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TOPIC HIGHLIGHT

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Cellular and molecular mechanisms in the pathogenesis of liver fibrosis: An update

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Abstract

There have been considerable recent advances towards a better understanding of the complex cellular and molecular network underlying liver fibrogenesis. Recent data indicate that the termination of fibrogenic processes and the restoration of deficient fibrolytic pathways may allow the reversal of advanced fibrosis and even cirrhosis. Therefore, efforts have been made to better clarify the cellular and molecular mechanisms that are involved in liver fibrosis. Activation of hepatic stellate cells (HSCs) remains a central event in fibrosis, complemented by other sources of matrix-producing cells, including portal fibroblasts, fibrocytes and bone marrow-derived myofibroblasts. These cells converge in a complex interaction with neighboring cells to provoke scarring in response to persistent injury. Defining the interaction of different cell types, revealing the effects of cytokines on these cells and characterizing the regulatory mechanisms that control gene expression in activated HSCs will enable the discovery of new therapeutic targets. Moreover, the characterization of different pathways associated with different etiologies aid in the development of disease-specific therapies. This article outlines recent advances regarding the cellular and molecular mechanisms involved in liver fibrosis that may be translated into future therapies. The pathogenesis of liver fibrosis associated with alcoholic liver disease, non-alcoholic fatty liver disease and viral hepatitis are also discussed to emphasize the various mechanisms involved in liver fibrosis.

Key words: Liver; Liver fibrosis; Cirrhosis; Fibrogenesis; Hepatic stellate cells; Myofibroblast; Extracellular matrix

Core tip: Liver fibrosis is a dynamic process that results from an imbalance between the production and dissolution of the extracellular matrix. Development of liver fibrosis is orchestrated by many cell types, including hepatic stellate cells (HSCs). The activation of HCSs is a complex process, leading to multiple potential sites for therapeutic interventions. Additionally, the differences between the pathogenesis of liver fibrosis associated with different etiologies may provide the determination of new therapeutic approaches. This review summarizes the most significant data that has contributed to the understanding of the cellular and molecular pathogenesis of liver fibrosis, which may be translated into future therapeutic strategies.

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INTRODUCTION

Liver fibrosis is a common pathological consequence of a variety of chronic stimuli, including viral, autoimmune, drug induced, cholestatic and metabolic diseases[1-4]. Liver fibrosis can be defined as a result of the progressive accumulation and decreased remodeling of the extracellular matrix (ECM), which disrupts the normal architecture of

the liver[2]. If left untreated, fibrosis can progress to liver cirrhosis, ultimately leading to organ failure and death. The characterization of the underlying mechanisms of liver fibrogenesis has indicated that fibrosis is driven by a dynamic process involving the increased synthesis of matrix components and a failure of physiological mechanisms of matrix turnover. Moreover, the capacity of the liver to undergo fibrosis regression following cessation of the liver insult has been highlighted[4-6]. These findings have provided progressed the understanding of the pathogenesis of chronic liver diseases and have presented opportunities for novel therapeutic approaches for the management of liver fibrosis.

This review presents key advances in the new insights into the cellular and molecular mechanisms that regulate liver fibrosis, which may represent future therapeutic targets.

ECM IN LIVER FIBROSIS

During chronic liver injury, an increase of fibril-forming collagen and the replacement of the low density, basement membrane-like interstitial matrix occurs[4,6,7]. There is also an accumulation of other matrix proteins, including elastin, hyaluronan, proteoglycans and fibronectin. This type of matrix has the capacity to activate quiescent HSCs, leading to the loss of hepatocyte microvilli and the disappearance of endothelial fenestrations (Figure 1)[4,7,8]. This architectural change of endothelial cells also impairs the transport of solutes from the sinusoid to the hepatocytes, further contributing to hepatocyte dysfunction[7]. Moreover, the accumulation of ECM itself provokes positive feedback pathways that further amplify fibrosis[8]. The alteration of ECM proteins influences cellular behavior *via* cell membrane receptors. The most potent proteins are integrins that permit communication between the ECM and the cytoskeleton[9-11]. Patsenker *et al*[11] demonstrated that the inhibition of integrin alpha-V-beta slows the progression of biliary fibrosis and suggested that this inhibition could have potential therapeutic utility.

ECM remodeling is critical in the preservation of homeostasis during liver injury. This homeostasis depends on the fine balance between matrix metalloproteinases (MMPs) and their inhibitors, tissue inhibitors of matrix metalloproteinases (TIMPs). While the excessive increase in the ECM is controlled by MMPs (especially MMP-1, 2, 8 and 13), progressive fibrosis is correlated with the marked increase of TIMPs (TIMP-1 and TIMP-2)[12,13]. Moreover, because TIMP-1 has also anti-apoptotic effects on HSCs, it induces fibrogenesis by promoting fibrogenic cell survival. Several studies have reported that the regulation of TIMPs in HSCs may accelerate the elimination of fibrotic liver tissue and the reversal of fibrosis[14,15]. Enhancing the degradation of excess ECM by increasing the activity of MMPs or decreasing that of TIMPs is an additional approach in the development of antifibrotic drugs.

Angiogenesis is another response to chronic liver injury that leads to sinusoidal remodeling and pericyte amplification[16-18]. Consequently, many potent angiogenic mediators are involved in the exaggerated wound healing response to chronic liver injury, leading to an excessive accumulation of ECM[17,18]. The ECM can also affect cell function indirectly by releasing cytokines. These include transforming growth factor β (TGF-β), platelet derived growth factor (PDGF), hepatocyte growth factor (HGF), connective tissue growth factor (CTGF), tumor necrosis factor-α (TNF-α), basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF)[19].

