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Role of the chemokine system in liver fibrosis: a narrative review

Kyle L. Poulsen[1,2], **Christina K. Cajigas-Du Ross**[1], **Jarod K. Chaney**[2], **Laura E. Nagy**[1,3,4]

[1]Center for Liver Disease Research, Department of Inflammation and Immunity, Cleveland Clinic, Cleveland, OH, USA;

[2]Department of Anesthesiology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA;

[3]Gastroenterology and Hepatology, Cleveland Clinic, Cleveland, OH, USA;

[4]Department of Molecular Medicine, Case Western Reserve University, Cleveland, OH, USA

Abstract

Background and Objective: Liver fibrosis is a disease with characteristics of an aberrant wound healing response. Fibrosis is commonly the end-stage for chronic liver diseases like alcohol-associated liver disease (ALD), metabolic-associated liver disease, viral hepatitis, and hepatic autoimmune disease. Innate immunity contributes to the progression of many diseases through multiple mechanisms including production of pro-inflammatory mediators, leukocyte infiltration and tissue injury. Chemokines and their receptors orchestrate accumulation and activation of immune cells in tissues and are associated with multiple liver diseases; however, much less is known about their potential roles in liver fibrosis. This is a narrative review of current knowledge of the relationship of chemokine biology to liver fibrosis with insights into potential future therapeutic opportunities that can be explored in the future.

Methods: A comprehensive literature review was performed searching PubMed for relevant English studies and texts regarding chemokine biology, chronic liver disease and liver fibrosis published between 1993 and 2021. The review was written and constructed to detail the intriguing chemokine biology, the relation of chemokines to tissue injury and resolution, and identify areas of discovery for fibrosis treatment.

Correspondence to: Kyle L. Poulsen, PhD. Department of Anesthesiology, McGovern Medical School, University of Texas Health Science Center at Houston, 6431 Fannin St., Houston, TX 77030, USA. kyle.l.poulsen@uth.tmc.edu.

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Key Content and Findings: Chemokines are implicated in many chronic liver diseases, regardless of etiology. Most of these diseases will progress to fibrosis without appropriate treatment. The contributions of chemokines to liver disease and fibrosis are diverse and include canonical roles of modulating hepatic inflammation as well as directly contributing to fibrosis via activation of hepatic stellate cells (HSCs). Limited clinical evidence suggests that targeting chemokines in certain liver diseases might provide a therapeutic benefit to patients with hepatic fibrosis.

Conclusions: The chemokine system of ligands and receptors is a complex network of inflammatory signals in nearly all diseases. The specific sources of chemokines and cellular targets lend unique pathophysiological consequences to chronic liver diseases and established fibrosis. Although most chemokines are pro-inflammatory and contribute to tissue injury, others likely aid in the resolution of established fibrosis. To date, very few targeted therapies exist for the chemokine system and liver disease and/or fibrosis, and further study could identify viable treatment options to improve outcomes in patients with end-stage liver disease.

Keywords

Chemokines; chemokine receptors; liver disease; fibrosis

Introduction

The inflammatory response is associated with the onset and progression of almost all diseases, including chronic liver disease. While inflammation is characteristic of all stages of liver injury, the specific etiology of chronic liver injury, i.e., alcohol- or metabolic-associated, viral, or autoimmune can modulate the characteristics of the inflammatory milieu within the liver (1). The inflammatory environment is governed by a complex mixture of cellular and soluble factors that interact in response to noxious stimuli in an effort to resolve the injury or infectious agent (1–3). Mechanistically, appropriate and effective immune-cell trafficking is essential for host defense from pathogens and in response to injury. Whereas cytokines, interleukins, and complement act directly on tissues in response to noxious stimuli, chemokines orchestrate the dynamics of cellular infiltration into sites of damage within tissues (4,5). Research into the system of chemokines over the past two decades has defined the many roles these inflammatory mediators play in liver disease. The focus of this review is to incorporate current knowledge of chemokine biology as it pertains to chronic liver disease and liver fibrosis and look forward to the opportunities the chemokine system presents for meaningful improvements in patients. We present the following article in accordance with the Narrative Review reporting checklist (available at https://dmr.amegroups.com/article/view/10.21037/dmr-21-87/rc).

Methods

A PubMed search was conducted on September 1, 2021 for this review. The search terms and keywords utilized are summarized in Table 1. The final selection of information included in this manuscript was performed upon review of the identified manuscripts by the authors.

Chemokine biology: structure and families

The name “chemokine” is a portmanteau formed by merging the term chemotactic cytokines (3,6). They are relatively small (6–14 kilodaltons), are made up of many basic amino acids, and are heparin-binding proteins best characterized as chemo-attractants for immune cell trafficking (7,8). In addition, the roles of chemokines may also include effects on tissue epithelium, growth and angiogenesis (9). Per the focus on fibrosis, chemokines can act on hepatic stellate cells (HSCs) to promote and sustain the fibrogenic phenotype in HSCs within the liver (2,10).

To date, at least 50 chemokine ligands and 20 receptors have been identified, and many have been implicated in many forms of chronic liver disease (3,9,11). A comprehensive table of chemokines, chemokines receptors, cellular source and targets, as well as potential role(s) in liver diseases and liver fibrosis, is presented in Table 2. The system of chemokine ligands and receptors is degenerate, that is to say multiple ligands exist for most receptors and a given receptor can bind multiple chemokines. It is unclear as to whether the system is simply redundant, with biochemically similar chemokines performing copycat functions of each other. Multiple studies, however, would suggest that it is more nuanced, with structurally similar chemokines that bind the same receptor having distinct functions on a target cell (12). Furthermore, the cellular source and targets of these biologically similar chemokine families likely act to fine tune the inflammatory response rather than just acting as duplicate ligands for the same receptors (13).

The chemokine families are grouped into four subfamilies by the arrangement of the N-terminal cysteine motifs, so-called C, CC, CXC and CX3C (3,6,14,15). Within the CXC family, there is an additional layer of structural distinction that is determined by the presence or absence of an amino acid motif of glutamic acid (E)-leucine (L)-arginine (R) (ELR) before the first cysteine of the C-X-C motif (ELR^+) or those without an ELR motif (ELR^-) (16). Despite chemokines being intrinsic to immune cell/leukocyte trafficking and inflammation, they are produced by a spectrum of cells within the liver, from resident macrophages to non-immune hepatic epithelial cells like hepatocytes, sinusoidal epithelial cells, cholangiocytes, as well as HSCs and fibroblasts (10). Preclinical experimental models of liver injury show that most cell types can express and release chemokines in an attempt to resolve cellular injury or toxic insult (9,17,18).

An intriguing aspect of chemokine biology is that the genes for chemokine families reside in clusters within the mammalian genome (19–21). The majority of CC chemokines are found on the human chromosome 17q11-q21 and the CXC chemokines on 4q21-q21 (19,20). Subregions exist within these clusters, with the CC chemokines including MIP and MCP subregions and the CXC cluster divided into the GRO and IP-10 regions (21,22). The MIP region of the CC cluster contains CCL5, CCL16, CCL14, CCL15. CCL23, CCL18, CCL3, and CCL4 and the MCP regions containing CCL2, CCL7, CCL11, CCL8, CCL13 and CCL1 (21). All are considered to be proinflammatory due to their chemotactic activity, with CCL1 is specifically linked to fibrogenesis (21). For CXC chemokines, the GRO region contains CXCL8, CXCL6, CXCL4L1, CXCL4, CXCL7, CXCL5, CXCL3 and CXCL2 and several of these are potent chemoattractants for neutrophils (22). In the IP-10 region

CXCL9, CXCL10, CXCL11 and CXCL13 are found and are not associated with neutrophil chemotaxis, but for T cells and B cells (23–25). This clustered organization suggests that regulation of chemokines has been evolutionarily honed to direct specific coordination of chemokine expression to best respond to noxious stimuli.

Standard chemokine nomenclature requires chemokine receptors to be named in parallel with their ligands, e.g., CCR for CC chemokine receptors and CXCR for CXC chemokine receptors. Chemokine receptors are mainly expressed on leukocytes and are classical G-protein coupled receptors (GPCR) with seven transmembrane domains (7,26). When a chemokine binds to a chemokine receptor, it initiates several intracellular signaling pathways necessary for leukocyte trafficking towards the chemokine source. The Gα1 and Gβ-γ subunits of the GPCR dissociate and activate phosphatidylinositol 3-kinase, small Rho guanosine triphosphatase which alters intracellular calcium flux inside the chemokine target cells (26). These signaling events change the conformation of pivotal integrins in the leukocyte targets of chemokines. Chemokine receptor signaling promotes the interactions with cellular adhesion markers, such as intracellular adhesion molecules (ICAMs) and vascular cell adhesion molecules (VCAMs) on the sinusoidal epithelium for leukocyte extravasation from the peripheral circulation (27). Chemokines favor binding to glycosaminoglycans found in the extracellular matrix or the sinusoidal endothelium which generates the localized chemokine gradients for effective trafficking towards the chemokine source (28). This interaction with the extracellular matrix is intriguing in a disease like liver fibrosis that has disrupted synthesis and turnover of the extracellular matrix (29). Although untested, this interaction suggests that chemokines maybe a relatively underappreciated orchestrators of inflammation and fibrosis.

