Hepatic stellate cell: a double-edged sword in the liver

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ALD	alcoholic liver disease
ECM	excessive extracellular matrix
HSCs	hepatic stellate cells
LRAT	lecithin retinol acetyl transferase
LSECs	liver sinusoidal endothelia cells
MMP	matrix metallo proteinase
NAFLD	non-alcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NPCs	non-parenchymal cells
PH	partial hepatectomy
PPARs	peroxisome proliferator-activated receptors
RBP	retinol-binding protein
rER	rough endoplasmic reticulum
TGF-β	transforming growth factor-β
VEGF	vascular endothelial growth factor
α-SMA	α-smooth muscle actin

Summary

Hepatic stellate cells (HSCs) are located in the space of Disse, between liver sinusoidal endothelia cells (LSECs) and hepatocytes. They have surprised and excited hepatologists for their biological characteristics. Under physiological quiescent conditions, HSCs are the major vitamin A-storing cells of the liver, playing crucial roles in the liver development, regeneration, and tissue homeostasis. Upon injury-induced activation, HSCs convert to a pro-fibrotic state, producing the excessive extracellular matrix (ECM) and promoting angiogenesis in the liver fibrogenesis. Activated HSCs significantly contribute to liver fibrosis progression and inactivated HSCs are key to liver fibrosis regression. In this review, we summarize the comprehensive understanding of HSCs features, including their roles in normal liver and liver fibrosis in hopes of advancing the development of emerging diagnosis and treatment for hepatic fibrosis.

I. Introduction

As a metabolic organ, the liver is known for its regenerative capacity, and plays an important role in the body such as synthesizing, breaking down, filtering, storing and producing bile (Grunsven 2017). The liver consists of parenchymal cells (hepatocytes) and non-parenchymal cells (NPCs) such as HSCs, LSECs, biliary epithelial cells, Kupffer cells, natural killer cells, B cells and macrophages (Mazza *et al.* 2017). Hepatic fibrosis is a dynamic process and results from chronic liver injury of different etiologies, containing chronic viral infection (e.g. HBC, HCV), alcoholic liver disease (ALD), fatty liver disease, non-alcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH) and other conditions (Sherman 2018). Hepatic fibrosis is considered as a reversible pathological process, characterized by excessive accumulation of ECM (Schildberg *et al.* 2015). HSCs play a vital role in the fibrogenesis, differentiating into myofibroblasts leading to hepatic fibrosis after activated (Friedman 2008b).

HSCs located in the perisinusoidal space of Disse are the main ECM-producers of the liver, and significantly contribute to its roles by interaction with adjacent cells (Lee *et al.* 2015). In a healthy liver, quiescent HSCs represent 15% of the total number of liver cells and preserve retinoid storage (Seki 2015). Upon liver injury, HSCs receive signals and become activated, transdifferentiating into ECM-producing myofibroblast-like cells, activated HSCs are proliferative and fibrogenic phenotype (Figure 1). This review focuses on the understanding of HSCs to grasp the characteristics of quiescent HSCs and activated HSCs, directing therapeutic targeting of anti-fibrotic strategy.

II. Embryonic origin and ultrastructure of HSCs

In 1876, the HSC was found by Kupffer using gold chloride method (Doherty 2016). As a vitamin A-storing mesenchymal cell type, HSC is crucial to liver regeneration and fibrosis (Koyama *et al.* 2017). The embryonic origin of HSCs is unclear because they express marker genes of the endoderm and mesodermal

(Friedman 2008a, Marrone *et al.* 2016). In the view of an endoderm origin, HSCs express CD34 and cytokeratin-7/8, which are typically localized to the endodermal during liver development (Eggert *et al.* 2017). In the view of a mesodermal origin, lineage tracing of the mesoderm transcriptional factor Foxf1 showed that HSCs develop from the septum transversum mesenchyme, suggestive of a mesodermal origin (Yanguas *et al.* 2016). Meanwhile, bone marrow- and neural-derived cells are also thought to contribute to both quiescent and activated HSCs (Zoubek *et al.* 2017).

HSC is one of the non-parenchymal cells in the liver, also known as fat-storing cell, Ito cells, lipocyte, interstitial cell, perisinusoidal cell or vitamin A-storing cell (Schumacher *et al.* 2016). HSCs are located in the space of Disse, communicating with the neighboring cell types such as hepatocytes, LSECs, biliary epithelial cells, hepatic progenitor cells, Kupffer cells and B cells via soluble mediators or cytokines (Thompson *et al.* 2015). HSCs in normal liver have irregular star-shaped cell bodies with round or oval nuclei (Koyama *et al.* 2016). In quiescent state, they do not or rarely express α-smooth muscle actin (α-SMA), with low proliferative activity and low capacity of collagen synthesis (Huang *et al.* 2017). Their perikaryons lie in recesses between hepatocytes and LSECs (Bansal 2016). They have small Golgi complex, rough endoplasmic reticulum (rER) and dendritic cytoplasmic protuberances (Kitano *et al.* 2016).

