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Review

Wnt signaling in liver fibrosis: Progress, challenges and potential directions

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ABSTRACT

Liver fibrosis is a common wound-healing response to chronic liver injuries, including alcoholic or drug toxicity, persistent viral infection, and genetic factors. Myofibroblastic transdifferentiation (MTD) is the pivotal event during liver fibrogenesis, and research in the past few years has identified key mediators and molecular mechanisms responsible for MTD of hepatic stellate cells (HSCs). HSCs are undifferentiated cells which play an important role in liver regeneration. Recent evidence demonstrates that HSCs derive from mesoderm and at least in part via septum transversum and mesothelium, and HSCs express markers for different cell types which derive from multipotent mesenchymal progenitors. There is a regulatory commonality between differentiation of adipocytes and that of HSC, and the shift from adipogenic to myogenic or neuronal phenotype characterizes HSC MTD. Central of this shift is a loss of expression of the master adipogenic regulator peroxisome proliferator activated receptor γ (PPARγ). Restored expression of PPARγ and/or other adipogenic transcription genes can reverse myofibroblastic HSCs to differentiated cells. Vertebrate Wnt and Drosophila wingless are homologous genes, and their translated proteins have been shown to participate in the regulation of cell proliferation, cell polarity, cell differentiation, and other biological roles. More recently, Wnt signaling is implicated in human fibrosing diseases, such as pulmonary fibrosis, renal fibrosis, and liver fibrosis. Blocking the canonical Wnt signal pathway with the co-receptor antagonist Dickkopf-1 (DKK1) abrogates these epigenetic repressions and restores the gene PPARγ expression and HSC differentiation. The identified morphogen mediated epigenetic regulation of PPARγ and HSC differentiation also serves as novel therapeutic targets for liver fibrosis and liver regeneration. In conclusion, the Wnt signaling promotes liver fibrosis by enhancing HSC activation and survival, and we herein discuss what we currently know and what we expect will come in this field in the next future.

1. Introduction

Liver fibrosis is a common wound-healing response to chronic liver injuries, including persistent alcoholic toxicity, viral infection and hereditary metal overload [1]. Hepatic stellate cells (HSCs) are undifferentiated cells capable to develop cells of endothelial and hepatocyte lineages, and activated HSCs are the most important source of extracellular matrix proteins during the disease process [2]. Much evidence confirms that activated HSCs induce the occurrence and development of liver fibrosis. In their quiescent stage, HSCs store retinoids and synthesize glial fibrillary acidic protein (GFAP). In activated stage, a gradual loss of retinoids and GFAP accompanies their development into myofibroblast-like cells with increased synthesis of extracellular matrix proteins and a-smooth muscle actin (a-SMA) [3,4]. Due to these properties, the majority of anti-fibrotic therapies are designed to inhibit the

Abbreviations: HSCs, hepatic stellate cells; GFAP, glial fibrillary acidic protein; a-SMA, a-smooth muscle actin; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; Gsk3β, glycogen synthase kinase 3β; Fz, frizzled; Lrp5/6, lipoprotein receptor-related protein 5/6; LEF, lymphoid enhancer binding factor; TCF, T-cell specific transcription factors; MMP, matrix metalloproteinase; MCP-1, monocyte chemotactic protein-1; MMPCs, mesoderm-derived multipotent mesenchymal progenitor cells; PDGF, platelet-derived growth factor; HCV, hepatitis C; CK1, casein kinase 1; APC, adenomatous polyposis coli; Dvl, disheveled; SFRP, secreted frizzled-related protein; DKK, Dickkopf; PCP, planar cell polarity; PKC, protein kinase C; CamKII, calmodulin kinase II; ROK, rho kinase; PPRE, PPAR response element; PITX2c, paired-like homeodomain transcription factor 2c; KEGG, kyoto encyclopedia of genes and genomes; HFFs, human foreskin fibroblasts; DLK1, Delta-like 1 homolog; PH, partial hepatectomy; AICAR, 5-aminoimidazole-4-carboxamide-1-beta-4-ribofuranoside; MeCP2, methyl-CpG binding protein 2; UUO, unilateral ureteral obstruction; RA, rheumatoid arthritis; FLS, fibroblast-like synoviocytes; 5-azadC, 5-aza-2′-deoxycytidine; ox-LDL, oxidized low-density lipoprotein; LOX-1, lectin-like ox-LDL receptor-1; PRA, polyphenolic rosmarinic acid; BC, baicalin; HPCs, hepatic progenitor cells.

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activation, proliferation, and synthetic products of HSCs. For example, the selective induction of HSC apoptosis by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) has been proposed as an anti-fibrotic treatment [5].

In the past few years, there have been notable advances toward a deeper understanding of the pathogenesis of liver fibrosis, leading to changes in the study and treatment of this disease [6]. Accumulated evidence shows that several signaling pathways are involved in the liver fibrosis pathogenesis, such as the Wnt signaling pathway, which is proved to play an important role during liver fibrosis [7]. For example, a literature in work showed that mice with hepatocyte-specific β-catenin deletion developed significantly higher steatohepatitis and fibrosis on the steatogenic methionine and choline-deficient diet compared with wild-type mice. Blocking of the Wnt signaling pathway in liver would lead to liver metabolic disorders and physiological dysfunction [8]. Recent evidence suggests that the Wnt signaling is activated in HSCs during liver fibrosis, and some elements of the Wnt signaling pathway are up-regulated and implicated in the process [9]. In absence of Wnt signaling, cytoplasmic β-catenin is recruited into a protein destruction complex that facilitates phosphorylation of β-catenin by glycogen synthase kinase 3β (Gsk3β) and its proteasomal degradation. Wnt ligands are capable to stimulate the Wnt signaling by binding to their receptors frizzled (Fz) and co-receptors lipoprotein receptor-related protein 5/6 (Lrp5/6), leading to phosphorylation of disheveled, a downstream scaffold protein of Wnt signaling, and disruption of the β-catenin destruction complex. This signaling finally results in inhibition of Gsk3β activity, reduced proteolysis of β-catenin and translocation of β-catenin into the nucleus. Then nuclear β-catenin alters expression of Wnt target genes by binding to the transcription factors lymphoid enhancer binding factor (LEF) and T-cell specific transcription factors (TCF) [8]. Base on these findings, it is confirmed that the Wnt signaling pathway is involved in the pathogenesis of liver fibrosis, and research in this area is beneficial to the treatment of this disease.

