



REVIEW ARTICLE OPEN

Immunopathobiology and therapeutic targets related to cytokines in liver diseases

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Chronic liver injury with any etiology can progress to fibrosis and the end-stage diseases cirrhosis and hepatocellular carcinoma. The progression of liver disease is controlled by a variety of factors, including liver injury, inflammatory cells, inflammatory mediators, cytokines, and the gut microbiome. In the current review, we discuss recent data on a large number of cytokines that play important roles in regulating liver injury, inflammation, fibrosis, and regeneration, with a focus on interferons and T helper (Th) 1, Th2, Th9, Th17, interleukin (IL)-1 family, IL-6 family, and IL-20 family cytokines. Hepatocytes can also produce certain cytokines (such as IL-7, IL-11, and IL-33), and the functions of these cytokines in the liver are briefly summarized. Several cytokines have great therapeutic potential, and some are currently being tested as therapeutic targets in clinical trials for the treatment of liver diseases, which are also described.

Keywords: T helper; ALD; NAFLD; Fibrosis; Inflammation

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INTRODUCTION

Liver disease is a leading cause of mortality, accounting for approximately 2 million deaths per year worldwide.^{1,2} Alcohol consumption, obesity, and hepatitis virus infection are the three major causes of liver diseases, resulting in alcohol-associated liver disease (ALD),³ nonalcoholic fatty liver disease (NAFLD),⁴ and viral hepatitis, respectively. In addition, autoimmune liver diseases, such as autoimmune hepatitis, primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC), are also often seen in the clinic.⁵ Drug-induced liver injury (DILI) is the most common cause of acute liver failure (ALF), with acetaminophen (APAP) being the leading cause of DILI in Western countries. Regardless of the etiology, chronic liver injury can eventually progress to the end-stage diseases, such as cirrhosis and hepatocellular carcinoma (HCC). Accumulating evidence suggests that inflammation plays a key role in controlling liver disease progression.^{6–8} In the current review, we discuss the immunopathobiology and therapeutic targets related to cytokines in liver diseases with a focus on interferons (IFNs) and T helper (Th) 1, Th2, Th9, Th17, interleukin (IL)-1 family cytokines, IL-6 and IL-6 family cytokines, and IL-20 family cytokines. Th cells are CD4⁺ T cells that play important roles in supporting the activity of other immune cells by releasing T cell cytokines. After activation and under specific conditions, naive T cells can differentiate into distinct effector subtypes, including Th1, Th2, Th9, Th17, and Th22 cells. Each subset of Th cells can produce a specific group of cytokines that play important roles in the pathogenesis of liver disease. In addition, several families of

cytokines, including the IL-1, IL-6, and IL-20 families, regulate liver inflammation, fibrosis, injury and repair, and some of these factors are currently being tested as therapeutic targets in clinical trials for several types of liver diseases. Hepatocytes are not only responsible for the production of 80–90% of circulating innate immunity-related proteins but can also produce some cytokines (such as IL-7, IL-11, and IL-33). The functions of these cytokines in the liver are briefly described in the current review.

IFNS

IFNs are typically divided into three classes: type I (IFN- α/β), type II (IFN- γ), and type III (IFN- λ). IFNs were the central focus of research in the field of hepatology in the past due to their critical roles in the control of viral hepatitis and their use as first-line drugs for the treatment of patients with viral hepatitis. Currently, direct-acting antiviral drugs are the first-line drugs for hepatitis C virus (HCV) infection and can effectively eliminate HCV. Nucleos(t)ide analogs are currently the most widely used antiviral drugs for the treatment of hepatitis B virus (HBV) infection, although IFN- α is still used for HBV treatment.

Interestingly, murine hepatocytes respond much more poorly to IFN- α/β and IFN- λ stimulation than human hepatocytes.^{9,10} Murine hepatocytes predominately express nonfunctional, truncated forms of IFN- α/β receptors, while human hepatocytes express the functional, full-length forms of IFN- α/β receptors, which explains the differential responses of murine and human

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hepatocytes to IFN- α/β stimulation.⁹ Thus, although IFN- α/β signaling has been implicated in controlling coxsackievirus B3 infection¹¹ and regulating the hepatic urea cycle,¹² in the murine liver, IFN- α/β signaling probably plays a more important role in the pathogenesis of human liver diseases. The poor and strong responses of murine and human hepatocytes to IFN- λ stimulation are due to the weak and strong expression of IFN- λ receptors on these cells, respectively.¹⁰ Remarkably, both human and murine hepatocytes respond well to IFN- γ stimulation, and IFN- γ has been well documented to promote hepatocyte death, inhibit liver regeneration, and induce liver inflammation (see the discussion in the Th1 cytokine section).

Type III IFN- λ is also known as IL-28B and is involved in the pathogenesis of liver diseases.^{13,14} The rs12979860 C>T polymorphism of the *IFNL4* locus was shown to be the major predictor of spontaneous and IFN- α -induced viral eradication during HCV infection. The *IFNL4* genotype is also associated with the severity of fibrosis in viral hepatitis and NAFLD patients, which is likely mediated by modulating the activation of innate immunity and inflammation in the liver.^{13,14}

TH1 CYTOKINES

Th1 cells can produce many cytokines that play important roles in the pathogenesis of liver diseases (Fig. 1). Among them, both IFN- γ and TNF α have been extensively investigated over the last three decades, and the related findings are summarized below. Other Th1 cytokines, such as IL-12 and IL-2, are also briefly discussed, although their roles in liver diseases have been less well characterized.

IFN- γ is a crucial cytokine in innate and adaptive immune responses against intracellular pathogens such as viruses, some bacteria and protozoans and in cancer elimination (immunosurveillance) through antitumor immunity. Cellular responses to IFN- γ are mediated by interactions with a heterodimeric cell-surface receptor consisting of IFN- γ receptor 1 (IFNGR1) and IFN- γ receptor 2 (IFNGR2), which mainly activates the canonical Janus kinase (JAK)-signal transducer and activator of transcription 1

(STAT1) pathway, ultimately leading to the expression of various downstream genes; however, the IFN- γ -mediated noncanonical signaling pathway has been shown to play an important role in host defense against intracellular bacterial infection. IFN- γ induces the phosphorylation of sorting nexin 8, which recruits I κ B kinase β (IKK β) to the JAK1 complex and subsequently promotes IKK β activation to trigger the induction of downstream genes.¹⁵

IFN- γ is predominantly secreted by Th1 cells, cytotoxic T lymphocytes, natural killer (NK) cells and natural killer T (NKT) cells and plays a key role in promoting antitumor and antiviral immunity. The antitumor immune activity of IFN- γ is well recognized, as indicated by the findings showing that IFN- γ protects mice from chemically induced, spontaneous, and transplanted tumors,¹⁶ but there have been some controversies. For example, in HBV-associated HCC, intrahepatic NK cell-derived IFN- γ accelerates HCC development through epithelial cell adhesion molecule-mediated epithelial-to-mesenchymal transition in HBV surface antigen (HBsAg)-positive hepatocytes in HBV-transgenic mice.¹⁷ Interestingly, CD8⁺ T cell-derived IFN- γ is a critical biomarker of the response to sorafenib treatment of HCC, as demonstrated by the fact that increases in IFN- γ ⁺CD8⁺ T cells are closely associated with improved progression-free survival and overall survival in HCC patients treated with sorafenib.¹⁸ The strong antiviral activity of IFN- γ in the liver is mediated by direct activation of the STAT1 signaling pathway in hepatocytes or by the regulation of immune cells. For example, CD4⁺ T cell-derived IFN- γ promotes C-X-C motif chemokine ligand 9 (CXCL9) production by liver-resident macrophages, which facilitates the retention of antiviral CD4⁺ T cells in the liver.¹⁹ In addition, CD4⁺ T cell-produced IFN- γ is positively correlated with a decrease in HBsAg levels during a flare, suggesting that IFN- γ favors HBV clearance in chronic HBV infection.²⁰

Similar to most autoimmune diseases, PSC and PBC are poorly understood chronic progressive biliary diseases characterized by biliary inflammation and fibrosis. Recently, Bae et al.²¹ demonstrated that mice with chronic expression of IFN- γ induced by ablation of the IFN 3'-untranslated region adenylate uridylylate-rich element developed the classic histological features of

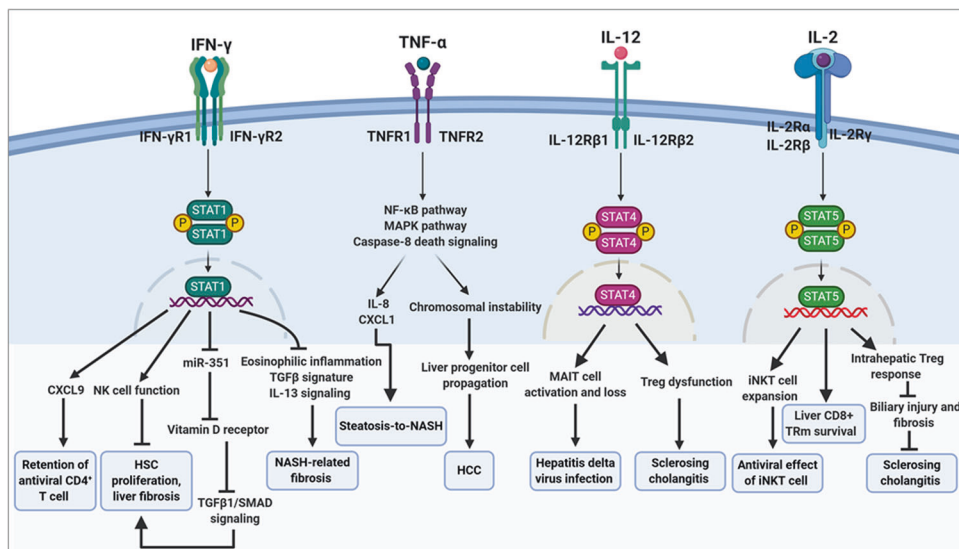


Fig. 1 Roles of Th1 cytokines in the pathogenesis of liver diseases. IFN- γ activates the STAT1 signaling pathway by binding to IFN- γ R1 and IFN- γ R2, which induces liver injury and inflammation but inhibits liver regeneration and fibrosis. IFN- γ /STAT1 signaling facilitates the retention of antiviral CD4⁺ T cells in the liver by inducing CXCL9 expression in liver-resident macrophages. TNF- α binding to TNFR1 and TNFR2 may promote steatosis-to-NASH and HCC progression by activating several pathways. IL-12 binds to the IL-12 receptor, which is composed of IL-12R β 1 and IL-12R β 2, leading to STAT4 activation. IL-12 is involved in the progression of hepatitis delta virus infection and sclerosing cholangitis by activating MAIT cells and inducing Treg dysfunction. IL-2 not only controls HBV infection but also harnesses the antiviral effects of iNKT cells by inducing STAT5 activation. In addition, IL-2 ameliorates biliary injury and fibrosis in murine sclerosing cholangitis by boosting the intrahepatic Treg response

autoimmune cholangitis, as evidenced by increases in total bile acid levels, spontaneous production of anti-mitochondria antibodies, and portal duct inflammation. Furthermore, the IFN- γ -induced Th1 response mediated through CD4⁺ but not CD8⁺ T-cell activation drives the progression of PBC. In addition, in patients with PSC and in a multidrug resistance gene (*Mdr2*)-deficient PSC mouse model, serum IFN- γ levels are significantly elevated and primarily derived from hepatic CD8⁺ T cells and NK cells. Genetic deletion of the *Ifng* gene reduces hepatic CD8⁺ T cell and NK cell cytotoxicity and shifts monocytes/macrophages toward an anti-inflammatory phenotype, thus ameliorating liver fibrosis in *Mdr2*-deficient mice.²² Another interesting study showed that T cell-induced experimental cholangitis was associated with reduced levels of unconjugated bile acids in the liver and increased serum and hepatic levels of conjugated bile acids,²³ suggesting that liver-infiltrating T cells are involved in controlling bile acid synthesis, catabolism, and anabolism. In principle, T cell-mediated bile acid metabolism is dependent on TNF and IFN- γ in PBC, as demonstrated by the fact that the inhibition of both of these cytokines restores the suppression of genes involved in bile acid synthesis, export and hepatic uptake in a farnesoid X receptor-dependent manner.²³ Taken together, these studies reveal that the IFN- γ -dependent immune response may be exploited to identify a novel therapeutic strategy and target for the treatment of cholangitis.

