Abstract

Pancreatic stellate cells (PSCs) are resident cells of the pancreas, found in both the exocrine and endocrine parts of the gland. Over the two decades since these cells were first isolated and cultured from rodent and human pancreas, research in this area has progressed at a rapid rate. Our knowledge of PSC biology in both health and disease has increased significantly. In health, PSCs are known to not only play a role in regulating normal extracellular matrix turnover but are also thought to have progenitor cell functions as well as a role in innate immunity. The critical roles of PSCs in inflammatory as well as malignant disease of the pancreas are now being increasingly elucidated. An improved understanding of PSC biology and of the interactions of PSCs with other pancreatic cells provides a strong platform for the development of novel therapeutic approaches for notoriously hard to treat diseases of the pancreas such as chronic pancreatitis and pancreatic cancer.

I. INTRODUCTION

Pancreatic fibrosis is a well-recognized histopathological feature of two major diseases of the pancreas – chronic pancreatitis and pancreatic cancer. In health, the process of fibrogenesis is a well-regulated dynamic process which is necessary for regular turnover of extracellular matrix (ECM) that allows remodeling and maintenance of normal pancreatic architecture. However, during injury, the equilibrium between production and degradation of fibrous tissue is disrupted leading to excessive deposition of extracellular matrix proteins resulting in fibrosis.

Pancreatic stellate cells (PSCs) are now considered to be the key contributors of pancreatic fibrosis (5, 11, 135). These cells were first observed by Watari et al. (144) in 1982, and later confirmed by Ikejiri (54) in 1990. The development of isolation and culture methods for PSCs in 1998 helped to unravel the mechanisms involved in the process of pancreatic fibrogenesis (5, 11) and also helped researchers to investigate the functions of these cells both in health and disease.

II. PANCREATIC STELLATE CELLS (PSCs)

A. PSCs in health

In a healthy pancreas, PSCs make up 4-7% (5) of the total parenchyma and are located around the
basolateral aspects of the acinar cells (Figure 1A). PSCs are also found around small pancreatic ducts (5, 11), pancreatic islets (163) and blood vessels. PSCs in their native state express abundant vitamin A (retinoids) containing droplets in their cytoplasm which is a characteristic feature of the "stellate cell system" in the body (138). The buoyancy imparted by the vitamin A containing vesicles was utilized by Apte et al. (5) to develop a density gradient centrifugation method for the isolation of quiescent PSCs from the pancreas. In early culture, PSCs are polygonal in shape with abundant lipid droplets in the cytoplasm (Figure 1B) and express stellate cell selective markers such as desmin, glial fibrillary acidic protein (GFAP), nestin, neural cell adhesion molecule, nerve growth factor, and synemin (34, 167). Due to the expression of neural markers, PSCs were initially thought to be of neuroectodermal origin. However, lineage tracing studies with hepatic stellate cells (counterparts of PSCs in the liver) have confirmed a mesenchymal origin for these cells (9). The fact that a proportion of PSCs are replenished from bone marrow further supports a mesenchymal origin for PSCs (120).

![Figure 1. (A) Normal rat pancreatic stellate cells stained for cytoskeletal protein desmin. Photomicrograph showing a normal rat pancreatic section immunostained for the stellate cell selective marker desmin (left) and a corresponding line diagram (right). Desmin-positive (brown) PSCs can be seen surrounding the basolateral aspects of pancreatic acini. (B) PSCs in an early culture showing a typical flattened polygonal shape with abundant vitamin A-containing lipid droplets in the cytoplasm. Source: Apte et al. 1998 (5). (Reproduced with permission from BMJ Publishing Group Ltd.).](image)

Islet stellate cells (ISCs) are similar to but differ in certain aspects with PSCs. ISCs have fewer vitamin-A containing droplets and undergo rapid activation compared to PSCs. Upon activation, they express more α-SMA but have reduced rates of proliferation and migration compared to exocrine PSCs (163).

PSCs are the primary producers of ECM proteins such as collagen I–IV, fibronectin, and laminin. At the same time, they also produce ECM degrading enzymes like matrix metalloproteinases (MMP) and their inhibitors - tissue inhibitors of matrix metalloproteinases (TIMPs) (101). In the normal pancreas, these enzymes maintain an equilibrium between the deposition and degradation of ECM proteins. However, it is now recognised that PSCs have functions beyond ECM remodeling in the normal pancreas. PSCs express receptors for the secretagogue cholecystokinin (CCK1 and CCK2) (14) and have the capacity to synthesize the neurotransmitter acetylcholine (ACh).

