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Review Article

Therapeutic Perspectives of IL1 Family Members in Liver Diseases: An Update

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Abstract

Interleukin (IL) 1 superfamily members are a cornerstone of a variety of inflammatory processes occurring in various organs including the liver. Progression of acute and chronic liver diseases regardless of etiology depends on the stage of hepatocyte damage, the release of inflammatory cytokines and disturbances in gut microbiota. IL1 cytokines and receptors can have pro- or anti-inflammatory roles, even dual functionalities conditioned by the microenvironment. Developing novel therapeutic strategies to block the IL1/IL1R signaling pathways seems like a reasonable option. This mode of action is now exploited by anakinra and canakinumab, which are used to treat different inflammatory illnesses, and studies in liver diseases are on the way. In this mini review, we have focused on the IL1 superfamily members, given their crucial role in liver inflammation diseases, specifically discussing their potential role in developing new treatment strategies.

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Introduction

Liver disorders are one of the major health care concerns worldwide[1] mostly because of chronic liver diseases such as nonalcoholic/metabolically associated fatty liver disease (NAFLD/MAFLD), alcoholic liver disease (ALD) and viral hepatitis.[2,3] In addition, acute liver disease can be associated with high mortality most frequently caused by drug associated liver injury, especially in Western countries.[4] Autoimmune hepatitis (AIH) is also a risk factor for the development of liver cirrhosis and hepatocellular carcinoma.[5] Therefore, exploring new therapeutic options for treatment of liver disease has become increasingly important in the past couple of decades. Given that inflammation, whether acute or chronic, and the production of proinflammatory cytokines play a key role in the progression of liver disease, it should not come as a surprise that the spotlight of recent pharmacotherapeutic research has been directed to immune processes and the development of molecules with immunomodulatory properties.[6–8] In this review, we have focused on the interleukin (IL) 1 cytokine superfamily as an important player in the development of liver damage regardless of etiology.[9]

Pathobiological effects of the IL1 family

The IL1 superfamily consists of 11 members of IL1 superfamily cytokines and 10 members of IL1 superfamily receptors and is divided into three subfamilies, the IL1 subfamily (IL1α, IL1β, and IL33, and IL1Ra), the IL18 subfamily (IL18 and IL37), and the IL36 subfamily (IL36α, β, γ, and IL38). They are primarily associated with inflammation injury; yet some of the members also improve defensive mechanisms and build immune response to infection. However, most of the IL1 family have nonspecific features. These cytokines may function as pro-inflammatory (IL1α, IL1β, and IL33) or anti-inflammatory (IL1Ra, IL36Ra, IL37, or IL38) cytokines; IL18 can act as either a pro- or anti-inflammatory cytokine[10–12] depending on the microenvironment. IL1 receptors (ILRs) consist of ligand binding subunits IL1R1, ST2, IL18Rα and IL36R, signaling subunits IL1RAcP, IL18Rβ, and a single immunoglobulin IL1-related receptor (SIGIRRs), alternatively named TIR8. SIGIRR/TIR8 has a regulatory function and is considered as an orphan receptor.[10] ILRs are comprised of two subunits, an extracellular immunoglobulin-like domains and an intracellular Toll/Interleukin1R (TIR) domain responsible for oligomerization of IL1R subunits after cell stimulation. Subsequently, MyD88 activates nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases) such as p38 and JNK pathways

Keywords: Interleukin 1 superfamily members; Inflammation; Acute liver disease; Chronic liver disease; Therapy.

Abbreviations: AIH, autoimmune hepatitis; ALD, alcoholic liver disease; ASH, alcoholic steatohepatitis; GSDMD, gasdermin D; GSDMD-N, cleaved GSDMD; HBV, hepatitis B virus; HCV, hepatitis C virus; IL, interleukin; ILR, IL1 receptor; NAFL, nonalcoholic fatty liver; NAFLD/MAFLD, nonalcoholic/metabolically associated fatty liver disease; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor-kappa B; NK cells, natural killer cells; NLRP3, NOD-like receptor family, pyrin domain containing 3; NSP, neutrophil serine protease; SIGIRR, single immunoglobulin IL1-related receptor; TIR, Toll/Interleukin1R.

