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Hepatic stellate cells as key target in liver fibrosis☆

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ABSTRACT

Progressive liver fibrosis, induced by chronic viral and metabolic disorders, leads to more than one million deaths annually via development of cirrhosis, although no antifibrotic therapy has been approved to date. Transdifferentiation (or "activation") of hepatic stellate cells is the major cellular source of matrix protein-secreting myofibroblasts, the major driver of liver fibrogenesis. Paracrine signals from injured epithelial cells, fibrotic tissue microenvironment, immune and systemic metabolic dysregulation, enteric dysbiosis, and hepatitis viral products can directly or indirectly induce stellate cell activation. Dysregulated intracellular signaling, epigenetic changes, and cellular stress response represent candidate targets to deactivate stellate cells by inducing reversion to inactivated state, cellular senescence, apoptosis, and/or clearance by immune cells. Cell type- and target-specific pharmacological intervention to therapeutically induce the deactivation will enable more effective and less toxic precision antifibrotic therapies.

Contents

Abbreviations: 5-HT(2B), 5-hydroxytryptamine 2B receptor; ACE, angiotensin-converting enzyme; AMPK, AMP-activated protein kinase; ARB, AT1R blocker; ASK1, apoptosis signal-regulating kinase 1; AT1R, angiotensin II type 1 receptor; ATX, autotaxin; BDL, bile duct ligation; CB, cannabinoid; CCL, C-C motif chemokine ligand; CCl4, carbon tetrachloride; CCR, C-C motif chemokine receptor; CpG, cytosine-phosphoguanine dinucleotide; CVCR, C-X-C motif chemokine receptor; CXCL, C-X-C motif chemokine ligand; DAMP, damage-associated molecular pattern; DKK1, Dickkopf-1; DNMT, DNA methyltransferase; ECM, extracellular matrix; EGF, epidermal growth factor; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; FGF, fibroblast growth factor; FXR, farnesoid-X-receptor; HBV, hepatitis B virus; HCV, hepatitis C virus; HGF, hepatocyte growth factor; Hh, hedgehog; HMGB1, high mobility group protein B1; HSC, hepatic stellate cell; IL, interleukin; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; LPA, lysophosphatidic acid; LRAT, lecithin-retinol acyltransferase; LSEC, liver sinusoidal endothelial cell; LY6C, lymphocyte antigen 6 complex; MeCP2, methyl-CpG binding protein 2; MMP, matrix metallopeptidase; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NF-kB, nuclear factor kBNK, natural killer; NO, nitric oxide; OCA, obeticholic acid; PAMP, pathogen-associated molecular pattern; PDGF, platelet-derived growth factor; PPAR, peroxisome proliferator-activated receptor; PRR, pattern recognition receptor; RAR, retinoic acid receptor; ROS, reactive oxygen species; RXR, retinoid X receptor; SREBP, sterol regulatory element-binding protein; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; Th, helper T; TLR, toll-like receptor; TNF, tumor necrosis factor; TWEAK, tumor necrosis factor-like weak inducer of apoptosis; TZD, thiazolidinedione; UPR, unfolded protein response; UTR, untranslated region; VAP-1, vascular adhesion protein 1; VDR, vitamin D receptor; VEGF, vascular endothelial growth factor.

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1. Introduction

Chronic tissue injury leads to a sustained scarring response that gradually disrupts normal cellular functional units and eventually causes failure in multiple epithelial organs such as liver, lung, and kidney, which is estimated to account for one-third of deaths worldwide [1]. Progressive liver fibrosis can be caused by chronic infection of hepatitis B virus (HBV) or hepatitis C virus (HCV), alcohol abuse, non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH), and other relatively rare conditions such as autoimmune hepatitis, hemochromatosis, Wilson's disease, and primary/secondary biliary cholangitis. Cirrhosis is the terminal stage of progressive liver fibrosis, which is estimated to affect 1% to 2% of global population and results in over 1 million deaths annually worldwide [2,3].

Lethal complications of cirrhosis include functional liver failure, portal hypertension-induced variceal bleeding, ascites, and hepatic encephalopathy, systemic bacterial infection, and liver cancer, especially hepatocellular carcinoma (HCC) [3]. Annual direct and indirect costs for the care of cirrhosis exceed $12 billion in the U.S. alone [4]. Although approved therapies directly targeting and reversing advanced fibrosis are still lacking, clinical studies have indicated that liver fibrosis and even cirrhosis can be regressed by therapeutic intervention aimed at the primary disease etiology [5]. In this review, we summarize recent findings relevant to direct therapeutic targeting of the major fibrogenic cell type in the liver, the activated hepatic stellate cell (HSC), as an antifibrotic strategy.