Accumulating evidence suggests that IFN- γ exerts antifibrotic effects in the liver by promoting STAT1 activation to stimulate the antifibrotic functions of NK cells, inhibiting hepatic stellate cell (HSC) proliferation^{24,25} and impairing profibrogenic transforming growth factor (TGF)- β signaling.^{26,27} Recently, another mechanism of the antifibrotic effect of IFN- γ has been reported, showing that IFN- γ negatively regulates microRNA (miR)-351 expression in HSCs through the activation of STAT1 and induction of IFN regulatory factor 2.²⁸ Elevated miR-351 expression in HSCs promotes liver fibrosis by targeting the vitamin D receptor, which is an antagonist of TGF- β /small mothers against decapentaplegic (SMAD) signaling.²⁸ Recent studies suggest that IFN- γ also plays an important role in limiting fibrosis in nonalcoholic steatohepatitis (NASH). Tosello-Tramont et al.²⁹ demonstrated that methionine and choline-deficient (MCD) diet feeding selectively activated conventional NKp46⁺DX5⁺ NK cells in the liver, which were mainly responsible for the increased IFN- γ production. Furthermore, depletion of NKp46⁺ cells exacerbated the progression of NASH-related fibrosis with elevated expression of several profibrogenic genes. Notably, the antifibrotic function of NK cells is mediated via IFN- γ production, as well the induction of M1 macrophage polarization, in NASH.²⁹ Another interesting finding is that *Ifng*-deficient mice develop accelerated NASH-related fibrosis, which is characterized by severe eosinophilic inflammation and increased TGF- β expression and IL-13 signaling.³⁰

Acute-on-chronic liver failure (ACLF) is a distinct clinical syndrome characterized by acute hepatic insult in the context of preexisting chronic liver disease, resulting in multiorgan failure. Recently, Xiang et al.³¹ found that serum IFN- γ levels were significantly elevated in ACLF patients and in a new mouse model of ACLF induced by a combination of chronic liver injury, acute hepatic insult and bacterial infection. The IFN- γ /STAT1 pathway was strongly activated to suppress liver regeneration in ACLF mice, suggesting that IFN- γ is a powerful inhibitory cytokine in ACLF-related liver regeneration.

TNF- α signals by binding to TNF receptor type 1 (TNFR1), which is paired with TNF receptor type 2 (TNFR2), followed by activation of the NF- κ B pathway, the MAPK pathway and caspase-8 death signaling, leading to systemic inflammation and an acute-phase reaction.³² TNF- α is primarily produced by activated macrophages but is also produced by many other cell types, such as Th1 cells, neutrophils and NK cells.³² Early studies suggested that TNF- α produced by Kupffer cells/macrophages plays a key role in the

pathogenesis of ALD in experimental models, but clinical trials have revealed that treatment with TNF α inhibitors fails to improve ALD due to worsening bacterial infection.³³ Emerging evidence suggests that TNF- α plays a role in promoting steatosis-to-NASH progression by stimulating hepatocytes to express IL-8 and the neutrophil-recruiting chemokine CXCL1.^{34–36} Thus, TNF- α blockers or combination therapies with other drugs may exert beneficial effects against NASH and deserve further investigation. In addition, increased TNF- α was also found in patients with acute hepatitis A and was produced by a high proportion of regulatory T cells (Tregs) after stimulation with anti-CD3 and anti-CD28 antibodies. These TNF- α -producing Tregs exhibit the features of Th17 cells, with elevated expression of ROR γ t, which is required to produce TNF- α .³⁷ Moreover, the frequency of TNF- α -producing Tregs in the peripheral blood is associated with severe liver injury in patients with acute hepatitis A.³⁷

Liver progenitor cell (LPC) propagation is associated with exacerbated inflammation in cirrhotic livers, suggesting that reactivation of the generative capacity of LPCs may increase their susceptibility to transformation, thereby initiating inflammation-induced hepatocarcinogenesis.³⁸ Interestingly, TNF- α but not IL-6 accelerates the malignant transformation and expansion of LPCs by inducing chromosomal instability in LPCs and promoting the self-renewal of LPCs, which synergistically drives the conversion of LPCs into liver cancer stem cells.³⁸ More importantly, elevated TNF- α levels are correlated with poor outcomes in HCC patients after sorafenib therapy. TNF- α promotes HCC cell proliferation and resistance to sorafenib treatment. As expected, blocking TNF- α markedly enhances the antitumor effect of sorafenib on HCC cells. Therefore, TNF- α may serve as a novel predictor of sorafenib sensitivity in HCC patients.³⁹

IL-12 belongs to the IL-12 family, which includes IL-12, IL-23, IL-27, and IL-35. Although these cytokines share many similarities in structure, receptors and downstream signaling components, they exert many different functions. IL-12 binds to the IL-12 receptor, which is a heterodimeric receptor composed of IL-12R β 1 and IL-12R β 2, leading to STAT4 activation. IL-12 is well known to play central roles in T cell-mediated responses in inflammation, such as naive T-cell differentiation and NKT cell activation.^{40,41} Recently, an interesting study suggested that after chronic hepatitis delta virus infection, IL-12 induces the activation and apoptosis of mucosa-associated invariant T (MAIT) cells,⁴² which are a recently identified subset of T cells with innate-like characteristics that play important roles in modulating immune responses in various types of liver diseases.⁴³ In addition, IL-12 production is necessary and sufficient to exert suppressive effects on the development of the Th2 response.⁴⁴ As discussed above, Treg functional impairment or deficiency is involved in the pathogenesis of cholangitis.⁴⁵ Interestingly, IL-12 causes hepatic Treg dysfunction by activating STAT4 in experimental sclerosing cholangitis, suggesting that neutralizing IL-12 may serve as a potential strategy for improving the course of cholangitis.⁴⁶

Adoptive immunotherapy with genetically engineered chimeric antigen receptor-modified T (CAR-T) cells has been shown to be a promising strategy for cancer treatment;⁴⁷ however, methods to enhance CAR-T cell efficacy remain obscure. One of the main solutions is to promote cytokine production by CAR-T cells to further facilitate antitumor immunity. It has been demonstrated that inducible expression of IL-12 can boost CAR-T cell efficacy in HCC, which may provide an alternative therapeutic strategy for treating HCC patients.⁴⁸ Thus, IL-12 acts as a proinflammatory cytokine that bridges innate and adaptive immunity, reprograms T cell suppressive functions, and exerts antitumor immune effects.

IL-2 is a potent growth factor that drives the expansion of activated T cells by inducing STAT5 activation.⁴⁹ IL-2 mediates its effect through binding with three classes of IL-2 receptors with different affinities: the low-affinity receptor containing only the IL-2R α -chain (IL-2R α), the intermediate-affinity receptor containing

the IL-2R β -chain (IL-2R β) and IL-2R γ -chain (IL-2R γ), and the high-affinity receptor containing IL-2R α , IL-2R β , and IL-2R γ .⁴⁹ Although hepatocytes do not express IL-2R, IL-2 still plays an important role in the pathogenesis of liver diseases by targeting immune cells. Activation of invariant NKT (iNKT) cells produces an antiviral immune response. The degree of iNKT cell defects is closely associated with liver injury and the HBV DNA load in patients with chronic HBV infection;⁵⁰ however, IL-2 administration rescues iNKT cell expansion and overcomes the hyporesponsiveness of iNKT cells in HBV patients, suggesting that IL-2 not only controls HBV replication but also harnesses the antiviral and immunosurveillance properties of iNKT cells.⁵⁰ In addition, the combination of IL-2 and IL-21 restores HBsAg-specific B-cell maturation, and these mature cells act as anti-HBV surface antibody-producing cells and are associated with the concept of a functional HBV cure.⁵¹ Intrahepatic specific tissue-resident memory T cells (T_{RM} S) but not circulating memory CD8⁺ T cells are preferentially expanded in patients with partial immune control of HBV infection or after the resolution of infection.⁵² These specific T_{RM} S perform local noncytolytic hepatic immunosurveillance. Strikingly, CD8⁺ T cell-autonomous IL-2 is enriched in the HBV-specific T_{RM} compartment, thus promoting liver CD8⁺ T_{RM} survival and maintaining functionality.⁵²

IL-2 is required for the maintenance of functional Tregs, whose functional impairment or deficiency has been identified in autoimmune diseases.^{53,54} Emerging studies have investigated the effects of Tregs on the phenotypic and functional properties of autoimmune hepatitis.^{45,55,56} Notably, treatment with a low dose of IL-2 enhances Treg survival and functional properties, thus attenuating inflammatory liver damage in mice and patients with autoimmune hepatitis.⁵⁷ Another interesting study suggests that IL-2 treatment boosts the intrahepatic Treg response and thereby diminishes the CD8⁺ T-cell response, ultimately ameliorating biliary injury and fibrosis in murine sclerosing cholangitis.⁵⁸ Mechanistically, IL-2 exerts its effect on Tregs by downregulating Treg CD39 expression, which stabilizes the suppressive activity of Tregs under inflammatory conditions.⁵⁹

TH2 CYTOKINES

The type 2 immune response counteracts tissue-damaging inflammation and promotes the resolution of inflammation and restoration of tissue homeostasis. The type 2 immune response has been traditionally thought to be initiated by helminth infection, and other factors, such as allergens, bacteria, viruses, and even host materials, have also been shown to trigger it. Dysregulation of host defense against these factors may cause chronic inflammatory diseases, such as asthma, rhinitis, dermatitis, and anaphylaxis. In addition, Th2 cytokines have also been shown to play important roles in the pathogenesis of liver diseases (Fig. 2).

IL-4 and IL-13 are the two major cytokines in the type 2 immune response and are secreted by Th2-polarized T cells, granulocytes, and monocytes/macrophages. IL-4 and IL-13 are required for the differentiation of Th2 cells, B cells and plasma cells, MHCII expression, M2 macrophage polarization, immunoglobulin isotype switching, mucus production, and innate cell recruitment to inflamed sites.^{60,61} IL-4 and IL-13 share 25% sequence similarity and are expressed in a coordinated manner by immune cells. For example, highly polarized Th2 cells coexpress IL-4 and IL-13, even at the single-cell level, although recent studies have also reported noncoordinated expression of IL-4 and IL-13.⁶² IL-4 and IL-13 signal through heterodimeric cell-surface receptors composed of three possible subunits, the IL-4R α , IL-13R α 1, and γ c chains, which create two types of receptor complexes for IL-4 and IL-13.⁶³ The IL-4R α and γ c chains together constitute the type 1 receptor, whereas the IL-4R α and IL-13R α 1 chains together constitute the type 2 receptor. IL-4 signals through both the type 1 receptor and

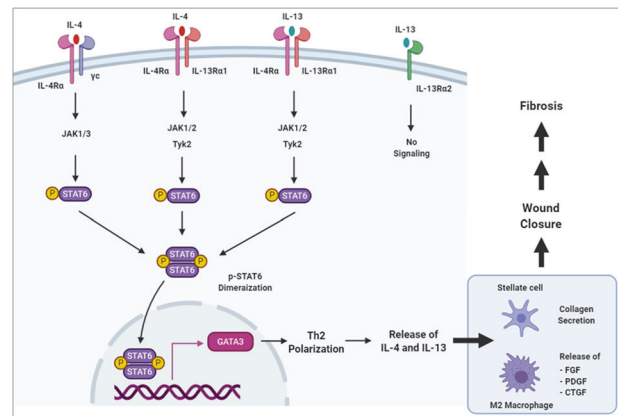


Fig. 2 Roles of Th2 cytokines in the pathogenesis of liver diseases. IL-4 and IL-13 signal through two distinct receptor complexes that are comprised of (1) IL-4R α and IL-13R α 1 (the type 1 receptor complex) and (2) IL-4R α and γ c (the type 2 receptor complex). The activation of the two receptor complexes leads to STAT6 phosphorylation and dimerization via the activation of JAK1/2 and Tyk2 (the type 1 receptor complex) and the activation of JAK1/3 (the type 2 receptor complex). The phosphorylated STAT6 dimer transactivates GATA3, thereby inducing Th2 polarization and the subsequent release of IL-4 and IL-13 by Th2 cells. The released IL-4 and IL-13 stimulate collagen secretion by HSCs and the release of FGF, PDGF, and CTGF by M2 macrophages for wound closure. However, overactivation of this process may result in hepatic fibrosis

the type 2 receptor, whereas IL-13 signals exclusively through the type 2 receptor. Type 1 receptor signaling activates JAKs and their downstream signaling molecules STAT6 and IRS-1/2, while type 2 receptor signaling preferentially activates STAT6. IL-4 binding to the type 1 receptor can also trigger the activation of PI3K and AKT. STAT6 phosphorylation by IL-4R α -mediated signaling leads to STAT6 dimerization and nuclear translocation and induces GATA3 expression. GATA3 promotes Th2 cytokine expression and its own transcription, thereby forming a positive loop to maintain the production of IL-4 and IL-13 in Th2 cells.⁶⁴ Another type of IL-13 receptor, IL-13R α 2, is commonly believed to not participate in signaling processes but rather to act as a decoy receptor for IL-13 and inhibit the activity of IL-13.⁶³ However, there is also emerging evidence that challenges this view. Several studies have shown that IL-13 binding to IL-13R α 2 attenuates IL-4 signaling.^{65,66} In addition, IL-13R α 2 is activated by TNF- α to promote activator protein 1-driven TGF- β production in monocytes.⁶⁷

