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Ezhilarasan, D.^a, Najimi, M.^b

Intercellular communication among liver cells in the perisinusoidal space of the injured liver: Pathophysiology and therapeutic directions

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^a Department of Pharmacology, Molecular Medicine and Toxicology Lab, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences (SIMATS), Tamil Nadu, Chennai, India

^b Laboratory of Pediatric Hepatology and Cell Therapy, Institute of Experimental and Clinical Research (IREC), UCLouvain, Brussels, Belgium

Abstract

Hepatic stellate cells (HSCs) in the perisinusoidal space are surrounded by hepatocytes, liver sinusoidal endothelial cells, Kupffer cells, and other resident immune cells. In the normal liver, HSCs communicate with these cells to maintain normal liver functions. However, after chronic liver injury, injured hepatocytes release several proinflammatory mediators, reactive oxygen species, and damage-associated molecular patterns into the perisinusoidal space. Consequently, such alteration activates quiescent HSCs to acquire a myofibroblast-like phenotype and express high amounts of transforming growth factor- β 1, angiopoietins, vascular endothelial growth factors, interleukins 6 and 8, fibril forming collagens, laminin, and E-cadherin. These phenotypic and functional transdifferentiation lead to hepatic fibrosis with a typical abnormal extracellular matrix synthesis and disorganization of the perisinusoidal space of the injured liver. Those changes provide a favorable environment that regulates tumor cell proliferation, migration, adhesion, and survival in the perisinusoidal space. Such tumor cells by releasing transforming growth factor- β 1 and other cytokines, will, in turn, activate and deeply interact with HSCs via a bidirectional loop. Furthermore, hepatocellular carcinoma-derived mediators convert HSCs and macrophages into protumorigenic cell populations. Thus, the perisinusoidal space serves as a critical hub for activating HSCs and their interactions with other cell types, which cause a variety of liver diseases such as hepatic inflammation, fibrosis, cirrhosis, and their complications, such as portal hypertension and hepatocellular carcinoma. Therefore, targeting the crosstalk between activated HSCs and tumor cells/immune cells in the tumor microenvironment may also support a promising therapeutic strategy. © 2022 Wiley Periodicals LLC.

Author Keywords

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Correspondence Address

Ezhilarasan D.; Department of Pharmacology, No.162, PH Rd, Tamil Nadu, India; email: ezhild@gmail.com

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