Matrix metalloproteinases and liver fibrosis (translational aspects)

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Abstract

Liver fibrosis, a reversible wound-healing response to chronic cellular injury, reflects a balance between liver repair and progressive substitution of the liver parenchyma by scar tissue. Complex mechanisms that underlie liver fibrogenesis are summarized to provide the basis for generating targeted therapies to reverse fibrogenesis and improve the outcomes of patients with chronic liver disease. This minireview presents some pathophysiological aspects of liver fibrosis as a dynamic process and elucidates matrix metalloproteinases (MMPs) and their role within as well as beyond matrix degradation. Open questions remain, whether inhibition of fibrogenesis or induction of fibrolysis is the key mechanism to resolve fibrosis. And a point of principle might be whether regeneration of liver cirrhosis is possible. Will we ever cure fibrosis?

Introduction

Liver fibrosis is a common pathologic consequence of a wide variety of chronic liver diseases, including hepatitis B and C virus infections, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD) especially nonalcoholic steatohepatitis (NASH), as well as primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and other autoimmune liver diseases (AIH). Fibrosis results from an accumulation of extracellular matrix (ECM) following the activation and proliferation of hepatic stellate cells (HSCs). Upon liver injury, excessive deposition of collagen from activated HSCs is the leading cause of liver fibrosis. The extent of liver fibrosis is the most important predictor of liver-related outcomes, including development of portal hypertension, decompensation events, cancer and death. Fig. 1 summarizes the common state of knowledge about etiologies and pathophysiological mechanisms of liver fibrogenesis as well as carcinogenesis. (Fig. 1).

One of the pathological features of liver fibrosis is the increased expression of collagen, fibronectins, proteoglycans, structural glycoproteins, hyaluronan, and thus a persistent new formation of ECM. A substantial change is the deposition of collagens, mainly fibril-forming types I, III, and IV, which increase in fibrotic ECM up to ten-fold [1,2,3]. Collagen is degraded by matrix metalloproteinases (MMPs), which together with their inhibitors, so-called TIMPs (tissue Inhibitor of metalloproteinases), play a key role fibrogenesis and fibrolysis [1,2,3]. The family of human MMPs already comprises >24 members and can be divided into the subgroups stromelysins, gelatinases, collagenases, matrilysins, metalloelastase, enamelysin, membrane-type MMPs, and others [1,2]. MMPs are secreted as proenzymes and activated in extracellular space. During fibrogenesis, the ECM is reworked, resulting in an approximately ten-fold increase in the collagens I, III, and IV in an already advanced cirrhosis [2]. Since several years MMPs as well as their specific tissue inhibitors, have been implicated in the pathogenesis of various liver diseases, especially liver fibrogenesis.

Some pathophysiological aspects of liver fibrosis as a dynamic process

In healthy liver homeostasis of ECM is precisely regulated by a permanent turn-over directed by a group of enzymes called MMPs and their specific

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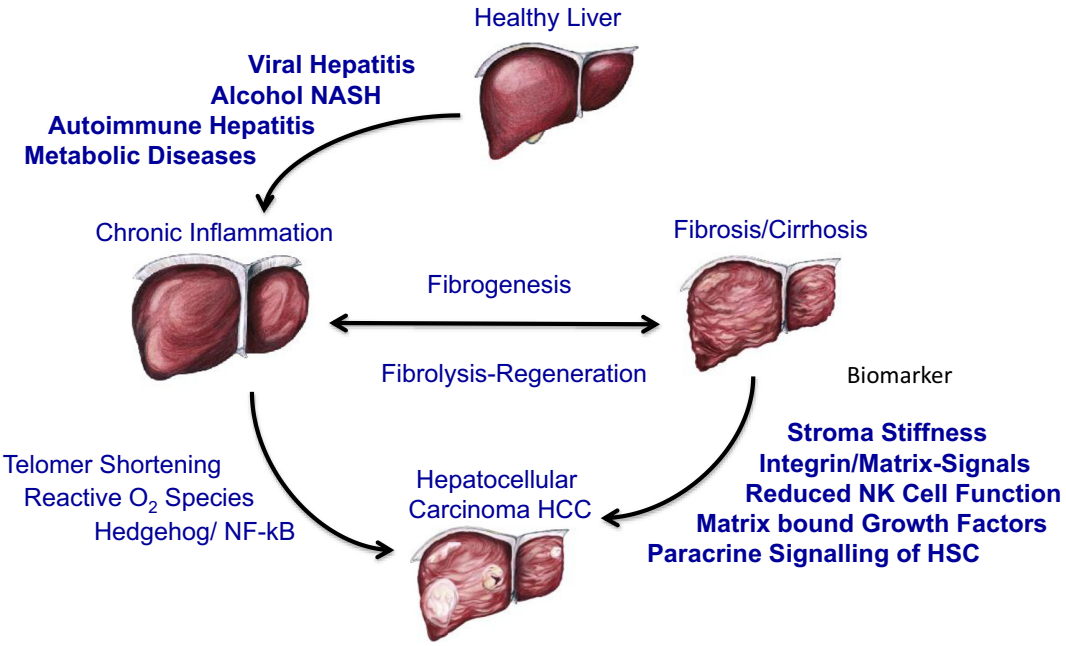

Fig. 1. Common causes of fibrogenesis and carcinogenesis.

inhibitors, TIMPs. Upon chronic damage of liver tissue, HSCs become activated and differentiate into a fibroblast-like phenotype. In activated HSCs, especially the expression of TIMP-1 is upregulated leading to the inhibition of MMP activity and subsequent accumulation of matrix proteins in the extracellular space [3]. In healthy liver tissue, there is a balance between TIMPs and MMPs, which control the removal and assembly of the ECM (Fig. 2). During fibrogenesis, this equilibrium is disturbed and increased expression of TIMPs and MMPs occurs with an excess of TIMPs and thus inhibition of matrix degradation [4]. However, activated HSCs can also contribute to the regression of fibrosis via the release of ECM-degrading proteases.

In addition lipid peroxidation in Kupffer cells leads to early HSC activation, such as activation of toll-like receptor 4 by LPS via NFkappaB and transcription of proinflammatory cytokines, e.g. tumor necrosis factor-α (TNF-α) and interferon-γ [5]. Bone marrow stem cells, CD34+ fibrocytes, portal fibroblasts, as well as capsular fibroblasts are also associated with

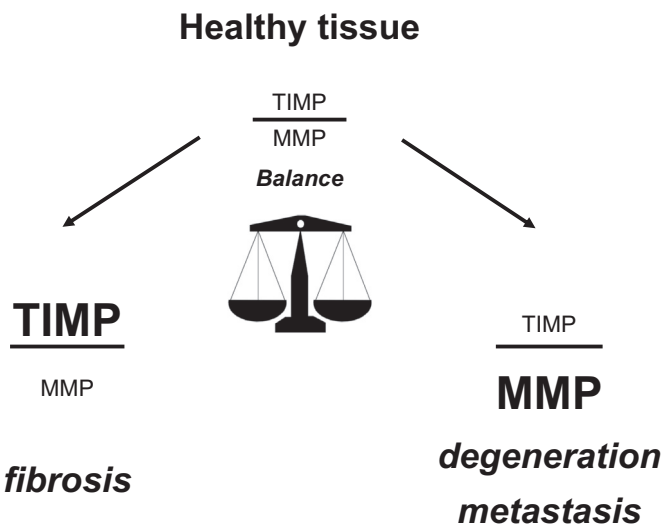

Fig. 2. Simplified scheme for the ECM.

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