

Pancreatic stellate cell: Pandora's box for pancreatic disease biology

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Abstract

Pancreatic stellate cells (PSCs) were identified in the early 1980s, but received much attention after 1998 when the methods to isolate and culture them from murine and human sources were developed. PSCs contribute to a small proportion of all pancreatic cells under physiological condition, but are essential for maintaining the normal pancreatic architecture. Quiescent PSCs are characterized by the presence of vitamin A laden lipid droplets. Upon PSC activation, these perinuclear lipid droplets disappear from the cytosol, attain a myofibroblast like phenotype and expresses the activation marker, alpha smooth muscle actin. PSCs maintain their activated phenotype *via* an autocrine loop involving different cytokines and contribute to progressive fibrosis in chronic pancreatitis (CP) and pancreatic ductal adenocarcinoma (PDAC). Several pathways (*e.g.*, JAK-STAT, Smad, Wnt signaling, Hedgehog *etc.*), transcription factors and miRNAs have been implicated in the inflammatory and profibrogenic function of PSCs. The role of PSCs goes much beyond fibrosis/desmoplasia in PDAC. It is now shown that PSCs are involved in significant crosstalk between the pancreatic cancer cells and the cancer stroma. These interactions result in tumour progression, metastasis, tumour hypoxia, immune evasion and drug resistance. This is the rationale for therapeutic preclinical and clinical trials that have targeted PSCs and the cancer stroma.

Key words: Pancreatic stellate cells; Pancreatic fibrosis;

Pancreatic cancer stroma; Physiological functions; Pancreatic stellate cells-cancer-stromal interactions; Therapeutic targets

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Core tip: Pancreatic stellate cells (PSCs) have emerged as one of the major effector cells in chronic pancreatitis and pancreatic ductal adenocarcinoma. In this review, we discuss the physiological function of PSCs and the profibrogenic mechanisms. We also discuss various pathways, transcription factors and miRNAs implicated in the inflammatory and profibrogenic functions mediated by PSCs. We further discuss the crosstalk among PSCs, pancreatic cancer cells and pancreatic cancer stroma and mechanisms that lead to cancer progression, metastasis, tumour hypoxia, immune evasion and drug resistance. We conclude with recent preclinical and clinical studies that have targeted PSCs and cancer stroma.

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HISTORICAL PERSPECTIVES

Stellate cells were described for the first time in the perisinusoidal spaces of the liver by Karl Wilhelm Von Kupffer in 1876 and were called "Sternzellen" (meaning star shaped cells). Later in 1951, Ito described the presence of lipid droplet containing cells in the perisinusoidal spaces of the liver and named them "Ito cells"^[1]. The Ito cells were shown to emit blue-green fluorescence due to the presence of vitamin A in the lipid droplets^[2]. Later in 1971, the usage of multiple techniques provided unequivocal evidence that the "sternzellen" reported by Kupffer and "Ito cells" identified by Ito were the same cell type: the hepatic stellate cells (HSCs)^[3,4]. In 1982, a cell type carrying vitamin A containing lipid droplets and exhibiting a transient blue-green fluorescence were described in mouse pancreas^[5]. In 1991, the cells exhibiting the vitamin A autofluorescence were identified in the healthy pancreatic sections from humans and rats^[6]. These cells are now identified as pancreatic stellate cells (PSCs), which localize the periacinar regions, with long cytoplasmic projections extending towards the basolateral aspects of the acinar cells. Later in 1998, the development of *in vitro* tools to isolate and culture the PSCs laid a strong foundation to characterize their basic biology^[7,8]. These cells also surround the perivascular and periductal regions. Sustained PSC cultures have helped to decipher the crucial factors that act in

the inflammatory mechanisms and their mechanistic role in the pancreatic fibrosis in chronic pancreatitis (CP) and pancreatic ductal adenocarcinoma (PDAC). However, in view of the challenges of limited viability of the PSCs in primary cultures, there had been several attempts to modify isolation and culture techniques. In this regard, techniques were developed to immortalize the normal and tumour associated PSCs. However, further validation studies will be required prior to their routine use in PSC research^[9-12]. Interestingly, even though PSCs were associated primarily with the exocrine pancreas, a recent study has reported isolation of PSCs from rat and human pancreatic islets too. These cells demonstrated certain morphologic and functional differences from the conventional PSCs in terms of fewer lipid droplets, lower rates of proliferation, migration and easier activation^[13,14].

BASIC BIOLOGY OF PANCREATIC STELLATE CELLS

Origin

The origin of PSCs is still being debated. Till date no direct studies have been executed to identify the origin of PSCs. However, the studies on the origin of HSCs have helped in gaining some insight into this aspect. Even though initially a neuroectodermal origin of PSCs was proposed, it was eventually negated in genetic cell lineage mapping studies^[15]. A recent study forwarded refreshing evidence supporting a mesodermal origin of HSCs by using the conditional lineage analysis approach^[16,17]. Since most of the characteristic features and functions that sketched the biology of PSCs are similar to HSCs, it is believed that even PSCs might have evolved from a mesodermal origin. Employing such similar tracer techniques might help in ascertaining the origin of PSCs.

In the context of CP and PDAC, even though most of the proliferating PSCs are derived from the resident PSCs within the pancreas, a proportion of PSCs are thought to originate in the bone marrow. This was proposed in a novel sex mismatched study, which evidenced that even bone marrow (BM) derived cells may also contribute to PSC population in CP and PDAC apart from the resident cells of pancreas^[18,19]. The speculation that bone marrow is another potential source of PSC was further supported by a recent study involving dibutyltin chloride induced CP wherein a model of stable hematopoietic chimerism by grafting enhanced green fluorescence protein (eGFP)-expressing BM cells was used. In this study, 18% of the PSCs in the pancreas was found to originate in the bone marrow^[20]. A recent study that used enhanced green fluorescent protein (EGFP)(+)CD45(-) cells transplanted from EGFP-transgenic mice in a carbon tetrachloride (CCL4) model suggested that infiltrating monocytes could also differentiate into stellate cells within the pancreas and liver under the influence of

Table 1 Function of pancreatic stellate cells in the quiescent state and after activation

| |
|--------------------------------------------------------------------------------------------------------|
| Physiological functions |
| Store fat and retinoids in their perinuclear droplets, expressing GFAP, desmin and vimentin |
| Secrete MMPs and TIMPs |
| Maintains ECM turnover |
| Involved in maintenance of pancreatic tissue architecture |
| No or limited secretion of cytokines, chemokines and growth factors |
| Function as an immune, progenitor and intermediary cell |
| Possible role in exocrine and endocrine secretions |
| Pathological functions |
| Exhibit cell proliferation and migration |
| Deranged ECM turnover due to loss of balance between MMPs and TIMPs |
| Secrete various cytokines, chemokines and growth factors and thereby contribute to inflammatory milieu |
| Stimulate cancer cell proliferation and migration and inhibit their apoptosis |
| Mediate invasion and metastasis of carcinoma cells |
| Mediate chemoresistance and radioresistance thereby promoting cancer cell survival |
| Contribute to the hypovascular and hypoxic tumour microenvironment |
| Promote angiogenesis, neural invasion and epithelial-mesenchymal transition |

GFAP: Glial fibrillary acidic protein; MMPs: Matrix metalloproteinases; TIMPs: Tissue inhibitors of matrix metalloproteinases; NGF: Nerve growth factor.

monocyte chemoattractant protein-1 (MCP-1)^[21].