CELL TYPES INVOLVED IN THE PATHOGENESIS OF LIVER FIBROSIS

Although the cellular source of ECM components in fibrotic liver has been a matter of controversy for many years, recent investigations have revealed that ECM accumulation during chronic liver injury is driven by a heterogeneous population of cells. Currently, it is accepted that liver fibrogenic cells (myofibroblasts) play a central role during liver fibrosis. Their origin has been extensively studied, and several sources of myofibroblasts (MFs) have been identified[3,20-27]. Because HSCs are the main ECM-producing cells in the injured liver[20] they are currently considered to be the major source of MFs[3,20-22]. Hepatic MFs may also originate from portal fibroblasts and bone marrow derived mesenchymal cells[24,28]. Two other minor contributors of fibrogenic cells are the epithelial-mesenchymal transition (EMT)[29,30] and endothelial to mesenchymal transition (Figure 2)[31,32].

HSCs

Activation of HSCs is recognized as a central event during liver fibrosis, and the molecular mechanisms of this cellular alteration continue to attract increasing attention, creating many new findings[33,34]. However, there is limited knowledge about HSC activation from the viewpoint of cell fate or lineage regulation[35-37]. Recently, many studies have shown that HSCs are derived from mesodermal-derived multipotent mesenchymal progenitor cells (MMPC), which also give rise to neural cells and other mesenchymal cells[38,39]. Supporting these findings, HSCs also express neural and mesenchymal lineage markers. Because cell types derived from MMPC may undergo transdifferentiation within their lineages, the notion that HSC transdifferentiation may reside in these mesenchymal lineages is reasonable[39]. In normal liver tissue, HSCs exist in a quiescent state, storing retinoids and synthesizing glial fibrillary acidic protein (GFAP)[40-43]. Following liver injury, HSCs are activated with a gradual loss of retinoids and GFAP, leading to a reduction in the expression of adipogenic/lipogenic factors. Meanwhile, a complex network of autocrine/paracrine fibrogenic signals promotes the transdifferentiation of HSCs to a myofibroblastic phenotype.

Portal fibroblasts

Portal fibroblasts are spindle shaped cells of mesenchy-

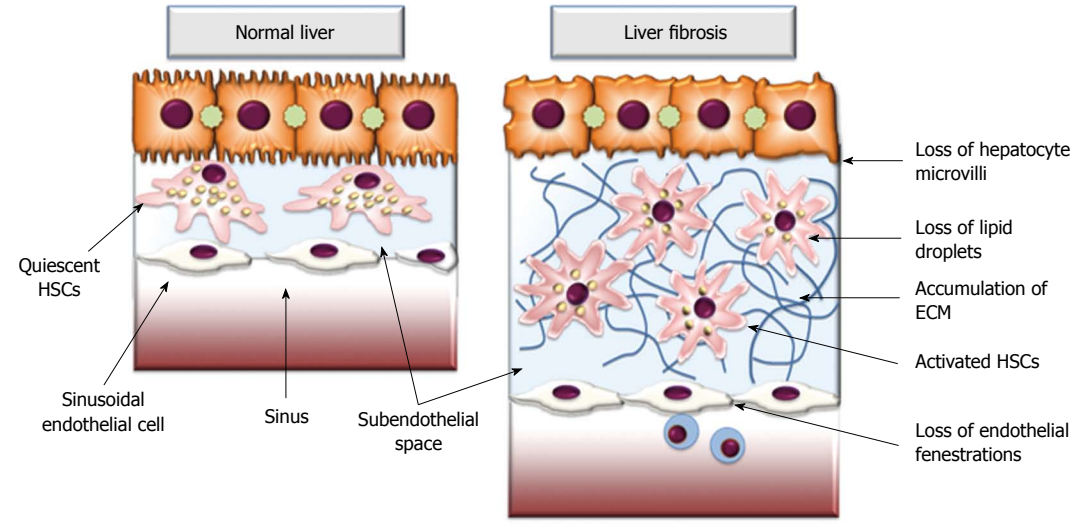

Figure 1 Extracellular matrix accumulation in subendothelial space activates quiescent hepatic stellate cells leading to the loss of hepatocyte microvilli and disappearance of endothelial fenestrations. These architectural changes impair transport of solutes from the sinusoid to the hepatocytes, further contributing to the hepatocyte damage. ECM: Extracellular matrix; HSCs: Hepatic stellate cells.

mal origin that undergo myofibroblastic differentiation, primarily in biliary and cholestatic liver injuries[44-46]. Although they possess biological similarities with activated HSCs, portal fibroblasts have different genetic profiles and signaling responses[45,46]. The latter could enable the development of disease specific antifibrotic therapies targeting these cells.

Fibrocytes

Fibrocytes originate from hematopoietic stem cells and have the ability to differentiate into MFs. In cases of tissue damage, fibrocytes proliferate and migrate to the injured organ and secrete growth factors that promote deposition of the ECM[47-49]. Several studies have suggested that the extent of fibrocyte differentiation into MFs depends on the organ and the type of injury[48,49]. Other studies have demonstrated that liver injury induces migration of fibrocytes to lymphoid organs[49], suggesting that the function of these cells may not be limited to ECM deposition.

Bone marrow-derived MFs

A fraction of hepatic MFs can also arise from bone marrow-derived mesenchymal stem cells (MSCs), which are defined as multipotent progenitor cells with the capacity to differentiate into lineage-specific cells[44,48,49]. Currently, it is not clear whether circulating MSCs significantly contribute to ECM deposition in the course of liver fibrosis or not, but they most likely represent a population that is distinct from hematopoietic-derived fibrocytes[49].

EMT

EMT is a process during which fully differentiated epithelial cells undergo phenotypic transition to fully differentiated mesenchymal cells. Liver cell culture studies have shown that hepatocytes and cholangiocytes may undergo EMT and acquire mesenchymal features, including FSP-1 expression[50-52]. However, more recent reports provide strong evidence against EMT in the liver as a source of MFs, convincingly arguing for an epithelial origin of ECM-producing cells[52,53].

