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**Crosstalk network among multiple inflammatory mediators in liver fibrosis**

Zhangdi HJ *et al.* Inflammatory mediators in liver fibrosis

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**Abstract**

Liver fibrosis is the common pathological basis of all chronic liver diseases, and is the necessary stage for the progression of chronic liver disease to cirrhosis. As one of pathogenic factors, inflammation plays a predominant role in liver fibrosis *via* communication and interaction between inflammatory cells, cytokines, and the related signaling pathways. Damaged hepatocytes induce an increase in pro-inflammatory factors, thereby inducing the development of inflammation. In addition, it has been reported that inflammatory response related signaling pathway is the main signal transduction pathway for the development of liver fibrosis. The crosstalk regulatory network leads to hepatic stellate cell activation and proinflammatory cytokine production, which in turn initiate the fibrotic response. Compared with the past, the research on the pathogenesis of liver fibrosis has been greatly developed. However, the liver fibrosis mechanism is complex and many pathways involved need to be further studied. This review mainly focuses on the crosstalk regulatory network among inflammatory cells, cytokines, and the related signaling pathways in the pathogenesis of chronic inflammatory liver diseases. Moreover, we also summarize the recent studies on the mechanisms underlying liver fibrosis and clinical efforts on the targeted therapies against the fibrotic response.

**Key words:** crosstalk network; inflammatory cell; cytokine signal pathway; liver fibrosis

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**Core tip:** Liver fibrosis is a chronic liver lesion with inflammation. Reciprocally, increased inflammatory response exacerbates the severity of liver disease. Clinical data reveal that an aberrant increase of inflammatory cytokines is highly correlated with poor outcome of patients with liver fibrosis. However, the mechanism underlying liver fibrosis is not completely understood. It is urgently needed to enrich the knowledge of liver fibrosis. This review focuses on the role of inflammation in liver fibrosis and discusses the crosstalk network involving immune cells, cytokines, and the related signaling pathways.

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**INTRODUCTION**

Chronic inflammatory lesions results in extracellular matrix accumulation and hepatic fibrosis, eventually leading to cirrhosis[1]. Liver cirrhosis is a life-threatening factor for human health in the world. Sustained stimulations by a series of pathogenic mediators impair the regeneration capacity of the liver and thus result in the development of liver fibrosis. Among many pathogenic factors, inflammation is a key inducer for liver fibrosis progression. Cross activation of hepatic stellate cells (HSCs), kupffer cells, and other immune cells is a hallmark for the pathogenesis of liver fibrosis. Furthermore, critical cell signal pathway-related apoptosis, autophagy, collagen and inflammatory cytokine production are involved in the development of liver fibrosis by crosstalk with immune cells. Chronic pathogenic factors activated abundant hepacytes to generate inflammatory cytokines and chemokine mediators, which subsequently form a crosstalk network in liver fibrosis. Until now, liver fibrosis is still a serious unsolved problem in chronic liver disease. This review focuses on this crosstalk network in liver fibrosis and discusses the detailed mechanism by which the process of liver fibrosis is modulated.

