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Modulation of hepatic stellate cells and reversibility of hepatic fibrosis

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ABSTRACT

Hepatic fibrosis (HF) is the pathological component of a variety of chronic liver diseases. Hepatic stellate cells (HSC) are the main collagen-producing cells in the liver and their activation promotes HF. If HSC activation and proliferation can be inhibited, HF occurrence and development can theoretically be reduced and even reversed. Over the past ten years, a number of studies have addressed this process, and here we present a review of HSC modulation and HF reversal.

1. Introduction

Hepatic fibrosis (HF) is a common wound-healing response to chronic liver injury [1] involving excessive deposition of extracellular matrix (ECM) [2] HF can be reversed if the cause of fibrosis formation is weakened or eliminated [3]. HF is an important pathological process by which chronic liver disease eventually develops into liver cirrhosis or hepatocellular carcinoma [4]. Hepatic stellate cells (HSC) are non-parenchymal cells that localize in the space of Disse. They were first described by Carl-von Kupffer 1876 [5], and have also been referred to as Ito cells, perisinusoidal stellate cells (fat-storing cells, interstitial cells, lipocytes), or vitamin A-storing cells. They were officially named HSC in 1995, and are the main collagen-producing cells in the liver [6]. In the normal liver, HSC are in quiescent state and the ECM is composed of macromolecules including collagens (types I, III, IV, V and VI) [7,8]. Matrix can be degraded by a variety of enzymes, but primarily by matrix degrading metalloproteinases (MMPs). Many types of liver cells including HSC, hepatocytes, Kupffer cells, neutrophils and recruited hepatic macrophages can express MMPs [9], and humans express MMP-1 while rodents express MMP-13 [10]. Activated MMPs are susceptible to inhibition by key extracellular inhibitors, tissue inhibitors of metalloproteinases (TIMPs) [9]. Moderate TIMP-2 expression regulates the TIMP-MMP balance in quiescent HSC [10]. In the healthy liver, extracellular matrix is degraded and thus does not accumulate causing fibrosis (Fig. 1).

In contrast, after the liver injury the TIMP-MMP balance is disturbed, and TIMPs are over-expressed contributing to ECM deposition and development of fibrosis [10]. When the liver is damaged by inflammatory or mechanical processes, HSC can be activated to produce activating cytokines which promote proliferation [11,12]. This activation to a myofibroblast-like phenotype increases expression of alpha smooth muscle actin, upregulating secretion of fibrillar collagens, elastins and matrix proteins [13–16]. TIMP-1 expression and secretion is strongly linked to HSC activation, in terms of numbers of activated cells and fibrosis activity, and remains at high levels during progressive fibrosis [17]. However, the expression of interstitial collagenase in humans (MMP-1) and rodents (MMP-13) remains relatively unaltered [17,18]. TIMP expression is also regulated by cytokines and growth factors. Pro-fibrogenic cytokines such as TGF-β1 may differentially affect MMP expression by downregulating interstitial collagenase expression while upregulating expression of gelatinase A, TIMP-1 and collagen-I [9]. The binding of TIMPs to active MMPs appears to cause irreversible ECM deposition, which leads to fibrosis. Both HSC activation and their numbers appears to be altered with specific changes in phenotype that accompany fibrogenesis in vivo [10].

These observations suggest that if HSC activation and proliferation can be inhibited, or the rate of apoptosis increased, the progression of HF may be inhibited or reversed (Fig. 2).

Abbreviations: HF, hepatic fibrosis; HSC, hepatic stellate cells; ECM, extracellular matrix; MMPs, matrix degrading metalloproteinases; TIMPs, tissue inhibitors of metalloproteinases; TGF-β, transforming growth factor-beta; NK, Natural killer; NKT, NK like T; NKG2D, natural killer group 2, member D; RAE1, retinoic acid early inducible 1; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; IL-30, interleukin-30; IFN-γ, interferon-gamma; CD, cluster of differentiation; Tregs, regulatory T cells; PPAR, peroxisome proliferator-activated receptor; 3-BrPA, 3-bromopyruvate; TCM, traditional Chinese medicine; PDGF, platelet-derived growth factor

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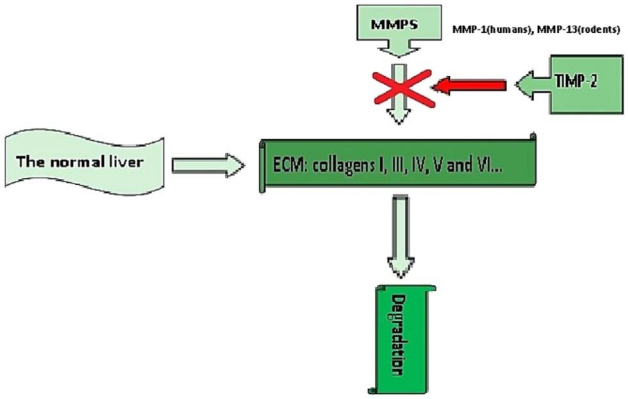

Fig. 1. Extracellular matrix degradation in normal liver. Healthy liver produces ECM composed of collagens (types I, III, IV, V and VI). Under the synergistic action of MMPS (humans express MMP-1 and rodents express MMP-13) and TIMP-2, the ECM is ultimately degraded and does not accumulate.

