*REVIEW*

# Cancer-associated fibroblasts in hepatocellular carcinoma

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## Abstract

The hepatic stellate cells in the liver are stimulated sustainably by chronic injury of the hepatocytes, activating myofibroblasts, which produce abundant collagen. Myofibroblasts are the major source of extracellular proteins during fibrogenesis, and may directly, or secreted products, contribute to carcinogenesis and tumor progression. Cancer-associated fibroblasts (CAFs) are one of the components of the tumor microenvironment that promote the proliferation and invasion of cancer cells by secreting various growth factors and cytokines. CAFs crosstalk with cancer cells stimulates tumor progression by creating a favorable microenvironment for progression, invasion, and metastasis through the epithelial-mesenchymal transition. Basic studies on CAFs have advanced, and the role of CAFs in tumors has been elucidated. In particular, for hepatocellular carcinoma, carcinogenesis from cirrhosis is a known fact, and participation of CAFs in carcinogenesis is supported. In this review, we discuss the current literature on the role of CAFs and CAF-related signaling in carcinogenesis, crosstalk with cancer cells, immunosuppressive effects, angiogenesis, therapeutic targets, and resistance to chemotherapy. The role of CAFs is important in cancer initiation and progression. CAF-targeted therapy may be effective for suppression not only of fibrosis but also cancer progression.

Key words: Cancer associated fibroblast; Hepatic stellate cell; Hepatocellular carcinoma; Immunosuppression; Therapeutic target

Core tip: Cancer-associated fibroblasts (CAFs) are one of the most crucial components of the tumor microenvironment that promote the carcinogenesis, proliferation and invasion of cancer cells by secreting various growth factors and cytokines. In hepatocellular

carcinoma (HCC), cirrhosis caused by chronic inflammation was considered the main reason for carcinogenesis, and field cancerization was explained by the epigenetic changes in fibroblasts in tissues surrounding the tumor. In this review, we discuss the findings from current literature on the role of CAFs in HCC. CAF-targeted therapy may be effective for suppression not only fibrosis but also cancer progression.

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the second most common cause of death from cancer worldwide, and accounted for nearly 746000 deaths in 2012[1]. Malignant tumors comprise cancer cells and stromal cells. For a long time, the malignant potential of the tumor was thought to be entirely due to the cancer cells because the stromal cells were not undergoing differentiation or activate proliferation[2]. Stromal cells were considered to simply surround the cancer cells and have a non-malignant function. Recent studies have clarified the origins, features, and roles of the stromal cells.

Fibroblasts in cancer tissues are similar in morphology to the myofibroblasts that are activated during the wound healing process[3]. Recent studies have shown the importance of cross talk between cancer cells and the fibroblasts called cancer-associated fibroblasts (CAFs)[4]. CAFs are active in a wound healing process similar to normal myofibroblasts[5], and promote tumor proliferation, invasion, and metastasis *via* secretion of various growth factors, cytokines and degradation of extracellular matrix proteins[6-8] (Figure 1).

CAFs are large spindle-shaped mesenchymal cells with positive immunostaining for vimentin, alpha smooth muscle actin, and developed fibronexus[9,10]. The types of surface marker proteins on CAFs and non-tumoral fibroblasts (NTFs), which are primary cells from cirrhotic tissue, can be detected by flow cytometry and immunofluorescence[4]. No significant difference between CAFs and NTFs in surface markers is evident, but mRNA expression of $\alpha SMA$ is higher in CAFs compared to NTFs[4]. It has been reported that DNA-methylation-based epigenetic changes have already occurred in activated hepatic stellate cells (HSC)[11,12]. Therefore, NTF, which are activated HSCs from cirrhotic tissue, may have already undergone a genetic change that affects surface markers. Collagen 11A1 expression is a remarkable biomarker of human carcinoma-associated stromal cells[13]. It was

reported that even without exposure to cancer cells, the tumor promoting characteristics of CAFs can be stably maintained[14]. There remains a persistent risk for HCC in patients with advanced fibrosis who have achieved a sustained virologic response (SVR)[15]. These observations indicate that genetic or epigenetic changes may have already existed in the CAFs independent of the original tumor[14]. Furthermore, activated HSCs can be stimulated by cancer cells, which then become CAFs. Details of differentiation into quiescent HSCs, HSCs, and CAFs is shown in the Table 1. Quiescent HSCs were characterized by the stored vitamin A with fat droplets[16] and are derived from the mesoderm[17]. HSCs have a function in wound healing and fibroblast production. Characterization of CAFs revealed that they were affected by cancer cells through "crosstalk".