Morphologic characteristics

Most of the characteristic features exhibited by quiescent as well as activated PSCs have been determined based on *in vitro* studies using rat and human PSC isolates. Cultured PSCs display prominent vitamin A containing lipid droplets with perinuclear localization in the cytoplasm. These lipid droplets elicit a fugacious blue-green autofluorescence when exposed to UV light at 328 nm or 350 nm wavelength. The expression of glial fibrillary acidic protein (GFAP) is specific to PSCs in the pancreas and presence of lipid droplets in the cytoplasm define the quiescent phenotype of PSCs^[5-8]. The underlying mechanisms involved in the accumulation and disappearance of lipid droplets are still not elaborately elucidated. It was demonstrated in a few studies that albumin colocalizes with the lipid droplets within quiescent PSCs. Activated PSCs, which are characterized by disappearance of lipid droplets, re-developed the lipid droplets and showed resistance against the activating effects of transforming growth factor- β (TGF- β) when transfected with the plasmids expressing albumin, thereby confirming the contribution of albumin in lipid droplet formation. The albumin was reported to be a downstream effector of peroxisome proliferator activated receptor- γ (PPAR- γ), a nuclear receptor that is known to inhibit PSC activation^[22,23]. The presence of lipid droplets together with expression of GFAP, desmin, nestin and vimentin is used to differentiate the PSCs from pancreatic fibroblasts^[24].

Using GFAP-*LacZ* transgenic mice model, it was proven that GFAP promoter activity was unique to PSCs alone in the pancreas^[25].

Autotransformation of quiescent PSCs to activated phenotype is observed *in vitro*. The basic phenotypic differences that were observed when the PSCs switch to activated phenotype include the disappearance of lipid droplets and transformation into a myofibroblast-like phenotype. The expression of α -smooth muscle actin (α -SMA) marks the transdifferentiation of the quiescent PSC to an activated phenotype. Figure 1 shows the morphology of PSCs in culture at different time points.

PSC functions

The physiological and pathological functions of PSCs have been summarized in Table 1. Under physiological conditions, PSCs are believed to contribute to the exocrine cell structure and function *via* maintenance of the normal basement membrane^[26,27] and carry out normal ductal and vascular regulation by virtue of their localization^[28]. Quiescent PSCs have a low mitotic index and bears the capability to synthesize matrix proteins and maintain the physiological extracellular matrix. The expression of matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs) are complementary to each other and is a prerequisite to poise the ECM turnover. Increased production of the ECM proteins fibronectin, periostin, MMPs and TIMPs are the most common features exhibited by the activated PSC phenotype^[29] and hence described as the effector cells contributing to the stroma associated with CP and PDAC. Besides laying and maintaining the ECM, PSCs have also been demonstrated to secrete acetylcholine that might function as an intermediate regulator for cholecystokinin mediated pancreatic exocrine secretion^[30].

Until recently, much attention was paid to unveil the functions of activated PSCs as a multiple cytokine producing profibrogenic cell type, which promotes self-proliferation, migration and fibrogenesis. However, recent advances have even demonstrated certain non-fibrogenic functions of PSCs, which projected PSCs as immune cells^[31], intermediary cell^[30,32] and also as a progenitor cell^[33-35]. An earlier study showed that PSCs could phagocytize senescent neutrophils in experimental acute pancreatitis (AP) and this was reduced by the presence of cytokines while augmented by presence of PPAR- γ ligand^[31]. The same group subsequently demonstrated that PSCs could also phagocytize necrotic acinar cells and themselves undergo cell death. No change in TGF- β concentration was detected in the PSC media and medium with PSC and acinar cells, thereby indicating that the death of PSCs could result in inhibition of fibrogenesis in the setting of AP^[36]. This role in innate immunity was further supported by the capacity of PSCs to recognize pathogen-associated molecular patterns *via* Toll-like receptors (TLRs) that are expressed on their surface^[37].

