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Molecular pathogenesis of hepatic fibrosis and current therapeutic approaches

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ABSTRACT

The pathogenesis of hepatic fibrosis involves significant deposition of fibrilar collagen and other extracellular matrix proteins. It is a rather dynamic process of wound healing in response to a variety of persistent liver injury caused by factors such as ethanol intake, viral infection, drugs, toxins, cholestasis, and metabolic disorders. Liver fibrosis distorts the hepatic architecture, decreases the number of endothelial cell fenestrations and causes portal hypertension. Key events are the activation and transformation of quiescent hepatic stellate cells into myofibroblast-like cells with the subsequent up-regulation of proteins such as α-smooth muscle actin, interstitial collagens, matrix metalloproteinases, tissue inhibitor of metalloproteinases, and proteoglycans. Oxidative stress is a major contributing factor to the onset of liver fibrosis and it is typically associated with a decrease in the antioxidant defense. Currently, there is no effective therapy for advanced liver fibrosis. In its early stages, liver fibrosis is reversible upon cessation of the causative agent. In this review, we discuss some aspects on the etiology of liver fibrosis, the cells involved, the molecular pathogenesis, and the current therapeutic approaches.

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1. Introduction

Fibrosis is the wound healing response to a variety of acute and/or chronic stimuli, including to name a few, ethanol, viral infection, drugs and toxins, cholestasis, and metabolic disease [1,2]. Hepatic fibrosis develops due to an increase in fibrillar collagen synthesis and deposition along with insufficient remodeling [3,4]. Fibrosis is associated with a number of pathological and biochemical changes leading to structural and metabolic abnormalities, as well as with increased hepatic scarring [5,6]. The progression of liver fibrosis leads to cirrhosis, a condition characterized by distortion of the normal architecture, septae and nodule formation, altered blood flow, portal hypertension, hepatocellular carcinoma, and ultimately liver failure [7].

2. Etiology of hepatic fibrosis

Most chronic liver diseases are associated with fibrosis and are characterized by parenchymal damage and inflammation. Alcohol abuse, chronic viral hepatitis (HBV and HCV), obesity, autoimmune hepatitis, parasitic diseases (i.e. schistosomiasis), metabolic disorders (hemochromatosis and Wilson's disease), biliary disease, persistent exposure to toxins and chemicals, and drug-induced chronic liver diseases are the most common causes of hepatic fibrosis.

2.1. Alcohol

Alcohol consumption is a predominant etiological factor in the pathogenesis of chronic liver diseases worldwide, resulting in fatty liver, alcoholic hepatitis, fibrosis/cirrhosis, and hepatocellular carcinoma [8]. Acetaldehyde, the product of alcohol metabolism via alcohol dehydrogenase, increases the secretion of transforming growth factor β1 (TGFβ1) and induces TGFβ type II receptor expression in hepatic stellate cells (HSC), the key collagen-producing cell within the liver [9]. Both, ethanol and acetaldehyde induce the *COL1A2* promoter and up-regulate collagen I protein expression [10]. In cultured human HSC, acetaldehyde up-regulates *COL1A1* mRNA expression via distinct mechanisms in the early and late responses [11]. Acetaldehyde-induced fibrogenesis involves a complex signaling pathway, which differs from that mediated by TGFβ1 in the early time points to up-regulate *COL1A2* gene expression [11].

TGFβ1 is a critical factor in the progression of alcoholic liver disease (ALD) in patients with steatosis and steatohepatitis [12]. Acetaldehyde does not alter the Smad3 and Smad4 protein concentration; however, it selectively induces phosphorylation of Smad3 but not of Smad2 [13]. Weng et al. [12] identified a significant

Abbreviations: ALD, alcoholic liver disease; AP1, activator protein 1; α-SMA, α-smooth muscle actin; CCl_4, carbon tetrachloride; CYP2E1, cytochrome P450 2E1; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HSC, hepatic stellate cells; JNK, c-*jun* N-terminal kinase; MCP1, monocyte chemoattractant protein 1; miRNA, micro RNA; MMP, matrix metalloproteinase; NFκB, nuclear factor kappa B; PDGF, platelet-derived growth factor; RAGE, advanced glycation-end products; ROS, reactive oxygen species; TGFβ1, transforming growth factor β1; TIMP1, tissue inhibitor of metalloproteinase 1.

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correlation of Smad2 phosphorylation with the fibrosis stage and the inflammation score. In addition, an association between serum pro-collagen III N-pro-peptide and TGFβ1 has been reported in patients with ALD [14]. These results demonstrate a significant role for TGFβ1 as mediator of alcohol-induced liver fibrosis.

Hepatic alcohol metabolism generates reactive oxygen species (ROS) causing significant cell death [15]. Indeed, oxidative stress, likely by increasing mitochondrial permeability transition, promotes hepatocyte necrosis and/or apoptosis. Generation of ROS within hepatocytes may be a consequence of an altered metabolic state, as it occurs in non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Alternatively, it could result from ethanol metabolism as in alcoholic steatohepatitis, with ROS being generated mainly by the mitochondrial electron transport chain, cytochrome P450 isoforms such as cytochrome P450 2E1 (CYP2E1), damaged mitochondria, xanthine oxidase, NADPH oxidase, and generation of lipid peroxidation-end products [16]. In addition, it is known that chronic alcohol consumption lowers glutathione levels; thus, contributing to liver injury [17]. ROS-derived mediators released by damaged neighboring cells can directly affect the HSC behavior. ROS up-regulate the expression of critical genes related to fibrogenesis including pro-collagen type I, monocyte chemoattractant protein 1 (MCP-1), and tissue inhibitor of metalloproteinase-1 (TIMP1), possibly via activation of a number of critical signal transduction pathways and transcription factors, including c-*jun* N-terminal kinases (JNKs), activator protein 1 (AP-1), and nuclear factor kappa B (NFκB) [18].

