

Update on the role of Chemokines and Chemokine Receptors in Liver Fibrosis

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ABSTRACT

Chemokines play a critical role in cell migration and activation through binding to G-protein coupled cell-surface receptors with seven transmembrane domains. Chemokines are subdivided into four superfamilies including the CC, the CXC, the CX3C and the C families and the receptors of chemokines also segregate into four families including the CCR, CXCR, CX3CR and XCR families. Most chemokine receptors can bind to more than one chemokine and some chemokines also can bind to more than one receptor. There is ligand-receptor restriction during the binding of chemokines and special receptors. Interaction between chemokines and their receptors exerts a critical role in liver fibrogenesis through recruiting a variety of inflammatory cells into injured liver. The roles of chemokines including the CC, CXC and CX3C families on liver inflammation and fibrosis were described by the Wasmuth HE team ten years ago. Abundant evidence for pro-fibrotic or anti-fibrotic roles of chemokines and their receptors in liver fibrosis has been provided in the past decade. This paper is drawing on new evidence that has come up over the past 10 years, and uses that evidence to advance the understanding of chemokines' roles.

Key words: chemokines – chemokine receptors – liver fibrosis.

Abbreviations: AH: alcoholic hepatitis; BDL: bile duct ligation; C, CC, CXC, CX3C: chemokine superfamilies; CCR, CXCR, CX3CR and XCR: receptors of chemokine families; CCl₄: carbon tetrachloride; CLD: chronic liver disease; CVC: cenicriviroc; DAA: direct antiviral agent; DC: dendritic cells; ECM: extracellular matrix; EMT: endothelial mesenchymal transition; HBV: hepatitis B virus; HCV: hepatitis C virus; HCC: hepatocellular carcinoma; HSC: hepatic stellate cells; IgG4-SC: IgG4-related sclerosing cholangitis; KC: Kupffer cell; LSEC: liver sinusoidal endothelial cell; LSM: liver stiffness measurement; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; NK: natural killer; NKT: natural killer T; PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis; ROS: reactive oxygen species; TAA: thioacetamide; UDCA: ursodeoxycholic acid.

Received: 14.10.2022

Accepted: 25.02.2023

INTRODUCTION

Chemokines, approximately 7 to 13kDa, are small heparin-binding proteins with 20 to 70 percent homology in amino acid sequences, which function as both chemotactic mediators and cytokines [1-3]. Chemokines are subdivided into four superfamilies including the CC, the CXC, the CX3C and the C families based on the position of cysteine residues. Both the CC and CXC families contain four cysteines, and the first two

cysteine residues are adjacent to each other in CC family, whereas one amino acid separates the first two cysteine residues in CXC family [3, 4]. In the CX3C family, the first two cysteine residues are separated by three amino acids and chemokine domains located in a mucin-like stalk. The C family lacks the first cysteine residue of the distinctive Cys-Cys or Cys-X-Cys motifs located in the NH₂-terminal [5, 6]. The CC family is the largest family including 28 members (CCL1 through CCL28) and the CXC family includes 17 members (CXCL1 through CXCL17). There is only one ligand (CX3CL1) in the CX3C family, whereas there are two ligands including XCL1 and XCL2 in the C family [3].

Chemokines play a critical role in cell migration and activation through binding to G-protein coupled cell-surface receptors with seven transmembrane domains. The receptors of chemokines also segregate into four families: CCR, CXCR,

CX3CR and XCR [3]. There are eight CC chemokine receptors, four CXC chemokine receptors, and one CX3C chemokines receptor [3]. Some receptors are widely expressed on various leukocytes, whereas others are restricted to certain cells. Moreover, chemokine receptors are constitutively expressed on some cells, whereas they are inducible on others. Most chemokine receptors can bind to more than one chemokine with ligand-receptor restriction. For example, CC receptors bind to only CC chemokines and CXC receptors bind to only CXC chemokines, which is related to chemokine' different quaternary structures [7, 8]. Some chemokines can bind to more than one receptor [9]. The receptors are divided into the homeostatic receptors such as CXCR4, which are expressed constitutively in specific tissues, and the inflammatory receptors such as CCR1, CCR2, which are induced during inflammation [10].

Liver fibrosis is characterized by accumulation of extracellular matrix (ECM) proteins and fibrous scar, which results from chronic liver inflammation. Inflammatory cells including bone-marrow-derived macrophages, Kupffer cells (KCs) (the resident macrophages of the liver), neutrophils, Th17 cells, $\gamma\delta$ T cells, etc. play an important role during liver fibrogenesis through releasing pro-inflammatory mediators to induce hepatocyte apoptosis and activate hepatic stellate cells (HSCs) [11-14]. Interaction between chemokines and their receptors exerts a critical role in liver fibrogenesis through recruiting a variety of inflammatory cells into injured liver. Wasmuth et al. [3] summarized the role of chemokines including the CC, the CXC and the CX3C families on liver inflammation and fibrosisten years ago. They described pro-fibrotic roles of the CCL2-CCR2 axis, the CCL5-CCR5/CCR1axis, the CXCL12-CXCR4 axis and the CXCL8 as recruiting bone marrow-derived macrophages or neutrophils to injured liver and stimulating proliferation of human HSCs during liver inflammation, wound healing and fibrogenesis [3]. CXCL4, which is produced by platelets early in fibrogenesis, mediates the migration and proliferation of murine HSCs, but does not show a direct pro-fibrotic role [3]. Moreover, some chemokines binding to the same receptor can exert opposing effects. For example, stimulation of CXCR3 by CXCL10 leads to a migration of HSCs, whereas binding of CXCR3 and CXCL9 inhibits the expression of collagen [3].

Abundant evidence for pro-fibrotic or anti-fibrotic roles of chemokines and their receptors in liver fibrosis has been provided in the past decade. This paper is drawing on new evidence that has come up over the past 10 years, and uses that evidence to advance the understanding of chemokines' roles that was previously summarized by Wasmuth et al [3].

CC CHEMOKINES AND RECEPTORS IN LIVER FIBROSIS

The CC family includes 28 members, and some of them play pro-fibrotic or anti-fibrotic roles in liver fibrogenesis through binding to special receptors. Evidence of the role of CCL1-CCR8 axis, CCL2-CCR2 axis, CCL3/CCL5-CCR1/CCR5 axis, CCL20-CCR6 axis and CCL25-CCR9 axis in liver fibrosis has accumulated over the past decade.