HSCS IN LIVER FIROSIS

During liver fibrogenesis, parenchymal injury and the resulting inflammatory reaction generate a large panel of signals that stimulate the induction of specific transcription factors and morphogens in quiescent HSCs, thereby initiating the activation and the acquisition of fibrogenic and proinflammatory properties. Sustained activation leads to discrete changes in hepatic stellate cell (HSC) behavior, including proliferation, chemotaxis, fibrogenesis, contractility, retinoid loss and WBC chemoattractant/cytokine release[1]. In these phases there is a release of proinflammatory, profibrogenic and promitogenic stimuli acting in an autocrine and paracrine manner (Figure 3).

ACTIVATION OF HSCS

Activation of HSCs by neighboring cells

In the early stage of injury, all neighboring cell types can contribute to the paracrine stimulation of HSC activation.

Hepatocytes

Hepatocyte apoptosis is a common feature in liver injury. This process is mediated partially by Fas and may also involve TNF-related-apoptosis-inducing ligand (TRAIL)[54-56]. Recent data have shown that the engulfment of the apoptotic bodies of hepatocytes by HSC lines results in a profibrogenic response and activates Kupffer cells[57,58]. A similar profibrogenic response can be observed following disruption of Bcl-xl (an anti-apoptotic mediator) that leads to hepatocyte apoptosis[59,60].

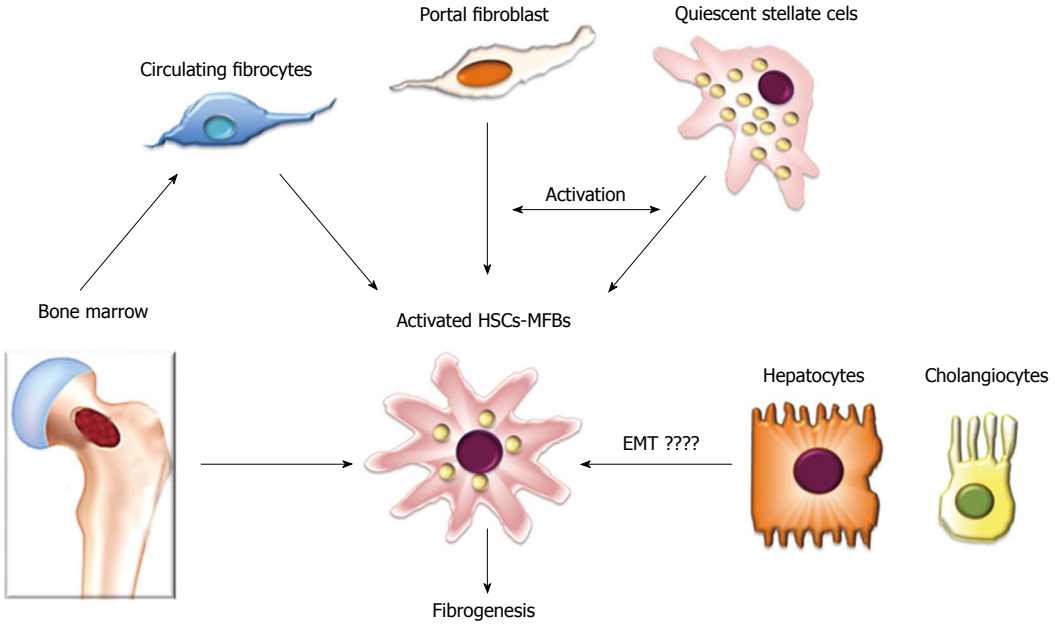

Figure 2 Hepatic myofibroblasts are a heterogenous population of fibrogenic cells. Hepatic stellate cells are considered to be a major source of liver fibrogenic cells followed by portal fibroblasts that play an important role in the fibrogenic process during cholestatic liver diseases. Other sources of hepatic myofibroblasts include circulating fibrocytes and bone marrow-derived cells that constitute a minor proportion of liver fibrogenic cells. The epithelial origin of liver fibrogenic cells is unlikely. EMT: Epithelial mesenchymal transition; MFBs: Myofibroblasts; HSCs: Hepatic stellate cells.

HSC activation by hepatocyte-derived apoptotic bodies is partially mediated by the interaction of hepatocyte DNA with Toll-like receptor 9 (TLR9) expressed in HSCs[61]. Hepatocytes also produce fibrogenic lipid peroxides[62]. Experimental studies have demonstrated that either blockage of hepatocyte apoptosis or selective stimulation of apoptosis in HSCs could be a therapeutic strategy for the prevention of fibrosis[63-66]. However, this approach has not been successful in clinical trials[26].

Liver sinusoidal endothelial cells

In response to injury, sinusoidal endothelial cells contribute to HSC activation, owing to their capacity to produce fibronectin, TGF-β1 and PDGF[67]. Conversely, recent data indicate that restoration of liver sinusoidal endothelial cell differentiation may contribute to fibrosis regression by promoting HSC quiescence[68-70]. It has been proposed that a loss of endothelial fenestration following injury leads to changes in liver sinusoidal endothelial cell differentiation and, consequently, HSC activation[3].

Kupffer cells

Kupffer cells and infiltrating monocytes express a number of chemokine receptors that influence fibrosis progression and resolution[71-74]. Indeed, different macrophage subsets have been described in experimental models; however, their molecular profile is incomplete and additional studies are warranted[74-78]. To date, profibrogenic macrophages have been shown to have high Gr1 (Ly6c) expression and to activate HSCs[74,78]. Additionally, another subset of monocytes (Gr1Io) is vital for fibrosis regression[79,80].

Lymphocytes

Lymphocytes, especially CD4 T-helper lymphocytes, may activate HSCs *via* cytokine production. Previous experimental models imply that during liver injury Th2 lymphocytes, a subset of T-helper lymphocytes, are more fibrogenic as compared to the Th1 lymphocytes subset[81,82].

