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REVIEW

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Key role of macrophages in the progression of hepatic fibrosis

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Abstract

Liver fibrosis is a pathological change characterized by excessive deposition of extracellular matrix caused by chronic liver injury, and the mechanisms underlying its development are associated with endothelial cell injury, inflammatory immune cell activation, and HSC activation. Furthermore, hepatic macrophages exhibit remarkable heterogeneity and hold central functions in the evolution of liver fibrosis, with different subgroups exerting dual effects of promotion and regression. Currently, targeted macrophage therapy for reversing hepatic fibrosis has been extensively studied and has shown promising prospects. In this review, we will discuss the dual role of macrophages in liver fibrosis and provide new insights into reversing liver fibrosis based on macrophages.

Keywords: liver fibrosis, macrophages, therapeutics

INTRODUCTION

Liver fibrosis is a pathological alteration that occurs in the reparative and healing processes as a result of the response to chronic liver injury, mainly including viral hepatitis and cholestatic injury. It is characterized by excessive deposition of extracellular matrix (ECM) within the liver and serves as a critical step in the progression of liver cirrhosis and hepatocellular carcinoma.[1–3] Additionally, liver fibrosis can lead to a series of complications, such as portal hypertension, liver failure, and HE. Moreover, liver cirrhosis and its complications cause approximately 1 million deaths worldwide each year, posing a significant public health concern.[4] However, the mechanisms underlying the development of liver fibrosis are complex and not fully elucidated. It is likely associated with the injury of endothelial cells, the recruitment of inflammatory immune cells, and the

Abbreviations: CCL2, chemokine ligand; CCR2, chemokine receptor 2; ECM, extracellular matrix; iNOS, inducible nitric oxide synthase; MDM, monocyte-derived macrophage; MMP, matrix metalloproteinase; ROS, reactive oxygen species.

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activation of HSCs, as the interactions between these cells contribute to the promotion of liver fibrosis.[5] Recently, the main approaches for treating hepatic fibrosis include removing the injurious factors causing chronic liver damage, eliminating or inactivating myofibroblasts, suppressing inflammatory responses, and degrading ECM.[6] However, significant breakthroughs in treatment have yet to be achieved.

Hepatic macrophages are a crucial component of the liver's innate immune system. In addition to their robust phagocytic ability and antigen-presenting function, they can recognize and eliminate pathogens, cellular debris, or apoptotic cells, and can also generate reactive oxygen species (ROS), inducible nitric oxide synthase (iNOS), reactive nitrogen species, cytokines, chemokines, and growth factors to trigger cascades of inflammatory reactions and other biological responses, playing a vital role in tissue repair, inflammatory responses, lipid metabolism, and tumor development.[7,8] Besides, hepatic macrophages, as key regulatory cells, play a crucial role in the progression of liver fibrosis, which is a dynamic and reversible wound-healing process that involves both progression and regression. Importantly, single-cell sequencing has revealed that distinct subpopulations of hepatic macrophages have dual effects, both promoting and resolving liver fibrosis.[9] This article provides a comprehensive review of the dual role of macrophages in liver fibrosis and explores new perspectives on how to reverse liver fibrosis based on macrophage-mediated mechanisms.

The origin of liver macrophages

Hepatic macrophages are composed of different subpopulations, primarily including resident hepatic macrophages, monocyte-derived macrophages (MDMs), and peritoneal macrophages. Using single-cell sequencing, hepatic macrophages can now be more accurately classified based on relevant selection markers[10] (Figure 1).