CCL1-CCR8 Axis

CCL1, also known as I-309 in humans and TCA-3 in mice, is predominantly expressed on the pancreatic duct epithelium, peribiliary glands, vascular endothelial cells and CCR8+ lymphocytes [15]. CCR8, which is the receptor for CCL1, is expressed on macrophages and can promote the trafficking of monocyte/macrophage, dendritic cells (DCs) and T-helper cell (Th) subsets [16].

CCR8 is involved in the infiltration of inflammatory monocytes into injured liver and in promoting preferential differentiation into macrophages with a pro-inflammatory phenotype. CCR8 is also related to the increase of neutrophils and natural killer (NK) cells and decrease of CD4+ Th1 cells [17]. CCR8 exhibits a pro-fibrotic role, which is up-regulated in liver fibrosis models induced by carbon tetrachloride (CCl4) or surgical bile duct ligation (BDL). CCR8-deficiency attenuates liver injury and fibrosis, improves hepatocyte apoptosis, and reduces intrahepatic monocytes/macrophages. In addition, CCL1-CCR8 interaction may function as lymphocytic recruitment in IgG4-related sclerosing cholangitis (IgG4-SC) [15]. The reports about pro-fibrotic role of CCL1-CCR8 axis in liver fibrosis is lacking lately, while CCL18, another ligand of CCR8, participates in pulmonary fibrosis. It is reported that interaction between CCL1 and CCR8 is involved in liver fibrosis, whereas interaction between CCL18 and CCR8 is related to pulmonary fibrosis [18].

CCL2-CCR2 Axis

CCL2, also termed monocyte chemotactic factor 1 (MCP-1) before, through binding to its specific receptor CCR2 [19, 20], recruits monocyte-derived macrophages to injured liver [21, 22]. CCL2 is secreted by hepatocytes, KCs, biliary epithelial cells and activated or non-activated HSCs after inflammation and liver injury [23-30]. Its receptor CCR2 can be found on various cells such as monocytes, immature dendritic cells (DCs), and T cells [3].

CCL2-CCR2 axis plays an important role in the progression of fibrosis [22, 31-34]. CCL2 is expressed at a high level in fibrotic and cirrhotic livers [35]. Inhibition of CCL2 leads to less disturbed architecture and the reduction of collagen I, collagen IV and pathogenic angiogenesis in the combined fibrosis-hepatocellular carcinoma (HCC) model [36]. CCL2-dependent infiltrating macrophages promote angiogenesis in progressive liver fibrosis [31]. Splenic macrophages can promote hepatic macrophage secretion of CCL2, increase the recruitment of splenic monocytes into the liver and aggravate liver fibrosis [37]. Similarly, monocytes-derived macrophages, expressing high levels of CCR2, can activate HSCs to release high amounts of the CCL2 counterpart and promote the progression of liver fibrosis [22, 32, 38-41]. Non-alcoholic steatohepatitis (NASH) severity and fibrosis stage is correlated to increased CCR2+ macrophages [42]. Deletion of the CCR2 gene improves liver fibrosis in mouse models induced by CCl4 and BDL [43]. CCL2-CCR2 axis leads to the polarization of macrophage to M2 phenotype, whereas the expression level of the M2 macrophage marker elevates during liver fibrosis progression and is associated with fibrosis severity [44, 45]. Activated HSCs (aHSCs) promote the development of the M2 phenotype macrophage and up-regulates the expression

of CCR2 on macrophages through secreting high level CCL2 [45, 46].

At present, CCL2-CCR2 axis has been used as the therapeutic target of liver fibrosis. Glucocorticoid-induced leucine zipper exerts anti-inflammatory effects similar to glucocorticoids and regulates liver fibrosis by inhibiting CCL2-mediated leukocyte recruitment [47]. Anti-CCL2 treatment reduces pro-inflammatory cytokines such as tumor necrosis factor (TNF), interferon- γ (IFN- γ), IL-6 and ameliorates steatosis and steatohepatitis [48].

CCL3/CCL5-CCR1/CCR5 Axis

CCL3, also called macrophage inflammatory protein-1 α (MIP-1 α), is primarily secreted by M1 phenotype macrophages in the liver, and through the binding with its receptors, CCR1 and CCR5, is associated with various inflammatory diseases such as non-alcoholic fatty liver disease (NAFLD) [49, 50].

The protein expression of CCL3 elevates after chronic liver injury and deletion of CCL3 attenuates liver fibrosis. CCL3 increases proliferation and migration of HSCs in mouse liver fibrosis models induced either by CCl4 or by a methionine- and choline-deficient diet [51]. CCL3 promotes macrophage infiltration into the liver and M1 polarization and CCL3 deficiency attenuates steatohepatitis and fibrosis in mouse model induced by a high-cholesterol and high-fat diet [52].

CCL5, also known as RANTES, functions as a pro-fibrotic factor in liver fibrosis. CCL5 is up regulated both in patients with chronic liver diseases (CLDs) and in murine liver fibrosis models after CCl4 treatment or BDL [53, 54]. CCL5-induced migration of HSCs depends on reactive oxygen species (ROS) formation and Akt- and extracellular signal regulated kinase (ERK)-signaling [54, 55]. Another newly discovered action of CCL5 is the recruitment of CCR5-positive liver progenitor cells during fibrogenesis and wound healing [56].

Both CCR5 and CCR1, being receptors for CCL3 as well as CCL5, are found to promote liver fibrosis in the event of chronic injury and deficiency of CCR1 or CCR5 is associated with significant improvement of liver fibrosis. CCR1 is predominantly expressed in macrophages, whereas CCR5 is expressed both in macrophages and HSCs in fibrotic liver [54]. CCR5 may mediate fibrogenic effects later in the fibrogenic process than CCR1 and through a mechanism distinct from that of CCR1. The function of CCR1 could be attributed to infiltrating immune cells (most likely Ly6C⁺ monocytes), and CCR5 exerts its actions primarily on resident hepatic non-parenchymal cells, most often on HSCs [54]. CCR1 expression is functionally important in bone marrow-derived macrophages, and the expression of CCR5 seems to be necessary in HSCs during active fibrogenesis. CCR5 elevates in rats with hypersplenism and liver cirrhosis induced by CCl4 and CCR5-deficiency inhibits HSCs activation [57, 58].