The type 2 immune response is crucial for tissue repair following injury; however, when this process becomes chronic, overactive, or dysregulated, pathological fibrosis results from the expansion of hepatocytes to restore the lost population and remodeling of the ECM.^{68,69} In injured liver tissues, polarized Th2 cells stimulate the release of IL-4 and IL-13, which directly act on activated fibroblasts to promote collagen secretion for wound closure. IL-4 and IL-13 also facilitate the release of growth factors such as fibroblast growth factor (FGF), connective tissue growth factor (CTGF), and platelet-derived growth factor (PDGF) by M2 macrophages.^{68,69} These factors support wound closure; however, in a highly polarized Th2 immune response, these factors are biased toward the activation of fibroblasts and the ensuing excessive deposition of ECM, which eventually causes fibrosis.^{68,69} Activated M2 macrophages release C-C motif chemokine (CCL)11 and CCL22 and recruit Th2 cells that release IL-4 and IL-13, which can further polarize the response.^{68,69} IL-13 signaling activates the secretion of CCL11 from epithelial cells and fibroblasts, which recruits eosinophils. In the presence of excessive type 2 signaling, inflammatory eosinophils participate in cytotoxicity and fibrosis, although these cells also play a beneficial role, such as promoting the proliferation of parenchymal cells through IL-4 secretion.^{68,69}

In liver tissue infected with parasitic helminths, such as *Schistosoma mansoni*, helminth eggs migrate to the hepatic vasculature and cause chronic irritation, granulomatous inflammation, and fibrosis. These deleterious events are largely mediated by IL-4, IL-13, and immune cells, including M2 macrophages and eosinophils.⁷⁰ IL-4 and IL-13 contribute to Th2 cytokine-driven fibrosis in various liver diseases other than parasitic helminth infection, such as viral hepatitis, biliary disease, autoimmune hepatitis, and NAFLD.^{68,69}

Expanding on the existing literature regarding the importance of the type 2 immune response in the exacerbation of liver fibrosis, recent studies have shown novel mechanistic insights into IL-4- and IL-13-induced fibrosis in the helminth-infected liver. He et al. demonstrated that in the fibrotic livers of mice infected with *Schistosoma japonicum*, IL-13 and TGF- β 1 upregulated miR-21 expression in HSCs via the activation of SMAD1/5, SMAD2, and SMAD3.⁷¹ Inhibition of miR-21 by an adeno-associated virus serotype 8 vector reduced hepatic fibrosis by enhancing the expression of SMAD7, which is an inhibitor of other SMADs, thereby inhibiting the TGF- β 1/SMAD and IL-13/SMAD pathways.⁷¹ A recent study using *Batf3*-deficient mice, which lack CD8a⁺ and CD103⁺ DCs, demonstrated that liver fibrosis induced by *S. mansoni* infection was exacerbated in mice in the absence of migratory CD103⁺ DCs and that the production of IL-12 by migratory CD103⁺ DCs was necessary and sufficient to repress the development of the type 2 immune response.⁴⁴

A comprehensive study using genetically modified mice with cell type-specific disruption of IL-13 signaling elucidated the role of IL-13 in different hepatic cell types, such as hepatocytes, myofibroblasts, and biliary cells, during hepatic regeneration, fibrosis, ductular reaction, and steatosis driven by either *S. mansoni* infection or hepatic IL-13 overexpression.⁷² This study demonstrated that IL-13 signaling in hepatocytes and/or biliary cells induced a ductular reaction but not fibrosis, whereas IL-13 signaling through PDGFRB⁺ fibroblasts was necessary for Th2-induced fibrosis, indicating that IL-13 differentially controls Th2-mediated fibrosis and regeneration.⁷² In addition, IL-13 signaling is able to induce lipogenesis, bile acid synthesis, and biliary-dependent steatosis.⁷² The pathogenic mechanisms of Th2 cytokines in biliary diseases have been further elucidated in recent papers.^{73,74} Mice deficient in the *Mdr2* gene have been used as a common model of PSC due to their defective secretion of phospholipids into bile. PSC accelerates the proliferation of cholangiocytes and subsequent ductular reaction, fibrosis and biliary cirrhosis. An interesting study exploring the therapeutic effect of liver stem cell-derived extracellular vesicles (LSCEVs) reported that let-7-containing LSCEVs attenuated the ductular reaction and biliary fibrosis in MDR2-deficient PSC mice through let-7-mediated inhibition of IL-13.⁷³

To inhibit the overactivation of Th2 signaling and resultant tissue dysfunction, STAT6 signaling, which promotes Th2 polarization, also exerts negative feedback by inducing suppressor of cytokine signaling 1 (SOCS1) expression.⁷⁵ The inhibitory effect of SOCS1 can be overcome by PPAR γ , which upregulates IL-4 and IL-13 expression.⁷⁶ In macrophages, IL-4 and IL-13 control profibrogenic programs by regulating miR-142-5p and miR-130a-3p, which target SOCS1 and PPAR γ , respectively.⁷⁷ Moreover, pharmacological reversal of the dysregulation of these miRNAs in carbon tetrachloride (CCl₄)-treated mice attenuated liver fibrosis, indicating the important role of posttranscriptional regulation in IL-4- and IL-13-induced fibrosis.

In experimental ALD, activated M2 macrophages suppress inflammation and promote tissue repair.⁶ Phagocyte gp91phox, which enhances the function of NADPH oxidase 2, was shown to support the tissue-restorative function of M2 macrophages in mice with ALD; however, the exact roles of M2 macrophages, IL-4 and IL-13 in ALD development are still unclear.^{6,78} In NASH, the involvement of type 1 and type 2 immune responses has been

demonstrated by the findings that the type 2 immune response attenuates metabolic disease but exacerbates NASH in mice and humans.³⁰ Mechanistically, eosinophilic type 2 liver inflammation promotes NASH progression, and IL-13 signaling contributes to fibrogenesis in combination with TGF- β .³⁰ In addition to the canonical functions of Th2 cytokines in inducing fibrosis, recent studies have also highlighted the ability of Th2 cytokines to modulate liver biology and pathology without directly impacting fibrogenic processes such as liver regeneration and tumorigenesis. For example, eosinophils and IL-4/IL-13 stimulate liver regeneration after partial hepatectomy and CCl₄-induced injury.⁷⁹ In addition, accumulating evidence supports the participation of M2 macrophages in immune escape and the progression of HCC.⁸⁰ More recently, it has been reported that osteopontin, a tumor cell-intrinsic factor that induces immune escape, contributes to M2 macrophage polarization and programmed death ligand 1 (PD-L1) expression through the activation of the colony stimulating factor-1 (CSF1) pathway.⁸¹ This activation leads to increased production of Th2 cytokines and HCC metastasis, highlighting the critical role of the osteopontin/CSF1 pathway in the immunosuppressive environment of HCC.⁸¹ Interestingly, several studies have also reported that IL-13 may inhibit HCC growth.^{82,83} Brunner et al. demonstrated that patients with high IL-13⁺ cell infiltration in tumor and distant liver tissues showed a trend toward prolonged survival, presumably in association with an increase in IL-13-producing NKT cells, indicating a complex role for IL-13 in tumor biology.⁸² Cytokine-induced killer (CIK) cell-based immunotherapy has been highlighted as a promising approach for the treatment of HCC; however, its efficacy in advanced HCC treatment has been low. Yu et al. reported that adoptive transfer of CIK cells into mice with HCC resulted in the induction of IL-13 and myeloid-derived suppressor cell (MDSC) infiltration into tumors, contributing to resistance to immunotherapy.⁸⁴ When MDSCs were suppressed by the administration of a phosphodiesterase-5 inhibitor, the efficacy of CIK cell therapy was improved, indicating the critical roles of IL-13 and MDSCs in limiting the efficacy of CIK cell therapy in advanced HCC.⁸⁴

IL-5 is a crucial player in eosinophil biology and is produced by several types of cells, including Th2 cells, type 2 innate lymphoid cells (ILC2s), mast cells, and eosinophils.⁸⁵ Multiple stimuli, such as allergens, viruses, and pollutants, can trigger the release of IL-5.⁸⁵ IL-5 functions as a homodimer and signals through its heterodimeric receptor complex, which consists of IL-5R α and IL-5R β c. High-affinity binding of IL-5 to the IL-5R α subunit triggers its binding to the β c dimer to initiate signal transduction.⁸⁶ The IL-5R α chain is expressed only in eosinophils, basophils, and mast cells in humans. IL-5 binding to its receptor complex activates JAK1 and JAK2, which relay the signal to downstream pathways such as STAT1, STAT3, STAT5, MAPKs, PI3K, and NF- κ B.⁸⁷ Activation of these pathways modulates a variety of the cellular functions in eosinophils, such as differentiation, degranulation, and adhesion.⁸⁵ In addition to modulating these functions, IL-5 drives the egress of eosinophils from the bone marrow in association with chemotactic factors such as CCL11 and primes eosinophils to be activated by mediators.⁸⁵ IL-5 also enhances the survival of eosinophils in combination with antiapoptotic factors, thereby leading to eosinophilia through the production of eosinophils and the inhibition of eosinophil death.⁸⁸

The role of IL-5 in liver diseases remains largely unknown. In mice, concanavalin A treatment induces T cell-mediated hepatitis that resembles the features of human immune-mediated hepatitis.⁸⁹ CD4⁺ T cell-induced liver damage stimulates hepatic ILC2s to produce IL-5 and recruit eosinophils, thereby amplifying inflammation.⁹⁰ Viral hepatitis can also stimulate ILC2s to release IL-5 and IL-13, which inhibit macrophage and T cell secretion of cytotoxic TNF- α ; this inhibition in turn attenuates hepatocyte death.⁹¹ As a member of the Th2 cytokine family that plays a critical role in parasitic infection, IL-5 has been recently reported to

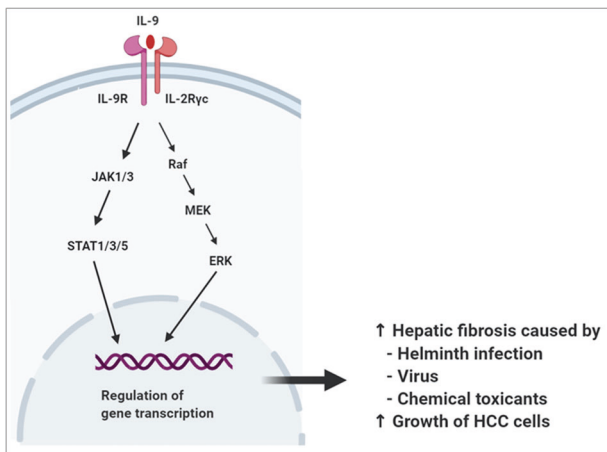


Fig. 3 Roles of the Th9 cytokine (IL-9) in the development of liver diseases. IL-9 signals through the receptor complex comprised of IL-9R and IL-2R γ c, the activation of which stimulates the JAK1/3-PI3K-Akt, JAK1/3-STAT1/3, and Raf-MEK-ERK pathways. The activation of these pathways promotes hepatic fibrosis caused by various factors, such as helminth infection (e.g., *Schistosoma japonicum* and *Echinococcus granulosus*), viruses (HBV), and chemical toxicants (e.g., CCl₄). During tumorigenesis, the growth of HCC cells is supported by IL-9 signaling

be involved in the immunopathology of parasitic infection. *S. japonicum* infection in mice increases IL-5 production by hepatic macrophages and splenocytes in response to IL-33.⁹² Liver fibrosis, which is the outcome of chronic parasitic infection, seems to also be related to IL-5. Sanches et al. reported that IL-5 may participate in *S. mansoni*-induced granuloma formation and collagen deposition in the livers of mice.⁹³

TH9 CYTOKINES

Th9 cells are a subset of effector T cells that mainly produce IL-9, which is a member of the IL-2R γ -chain cytokine family.⁹⁴ In addition to Th9 cells, other types of cells, such as ILC2s, mast cells, and NKT cells, also produce IL-9.⁹⁴ IL-2, IL-4, and TGF- β together promote the conversion of naive CD4⁺ T cells into IL-9-producing cells known as Th9 cells.⁹⁴ IL-4 alone cannot strongly induce IL-9 production and requires the presence of IL-2 and TGF- β for full activation of IL-9 production, while IFN- γ inhibits CD4⁺ T cell production of IL-9.⁹⁴ IL-4 production is inhibited when CD4⁺ T cells become dedicated to IL-9 production. IL-4-mediated repression of Foxp3 expression in CD4⁺ T cells causes CD4⁺ T cells to become IL-9-producing Th9 cells.⁹⁴ Thymic stromal lymphopoietin also promotes IL-9 production when combined with other IL-9-inducing factors, such as IL-2, IL-4, and TGF- β .⁹⁴ The expression of IL-9 has been reported to be influenced by various transcription factors, such as PU.1, NF- κ B, STATs, FOXO1, NFAT, and IRF family members.⁹⁴

IL-9 signals through a receptor complex that comprises the IL-9R and IL-2R γ c subunits. Activation of the receptor complex leads to signal transduction through JAK1 and JAK3, which primarily results in the activation of STAT1, STAT3, and other signaling pathways, such as the PI3K-Akt and MAPK pathways, to regulate multiple cellular functions. IL-9 is a crucial factor in mast cell growth and stimulates mast cells to produce cytokines such as IL-5, IL-6, IL-9, IL-10, and IL-13, thereby promoting allergic inflammation.^{95,96} Autoimmune inflammation can also be amplified by IL-9 through Th17 cell expansion.^{97,98} IL-9 protects against parasitic infections through epithelial protection and enhances antitumor immunity through the actions of CD8⁺ cytotoxic T cells.⁹⁹ However, IL-9 exacerbates allergic diseases in mice and is strongly correlated with elevated IgE levels.^{100,101} IL-9 is also

considered to contribute to transplant tolerance and autoimmune disease development. These diverse functions highlight IL-9 as a pleiotropic cytokine with both protective and pathogenic roles.