Upon exposure to physiological levels of CCK, PSCs have been shown to secrete ACh which, in turn, acts on the muscarinic receptors on acinar cells and induces amylase secretion. (102). PSCs also play an important role in innate immunity through the expression of Toll-like receptors (TLRs) 2, 3, 4 and 5 (78) which can recognise pathogen-associated molecular patterns (PAMPs), alarmins and endogenous molecules released by tissue damage (DAMPs). These cells also possess the ability to phagocytose polymorphonuclear neutrophils and cell debris, which is mediated by CD36 via peroxisome proliferator-activated receptor γ (116). PSCs may also possess progenitor-like capabilities since they express several stem cell markers, including CD133, SOX9, nestin, and GDF3 (64, 83). They can differentiate into other cell types including insulin-secreting cells under the influence of relevant growth factors (14, 41, 83, 88, 118).

B. PSCs in disease

In the event of pancreatic injury, PSCs are activated, leading to loss of the vitamin A-containing lipid droplets and transform to a myofibroblast-like phenotype that expresses alpha
smooth muscle actin (αSMA), fibroblast activation protein-α (FAP-α), fibroblast specific protein-1 (FSP-1), and fibrinogen (34). These cells also exhibit increased proliferation, migration, and ECM synthesis (4, 44). Activated PSCs produce collagenous stroma during pancreatic injury (8, 145, 152) which overwhelms the ECM degrading capacity of MMPs, leading to fibrosis. A comparison of resting and activated PSCs is given in Table 1.

| Characteristic                          | Quiescent PSCs | Activated PSCs |
|----------------------------------------|----------------|---------------|
| Vitamin A lipid containing droplets    | Abundant       | Absent        |
| Alpha smooth muscle actin              | Not expressed  | Expressed     |
| Proliferation                          | Basic          | Enhanced      |
| Ability to migrate                     | No             | Yes           |
| Collagen production                    | Limited        | Increased     |
| Activity of matrix metalloproteinases (MMP) and tissue inhibitors of matrix proteinases (TIMP) | In equilibrium | TIMP > MMP |
| Cytokine production                    | Limited        | Increased inflammatory cytokines (PDGF, TGFβ, CTGF, IL-1, IL-6, IL-15) |
| Ability for phagocytosis               | No             | Present (CD6 mediated) |
| Protein expression                     | Basal expression | Differential expression |

Table 2. Factors causing activation of pancreatic stellate cells

| Factor                                      |
|---------------------------------------------|
| Angiotensin                                 |
| Cyclooxygenase 2 (COX-2)                    |
| Endothelin-1                                |
| Endotoxin                                    |
| Ethanol and its metabolites (acetaldehyde, fatty acid ethyl esters) |
| Fibrinogen                                   |
| Galectin-1                                   |
| Hyperglycemia                               |
| Hypoxia                                      |
| Inflammatory mediators (cytokines, growth factors, complement) |
| Oxidant stress                               |
| Parathyroid hormone-related protein (PTHrP) |
| Pigment epithelium-derived factor            |
| Proteases                                    |

Several pathways that mediate PSC activation have now been identified (summarized in Table 3). A number of these pathways interact with each other leading to significant redundancy in terms of the modulation of PSC activation (81, 85). Furthermore, studies have also shown that numerous signaling pathways can converge causing aberration of a common secondary messenger, namely, sustained increase in intracellular calcium within the PSCs (42, 48, 147). Recently microRNAs, (small noncoding RNAs), which are implicated in cell functions such as proliferation, differentiation, apoptosis, and protein synthesis, have been shown to differentially express between quiescent and activated PSCs (79). Other studies have implicated miR15b and 16 (known to regulate PSC apoptosis (113) and miR21 as possible cofactors in connective tissue growth factor (CCN2)-mediated PSC activation (22).
Table 3. Signalling pathways involved in the interactions between PSCs and cancer cells.

