

The Dual Role of IP-10/CXCL10 in Liver Injury: From Pathogenic Mediator to Clinical Biomarker and Therapeutic Target

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Abstract: A complex interplay of immune and inflammatory mechanisms underlies liver injury, with the chemokine interferon-gamma-induced protein 10 (IP-10/CXCL10) playing a decisive role. Recent findings identify IP-10 as a key pathogenic mediator; by binding its receptor CXCR3, it directly recruits cytotoxic T lymphocytes and NK cells to the liver, promoting hepatocyte apoptosis and driving inflammation. This chemokine also activates hepatic stellate cells (HSCs), stimulating fibrogenesis and disease progression in conditions ranging from viral hepatitis to metabolic steatotic liver disease (MASLD) and cirrhosis. Consequently, IP-10 has emerged as a sensitive biomarker for liver inflammation and fibrosis. This review highlights these mechanistic insights, linking CXCL10's causal roles to its diagnostic, prognostic, and therapeutic potential. We examine its utility in early detection, risk stratification, and targeted therapies to modulate immune responses and reduce fibrosis. We also discuss innovative applications in personalized medicine and precision diagnostics that offer new opportunities to improve outcomes in viral hepatitis and other liver diseases. By integrating mechanistic understanding with clinical implications, this work clarifies the multifaceted role of CXCL10 and identifies future research directions to optimize its therapeutic and diagnostic applications.

Keywords: clinical value, CXCR3, IP-10, liver injury, mechanism

Introduction

The liver, a vital organ responsible for detoxification, metabolism, and protein synthesis, is constantly exposed to various impairments, including viral infections and metabolic disorders.¹ When these impairments overwhelm the liver's natural defenses, a complex cascade of events leads to inflammation and ultimately to liver damage. Understanding the mechanisms underlying this process is crucial for developing effective diagnostic tools, therapeutic strategies, and prognostic indicators.^{2,3} In recent years, chemokines have emerged as key factors in the pathogenesis of liver damage. Among them, interferon gamma-induced protein 10 (IP-10), also known as CXCL10, has attracted considerable attention due to its potent chemotactic activity and its association with various liver diseases.^{4,5} IP-10 is best known for attracting cytotoxic T lymphocytes and NK cells to sites of inflammation. However, it also plays a crucial role in inhibiting the migration of activated T cells to lymph nodes, thus modulating the immune response.⁶ In liver disease, IP-10 expression is often dysregulated, with levels significantly elevated in the serum of patients with viral hepatitis and other forms of liver damage.^{7,8} This abnormal expression correlates with disease progression and severity, emphasizing the importance of IP-10 in the pathological process of liver disease.

The biological activity of CXCL10 is primarily mediated by its binding to CXCR3, a G protein-coupled receptor highly expressed on activated T cells, natural killer (NK) cells, and dendritic cells (DCs). Upon ligand binding, CXCR3 activates several downstream signaling cascades, including the JAK/STAT, PI3K/Akt, and MAPK/ERK pathways.⁹

These pathways are essential for directing the chemotaxis, adhesion, and transendothelial migration of CXCR3-expressing immune cells to sites of inflammation. Additionally, CXCL10 signaling can directly affect hepatocyte fate by activating pro-apoptotic pathways, contributing to liver injury beyond its chemotactic functions.¹⁰ Dysregulation of the CXCL10/CXCR3 signaling axis is a central mechanism in the pathogenesis and progression of various liver diseases.

The significance of IP-10 in liver diseases is complex. As a biomarker, IP-10 has shown both sensitivity and specificity in indicating inflammatory liver injury,^{11,12} making it a valuable diagnostic tool. Dynamic changes in IP-10 levels over time can also serve as a prognostic indicator, providing physicians with insight into disease progression and the likelihood of response to therapy.¹³ IP-10 also has therapeutic potential. Targeted interventions in the IP-10 signaling pathway could modulate the inflammatory response and provide a new approach to treating liver injury.¹⁴ This is particularly relevant in viral hepatitis, where current treatments often fail to achieve a cure or alleviate the long-term consequences of liver damage. Research on IP-10 in the context of liver disease treatment has concrete implications for clinical practice.¹⁵ This could lead to the development of more effective diagnostic tools, targeted therapies, and personalized treatment strategies.¹⁶

This review discusses recent research on the multifaceted role of IP-10 in the pathogenesis of various types of liver injury.^{2,12} We examine its potential as a diagnostic tool, prognostic indicator, and therapeutic target, highlighting its importance in the clinical management of liver disease. This work also provides valuable insights into future research directions and clinical applications that may contribute to developing more effective strategies for the prevention and treatment of liver disease.¹⁷ Additionally, this review makes an initial contribution to addressing the gap in this field.

Overview of IP-10 and CXCR3

IP-10 belongs to the CXC chemokine family and plays a central role in immune regulation and inflammatory responses.¹⁸ CXCR3 is the only receptor for IP-10 and belongs to the family of G-protein-coupled receptors and has a structure with seven transmembrane domains.¹⁹ Together with CXCL9 (also named monokine induced by interferon- γ , MIG) and CXCL11 (interferon-inducible T cell- α chemoattractant, I-TAC), IP-10 binds to the CXCR3, which is predominantly expressed on activated T cells, NK cells, and dendritic cells (DCs). Together, these ligands ensure the recruitment of immune cells to sites of inflammation or in the tumor microenvironment, thereby modulating immune surveillance and the antitumor response.²⁰ In addition, IP-10 is characterized by its strong chemoattractant properties for Th1 lymphocytes and its involvement in metabolic pathways that are crucial for the progression of hepatocellular carcinoma (HCC), such as angiogenesis, metastasis, and immune evasion.²¹ While the functions of CXCL9 and CXCL11 overlap with those of IP-10, the unique induction of IP-10 by interferon- γ and its broader expression profile under pathological conditions highlight its particular importance in HCC. The interplay between IP-10/CXCR3 and other chemokine axes underscores its potential as a therapeutic target, especially for remodeling the tumor microenvironment to enhance immune infiltration and counteract immunosuppressive signals.²²