Ⅲ. **Activation and deactivation of HSCs**

HSCs are quiescent in normal liver, the functions of quiescent HSCs mainly include vitamin A-metabolizing and -storing, fat-storing, synthesis of matrix metallo proteinase (MMP) and tissue inhibitor of metallo proteinase (TIMP-1), expression of cytokines and receptors, and regulation of liver sinusoidal blood (Tsuchida *et al.* 2017). HSCs are activated when the liver is damaged by inflammation or mechanical stimulation, its features contain expression of α-SMA, secretion of ECM and so on (Shang *et al.* 2018). The mechanism of HSCs activation is complex, including cellular events, molecular dysregulation, and other complex factors (Seki 2015). As the predecessors of proliferative myofibroblasts, activated HSCs spark efforts to understand their phenotypes transdifferentiation and how they contribute to liver

fibrosis (Jung *et al.* 2017). Quiescent HSC is identified in a nonproliferative state, with a distinctive feature of cytoplasmic lipid droplets (Hellerbrand 2013). Upon liver injury, HSCs become activated, transdifferentiating to myofibroblasts (Preziosi *et al.* 2017). These activated HSCs are proliferative, contractile, and characterized by excessive ECM production (Zhang *et al.* 2016). Other resident liver cells promote or inhibit HSCs activation via released or secreted factors (Figure 2). The sequence of HSC activation featuring initiation followed by perpetuation (Hsieh *et al.* 2015). Initiation is characterized by events rendering the HSCs responsive to many extracellular signals (Seo *et al.* 2016). Development of a contractile and fibrogenic phenotype, modulation of growth factor signaling, as well as are initiation phase features (Zhou *et al.* 2014). Perpetuation characterizes amplification of the activated phenotype (Elpek 2014). The perpetuation phase results in fibrogenesis through matrix production, contractility, proinflammatory signaling and enhanced HSC proliferation (Tsuchida *et al.* 2017).

There are three ways of activated HSCs elimination: reversion, senescence and apoptosis (Friedman 2008b). The reversion of activated HSCs to inactivated state has shown a vital role in hepatic fibrosis regression, suggesting the expression of fibrogenic genes relative to activated HSCs was reduced. HSC senescence also plays a crucial role in liver fibrosis recovery, senescent HSCs represented reduced ECM component production (DeRossi *et al.* 2019). In the liver, HSC apoptosis has been reported during hepatic fibrosis reversion through two approaches: mitochondrial dependence and death receptors (Tao *et al.* 2019). The mechanisms of HSCs activation and deactivation could provide antifibrotic targeted therapeutic strategies (Wang *et al.* 2020).

IV. HSCs in normal liver

A fundamental understanding of the feature and function of HSCs in normal liver is essential to explore their role in liver diseases. Researches of HSCs in normal liver have showed that they play a vital role during liver development, regeneration, vitamin A storage and other processes (Figure 3).

A. HSCs in liver development

Throughout the liver development, HSCs are closely related to hematopoietic cells, liver progenitor cells, biliary epithelial cells, LSECs, hepatocytes and Kupffer cells (Lee *et al.* 2015). It suggests that HSCs may contribute to hepatic organogenesis via regulating the growth, differentiation, or morphogenesis of these cells (Arab *et al.* 2020). As is well-known, the liver is the primary site of hematopoiesis during mammalian embryogenesis. HSCs are involved in fetal liver hematopoiesis through the secretions of Hlx and CXCL12 (Friedman 2008a, Yin *et al.* 2013). HSCs also can promote the progenitor cells maturation through its markers (α-SMA, desmin and vimentin) (Arriola *et al.* 2019). Quiescent HSCs express mesenchymal morphogenic proteins pleiotrophin and epimorphin, which are contribute to liver regeneration after partial hepatectomy (Chen *et al.* 2020).