The interactions between chemokines and their receptors, as well as the sources and targets of chemokines and expression of receptors in chronic liver disease and fibrosis are summarized in Table 2. An atypical chemokine is included in this list, macrophage migration inhibitory factor (MIF) (30,31). MIF is a pleiotropic cytokine/chemokine which can interact with CXCRs to promote leukocyte chemotaxis, but our understanding of MIF's role in liver disease has evolved over the past decade of research (18,32–36). The role of MIF in fibrosis is somewhat controversial, as studies in genetic knockout models reported contrasting roles for MIF in fibrosis. However, recent studies indicate that MIF's role in fibrosis is likely dependent on the context of disease and/or cellular source of MIF (35,37–39). The roles of MIF in fibrosis include indirect effects in signaling pathways regulated by MIF, including cytokine- and chemokine-like functions. Our group has recently shown MIF is a potent regulator of coordinated chemokine expression in murine models of alcohol-associated liver disease (ALD). Importantly, MIF concentration in supra-hepatic circulation was associated with disease severity in patients with alcohol-associated hepatitis (AH) (18). Further research into the role of MIF in specific liver diseases associated with susceptibility to the development of fibrosis could lead to re-defining the potential efficacy of therapeutic targeting of inflammation to treat liver fibrosis.

At present, the abundance of data regarding the involvement of chemokines and/or chemokine receptors in chronic liver disease has yielded only a few clinically relevant therapeutic candidates, such as cenicriviroc, a dual CCR2/CCR5 inhibitor (40,41). The

CCR2/CCR5 signaling axis was identified as an attractive target to treat metabolic-associated fatty liver disease [MAFLD; note: here we are using the newly recommended term of MAFLD/metabolic-associated steatohepatitis (MASH) to replace the previous term of non-alcoholic fatty liver disease (NAFLD) and non-alcohol associated steatohepatitis (NASH)] and has shown promise in treating MAFLD-associated liver fibrosis. Mounting evidence from studies in the era of anti-viral therapies for viral hepatitis suggests that hepatic fibrosis and even cirrhosis can be reversed with removal of the noxious stimuli (29,42,43). Despite this evidence, the chemokine system is largely underutilized as a therapeutic target in liver fibrosis. Appropriate immune cell trafficking to enable elimination of excessive matrix and resolve inflammation would require specific chemokines to direct this act of cleanup in the resolution of fibrosis. In essence, the upregulation of chemokines and chemokine receptors in chronic liver disease represents a link between the liver's response to injury that can feed forward into maladaptive inflammation and severe tissue injury. However, further investigations into the chemokine system might also reveal novel roles that contribute to the regression of fibrosis.

Cell recruitment by chemokines in liver injury

Since we have covered the disease-related upregulation of chemokines, we will now briefly define some of the leukocytes that are recruited during liver injury that are likely to participate in fibrogenesis or fibrosis. Summarized in Table 2, the target cells of chemokines are diverse and include monocytes/macrophages, natural killer (NK) and natural killer T (NKT) cells, neutrophils and T lymphocytes.

Monocytes and macrophages

The recruitment of monocytes and macrophages to the injured or inflamed liver is a common feature of chronic liver disease. In addition, Kupffer cells, the liver-resident macrophage, are consistently associated with pro-inflammatory functions in liver disease. Several studies confirm the profibrogenic response of monocytes and macrophages in liver disease since depletion of macrophages decreases liver fibrosis (44–47). Monocytes/macrophages are recruited by chemokines including CCL1, CCL2, and members of the GRO family of CXC chemokines. However, recruited monocytes/macrophages can have both restorative and damaging function, both producing multiple chemokines that can lead to feed-forward inflammation and promotion of fibrosis through HSC activation and promoting the resolution of fibrosis through expression of matrix metalloproteinases or killing of activated HSCs (48).

Neutrophils

The role of neutrophils in fibrogenesis and injury resolution is controversial (49). The functional role of neutrophils in liver injury is likely context-dependent (50) with studies reporting that neutrophils contribute to exacerbated injury in acute liver inflammation or both protection or exacerbation in chronic injury (49). Initial evidence demonstrating that decreasing neutrophil infiltration/accumulation, either by administration of neutrophil anti-serum to rats undergoing bile duct ligation, or α-naphthylisothiocynate to CXCR2-deficient mice, suggested a limited role for neutrophils in fibrosis (48). However, neutrophils

can orchestrate leukocyte infiltration through modulation of chemokine receptors, which can indirectly modulate fibrogenesis (51,52). Neutrophils will downregulate CXCR2 and upregulate inflammatory CC receptors CCR1, CCR2, and CCR5 in an effort to activate phagocytic activity and reactive oxygen species (ROS) production (53). Neutrophils also promote recruitment of T lymphocytes by producing Th1 chemokines CXCL9, CXCL10, and CXCL11 (54).

NK and NKT cells

NK and NKT are immune cells that connect the innate and adaptive immune systems with multiple roles in liver injury and fibrosis (44,55,56). They are targets of CCL3 and CCL4, IFN-γ-dependent chemokines CXCL9, CXCL10, and CXCL1, as well as CXCL16. NK and NKT cells have clearly defined roles in response to infection and in tumor surveillance, but also in both promotion and resolution of fibrosis in both direct pro-inflammatory functions but indirectly on HSC activation.

T lymphocytes

The adaptive immune response plays an important role in liver disease and fibrosis. The T cell subsets exert both pro- and anti-inflammatory functions dependent upon the subtype of T cell; Th1, Th17, CD8 T are pro-inflammatory where as Th2 and regulatory T cells (Tregs) can dampen inflammation or promote injury resolution (15,57). Many studies involving chemically-induced fibrosis suggest little involvement for T cells in fibrogenesis and/or fibrosis, but this might represent a limitation of preclinical models of liver fibrosis (58,59). In liver diseases where an adaptive immune response is prominent, T cell migration to the liver might be protective in subsequent fibrosis. Many of the chemokines that recruit NK and NKT cells are similar for T lymphocytes, e.g., CCL3, CCL4, CXCL9, CXCL10, CXCL11, as well as CCL17 and CCL22 for Tregs (15,57).

Other granulocytes: mast cells and eosinophils

The leukocytes mentioned previously are the most studied in liver disease and immunology, but recent studies in other cell types describe intriguing functions for the other granulocytes, like mast cells and eosinophils. Mast cells were traditionally associated with allergic responses, but recently have been shown to play many roles in models of liver injury such as MAFLD, ALD and fibrosis (60–62). Mast cell chemotaxis has been observed in response to CXCL1, CXCL5, CXCL8, CXCL14, as well as CX3CL1 and CCL5 and CCL11 (63). Furthermore, in addition to chemotaxis, the interactions of chemokines at receptors on mast cells can also lead to their activation and degranulation (64) and feed-forward production of more chemokines (65). The other granulocyte mentioned are eosinophils which are associated with parasitic infection and allergic responses, but also have been described to play roles in tissue injury and resolution (66). Eosinophils express a number of chemokine receptors that will lead to migration towards a site of tissue injury or infection which include CXCR1, CXCR2, CXCR3, CXCR4, as well as CCR1, CCR2, CCR3, CCR6 and CCR8 (67). Similar to most immune cells, eosinophils are also important sources of chemokines. A recent study showed that eosinophils are protective against chemically-induced fibrosis as well as acute liver injury (66). The study went on to show that the chemokines responsible for eosinophil chemotaxis were due to CCL24 produced by macrophages in a dynamic

crosstalk, further demonstrating how tightly controlled the chemokine system can be in disease and homeostasis (66).

Liver diseases associated with fibrosis

The dynamics of chemokine regulation and cellular recruitment in chronic liver diseases likely impacts the ability of the chemokine system to both contribute to and promote the resolution of fibrosis. Therefore, here we highlight liver disease-specific changes in expression and release of chemokines.

Fatty liver diseases—ALD and MAFLD

The progression of fatty liver disease to fibrosis and eventual cirrhosis are similar on a clinical level for both ALD and MAFLD (4,68–70). Initial stages include steatosis, whether due to excessive intake of alcohol or nutrients in ALD and MAFLD, respectively. Steatosis is reversible with cessation of drinking alcohol or with decreases in caloric intake and/or increases in energy expenditure (69,71). Although steatosis is relatively benign, it is considered a necessary step to the latter stages of fatty-liver disease. In addition, steatosis is characterized by increased hepatic inflammation as measured by increased expression of pro-inflammatory cytokines like tumor necrosis factor-alpha, interleukin-6, and many chemokines (1,3). With continued drinking and/or metabolic stress, fatty liver disease can progress to fibrosis, cirrhosis, and eventually hepatocellular carcinoma (4,68–70). Within ALD, a particularly inflammatory stage of ALD is AH (4,69,72). AH can superimpose along the spectrum of ALD and is associated with high patient mortality. In fact, most patients who present with AH have some form of underlying fibrosis (69,73).

ALD is now one of the leading causes of preventable liver disease and patient mortality worldwide (69,74,75). The incidence of ALD is increasing, however, there are limited therapeutic options other than off-label glucocorticoid use and, for patients with cirrhosis, orthotopic liver transplant (72). From steatosis through cirrhosis, inflammatory infiltrates including monocytes and neutrophils are well-described in clinical studies as well as in preclinical models in ethanol-fed mice (1,76). The initial studies almost 30 years ago regarding chemokines in ALD reported that upregulation of CXCL8 in patients with AH was associated with a poor prognosis and that hepatocytes exposed to ethanol upregulated expression of CXCL8 (77). As CXCL8 is the prototypical ELR^+ CXC chemokine and neutrophil chemoattractant, it suggested a role for neutrophils in ALD, AH and by extension, alcohol-associated fibrosis. Several studies have confirmed the prominent role for neutrophil infiltration in ALD and AH, however, it is still unclear whether neutrophils contribute to both injury and/or repair (73).

