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Pericytes in the liver

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Abstract

Liver pericytes, commonly named hepatic stellate cells (HSCs), reside in the space between sinusoidal endothelial cells (LSECs) and hepatocytes. They display important roles in health and disease. HSCs ensure the storage of the majority of vitamin A in a healthy body, and they represent the major source of fibrotic tissue in liver disease. Surrounding cells, such as LSECs, hepatocytes and Kupffer cells, present a significant role in modulating HSC behavior. Therapeutic strategies against liver disease are being currently developed, where HSCs represent an ideal target. In this chapter, we will discuss HSC quiescence and activation in the context of healthy liver and diseases, such as fibrosis, steatohepatitis and hepatocellular carcinoma.

Keywords

liver; hepatic stellate cells; pericytes; healthy liver; regeneration; fibrosis; NASH; NAFLD; hepatocellular carcinoma; hepatocytes; sinusoidal endothelial cells; Kupffer cells

Introduction

The liver specific pericytes are called hepatic stellate cells (HSCs). They reside in the subendothelial space of Disse, defined as the space between the liver sinusoidal endothelial cells and the parenchymal cells. HSCs were first described in 1876 by the German anatomist Carl von Kupffer who visualized them using gold chloride preparations of human liver. He called these cells « sternzellen » meaning stellate cells due to their shape (Kupffer 1876). In 1952, Toshito Ito described perisinusoidal cells as fat-storing cells based on their capacity to accumulate lipid droplets (Ito and Nemoto 1952), also called later lipocytes or Ito cells. The term HCS was reused in 1971 by the Japanese Kenjiro Wake (Wake 1971), who also described the storage of vitamin A in rat quiescent HSCs (Wake 1974) and who opened the era of their characterization. The existence of many names describing the same cell, such as Ito cell, fat-storing cell, lipocyte, perisinusoidal or parasinusoidal cell, prompted the investigators of the field in 1996 to standardize the term HSC when referring to these cells (Hepatology 1996;23:193). In this chapter, we will discuss the origin of HSCs, their role in the adult healthy liver and finally their implication in liver diseases where HSCs are designated as the main mediators of fibrosis.

The origin of HSCs during development

The developmental origin of HSCs has been debated since they express both neuronal and mesenchymal cell markers, such as nestin, glial fibrillary acidic protein (GFAP), p75 neurotrophin receptor (p75^{NTR}), desmin, type 1 collagen and vimentin. For this reason, it has been thought that HSCs derive from neural crest and from the mesenchyme (Asahina 2012). To investigate the neural crest origin of HSCs, yellow fluorescent protein (YFP)⁺ neural crest descendants were obtained by crossing wingless-type MMTV integration site family member 1 (Wnt1)^{Cre} mice with Rosa26^{YFP} reporter mice (Cassiman et al. 2006). In this model, HSCs failed to express the YFP leading to the conclusion that they do not derive from the neural crest (Cassiman et al. 2006). Nevertheless, a more recent study shows that in zebrafish, HSCs express heart and neural crest derivatives expressed 2 (hand2), a mesoderm and neural crest marker suggesting a link between HSCs and neural crest (Yin et al. 2012). This controversy may be explained by inter-species differences and needs further investigation.

The most accepted developmental origin for HSCs is a sheet of mesoderm that develops along the foregut endoderm near the cardiac mesoderm, called the septum transversum (Asahina et al. 2009, 2011, Loo and Wu 2008, Pérez-Pomares et al. 2004, Toi et al. 2018). The septum transversum is also important for the pre-natal development of the liver by secreting bone morphogenetic proteins (BMPs) and fibroblast growth factors (FGFs) (Zaret 2002). To test whether septum transversum contributes to HSC population in mice, Wilm's tumor 1 (WT1) was used as a marker. Before liver development, WT1 is only expressed in the septum transversum, while in later stages of liver morphogenesis WT1 is expressed in mesothelial and submesothelial cells. These cells give rise to WT1⁻/β-galactosidase⁺ HSCs (Asahina et al. 2011). The septum transversum origin of HSCs is also demonstrated in rats and in developing human liver (Toi et al. 2018, Loo and Wu 2008). Moreover, in human fetuses a cell population expressing hematopoietic stem cell markers (CD34 and cytokeratin 7/8) and HSC markers (desmin and α-smooth muscle actin (αSMA)) was identified suggesting a link between hematopoietic and hepatic systems (Suskind and Muench 2004). In addition to these studies, further investigation is necessary to understand the developmental origin of HSCs in different species and whether there exist several sub-populations of HSCs deriving from different precursors.