HSCs may also be critical to the morphogenesis of intrahepatic bile ducts via interacting with biliary epithelial cells (Chen *et al.* 2020). Fetal HSCs secrete hepatocyte growth factor (HGF), this growth factor has significant effects on the development of biliary epithelial cells during hepatic organogenesis (Das *et al.* 2020). In the injured liver, HSCs expressed hepatocyte and epithelial cell markers. The role of these cells in biliary epithelial cells differentiation is not quite clear, which may be mediated by cell-cell contacts (Dong *et al.* 2020). In both fetal and adult livers, HSCs and LSECs have been proposed to share a common precursor because of their location proximity and coexpression of angiogenic factors, their communication by means of paracrine signaling (Hoffmann *et al.* 2020). During angiogenesis, HSCs are thought to have the same effect on the vascular tube maturation and integrity with LSECs when the liver responds to injury, understanding their interactions during growth is vital for liver injury recovery (Kong *et al.* 2020).

B. HSCs in liver regeneration

A deep understanding of the relationship between HSCs and liver regeneration has important significances for stimulating liver recovery following partial hepatectomy (PH) (Forbes *et al.* 2016). Activated HSCs have involved in liver regeneration through producing hepatocyte proliferation factors, angiogenic factors and remodeled ECM,

these cytokines and chemokines directly promote the proliferation of hepatocytes, and act indirectly through LSECs or Kupffer cells to stimulate regeneration (Li *et al.* 2020). Activated HSCs-derived HGF can promote hepatocytes proliferation during liver injury. However, HSCs also can inhibit the hepatocyte proliferation, HSCs-derived transforming growth factor-β (TGF-β) is the antiproliferative factor, and even induces apoptosis (Yin *et al.* 2013). Therefore, liver regeneration is a complex process, HSCs modulate the process both the initiation and termination.

Quiescent HSCs are critical to the liver regenerative response in injured liver, they contribute to hepatocellular development following injury, reducing hepatic fibrosis and diminishing the expression of α-SMA (Friedman 2008a). At the same time, activated HSCs can increase liver cell injury and even apoptosis. The role of HSCs in liver injury and repair is unclear because they have quiescence and activation phenotypes (Li *et al.* 2020). An advanced model in vivo and in vitro is necessary to clarify the function of these enigmatic cells.

C. Vitamin A storage and metabolism

In normal liver, HSCs present a quiescent state, which are characterized by vitamin A in their cytoplasmic droplets in the form of retinyl esters. There are two types of vitamin A droplets: type I and type II (Friedman 2008a). Under physiological conditions, the vast majority of vitamin A in the liver is stored in HSCs, showing a heterogeneous pattern. Under liver injury, HSCs become activated and lose these characteristic droplets (Lv *et al.* 2020). The form of vitamin released outside the activated HSCs is retinol, indicating that there is intracellular hydrolysis of esters, rather than export. Several nuclear retinoid receptors secreted by HSCs mediate vitamin A metabolism in the liver, such as retinol-binding protein (RBP), lecithin retinol acetyl transferase (LRAT) and peroxisome proliferator-activated receptors (PPARs). The roles of vitamin A storage and metabolism in the HSCs of liver merit further investigation (Miyazoe *et al.* 2020).

V. HSCs in liver fibrosis

The facilitation of liver development and regeneration may be feasible in normal liver, HSCs can also be related with liver diseases, especially liver fibrosis. The

overwhelming majority of hepatic fibrosis result in the hepatic carcinoma, the relationship between HSCs and liver fibrosis has been recognized (Nagasaki *et al.* 2020). Studies suggest that activated HSCs can be involved in hepatic fibrogenesis due to the production of extracellular matrix accumulation. Phenotypic transformation from quiescent HSCs to activated HSCs contributes to many forms of liver fibrosis, at least there are three activated HSCs clearance approaches: apoptosis, senescence, and reversion (Tao *et al.* 2020). Each clearance way of activated HSCs contributes to a decrease in the number of this ECM-producing cell type, resulting in the regression of hepatic fibrosis. Targeting HSCs provide anti-fibrotic strategies for liver fibrosis therapies. Therefore, the comprehensive understanding of HSCs is necessary to promote the resolution of liver fibrosis (Wang *et al.* 2020).

A. ECM-producing cell

Liver fibrosis is caused by chronic liver injury and considered as ECM excess. The unbalance between synthesis and degradation of ECM results in hepatic fibrogenesis, HSCs are the central regulators of liver fibrosis (Wang *et al.* 2020). In normal liver, HSCs have key roles in vitamin A storage and metabolism. Under liver injury, quiescent HSCs are activated via the mediation of ROS, MCP-1, HGF, CXCR4, CCL2, and activated HSCs are the major ECM producer (Yang *et al.* 2020). The activated phenotype is characterized as proliferation, contractility, fibrogenesis and retinoid loss, promoting the accumulation of ECM by increasing the expression of collagen type I and decreasing the expression of MMP (Zhang *et al.* 2020).

