REVIEW

Liver fibrosis and hepatic stellate cells: Etiology, pathological hallmarks and therapeutic targets

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Abstract

Liver fibrosis is a reversible wound-healing process aimed at maintaining organ integrity, and presents as the critical pre-stage of liver cirrhosis, which will eventually progress to hepatocellular carcinoma in the absence of liver transplantation. Fibrosis generally results from chronic hepatic injury caused by various factors, mainly viral infection, schistosomiasis, and alcoholism; however, the exact pathological mechanisms are still unknown. Although numerous drugs have been shown to have antifibrotic activity *in vitro* and in animal models, none of these drugs have been shown to be efficacious in the clinic. Importantly, hepatic stellate cells (HSCs) play a key role in the initiation, progression, and regression of liver fibrosis by secreting fibrogenic factors that encourage portal fibrocytes, fibroblasts, and bone marrow-derived myofibroblasts to produce collagen and thereby propagate fibrosis. These cells are subject to intricate cross-talk with adjacent cells, resulting in scarring and subsequent liver damage. Thus, an understanding of the molecular mechanisms of liver fibrosis and their relationships with HSCs is essential for the discovery of new therapeutic targets. This comprehensive review outlines the role of HSCs in liver fibrosis and details novel strategies to suppress HSC activity, thereby providing new insights into potential treatments for liver fibrosis.

Key words: Liver cirrhosis; Fibrosis; Hepatic stellate cells; Etiology; Pathology; Treatment

Core tip: This review discusses the molecular mechanisms of liver fibrosis with respect to hepatic stellate cells (HSCs). In particular, we describe the functional significance of HSCs with respect to major events triggering fibrosis and novel therapeutic strategies to suppress the activity of activated HSCs.

INTRODUCTION

Liver fibrosis is a complex fibrogenic and inflammatory process that results from chronic liver injury and represents an early step in the progression of liver cirrhosis. Cirrhosis is a major health problem worldwide, owing to the lack of effective treatment methods[1,2]. During hepatic fibrosis, continuous accumulation of extracellular matrix (ECM) extremely rich in collagen I and III leads to scar deposition and liver fibrosis[3,4]. When left untreated, this condition can develop into cirrhosis and subsequent portal hypertension, hepatic encephalopathy, and/or liver failure, and lead to an increased risk of hepatocellular carcinoma (HCC), which can ultimately cause organ failure and death[2,4]. Liver transplantation is currently regarded as the only treatment method for cirrhosis and is generally inadequate[3]. During chronic liver disease, ongoing liver injury results in excessive ECM deposition with limited remodeling, which inevitably leads to scarring and fibrosis[5]. In comparison, the liver can quickly reestablish its structural integrity in response to acute injury, even when a substantial portion of the organ is damaged[6].

Hepatic stellate cells (HSCs) localize to the perisinusoidal space between hepatocytes and sinusoidal endothelial cells and are the primary source of activated myofibroblasts and portal fibroblasts that drive the fibrogenic process[7]. Quiescent HSCs (qHSCs) mostly function as vitamin A reserves[8]. In response to liver injury, inflammatory mediators promote HSC activation and subsequent differentiation into myofibroblasts[9]. Activated HSCs (aHSCs) are a major source of collagen in the liver and can abundantly secrete ECM proteins, tissue inhibitors of metalloproteinases, and matrix metalloproteinases (MMPs) that elicit liver architecture remodeling[9,10]. Importantly, HSCs are responsible for as much as 80% of total fibrillar collagen I in the fibrotic liver[8-11]; thus, aHSC depletion is critical for the resolution of fibrosis.

Based on these findings, we provide a comprehensive review summarizing the etiology and pathological characteristics of hepatic fibrosis, and detail the potential therapeutic targets for suppression of aHSC function.

