



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

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**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.

**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

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## 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,

**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

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 CX<sub>3</sub>C (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*<sup>+</sup>) or those without an ELR motif (*ELR*<sup>-</sup>) (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 G $\alpha$ 1 and G $\beta$ - $\gamma$  subunits of the GPCR dissociate and activate phosphatidylinositol 3-kinase, small Rho guanine 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

**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-1 $\alpha$	CCR1, CCR5	BECs	CD8 T, NK, Th1	HCV, MAFLD, PBC, fibrosis
CCL4	MIP-1 $\beta$	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-3 $\alpha$	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- $\alpha$	CXCR2	Hepatocytes, Kupffer cell	Neutrophils, monocytes	Inflammation, ALD, MAFLD
CXCL2	GRO- $\beta$	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.

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  $\alpha$ -naphthylisothiocyanate 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- $\gamma$ -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*<sup>+</sup> 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*<sup>-/-</sup> 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<sub>4</sub>)-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*<sup>-/-</sup> 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*<sup>-/-</sup> 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*<sup>-/-</sup> 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<sub>4</sub> 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<sub>4</sub> treatment, the recruited

monocytes converted to a restorative-type macrophage. The *Ccr2*<sup>+</sup> 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 CXCL2. 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*<sup>-/-</sup> 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*<sup>-/-</sup> 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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