Role of HSCs in healthy liver

In a healthy adult liver, quiescent HSCs represent ~10% of total resident cells (Tsuchida and Friedman 2017). They are mainly recognized for their role in storage and controlled release of vitamin A. Storage of retinols or vitamin A in cytoplasmic lipid droplets is the most distinctive feature of quiescent HSCs. These lipid droplets are routinely used for HSC isolation and are autofluorescent when excited with the light of ~328 nm (Popper 1944) (Figure 1). In a healthy liver, 50–80% of total body retinol is stocked in the liver (Blomhoff et al. 1990), of which 80–90% is stored in HSCs (Hendriks et al. 1985). While it remains unknown how retinol is transferred to HSCs, more studies exist regarding retinol metabolism in HSCs. Upon entering in HSCs, retinol is esterified and mostly stored as retinyl esters by lecithin retinol acyltransferase (LRAT) (Friedman 2008). Retinyl esters constitute 30–50%

of the lipids of HSC lipid droplets (Senoo 2004). Vitamin A is important for maintaining HSCs in quiescence since treatment of cultured HSCs with vitamin A induced its accumulation in cytoplasmic lipid droplets and decreased the expression of HSC activation markers (Yoneda et al. 2016). Moreover, all-trans retinoic acid, a derivative of vitamin A, was demonstrated to reduce HSC activation (Shimizu et al. 2017). However, the absence of lipid droplets in LRAT-deficient mice was not associated with liver fibrosis (Kluwe et al. 2011). This controversy raises the question whether vitamin A loss is the cause or the consequence of HSC activation, leading to the need of further studies to elucidate this question.

HSCs also secrete molecules that act in an autocrine or paracrine manner, part of which are lipoproteins, growth factors and cytokines (Friedman 2008). As other quiescent perivascular cells, HSCs secrete apolipoprotein E (ApoE) (Ramadori et al. 1989). At basal level, ApoE-deficient mice showed increased transforming growth factor beta (TGF β), monocyte chemoattractant protein (MCP-1) and tissue inhibitor of metalloproteinase 1 (TIMP-1) expression in the liver when compared to wild-type (WT) mice (Ferré et al. 2009), suggesting a role for ApoE in maintaining liver homeostasis. It would have been interesting to investigate whether HSC-specific ApoE deletion would have an incidence on liver injury. Follistatin and interleukin 10 (IL-10) are other molecules secreted by HSCs that have shown anti-fibrotic effects (Friedman 2008). Indeed, treatment of carbon tetrachloride (CCl₄)-exposed rats with follistatin reduced liver fibrosis and constrained HSC proliferation (Patella et al. 2006). Nevertheless, another study showed that follistatin is expressed only by activated HSCs and could be a marker of liver fibrosis (Boers et al. 2006). HSCs can also secrete IL-10, a hepatoprotective cytokine recognized for its role in reducing liver injury (Thompson KC et al. 1998, Byun et al. 2013). Indeed, IL-10-deficient mice develop more severe liver fibrosis following CCl₄ administration (Thompson K et al. 1998). The anti-fibrotic molecules produced by HSCs deserve more elucidation as they have a therapeutic potential.