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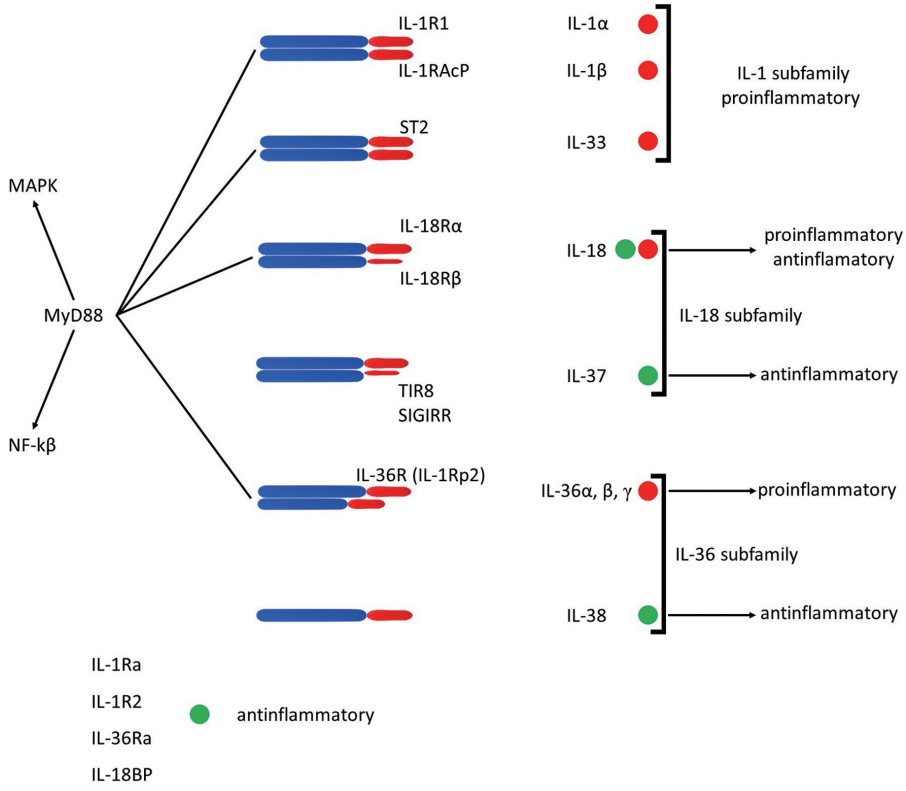

Fig. 1. Three subfamilies of IL1 family. The IL1 subfamily (IL1α, IL1β and IL33, IL1Ra), IL18 subfamily (IL18 and IL37), and IL36 subfamily (IL36 α, β, γ, and IL38). These cytokines may have a dual function: proinflammatory (IL1α, IL1β, IL33) and anti-inflammatory (IL1Ra, IL36Ra, IL37, or IL38) while IL18 can act as pro- or anti-inflammatory cytokine. IL1 receptors (ILR) consist of ligand binding subunits IL1R1, ST2, IL18Rα and IL36R, and signaling subunits IL1RAcP, IL18Rβ, and SIGIRR. After cell stimulation, oligomerization of IL1R subunits takes place recruiting MyD88 and activating NF-κB and MAPK such as p38 and JNK pathways eliciting inflammation. IL1α and IL1β have a decoy receptor IL1R2 inhibiting their signaling, and IL1 and IL36 actions are antagonized by IL 1Ra and IL 36Ra. IL18 signaling is inhibited by IL18B, IL18BP, IL18-binding protein; MAPK, mitogen-activated protein kinase; c-Jun N-terminal kinase; NF-κB, nuclear factor-kappa B; PST2, suppression of tumorigenicity 2; SIGIRR, single immunoglobulin IL1-related receptor.

eliciting inflammation (Fig. 1).[10]

IL1 superfamily members lack a signaling peptide for excretion. For instance, activation of IL1β, IL18, and IL37 depends on caspase-1, which is triggered by the NOD-like receptor family, pyrin domain containing 3 (NLRP3)-inflammasome, converting procaspase-1 into the active caspase.[12] In contrast, IL1α is a biologically active precursor and is activated in liver necrosis.[11] IL1α and IL33 have dual functions. They not only prevent inflammation induced by proapoptotic signals, but also act as proinflammatory factors following tissue necrosis, as part of a damage-associated molecular pattern or DAMP.[11]

NAFLD

NAFLD is a serious public health issue because of its high incidence and increased risk of its progression to liver cirrhosis and hepatocellular carcinoma.[13] NAFLD consists of nonalcoholic fatty liver (NAFL), characterized by accumulation of triglycerides in the absence of inflammation. Nonalcoholic steatohepatitis (NASH), a more severe form of NAFLD characterized by cell damage and infiltration by inflammatory cells.[14] In NAFL, liver damage is usually absent or insignificant because inflammation and pyroptosis are absent or mild. In NASH, stage inflammation and pyroptosis are more serious, and the damage is significant.[15] In recent years, researchers have been increasingly interested in the association of NAFLD with inflammasomes, mostly NLRP3, and to some extent NLRP1, which is less understood, and pyroptosis.