ETIOLOGY AND PATHOLOGICAL CHARACTERISTICS OF HEPATIC FIBROSIS

Liver fibrosis is a complex process that results from various forms of chronic hepatic disease and is associated with excess hepatocellular death[2,12,13]. The main etiologies of liver fibrosis are schistosome and chronic viral hepatitis infection, nonalcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), and cholestatic and autoimmune liver disease[1,14-17]. Liver fibrosis, which is characterized by the excessive deposition ECM proteins[18], involves both parenchymal and nonparenchymal hepatic cells, as well as infiltrating immune cells[3,19]. Furthermore, different organs, such as the adipose tissue, bile duct, intestine, and muscle, can also affect the development of liver fibrosis. Moreover, several essential signaling pathways have important roles in fibrosis. The complex interactions among these signaling pathways, diverse cells, and different organs contribute to the progression of liver fibrosis[20]. Upon fibrogenic initiation, qHSCs differentiate into aHSCs, upon which they lose the intracellular lipid droplets and acquire a myofibroblastic phenotype characterized by marked upregulation of a-smooth muscle actin (a-SMA, ACTA2), desmin (DES), and type I collagen (COL1A1)[8-10]. The sustained buildup of collagens distorts the liver parenchyma and vascular architecture, resulting in impaired liver function, scar deposition, and liver fibrosis[1,2,12,14,17]. The initiation, progression, and resolution of liver fibrosis involving HSCs are present in Figure 1.

Viral and schistosome infection

Viral infections such as those caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) induce hepatic inflammation and thereby contribute to the cyclical process of inflammation, necrosis, and regeneration[21]. Within this inflammatory microenvironment, continuous infiltration of immune cells and secreted inflammatory cytokines leads to liver injury, triggering a progressive cascade of hepatic lobule reconstruction that promotes liver fibrosis and cirrhosis[22].

Schistosomiasis is a major chronic disease that occurs in humans living in endemic regions, owing to substantial pathologic liver fibrosis caused by from an accumulation of parasitic eggs[23]. Ongoing antigenic stimulation from the trapped ova results in immune cell recruitment to the sites of infection, leading to the formation of periovular granulomas and eventual fibrosis[24]. Liver fibrosis often begins 6 wk after infection, when the Th2 immune response predominates
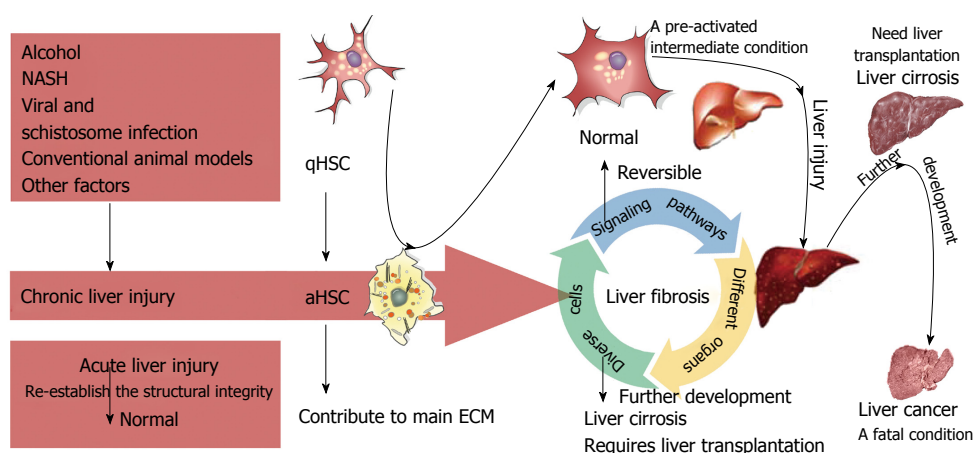
Figure 1 Initiation, progression, and resolution of liver fibrosis involving hepatic stellate cells. Upon various types of chronic injury - including that caused by alcohol, viral and schistosome infection, nonalcoholic steatohepatitis (NASH), and other factors - hepatic stellate cells (HSCs) transdifferentiate from quiescent HSCs to activated HSCs, the latter of which secrete abundant extracellular proteins that contribute to liver fibrosis. Liver fibrosis is thought to be a reversible condition owing to the elimination of causative agents and different strategies of limiting HSC activation; however, they cannot totally return to a quiescent status of the naive HSCs. Instead, they exhibit a pre-activated intermediate condition with an increased sensitivity to injury. Thus, preventing recurrent chronic liver injury is of great importance in patients undergoing treatment for liver fibrosis. Untreated or relapsed fibrosis progresses to liver cirrhosis, which often requires hepatic transplantation.