Lenicriviroc (CVC), an oral, dual CCR2/CCR5 antagonist, causes anti-inflammatory and antifibrotic effects by reducing monocyte/macrophage recruitment and collagen deposit [42, 59-62]. Liver fibrosis in patients with NASH is improved, while body weight, level of transaminases, liver function and insulin resistance are not improved after 1 year of CVC treatment in a randomized, double-blind, multinational phase 2b study (CENTAUR trial, NCT02217475) [63-65]. A phase

3 study of CVC (AURORA, NCT03028740) and phase 2b study of both of CVC and TXR (TANDEM, NCT03517540) effects on patients with NASH and liver fibrosis are currently underway [66-68].

CCL20-CCR6 Axis

CCL20, also known as macrophage inflammatory protein-3 α (MIP-3 α) and liver activation-regulated chemokine (LARC), is the only ligand for CCR6. CCL20 is expressed predominantly in macrophages, HSCs, epithelial cells, endothelial cells, monocytes and injured hepatocytes. CCR6 is mainly expressed on T cells including T-helper 17 (Th17) lymphocytes, regulatory T lymphocytes (Treg) and $\gamma\delta$ T cells and on some hepatocytes [69-71].

CCL20 recruits macrophages and HSCs, then activates HSCs and exerts pro-inflammatory and pro-fibrogenic effects. The expression of CCL20 elevates in patients with alcoholic hepatitis (AH), fibrosis and cirrhosis correlated with NAFLD and hepatitis C virus (HCV) infection [72-75]. Blocking or knockdown of CCL20 significantly decreases the expression levels of collagen I, collagen III, α -SMA, fibronectin, connective tissue growth factor (CTGF), metalloproteinase (MMP) 2, tissue inhibitor of matrix metalloproteinase (TIMP) 1 and CCR6 [76,77]. Over-expression of NOD-like receptor 6 (NLRP6) reduces the expression of CCL20 in the AH mouse model [74, 78].

As CCR6 is the only receptor for CCL20, CCR6 expression elevates in patients with liver fibrosis and cirrhosis as well, and CCR6 levels are higher in cirrhosis than in fibrosis [79]. However, CCR6 exhibits a protective role, which is totally opposite to CCL20, during chronic liver injury and liver fibrogenesis. The CCR6-dependent recruitment of $\gamma\delta$ T cells into injured liver restricts hepatic inflammation and fibrogenesis and promotes HSCs apoptosis [71]. CCR6 deficiency causes increased recruitment of CD4⁺ T cells and monocyte-derived macrophages, elevated inflammatory M1 macrophage cytokines and reduction of Th17⁺ T cells, followed by exacerbated liver inflammation [79-81]. The above apparent opposite effects between CCL20 and CCR6 deserve further investigation.

CCL25-CCR9 Axis

CCL25, also known as thymus-expressed chemokine (TECK), is the specific ligand for CCR9. CCL25 is mainly expressed in the thymus and intestinal epithelium, and the source of CCL25 in the thymus is thymic dendritic cells, which can recruit immature T cells into the thymus to mature and release. CCL25 is also produced by liver sinusoidal endothelial cells (LSECs), portal DCs, vascular endothelial cells and other parenchymal cells [82, 83].

CCR9 is mainly distributed in immature T lymphocytes and on the surface of intestinal cells, and it plays a role in T lymphocyte development and tissue-specific homing when bound to its specific ligand, CCL25. CCR9 expression has been identified in activated B cells, a certain proportion of CD4 and CD8 T cells, plasmacytoid dendritic cells, macrophages and HSCs. In the peripheral tissues, CCR9⁺ cells are mostly concentrated in the colon, thymus, and small intestine. CCL25 is associated with chemotactic activity for activated

macrophages, dendritic cells, and thymocytes through binding to CCR9 [84].

The CCL25-CCR9 axis plays an important role in a variety of liver diseases. The expression of CCL25, which is mainly on LSECs and portal DCs, elevates in inflamed livers of patients with primary sclerosing cholangitis (PSC). The hepatic inflammation in PSC is also related to the increase of CCR9 positive T cells [85]. In addition, the CCL25-CCR9 axis plays an important role in macrophage recruitment and fibrosis formation in mice with NASH. CCR9-deficiency in HSCs ameliorates liver fibrogenesis and administration of a CCR9 antagonist hampers further fibrosis progression. Serum CCL25, hepatic CCL25 and CCR9 were elevated in patients with NASH [86]. The CCL25-CCR9 axis has also been confirmed to be associated with HCC [87].

Collectively, CCL1-CCL8 axis [15, 17, 18], CCL2-CCR2 axis [22, 31-48], CCL3/CCL5-CCR1/CCR5 axis [51-58], CCL20 [72-78] and CCL25-CCR9 axis [84-86] exhibit pro-fibrotic role through recruiting inflammatory monocytes into injured liver, promoting differentiation into M2 macrophages, increasing proliferation and migration of HSCs, activating HSCs. Glucocorticoid-induced leucine zipper regulates fibrosis by inhibiting CCL2-mediated leukocyte recruitment [47] and CVC attenuates liver fibrosis by inhibiting CCR2 and CCR5 [42, 59-68]. However, CCL3 promotes macrophage infiltration into the liver and leads to M1 not M2 polarization [52]. What's more interesting is that as the only receptor for CCL20, CCR6 exhibits a protective role opposite to CCL20 [71, 79].

The roles of CC chemokines and receptors in liver fibrosis are listed in Table I and the expressions of CC and their CCR participated in liver fibrosis in this paper are illustrated in Fig. 1.

CXC CHEMOKINES AND RECEPTORS IN LIVER FIBROSIS

CXC chemokines, characterized by a nonconserved single amino acid between the N-terminal cysteine residues, are the second largest group of chemokines. The CXC chemokines with the sequence glutamic acid leucine-arginine near the N terminal such as interleukin-8 (IL-8) are chemotactic for neutrophils and monocytes/macrophages, whereas those without the sequence are chemotactic for lymphocytes [3, 88].

CXCL1-CXCR2 Axis

CXCL1 is a strong neutrophil chemoattractant and is also known as growth-related oncogene-(GRO- α), keratinocyte-derived chemokine (KC) and cytokine-induced neutrophil chemoattractant 1 (CINC-1) [89, 90]. CXCL1 is mainly expressed in neutrophils, macrophages, and epithelial cells and exerts its effect via binding to its receptor CXCR2, which is expressed on neutrophils and other types of cells [91].

