Clinics and Research in Hepatology and Gastroenterology (2015) 39, S98—S103

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MINI REVIEW

Pancreatic stellate cells: A dynamic player of the intercellular communication in pancreatic cancer☆

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Available online 16 July 2015

Summary There is accumulating evidence that activated pancreatic stellate cells (PSCs) play a pivotal role in the development of pancreatic fibrosis within the pancreatic cancer tissue. Not only do they produce extracellular matrix components, PSCs dynamically interact with other cell types to constitute the cancer-conditioned microenvironment. There exist bidirectional interactions between PSCs and pancreatic cancer cells. Pancreatic cancer cells promote the proliferation, migration, extracellular matrix production and degradation, and angiogenetic responses in PSCs. In turn, PSCs promote the proliferation and migration, and inhibit the apoptosis of pancreatic cancer cells. PSCs also induce epithelial-mesenchymal transition and stem cell like phenotypes in pancreatic cancer cells, resulting in resistance to conventional therapies, distant metastasis, and recurrence. PSCs interact with endothelial cells, neural cells and β-cells, leading to angiogenesis, neurogenesis and β-cell dysfunction and apoptosis. PSCs cause impaired immune responses and help pancreatic cancer cells escape from host immune-surveillance. PSCs induce the differentiation of myeloid-derived suppressor cells, induce the apoptosis of T cells, inhibit the infiltration of T cells, and induce the activation of mast cells. Overall, these interactions appear to promote the progression of pancreatic cancer, and anti-stroma therapies targeting PSCs are under intense investigation. Further elucidation of these interactions could lead to the identification of novel therapeutic targets in pancreatic cancer.

Abbreviations: CSC, cancer stem cell; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; IL, interleukin; MDSC, myeloid-derived suppressor cells; miRNA, microRNA; PSC, pancreatic stellate cells; Shh, Sonic hedgehog; SMA, smooth muscle actin; VEGF, vascular endothelial growth factor.

☆ This article is part of the special issue ''Alcohol, Virus and Steatosis evolving to cancer'' featuring the conference papers of the 10th International Symposium organized by the Brazilian Society of Hepatology in São Paulo, Brazil, September 30th—October 1st, 2015.

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http://dx.doi.org/10.1016/j.clinre.2015.05.018
2210-7401/

Introduction

Pancreatic ductal adenocarcinoma is a highly malignant phenotype characterized by rapid progression, early metastasis, and a limited response to chemotherapy and radiotherapy [1]. The abundant desmoplastic/stromal reaction, accounting for up to 90% of the tumor volume, is a characteristic feature of pancreatic cancer [1—3]. It has been controversial whether the stroma drives the progression of pancreatic cancer or acts as a defense against pancreatic cancer [2—4]. A major breakthrough in this research field was the identification and characterization of the star-shaped cells in the pancreas, namely pancreatic stellate cells (PSCs), in 1998 [5,6]. There is accumulating evidence that activated PSCs play a pivotal role in the development of pancreatic fibrosis within the pancreatic cancer tissue [7—11]. Not only do they produce extracellular matrix (ECM) components, PSCs dynamically interact with other cell types to constitute the cancer-conditioned microenvironment. In this mini-review, we will briefly summarize our current knowledge in this field.

Stroma in pancreatic cancer

The stroma consists of a variety of components including fibroblasts and myofibroblasts, blood vessels, inflammatory and immune cells, ECM and matricellular proteins [3,4]. It has been shown that high stromal activity, as assessed by α-smooth muscle actin (α-SMA) expression, is associated with a poor prognosis in patients with pancreatic cancer [2]. Similarly, the high expression of matricellular matrix proteins such as secreted protein acidic and rich in cysteine [12] and periostin [13] is associated with a poor prognosis. These results suggest that the stroma has a clinical impact on the progression of pancreatic cancer. It has been controversial whether the stroma drives the progression of pancreatic cancer or acts as a defense against pancreatic cancer [3,4]. The stroma might stimulate the aggressive behaviors of pancreatic cancer cells and help them escape from host immune-surveillance. On the other hand, the stroma might provide a barrier limiting the dissemination and metastasis of pancreatic cancer cells. Another aspect of the stroma is low blood perfusion and hypoxia. The dense stroma impairs drug delivery by several mechanisms such as by providing a physical barrier and high interstitial pressure [14].

Identification and characterization of PSCs

A major breakthrough in this research field was the identification and characterization of PSCs in 1998 [5,6]. PSCs are mainly located around acinar cells, and account for about 4% of all pancreatic cells [5]. PSCs are morphologically and functionally very similar to hepatic stellate cells, which are major effector cells in liver fibrosis. In normal pancreas, stellate cells are quiescent and can be identified by the presence of vitamin A-containing lipid droplets in the cytoplasm [5,6,9]. In response to pancreatic injury or inflammation, quiescent PSCs undergo morphological and functional changes to become myofibroblast-like cells, which express α-SMA. This step is called ''activation'' [7]. The mechanism responsible for the activation of PSCs remains to be fully clarified, but includes the activation of intracellular signaling pathways such as mitogen-activated protein kinases [7,15]. The expression profile of microRNAs (miRNAs) in PSCs is dramatically altered upon activation, suggesting that microRNAs have a role in the activation process [16]. Activated PSCs lose lipid droplets, actively proliferate, migrate, and produce large amounts of ECM components such as type I collagen and fibronectin. It has been established that PSCs play a pivotal role in the development of pancreatic fibrosis in pancreatic cancer [8—11]. Importantly, in vitro culture of PSCs provides a useful and unique platform to investigate the interactions between stromal cells and cancer cells.

Dynamic interactions between PSCs and other cell types in pancreatic cancer microenvironment

It has been increasingly recognized that dynamic interactions exist between PSCs and other cell components in pancreatic cancer.

PSC-cancer cell interactions

Previous in vitro studies have shown bidirectional interactions between PSCs and pancreatic cancer cells [10]. Pancreatic cancer cells promote proliferation, migration, ECM production and degradation, and angiogenetic responses in PSCs. In turn, PSCs promote the proliferation and migration, and inhibit the apoptosis of pancreatic cancer cells [17]. These interactions are likely to be mediated mainly by cytokines and growth factors such as platelet-derived growth factor, transforming growth factor-β and fibroblast growth factor [18]. In an orthotopic model of pancreatic cancer, the size of a local tumor was greater if pancreatic cancer cells were injected with PSCs [17,19]. In addition, the number of mice with distant metastasis was increased if PSCs were injected together with pancreatic cancer cells [17,19]. Thus, PSCs promote local tumor growth and distant metastasis. Kikuta et al. [20] reported that PSCs-induced epithelial-mesenchymal transition (EMT) in pancreatic cancer cells. PSCs induced the fibroblast-like cell morphology, decreased the expression of epithelial markers E-cadherin and cytokeratin, and increased the expression of mesenchymal markers such as vimentin. EMT is a developmental process that allows a polarized epithelial cell to undergo multiple biochemical changes that enable it to assume a mesenchymal phenotype [21]. The EMT phenotype includes enhanced migratory capacity, invasiveness, elevated resistance to apoptosis, and greatly increased production of ECM components. EMT is now considered a critical process in cancer progression, and EMT induction in cancer cells results in the acquisition of invasive and metastatic properties as well as resistance to conventional therapies [21]. The molecular mechanisms responsible for PSC-induced EMT in pancreatic cancer cells remain to be fully clarified, but miRNAs might be involved. Takikawa et al. [22] identified miR-210 as an upregulated miRNA in pancreatic cancer cells by co-culture with PSCs. Inhibition