IP-10 and Various Liver Injury

The role of IP-10 in various liver diseases, including viral hepatitis, liver fibrosis, cirrhosis, PLC, MASLD/MASH, DILI, PBC, and liver failure, is discussed below. Table 1 presents the liver cell types that express CXCL10 and the specific immune cell types regulated by CXCL10 in these diseases. Figure 1 illustrates how CXCL10 activation of the CXCR3 receptor mediates signal transduction in these liver diseases.

IP-10 and Chronic Hepatitis B (CHB)

IP-10 plays a vital role in liver injury by mediating immune cell recruitment and directly inducing apoptosis of hepatocytes. During HBV clearance, immune cells, particularly cytotoxic T lymphocytes (CTLs), play a crucial role in the anti-HBV immune response.²³ Studies have shown that patients infected with HBV have a high expression of IP-10.^{11,24} In addition, a longitudinal analysis of biopsies from treated patients showed that anti-HBV treatment was associated with a significant decrease in inflammation.²⁵ When IP-10 was blocked, CTL cell infiltration in the liver decreased significantly, and liver tissue damage was reduced. This suggests that increased IP-10 mediates the infiltration of inflammatory cells into liver tissue after HBV infection.²⁶ However, IP-10 activates and attracts CXCR3+ T cells, monocytes, NK cells, and other

Table 1 Liver Cell Types That Express CXCL10 and Immune Cells Regulated by CXCL10 in Various Liver Diseases

Liver Disease (Injury)	Primary Liver Cell Types Expressing CXCL10	Activated/Recruited Immune Cell (T-cell Subtype and Others)	Proposed Roles of CXCL10
Chronic Hepatitis B (CHB)	Hepatocytes, Hepatic Stellate Cells (HSCs), Biliary epithelial cells	CD8+ Cytotoxic T-cells, CD4+ Th1 cells, NK cells	1) Critical for both viral control and liver damage. 2) High levels correlate with inflammation and disease activity
Chronic Hepatitis C (CHC)	Hepatocytes, HSCs, Liver Sinusoidal Endothelial Cells (LSECs)	CD8+ Cytotoxic T-cells, CD4+ Th1 cells, NK cells	1) Induced by the HCV core protein, it recruits cells that contribute to chronic inflammation and fibrosis
Liver Fibrosis & Cirrhosis (LF&LC)	Activated HSCs, Hepatocytes, LSECs	CD4+ Th1 cells, NKT cells, Monocytes/Macrophages	1) HSCs become a major source, creating a profibrotic and inflammatory feedback loop
Hepatocellular Carcinoma (HCC)	Tumor-associated macrophages, Tumor cells (in some cases), Stromal cells,	CD8+ Cytotoxic T-cells, CD4+ Th1 cells, NK cells	1) Can promote anti-tumor immunity or drive inflammation-induced tumor progression
MASH / MASLD	Hepatocytes, HSCs, LSECs	CD8+ Cytotoxic T-cells, CD4+ Th1 cells, Monocytes/Macrophages	1) Driven by metabolic stress and lipotoxicity, it recruits inflammatory cells that worsen steatosis and initiate fibrosis
Drug-Induced Liver Injury (DILI)	Hepatocytes, Biliary epithelial cells	CD8+ Cytotoxic T-cells, CD4+ Th1 cells, NK cells	1) The haptenated drug or neoantigen triggers an adaptive immune response similar to that seen in viral hepatitis
Primary Biliary Cholangitis (PBC)	Biliary Epithelial Cells (BECs), Hepatocytes, Infiltrating immune cells	CD4+ Th1 cells, CD8+ T-cells, Autoreactive T-cells	1) BECs are the primary target; CXCL10 recruits T cells that destroy the small intrahepatic bile ducts
Liver Failure (Acute)	Hepatocytes, LSECs, Biliary epithelial cells	CXCR3+ Monocytes/Macrophages, Neutrophils, T-cells	1) As part of a massive "cytokine storm", it recruits innate and adaptive immune cells, leading to widespread destruction of parenchymal tissue

Notes: This provides a general overview. Specific cellular interactions may vary depending on disease stage, individual patient factors, and treatment status.

inflammatory cells to migrate, become activated, and participate in the antiviral immune response against HBV-infected liver tissue.²⁷

Kan et al, suggested that plasma IP-10 level is a predictive factor for spontaneous hepatitis B surface antigen seroclearity in CHB patients.¹² Our team shows that IP-10 gene expression in liver tissue and IP-10 protein expression in the serum of CHB patients are significantly higher than in the healthy donor group. In addition, the slow decline of IP-10 levels in CHB patients during antiviral treatment suggests that these patients have a high serum HBeAg conversion rate.¹¹ IFN- γ and TNF- α secreted by activated T cells in hepatitis B patients stimulate liver cells to secrete IP-10. The IP-10 mRNA level in peripheral blood mononuclear cells (PBMCs) of CHB patients is positively correlated with plasma IP-10 concentration, alanine aminotransferase (ALT), and HBV DNA levels.²⁸ For example, Figure 2 shows the role of the CXCL10/CXCR3 pathway in the outcome of HBV infection in liver cells.