With the advent of transcriptomics, a seminal study from Dominguez *et al.* found that hepatic expression of chemokines CXCL1, CXCL5, CXCL6, CXCL8, CXCL10 and CXCL4 was upregulated in patients with AH, as well as CCL2 and CCL20 (78). In particular, the expression of CXC chemokines was associated with hepatic dysfunction and patient mortality, including portal hypertension, a known feature of the fibrotic liver (29). Follow-up *in vivo* studies in mouse models of ethanol feeding defined the roles of CCL2 and CCL20 in hepatic injury which served to link ethanol-mediated inflammation to steatosis,

hepatocyte injury and eventual fibrosis (78–80). Interestingly, although *Ccl2*$^{-/-}$ mice were protected from ethanol-induced liver injury, *Ccr2* deficiency was not protective. This disconnect between a chemokine and its receptor suggests that a binary relationship between ligand and receptor is insufficient to explain the role of a specific chemokine-receptor combination in any disease and that the system requires a broader, more comprehensive approach when considering targeted therapies.

A recent study from our group expanded on previous studies highlighting the roles of specific chemokines in ALD. Patients with AH exhibited a very specific chemokine expression signature as compared to other disease etiologies such as MAFLD and viral hepatitis including CCL2, CCL20, CXCL1, CXCL5, CXCL6, and CXCL8 (18). The next step was to determine what drives the transcriptional program in livers of these patients, as both CC and CXC chemokines were upregulated in a strong association with one another, despite being found in distinct regions of the genome (21). Since MIF is known to control expression of chemokines, we tested if hepatocyte-derived MIF drove this expression in ethanol-fed mice. Upregulation of mRNA expression for CXC and CC chemokines was dependent upon hepatocyte-derived MIF and when MIF signaling was interrupted by a small molecule inhibitor, expression of these chemokines was prevented in murine hepatocytes. MIF, was therefore a likely upstream mediator of pro-inflammatory functions in ALD, and could contribute to fibrosis through expression of hepatic chemokines. In another study, MIF was shown to control expression of *Ccl2* in a model of carbon tetrachloride (CCl_4)-induced fibrosis in mice (39). *Ccl2* is consistently associated with hepatic inflammation and chronic liver disease in many modalities of injury, adding to the evidence for MIF as an important controller of chemokine expression in the liver. Taken together, the intricate regulation of chemokine expression in ALD is necessary to drive maladaptive inflammation in the liver, and might be coordinately regulated by MIF.

MAFLD has several similarities in the clinical presentation of liver pathophysiology to ALD; however, MAFLD also has unique aspects with respect to the role of chemokines to disease progression. The upregulation of hepatic inflammation via chemokine expression and leukocyte trafficking is well-established (3,11). Many chemokines, including CCL2, CCL5, CXCL1, and CXCL8 are implicated in the progression of MAFLD to MASH and eventual fibrosis. There is some controversy in experimental results that contrast with respect to CCL2, however, this is largely dependent upon the source of the chemokine. CCL2 expression in hepatocytes is associated with steatosis, insulin resistance and obesity (81). Targeting *Ccr2* prevents macrophage accumulation in the liver as well as steatosis, as expected (82–84). Models of MAFLD also reveal a prominent role for CCL2 expression and leukocyte recruitment to the adipose tissue, which contributes to liver injury (85–87). Interestingly, some studies show that *Ccl2* knockout mice are not protected from adipose tissue macrophage recruitment nor insulin resistance (87,88), yet *Ccr2*$^{-/-}$ mice or pharmacological antagonists of CCR2 are effective interventions in experimental models (89), suggesting that the other ligands for CCR2, such as CCL7, CCL8 and CCL13, are important for disease progression (3). CCR2, therefore, might play a more prominent role in experimental MAFLD and MASH development compared to ALD. CCL2 is also known to be an activator and recruiter of HSCs. HSCs can in turn also produce chemokines like

CCL2, CCL5, as well as CXCL9, CXCL10 and CX3CL1, adding more players in the complex chemokine response in MAFLD (82,90,91).

CCL5, produced by many of the same cell types in the liver that produce CCL2, is associated with MAFLD, MASH and fibrosis (92,93) and CCL5 binds several receptors including CCR1, CCR3 and CCR5 (3,94). Hepatic expression of CCL5 is upregulated in obese humans and murine models of MASH, and is likely produced by fat-laden hepatocytes, targeting macrophages and HSCs (93,94). CCR5 appears to play a pivotal role in HSC migration and activation, macrophage polarization and subsequent insulin resistance in models of MASH (91,93). Therefore, both CCR2 and CCR5 signaling are among the most important players in the development of MAFLD-associated fibrosis within the chemokine system.

Neutrophil chemotaxis via the GRO family is well established in studies of MASH and in patient samples of MASH. Markers of neutrophil infiltration including neutrophil elastase (NE), myeloperoxidase (MPO), and neutrophil extracellular traps are elevated in the patients with MAFLD (95–97). In addition, elevated levels of neutrophil-secreted MMP9 drives MASH-related fibrosis progression (98). Neutrophils also release factors that play a role in MAFLD. NE, a regulator of insulin signaling contributes to liver damage through decreased insulin sensitivity, and MPO in granules of neutrophils catalyzes ROS to induce hepatocyte death (99,100). Although indirect, the generation of ROS and cellular damage from GRO-dependent neutrophil recruitment to the liver in MAFLD is likely important to hepatic fibrosis but some evidence suggests that neutrophils could promote resolution of fibrosis (101).

CXCL9 and CXCL10 are also implicated in MASH, with their receptor CXCR3 expressed on macrophages, T cells and NK cells (102,103). Both CXCL9 and CXCL10 are typically expressed at low levels, but are robustly induced in pathophysiological conditions. CXCL9 expression is upregulated in the liver sinusoidal epithelium and its expression is induced in MASH patients and in models of MASH in mice (103,104). Furthermore, CXCL10 is known to play a role in MASH pathophysiology through promotion of inflammation and steatosis (105). The studies regarding CXCL9, CXCL10 and CXCL11 in MAFLD suggest a prominent role for CXCR3 in the development of experimental models of MAFLD and fibrosis and are corroborated in patient samples (106).

In contrast to ALD, the role of MIF in experimental MASH and MAFLD has been somewhat controversial. In models of high fat diet feeding and methionine- and choline-deficient (MCD) diets, *Mif*$^{-/-}$ mice had exacerbated liver injury, inflammation and steatosis, including increased expression of CCL2 in the liver (36). Interestingly, inflammation in the adipose tissue was decreased in *Mif*$^{-/-}$ mice, suggesting that the protective role of MIF in MASH or MASH-associated fibrosis might be through suppression of inflammation, but expression of only a few chemokine genes was assessed in this study (36). A more recent study, however, found that MIF deficiency protected from MCD diet-induced steatohepatitis and fibrogenesis, but more importantly that hepatocyte-derived MIF deficiency was also protective, but through a unique mechanism. MIF signaling, via CXCR2, skewed the infiltrating NKT cell phenotype towards proinflammatory (38). We have reported that

upregulation of chemokines in livers of MAFLD patients is not as robust as it is in ALD or viral hepatitis (18). MIF might not act as a regulator of chemokine expression in metabolic liver disease or the subsequent fibrosis, but as a chemokine signaling through CXCR2, highlighting an etiology-specific role for MIF in liver fibrosis.

Infection-related hepatitis

Fibrosis can develop in response to both viral and parasitic infections. While some data is available demonstrating a role of chemokines in fibrotic responses to schistosome infection (107,108), the role of chemokines in viral hepatitis is better understood. Viral hepatitis is of particular interest with respect to chemokines and liver disease progression, as it represents an inflammatory response to infectious disease rather than the sterile inflammation driving ALD and MAFLD (109). Schistosoma infection is also an important cause of liver fibrosis. Chemokines perform classical roles of directing the inflammatory response to the liver in the anti-viral response, but also are associated with upstream development of the inflammatory environment that can eventually lead to fibrosis (110,111). Although an efficient and targeted response to the viral pathogens helps in clearance of the hepatitis C virus (HCV), a prolonged and unresolved infection could progress to more extensive injury and fibrosis. CXCR3, the receptor for interferon-gamma inducible chemokines CXCL9, CXCL10 and CXCL11 released by the sinusoidal endothelium and hepatocytes, is critical for T-cell recruitment to the liver (27,112–115). In response to HCV particles in the liver, CCL5 expression and release is increased, and expression of the CXCR3 and CCR5 ligands (CCL3–5) are increased in the liver (112,116). Furthermore, these ligands, specifically CXCL10, could serve as biomarkers for infection (114,117) CXCL10 expression is associated with the likelihood of the development of fibrosis in patients with HCV who have received a previous liver transplant (118).

Outside the adaptive immune response, NK cells are also recruited by ligands for CCR1, CCR5 and CX3CR1, as well as CXCR3, CCR5 and CCR7 (119,120). Although recruitment of NK cells is necessary for their anti-viral functions, they are associated with the development of fibrosis. Interestingly, despite the robust accumulation of these NK cells in the liver in viral hepatitis, they appear to be dysfunctional, suggesting a more complex biology than the chemokine ligand-receptor interaction in this disease (121).

One final chemokine worthy of mentioning in viral hepatitis is CXCL16. It is upregulated in sinusoidal epithelium in viral hepatitis and interacts with CXCR6 and is thought to be critical in recruitment of memory NK cells that recruit and concentrate cytotoxic NK cells to the liver (120,122). As stated previously, with the advent of direct acting antivirals, the resolution of HCV-mediated liver injury and subsequent fibrosis is likely to continue to decrease in the future, but could also serve as a rich source of clinical data to investigate the role(s) that the chemokine system can play in fibrosis regression.

