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TOPIC HIGHLIGHT

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Pathogenesis of liver cirrhosis

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Abstract

Liver cirrhosis is the final pathological result of various chronic liver diseases, and fibrosis is the precursor of cirrhosis. Many types of cells, cytokines and miRNAs are involved in the initiation and progression of liver fibrosis and cirrhosis. Activation of hepatic stellate cells (HSCs) is a pivotal event in fibrosis. Defenestration and capillarization of liver sinusoidal endothelial cells are major contributing factors to hepatic dysfunction in liver cirrhosis. Activated Kupffer cells destroy hepatocytes and stimulate the activation of HSCs. Repeated cycles of apoptosis and regeneration of hepatocytes contribute to pathogenesis of cirrhosis. At the molecular level, many cytokines are involved in mediation of signaling pathways that regulate activation of HSCs and fibrogenesis. Recently, miRNAs as a post-transcriptional regulator have been found to play a key role in fibrosis and cirrhosis. Robust animal models of liver fibrosis and cirrhosis, as well as the recently identified critical cellular and molecular factors involved in the development of liver fibrosis and cirrhosis will facilitate the development of more effective therapeutic approaches for these conditions.

Key words: Cirrhosis; Pathogenesis; Hepatic stellate cells; Cytokine; miRNA; Animal model; Therapy

Core tip: Cirrhosis is the end-stage condition of many types of chronic liver diseases but the underlying mechanisms are far from being clarified. Multiple cellular and molecular factors might be involved in the initiation and progression of cirrhosis. Activation of hepatic stellate cells is a pivotal event in the development of cirrhosis. Animal models are crucial for understanding the pathogenesis and the development of more efficient therapeutic strategies for cirrhosis, with which cirrhosis may become a treatable or even a reversible disease.

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INTRODUCTION

Liver cirrhosis is the final common pathological pathway of liver damage arising from a wide variety of chronic liver diseases[1-3]. The etiology of cirrhosis varies geographically, with alcoholism, chronic hepatitis C virus infection, and nonalcoholic fatty lives disease (NAFLD) being the most common causes in western countries[4-6], whereas chronic hepatitis B is the primary cause of liver cirrhosis in the Asia-Pacific region[7-9]. Liver cirrhosis has many other causes, include inherited diseases such as hemochromatosis and Wilson's disease[10-14], primary biliary cirrhosis, primary sclerosing cholangitis[15-18], and autoimmune hepatitis[14,19]. Some cases are idiopathic or crypto-

genic. In recent decades, NAFLD has become a leading cause of chronic liver disease in Western countries such as the United States, with a prevalence of as high as 30% in the general population[20]. Thus, NAFLD has attracted extensive attention as an important cause of chronic liver diseases[21-23].

Although the causes of liver cirrhosis are multifactorial, there are some pathological characteristics that are common to all cases of liver cirrhosis, including degeneration and necrosis of hepatocytes, and replacement of liver parenchyma by fibrotic tissues and regenerative nodules, and loss of liver function[24-27]. Fibrosis as a precursor of cirrhosis is a pivotal pathological process in the evolution of all chronic liver diseases to cirrhosis[2,28]. At present, effective strategies to treat liver cirrhosis are still lacking, partially because of a poor understanding of the molecular mechanisms leading to cirrhosis. Thus, a better understanding of the pathogenesis of liver cirrhosis would facilitate the development of more effective treatment options.

In this review, we aim to summarize the recent advance in the molecular pathogenesis, animal models, and therapeutic strategies for liver cirrhosis.

MULTIPLE CELL TYPES CONTRIBUTE TO PATHOGENESIS OF LIVER CIRRHOSIS

The liver is formed by parenchymal cells (*i.e.*, hepatocytes) and other cells commonly known as nonparenchymal cells. The walls of hepatic sinusoids are lined by three different nonparenchymal cells: liver sinusoidal endothelial cells (LSECs), Kupffer cells (KCs), and hepatic stellate cells (HSCs). Both hepatic parenchymal and nonparenchymal cells are involved in the initiation and progression of liver fibrosis and cirrhosis.