IP-10 and Chronic Hepatitis C (CHC)

Similar to CHB, IP-10 is also a crucial mediator in chronic hepatitis C (CHC), although its effects are characterized by the different viral pathogenesis. One study has shown that serum IP-10 levels increase after HCV infection,²⁹ and also increase in the peripheral blood of CHC patients. IP-10 levels in the livers of CHC patients were significantly higher than in the normal control group and correlated positively with both the number of NK and T cells infiltrating the liver and the degree of liver inflammation in these patients.³⁰ However, studies by Wiegand et al show that serum IP-10 levels are higher in patients with HCV infection than in those with HBV infection.³¹ It is currently hypothesized that IP-10 produced by liver parenchymal cells at the site of liver inflammation may recruit lymphocytes to the infected area and participate in the anti-HCV immune response.³² During acute hepatitis C infection, IP-10 expression is upregulated and recruits CXCR3+ effector T cells, which accumulate in the liver, trigger an adaptive immune response and clear HCV. However, because virus-specific T cells are unable to inhibit HCV replication, IP-10 production in the liver continues to

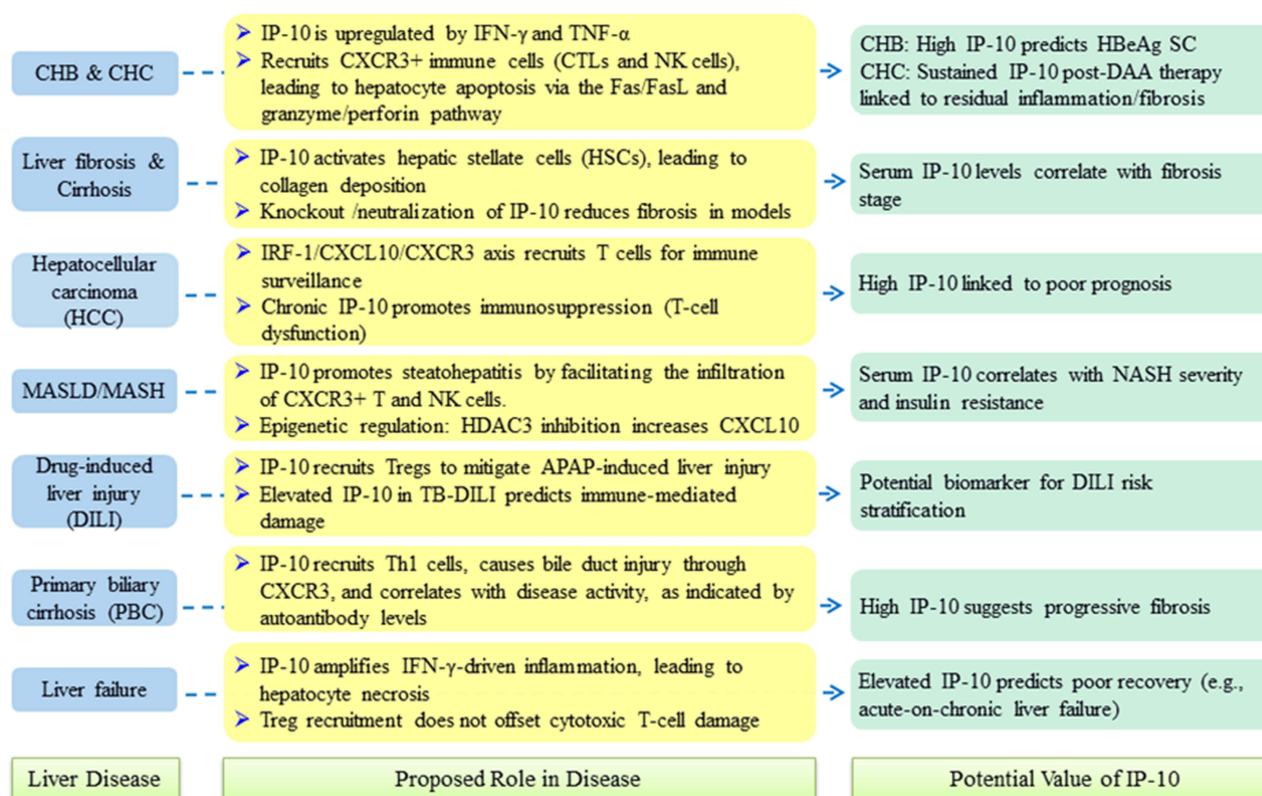


Figure 1 Role and potential value of IP-10/CXCL10 signal transduction in various liver injuries.

Abbreviations: CHB, chronic hepatitis B; CHC, chronic hepatitis C; DILI, drug-induced liver injury; IP-10, Interferon gamma-induced protein -10; LF&LC, liver fibrosis and cirrhosis; MASH, metabolic dysfunction associated steatohepatitis; MASLD, metabolic dysfunction associated steatotic liver disease; PBC, primary biliary cirrhosis; PLC, primary liver cancer.

increase and recruits non-specific T cells that produce cytokines, triggering liver fibrosis and leading to liver inflammation. Therefore, IP-10 expression in the acute and chronic stages of HCV infection can result in completely different prognoses.³³ Furthermore, the serum IP-10 level is positively correlated with the histopathology score (HAI) in patients infected with HCV genotype 1.³⁴

