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Pancreatic cancer associated stroma production

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Abstract

One of the defining features of pancreatic ductal adenocarcinoma is the presence of extensive desmoplasia. The desmoplastic stroma consists of proliferating fibroblasts and pancreatic stellate cells that produce and deposit fibronectin and collagens, inflammatory cells and macrophages that produce chemokines and cyokines, nerve fibers that release nerve growth factors, and marrow derived stem cells. Stroma production is facilitated by the abundance of growth factors, including fibroblast growth factors, 1 epidermal growth factor receptor ligands, transforming growth factor beta isoforms, and connective tissue growth factor. Due to its location in the pancreas, stromal cells and pancreatic cancer cells are also exposed to high insulin levels. The stromal compartment stores and synthesizes multiple growth factors and the heparan sulfate proteoglycans glypican-1 and syndecan-1. This unique microenvironment harbors and nourishes the cancer cells, facilitating their invasive and metastatic potential. Targeting the stroma may thus provide novel therapeutic options in this deadly malignancy.

Keywords

pancreatic cancer; stroma; growth factors; heparan sulfate proteoglycans; tumor microenvironment; targeted therapy

Introduction

Pancreatic Ductal Adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer related mortality in the United States and other industrialized countries. The prognosis of patients with PDAC is extremely poor, with a median survival of 6 months and an overall 5-year survival rate that is less than 5% [1–3]. The diagnosis of PDAC is often established at an advanced stage, precluding patients from undergoing tumor resection. This delay in diagnosis is due to the indolent growth of the tumors within the pancreas, the absence of truly effective conventional radiological tests that will identify early disease, and the absence of specific and sensitive diagnostic serum markers. Although endoscopic ultrasonography is providing an enhanced ability to identify smaller pancreatic lesions, the tumor has a propensity to metastasize even when small, and the cancer cells are generally resistant to chemotherapy and/or radiotherapy [3–5]. Moreover, in view of our aging population, it is likely that PDAC may become a more serious problem in the future. An improved understanding of the mechanisms

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that contribute to pancreatic tumor growth and metastasis is therefore urgently needed. It is in this context that the NCI sponsored a Report of the Pancreatic Cancer Progress Review Group which pointed to important gaps in our understanding of the pathobiology of this malignancy [6].

Molecular Aspects of Pancreatic Cancer

PDAC is known to overexpress many mitogenic growth factors and their corresponding high affinity tyrosine kinase receptors [7], and to harbor a high frequency of mutations in the K-*ras* oncogene, the p53 and Smad4 tumor suppressor genes, the p16 cell cycle inhibitory gene [8]. In addition, there is excessive activation of downstream signaling pathways such as the src, NFκB and Stat3 signaling pathways [9–11]. Together, these alterations enhance cancer cell proliferation, suppress pro-apoptotic pathways, and promote tumor spread and metastasis. This high metastatic potential is facilitated by altered epithelial-mesenchymal interactions that are due, in part, to the abundance of stromal elements within the pancreatic tumor mass. This review will focus on our increasing understanding of the contribution of cancer associated stroma to the pathobiology of PDAC.

Origin of Pancreatic Cancer and Its Associated Stroma

The exact cell type that gives rise to PDAC is not known. In theory, PDAC may arise from a poorly differentiated ductal cell, a de-differentiated acinar or islet cell, a progenitor cell, or a stem cell. In recent years there has been a growing appreciation that pancreatic intraepithelial neoplasia or PanINs constitute pre-cancerous lesions that lead to PDAC [12,13]. Low-grade lesions are termed PanIN-IA and PanIN-1B, and these lesions often harbor activating K-*ras* mutations. Intermediate grade lesions are classified as either PanIN-2A or PanIN2B, and exhibit, in addition to K-ras mutations, loss of cyclin dependent kinase 2A (CDKN2A or p16). Progression to carcinoma *in situ* yields PanIN-3 lesions, which are characterized by marked nuclear atypia, budding of cells into the lumen of the duct-like structures, the presence of mitotic figures that are a reflection of the increased rate of cellular proliferation, and the occasional presence of p53 mutations [12–14]. Mice carrying an activate K-*ras* allele and harboring either a partially inactivated p53 gene or a deletion in the Ink4a locus exhibit accelerated tumor progression and develop distant metastases [15,16], underscoring the importance of multiple hits in the progression of PanINs to PDAC.

Early PanIN lesions may be associated with small amounts of normal stroma surrounding the normal pancreatic ducts from which the PanINs arise. By contrast, with PanIN III lesions there may be the beginning of enhanced stroma formation, and progression to invasive carcinoma is often associated with a readily evident increase in stroma formation that ultimately results in extensive stroma. Often, there is an associated inflammatory infiltrate.