2.2. Chronic viral hepatitis

Chronic hepatitis B and C virus are the most common causes of liver disease worldwide, with an estimated 350 and 170 million of individuals with chronic infection, respectively [19]. In addition, these infections are the primary cause of hepatocellular carcinoma (HCC). In both cases, there is significant chronic liver injury with subsequent progression to advanced liver fibrosis and in many cases cirrhosis. While HBV can be integrated into the host genome leading to changes in genomic function or chromosomal instability, HCV cannot integrate into the host genome. Various HCV proteins, including the HCV core protein, the envelope and non-structural proteins present oncogenic properties. In HBV infection, antiviral therapy and vaccination decrease the risk of HCC. Current antiviral therapies for HCV such as ribavirin significantly reduce the risk of HCC.

2.3. Other causes of hepatic fibrosis

In addition to alcoholism and chronic viral hepatitis, other factors contributing to hepatic fibrosis are obesity and steatosis, which can lead to nonalcoholic fatty liver disease and to chronic steatohepatitis. Nonalcoholic fatty liver disease has also been reported in non-obese individuals in developing countries [20].

Autoimmune hepatitis, the anomalous presentation of human leukocyte antigen class II in hepatocytes, causes cell-mediated immune responses against the host liver, and may lead to liver fibrosis as well [21]. Parasitic infections like schistosomiasis, have been shown to trigger advanced liver fibrosis and portal hypertension [22].

Metabolic disorders such as hemochromatosis and Wilson's disease are typically accompanied by chronic hepatitis and fibrosis [23]. In hereditary hemochromatosis, the excessive absorption and accumulation of iron in tissues and organs including liver is related to mutations in the *HFE* (High-iron) gene [24]. Wilson's disease or hepatolenticular degeneration is a genetic disorder leading to copper accumulation in the liver and it is due to a mutation in the APTase (ATP7B) that transports copper [25].

Lastly, cholestasis due to bile duct obstruction, leads to chronic portal fibrosis and eventually cirrhosis. Moreover, chronic exposure to toxins or chemicals such as N-nitrosodimethylamine, carbon tetrachloride (CCl_4) or thioacetamide leads to severe hepatic fibrosis in experimental animal models [26–28]. Exposure to these chemicals in humans is rare and generally occurs in the industry during manufacture and in places where these chemicals are routinely used.

3. Cell types involved in the pathogenesis of hepatic fibrosis

3.1. Hepatic stellate cells

Several cell types are involved in the pathogenesis of hepatic fibrosis. HSC reside in the *space of Disse* between hepatocytes and sinusoidal endothelial cells [29]. Quiescent HSC are characterized by significant expression of desmin and vitamin A storage. Following liver injury, HSC lose their vitamin A content, increase the expression of α-smooth muscle actin (α-SMA), acquire a myofibroblast-like phenotype losing their typical star-shape, become proliferative, motile, pro-fibrogenic, contractile, and show abundant rough endoplasmic reticulum [30].

Many factors have been identified to contribute to HSC activation. Damage to hepatocytes and Kupffer cell activation are still considered the primary effectors driving HSC activation [31,32]. Mediators released from damaged hepatocytes, such as lipid peroxidation products, intermediate metabolites of drugs or hepatotoxins, acetaldehyde, and 1-hydroxyethyl radical from alcohol metabolism as well as ROS (hydrogen peroxide, superoxide radical, and others) are strong inducers of HSC activation.

Activated Kupffer cells release ROS and cytokines that are crucial for HSC activation as well [32]. They are a major source of TGFβ and platelet-derived growth factor (PDGF), two potent profibrogenic cytokines that traditionally have been considered key fibrogenic and proliferative stimuli to HSC, respectively [33]. In addition, the Kupffer cell phagocytic activity generates large amounts of ROS that could further activate HSC and induce their fibrogenic potential.

We have previously demonstrated that cytochrome P450 2E1-dependent generation of ROS is critical for increased collagen I protein synthesis in co-cultures of hepatocytes and HSC [31]. Furthermore, addition of ethanol and arachidonic acid synergized to activate Kupffer cells and modulated the fibrogenic response by a mechanism involving TNFα, reduced glutathione and TGFβ [34].

It has been also demonstrated that *in vivo* ablation of TNFα, TLR4, CD14, and lipopolysaccharide-binding protein protects from the fibrogenic response [35]. Despite the close association of inflammation and fibrosis, little is known on the crosstalk between these two key events and the intracellular signal transduction pathways activated. For example, TLR4 is activated by lipopolysaccharide in Kupffer cells leading to NFκB and IRF3 activation, and the subsequent transcriptional activation of pro-inflammatory mediators such as TNFα and IFNγ. Moreover, TNFα activates the NFκB signaling pathway in hepatocytes, which is key for their survival [8,36]. However, there is no crosstalk with the TGFβ pathway that results in the activation of Smad3 and Smad4 and the associated induction of TGFβ-responsive genes.

3.2. Portal fibroblasts

The portal connective tissue in healthy liver is surrounded by quiescent portal fibroblasts, which constitute a second population of liver cells implicated in portal fibrosis [37]. Derived from small

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