HSCs

HSCs, formerly known as fat-storing cells, Ito cells, lipocytes, perisinusoidal cells, or vitamin A-rich cells, reside in the space of Disse in the normal liver and their main function is storage of vitamin A and other retinoids[27,29]. Following multiple injurious insults and/or exposure to inflammatory cytokines such as platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β, tumor necrosis factor (TNF)-α, and interleukin (IL)-1, HSCs undergo the transition from a quiescent to activated state. HSC activation is a pivotal event in initiation and progression of hepatic fibrosis and a major contributor to collagen deposition[30,31]. Activation of HSCs is characterized by cell proliferation and migration, contraction after transforming into myofibroblasts, generation of a large amount of collagen and other extracellular matrix (ECM), ultimately leading to liver fibrosis[32-34].

LSECs

LSECs constitute the sinusoidal wall, also called the endothelium, or endothelial lining. The structural characteristic of LSECs is the fenestrae on the surface of the endothelium[28,35,36] The endothelial fenestrae measure 150-175 nm in diameter, and act as a dynamic filter facilitating the exchange of fluids, solutes and particles between sinusoidal blood and the parenchymal cells[37-39]. LSECs have high endocytotic capacity[28,40]. Chronic alcohol abuse could result in defenestration, and a decrease in the number of fenestrae[37,41]. In cirrhotic liver, defenestration of sinusoidal endothelium and the presence of a subendothelial basement membrane are frequently present[35,42]. It is known that retinol deficiency can activate and transform HSCs into myofibroblasts with enhanced ECM production, resulting in perisinusoidal fibrosis and ultimately in cirrhosis[24,35]. Defenestration and capillarization of the hepatic endothelium are believed to be important in the initiation of perisinusoidal fibrosis by altering retinol metabolism. Studies in animals and humans have revealed that LSECs can secrete the cytokine IL-33 to activate HSCs and promote fibrosis[43]. Defenestration and capillarization of LSECs lead to impaired substrate exchange and are considered major contributing factors for hepatic dysfunction in liver cirrhosis[39]. On the contrary, differentiated LSECs can promote reversion of activated HSCs to quiescence and thereby accelerate regression and prevent progression of fibrosis through vascular endothelial growth factor (VEGF)-stimulated NO production[44,45].

KCs

KCs, also known as Browicz-Kupffer cells and stellate macrophages, are specialized macrophages located in the lining walls of the sinusoids of the liver that form part of the reticuloendothelial system (RES)[46]. Studies in animal models have shown that KCs are implicated in the pathogenesis of various liver diseases[47,48]. KCs can be activated by many injurious factors such as viral infection, alcohol, high-fat diet, and iron deposition. Activated KCs destroy hepatocytes by producing harmful soluble mediators and serving as antigen-presenting cells during viral infection[47]. KC-mediated hepatic inflammation is considered to aggravate liver injury and fibrosis[49,50]. KCs are involved in the activation of HSCs and formation of fibrosis. *In vitro* studies have shown that KC-conditioned medium can promote activation of cultured rat HSCs with enhanced matrix synthesis and cell proliferation by eliciting expression of PDGF receptor in HSCs[51]. KC-derived TGF-β1 stimulates proliferation and collagen formation of HSCs derived from rats fed with high-fat diet and ethanol[52,53]. Alcohol can induce the circulating level of Gram-negative bacterial lipopolysaccharide (LPS), which is a strong activator of KCs[54]. In genetic hemochromatosis, iron overload in KCs could induce the expression of intercellular adhesion molecule (ICAM)-1 on hepatocytes, therefore facilitating activation of HSCs and collagen deposition in the hepatic tissues[55]. Gelatinase secreted by activated KCs triggers the phenotypic change in HSCs by degrading collagen type Ⅳ[56]. KCs engulf apoptotic bodies and produce death ligands, in-

cluding Fas ligand and TNF-α, thereby promotes inflammation and fibrogenesis[57]. In addition, KCs activated by β-glucans increase portal pressure through the release of thromboxane A2 in normal and fibrotic livers[58].