HSCs have also been shown to have an important role in liver regeneration following a partial hepatectomy (Preziosi and Monga 2017). In the earlier phase of liver regeneration, they regulate matrix degradation by secreting matrix metalloproteinase and several proteoglycans and induce hepatocyte proliferation by secreting pleiotrophin and the potent mitogen hepatocyte growth factor (HGF) (Asahina et al. 2002, Taub 2004, Preziosi and Monga 2017). When HSC death was caused by gliotoxin 24 hours before partial hepatectomy, hepatocyte proliferation was significantly impaired due to a lack of HGF (Nejak-Bowen et al. 2013). At later phases of liver regeneration, HSCs secrete the mitoinhibitory TGF β to inhibit hepatocyte proliferation (Preziosi and Monga 2017). When gliotoxin was administered 5 days after partial hepatectomy, hepatocyte proliferation was prolonged due to decreased HSC-derived TGF β and collagen deposition (Nejak-Bowen et al. 2013). An increasing interest has been shown on the aspect of HSCs as progenitor cells. Several groups have demonstrated that HSCs can differentiate in hepatocytes during liver regeneration (Yang et al. 2008b, Kordes et al. 2014), suggesting a mesenchymal stem cell role. All these studies show that HSC presence is essential for normal liver function and regeneration. Nevertheless, further investigation is needed to elucidate the existing controversy on the role of HSC-derived signaling in healthy liver.

Role of HSCs in liver disease

HSCs have mainly been studied in liver diseases, due to their capacity to transdifferentiate in myofibroblasts, the major source of collagen deposition during fibrogenesis. In this subchapter, the HSC behavior will be discussed in the context of liver fibrosis, steatohepatitis and hepatocellular carcinoma.

HSCs and liver fibrosis

Liver fibrosis is the deposition of excessive scar tissue in response to a chronic injury. The identification of HSC activation in hepatic fibrosis has been a significant discovery in the understanding of liver's response to injury. HSC activation refers to the passage from a quiescent vitamin-rich cell to a proliferative, contractile, migratory and fibrogenic cell (Friedman 2008) (Figure 1). Some of the most studied signals that activate HSCs are platelet growth factor (PDGF), TGF β , Fas cell surface death receptor (Fas), apoptotic bodies, extracellular vesicles and stiffness (Friedman 2008, Kostallari and Shah 2016, Dou et al. 2018). These signals derive from several cell types, such as sinusoidal endothelial cells (SECs) (Kostallari and Shah 2016), Kupffer cells (Bilzer et al. 2006), injured hepatocytes (Canbay et al. 2002, 2003), and HSCs (Kostallari et al. 2018) (Figure 2).

In liver injury, SECs become activated or capillarized by losing their fenestrae (Brunt et al. 2014). Defenestrated SECs increase endothelin 1 (ET-1) secretion and decrease nitric oxide (NO) release, which contribute to HSC contraction (Kostallari and Shah 2016, Tsuchida and Friedman 2017). ET-1 is found to also be secreted by HSCs and to act in an autocrine manner (Pinzani et al. 1996). SECs stimulate HSC migration by producing stromal derived factor 1 (SDF-1)/C-X-C motif chemokine ligand 12 (CXCL12) (Kordes and Häussinger 2013) and releasing sphingosine kinase (SK)-1-containing EVs (Wang et al. 2015). Moreover, in liver fibrogenesis, SECs upregulate fibroblast growth factor receptor 1 (FGFR1) and C-X-C motif chemokine receptor 4 (CXCR4) expressions, enforcing the fibrogenic phenotype of HSCs (Ding et al. 2014). Another cell type influencing HSC behavior is the Kupffer cell. Kupffer cells are the liver resident macrophages lying in the sinusoids and penetrating between the hepatocytes during liver injury. They have an important role in HSC migration through PDGF secretion and HSC differentiation into myofibroblasts through TGF β and reactive oxygen species (ROS) release (Tsuchida and Friedman 2017, Kiagiadaki et al. 2018). Moreover, Kupffer cells secrete MCP-1 in a SK-1-dependent manner (Lan et al. 2018). MCP-1 binds to C-C motif chemokine receptor 2 (CCR2), which is expressed by both HSCs and Kupffer cells, leading to their respective migration (Marra et al. 1999, Lan et al. 2018) and ultimately to liver fibrosis (Seki et al. 2009). Treatment of mice with a specific inhibitor of SK-1 prevented liver fibrosis in CCl₄- and bile duct ligation (BDL)-induced liver injuries (Lan et al. 2018). Hepatocytes, which constitute 70–85% of the liver mass, also have a role in HSC activation. In a healthy liver, hepatocytes are polarized cells presenting microvilli, which contribute to the absorption of proteins and other molecules coming from the blood. Injured hepatocytes lose their microvilli and can participate to HSC activation (Canbay et al. 2003, Tsuchida and Friedman 2017). Indeed, injured hepatocytes underwent apoptosis through a Fas-dependent mechanism and released apoptotic bodies, which were engulfed by HSCs (Canbay et al.