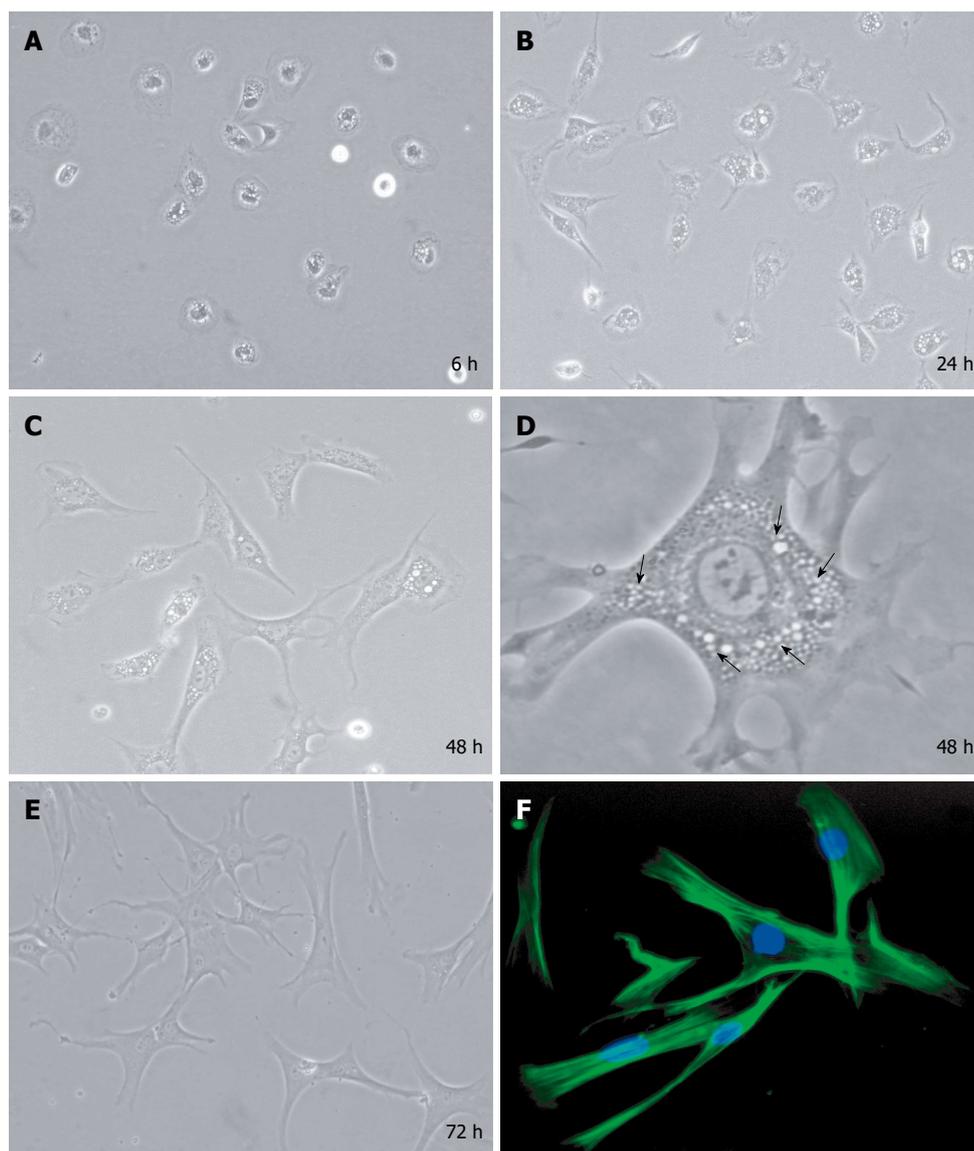


Figure 1 Morphological changes observed in cultured rat pancreatic stellate cells at different time points after isolation. A: Quiescent pancreatic stellate cells (PSCs) in culture exhibiting a flattened shape with lipid droplets, 6 h after isolation ($\times 20$); B, C: PSCs showing flattened angular appearance and exhibiting cytoplasmic extensions with lipid droplets after 24 and 48 h respectively in cultures ($\times 20$); D: PSCs exhibiting dense lipid droplets (lipid droplets are indicated with black arrows) in the cytoplasm ($\times 40$); E: Activated PSCs showing long cytoplasmic processes with no lipid droplets in the cytoplasm after 72 h in cultures ($\times 20$); F: Passage 2 rat PSCs in culture, immunostained for α -smooth muscle actin (α -SMA), a cytoskeletal marker for activated PSCs. Green striations indicate α -SMA and blue spots indicate nuclei, stained with DAPI ($\times 20$).

Studies have now also proposed a regenerative role especially in the context of AP, where the interaction between extracellular matrix laid by PSCs and acinar surface integrin receptors could result in a scaffold for acinar regeneration. Excess matrix deposition could also potentially be ameliorated by matrix degrading enzymes and apoptosis/cytolysis of activated PSCs^[38].

In addition to the above-mentioned functions of PSCs, it is now becoming more evident that these multifunctional cells also affects endocrine secretion in CP. This speculation surfaced from experiments that demonstrated increased numbers of PSCs in rat pancreas in a Type 2 diabetic model^[39]. Extension of this study *in vitro* showed that PSCs could reduce insulin

secretion and induce β -cell apoptosis^[40-42]. On the contrary, another study showed that PSCs increase insulin secretion from mouse islets^[43]. Interestingly, INS-1 cell culture supernatants reduced the secretion of proinflammatory cytokines (that mediate β -cell dysfunction) and ECM proteins from PSCs^[44]. Moreover, the expression of regenerating islet-derived protein-1 was high in islet stellate cells (ISCs) isolated from the diabetic mice, which inhibited the viability, migration, synthesis and secretion of ECM proteins in ISCs *in vitro*^[45]. As the *in vitro* results are more divergent, meticulous studies need to be designed and executed to understand the precise role played by these cells during their reciprocal interaction.

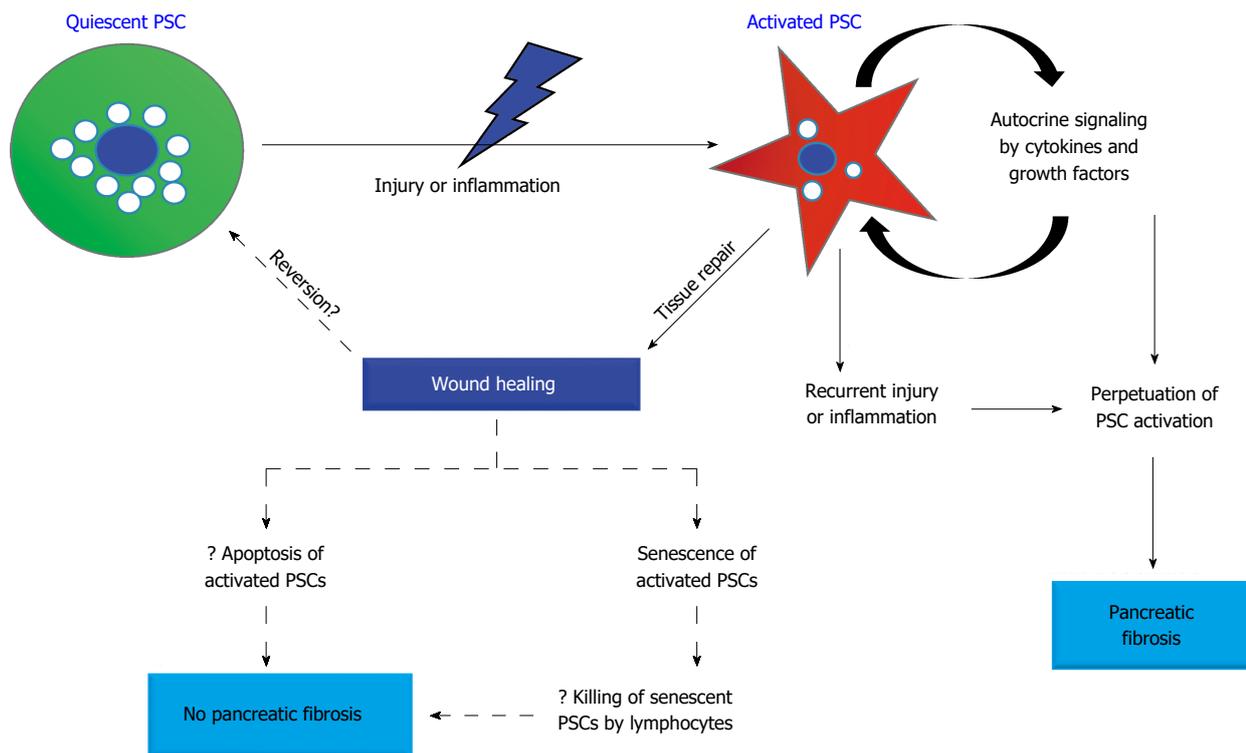


Figure 2 Fate of activated pancreatic stellate cells. The fate of activated pancreatic stellate cells (PSCs) could be potentially two pronged-sustained inflammation and/or autocrine mode of PSC activation may perpetuate its activated phenotype, even in the absence of its paracrine triggers, resulting in the development of pancreatic fibrosis or PSCs might undergo either reversion to quiescent phenotype or apoptosis or may become senescent and further cleared by lymphocytes. In the latter situation, there should not be fibrosis.