**CELLS INVOLVED IN LIVER FIBROSIS**

***HSCs***

As the precursor of myofibroblasts, HSCs differentiate into an activated myofibroblastic phenotype with the assistance of kupffer cells and cytokine-cytokine receptor signaling pathways. HSCs comprise 15% of total resident cells in the normal human liver. Through secretion of interleukins and chemokines, HSCs communicate with kupffer cells and other liver cells in quiescent conditions[2]. However, deregulation of HSC activation can initiate inflammation and enhance the susceptibility to liver fibrosis. Activated HSCs produce endothelin-1 to promote fibrogenesis[3]. A homologous protein of YB1 (a negative mediator for liver fibrosis) mediated anti-fibrotic activity by suppressing the expression of collagen type I in HSCs[4]. Moreover, Wnt signaling can also enhance HSC activation and promote liver fibrosis[5]. Some data showed that loss of interleukin (IL)-1Ra in mice decreased the number of HSCs and Kupffer cells in the liver compared to the other groups, which suggested that IL-1 signaling is also involved in this process[6]. Additionally, mature HSCs have been reported to stimulate allogeneic regulatory T cell proliferation in a cell-cell contact-dependent manner[7]. Mast cells might crosstalk with HSCs to inhibit liver fibrosis *via* the HLA-G-mediated decrease of collagen I, and IL-10 also mediates crosstalk between mast cells and HSCs[8]. Endothelial progenitor cells dramatically inhibit the proliferation, adhesion, and migration of HSCs, promote the apoptosis of HSCs, and down-regulate the mRNA and protein expression of collagen I and collagen Ⅲ in HSCs[9]. Epigenetic crosstalk between histone acetylation and miRNAs inhibited HSC activation[10]. Researchers have explored drugs targeting HSCs. A number of protein markers were found to be overexpressed in activated HSCs, and their ligands have been utilized to specifically deliver various anti-fibrotic agents[11]. natural killer (NK) cells are important in regulating hepatic fibrosis, and their cytotoxic killing of HSCs has been reported. Activated NK cells lead HSCs to death in a TRAIL-involved mechanism *via* the p38/PI3K/AKT pathway, which suggested that the p38/PI3K/AKT pathway in NK cells may be a novel drug target to inhibit liver fibrosis[12]. It has been confirmed that activation of HSCs could be inhibited by reducing the production of transforming growth factor-β1 (TGF-β1) in HSCs *via* inhibition of the NF-κB pathway through downregulation of the TGF-β1/Smad3 pathway[13].

***Kupffer cells***

Kupffer cells as resident macrophages are one of important liver inflammatory cell types, and account for 30% of sinusoidal cells[14]. Activated Kupffer cells secrete abundant cytokines and signaling molecules, which enhance liver immunopathology. Activated Kupffer cells participate in the initial injury/fibrogenic response to TGF-β1 and methotrexate, which results in upregulated production of cytokines, including IL-10, IL-4, IL-6, and IL-13[15]. CXCL6 stimulates the phosphorylation of epidermal growth factor receptor (EGFR) and the expression of TGF-β in cultured Kupffer cells, thereby resulting in activation of HSCs[16]. In response to liver injury induced by endotoxin, IL-35 can promote Kupffer cells to secrete IL-10 and reduce acute liver injury[17]. A crosstalk network including Ly6C+ monocytes, CCL2-CCR2, and kupffer cells determines HBV clearance/tolerance, and manipulation of these two cell types may be a potential strategy for immunotherapy of HBV-related liver diseases[18]. Activation of Kupffer cells by pathogens and the CCL2/CCR2 axis can be the key factor to recruit innate effector cells to the injured liver[19]. In alcoholic liver disease mice, a crosstalk network including kupffer cells, T cells, CCL2/CCR2, and CCL5/CCR5 sensitizes hepatocytes[20]. NLRP3 inflammasome from kupffer cells is involved in the occurrence of schistosomiasis-induced liver fibrosis (SSLF) *via* NF-κB signaling and IL-1β in serum increased strongly[21]. An effective method of isolating kupffer cells was explored to eliminate endothelial cell contamination, which could be meaningful for illuminating kupffer cell function and mechanism in diseases[22]. RAMP 1 in kupffer cells mediates a crosstalk network involving infiltration of immune cells and pro-inflammatory cytokines secreted by Kupffer cells and splenic T cells, and such crosstalk network can regulate the immune response[23]. ATG5-dependent autophagy involved in crosstalk between kupffer cells and cytokines (IL-6 and IL-10) mediated acute liver injury response[24]. The cross communication of Sphk1 with HSCs and kupffer cells regulated the CCL2-CCR2 axis in liver fibrosis[25]. Fas ligand stimulated Fas-expressing Kupffer cells or macrophages to secrete active IL-18 in a caspase-1-independent manner and finally resulted in acute liver injury in mice[26]. Kupffer cells with high expression of CD1d only presented lipid antigen to NKT cells for activation of the pro-inflammatory cytokine pathway[27]. Huangqi decoction activated Kupffer cells to promote liver fibrosis[28]. The crosstalk between Th2 microenvironment and kupffer cells promoted liver fibrodsis[29]. The interaction between NK cells and kupffer cells mediated by the CD205-TLR9-IL-12 axis promoted liver injury[30]. MM9 from Kupffer cell can remodel the matrix and repair the architecture during liver fibrosis regression[31]. Taken together, multiple functions of Kupffer cells modified by different molecules, signal pathways, inflammatory cytokines, and immune cells are essential in the development of liver fibrosis.

