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Review Article 133

New Concepts on Reversibility and Targeting of Liver Fibrosis; A Review Article

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ABSTRACT

Currently, liver fibrosis and its complications are regarded as critical health problems. With the studies showing the reversible nature of liver fibrogenesis, scientists have focused on understanding the underlying mechanism of this condition in order to develop new therapeutic strategies. Although hepatic stellate cells are known as the primary cells responsible for liver fibrogenesis, studies have shown contributing roles for other cells, pathways, and molecules in the development of fibrosis depending on the etiology of liver fibrosis. Hence, interventions could be directed in the proper way for each type of liver diseases to better address this complication. There are two main approaches in clinical reversion of liver fibrosis; eliminating the underlying insult and targeting the fibrosis process, which have variable clinical importance in the treatment of this disease. In this review, we present recent concepts in molecular pathways of liver fibrosis reversibility and their clinical implications.

KEYWORDS:
Fibrosis, Genetic therapy, Liver cirrhosis, Therapeutics, Gene targeting

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INTRODUCTION

Cirrhosis, which is the final stage of liver fibrosis, is one of the major health-related concerns worldwide. According to the global reports, cirrhosis results in about 1 million deaths annually.[1] Among chronic diseases, after coronary artery disease, cerebrovascular accidents, and chronic obstructive pulmonary disease, cirrhosis is the fourth leading cause of lost life years.[1] Liver fibrosis, the healing process as a response to a wide spectrum of chronic complications, including viral hepatitis, and alcoholic or non-alcoholic fatty liver disease,[2] can encapsulate the injury in the first stages of the insult and is regarded as a protective and reversible response of the liver tissue to these subset of injuries.[3] However, if the damage remains for a longer period, liver fibrosis will lead to cirrhosis, which causes further life-threatening complications such as hepatocellular carcinoma.[4]

Fibrosis formation is caused by imbalances in extracellular matrix (ECM) formation and its degeneration, which are regulated by extracellular enzymes; matrix metalloproteinases (MMPs) and their inhibitors; and tissue inhibitors of metalloproteinase (TIMPs), respectively.

Although a wide range of cells contribute to hepatic fibrogenesis,

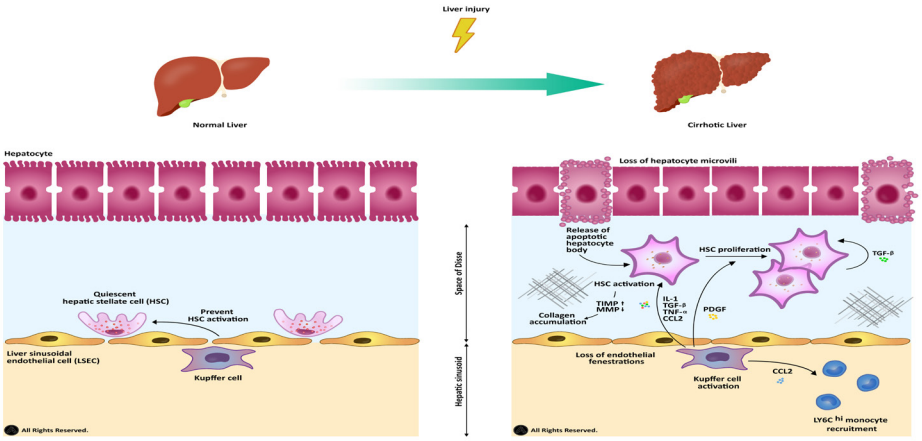

Fig.1: Molecular and cellular mechanisms involved in liver fibrogenesis

Liver fibrosis happens as a result of interactions between several molecular and cellular processes. Chronic hepatic injury promotes hepatocytes into apoptosis, and apoptotic hepatocyte bodies induce secretion of proinflammatory cytokines (TNF-α, TGF-β, PDGF, and IL-1) from KCs leading to HSCs activation and proliferation. Activated macrophages also release CCL2 that recruits LY6Chi monocytes and intensify inflammatory state. Moreover, activated HSCs express collagen fibers in addition to TIMP-1 that inhibits MMP activities and result in ECM accumulation. Tumor necrosis factor α, TNF-α; Transforming growth factor β, TGF-β; Platelet-derived growth factor, PDGF; Interleukin 1, IL-1; Kupffer cells, KCs; Hepatic stellate cells, HSCs; C-C Motif Chemokine Ligand 2, CCL2; Tissue inhibitors of metalloproteinase 1, TIMP-1; Matrix metalloproteinases, MMP; Extracellular matrix, ECM