CXCL1 is involved in fibrosis of various organs including liver fibrosis, pulmonary fibrosis and cardiac fibrosis [89, 92]. CXCL1 plays a pro-fibrotic role in liver fibrosis and is secreted by HSCs and participates in the activation of HSCs. Reduced expression of CXCL1 ameliorates liver fibrosis by accelerating apoptosis of activated HSCs [93-95]. Inhibition of CXCL1 expression by adipose-derived mesenchymal stem cells (ADMSCs)-derived EVs containing miR-150-5p down-

regulates hepatic neutrophil infiltration and attenuates liver fibrosis [96, 97]. Glycolysis promotes CXCL1 expression through nuclear pore changes and increases in NF- κ B translocation and inhibition of glycolysis attenuates a stiffness-induced CXCL1-dominant angiocrine signaling in LSECs and improves liver fibrosis induced by CCl₄ [98]. However, contrasting the above results, another report, which found higher peripheral CXCL1 levels in patients with less severe liver fibrosis, suggests that CXCL1 may play a protective role against liver fibrosis [99]. Recruitment of neutrophils into injured liver through CXCL1 expression alleviates liver fibrosis induced by CCl₄ [100].

CXCL4-CXCR3B Axis

CXCL4, also known as platelet factor 4 (PF4), is a platelets-derived chemokine, and is produced by activated platelets, megakaryocytes, and mast cells [101-103]. CXCR3B, a splice variant of CXCR3, is identified as a high-affinity receptor of CXCL4 and is expressed in human micro-vascular endothelial cell [104].

CXCL4 has immune-modulatory functions including inducing the differentiation of monocyte-derived dendritic cells (moDCs) and modulating DC-mediated T cells activation [105-108]. In addition, CXCL4 plays a pro-inflammatory role through promoting production of IL-6, tumor necrosis factor alpha (TNF- α) and IL-17 and shows anti-angiogenic activity [109, 110]. Furthermore, CXCL4 is a key component in fibrosis development and CXCL4 deficiency ameliorates fibrosis in the skin, lungs and heart. Meanwhile, CXCL4 drives fibrosis through inhibiting the expression of the anti-fibrotic cytokine IFN- γ , up-regulating pro-fibrotic cytokines IL-4 and IL-13 and promoting endothelial mesenchymal transition (EMT) and collagen synthesis [111].

The expression of CXCL4 increases significantly both in patients with hepatic fibrosis and in various liver fibrosis models induced by ethanol, CCl₄, thioacetamide (TAA) or BDL, and deletion of CXCL4 is found to inhibit liver fibrosis [102, 112]. CXCL4 promotes proliferation, chemotaxis, and expression of other chemokines such as CCL5 and CXCL1 in HSCs and thereby regulates the infiltration of immune cells and amplifies the inflammatory infiltrate within the liver [102]. CXCL4 inhibits proliferation of endothelial cells and reduces transcription factor FLI1, a negative regulator of collagen synthesis [113]. Recent research, which found that the level of CXCL4 was not correlated with improvement of liver stiffness in HCV-infected patients after direct antiviral agents (DAAs) therapy, suggested that CXCL4 measurements was not an effective factor of monitoring fibrosis changes [114].

CXCL8-CXCR1 Axis

CXCL8, which belongs to glutamate-leucine-arginine (ELR)-positive CXC chemokines, is synthesized by several cells including monocytes, macrophages, and endothelial cells [88]. Both CXCR1 and CXCR2 are receptors of CXCL8 and expressed on monocytes/macrophages, neutrophils, and T-cells [115, 116]. However, CXCL8-CXCR1 axis is predominantly involved in the progression of CLDs.

CXCL8 and CXCR1, not CXCR2, levels elevate significantly in patients with CLDs, especially in decompensated, Child Pugh

C staged liver cirrhosis [88, 117]. CXCL8 participates in hepatic neutrophil infiltration, liver inflammation and activation of HSCs and exerts pro-fibrogenic functions. In patients with primary biliary cholangitis (PBC), elevated CXCL8 and CXCR1 levels are associated with neutrophil infiltration, while in patients with non-cholestatic cirrhosis, they are related to hepatic macrophage accumulation, especially the non-classical CD16⁺ monocyte-derived macrophages subtype [88, 118, 119].

CXCL9-11-CXCR3 Axis

CXCL9 (monokine induced by IFN- γ , MIG), CXCL10 (IFN- γ -inducible protein 10, IP-10) and CXCL11 (IFN-inducible T cell chemoattractant, I-TAC; interferon- γ -inducible protein 9, IP-9) are all T cell chemoattractants. CXCL9, CXCL10 and CXCL11, which are ELR-negative CXC chemokines, are predominantly produced by monocytes, endothelial cells and fibroblasts in response to IFN- γ . CXCL9, CXCL10 and CXCL11 share the receptor CXCR3, which is expressed on activated T cells, especially Th1 cells, natural killer (NK) cells, natural killer (NKT) cells, epithelial cells and endothelial cells. Among the three ligands, CXCL11 has the highest affinity for CXCR3, followed by CXCL10 and CXCL9. The binding domain of CXCL11 on CXCR3 is different from that of CXCL9 and CXCL10 [120, 121].

CXCL9-11 polymorphisms are associated with liver fibrosis. CXCL9 rs10336 AG, CXCL10 rs3921 CG and CXCL11 rs4619915 AG are related to the decreased values of the liver stiffness measurement (LSM) and CXCL9 rs10336 AA, CXCL10 rs3921 CC and CXCL11 rs4619915 AA are related to the increased values of LSM. The degree of fibrosis and cirrhosis was reduced in patients with the genotypes noted above [122]. However, a recent study found a completely different result: CXCL9 rs10336, CXCL10 rs3921 and CXCL11 rs4619915 were not associated with liver fibrosis among a Brazilian population of patients with chronic hepatitis C [123].

Levels of CXCL9-11 and CXCR3 are increased in patients with hepatitis B virus (HBV) related decompensated liver cirrhosis [124-126]. Elevated levels of CXCL9-11 are associated with shorter survival of cirrhotic patients with severe portal hypertension receiving transjugular intrahepatic portosystemic shunt (TIPS) [127-129]. CXCL9 gene expression is higher in patients with NASH without fibrosis [130]. However, other reports suggest that CXCL9-CXCR3 axis plays anti-fibrotic role by inhibiting the expression of transforming growth factor- β (TGF- β) and collagen 1A1 and down-regulation of CXCL9 aggravates liver fibrosis [131, 132]. CXCL10 levels are correlated with early recurrence of liver fibrosis after liver transplantation due to HCV infection [133]. CXCL10 promotes the migration of HSCs by the interaction with CXCR3 receptor on HSCs [134]. CXCL10 enhances the expression of IL-9 in the liver, and overexpression of IL-9 aggravates liver fibrosis induced by CCl₄ [135]. CXCL11 levels are mainly increased in patients with non-alcoholic cirrhosis and high portal pressure and CXCL11-levels are related to the severity of liver fibrosis [129].

