Review

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Pancreatic Cancer: The Role of Pancreatic Stellate Cells in Tumor Progression

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Pancreatic cancer, treatment · Stellate cells · Desmoplasia · Signal transduction

Abstract
Pancreatic ductal adenocarcinoma is an aggressive and highly lethal disease frequently characterized by a dense stromal or desmoplastic response. Accumulating evidence exists that tumor desmoplasia plays a central role in disease progression and that e.g. activated pancreatic stellate cells (PSCs) are responsible for the excess matrix production. The mechanisms underlying the tumor versus stroma interplay are complex. Pancreatic cancer cells release mitogenic and fibrogenic stimulants, such as transforming growth factor β_1, platelet-derived growth factor (PDGF), sonic hedgehog, galectin 3, endothelin 1 and serine protease inhibitor nexin 2, all of which may promote the activated PSC phenotype. Stellate cells in turn secrete various factors, including PDGF, stromal-derived factor 1, epidermal growth factor, insulin-like growth factor 1, fibroblast growth factor, secreted protein acidic and rich in cysteine, matrix metalloproteinases, small leucine-rich proteoglycans, periostin and collagen type I that mediate effects on tumor growth, invasion, metastasis and resistance to chemotherapy. This review intends to shed light on the mechanisms by which PSCs in the stroma influence pancreatic cancer development. The increased understanding of this interaction will be of potential value in designing new modalities of targeted therapy.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a devastating disorder for most people who are afflicted, with a reported 5-year survival of less than 1% [1]. In Western countries, pancreatic adenocarcinoma comprises the fourth most common cause of malignancy-related death, and the annual incidence has been estimated to be approximately 10 cases per 100,000 population [2]. Cigarette smoking, advanced age and genetic disorders (e.g. hereditary pancreatitis, familial breast cancer and hereditary nonpolyposis colon cancer) are recognized as established risk factors.

The current model of progression of normal ductal epithelium, via pancreatic intraepithelial neoplasias, to invasive ductal adenocarcinoma, includes activating point mutations in K-ras, and loss of p53, p16 and SMAD4/DPC4 tumor suppressors. More recently, the microenvironment surrounding the pancreatic cancer cells has received increased attention. The cancer microenviron-

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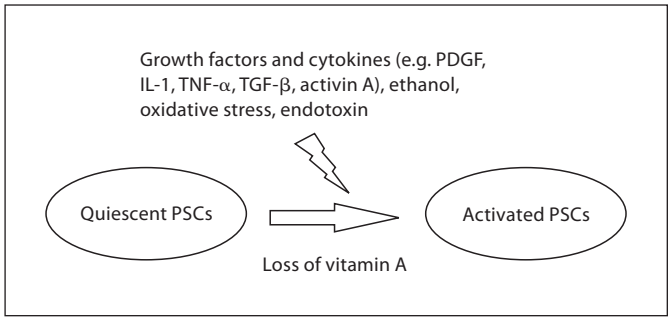

Fig. 1. A central feature of the desmoplastic response is the transformation of PSCs from quiescent vitamin-A-containing cells into activated myofibroblast-like cells. A variety of factors released during pancreatic injury or cancer, such as cytokines, growth factors, ethanol, oxidative stress and endotoxin, participate in the induction of PSC activation. IL = Interleukin; TNF = tumor necrosis factor.

ment is characterized by a desmoplastic reaction with the stromal part often being greater than the epithelial component of the tumor itself [3]. The stroma is a dynamic milieu, where fibroblasts, pancreatic stellate cells (PSCs), extracellular matrix (ECM), matrix metalloproteinases (MMPs), tissue inhibitors of MMP, inflammatory cells, nerve fibers, stem cells, endothelial cells as well as different growth factors and cytokines can interact with cancer cells and alter their behavior. Although it has been postulated that the cancer-associated stroma may represent a host defense against malignant spread [4], most lines of evidence indicate that the desmoplasia of pancreatic cancer is paramount to tumor promotion and progression [5–10].

This review will summarize recent advances in the understanding of the mechanisms involved in tumor-stroma interactions, with particular focus on PSCs and future directions in stroma-targeted therapies.

The Pancreatic Stellate Cell

In 1998, the star-shaped cells in the pancreas were identified and characterized, termed PSCs [11, 12]. These cells are considered to be critical for the development of the desmoplastic reaction associated with chronic pancreatitis, as well as pancreatic cancer. In the normal pancreas, PSCs represent approximately 4% of the resident cells and are located in the periacinar and interlobular space. A central feature of the desmoplastic response is the transformation of PSCs from quiescent vitamin-A-containing cells into activated myofibroblast-like cells. Characteristic features of this transition include an increase in the production of ECM, including type I and III collagens, laminin, fibronectin, as well as MMPs and tissue inhibitors of metalloproteinases. Other important features of activation include loss of vitamin A lipid droplets, proliferation, enhanced α-smooth muscle actin expression and upregulation of various cytokines and growth factors. Included in this latter group are transforming growth factor β_1 (TGF-β_1), platelet-derived growth factor (PDGF) and vascular endothelial growth factor [13]. During pancreatic injury or cancer, a variety of factors, such as epidermal growth factor (EGF), PDGF, interleukin 1, tumor necrosis factor α, fibroblast growth factor (FGF) and TGF-β_1, participate in the induction of PSC activation. PSCs may also be activated by ethanol and its metabolites, oxidant stress and endotoxin (fig. 1). Sustained activation of PSCs is further maintained by autocrine signaling via e.g. TGF-β_1, PDGF, connective tissue growth factor, interleukins 1β and 15, and endothelin 1 (ET-1). Moreover, activin A, a member of the TGF-β family, also has autocrine properties, increasing the secretion and expression of collagen and TGF-β [14]. Several signal transduction molecules involved in PSC activation have successfully been characterized, including mitogen-activated protein (MAP) kinase, peroxisome proliferator-activated receptor γ, phosphatidylinositol 3-kinase/Akt, ρ-kinase, AP-1, NF-κB, JAK/signal transduction and activation of transcription factor (STAT), TGF-β/SMADs, and reactive oxygen species [15].

Cancer Cells Stimulate PSCs

Pancreatic cancer cells can specifically activate surrounding PSCs. This may occur by cancer-cell-induced release of mitogenic and fibrogenic factors, such as PDGF, FGF2 and TGF-β_1. PDGF induces proliferation of PSCs through Src-dependent activation of the JAK2-STAT3 pathway [16] and the MAP kinase pathway extracellular signal-regulated kinases (ERK) 1/2 [17, 18] and p38 [19]. Pancreatic cancer cells also possess an attracting effect on PSCs. PDGF can induce migration of PSCs through activation of the phosphatidylinositol 3-kinase/Akt pathway [18, 20]. TGF-β_1 exerts its effects on PSCs through SMADs 2, 3 and 4 as well as SMAD-independent pathways such as MAP kinases [21]. Moreover, cancer cells express a surface glycoprotein known as ECM metalloproteinase inducer, which has been demonstrated to induce MMP-2 synthesis in PSCs [13, 22]. MMPs are asso-