activation of hepatic stellate cells (HSCs), one of the non-parenchymal cells in the liver, is shown to play a pivotal role in this process.[5] HSCs are the major source of cells that transform to myofibroblasts (MFs). These cells are the highly proliferative lineage that could accumulate at injury sites and promote ECM deposition.[6,7] Due to hepatic injury, autocrine and paracrine secretion of fibrogenic cytokines promote HSCs to transform from a quiescent form into an activated myofibroblastic state, which has a migratory and highly proliferative characteristic. Tumor necrosis factor α (TNF-α), transforming growth factor β (TGF-β), platelet-derived growth factor (PDGF), and interleukin 1 (IL-1) are among the known cytokines involved in fibrogenesis pathways. Activated HSCs express fibrogenic proteins and α-smooth muscle actin (α-SMA) while they lose their vitamin A storage.[2,8,9] Moreover, it is shown that extrahepatic cells, such as portal fibroblasts and bone marrow derived mesenchymal cells could also contribute to ECM synthesis as MF.[6,7]

Furthermore, chronic hepatic insult induces hepatocyte apoptosis and these apoptotic bodies promote HSCs activation as well as secretion of fibrogenic cytokines from Kupffer cells (KCs). In response to liver injury, KCs evolve into their activated forms and express chemokine receptors, secrete inflammatory cytokines including C-C Motif Chemokine Ligand 2 (CCL2), and more importantly induce HSCs activation (Figure 1).[2,10]

Reversibility of Liver Fibrosis

In most references, "regression" of liver fibrosis is referred to as resolution of fibrotic septa in the liver microstructure while "reversion" is considered as the more profound resolution to near normal pathology.[11] We use these terms accordingly in this review.

Molecular pathways of fibrosis reversibility

An array of cells and cytokines are involved in the evolution of liver fibrosis. Among them, HSCs and MFs regardless of their origin [12] have more central role.[13-15] MFs secrete high amounts of collagen I/III,[16] express high levels of TIMP-1, regulate hepatic angiogenesis and vascular remodeling,[17-19] and increase vascular resistance by contractility properties.[20]

Induction of MF apoptosis is believed to result in decreased amount of fibril-forming collagens, activation of MMPs that degrade collagens from ECM, and decreased vascular resistance in hepatic

Table 1: Receptor-ligand mediated myofibroblast apoptosis

Ligand	Receptor	Molecular Mediation/Pathway	Reference(s)
Adiponectin	Adipo-R1	Decreasing TGF-β1 expression	[21]
	Adipo-R2	Suppressing PDGF-stimulation for HSCs proliferation	
		Suppressing MF proliferation	
		Inhibiting NF-κB and MF apoptosis	
Cannabinoids	CB2R*	Inducing intracellular oxidative stress and MF apoptosis	[22-26]
Nerve growth factor	TrkA neurotrophin	Inhibiting NF-κB and promoting MF apoptosis	[27,28]
	TrkB neurotrophin		
	TrkC neurotrophin		
Hepatocyte growth factor	c-Met	Suppressing PDGF-stimulation for HSCs proliferation	[29-31]
		Suppressing MF proliferation	
		Inhibiting TGF-β expression	
		Promoting MF apoptosis	

* Cannabinoids may interact with CB1 receptor and promote fibrogenic processes by transdifferentiating HSCs to MF. CB1 receptor antagonists (SR141617A) may prevent fibrosis by blocking this pathway.[23]
Cannabinoids, CB; Hepatic stellate cell, HSCs; Nuclear factor-κB, NF-κB; Transforming growth factor, TGF-β; Platelet derived growth factor, PDGF; Myofibroblast, MF

vasculature. The ultimate outcome in this process is the regression of liver fibrosis. Apoptosis of MFs can be induced by four mechanisms as described below:

1- Receptor-ligand mediated MF apoptosis

Table 1 summarizes some of the most important ligands, which interact with specific receptors and eventually lead to HSC or MF apoptosis. As described, other mechanisms contributing to fibrosis regression might be perpetuated by receptor-ligand interactions.