| Mediator                      | Signalling pathway                                      | Functional role                                                                 | Reference |
|-------------------------------|---------------------------------------------------------|---------------------------------------------------------------------------------|-----------|
| PSC-derived CXCL12 (SDF-1)    | CXCL12 (SDF-1) signalling                               | Immunosuppression                                                               | (38)      |
| PSC-derived SDF-1             | Galectin-1                                              | Proliferation of PSC and chemokine production facilitating PCC metastasis      | (106)     |
| Smo, Gli                      | Hedgehog pathway                                        | PSC activation, ECM synthesis, migration, desmoplasia, angiogenesis, PCC proliferation, migration and chemoresistance | (109)     |
| HGF                           | HGF/c-MET pathway                                       | PSC promote proliferation and metastasis of tumour cells                        | (104)     |
| CCL2                          | Hypoxia inducible factor 1 (HIF-1)                     | PSC activation, Macrophage recruitment                                         | (69)      |
| IL-6 Kindlin-2                | IL6/JAK/STAT Integrin                                   | PSC activation and proliferation                                               | (63)      |
| MAPK                          | Mitogen-activated protein kinase (MAPK) signalling path | PSC proliferation, TIMP-1 production                                            | (160)     |
| Periostin                     | Periostin pathway                                       | Periostin secreted by PSCs promoting PCC proliferation, EMT and resistance to nutrient deprivation and hypoxia | (71)      |
| PPAR-γ ligands                | Peroxisome proliferator-activated gamma (PPARγ)        | Inhibition of PSC activation, proliferation, and collagen synthesis             | (116)     |
| PDGF Hyperglycaemia           | PI3-Kinase pathway                                      | PSC migration and proliferation                                               | (85)      |
| Suppression of miRNA-21       | Protein kinase C                                        | PSC proliferation, α-SMA, collagen-I production, angiogenesis                 | (122)     |
| Rho-associated protein kinase | Reactive oxygen species (ROS)                          | PSC activation and induction of glycolysis                                       | (157)     |
| SMAD-2,3                      | Rho-ROCK pathway                                        | Activation of PSC, collagen I synthesis and fibrosis                           | (76)      |
| SMAD5                         | SMAD5                                                   | PSC activation, proliferation, ECM deposition, transdifferentiation, TGF-β1 expression | (95)      |
| TLR9                          | Toll-like receptor (TLR) signalling                    | Immunosuppression; PSC-derived cytokine production                              | (162)     |
| Vitamin D                     | Vitamin D receptor                                      | PSC quiescence; Decreased chemoresistance                                       | (114)     |
| β-catenin                     | Wnt/β-catenin signalling                                | Invasion of PCCs                                                                | (32)      |

α-SMA, alpha smooth muscle actin; c-MET, tyrosine-protein kinase of Met; CCL, chemokine ligand; CXCL, chemotactic cytokine ligand; ECM, extracellular matrix; JAK/STAT, Janus kinase/signal transducers and activators of transcription; HGF, hepatocyte growth factor; PSC, pancreatic stellate cells; PCC, pancreatic cancer cells; SDF, stromal derived factor; PDGF, platelet-derived growth factor; SMAD, small worm mothers against decapentaplegic.
The past two decades have seen a considerable improvement in our understanding of the role of PSCs in pancreatic inflammation (both acute and chronic pancreatitis) as well as pancreatic cancer. Acute pancreatitis is usually a self-limiting disease where PSCs aid remodeling and repair of tissue architecture, while both chronic pancreatitis and pancreatic cancer are characterized by pathological accumulation of fibrous tissue.

III. ACUTE PANCREATITIS

Acute pancreatitis is a condition which results from acute inflammation of the pancreatic parenchyma, ranging from mild inflammation to extensive pancreatic necrosis. Most of the cases are mild and self-limiting with a mortality rate <1%. The most common causes of acute pancreatitis are gallstones and alcohol excess (33). In response to inflammatory cytokines and chemokines secreted by damaged acinar cells and inflammatory cells, PSCs are activated and proliferate early in acute pancreatitis (26). The majority of the increased numbers of activated PSCs, in the inflamed areas, are a result of local proliferation of resident PSCs. However, a small proportion (7–18%) are derived from circulating bone marrow cells (120). Activated PSCs secrete increased ECM proteins that act as a scaffold for regenerating ductal and acinar cells during the repair process. These ECM proteins are also important for differentiation and cell growth via integrin mediated interactions between cell membranes and the surrounding matrix (16). Indeed, using β1-integrin knockout animals, it has been shown that the lack of integrin-mediated interactions results in decreased ECM production by PSCs and increased apoptosis and decreased proliferation of acinar cells, thereby impeding pancreatic repair (108).

PSCs may also play an important role in remodeling and regeneration after acute necrotizing pancreatitis. Zimmerman et al. (168) observed that pilot ductules that originate from hypercellular regenerative spheres (islands of vascular granulation tissue, ductular cells, stellate cells, and residual lobular elements) grow outwards in close association with activated PSCs. The authors have suggested that these PSCs may be able to support differentiation of cells to mature duct and acinar cells, thereby playing a role in the reconstitution of the cell population after acute injury. The process of regeneration also requires removal of excess ECM, a task that is aided by the fibrinolytic activity of PSCs via the production of matrix degrading enzymes (MMPs).