2002, 2003). This induced HSC fibrogenic activity by increasing collagen $\alpha 1$, TGF β 1 and α SMA expression (Canbay et al. 2003). Moreover, damaged hepatocytes release ROS, which activate HSCs and lead to liver fibrogenesis (Jiang et al. 2010, Tsuchida and Friedman 2017).

Besides SECs, Kupffer cells and hepatocytes, activated HSCs can also release signals in a paracrine manner, which contribute to fibrosis. Activated HSCs are well recognized to secrete the canonical pro-fibrogenic molecules such as collagen 1 α 1, TGF β and PDGF-BB (Drinane et al. 2017, Friedman 2008). Moreover, a decrease of retinoic acid signaling in HSCs is associated with induction of TGF β 1 expression and activation of HSCs, suggesting a role for retinoic acid in HSCs quiescence (Ohata et al. 1997). The presence of bacterial lipopolysaccharide (LPS), due to increased gut permeability in liver disease, has been shown to have a significant role in retinoic acid signaling decrease by inducing the autophagy of HSC lipid droplets and leading to HSC activation (Chen et al. 2017). LPS-dependent activation of HSCs induces interferon beta (IFN β) release, which promotes hepatocyte apoptosis (Dangi et al. 2016). In turn, apoptotic hepatocytes participate to further activation of HSCs (Canbay et al. 2002, 2003). Moreover, activated HSCs and myofibroblasts secrete vascular endothelial growth factor (VEGF), a potent angiogenic molecule that binds to VEGF receptor (VEGFR) expressed by SECs, and induce fibrosis-associated angiogenesis (Das et al. 2010). In a recent study, activated HSCs also secrete PDGFR α -enriched EVs, which have a paracrine effect in promoting *in vitro* cell migration and *in vivo* fibrogenesis (Kostallari et al. 2018). The PDGFR α enrichment in HSC-derived EVs is SHP2 dependent and treatment of mice with SHP2 inhibitor, SHP099, reduced significantly liver fibrosis (Kostallari et al. 2018). Interestingly, G protein-coupled receptors (GPCRs) are emerging as new targets in liver fibrosis. Indeed, protease-activated receptor-2 (PAR2) is expressed in activated HSCs. Inhibiting PAR2 by PZ-235 decreased HSC proliferation and collagen deposition (Shearer et al. 2016).

Another interesting stimulator of HSC activation is liver stiffness. Indeed, when plated on a soft substrate freshly isolated HSCs maintain their lipid droplets and high levels of PPAR γ . However, when plated on a stiff substrate HSCs lose their lipid droplets and upregulate α SMA and collagen1 expression (et al. 2014). Moreover, in a recent study, it has been demonstrated that substrate stiffness induces HSC activation through translocation into the nucleus of histone acetyltransferase p300, which upregulated transcription of HSC activation genes (Dou et al. 2018). In line with these studies and in a therapeutic perspective, it could be of interest to further investigate the cause of the stiffness in order to modulate it *in vivo* and to explore the role of other GPCRs in liver fibrosis.