Fate of PSCs

The fate of activated PSCs is an important question that remains unresolved. Figure 2 depicts a schematic representation of the fate of PSCs. One of the two possible explanations that were proposed is that sustained inflammation may perpetuate PSC activation, leading to fibrosis; while the other explanation proposed that the activated PSCs may undergo apoptosis or may revert back to the native phenotype if the inflammation or injury is ceased. Recently, Fitzner *et al*^[46] proposed that activated PSCs could undergo senescence as evidenced by increased senescence-associated β -galactosidase, higher expression of CDKN1A/p21, mdm2 and interleukin (IL)-6. On the contrary, there was lower expression of α -smooth muscle actin. The authors also observed that senescence increased the susceptibility of PSCs to cytolysis and concluded that inflammation, PSC activation and cellular senescence were coupled processes that took place in the same inflammatory microenvironment of CP^[46]. In the setting of AP, PSCs could undergo death after phagocytizing necrotic acinar cells^[36].

PSCS AND FIBROSIS

A pathological hallmark of CP and PDAC is progressive fibrosis that is mediated by the PSCs. One of the earliest cellular events at the initiation of fibrosis is activation of PSCs, which can be mediated concomitantly by

a variety of factors, such as oxidative stress, cytokines, growth factors, activin-A, angiotensin, hyperglycemia and pressure, to name a few. Interestingly, activation of PSCs can occur by both autocrine and paracrine mechanisms, which imply that the effects of PSC activation, primarily inflammation and resultant fibrosis can progress, even after removing the primary source. The distinctive sources of exogenous factors that actuate the PSC include activated macrophages, monocytes, pancreatic acinar cells, endothelial cells, pancreatic cancer cells and platelets in inflamed pancreas^[47-50]. Figure 3 depicts the autocrine and paracrine mechanisms of PSC activation and the resulting fibrosis.

Alcohol, smoking and PSC activation

Alcohol and smoking are now recognized as independent risk factors for the development of CP. It is known that pancreatic acinar cells can metabolize alcohol to form toxic metabolites that results in oxidative stress. This results in inflammation and PSC activation^[51-53]. Furthermore, PSCs themselves can metabolize ethanol to acetaldehyde and generate oxidative stress, thus promoting their own activation and lipid peroxidation. The above findings have been confirmed by immunostaining for 4-hydroxy-nonenal (4-HNE), a reactive product of lipid peroxidation, that demonstrated localization of 4-HNE stained PSCs in fibrotic areas adjacent to acinar cells^[54-56]. Ethanol activated PSCs

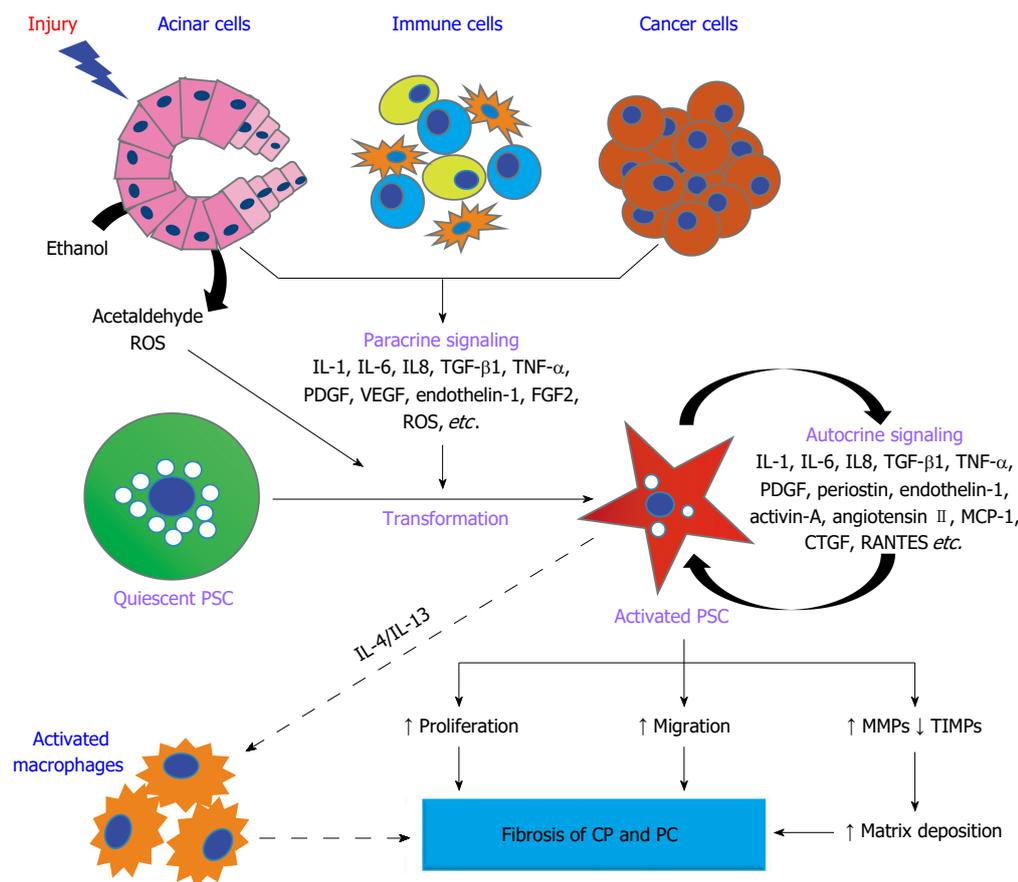


Figure 3 Autocrine and paracrine factors mediating pancreatic stellate cell activation. Cytokines and growth factors secreted by injured acinar cells, immune cells and cancer cells activate the pancreatic stellate cells (PSCs) in a paracrine fashion and stimulate them to secrete various factors. These factors secreted by PSCs in turn acts in a paracrine fashion and sustains its activation. This autocrine and paracrine signal cycles may help PSCs to retain its activated phenotype, resulting in excess ECM deposition, culminating to pancreatic fibrosis. ROS: Reactive oxygen species; PC: Pancreatic cancer; FGF: Fibroblast growth factor; PDGF: Platelet derived growth factor; TGF- β : Transforming growth factor- β ; VEGF: Vascular endothelial growth factor; TNF- α : Tumor necrosis factor- α ; MMP: Matrix metalloproteinase; CP: Chronic Pancreatitis; TIMPs: Tissue inhibitors of matrix metalloproteinases; CTGF: Connective tissue growth factor; IL: Interleukin.

showed increased proliferation by enhancing the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system stimulated by platelet derived growth factor (PDGF)^[57]. Also shown was expression of connective tissue growth factor (CCN2/CTGF) that was attributed to production of acetaldehyde and oxidant stress in ethanol stimulated PSCs, which rendered the properties of cell adhesion, migration and collagen synthesis when stimulated with profibrogenic molecules^[58]. Recently, CCN2 was also shown to increase miR-21 expression that in turn enhanced collagen α 1 expression in a murine alcoholic CP model. CCN2 and miR-21 were shown to be colocalized in PSC derived exosomes that were positive for cluster of differentiation (CD) 9. *In vitro* studies revealed that these exosomes serve as molecular cargos to activate and transfer fibrogenic signals to the adjacent PSCs^[59].

