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Editorial

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# Cancer Associated Fibroblasts and Hepatocellular Carcinoma

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Hepatocellular Carcinoma (HCC) ranks the fifth most common cancer worldwide, and high recurrent rate and metastasis are the major hurdles for effective therapies of this disease. Recently, increasing evidence shows that Cancer-associated Fibroblasts (CAFs), one of the most abundant cell types inside the tumor stroma, plays a prominent role in progression of various cancer types. Since most of the HCC cases are developed with cirrhosis background in which activated myofibroblasts are enriched, the role of CAFs in HCC progression is currently being investigated.

The origin of CAFs in HCC remains controversial. Recent studies revealed that it has multiple origins including activation of resting fibroblasts, trans-differentiation of hepatic stellate cells during liver injury, or direct contribution of hepatocytes through epithelial to Mesenchymal Transition (EMT) [1,2]. Mazzocca et al. [3] has found that HCC cells could stimulate the differentiation of peritumoral fibroblasts to a more CAF like myofibroblast phenotype through the secretion of lysophostatidic acid. These activated fibroblasts or CAFs could remodel the Extra-cellular Matrix (ECM), which release a number of signaling molecules like growth factors and cytokines which aggravate HCC development and progression. These growth factors, for instance like Epidermal Growth Factor (EGF), Hepatocyte Growth Factor (HGF), and chemokines like CCL2 and Stromal Cell-Derived Factor 1(SDF-1) were also found to be directly secreted by CAFs in other cancer types [4-7].

It was shown that CAFs could also directly promote HCC cells growth. HCC cells stimulated the proliferation of CAFs by secreting CTGF through TGF-β induction, and CAFs reciprocally promote growth of HCC cells. This highlights the significance of their cross-talk in tumor development [3,8]. Targeting TGF-β receptor type I by LY2109761 yielded an antistromal therapy to suppress HCC progression. Study from the same group also showed that CAFs was able to enhance the metastatic potential and intravasation of HCC [8]. Disrupting the cross-talk between CAFs and HCC cells by down-regulating CTGF could inhibit stromal growth and metastasis. Besides, a hepatic stellate cell which was activated to a myofibroblast like phenotype (as indicated by the expression of α-smooth muscle actin) was found to be responsible for the production of excessive peritumoral collagen and colorectal metastasis [9]. In another study, van Zijl et al. [10] found that the co-injection of myofibroblasts and malignant hepatocytes not only enhanced tumor growth, but also promoted HCC invasiveness through TGF-β/ PDGF signaling axis. All in all, these studies demonstrate the role of CAFs in exaggerating HCC progression and metastatic spread. Besides its direct effect on cancer cells, CAFs was found to create a cancer favorable environment by interacting with immune cells inside the tumor stroma such as the NK cells. NK cells mediate the cytotoxic effect towards cancer cells and has prominent role in anti-tumor defense mechanism, and its activity is significantly lowered in HCC [11]. CAFs were found to produce PGE2 and IDO to suppress the activity of NK cells, lowering their cytotoxic effects on HCC cells and thereby promoting cancer progression [12].

Despite the advances in various treatments, the long-term prognosis of HCC remains unsatisfactory due to the high recurrent rate. Recently, "Cancer Stem Cell" theory proposed that a small population of Cancer Stem Cells (CSCs) which are resistant to chemo-therapy are the root of tumor development. Phenotypes of CSCs were reported to be tightly regulated by CAFs in certain cancer types. Li et al. and Giannoni et al. [12,13] found that CAFs could promote cancer stemness of prostate cancer cells by activating the EMT pathways. In colon cancer, myofibroblasts was also able to increase cancer stemness via the secretion of HGF [14]. Although various liver CSC markers have been identified, there is no report showing the regulatory role of CAFs on liver CSCs. However, the role of CAFs on regulation of liver CSCs cannot be underestimated. In order to achieve the goal of developing an effective therapy for HCC by specifically eliminating liver CSCs, further investigation on the molecular mechanism of how CAFs regulate liver CSCs is highly warranted.

To conclude, recent findings highlighted the contribution of CAFs to tumor cell proliferation, metastasis, and self-renewal and immune evasion in various cancers. Given the crucial contribution of CAFs in promoting tumor progression, it has gained increasing interest as a potential therapeutic target for anti-tumor therapies. Thus far, only limited reports have shown the role of CAFs in HCC. Therefore, it would be interesting to further investigate the interactions between CAFs and HCC cells for identification of therapeutic targets against HCC. Disrupting the cross-talks between CAFs and HCC cells may potentially open a novel avenue to improve the clinical outcome of HCC treatment.

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