***Other inflammation-related cells***

NKT cells are activated in an NKG2D-dependent manner, and the crosstalk of IL-30 with NKG2D activates NKT cells to remove collagen-produced HSCs[32]. Regulatory CD4 T cells modulate the crosstalk network between NK cells and HSCs[33]. Neutrophils are the source of many inflammation cytokines and important inflammatory cells for acute liver injury and chronic fibrosis. Neutrophil-to-lymphocyte ratio is determined to be related with inflammatory activity and fibrosis in non-alcohol fatty liver disease[34]. A latest report shows that Th22 cells are closely associated with chronic liver fibrosis; moreover, the close crosstalk in the cell number of CD4+ T cells and Th22 cells suggests that Th22 plays an important role in chronic liver fibrosis[35]. One report demonstrates that NK cells migrate into the fibrosis scar and play a role in immune surveillance by clearing senescent activated HSC cells[36]. However, the chemokine CXCL-10 reverses NK cell-mediated HSC inactivation function and promotes liver fibrosis[37]. Therefore, liver fibrosis progresses in the inflammatory mediator crosstalk network microenvironment.

***Inflammatory cytokines***

**Proinflammatory cytokines**: IL-17A in combination with TGF-βRI can phosphorylate SMAD2/3 in HSCs to activate liver fibrosis[38]. A cross communication involving BM-MSCs and IL-6/STAT3 can down-regulate IL-17 and affect liver fibrosis[39]. In a new mouse model with a pre-injured liver (Abcb4/Mdr2-/-), IL-6-driven inflammatory response may determine the outcome of acute liver injury[40]. IL-6 is a primary regulator of both acute and chronic inflammation, which exhibits two contrasting functions. It acts as a pro-inflammatory cytokine in models of chronic inflammatory diseases[41], and contrarily shows anti-inflammatory effects in acute inflammation. Therefore, as a classic pro-inflammatory cytokine biomarker, IL-6 is used to clinically diagnose chronic liver fibrosis[42]. A crosstalk axis involving IL-6 and polymorphism of its gene (C174G) accelerates progression of chronic liver fibrosis[43]. As a potent chemoattractant for neutrophils, IL-8 and its receptor CXCR1 are involved in inflammation activation and liver fibrosis[44]. As potent predictors of liver injury, IL-8, MCP-1, and OPN are associated with advanced liver fibrosis in nonalcoholic fatty liver disease[45]. CXCL-6 can phosphorylate EGFR and activate the TGF-β pathway in Kupffer cells in liver fibrosis[16]. A latest report shows that IL-9-derived interaction between Raf/MEK/ERK and CXCL-10 can promote liver fibrosis[46]. As a profibrogenic factor, IL-34 may become a diagnostic biomarker for liver fibrosis[47]. In a mouse model, the crosstalk between IL-13 and STAT6 signaling pathways activates schistosomiasis-induced liver fibrosis[48]. In non-alcoholic fatty liver disease, fibroblast-derived marker IL-34 is developed as a feasible diagnostic marker[49]. IL-34, together with macrophage colony-stimulating factor, activates HSCs to promote collagen synthesis[50]. Plasma IL-18 in children with nonalcoholic fatty liver disease has been proposed as a novel biomarker for liver fibrosis[51]. CCL2-dependent monocytes may promote angiogenesis induced by inflammation in the progression of liver fibrosis[52]. The communication of TGF-β with JAK1-STAT3 may promote HSC proliferation as well as collagen I and α-SMA up-regulation in CCL4-derived live fibrosis[53]. In fibrotic liver, activated HSC-derived CTGF may respond to TGF-β stimulation in order to form a crosstalk regulatory network, and this crosstalk contributes to extracellular matrix production in a STAT3-dependent mode[54]. Alternatively, the interaction of TGF-β with long non-coding RNA-21 may promote hepatocyte apoptosis in liver fibrosis[55]. Neutralizing of IL-1α and IL-1 can inhibit the progression of liver fibrosis, which suggests that IL-1α and IL-1β promote inflammatory liver fibrosis[56]. Higher IL-9-derived Th9 cell expression was investigated in patients with HBV associated liver cirrhosis, and the result suggested that IL-9 may relate closely to the liver fibrosis. IL-9 is reported to promote hepatic dysfunction in CCL4-mediated liver fibrosis[57].