2- Transcriptional factors involved in MF apoptosis

There are many transcriptional regulators, which may promote HSC/MF toward apoptosis or survival. The most important is nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which interact with Bcl-2 protein family, p53, and many other factors within MF cells.[32-36] Expression of NF-κB guarantees MF survival. NF-κB in MF nucleus produces two anti-apoptotic proteins, namely Gadd45β and anti-apoptotic Bcl-2. Gadd45β has negative control on c-Jun N-terminal kinases (JNKs).[37] In the cytoplasm, JNKs themselves regulate pro-apoptotic factors such as p53 and pro-apoptotic Bcl-2 (Bax and PUMA),[38] which lead to cytochrome c release from mitochondria and promote caspase-3 dependent apoptosis of MF.[33,39,40]

Another important transcription factor in the resolution of hepatic fibrosis is peroxisome proliferator-activated receptor gamma (PPAR-γ). PPAR-γ yields its effects through inhibition of PDGF-stimulated HSC activation,[41] TGF-β expression,[42] and decreasing collagen production.[41] Both in vitro and in vivo studies have demonstrated that expression of PPAR-γ decreases during fibrogenic processes.[41,43,44] Re-expression of PPAR-γ may revert HSCs activation and may be of worth in resolution of hepatic fibrosis.

3– Role of ECM in MF apoptosis

It is well known that ECM components influence liver fibrosis. Intact collagen I and TIMP-1 promote MF survival [45,46] while MMPs especially MMP-2 [47] oppose with collagen production and liver fibrosis. These interactions are mainly regulated by α/β integrin transmembrane proteins. α3/β2 integrin can prevent mitochondrial pathway of apoptosis in contrast to its antagonist that may activate p53 and give rise to apoptosis in MF cells.[48] Disruption in α3/β2 integrin causes increased amount of MMPs and a decrease in expression of TIMP-1; both of which promote MF apoptosis.[48]

4- Immune cells and their roles in fibrosis regression

Fibrosis formation in the liver is under close monitoring of the immune system. NK cells and IFN-γ play important role in resolution of hepatic fibrosis. NK cells have antifibrotic properties, which decrease with progression of liver fibrosis.[49] NK cells directly invade MF cells and induce MF apoptosis.[50,51] This process is mediated by TNF-related apoptosis-inducing ligand (TRAIL).[52,53] IFN-γ enhances the ability of NK cells in killing MFs and may induce HSC apoptosis.

It is noteworthy that TLR3 induces NK cells' activation.[54] IFN-γ mediates HSCs apoptosis [55] and inhibition of HSCs proliferation by producing type 1 IFN-β are other possible pathways acting under control of Toll-like receptor 3 (TLR3).[56]

Clinical Implications

Thanks to the recent molecular discoveries of the pathogenesis of liver fibrosis, applying interventions to reverse the process of fibrogenesis seems imminent. Two main approaches are pursued in clinical reversion of liver fibrosis. First, eliminating the underlying insult from the hepatocytes and the second, pointing to the fibrosis process after the effect of injuries on different components of liver tissues has ensued.

Eliminating the underlying injuries

The first line of battling liver fibrosis is to eliminate the inciting stimulus. Spontaneous reversion of liver fibrosis is rarely reported, but there are many reports of fibrosis reversal following treatment of different types of underlying liver diseases, including autoimmune hepatitis,[57-59] hemochromatosis,[60,61] and biliary cirrhosis.[62] In the following paragraphs, reversibility of viral hepatitis, alcoholic hepatitis, and non-alcoholic steatohepatitis (NASH) are discussed in more details.

- Viral hepatitis

Randomized clinical trials (RCTs) have shown that treatment of chronic hepatitis B with oral nucleoside analogues not only delays fibrosis progression, but also prevents decompensation in patients with advanced liver fibrosis.[63] Regression have been reported by lamivudine,[64] telbivudine,[65] entecavir,[66] adefovir [67] and tenofovir.[68] Also, interferon-based therapies improve histological outcomes, and decrease the incidence of cirrhosis, and the occurrence of hepatocellular carcinoma (HCC).[69,70]