Hepatic autoimmunity

For the purposes of hepatic autoimmunity, we will focus on the role of chemokines in primary biliary cholangitis (PBC) and in autoimmune hepatitis (AIH). Consistent with metabolic-related and viral hepatitis, both PBC and AIH exhibit profound leukocyte

infiltration into liver, including monocytes, macrophages, NK cells, and T cells. Moreover, many of the same chemokines previously detailed in other liver diseases are upregulated in the liver and play important roles in the pathogenesis of PBC and AIH. Within PBC, CCL2 and CXCL8 are detected around damaged bile duct epithelium and are likely expressed by these cells as well (15,119,123). They are likely indirect participants in damage to the bile ducts due to the inflammatory infiltrates, induction of feed-forward expression of cytokines and other fibrogenic factors in these areas (15). CCL3, CCL4 and CCL5 are also upregulated in the bile duct epithelium leading to enhanced chemotaxis of infiltrating mononuclear cells (124). Finally, CXCL9 and CXCL10 are significantly increased in the circulation of patients with PBC, as is the expression of CXCR3, suggesting an important role for these chemokines in attracting Th1 cells to participate in liver injury in PBC (15). In AIH, the secretion of CXCL9, CXCL10 and CXCL11 recruit T helper type 17 lymphocytes expressing CXCR3 and CCR6 which in turn attract T helper type 1 lymphocytes (57). Hepatic secretion of CXCL16 leads to migration of NKT cells via interaction with CXCR6 (125,126). Resident NKT cells expressing CXCR6 migrate in response to the local secretion of CXCL16 (127). Despite less information regarding chemokines in hepatic autoimmunity, there are consistent players amongst all of these diseases, suggesting consistent chemokine players, e.g., CCL2, CXCL8, CXCL9, CXCL10 and CXCL16, within the liver to most injurious stimuli, highlighting their importance to pathophysiology in the liver.

Direct roles of chemokines in HSCs and fibrosis

The consistent and sustained inflammatory environment in chronic liver diseases contributes to the fibrogenic phenotype with the chronic inflammation and wound healing responses that cannot appropriately resolve. The consequence of this pathophysiological response is excess production of extracellular matrix (29). Different cells within the liver can contribute to excess collagen production, but the activation of HSCs from their quiescent phenotype is necessary for the generation of myofibroblasts, a pivotal step in fibrogenesis (43,128). While there are multiple indirect roles for chemokines in fibrosis, as detailed above, there are also several chemokines that either act on HSCs or have been shown to be produced by HSCs to amplify their pro-fibrotic milieu.

Within the CC chemokine family, several members can activate HSCs, promote their fibrogenic activity, and can be produced by HSCs. CCL2, produced by multiple cell types in the inflamed liver, promotes the migration of HSCs and activates HSCs (129,130). CCL5 is upregulated in livers of patients with fibrosis, and interfering with CCL5 and its receptor CCR5 prevents experimentally-induced activation of HSCs and fibrosis (91,93,131). CCL5 promotes the migration and pro-fibrogenic functions of HSCs (132). CCL20 is also produced by resident cells in the liver, including damaged hepatocytes and cholangiocytes, and is prominently upregulated in livers of patients with AH (78,80). CCL20 promotes HSC-mediated fibrogenesis and can be produced by activated HSCs. In the CXC family, the CXCL10 directly acts on HSCs to be profibrogenic but also can prevent NK-mediated inactivation of HSCs (133). HSCs are also a source of CXCL9 and CXCL10, but CXCL9 might be anti-fibrogenic (115,134,135).

Chemokines and injury resolution in fibrosis

Although the pro-inflammatory and pro-fibrogenic roles of chemokines are implicated in chronic liver diseases, evidence also exists as to chemokine-receptor interactions that might promote resolution and thus be anti-fibrogenic. This is not as well understood due to our nascent understanding of the mechanisms for regression of fibrosis in patients, but has shown promise in preclinical models of fibrosis.

The chemokine CX3CL1, also known as fractalkine, is rather unique in chemokine biology. It is the only known member of the CX3C chemokine family that signals through CX3CR1 (136–138). There remains some controversy as to whether CX3CL1 is always pro-resolution, but several studies show that the interaction with CX3CR1 on macrophages decreases hepatic inflammation, enhances macrophage survival and promotes a switch in phenotype to an anti-inflammatory cell (139). If CX3CL1 or CX3CR1 are knocked out in mice, they are more likely to develop fibrosis, providing a functional link to CX3CR1-CX3CL1 signaling and a protective role in liver fibrosis.

In AIH, CCR4-expressing T helper type 2 lymphocytes migrate into the liver due to CCL17 and CCL22, and dampen the expansion of pro-inflammatory cells (57,140–142). Tregs expressing CXCR3 are also attracted by the secretion of CXCL9 in AIH, which can also attenuate the pro-inflammatory environment (143–145). Identifying the chemotactic signals for anti-inflammatory cells like Th2 or Tregs could be an important area of discovery, especially in liver diseases with prominent adaptive immune responses like in viral hepatitis and autoimmune disease

Neutrophils may have a role in fibrotic injury resolution, with neutrophil-derived MMP expression contributing to collagen breakdown in the context of biliary obstruction (146) and CCl_4 liver injury model where neutrophil recruitment was driven by an artificial increase in bone marrow-derived macrophages (146,147). Neutrophils were also found to mediate resolution of liver inflammation and fibrosis through expression microRNA (miR)-223 prompting macrophage polarization to a restorative phenotype (101).

Another potential link to fibrosis resolution and chemokines comes from a seminal study by the Iredale group which detailed the resolution of chemically-induced fibrosis. After ceasing CCl_4 treatment, the recruited monocytes converted to a restorative-type macrophage. The *Ccr2*$^{+}$ monocytes were likely recruited by the chemokines released in response to liver damage in this model, but undergo a phenotypic switch which could be tied to increased expression of CX3CL1 and CX3CR1 (42,148). These cells also decrease expression of pro-fibrogenic chemokines like CXCL10 and CXL2. Interestingly, these restorative macrophages also have increased expression of MIF and the MIF receptor CD74, highlighting a potential mechanism of MIF-dependent anti-fibrosis, supported by the exacerbated liver injury in *Mif*$^{+/-}$ mice in models of chemically-induced fibrosis.

Therapeutic targeting of chemokine axes in liver fibrosis

To date, there are few options for anti-fibrotic therapies, and many are still in clinical trials (136). By extension, this is certainly true for therapies that might modulate the chemokine

system in chronic liver disease or in liver fibrosis. The extensively interconnected web of chemokines, receptors and cell types requires further comprehensive studies to analyze the spatial, and temporal relationships of chemokine expression and chemokine activities in liver disease that could result in fibrosis. Furthermore, the specific sources of chemokines could also represent viable targets for neutralization of proinflammatory and profibrotic chemokines, e.g., CCL2 or CXCL10, or even the over expression of chemokines that can induce and anti-inflammatory phenotype or lead to fibrosis regression, e.g., CX3CL1 or CXCL9.

Most recently, the dual CCR2/CCR5 inhibitor, cenicriviroc, was evaluated in clinical trials as a therapy to treat liver fibrosis in adults with MASH. The results suggested that cenicriviroc was well-tolerated and effective as an antifibrotic therapy, without affecting the underlying steatohepatitis. The disconnect between the persistent underlying disease but effective fibrosis regression is unknown, but demonstrated the feasibility of specific targeting of the chemokine system as a means to resolve fibrosis (41).

Targeting of specific sources of chemokines is another avenue for discovery, with respect to the immune master regulator, MIF. Hepatocyte-derived MIF is now implicated as a controller of the coordinated chemokine signature in ALD and possibly required for NK cell-mediated injury and fibrogenesis in a model of MAFLD (18,38). In contrast, the first studies to investigate the role of MIF in liver fibrosis described protective functions of MIF with respect to hepatocellular signaling and the recruitment of scar-associated macrophages in global *Mif*$^{-/-}$ mice (35,37). The dichotomous roles MIF might play in fibrosis could be due to the pleiotropic nature of MIF, the temporal relationship to onset of fibrosis, or etiology of underlying chronic liver disease. Thus, MIF serves as an exciting target of discovery in chemokine biology and fibrosis as it highlights the dynamic relationship within the chemokine system, from the source(s) to the target(s).

An effective therapeutic in fibrosis could come from several facets of the chemokine system; designed as preventatives, therapies to lessen fibrogenesis, and/or to resolve established fibrosis. First and most directly, specific inhibitors of chemokines or their receptors could prevent sustained recruitment of leukocytes that might contribute to sustained and maladaptive inflammation. Secondly, targeting chemokines that act on HSCs or are produced by HSCs could help to augment the pro-fibrogenic phenotype in these cells, decrease or prevent the activation of HSCs. Third, a chemokine-type therapy that could enhance chemotaxis of leukocytes that would decrease extracellular matrix deposition in established fibrosis. It is important to note the potential challenges associated with targeting chemokines for the treatment human diseases because their role in driving and regulating various aspects of the immune response are crucial for the ability of a patient to survive viral, fungal, and bacterial infection. For example, clinical trials using CXCR1 and CXCR2 inhibitors proved successful in treating patients with chronic disease, but their use was harmful in patients with viral infection (149).

Discussion/summary

In summary, the role of the chemokine system in liver fibrosis is dynamic and our understanding of it is still developing. Despite robust upregulation of chemokine expression in nearly all liver pathologies, profound roles of infiltrating leukocytes in inflammatory biology, as well as the effects of chemokines on activation and proliferation of HSCs, they are still relatively fewer studies about the roles of chemokines in liver fibrosis. The multiple sources of chemokines in the liver and increased chemokines in circulation in most chronic liver diseases are important features in the progression of liver fibrosis. Future studies into the chemokine system in fibrosis could represent a shift in the therapeutic interventions which target HSC activation and possibly the prevention of fibrosis in susceptible populations of patients, e.g., patients with fatty liver disease, viral hepatitis or hepatic autoimmune disease.

