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Crosstalk between hepatic stellate cells and tumor cells in the development of hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) ranks sixth in population age-standardized incidence (ASI) and fourth in population age-standardized mortality (ASM) globally and is the fourth ASI and the second ASM, respectively, of the cancer spectrum in China.[1] HCC usually develops as a result of chronic hepatitis B, the major underlying etiology of HCC in China. Concerning the tumor microenvironment, a growing body of research has focused on the intercellular and molecular crosstalk between tumor cells and the surrounding hepatic stromal cells, including hepatic stellate cells (HSCs), liver stromal endothelial cells (LSECs), and immune cells. Among stromal cells, HSCs play a central role in the crosstalk between tumor and stroma, which contributes significantly to HCC progression.

HSCs reside in the space of Disse in a quiescent and non-proliferative state, storing vitamin-A in normal liver. However, following persistent liver injury and inflammation, HSCs are activated and become crucially involved in the production of growth factors, extracellular matrix (ECM), matrix metalloproteinases (MMPs), and other cytokines. As known, HSC is closely related to fibrosis and cirrhosis, and the remodeling and reorganization of ECM simultaneously creates a stiff tumor microenvironment. As a central modulator of the tumor microenvironment, activated HSCs, as well as cancer-associated fibroblasts (CAF) predominantly originated from HSC, have multiple roles in HCC progression. *In vitro* studies have shown that HSCs directly induce the malignant phenotype of cancer cells through the secretion of growth factors, ECM, and MMPs.[2,3] Activated HSCs also play a pivotal role in the promotion of angiogenesis through upregulating the expression of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), and fibroblast growth factor (FGF) during HCC development.[4] Another role of HSC in HCC development is the reduction of immune surveillance by recruiting immunosuppressive inflammatory cells such as regulatory T-cells, M2 macrophages, or myeloid-derived suppressor cells (MDSCs), which drive tumor progression. Evidence suggests that HSCs induce MDSCs through interleukin-6 (IL-6) signaling and produce inhibitory enzymes to inhibit T-cell immunity, thereby creating an immunosuppressive microenvironment.[5] In stark contrast, a study reports that HSCs are negative regulators of HCC progression through upregulating endosialin expression in HCC. Endosialin is capable of inhibiting tumor-promoting cytokines, including insulin-like growth factor 2, retinol-binding-protein 4, dickkopf-1, and C-C chemokine ligand 5.[6] Thus, it appears that there is a complex, at least dual, function of HSC in HCC progression. Mechanistically, HSCs can influence HCC cells, with the secretion of growth factors, ECM, MMPs, and other cytokines mediating the HSC–HCC crosstalk.

TGF-β, mainly secreted by HSC, is a key cytokine modulating the HSC–HCC crosstalk. TGF-β binds to its receptors TGF-beta receptor type I and TGF-beta receptor type II, respectively, and induces Smad and non-Smad signaling pathways, resulting in HSC activation, macrophage polarization, and LSEC capillarization. Furthermore, TGF-β has a dual role during cancer progression. The tumor-suppressing activity of TGF-β in early phases of hepatocarcinogenesis is mediated by inducing cytostasis and apoptosis of hepatocytes, preventing inflammation and counteracting the effects of stroma-released mitogens. In the later phases of HCC, TGF-β is a tumor promoter by orchestrating processes such as fibrogenesis, invasion and migration, epithelial–mesenchymal transition (EMT), and tumor–stromal cells crosstalk in HCC, probably by

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upregulating nuclear β-catenin accumulation in malignant hepatocytes. As a TGF-β superfamily member, growth differentiation factor 15 (GDF15) upregulation in HCC cells, induced by cisplatin and hypoxia treatment, also participates in HSC promotion and acceleration of HCC progression through activating ERK1/2- and Smad3-dependent signaling pathways.[7]

PDGF is a key element in HSC signaling and acts synergistically with TGF-β to activate HSC. PDGF binds to its receptors PDGF-Rα or PDGF-Rβ to activate phosphatidylinositol-3-kinase, rat sarcoma, and phospholipase C-gamma signaling pathways. PDGF also plays a pro-tumorigenic role in diverse stages of HCC development through upregulating TGF-β receptors and inducing pro-carcinogenic factors such as β-catenin, VEGF, and FGF. A recent study in transgenic mice over-expressing PDGF-C indicates that PDGF-C activates TGF-β/Smad3 signaling pathway to promote HSC activation, leading to HCC progression.[8]

Hepatocyte growth factor (HGF), mostly produced by HSC, also acts as crucial growth factor in regulating the HSC-HCC interaction. HGF binds to its receptor *c-Met* and triggers subsequent phosphorylation cascades. The HGF/c-Met signaling pathway is considered as a promoter during hepatocarcinogenesis, as it accelerates tumor cell proliferation, angiogenesis, invasion, and EMT in HCC. Consistently, evidence suggests that HSC-derived HGF regulates Keratin 19 expression via a MET-ERK1/2-AP1 and SP1 axis to promote the aggressive hepatoma growth.[2]

Connective tissue growth factor (CTGF), mainly derived from HSC, is a downstream mediator of TGF-β signaling and induced by TGF-β via STAT3 and Smad2/3 signaling pathways. CTGF acts in a pro-carcinogenic role in HCC development by increasing DNA synthesis, cell-cycle progression, and invasion and migration abilities; and it induces resistance to doxorubicin and TNF-related apoptosis-inducing ligand apoptosis in HCC cells. CTGF secreted also by tumor cells is reported to promote HSC activation and accelerate HCC development. Additionally, CTGF-mediated crosstalk between HSC and HCC induces IL-6 production, which stimulates hepatoma advancement.[9]