## CARCINOGENESIS

It is well established in other systems that complex intercellular signaling networks exist between tumors and CAFs, contributing to cancer initiation, growth, and progression[18-22]. Tumor secretion of cytokines, such as transforming growth factor-$\beta$ (TGF-$\beta$), stimulate myofibroblast activation leading to profound changes in extracellular matrix composition and organization. The role of mesenchymal stroma alterations in cancer initiation was proposed in the context of colon[23] and prostate[24] cancers. Chronic liver injuries caused by viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, and non-alcoholic steatohepatitis activate and transform quiescent fibroblasts into activated myofibroblasts through the actions of increased growth factors and continued expression of inflammatory cytokines such as PDGF, TGF-$\beta$, TNF-$\alpha$, IL-6, and IL-1$\beta$[25,26]. Fibroblasts might be directly activated by hepatitis C infection, which leads to production of reactive oxygen species and TGF-$\beta$[27]. The activated fibroblasts produce massive amounts of extracellular matrix proteins, including type I collagen, which leads to liver fibrosis[28]. Persistent inflammation in chronic hepatitis plays a major role in the development of HCC[29-31]. There remains a persistent risk for HCC in patients with advanced fibrosis who have achieved SVR[15]. Around 90% of HCC cases are associated with fibrotic or cirrhotic livers[32,33].

Dotto[34] suggested that while changes in tumor stroma are frequently viewed as secondary to changes in the epithelium, recent evidence indicates that they can play a primary role in both cancer progression and initiation. These changes include epigenetic events such as loss of p53[35-37]. These processes may explain the phenomenon of field cancerization, namely the occurrence of multifocal and recurrent epithelial tumors that are preceded by and associated with widespread changes of surrounding tissue or organ fields[34]. It thought that epigenetic changes affect CAFs in HSCs in cases of liver cirrhosis that include
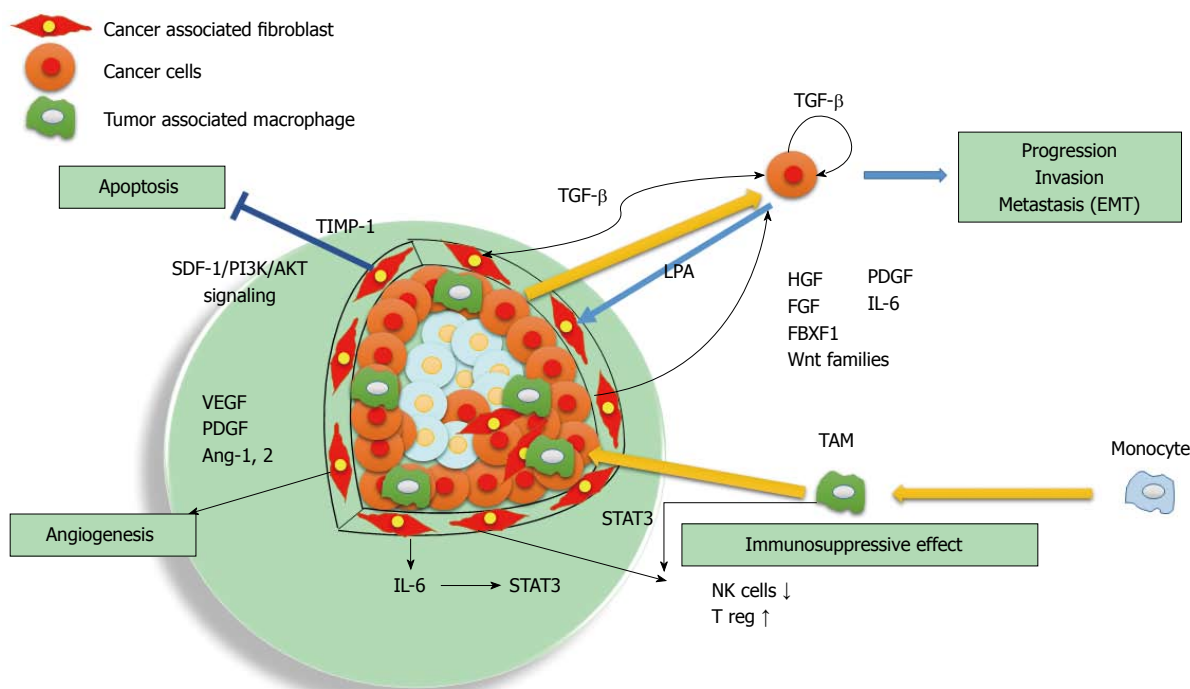
**Figure 1 Microenvironment to be formed with cancer-associated fibroblasts and tumor-associated macrophages.** Cancer-associated fibroblasts (CAFs) mainly located at the tumor marginal zone and secreted the various cytokines such as HGF and crosstalk with hepatocellular carcinoma cells and stimulate the tumor progression, invasion and metastasis through the epithelial mesenchymal transition. TIMP-1 suppressed the tumor cell apoptosis *via* SDF-1/PI3K/AKT signaling. Angiogenesis is occured by the angiogenic factors including VEGF, PDGF, ang-1 and ang-2 secreted by CAFs. TAMs and CAFs make the microenvironment to the immunosuppressive condition to create favorable microenvironment for tumor progression. TAM: Tumor associated macrophage.