Research of the past two decades has revealed the dynamics of the chemokine system as critical mediators of inflammation and chronic disease. In striking parallel, both inflammation and chronic disease states are associated with the development of liver fibrosis. In general, despite the growing body of knowledge showing the pivotal roles played by chemokines in liver disease, they remain relatively understudied in the field as compared to cytokines, with only one clinical trial for cenicriviroc in MAFLD patients showing some benefits. Increased research into the chemokine system could uncover specific and potent targets to either prevent fibrosis in susceptible populations or help to stabilize or reverse the progression of fibrosis to improve the quality of life in these patients with liver disease.

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References

1. Gao B, Ahmad MF, Nagy LE, et al. Inflammatory pathways in alcoholic steatohepatitis. J Hepatol 2019;70:249–59. [PubMed: 30658726]
2. Seki E, Brenner DA. Recent advancement of molecular mechanisms of liver fibrosis. J Hepatobiliary Pancreat Sci 2015;22:512–8. [PubMed: 25869468]
3. Marra F, Tacke F. Roles for chemokines in liver disease. Gastroenterology 2014;147:577–594.e1. [PubMed: 25066692]
4. Nagy LE. The Role of Innate Immunity in Alcoholic Liver Disease. Alcohol Res 2015;37:237–50. [PubMed: 26695748]
5. Mathews S, Xu M, Wang H, et al. Animals models of gastrointestinal and liver diseases. Animal models of alcohol-induced liver disease: pathophysiology, translational relevance, and challenges. Am J Physiol Gastrointest Liver Physiol 2014;306:G819–23. [PubMed: 24699333]
6. Charo IF, Ransohoff RM. The many roles of chemokines and chemokine receptors in inflammation. N Engl J Med 2006;354:610–21. [PubMed: 16467548]
7. Rossi D, Zlotnik A. The biology of chemokines and their receptors. Annu Rev Immunol 2000;18:217–42. [PubMed: 10837058]
8. Kim CH, Broxmeyer HE. Chemokines: signal lamps for trafficking of T and B cells for development and effector function. J Leukoc Biol 1999;65:6–15. [PubMed: 9886241]

9. Hughes CE, Nibbs RJB. A guide to chemokines and their receptors. FEBS J 2018;285:2944–71. [PubMed: 29637711]
10. Saiman Y, Friedman SL. The role of chemokines in acute liver injury. Front Physiol 2012;3:213. [PubMed: 22723782]
11. Roh YS, Seki E. Chemokines and Chemokine Receptors in the Development of NAFLD. Adv Exp Med Biol 2018;1061:45–53. [PubMed: 29956205]
12. Schall TJ, Proudfoot AE. Overcoming hurdles in developing successful drugs targeting chemokine receptors. Nat Rev Immunol 2011;11:355–63. [PubMed: 21494268]
13. Dyer DP, Medina-Ruiz L, Bartolini R, et al. Chemokine Receptor Redundancy and Specificity Are Context Dependent. Immunity 2019;50:378–389.e5. [PubMed: 30784579]
14. Zlotnik A, Yoshie O. Chemokines: a new classification system and their role in immunity. Immunity 2000;12:121–7. [PubMed: 10714678]
15. Choi J, Selmi C, Leung PS, et al. Chemokine and chemokine receptors in autoimmunity: the case of primary biliary cholangitis. Expert Rev Clin Immunol 2016;12:661–72. [PubMed: 26821815]
16. Belperio JA, Keane MP, Arenberg DA, et al. CXC chemokines in angiogenesis. J Leukoc Biol 2000;68:1–8. [PubMed: 10914483]
17. Roh YS, Zhang B, Loomba R, et al. TLR2 and TLR9 contribute to alcohol-mediated liver injury through induction of CXCL1 and neutrophil infiltration. Am J Physiol Gastrointest Liver Physiol 2015;309:G30–41. [PubMed: 25930080]
18. Poulsen KL, Fan X, Kibler CD, et al. Role of MIF in coordinated expression of hepatic chemokines in patients with alcohol-associated hepatitis. JCI Insight 2021;6:141420. [PubMed: 33945507]
19. Naruse K, Ueno M, Satoh T, et al. A YAC contig of the human CC chemokine genes clustered on chromosome 17q11.2. Genomics 1996;34:236–40. [PubMed: 8661057]
20. Modi WS, Chen ZQ. Localization of the human CXC chemokine subfamily on the long arm of chromosome 4 using radiation hybrids. Genomics 1998;47:136–9. [PubMed: 9465307]
21. Zlotnik A, Yoshie O, Nomiyama H. The chemokine and chemokine receptor superfamilies and their molecular evolution. Genome Biol 2006;7:243. [PubMed: 17201934]
22. Nomiyama H, Osada N, Yoshie O. The evolution of mammalian chemokine genes. Cytokine Growth Factor Rev 2010;21:253–62. [PubMed: 20434943]
23. Loetscher P, Clark-Lewis I. Agonistic and antagonistic activities of chemokines. J Leukoc Biol 2001;69:881–4. [PubMed: 11404371]
24. Hardtke S, Ohl L, Förster R. Balanced expression of CXCR5 and CCR7 on follicular T helper cells determines their transient positioning to lymph node follicles and is essential for efficient B-cell help. Blood 2005;106:1924–31. [PubMed: 15899919]
25. Gunn MD, Ngo VN, Ansel KM, et al. A B-cell-homing chemokine made in lymphoid follicles activates Burkitt's lymphoma receptor-1. Nature 1998;391:799–803. [PubMed: 9486651]
26. Mellado M, Rodríguez-Frade JM, Mañes S, et al. Chemokine signaling and functional responses: the role of receptor dimerization and TK pathway activation. Annu Rev Immunol 2001;19:397–421. [PubMed: 11244042]
27. Oo YH, Shetty S, Adams DH. The role of chemokines in the recruitment of lymphocytes to the liver. Dig Dis 2010;28:31–44. [PubMed: 20460888]
28. Proudfoot AE, Handel TM, Johnson Z, et al. Glycosaminoglycan binding and oligomerization are essential for the in vivo activity of certain chemokines. Proc Natl Acad Sci U S A 2003;100:1885–90. [PubMed: 12571364]
29. Friedman SL. Liver fibrosis -- from bench to bedside. J Hepatol 2003;38 Suppl 1:S38–53. [PubMed: 12821042]
30. Bernhagen J, Calandra T, Mitchell RA, et al. MIF is a pituitary-derived cytokine that potentiates lethal endotoxaemia. Nature 1993;365:756–9. [PubMed: 8413654]
31. Kapurniotu A, Gokce O, Bernhagen J. The Multitasking Potential of Alarmins and Atypical Chemokines. Front Med (Lausanne) 2019;6:3. [PubMed: 30729111]

32. Barnes MA, McMullen MR, Roychowdhury S, et al. Macrophage migration inhibitory factor contributes to ethanol-induced liver injury by mediating cell injury, steatohepatitis, and steatosis. Hepatology 2013;57:1980–91. [PubMed: 23174952]
33. Marin V, Poulsen K, Odena G, et al. Hepatocyte-derived macrophage migration inhibitory factor mediates alcohol-induced liver injury in mice and patients. J Hepatol 2017;67:1018–25. [PubMed: 28647568]
34. Poulsen KL, McMullen MR, Huang E, et al. Novel Role of Macrophage Migration Inhibitory Factor in Upstream Control of the Unfolded Protein Response After Ethanol Feeding in Mice. Alcohol Clin Exp Res 2019;43:1439–51. [PubMed: 31009094]
35. Heinrichs D, Knauel M, Offermanns C, et al. Macrophage migration inhibitory factor (MIF) exerts antifibrotic effects in experimental liver fibrosis via CD74. Proc Natl Acad Sci U S A 2011;108:17444–9. [PubMed: 21969590]
36. Heinrichs D, Berres ML, Coeuru M, et al. Protective role of macrophage migration inhibitory factor in nonalcoholic steatohepatitis. FASEB J 2014;28:5136–47. [PubMed: 25122558]
37. Barnes MA, McMullen MR, Roychowdhury S, et al. Macrophage migration inhibitory factor is required for recruitment of scar-associated macrophages during liver fibrosis. J Leukoc Biol 2015;97:161–9. [PubMed: 25398607]
38. Heinrichs D, Brandt EF, Fischer P, et al. Unexpected Pro-Fibrotic Effect of MIF in Non-Alcoholic Steatohepatitis Is Linked to a Shift in NKT Cell Populations. Cells 2021;10:252. [PubMed: 33525493]
39. Xie J, Yang L, Tian L, et al. Macrophage Migration Inhibitor Factor Upregulates MCP-1 Expression in an Autocrine Manner in Hepatocytes during Acute Mouse Liver Injury. Sci Rep 2016;6:27665. [PubMed: 27273604]
40. Friedman SL, Ratziu V, Harrison SA, et al. A randomized, placebo-controlled trial of cenicriviroc for treatment of nonalcoholic steatohepatitis with fibrosis. Hepatology 2018;67:1754–67. [PubMed: 28833331]
41. Ratziu V, Sanyal A, Harrison SA, et al. Cenicriviroc Treatment for Adults With Nonalcoholic Steatohepatitis and Fibrosis: Final Analysis of the Phase 2b CENTAUR Study. Hepatology 2020;72:892–905. [PubMed: 31943293]
42. Campana L, Iredale JP. Regression of Liver Fibrosis. Semin Liver Dis 2017;37:1–10. [PubMed: 28201843]
43. Kisseleva T, Brenner D. Molecular and cellular mechanisms of liver fibrosis and its regression. Nat Rev Gastroenterol Hepatol 2021;18:151–66. [PubMed: 33128017]
44. Seki E, Schwabe RF. Hepatic inflammation and fibrosis: functional links and key pathways. Hepatology 2015;61:1066–79. [PubMed: 25066777]
45. Duffield JS, Forbes SJ, Constandinou CM, et al. Selective depletion of macrophages reveals distinct, opposing roles during liver injury and repair. J Clin Invest 2005;115:56–65. [PubMed: 15630444]
46. Pradere JP, Kluwe J, De Minicis S, et al. Hepatic macrophages but not dendritic cells contribute to liver fibrosis by promoting the survival of activated hepatic stellate cells in mice. Hepatology 2013;58:1461–73. [PubMed: 23553591]
47. Seki E, De Minicis S, Osterreicher CH, et al. TLR4 enhances TGF-beta signaling and hepatic fibrosis. Nat Med 2007;13:1324–32. [PubMed: 17952090]
48. Pellicoro A, Ramachandran P, Iredale JP, et al. Liver fibrosis and repair: immune regulation of wound healing in a solid organ. Nat Rev Immunol 2014;14:181–94. [PubMed: 24566915]
49. Tang J, Yan Z, Feng Q, et al. The Roles of Neutrophils in the Pathogenesis of Liver Diseases. Front Immunol 2021;12:625472. [PubMed: 33763069]
50. Weston CJ, Zimmermann HW, Adams DH. The Role of Myeloid-Derived Cells in the Progression of Liver Disease. Front Immunol 2019;10:893. [PubMed: 31068952]
51. Saito JM, Bostick MK, Campe CB, et al. Infiltrating neutrophils in bile duct-ligated livers do not promote hepatic fibrosis. Hepatol Res 2003;25:180–91. [PubMed: 12644055]
52. Xu J, Lee G, Wang H, et al. Limited role for CXC chemokines in the pathogenesis of alpha-naphthylisothiocyanate-induced liver injury. Am J Physiol Gastrointest Liver Physiol 2004;287:G734–41. [PubMed: 15130876]