B. Angiogenesis in liver fibrogenesis

Angiogenesis has a key role in liver fibrogenesis and progression. HSCs also mediate angiogenesis through the stimulation of vascular endothelial growth factor (VEGF), which is pro-angiogenic factor. The overexpression of VEGF is associated with liver fibrosis grade and portal hypertension, indicating the important role of pro-angiogenic factor VEGF in liver fibrogenesis (Zou *et al.* 2019). Activated HSCs are considered to secrete pro-angiogenic factors such as VEGF, IGF1, TGF-β and EGF, and express angiogenic growth factor receptors (Chen *et al.* 2020, Moon *et al.* 2019). In liver fibrosis, these factors contribute to pro-angiogenic microenvironment,

and their upregulation induces liver fibrogenesis.

Ⅵ. Conclusion and perspectives

As summarized in this review, the HSCs play a critical role in liver development, liver regeneration and hepatic fibrogenesis. Vital regulators of liver fibrosis have been characterized, and HSCs have been identified as potential therapeutic targets for hepatic fibrosis (Dong *et al.* 2020, Zhang *et al.* 2019). Concerted efforts to explore the mechanisms that HSCs activation and clearance will enhance the efficiency of targeting these cells in liver fibrosis. The application of targeting HSCs in clinical trials requires further investigation, the function of HSCs and their regulation mechanisms in other tissue are unclear (Zhai *et al.* 2019). Furthermore, advanced models are necessary for in vivo and in vitro studies of HSCs in the liver, to probe the regulation of phenotypic reversion from activation to quiescence.

Although the advanced understanding of the phenotype reversion of the activated HSCs has been made remarkable progress, treatment options for therapeutic strategy for the control of liver fibrogenesis are still severely limited (Yuan *et al.* 2019). It is urgent to establish the specific, effective, and safe anti-fibrotic therapeutic strategy, either by apoptosis, senescence, HSC phenotypic reversion, or inhibition of the HSC-mediated angiogenesis. Recently, mounting evidence has demonstrated that HSCs are critical modulators of liver fibrogenesis via the reversal of their phenotype (Wei *et al.* 2019). In the near future, nanotechnology could be very promising in the innovative therapeutic approaches of liver fibrosis via targeting HSCs (Li *et al.* 2020, Tao *et al.* 2019). For example, targeted therapy reverses hepatic fibrosis via exosome mediated delivery system.

In conclusion, this study has offered significant insights regarding HSCs in the liver, providing prospects for emerging target therapies in patients with liver fibrosis.