2. Cellular sources of matrix-producing myofibroblasts

2.1. Myofibroblasts: driver of tissue fibrogenesis in multiple organs

In chronic fibro-proliferative diseases, affecting multiple organs such as lung, kidney, and liver, presence of myofibroblasts is a key common feature [6]. The myofibroblast is a fibroblast-like cell with contractile properties, which is derived typically from cells of mesenchymal lineage via transdifferentiation, often referred to as "activation". Proliferating myofibroblasts are the key source of excess extracellular matrix (ECM) molecules such as collagen type I and III as well as other proteins that constitute pathologic fibrous tissues [7]. Paracrine factors such as platelet-derived growth factor (PDGF), transforming growth factor β (TGFβ), and connective tissue growth factor (CTGF), together with other growth

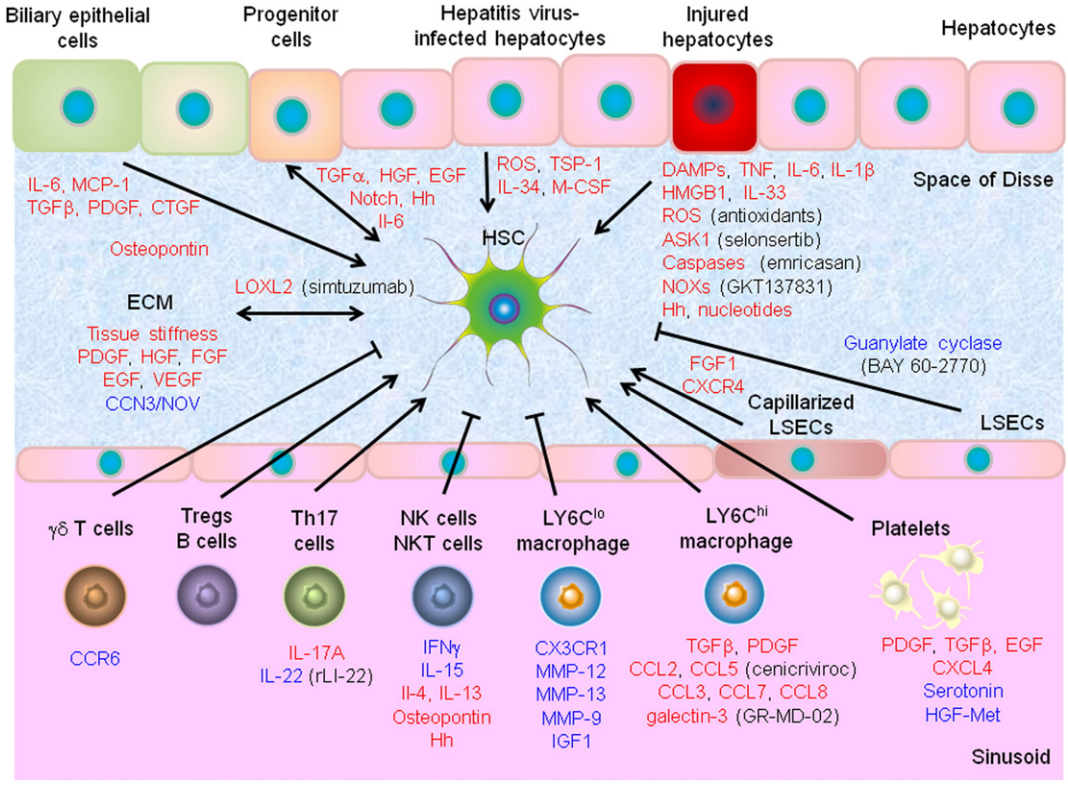

Fig. 1. Extracellular regulation of HSC activation. HSC activation is promoted (sharp arrow) or inhibited (blocked arrow) by liver resident cells, ECM, and circulating cells via paracrine factors. Red and blue font colors indicate positive and negative regulators of HSC activation, respectively. Pharmacological intervention to each candidate target is shown in parenthesis.