53. Rudd JM, Pulavendran S, Ashar HK, et al. Neutrophils Induce a Novel Chemokine Receptors Repertoire During Influenza Pneumonia. Front Cell Infect Microbiol 2019;9:108. [PubMed: 31041196]
54. Tecchio C, Cassatella MA. Neutrophil-derived chemokines on the road to immunity. Semin Immunol 2016;28:119–28. [PubMed: 27151246]
55. Radaeva S, Sun R, Jaruga B, et al. Natural killer cells ameliorate liver fibrosis by killing activated stellate cells in NKG2D-dependent and tumor necrosis factor-related apoptosis-inducing ligand-dependent manners. Gastroenterology 2006;130:435–52. [PubMed: 16472598]
56. Melhem A, Muhanna N, Bishara A, et al. Anti-fibrotic activity of NK cells in experimental liver injury through killing of activated HSC. J Hepatol 2006;45:60–71. [PubMed: 16515819]
57. Czaja AJ. Review article: chemokines as orchestrators of autoimmune hepatitis and potential therapeutic targets. Aliment Pharmacol Ther 2014;40:261–79. [PubMed: 24890045]
58. Muhanna N, Horani A, Doron S, et al. Lymphocytehepatic stellate cell proximity suggests a direct interaction. Clin Exp Immunol 2007;148:338–47. [PubMed: 17437422]
59. Novobrantseva TI, Majeau GR, Amatucci A, et al. Attenuated liver fibrosis in the absence of B cells. J Clin Invest 2005;115:3072–82. [PubMed: 16276416]
60. Jarido V, Kennedy L, Hargrove L, et al. The emerging role of mast cells in liver disease. Am J Physiol Gastrointest Liver Physiol 2017;313:G89–G101. [PubMed: 28473331]
61. Kennedy L, Meadows V, Sybenga A, et al. Mast Cells Promote Nonalcoholic Fatty Liver Disease Phenotypes and Microvesicular Steatosis in Mice Fed a Western Diet. Hepatology 2021;74:164–82. [PubMed: 33434322]
62. Meadows V, Kennedy L, Ekser B, et al. Mast Cells Regulate Ductular Reaction and Intestinal Inflammation in Cholestasis Through Farnesoid X Receptor Signaling. Hepatology 2021;74:2684–98. [PubMed: 34164827]
63. Juremalm M, Nilsson G. Chemokine receptor expression by mast cells. Chem Immunol Allergy 2005;87:130–44. [PubMed: 16107768]
64. Willox I, Mirkina I, Westwick J, et al. Evidence for PI3K-dependent CXCR3 agonist-induced degranulation of human cord blood-derived mast cells. Mol Immunol 2010;47:2367–77. [PubMed: 20627397]
65. Mukai K, Tsai M, Saito H, et al. Mast cells as sources of cytokines, chemokines, and growth factors. Immunol Rev 2018;282:121–50. [PubMed: 29431212]
66. Xu L, Yang Y, Wen Y, et al. Hepatic recruitment of eosinophils and their protective function during acute liver injury. J Hepatol 2022. [Epub ahead of print].
67. Carr TF, Berdnikovs S, Simon HU, et al. Eosinophilic bioactivities in severe asthma. World Allergy Organ J 2016;9:21. [PubMed: 27386041]
68. Tacke F, Weiskirchen R. Non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH)-related liver fibrosis: mechanisms, treatment and prevention. Ann Transl Med 2021;9:729. [PubMed: 33987427]
69. Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology 2011;141:1572–85. [PubMed: 21920463]
70. Lee YA, Friedman SL. Inflammatory and fibrotic mechanisms in NAFLD-Implications for new treatment strategies. J Intern Med 2022;291:11–31. [PubMed: 34564899]
71. Schuppan D, Surabattula R, Wang XY. Determinants of fibrosis progression and regression in NASH. J Hepatol 2018;68:238–50. [PubMed: 29154966]
72. Louvet A, Thursz MR, Kim DJ, et al. Corticosteroids Reduce Risk of Death Within 28 Days for Patients With Severe Alcoholic Hepatitis, Compared With Pentoxifylline or Placebo-a Meta-analysis of Individual Data From Controlled Trials. Gastroenterology 2018;155:458–468.e8. [PubMed: 29738698]
73. Altamirano J, Miquel R, Katoonizadeh A, et al. A histologic scoring system for prognosis of patients with alcoholic hepatitis. Gastroenterology 2014;146:1231–9. e1–6. [PubMed: 24440674]
74. Mellinger JL, Winder GS. Alcohol Use Disorders in Alcoholic Liver Disease. Clin Liver Dis 2019;23:55–69. [PubMed: 30454833]

75. Dang K, Hirode G, Singal AK, et al. Alcoholic Liver Disease Epidemiology in the United States: A Retrospective Analysis of 3 US Databases. Am J Gastroenterol 2020;115:96–104. [PubMed: 31517639]
76. Nagy LE, Ding WX, Cresci G, et al. Linking Pathogenic Mechanisms of Alcoholic Liver Disease With Clinical Phenotypes. Gastroenterology 2016;150:1756–68. [PubMed: 26919968]
77. Shiratori Y, Takada H, Hikiba Y, et al. Production of chemotactic factor, interleukin-8, from hepatocytes exposed to ethanol. Hepatology 1993;18:1477–82. [PubMed: 8244273]
78. Dominguez M, Miquel R, Colmenero J, et al. Hepatic expression of CXC chemokines predicts portal hypertension and survival in patients with alcoholic hepatitis. Gastroenterology 2009;136:1639–50. [PubMed: 19208360]
79. Mandrekar P, Ambade A, Lim A, et al. An essential role for monocyte chemoattractant protein-1 in alcoholic liver injury: regulation of proinflammatory cytokines and hepatic steatosis in mice. Hepatology 2011;54:2185–97. [PubMed: 21826694]
80. Affò S, Morales-Ibanez O, Rodrigo-Torres D, et al. CCL20 mediates lipopolysaccharide induced liver injury and is a potential driver of inflammation and fibrosis in alcoholic hepatitis. Gut 2014;63:1782–92. [PubMed: 24415562]
81. Rull A, Rodríguez F, Aragonès G, et al. Hepatic monocyte chemoattractant protein-1 is upregulated by dietary cholesterol and contributes to liver steatosis. Cytokine 2009;48:273–9. [PubMed: 19748796]
82. Miura K, Yang L, van Rooijen N, et al. Hepatic recruitment of macrophages promotes nonalcoholic steatohepatitis through CCR2. Am J Physiol Gastrointest Liver Physiol 2012;302:G1310–21. [PubMed: 22442158]
83. Tamura Y, Sugimoto M, Murayama T, et al. C-C chemokine receptor 2 inhibitor improves diet-induced development of insulin resistance and hepatic steatosis in mice. J Atheroscler Thromb 2010;17:219–28. [PubMed: 20179360]
84. Baeck C, Wehr A, Karlmark KR, et al. Pharmacological inhibition of the chemokine CCL2 (MCP-1) diminishes liver macrophage infiltration and steatohepatitis in chronic hepatic injury. Gut 2012;61:416–26. [PubMed: 21813474]
85. Xu ZM, Zhao SP, Li QZ, et al. Atorvastatin reduces plasma MCP-1 in patients with acute coronary syndrome. Clin Chim Acta 2003;338:17–24. [PubMed: 14637261]
86. Kanda H, Tateya S, Tamori Y, et al. MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. J Clin Invest 2006;116:1494–505. [PubMed: 16691291]
87. Inouye KE, Shi H, Howard JK, et al. Absence of CC chemokine ligand 2 does not limit obesity-associated infiltration of macrophages into adipose tissue. Diabetes 2007;56:2242–50. [PubMed: 17473219]
88. Kirk EA, Sagawa ZK, McDonald TO, et al. Monocyte chemoattractant protein deficiency fails to restrain macrophage infiltration into adipose tissue corrected. Diabetes 2008;57:1254–61. [PubMed: 18268047]
89. Weisberg SP, Hunter D, Huber R, et al. CCR2 modulates inflammatory and metabolic effects of high-fat feeding. J Clin Invest 2006;116:115–24. [PubMed: 16341265]
90. Baeck C, Wei X, Bartneck M, et al. Pharmacological inhibition of the chemokine C-C motif chemokine ligand 2 (monocyte chemoattractant protein 1) accelerates liver fibrosis regression by suppressing Ly-6C(+) macrophage infiltration in mice. Hepatology 2014;59:1060–72. [PubMed: 24481979]
91. Seki E, De Minicis S, Gwak GY, et al. CCR1 and CCR5 promote hepatic fibrosis in mice. J Clin Invest 2009;119:1858–70. [PubMed: 19603542]
92. Henao-Mejia J, Elinav E, Strowig T, et al. Inflammasomes: far beyond inflammation. Nat Immunol 2012;13:321–4. [PubMed: 22430784]
93. Berres ML, Koenen RR, Rueland A, et al. Antagonism of the chemokine Ccl5 ameliorates experimental liver fibrosis in mice. J Clin Invest 2010;120:4129–40. [PubMed: 20978355]
94. Kirovski G, Gäbele E, Dorn C, et al. Hepatic steatosis causes induction of the chemokine RANTES in the absence of significant hepatic inflammation. Int J Clin Exp Pathol 2010;3:675–80. [PubMed: 20830238]