IP-10 and Liver Fibrosis and Cirrhosis

The persistent inflammation caused by IP-10 in viral hepatitis (CHB and CHC) often leads to fibrogenesis. Ongoing liver injury can activate hepatic stellate cells (HSC), myofibroblasts, and fibroblasts, promoting liver fibrosis. Studies have shown that high IP-10 expression in serum and liver is associated with the stage of liver fibrosis and that IP-10 expression increases significantly as fibrosis progresses.³⁵ Hintermann et al,³⁶ found that IP-10 mRNA expression was significantly increased in the HSCs of wild-type mice in a mouse model of liver fibrosis. Compared to wild-type mice, the numbers of infiltrating B cells, T cells, and dendritic cells were significantly reduced in the livers of IP-10 gene knockout mice, as were the number and activity of HSCs and the degree of fibrosis. In addition, blocking IP-10 with neutralizing antibodies produced a significant anti-fibrotic effect, suggesting that targeting IP-10 may represent a new approach for the treatment of liver fibrosis. In the context of liver cirrhosis, Katoh et al,³⁷ found that serum IP-10 levels decreased from high levels in patients with chronic hepatitis or compensated cirrhosis and decompensated cirrhosis (dLC) with a favorable prognosis, while they were elevated in patients with dLC without a favorable outcome.

IP-10 and Primary Liver Cancer (PLC)

As for PLC, MIG (CXCL9) and IP-10 can promote lymphocyte aggregation in the tumor microenvironment, which is closely associated with tumor immunity.³⁸ Our group has shown that the expression of IP-10 mRNA is significantly

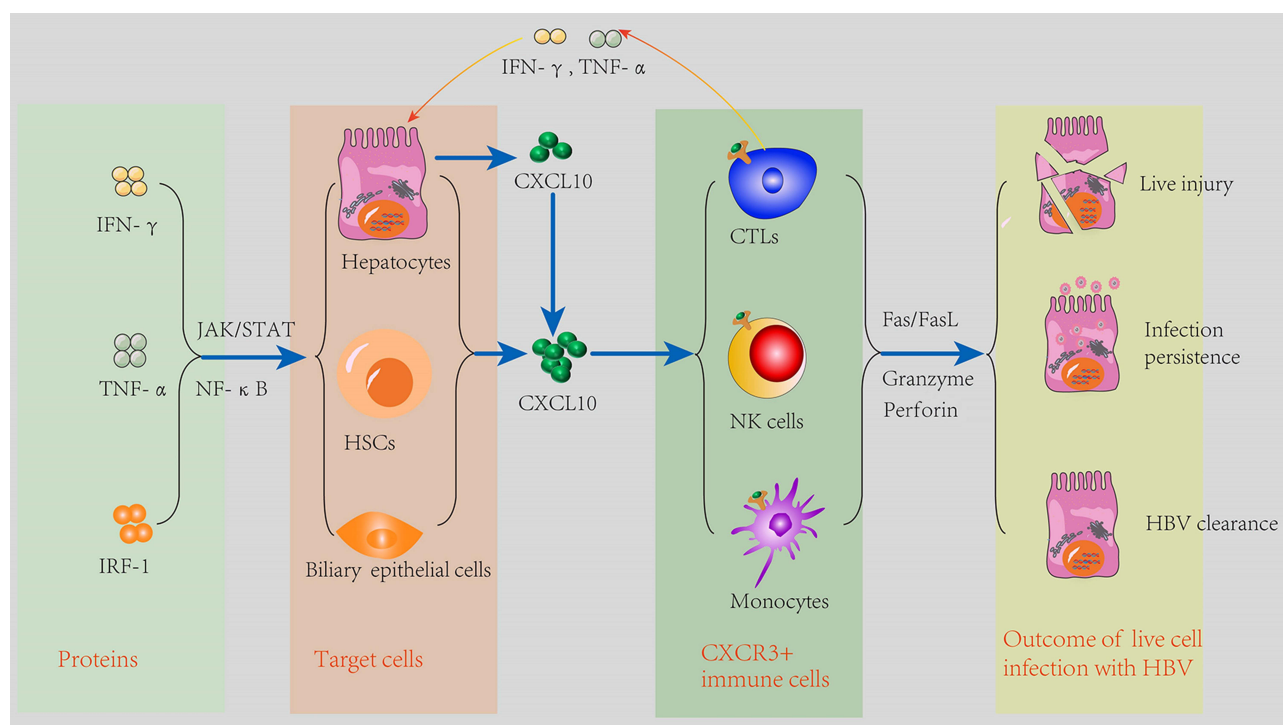


Figure 2 Immune cells cause liver injury or exert an anti-HBV infection effect in chronic hepatitis B through the CXCL10–CXCR3 axis. In CHB, IFN- γ , TNF- α , and IRF-1 promote CXCL10 expression at the transcriptional level in hepatocytes, HSCs, and biliary epithelial cells by activating the JAK/STAT and NF- κ B signaling pathways. CXCL10-positive cells recruit CXCR3-positive immune cells, including CTLs, NK cells, and monocytes, which express effector molecules such as granzyme, perforin, and components of the Fas/FasL pathway. This leads to liver injury, infection persistence, or HBV clearance, depending on immune homeostasis, and may involve additional signaling pathways. Additionally, IFN- γ and TNF- α secreted by activated T cells in hepatitis B patients stimulate liver cells to secrete CXCL10.