The levels of CXCL9 and CXCL10 elevate in patients with PBC and in animals with autoimmune cholangitis and are correlated with the progression of liver fibrosis. Moreover, treatment with ursodeoxycholic acid reduces levels of CXCL9,

CXCL10 and CXCR3 in the serum of patients with PBC [136, 137]. Overexpression of CXCL9 promotes umbilical cord mesenchymal stem cells (UC-MSCs) homing to injured liver and ameliorates liver fibrosis in rats [138].

The expression of CXCR3 elevates in cirrhotic and hypersplenic rat model induced by CCl₄ [62]. Down-regulating the expression of CXCR3 decreases COL1A1 levels and inhibits the development of liver cirrhosis into liver cancer [139, 140]. CXCR3 deficiency, which causes Th2-polarized immune response in the liver by reduction of infiltration of IFN- γ -positive T cells into the liver, attenuates liver fibrosis in mouse model induced by CCl₄ or TAA [132, 141-147].

CXCL12-CXCR4/CXCR7 Axis

CXCL12, also called stromal derived-cell factor 1 (SDF-1), is certified as the ligand for CXCR4 and CXCR7. CXCL12 is secreted by bone-marrow stromal cells and is chemotactic for various cells including neutrophils, monocytes, T lymphocytes and CD34-positive cells. CXCR7 expresses specifically in LSECs, while CXCR4 expresses in a variety of cells including neutrophils, monocytes, T lymphocytes, endothelial cells, epithelial cells, fibroblasts, hematopoietic stem cells and different tissue cells [3, 148-150]. CXCL12 expression is regulated by interleukin 1 β , hypoxia-inducible factor-1 α , epithelial growth factor and vascular endothelial growth factor [151-153].

CXCL12-CXCR4/CXCR7 axis plays an important role in the development of liver fibrosis. CXCL12 is presented by LSECs to lymphocytes within the sinusoidal lumen and it might be closely related to the recruitment of inflammatory cells into the liver by transendothelial migration [154, 155]. CXCL12 is expressed by bile duct epithelial cells in the portal tracts in normal liver, and in cirrhotic liver, CXCL12 is strongly expressed in bile ducts and blood vessels proliferating along the fibrotic diaphragm [156]. Hypoxia following chronic liver injury up-regulates CXCL12 in primary mouse hepatocytes dependent on hypoxia-inducible factors (HIFs) and TGF- β [157]. CXCL12 plays an important role in regeneration via its receptor CXCR7 or in liver fibrosis via its another receptor CXCR4 in both chronic injury model induced by CCl₄ and BDL [148]. Serum levels of CXCL12 are related to the aggravation of liver fibrosis in patients with HCV and HBV infection [156]. CXCL12, which plays a pro-fibrogenic role, activates HSCs by stimulating the receptor CXCR4 and enhances the expression of collagen [158]. Human urine-derived stem cells (USCs) can differentiate into functional hepatocytes and elicit the recovery of injured liver tissue, induced by hypoxia pretreatment, through enhancing the expression of the receptor CXCR4 [159]. Moreover, CXCL12 secreted by LSECs stimulates the migration of HSCs [160, 161].

Increased CXCR4 expression levels are correlated with portal inflammation, piecemeal necrosis, and severity of fibrosis [162, 163]. The expression of CXCR4 increases in mouse liver fibrosis model induced by CCl₄ and leads to blood progenitor cells' homing to liver from bone marrow [164-166]. Chronic liver injury causes the shift in CXCL12 signaling from pro-regenerative response via CXCR7 to pro-fibrotic response via CXCR4 in LSECs [148].

Inhibiting the CXCL12/CXCR4 axis, which up-regulates canonical Wnt pathway, can impede chemotaxis of fibrocytes, reduce collagen deposition, inhibit angiogenesis, dampen HSCs activation, then attenuate liver fibrogenesis [166-171]. Cyclam-modified polyethyleneimine (PEI-Cyclam) exhibits anti-fibrotic effects in liver fibrosis mouse model induced by CCl₄ through effectively inhibiting CXCR4 and TGF- β [173]. Curcumin improves liver fibrosis and inhibits the activation of HSCs through reducing the expression of CXCL12 and CXCR4 [173]. However, the inhibition of CXCR4 with AMD3100, a CXCR4 small molecule inhibitor, increases intrahepatic neutrophils, promotes HSCs activation, and aggravates liver inflammation and liver fibrosis induced by CCl₄ [174, 175]. Further study should clarify whether inhibiting CXCL12-CXCR4 axis can improve liver fibrosis.

CXCL16-CXCR6 Axis

CXCL16 is dominantly expressed on endothelial cells, macrophages, cholangiocytes, LSECs, and hepatocytes, and CXCR6 is mainly expressed on NKT cells, NK cells, CD4⁺ T cells, CD8⁺ T cells and the subset M1 macrophage in murine liver [176, 177].

The levels of CXCL16 and CXCR6 in liver are higher in patients with CLDs. Elevated CXCL16, which is stimulated by pro-inflammatory cytokines and HIF-1, enhances ROS, lipid accumulation and ECM [178-180]. CXCL16 induces the migration and activation of HSCs [181]. CXCR6 promotes inflammatory response by enhancing NKT cells accumulation, which secrete IFN- γ and IL-4 during liver injury [182-184]. Inhibition of CXCR6 expression protects from chronic liver damage and fibrosis induced by CCl₄ and methionine-choline-deficient (MCD) diet respectively [184, 185]. In NAFLD, hepatocytes produce CXCL16, which activates HSCs that produce collagen and transform into myofibroblasts [186].

Furthermore, the CXCL16-CXCR6 axis worsens PBC by recruiting circulating TCR $\gamma\delta^{\text{low}}$ cells into liver during inflammation and is related to ursodeoxycholic acid (UDCA) response [187-189].