**Table 1  Differentiation into quiescent hepatic stellate cells, hepatic stellate cells, and cancer-associated fibroblasts**

| | Quiescent hepatic stellate cells (fibroblast) | Hepatic stellate cells (myofibroblast) | Cancer associated fibroblasts |
| --- | --- | --- | --- |
| Morphology | Spindle shape with numerous intracellular droplets[16] | Spindle shape | Spindle shape |
| Origin | Mesoderm[17] | Quiescent hepatic stellate cells | Activated hepatic stellate cells |
| Location | Space of Disse, sinusoidal spaces | Periportal lesion | Tumor stroma |
| Biological markers | Desmin[17] | αSMA, p75NTR[17] | αSMA, COL11A1[13] |
| Function | Store the vitamin A and fat | Wound healing fibrosis | Tumor progression |
| Cytokines | - | Production of the collagens, PDGF, TGF-β, TNF-α, IL-6, IL-1β[25,26] | production of the collagens, TGF-β, HGF, FGF, VEGF, IL-6[42-58], *etc* |

p75NTR: p75 neurotrophin receptor; αSMA: Alpha smooth muscle actin; COL11A1: (pro)collagen 11A1; TGF-β: Transforming growth factor-β; HGF: Hepatocyte growth factor; FGF: Fibroblast growth factor; PDGF: Platelet-derived growth factor; VEGF: Vascular endothelial frowth factor; IL-6: Interleukin-6.

abundant fibrosis. However, gene analysis is not performed often enough in human HSCs of the liver cirrhosis or CAFs[38].

# CROSSTALK BETWEEN CANCER-ASSOCIATED FIBROBLASTS AND HCC CELLS

Recent studies have shown the importance of crosstalk between cancer cells and their stromal microenvironment, including HCC[4,39,40]. CAFs are the most important cell type in the stroma and play a critical role in modulating neighboring cancer cells[41]. CAFs stimulate malignant cell proliferation by providing different types of growth factors and cytokines in a context-dependent manner[20] such as SDF-1[42-45], HGF[46-48], members of the epidermal growth factor family[49], fibroblast growth factor (FGF)[50,51], Wnt families[52], forkhead box F1[53], IL-6[54-56], TGF-β[57,58], and EGF. When HCC cells are co-cultured with CAFs, CAFs induced by TIMP-1 repress HCC apoptosis with an increased Bcl-2/BAX ratio through SDF-1/CXCR4/PI3K/AKT signaling[44]. Moreover, CAFs upregulated gene expressions of TGF-β and FAP, whereas NTFs did not induce the expression of either gene[4]. HGF is expressed by CAFs, HSCs, and myofibroblasts[48,59,60], and it is a highly potent hepatocyte growth factor regulating cell proliferation, migration, survival, and angioneogenesis[61-64]. IL-6 stimulated progranulin

expression contributes to the malignancy of HCC cells by activating mTOR signaling[56]. After the IL-6/STAT3 pathway is activated, malignant cells proliferate much faster and their anti-apoptosis ability increases significantly[65]. TGF-β complex is secreted by most cell types, including human HSCs and hepatocytes[66,67]. TGF-β signaling promotes HCC progression by two mechanisms: first, *via* an intrinsic activity as an autocrine or paracrine growth factor, and second, *via* an extrinsic activity by inducing microenvironment changes, including CAFs activation, T regulatory cell increases, and inflammatory mediators[68]. A recent study using transgenic mice suggested that PDGF-C overexpressing hepatocytes causes activation of HSC, which in turn produces HGF and cytokines, resulting in the development of HCC[69]. Crosstalk between TGF-β and PDGF signaling supports epithelial mesenchymal transition (EMT), which is crucial for tumor growth and the acquisition of an invasive phenotype[70]. MRC-5 fibroblast-conditioned medium influences multiple pathways regulating invasion in HCC[71].