Natural killer cells

Recent findings indicate that natural killer (NK) cells inhibit liver fibrosis by directly killing activated HSCs[83-86]. In cases of liver injury, NK cells induce apoptosis of HSCs by IFN-γ. Moreover, IFN-γ not only inhibits HSC activation directly but also amplifies NK cell cytotoxicity against HSCs *via* upregulation of NKG2D (best defined natural cytotoxicity receptor) and TRAIL expression on NK cells[87-90]. It has been shown that HSCs in the early stages of activation are more prone to be killed by NK cells than quiescent or fully activated HSCs, because they still produce retinoic acid that is important in the induction of NK cell-activating ligands (MICA in humans)[91]. Thus, activation of NK cells could be a novel, therapeutic target to treat liver fibrosis[91,92]. It should be noted that another T cell subset, NKT cells, has diverse effects on liver fibrosis depending on the stage of the disease[91-93].

Leukocytes recruited to the liver during injury produce compounds that modulate HSC behavior. Neutrophils are an important source of reactive oxygen species (ROS) that also produce nitric oxide (NO), which may counteract the effect of superoxide on collagen production[94,95].

Platelets that produce TGF-β1, PDGF and epidermal growth factor (EGF) are also an important source of

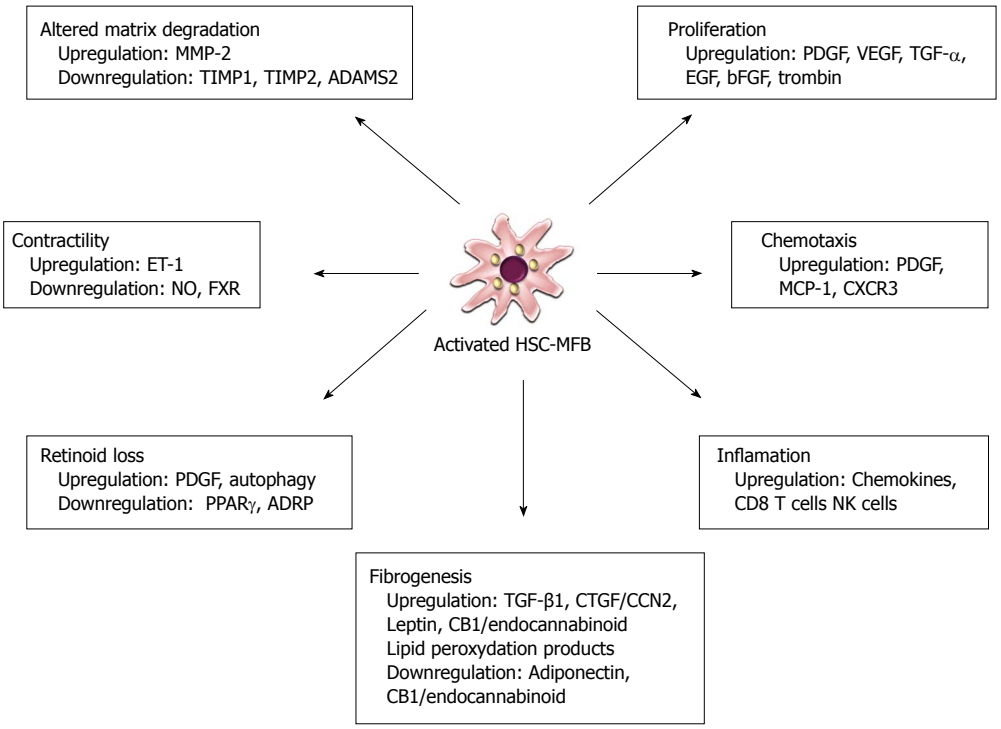

Figure 3 Hepatic myofibroblasts myofibroblasts have multiple functions during liver fibrogenesis. In the activated form, hepatic stellate cells show *de novo* properties, including increased proliferation, fibrogenesis, contractility, chemotaxis, matrix degradation, retinoid loss and secretion of chemokines. Each of these properties is controlled by the release of many cytokines acting in an autocrine and paracrine manner offering many potential sites for therapeutic intervention. MMP: Matrix metalloproteinase; TIMP: Tissue inhibitor of matrix metalloproteinase; ADAMS2: A disintegrin and metalloproteinase 2; PDGF: Platelet derived growth factor; VEGF: Vascular endothelial growth factor; TGF-α: Transforming growth factor-α; EGF: Epidermal growth factor; bFGF: Basic fibroblast growth factor; TGF-β1: Transforming growth factor-β1; CTGF/CCN2: Connective tissue growth factor; ET-1: Endothelin 1; NO: Nitric oxide; FXR: Farnesoid X receptor; PPARγ: Peroxisome proliferators activated nuclear receptorsγ; ADRP: Adipose differentiation related protein.

paracrine stimuli in HSC activation and fibrogenesis[96-98].

Molecular activation of HSCs

ROS: ROS that are generated through lipid peroxidation have the ability to activate HSCs and stimulate the progression of fibrosis[99,100] They can originate from hepatocytes, macrophages, cholangiocytes and inflammatory cells[99,100]. Moreover, ROS can also be produced by HSCs in response to several fibrogenic mediators, such as PDGF, TGF-β leptin and Angiotensin Ⅱ[101-104]. Although it has been suggested that the loss of antioxidant capacity in activated HSCs amplifies the effects of lipid peroxidation products, more recent studies have indicated that activated HSCs have an increased ROS-detoxifying capacity compared to quiescent HSCs[62,105-107]. It has also been demonstrated that increased glutathione levels and hydrogen peroxide detoxifying enzymes protect HSCs from ROS-induced necrosis and apoptotic cell death, respectively[107]. Because ROS can activate signal transduction pathways and transcription factors, including JNK and NFκB, they also upregulate the expression of fibrosis-associated genes, including COL1A1, COL1A2, MCP1 and TIMP1 in HSCs[102-104]. At the cellular level, ROS are generated *via* mitochondrial damage, mitochondrial transport chain or *via* activation of cytochrome P450 (especially cytochrome P450 2E1), xanthine oxidase and NADPH oxidase[108]. It has been demonstrated that, through the induction of oxidative stress, homologs of NADPH oxidase (NOX) might contribute not only to HSC activation but also to the activation of Kupffer cells and macrophages[109]. More recently it has been shown that the phagocytic NADPH oxidase NOX2 is expressed in HSCs and its activation leads to the induction of fibrogenic cascades[110,111]. Angiotensin Ⅱ-mediated induction of NOX1 was also described as profibrogenic[111,112]. In a recent study, Jiang *et al*[113] demonstrated that NOX4 plays an important role in ROS production and HSC activation. They proposed that inhibition of NOX4 might be a promising new strategy for translational trials in liver fibrosis. The cytochrome P450 2E1 (CYP2E1) may also contribute to activation of HSCs *via* the generation of ROS. In the presence of cells that express CYP2E1 (E47 cells), the production of collagen by HSCs is increased[114,115]. Conversely, in the presence of antioxidants or a CYP2E1 inhibitor the increase in collagen production is blocked, suggesting that the CYP2E1 derived ROS are responsible for the increased collagen production[115].