As major components of ECM, proteoglycans, laminins, and fibronectin, mostly secreted by HSC, can also interact with tumor cells. It has also been demonstrated that HSC-derived cartilage oligomeric matrix protein stimulates HCC development by inducing MEK/ERK and phosphatidylinositol-3-kinase/AKT signaling pathways in a CD36-dependent manner.[10] Besides, the fibrinogen promotes HSC activation by binding to integrin αvβ5 to induce hepatocarcinogenesis, indicating a novel interaction between HCC and HSC in a zebrafish HCC model.[3]

Apart from the aforementioned factors, HSCs secrete other cytokines that mediate the HSC-HCC crosstalk. For instance, the senescence-associated secretory phenotype (SASP) in HSC plays a pro-tumorigenic role by down-regulation of cytoplasmic DNases, and the blockage of the SASP in HSC senescence results in a decline of obesity-associated HCC development in mice.[11]

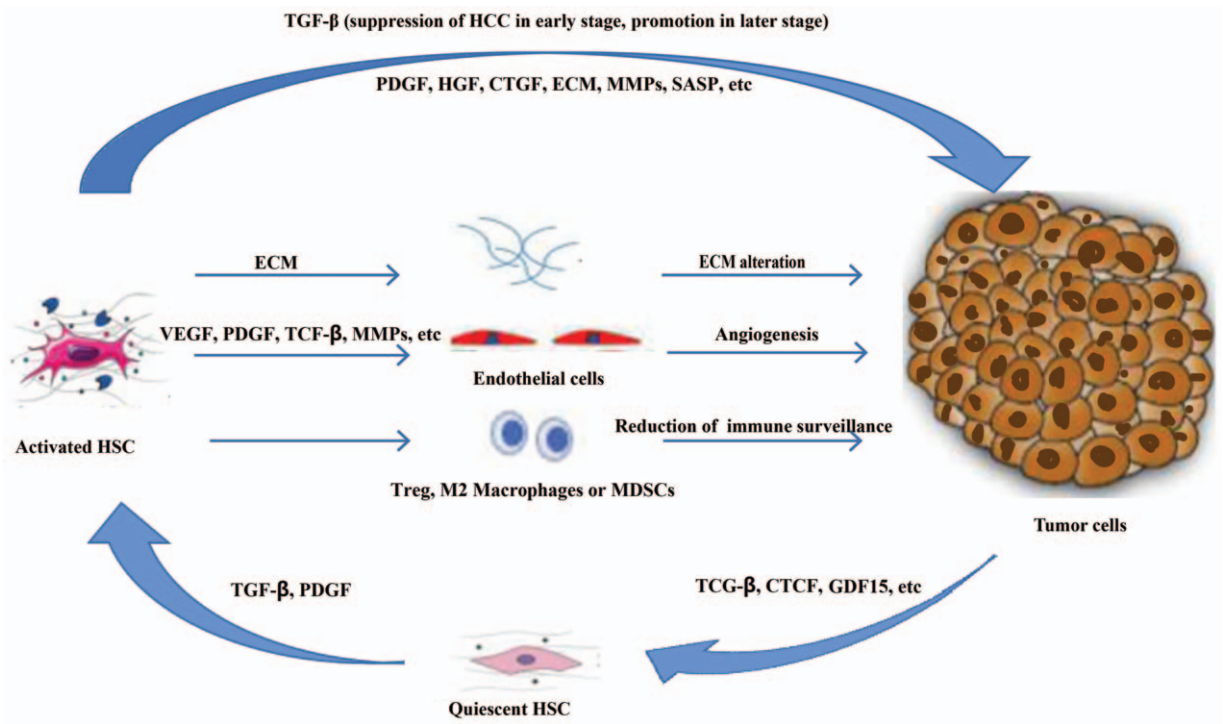

Figure 1: The mechanisms of bidirectional crosstalk between HSC and tumor cells. CTGF: Connective tissue growth factor; ECM: Extracellular matrix; GDF15: Growth differentiation factor 15; HCC: Hepatocellular carcinoma; HGF: Hepatocyte growth factor; HSC: Hepatic stellate cells; MDSCs: Myeloid-derived suppressor cells; MMPs: Matrix metalloproteinases; PDGF: Platelet-derived growth factor; SASP: Senescence-associated secretory phenotype; TGF-β: Transforming growth factor-β; VEGF: Vascular endothelial growth factor.

As an oncogene, by the way, STMN1 is reported to mediate the HSC-HCC crosstalk through inducing HGF/c-Met signaling pathway. STMN1 overexpression in HCC cells enhanced by HGF converts HSC into CAF, which promotes HCC development.[12] The HSC-HCC interaction is also modulated by tumor-derived exosomes. An investigation has revealed that tumor-secreted miRNA-21 facilitates HSC activation to acquire CAF features via PTEN/PDK1/AKT signaling pathway. Moreover, CAF exhibit increased angiogenic factors like VEGF, MMP2/9, TGF-β, and FGF to accelerate HCC development.[13]

To summarize, crosstalk between HSC and tumor cells is indispensable for HCC progression. The interaction between these two cell types is bidirectional. HSCs do directly affect tumor growth by the secretion of growth factors, ECM, MMPs, and other cytokines. Moreover, HSCs influence the advancement of HCC through altering components of the ECM, promoting angiogenesis and reducing immune surveillance. At the same time, tumor cells secrete multiple factors that alter HSC towards a more pro-tumoral phenotype, which in turn affect HCC progression in a vicious feedback loop [Figure 1]. The complex molecular network of HSC-HCC cells crosstalk is crucial for the development of HCC[14]; hence, innovative therapeutic strategies targeting their interaction need to be explored to improve treatment of this deadly cancer.

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Conflicts of interest

None.

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