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

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. Among chronic diseases, after coronary artery disease, cerebrovascular accidents, and chronic obstructive pulmonary disease, cirrhosis is the fourth leading cause of lost life years. 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, 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. 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.

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,
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.\(^6,7\)

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
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.

| 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 | Suppressing PDGF-stimulation for HSCs proliferation            |              |
|                 | TrkC neurotrophin | Suppressing MF proliferation                                    |              |
|                 | c-Met    | Suppressing PDGF-stimulation for HSCs proliferation              | 29-31        |
|                 |          | 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

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, TGF-β expression, and decreasing collagen production. Both in vitro and in vivo studies have demonstrated that expression of PPAR-γ decreases during fibrogenic processes. 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 while MMPs especially MMP-2 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. Disruption in α3/β2 integrin causes increased amount of MMPs and a decrease in expression of TIMP-1; both of which promote MF apoptosis.
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 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 adefovir⁶⁷ 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.⁷⁶ 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
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. 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. 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.

**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. 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. Further studies are needed to address these issues.
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 category, along with their mechanisms of action are discussed in detail elsewhere | 84             |
| 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                                | 101-105      |
| 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      |
| 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      |
| CB2R agonist                 | CB2R                    | Inhibits MF proliferation                                                   | 129,130      |
|                              |                         | Induces MF apoptosis via induction of intracellular oxidative stress        |              |
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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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There is nothing to be declared.

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

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