As mentioned above, CXC chemokines and receptors play an important role in liver fibrosis. CXCL1, CXCL4-CXCR3B axis, CXCL8-CXCR1 axis, CXCL9-11-CXCR3 axis, CXCL12-CXCR4 axis, CXCL16-CXCR6 axis and CX3CL1-CX3CR1 axis drive liver fibrosis through multiple mechanisms including up-regulating anti-fibrotic cytokines and down-regulating pro-

fibrotic cytokines, promoting EMT, increasing angiogenesis and collagen synthesis, activating HSCs [88, 93-95, 105-114, 117-119, 122-130, 133-147, 154-171, 178-189]. However, the inhibition of CXCR4 with AMD3100 aggravates liver inflammation and liver fibrosis induced by CCl₄ [174, 175], so further study should clarify whether inhibiting CXCL12-CXCR4 axis can improve liver fibrosis. In addition, CXCL1 and CXCL9 are also reported to inhibit liver fibrosis by decreasing TGF- β and collagen 1A1 [99, 100, 131, 132].

The roles of CXC chemokines and receptors in liver fibrosis are well documented in Table I and the expressions of CXC chemokines and their receptors in liver resident cells in this paper are illustrated in Fig. 1.

CX3C CHEMOKINE AND RECEPTOR IN LIVER FIBROSIS

There is only one chemokine (CX3CL1) and one receptor (CX3CR1) in the CX3C chemokine and receptor family. CX3CL1, also known as fractalkine, is involved in the pathogenesis of CLD. CX3CL1 is expressed on HSCs and KCs/macrophages, and its receptor CX3CR1 is dominantly expressed on KCs and hepatocytes in the liver [190, 191].

Patients with progressive liver fibrosis or cirrhosis are found higher CX3CL1 in the circulation and lower CX3CR1 intrahepatically, and CX3CR1 deficiency attenuates liver fibrosis induced by CCl₄ and BDL [192]. And CX3CR1 mediates the adhesion of CD16⁺ monocytes to LSECs, which is an important step in the extravasation of leukocytes during inflammatory processes [193, 194]. Interaction between CX3CL1 and CX3CR1 aggravates liver fibrosis induced by Schistosomiasis [195]. CX3CL1 and CX3CR1 are up-regulated in biopsies of patients with acute and chronic liver injury and cholestatic diseases [196-198].

On the one hand, the mRNA levels of CX3CR1 rise in patients with HCV-induced advanced liver fibrosis. The CX3CR1 V249I variant, which contributes to a directed migration of HSCs toward infected or sublethally injured hepatocytes, aggravates HCV-induced advanced liver fibrosis [199]. On the other hand, the number of CD14⁺CD16⁺ monocytes increase in end-stage cirrhosis and CX3CR1 limits liver fibrosis by controlling the differentiation and survival of intrahepatic monocytes [22, 35]. CX3CR1 signaling prevents liver inflammation by reducing pro-inflammatory factors

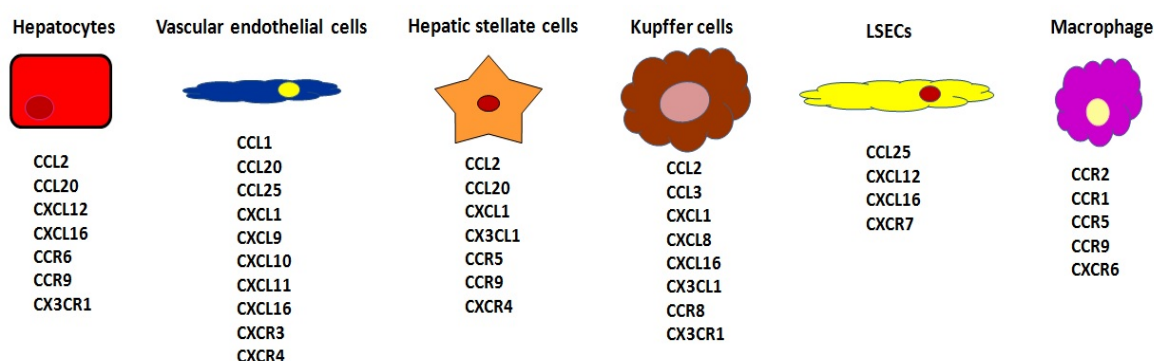


Fig. 1. Expression of chemokines and their receptors in liver resident cells. LSEC: liver sinusoidal endothelial cell.

including TNF- α , nitric oxide (NO) and TGF- β and increasing the expression of the anti-inflammatory markers such as IL-10 and activating anti-apoptotic and anti-inflammatory signals in hepatic macrophages [190]. Moreover, the CX3CL1-CX3CR1 axis is also involved in PBC-associated inflammation. Ursodeoxycholic acid reduces the infiltration of T-cells into the liver by decreasing CX3CL1 expression in PBC [200].

The roles of the CX3CL1-CX3CR1 axis in liver fibrosis are summarized in Table I and the expressions of CX3CL1 and CX3CR1 in liver resident cells are illustrated in Fig. 1.

C CHEMOKINES AND RECEPTORS IN LIVER FIBROSIS

There are two ligands including XCL1 and XCL2 in the C family. High levels of conventional dendritic cells (cDCs), especially type 1 cDCs (cDC1), have been identified in NASH-related liver inflammation and fibrosis. Depleting cDC1 in XCR1^{DTA} mice or using anti-XCL1-blocking antibody significantly attenuates liver pathology in NASH mouse models. XCR1+ cDC1 acts as an important driver of liver pathology