Hepatocytes

Hepatocytes are the primary liver parenchymal cells, and play complicated roles in fibrosis and cirrhosis. Hepatocytes are targets for most hepatotoxic agents, including hepatitis viruses, alcohol metabolites, and bile acids[59]. Chronic liver diseases either promotes apoptosis or trigger compensatory regeneration of hepatocytes[60]. Damaged hepatocytes release reactive oxygen species (ROS) and fibrogenic mediators, induce activation of HSCs, and stimulate the fibrogenic actions of myofibroblasts[59]. Apoptosis of hepatocytes is a common event in liver injury and contributes to tissue inflammation, fibrogenesis, and development of cirrhosis. Steatohepatitis enhances Fas-mediated hepatocyte apoptosis, which correlates with active nuclear factor (NF)-κB and disease severity[61]. Both HCV infection and ethanol consumption induce hepatocyte apoptosis in animal models and humans, and induction may be related to downregulation of Bcl-2 signaling[62]. Chronic HCV infection can induce hepatocyte G1 arrest and impair hepatocellular function and limit hepatic regeneration[63,64]. In CCl_4-induced liver injury, hepatocyte apoptosis is induced at the early phase, which is followed by constant proliferation and if it persists, liver cirrhosis ensues at a later stage[65]. Hepatocytes are the major sources of matrix metalloproteinases (MMP-2, MMP-3 and MMP-13) and tissue inhibitors of matrix metalloproteinases (TIMP-1 and TIMP-2); all of which are involved in the pathogenesis of liver cirrhosis in CCl_4-induced liver cirrhosis in rats[66]. In the last fibrotic stage or cirrhosis, hypoxic hepatocytes become a predominant source of TGF-β1, further exacerbating hepatic fibrogenesis[67]. Recently, it has been shown that hepatocyte telomere shortening and senescence can result in fibrotic scarring at the cirrhosis stage, presenting a novel explanation for the pathophysiology of cirrhosis[68].

ROLE OF CYTOKINES IN LIVER FIBROSIS AND CIRRHOSIS

Liver cirrhosis is orchestrated by a complex network of cytokine-mediated signaling pathways regulating the activation of HSCs and fibrogenesis.

PDGF

PDGF is the strongest mitogen to HSCs among all polypeptide growth factors. PDGF family has four members, PDGF-A, -B, -C and -D[69]. PDGF and its receptors are markedly overexpressed in fibrous tissues, and its activity increases with the degree of liver fibrosis[70-72]. A variety of factors such as viruses, chemicals, or mechanical damage to hepatocytes can induce KCs to synthesize and release PDGF[73]. Upon binding to its specific receptor on the membrane of HSCs, PDGF activates corresponding signal molecules and transcription factors, leading to the activation of its downstream target genes and activation of HSCs[74,75]. PDGF has been shown to upregulate the expression of MMP-2, MMP-9 and TIMP-1, and inhibit the activity of collagenase, thereby reducing ECM degradation[69,75]. PDGF-B and PDGF-D are potent PDGF isoforms in PDGF receptor (PDGFR)β signaling within HSCs, as evidenced by PDGFRβ autophosphorylation and activation of extracellular signal-regulated kinase (ERK)1/2, C-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), and protein kinase (PK)B/Akt pathways[75-77]. PDGF-D can activate HSCs and exerts mitogenic and fibrogenic effects, and therefore plays an important role in matrix remodeling in liver fibrosis[72].

TGF-β

TGF-β is the strongest known inducer of fibrogenesis in hepatic fibrosis[78,79]. TGF-β is mainly synthesized by HSCs/myofibroblasts, KCs, LSECs, and hepatocytes in the liver. The TGF-β1 family is composed of six members, and among them, TGF-β1 has been shown to play a key role in the initiation and maintenance of liver fibrosis[78-82]. The expression level of TGF-β1 is increased in fibrotic liver and reaches a maximum at cirrhosis[67]. The pro-fibrogenesis effect of TGF-β1 is complicated, involving multiple aspects: the primary effect of TGF-β1 is to stimulate activation of HSCs, and the TGF-β1 autocrine loop in activated HSCs is an important positive feedback to the progression of liver fibrosis[80,81]. TGF-β1 induces expression of the matrix-producing genes and inhibits degradation of ECM by downregulating expression of MMPs and promoting TIMP, leading to excessive deposition of collagenous fibers and promoting the development of liver fibrosis[82,83]. In addition, TGF-β1 has been shown to inhibit DNA synthesis and induces apoptosis of hepatocytes. TGF-β1-induced apoptosis is thought to be responsible for tissue loss and decrease in liver size seen in cirrhosis[78]. Given the critical role of TGF-β1 in the pathogenesis of liver cirrhosis, specific blockade of TGF-β1/Smad3 signaling has shown some therapeutic value for liver fibrosis[82].