NLRP3 inflammasomes are associated with various pathological events in different organs including fibrosis in the liver, heart, kidneys, lungs, and others.[16] In the liver, activation of NLRP3 inflammasomes stimulates activation of caspase-1, leading to pyroptosis.[15] NLRP3 recognizes microbial and non-microbial signals of cell damage, and in NAFLD it is activated by lipotoxic ceramides[17] and triggers aseptic inflammation[18] by transferring the signal to apoptotic-related spot protein to activate caspase-1, a key processing mediator of interleukin 1 family of cytokines and gasdermin D (GSDMD) cleavage.[12,19] GSDMD-N (cleaved GSDMD) then regulates adipogenesis by activating the NF-κB signaling pathway and increases secretion of inflammatory cytokines.[20]

Pyroptosis is a form of programmed cell death, different form apoptosis and autophagy, triggered by proinflammatory signals, and dependent on inflammatory caspase-1 and caspases4, 5, and 11, with a series of inflammatory responses.[15] It is characterized by the creation of membrane pores that dissipate ion gradients of the cells allowing influx of water, cell swelling, osmotic dissolution, and release of proinflammatory substances inside of the cell, including IL1β, IL18, IL33), IL37, high mobility group protein box-1, and heat shock protein .[7,21–23]

The involvement of NLRP3 inflammasome activation in the severity of NAFLD has been elucidated by numerous animal studies. Inflammation and fibrogenesis in liver damage, was reduced in NLRP3 knockout mice fed a

choline-deficient amino acid diet, moreover arsenic trioxide induced pyroptosis by NLRP3 activation through cytoplasmic cathepsin that led to NAFLD development.[24] MCC950, a selective inhibitor of NLRP3, significantly suppressed inflammation and fibrosis in NAFLD by reducing expression of caspase-1 and monocyte chemoattractant protein-1, IL1β and IL6 levels, and hindered migration of neutrophiles and macrophages in obese diabetic mice.[25] Levels of IL33, also processed by NLRP3 inflammasomes, were increased in serum of mice fed a high-fat diet, and administration of IL33 to the mice attenuated hepatic steatosis but increased fibrosis.[26,27] Anakinra, an IL1 receptor antagonist, as a treatment in type 2 diabetes patients, resulted in a significant decrease of inflammation and insulin resistance. In the treatment of ethanol-induced liver injury, it resulted in a significant reduction of hepatic inflammation, steatosis, and neutrophil infiltration. This raises the possibility of its potential use for treatment of NAFLD.[28–30] The evidence is consistent with other reports that inhibition of NLRP3 inflammasomes and GSDMD significantly reduced inflammation and fibrosis by regulating pyroptosis pathways.[31–34]

Another inflammasome important for the development of NAFLD is NLRP1. It is activated in nonhematopoietic cells and interacts with caspase-1, caspase-5, and most likely with apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain to form an inflammasome that activates both ILβ and IL18,[7,35,36] but with a preference for IL18, at least in insulin-responsive tissue like adipocytes, muscle, and liver.[35] Although the effects of activation of this inflammasome are not completely clear in the development of NAFLD, it has been shown that IL18 has protective effects in animal models of NAFLD.[37] However, that was not confirmed in type 2 diabetes patients or in obese children, in whom IL18 had the opposite correlation.[17,38] Henao-Mejia *et al.*[39] reported that inflammasomes and their effector protein IL18 negatively regulated NAFLD/NASH progression by modulation of the gut microbiota and gut leakage. In mouse models associated with inflammasome-deficiency, IL18 changed the configuration of gut microbiota in a way that exacerbated hepatic steatosis and inflammation through influx of TLR4 and TLR9 agonists into the portal circulation, activating TNF-α expression that driving NASH progression.[39]

Furthermore, the anti-inflammatory cytokine IL37, was found to cause increases of circulating adiponectin and insulin sensitivity in mice transgenic for human IL37 fed a high-fat diet and in mRNA expression in human adipose tissue was correlated with insulin sensitivity.[40] In the same transgenic mice fed ethanol, IL37 expression was lower than in pair-fed transgenic mice with the same extent of liver damage. In patients with alcoholic steatohepatitis, IL37 levels were lower than they were in patients with NAFLD.[41] It is important to note that no mouse homolog of IL37 has been described, and for that reason, only transgenic expression of human IL37 allows study its effects in a mouse model.