First, hepatic resident macrophages, also known as KCs, originate from the yolk sac erythro-myeloid progenitors and play a dominant role among hepatic macrophages, thereby, serving as the first line of defense in immune responses within the liver. In addition, KCs are activated by inflammatory factors, lipid mediators, and dysbiosis of the gut microbiota, and recruit circulating bone marrow-derived macrophages to the liver for differentiation and replenishment.[11,12] Current studies have found that mouse KCs can specifically express CLEC4F,[13] TIM4,[14] CLEC2,[15] etc., to distinguish them from monocyte-derived macrophages (MDMs); for example, the specific expression markers of mouse KCs include $CD45^+$ chemokine receptor 2 $(CCR2)^-CD11b^+F4/80^{++}CD68^+CD11c^{+/-}CLEC4F^+$-$TIM4^+CLEC2^+$. Blériot et al[16,17] have classified mouse KCs into 2 subpopulations, KC1 ($CD206^{lo}ESAM^-$) and KC2 ($CD206^{hi}ESAM^+$), based on the expression of CD206 and ESAM. These 2 subpopulations exhibit distinct functional characteristics, with KC1 showing stronger immunological features, while KC2 specifically expresses genes involved in cell adhesion and hepatic lipid metabolism pathways. In humans, KCs exhibit high expression of TIM4 and MARCO, therefore, the surface markers for human KCs are $CD68^+CD32^+MARCO^+$-$TIM4^+$. Furthermore, a study[18] using spatial transcriptomics has revealed that KCs ($CD68^+MARCO^+$) are localized in the portal area, while recruited MDMs ($CD68^+MARCO^-$) are located near the central vein.

Second, MDMs primarily consist of those originating from the bone marrow and the spleen, possessing immunogenicity and acquiring different phenotypes and functions under the influence of the local microenvironment.[19] Interestingly, in mice, studies have shown that MDMs can differentiate into macrophages with different phenotypes in response to the distinct microenvironment within the liver, known as Ly-$6C^{hi}$ and Ly-$6C^{lo}$. The Ly-$6C^{hi}$ subset primarily originates from the bone marrow, while the Ly-$6C^{lo}$ subset is derived from the spleen.[20] Furthermore, studies in mice have found that MDMs with high expression of Ly6C ($Ly6C^{hi}CD11b^+CCR2^{++}CX3CR1^+$) exhibit a proinflammatory and profibrotic phenotype, while MDMs with low expression of Ly6C ($Ly6C^{lo}CD11b^+CCR2^{++}CX3CR1^+$) display a prorepair and antifibrotic phenotype.[21,22] In humans, based on the expression of CD14 and CD16, macrophages can be classified into 3 subtypes: $CD14^+CD16^-$, $CD14^+CD16^+$ and $CD14^-CD16^+$ subsets. Moreover, in humans, there is no antigen equivalent to mouse Ly-6C. It is generally believed that $CD14^+CD16^-$ monocyte-derived macrophages are similar to mouse $Ly6C^{hi}$ macrophages, while $CD14^+CD16^+$ monocyte-derived macrophages are similar to $Ly6C^{lo}$ macrophages.[23] However, $CD14^+CD16^+$monocyte--derived macrophages accumulate and release inflammatory factors in the damaged liver, contrary to the role of mouse Ly-$6C^{lo}$ macrophages. Consistently, both cell types can promote ECM degradation or fibrinolysis.

Finally, peritoneal macrophages are located in the subcapsular region of the liver and have been confirmed to exist in both humans and mice[24] (Figure 1). They express common macrophage markers, such as F4/80 and CD64, but do not express markers specific to KCs, such as VSIG4, CLEC4F, FOLR2, or CLEC2.[25] In addition to bone marrow–derived macrophages, peritoneal macrophages also undergo self-renewal and promote liver regeneration through their migration via the mesothelial cells when the liver injury occurs.

In general, activated macrophages undergo differentiation or polarization into two distinct subtypes, namely M1 (proinflammatory) and M2(prorepair)[26] (Figure 1). Lipopolysaccharide, TNF-α, and colony-stimulating