TNF-α

TNF-α is mainly produced by monocyte, macrophage, HSCs, and KCs. It has proinflammatory activities and cytotoxic effects in these cells. In the process of liver fibrosis, TNF-α plays an important role in the activation of HSCs and synthesis of ECM[84,85]. TNF-α can reduce the spontaneous apoptosis of activated rat HSCs by upregulating the antiapoptotic factors NF-κB, Bcl-XL and $p21^{WAF1}$, as well as downregulating the proapoptotic factor p53[86]. However, the effects of TNF-α on HSCs and fibrosis are complicated and even paradoxical, as demonstrated by studies showing that TNF-α could induce apoptosis in HSCs[87]. TNF-α has also been shown to exert antifibrogenic effect in rat HSCs by reducing

glutathione and inhibiting pro-collagen α1 expression[88]. In a rat model of nonalcoholic steatohepatitis (NASH), TNF-α antibody was shown to reduce the inflammation, necrosis and fibrosis in liver[89]. TNF-α signaling through activation of KCs plays an essential role in the pathogenesis of liver fibrosis in animal models of NASH[90].

Interferon

Interferon (IFN) is a family of soluble extracellular signaling molecules. Leukocytes synthesize IFN-α and IFN-β in response to virus infection, and T cells secrete IFN-γ upon stimulation with various antigens and mitogens. IFNs possess antiviral activity and is well-recognized for their antiviral effects[91]. Patients treated with IFNs exhibit a regression of liver fibrosis even if viral eradication is not achieved, indicating that IFN itself has antifibrotic activity via triggering the apoptosis of HSCs[92]. IFN-β could inactivate HSCs and decrease their production of α-smooth muscle actin (SMA) and collagen through inhibition of the TGF-β and PDGF pathways[93]. Similarly, IFN-γ has been demonstrated to reduce ECM deposition *in vivo* by inhibiting HSC activation via TGFβ1/Smad3 signaling pathways[94,95]. Treatment of rats with fibrosis by IFN-γ led to a reduced production and deposition of collagen, laminin, fibronectin, and pro-collagen type I in liver[95]. However, the effect of IFNs on fibrosis is not consistent, as demonstrated by a recent study showing that IFN-α and IFN-γ may exert opposite effects on apoptosis in HSCs. IFN-α was shown to elicit an antiapoptotic effect on activated HSCs, whereas IFN-γ was found to exert pro-apoptotic effect on HSCs by downregulating heat-shock protein 70[96].

ILs

ILs are a group of cytokines initially found to be expressed by leukocytes, but later on were shown to be produced by a wide variety of cells, such as CD4 T lymphocytes, monocytes, macrophages, and endothelial cells. ILs have a complicated role in immune response, inflammation, and liver fibrogenesis.

Pro-fibrogenic ILs: KCs and SECs can rapidly produce ILs in response to liver tissue damage. IL-1 can directly activate HSCs and stimulate them to produce MMP-9, MMP-13 and TIMP-1, resulting in liver fibrogenesis. In contrast, IL-1-receptor-deficient mice are less likely to sustain liver damage and exhibit reduced susceptibility to develop fibrosis[97]. Deficiency of IL-1α or IL-1β also makes the mice less susceptible to develop liver fibrosis in animal models of steatohepatitis[98]. Similarly, IL-1 receptor antagonists were found to protect rats from developing liver fibrosis in response to dimethylnitrosamine[99], and blocking IL-1 signaling could markedly attenuate alcohol-induced liver inflammation and steatosis. IL-1β was reported to increase the inflammatory and pro-steatotic chemokine monocyte chemoattractant protein-1 in hepatocytes, and augment Toll-like receptor (TLR4)-dependent upregulation of inflammatory signaling in macrophages[100].

Another profibrotic cytokine is IL-17, whose expression level increases with degree of liver fibrosis[101,102], indicating that IL-17 may be involved in disease progression and chronicity[101]. Studies in mice have shown that IL-17 induces liver fibrosis through multiple mechanisms, including upregulation of TNF-α, TGF-β1, and collagen 1α, which is dependent on signal transducer and activator of transcription (STAT)3 signaling pathway, and promotion of myofibroblast-like change of HSCs[102,103].