**Anti-fibrosis cytokines:** As an autophagy inhibitor, IL-10 crosstalks with STAT3 to exert an anti-fibrogenic function in liver injury[58]. IL-10 producing regulatory B cells can enhance regulatory T cell function in chronic liver fibrosis mediated by HBV[59]. Through restriction fragment length polymorphism (RFLP) analysis, IL-10 gene promoter (rs1800896) polymorphism was correlated with an increased risk of chronic liver fibrosis, especially that mediated by HBV[60]. IL-22 belongs to the IL-10 family and is produced by Th17 cells, Th22 cells, and NKT cells. IL-22 crosstalks with the microRNA (miRNA) and inflammatory cytokine pathways to attenuate HSC activation and inhibit liver fibrosis[61,62]. Crosstalk of IL-22 with p53-p21 in a STAT3 dependent way may induce the senescence of activated HSCs in liver fibrosis[63]. Crosstalk of IL-22 with Nrf2-keap1-ARE inhibits acetaldehyde-induced HSC activation and proliferation[64]. As a liver protector, IL-22 may activate liver cell STAT3 to inhibit liver injury[65]. Moreover, IL-22 inhibits ConA-induced acute liver inflammation[66]. Crosstalk of IL-22 with STAT3 exerts an anti-apoptotic and mitogenic activity[67]. IL-22 is up-regulated strongly in patients with HCV infection, and administration of IL-22 promotes α-SMA expression and collagen production from HSCs[68]. However, crosstalk between IL-22 and HSC-derived IL-22-R1 may induce up-regulation of HSC-derived chemokines (CXCL10 and CCL20) to recruit Th17 cells to migrate into the inflammatory liver in response to chronic liver inflammation and fibrosis mediated by HBV. Therefore, the ultimate effect of IL-22 in liver fibrosis needs to be determined by the balance between induction of HSC apoptosis and promotion of liver inflammation[69]. Crosstalk between IL-22 and the TGF-β1/Notch signaling pathway may induce HSC inactivation and inhibit liver fibrosis[70]. Therefore, liver fibrosis progresses gradually *via* a crosstalk regulatory network involving multiple cytokines and their related downstream signaling pathways. IL-23 produced by Th2 cells down-regulates proinflammatory cytokines and inhibits liver fibrosis[71]. High expression of IL-23R on the Th17 cell surface in acute-on-chronic liver injury patients suggests that it strongly correlates with liver disease severity[72]. High expression of IL-23 in monocyte-derived dendritic cells presents in a TRAF6/NF-κB dependent manner and is closely associated with HBV-mediated acute-on-chronic liver injury[73]. Besides, IL-23 on the basis of IL-17A-producing γδT cells has a protective effect against ConA-mediated liver injury[74].

