:25–31.
[130] Gieling RG, Wallace K, Han YP. Interleukin-1 participates in the progression from liver injury to fibrosis. Am J Physiol Gastrointest Liver Physiol 2009;296:G1324–G1331.
[131] Zhu RZ, Xiang D, Xie C, Li JJ, Hu JJ, He HL, et al. Protective effect of recombinant human IL-1Ra on CCl4-induced acute liver injury in mice. World J Gastroenterol 2010;16:2771–2779.
[132] Barak V, Selmi C, Schlesinger M, Blank M, Aqmon-Levin N, Kalickman I, et al. Serum inflammatory cytokines, complement components, and soluble interleukin 2 receptor in primary biliary cirrhosis. J Autoimmun 2009;33:178–182.
[133] Ritter M, Gross O, Kays S, Ruland J, Nimmerjahn F, Saijo S, et al. Schistosoma mansoni triggers Dectin-2, which activates the Nlrp3 inflammasome and alters adaptive immune responses. Proc Natl Acad Sci USA 2010;107:20459–20464.
[134] Sakamoto T, Higaki Y, Hara M, Ichiba M, Horita M, Mizuta T, et al. Interaction between interleukin-1beta -31T/C gene polymorphism and drinking and smoking habits on the risk of hepatocellular carcinoma among Japanese. Cancer Lett 2008;271:98–104.
[135] Fujikawa K, Shiraki K, Sugimoto K, Ito T, Yamanaka T, Takase K, et al. Reduced expression of ICE/caspase1 and CPP32/caspase3 in human hepatocellular carcinoma. Anticancer Res 2000;20:1927–1932.
[136] Vidal-Vanaclocha F, Fantuzzi G, Mendoza L, Fuentes AM, Anasagasti MJ, Martin J, et al. IL-18 regulates IL-1beta-dependent hepatic melanoma metastasis via vascular cell adhesion molecule-1. Proc Natl Acad Sci USA 2000;97:734–739.
[137] Roth GA, Faybik P, Hetz H, Hacker S, Ankersmit HJ, Bacher A, et al. Pro-inflammatory interleukin-18 and Caspase-1 serum levels in liver failure are unaffected by MARS treatment. Dig Liver Dis 2009;41:417–423.
[138] Bémeur C, Qu H, Desjardins P, Butterworth RF. IL-1 or TNF receptor gene deletion delays onset of encephalopathy and attenuates brain edema in experimental acute liver failure. Neurochem Int 2010;56:213–215.
[139] Alfonso-Loeches S, Pascual-Lucas M, Blanco AM, Sanchez-Vera I, Guerri C. Pivotal role of TLR4 receptors in alcohol-induced neuroinflammation and brain damage. J Neurosci 2010;30:8285–8295.
[140] Kelly A, Ramanan AV. A case of macrophage activation syndrome successfully treated with anakinra. Nat Clin Pract Rheumatol 2008;4: 615–620.
[141] Lurati A, Teruzzi B, Salmaso A, Demarco G, Pontikati I, Gattinara M, et al. Macrophagic activation sindrome (MAS) during anti-IL1 receptor therapy (anakinra) in a patient affected by systemic onset idiopathic juvenile arthritis (soJIA). Pediatr Rheumatol Online J 2005;3:79–85.
[142] Canna S, Frankovich J, Higgins G, Narkewicz MR, Nash SR, Hollister JR, et al. Acute hepatitis in three patients with systemic juvenile idiopathic arthritis taking interleukin-1 receptor antagonist. Pediatr Rheumatol Online J 2009;7:21.
[143] Maelfait J, Vercammen E, Janssens S, Schotte P, Haegman M, Magez S, et al. Stimulation of Toll-like receptor 3 and 4 induces interleukin-1β maturation by caspase-8. J Exp Med 2008;205:1967–1973.
[144] Netea MG, Simon A, van de Veerdonk F, Kullberg BJ, Van der Meer JW, Joosten LA. IL-1beta processing in host defense: beyond the inflammasomes. PloS Pathog 2010;6:e1000661.
[145] Zaki MH, Boyd KL, Vogel P, Kastan MB, Lamkanfi M, Kanneganti TD. The NLRP3 inflammasome protects against loss of epithelial intergrity and mortality during experimental colitis. Immunity 2010;32:379–391.
[146] Ippagunta SK, Malireddi RK, Shaw PJ, Neale GA, Walle LV, Green DR, et al. The inflammasome adaptor ASC regulate the function of adaptive immune cells by controlling Dock-2 mediated Racactivation and actin polymerization. Nat Immunol 2011;12:1010–1016.
[147] Taxman DJ, Holley-Guthrie EA, Huang MT, Moore CB, Bergstralh DT, Allen IC, et al. The NLR adaptor ASC/PYCARD regulates DUSP10, mitogen-activated protein kinase (MAPK), and chemokine induction independent of the inflammasome. J Biol Chem 2011;286:19605–19616.
[148] Vande WL, Kanneganti TD, Lamkanfi M. HMGB1 release by inflammasomes. Virulence 2011:162–165.
[149] Kayagaki N, Warming S, Lamkanfi M, Walle LV, Louie S, Dong J, et al. Non-canonical inflammasome activation targets caspase-11. Nature 2011;479:117–122.
[150] Elinav E, Strowig T, Kau AL, Henao-Meija J, Thaiss CA, Booth CJ, et al. NLRP6 inflammasome regulates colonic microbial ecology and risk for colitis. Cell 2011;145:745–757.