Table I. Roles of chemokines and receptors relevant to liver fibrosis

Family	Chemokines	Receptors	Roles in liver fibrosis	References
CC	CCL1	CCR8	Promoting the infiltration of inflammatory monocytes into injured liver Increasing neutrophils and NK cells Decreasing CD4+ Th1 cells Playing a pro-fibrotic role in liver fibrosis induced by CCL4 or BDL Playing a role in lymphocytic	[15, 17, 18]
	CCL2	CCR2	Increasing the recruitment of splenic monocytes into the liver leading to the polarization of macrophage to M2 phenotype Promoting the infiltration of macrophages and angiogenesis Aggravating liver fibrosis	[22, 31-48]
	CCL3/ CCL5	CCR1/ CCR5	Play pro-fibrotic role Increasing proliferation and migration of HSCs Promoting macrophage infiltration and M1 polarization Recruitment of CCR5-positive liver progenitor cells during fibrogenesis	[51-58]
	CCL20	CCR6	Recruiting macrophages and HSCs Activating HSCs Exerting pro-inflammatory and pro-fibrogenic effects CCR6 playing a protective role (opposite to the role of CCL20)	[72-81]
	CCL25	CCR9	Recruiting macrophage Promoting fibrosis formation	[84-86]
CXC	CXCL1	CXCR2	Participating in the activated of HSCs Accelerating apoptosis of activated HSCs Up-regulating hepatic neutrophil infiltration	[89-100]
	CXCL4	CXCR3B	playing a pro-inflammatory role Driving fibrosis Promoting EMT and collagen synthesis Promoting pro-fibrotic cytokines IL-4 and IL-13 Inhibiting anti-fibrotic cytokine interferon- γ Promoting proliferation, chemotaxis of HSCs Regulating the infiltration of immune cells and amplifying the inflammatory infiltrate within the liver	[105-114]
	CXCL8	CXCR1	Exerting pro-fibrogenic functions Participating in hepatic neutrophil infiltration, liver inflammation and activation of HSCs	[88, 117-119]
	CXCL9-11	CXCR3	Decreasing liver stiffness Inhibiting angiogenesis and progression of liver fibrosis Inhibiting the expression of TGF- β and collagen 1A1 Promoting the migration of HSCs	[122-147]
	CXCL12	CXCR4/ CXCR7	Playing an important role in regeneration via CXCR7 in LSECs Playing an important role in liver fibrosis via CXCR4 in LSECs Stimulating the migration of HSCs Increasing chemotaxis of fibrocytes and collagen deposition	[154-171]
	CXCL16	CXCR6	Enhancing ROS, lipid accumulation and ECM Activating HSCs Promoting inflammatory response	[178-189]
CX3C	CX3CL1	CX3CR1	Promoting the progression of liver fibrosis Reducing pro-inflammatory factors	[192-200]
C	XCL1	XCR1	Playing a pro-inflammatory role	[201]
	XCL2	XCR1		

BDL: bile duct ligation; CCL4: carbon tetrachloride; ECM: extracellular matrix; EMT: endothelial mesenchymal transition; HSC: hepatic stellate cell; IgG4-SC: IgG4-related sclerosing cholangitis; LSEC: liver sinusoidal endothelial cell; ROS: reactive oxygen species.

and modulation of cDC1 may be a possible immunotherapy approach for NASH [201]. Table I demonstrates the roles of C chemokines and receptors in liver fibrosis.

ROLES OF CHEMOKINES AND RECEPTORS RELEVANT TO LIVER FIBROSIS CAUSED BY DIFFERENT DISEASES

Nonalcoholic liver disease, alcoholic liver disease, chronic hepatitis B, chronic hepatitis C, as well as autoimmune liver diseases such as PBC, PSC, are common etiologies of liver fibrosis. A variety of chemokines and their receptors are involved in liver fibrosis caused by above diseases. CCL2-CCR2 axis, CCL3-CCR5 axis, CCL20, CCL25-CCR9 axis, CXCL9, CXCL16-CXCR6 axis, and XCL2-XCR1 axis are observed elevated levels in patients with NASH or NASH, and aggravate steatohepatitis and liver fibrosis. Nonalcoholic steatohepatitis severity and fibrosis stage is correlated with increased CCR2+ macrophages [42] and anti-CCL2 treatment reduces pro-inflammatory cytokines, ameliorates steatosis and steatohepatitis as well [48]. CCL3 deficiency attenuates steatohepatitis and fibrosis in mouse model induced by a high-cholesterol and high-fat diet [52]. Liver fibrosis in patients with NASH is improved after 1 year of CVC treatment in a randomized, double-blind, multinational phase 2b study (CENTAUR trial, NCT02217475) [63-65]. The expression of CCL20 elevates in patients with AH, as well as in patients with fibrosis and cirrhosis correlated with NAFLD and HCV infection [72-75]. Serum CCL25, hepatic CCL25 and CCR9 elevate in patients with NASH [86]. CXCL9 gene expression is higher in patients with NASH without fibrosis [130]. In NAFLD, CXCL16 produced by hepatocytes, activates HSCs and produces collagen [186]. XCR1+ cDC1 acts as an important driver of liver pathology and modulation of cDC1 may be a possible immunotherapy approach for NASH [201].

In addition, some chemokines and their receptors are related to liver fibrosis caused by chronic HBV or HCV infection. The levels of CXCL9-11 and CXCR3 are increased in patients with HBV-DLC [124-126]. CCL11 is independently associated with LSM in patients with chronic HBV virus infection [202]. CXCL4, CXCL10 and CX3CR1 are related to HCV-induced liver fibrosis. A recent in-depth study found that the level of CXCL4 is not correlated with improvement of liver stiffness in HCV-infected patients after DAA therapy, and suggests that CXCL4 measurements is not an effective factor of monitoring fibrosis changes [114]. CXCL10 levels are correlated with early recurrence of liver fibrosis after liver transplantation due to HCV infection [133]. CXCL10 level normalizes after DAA treatment in patients with chronic hepatitis C and dynamic declines of CXCL10 during DAA treatment predicts the sustained virologic responses [203-206]. Another observation that CXCL10 significantly declines among non-responder group of DAA treatment, seems to argue against above conclusion [207]. CCL5 level declines before DAA treatment and increases during the first 4 weeks of DAA treatment. However, a subsequent return to baseline or lower levels is observed at 12 and 24 months post-DAA and probably suggests other infections or immune-mediated disorders [206].

Serum levels of CXCL12 are related to the aggravation of liver fibrosis in patients with HCV and HBV infection [156]. Significant decline of CCL2 within 4 weeks after initiation of DAA treatment is associated with HBV reactivation in patients with CHC [208].

Moreover, some chemokines and their receptors also play an important role in autoimmune liver diseases. Elevated levels of CXCL8-CXCR1 axis are observed in patients with PBC [88, 119]. The levels of CXCL9/10-CXCR3 axis elevate in patients with PBC, and treatment with ursodeoxycholic acid reduces levels of CXCL9, CXCL10 and CXCR3 in the serum of patients with PBC [136, 137]. And the CXCL16-CXCR6 axis worsens PBC and is related to UDCA response [187-189]. The CX3CL1-CX3CR1 axis is involved in PBC-associated inflammation and UDCA reduces the infiltration of T-cells into the liver by decreasing CX3CL1 expression in PBC [200]. Furthermore, the expression of CCL25 elevates in patients with PSC [85]. In addition, CX3CL1-CX3CR1 axis leads to the progression of liver fibrosis induced by schistosomiasis [195].

Roles of chemokines and receptors relevant to liver fibrosis caused by different diseases are listed in Table II.

