Short Communication

Role of Hepatic Stellate Cells in Human Health and its Regulating Factors

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DESCRIPTION

Hepatic Stellate Cells (HSCs) are specialized cells that reside in the liver within the space of Disse, the area between the sinusoidal endothelial cells and the surface of hepatocytes. HSCs constitute about 5% of the total number of liver cells and have multiple long protrusions that extend from the cell body and wrap around the sinusoids. HSCs are also known as perisinusoidal cells, Ito cells, lipocytes, or fat-storing cells, because they store vitamin A as retinol ester in lipid droplets in their cytoplasm [1]. HSCs can exist in two different states i.e., quiescent and activated. In normal, healthy livers, HSCs are in a quiescent state, where they have a low proliferation rate, a low contractility, and a low expression of Extracellular Matrix (ECM) proteins [2]. The function and role of quiescent HSCs are not fully understood, but some studies suggest that they may act as liver-resident antigen-presenting cells, presenting lipid antigens to Natural Killer T (NKT) cells and stimulating their proliferation. When the liver is damaged by various factors, such as toxins, viruses, alcohol, or metabolic disorders, HSCs can change into an activated state. The activated state of HSCs is characterized by a high proliferation rate, a high contractility, a high chemotaxis, and a high expression of ECM proteins. Activated HSCs lose their vitamin A content and their cellular extensions and acquire a myofibroblastic phenotype. Activated HSCs are the major source of ECM production in liver injury, which leads to fibrosis and cirrhosis [3-4].

The activation of HSCs is a complex and dynamic process that involves multiple signaling pathways and interactions with other cell types [5]. Some of the factors that can trigger HSC activation include oxidative stress, cytokines, growth factors, chemokines, matrix metalloproteinases, endocannabinoids, and bile acids. These factors can activate various receptors and intracellular mediators in HSCs, such as Transforming Growth Factor Beta (TGF-β), Platelet-Derived Growth Factor (PDGF), Nuclear Factor Kappa B (NF-κB), c-Jun N-terminal Kinase (JNK), Smad proteins, Rho GTPases, and Peroxisome Proliferator-Activated Receptors (PPARs) [6].

The activation of HSCs results in several changes in their structure and function. Activated HSCs increase their synthesis and secretion of ECM proteins, such as collagen type I, collagen type III, fibronectin, laminin, and proteoglycans. These proteins accumulate in the space of Disse and form scar tissue that disrupts the normal architecture and function of the liver. Activated HSCs also increase their contractility by expressing Alpha Smooth Muscle Actin (α-SMA) and modulating intracellular calcium levels [7]. This leads to increased sinusoidal resistance and portal hypertension. Activated HSCs also increase their chemotaxis by expressing chemokine receptors such as CCR2 and CXCR4. This allows them to migrate to sites of injury and inflammation. Activated HSCs also increase their production of pro-inflammatory cytokines such as Interleukin-1 Beta (IL-1β), Interleukin-6 (IL-6), Tumor Necrosis Factor Alpha (TNF-α), and Interferon Gamma (IFN-γ) [8]. These cytokines can further stimulate HSC activation and recruit other inflammatory cells such as macrophages, neutrophils, lymphocytes, and NKT cells. The consequences of HSC activation are detrimental for liver health. The excessive ECM deposition by activated HSCs leads to fibrosis and cirrhosis, which are characterized by the loss of liver parenchyma and the formation of regenerative nodules surrounded by fibrous septa [9,10]. Fibrosis and cirrhosis impair liver function by reducing blood flow, oxygen supply, nutrient exchange, bile secretion, drug metabolism, and detoxification. Fibrosis and cirrhosis also increase the risk of developing complications such as portal hypertension, variceal bleeding, ascites, hepatic encephalopathy, hepatocellular carcinoma, and liver failure. The pivotal role of HSCs in liver fibrosis and cirrhosis makes them an attractive target for therapeutic interventions.

CONCLUSION

Several strategies have been proposed to modulate HSC activation and function, such as Antioxidants can reduce oxidative stress and inhibit HSC activation. Examples of antioxidants include vitamin E, N-acetylcysteine, silymarin, and curcumin. Anti-fibrotic agents can inhibit the synthesis or degradation of ECM proteins by HSCs. Examples of anti-fibrotic

agents includes pirfenidone, tranilast, halofuginone, and losartan. Anti-inflammatory agents can suppress the production or action of pro-inflammatory cytokines by HSCs. Examples of anti-inflammatory agents includes pentoxifylline, thalidomide, infliximab, and etanercept. Anti-proliferative agents can inhibit the growth or induce the apoptosis of HSCs. Examples of anti-proliferative agents include rapamycin, sorafenib, imatinib, and fasudil. Cell-based therapies can replace or regenerate damaged liver tissue by using stem cells or hepatocyte-like cells derived from various sources. Examples of cell-based therapies include bone marrow-derived mesenchymal stem cells, adipose-derived stem cells, induced pluripotent stem cells, and hepatocyte-like cells.

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