IV. CHRONIC PANCREATITIS

Chronic pancreatitis is a progressive disease characterized by fibrosis, acinar cell loss, distorted ducts, and inflammatory cell infiltration, eventually leading to significant exocrine and endocrine dysfunction (62) (Figure 2).

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The presence of activated PSCs was confirmed in the areas of fibrosis using dual staining techniques ( Sirius Red for collagen and immunostaining for αSMA) (44) (Figure 3), while dual staining for αSMA and procollagen mRNA has shown that activated PSCs are the predominant source of collagen I in the fibrotic areas (44) (Figure 4). Interestingly, the fibrosis of chronic pancreatitis was found not to be limited to the exocrine

Figure 2. A section from a patient with chronic pancreatitis showing colocalization of staining for the PSC activation marker alpha smooth muscle actin (αSMA, brown) and collagen (using Sirius Red) (red) in fibrotic areas of the pancreas. Source: Haber et al. 1999 (44). (Reproduced with permission of Elsevier).
parenchyma. Activated PSCs have been demonstrated within and surrounding pancreatic islets and are co-localized in fibrotic areas around the islets in diabetic Goto–Kakizaki rats (163) and db/db mice (obesity, diabetes, and dyslipidemia model due to leptin receptor deficiency) (150). Additionally, activated PSCs can inhibit insulin secretion and cause beta cell apoptosis, effects which are further aggravated by hyperglycemia (60). These findings suggest that PSCs can modulate islet cell function, suggesting a direct role for these cells in the diabetes of chronic pancreatitis.

Figure 3. Colocalization of collagen and alpha SMA staining in pancreatic cancer. A representative pair of serial paraffin sections of the pancreas from a patient with pancreatic cancer demonstrating that stromal areas exhibit strong positive staining for collagen as well as for alpha SMA, indicative of the presence of activated PSCs in the desmoplastic reaction in pancreatic cancer. Original magnification, × 100. Source: Apte et al. 2004 (6). (Reproduced with permission of Wolter Kluwer).

Figure 4. Desmoplasia in a human pancreatic cancer section. A representative photomicrograph of a hematoxylin and eosin stained human pancreatic cancer section showing malignant elements (duct-like and tubular structures- indicated by asterisks) embedded in highly fibrotic stroma (indicated by arrows). Source: Apte et al. 2015 (8). (Reproduced with permission of Elsevier).

Many factors are known to activate PSCs during chronic pancreatitis including the profibrogenic growth factor TGFβ, platelet-derived growth factor (PDGF) (44), nerve growth factor (NGF) (31) and oxidative stress (110). It is now known that PSC-activating factors such as TGFβ, PDGF, oxidant stress and other cytokines are upregulated early during pancreatic injury leading to PSC proliferation and ECM synthesis. As noted earlier, PSCs can be maintained in a perpetually activated state through autocrine effects of endogenous cytokines, leading to pathological fibrosis.

Animal models provide an invaluable tool for understanding the pathogenesis of chronic pancreatitis. Several methods of inducing experimental chronic pancreatitis have been reported in the literature - repeated intravenous injections of caerulein (89) or superoxide dismutase inhibitor (84), instillation of toxins into the pancreatic duct (28, 44); chronic ethanol administration followed by secondary challenge with caerulein (129, 131), cyclosporin (43) or endotoxin (136). Regarding alcoholic chronic pancreatitis, endotoxin is a relevant trigger factor, given that gut permeability is known to be increased by alcohol and elevated serum endotoxin levels have been reported in drinkers (35). Further, endotoxin (lipopolysaccharide, LPS) challenge was shown to enhance fibrosis in Sprague-Dawley rats fed Lieber de Carli alcohol liquid diet (124). Transgenic models of CP include animals overexpressing cytokines or profibrogenic factors such as IL-1β, TGFβ, and heparin-binding EGF-like growth factor (HB-EGF) (15, 75) and WBN–Kob rats (93) and Goto–Kakizaki rats with type 2 diabetes (19). More recently, the effects of smoking on pancreatic fibrosis have been studied, given the close association of drinking, and smoking as lifestyle factors. Lugea and colleagues (73) have shown that smoking significantly worsened tissue injury as well as fibrosis in a rat model of alcoholic pancreatitis. The increased fibrosis could be due to direct activation of PSCs.
by i) nicotine and NNK via nicotinic acetylcholine receptors (nAChRs) on the cells and/or ii) IL-22 secreted by infiltrating macrophages in response to smoke compounds (via Aryl hydrolase receptors) (154).