and subsequently subsides at 12 wk postinfection. The Th17 response has also been associated with severe hepatic inflammation; however, the function of B cells in schistosome-induced pathology remains controversial. Because immune cell-derived chemokines play a vital role in schistosome-induced pathology[25,26], one method to hamper disease progression could be by modulating chemokine production to limit hepatic eosinophil recruitment[27]. Importantly, although praziquantel therapy effectively kills adult *Schistosoma*, it has diminutive effects on liver fibrogenesis or portal hypertension[28,29]; thus, new strategies to treat schistosomiasis are urgently needed.

Alcohol

Excessive alcohol abuse causes steatohepatitis that can progress to ALD. Most patients are generally asymptomatic, and ALD is easily reversible when patients abstain from alcohol consumption. Otherwise, they will develop into liver fibrosis. Acetaldehyde is regarded as a major intermediate in alcohol-induced fibrogenesis[30,31], and recent studies have delineated the mechanisms through which transforming growth factor (TGF)-β/small mother against decapentaplegic (SMAD) signaling is enhanced by acetaldehyde[32]. Additionally, acetaldehyde-induced fibrogenesis is also thought to involve members of the basic transcription element binding protein[33,34], CAAT/enhanced-binding protein[35,36], and acetaldehyde-responsive element[37]. Cytochrome P450 2E1 (CYP2E1) protein is a member of the microsomal ethanol oxidizing system responsible for ethanol metabolism and is crucial for alcohol-induced fibrogenesis[38]. This mechanism is readily observed in hepatocyte and HSC cocultures with enhanced collagen Ⅰ protein synthesis resulting from CYP2E1-dependent reactive oxygen species generation[39]. Correspondingly, ethanol-mediated lipid peroxidation is effectively

blocked in *CYP2E1*^{-/-} mice[40], whereas oxidative stress and hepatic fibrogenesis is elevated in transgenic mice with CYP2E1 overexpression[41]. Moreover, the calcium regulatory protein osteopontin (OPN) has demonstrated protective effects in early alcohol-induced liver injury by binding lipopolysaccharide and blocking tumor necrosis factor-alpha (TNF-α) function in the liver[42]. OPN is also positively correlated with fibrosis in patients with ALD[43].

Nonalcoholic steatohepatitis

Nonalcoholic steatohepatitis (NASH) is a relatively common chronic liver disease with histological characteristics similar to that of ALD[44]. NASH presents as balloon-like hepatocellular injury with or without hepatic fibrosis in liver biopsies[45] and is the intermediate between NAFLD and cirrhosis[46]. NASH occurs when sustained oxidative stress prevents the proliferation of mature liver cells, resulting in excess necrosis and an overgrowth of liver progenitor cells (oval cells)[47]. In addition, the inflammatory response to cellular necrosis induces the progressive release of platelet-derived growth factor, TGF-β, TNF-α, and other inflammatory factors, such as interleukin (IL)-1, by resident immune cells[48]. These inflammatory signals result in the activation and proliferation of HSCs and induce differentiation of HSCs into myofibroblasts, further driving ECM synthesis and ultimately liver fibrosis[49].