ALD

ALD includes acute and chronic forms that can progress to liver fibrosis or cirrhosis. Alcohol causes increased production of the proinflammatory cytokine ILβ through activation of the inflammasome NLRP3-caspase 1.[42,43] In addition, microRNA-148a, which is responsible for the inhibition of NLRP3 inflammasomes is decreased by alcohol consumption through the transcriptional regulator forkhead box protein O1. A recently identified target molecule of microRNA -148a, thioredoxin-interacting protein, was found to be overexpressed during ALD-induced inflammation in the liver through NLRP3 inflammasome activation and pyroptosis.[44] ILβ also triggers invariant natural killer T lymphocyte activation leading to polymorphonucleocyte invasion and further liver damage.[45,46] At the same time, several DAMPs such as ATP and uric acid are produced by hepatocytes,[47] further promoting liver damage. Development of new therapeutic options to block the IL1/IL1R signaling pathways seems reasonable. For now, anakinra and canakinumab, drugs used to treat other inflammatory diseases, but not liver disease, have that mechanism of action. Anakinra is an ILR antagonist with an excellent safety profile, and is used to treat adult rheumatoid arthritis by blocking the biologic activity of IL1.[48] The results of a study that found blockage of IL1 signaling caused reduced liver inflammation and increased in liver regeneration in a mouse model of acute-on-chronic liver injury induced by ethanol also support the hypothesis.[49] In another animal study, administration of IL1Ra led to inhibition of IL1β signaling by down-regulation of Caspase-1 activity and inflammasome activation, thus reducing liver steatosis, inflammation, and damage. Administration of anakinra, an antagonist of IL1α and β receptors was more effective than inhibition of IL1β alone.[28]

Considering that human studies are lacking, data from the Defeat Alcoholic Steatohepatitis (DASH) study, a multicenter, randomized, double-blind controlled trial are eagerly awaited. The primary objective is assessment of the safety and efficacy of a combination of an ILR1 antagonist, anakinra to suppress acute inflammation, pentoxifylline for hepatorenal syndrome prevention, and zinc sulfate compared with methylprednisolone, a standard of care in alcoholic steatohepatitis (ASH).[29] The results of phase 2 trials demonstrating the superiority of combination therapy regarding the survival rate after 3 and 6 months compared with glucocorticoid therapy are encouraging.[50] Other treatment options such as canakinumab, which targets IL1β and not IL1α seem to be less favorable compared with anakinra for treatment of liver disease.[48]

On the other hand, IL18 has shown a proinflammatory role in ALD by promoting inflammation and intestinal cell permeability in animal models.[51] However, a study by Khanova *et al*.[52] using RNA sequencing and proteomic analyses in a mouse binge-drinking model, showed that the CASP11/4- GSDMD pathway was associated with pyroptosis in ASH that was promoted by IL18 deficiency, indicating dual properties of IL18.[52] Thus, depending on the microenvironment, IL18 has the potential to either promote or inhibit inflammation and liver damage, but studies in humans are lacking.

The IL1RL1 chain (also called ST2 or suppression of tumorigenicity 2, T1/ST2, or IL1-R4) is also a potential therapeutic target. IL33 is a soluble form of a decoy receptor shown to correlate with ALD severity in human patients.[48] In the early stages of the disease, ST2 has a protective role mediated by NF-κB inhibition in liver macrophages. It is independent of IL33, as was shown in an animal model comparing alcohol-induced liver injury, inflammation, and hepatic macrophage activation in wild-type, $IL33^{-/-}$ and $ST2^{-/-}$ mice. However, in the same study, which included ALD patients, only individuals with severely decompensated ALD had increases in serum IL33 and ST2.[53,54] Hence, ST2/IL33 potentially has a dual mode of action that is protective in the early stages of disease and damaging as liver injury and inflammation progress.

In a study investigating IL37 in humans and an animal model, IL37 transgenic mice had decreased expression of IL37 compared with pair-fed transgenic mice. Moreover, infusion of human recombinant IL37 improved liver inflammation in a mouse binge-drinking model of ALD. In addition, IL37 expression was compared in liver samples of NAFLD and ASH patients confirming, the anti-inflammatory activity of IL37 in ASH patients, as its expression was decreased when compared to NAFLD patients.[41] Enhancing IL-37 action could present a possible therapeutic option in treating ALD.