Abbreviations: IRF-1, Interferon regulatory factor 1; JAK/STAT, Janus kinase-signal transducer and activator of transcription; NF- κ B, Nuclear factor activated B cell kappa light chain.

increased in patients with HCC and that its level is closely related to the number of infiltrating lymphocytes, suggesting that high IP-10 levels are associated with lymphocyte dysfunction in blood and tumor tissue, which may impair tumor immune defense.³⁹ In vitro experiments have shown that IP-10 has a weaker chemotactic effect on CD4⁺ and CD8⁺T cells from liver cancer cells, but a stronger chemotactic effect on T cells from normal tissue.⁴⁰ Currently, the detection of tumor markers in serum is widely used for clinical diagnosis and tumor efficacy monitoring. Alpha-fetoprotein (AFP) in serum is considered the most specific diagnostic marker for PLC, but its sensitivity is low. Therefore, the combined detection of several tumor markers is more useful for the early detection and differential diagnosis of tumors. IP-10 as a combined serologic marker for liver cancer should be further investigated in an extended case.⁴¹ Mechanistically, the IRF-1/CXCL10/CXCR3 axis contributes to the antitumor microenvironment in hepatocellular carcinoma (HCC). IRF-1 regulates CXCL10, which attracts CXCR3-expressing immune cells, such as cytotoxic T cells, NKT and natural killer cells, to the tumor. This axis enhances immune-mediated tumor suppression by promoting T cell infiltration and activation, and inhibiting angiogenesis and tumor proliferation.⁴² Consequently, the IRF-1/CXCL10/CXCR3 axis represents a promising immunotherapeutic target for the treatment of HCC.

IP-10 and Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD)

In MASLD (formerly known as non-alcoholic fatty liver disease, NAFLD), the expression level of CXCL10 is closely related to disease progression.⁴³ MASLD is a liver disease associated with metabolic syndrome and ranges from simple steatosis to non-alcoholic steatohepatitis (NASH) and can lead to liver fibrosis, cirrhosis and even liver cancer.⁴⁴ The inflammatory response and the infiltration of immune cells in the liver are key factors in the progression of MASLD. CXCL10 attracts activated T cells and natural killer (NK) cells to the liver by binding to its receptor CXCR3, thereby promoting local inflammatory responses. Studies have shown that the expression of CXCL10 is significantly increased in

the liver of NASH patients and that serum levels of CXCL10 correlate positively with the severity of liver damage.⁴⁵ Therefore, CXCL10 not only plays an important role in the pathogenesis of MASLD, but could also serve as a potential biomarker for the diagnosis and monitoring of MASLD.⁴⁶ In terms of treatment, the FDA has conditionally approved RESMETIROM for the treatment of MASH,⁴⁷ which is one of the more serious diseases of MASLD and affects about 30% of the world's population. In summary, a detailed investigation of the mechanism of action of CXCL10 in MASLD could provide new ideas and starting points for the early diagnosis and treatment of the disease.

IP-10 and Metabolic Dysfunction Associated Steatohepatitis (MASH)

The former name for MASH was non-alcoholic steatohepatitis (NASH), a severe form of non-alcoholic fatty liver disease (NAFLD).⁴⁶ Recent research has emphasized the importance of IP-10 in the pathogenesis of NASH. NASH is characterized by hepatic steatosis, inflammation and fibrosis, which can progress to cirrhosis and HCC. However, the diagnosis and monitoring of NASH remains difficult due to the lack of reliable biomarkers. Elevated serum levels of IP-10 have been observed in NASH patients, which correlate with disease severity and fibrosis stage. Since IP-10 measurement is non-invasive, Wada et al, suggested that insulin resistance with bacterial-induced TLR-2 stimulation could induce IP-10 production by monocytes, and that insulin resistance should be intensively controlled to prevent progression from NAFL to NASH.⁴⁸

In addition, IP-10 has been shown to promote the activation of hepatic stellate cells (HSC), which play a key role in the fibrogenesis of NASH.⁴⁹ The interaction of this chemokine with its receptor, CXCR3, on HSC and immune cells further enhances the inflammatory and fibrotic responses. However, targeting the IP-10/CXCR3 axis has been shown to be a potential therapeutic strategy for NASH.⁵⁰ Inhibiting this signaling pathway could reduce liver inflammation and fibrosis and thus halt disease progression. Understanding the precise mechanisms by which IP-10 affects the pathophysiology of NASH could pave the way for new treatments aimed at reducing the burden of this increasingly prevalent liver disease. Accordingly, a number of different cytokines and chemokines,⁵¹ including IP-10, could be considered as biomarkers for differentiating NASH from NAFLD.⁴⁵

IP-10 and Drug-Induced Liver Injury (DILI)

Drug-induced liver injury (DILI) is a relatively common pathophysiologic phenomenon that seriously affects human health. Zhan et al,⁵² investigated the role of Chitinase 3-like protein 1 (YKL-40) and found that it increased the expression of chemokines such as CCL2 and IP-10. These chemokines are known to play a critical role in the recruitment of immune cells to sites of inflammation, suggesting that YKL-40 may be an important regulator of inflammatory responses in the liver. Building on this, Wang et al,⁵³ investigated the specific function of IP-10 in the context of liver injury caused by acetyl-p-acetaminophen (APAP), a common analgesic. Their study showed that Th1 and regulatory T cells (Treg cells) are significantly involved in the body's response to APAP-induced liver damage. They found that the recruitment of Treg cells in the liver, which is promoted by the chemokine CXCL10, can mitigate the damage caused by APAP. This finding underscores the therapeutic potential of modulating Treg cell recruitment in the treatment of DILI. In addition, Ma et al pointed to a link between DILI and novel human leukocyte antigen gene polymorphisms.⁵⁴

In addition, Ho et al,⁵⁵ focused their prognostic model on predicting and preventing DILI in patients treated for tuberculosis (TB). Using the Roussel-Uclaf Causality Assessment Method (RUCAM), they identified treatment levels of interleukin-22 binding protein (IL-22BP) as a protective biomarker against DILI. They also developed a scoring system that incorporates additional risk factors such as IP-10 and soluble CD163 (sCD163), which can effectively predict the likelihood of patients developing DILI during treatment.