Lysophosphatidic acid (LPA) is a lipid mediator that is involved in multiple cellular events associated with tumor initiation and progression, invasion, and metastasis[72,73]. LPA is secreted by HCC cells and promotes transdifferentiation of myofibroblasts by the paracrine mechanism and has been clearly shown to be a therapeutic target for tumor-CAF interactions in HCC[41,74]. MMP-9 is downstream of LPA and has been postulated to have a critical role in HCC cell invasion and metastasis[73] by secreting various matrix-degrading proteases as well as their activators such as uPA[75].

These functions of CAFs in supporting HCC growth were confirmed by *in vitro* experiments involving co-culture of HCC cell lines with CAFs[4]. Remarkably, the activation of CAFs was maintained after their isolation from cells of various cancer types such as squamous skin carcinoma, lung carcinoma, breast carcinoma, and scirrhous gastric cancer[76-78]. Exposure to leukemia inhibitory factor initiates an epigenetic switch causing the constitutive activation of JAK1/STAT3 signaling, which results in sustained activation of CAFs[79]. DNA methylation plays critical roles in the control of sustained and constitutive activation of signaling pathways[80]. CAF activation is accompanied by stromal cell senescence[81,82]. Concomitant loss of CSL (also known as RBP-Jk) and p53 overcomes fibroblast senescence, enhances expression of CAF effectors, and promotes stromal and cancer cell expansion[81] through β-galactosidase[83], IL-6, and IL-8[82] respectively. Xenografts in nude mice also demonstrated *in vivo* tumor growth enhancement by CAFs[48].

### Immunosuppression by CAFs

There is an impaired anti-tumor response within the HCC microenvironment due to various immune suppressive elements[84], including regulatory T cells (Tregs)[85], tumor-associated macrophages (TAMs)[86], and tumor-associated neutrophils (TANs)[87,88]. Among the immune cell types present within the HCC, TAMs play a leading role in the setting of the crosstalk between tumor and stromal cells[89]. TAMs are mainly polarized towards an M2 phenotype, which is a major component of leukocyte infiltration of tumors and plays a pivotal role in tumor progression of HCC[90]. Increased TAMs are correlated with angiogenesis, metastasis, and poor prognosis[91-94]. STAT3 activation is correlated with aggressive behavior of HCC and may be mediated *via* TAMs[95].

CAFs educate NK cells to acquire a deactivated phenotype and create an unresponsive condition in tumors[96]. This suppression is eliminated by indoleamine 2,3-dioxygenase (IDO) and/or PGE2 inhibitors[96]. CAFs recruit regulatory dendritic cells and educate them to acquire a tolerogenic phenotype through IL-6 mediated STAT3 activation[97] and upregulate the production of Tregs by secreting TGF-β in tumor microenvironments[98]. The mechanisms underlying CAFs' immunomodulatory effects in HCC may be mediated *via* upregulation of human B7 homolog 1 (B7-H1) in CAFs[99]. B7-H1/programmed death 1 (PD-1) signaling promotes Treg cell induction and immunosuppressive function through the down regulation of mTOR and AKT phosphorylation[100]. Using these immunosuppression effects, CAFs that receive cytokine signals from cancer cells produce an environment that is convenient for cancer cells.

## ANGIOGENESIS

A hypoxic condition activates Akt, which increases the expression of vascular endothelial growth factor (VEGF), the most important angiogenic factor. The rapid growth of the HCC requires new vessels. CAFs secrete angiogenic factors, including VEGF, PDGF, MMPs, FDF, TGF-β1, EGF, angiopoietin-1, and angiopoietin-2, which have a critical role in HCC initiation, progression, and metastasis, and creates new vessels[101-105]. VEGF receptor, PDGF receptor, and Tie-2 upregulation also occur during CAFs activation, resulting in increased mitogenesis in response to VEGF[19,106-108]. VEGF secretion by HSCs can be hormonally induced by leptin, or by physical stress such as hypoxia, and is upregulated in HCC[104,106,109]. Conditioned medium from HCC cells can activate CAFs and stimulate VEGF production. Oxidative stress enhances the malignant potential of HCC through the stimulation of angiogenesis by activation of the Akt-VEGF pathway[110]. Angiogenesis is also facilitated by TAM-derived proteases because extracellular proteolysis is necessary for new vessel formation. The most prominent proteinases that promote tumor-directed angiogenesis include matrix metalloproteinase, plasmin, and urokinase-type plasminogen activator and its receptor[111,112].