Fibrosis

Hepatic fibrosis is a major characteristic of chronic inflammatory liver disease progression and a risk factor for development of hepatocellular carcinoma (HCC). Immunoregulatory mediators such as cytokines, including the IL-1 family, play an important role in fibrinogenesis. Activation of NOD-like receptor NLRP3 inflammasomes has been identified as important factor in hepatocyte pyroptosis, liver inflammation and fibrosis, which can initiate and facilitate progression of fibrosis.[55] These findings propose blockade of NLRP3 pathway as a therapeutic target to reduce liver inflammation and fibrosis. IL-1 and its role in hepatic fibrosis has been extensively investigated. Gieling *et al*. conducted an *in vivo* study which found that IL-1 receptor-deficient mice exhibited decreased hepatic tissue damage and reduced fibrogenesis, indicating that IL-1 participates in the progression from liver injury to fibrosis.[56] In a similar study, mice with steatosis induced by a high-fat diet, and deficient in either IL1α or IL1β had a significantly reduced transformation of steatosis to fibrosis. The result supports neutralizing IL1α and IL1β as a potential therapeutic option in the progression of liver fibrosis.[57] Anakinra, an IL1R antagonist, has shown significant, beneficial modulation of liver inflammation and fibrosis in several *in vivo* studies.[7,28,58] On the other hand, in animal and human studies, IL33 activated hepatic stellate cells and worsened fibrosis.[59,60]

HCC

The IL1 family participates in signaling pathways in tumorigenesis. The most extensively studied family members are IL1 and IL18. An epidemiological study in South Korea showed IL1β polymorphisms were associated with either increased or decreased HCC risk.[61] IL1α is produced in hepatocytes damaged by reactive oxygen species, and promoted carcinogenesis in a mouse model of carcinogen-induced liver cancer. Targeting IL1R signaling may thus be a preventive or therapeutic option in HCC.[62] Bermekimab, an IL1α-specific monoclonal antibody, was recently used in a phase III trial in treatment of metastatic colorectal cancer. The study showed no survival benefit of bermekimab, but cancer-associated cachexia was improved.[63] There is strong evidence that the IL18/IL18R axis is a checkpoint in immunological processes regulating carcinogenesis.[9] Absence of IL18 production leads to loss of antitumor activity, partially because of the absence of the FasL-dependent cytotoxicity of hepatic natural killer (NK) cells. Reduced production of IL18 is also associated with increased liver metastasis of colorectal cancer.[64] Currently, there are several clinical trials targeting the IL18 signaling pathway, including recombinant IL18 and a monoclonal anti-IL18 neutralizing antibody.[65] Elevated IL33 has been detected in HCC patients, and several animal model studies demonstrated antitumoral and antimetastatic activity of IL33. Some studies found decreased IL33 levels and its diminished effects as a protective factor in HCC, highlighting the need for further research of the mechanisms.[66] Regarding IL37, current data suggests that it has antitumor activity in HCC, with strong evidence associating elevated hepatic levels with improved survival.[67]

Drug-induced liver injury

Acute liver injury is also mediated by IL1 superfamily members. In murine-model studies of IL1α and IL1β knockout mice, acute liver injury was diminished compared with wild-type mice.[68] In addition, IL18[69] and IL33[70,71] promoted acetaminophen-induced liver injury, and IL36 exhibited a protective role by induction of CCL20, a protective chemokine.[72] Furthermore, in animal studies, IL37 was shown to have a dual function, with protection through TNF-α inhibition, and destruction by increasing liver injury.[73,74] In acetaminophen-induced liver injury, increased production of IL1β and IL18 by Kupffer cells have shown to induce IFN-γ and TNF-α secretion by Th1 and NK cells, resulting in acute drug-induced liver injury.[69]

Viral hepatitis (A, B, C)