IP-10 and Primary Biliary Cirrhosis (PBC)

PBC is a chronic progressive cholestatic disease mediated by autoimmune mechanisms that can lead to liver fibrosis, cirrhosis and ultimately liver failure.⁵⁶ The etiology and exact pathogenesis of PBC are not fully understood and may be related to abnormalities in various signaling pathways and cytokines.⁵⁷ The interaction between chemokines and their receptors mediates the migration, colonization and redistribution of immune cells to specific tissues. Studies have shown that the chemokine receptors CCR5, CXCR3 and CXCR6 are associated with the directed migration of T cells into liver

tissue.⁵⁸ When initial T cells are activated and differentiate into effector T lymphocytes, their expression of CXCR3 increases.⁵⁹ Moreover, inflammatory chemokines in tissues can also induce the expression of their receptor, CXCR3.⁶⁰ Liao et al report abnormal demethylation of the CXCR3 promoter in PBC and highlight the role of CXCR3 in the natural history of PBC.⁶¹

Studies have shown that IP-10 levels are elevated in the serum and liver tissue of patients with PBC compared to healthy controls. This elevation is believed to result from increased immune activation and inflammation in the liver. The presence of high IP-10 levels in PBC patients suggests that it may serve as a biomarker of disease activity and progression.⁶² In addition, IP-10 may play a functional role in recruiting immune cells to the liver, contributing to the inflammation and fibrosis seen in this disease. Further research into the role of IP-10 in PBC could provide insights into the underlying mechanisms of the disease and potentially identify new therapeutic targets.⁶³

IP-10 and Liver Failure

The relationship between IP-10 and liver failure is a complex and fascinating area of research. From a pathophysiological perspective, acute liver failure results from extensive necrosis of liver cells, which triggers a strong inflammatory immune response in the liver.⁶⁴ Immune cells that invade the liver, including T cells, NK cells, and natural killer T (NKT) cells, secrete various proinflammatory chemokines and cytokines that cause lasting damage to liver cells.^{64,65} Increased IFN- γ can strongly activate the transcription of the chemokines CXCL9, CXCL10 and CXCL11, leading to the recruitment of CXCR3+ Treg in liver cells.⁶⁶ Although Treg cells can attenuate the inflammatory response of liver tissue to some extent, IFN- γ and IP-10 have a reciprocal promoting effect. Increased secretion of IP-10 causes more T cells to aggregate, infiltrate, and activate in the liver, leading to overexpression of IFN- γ and resulting in liver damage.⁶⁷

In addition, IP-10 could predict the progression of liver fibrosis in CHB patients.⁶⁸ It can stimulate the production of extracellular matrix proteins, leading to collagen deposition and the development of fibrosis. This fibrotic reaction can further impair liver function and increase the risk of liver failure. Conversely, targeting IP-10 or its signaling pathways could modulate the immune response and reduce inflammation and fibrosis, thereby slowing the progression of liver disease to liver failure. Further research is needed to fully elucidate the mechanisms by which IP-10 contributes to liver failure and to develop effective strategies for therapeutic intervention.⁶⁹

Summary and Outlook

In summary, IP-10/CXCL10 plays a crucial role in the pathogenesis of various liver lesions, including viral hepatitis. Abnormal IP-10 expression is associated with the progression and severity of liver injury,⁷⁰ and IP-10 provides valuable insights into the underlying mechanisms of this disease. Due to its potential as a diagnostic tool, therapeutic target, and prognostic indicator, IP-10 holds significant clinical value for liver diseases.⁷¹ Moreover, CXCL10 has two opposing functions in immune responses. It is crucial for recruiting immune cells to infection sites and promoting pathogen elimination. However, excessive CXCL10 can trigger chronic inflammation, leading to liver tissue damage.^{24,72} Although CXCL10 is essential for immunity, its overexpression can worsen pathological conditions, highlighting its complex dual role in health and disease.⁷³ The role of IP-10 in liver injury and future research prospects are summarized below.

IP-10 as a Key Mediator of Liver Injury

IP-10/CXCL10 mediates liver damage through a two-pronged mechanism: it acts as a potent chemoattractant for immune cells and directly induces apoptotic pathways in hepatocytes. Its expression is primarily regulated by proinflammatory cytokines, particularly interferon-gamma (IFN- γ) and tumor necrosis factor-alpha (TNF- α), which are elevated in various liver diseases,⁷⁴ as shown in Table 2. These cytokines activate the JAK/STAT and NF- κ B signaling pathways, respectively, leading to transcriptional upregulation of IP-10. Additionally, activation of Toll-like receptors (TLRs) by pathogen-associated molecular patterns (PAMPs) during viral infections or tissue damage increases IP-10 production.⁷⁵ The mechanisms by which IP-10 contributes to liver injury are summarized below.

Table 2 CXCL10 Production in Hepatic Immune Cells Regulated by IFN- γ , TNF- α , and IRF-I

Hepatic Immune Cells	IFN- γ	TNF- α	IRF-I
NK-T Cells	↑↑	↑	↑↑
Kupffer Cells	↑↑	↑↑	↑↑
Hepatic Stellate Cells	↑↑	↑	↑↑
Hepatocytes	↑↑	↑	↑↑
Liver Sinusoidal Endothelial Cells (LSECs)	↑	↑	↑

Notes: ↑↑, Strong Increase; ↑, Increase. IRF-I is a critical transcription factor induced by both IFN- γ and TNF- α . It binds to the CXCL10 promoter to drive its expression. Therefore, the strong increase in CXCL10 from IFN- γ and TNF- α is often mediated through the upregulation and activation of IRF-I. IRF, Interferon regulatory factor I; CXCL10 (also name IP-10), Interferon-gamma-induced protein 10.