V. REVERSAL OF PANCREATIC FIBROSIS IN CHRONIC PANCREATITIS

The study of mechanisms underlying PSC activation and fibrosis can help in developing novel anti-fibrotic treatments. Several antifibrotic strategies have been successfully evaluated to counter CP in experimental animal models including (i) inhibition of profibrogenic growth factors TGFβ and tumor necrosis factor alpha (TNFα) (52, 86, 99, 154); (ii) antioxidants such as vitamin E (40), ellagic acid, a plant polyphenol (125), and salvianolic acid, a herbal medicine (72); (iii) protease inhibitors (39); (iv) modulation of signaling molecules (e.g., troglitazone binding to the peroxisome proliferator receptor gamma, PPARγ) (117); retinoic acid-induced PSC quiescence via suppression of the Wnt–catenin pathway (148); (v) collagen siRNA (55); (vi) an anthraquinone derivative Rhein, and a flavonoid, apigenin; (vii) a prostacyclin analogue ONO-1301, which inhibits proinflammatory and profibrogenic cytokine production (91); and (viii) alcohol withdrawal in alcohol induced pancreatitis (134).

Amygdalin was shown to inhibit PSC activation and attenuate fibrosis by decreasing production of profibrotic cytokines in a rat CP model induced by injecting dibutyltin dichloride (DBTC) (165). An experimental compound miR-200a inhibited TGF-β1-induced pancreatic stellate cell activation and extracellular matrix formation through inhibition of PTEN /Akt/mTOR pathway (149). In chronic pancreatitis induced by dibutyltin dichloride in rats, 3-methyladenine (3-MA), a PI3K inhibitor decreased fibrosis by decreasing autophagy in PSCs (68).

Several plant compounds have shown promising antifibrotic activity in several studies. Curcumin (a polyphenol found in turmeric) was reported to inhibit activation of PSCs through the inhibition of IL1β and TNFα-induced activation of activator protein-1 (AP-1) and mitogen-activated protein (MAP) kinases (ERK, c-Jun N-terminal kinase (JNK), and p38 MAP kinase) (82). Conophyline, a plant alkaloid, decreased fibrosis through the inhibition of ERK1/2 in PSCs (127). In an in vitro study, resveratrol, a natural polyphenol, decreased oxidative stress induced activation and glycolysis in PSCs mediated by ROS/miR-21 (157). Genestein, a natural isoflavone decreased fibrosis in human PSCs transfected with let-7d to express thrombospondin 1, a marker of fibrosis (10). Saikosponin A, the active component of the Chinese medicine chaïhu, was shown to decrease PSC activation, viability, proliferation and migration and to promote apoptosis by inhibiting autophagy and the formation of NLRP3 inflammasome via the AMPK/mTOR pathway (24). Similarly, date palm fruit extract decreased fibronectin-1 and αSMA, markers of fibrosis in PSCs activated by TNF-α (1).

Vitamins such as D and its isoforms D2 and D3 are reported to decrease in vitro PSC activation by decreasing IL-6 (139). Furthermore, in vivo studies with the vitamin D ligand calcipotriol have shown significant attenuation of the fibrosis of chronic pancreatitis in mice (114). Since storage of vitamin A is associated with PSC quiescence, administration of vitamin A (retinol) or its metabolites such as retinoic acid, has been assessed in models of chronic pancreatitis. In this regard, Vitamin A-containing liposomes combined with TLR4-silencing shRNA has been reported to inhibit pancreatic fibrosis in mouse models of chronic pancreatitis (166).

Other compounds known to induce quiescence of activated PSCs include melatonin, the anthraquinone derivative rhein (128), bone morphogenic protein (37), troglitazone (a ligand for the peroxisome proliferator activated receptor PPARγ) (117). Recently, kinase inhibitors such as sorafenib, sunitinib, trametinib, and dactolisib have been shown to inhibit PSC proliferation and ECM synthesis (27, 146). Interestingly, trametinib also
decreases the expression of two autocrine mediators of PSC activation, IL6 and TGFβ (146). Coenzyme Q10 suppresses PSC activation by inhibiting autophagy through PI3K/ATK/mTOR signaling (155). Inhibition of cyclo-oxygenase by indomethacin, an anti-inflammatory drug also results in decreased activation of PSCs (123).