Antifibrogenic ILs: IL-10 is a cytokine that downregulates the proinflammatory response and has a modulatory effect on hepatic fibrogenesis[104,105]. IL-10 may have therapeutic potential for patients with HCV-related liver fibrosis who do not respond to IFN-based therapy[105]. IL-10 has been shown to exert antifibrotic effects through inhibiting HSC activity[106], and this was demonstrated in a rat model in which exogenous IL-10 was shown to reverse CCl_4-induced hepatic fibrosis by inhibiting the expression of TGF-β1, MMP-2 and TIMP-1[104,106,107].

IL-22 is known to play a key role in promoting antimicrobial immunity, inflammation, and tissue repair at barrier surfaces. IL-22 has been shown to induce HSC senescence, restrict liver fibrosis, and accelerate the resolution of liver fibrosis during recovery in a mouse model[108].

IL-6 is a pleiotropic cytokine involved in inflammatory pathways, hematopoiesis and immune regulation. IL-6 can attenuate apoptosis and promote regeneration of hepatocytes through NF-κB signaling and the Ras-MAPK pathway[109]. IL-6 reduces CCl_4-induced acute and chronic liver injury and fibrosis[110]. Pretreatment of fibrotic liver with IL-6 improves hepatic microenvironment and primes it for mesenchymal stem cell transplantation, leading to improvement in liver injury after fibrosis[111]. Meanwhile, increased blood level of IL-6 has been found in patients with NAFLD, and IL-6 could induce insulin resistance and inflammation in the liver[112,113], suggesting that IL-6 may play a role in the development of NAFLD.

miRNAS AND CIRRHOSIS

miRNAs represent a family of small noncoding RNAs controlling translation and transcription of many genes, which have recently emerged as post-transcriptional regulators. miRNAs play a key role in various hepatic pathologies, including hepatitis, cirrhosis and hepatoma[34,114]. miRNAs may play pro- and antifibrogenic roles, depending on cellular context and the nature of the stimuli.

Profibrogenic miRNA

miR-21 has an important role in the pathogenesis and progression of hepatic fibrosis. miR-21 can downregulate TGF-β expression and suppress HSC activation[115]. TGF-β1 induces expression of miR-181a and miR-181b,

and the latter can promote HSC proliferation by regulating p27 and the cell cycle. Elevation of serum level of miR-181b is suggested as a potential diagnostic biomarker for patients with cirrhosis[116].

miR-214-5p can increase expression of fibrosis-related genes (such as MMP-2, MMP-9, α-SMA, and TGF-β1) in LX-2 cells, and therefore, it may play crucial roles in HSC activation and progression of liver fibrosis[117].

miR-221 and miR222 are upregulated in human liver in a fibrosis progression-dependent manner and in mouse models of liver fibrosis. TGF-α or TNF-α induce expression of miR-222, which can bind to the CDKN1B (p27) 3'-untranslated region (UTR) and regulate expression of the corresponding protein[118].

Other fibrosis-associated miRNAs have been identified. For example, miR-199a, miR-199a*, miR-200a, and miR-200b were positively and significantly correlated with progression of liver fibrosis in both mouse and human studies. Overexpression of these miRNAs significantly increases the expression of fibrosis-related genes in HSCs[119]. miR-571 is upregulated in human hepatocytes and HSCs in response to TGF-β[120].

Antifibrogenic miRNAs

miRNA-150 and miRNA-194 are reduced in HSCs isolated from experimental rats with liver fibrosis. It has been demonstrated that these two miRNAs inhibit HSC activation and ECM production, at least in part, via inhibition of c-myb and rac1 expression[121]. In contrast, several miRNAs such as miR-29, miR 19b, miR-146a, and miR-133a are markedly downregulated in HSCs isolated from experimental animals with liver fibrosis, and restoration of these miRNAs attenuates hepatic fibrogenesis[30,122,123].

It is now thought that miRNAs can serve as biomarkers for HSC activation and liver fibrosis progression, and may represent therapeutic targets for hepatic fibrosis and cirrhosis.