95. Mirea AM, Toonen EJM, van den Munckhof I, et al. Increased proteinase 3 and neutrophil elastase plasma concentrations are associated with non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes. Mol Med 2019;25:16. [PubMed: 31046673]

96. Rensen SS, Slaats Y, Nijhuis J, et al. Increased hepatic myeloperoxidase activity in obese subjects with nonalcoholic steatohepatitis. Am J Pathol 2009;175:1473–82. [PubMed: 19729473]

97. van der Windt DJ, Sud V, Zhang H, et al. Neutrophil extracellular traps promote inflammation and development of hepatocellular carcinoma in nonalcoholic steatohepatitis. Hepatology 2018;68:1347–60. [PubMed: 29631332]

98. D'Amico F, Consolo M, Amoroso A, et al. Liver immunolocalization and plasma levels of MMP-9 in non-alcoholic steatohepatitis (NASH) and hepatitis C infection. Acta Histochem 2010;112:474–81. [PubMed: 19604544]

99. Talukdar S, Oh DY, Bandyopadhyay G, et al. Neutrophils mediate insulin resistance in mice fed a high-fat diet through secreted elastase. Nat Med 2012;18:1407–12. [PubMed: 22863787]

100. Aratani Y Myeloperoxidase: Its role for host defense, inflammation, and neutrophil function. Arch Biochem Biophys 2018;640:47–52. [PubMed: 29336940]

101. Calvente CJ, Tameda M, Johnson CD, et al. Neutrophils contribute to spontaneous resolution of liver inflammation and fibrosis via microRNA-223. J Clin Invest 2019;129:4091–109. [PubMed: 31295147]

102. Braunersreuther V, Viviani GL, Mach F, et al. Role of cytokines and chemokines in non-alcoholic fatty liver disease. World J Gastroenterol 2012;18:727–35. [PubMed: 22371632]

103. Schrage A, Wechsung K, Neumann K, et al. Enhanced T cell transmigration across the murine liver sinusoidal endothelium is mediated by transcytosis and surface presentation of chemokines. Hepatology 2008;48:1262–72. [PubMed: 18697212]

104. Semba T, Nishimura M, Nishimura S, et al. The FLS (fatty liver Shionogi) mouse reveals local expressions of lipocalin-2, CXCL1 and CXCL9 in the liver with non-alcoholic steatohepatitis. BMC Gastroenterol 2013;13:120. [PubMed: 23875831]

105. Zhang X, Shen J, Man K, et al. CXCL10 plays a key role as an inflammatory mediator and a non-invasive biomarker of non-alcoholic steatohepatitis. J Hepatol 2014;61:1365–75. [PubMed: 25048951]

106. Zhang X, Han J, Man K, et al. CXC chemokine receptor 3 promotes steatohepatitis in mice through mediating inflammatory cytokines, macrophages and autophagy. J Hepatol 2016;64:160–70. [PubMed: 26394162]

107. Souza AL, Sousa-Pereira SR, Teixeira MM, et al. The role of chemokines in Schistosoma mansoni infection: insights from human disease and murine models. Mem Inst Oswaldo Cruz 2006;101 Suppl 1:333–8. [PubMed: 17308793]

108. Chuah C, Jones MK, Burke ML, et al. Cellular and chemokine-mediated regulation in schistosome-induced hepatic pathology. Trends Parasitol 2014;30:141–50. [PubMed: 24433721]

109. Fahey S, Dempsey E, Long A. The role of chemokines in acute and chronic hepatitis C infection. Cell Mol Immunol 2014;11:25–40. [PubMed: 23954947]

110. Negash AA, Ramos HJ, Crochet N, et al. IL-1β production through the NLRP3 inflammasome by hepatic macrophages links hepatitis C virus infection with liver inflammation and disease. PLoS Pathog 2013;9:e1003330. [PubMed: 23633957]

111. Bataller R, Paik YH, Lindquist JN, et al. Hepatitis C virus core and nonstructural proteins induce fibrogenic effects in hepatic stellate cells. Gastroenterology 2004;126:529–40. [PubMed: 14762790]

112. Nguyen N, de Esch C, Cameron B, et al. Positioning of leukocyte subsets in the portal and lobular compartments of hepatitis C virus-infected liver correlates with local chemokine expression. J Gastroenterol Hepatol 2014;29:860–9. [PubMed: 24236853]

113. Butera D, Marukian S, Iwamaye AE, et al. Plasma chemokine levels correlate with the outcome of antiviral therapy in patients with hepatitis C. Blood 2005;106:1175–82. [PubMed: 15860662]

114. Zeremski M, Shu MA, Brown Q, et al. Hepatitis C virus-specific T-cell immune responses in seronegative injection drug users. J Viral Hepat 2009;16:10–20. [PubMed: 18647233]

115. Tacke F, Zimmermann HW, Berres ML, et al. Serum chemokine receptor CXCR3 ligands are associated with progression, organ dysfunction and complications of chronic liver diseases. Liver Int 2011;31:840–9. [PubMed: 21645215]

116. Larrubia JR, Calvino M, Benito S, et al. The role of CCR5/CXCR3 expressing CD8+ cells in liver damage and viral control during persistent hepatitis C virus infection. J Hepatol 2007;47:632–41. [PubMed: 17560677]

117. Sahin H, Borkham-Kamphorst E, do O NT, et al. Proapoptotic effects of the chemokine, CXCL 10 are mediated by the noncognate receptor TLR4 in hepatocytes. Hepatology 2013;57:797–805. [PubMed: 22996399]

118. Berres ML, Trautwein C, Schmeding M, et al. Serum chemokine CXC ligand 10 (CXCL10) predicts fibrosis progression after liver transplantation for hepatitis C infection. Hepatology 2011;53:596–603. [PubMed: 21274880]

119. Zimmermann HW, Seidler S, Gassler N, et al. Interleukin-8 is activated in patients with chronic liver diseases and associated with hepatic macrophage accumulation in human liver fibrosis. PLoS One 2011;6:e21381. [PubMed: 21731723]

120. Rehermann B Pathogenesis of chronic viral hepatitis: differential roles of T cells and NK cells. Nat Med 2013;19:859–68. [PubMed: 23836236]

121. Eisenhardt M, Glässner A, Krämer B, et al. The CXCR3(+)CD56Bright phenotype characterizes a distinct NK cell subset with anti-fibrotic potential that shows dys-regulated activity in hepatitis C. PLoS One 2012;7:e38846. [PubMed: 22792160]

122. Paust S, Gill HS, Wang BZ, et al. Critical role for the chemokine receptor CXCR6 in NK cell-mediated antigen-specific memory of haptens and viruses. Nat Immunol 2010;11:1127–35. [PubMed: 20972432]

123. Tsuneyama K, Harada K, Yasoshima M, et al. Monocyte chemotactic protein-1, −2, and −3 are distinctively expressed in portal tracts and granulomata in primary biliary cirrhosis: implications for pathogenesis. J Pathol 2001;193:102–9. [PubMed: 11169522]

124. Shimoda S, Harada K, Niiro H, et al. Biliary epithelial cells and primary biliary cirrhosis: the role of liver-infiltrating mononuclear cells. Hepatology 2008;47:958–65. [PubMed: 18181218]

125. Omenetti A, Syn WK, Jung Y, et al. Repair-related activation of hedgehog signaling promotes cholangiocyte chemokine production. Hepatology 2009;50:518–27. [PubMed: 19575365]

126. Abel S, Hundhausen C, Mentlein R, et al. The transmembrane CXC-chemokine ligand 16 is induced by IFN-gamma and TNF-alpha and shed by the activity of the disintegrin-like metalloproteinase ADAM10. J Immunol 2004;172:6362–72. [PubMed: 15128827]

127. Wehr A, Baeck C, Heymann F, et al. Chemokine receptor CXCR6-dependent hepatic NK T Cell accumulation promotes inflammation and liver fibrosis. J Immunol 2013;190:5226–36. [PubMed: 23596313]