IL-9 has been shown to promote hepatic fibrogenesis in part through activation of the Raf/MEK/ERK signaling pathway (Fig. 3).¹⁰² Liver fibrosis, along with granulomatous inflammation in the liver, is a key feature of *S. japonicum* infection.¹⁰³ Two recent studies reported that IL-9 neutralization decreased the level of fibrosis in mice infected with *Schistosoma japonicum*, suggesting a stimulatory role for IL-9 in schistosomiasis-induced fibrosis.^{104,105} In the livers of cystic echinococcosis patients with *Echinococcus granulosus* infection, IL-9 expression is elevated and positively correlated with the degree of liver inflammation. TGF- β /Smad signaling is activated by *Echinococcus* infection, which promotes the differentiation of IL-9-producing CD4⁺ T cells and enhances immunopathological damage.¹⁰⁶

Recent studies have shown that IL-9 is implicated in the pathogenesis of HBV and the development of hepatic fibrosis. In chronic HBV patients with hepatic fibrosis, the percentage of Th9 cells and plasma levels of IL-9 are elevated.¹⁰⁷ In addition, CCl₄-induced hepatic fibrosis is associated with an increase in plasma IL-9 levels and hepatic expression of IL-9.¹⁰⁷ Neutralization of IL-9 with an anti-IL-9 monoclonal antibody attenuates liver fibrosis in mice, indicating the detrimental effect of IL-9 in hepatic fibrogenesis.¹⁰⁷ Th9 cells and IL-9 are known to be unrelated to the progression of HBV-related liver injury.¹⁰⁸ Unlike the data on HBV-related pathology, the data on the role of IL-9 in HCV infection is controversial.¹⁰⁹ IL-9 is known to support the growth of tumor cells that express the IL-9 receptor, including HCC cells.¹¹⁰ A recent study further revealed the involvement of the CCL20 and STAT3 pathways in the acceleration of HCC by IL-9 and Th9 cells.¹¹¹

TH17 CYTOKINES

Th17 cells are a subset of Th cells that play critical roles in host defense against bacterial and fungal pathogens. The functions of Th17 cells are mediated via the production of several cytokines, including IL-17A and IL-22. Dysregulation of IL-17 signaling is linked to defective extracellular pathogen clearance and autoimmune diseases, such as asthma, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and multiple sclerosis, as well as lung, liver, and skin fibrosis.^{112–116} Recent studies have implicated Th17 cells in a variety of chronic liver diseases that develop in response to toxic or metabolic injury, such as HBV/HCV infections, NASH, ALD, HCC, and cholestatic liver diseases (Fig. 4).^{116,117}

Th17 cell differentiation from naive Th0 cells is triggered by TGF- β 1 and IL-6 via the activation of the transcription factor retinoic acid receptor-related orphan nuclear receptor gamma t (ROR γ t), which is a key transcriptional regulator that controls IL-17-producing Th17 cells, γ δ T cells, and innate lymphoid cells in both humans and mice.¹¹³ IL-23 is required for Th17 cell proliferation,¹¹⁸ while IL-27 directly antagonizes the expansion of Th17 cells¹¹⁹ or inhibits IL-23-producing cells; both IL-23 and IL-27 are produced mainly by myeloid cells.¹²⁰ Moreover, IL-25 (also named IL-17E) blocks Th17 cell proliferation by inhibiting IL-23, IL-1 β and IL-6 secretion by DCs (and other cells).¹¹³ IL-25 also drives the expression of IL-13,¹²¹ which is required for the suppression of Th17 responses.¹²² Th17 cells secrete the IL-17 family cytokines IL-17A, IL-17F, IL-17B, IL-17C and IL-17E.¹¹⁴

The IL-17A homodimer (also known as IL-17) is the most abundant IL-17 cytokine in Th17 cells, exhibits relatively high biological activity and signals through the receptors IL-17RA and IL-17RC.¹¹³ IL-17A is mainly produced by CD4⁺ Th17 cells but can also be produced by other cells, including subsets of γ δ T cells, CD8⁺ T cells, NKT cells, NK cells, and innate lymphoid cells (such as type 3 innate lymphoid cells [ILC3s]).^{113,123} IL-17RA is ubiquitously expressed and strongly induced in hematopoietic cells¹²⁴ and

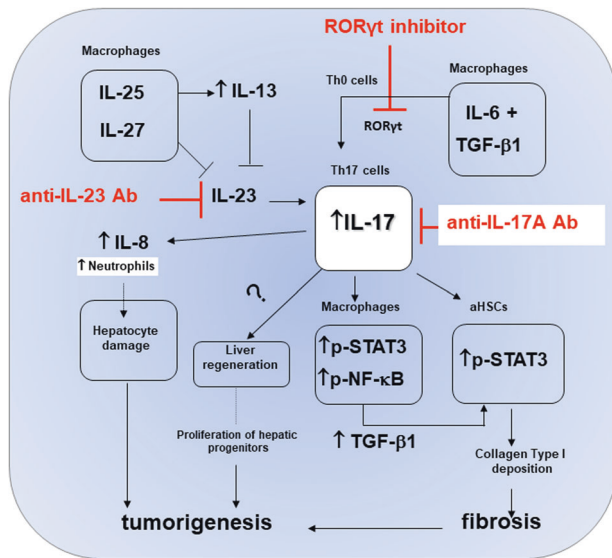


Fig. 4 IL-17 regulation, signaling, and functions in the liver. Th17 cells differentiate from naive Th0 cells via the TGF- β 1/IL-6-dependent activation of retinoid-related orphan receptor γ t (ROR γ t). IL-23 drives the expansion of Th17 cells, while IL-25 and IL-27 inhibit the proliferation of Th17 cells. In the fibrotic liver, IL-17A is primarily produced by CD4⁺ Th17 cells, stimulates cytokine secretion in neutrophils and macrophages, directly activates collagen type I production in activated HSCs (aHSCs), and regulates lipogenesis in steatotic hepatocytes. Several classes of IL-17A/Th17 cell inhibitors have been developed and may have great therapeutic potential for the treatment of liver diseases. These inhibitors include anti-IL-17A neutralizing Abs, anti-IL-23 neutralizing Abs, and ROR γ t inhibitors

fibroblasts¹²⁵ in response to stress. IL-17A activates specific signaling in target cells via the activation of the NF- κ B and STAT3 signaling pathways.^{117,124}

IL-17B is produced mostly by chondrocytes and neurons and signals via the IL-17RA and IL-17RB complex.¹²⁶ IL-17C is secreted by CD4⁺ T cells, DCs, and a subset of keratinocytes. Both IL-17B and IL-17C have been implicated in promoting neutrophil recruitment and inflammatory responses in target cells.¹²⁷ IL-17D is expressed by T and B cells.¹²⁸ Although the functions of IL-17D remain largely unknown, IL-17D stimulates the production of MCP-1 in endothelial cells, the recruitment of NK cells and M1 macrophages, and the development of adaptive immune responses.¹²⁹ Interestingly, IL-17E (IL-25)¹²² and IL-22 (see the discussion in other sections) exhibit functions distinct from those of other Th17 cytokines.¹³⁰ IL-17E propagates allergic responses¹³¹ by binding to IL-17RA and IL-17RB heterodimers (among which IL-17RB represents an IL-17E-specific moiety¹³²) and induces AKT1-dependent activation of the NF κ B signaling pathway in target cells.¹³³ Finally, IL-17F¹³⁴ forms homodimers or heterodimers with IL-17A, suggesting that both of these cytokines exhibit synergistic functions. In support of this hypothesis, genetic ablation of IL-17A results in compensatory upregulation of the expression of IL-17F, which signals through the same receptors (IL-17RA and IL-17RC) as IL-17A, and conversely, IL-17A expression is upregulated in IL-17F^{-/-} mice.¹³⁵ Hence, IL-17A homodimers (but not IL-17A/IL-17F heterodimers) have been identified as a major Th17 cytokine contributing to toxic fibrosis in mice,^{112,136–138} therefore, the role of IL-17A in fibrogenic liver diseases will be discussed in further detail (Fig. 4).

In response to NASH or alcohol-induced liver injury, neutrophils are rapidly recruited to the liver, where they facilitate hepatocyte injury and macrophage activation.¹¹⁶ Th17 cells release IL-17A, which stimulates the induction of IL-8 and CXCL1, recruiting

neutrophils to the damaged liver. Moreover, IL-17A stimulates hepatic macrophages to secrete the cytokines IL-6, IL-1 β , TNF- α , and TGF- β 1.¹¹² Genetic deletion of either IL-17A or IL-17RA in immune cells decreases liver fibrosis by 50–55%, and this effect is attributed to reduced TGF- β 1 production in myeloid cells. Consistently, deletion of IL-17RA in myeloid cells has been shown to prevent the development of toxic liver injury in experimental models established in CCl₄, NASH- and ALD-injured mice,^{136,139,140} suggesting that myeloid cells are the primary targets of IL-17 signaling. In addition, deletion of IL-17RA in nonimmune cells was shown to attenuate CCl₄-mediated liver fibrosis by 25%.¹¹² IL-17A was shown to stimulate collagen type I production either directly or via autocrine secretion of IL-6 in activated HSCs¹¹² but had no effect on normal hepatocytes. While nonsteatotic (CCl₄-injured) hepatocytes seem to lack responses to IL-17A, metabolically injured steatotic hepatocytes strongly respond to IL-17 signaling, resulting in upregulation of the expression of IL-17RA, IL-6, TNFR1, TNF, CXCL1 and other factors and increased synthesis of cholesterol/fatty acids. Notably, NASH- and ALD-induced liver injury, steatosis, and fibrosis (but not inflammation) are markedly reduced in hepatocyte-specific IL-17RA^{-/-} mice,¹³⁶ suggesting that, similar to IL-17 signaling in myeloid cells, IL-17 signaling in steatotic hepatocytes is important in the pathogenesis of NASH and ALD. Moreover, IL-17A was identified as a tumor-promoting cytokine that critically regulates inflammatory responses and cholesterol synthesis in NASH- and ALD-injured steatotic hepatocytes.¹³⁶ ALD- and NASH-induced hepatocyte-specific IL-17RA^{-/-} mice that were challenged with diethylnitrosamine (DEN) developed less HCC than wild-type mice, while the expression levels of the cytokines TNF, IL-6, and IL-1 β were not significantly changed in these mice (compared to wild-type mice).¹³⁶ In addition, recent studies also suggest that γ δ T cells play an important role in producing IL-17 and contribute to ALD in an experimental model.^{141,142}

A novel TNF-TNFR1-dependent caspase-2-S1P-SREBP-DHCR7-mediated cholesterol synthesis pathway, which is activated in response to IL-17 signaling, has been recently identified in experimental and clinical NASH and ALD.^{136,143} Deletion of IL-17RA in steatotic hepatocytes (but not normal hepatocytes) was shown to result in the downregulation of TNFR1, SREBP1/2, and DHCR7 protein expression in steatotic hepatocytes, causing a defect in the biosynthesis of cholesterol/fatty acids (a critical source of energy and structural components of lipid membranes).¹⁴⁴ As a result, hepatocyte-specific IL-17RA^{-/-} mice were protected from hepatic steatosis and HCC.¹³⁶

Hepatic lipogenesis is driven by the transcription factors SREBP1 and 2, which control fatty acid and cholesterol biosynthesis in NASH- and ALD-injured hepatocytes, respectively.¹⁴⁵ SREBP1 and 2 activity is regulated on several levels, including the canonical INSIG:SREBP cleavage activating protein (SCAP) pathway and nonapoptotic caspase-2-dependent pathway, which mediates SCAP-independent SREBP cleavage and processing.^{143,145} SREBP1/2 translocate to the nucleus, triggering transcription of lipogenic genes, such as HMGCR, FASN, DHCR7, and DHCR24.¹⁴⁵ Although it is unknown whether IL-17 signaling controls the SREBP1/2 pathway directly or via its target genes, suppression of TNF-TNFR1 signaling and subsequent SREBP1/2 activation may be responsible for the downregulation of DHCR7 expression in steatotic IL-17RA-deficient hepatocytes.¹³⁶ DHCR7, the sole enzyme that converts 7-dehydrocholesterol into cholesterol, plays a critical role in physiological cholesterol maintenance and turnover. Therefore, IL-17RA-deficient hepatocytes exhibit defects in desmosterol/cholestanol and cholesterol synthesis. Ablation of the *dhcr7* gene in mice results in the complete loss of endogenous cholesterol biosynthesis and lethality in mice,¹⁴⁶ which can be rescued by overexpression of DHCR7 in the liver and brain.^{147,148} Furthermore, a lack of DHCR7 in IL-17RA-deficient steatotic hepatocytes decreases the conversion of 7-dehydrocholesterol