**SIGNALING PATHWAY CROSSTALK IN LIVER FIBROSIS**

***TGF-β signaling pathway***

A crosstalk involving TGF-β and TGF-β R exerts a regulatory effect on cell plasticity in liver fibrosis (Figure 1). In CCL4 induced acute liver injury mice, CCL2/CCR2 recruits monocytes to infiltrate to the injury liver, then monocytes differentiate preferentially into inducible nitric oxide synthase-producing macrophages exerting pro-inflammatory and pro-fibrogenic actions, *e.g.*, promoting HSC activation *via* the TGF-β pathway[75]. Collagen triple helix repeat containing 1 (CTHRC1) promotes HSC proliferation, migration, and contractility for supporting liver fibrosis *via* crosstalk with the TGF-β signal pathway[76]. IL-13 activates the TGF-β signaling pathway to promote HSC proliferation and cell viability[77]. M2 Kupffer cells produce TGF-β and IL-10, which mediate immune tolerance in mouse liver injury by down-regulating the production of TNF-α and IL-12. In addition, M2 polarization of Kupffer cells contributes to the apoptosis of M1 Kupffer cells in fatty liver disease[78]. Therefore, TGF-β is critical for the activation of HSCs to transdifferentiate into fibrogenic myofibroblasts. Crosstalk between TGF-β and SMAD3 contributes to CCL4-induced liver fibrosis[79]. Activated HSCs may impair NK cell-mediated anti-fibrosis function through crosstalk with TGF-β in HBV-induced chronic liver fibrosis[80]. Some small compounds may crosstalk with the TGF-β pathway and exert an effect on liver fibrosis. Crosstalk of paeoniflorin with the TGF-β pathway may exert a protective role in radiation-induced liver fibrosis[81]. Sauchinone also reduces activation of HSCs and liver fibrosis through crosstalk with the TGF-β1 pathway[82]. Isorhamnetin may control liver fibrosis progression through inhibitive crosstalk with TGF-β1 and relieving oxidative stress[83]. Synthetic oligodeoxynucleotide may prevent fibrogenesis and deposition of collagen by targeting the TGF-β1/Smad pathway[84]. Platelets are a rich source of TGF-β1 and platelet TGF-β1 deficiency decreases liver fibrosis in a mouse model of live injury[85]. TGF-β mediates the transformation of mesothelial cells to myofibroblast[86].

***MiRNA signaling pathways***

MiRNAs as an important regulatory element are involved in liver fibrosis. Crosstalk between miR-101 and the PI3K/Akt/mTOR signaling pathway presents an anti-fibrotic effect in a CCL4 induced mouse model[87]. MiRNA-29b can target the PI3K/AKT pathway to prevent liver fibrosis by attenuating HSC activation and inducing apoptosis[88]. MiRNA-29b and its crosstalk with the TGF-β1/Smad3 may suppress HSC activation[89]. MiRNA-34a-5p inhibits liver fibrosis by regulating the TGF-β1/Smad3 pathway in HSCs[90]. A cross-communication between miR-130a-3p and its down-regulatory TGFBR1 and TGFBR2 induces HSC apoptosis[91]. MiR-19b can down-regulate CCL2 in HSCs and further inhibit liver fibrosis[25]. A crosstalk involving miRNA-21 and the NLRP3 inflammasome/IL-1β axis mediates angiotensin II-induced liver fibrosis[92]. As a wnt/β-catenin activator, miR-17-5p contributes to progression of liver fibrosis *via* activating HSCs[93]. Much evidence suggests that miR-17-5p promotes HSC proliferation and activation, on the contrary, down-regulation of miR-17-5p expression contributes to the suppression of activated HSCs[94]. MiRNA-142-3p inhibits TGF-β-induced fibrosis by targeting the TGF-RI pathway and was found to decrease the plasma of chronic liver fibrosis patients[95]. A considerable amount of evidence has shown that miRNA-200 participates in fibrosis[96]. As a PI3K/Akt pathway activator, interaction of miR-200c with its related FOG2 results in HSC activation and liver fibrosis[97]. MiRNA-181b-3p and its target importin α5 may regulate sensitivity of TLR4 in Kupffer cells[98]. MiRNA-193a/b-3p relives liver fibrosis by inhibiting the activation and proliferation of HSCs[99]. MiRNA-26b-5p inhibits mouse liver fibrosis by targeting platelet-derived growth factor receptor-β[100]. MiRNA-219 plays a protective role in liver fibrosis by targeting TGF-βRII[101]. MiRNA-145 promotes HSC activation by targeting Krüppel-like factor 4[102]. The effects of alcohol on DNA methylation in hepatocytes in liver fibrosis and miRNA regulation have been elucidated[103]. Therefore, the core miRNAs and the related downstream targets form a complicate regulatory miRNA-mRNA communication network in liver fibrosis, and this provides a basis for the development of more effective therapy for liver fibrosis.