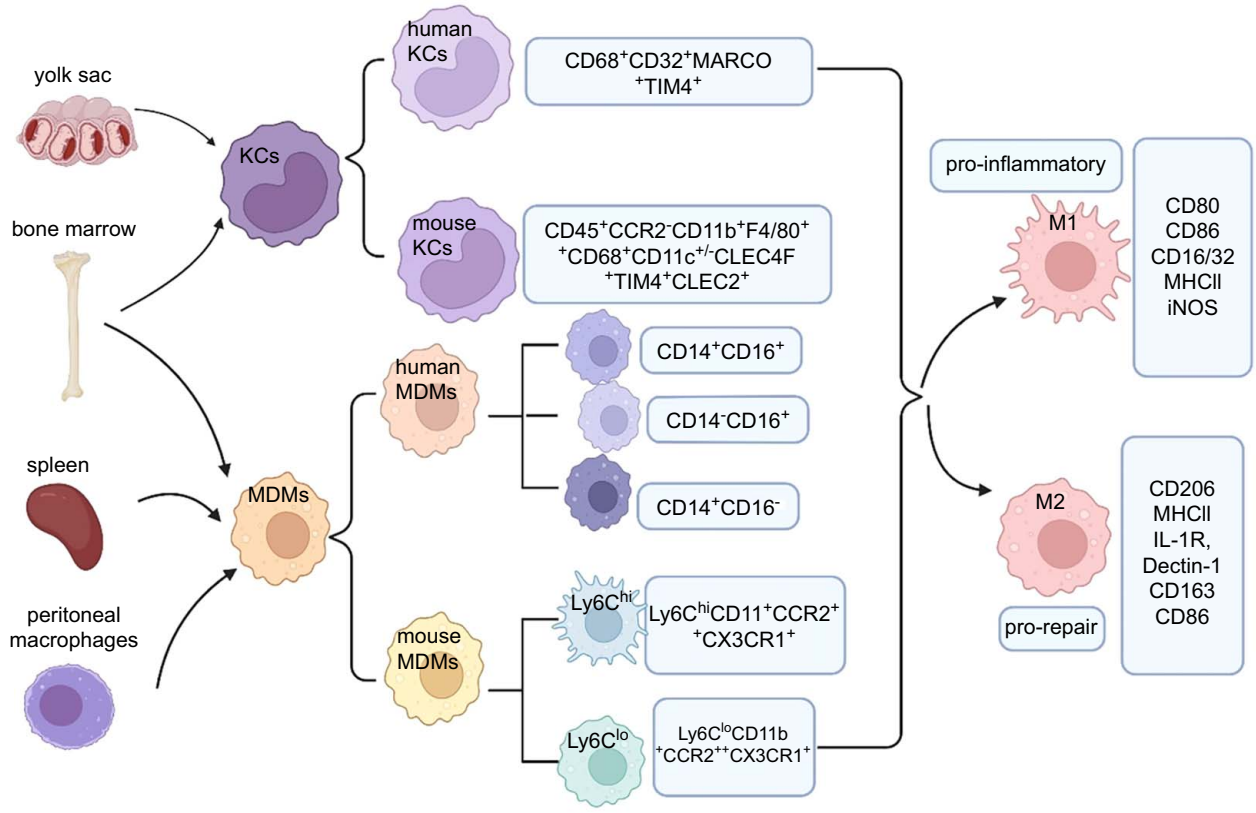

FIGURE 1 The origin of hepatic macrophage subsets in mice and humans. Hepatic macrophages are mainly comprised of KCs and MDMs. KCs are located in the sinusoid of the liver with a yolk sac or bone marrow origin. Infiltrating monocytes are categorized into 2 subsets: Ly6C^{hi} and Ly6C^{lo} monocytes, mainly derived from the bone marrow as well as the spleen. The peritoneal macrophages originating from the peritoneum also contribute to the infiltrating monocytes. Activated macrophages undergo differentiation or polarization into 2 distinct subtypes, namely M1 (proinflammatory) and M2 (prorepair). Abbreviations: MDMs, monocyte-derived macrophages; MHC, major histocompatibility complex.