2. HSC

2.1. The origin of HSCs

It is well known that HSCs develop into critical effector cells which are thought to contribute to liver fibrogenesis. Activation of HSCs is recognized as the central event during liver fibrosis, and the molecular mechanisms of this cellular alternation attract more and more attention [10,11]. This has led to the generation of an explosive amount of new findings including gene regulation, identification of mediators, and intracellular signaling that control the expression of activation-associated molecules such as cytokines, collagens, extracellular matrix degradation enzymes and inhibitors (matrix metalloproteinase, MMP), monocyte chemotactic protein-1 (MCP-1), tissue inhibitors of metalloproteinases, renin-angiotensin system, and nicotinamide adenine dinucleotide phosphate oxidase [12,13]. However, there is limited knowledge about HSC activation from the viewpoint of cell fate or lineage regulation. Obviously, this question cannot be clarified without understanding the embryonic origin of HSC [14]. In the past years, since HSC express many neuronal or glial cell markers, many reports suggest that HSCs are derived from neuroectoderm [15,16]. But subsequent experimental results using the Wnt1-Cre and ROSA26 reporter mice show that this view is incorrect [16]. Recently, many reports demonstrate that HSCs derive from mesoderm-derived multipotent mesenchymal progenitor cells (MMPCs) and at least in part via septum transversum and mesothelium, because MMPCs give rise to neural cells and other mesenchymal lineages for chondrocytes, smooth muscle cells, adipocytes, and osteoblasts whose markers are also expressed by HSCs [17,18]. The findings in cell fate regulation of different mesenchymal cell types derived from MMPC are that they will undergo trans-differentiation within their lineages in culture upon addition of mediators [19]. Base on these findings, we should accept the notion that HSC trans-differentiation may reside in these mesenchymal lineages.

2.2. The function of HSCs

There is evidence that HSCs are progenitor cells with the capacity to differentiate into cells of hepatocyte and endothelial lineages [20,21]. HSCs are the major mesenchymal cell type in liver tissue with several known functions, such as control of sinusoidal vascular tone, vitamin A storage, wound healing, and mesenchymal–epithelial interaction [22]. Although the storage of lipid-soluble retinyl esters is primarily considered as the main physiological function, HSCs also store other lipids, particularly neural lipids. Thus Toshio Ito and colleagues who recognize this lipid-storing phenotype term the cells “fat storing cells” [23]. Since then, this intriguing aspect of HSC was in large left unexplored. Several reports propose that there was a regulatory commonality between HSCs and adipocytes differentiation [24,25]. HSC trans-differentiation is similar to adipocyte and preadipocytic fibroblast de-differentiation, and this notion is based on several similarities found between two processes. First, both differentiated HSCs and adipocytes share a fat storing phenotype, as discussed in reference to Professor Ito and Tsukamoto’s work. Second, both differentiated HSCs and adipocytes primarily express type IV collagen while trans- differentiated HSCs and preadipocytic fibroblasts primarily express interstitial collagens. Third, intracellular lipids are lost during HSC trans-differentiation and adipocytes dedifferentiation. Fourth, cultivation with cell differentiation regulators known to suppress adipocyte differentiation such as platelet-derived growth factor (PDGF), TNFα, MCP-1, and leptin also can promote the HSC activation. Last, differentiated HSCs are known to express adipocyte-specific genes including adipsin, leptin, and adiponectin [26–28]. Since the PPARγ promotes the storage of intracellular fat including retinyl esters in HSC and suppresses the α1 (I) collagen gene via the inhibition of p300-facilitated NF–I binding to its promoter, central to this proposal is the expression and regulation of the adipogenic transcription gene PPARγ, which is essential for both adipocyte and HSC differentiation [29]. Animal models of liver fibrosis also show the efficacy of PPARγ ligands in this disease treatment, thus PPARγ is considered as a potential therapeutic target for liver fibrosis [30,31].

2.3. HSCs and liver fibrosis

HSCs reside in the space of Disse between hepatocytes and sinusoidal endothelial cells in the liver and extend their dendritic processes along the wall of the sinusoid. One of the unique features of HSCs is that they store vitamin A lipids in their cytoplasm. Upon liver injury, they lose their stored vitamin A lipids, and quiescent HSCs radically change their phenotype into an activated state, begin expressing SMA and synthesizing both proinflammatory cytokines and extracellular matrix proteins. It is confirmed that activated HSCs become myofibroblasts in injured liver and participate in the pathogenesis of liver fibrosis. Therefore, the activation step of HSC has been considered as a possible therapeutic target for suppression of cirrhosis and liver fibrosis treatment [32]. Recently, many experimental studies have revealed the role of cytokines in liver fibrosis. For example, TGF-β is known to induce activation of HSCs and suppression of TGF-β signaling is shown to ameliorate liver fibrosis. In activated HSCs, TGF-β1 up-regulates the expression of

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