Because ROS constitute a heterogeneous group of species with widely varying chemical reactivity and biological properties, the blockade of oxidative stress as a therapeutic target is still under investigation. Early results demonstrated that the use of an antioxidant mitoquinone might decrease liver inflammation possibly through the induction of the antioxidant transcription factor Nrf2[116].

In a more recent study, chloride channels that are involved in HSC activation by superoxide anion radicals were proposed as a potential target for new anti-fibrotic drugs[117].

Toll-like receptors: Toll-like receptors (TLRs), receptors for microbial products, are present in HSCs and Kupffer cells, introducing a role of immunity in HSC activation and hepatic fibrosis. In chronic liver diseases, increased intestinal permeability results in an enhanced portal inflow of gut-derived microbial products, lipopolysaccharides (LPS), bacterial DNA, peptidoglycan and viral and fungal components[118]. The impact of intestinal decontamination on liver fibrogenesis has been reported. Parallel to this data, mice with a knockout of TLR4 (the LPS receptor), TLR2 and TLR9 were shown to be protected from liver fibrosis[118]. The stimulation of HSCs by LPS or bacterial products through TLR4, TLR9 and TLR2 has been shown to induce a proinflammatory response[118,119]. The activation of HSCs in response to LPS and its receptor TLR4 may elicit a fibrogenic response by down-regulating a transmembrane suppressor of TGF-β-1, BAMBI[119-121]. By contrast, it has been indicated that in addition to LPS (exogenous ligand) TLR4 signaling may also be activated by endogenous ligands from cellular compartments that are released and/or increased during tissue injury, including high mobility group box 1 protein (HMGB1)[122,123]. This chromatin-associated, highly conserved nuclear protein has been shown to be upregulated during liver fibrosis. *In vitro* studies have demonstrated that HMGB1 activates TLR4 signaling in HSCs to enhance their inflammatory phenotype, indicating that TLR4 signaling need not rely solely on gut-derived LPS for activation during liver injury[123]. HMGB1 also has a synergistic effect with TGF-β1 to stimulate fibrogenic protein expression, which is likely to be TLR4-dependent[123]. It has been suggested that inhibition of HMGB1 and TLR4 signaling activity may therefore be important targets of antifibrotic therapy, warranting further investigation by *in vitro* and *in vivo* studies[122,123].

Gene regulations in activated HSCs

There are countless changes in gene transcription that may take place after HSC activation. Among the many target genes of transcription factors described in HSCs include: Type 1 collagen, α-SMA, TGF-β-1, TGF-β receptors, MMP-2, TIMPs 1 and 2[124-126]. The transcription factors that activate these downstream targets are Ets-1, Mef2, CREB, Egr-1, Vitamin D receptor, Foxf1, JunD and C/EBPβ[127].

HSCs also express many nuclear receptors, such as the retinoid responsive RxR and RAR, the farnesoid X receptor (FXR), the pregane X receptor (PXR) and peroxisome proliferators-activated nuclear receptorsγ (PPARγ)[128-130]. While RXR an FXP suppress collagen production, PXR is activated by steroids and antibiotics, dimerizes RXR to induce cytochrome p450 and thereby induces fibrosis[128]. By contrast, PPARγ down-regulates HSC activation and reduces collagen production[128-130].

MicroRNAs: Micro RNAs (mi-Rs) regulate posttranscriptional gene repression by decreasing target mRNA levels. Many mi-Rs are expressed in HSCs and control fibrosis progression[131] including mi-R29, mi-R19b and miR 221/222, among others[132-134]. Based on gene array analysis, mi-R29, which is a physiological inhibitor of various ECM proteins, including collagens, is down regulated by TGF-β and LPS in cultured HSCs[132,133]. MiR-19b is an inhibitor of TGF-β signaling and its expression is decreased in patients with advanced fibrosis, while its overexpression in HSCs blocks activation[132]. In contrast, miR-221/222 is upregulated in human livers in parallel with progression of liver fibrosis. Its expression also increases during HSC activation, and its contribution to HSC proliferation has been proposed[134].

DNA methylation and histone modifications: DNA methylation of genes expressed in quiescent HSCs contributes to the maintenance of the quiescent phenotype. During activation, HSCs express DNA-methyl binding proteins (MeCP2). These proteins promote the silencing of antifibrogenic genes and increase the expression of histone methyl transferases, leading to enhanced transcription of collagen, TIMP-1 and TGF-β[135-137].

It is noteworthy that epigenetic changes can also modulate fibrosis susceptibility[136]. In a recent study, offspring from the progeny of male fibrotic rat ancestors are found to be more resistant to liver fibrosis than their counterparts with no previous history of fibrosis[137]. In experimental models, DNA methylation and histone acetylation in the sperm of rats with fibrosis may also take place in the resistance to the wound healing process, leading to hypomethylation of the PPARγ gene, resulting in elevated hepatic expression of this antifibrogenic transcription factor in adult offspring[137].