1. Recruitment of immune cells and damage to hepatocytes

IP-10 attracts CXCR3-expressing immune cells, such as cytotoxic T lymphocytes (CTL) and natural killer (NK) cells, to the liver. These cells release cytotoxic granules (eg, perforin, granzyme B) and proinflammatory cytokines (eg, IFN- γ , TNF- α), which promote necrosis and apoptosis of hepatocytes.⁷⁶

2. Direct apoptotic signaling pathway in hepatocytes

Beyond chemotaxis, IP-10 directly induces hepatocyte apoptosis by activating caspase-3 and the Fas/FasL signaling pathway through CXCR3 binding. This noncanonical function highlights IP-10 as both an immune recruiter and a pro-apoptotic mediator.⁷⁷

3. Epigenetic modulation

Recent studies show that inhibiting histone deacetylase 3 (HDAC3) enhances IP-10-mediated migration of immune cells, establishing a link between epigenetic regulation and IP-10-induced liver injury.⁷⁸

4. Fibrogenic and tumor-promoting functions

In chronic injury, IP-10 promotes hepatic stellate cell (HSC) activation and collagen deposition, leading to fibrosis.⁷⁹ In cholangiocarcinoma (CCA), IP-10 contributes to an immunosuppressive tumor microenvironment that facilitates immune evasion and tumor progression.⁸⁰

IP-10 as a Novel Biomarker in Liver Injury

Recent advances in biomarker research have identified IP-10 as a groundbreaking, noninvasive indicator of liver inflammation and damage. Unlike conventional biomarkers, IP-10 shows exceptional sensitivity and specificity in detecting liver injury from various causes, including viral hepatitis, alcoholic liver disease, and nonalcoholic fatty liver disease (NAFLD).⁵¹ In particular, IP-10 has been shown to be a key factor in assessing the severity of liver fibrosis and predicting disease progression, providing a dynamic and accurate alternative to conventional diagnostic methods.⁸¹ The clinical utility of IP-10 lies in its potential to replace or complement invasive procedures such as liver biopsies. By enabling reliable measurements through simple blood tests, IP-10 improves patient convenience and facilitates real-time monitoring of liver health. In addition, IP-10 outperforms conventional markers such as alanine aminotransferase (ALT) in responsiveness to liver changes and allows earlier detection of disease activity and therapeutic response.⁸² By leveraging the unique properties of IP-10, clinicians may soon adopt a minimally invasive, precision medicine approach to hepatology that improves patient outcomes and redefines standards of care. The drugs that may decrease serum levels of IP-10/CXCL10 in liver diseases are listed in [Table S1](#).

Therapeutic Target of IP-10/CXCR3 in Liver Injury

Targeting the IP-10/CXCR3 axis offers significant therapeutic potential for chronic liver diseases.⁸³ Future strategies should focus on developing selective CXCL10 inhibitors or CXCR3 antagonists that target specific liver cell types, such as hepatocytes or HSCs. This cell-type-specific approach could maximize efficacy in reducing inflammation and fibrosis

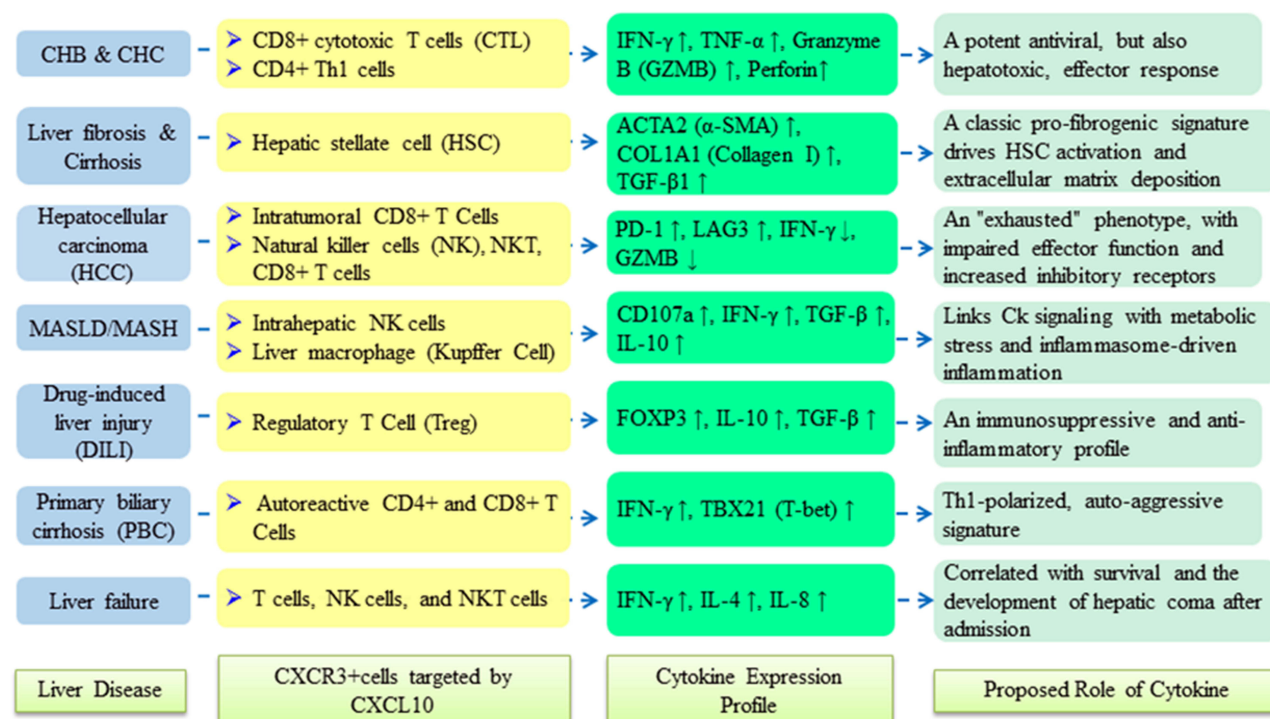


Figure 3 Interaction of CXCL10 with CXCR3+ target cells in various liver diseases and the cytokine expression profiles of these cells.