***TLR pathway in liver fibrosis***

TLR has the ability to recognize pathogens and contains ten members: TLR1-10. Among the TLR family, TLR3, 7, 8, 9, and 10 are located in the endolysosome[104,105], and TLR1, 2, 4, 5, and 6 are located on the membrane. A crosstalk between TLR and their ligands activates the liver fibrosis pathway (Figure 2). TLR2 and its ligand stimulate Kupffer cells to secret IL-10 in HBV-dependent liver fibrosis[106,107]. In HBV-induced chronic liver fibrosis, TLR2 acts in a homodimer form or in a heterodimer form with TLR1 or TLR6 and activates NF-kB in a MyD-88 dependent manner[108]. TLR3 silencing induces HSC and kupffer cell activation, suggesting that TLR3 is related closely to liver injury. This supports the basis for TLR3-targeted therapy of liver disease[109]. Crosstalk between TLR3 and CCL5 plays a key role in HCV- mediated liver fibrosis[110]. Exosome-mediated TLR3 promotes liver fibrosis by enhancing IL-17A production from γδT cells[111]. In a non-alcoholic steatohepatitis rat model, TLR4-p38 MAPK signaling may induce kupffer cell activation, suggesting that TLR4 is closely associated with steatofibrosis[112]. Ethyl pyruvate may protect the liver from CCL4-mediated fibrosis by inhibition of TLR4[113]. TLR5 promotes liver bacterial clearance and protects from liver injury and fibrosis[114]. Bioactive compound luteolin may protect the liver from fibrosis through up-regulation of TLR5, and knockdown of TLR5 induces metabolic syndrome[115]. These data suggest that TLR5 is a possible key transcription factor for preventing lipotoxicity. TLR2, together with the TLR9-dependent myD88-dependent pathway, may activate HSCs to secret CXCL1, and the CXCL1/CXCR2 axis recruits neutrophils to the liver, which contributes to the development of alcohol-mediated liver injury[116]. TLR7 may activate dendritic cells to secret type I interferon (IFN) to activate kupffer cells to produce profibrogenic IL-1ra. The TLR7/type I IFN/IL-1ra axis opens a selective target therapy for liver fibrosis[117]. Besides TLR3, other TLR family members are dependent on the MyD88 pathway. Curcumin promotes apoptosis of activated HSCs by inhibiting the MyD-88 pathway[118].

***Other signaling pathways***

There are other signaling pathways, such as STAT-3, Wnt/β-catenin, and NF-кB signaling pathways, involved in liver fibrosis (Figure 3). A crosstalk involving IL-17 and the STAT3 signaling pathway activates HSCs to produce collagen I[119]. A crosstalk network involving IL-6 and IL-10 with STAT3 may protect the liver against alcohol-mediated inflammation and injury[120]. STAT3/IL-10/IL-6 signaling regulates hepatocyte proliferation and is a key factor associated with acute injury and chronic liver fibrosis[121]. Moreover, crosstalk of IL-22 with STAT3 induces senescence of HSCs in liver fibrosis[53]. STAT3 is required to for TGF-β-induced proliferation and fibrosis in LX-2 cells, and this supports that there is a close crosstalk between the TGF-β and STAT3 pathways[122]. STAT3-EGFR signaling promotes liver protective function in cholestatic liver injury and fibrosis[123]. STAT3 and MAPK are necessary for IL-6-mediated liver fibrosis[63]. STX-0119 reduces liver fibrosis by inhibition of STAT3 and inactivation of HSCs in mice[124]. Crosstalk of FGF21 with the NF-кB and JNK signaling pathways protects the liver from inflammation and fibrosis[125]. Crosstalk between NF-κB and type I IFN signaling promotes liver inflammation and fibrosis, while crosstalk of ADAR1 with this pathway restrains this function[126]. The Wnt/β-catenin pathway exerts a function in HSC activation induced collagen I formation and liver fibrosis, and crosstalk of hBM-MSC with this pathway may inhibit liver fibrosis[127]. HGF activation promotes HSC apoptosis through the Rho pathway[128].