factors for granulocytes and macrophages can induce polarization of macrophages toward M1 phenotype.[27] Current researches indicate that M1 macrophages can be polarized via the toll-like receptor-4/NF-κB, JAK/STAT1, and Notch signaling pathway,[28–31] characterized by specific markers such as CD80, CD86, CD16/32, major histocompatibility complex II, and iNOS, producing a large amount of proinflammatory cytokines and chemokines such as IL-1b, IL-6, IL-12, IL-23, TNF-a, CXCL1~3, CXCL8~10, chemokine ligand (CCL2)~5, and CCL11,[32] and mainly exerting antigen-presenting function, , as well as proinflammatory and pathogenic microorganism scavenging capabilities. On the other hand, M2 macrophages, known as anti-inflammatory macrophages, are primarily activated by IL-4 and IL-13, secreting anti-inflammatory factors such as IL-10, IL-4, IL-13, TGFβ, etc.; therefore, have the ability to suppress inflammation, promote tissue remodeling and prevent parasitic infections. In addition, common mechanisms for M2 macrophage polarization include the JAK/STAT6 and TGFβ/Smads signaling pathways.[33,34] In accordance with the expression of activation markers and various functions, M2 macrophages are typically categorized into 4 subpopulations: M2a, M2b, M2c, and M2d subtypes.[35] First, induced M2a macrophages are characterized by specific markers, such as CD206, major histocompatibility complex II, IL-1R, and Dectin-1, having various functions, including anti-inflammation, wound healing, and Th2 immune response;[36] second, M2b macrophages are characterized by specific markers such as CD206, major histocompatibility complex II, and CD86, which have functions of immune regulation, protumor and pro-infection;[37] third, M2c macrophages are characterized by specific markers, such as CD206 and CD163, that have functions of phagocytosis, immunosuppression, and tissue remodeling.[37] Finally, M2d macrophages are characterized by specific marker CD206, and have functions of promoting tumor growth and angiogenesis.[38] Furthermore, transcriptomic studies have revealed that the phenotypes of Ly-6C^{hi} and Ly-6C^{lo} cells do not strictly correspond to M1 and M2 macrophage types.[39] However, it is now recognized that the M1/M2 dichotomy is too simplistic and limited to describe the many distinct polarization phenotypes unraveled by single-cell RNA sequencing. Nevertheless, the M1/M2 phenotyping of liver macrophages can still reflect various dynamic pathological changes in the liver.

The dual role of macrophages in the formation of liver fibrosis

ECM is a complex structure composed of various molecules, including type I and III collagen fibers, fibronectin, laminin, and glycosaminoglycans.[40] Liver fibrosis formation is a process characterized by excessive deposition of ECM components produced by myofibroblasts. In fibrotic liver, the primary sources of fibrogenic myofibroblasts have been identified as liver-resident–activated HSCs and activated portal fibroblasts.[1] The activation of HSCs and their transformation into myofibroblasts are key steps in the formation of liver fibrosis, while liver macrophages play a crucial role in regulating HSC activation.[41] Different subsets of macrophages exhibit distinct polarization states, as changes in the tissue microenvironment can induce macrophages of different origins to adopt different phenotypes, hence crucial in promoting or resolving fibrosis at different stages of liver fibrosis.[42] During the initiation and progression of liver fibrosis, activated hepatic macrophages upregulate profibrotic factors and inflammatory cytokines, such as TGF-β, PDGF, CCL2/CCR2), TNF-α, IL-1β, and so on. These factors activate HSCs and contribute to the deposition of ECM and liver fibrosis.[43] However, in the late stage of liver fibrosis, under various exogenous stimuli, hepatic macrophages can also degrade ECM by producing matrix metalloproteinases (MMPs), and produce large amounts of IL-4, IL-5, and IL-10, working together with IL-13 to exert antifibrotic effects[44,45] (Figure 2). Therefore, hepatic macrophages play a dual role in liver fibrosis progression and its resolution.

Macrophages promote liver fibrosis progression

Activated KCs can upregulate proinflammatory and profibrotic factors through pattern recognition receptors,[46] classical TGF-β,[47] and PDGF[48] pathway, thereby promoting liver fibrosis. When liver injury occurs, pathogen-associated molecular patterns and damage-associated molecular patterns can be recognized by pattern recognition receptors on the cell surface or within the cells, such as toll-like receptors and nod-like receptors. This recognition triggers the production of inflammatory mediators, such as TNF-α, IL-6, IL-12, IL-1β, and CCL2, promoting the activation and proliferation of HSCs, leading to the deposition of ECM and the development of liver fibrosis[49] (Figure 2). Moreover, various cytokines secreted by macrophages can activate and enhance T-cell functions.[50] For example, IL-6 can promote the differentiation of Th17 cells and IL-4 promotes the differentiation of Th2 cells. Th17 cells can secrete pro-inflammatory factors, such as IL-17, IL-22, and IL-23, to activate HSCs and promote liver fibrosis.[51,52] Current studies suggest that when there is an imbalance between Th17 cells and regulatory T cells, HSCs become activated and stimulate liver fibrosis.[52,53] Th2 cells produce cytokines IL-4 and IL-13 to activate HSCs, leading to ECM proliferation and promoting liver fibrosis.[54,55] Indeed, the most potent inducers of liver fibrogenesis are TGF-β and PDGF, which are primarily secreted by KCs. During liver injury, KCs produce a significant amount of TGF-β, which binds to the highly affinitive TGF-β receptor on the surface of HSCs, then induces sustained phosphorylation of downstream membrane receptor-regulated Smad, downregulates inhibitory Smad expression, facilitates the translocation of the signal into the cell nucleus and triggers the activation of HSCs as well as the development of fibrosis.[56] Whereas, PDGF secreted by hepatic macrophages during liver injury binds to its receptors on HSCs, leading to the dimerization and autophosphorylation of its subunits, thereby inducing sustained activation of HSCs.[57]

