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MINI REVIEW

Liver fibrosis: Common mechanisms and antifibrotic therapies☆

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Summary Liver fibrosis and in particular cirrhosis have become major endpoints in clinical trials of patients with chronic liver diseases. Here, viral hepatitis, alcoholic and non-alcoholic steatohepatitis have become the major etiologies. We have made great progress in our understanding of the mechanisms and the cell biology of liver fibrosis and have already made the transition from preclinical testing of antifibrotic agents and strategies towards clinical translation. There continues to be an urgent need for specific antifibrotic therapies, despite the advent of highly potent antiviral agents that can even induce regression of advanced fibrosis. This review addresses central mechanisms and cells to be targeted, current antifibrotic drug trials, and the state of non-invasive biomarker development that is key to rapid clinical progress and to a personalized treatment of fibrosis.

Relevance of liver fibrosis

Chronic liver diseases are characterized by a protracted wound healing response, which often progress to advanced fibrosis and cirrhosis, which is accompanied by severe distortion of the liver vascular architectural. Patients with compensated cirrhosis run a yearly risk of 2—7% for decompensation and a 1—7% risk to develop primary hepatocellular carcinoma (HCC). Importantly, established cirrhosis causes complications of portal hypertension and progressive loss of liver function, often despite the use of agents that address the underlying liver disease, such as immunosuppressive, antiviral or anti-inflammatory drugs [1].

Abbreviations: HSC, Hepatic stellate cell; MF, Myofibroblast; PDGF, Platelet-derived growth factor; ECM, Extracellular matrix; MMP, Matrix metalloproteinase; TGFβ, Transforming growth factor beta; TIMP, Tissue inhibitor of metalloproteinases.

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As reviewed recently [2—6], development of antifibrotic therapies for chronic liver disease has become an important focus especially for the following reasons:

- the public health burden of alcoholic (ASH) and non-alcoholic steatohepatitis (NASH), of viral hepatitis B and C — despite the advent of highly effective antiviral therapies —, and of (pediatric) metabolic, biliary and autoimmune liver diseases;
- our improved understanding of the pathogenesis of hepatic fibrosis progression and reversal leading to the identification of key therapeutic targets and agents;
- improved clinical study design and (non-invasive) surrogates.

Mechanisms of hepatic fibrogenesis

Fibrosis results from excessive accumulation of scar tissue (extracellular matrix, ECM). This goes hand in hand with altered angiogenesis, finally leading to the severe architectural changes of cirrhosis [1]. Collagens are the most abundant ECM components in fibrosis, increasing up to ten-fold in cirrhosis, but there are numerous other ECM molecules that are either indicators or therapeutic targets of liver fibrosis [7—9]. There are a variety of stimuli that cause chronic liver diseases, such as toxins, viruses, cholestasis, hypoxia, or insulin resistance that may lead to hepatocyte lipoapoptosis and NASH, all usually in the context of inflammation. They all are important triggers of fibrogenesis, i.e., de novo ECM formation, either indirectly by induction of profibrogenic cytokines/growth factors and other mediators, or directly by exposing the major responding cells and downstream effectors of fibrosis, namely activated hepatic stellate cells (HSC) and myofibroblasts (MF) to an altered ECM environment that these cells sense as enhanced mechanical stress [1—6] (Fig. 1). The figure also stresses the common finding that patients with rapid fibrosis progression usually have several ''hits'', such as HCV infection combined with alcoholic liver disease, or NASH. Therefore, the elimination or appropriate treatment of these ''second hits'' will alleviate advanced fibrosis progression and decrease the risk of development of fibrosis, cirrhosis and HCC.

In early liver disease, fibrogenesis is matched by an upregulated fibrolysis (removal of excess ECM by proteolytic enzymes), mainly via the ECM degrading matrix metalloproteinases (MMPs), such as MMP-1, -3, -8, -9, -12, and -13 [1,3]. Upon protracted injury, fibrogenesis prevails over fibrolysis, resulting in excess ECM deposition, which is accompanied by a downregulation of MMP secretion and activity, and by an increase of the tissue inhibitors of MMPs (TIMPs), especially

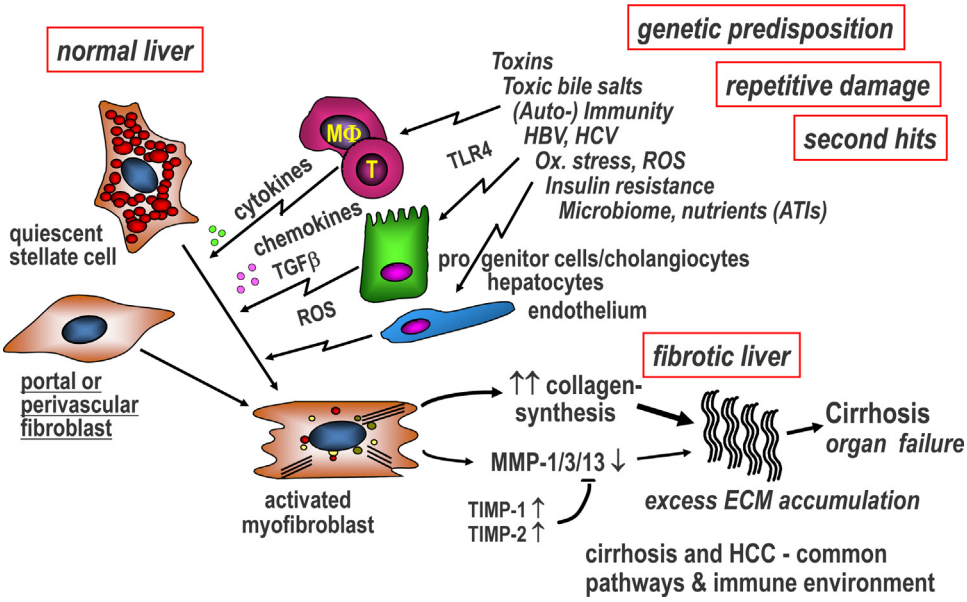

Figure 1 Common cellular mechanisms of liver fibrogenesis. Activated hepatic stellate cells and (portal) myofibroblasts (HSC/MF) are prime effectors of liver fibrogenesis. They are characterized by increased proliferation, migration and contractility, and a relative resistance to apoptosis. In addition, activated cholangiocytes, which share common characteristics with fibrogenic progenitor cells have emerged as important drivers of fibrogenesis. Apart from an upregulation of the synthesis and deposition of various ECM components, fibrolysis is further compromised via an increased synthesis of TIMP-1 and a decreased production of fibrolytic MMPs, both by HSC/MF and by Kupffer cells/macrophages. Other cell types and various stimuli can contribute to fibrogenesis or fibrolysis. Usually, more than a single, primary hit (the primary etiology) needs to be present, to promote progression to cirrhosis. These second hits can partly be addressed prophylactically, e.g., by alcohol abstinence or weight loss and physical exercise in case of non-alcoholic fatty liver disease. Once these triggers subside and with the help of antifibrotic agents, fibrosis can regress, largely via proteolytic removal of excess ECM, often by the same cells that play a central role in fibrogenesis, such as activated HSC/MF and macrophages/Kupffer cells. ATIs: wheat amylase trypsin inhibitors (nutritional TLR4 activators); ECM: extracellular matrix; MMP: matrix metalloproteinase; ROS: reactive oxygen species; TGFβ: transforming growth factor beta; TIMP: tissue inhibitor of metalloproteinases; TLR4: toll-like receptor 4.