Pancreatic stellate cells promotes the perineural invasion in pancreatic cancer

Yu Zhou¹, Quanbo Zhou¹, Rufu Chen*

Department of Hepatobiliary Surgery, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

ABSTRACT

Perineural invasion is a prominent characteristic of pancreatic cancer. Pancreatic cancer has an extremely high incidence of perineural invasion which has been associated with poor survival. Early studies mostly focus on the interaction between cancer cells and nerves. Recently, the effect of pancreatic stellate cells in progression of pancreatic cancer has been paid more attention. Both in vitro studies and in vivo ones revealed that pancreatic stellate cells can enhance the proliferation, migration and invasion of pancreatic cancer cells. Pancreatic stellate cells can also regulate the expression and effect of molecules involved in perineural invasion. In addition, pancreatic stellate cells seems to associated with the generation of neuronal plasticity in pancreatic cancer. Herein the hypothesis that pancreatic stellate cells play a potential role in promote the perineural invasion in pancreatic cancer through three mechanisms. One is that pancreatic stellate cells enhance the proliferation, migration and invasion directly through releasing a variety of stimuli and providing a suitable microenvironment. Pancreatic stellate cells also regulate the expression and effects of molecules involved in perineural invasion such as nerve growth factor. Another is that pancreatic stellate cells induce neuronal plasticity, which makes nerves more vulnerable to be invaded. We can conclude that pancreatic stellate cells play a central role in regulating the perineural invasion process by producing different effects on cancer cells and nerve. To inhibit the activity of pancreatic stellate cells or block the interaction between pancreatic stellate cells and cancer cells or nerve tissue might reduce the perineural invasion in pancreatic cancer.

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Introduction

Pancreatic cancer (PanCa) is an aggressive and highly lethal disease with a reported 5-year survival of less than 1% [1]. In addition to the difficult early diagnosis, metastasis and recurrence are key factors with its dismal prognosis. It has long been known that PanCa is characterized by extremely high frequency of perineural invasion (PNI) [2], which serve as an alternative route for dissemination and may be responsible for some cases of lymphatic spread [3]. Although surgery has been shown to be an effective therapeutic approach, there is an inevitable tendency for recurrence for what the involved nerve tissue is an important source [4].

In 1998, the star-shaped cells in the pancreas, called pancreatic stellate cells (PSCs), were identified and characterized [5]. In health, PSCs exist in a quiescent state. In diseased states, under the influence of growth factors, cytokines, and oxidant stress, PSCs transform into a myofibroblast-like phenotype secreting excess amounts of extracellular matrix (ECM) as well as matrixdegrading enzymes [6]. For over a decade, there has been accumulating evidence that activated PSCs play a pivotal role in the development of pancreatic fibrosis in chronic pancreatitis and in pancreatic cancer [7,8]. In recent years, the integral role of PSCs in pancreatic tumor progression is becoming increasingly clear. Conditioned medium of PSCs has been shown to induce proliferation, migration and invasion of pancreatic cancer cells (PCCs) in a dose-dependent manner [9,10]. Unfortunately, the potential important role of PSCs in PNI has been ignored.

The mechanism of PNI in PanCa

The mechanism of neural invasion in pancreatic cancer is not fully understood. It is considered that the numerous innervation of pancreas and nearby nerve plexus around the pancreatic parenchyma are the proper anatomical basis. Mechanically, cancer cells may invade nerves through two likely mechanisms: tumor invasion into the perineural cavities after direct destruction of the perineurium and invasion via the perforating vessels of the perineurium [3]. The molecular mechanisms can be explained by the highly coordinated signalling events between the cancer cells and nerves. A large number of molecules including neurotrophins and their receptors, cytokines, chemokines and cell-surface ligands and receptors have been implicated in the process of PNI [11–15].

* Corresponding author. Address: Department of Hepatobiliary Surgery, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, 107 Yan-Jiang Xi Road, Guangzhou 510120, China. Tel.: +86 13 2868 87779; fax: +86 21 8133 2020. E-mail address: zyzysmile@163.com (R. Chen).

¹ These authors contributed equally to this work.
PSCs enhance the progression of pancreatic cancer

PSCs can regulate the progression of pancreatic cancer through a paracrine pathway. Conditioned medium of PSCs has been shown to induce proliferation, migration and invasion of pancreatic cancer cells in a dose-dependent manner [16,17]. The proliferation of pancreatic cancer cells is partly mediated by platelet-derived growth factor secretion from PSCs. Other factors that are suspected to promote proliferation of cancer cells are stromal-derived factor 1, EGF, insulin-like growth factor 1 and FGF [16]. In addition, PSCs can activate the Notch signaling pathway in PCCs by direct cell–cell contact, cancer cell proliferation significantly increased in direct culture system compared with the indirect coculture system [18]. In vivo studies with xenograft and orthotopic models in nude mice revealed that the presence of stromal cells significantly enhances pancreatic tumor growth rate as well as regional and distant metastasis, human PSCs accompany cancer cells to metastatic sites, stimulate angiogenesis, and are able to intravasate/extravasate to and from blood vessels [16,19].