Lee *et al*^[60] has recently demonstrated that PSCs express nicotinic acetylcholine nAChRs (isoforms α 3, α 7, β , ϵ). Furthermore, nicotine and nicotine-derived nitrosamine ketone and cigarette smoke extracts were shown to activate PSCs both in the presence and absence of alcohol. This reiterates the clinical obser-

vation of role of smoking as an independent risk factor in the initiation and progression of CP^[61].

Pressure and PSC activation

Ductal hypertension resulting from obstructing pancreatic ductal calculi or stricture has been long believed to be a major contributor of pain in CP. This formed the rationale for ductal clearance of stone/stricture by endotherapy and/or surgery in an attempt to ameliorate pain in CP. Experimental evidence to support this concept came forward from studies by Asaumi *et al*^[62] where externally applied pressure of 80 mmHg induced activation of PSCs and generation of reactive oxygen species (ROS) within the activated PSCs^[63]. ROS generation was observed as early as 30 min after application of pressure and reached peak by 1 h.

Hyperglycemia and PSC activation

In a study by Ko *et al*^[64], exposure of PSCs to high glucose concentration resulted in stimulation of α -SMA expression, proliferation and expression of extracellular matrix proteins such as CTGF and collagen type IV. PSC activation by hyperglycemia was also confirmed

by subsequent studies by Nomiya *et al.*^[65] and Hong *et al.*^[39] and the latter study also suggested an additive effect of hyperglycemia and hyperinsulinemia in inducing PSC activation and islet fibrosis in the context of Type 2 diabetes. Observations from these studies have provided an insight into the role of hyperglycemia in preserving the activated phenotype and also in the context of secondary diabetes in patients with CP. A more recent study has indicated that hyperglycemia could result in induction of Cysteine-X-Cysteine ligand (CXCL) 12 production by the PSCs and its receptor, CXCR4 on cancer cells^[66].

Cytokines and other activation factors that mediate proinflammatory function of PSCs

Fibrous tissue in CP and PDAC abounds in type I collagen. Among the cytokines that can cause PSC activation, TGF- β stands among the most important. Studies have shown increased collagen synthesis and upregulation of MMP1 in PSCs that were stimulated with TGF- β and TGF- α ^[67,68]. Other activators of PSCs include interleukin-8 (IL-8), MCP-1 and RANTES (Regulated on Activation, Normal T-cell Expressed and Secreted), which promote PSC activation *via* autocrine pathways^[69]. Activin-A and angiotensin II have also been identified as the autocrine activators of PSCs, contributing to further TGF- β 1 expression and PSC proliferation^[70,71]. Expression of TGF- β 1 and collagen secretion, has also been shown to result from application of external pressure and with hyperglycemia^[63-65].

Migration and proliferation of PSCs are other important properties that go parallel along with the proinflammatory and profibrotic cascade. Proliferation and migration of PSCs is mediated by PDGF^[57,72,73] (which is expressed after TGF- β mediated activation) and endothelin-1^[74,75]. A proinflammatory chemokine, CX3CL1 (fractalkine), reported to circulate in the serum of patients with alcoholic chronic pancreatitis, was demonstrated as an activation and proliferation factor for PSCs and PSCs were shown to express the receptor (CX3CR1) for this chemokine^[76,77]. Interestingly, this chemokine and its receptor system was reported to regulate the insulin secretion by β -cells^[78]. Recently, another new activation factor, namely parathyroid hormone related protein (PTHrP) was demonstrated to be expressed by acinar cells during experimental pancreatitis using an acinar cell specific *PTHrP* gene knock-out model. Receptor for this factor (PHT1R) has been shown to be expressed in PSCs and receptor-ligand interaction between the two resulted in fibrogenesis^[79]. Of note, IL-6 has been shown to inhibit both PSCs proliferation and collagen synthesis^[80]. Recently it was also demonstrated that IL-4 and IL-13 secreted by PSCs mediate macrophage activation, which in turn participate in promoting the pancreatic fibrosis^[81].

To summarize the effect of the above experimental evidence, different paracrine factors released during the injury will result in activation, proliferation and migra-

tion of PSCs and the activated phenotype is further retained by an autocrine loop, even in the absence of paracrine triggers.

MOLECULAR PATHWAYS, MICRORNAS, TRANSCRIPTION FACTORS AND PROTEOMICS IN PSC MEDIATED PANCREATIC FIBROSIS

Studies conducted over the past decade have implicated the involvement of several proteins and molecular pathways (Figure 4) in perpetuating the profibrogenic role of PSCs.

MAPK, JAK-STAT and PI3K signaling pathways

Mitogen activated protein kinases (MAPKs) are serine/threonine protein kinases with three families: extracellular signal regulated kinase (ERKs), c-Jun N-terminal kinase (JNK) and p³⁸^[82], and all the three MAPKs have been studied extensively for their role in PSCs activation. *In vitro* studies demonstrated that the activation of ERK1/2 is the initial pathway that precedes the transformation of PSCs into activated phenotype and PDGF was shown to mediate ERK1/2 and Activator protein-1 (AP-1) dependent proliferation and migration of PSCs^[72,73]. Studies have also demonstrated involvement of the Janus-activated kinase-signal transducers and activators of transcription (JAK2-STAT3) pathway in PDGF-BB induced PSC proliferation^[83]. PI3K and all the MAPKs were described in human PSCs to express IL-32 α and IL-33 when treated with proinflammatory cytokines. IL-33 was shown to activate PSCs^[84-86]. HNE was reported to activate all the 3 classes of MAPKs and AP-1. PSCs treated with HNE showed increased production of type I collagen with no significant effect on proliferation and transformation, implicating oxidative stress mediated pathogenesis of pancreatic inflammation and fibrosis^[87]. All the three MAPKs including AP-1 were triggered in PSCs when stimulated with ethanol and acetaldehyde. Inhibition of p³⁸, JNK and Rho associated protein kinase (ROCK) pathways demonstrated the inhibition of PSC activation, supporting the involvement of above mentioned pathways in the pathogenesis of alcohol induced pancreatic injury^[54,88,89].

Smad signaling pathway

TGF- β 1, which is a proven profibrogenic cytokine, is required in the regulation of PSC activation^[90]. Smads are the signaling effectors of TGF- β mediated functions and have also been ascribed a regulatory role in PSC functions. Results from co-expression of Smad2/3 with dominant negative Smad2/3 mutants and inhibition of ERK showed that the activation, proliferation and TGF- β 1 mRNA expression are mediated through the Smad2/3 and ERK dependent pathways in PSCs^[91]. The autocrine loop between IL-1 β and TGF- β 1 and the one existing between the IL-6 and TGF- β 1 were