The role of IL1 superfamily members in viral hepatitis-induced liver inflammation has been widely studied and documented. Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection can lead to liver fibrosis, cirrhosis, and HCC. *In vitro* studies in cell cultures have shown that monocyte-derived human macrophages, peripheral blood mononuclear cell – derived primary human macrophages, and Kupffer cells incubated with HCV demonstrated enhanced IL18 and/or IL1β production through mechanisms involving NF-κB signaling, caspase-1 activation, and NLRP3 inflammasomes. Strategies targeting those interleukins may offer new therapeutic options to reduce hepatic inflammation induced by HCV infection.[75,76] Increased secretion of IL18 has also been observed in patients with hepatitis A virus (HAV) infection. A rare fulminant form of viral hepatitis has been reported in patients infection with HAV has been reported in patients with HAV infection and IL18 binding protein (IL18BP) deficiency. IL18BP acts as inhibitory ligand, and its absence has been associated with uncontrolled NK cell activation by IL18 resulting in hepatotoxicity, thus highlighting its potential in treatment and prevention of HAV induced acute liver.[77] However, IL18-mediated stimulation of T cells, NK cells, and NKT cells leading to IFN-γ production has shown to significantly inhibit HBV replication, suggesting that IL18 has potential therapeutic value in HBV infected patients.[78] Elevation of another member of the IL1 superfamily, IL33 has been observed in patients with HBV and HCV, especially in those with the most severe forms of hepatitis. It has been suggested that it increases liver inflammation through activation of monocytes, TNFα, IL6, and IL1β.[79]

AIH

AIH is a chronic inflammatory liver disease with poorly understood pathophysiological mechanisms. Studies in animal models with concanavalin A – induced hepatitis show rapid neosynthesis of IL33, which demonstrates protective activity , possibly due to induction of anti-apoptotic factors and recruitment of Treg which might be an important mechanism of liver repair.[80] Another study suggests that NLRP3 inflammasome-induced IL1β production has an important role in the pathogenesis of concanavalin A – induced hepatitis, providing valuable findings regarding new therapeutic strategies for AIH by blocking NLRP3 inflammasome and IL1β.[81]

Therapeutic perspectives in liver disease

Current therapies for liver diseases are still quite modest, especially with regard to ALD or NAFLD. Therapeutic options targeting specific members of the IL1 superfamily seem to be very promising in the development of new drugs, and are summarized in Table 1.[25,27–30,39–41,49,51,53,54,58–60,65,66,69,82–84] In addition, some cytokines/receptors have anti-inflammatory action (IL37), and others like IL1α, IL1β, and IL18 have pro-inflammatory activity, which could be very useful

Table 1. Potential therapeutic options of IL1 family members in liver disease

Target pathway	Drug	Disease	Study model	Main findings	Author, year
Inhibition of ILα and ILβ receptors	Anakinra	ALD	Mouse	Reduction of liver steatosis, inflammation, and damage	Iracheta-Vellve *et al*., 2017;[49] Petrasek *et al*., 2012[28]
			Human	Superiority of combination therapy (anakinra, pentoxyfilline, zinc) regarding survival rate after 3 and 6 months compared to glucocorticoid therapy	Dasarathy *et al*., 2020[29]
	Anakinra	DMT2	Human	Decrease in insulin resistance and inflammation	Larsen *et al*., 2007[30]
	IL1Ra	Fibrosis		IL1Ra worsened fibrosis in a CCl_4 model, but it had protective effect in the BDL model	Meier *et al*., 2019[58]
Inhibition of ILβ receptor	Canakimumab	DMT2	Human	Decrease in glucose levels during a period of 1 year	Everett *et al*., 2018[83]
		CVD	Human	Decrease in CVD events	Ridker *et al*., 2017[82]
Selective NLRP3 inflammasome inhibitor	MCC950	NAFLD	Diabetic mouse	Suppression of inflammation and fibrosis in NAFLD	Qu *et al*., 2019[25]
NLRP3 inflammasome inhibitor	Sulforaphane	NAFLD	Mouse	Decrease in liver steatosis and inflammation	Yang *et al*., 2016[66]
IL18	/	ALD, NAFLD	Mouse	Increasing gut permeability and gut leakage fueling inflammation	Gyongyosi *et al*., 2019;[51] Henao-Mejia *et al*., 2012[39]
	/	ALI	Mouse	Promoting APAP induced liver injury	Bachmann *et al*., 2018[69]
	Monoclonal recombinant IL18/neutralizing anti-IL18 antibody	HCC	Mouse, Human	Inhibition of IL18 production increases anti-tumoral activity	Birbrair *et al*., 2020[65]
IL37	Recombinant human anti-IL37 antibody	ALD	Mouse	Infusion of human recombinant IL37 improved liver inflammation	Grabherr *et al*., 2018[41]
	/	ALD	Human	Decreased expression of IL37 in ALD patients compared to NAFLD	Grabherr *et al*., 2018[41]
	/	NAFLD	IL37-transgenic mouse	Increased insulin sensitivity and adiponectin levels	Ballak *et al*., 2014[40]
	/		Humans	Insulin sensitivity correlated with expression of IL37 mRNA in fat tissue	
ST2/IL33	/	ALD	Mouse, human	At early stages, ST2 has a protective role independent of IL33. In severe liver damage, IL33 increases liver injury	Wang *et al*., 2017;[54] Sun *et al*., 2019[53]
		NAFLD	Mouse	IL33 diminished liver steatosis but worsened fibrosis	Gao *et al*., 2016[27]
	/	Fibrosis	Mouse, human	Activation of HSC and induction of fibrosis	Kotsiou *et al*.,2018;[59] Tan *et al*., 2018[60]
	Recombinant IL233–hybrid cytokine with IL2 and IL33 properties	Possibly ALI, no studies available	Mouse	Prevents acute renal injury enhancing Treg activity	Stremska *et al*., 2017[84]