ANIMAL MODELS OF LIVER FIBROSIS AND CIRRHOSIS

Animal models are crucial to understanding the pathogenesis and development of therapeutic strategies for liver fibrosis and cirrhosis. So far, many types of animal model have been developed in mice, rats, rabbits, and pigs to mimic the complicated process of fibrosis and cirrhosis. Animal models of liver fibrosis and cirrhosis can be induced by one of the following approaches: (1) Fibrosis induced by chemical compounds and toxins. These agents cause direct injury to hepatocytes and trigger secondary inflammatory reaction in the liver, which in turn activate HSCs and result in fibrosis. Commonly used chemical agents include CCl_4[124-126], thioacetamide[127,128] dimethylnitrosamine[129,130], dioxin[131], sodium arsenate[132], and ethanol[126,133,134]. These agents can be administered to experimental animals alone or in combination; (2) Special diet, such as choline-deficient, *L*-amino acid-defined, methionine-deficient diet[89,135,136], and high-fat diet[134,137,138]. Animals develop NAFLD and cirrhosis when they are fed these diets alone or in combination with other chemical agents; (3) Physical methods. Bile duct ligation creates obstruction of the extrahepatic bile duct[139,140], leading to cholestasis and subsequent injury to biliary epithelial cells and hepatocytes, infiltration of inflammatory cells in the portal area, fibrous tissue proliferation, and formation of liver fibrosis; (4) Fibrosis induced by immune reaction. Antigen-antibody complexes can provoke type Ⅲ hypersensitive reactions. Deposition of immune complexes in the portal area and around the central vein area causes allergic reaction and inflammation, stimulating HSCs to secrete collagen, and fibrosis formation. Common immunogens include plant protein concanavalin A[141] and xenogenic serum[142,143], such as serum from pigs, cattle, humans, and schistosoma. It was reported that 85.5% of rats immunized with subcutaneous injection of human serum albumin develop liver fibrosis and cirrhosis[144]. Similarly, injection of the excretory-secretory (ES) antigens of *Ascaris suum* into golden hamsters also successfully induces hepatic fibrosis[144]; and (5) Genetic modification. Forced overexpression of critical profibrotic genes and/or silencing of antifibrotic genes has been shown to induce cirrhosis in animals. For example, high-speed intravenous injection of naked plasmid DNA of TGF-β1 can induce transient and reversible liver fibrosis in mice[145]. Mice with liver-specific deletion of CYLD exon7/8 [CYLD(FF)xAlbCre] exhibit a prominent biliary phenotype with ductular reaction and biliary-type fibrosis[146].

THERAPY OF LIVER FIBROSIS AND CIRRHOSIS

Recent developments in our understanding of the process of hepatic fibrogenesis have revealed that the process is dynamic and reversible. Animal and clinical evidence has confirmed that any degree of fibrosis and even cirrhosis are potentially reversible by reasonable therapeutic strategies[147-149]. At present, the therapeutic strategies for liver fibrosis include the following.

Therapies to eliminate the etiological factors

Removing the etiological factors is the most direct and perhaps most effective method of treating liver fibrosis. As such, treatments against HBV and HCV infections[150,151], abstinence from alcohol abuse, weight and blood lipid control, chelation of overloaded iron and copper[152] are considered potentially effective therapies for a large proportion of liver fibrosis cases. In particular, the commonly used antiviral agents such as IFN-α, ribavirin, lamivudine, adefovir, entecavir, and especially pegylated IFN-α have been shown to exert antifibrotic effects[91,151,153-156].

Anti-inflammatory and immunosuppressive therapies

Intrahepatic inflammation and immune response are direct causes of injury to hepatocytes and activation of HSCs. Therefore, anti-inflammatory and immunosup-

pressive therapies are important measures to inhibit fibrogenesis, especially for fibrosis and cirrhosis resulting from viral hepatitis, autoimmune hepatitis, and primary sclerosing cholangitis. The anti-inflammatory drug celecoxib[157] and antioxidative agents taurine and vitamin E[158,159] all show some degree of antifibrotic effect. Likewise, glucocorticoids, azathioprine[160], colchicines[161] and rapamycin[162,163] appear to exert anti-inflammatory, antifibrotic and immunomodulatory effects, and therefore may potentially be useful in the treatment of liver fibrosis.