Animal models of liver fibrogenesis

Liver fibrosis takes years to develop in most patients and results from an interplay of several risk factors, including HBV and HCV infection, alcohol abuse, and metabolic syndromes attributed to obesity, insulin resistance, and diabetes[50]. Accordingly, animal models used to study the pathophysiology of liver fibrosis,

cirrhosis, and HCC should mimic the general disease patterns found in human counterparts.

Currently, *in vivo* models of liver fibrosis can be divided into five categories based on etiology: chemical, dietary, surgical, genetically modified, and infection[51]. The chemicals commonly used to cause hepatic lesions and induce liver fibrosis include ethanol, carbon tetrachloride (CCl_4)[52], thioacetamide[53], dimethylnitrosamine[54], and diethylnitrosamine[55]. A number of specific diets, such as the methionine- and choline-deficient diet[56], high-fat diet[57], and choline-deficient ʟ-amino acid-defined diet[58], can be used to induce progression of NAFLD to hepatic fibrosis in experimental animals. Moreover, common bile duct ligation (BDL) can also lead to cholestatic injury and periportal biliary fibrosis[59]. In the past decade, multidrug resistance-associated protein 2-deficient ($Mdr2^{-/-}$) mice[60] and $Alms1^{foz/foz}$ fat Aussie mice[61] have been used to study the functional relevance of specific signaling pathways in the formation of liver fibrosis and identify novel drug targets. Finally, infections with HBV[62] and *Schistosoma* parasites[63] are also popular models of liver fibrosis.

NOVEL THERAPEUTIC TARGETS IN LIVER FIBROSIS

Liver fibrosis was once deemed irreversible; however, early liver fibrosis is now managed by clinical treatment, and overwhelming evidence suggests that advanced fibrosis may likely be reversible once the injurious stimulus is removed[64]. Since aHSCs are the primary mediators of liver pathology in this process, several molecules required for HSC activation are considered potential therapeutic targets[9,64,65]. The following section details recent novel targets identified for the treatment of liver fibrosis through suppression of HSC activation.

Key molecules in liver fibrosis

Mitra and colleagues reported that IL-30 attenuates hepatic fibrosis by inducing natural killer group 2D (NKG2D)/ribonucleic acid export 1 crosstalk between aHSCs and natural killer T (NKT) cells and is therefore an ideal therapy for liver fibrosis. Mechanistically, IL-30 treatment promotes surface NKG2D expression on liver NKT cells to subsequently enhance their cytotoxic activity towards aHSCs, thereby inhibiting liver fibrosis[66]. Another molecule, hydrogen peroxide-inducible clone-5 (Hic-5) is a TGF-β1-inducible focal adhesion protein that facilitates cell proliferation and ECM expansion in various organs[67]. Previous studies have shown that Hic-5 contributes to vascular restoration and restructuring[67,68]; however, a recent study revealed that Hic-5 expression also plays a critical role in attenuating fibrosis by enhancing TGF-β-induced Smad2 phosphorylation via the downregulation of Smad7 in both human and mouse aHSCs[69].

Taken together, these data indicate that Hic-5 is a novel therapeutic target and a potential marker of activated HSCs. Additionally, acyl-coenzyme A: cholesterol acyltransferase (ACAT) is comprised of two isoenzymes-ACAT1 and ACAT2-and functions as a catalyst to convert free cholesterol (FC) to cholesteryl esters[70]. FC accumulation has been shown to regulate HSC activation and the development of liver fibrosis by promoting Toll-like receptor 4 signal transduction. Because ACAT1 plays an essential role in regulating FC accumulation in HSCs[71], studies have focused on developing new ACAT1-directed therapeutic interventions for the treatment of liver fibrosis. The roles of IL-30, Hic-5, and ACAT1 in liver fibrosis are presented in Figure 2.