VI. PANCREATIC CANCER

Pancreatic ductal adenocarcinoma (PDAC) is characterized by extensive stroma/desmoplasia (Figure 5) which constitutes 80 - 90% of the tumor volume (47). This stroma consists of extracellular matrix proteins including collagen type I, fibronectin and laminin, non-collagenous factors such as glycoaminoglycans (e.g., hyaluronan), glycoproteins, and proteoglycans, and several cell types, including stellate cells, endothelial cells, neural elements and immune cells (30). Just as with the fibrosis of chronic pancreatitis, activated PSCs are now also recognised as the primary source of the collagenous stroma in PDAC (6). The detection of activated PSCs expressing periostin (a cell adhesion protein), galectin-1 (a glycan binding protein) and αSMA (an activation marker) in precursor pancreatic intraepithelial neoplasms (PanINs) (Figure 6) and intra-ductal papillary mucinous neoplasms (IPMN) suggests that activation of PSCs is an early event in PDAC (7, 56). Studies have also shown a positive correlation between extent of PSC activation in the stroma and poor clinical outcome (29, 141). It is now known that functionally different subsets of PSCs exist within the stroma of pancreatic cancer. Yuzawa et al. (161) observed the presence of fibroblasts with varying expression of αSMA and PDGFRβ while Ohlund et al. (94) observed that cancer-associated fibroblasts (CAFs) / pancreatic stellate cells in proximity to cancer cells exhibit higher αSMA expression compared to those located at a distance from cancer cells. The authors termed the PSCs close to cancer cells as (myofibroblastic) myPSCs and those at some distance from cancer cells as (inflammatory) iPSCS, based on their cytokine secretion profile.

Figure 5. Dual staining for alpha smooth muscle actin (αSMA) and collagen mRNA in a human pancreatic cancer section. Immunostaining for αSMA (brown) combined with in situ hybridization for collagen mRNA (blue) reveals colocalization of the two stains in stromal areas of the section with no staining in tumor cells. This pattern of staining indicates that pancreatic stellate cells are the main source of collagen in pancreatic cancer stroma. Source: Apte et al. 2004 (6). (Reproduced with permission of Wolters Kluwer).

Figure 6. Activated PSCs in early pancreatic intraepithelial neoplasia (PanIN). A section from an 8-week old transgenic KrasG12D P53R172H Cre (KPC) mouse showing staining for the PSC-activation marker alpha smooth muscle actin (αSMA, brown) around PanINs in a section of the pancreas. (Magnification 20x).

Studies involving in vitro and in vivo models have established that PSCs interact bidirectionally with cancer cells to facilitate local tumor growth and distant metastasis (8). PSCs also interact with other cells in the stroma including immune cells resulting in a complex cascade of events (Figure 7). PSCs promote cancer cell progression, migration, and cancer cell survival (132, 153) while in turn, cancer cells promote PSC proliferation, migration, and extracellular matrix synthesis (53, 132). Several in vitro studies have shown that
cancer cells increase PSC proliferation and ECM synthesis mediated by PDGF, FGF2, and TGFβ1 (12) and also promote the secretion of matrix metalloproteinases by PSCs (97) through ECM metalloproteinase inducer (EMMPRIN) secretion (111) and TGFβ1 signalling (132, 133). Cancer cells can also induce autophagy in PSCs leading to release of alanine which acts as an alternative carbon source for the TCA cycle and lipid synthesis in cancer cells, thus improving cancer cell survival in the nutrient-poor and hypoxic environment of PDAC (51, 119).

Figure 7. Bi-directional interactions of pancreatic stellate cells with cancer cells. Activated PSCs promote proliferation, invasion, metastasis, survival, and chemoresistance as well as radio-resistance of cancer cells while cancer cells in turn promote ECM synthesis, proliferation, and migration of PSCs.

Epithelial mesenchymal transition (EMT) and stemness, two processes that play an important role in cancer metastasis and recurrence, are known to be induced by PSCs. (45, 61). Studies have shown that stromal signalling is indispensable for cancer progression. Sherman and colleagues have reported that KRas mutation alone is insufficient for pancreatic cancer and that stromal cues, collagen and cytokines derived from cancer associated PSCs, are essential to this process (115). Furthermore, in both subcutaneous and orthotopic xenograft models, co-injection of cancer cells and stromal cells (PSCs) resulted in larger tumors with significant desmoplasia compared to injection of cancer cells alone (53, 104, 132). An intriguing report published some years ago suggested that PSCs may also facilitate seeding of cancer cells at metastatic sites. Using a gender mismatch approach and an orthotopic model of pancreatic cancer, the authors of this study found PSCs from the primary tumor within metastatic nodules at distant sites, indicating that, in addition to cancer cells, PSCs can also disseminate via the circulation (153). Similar observations were made by Suetsugu et al. (121) who injected a mixture of PSCs and pancreatic cancer cells into the spleen and observed that both cell types co-migrated from the spleen to metastatic nodules. In a recent groundbreaking study, Pang et al. (98) have identified the presence of circulating PSCs alongside circulating tumor cells (CTCs) in the blood of orthotopic tumor bearing mice.