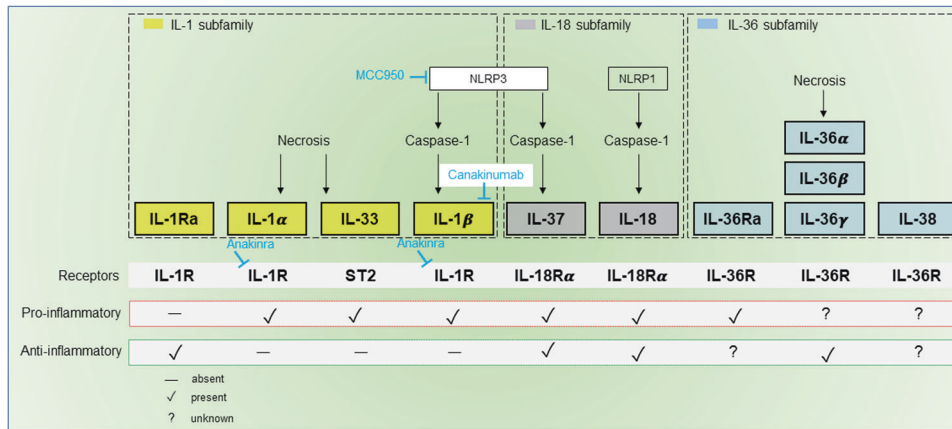


Fig. 5 Role of the IL-1 family members in liver diseases. IL-1 α and IL-1 β play proinflammatory roles in liver diseases through interactions with IL-1R, while the interaction of IL-1Ra with IL-1R has an anti-inflammatory effect. IL-33 binds to the ST2 receptor and triggers proinflammatory responses. Both IL-37 and IL-18 bind to IL-18R α and exert pro- or anti-inflammatory responses that depend on the context of the liver disease. IL-36 α , β or γ interacts with IL-36R and plays an anti-inflammatory role. The inhibition of NLRP3 by MCC950 decreases IL-1 β and IL-37 production. The monoclonal antibody canakinumab blocks IL-1 β responses. Anakinra prevents the interaction of IL-1 α and IL-1 β with IL-1R, reducing the inflammatory process

into cholesterol but increases its conversion into vitamin D₃, which exerts hepatoprotective effects.¹⁴⁹ Suppression of DHCR7-mediated cholesterol synthesis through the prevention of IL-17 signaling or SREBP1/2 or DHCR7 activation may provide a new direction for pharmacological targeting of steatosis-related liver diseases.

Three classes of IL-17A/Th17 cell inhibitors have been developed and are being assessed in clinical trials. These inhibitors include anti-IL-17A neutralizing antibodies,¹⁵⁰ ROR γ t inhibitors¹⁵¹ that prevent the differentiation of naive Th0 cells into Th17 cells, and anti-IL-23 blocking antibodies that suppress the expansion of Th17 cells. In experimental models, therapeutic blockade of IL-23 has been shown to successfully suppress steatosis, fibrosis and HCC progression by 70% in ALD-injured DEN-challenged mice,¹³⁶ suggesting the therapeutic potential of IL-17 blockers for the treatment of ALD.

Experimental models of ALD and alcohol dependence in mice have demonstrated that IL-17A facilitates the alcohol-induced damage of the liver-brain axis associated with advanced stages of ALD,¹⁵² suggesting that a broad range of systemic effects are mediated by IL-17A and may also contribute to brain disorders. Patients with ALD often exhibit elevated serum levels of IL17A, which correlates with the severity of alcoholic steatohepatitis and fibrosis.¹¹⁶ Increased numbers of circulating Th17 cells have been reported in active drinkers but not in abstinent patients with alcohol abuse. Recent studies have linked IL-17A to brain disorders, such as the development of neuroinflammation and anxiety-related behavior in alcohol-fed mice,¹⁵³ suggesting that IL17 signaling may link excessive alcohol consumption associated with alcohol addiction to alcohol-induced liver and brain pathology. Although the role of IL-17 signaling in the pathogenesis of chronic alcohol abuse has not been investigated, several lines of evidence suggest that IL-17A may be one of the missing mediators.¹⁵² Therapeutic blockade of IL-17 signaling by pharmacological inhibitors (a neutralizing anti-IL-17 antibody or ROR γ t inhibitor targeting Th17 cells) not only reverses alcohol-induced damage to the liver/brain axis (reduced activation of microglia and astrocytes) in mice with severe alcohol-induced liver injury but also suppresses voluntary alcohol drinking in alcohol-dependent mice,¹³⁷ indicating that IL-17 signaling may stimulate excessive alcohol consumption in patients.

Overall, IL-17A is a critical mediator of chronic liver injury that mediates the crosstalk among hepatic macrophages/Kupffer cells, HSCs and steatotic hepatocytes. Blocking IL-17 signaling suppresses inflammation, fibrosis, hepatic steatosis, systemic

inflammation and neuroinflammation in experimental models of NASH and ALD (Fig. 4).

IL-1 FAMILY CYTOKINES

The IL-1 family comprises 11 members divided into three subfamilies: the IL-1 subfamily (IL-1 α , IL-1 β and IL-33, and IL-1Ra), the IL-18 subfamily (IL-18 and IL-37), and the IL-36 subfamily (IL-36 α , β , γ , IL-36Ra and IL-38). IL-1 α , IL-1 β , or IL-33 triggers proinflammatory responses, and other members, such as IL-1Ra, IL-36Ra, and IL-38, play anti-inflammatory roles by acting as receptor antagonists, while IL-37 is an anti-inflammatory cytokine, and IL-18 can be pro- or anti-inflammatory in different contexts (Fig. 5).¹⁵⁴

IL-1-type cytokines are produced by immune cells and nonhematopoietic cells in different organs. IL-1 α is biologically active as a precursor molecule. In contrast, IL-1 β , IL-18, and IL-37 require processing by inflammatory caspases (caspase-1) or other enzymes (neutrophil elastase and proteinase-3). The activation of caspase-1 requires the assembly and activation of the inflammasome, a multiprotein complex composed of three proteins (a sensor, such as NLRP3; an adapter, such as ASC; and an effector, such as caspase-1).¹⁵⁵

The IL-1 α precursor is constitutively present in the liver and is released through necrosis. In contrast to IL-1 α , IL-1 β is expressed at low levels in the healthy liver.¹⁵⁶ IL-1 α and IL-33 are dual function cytokines.¹⁵⁷ Proapoptotic signals result in nuclear translocation of IL-1 α and inhibit inflammation. However, when the cell is exposed to necrosis, IL-1 α released by cells is highly proinflammatory and acts as a DAMP.¹⁵⁷ In normal livers, IL-1Ra is also highly expressed, which seems to counteract the contribution of IL-1 β to liver tissue homeostasis. However, the levels of IL-1Ra are increased in the acute-phase response.¹⁵⁸

IL-1-type cytokines activate target cells via 10 specific IL-1 receptors (IL-1R). IL-1 receptors are composed of two subunits that are members of the IL-1R family and are characterized by an extracellular Ig-like domain, a transmembrane domain and an intracellular Toll/Interleukin-1R (TIR) domain that is responsible for intracellular signaling. After ligand binding, IL-1R subunits oligomerize and recruit MyD88 to activate both nuclear factor- κ B (NF- κ B) and mitogen activated protein kinases (MAPKs), consequently triggering proinflammatory responses.¹⁵⁹

In NAFLD, IL-1 α and IL-1 β are the most widely studied members of the IL-1 family. Animal models of diet-induced NAFLD have been used to elucidate the roles of IL-1 family members in disease

pathogenesis. Kamari and colleagues demonstrated a significant increase in hepatic expression of IL-1 α and IL-1 β in NASH animals compared to controls.¹⁶⁰ Both IL-1 α - and IL-1 β -deficient mice exhibited less inflammation and fibrosis than control mice after 18 weeks of an atherogenic diet. However, only IL-1 α -KO mice exhibited increased hepatic and plasma cholesterol levels, suggesting that IL-1 α and IL-1 β play distinct roles in steatosis establishment.¹⁶⁰ In a recent study, Kamari et al. demonstrated that, compared to WT mice, IL-1 α -deficient mice fed an HFD for 16 weeks exhibited improved insulin resistance and diminished adipocyte size and triglyceride accumulation in the liver.¹⁶¹ The IL-1 α produced in mice fed an atherogenic diet was derived from hepatic macrophages/Kupffer cells, since macrophage-specific IL-1 α -KO mice exhibited less steatohepatitis than WT mice.¹⁶² In addition, Pan et al. demonstrated that in NASH, IL-1 β was released mainly by Kupffer cells through the activation of NLRP3 by mitochondrial DNA.¹⁶³

When fed an HFD, mice deficient in three genes that activate IL-1 β (caspase-1, neutrophil elastase, and proteinase-3) demonstrated less steatosis and inflammatory markers in adipose tissue than control mice.¹⁶⁴ During the progression of murine NAFLD from steatosis to steatohepatitis, the increase in liver IL-1-type cytokines has been demonstrated through transcriptome analysis.¹⁶⁵ Cleaved gasdermin D (GSDMD-N) is a membrane pore-forming protein responsible for IL-1 β and IL-18 release. To examine the role of GSDMD in NASH, Xu et al. challenged GSDMD-KO mice with a NASH-inducing diet and observed reduced hepatic secretion of IL-1 β , inflammation, and fibrosis compared to those of WT littermates. Similar to those of animal models of NAFLD, increased hepatic levels of NLRP3, GSDMD, and IL-1 β have been detected in patients with NASH.¹⁶⁶ In a recent paper on morbidly obese patients, serum levels of IL-1 β were associated with the severity of steatosis.¹⁶⁷

In contrast to IL-1, IL-18 has been reported to be protective in animal models of NAFLD. IL-18-KO mice fed an HFD showed weight gain, insulin resistance, and steatosis. In addition, treatment of IL-18-deficient mice with recombinant IL-18 protein reduced hepatic lipid accumulation and insulin resistance.¹⁶⁸ Nonhematopoietic cells are the primary source of IL-18 in HFD-fed mice after activation of the NLRP1 inflammasome.^{169,170} In both obese type 2 diabetes mellitus (T2D) patients and obese children, serum levels of IL-18 were significantly higher than those of nonobese controls, and in obese children, IL-18 positively correlated with systemic inflammation, liver lipid accumulation, and liver injury.^{171,172} However, treatment of T2D patients with anti-IL-18 monoclonal antibodies did not improve insulin sensitivity.¹⁷³

Treatment of obese diabetic mice with the NLRP3 inhibitor MCC950 decreased circulating levels of IL-1 β , IL-6, and MCP-1 and improved liver inflammation and hepatic steatosis.¹⁷⁴ In addition, NLRP3-deficient mice challenged with palmitic acid developed less liver inflammation than WT mice.¹⁷⁵ The administration of sulforaphane, a pharmacological inhibitor of the NLRP3 inflammasome, decreased hepatic steatosis and inflammation induced by HFD in mice.¹⁷⁶ In a clinical setting, T2D patients treated with anakinra (IL-1Ra) exhibited decreases in insulin resistance and overall inflammation.¹⁷⁷ In contrast to the clinical administration of anakinra to treat T2D, the treatment of these patients with canakinumab, a monoclonal antibody targeting IL-1 β , demonstrated improvements in glucose homeostasis only during the first year of treatment.¹⁷⁸ These animal and clinical studies suggest potential benefits of MCC950, anakinra, and canakinumab in treating patients with NAFLD.