Regulatory CD4+ T cells

Regulatory T (Treg) cells function to modulate HCV-dependent liver fibrosis by regulating the interaction between NK cells and aHSCs[72,73]. Specifically, Treg cells act in a cell-contact-dependent manner to reduce NK cell activity against HSCs and downregulate vital NKT-activating ligands on HSCs by secreting soluble IL-8 and/or TGF-β1[73]. This mechanism may also be present in fibrosis, resulting from other etiologies; however, further studies are needed to confirm this hypothesis.

Macrophages

Macrophages, which can be classified as M1 (classically activated) macrophages and M2 (alternatively activated) macrophages, play dual roles in the progression and resolution of liver fibrosis. Typically, M1 macrophages produce inflammatory cytokines, whereas M2 macrophages regulate inflammatory responses and tissue repair. The imbalance of M1 and M2 macrophages mediates the progression and resolution of liver fibrosis[74]. During the early stages of liver injury, bone marrow-derived monocytes are extensively recruited to the liver and then differentiate into inflammatory macrophages (mostly M1 macrophages) to produce pro-inflammatory and profibrotic cytokines, thereby promoting inflammatory responses and HSC activation. Afterwards, recruited macrophages switch their phenotypic (mostly M2 macrophages) to secrete MMPs, the main enzymes degrading ECM, to facilitate fibrosis resolution[20,75,76].

Role of signal transduction in the progression of liver fibrosis

Several intracellular signaling pathways are involved in the pathophysiology of liver fibrosis. In this section, we detail the functional significance of three key signaling axes in this process: Gas6/Axl, TGF-β/Smad, and target of Wnt signaling pathway (Figure 3).

Gas6/Axl pathway: The TAM (Tyro3, Axl, Mer) receptor ligand Gas6 is a vitamin K-dependent protein with an extremely high affinity for the Axl receptor.
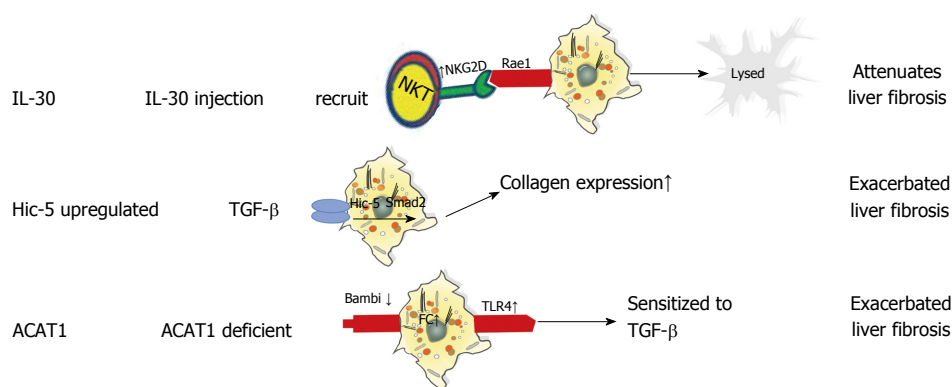
Figure 2 Roles of interleukin-30, hydrogen peroxide inducible clone 5, and cholesterol acyltransferase 1 in liver fibrosis.
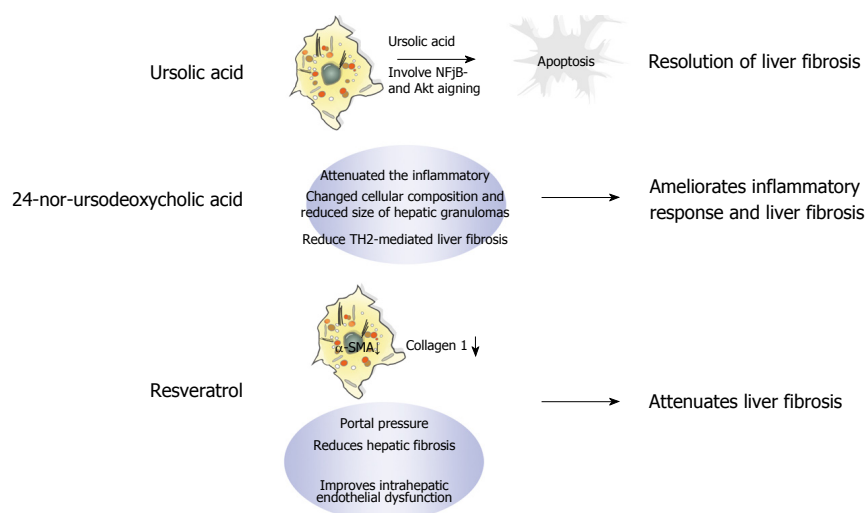