Suppressing activation and promoting apoptosis of HSCs

HSCs play a critical role in hepatic fibrogenesis, and therefore are potential target cells of antifibrotic therapy[164]. As such, inhibition of HSC activation is an attractive therapeutic approach for liver fibrosis. Inactivation of HSCs can be achieved by inhibiting the TGF-β1 signaling pathway and PDGF-B[165-167], and activated HSCs can be removed by inducing these cells to undergo apoptosis[27,31,164]. Some cytokines and growth factors such as insulin-like growth factor-1, IFN-α and IFN-γ have been found to induce apoptosis of HSCs[90,96,168]. Inhibitors of IκB kinase has also been shown to promote apoptosis of HSCs and exert antifibrotic effectd[31]. Other pharmacological agents such as gliotoxin, sulfasalazine, benzodiazepine ligands, curcumin and tanshinone I have been explored for their effects in inducing HSC apoptosis[27].

Protect liver function and promote hepatocyte regeneration

The hepatoprotective agent silymarin has been widely used in the management of chronic liver diseases and cirrhosis[129,169]. Ursodeoxycholic acid and tauroursodeoxycholic acid have shown protective effects against hepatocyte organelle injury, and have been confirmed as effective agents for the treatment of primary sclerosing cholangitis[170,171]. Calcium channel blockers (*e.g.*, verapamil) also show hepatoprotective and antifibrotic effects by stabilizing the hepatic cellular membrane[172] and lowering the portal vein pressure.

Hepatocyte apoptosis is a common event in liver injury and contributes to fibrogenesis and development of cirrhosis. Hence, preventing the hepatocytes from undergoing apoptosis and promoting hepatocytes regeneration can be useful therapeutic strategies for liver fibrosis and cirrhosis. Hepatocyte growth factor (HGF), an antifibrotic growth factor that induces apoptosis in HSCs and stimulates hepatocyte regeneration[173,174], has been attempted as a therapeutic agent for liver cirrhosis. In this respect, infusion of bone-marrow-derived cells and mesenchymal cells have been reported as a potentially effective method for the treatment of liver cirrhosis[175-177], because these cells can differentiate into hepatocyte-like cells in the liver and stimulate proliferation of hepatocytes by secreting some growth factors such as HGF. Furthermore, HGF-overexpressing human umbilical-cord-blood-derived mesenchymal stem cells have shown promising therapeutic effects on liver fibrosis[178].

Gene therapy and targeted therapy

Several critical genes implicated in the pathogenesis of liver cirrhosis such as TGF-β, PDGF-β, CTGF, and TIMP have been investigated as therapeutic targets for liver cirrhosis[179]. Antisense oligonucleotides[167,180,181] and siRNAs[182-184] against these genes have been tested *in vitro* and *in vivo*. Recently, miRNA has been found to play a regulatory role in the pathogenesis of liver fibrosis and cirrhosis through regulating the expression of profibrotic or antifibrotic genes, and influencing the proliferation and activation of HSCs. As such, miRNA-based therapy can potentially be useful for the treatment of liver fibrosis[185]. Furthermore, in order to target more directly the fibrogenic cells, attempts have been made to target the receptors of the profibrogenic proteins expressed on HSCs[184,186,187].

Complementary and alternative medicine

Evidence indicates that some traditional Chinese herbal medicines are effective in the treatment of liver fibrosis and cirrhosis, and have thus gained popularity worldwide[188,189]. These herbal medicines include the following categories: pure compounds (*e.g.*, salvianolic acid B[190] and oxymatrine[143]). The mechanisms by which tetrandrine[191], glycyrrhetinic acid[192] and curcumin[193]), single agents (*e.g.*, *Salvia miltiorrhiza*[194] and *Ganoderma lucidum*[195]), and composite formulae (*e.g.*, Fuzheng Huayu Capsule[196], Biejiajian[197], Yi-Gan-Kang granule[198] and Qinggan Huoxuefang[199]). Chinese herbal medicines exert antifibrotic effect are far from clear but may include antiviral and anti-inflammatory effects, immune regulation, inhibition of HSC activity, and promotion of collagen degradation. Further randomized controlled clinical trials are needed and the possible adverse effects should be carefully evaluated.

CONCLUSION

In summary, the etiology of cirrhosis is multifactorial and the mechanisms underlying pathogenesis of cirrhosis are far from being clarified. Further studies, particularly with appropriate animal models, to unveil the molecular mechanisms leading to liver fibrosis and cirrhosis are essential for the development of effective therapeutic approaches.

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