

Editorial

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Tumor Microenvironment and Pancreatic Cancer

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Pancreatic cancer is the fourth leading cause of cancer-related deaths in both men and women (preceded by lung, prostate/breast and colon-rectum) in the United States, with a 5-year survival rate of less than 5% [1]. Despite the rapid advances in diagnostic and operative techniques, the patient survival has little improvement in the last decade. Chemoresistance [2,3], early metastases, and late clinical presentation [4] are the major reasons for the poor clinical outcomes. This discouraging reality strongly suggests an urgent demand of new research directions and alternative/complementary approaches to improve the clinical outcome of pancreatic cancer.

Efforts through intensive genomic and histologic research over the last several decades have progressively increased our understanding of pancreatic carcinogenesis which is characterized by the accumulation of genetic alterations and concomitant morphological and histological changes in pancreatic ductal cells. However, the growth of our knowledge has not achieved the transition into more effective clinical approaches as expected. It has been documented that pancreatic cancer cells *in vitro* displayed a similar response to chemotherapeutic agents compared to the cell lines derived from other solid tumors [5]. However, pancreatic cancer patients have lower drug responses (e.g. paclitaxel) compared to breast and prostate patients [5], indicating that other cells in the pancreatic tumors also play important roles in chemoresistance. A major histopathological feature of pancreatic cancer is its prominent desmoplastic reaction, a pronounced increase in connective tissue around the tumor elements, and the stroma can form up to 90% of the tumor [5,6]. It has also been reported that pancreatic tumor desmoplasia correlates with its biological and clinical aggressiveness [6,7]. Therefore, attention has been steadily expanded to the tumor microenvironment including fibroblasts, peritumor nerves, endothelial cells, and macrophages [8], among which, pancreatic stellate cell (PSC) is considered to be a rising star in pancreatic cancer research.

Pancreatic stellate cells were first observed as fat-storing cells in pancreas with the functional similarity with hepatic stellate cells, counterpart cells in the liver [9]. PSCs were first isolated in 1998, and are the resident cells primarily located in peri-acinar, peri-ductal, and perivascular area of the pancreas [10,11]. First isolated, the PSCs were characterized in a quiescent state by the presence of intracellular fat droplets and absence of α -smooth muscle actin (α -SMA). Activation of primary PSCs occurs in pancreatic injury or under cultivation, and PSCs attain a myofibroblast-like phenotype with the expression of α -SMA and extracellular matrix (ECM) proteins and disappearance of intracellular fat droplets [10,11]. An growing body of studies of primary PSCs in culture have identified several potential activators, such as growth factors (PDGF and TGF- β 1) [12,13], cytokines (IL-1, IL-6, IL-8, and TNF- α) [14,15], angiotensin II [16], and reactive oxygen species (ROS) released by the recruited leukocytes in response to pancreatic injury [17]. Furthermore, evidence is accumulating to suggest the bidirectional interplay between pancreatic tumor cells and activated PSCs promotes the tumor progression [18-20]. Bachem et al. [11] has demonstrated the tumor growth rate is markedly increased when the PSCs are co-injected with the pancreatic cancer cells *in vivo* [19]. Pancreatic cancer cells attract and promote the activation, proliferation, and the capability to remodel the ECM of PSCs by secretion of the aforementioned mediators [18,19,21,22]. Meanwhile, PSCs secrete various growth factors (PDGF, IGF-1, EGF), ECM proteins (matrix

metalloproteinases, collagen-I) which enhance the survival of the tumor cells by increased proliferation and reduced apoptosis [23,24], and promote the invasion of the tumor cells [25,26]. It has also been documented that PSCs promote epithelial-mesenchymal transition (EMT) via the production of increased fibrosis [27].

Several major signaling pathways involved in the functions of PSCs have been identified. MAPK/ERKs, initiated by growth factors and ethanol, have been suggested as key signal molecules regulating the functions of PSCs [28,29]. Activation of CXC-chemokine receptors is one of the up-stream signaling events of MAPK/ERKs signaling pathway. It has been reported that over expression of CXC-chemokine receptors (such as CXCR2 and CXCR4) and their cognate ligands correlates with high tumor grade and stage in pancreatic adenocarcinoma [30-32]. Moreover, an increasing body of evidence has shown that blocking the CXC-chemokine receptor signaling represent an effective intervention to reduce proliferation [32,33], invasion [34], and tumor-induced angiogenesis [32,34,35] both *in vitro* and *in vivo*. However, there are very few studies focusing on the CXC-chemokine signaling on PSC cells, which could improve our knowledge of the partially-understood mechanisms of the rapid tumor growth [19], enhanced epithelial-mesenchymal transition leading to metastasis [27], and poor delivery of chemotherapies [36] caused by PSCs and the prominent desmoplastic reactions.

A variety of PDZ (PSD-95/DlgA/ZO-1) domain-containing proteins (also referred to as PDZ scaffolding proteins) have been reported to nucleate the formation of compartmentalized multi-protein complexes that are critical for efficient and specific cell signaling [37-42]. These PDZ scaffolding proteins preferentially localize at the membrane and interact with membrane proteins (such as receptors, channels) and their downstream effectors. Characterizing the PDZ domain-mediated chemokine receptor macromolecular signaling complex in PSCs could be an innovative way to study the molecular mechanisms of tumor-stroma interactions in pancreatic cancer, and furthermore could be an alternative way to improve the transition into more effective chemotherapies.

In summary, the patient survival in pancreatic cancer has been limitedly improved in the last decade, indicating that alternative approaches other than targeting cancer cells alone is in urgent demand. PSCs are the key mediators of the prominent desmoplastic reactions, a unique feature of pancreatic cancer. The interplay between pancreatic cancer cells and PSCs facilitates tumor progression, tumor-induced

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angiogenesis, and metastasis. Various chemokine receptors and their cognate ligands are over expressed in the human pancreatic tumor, and correlates with the chemoresistance and poor prognosis. Targeting PDZ domain-mediated macromolecular complex of chemokine receptors in PSCs may represent a novel strategy to tackle pancreatic cancer.

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