ALD, alcoholic liver disease; ALI, Acute liver injury; APAP, Acetaminophen; BDL, Bile duct ligation; CCl_4, Carbon tetrachloride treatment; CVD, cardiovascular disease; DMT2, diabetes mellitus type 2; HCC, Hepatocellular carcinoma; HSC, Hepatic stellate cells; NAFLD, nonalcoholic fatty liver disease; NLPR3, NOD-like receptor family, pyrin domain containing 3; ST2, Suppression of tumorigenicity 2; Treg, $CD4^+Foxp3^+$ regulatory T cell.

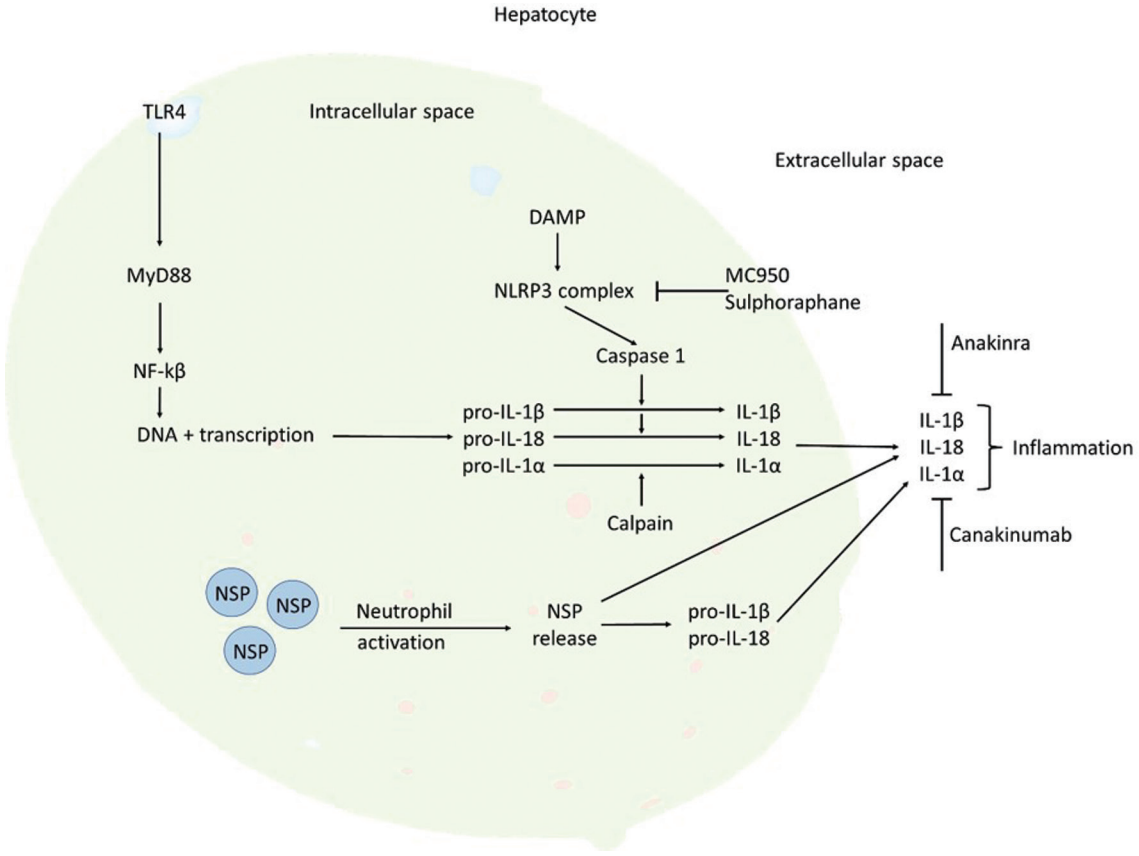

Fig. 2. IL1 family cytokine activation by NLRP3 inflammasomes, neutrophil serine proteases, and potential therapeutic targets. At first, in hepatocytes, activation of NF-κB via recruitment of MyD88 upon TLR4 receptor stimulation occurs. Then, NF-κB promotes the transcription of IL1α, IL1β, and IL18 encoding genes as well as NLRP3 inflammasomes. Activation of caspase-1 is stimulated by DAMP signaling mediated by the NLRP3 inflammasome complex. Pro-IL1β and pro-IL18 are activated via cleavage by caspase-1. while pro-IL1α is secreted as a biologically active precursor activated by calpain. Upon activation, IL1α, IL1β, and IL18 are transported to the extracellular space, promoting inflammation. Conversely, neutrophil activation causes release of NSPs, activating pro-inflammatory cytokines in the intra- and extracellular spaces. Inhibition of the signaling cascade represents potential therapeutic targets in liver disease. Currently available are anakinra, an IL1R antagonist, canakinumab, a monoclonal antibody inhibiting IL1β action and sulforaphane and MC950, which are both NLRP3 inflammasome inhibitors. DAMP, damage-associated molecular pattern; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor-kappa B; NLRP3, NOD-like receptor associated protein 3; NSP, neutrophil serin protease; TLR4, toll-like receptor; (pro)-IL1β, (pro) interleukin-1β; (pro)- IL18, (pro)- interleukin 18; (pro)-IL1α, (pro) interleukin-1α.

by enabling us to act in two opposite ways on inflammatory liver disease, depending on whether agonist or antagonist properties are activated. Also, several cytokines share the same receptor. Hence, by its stimulation or inhibition, it is possible to influence several inflammatory processes mediated by those molecules. For example, IL1RAcP is shared by IL1α, IL1β, IL33, and IL36. Interestingly, some family members, ST2 / IL33. Depending on the stage of damage or inflammation, it may have a protective effect in the early phase by ST2 activation. It