PROLIFERATION OF HSCS

The most potent mitogen in HSCs is PDGF. Other mitogens that stimulate HSC proliferation are VEGF, thrombin and its receptors, EGF, TGFα and bFGF[3,104]. Downstream pathways in HSCs include PI3 kinase and ERK/MAP kinase, among others[104,138]. PDGF signaling at the cell membrane of HSCs can also be enhanced by a co-receptor, neuropilin-1[139]. In addition to its mitogenic effect, PDGF also stimulates Na^+/H^+ exchange, providing a potential site for therapeutic intervention by blocking ion transport[140]. Signaling pathways for these mitogens have been clearly identified in HSCs, offering many potential sites for therapeutic intervention[141,142].

CHEMOTAXIS OF HSCS

HSCs can migrate towards many chemokines, including VEGF, PDGF, MCP-1, CXCR4 and CXCR3[3]. For example, CCR5 and its ligand RANTES stimulate the mi-

gration of HSCs[143]. Hypoxia is another activator of HSC migration. In hypoxic conditions the motility of HSCs is not only induced by ROS but also by VEGF in an autocrine manner because prolonged hypoxia induces HSCs to produce and secrete VEGF in an HIF-1α-dependent manner[144].

The role of ECM in migratory behavior of HSCs has been previously described. Additionally, cellular fibronectin containing an alternatively spliced domain A (EⅡA) has been shown to induce motility of HSCs, supporting the role of ECM in HSC behavior[145].

Interestingly, while adenosine blunts chemotaxis and fixes cells at sites of injury *via* the loss of actin fibers, enhanced adenosine signaling may also stimulate HSC fibrogenesis[146,147]. Therefore, understanding the dual role of adenosine will be important in the development of antifibrotic agents. Recent epidemiologic studies demonstrated that caffeine exerts its protective effect by inhibiting adenosine signaling in HSCs[148,149].

HSCS IN FIBROGENESIS

Production of the ECM, in particular collagen type Ⅰ, is a major characteristic of HSCs. The expression of collagen type Ⅰ in HSCs is regulated posttranscriptionally by multiple stimuli and pathways. Prominent among these is TGF-β, the most profibrogenic cytokine in the liver[150,151]. TGF-β is produced by Kupffer cells, liver sinusoidal endothelial cells, hepatocytes and HSCs and has paracrine/autocrine effects on HSCs[150,151]. It has three major isoforms: TGF-β1, TGF-β2 and TGF-β3. In addition to its role in the stimulation of collagen type Ⅰ, TGF-β also stimulates the production of other matrix components, including cellular fibronectin and proteoglycans[150,151]. Although none appears to be as potent as TGF-β, a variety of other factors have profibrogenic effects on HSCs, including retinoids and angiotensin Ⅱ[103,152]. TGF-β1 is stored as an inactivated protein and, when activated, signals *via* its receptors to Smad proteins, which enhance the transcription of target genes, such as procollagens Ⅰ and Ⅲ[150,151]. The response of SMADs in HSCs differs between acute and chronic injury to further favor matrix production[151]. Because TGF-β1 may also contribute to liver homeostasis during regeneration, therapeutic antagonization of TGF-β1 is challenging[153].

Connective tissue growth factor (CTGF/CCN2) is a growth factor protein that is upregulated by hyperglycemia, hyperinsulinemia and alcohol-induced cellular injury[154,155]. While the stimulation of CTGF/CCN2 in hepatocytes is TGF-β dependent, this stimulation in HSCs is independent of TGF-β, highlighting the fact that, in exception to the general rule, cytokine signaling in HSCs is not always autocrine[156].

Adipokines are polypeptides mainly secreted in adipose tissue and, to lesser extent, by stromal cells. In the liver, they not only contribute to the hepatic manifestation of obesity but are increasingly recognized as key mediators of liver fibrogenesis. Leptin, adiponectin and ghrelin are the main adipokines that contribute to liver injury[157-161]. Leptin is an adipogenic hormone that promotes HSC fibrogenesis and activates Kupffer cells, macrophages and endothelial cells to produce TGF-β1[162]. It modulates the HSC phenotype through the leptin receptor (OB-R), which leads to stimulation of the Janus kinase 2 (JAK 2) and signal transducer and activator of transcription 3 (STAT 3) pathways[157]. Leptin also partially suppresses PPARγ, which can reverse HSC activation and maintain senescence[163]. Recently, it has been demonstrated that leptin deficiency may reduce the activity of norepinephrine, thereby reducing fibrogenesis[164]. Reduced activity of norepinephrine leads to decreased activity of NK cells and attenuates the release of profibrogenic cytokines and reduces ECM production[164]. Adiponectin, a counter-regulatory hormone of leptin, inhibits hepatic fibrogenesis both *in vivo* and *in vitro*[160,162]. Ghrelin also appears to attenuate hepatocellular damage and fibrosis in experimental studies[161].

Neurochemical and neurotrophic factors also contribute to the fibrogenic function of HSCs. Following liver injury, activated HSCs express specific receptors (CB1 and CB2) that are components of the endocannabinoid system that regulates the fibrogenic cascade[165-168]. Two receptors exert opposing effects; while CB1 stimulation induces fibrogenesis, the stimulation of the CB2 receptor is anti-fibrotic and hepatoprotective[165-167]. The overexpression of these receptors is observed both in experimental models of liver fibrosis and in the livers of patients with chronic liver disease[165,167]. Therefore, efforts for therapeutic strategies are being directed to either antagonize CB1 or agonize CB2. Non-brain penetrant CB1 antagonists have shown promising results in experimental models[168]. Similarly, opioids that contribute to fibrogenesis by stimulating HSCs can be antagonized by naltrexone[169,170]. Serotonin and thyroid hormones are also involved in fibrogenesis, with agonists or antagonists for these mediators already in existence[41,171].