HSCs and steatohepatitis

Steatohepatitis is one of the leading causes of liver diseases in the United States. It can occur due to a high consumption of alcohol leading to alcoholic steatohepatitis (ASH), or a high fat diet leading to non-alcoholic steatohepatitis (NASH). Despite the different etiologies, these two entities have similar pathogenic mechanisms. They usually start with steatosis, which is the fat accumulation within the hepatocytes (ballooned hepatocytes), followed by hepatocyte cell death response, inflammation and ultimately fibrogenesis (Greuter et al.

2017, Ibrahim et al. 2018). HSCs have a significant role in driving inflammation and fibrogenesis in ASH and NASH by receiving and emitting signals. Lipotoxicity-induced hepatocyte-derived extracellular vesicles promote HSC activation, proliferation and migration by inhibiting the quiescence marker peroxisome proliferator-activated receptor gamma (PPAR γ) through miR-128-3p (Povero et al. 2015). Lipotoxicity-induced hepatocyte can also secrete sonic hedgehog (Shh), which is an activator of HSCs (Yang et al. 2008a, Rangwala et al. 2011). In turn, activated HSCs can increase the inflammatory reaction by secreting pro-inflammatory cytokines such as MCP1, IL6, TGF β and neural cell adhesion molecules (Friedman 2008, Lee and Jeong 2012).

In alcoholic and non-alcoholic liver disease, intestinal epithelial permeability is increased, which can be detected by a high level of bacterial LPS in the liver. LPS can stimulate HSCs through Toll-like receptors (TLRs) (Tsuchida and Friedman 2017). HSCs express several TLRs, such as TLR2, TLR3, TLR4, TLR7 and TLR9 (Seki et al. 2007, Gäbele et al. 2008, Chou et al. 2012, Miura et al. 2013, Byun et al. 2013). In some mouse models of steatohepatitis, activation of TLR4 induces Kupffer cell chemotaxis and inflammation (Seki et al. 2007, Guo et al. 2009). Moreover TLRs activation in HSCs induces liver fibrosis (Huang et al. 2007, Seki et al. 2007). HSCs nuclear receptors, such as farnesoid X receptor (FXR), peroxisome proliferator-activated receptor (PPAR) or vitamin D3 receptor (VDR), are other factors involved in liver disease. Indeed, deficiency of FXR in HSCs promotes hepatic inflammation and fibrosis (Kong et al. 2009). Furthermore, a dual PPAR α -PPAR δ agonist, GFT505 that may target both hepatocytes and HSCs, protects liver from steatosis, inflammation and fibrosis in several mouse models (Staels et al. 2013). In line with this, inhibition of VDR signaling by sequestosome 1 (SQSTM1/p62) knock out attenuates liver inflammation and fibrosis in experimental steatohepatitis (Beilfuss et al. 2015, Duran et al. 2016).

The interaction between HSCs and neutrophils also seems to play an important role in the establishment of steatohepatitis through HSCs. Indeed, neutrophils stimulate the secretion of HSC-derived GM-CSF and IL-15, which in turn prolong neutrophil survival and may serve as a positive forward loop to promote liver damage and fibrosis (Zhou et al. 2018). Cholesterol, a component of high-fat diet, is another factor that can accumulate in HSCs and induce their activation (Tomita et al. 2014). Cholesterol-lowering drugs, such as ezetimibe or statins, attenuate steatohepatitis and fibrosis in a mouse model of NASH (Van Rooyen et al. 2013). Nevertheless, the effect of activated HSCs on recruiting pro-inflammatory cells is not fully understood and deserves further investigation.