The role of IL-33 in NAFLD has also been demonstrated in animal models of HFD-induced steatohepatitis. Levels of IL-33 were upregulated in the serum and livers of HFD-fed mice, but mice deficient in IL-33 were not protected from liver inflammation and fibrosis compared to WT mice.¹⁷⁹ The administration of IL-33

to HFD-fed mice attenuated hepatic steatosis but intensified fibrosis.¹⁸⁰ The role of the IL-36 subfamily in NAFLD remains unclear. However, mice lacking IL-36Ra and fed an HFD exhibited decreased adiposity and serum glucose levels, as well as improved insulin sensitivity, compared to those of WT mice, suggesting a proinflammatory role of IL-36Ra and/or a protective role of IL-36 cytokines in obesity.¹⁸¹ The role of the anti-inflammatory cytokine IL-37 in obesity was demonstrated in a transgenic mouse overexpressing human IL-37. After HFD feeding for 16 weeks, IL-37-transgenic mice exhibited increased circulating levels of adiponectin and insulin sensitivity. Notably, in humans, the mRNA expression of IL-37 in adipose tissue correlated with insulin sensitivity.¹⁸²

In ALD, the importance of IL-1 signaling in disease pathogenesis was revealed by using mice deficient in different components of the IL-1 pathway, such as caspase-1, IL-1R1, and ASC. Mice deficient in these components developed less steatosis, inflammation, and fibrosis than WT mice after ethanol challenge.¹⁸³ The dependence of the NLRP3 inflammasome on IL-1 β production was demonstrated by the finding that NLRP3-deficient mice were protected from alcohol-induced liver inflammation, liver injury, and steatosis.¹⁸⁴ Notably, patients with ALD had elevated levels of IL-1 β , IL-18, and caspase-1 in the liver, which was positively correlated with disease severity.¹⁸⁵ IL-1 β derived from Kupffer cells in ALD induces iNKT recruitment, which triggers liver injury through TNF- α production and neutrophil recruitment to the liver.¹⁸⁶ In addition, acute-on-chronic alcohol feeding in mice resulted in inflammasome-mediated IL-18 activation in the proximal small intestine, contributing to gut leakiness in ALD.¹⁸⁷ In an alcoholic hepatitis mouse model, intragastric administration of alcohol with HFD ad libitum increased IL-18 serum levels compared to those of control mice. However, IL-18-KO mice exposed to the AH diet exhibited increased hepatocyte pyroptosis and neutrophil infiltration in the liver.¹⁸⁸

In addition to the positive effects of anakinra on T2D, it has been shown that interfering with IL-1 β signaling in ALD in the context of anakinra treatment in vivo significantly reduced hepatic inflammation, hepatic injury, steatosis, and neutrophil infiltration induced by ethanol.¹⁸³ Anakinra was also used in a mouse model of acute-on-chronic liver injury to observe the effect of the antagonist on liver inflammation and hepatocyte regeneration in AH. Anakinra treatment decreased liver inflammation and neutrophil infiltration and resulted in enhanced hepatocyte regeneration and an increased rate of recovery from liver injury.¹⁸⁹ Based on in vivo studies, anakinra combined with zinc and pentoxifylline administration is currently being evaluated in a phase 2 clinical trial with 103 severe AH patients in comparison to methylprednisolone treatment of patients. The survival rate between the groups was similar at 30 days. However, at 3 and 6 months, an increasing trend in survival was observed.¹⁹⁰

Mice deficient in IL-1R-like 1 (IL1RL1 and ST2), a receptor for IL-33 were subjected to an alcohol diet and exhibited reduced inflammatory activation of hepatic macrophages. The authors also demonstrated that substantial cell death in severe liver injury resulted in the release of IL-33, which signaled through ST2 to activate immune cells in the liver, such as iNKT cells and ILC2s, increasing tissue damage.^{191,192} Importantly, in humans, the plasma levels of soluble ST2 were positively correlated with the severity of ALD.¹⁹³ A recent paper demonstrated that the IL-33/ST2 pathway was dysregulated in neutrophils in severe AH patients, which was related to an increased risk of developing infection.¹⁹⁴

The anti-inflammatory cytokine IL-37 has also been shown to play a role in ALD. Chronic ethanol-fed IL-37 transgenic mice exhibited less hepatic expression of IL-37 than WT mice and had similar amounts of liver damage. In addition, in a binge-drinking model, the administration of recombinant IL-37 to WT mice resulted in reduced hepatic inflammation. Consistent with the

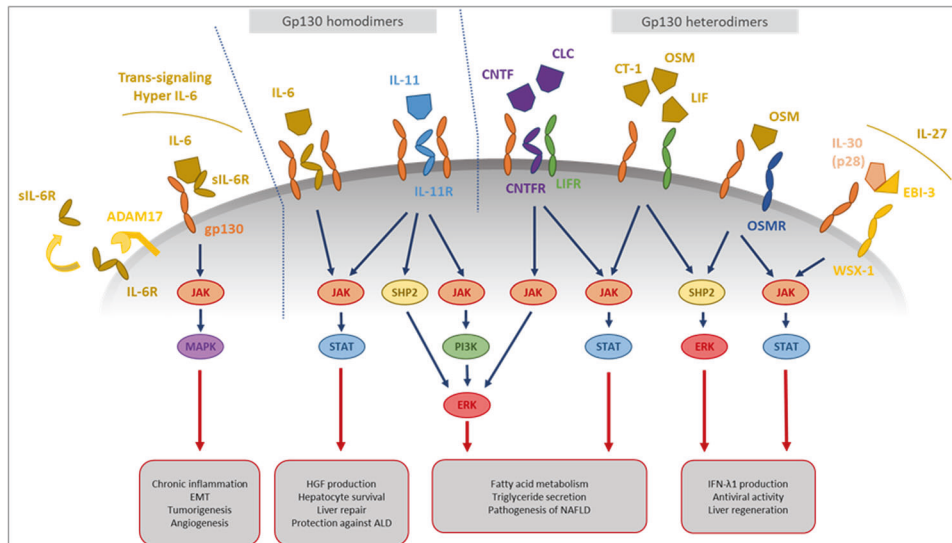


Fig. 6 Members of the IL-6 cytokine family and their associated receptors. The signaling pathways of IL-6 and IL-11 are shown on the left and mainly trigger proinflammatory responses. In contrast, the classic signaling pathways of all IL-6 family cytokines are shown on the right and lead to anti-inflammatory cascades and exert many important functions in the liver

murine results, patients with alcoholic steatohepatitis showed decreased expression of IL-37 in the liver compared to NAFLD patients.¹⁹⁵

In chronic liver diseases, such as ASH and NASH, fibrosis is characterized by the deposition of extracellular matrix (ECM), which contributes to organ failure. Gieling et al. highlighted the role of IL-1 in the activation of HSCs, enabling the transition from liver injury to fibrosis.¹⁹⁶ IL-1 β derived from myeloid cells stimulates IL-17 and TNF- α and perpetuates liver fibrosis.¹⁹⁷ A recent paper demonstrated that IL-1Ra plays distinct roles in the bile duct ligation (BDL)- and CCl₄-induced fibrosis models. In the CCl₄ model, IL-1Ra was harmful, while in the BDL model, it was protective against liver fibrosis.¹⁹⁸ IL-1 α and IL-1 β seem to distinctly influence the onset of acute-on-chronic liver failure in human and experimental cirrhosis.¹⁹⁹ The role of IL-33 in fibrosis has been extensively studied in human and animal models, demonstrating the crucial role of IL-33 in HSC activation and liver fibrogenesis.^{200,201}

The IL-1 family also plays a role in acute liver injury (ALI). A study by Sultan et al. demonstrated the important roles of IL-1 α and IL-1 β in the liver injury caused by LPS and D-galactosamine (GalN) using IL-1 α - and IL-1 β -KO mice, respectively.²⁰² Liver inflammation, injury and hepatocyte death were attenuated in the IL-1 α - and IL-1 β -KO mice in comparison to WT mice.²⁰² In addition, mice with hepatocyte-specific deletion of IL-1R that were challenged with LPS/GalN developed less systemic and liver inflammation than WT mice.²⁰³ In another model of ALI induced by APAP, IL-1 α plays a crucial role in APAP-induced liver injury, while IL-1 β is not required.²⁰⁴ IL-18 has been shown to induce liver injury in mouse models of concanavalin A (Con A)- or APAP-induced ALI by inducing the expression of IFN- γ and FasL in the liver.^{205,206}

Antunes et al. recently investigated the role of IL-33 in APAP-induced liver injury and showed that IL-33 released by necrotic hepatocytes promoted liver injury by neutrophil infiltration into the liver.²⁰⁷ Furthermore, in a liver ischemia and reperfusion mouse model, IL-33 was mainly produced by liver sinusoidal endothelial cells and was shown to drive neutrophil infiltration, subsequently inducing neutrophil extracellular trap formation, which promoted excessive liver injury.²⁰⁸

APAP challenge also promotes IL-36 release from hepatocytes, which in turn induces expression of the protective chemokine CCL20. Accordingly, treatment of APAP-challenged mice with an IL-36 receptor antagonist worsens liver injury.²⁰⁹ The cytokine IL-

37 seems to have contradictory roles in ALI. In a mouse model of repeated Con A challenge, IL-37 decreased hepatic production of TNF- α and induced hepatic M2 macrophage polarization.²¹⁰ Another study showed that AAV-IL-37 injection exacerbated liver inflammation in Con A-challenged mice via the activation of recruited NK cells.²¹¹

IL-6 FAMILY CYTOKINES

Since it was first cloned in 1986, IL-6 has been the focus of many studies that contributed to the discovery of the entire IL-6 family of cytokines. IL-6 family cytokines are composed of seven variants of four-helix cytokines: IL-6, IL-11, ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), oncostatin M (OSM), cardiotrophin 1 (CT-1), and cardiotrophin-like cytokine (CLC). In addition, a newly discovered cytokine known as IL-27, a heterodimeric cytokine formed by the four-helix protein p28 and the soluble cytokine receptor Epstein-Barr virus-induced gene 3, has been included in the IL-6 family (Fig. 6). All IL-6 family cytokines bind to receptor complexes composed of one or two gp130 molecules. As shown in Fig. 6, IL-6 and IL-11 receptors include two gp130 molecules (gp130 homodimers), while the other cytokine receptors include one gp130 molecule that forms a heterodimer with other cytokine receptors. The IL-6 receptor (IL-6R) exists in two forms: a transmembrane receptor (mIL-6R) and a soluble receptor (sIL-6R). By binding to mIL-6R, IL-6 activates the canonical signaling pathway and subsequently triggers anti-inflammatory responses. On the other hand, in cells that do not express mIL-6R, IL-6 can activate the signaling pathway by binding to sIL-6R.²¹² Similarly, IL-11 can activate the signaling pathway via sIL-11R.²¹³ sIL-6R and sIL-11R are derived through the cleavage of the corresponding transmembrane receptors by the proteases ADAM17 and ADAM10, respectively.²¹³ After binding to the IL-6Ra subunit, IL-6/IL-6Ra can induce the dimerization of two gp130 molecules, leading to the formation of a tetramer and further activating the JAK/STAT signaling pathway. As shown in Fig. 6, the second class of gp130 receptors is gp130 heterodimers. For example, OSM can bind to gp130/OSMR and gp130/LIFR. The latter heterodimer is also the receptor for CT-1 and LIF. The heterodimeric receptor composed of gp130/LIFR can also bind to the CNTFR α chain expressed by hepatocytes and act as a receptor for both CNTF and CLC. Finally, the heterodimer composed of gp130 and WSX-1 binds to IL-27. In summary, gp130 is the only

receptor subunit present on all cell types, while the other IL-6 family receptor subunits are expressed specifically in a variety of cell types. Therefore, the sensitivity and ability of a cell type to respond to a given cytokine is determined by the distribution of these heterodimeric receptors.²¹⁴

IL-6 performs a large variety of functions and is mainly produced by immune cells but can also be expressed by hepatocytes.²¹⁵ Earlier studies in the 1980s first reported that IL-6 plays a key role in promoting liver regeneration after partial hepatectomy, but later studies have suggested that IL-6 plays a more important role in promoting hepatocyte survival rather than proliferation. The hepatoprotective effects of IL-6 have been well documented in many models of ALI, but IL-6 may promote liver inflammation during chronic liver injury. Following ALI, regardless of etiology, hepatocytes can self-renew by entering the cell cycle to restore liver mass and function. In the context of acute liver stress, IL-6 family cytokines play crucial roles in regulating liver regeneration and promoting hepatocyte survival.²¹⁶ For example, Gao et al.²¹⁷ recently provided evidence suggesting that hypoxia-inducible factor 2 α reprograms hepatic macrophages to produce the hepatoprotective cytokine IL-6, thereby ameliorating DILI in mice. In a partial hepatectomy model, hepatocytes contribute to IL-6 production, which is dependent on the HGF/cMET signaling pathway, thereby promoting liver repair.²¹⁵ IL-6 promotes liver regeneration by activating STAT3 via the canonical signaling pathway, but a recent study suggested that IL-6 signaling through sIL-6ra also controls liver regeneration after partial hepatectomy.²¹² In addition, the role of IL-6 in the pathogenesis of fatty liver disease has been reported. Early studies showed that serum and hepatic IL-6 levels were elevated and protected against ALD in animal models.²¹⁸ Elevated IL-6 levels were also observed in serum and liver and adipose tissues from NASH patients, implicating IL-6 in insulin resistance, steatosis, and liver injury.²¹⁶ IL-6 levels are also elevated in high-fat diet (HFD)-fed mice, and genetic deletion of *Il6* enhances HFD-induced NAFLD.²¹⁹ In contrast, *Il6* deletion attenuates liver injury and inflammation in another model of NASH induced an MCD diet.²²⁰ These conflicting data on the role of IL-6 in NAFLD may be due to the different models used and wide expression of mIL-6R and its signaling subunits gp130, sIL-6R, and sgp130.²¹⁶ Further studies are required to elucidate the cell-specific IL-6 functions in NAFLD, which may help us to better understand the pathogenesis of this disease. IL-6 and other IL-6 family cytokines may play important roles in controlling bacterial infection by stimulating hepatocytes to produce a large number of antibacterial proteins. For example, in murine models of bacterial infection with *Klebsiella pneumoniae* and *Escherichia coli*, IL-6 has been shown to play a beneficial role by stimulating hepatocytes to produce lipocalin 2 (LCN2), which inhibits bacterial infection.²²¹ In summary, IL-6 exhibits both pro- and anti-inflammatory properties and contributes to liver homeostasis by regulating metabolic functions, regeneration, and defense against infection.²¹⁶

Elevated serum IL-6 levels are associated with an increased risk of HCC.²²² In human HCC, the number of infiltrating tumor-associated macrophages (ATMs) is inversely correlated with prognosis in HCC patients, and it was shown that IL-6 secreted by ATMs promotes the expansion of HCC cancer stem cells through STAT3 activation.²²³ In a murine model of HCC induced by the administration of DEN followed by injections of 3,3',5,5'-tetrachloro-1,4-bis(pyridyloxy) benzene (TCPOBOP), p53-dependent apoptosis was suppressed by IL-6 signaling.²²⁴ Interestingly, upon carcinogen-induced DNA damage, monocytes were recruited to the liver and produced high levels of sIL-6R, which increased IL-6 signaling.²²⁴ Tumor angiogenesis was also increased by IL-6 signaling in those mice.²²⁴ Thus, strategies aimed at blocking IL-6 signaling represent an interesting therapeutic option to prevent HCC development.