In recent years, there has been considerable focus on the role of exosomes (nanosized vesicles secreted by most cell types) in a variety of diseases. These exosomes carry a cargo of proteins, lipids, DNA, mRNA, and microRNA) which can influence the function of cells remote from the source of the exosomes. Regarding pancreatic cancer, Takikawa et al. (126) have demonstrated that exosomes derived from PSCs contained a variety of microRNAs and an abundance of miR-21-5p and miR-451a which mediated PSC-induced proliferation and migration of PSCs. Similarly, exosomes derived from PSCs were found to stimulate activation, proliferation, and migration of PSCs through upregulation of transforming growth factor β1 (TGFβ1) and tumor necrosis factor (TNF).

Several studies have shown that pancreatic desmoplasia can contribute to chemoresistance by affecting the kinetics of chemotherapeutic agents. Hessmann et al. (50) found that cancer associated activated fibroblasts are resistant to gemcitabine and tend to accumulate and rapidly convert gemcitabine into an inactive metabolite 2',2'-difluorodeoxyuridine thus contributing to decreased efficacy of gemcitabine on tumor cells. Moreover, growing evidence suggests that PSCs may also directly alter the response of cancer cells to chemotherapeutic agents. Autocrine secretion of IL-6 by PSCs in response to stromal-derived factor 1α (SDF-1α), demonstrated a protective effect on cancer cells from the apoptotic effect of gemcitabine (164). Owing to their chemoresistance, post therapy, PSCs can facilitate
proliferation of residual cancer stem-cells leading to recurrence (18).

VII. STRATEGIES TO COUNTER STROMAL-TUMOR INTERACTIONS IN PANCREATIC CANCER

As PSC-cancer cell interactions play an important role in the progression of PDAC, several strategies have been developed to counter these interactions. Several chemicals including phytochemicals and hormones have been shown to decrease stromal-tumor interactions in experimental studies. Metformin, an activator of AMP-activated protein kinase reduced the production of fibrogenic cytokines from cancer cells and inhibited PSC activation in co-culture studies and decreased tumor growth and enhanced chemosensitivity to gemcitabine in an orthotopic xenograft model (25). ProAgioQ20, which targets an Integrin α(v)β(3) overexpressed in PSCs, caused apoptosis of cancer associated PSCs, reabsorbed collagen, inhibited tumor growth, and drug penetration in subcutaneous, orthotopic xenograft and transgenic KPC model (21). Similarly, inhibition of cyclic AMP-response element binding protein-binding protein (CBP)/β-catenin signaling using ICG-001 resulted in decreased activation of PSCs and PSC-induced migration of PANC-1 cancer cells in a transwell migration assay (23). Curcumin, the active compound of turmeric was shown to inhibit IL-6 in PSCs under hypoxic conditions leading to suppression of EMT and PSC-mediated cancer cell migration in vitro (70). Relaxin-2, an endogenous hormone combined super magnetic iron oxide nanoparticles decreased fibrosis and tumor growth besides potentiating the effects of co-administered gemcitabine in an orthotopic xenograft model (74).

Several pathways are shown to be key regulators of cancer cell-PSC interactions and inhibition of these pathways in animal studies has been reported to decrease fibrosis, tumor growth and metastasis. In this regard, Hedgehog pathway is significant as the ligand sonic hedgehog (Shh) is expressed in tumor cells while the receptor, Smo, is located mainly on cancer-associated fibroblasts (140). In animal models, inhibitors of this pathway such as ormeloxifene (59) and IPI-926 (96) decreased desmoplasia and tumor growth and improved chemosensitivity to co-administered gemcitabine. Interestingly, in an orthotopic tumor model where cancer and PSCs are co-injected, a triple combination of CXCR4 antagonist (AMD3100), hedgehog inhibitor (GDC0449) and gemcitabine resulted in complete remission of tumor growth (58).