HSCs and hepatic metastases

The combination of the unique microenvironment and its hemodynamics characteristics makes the liver one of the most targeted organs of cancer metastasis. Furthermore, liver metastases are dependent on the interactions between the tumor cells and the hepatic stromal cells, such as HSCs. HSCs have several important roles in liver tumors, such as promoting tumor growth, releasing growth factors and cytokines, regulating extracellular matrix (ECM) turn-over, tumor-associated angiogenesis and suppressing anti-tumor immune response (Kang et al. 2011). In 130 cases of hepatocellular carcinoma, peritumoral activated HSCs

independently contributed to high recurrence or death rates (Ju et al. 2009). Similarly to liver fibrosis, tumor-stimulated HSCs differentiate into myofibroblasts, upregulate α SMA expression, proliferate, migrate and contribute significantly to collagen deposition (Vidal-Vanaclocha 2008). This behavior is stimulated by tumor cells through paracrine signaling, including secretion of TGF β (Kang et al. 2011). In turn, activated HSCs induce tumor cell proliferation, migration and invasion through secretion of several secreted growth factors and cytokines, such as TGF β , HGF, PDGF, SDF-1, VEGF and CXCL12 (Okabe et al. 2009, Amann et al. 2009, Zhao et al. 2011, Kang et al. 2011, Yaqoob et al. 2012, Dou et al. 2018) and by downregulating other molecules such as endosialin (Mogler et al. 2017). Indeed, conditioned media of activated HSCs promoted tumor cell invasion and proliferation *in vitro* (Okabe et al. 2009, Amann et al. 2009) and *in vivo* (Dou et al. 2018). Furthermore, HSCs cultured on a stiff environment induced a higher tumor growth than HSCs cultured on soft matrix (Dou et al. 2018), suggesting a role for stiffness in tumor progression.

Activated HSCs at the invasive front of liver metastasis can regulate the ECM by producing matrix metalloproteinase 2 (MMP2), TIMP2 and a disintegrin and metalloproteinase 9 (ADAM9) allowing cancer cells to increase their invasive behavior (Musso et al. 1997, Mazzocca et al. 2005). Furthermore, HSC-derived ECM components, such as collagen, fibronectin, laminin and CCN family member 1 (CCN1), regulate adhesion, migration and survival of tumor cells by activating the integrins on tumor cell surface (Kang et al. 2011, Azzariti et al. 2016, Li et al. 2018). For example, inhibiting α 3 integrin on HCC cells abrogated the anti-apoptotic effect of laminin-332 (Azzariti et al. 2016). Moreover, the expression of neuropilin-1 by HSC-derived myofibroblasts promoted the secretion of fibronectin and therefore the increase of tumor microenvironment stiffness leading to a greater tumor growth (Yaqoob et al. 2012).

Activated HSCs can also promote tumor-associated angiogenesis since they release VEGF, angiopoietins and IL-8 (Semela et al. 2008, Taura et al. 2008, Das et al. 2010, Zhu et al. 2015). Indeed, IL-8 derives mainly from activated HSCs and IL-8 inhibition with a blocking antibody significantly reduced angiogenesis (Zhu et al. 2015). Moreover, activated HSCs protect the hepatic tumor by inhibiting anti-tumor cytotoxic T cells (Xia et al. 2017). Indeed, tumor-associated HSCs induce dendritic cell-derived immunoglobulin receptor 2 (DIgR2) in dendritic cells, which in turn inhibit the inflammatory response of T cells (Xia et al. 2017). It could be of interest to better understand the role of activated HSCs on the inflammatory cell behavior in the context of HCC.