CONTRACTILITY OF HSCS

Activation of HSCs is accompanied by an increase in expression of proteins characteristic of contractile cells[172]. In the process of becoming contractile, HSCs develop an increased expression of the cytoskeletal protein α-smooth muscle actin (α-SMA)[172]. It has also been reported that HSC contraction is mediated by both Ca^{2+} dependent and Ca^{2+} independent mechanisms[173,174]. Contractility of HSCs has a multitude of effects in the injured liver, including perisinusoidal constriction and portal hypertension, leading to an increase in portal resistance during liver fibrosis[174]. Contractile HSCs impede portal blood flow by constricting sinusoids and by contracting the cirrhotic liver[174-177]. This contractility is likely associated with multiple different systems, including endothelin-1. Endothelin-1 receptors are expressed in both quiescent and activated HSCs[176]. Nuclear receptor FXR antagonizes endothelin 1[176]. There is a shift in the

predominant type of endothelin receptor and increased sensitivity to endothelin-1 after activation of HSCs[178]. The effect of endothelin-1 may also be reversed by locally produced vasodilator substances; particularly, nitric oxide (NO) may counteract the constrictive effects of endothelin-1[179]. Similarly, carbon monoxide also mediates sinusoidal dilatation[179].

RETINOID LOSS OF HSCS

Retinoid is stored as retinyl esters in the form of perinuclear droplets in the cytoplasm of quiescent HSCs. Activation of HSCs is accompanied by the loss of these characteristic droplets. The form of retinoid released outside the cell during activation is retinol, suggesting that there is intracellular hydrolysis of esters prior to export[127]. Several nuclear retinoid receptors have been identified in HSCs. Lecithin retinol acetyl transferase (LRAT) catalyzes the esterification of retinol into retinyl ester in liver[180]. In liver injury models, LRAT-deficient animals exhibit increased fibrogenesis in the liver[181]. In contrast, treatment with retinoid acid decrease activation of HSCs by inhibiting TGF-β[182].

PPARs regulate glucose and lipid metabolism[129]. Their expression decreases with the activation of HSCs[128,130]. In contrast, forced expression of PPARγ in activated HSCs inhibits collagen expression, blocks TGF-β1 signaling and increases cytoplasmic lipid droplets[129].

Adipose differentiation related protein (ADRP), an intracellular lipid storage protein, is present in quiescent HSCs and its expression is reduced during HSC activation. ADRP is induced by retinoid exposure, suggesting that ADRP may have a regulatory role between lipid content and cellular activation through an unknown mechanism[183,184].

Because energy homeostasis is maintained through autophagic digestion of lipid droplets in many cells, it has been hypothesized that autophagy drives HSC activation by digesting lipid droplets, thereby providing energy required for the activation process[185,186]. Recent studies have demonstrated that inhibition of autophagy downregulates the fibrogenic properties of HSCs, revealing HSC autophagy as a therapeutic target[185-187].

HSCS IN INFLAMMATION AND WBC CHEMOATTRACTION

HSCs may produce chemokines that amplify inflammatory responses by inducing migration of inflammatory cells[141,188]. Additionally, cell surface expression of chemokines by HSCs promotes ICAM-1- and VCAM-1-dependent adhesion and migration of lymphocytes[189]. Therefore, some of these chemokines are attractive therapeutic targets[188]. The interaction of HSCs with immune cells (especially with T cells) promotes or inhibits their maturation[190]. The results from a recent proteomics analysis supports the immunosuppressive role of activated HSCs[191]. It has been suggested that HSCs also have the capacity to interact with bacterial LPS because they express TLRs[94,118,119].

PATHOGENESIS OF FIBROSIS ASSOCIATED WITH VARIOUS ETIOLOGIES

Alcoholic liver disease

The pathogenesis of liver fibrosis in alcoholic liver disease (ALD) is complex and may be cell specific and controlled through feedback mechanisms and cross-talk between neighboring and distant cells. The development of liver fibrosis in alcoholics has been linked to the oxidation of ethanol to the highly reactive compound acetaldehyde. After alcohol consumption, acetaldehyde stimulates type I collagen synthesis and gene transcription in cultured rat and human HSCs through the activation of protein kinase C (PKC)[192]. Acetaldehyde was also shown to increase NFκB (p65) and its binding to the α2(I) collagen promoter as well as to enhance NFκB by a mechanism dependent on H_2O_2 accumulation[90,193-195]. The activity of cytochrome P450 isoform 2E1 (CYP2E1) is an important source of ROS in alcohol-induced injury. It has been reported that the inhibition of CYP2E1 activity prevented the induction of collagen I gene expression in rat stellate cells overexpressing CYP2E1[196]. Oxidative stress also activates c-Jun N-terminal kinase (JNK), a protein that regulates the secretion of proinflammatory cytokines in cultured HSCs[144]. The results of a recent study indicated that butein inhibited ethanol- and acetaldehyde-induced activation of HSCs at different levels, acting as an antioxidant and inhibitor of ethanol-induced MAPK, TGF-β and NFκB/IκB transduction signaling; therefore, butein is a promising agent for antifibrotic therapies[197].

Alcohol inhibits the anti-fibrogenic effects of NK cells by stimulating TGF-β production by HSCs, inducing suppressors of cytokine signaling (SOCS-1) and ROS in hepatocytes, thereby sustaining HSC activation and reducing HSC apoptosis[90,198]. Recently, it has been suggested that alcohol increases the binding of the early growth response-1 (Egr-1) transcription factor to the TNF-α promoter and enhances macrophage sensitivity to LPS in the progression of liver injury to fibrosis[199]. Recent discoveries have revealed that alcohol inhibits PPARα, suppressing sterol-regulatory element binding protein-1 (SREBP-1), which is involved in fatty acid synthesis, leading to the activation of HSCs and ultimately fibrosis[90,200]. Other recently identified novel molecules and physiological/cell signaling pathways include hedgehog (Hh) signaling, fibrinolysis and involvement of novel cytokines such as osteopontin. Alcohol increases liver progenitor cell accumulation by providing an increase of Hh and Hh ligands in an autocrine manner[201]. Osteopontin (OPN), which is secreted by several cell types in the presence of alcohol, activates NFκB and activator protein 1 (AP-1) as well as several other genes, including urokinase plasmino-

gen activator (uPA), MMPs and TGF-β[202,203]. Moreover, the profibrogenic plasminogen activator inhibitor (PAI-1) was increased in liver cells after alcohol consumption, leading to the inhibition of uPA, plasmin and fibrinolysis, thereby tipping the balance in favor of fibrosis[204].