128. Mederacke I, Hsu CC, Troeger JS, et al. Fate tracing reveals hepatic stellate cells as dominant contributors to liver fibrosis independent of its aetiology. Nat Commun 2013;4:2823. [PubMed: 24264436]

129. Ramm GA. Chemokine (C-C motif) receptors in fibrogenesis and hepatic regeneration following acute and chronic liver disease. Hepatology 2009;50:1664–8. [PubMed: 19877298]

130. Marra F Hepatic stellate cells and the regulation of liver inflammation. J Hepatol 1999;31:1120–30. [PubMed: 10604588]

131. Heinrichs D, Berres ML, Nellen A, et al. The chemokine CCL3 promotes experimental liver fibrosis in mice. PLoS One 2013;8:e66106. [PubMed: 23799074]

132. Schwabe RF, Bataller R, Brenner DA. Human hepatic stellate cells express CCR5 and RANTES to induce proliferation and migration. Am J Physiol Gastrointest Liver Physiol 2003;285:G949–58. [PubMed: 12829440]

133. Hintermann E, Bayer M, Pfeilschifter JM, et al. CXCL10 promotes liver fibrosis by prevention of NK cell mediated hepatic stellate cell inactivation. J Autoimmun 2010;35:424–35. [PubMed: 20932719]

134. Wasmuth HE, Weiskirchen R. Pathogenesis of liver fibrosis: modulation of stellate cells by chemokines. Z Gastroenterol 2010;48:38–45. [PubMed: 20072995]

135. Sahin H, Borkham-Kamphorst E, Kuppe C, et al. Chemokine Cxcl9 attenuates liver fibrosis-associated angiogenesis in mice. Hepatology 2012;55:1610–9. [PubMed: 22237831]
136. Bazan JF, Bacon KB, Hardiman G, et al. A new class of membrane-bound chemokine with a CX3C motif. Nature 1997;385:640–4. [PubMed: 9024663]
137. Imai T, Hieshima K, Haskell C, et al. Identification and molecular characterization of fractalkine receptor CX3CR1, which mediates both leukocyte migration and adhesion. Cell 1997;91:521–30. [PubMed: 9390561]
138. White GE, Greaves DR. Fractalkine: a survivor's guide: chemokines as antiapoptotic mediators. Arterioscler Thromb Vasc Biol 2012;32:589–94. [PubMed: 22247260]
139. Karlmark KR, Zimmermann HW, Roderburg C, et al. The fractalkine receptor CX_3CR1 protects against liver fibrosis by controlling differentiation and survival of infiltrating hepatic monocytes. Hepatology 2010;52:1769–82. [PubMed: 21038415]
140. Imai T, Nagira M, Takagi S, et al. Selective recruitment of CCR4-bearing Th2 cells toward antigen-presenting cells by the CC chemokines thymus and activation-regulated chemokine and macrophage-derived chemokine. Int Immunol 1999;11:81–8. [PubMed: 10050676]
141. Andrew DP, Chang MS, McNinch J, et al. STCP-1 (MDC) CC chemokine acts specifically on chronically activated Th2 lymphocytes and is produced by monocytes on stimulation with Th2 cytokines IL-4 and IL-13. J Immunol 1998;161:5027–38. [PubMed: 9794440]
142. Sallusto F, Lanzavecchia A, Mackay CR. Chemokines and chemokine receptors in T-cell priming and Th1/Th2-mediated responses. Immunol Today 1998;19:568–74. [PubMed: 9864948]
143. Sebastiani S, Allavena P, Albanesi C, et al. Chemokine receptor expression and function in CD4+ T lymphocytes with regulatory activity. J Immunol 2001;166:996–1002. [PubMed: 11145678]
144. Müller M, Carter SL, Hofer MJ, et al. CXCR3 signaling reduces the severity of experimental autoimmune encephalomyelitis by controlling the parenchymal distribution of effector and regulatory T cells in the central nervous system. J Immunol 2007;179:2774–86. [PubMed: 17709491]
145. Saeki C, Nakano M, Takahashi H, et al. Accumulation of functional regulatory T cells in actively inflamed liver in mouse dendritic cell-based autoimmune hepatic inflammation. Clin Immunol 2010;135:156–66. [PubMed: 20080065]
146. Harty MW, Muratore CS, Papa EF, et al. Neutrophil depletion blocks early collagen degradation in repairing cholestatic rat livers. Am J Pathol 2010;176:1271–81. [PubMed: 20110408]
147. Thomas JA, Pope C, Wojtacha D, et al. Macrophage therapy for murine liver fibrosis recruits host effector cells improving fibrosis, regeneration, and function. Hepatology 2011;53:2003–15. [PubMed: 21433043]
148. Ramachandran P, Pellicoro A, Vernon MA, et al. Differential Ly-6C expression identifies the recruited macrophage phenotype, which orchestrates the regression of murine liver fibrosis. Proc Natl Acad Sci U S A 2012;109:E3186–95. [PubMed: 23100531]
149. Capucetti A, Albano F, Bonecchi R. Multiple Roles for Chemokines in Neutrophil Biology. Front Immunol 2020;11:1259. [PubMed: 32733442]

Table 1

The search strategy summary

Items	Specification
Date of search	September 1, 2021
Databases and other sources searched	PubMed
Search terms used	“Chemokines” AND “Liver Fibrosis”
	“Chemokines” AND “Chronic Liver Disease”
	“Chemokines” AND “Fibrogenesis”
	“Inflammation” AND “Liver Fibrosis”
	“Inflammation” AND “Liver Disease”
Timeframe	1993–2021
Inclusion and exclusion criteria	Inclusion criteria: (I) Basic and clinical studies (II) English language (III) Full text available
Selection process	Selection by all authors

Table 2

A comprehensive table of chemokines, chemokines receptors, cellular source and targets, as well as potential role(s) in liver diseases and liver fibrosis

Chemokine	Common name	Receptor	Cellular source in fibrosis	Target cells	Role in liver disease
CCL1	I-309, TCA-3	CCR8	BECs, LSECs	Macrophages, monocytes	Fibrosis
CCL2	MCP-1	CCR2	BECs, hepatocytes, HSCs, Kupffer cell, macrophages, monocytes	HSCs, macrophages, monocytes	Inflammation, fibrosis, ALD, MAFLD, PBC
CCL3	MIP-1α	CCR1, CCR5	BECs	CD8 T, NK, Th1	HCV, MAFLD, PBC, fibrosis
CCL4	MIP-1β	CCR1, CCR5	BECs	CD8 T, NK, Th1	HCV, MAFLD, PBC, fibrosis
CCL5	RANTES	CCR1, CCR5	BECs, hepatocytes, HSCs, Kupffer cell, macrophages, monocytes	CD8 T, HSCs, NK, Th1	HCV, MAFLD, PBC, fibrosis
CCL17	TARC	CCR4	–	Tregs	HCV
CCL19	ELC	CCR7	–	CD8 T, DCs	HCV
CCL20	MIP-3α	CCR6	BECs, hepatocytes, HSCs, macrophages, monocytes	gd T, Th17, HSCs	ALD, fibrosis, HCV
CCL21	SLC	CCR7	–	CD8 T, DCs	HCV
CCL22	MDC	CCR4	–	Tregs	HCV
CCL25	TECK	CCR8	–	HSCs, macrophages, monocytes	Fibrosis
CXCL1	GRO-α	CXCR2	Hepatocytes, Kupffer cell	Neutrophils, monocytes	Inflammation, ALD, MAFLD
CXCL2	GRO-β	CXCR2	BECs, hepatocytes	Neutrophils, monocytes	Inflammation, ALD, MAFLD
CXCL5	ENA-78	CXCR2	Hepatocytes	Neutrophils	ALD, fibrosis
CXCL6	GCP-2	CXCR1, CXCR2	Hepatocytes	Neutrophils, monocytes	ALD
CXCL8	IL-8	CXCR1, CXCR2	Hepatocytes	Neutrophils, monocytes	Inflammation, ALD, MAFLD, PBC
CXCL9	MIG	CXCR3	Hepatocytes, HSCs, LSECs	NK, Th1, Th17	HCV, fibrosis, PBC, AIH
CXCL10	IP-10	CXCR3	Hepatocytes, HSCs, LSECs	NK, Th1, Th17, HSCs	HCV, MAFLD, fibrosis, PBC, AIH
CXCL11	I-TAC	CXCR3	Hepatocytes, LSECs	NK, Th1, Th17	HCV, fibrosis, AIH
CXCL12	SDF-1	CXCR4, CXCR7	BECs, LSECs	HSCs, LSECs	Fibrosis
CXCL13	BCA-1	CXCR5		B cells	HCV
CXCL16	SRPSOX	CXCR6	Kupffer cell, LSECs	NKT cells	HCV, fibrosis (pro and anti), AIH
CX3CL1	FRACTALKINE	CX3CR1	Hepatocytes, HSCs, Kupffer cell	Macrophages, monocytes	HCV, fibrosis (anti)
MIF	N/A	CXCR2, CXCR4, CXCR7	BECs, hepatocytes, macrophages, monocytes	Macrophages, monocytes, neutrophils, NKT cells	ALD, MAFLD, fibrosis (pro and anti)

BECs, biliary epithelial cells; LSECs, liver sinusoidal endothelial cells; HSCs, hepatic stellate cells; NK, natural killer; Treg, regulatory T cell; DCs, dendritic cells; NKT, natural killer T; ALD, alcohol-associated liver disease; MAFLD, metabolic-associated fatty liver disease; PBC, primary biliary cholangitis; HCV, hepatitis C virus; AIH, autoimmune hepatitis.