Multiple trials have proven the effectiveness of treatment against hepatitis C.[71] Older treatment options for hepatitis C with peginterferon and/or ribavirin were associated with regression of liver fibrosis,[72] along with new options such as daclatasvir, sofosbuvir, and simeprevir.[73-75] The advent of highly efficacious direct antiviral agents (DAAs) with high rates of sustained virological response (SVR) in patients with hepatitis C is expected to be associated with promising effects on histology including fibrosis regression.[75] This regression in fibrosis results in decreased morbidity and mortality in patients with hepatitis C.[76] Recent studies have shown that statins may be associated with reduced risk of fibrosis progression in chronic hepatitis C.[77,78]

- Alcoholic hepatitis

Alcohol abstinence is the mainstay for fibrosis regression in alcoholic liver disease, and is accompanied by clinical and histological improvement.[79-81] Other drugs such as pentoxifylline, silymarin, and polyenylphosphatidylcholine (lecithin) might be of clinical importance in reversing fibrosis in alcoholic hepatitis.[82]

- Non-alcoholic steatohepatitis

Numerous drugs have been investigated to reverse fibrosis in NASH, the most advanced type of NAFLD. Based on meta-analyses, none is associated with regression in liver fibrosis.[83-85] Recent studies have shown that liraglutide, obeticholic acid, and telmisartan may reverse hepatic fibrosis in human subjects with NASH.[86-88] Weight loss has significant effect on histological features of NASH including liver fibrosis.[89,90] Several studies have shown improvement of steatosis and inflammation in patients with NAFLD after bariatric surgery. In a meta-analysis, authors looked at 766 paired liver

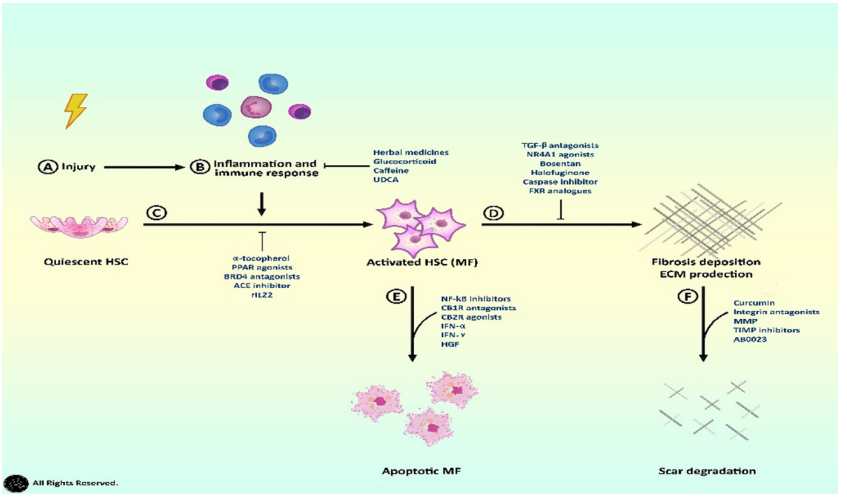

Fig.2: Different strategies to oppose liver fibrosis

The most effective way is to eliminate the underlying insults (A), but some agents like glucocorticoid and UDCA decrease fibrogenesis by reducing the background inflammation and immune response (B). PPAR agonists, rIL-22, and some others target HSCs trans-differentiation (C), while TGF-β antagonists, bosentan, and caspase inhibitors inhibit downstream response cascade after HSCs activation (D). NF-κB inhibitors, melatonin, CB1R antagonists, CB2R agonists, and NK cells activators promote MF into apoptosis (E) but MMPs and TIMP inhibitors along with AB0023 (LOXL2 monoclonal antibody) augment scar degradation (F).
Ursodeoxycholic acid, UDCA; Proliferator-activated receptor, PPAR; Interleukin 22-recombinant protein, rIL-22; Hepatic stellate cell, HSCs; Transforming growth factor β, TGF-β; Nuclear factor-κB, NF-κB; Cannabinoid receptor type 1, CB1R; Cannabinoid receptor type 2, CB2R; Natural killer, NK; Myofibroblast, MF; Matrix metalloproteinases, MMPs; Tissue inhibitor of metalloproteinases, TIMP; Lysyl oxidase like 2, LOXL2;

biopsies from 15 different studies. The combined results showed that 91.6% of the patients had improvement in steatosis, 81.3% of the patients had improvement in steatohepatitis, and 65.5% of them had improvement in fibrosis.[91] Another Cochrane systematic review of 21 studies with histological outcomes of bariatric surgery looked at 21 prospective or retrospective cohort studies, which showed improvement of steatosis or inflammation in most studies except for four studies that showed worsening of fibrosis.[92] The fact that some studies showed worsening of liver fibrosis cannot be overlooked. Further long-term and well-designed prospective studies are needed to address these issues. Interestingly, in a meta-analysis, Singh and colleagues showed that up to 8% of patients with NAFL and 25% of patients with NASH have spontaneous improvement in the amount.[93]