Non-alcoholic fatty liver diseases and non-alcoholic steatohepatitis

Although the role of HSC activation in non-alcoholic fatty liver disease (NAFLD) has not been completely clarified, several studies have reported increased HSC activation in non-alcoholic steatohepatitis (NASH)[205]. Although the TGF-β signaling pathway plays a major role in the activation of HSCs in liver fibrosis, many other signaling pathways are implicated in liver fibrosis in NAFLD, including the hedgehog (Hh), PI3K/AKT and JAK/STAT signaling pathways[206].

Several studies have demonstrated that insulin resistance is associated with advanced stages of fibrosis in NAFLD[206,207]. Because insulin promotes HSC activation and insulin sensitizers can attenuate hepatic fibrosis in NASH, it has been suggested that insulin resistance plays an important role in NASH-related fibrogenesis[208,209].

It is understood that oxidative stress induces the activation of HSCs in NASH[108]. The role of oxidative stress in fibrogenesis is supported by the finding that antioxidants, such as vitamin E and astaxanthin, can decrease NASH-related fibrogenesis[210].

Recently reported data also indicate that adipokines affect not only lipid metabolism but also inflammatory and fibrotic processes in NAFLD[157] (the adipokines are described in more detail in the section "HSCs in fibrogenesis"). Recent data related to the newly described adipokines visfatin, chemerin and vaspin in NASH fibrogenesis is limited, warranting further studies to better understand their importance in the pathogenesis of NASH[211,212].

It has been hypothesized that various factors might contribute to the development of liver fibrosis in NAFLD, including LPS-derived from gut bacteria. Because LPS presents its effects by binding TLRs and because a recent finding in a murine NAFLD model demonstrated that TLR9 knockout mice demonstrate less steatohepatitis and liver fibrosis than controls, a role for TLRs in the progression of fibrosis of NASH have been proposed[213]. Recently, it has also been suggested that NK cells may play a pivotal role in NAFLD-related liver fibrogenesis. Although the population of hepatic NK cells in NAFLD patients is controversial, it has been shown that activation of the Hh pathway lead to hepatic accumulation of NK cells, resulting in progression of liver fibrosis in NASH[214].

In experimental studies as well as studies in patients with NASH, PPARγ agonists and especially pioglitazone have been shown to diminish liver fibrosis[209,215]. These data support the key role of PPARs in fibrosis in NASH. Among the other nuclear receptor family, liver X receptors (LXRs) play important roles in the regulation of cholesterol absorption, efflux, transport and excretion. In a more recent experimental study LXR ligands were found to suppress the activation of HSCs and the expression of fibrosis related genes[216].

Chronic viral hepatitis

During liver fibrogenesis, hepatotrophic viruses can induce HSC activation through several mechanisms. Immune cell types, especially NK cells, are engaged in the hepatitis B virus (HBV)-related acceleration of fibrosis[217]. It has been demonstrated that hepatitis B virus X protein (HBx) expression in hepatocytes leads to paracrine activation and proliferation of HSCs[218]. Moreover, in patients with chronic HBV, superinfection of hepatitis delta virus (HDV) accelerates the progression of fibrosis. The large isoform of hepatitis delta antigen (LHDAg) can induce liver fibrosis through the regulation of TGF-β-mediated signal transduction. LHDAg synergistically activates HBx protein-mediated TGF-β and AP-1 signaling, enhancing the level of TGF-β-induced PAI-1[219].

It has been found that the biology of activated HSCs is modulated by hepatitis C virus (HCV)-derived proteins in a profibrogenic manner[220]. Recent findings indicate that both oxidative stress and mitochondrial dysfunction are related to HCV pathogenesis. The blockade of oxidative stress as a therapeutic target in patients with HCV hepatitis remains under investigation[221,222]. Recent studies have indicated that hepatic iron accumulation is also correlated with histologic disease severity and with HSC numbers in patients with HCV infection, supporting the assumption that hepatic iron concentration may also influence fibrogenesis[223]. Huang *et al*[224] demonstrated that specific single nucleotide polymorphisms of TLR4 are related to the rate of progression of fibrosis in patients with HCV hepatitis. It has been suggested that this finding presents a link between a genetic marker and disease pathogenesis.

Although a correlation between HCV viral load and the progression of fibrosis has not been demonstrated in HCV hepatitis, HIV RNA levels predict the fibrogenic progression of chronic hepatitis in HCV/HIV-co-infected individuals[225,226]. In contrast, patients infected with HIV alone do not show significant liver fibrosis, indicating that HIV infection is not profibrogenic per se but rather accelerates the fibrogenic process in the presence of hepatic damage induced by hepatotropic viruses[225-227]. A recent, elegant study by Bruno *et al*[228] demonstrated that HIV gp120 modulates HSC behavior, including directional cell movement and expression of proinflammatory cytokines. They concluded that these results identify a direct pathway that most likely links HIV infection with liver fibrosis *via* envelope proteins, presenting new prospective strategies for the management of liver diseases in HCV/HIV-co-infected patients.

CONCLUSION

In conclusion, there have been considerable advances in the understanding of the mechanisms that underlie he-

patic fibrogenesis. A critical event in liver fibrogenesis is that the ECM is a dynamic structure, and even advanced fibrosis may be reversible. Multiple interactions between the ECM, HSCs, endothelial cells and immune cells have been identified. The central event in fibrogenesis appears to be the activation of HSCs, which is a complex process, leading to multiple potential sites for therapeutic interventions. Although specific, effective and safe antifibrotic therapies are not currently available for the identification of potential new therapeutic agents, once available, they will mediate the progression of hepatic fibrogenesis.

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