IL-6 and other IL-6 family cytokines have been implicated in the pathogenesis of viral hepatitis. For example, IL-6 and IFNs were

reported to promote direct antiviral effects to limit the replication of HBV in hepatocytes.²²⁵ Interestingly, it has recently been demonstrated that HBV can modulate liver macrophage differentiation and function to promote HBV infection in hepatocytes by significantly reducing the production of IL-6 and proinflammatory cytokines.²²⁶ IL-6 is also known to be important to both T lymphocytes and B lymphocytes, as it is a cofactor of cytotoxic T lymphocytes and induces B-cell differentiation into antibody-producing cells, playing an important role in inhibiting HBV infection.²²⁷ IL-27 has also been shown to have antiviral properties that defend against HBV by stimulating IFN- λ 1 via the activation of the ERK1/2 and NF- κ B signaling pathways.²²⁸ HCV infections are characterized by inflammation that results from the recognition and interaction of HCV RNA and proteins with pathogen pattern recognition receptors or other host receptor complexes. These interactions in turn trigger downstream signal transduction pathways that contribute to the modulation of immune responses and inflammation. HCV patient livers exhibit increased expression of a variety of immunomodulatory gene products associated with inflammatory responses, including OSM and IL-6.²²⁹ OSM has been shown to have beneficial effects on HCV infection.²³⁰ OSM levels are correlated with CD40L expression on antigen-presenting cells, and exposure of Huh7 Core-3' cells to supernatant from CD40L-stimulated antigen-presenting cells represses HCV replication.²³⁰ Furthermore, OSM neutralization by antibodies or silencing techniques abrogates these effects.²³⁰

IL-11 is a multifunctional cytokine that is mainly produced by fibroblasts. A previous study suggested that IL-11 exerted anti-inflammatory and hepatoprotective effects in a liver ischemia/reperfusion (I/R) model,²³¹ but a recent study suggested that IL-11 played a detrimental role in promoting NASH in mice, as the administration of an anti-IL-11 antibody or IL-11RA prevented, stopped and even reversed steatosis and fibrosis in mouse models of NASH.²³² Similar to IL-11, OSM has been suggested to be a key factor in the induction of steatohepatitis and fibrosis.²³³ Patients with steatosis and NASH have been reported to have elevated serum levels of OSM.²³³ Consistently, in murine models, OSM has been shown to promote liver fibrosis by stimulating HSCs and macrophages.^{233,234} In contrast to OSM, CNTF has been shown to protect against NAFLD, as recombinant CNTF administration improved liver injury and NAFLD in a rat model induced by HFD feeding.²³⁵ LIF and CNTF are predominantly involved in fatty acid metabolism, particularly by stimulating hepatic triglyceride secretion, and thereby play roles in the pathogenesis of NAFLD.²³⁶

IL-27 is mainly produced by antigen-presenting cells and has been described as having anti-inflammatory effects; IL-27 has been shown to reduce liver damage by directly modifying CD4⁺ and CD8⁺ T cell responses and promoting IL-10 and Treg functions and liver regeneration.²³⁷ In cases of severe hepatic injury, which are characterized by massive hepatocyte destruction and chronic inflammation, the proliferation of the remaining healthy hepatocytes is not sufficient to restore the initial liver mass and hepatic functions. In this context, bipotent LPCs are activated and contribute to the regenerative process through the differentiation of these progenitor cells into biliary cells and hepatocytes. The murine model established with choline-deficient, ethionine-supplemented diet feeding recapitulates this chronic liver injury and stimulates LPC accumulation and proliferation. In this model, IL-27 has recently been shown to play a pivotal role in liver regeneration by promoting progenitor cell differentiation into hepatocytes.²³⁷ In fact, IL-27 has a direct effect on LPCs in vitro, promoting their differentiation into a hepatocyte-like phenotype. In contrast, disruption of WSX-1 signaling prevents LPC accumulation and further leads to a significant reduction in the recruitment of macrophages, which are known to be central actors in the expansion of LPCs.²³⁷ These properties highlight the essential role of IL-27 in liver regeneration mediated by promoting the activation and expansion of the LPC compartment. Finally, CT-

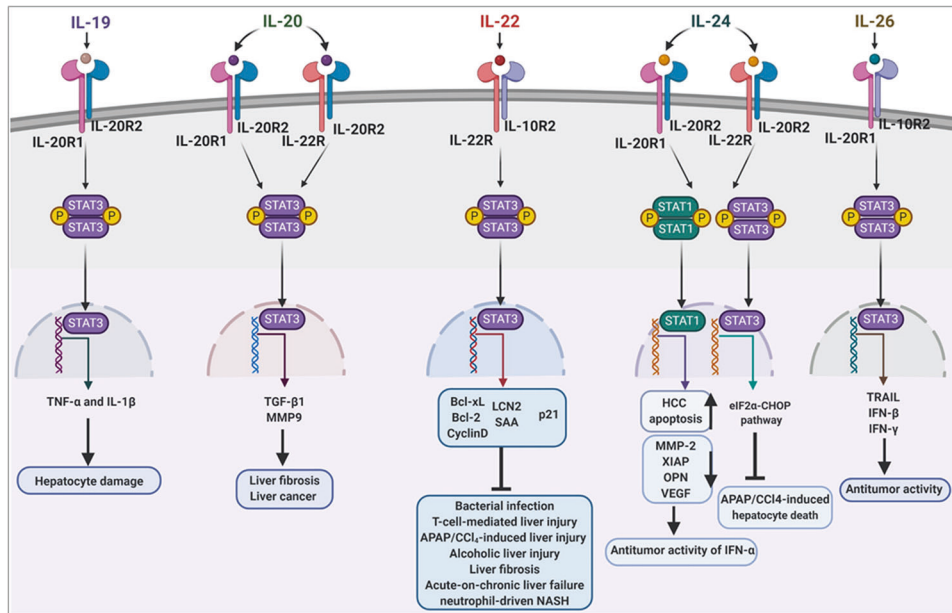


Fig. 7 Roles of IL-20 family cytokines in liver diseases. IL-22 strongly activates STAT3 in hepatocytes through a receptor complex composed of IL-22R1 and IL-10R2, which subsequently triggers the expression of several genes involved in cell survival and protection against bacterial infection. IL-22/STAT3 signaling limits bacterial infection, inhibits liver injury and fibrosis, and ameliorates neutrophil-driven NASH and acute-on-chronic liver failure. In contrast, IL-19 promotes hepatocyte damage by upregulating TNF- α and IL-1 β expression. By binding to IL-22R/IL-20R2 or IL-20R1/IL-20R2, IL-20 accelerates liver injury and fibrosis by increasing TGF- β 1 and MMP9 expression in HSCs. IL-24 activates the STAT1 and STAT3 signaling pathways through the same receptor complex as IL-20, thereby promoting antitumor activity and inhibiting APAP/CCl₄-induced liver injury. IL-26 exerts antiviral immune effects mainly by inducing STAT3 activation through a receptor composed of IL-20R1 and IL-10R2

1 is mainly produced by myocytes and is involved in cardiac functions, but it was also shown to have interesting hepatoprotective properties, as demonstrated in several models of liver injury.²³⁸

In summary, the IL-6 cytokine family represents a wide group of cytokines with multiple functions and anti- and/or proinflammatory properties (Fig. 6). The variety of receptors in this family is responsible for the diversity of intracellular responses triggered by IL-6 family cytokines, such as the stimulation of immune cell proliferation and activation. Therefore, blocking or stimulating those cytokines can be either beneficial or detrimental depending on the pathology. In conclusion, IL-6 family cytokines represent a very interesting group of inflammatory factors that could be targeted in the field of hepatology to develop promising novel therapeutic strategies based on hepatic pathophysiology.

IL-20 FAMILY CYTOKINES

The IL-20 subfamily includes IL-19, IL-20, IL-22, IL-24, and IL-26, which all facilitate communicating between leukocytes and epithelial cells in different tissues, thereby enhancing innate defense mechanisms and tissue repair processes at epithelial surfaces. All IL-20 subfamily cytokines signal through the JAK-STAT pathway and primarily activate STAT3 by binding heterodimeric receptors composed of the IL-20 receptor β -subunit (IL-20R2) or IL-10R2 paired with either the IL-20 receptor α -subunit (IL-20R1) or IL-22R1 (Fig. 7). To date, the role of IL-22 in liver diseases has been extensively investigated; however, little is known about the roles of other IL-20 family members in liver diseases.

IL-22 is mainly produced by immune cells such as T cells (especially Th17 and Th22 cells), NK cells, and NKT cells.^{239,240} However, the target cells of IL-22 are not immune cells, since one of its receptor subunits, IL-22R1, is absent from cells of hematopoietic origin.^{241,242} In the liver, the target cells of IL-22 include hepatocytes, LPCs and HSCs.^{243–245} The main downstream signaling

outcome of IL-22 stimulation is the activation of STAT3 through a receptor complex composed of IL-22R1 and IL-10R2, which subsequently triggers the expression of genes involved in cell survival and proliferation, such as Bcl-xL, Bcl2, and cyclin D.²⁴³ IL-22 may also activate the STAT5, ERK, JNK, and p38 MAPK signaling pathways.²⁴⁶ In addition, IL-22 is a strong inducer of many antibacterial proteins, such as LCN2, serum amyloid A and Reg family proteins.^{247–249} Thus, IL-22 originates from activated immune cells but functions as a tissue-protective cytokine during liver injury.

The hepatoprotective effects of IL-22 have been well documented in several models of liver disease. Early studies mainly focused on immune-mediated liver injury models. Treatment with recombinant IL-22 or the overexpression of IL-22 very effectively ameliorated liver damage caused by the activation of T cells or macrophages/Kupffer cells, while treatment with anti-IL-22 neutralizing antibodies enhanced liver damage in these models.^{243,250–253} In addition, mice lacking IL-22 or with deficient IL-22 production were more susceptible to immune cell-mediated liver injury than wild-type mice.^{254,255} In chemical-induced liver injury and DILI models, IL-22 significantly reduced liver damage caused by CCl₄ or APAP.^{256–258} STAT3 activation and enhanced autophagic flux were implicated in the protective effects of IL-22 on APAP-induced liver injury.^{257,259} In addition, in a clinical study, relatively high plasma IL-22 levels were associated with improved outcomes in patients with DILI.²⁶⁰ The hepatoprotective effect of IL-22 was also demonstrated in a well-established chronic-plus-binge ALD model.²⁶¹

Since IL-22R1 is expressed on HSCs, the effects of IL-22 on liver fibrosis models have been evaluated. IL-22 induces HSC senescence by activating the p53-p21 pathway, which accelerates the resolution of liver fibrosis.²⁴⁵ The antifibrotic effects of IL-22, which have different mechanisms, have also been observed in several studies,^{262–264} however, IL-22 was also suggested to be a profibrotic factor in chronic HBV infection.^{265,266} It is plausible that IL-22 protects against liver fibrosis by inducing HSC

senescence and reducing liver injury but may exacerbate liver fibrosis by promoting inflammation during chronic liver injury.