Conclusion

In this chapter, we have identified HSCs as a crucial cell for liver development, homeostasis and disease through paracrine and autocrine signaling, which includes growth factors, cytokines and extracellular vesicles. While most of the studies describe HSC-dependent ECM regulation in response to microenvironment stimuli, less attention is brought to the understanding of other HSC-derived signals and their effect on the surrounding cell types. The HSC-derived signaling study remains incomplete, especially in the context of HSC heterogeneity. The isolation of different HSC sub-populations and specifically targeting the most fibrogenic ones are essential for developing novel therapies. Several encouraging

antifibrotic strategies aiming the prevention or reversal of HSC-induced liver fibrosis have been or are being developed (Schuppan et al. 2018). Recently, a dual C-C chemokine receptors type 2 and 5 (CCR2/CCR5) antagonist, cenicriviroc, is in phase 2 clinical trial and is being evaluated in liver inflammation and fibrosis in the context of NASH (Friedmann et al. 2016). This is the first prospective study of an oral agent in patients with exclusively NASH and liver fibrosis, which aims to assess correlations between inflammation and fibrosis (Friedmann et al. 2016). In parallel, other clinical trials are ongoing (clinicaltrials.gov) and throw a glimmer of hope in finding treatments for liver diseases.

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Quiescent Activated

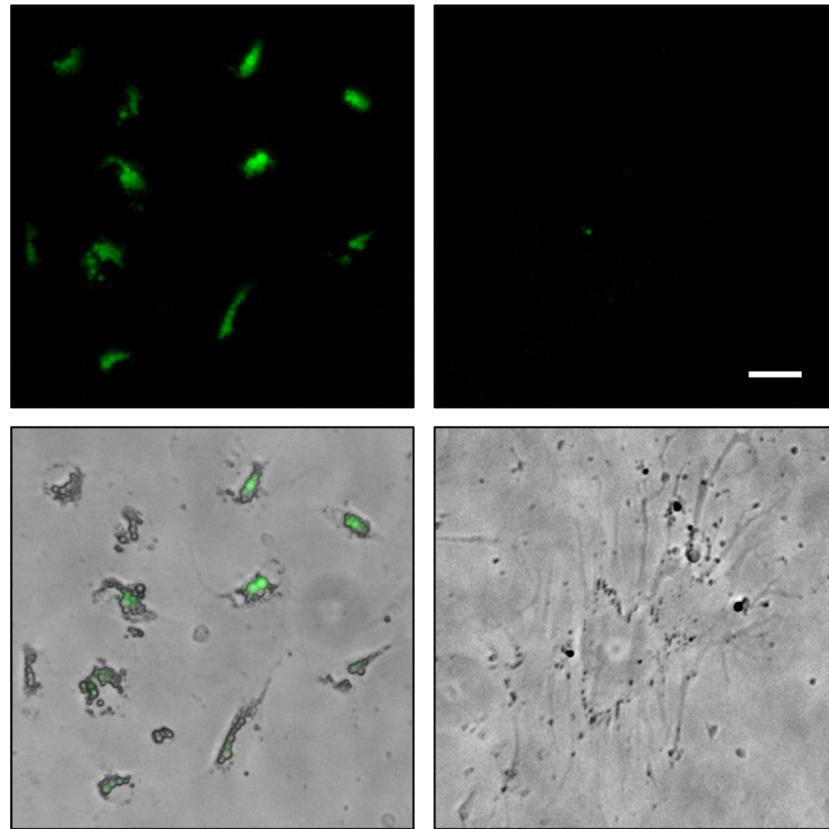


Figure 1:

Left: primary quiescent HSCs isolated from mouse liver presenting autofluorescent lipid droplets (day 1 after isolation). Right: primary activated HSC isolated from mouse liver (day 10 after isolation). It presents several processes, and lipid droplets are absent. Upper panels: autofluorescent lipid droplets. Lower panels: brightfield capture of the cells merged with the autofluorescent lipid droplets. Scale bar: 10 μ m.