Furthermore, during liver injury, recruited MDMs in the liver can activate HSCs and promote liver fibrosis by releasing inflammatory mediators, such as ROS,[58] iNOS,[59] and reactive nitrogen species.[60] Nicotinamide adenine dinucleotide phosphate oxidase 2 is an inflammatory mediator that promotes apoptosis in hepatocytes. Also, it has been reported that ROS generated by nicotinamide adenine dinucleotide phosphate oxidase 2 released from MDMs can exacerbate liver fibrosis induced by CCl4.[61] MDMs can catalyze the production of a large amount of proinflammatory macrophage factor, nitric oxide, by inducing the expression of iNOS from L-arginine, which can increase the production of prostaglandin E2 through the activation of cyclooxygenase, thereby promoting the occurrence of liver fibrosis.[62] Additionally, the reduced form of nitric oxide can react with ROS to form reactive nitrogen species, such as the highly reactive and toxic peroxynitrite anion (ONOO-), which can activate HSCs.[60] In the early stages of liver injury, Ly6C^{hi} monocyte-derived macrophages are recruited to the injured liver through the action of the CCL2/CCR2 axis. Then, these macrophages release various inflammatory and profibrotic factors that act on HSCs, promoting their proliferation and activation, thereby driving the development of liver fibrosis[1] (Figure 2). In the human body, CD14+ CD16+ monocyte-derived macrophages in MDMs are the main cell types involved in the formation of liver fibrosis, accumulating in the damaged liver and releasing inflammatory and fibrotic factors to promote the development of liver fibrosis[22] (Figure 2).

Macrophages are involved in the regression of liver fibrosis

Several studies[36–38] have demonstrated that liver fibrosis is reversible. The regression of liver fibrosis