Pointing to the fibrosis process

Opposing to fibrosis process, researchers have worked on different aspects of fibrosis development. Table 2 summarizes the most important aspects of fibrosis process, which are being targeted in order to reverse fibrosis progression. Figure 2 depicts various aspects of fibrosis process targeted by investigational agents.

Future Prospect

As discussed earlier, understanding molecular and cellular mechanisms involved in fibrosis progression could be translated into therapeutic targets in the future. Epigenetic mechanisms, including DNA methylation, non-coding RNAs, and histone modification has been shown to modify fibrogenesis process and are new frontiers in developing therapeutic approaches. Recent findings show that DNA methylation orchestrates HSCs trans-differentiation from quiescent state to activated form, suggesting that enzymes, which catalyze DNA methylation, could be potential new targets in battling fibrosis.[149-151] Another new area of research is the role of microRNA-122 in amplification of HCV replication. While in vivo targeting of microRNA-122 and decreasing its level lead to reductions in HCV RNA level and also cholesterol, microRNA-122 deletion leads to recruitment of inflammatory cells and an increase in inflammatory mediators.[152-155] Further studies are

Table 2: Different strategies for reversing hepatic fibrosis

Agent	Target	Mechanism(s)	Reference(s)
1: Reducing inflammation and immune response before HSCs activation			
Herbal medicines	Different agents in this categories along with their mechanisms of action are discussed in detail elsewhere		94
Glucocorticoids	Immune system	Reduction of inflammation mostly in autoimmune hepatitis	57
Caffeine	NA	NA	95-98
Ursodeoxycholic acid (UDCA)	Cholangiocytes	Reduction in the cytotoxicity of bile acids	99
		Protection of hepatocytes against bile acid-induced apoptosis	
2: Inhibiting HSCs activation			
α-tocopherol	Oxidative stress pathway	Decreasing oxidative stress	100
Thiazolidinediones	PPAR Family	Inhibition of PDGF stimulated HSCs activation	101-103
Oleoylethanolamide		Modulation of the TLR4-mediated signaling pathway	
ESM (PPAR agonist)			
JQ1 (BRD4 antagonist)	BRD4	Abrogates cytokine-induced activation of HSCs	104
Imatinib mesylate	PDGF	Suppresses PDGF receptor phosphorylation and HSCs activation	105
ACE Inhibitors	RAS	Down regulate angiotensin II receptor on HSCs, which is responsible for HSCs proliferation and contraction	106-110
		Suppress activation of HSCs by TGF-β expression	
Recombinant IL-22	Th22	Attenuation of HSC activation	111
		Downregulation of the levels of inflammatory cytokines	
3: Inhibiting response cascade after HSCs activation			
GW6604 (TGF-β antagonist)	TGF-β	Inhibition of TGF-β signal transduction	112
cytosporone B (NR4A1 gene agonist)	TGF-β	Termination in TGF-β signaling	113
Bosentan	Endothelin	Endothelium-receptor antagonist	114
Halofuginone		Blocking collagen expression via inhibition of Smad3 phosphorylation downstream of the TGFβ signaling pathway	115,116
Caspase inhibitors	Caspase	Inhibit effector of apoptosis signaling in hepatocytes	117
FXR analogues	FXR	Improve hepatocyte integrity	118,119
		Reduce HSCs contractility	
		Reduce collagen I levels	
		Inhibit TIMP-1	
4: Promoting activated HSCs (myofibroblasts) into apoptosis			
Gliotoxin	NF-κB	Inhibition of NF-κB pathway	120,121
Sulfasalazine	NF-κB	Inhibition of NF-κB pathway	122
Thalidomide	NF-κB	Inhibition of NF-κB pathway	123
		Suppression of TNF-α and TGF-β1 production of Kupffer's cells	
Melatonin	NF-κB	Inhibiting necroptosis-associated inflammatory signaling	124,125
CB1R antagonists	CB1R	Inhibition of Smad3 phosphorylation downstream of the TGFβ signaling pathway	126-128
		Reduce cellular proliferation	
		Promote myofibroblasts apoptosis	
CB2R agonist	CB2R	Inhibits MF proliferation	129,130
		Induces MF apoptosis via induction of intracellular oxidative stress	