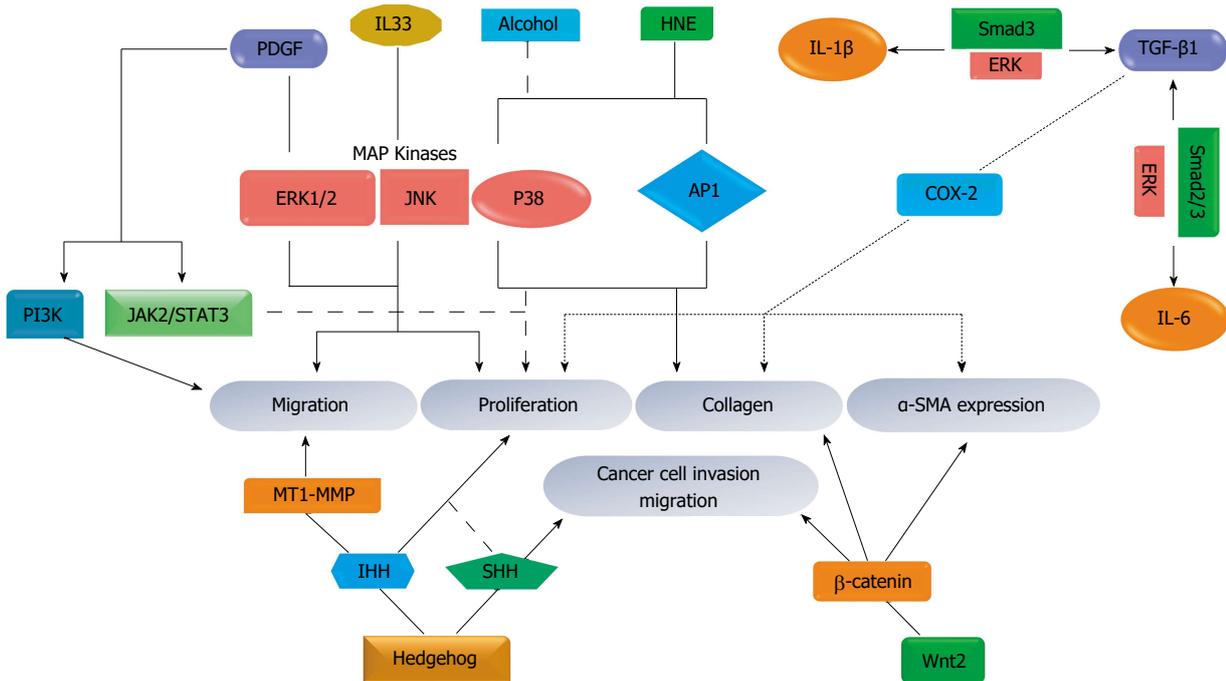


Figure 4 Signaling pathways mediating pancreatic stellate cell activation. Expression of α -SMA, proliferation, migration and deposition of matrix proteins are the important properties attained by activated pancreatic stellate cells (PSCs) when stimulated with various growth factors and proinflammatory cytokines. Proliferation and migration is mediated through the MAP kinase and PI3K pathways when PSCs are stimulated with HNE, alcohol, PDGF and IL-33 and other cytokines. TGF- β 1 induces the Smad proteins and stimulates the proliferation and collagen secretion by PSCs. Activation of Indian Hedgehog (IHH) signaling in PSCs promotes their migration, proliferation and collagen deposition. PSC mediated Sonic Hedgehog (SHH) signaling promotes cancer cell invasion and migration. Wnt signaling can cause collagen deposition and cancer progression. PDGF: Platelet derived growth factor; HNE: Hydroxy-nonenal; ERK: Extracellular signal-regulated kinases; JNK: c-Jun N-terminal kinase; TGF- β : Transforming growth factor- β ; α -SMA: α -smooth muscle actin; COX-2: Cyclooxygenase-2; IL: Interleukin.

mediated by Smad3/ERK dependent and Smad2/3 and ERK dependent pathways. Further investigations had confirmed the existence of a TGF- β 1 autocrine loop and supported the role of PSCs in preserving the activated phenotype and collagen synthesis^[92,93]. TGF- β 1 induced expression of cyclooxygenase-2 (COX-2) by PSCs also followed Smad2/3 dependent pathway in response to proinflammatory cytokines^[94]. This pathway has been suggested to be protective against the inhibitory activity of reversion-inducing-cysteine-rich protein with kazal motifs (RECK), a membrane anchored MMP inhibitor in the activated PSCs^[95]. The stimulation of activated PSCs with TGF- β unveiled the possible role of Ras-ERK and PI3/Akt pathways in the expression of MMP-1^[68].

Wnt signaling and β -catenin pathway

Yet another signaling pathway aberration that could result in PSC activation, proliferation and transformation into a profibrotic phenotype is that of Wnt signaling. This observation came from an experimental CP model by Hu *et al*^[96] where the authors have shown that there was increased expression of Wnt and its second messenger β -catenin and that this imbalance could result in persistent activation of PSCs. Yet another study by Xu *et al*^[97] showed that cancer cell invasion and migration are promoted by Wnt2 protein

secreted by the PSCs.

Hedgehog signaling pathway

Indian hedgehog (IHH) and sonic hedgehog (SHH) are the other important pathways in PSCs. Receptors, namely smoothed and patched-1, for the IHH protein are expressed on the surface of PSCs and the receptor-ligand binding results in localization of the membrane-type 1 matrix metalloproteinase on PSC plasma membrane, which in turn could mediate PSC migration^[98]. SHH was shown to influence the PSC mobility and differentiation^[99] and also perineural invasion, metastasis, tumour growth and pain in pancreatic cancer^[100,101].

microRNAs

Implications on the involvement of microRNAs (miRs) has recently been reported frequently in the context of CP and PSCs. A recent study reported upregulation and downregulation of 42 miRs each in activated PSCs^[102]. miR-15b and 16 have been shown to induce apoptosis of rat PSCs *via* influencing the anti-apoptotic Bcl-2 protein^[103]. An even more recent study demonstrated a paracrine pathway wherein CCN2 mRNA and miR-21 containing exosomes liberated by PSCs were engulfed by surrounding PSCs. This results in further expression of the CCN2 and miR-21 by the activated PSCs^[59].

Transcription factors and interactions with cytokines

Different cytokines exert their effect by inducing various transcription factors such as nuclear factor- κ B (NF- κ B), Activator protein-1 (AP-1), STAT proteins and Gli, to name a few. NF- κ B is stimulated by various cytokines associated with different cellular functions^[104]. Activated PSCs showed NF- κ B mediated expression of intracellular adhesion molecule when stimulated with IL-1 β and tumor necrosis factor (TNF)- α , which was not observed in the quiescent phenotype^[105]. Expression of MCP-1, cytokine induced neutrophil chemoattractant-1, IL-6, IL-8 and RANTES was observed *via* NF- κ B activation when induced with galectin-1, various ligands of TLR and cytokines, substantiating the role of PSCs in mediating the infiltration and accumulation of inflammatory cells^[106-108].

Proteomics

Proteomic studies using the immortalized PSC lines from *Mus musculus* and *Rattus norvegicus* showed the expression of cytoskeletal and ribosomal proteins by activated PSCs. The studies also demonstrated proteins involved in protein degradation, MAPK 3 and Ras related proteins by pseudo-quiescent PSCs^[109,110]. Proteomic profiling of mild and severe CP by label free quantitative proteomic approach displayed varied expression of proteins with a relative change in the proteins related to ECM and PSC activation which includes periostin, fibrillin 1, transgelin and a group of collagens. An accompanying study showed increased expression of transgelin in stromal and periacinar regions of CP, confirming its role in PSC activation^[111,112].