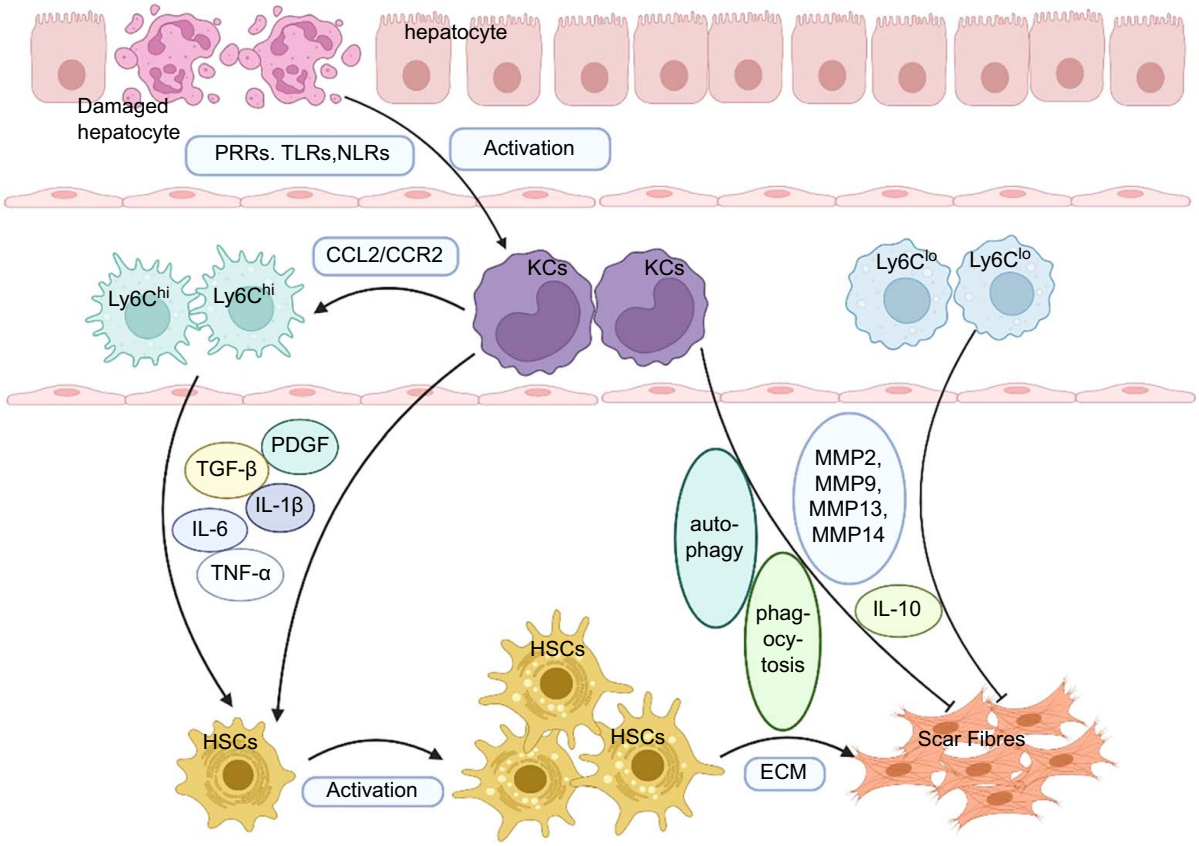

FIGURE 2 The dual role of hepatic macrophages in the progression and regression of liver fibrosis. KCs are activated by damaged hepatocytes and upregulate TGF-β, PDGF, CCL2/ CCR2, TNF-α, IL-1β, and so on. The increased levels of CCL2/CCR2 promote the recruitment of Ly-6C^{hi} monocytes to the liver injury. The activated KCs and Ly6C^{hi} monocytes both exert profibrotic effects by promoting the activation of HSCs, leading to the excessive deposition of ECM and scar formation. On the contrary, under various exogenous stimuli, KCs and Ly6C^{lo} monocytes can degrade ECM by producing MMPs and IL-10 to exert antifibrotic effects. In addition, autophagy and phagocytosis of KCs can promote the regression of liver fibrosis. Abbreviations: CCL2/CCR2, chemokine ligand 2/chemokine receptor 2; ECM, extracellular matrix; MMPs, matrix metalloproteinases; NLRs, nod-like receptors; PRRs, pattern recognition receptors; TLRs, toll-like receptors.

may be associated with a decrease in proinflammatory or profibrotic cytokine production, an increase in collagen degradation activity,[63] the elimination of hepatic myofibroblasts,[59] the inhibition of ECM production, and the resolution of fibrous scar tissue. Moreover, KCs can promote the regression of liver fibrosis through various mechanisms, such as producing anti-inflammatory factors like IL-10, recruiting natural killer cells to induce apoptosis of activated HSCs, phagocytosing damaged liver cells, and producing MMPs that degrade the ECM, including MMPs-2, 9, 13, and 14[64,65] (Figure 2). Furthermore, IL-10 and IL-12 secreted by macrophages promote the differentiation and proliferation of regulatory T cells and Th1 cells, respectively. Regulatory T cells not only directly inhibit the activation and proliferation of HSCs, thereby reducing the deposition of ECM, but they also suppress the activation of Ly6C^{hi} macrophages, by reducing chronic inflammation and alleviating liver fibrosis.[50,66,67] Th1 cells can produce interferon-γ to decrease the activation of HSCs and the accumulation of ECM, as well as enhance natural killer cell activity and promote apoptosis of HSCs.[68] Additionally, hepaticmacrophages in the liver synthesize and secrete TRAIL, which can induce apoptosis in HSCs via decreasing the expression of TIMPs in HSCs, thereby promoting extracellular matrix degradation and exerting an antifibrotic effect.[69]

During the regression of liver fibrosis, the population of Ly6C^{lo} subset is enriched in the mouse liver, which exhibits reduced secretion of proinflammatory factors and can secrete multiple proteins, including MMP9 and MMP2, that degrade the ECM[70] (Figure 2).