Agent	Target	Mechanism(s)	Reference(s)
IFN-α	NK cells	Promotes NK cell activity	131,132
IFN-γ		Promotes HSCs killing	
		Inhibits HSCs activation	
HGF	-	Inhibition of TGF-β signaling and hepatocyte apoptosis	133-135
		Suppression of TGF-β	
		Induction of collagenase expression	
		Growth inhibition and apoptosis of HSCs	
CYD0682	HSCs	Promotes HSCs apoptosis	136
		Inhibition of HSC proliferation	
		Downregulation of ECM proteins in activated HSC	
Green Asparagus	TNF-α	Inactivation of TGF-β1/Smad signaling and c-Jun N-terminal kinases	137
5: Enhancing scar degradation			
Curcumin	TGF-β	Oppose TGF-β signaling and aid matrix degradation	138-141
TGF-β antagonist			
recombinant Smad7			
αVβ6 integrin antagonist	Integrin	Prevents TGF-β signaling	142,143
		Promotes HSCs apoptosis	
MMP-s	MMP	Suppress trans-differentiation of HSCs to MF	144,145
		Increase HSCs apoptosis	
		Degrade collagens in extracellular matrix	
TIMP inhibitors	TIMP	Decrease in HSC activation and MMP-2 activity	146
AB0023	LOXL2	Catalyzing the cross linking of extracellular collagens	147,148
(LOXL2 monoclonal antibody)		Reduction in activated fibroblasts	
		Decreased production of growth factors and cytokines	
		Decreased TGF-β pathway signaling	

Lysyl oxidase like 2, LOXL2; Bromodomain-containing protein 4, BRD4; Nuclear receptor 4 A1, NR4A1; Farnesoid X receptor, FXR; Renin angiotensin system, RAS; Eggshell membrane, ESM; Angiotensin converting enzyme, ACE; Tissue inhibitor of metalloproteinase, TIMP; Matrix metalloproteinase, MMP; Hepatocyte growth factor, HGF; Interferon, IFN; Cannabinoid receptor, CBR; Interleukin, IL; Helper T cell, Th; Cannabinoids, CB; Hepatic stellate cell, HSC; Nuclear factor-κB, NF-κB; Transforming growth factor, TGF; Platelet derived growth factor, PDGF; Myofibroblast, MF; not available, NA

needed to differentiate between pharmacological targeting and genetic deletion of microRNA-122. Accordingly, epigenetic modifications are novel therapeutic targets in drug development and can potentially be used as non-invasive markers for assessing fibrosis.

Recent advances offer cell therapy, more precisely cell transplantation, as a propitious candidate for treating liver fibrosis.[156,157] Mesenchymal stem cells (MSCs) have been shown to induce improvement in fibrotic liver due to their capacity to secrete anti-inflammatory and immunomodulatory factors, in addition to trans-differentiation to hepatocyte.[158] Baligar and colleagues have recently demonstrated that bone marrow-derived CD45 (BM-CD45) cells are superior candidates for the treatment of the liver fibrosis through functional and structural improvement in fibrotic tissues.[159] Future trials are needed to validate effectiveness, and safety, and investigate the role of cell transplantation in treating hepatic fibrosis.

CONCLUSION

Since liver fibrogenesis and ECM synthesis are dynamic and reversible phenomena, the process of HSCs activation is regarded as the main potential target for therapeutic interventions besides resolving the underlying insult. Future research will validate safety, effectiveness, and accuracy of therapeutic interventions and non-invasive strategies for

assessing hepatic fibrosis. Interfering molecular mechanisms along with cell therapy and gene therapy are among the most valuable strategies for battling liver fibrosis. Future basic studies and then, animal and clinical trials will be prerequisites for reversing and targeting liver fibrosis.

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ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The author declares no conflict of interest related to this work.

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