A comparative proteomic profiling of human HSC and PSC lines LX-2 and RLT-PSCs identified 1223 different proteins. Among 1223 proteins 1222 were found to be commonly expressed in both cell lines and a single protein (amino transferase) was found expressed in HSCs alone. The proteins in abundance from human PSC lines in this study were implicated for their role in maintaining the cellular structure^[113]. The proteomic analysis of nicotine treated human, mouse and rat PSCs by GeLC-MS/MS approach demonstrated the differential expression of proteins and signaling pathways, while the expression of integral protein 2B, procollagen type VI alpha, toll interacting protein and amyloid interacting proteins was found to be common^[114]. Expression of lysosomal proteins, indicators of pancreatic disease, proteins involved in defense mechanism and alteration in the phosphorylation sites were observed in another study^[115]. Few other proteomic studies of similar kind have reported the expression of proteins related to inflammation, fibrosis, apoptosis, wound healing and proliferation^[116]. The change in the expression profile of the proteome in response to various (TNF- α , FGF-2, CCL4 and IL-6) proinflammatory factors on immortalized human PSCs described their unique functions^[117].

PSCS-PANCREATIC CANCER CELLS-CANCER STROMAL INTERACTIONS

It has now been conclusively demonstrated that majority (50%-80%) of PDAC volume is composed of a fibrous stroma, amidst which lay the islands of cancer cells^[118]. There has been increasingly accumulating evidence that supports substantial two-way interactions between the stromal components and cancer cells and the association between the cancer cells and cancer associated PSCs have received several monikers such as "*dangerous liaisons*"^[119], "*friend or foe*"^[120] and "*unholy alliance*"^[121]. The stroma in pancreatic cancer consists predominantly of collagenous fibres laid down by the PSCs, along with other cellular [mast cells, macrophages, lymphocytes, myeloid derived suppressor cells (MDSC) and endothelial cells]^[122-131] and non-cellular (ECM proteins such as collagen, laminin, fibronectin, glycoproteins, proteoglycans and glycosaminoglycans; non-ECM proteins such as growth factors, osteopontin, periostin and serine protein-acidic and rich in cysteine) components^[132,133]. These stromal components can mediate the interaction between the PSCs and cancer cells and eventually influence the biological behavior and clinical outcomes of PDAC. Apart from vascular endothelial growth factor (VEGF) and angiopoietin-1, PSCs also secrete hepatocyte growth factor (HGF) and mediators responsible for endothelial cell proliferation and tube formation. This appears to operate through the HGF/c-MET pathway *via* induction of the downstream PI3K and p38 signaling pathways^[134]. Of note, upon neutralizing the HGF activity, proliferation and migration of cancer cells could be inhibited and apoptosis could be induced^[135].

Even though fibrosis that was observed early in development of PDAC led to the belief that PSC produced stroma is protective, this eventually shifted towards the concept of the stroma having a tumour permissive effect. However, the current opinion holds that PSC-stroma-cancer cell interaction is dynamic and stage-dependent, with protective effect in the earliest stage and harmful effect in later stages^[38]. The mechanism of PSC induced fibrosis in PDAC is similar to that seen in CP. Therefore, in the next section we will discuss only the cancer specific interactions and phenotypic effects of stroma-cancer cell interactions. While the PSC-pancreatic cancer cell interactions result in cancer growth and PSC activation, interaction between PSCs and stromal cells may be instrumental in metastasis, immune evasion, tumour hypoxia and resistance to chemoradiotherapy.

PSC-PDAC crosstalk

Pancreatic intraepithelial neoplasia (PanINs) are the precursor lesions of PDAC. It is now well known that PSCs get activated even at the early PanIN stages of

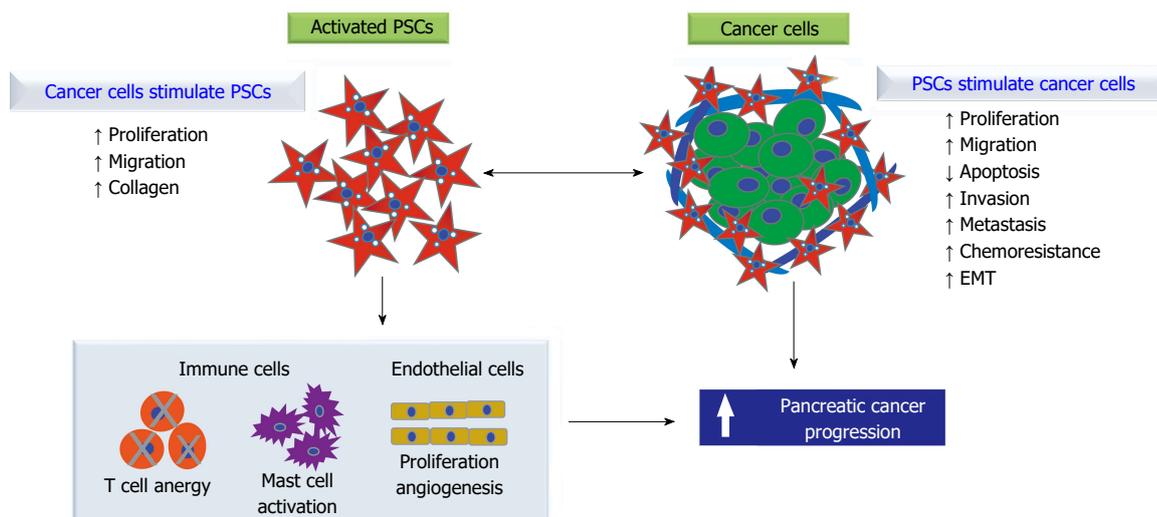


Figure 5 Crosstalk between pancreatic stellate cells and pancreatic cancer cells. Pancreatic stellate cells (PSCs) promote cancer cell proliferation, migration, invasion, EMT and metastasis. They also promote the cancer cell survival by decreasing cancer cell apoptosis and helps in chemoresistance. The cancer cells in turn promote PSC proliferation, contractility, migration and increased collagen synthesis. Apart from this, PSCs induce T cell anergy, activate mast cells and promote endothelial cell proliferation and tube formation. Together, these events mediated by PSCs and pancreatic cancer cells further aggravate pancreatic cancer progression. EMT: Epithelial-mesenchymal transition.

PDAC and initiates fibrosis around these precursor lesions. Several *in vitro* and *in vivo* studies have provided insight into the bipolar interactions between the PSCs and PDAC. *In vitro* co-culturing of PSCs with pancreatic cancer cells accelerated the proliferation and increased survival by inhibiting apoptosis^[49,136]. Furthermore, co-culturing also resulted in epithelial-mesenchymal transition (EMT) as evidenced by increased expression of vimentin and snail (mesenchymal marker) with corresponding reduction in E-cadherin and cytokeratin (both epithelial markers)^[137]. This was associated with migration of the cancer cells, which indicate the capability of PSCs to trigger the metastasis of pancreatic cancer cells^[138].