may worsen inflammation and accelerate progression of fibrosis in the late phase by increased IL33 secretion. However, the story behind the IL1 superfamily is not simple, as the activation of IL1β and IL18 involves not only the classical NLRP3/inflammatory caspase-1 cytokine activation pathway, but also neutrophil serine proteases (NSPs), as shown in Figure 2, which explains why inhibition of NLRP3 and NLRP1 inflammasomes had low potency.[85,86] Thus, in the future, development of therapeutic options focus on targeting all of the mediators involved in the activation signaling pathway of all or several pro-inflammatory cytokines, like alpha-1 antitrypsin an inhibitor of NSPs that protects against NAFLD development in animal models.[6,87,88] However, a recombinant human IL1Ra, anakinra, has shown promising results in treating ALD, NAFLD in diabetic patients, and fibrosis. In addition, cankinumab, a human monoclonal anti-IL1β antibody demonstrated groundbreaking outcomes in the CANTOS trial, preventing atherosclerosis progression and reducing cardiovascular events.[82] Given that administration of canakinumab in diabetic patients led to an improvement in hyperglycemia over a period of 1 year, it may have potential as an NAFLD treatment.[83]

In conclusion, most of the evidence presented in this mini review originates from preclinical studies, but evidence of the efficacy of these therapeutic options in humans is very scarce. Furthermore, the functions of all IL1 family members, including IL36 and IL38, are not fully understood. We are still a long way from using the potential therapeutic advantages of IL1 family members in routine clinical practice because of lack of clinical data, high cost, and limited availability. Thus, more studies of the function of these cytokines and whether they truly represent a valid therapeutic target are needed.

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Conflict of interest

GYW has been an editor-in-chief of *Journal of Clinical and Translational Hepatology* since 2013. MS has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflict of interests related to this publication.

Author contributions

Conceptualization (MS, RS), original draft preparation (IBC), writing, review and editing (IBC, TK, AP), figure generation (TK), supervision (MS, RS), funding acquisition (IBC), and editing for important intellectual content (GYW, AT).

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