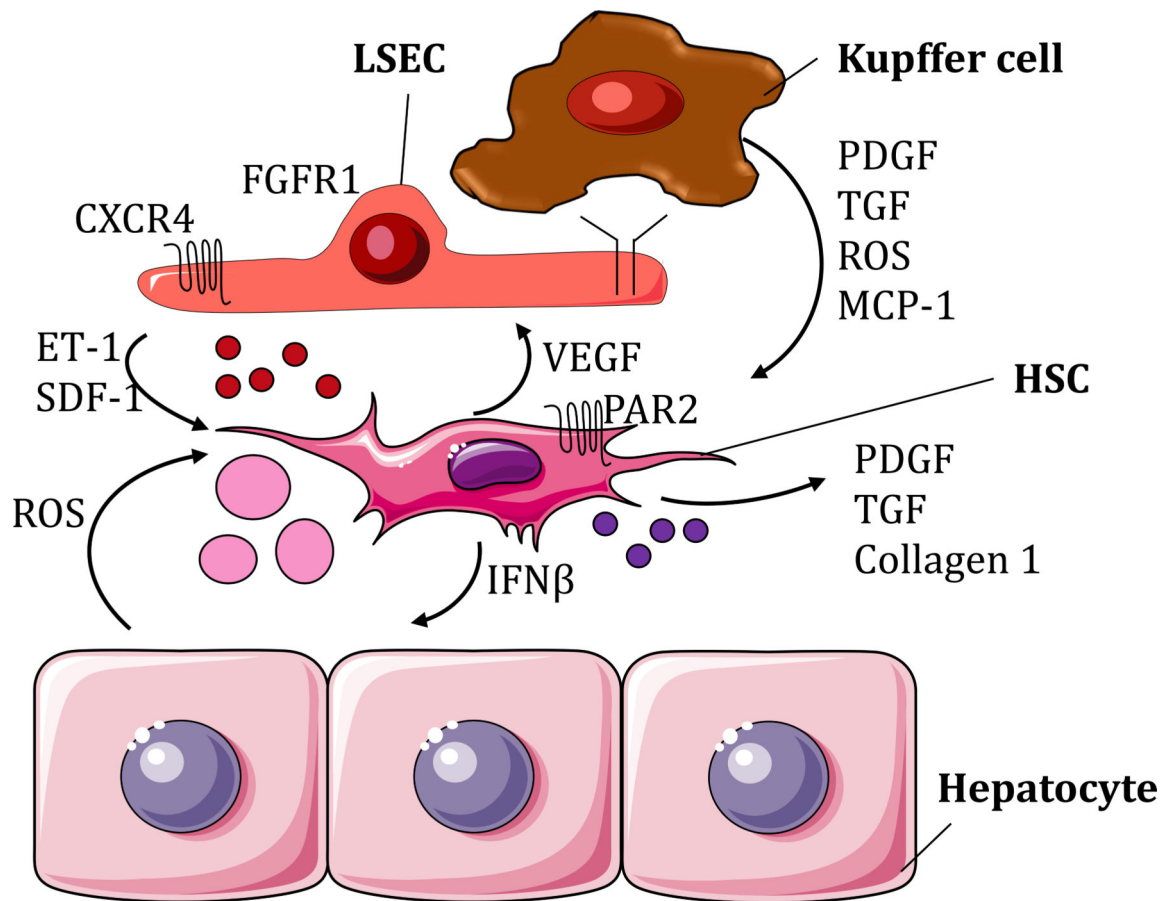


Figure 2:

Cross-talking between HSCs and the surrounding cells in the context of liver fibrosis. Defenestrated LSEC upregulate the expression of CXCR4 and FGFR1 and secretion of ET-1, SDF-1 and SK-1-containing EVs (small red circles), which induce HSC activation. Kupffer cells participate in this process by secreting PDGF, TGF, ROS and MCP-1. ROS are also released by injured hepatocytes. HSCs secrete PDGF, TGF collagen 1 and PDGFR α -enriched EVs (small purple circles) which act in an autocrine manner. In addition, activated HSCs release IFN β that induces hepatocyte apoptosis and hepatocyte-derived apoptotic bodies (pink circles) implicated in HSC further activation.