Research Progress on the Association Between PU.1 and Liver Fibrosis

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Abstract: Liver fibrosis is a pathophysiological process characterized by excessive proliferation of intrahepatic connective tissue induced by chronic hepatic injury. Its molecular mechanisms include inflammation-mediated macrophage activation, hepatic stellate cell activation, and various fibrogenic pathways. Early fibrosis is reversible, which is why early diagnosis and treatment are essential.The emerging evidence underlines the importance of the transcription factor PU.1 in liver fibrosis development. This review is done to relate PU.1 with liver fibrosis for diagnosis and therapy insight into the condition.
***Keywords*:** liver fibrosis, PU.1, hepatic macrophages, hepatic stellate cells, signaling pathways

1. Introduction

Hepatic fibrogenesis manifests as a pathological condition marked by the abnormal accumulation of extracellular matrix components (particularly collagen) within the liver parenchyma, which primarily results from persistent damage to hepatocytes. This progressive tissue remodeling process is driven by chronic inflammatory insults to the hepatic microenvironment. It is characterized by excessive extracellular matrix (ECM) accumulation, driven by various etiological factors.Central to this pathogenesis is the transdifferentiation of quiescent hepatic stellate cells (HSCs) into myofibroblast-like phenotypes, which drives ECM component synthesis. Concurrently, macrophage-mediated inflammatory responses synergize with key molecular pathways—notably the transforming growth factor-beta/Smad axis—to orchestrate fibrotic progression. If untreated, hepatic fibrosis will lead to cirrhosis or even hepatocellular carcinoma (HCC), while early fibrosis is usually reversible. So, it's very important to diagnose and give timely treatment to the disease patients. [1]

2. Overview of PU.1

SPI1 (officially designated PU.1) operates through its ETS DNA-binding domain to recruit epigenetic modifiers like histone acetyltransferases, establishing dynamic chromatin states. Its pleiotropic functions include Hematopoietic Regulation, Immune Modulation and Metabolic Crosstalk. [2]

Recently, more and more studies have pointed to the important role of PU.1 in fibrosis. PU.1-dependent signaling is critical for fibrosis progression. Its inhibition attenuates collagen deposition through dual mechanisms: interrupting profibrotic networks and reverting myofibroblasts to quiescent CD34+ states, thereby restoring tissue homeostasis. [3,4] Meanwhile, PU.1 has also been implicated in fibrosis in several organs, including the heart and liver. [5]

PU.1 contributes to fibrosis progression through multiple pathways and plays a key role in hepatic fibrosis.

3. The Association Between PU.1 and Liver Fibrosis

3.1 PU.1 and Hepatic Macrophages

Hepatic macrophages consist mainly of Kupffer cells and monocyte-derived macrophages, both of which play key roles in liver fibrosis.

Kupffer cells are hepatic-specific macrophages maintaining liver immune homeostasis. Following liver injury, they produce TNF-α and TGF-β1, two pro-inflammatory cytokines that contribute to the initiation of HSCs proliferation and differentiate them into myofibroblast. That brings about excessive extracellular matrix deposition, leading to the development of liver fibrosis. [6] Besides activation of ECM, Kupffer cells increase local inflammation and fibrosis with interactions with various other immune cells. Its interaction with endothelial cells promotes recruitment and localization of HSCs, accelerating the development of liver fibrosis. [6]

Besides, Monocyte-derived macrophages polarize into M1 or M2 phenotype macrophages according to the microenvironment. Macrophages of these two phenotypes have pro-inflammatory or anti-inflammatory activities, respectively. They regulate the hepatic inflammatory response and hence fibrosis by secreting relevant cytokines. [7]

In summary, PU.1 is a crucial transcription factor that regulates immune functions, differentiation and metabolism, gene expression of hepatic macrophages, and is required for the development and maintenance of Kupffer cells.[8] In addition,

PU.1 is also implicated in liver metabolism, and the inhibition of PU.1 has been found to enhance glucose metabolism and liver function, suppress liver injury, and prevent liver fibrosis. [9] Taken together, PU.1 regulates hepatic fibrogenesis through its regulatory effects on the immune function, differentiation, metabolic activity and gene expression of hepatic macrophages.

3.2 PU.1 and Hepatic Stellate Cells

HSCs are mesenchymal cells resident in the Disse's space of liver interstitium.They reside in a quiescent state under physiological conditions and, upon liver injury, become activated and differentiate into myofibroblast-like cells that produce abundant extracellular matrix responsible for liver fibrosis. Moreover, HSCs interact with immune cells, and pro-inflammatory cytokines secreted by immune cells maintain the activation of HSCs, thus further aggravating hepatic fibrosis. Persistent activation of HSCs has been considered a pivotal pathological mechanism related to liver fibrosis and even cirrhosis. [10]

Sirt1 is a molecule with anti-fibrotic effects in HSCs, and PU.1 promotes the transcription of miR-34a and miR-29c, thereby inhibiting Sirt1 expression. By inhibiting Sirt1, PU.1 enhanced the activation of HSCs and promoted the progression of fibrosis. The role of PU.1 in liver fibrosis was further confirmed by studies showing that PU.1-deficient mice exhibited anti-fibrotic ability in a thioacetamide (TAA)-induced liver fibrosis model. [11] PU.1 is an important regulator in the development of liver fibrosis.

3.3 PU.1 and Signaling Pathways in Liver Fibrosis

The progression of hepatic fibrosis is orchestrated through an intricate network of molecular interactions, with critical contributions from the TGF-β/Smad axis, NF-κB inflammatory cascade, PI3K/AKT survival cascade, Wnt-dependent β-catenin translocation, and Notch-mediated cell fate determination pathways — emerging as dominant regulators of extracellular matrix dysregulation. [12,10]

TGF-β/Smad pathway: TGF-β is a core regulator of hepatic fibrosis, activating HSCs mainly through phosphorylation of Smad protein, which in turn promotes the secretion of large amounts of collagen and extracellular matrix (ECM), while inhibiting ECM degradation, further exacerbating fibrosis.PU.1 Activation of Smad protein through regulation of the downstream effects of TGF-β promotes the synthesis and deposition of ECM. Accordingly, inhibition of PU.1 reduces TGF-β-mediated fibrosis. [5] Inhibition of PU.1 has been shown to reduce TGF-β-mediated fibrotic effects. [13]

NF-κB signaling pathway: Previous studies indicate that TNF-α can activate the NF-κB cascade, subsequently provoking inflammatory processes within liver cells. Furthermore, this signaling cascade contributes to hepatic fibrogenesis through its regulatory effects on hepatic HSCs activation. [14] PU.1 may modulate the expression of TNF-α-related genes in macrophage cells followed by activation of inflammatory pathways such as NF-κB to impact in the fibrosis process. Some investigations have indicated that TNF-α indirectly may upregulate the expression of PU.1 protein in the HSCs. [15]

Metabolic signaling pathway: PU.1 also affects hepatic metabolic function by regulating lipid metabolism-related signaling pathways, such as AMPK and mTOR, which influences the progression of liver fibrosis. [16]

In conclusion, PU.1 participates in multiple hepatic fibrosis-related signaling pathways, modulating further the occurrence and development of liver fibrosis.

4. Conclusion

Liver fibrosis is a reparative response that has excessive ECM deposition due to chronic liver injury. Early hepatic fibrosis is reversible; therefore, the necessity of an early diagnosis and early treatment follows. PU.1 is a close participant with the hepatic macrophages and HSCs and those signaling pathways relevant to fibrosis in influencing the development of the fibrosis. Thus, it may be an important target to explore further. This may provide new insights into diagnosing and treating liver fibrosis.

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