2. Evidence of HF reversibility

Several clinical reports have shown that HF is a dynamic process influenced by the balance between the ECM deposition and degradation [19]. Recently clinical studies have shown that HF is reversible, not only in experimental models of liver fibrosis, but also in humans (Table 1). However, whether end-stage cirrhosis can completely revert to a healthy liver architecture remains unknown [30]. Unfortunately, few of these studies have demonstrated a clear distinction between HF reversal in early and advanced stages of fibrosis.

3. Mechanism of HF reversibility

During HF reversal the number of activated HSC is decreased primarily by apoptosis or phenotypic conversion (reversion to a quiescent state) [31]. Other studies have reported that in addition to apoptosis and phenotype reversion, activation restriction, immune clearance and senescence are also involved in the clearance of activated HSC [32]. The occurrence and development of HF can, therefore, theoretically be inhibited , or even reversed, by stimulating these mechanisms (Fig. 3).

3.1. Prevention of HSC activation

HSC activation is affected by interactions with neighboring parenchymal and non-parenchymal cells (immune cells, capillarized liver sinusoidal endothelial cells), and by cell matrix components, interactions mediated through integrins, and matrix stiffness [33]. HSC activation is supported by transforming growth factorβ (TGF-β). Production of TGF-β1 promotes and maintains collagen gene expression in an autocrine loop, and upregulates TIMP expression. TIMPs inhibit metalloproteinases and have an anti-apoptotic effect on HSC [34]. However, which pathway is the most effective remains unknown. One study confirmed that relaxin not only inhibits HSC contribution to HF progression, but also promotes clearance of fibrillar collagen through the relaxin receptor [35]. HSC activation depends on an uninterrupted supply of intracellular energy. If this energy supply is blocked, synthesis and secretion of ECM will be halted. In a recent preclinical study, a sublethal dose of the energy blocker, 3-bromopyruvate (3-BrPA) promoted phenotypic alteration of activated HSC into a less-active form, and reduced ECM secretion by interfering with energy metabolism [36]. A deeper understanding of the mechanisms underpinning this effect, and the role of energy blockers, might reveal a valuable therapeutic target for human HF.

3.2. Reversal of HSC activation

Although the HSC phenotype is difficult to reverse after activation, reversal is not impossible [37]. Phenotypic conversion can restore the quiescent state of HSC, reduce pre-fibrosis cytokine secretion and the ECM deposition [38]. However, deactivated HSC do not fully revert to a quiescent state, but retain a preactivated intermediate state, and are more susceptible to subsequent insult [33]. Proteolytic clearance of non-fibrin matrix components can restore the quiescent HSC phenotype by plasminogen [39]. Even after activation to myofibroblasts, HSC can also revert to a quiescence-like phenotype by up-regulating the anti-apoptotic genes Hspa1a/b [40]. Nevertheless, identification of HSC activation state and regulating phenotype reversal remains to be studied. The major determinants of HF, gene expression, epigenetic mechanisms including DNA methylation, histone posttranslational modifications and noncoding RNA, can maintain HSC in a partially quiescent state [41]. Further research will be required to understand how to control reversibility of deactivated HSC, and develop mechanisms by which HSC can be reverted to a quiescent state, avoiding further episodes of liver injury.

3.3. HSC elimination

3.3.1. Innate immune cells

HSC can amplify inflammatory responses in the injured liver by promoting inflammatory cell recruitment [42]. The number of acti-

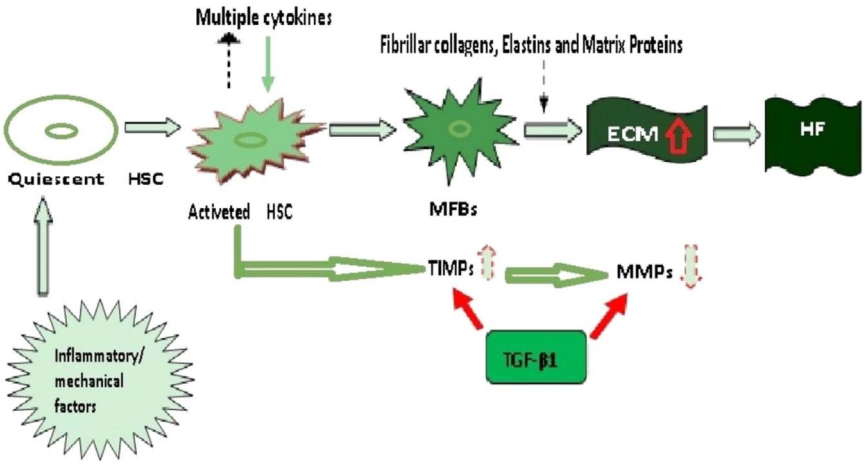

Fig. 2. Extracellular matrix degradation in injured liver. In response to acute or chronic parenchymal injuries, quiescent HSC are activated by inflammatory and mechanical factors. HSC can produce multiple cytokines which promote HSC development into myofibroblastic cells which secrete fibrillar collagens, elastins and matrix proteins. Additionally, TIMP expression and secretion increases during progressive fibrosis and MMPs expression is regulated by TGF-β1. Thus ECM deposition causes HF.