CONCLUSIONS AND PERSPECTIVES

Chemokines are subdivided into four superfamilies - the CC, the CXC, the CX3C and the C families - based on the position of cysteine residues. Chemokines play a critical role in cell migration and activation by binding to G-protein coupled cell-surface receptors with seven transmembrane domains. The receptors of chemokines also segregate into four families - CCR, CXCR, CX3CR and XCR. Most chemokine receptors can bind to more than one chemokine; however, there is ligand-receptor restriction. Some chemokines can bind to more than one receptor.

Interaction between chemokines and their receptors play a critical role in liver fibrogenesis by recruiting a variety of inflammatory cells into injured liver. Most chemokines and their receptors play pro-fibrotic roles including CCL1-CCR8 axis, CCL2-CCR2 axis, CCL3/CCL5-CCR1/CCR5 axis, CCL20, CCL25-CCR9 axis, CXCL4-CXCR3B axis, CXCL8-CXCR1 axis, CXCL12-CXCR4 axis, CXCL16-CXCR6 axis and CX3CL1-CX3CR1 axis. They aggravate liver fibrosis by the following mechanisms: recruiting monocytes/macrophages, neutrophils, immunocytes into injured liver, promoting angiogenesis, prompting migration, proliferation and activation of HSCs, up-regulating pro-fibrotic cytokines. Meanwhile, CXCL9-11-CXCR1 axis are involved in the inhibition of angiogenesis and progression of liver fibrosis. Moreover, CXCL12 plays a dual role in regeneration or liver fibrosis via its receptors CXCR7 or CXCR4 respectively. CXCL12 has pro-fibrogenic effects and activates HSCs by binding the receptor CXCR4.

CCL20 exerts pro-inflammatory and pro-fibrogenic effects, while its receptor CCR6 plays a protective role (opposite to the role of CCL20). More interestingly, it is reported by different teams that CXCL1-CXCR2 axis may play a pro-fibrotic role or an anti-fibrotic role.

Cenicriviroc, an oral, dual antagonist of CCR2 and CCR5, improved liver fibrosis in patients with NASH in a randomized, double-blind, multinational phase 2b study (CENTAUR trial,

Table II Roles of chemokines and receptors relevant to liver fibrosis caused by different diseases

Diseases	Chemokines	Receptors	Roles in liver fibrosis caused by different diseases	References
NAFLD/NASH	CCL2	CCR2	Increased CCR2+ macrophages are correlated to NASH severity and fibrosis stage Inhibition of CCL2 or CCR2/CCR5 improves liver fibrosis in patients with NASH	[42, 59-68, 73, 77, 84, 86]
	CCL3	CCR5	CCL3 aggravates steatohepatitis and fibrosis	[52, 59-68]
	CCL20		The expression of CCL20 elevates in patients with NAFLD	[73]
	CCL25	CCR9	The expression of CCL25 and CCR9 elevates in patients with NASH	[86, 87]
	CXCL9		CXCL9 gene expression is increased in the patients with nonalcoholic steatohepatitis without fibrosis	[130]
	CXCL16	CXCR6	CXCL16 activating HSCs in NAFLD	[186]
	XCL1	XCR1	XCL1-XCR1 drives liver pathology in NASH	[201]
ALD/AH	CCL20		The expression of CCL20 elevates in patients with AH	[74, 78]
Hepatitis B	CCL11	CCR3	CCL11 is independently associated with LSM in patients with CHB	[202]
	CCL20		The expression of CCL20 elevates in patients with HBV infection	[75]
	CXCL9/ CXCL10/ CXCL11	CXCR3	The levels of CXCL9, CXCL10 and CXCL11, as well as of CXCR3 elevate	[124-126]
Hepatitis C	CCL2		Significant decline of CCL2 within 4 weeks after initiation of DAA treatment is associated with HBV reactivation in patients with CHC	[208]
	CCL5	CCR1/CCR5	CCL5 level declines before DAA treatment and increases during the first 4 weeks of DAA treatment. However, a subsequent return to baseline or lower levels is observed at 12 and 24 months post-DAA	[206]
	CXCL4		Level of CXCL4 is not correlated with improvement of liver stiffness in patients with HCV infection after DAA therapy	[114]
	CXCL10		CXCL10 level is correlated with early recurrence of liver fibrosis after liver transplantation for HCV infection CXCL10 level normalizes after DAA treatment in patients with CHC CXCL10 significantly declines among non-responder group of DAA treatment	[133, 202-207]
		CX3CR1	The mRNA level of CX3CR1 elevates in the patients with HCV-induced advanced liver fibrosis	[199]
PBC	CXCL8	CXCR1	Elevated CXCL8 and CXCR1 levels are associated with prognosis in patients with PBC	[119]
	CXCL9/ CXCL10	CXCR3	The expression levels of CXCL9 and CXCL10 elevate in patients with PBC	[145, 146]
	CXCL16	CXCR6	CXCL16 and CXCR6 are related to severity of PBC and UDCA response	[189]
IgG4-SC	CCL1	CCR8	CCL1-CCR8 interaction may function as lymphocytic recruitment	[15]
PSC	CCL25	CCR9	The expression of CCL25 elevates in patients with PSC	[85]
Schistosomiasis	CX3CL1	CX3CR1	Interaction between CX3CL1 and CX3CR1 is involved in the progression of liver fibrosis induced by schistosomiasis	[195]

AH: alcoholic hepatitis; ALD: alcoholic liver disease; CHB: chronic hepatitis B; HCV: hepatitis C virus; HSC: hepatic stellate cell; IgG4-SC: IgG4-related sclerosing cholangitis; LSM: liver stiffness measurement; LSEC: liver sinusoidal endothelial cell; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic liver disease; PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis; UDCA: ursodeoxycholic acid.

NCT02217475). Phase 3 study of CVC (AURORA, NCT03028740) and phase 2b study of combination of CVC and TXR (TANDEM, NCT03517540) are currently underway in patients with NASH and liver fibrosis. However, there are no ongoing clinical trials of antagonists or agonists of other chemokines or their receptors. Developing chemokine or receptor antagonists needs to consider the complex effects and further test in clinical trials.

Conflicts of interest: None to declare.

Acknowledgement: This work was supported by National Natural Science Foundation of China (No. 82274323) and Sichuan Science

and Technology Program (No. 2020YFS0379). Thank Claire Phillips and Miao Long for proofreading this manuscript.

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