## CAFS AS THERAPEUTIC TARGETS IN HCC

Anti-cancer therapy targeting CAFs or inhibitors of the cytokines secreted by CAFs has been actively investigated recently. Inhibitors of TGF-β signaling have been shown to block HCC growth and progression by modulating EMT in different experimental models, leading to the clinical investigation of a TGF-β inhibitor monohydrate in HCC[68]. Several receptor tyrosine kinase inhibitors target VEGF and PDGF. Linifanib is a potent inhibitor of VEGF, PDGF, PDGFR-β, KDR, and colony stimulating factor-1-receptor (CSF). Sunitinib inhibits receptors for PDGF and VEGF, as well as other receptor tyrosine kinases such as CSF. Some groups have explored active targeting of CAFs to deliver therapeutic compounds. This involves coupling the selected compound to a carrier possessing a specific receptor binding ligand or an antibody. Carriers employed have included an antibody to the synaptophysin receptor on CAFs, and a liposome specific to the vitamin A receptor on CAFs[68,113,114].

These therapeutic targets are several cytokines secreted by CAFs or signals from CAFs that stimulate the HCC. Liver fibrosis is treated with anti-fibrotic drugs that inhibit the activation of quiescent HSCs and promote cell death in activated HSC. If CAFs are an activated state of HSC, it is possible that these drugs were effective for CAFs. A recent report suggested some anti-fibrotic drugs, such as PRI-724[115], conophylline[116], armepavine[117], follistatin[118], salvianolic acids[119], ursolic acid[120], gliotoxin[121], curcumin[122], sulfasalazine[123], benzodiazepine[124] and tanshinone I[125], which suppress activated HSCs and/or induce apoptosis. It is thought that these drugs not only control the fibrosis, but also suppress the HCC by controlling the function of CAFs. Restraining fibrosis may lead to controlling further carcinogenesis according to the theories about field cancerization.

Fibrolamellar HCC was surrounded by laminated fibrous stroma[126]. It was reported the overexpression of fibroblast growth factor receptor 1 in fibrolamellar HCC[127]. CAFs stimulate tumor cells by FGF[50,51] and produced fibrosis. Treatment targeting CAFs is might be effective in a fibrolamellar HCC.

CAFs stimulate malignant cell proliferation by providing different types of growth factors and cytokines in a context-dependent manner[20] such as SDF-1[42-45], HGF[46-48], members of the epidermal growth factor family[49], fibroblast growth factor (FGF)[50,51].

## CHEMORESISTANCE

After undergoing EMT, malignant cells become more resistant to chemotherapy, and those expressing surface molecules of stem cells increase, suggesting a close link between CAF-induced EMT, tumor stem cells, and chemoresistance of tumor cells[128,129]. miR-27

is associated with chemoresistance in esophageal cancer through transformation of normal fibroblasts to cancer-associated fibroblasts[130]. Tumors with stromal phenotypes are more chemoresistant and share more characteristics with tumor stem cells[131]. CAFs are primarily resistant to chemotherapy due to a small proportion of proliferating cells in contrast to malignant cells[132]. CAFs induce high mobility group box 1 and contribute to resistance to doxorubicin in breast cancer cells[133]. CAFs attenuate the sensitivity to cisplatin in ovarian cancer cells by promoting STAT3 signaling[134]. These findings about a connection between CAFs and chemoresistance are from recent studies, and the mechanisms of resistance are still unclear.

## CONCLUSION

CAFs are one of the most crucial components of the tumor microenvironment that promote the growth and invasion of cancer cells by various mechanisms. Chronic inflammation was previously considered the main reason for carcinogenesis leading to HCC. However, there remains a persistent risk for HCC in patients with advanced fibrosis who have achieved SVR[15]. These results suggest that procancer stromal alterations were made by the CAFs and CAFs related cells. In conclusion, CAFs are important for cancer cell initiation and progression, and therapy targeting CAFs may be effective for treating fibrosis and preventing HCC progression.

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