**TARGETED THERAPIES FOR LIVER FIBROSIS**

There are currently some drugs available for the therapy of liver fibrosis, however, their efficacy is limited (Table 1). It is the time to explore promising drugs to improve the treatment of liver fibrosis by developing promising therapeutic strategies, such as inhibition of HSC activation and anti-inflammation. Following molecular targeted therapy increasingly development, protein marker on HSC, signal pathway molecule may be potential marker to be selected for improving liver fibrosis. Many anti-fibrotic compounds are being on road. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) has been evaluated to improve liver fibrosis. TRAIL can reverse liver fibrosis by promoting apoptosis of primary HSCs and inhibiting kupffer cells in a CCL4-mediated liver fibrosis model. Therefore, TRAIL-based therapy is a useful direction for exploring new anti-fibrotic drugs[129]. Wnt/β-based ICG-001 has been assessed to selectively induce target cell apoptosis, with encouraging results obtained in terms of reversing fibrosis and improving survival rate of model animals[130]. 24-nor-ursodeoxycholic acid (norUDCA) has been found to have anti-fibrotic effects and improve inflammation-mediated liver fibrosis[131]. Cenicriviroc, an inhibitor of CCR2/CCR5, is on a phase III clinical trial, which presents an anti-liver fibrosis effect[132]. Accumulating experiments of tyrosine kinase inhibitors make it possible to exploit their beneficial effects on fibrotic disease, although it should not also neglect the side effects of TK inhibitors for liver fibrosis, such as rash and gastrointestinal symptoms[133]. Taken together, these new drug therapies will provide a new avenue for the treatment of liver fibrosis.

**CONCLUSION**

A better understanding of the crosstalk among inflammation-related cells, cytokines, and signaling pathways in liver fibrosis could help clarify the pathogenesis of liver fibrosis. The aim of this review is to describe the present knowledge about inflammation-related crosstalk networks, which effectively perform regulatory functions in HSC activation and liver fibrosis. Moreover, we discuss different interactions among crosstalk-related members in liver fibrosis. The crosstalk-related complex regulatory network modulates several important aspects of cell function, including proliferation, activation, and differentiation (Table 1, Figure 4). Targeting each node of the crosstalk network can be a promising direction for liver fibrosis treatment. Interaction of IL-34 with the PI3K/Akt signal pathway promotes the M2 polarization of Kupffer cells to inhibit acute rejection in rat liver transplantation[134]. IL-17 stimulates Kupffer cells to secret TGF-β and activates HSCs to form myofibroblasts by stimulating collagen synthesis *via* the STAT3 signal pathway. In the future, we will focus on the function of IL-22 in the crosstalk between Kupffer cells and the CCL2-CCR2 pathway in order to enrich our knowledge on inflammatory cytokines in liver fibrosis. This will provide a basis for the therapy of liver fibrosis[118]. In addition, it should be noted that impaired macroautophagy/autophagy is involved in the pathogenesis of hepatic fibrosis.

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**Figure 1 transforming growth factor-β mediated crosstalk network in liver fibrosis.** TGF-β is primarily signaled by intracellular Smads. TGF-β: transforming growth factor-β; HSC: hepatic stellate cell; NK: natural killer.



**Figure 2 Toll-like receptor mediated crosstalk network in liver fibrosis.** Toll-like receptor is a member of DAMPs that recognize pathogen-associated molecules and thereby transmit inflammatory signals that cause inflammatory responses. TLR: Toll-like receptor; MAPK: mitogen-activated protein kinase; NF-кB: Nuclear factor-кB; HSC: hepatic stellate cell; DC: Dendritic cells; NK: natural killer.