The stroma in PDAC is a complex structure. It consists of proliferating fibroblasts and pancreatic stellate cells (PSC) that produce and deposit fibronectin and collagens I and III [17]. The cancer cells are also capable of synthesizing and releasing collagens. In addition, the matrix contains aberrant endothelial cells, pericytes, foci of inflammatory cells and macrophages that produce chemokines and cyokines, many of which are mitogenic towards both fibroblasts and PSC [18]. The stroma also contains nerve fibers that release nerve growth factors (NGFs), and bone marrow derived stem cells that may have the capacity to differentiate into PSC and fibroblasts, and endothelial cells [19,20]. Moreover, due to its location in the pancreas, pancreatic cancer cells are exposed to high levels of insulin deriving from the adjacent endocrine islets. The net result is a unique microenvironment in which the pancreatic cancer cells can thrive, and from which they can readily metastasize.

Potential Role of Stroma in Pancreatic Cancer Invasion and Metastasis

Several types of tumor-stroma interactions have been implicated as having the potential to promote pancreatic cancer cell invasion and metastasis. Cancer cell derived growth factors, such as fibroblast growth factors (FGFs), transforming growth factor-betas (TGF-βs), insulin-like growth factor-1 (IGF-1) and platelet-derived growth factor BB (PDGF-BB), become sequestered within the stroma, which thus acts as a storage site for these factors. The invading cancer cells produce matrix metalloproteinases (MMPs) that release these growth factors. The cancer cells also shed glypican-1 and syndecan-1 [21,22] which are heparan sulfate proteoglycans that facilitate the interactions between those growth factors that are heparin binding (such as FGFs) and their cognate, high-affinity receptors. Moreover, the high insulin levels may lead to activation of the overexpressed IGF-1 receptor on the cancer cells and paracrine mitogenic effects on fibroblasts and PSC. In addition, the NGFs mentioned above that bind and activate NGF receptors on the cancer cells [23], and promote cancer cell proliferation and invasion.

In conjunction with the changes observed in the cancer cells, there is an altered gene expression profile in the cancer-associated stroma, including altered integrin expression that may act to promote cancer cell motility, increased expression of cyclooxygenase-2 (Cox-2) and VEGF-A and collagen I that enhance stromal neo-vascularization and promote cancer cell growth [24–28]. Together, these types of alterations result in aberrant epithelial-mesenchymal interactions that promote cancer cell proliferation and invasiveness, thereby enhancing tumor spread while suppressing cancer directed immune mechanisms.

Stroma-targeted Therapeutics

The conclusion that the stroma and aberrant stromal-epithelial interactions contributes to pancreatic cancer spread and metastasis raises the possibility that targeting the stroma may be represent an additional approach for treating pancreatic cancer. In this regard, any agents that target pro-fibrotic growth factors, such as small molecule tyrosine kinase inhibitors that interfere with EGF receptor, FGF receptor, PDGF receptor, or IGF-1 receptor signaling, may be useful in suppressing the proliferation of fibroblasts and stelate cells. Moreover, targeting factors produced by stromal cells that are known to stimulate cancer cells growth and/or endothelial cell proliferation, may also be a useful strategy. For example, VEGF Trap may act to inhibit the VEGF-A-mediated pro-angiogenic signal that is produced by stromal cells [29]. Similarly, expression of a soluble form of the type II TGF-β receptor in pancreatic cancer cells leads to attenuated tumor growth, decreased neo-angiogenesis, and decreased expression of metastasis-promoting genes, such as plasminogen activator inhibitor 1 (PAI-1) and urokinase plasminogen activator [30–31].

TGF-β isoforms are markedly up-regulated in PDAC [32], and they, in turn, enhance the expression of connective tissue growth factor (CTGF), a pro-fibrotic factor that increases pancreatic cancer cell proliferation and invasiveness [33]. Moreover, CTGF is abundant in both the cancer cells and PSC in PDAC [34]. The potential importance of CTGF in PDAC is underscored by the observation that a highly specific, fully human monoclonal antibody against CTGF (FG-3019) can attenuate tumor growth, metastasis and angiogenesis in an orthotopic mouse model of PDAC [33]. Similarly, Cox-2 was shown to be expressed at high levels in both the cancer cells and stroma cells in PDAC, and COX-2 inhibitors were shown to decrease pancreatic cancer cell invasiveness that was acquired through tumor-stromal interactions [25]. Taken together, these observations suggest that targeting the stroma may interrupt multiple aberrant autocrine and paracrine pathways that promote pancreatic cancer cell growth, invasion, metastasis, and angiogenesis. Devising strategies for targeting the stroma may thus ultimately provide novel therapeutic options in PDAC.

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