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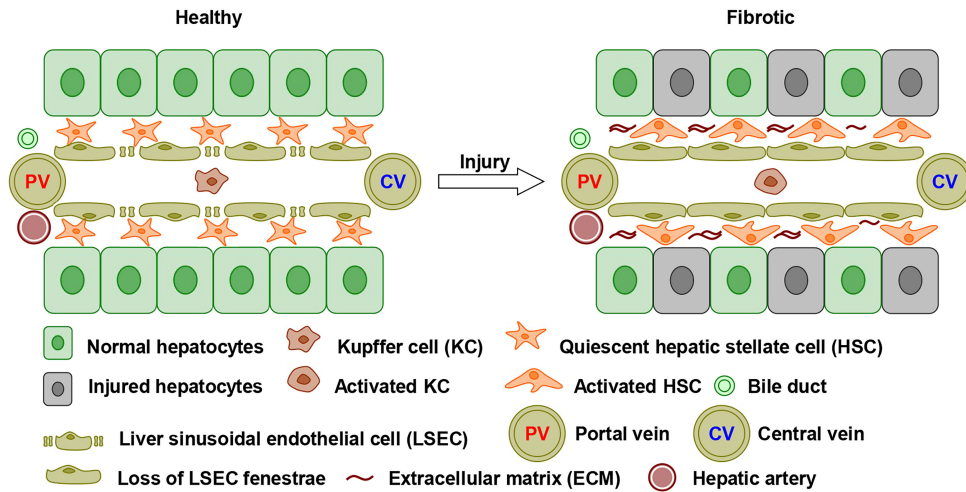
Fig. 1. Anatomical position of HSCs and liver sinusoids to injury. HSCs are located in the space of Disse, between LSECs and hepatocytes. Under liver injury, HSCs convert to a pro-fibrotic state, producing the excessive ECM and promoting the liver fibrogenesis.
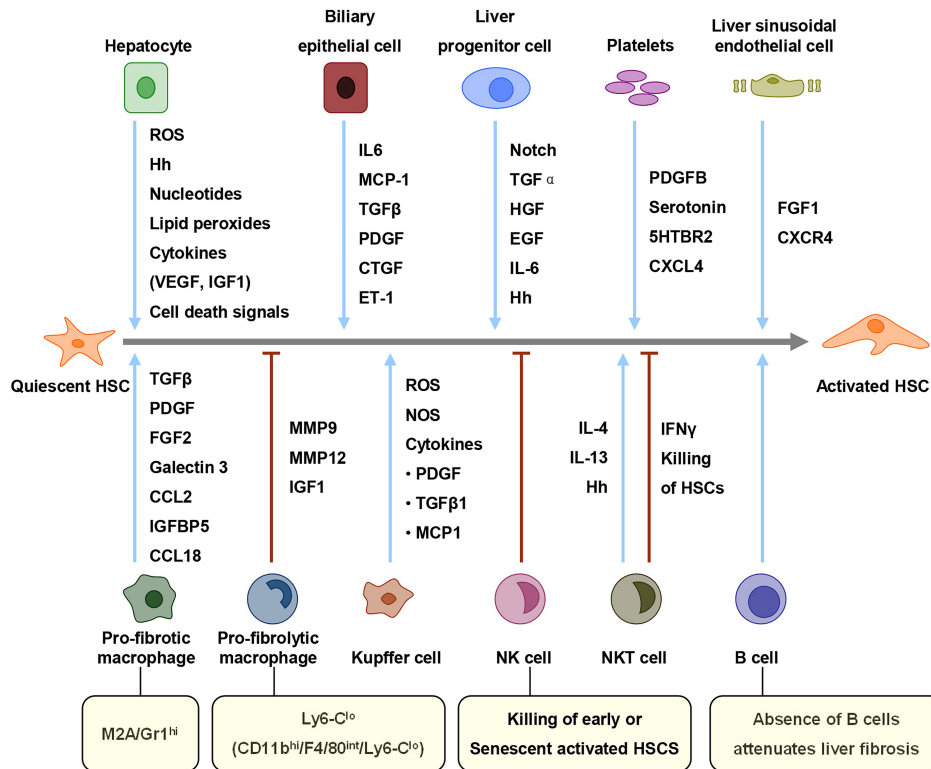
Fig. 2. Liver resident cells modulators of HSCs activation. HSCs activation is promoted or suppressed by multiple cell types. Liver resident cells promote (green lines) or suppress (red lines) quiescent HSCs to activated HSCs. ROS, reactive oxygen species; Hh, hedgehog; VEGF, vascular endothelial growth factor; IGF1, insulin-like growth factor 1; IL6, inter leukin 6; MCP-1, monocyte chemoattractant protein-1; TGFβ, transforming growth factor β; PDGF, platelet-derived growth factor; CTGF, connective tissue growth factor; ET-1, endothelin-1; HGF, hepatocyte growth factor; EGF, epidermal growth factor;FGF1, fibroblast growth factor 1; IFNγ, interferon-γ; NOS, nitric oxide synthase; IGFBP5, insulin-like growth factor binding protein 5; NKT, natural killer T; NK, natural killer.
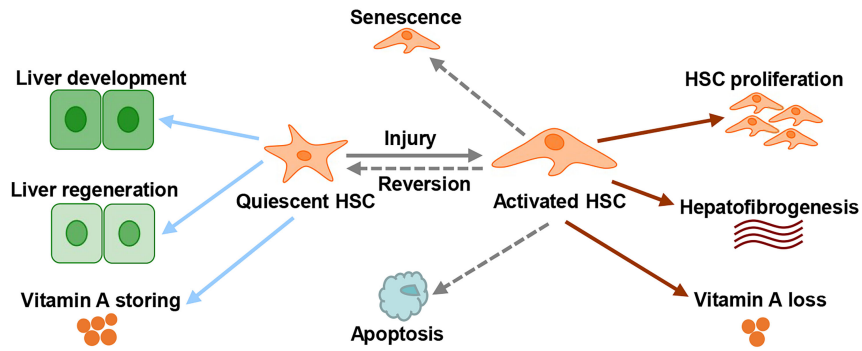
Fig. 3. Functions, features and phenotypes of HSC in normal and liver fibrosis, and activated HSC clearance approaches. Quiescent HSC in normal liver plays a vital role during liver development, regeneration, and vitamin A storage. Activated HSC is related with liver fibrosis. There are three activated HSCs clearance approaches: apoptosis, senescence, and reversion.