Abbreviations: $\uparrow$, Increase; $\downarrow$, Decrease; ACTA2, Actin alpha 2; FOXP3, Fork head box protein P3; GZMB, Granzyme B; LAG3, Lymphocyte activation gene 3, or CD223; PD-1, Programmed death-1; TBX21, T-box 21, or T-bet; TGF β 1, Transforming growth factor beta 1.

while minimizing systemic side effects, providing a more precise therapeutic option for conditions such as viral hepatitis and metabolic liver diseases. Moreover, Figure 3 shows the interaction of CXCL10 with CXCR3+ target cells and the potential gene expression profiles in selected cell types.

1. Neutralizing antibodies

Preclinical studies show that anti-IP-10 antibodies reduce immune cell infiltration and liver injury in models of viral hepatitis and fibrosis.^{26,36} For example, in chronic hepatitis B (CHB), IP-10 blockade attenuated cytotoxic T lymphocyte (CTL)-induced hepatocyte injury, while in liver fibrosis, it suppressed hepatic stellate cell (HSC) activation and collagen deposition.

2. CXCR3 antagonists

Small molecule CXCR3 antagonists (eg, AMG487, NBI-74330) interrupt IP-10 signaling, and reduce inflammation and fibrosis. In HCV infections, inhibition of CXCR3 reduced immune-mediated liver damage without affecting viral clearance. In HBV/HIV coinfections, these agents also reduced liver enzyme levels, suggesting a protective effect against immune-mediated damage.⁸⁴ Moreover, Targeting the IP-10/CXCR3 axis holds therapeutic promise but raises concerns about impairing antiviral immunity.⁸⁵ CXCR3 blockade may reduce immune-mediated liver injury but could also impair pathogen clearance by limiting T cell recruitment. The balance between immune modulation and antiviral efficacy is critical, especially in chronic infections such as HBV and HCV. Further research is needed to optimize strategies that reduce liver damage without compromising host defense or causing immune dysregulation.

3. Combination therapies

The combination of regorafenib with anti-PD1 can inhibit tumor growth and prolong survival by normalizing tumor vasculature and increasing intratumoral CXCR3+CD8 T cell infiltration.⁸⁶ Activation of the CT10 Regulator of Kinase-like (CRKL)/ β -catenin/VEGF α and CXCL1 axis is a critical obstacle to successful anti-PD-1 therapy.

Therefore, CRKL inhibitors in combination with anti-PD-1 may be useful for the treatment of HCC.⁸⁷ In addition, the combination of peg-IFN α and PD-1 blockade could be a promising strategy for HCC.⁸⁸

4. Challenges and future directions

Clinical translation, while promising, requires investigation of the context-dependent role of IP-10, eg, its dual proinflammatory and immunosuppressive effects in HCC.³⁹ Biomarker-driven studies (eg, stratification by IP-10 levels) could optimize patient selection. New epigenetic therapies (eg, HDAC3 inhibitors) that indirectly modulate IP-10 expression should also be explored.⁷⁸ By combining mechanistic insights with translational strategies, targeting IP-10/CXCR3 offers a versatile approach to ameliorate liver injury from various etiologies.⁸⁹

Perspective Representation

IP-10/CXCL10 is traditionally recognized as a proinflammatory cytokine that recruits T cells to sites of liver injury. However, emerging research indicates that its role is multifaceted and extends beyond chemotaxis to influence liver regeneration and the balance between hepatoprotection and hepatotoxicity.^{7,84} Recent findings highlight the dual role of IP-10: it causes immune-mediated damage and affects tissue repair pathways.⁹⁰ This broader understanding underscores the need to further investigate IP-10 mechanisms in liver homeostasis and opens new opportunities for therapeutic targeting and biomarker development.⁹¹ Future studies should examine the context-dependent functions of IP-10 to optimize its clinical applications.

The following research directions and possibilities are suggested for the future: How can the specific mechanisms of CXCL10 be thoroughly explored to optimize targeted therapy;⁹² How can large-scale, randomized, double-blind clinical trials be conducted to validate the efficacy and safety of CXCL10-targeted therapies? How can comprehensive treatment strategies be investigated to achieve optimal clinical outcomes? In addition, single-cell RNA sequencing will clarify the intercellular communication network of IP-10, providing insights into the role of IP-10 in intercellular communication during liver injury and identifying potential therapeutic targets.⁹³

Abbreviations

CHB, chronic hepatitis B; CHC, chronic hepatitis C; CXCR3, CXC receptor 3; HDAC3, histone deacetylase; IP-10, interferon gamma-induced protein 10; IRF-1, Interferon regulatory factor 1; MASH, metabolic dysfunction associated steatohepatitis; MASLD, metabolic dysfunction associated steatotic liver disease; MCP-1, monocyte chemotactic protein-1; MIG, monokine induced by interferon- γ (also as IP-9); NAFLS, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Disclosure

The authors report no conflicts of interest in this work.

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