Figure 3 Roles of the Wnt, TGF-β/Smad, and Gas6/Axl signaling pathways in the progression of liver fibrosis.

Gas6 is primarily expressed by Kupffer cells, whereas Axl is found in both macrophages and qHSCs in the normal liver[77,78]. Study has demonstrated that CCl4-induced liver fibrosis elicits Gas6/Axl pathway activation to promote HSC activation. Notably, Axl knockout disrupts this pathway, thereby attenuating hepatic fibrosis[78]. Clinical trials have also shown increased Gas6 and Axl serum levels in patients with HCV infection and ALD[78]. As such, targeting Axl may be a potential method to remediate liver fibrosis.

TGF-β/Smad signaling: TGF-β regulates ECM metabolism and tissue fibrosis through the overproduction of type Ⅰ collagen in both mice and humans. Recent studies have demonstrated that TGF-β/Smad signaling plays a crucial role in the progression of hepatic fibrosis caused by parasitic infection, including *Schistosoma*, *Clonorchis sinensis*, and *Echinococcus multilocularis*, as well as other etiological factors[79,80]. More specifically, TGF-β1 ligation to TGF-β type Ⅰ (TGFβRI) and type Ⅱ receptors induces Smad2/3 phosphorylation and its subsequent interaction with Smad4. The Smad2/3/4 complex can then translocate to the nucleus and induce the expression of profibrotic genes, namely

collagen type Ⅰ. Strikingly, Smad7 can block TGF-β signaling through various means[80-82], such as binding TGFβRI to inhibit the interaction-dependent activation of Smad2, collaborating with other effectors to induce TGFβRI degradation, and regulating the Wnt/β-catenin pathway to influence TGF-β-induced apoptosis[83]. Similarly, targeting of Smad7 enhances TGF-β pathway activation[84].

Wnt pathway: Several studies have demonstrated that aberrant Wnt/β-catenin signaling affects the progression of fibrotic disorders. Wnt comprises an evolutionarily conserved family of excreted lipid-modified glycoproteins that can be classified into at least three signaling pathways: Necdin-Wnt, noncanonical (β-catenin-independent), and canonical (β-catenin-dependent). In the Necdin-Wnt pathway, HSC activation and differentiation require the down-regulation of peroxisome proliferator-activated receptor γ (PPARγ). Necdin is a melanoma antigen family protein preferentially expressed in aHSCs that promotes myogenic and neuronal differentiation while suppressing adipogenesis. Notably, Necdin silencing restores PPARγ-mediated Wnt pathway inhibition to

effectively reverse HSC activation[85,86]. In the canonical pathway, Wnt ligation to cell surface receptors elicits downstream signaling that stabilizes β-catenin, which can then translocate into the nucleus, bind T cell factor/lymphoid enhancer-binding factor (TCF/LEF) promoter, and induce gene expression to exert biological effects[87,88]. Alternatively, noncanonical Wnt signaling occurs *via* the β-catenin-independent planar cell polarity and noncanonical Wnt/Ca^{2+} pathways. Thus, a collective understanding of Wnt signaling mechanisms may provide novel insights into the pathophysiology of liver fibrosis. A recent study also showed that DKK2 (a Wnt antagonist and target of the Wnt pathway) connects Sept4 (a subunit of the septin cytoskeleton expressed in qHSCs) and the activation of HSCs, thereby mediating the progression of liver fibrosis. The expression of DKK2 is high in primary cultured HSCs. However, DKK2 expression is reduced when Sept is not expressed in a mice model of CCL4-induced fibrosis. The high expression of DKK2 in qHSCs inhibits Wnts and thereby affects downstream β-catenin signaling. This results in suppression of the Wnt signaling pathway, leading to increased expression of Sept4 and preventing HSC activation[87].