New ideas for macrophage-based treatment of liver fibrosis

Due to the significant role of hepatic macrophages in the development and regression of liver fibrosis, there is currently a growing number of researches focused on macrophage-based therapies to improve liver fibrosis, which holds promising prospects.[20] So far, the main therapeutic strategies for reversing fibrosis based on macrophages include antifibrotic treatments targeting

TABLE 1 Targeting hepatic macrophages as a therapeutic strategy for liver fibrosis

Categories	Therapeutics	Mechanism	Drugs	References
Targeting macrophage immune metabolism	ACC inhibitor	Prevent macrophage activation and infiltration	WZ66	[68,73]
	PPAR	Promoting macrophage differentiation toward M2	Elafibranor	[69–71]
	FXR	Increasing cholesterol transport in macrophages	Obeticholic acid	[72]
Targeting macrophage-related signaling pathways	Antibiotics	Removes intestinal bacteria and inhibits macrophage activity	Rifaximin	[74]
	IL-1β antagonists	Inhibit the activation of inflammasomes	IL-1Ra	[75]
	CCR2/5 antagonists	Inhibition of monocyte recruitment	Cenicriviroc	[76,77]
	Gal-3 antagonists	Inhibition of inflammatory macrophage function	GR-MD-02	[78,79]
Targeting autologous macrophages	CD45+CD14+25F9^{hi} cells	Proreparative macrophages reverse liver fibrosis	—	[64]

Abbreviations: ACC-inhibitor, acetyl-CoA carboxylase-inhibitor; CCR2/5, chemokine receptor 2/5; FXR, farnesoid X receptor; Gal-3 antagonists, galectin-3 antagonists; PPAR, peroxisome proliferator-activated receptors.

macrophage immune metabolism,[71] anti-liver fibrosis treatments targeting macrophage-related signaling pathways,[72] and the use of autologous macrophages for treating liver fibrosis[73] (Table 1).

The metabolic reprogramming of macrophages in response to changes in the local microenvironment of the liver after injury can influence the polarization of macrophage subsets toward proinflammatory or anti-inflammatory phenotypes, thereby affecting the activation of HSCs.[80] In addition, M1 and M2 macrophages exhibit distinct metabolic characteristics: M1 macrophages are primarily involved in the enhancement of glycolysis and the pentose phosphate pathway, and the activation of tricarboxylic acid cycle, whereas, M2 macrophages are primarily involved in the enhancement of fatty acid oxidation and arginase pathway, and the activation of the tricarboxylic acid cycle.[74] Previous studies have demonstrated that the glycolytic pathway promotes the polarization of macrophages toward the M1 phenotype, activating inflammation pathways and releasing inflammatory cytokines such as TNF-α, IL-1β, IL-6, etc.[75] Targeting macrophage metabolism has a unique advantage in improving liver fibrosis and reducing drug side effects. Recently, relevant studies have shown that targets based on macrophage immune metabolism include the inhibitor WZ66 of acetyl-CoA carboxylase (ACC), which is involved in lipid metabolism,[76] peroxisome proliferator-activated receptors (PPAR),[77–79]and farnesol X receptor, which induces the expression of genes related to lipoprotein metabolism.[81] Gao et al[76] demonstrated that by using the acetyl-CoA carboxylase inhibitor WZ66, acetyl-CoA carboxylase could be inhibited and, therefore, prevent macrophage activation and infiltration and reduce HSC activation so as to alleviate hepatic steatosis. Notably, the peroxisome PPARs are a family of nuclear transcription factors, including four subtypes: α, β, δ, and γ, which are involved in the regulation of lipid metabolism and glucose metabolism. Previous studies have found that during liver inflammation, PPARα is redistributed from hepatocytes to KCs, and activation of PPARα can induce a phenotypic transformation of macrophages into the M2 phenotype.[83] On the other hand, farnesoid X receptor is a bile acid receptor that can inhibit gene expression related to hepatic triglyceride synthesis and regulate lipid metabolism. Currently, clinical trials are underway for the farnesol X receptor agonist obeticholic acid in patients with liver fibrosis.[81] However, metabolic targets are nonspecific, and it is necessary to accurately describe the spatiotemporal characteristics of macrophage metabolism to make targeted macrophage metabolism therapy more precise.