Similar to the hedgehog pathway, the HGF/c-MET pathway is involved in cancer proliferation, invasion and metastasis. The ligand HGF is produced by PSCs while its receptor, c-MET, is located on cancer cells and endothelial cells (103). In transgenic KPC mice, dual inhibition of both sonic hedgehog and HGF/c-MET pathways were found to sensitize PDAC to gemcitabine (109). In a subcutaneous xenograft mouse model, combination of c-Met inhibitor XL184 with gemcitabine significantly decreased tumor growth compared to individual treatments (67). Xu et al. (151) used a triple therapy approach consisting of HGF and c-Met inhibitors plus gemcitabine in an advanced model of orthotopic pancreatic cancer. Triple therapy not only reduced tumor size, but importantly, eliminated metastasis. Further, the authors reported that the combination therapy was successful in overcoming gemcitabine-stimulated stemness and aggressiveness of cancer cells. These findings corroborate the findings of previous studies that reported that gemcitabine alone increases stemness of cancer cells in PDAC (49, 107).

Extracellular signal-regulated kinases (ERKs) regulate cellular processes such as proliferation, differentiation, transcription and development and this pathway has been shown to be strongly expressed in cancer-associated PSCs. Dual inhibition of ERK1/2 and autophagy in PSCs with S7101 and chloroquine respectively resulted in PSC senescence and suppressed liver metastasis...
in a splenic pancreatic cancer organoid mouse model (158).

Vitamins inducing PSC quiescence have been successfully demonstrated to improve the outcome of pancreatic cancer in both preclinical and clinical studies. PEGylated gold nanoparticles containing all trans retinoic acid (ATRA) combined with siRNA against heat shock protein (HSP-47, known to activate PSCs) was used to induce PSC quiescence and inhibited ECM hyperplasia, thereby promoting drug delivery to pancreatic tumors in an orthotopic model developed by co-inoculation of cancer cells and PSCs (46). Similarly, the vitamin D analogue calcipotriol, combined with gemcitabine, induced quiescence of activated PSCs and decreased fibrosis in KPC mice (114). Based on this study, a vitamin D analogue paricalcitol, in combination with gemcitabine, and nab-paclitaxel is currently being evaluated in a clinical trial (NCT03520790) (100).

As epigenetic modifications also play an important role in PDAC, some studies have targeted epigenetic pathways to reprogram the tumor microenvironment in a bid to improve outcomes (90, 156). Common epigenetic targets relevant to PDAC include DNA methylation, histone modifications and bromodomain and extra-terminal domain (BET) family proteins. A DNA methyl transferase inhibitor, 5-Azacitidine, in combination with abraxane and gemcitabine is currently being tested in a Phase II clinical trial in resected PDAC patients (NCT01845805). Inhibiting epigenetic bromodomain and the extraterminal domain (BET) family of proteins using iBET151, and SB 203580, a MAPK inhibitor, decreased YAP-1 levels resulting in decreased PSC activation (51).

Myeloid derived suppressor cells (MDSC) help to maintain an immunosuppressive environment in PDAC by eliminating effector T cells (36). Therefore, therapies that boost effector T cell infiltration into tumor are gaining attention. The desmoplastic reaction in PDAC is shown to sequester cytotoxic CD8+ T cells and hinder drug penetration. In transgenic spontaneous pancreatic cancer bearing KC mice (KrasG12D, Cre) challenged with caerulein, an inhibitor of rho/ MRTF pathway, CCG-222740 not only decreased PSC activation but also decreased infiltration of macrophages, CD4+ T cells and B cells suggesting inhibition of PSC activation improves local immunity (66). Similarly, inhibiting stroma through an acidic-pH-responsive-nanoparticle cluster containing TGF-β inhibitor (LY2157299) and PD-L1 (siRNA) improved local tumor immunity by increasing CD8+ T cell infiltration in a subcutaneous xenograft orthotopic model (143). Tumor associated macrophages (TAM), which are derived from MDSCs, are shown to rapidly inactivate gemcitabine and depletion of TAM using clodronate resulted in increased concentration of active gemcitabine in desmoplastic tumors of KPC mice compared to either PanINs or normal pancreas (17).

**VIII. CONCLUSION**

PSCs play manifold roles in both health and disease. In the healthy pancreas they are responsible for maintaining ECM turnover and may also have additional roles in innate immunity and CCK-mediated exocrine secretion. In diseased conditions, PSCs are activated by a variety of factors known to be upregulated in the injured pancreas. The last two decades have seen an explosion of findings regarding the interaction of PSCs with other cells in the pancreas, in health and in disease. These findings have vastly improved our understanding of the physiology and pathology of pancreatic disease, raising hopes for innovative new treatments. Once activated, they become the primary contributors to the pathological fibrosis of both pancreatic inflammation and PDAC and impact on the function of beta cells of islets (or some reference to endocrine pancreas). Research efforts are now directed towards understanding the mechanisms underlying PSC-mediated fibrogenesis to develop novel therapies to treat fibrotic diseases of the pancreas.
IX. REFERENCES

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