HAb18G/CD147: HAb18G/CD147 is induced by TGF-β1 stimulation and is highly expressed on sinusoidal aHSCs, where it colocalizes with a-SMA. Transient transfection of CD147 in LX-2 cells results in increased expression of mRNAs encoding α-SMA, TIMP-1, α1(I) collagen, and TGF-β1. In contrast, MMP-13 and MMP-2 levels are markedly reduced, suggesting that HAb18G/CD147 promotes HSC activation. Consistent with this, HAb18G/CD147-targeting antibodies block HSC activation, thereby inhibiting liver fibrogenesis[89]. These data support the potential role for HAb18G/CD147 in liver fibrosis; however, further studies are needed to confirm these findings.

microRNAs and HSCs in liver fibrosis

Recently, microRNAs (miRNAs) have also been found to play multifaceted roles in hepatic fibrosis, including those in HSC activation and proliferation and production of ECM proteins[3,11]. Previous studies have indicated that human and murine miRNAs participate in liver fibrosis. For example, *miR-199a*, antisense *miR-199a**, *miR-200a*, and *miR-200b* are dramatically upregulated in a mouse model of liver fibrosis[90]. Conversely, the *miR-29* family is downregulated in aHSCs when compared with that in qHSCs, both *in vivo* and *in vitro*[91].

miR-133a is specifically downregulated in HSCs during fibrogenesis, but is overexpressed in primary murine HSC, resulting in attenuation of collagen expression[91]. Similarly, CCL4-induced *miR-122* expression is markedly lower in aHSCs and fibrotic liver tissue. Cell experiments have also shown that *miR-133a* overexpression inhibits both LX2 and primary murine HSC proliferation and prevents the progression

of liver fibrosis[92-94]. Furthermore, both *miR-15b* and *miR-16* facilitate qHSC apoptosis by targeting Bcl-2 and the caspase signaling cascade[95].

Promising therapies for liver fibrosis

Although several antifibrotic drug candidates have recently been evaluated, these drugs have failed to show increased therapeutic efficacy over those drugs currently used in the clinic, *e.g.*, ursolic acid (UA), 24-nor-ursodeoxycholic acid (norUDCA), and resveratrol. UA is a pentacyclic triterpenoid compound with a wide spectrum of pharmacological activities found in various edible fruits and medicinal plants. Studies have demonstrated that UA induces apoptotic culture-activated HSC death due to inhibition of nuclear factor kappa B and AKT in HSCs, but not in isolated qHSCs *in vitro*. In addition, UA alleviates liver fibrosis induced by both BDL and chronic thioacetamide administration *in vivo*. As shown in Figure 4, the mechanism of UA-induced apoptosis may be attributed to its suppression of cell survival pathways and the activation of downstream caspases via the mitochondrial permeability transition[96].

The bile acid derivative norUDCA is a promising new treatment option for liver fibrosis that significantly reduces liver fibrosis in chronically infected *Schistosoma mansoni* mice by limiting T-cell proliferation and IL-13 and IL-4 serum levels (Figure 4). Moreover, norUDCA has anti-inflammatory properties demonstrated by the low expression of MHC class Ⅱ on dendritic cells and macrophages after norUDCA treatment[28].