Currently, the development of drugs targeting macrophage-related signaling pathways is also a hot topic in the context of anti-liver fibrosis. Antibiotics such as rifaximin, vancomycin, gentamicin, and meropenem have been shown to clear the gut microbiota to inhibit macrophage activation, thereby reducing inflammatory responses and alleviating liver fibrosis.[84] In addition, IL-1β signaling pathway antagonists,[85] chemokine receptor 2/5 (CCR2/5) antagonists,[86,87]and galectin-3 antagonists[88] have been shown to inhibit the activation of inflammasomes produced by KCs and suppress the recruitment of monocytes. Additionally, IL-1Ra is an antagonist of IL-1β that binds to IL-1R to regulate inflammation. Current clinical trial is underway to monitor the levels of endotoxins, IL-1, TNF-α, and other markers in patients' serum to evaluate the efficacy of IL-1Ra (anakinra) in treating liver diseases.[85] Mulder et al[87] found that CCR2 plays a crucial role in recruiting immune cells to white adipose tissue and the liver, but the CCR2 inhibitor (cenicriviroc) can alleviate liver inflammation and the progression of liver fibrosis. Also,

galectin-3, a lectin protein, is a required factor for TGF-β–mediated myofibroblast activation and ECM generation. Notably, in the model of schistosome-induced liver fibrosis, KCs are recruited to the fibrotic tissue and exhibit high expression of Galectin-3.[89] Currently, clinical studies are underway for testing the efficacy of these agents.

A large recruitment of bone marrow-derived proreparative macrophages in the liver has been shown to reverse liver fibrosis by secreting MMPs and degrading ECM. Previous research has proposed the use of autologous macrophage therapy for the treatment of liver fibrosis. For example, Moroni and colleagues isolated $CD45^{+}CD14^{+}25F9^{hi}$ cells from peripheral blood monocytes of patients with liver cirrhosis using macrophage colony-stimulating factor and then infused these cells back into the patients. Follow-up assessments of liver fibrosis indicators such as transient elastography, pro-collagen type III, and type III collagen protein degradation products showed a decrease in their levels.[73] This study demonstrated the potential application of autologous macrophages $CD14^{+}25F9^{+}$ in the treatment of liver fibrosis. However, further clinical research data is needed to supplement and confirm these findings. Additionally, it remains to be elucidated whether other cell subpopulations have similar functions in the context of liver fibrosis treatment.

CONCLUSIONS

With the application of single-cell sequencing, subpopulations of liver macrophages can be accurately classified based on relevant selection markers. These subpopulations of liver macrophages play a dual role in the process of liver fibrosis. In the early stages of liver injury, $Ly6C^{hi}$ monocyte-derived macrophages are recruited to the liver and release various inflammatory and profibrotic factors, which activate and proliferate HSCs. While, during the resolution phase of fibrosis, $Ly6C^{lo}$ monocyte-derived macrophages can degrade ECM by secreting various MMPs such as MMP-12 and MMP-13. Therefore, macrophage-based therapies have become a promising approach for improving liver fibrosis, with extensive research being conducted in this area. These include antifibrotic treatments targeting macrophage immune metabolism, anti-liver fibrosis treatments targeting macrophage-related signaling pathways, and the use of autologous macrophages for liver fibrosis treatment, all of which are currently in clinical trial stages. Further identification of reparative macrophage subpopulations and clarification of their differentiation pathways and regulatory mechanisms will provide new strategies and hope for the treatment of liver fibrosis in the future.

AUTHOR CONTRIBUTIONS

Drafting of the article: Jinqiu Ran, Shengxia Yin, and Rahma Iss. Study review and/or revision of the manuscript: all authors. Study concept and study supervision: Jie Li, Chao Wu, Qun Zhang.

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CONFLICTS OF INTEREST

The authors have no conflicts to report.

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