**Figure 3 STAT3-mediated inflammatory mediator crosstalk network in liver fibrosis.** EGFR: epidermal growth factor receptor; HSC: hepatic stellate cell; TGF-β: transforming growth factor-β; MAPK: mitogen-activated protein kinase; IL: interleukin.



**Figure 4 Inflammatory mediator network between cytokines and signaling pathway in liver fibrosis.** TGF-β: transforming growth factor-β; IL: interleukin.

**Table 1 Signal pathway-inflammatory mediator crosstalk network in liver fibrosis**

|  |  |  |  |
| --- | --- | --- | --- |
| **Crosstalk family member** | **mechanism** | **Function in liver fibrosis** | **Biological basis as therapeutic target** |
| TGF-β | Proliferationmigrationcollagen productioncrosstalk with small compoundsinduces NK cell tolerance | Fibrosis activator | Deficiency of TGF-β inhibits liver fibrosis |
| Wnt/β-catenin | promotes activation of HSCcollagen I production | Fibrosis activator |  |
| TLR-2TLR1/2TLR2/6 | activates NF-kB pathwaypro-inflammatory cytokinesactivates Kupffer celland IL-10 production | Inducer or suppressor in liver fibrosis |  |
| TLR-3 | crosstalk with IL-17A and γδT cellcrosstalk with CCL5 | Inducer or suppressor in liver fibrosis | Loss of TLR3 aggravatesliver inflammation |
| TLR-4 | pro-inflammatory cytokine production | Fibrosis activator | Inhibition of TLR4 promotes liver protection |
| TLR-5 | crosstalk other pathwayregulates metabolismanti-inflammatory cytokine production | Fibrosis inhibitor | Activation of TLR5 reduces liver fibrosis |
| TLR7 | pro-inflammatory cytokine productionactivates DCscrosstalk with IFN signaling pathway | Fibrosis inhibitor |  |
| TLR-9 | CXCL1 productionneutrophil infiltration | Fibrosis activator |  |
| STAT3 | crosstalk with IL-17, IL-10, and IL-6crosstalk with other signal pathways | Fibrosis activatoror suppressor | Inhibition of STAT3 may inactivate HSCs and prevent liver fibrosis |
| miR-29b | crosstalk with PI3K/AKT pathwaycrosstalk with TGF-β1/SMAD3 pathwayinduces HSC apoptosis | Fibrosis inhibitor |  |
| miR-34a-5p | crosstalk with TGF-β1/SMAD3 | Fibrosis inhibitor |  |
| miR-130a-3p | crosstalk with TGFBR1 and TGFBR2induces HSC apoptosis | Fibrosis inhibitor |  |
| miR-19b | Crosstalk with HSC CCL2 | Fibrosis inhibitor |  |
| miR-21 | Crosstalk with NLRP3 inflammasome/IL-1β axis | Fibrosis regulator |  |
| miR-17-5p | crosstalk with Wnt/β-cateninActivation of HSCs | Fibrosis promoter |  |
| miR-142-3p | crosstalk with TGF-β | Fibrosis inhibitor |  |
| miR-200c | crosstalk with PI3K/Akt | Fibrosis promoter |  |
| miR-181b-3p | crosstalk with TLR4Kupffer cells | Fibrosis regulator |  |
| miR-193a/b-3p | Inhibits activation of HSCs | Fibrosis regulator |  |
| miR-26b-5p | Crosstalk with platelet-derived growth factor receptor-β | Fibrosis inhibition |  |
| miR-219 | Crosstalk with TGF-βRII | Fibrosis inhibition |  |
| miR-145 | Crosstalk with Krüppel-like factor 4promotes activation of HSCs | Fibrosis inhibition |  |

TGF-β: transforming growth factor-β; TLR: Toll-like receptor; NF-кB: Nuclear factor-кB; HSC: Hepatic stellate cell; DCs: Dendritic cells; NK: Natural killer; IL: interleukin.