PSCs and molecular factors involved in PNI

Evidence indicate that PSCs may play a regulatory role in the interaction between cancer cells and nerves. Transforming growth factor-β (TGF-β), a growth factor secreted by PSCs, can induces nerve growth factor expression in pancreatic stellate cells by activation of the ALK-5 pathway [20]. Chemotactic activity of NGF which promotes microglial migration was increased in the presence of low concentrations of TGF-β [21]. The ECM protein laminin which is mainly secreted by PSCs in pancreatic cancer can enhance the neurite outgrowth by down regulate the low affinity neurotrophin receptor, p75NTR, whose expression was inversely associated with PNI [22]. Increased expression of MMP2 and MMP9 in response to the stimulation of GDNF and NGF in pancreatic cancer cells is thought to contribute to the PNI [23–25]. It is noteworthy that cultured rat PSCs have the capacity to synthesis a number of matrix metalloproteinases and regulate their activities [26]. L1CAM and NCAM are typical cell-surface molecules involved in PNI, it is reported that upregulation of NCAM expression is an early event upon loss of E-cadherin function and epithelial-mesenchymal transition (EMT) in breast cancer cell lines, and the EMT associated transcription factor Slug can activate the L1CAM promoter and thus increase L1CAM expression in endometrial carcinoma cells [27,28]. For the PSCs can promote EMT in PCCs [29], it may regulate cell-surface molecules in PCCs by this pathway.

PSCs-nerve interaction

Human chronic pancreatitis and pancreatic cancer show prominent neuroplastic changes unparalleled by any other GI disorder: intrapancreatic nerves are strikingly hypertrophy and increased in neural density [30,31], a comprehensive pathomorphological study revealed that The aggressiveness of neural cancer cell invasion was related to neuropathic changes, desmoplasia, and pain [32]. A neurotrophic role of human pancreatic stellate cells (hPSC) in pancreatic cancer is increasingly recognized: immortalized hPSC lines can secrete NGF when stimulated by TGF-β [20], and supernatants of hPSC strongly stimulated neurite outgrowth [33]. An in vivo study about prostate cancer, another cancer also has neuro-invasive ability, showed that the number of nerves around the tumor tissue and the NGF expression in the group treated with CXCL12 was significantly higher than that found in the control group. Interestingly, PSCs but not PCCs express CXCL12 in pancreatic cancer [34], while CXCR4 exists on both PCCs and nerve tissue.

The hypothesis

Pancreatic cancer is characterized by extremely high frequency of perineural invasion, which has been associated with poorer survival. Much of the current research on PNI has focused on the interaction between cancer cells and nerves. Very few studies have examined the roles of tumour stromal elements—including pancreatic stellate cells, fibroblasts, infiltrating immune cells and ECM proteins in the PNI process [35]. We present the hypothesis that PSCs promote PNI through three mechanisms. One is that PSCs enhance the proliferation, migration and invasion directly through releasing a variety of stimuli and providing a suitable microenvironment. PSCs also regulate the expression and effects of molecules involved in PNI. Another is that PSCs induce neuronal plasticity, which makes nerves more vulnerable to be invaded. We can conclude that PSCs play a central role in regulating the PNI process by producing different effects on cancer cells and nerve.

Discussion

Pancreatic cancer is still a lethal malignancy with extremely high rate of metastasis and recurrence. Much evidence indicate that PNI is associated with the high incidence of disease relapse and the poor survival of patients with pancreatic cancer [36–38]. Therefore, treatment targeting PNI shows a potentially attractive therapeutic value for pancreatic cancer. As mentioned above, the activated PSCs which supports proliferation and invasion of PCCs may play an central role in regulating the process of PNI in pancreatic cancer. The distinctive presence of PSCs presents a unique opportunity for a better understanding of the mechanism that are involved in PNI. To attenuate the PNI process in pancreatic cancer, we can either inhibit the activity of PSCs or block the interaction between PSCs and PCCs or nerve tissue. Thus, targeting PSCs, in addition to those signalling pathways that just involved in the PCCs-nerve interaction, may be needed to improve the treatment effect of patients with pancreatic cancer. It is different from current studies focused on PCCs and nerves, studies provides insight into mechanisms by which PSCs influence PNI shall target three factors including PSCs, PCCs and nerves. Therefore, a three-dimensional culture system is needed for in vitro study. In addition, improvements in animal models that closely recapitulate the development of PNI will also be crucial to accelerating the discoveries.

Conflict of interest statement

We declare that there is no conflicts of interest.

References