Emerging evidence suggests that IL-22 promotes hepatocyte proliferation both in vitro and in vivo.^{251,267} Overexpression of IL-22 or treatment with recombinant IL-22 protein accelerates liver regeneration after partial hepatectomy in not only healthy livers but also previously damaged livers.^{251,268} Recent studies have shown that serum levels of IL-22 are increased in ACLF patients.^{269,270} The beneficial effects of IL-22 were analyzed in a newly established mouse model of ACLF.³¹ In this ACLF model, liver regeneration was severely impaired in association with the dysregulation of STAT1/STAT3 signaling. Treatment with IL-22 reversed the imbalance in STAT1 and STAT3 signaling, subsequently promoting liver repair and reducing bacterial infection.³¹ Moreover, IL-22 was also analyzed in a model of HFD-induced NAFLD.²⁷¹ In this model, IL-22 treatment reduced hepatic expression of lipogenesis-related transcription factors and enzymes, thereby improving liver steatosis.²⁷¹ Very recently, Hwang et al. demonstrated that IL-22 treatment ameliorated inflammation, liver fibrosis, and oxidative stress in a new model of neutrophil-driven NASH.³⁶ IL-22 treatment strongly upregulated hepatic expression of the antioxidant gene metallothionein and reduced hepatocyte release of inflammatory extracellular vesicles, thereby ameliorating NASH.³⁶

In viral hepatitis, serum IL-22 levels are elevated in both HBV-infected patients and HCV-infected patients.^{251,272,273} Infiltrated Th17 cells are considered to be the main source of IL-22 in these viral hepatitis patients.^{274–276} IL-22 does not directly impact the replication of HBV or HCV; however, IL-22 may trigger the infiltration of inflammatory cells by stimulating chemokine expression in the liver.^{272,277} The role of IL-22 in viral hepatitis needs to be clarified in future studies. As an activator of the oncogenic transcription factor STAT3, IL-22 has been studied in HCC in patients and mouse models. IL-22 expression is upregulated in infiltrated leukocytes in HCC tumors, and high levels of IL-22 are associated with the growth of HCC.²⁷⁸ Relatively high serum IL-22 levels and tumor-infiltrating IL-22-producing cells are also associated with unfavorable outcomes in HCC patients.^{279,280} Mice overexpressing IL-22 are more susceptible to DEN-induced HCC than wild-type mice.²⁵¹ However, no spontaneous tumors were observed in IL-22-overexpressing mice in the absence of DEN treatment, suggesting that IL-22 does not initiate tumorigenesis.²⁵¹

Finally, two phase 1 clinical trials have revealed that IL-22 treatment is safe and well tolerated in healthy human subjects.^{281,282} In a recently published phase 2 open-label dose escalation clinical trial, IL-22 treatment was associated with a relatively high improvement rate and reduced inflammation marker levels in patients with moderate or severe alcoholic hepatitis. No serious adverse effects were observed in this trial.²⁸³ These promising preliminary results support the need for randomized placebo-controlled multicenter trials of IL-22 to test the efficacy of IL-22-based treatments of alcoholic hepatitis.²⁸⁴

One concern regarding IL-22Fc therapy is liver tumor growth because IL-22 promotes liver cancer cell proliferation and survival.^{243,251,278} However, there is no evidence that IL-22 itself initiates tumor development, including HCC, as demonstrated by the fact that transgenic mice with high levels of IL-22 (~6000 pg/ml) do not have a higher incidence of spontaneous tumor development than wild-type mice.²⁵¹ Thus, clinical studies have focused on short-term (such as 4 weeks) treatment with IL-22 in patients without obvious liver cancer to avoid concerns regarding IL-22 and HCC.

IL-19 is preferentially expressed in monocytes.²⁸⁵ IL-19 signals by binding to IL-20R1, which is paired with IL-20R2, thus inducing STAT3 activation. Recently, a study showed that LPS injection induced IL-19 expression and elevated IL-20R2 expression in the liver and spleen,²⁸⁶ suggesting that the liver may be a potential target organ for IL-19. In addition, IL-19 promoted hepatocyte damage by upregulating TNF- α and IL-1 β expression.²⁸⁷ Thus,

blocking IL-19 signaling may provide a novel and potent therapeutic strategy to control liver inflammation.

IL-20 was discovered almost 19 years ago by utilizing a structural, profile-based algorithm.²⁸⁸ IL-20 is mainly produced by monocytes, granulocytes, epithelial cells, and DCs.²⁸⁹ IL-20 signals by binding to IL-22R/IL-20R2 or IL-20R1/IL-20R2. Recently, Chiu et al.²⁹⁰ showed that IL-20 expression was significantly elevated in hepatocytes and HSCs in liver biopsies from patients with fibrosis and HCC. IL-20 promoted CCl₄-induced liver fibrosis by activating quiescent HSCs and upregulating TGF- β 1 expression.²⁹⁰ Furthermore, *Il20r1*-deficient mice were protected against CCl₄-induced ALI and liver fibrosis. In addition, an anti-IL-20 monoclonal antibody inhibited HCC cell migration and invasion in vitro and suppressed liver tumor growth in vivo.^{291,292} However, the exact role and underlying mechanism of IL-20 in liver diseases remain unclear and need to be further clarified.

IL-24 (also named melanoma differentiation-associated gene-7 [MDA-7]) signals through the same receptor complex as IL-20. IL-24 is well known to exhibit antitumor activity in vitro and in vivo, as demonstrated by the findings that elevated IL-24 expression inhibits tumor growth and promotes apoptosis and toxic autophagy in a broad array of cancer cells, including liver cancer cells.²⁹³ For example, intramuscular electroporation of IL-24 inhibits hepatoma cell growth and tumor vascularization.²⁹⁴ IL-24 promotes the antitumor activity of IFN- α in HCC both in vitro and in vivo by upregulating STAT1-mediated apoptosis and downregulating STAT3-mediated expression of downstream proteins, including the metastatic and angiogenic proteins MMP-2, XIAP, OPN, and VEGF.²⁹⁵ In addition, gene-viro-therapy targeting liver cancer was performed with a dual-regulated oncolytic adenoviral vector harboring IL-24 and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL).²⁹⁶ Recently, in a phase 1/2 clinical trial, delivery of IL-24 by replication-incompetent adenovirus showed clinical efficacy in patients with advanced cancers.^{297,298} Thus, IL-24, a novel dual-acting cytokine, may be associated with specific aspects of the immune system in normal physiological processes and lead to tumor growth and cancer-specific apoptosis.²⁹⁹ In addition to the antitumor effects of IL-24, disruption of the *Il24* gene was shown to accelerate hepatocyte death in CCl₄-induced and APAP-induced ALI in a recent study.³⁰⁰ Mechanistically, a lack of IL-24 impairs endoplasmic reticulum homeostasis by regulating eIF2 α -CHOP pathway-mediated stress signaling.³⁰⁰ Overall, although the role of IL-24 in liver cancer has been extensively studied, the functions of IL-24 in other types of liver diseases remain obscure and require further exploration.

IL-26 was originally described in virus-transformed human T cells.³⁰¹ IL-26 mainly induces STAT3 activation through a receptor composed of IL-20R1 and IL-10R2.³⁰² Recently, a study showed that CD3⁺ T cell-derived IL-26 levels were elevated in chronically HCV-infected patients and that IL-26-stimulated NK cells had enhanced abilities to kill HCV-infected hepatocytes by increasing TRAIL expression.³⁰³ In addition, IL-26 also exerts antiviral immune activity by promoting IFN- β and IFN- γ production.³⁰³ Finally, hepatic IL-26 levels have been suggested to be a novel biomarker for predicting the prognosis of patients with HCC after surgical resection.³⁰⁴

CYTOKINES PRODUCED BY HEPATOCYTES

Hepatocytes are the major parenchymal cells in the liver, produce a variety of innate immune proteins that enter the blood after receiving pathogenic and inflammatory signals from other cell types, and play a key role in innate immunity.³⁰⁵ Interestingly, hepatocytes also produce several cytokines, including IL-33, IL-6, IL-11, and IL-7, that control liver injury, repair, and inflammation in liver diseases (Fig. 8).

IL-33 is a recently identified member of the IL-1 cytokine family and signals through its specific heterodimeric receptor composed

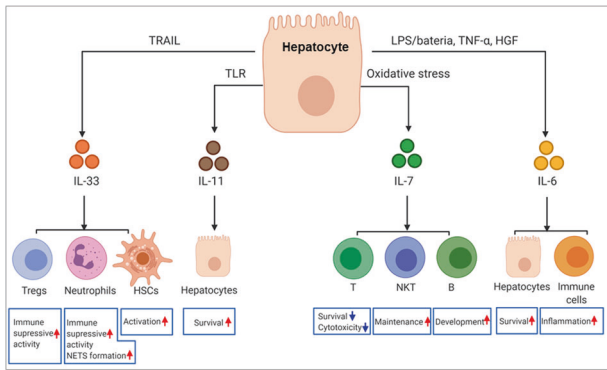


Fig. 8 Roles of hepatocyte-derived cytokines in liver diseases. The induction of IL-33 in hepatocytes by TRAIL exerts a protective effect by regulating Treg activity. IL-33 protects against liver injury in viral hepatitis by inducing immunosuppressive neutrophils. IL-33 exacerbates liver I/R injury by promoting neutrophil extracellular trap (NET) formation. IL-33 also promotes experimental bile duct ligation (BDL)-induced liver fibrosis by activating HSCs. IL-11 secreted by dying hepatocytes protects against adjacent healthy hepatocyte damage by activating STAT3. Hepatocyte-derived IL-7 regulates the T-cell response by inhibiting CD4⁺ and CD8⁺ T-cell survival and CD8⁺ T-cell cytotoxicity. IL-7 also plays a key role in the maintenance of NKT and T cells and the development of B cells. LPS/bacteria, TNF- α or HGF induces IL-6 production in hepatocytes. IL-6 promotes hepatocyte survival and immune cell-mediated inflammation

of IL-1 receptor-like 1 (IL-1RL1, also known as suppression of tumorigenicity 2 [ST2]) and IL-1 receptor accessory protein (IL-1RAcP).³⁰⁶ IL-33 is widely expressed in various types of tissues, and endothelial cells, epithelial cells and hepatocytes being the major sources of IL-33. Interestingly, TRAIL but not TNF- α or Fas ligand is responsible for the induction of IL-33 in hepatocytes in Con A-induced acute hepatitis.³⁰⁷ The functions of IL-33 in the pathogenesis of liver diseases are discussed in the section on IL-1 family cytokines.

IL-7 plays essential roles in controlling lymphocyte development and survival through IL-7R, which consists of the common cytokine receptor γ -chain and the unique IL-7R α -chain (IL-7R α).³⁰⁸ Hepatocyte-derived IL-7 production is dependent on Toll-like receptor signaling, which is an acute-phase response. It is believed that hepatic IL-7 regulates the T-cell response by inhibiting CD4⁺ and CD8⁺ T-cell survival and CD8⁺ T-cell cytotoxic activity.³⁰⁹ In addition, hepatocyte-derived IL-7 also plays a key role in the maintenance of NKT and T cells and the development of B cells, as demonstrated by the findings that hepatocyte-specific *Il7*-knock-out mice have reduced numbers of NKT cells and impaired B-cell development.³¹⁰

IL-6 is produced by various proinflammatory cells and many other types of cells, including hepatocytes, as described in the section on IL-6 family cytokines. However, the degree to which hepatocytes contribute to IL-6 production in vivo has not been investigated.

IL-11, a member of the IL-6 family of cytokines, is mainly produced by hepatocytes in an oxidative stress-dependent manner upon ALI.³¹¹ IL-11 is secreted by dying cells and protects adjacent healthy hepatocytes from damage by activating STAT3.³¹¹ Blockade of IL-11 signaling by using an IL-11R agonist or *Il11r*-deficient mice exacerbated APAP-induced liver injury,³¹¹ suggesting that the manipulation of the IL-11 signaling pathway may be a novel strategy to treat ROS-related liver injury.

CONCLUSIONS AND FUTURE PERSPECTIVES

To date, a large number of cytokines have been discovered, and some have been shown to play important and complex roles in

the pathogenesis of liver diseases, while many have still not been carefully investigated in the liver. Identification of the functions of these cytokines in the liver will not only help us understand liver disease development and progression but may also lead to the discovery of novel and effective therapeutic interventions for the treatment of liver diseases. Many cytokines have been shown to have therapeutic potential for the treatment of liver diseases in preclinical studies. Some of these cytokines are currently being tested in clinical trials for the treatment of liver diseases, including a recombinant IL-22 protein, IL-1 inhibitors, and a recombinant G-CSF protein for the treatment of patients with severe alcoholic hepatitis. More clinical trials using cytokines as therapeutic targets for the treatment of liver diseases are expected to be conducted in the future.

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AUTHOR CONTRIBUTIONS

Y.H. and S.H. share first authorship. Y.H. wrote the sections on Th1 and IL-20 family cytokines and hepatocyte-derived cytokines; S.H. wrote the sections on Th2 and Th9 cytokines; Y.A.A. and F.L. wrote the section on IL-6 family cytokines; D.F. wrote the section on IL-22 cytokine; N.L. and T.K. wrote the section on IL-17 family cytokines; M. R. and G.S. wrote the section on IL-1 family cytokines; and B.G. initiated and supervised the paper writing process and edited the paper. Y.A.A. was a participant in the NIH Graduate Partnerships Program and a graduate student at the Université Paris-Est, France and is affiliated with the Université Paris-Est and the NIH Graduate Partnerships Program.

ADDITIONAL INFORMATION

Competing interests: G.S. consults for Allergan, Alnylam, Arrow, Durcect Corporation, Generon, Glympe Bio, Terra Firma, Quest Diagnostics, Pandion Therapeutics, Surrozen, and Zomagen. She has received grants from Gilead, Genfit, Intercept, Novartis, SignaBlok, and Shire. She holds intellectual property rights with Up to Date. The other coauthors declare no competing interests.

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