Finally, the natural polyphenol flavonoid resveratrol has a broad range of beneficial biological functions, including anti-inflammatory[97] and antioxidant[98] properties[99]. In addition, resveratrol is believed to ameliorate obesity-related complications by mimicking caloric restriction[100] through activation of key metabolic regulators, including NAD$^+$-dependent deacetylase (SIRT1)[101], AMP-activated protein kinase[102], and nuclear factor erythroid-2 related factor 2[103]. Furthermore, oxidative damage and inflammation are closely related to the HSC activation process. For example, SIRT1 activation inhibits the expression of muscle-related genes, such as *MyoD*[104]. Moreover, studies have demonstrated the beneficial effects of resveratrol in different models of liver steatosis[105-108]. Superoxide dismutase activity is necessary for the reduction of oxygen free radicals and protects against lipid peroxidation, thereby inhibiting HSC activation and limiting the progression of liver fibrosis[109]. The mechanisms through which resveratrol alleviates fibrosis are shown in Figure 4. Although resveratrol has been shown to have beneficial biological functions in the antifibrotic response, its efficacy in NAFLD is insignificant; indeed, a meta-analysis conducted by Zhang *et al*[110] indicated that resveratrol can only improve LDL and total cholesterol levels in patients with NAFLD.
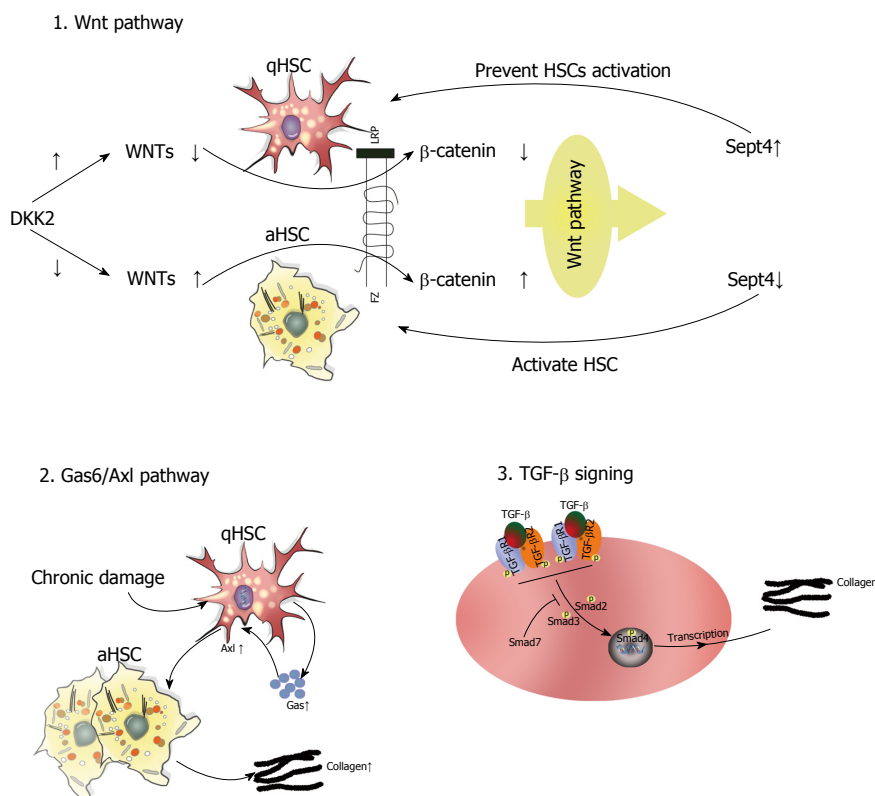
Figure 4 Mechanism of action of three potential therapeutic drugs-ursolic acid, 24-nor-ursodeoxycholic acid, and resveratrol-for treating fibrosis.

CONCLUSION

In this review, we outlined some major etiological and pathological characteristics of hepatic fibrosis and described several promising approaches for liver fibrosis therapy. We strongly believe that liver fibrosis will be cured through the combined application of these therapeutics; however, further studies are necessary to support this hypothesis.

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