Recurrence of PDAC after therapy has been postulated to be an effect of persistence of a treatment resistant cancer stem cell niche. PSCs have been shown to regulate the genesis of a cancer stem cell niche as marked by increased expression of stem cell markers such as ABCG-2, Lin28 and nestin, while also attaining capability to form spheroids *in vitro*^[139]. Interestingly, it has been shown that the same PDAC can contain a heterogeneous population of PSCs based on the expression of CD10, which is a cell-membrane associated MMP. CD10(+) cells are associated with a higher propensity to proliferate and invade, thereby indicating that the relative proportion of PSC subtypes could also determine the disease biology and prognosis^[140].

While the foregoing paragraphs discussed the effect of PSCs on pancreatic cancer cells, the cancer cells also induce profound effects on the PSCs. Pancreatic cancer cells produce factors such as PDGF, trefoil factor 1^[141] and COX-2, which could induce PSC proliferation. COX-2 expression is upregulated not only in the cancer cells, but also in the PanINs and PSCs exposed

to conditioned medium from cancer cell lines^[142-145]. Galectin-1 and Galectin-3, members of galectin family of β -galactoside binding proteins, are also important drivers of the PSC-PDAC crosstalk. Galectin-3 expression by pancreatic cancer cell lines was found to promote its own proliferation along with PSCs^[146,147]. Figure 5 outlines the overall crosstalk between PSCs and pancreatic cancer cells.

Role of PSCs on invasion and metastasis

Galectin-3^[147], thrombospondin-2^[148], stromal cell derived factor^[149] and nerve growth factor (NGF)^[150] expressed by PSCs are shown to drive the invasion of PDACs. Studies on xenograft models showed that PSCs exert a modulatory function and potentiate the invasiveness of SUIT2 pancreatic cancer cells expressing serine protease inhibitor nexin2 (SERPINE2)^[151,152]. Pancreatic cancer cells and PSCs express fibroblast growth factor (FGF) and fibroblast growth factor receptor (FGFR) that have been shown to mediate interaction between the tumour and stromal cells resulting in development of an invasive phenotype^[153]. A recent study confirmed that pro-invasive character results from nuclear localization of FGFR1 and FGF2 in PSCs^[154]. Perhaps the most convincing and concept changing data on the role of PSCs in metastasis was reported in the study by Xu *et al.*^[155] which showed that the PSCs could rapidly acquire a tumour inductive property even after a short exposure of pancreatic cancer cells, thereby facilitating tumour growth and metastasis. The authors used a gender mismatch approach in which they injected a combination of female pancreatic cancer cells and male human PSCs into the pancreas of female nude mice. Interestingly, they could demonstrate Y-chromosome positive (*i.e.*,

the injected male human PSCs) in metastatic liver nodules. This implied that the PSCs from the liver could intravasate blood vessels, transport in circulation and extravasate into metastatic nodules alongside the metastatic cancer cells. The findings also suggest that the metastatic PSCs could mount an active stromal reaction even in the metastatic nodule. The property of transendothelial migration of the PSCs was further supported by *in vitro* studies and was found to be mediated by PDGF.

Besides contributing to distant metastasis, PSCs have also been implicated in neural invasion. This notion has been supported by studies that reported expression of neurotrophic factors such as glial derived neurotrophic factor and brain derived neurotrophic factor and stimulation of neurite formation towards pancreatic cancer cells by activated PSCs. These effects appear to be mediated by SHH paracrine signaling pathway^[100,101].

Tumour hypoxia and resistance

Similar to CP, PDAC is also characterized by hypoxic microenvironment. Tumour hypoxia arising from fibro-inflammatory environment is shown to induce the expression of hypoxia-inducible factor-1 α (HIF-1 α) and stimulate the secretion of SHH ligand by cancer cells, leading to stromal deposition by tumour associated fibroblasts. Organotypic culture of thick pancreatic sections under hypoxic conditions depicted the activation (α -SMA) and proliferation (Ki67) of PSCs along with higher expression of HIF-1 α , mediating the activation of hypoxic pathways^[156]. *In vitro* studies on the role of hypoxic milieu on the interactions between PSCs and PDACs led to interesting observations. The hypoxia exposed PSCs expressed type I collagen and VEGF, showed increased migration and also promoted the endothelial cell proliferation, migration and angiogenesis^[157]. Another study also yielded similar results where the hypoxia induced PSCs showed increased expression of periostin, collagen type I, VEGF and fibronectin. In co-cultures, the hypoxia treated PSCs enhanced the endostatin production by cancer cells and increased the endothelial cell growth^[158]. A similar kind of study using 3D matrices also reported that the hypoxia induced procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2 (PLOD2) in PSCs promotes cancer cell migration^[159]. Periostin, a matrix protein, with its persevered autocrine loop was shown to promote ECM synthesis and cancer cell growth under hypoxia and starvation during chemotherapy by maintaining the activated phenotype of PSCs^[160]. PSCs were also shown to express miR-21 and miR-210 under hypoxic conditions, where miR-210 was reported to regulate the interactions between PSCs and PDACs *via* ERK and Akt pathways^[161] and miR-21 contributing to cancer cell invasion and metastasis^[162]. Apart from these 2 miRs, miR-199a and miR-214 expressed by PSCs shown to have a pro-tumoral effect and also promote their own proliferation and migration^[163]. Overexpression

of miR-29, the expression of which was lost during the transformation of PSCs into activated phenotype, resulted in the reduction of collagen deposition, cancer cell growth and viability^[164].

The outcomes of the above studies not only confirmed the central role of PSCs in desmoplasia but also exhibited the proangiogenic functions mediated by them in tumour hypoxia.

Immune escape of PDAC

Emerging data over the recent years have strongly suggested that pancreatic cancer cells could evade host immune surveillance. One of the major factors that mediate immune evasion of pancreatic cancer cells is by sequestration of CD8(+) cells within the stroma, thereby preventing them from invading peritumoral areas where they could mediate immune mediated injury to the cancer cells. This appears to be mediated by the chemokine CXCL12^[165]. The other important mediator that sustain an immunosuppressive milieu is the β -galactoside binding lectin galectin-1, which is overexpressed by PSCs in pancreatic cancer. Using siRNA induced knockout and overexpression studies, it was shown that galectin-1 could induce T-cell apoptosis and reduced Th-1 response (with concomitant increase in Th-2 responses) and thereby reducing the immune mediated injury to the cancer cells. This was further reconfirmed and was shown that the effects were significantly higher in poorly differentiated tumours compared to the well-differentiated ones^[166].

Other PSC mediated mechanisms that has been proposed to result in disruption of anti-tumour immunity are cytokine secretion by macrophages^[167] and expression of the fibroblast activation protein- α ^[168], migration of MDSC^[130], mast cell degradation leading to release of tryptase and IL-13^[124].

THERAPEUTIC IMPLICATIONS

Given the background of substantial understanding of the mechanisms of PSC involvement in pancreatic fibrosis and pancreatic cancer, several experimental, preclinical and early phase clinical studies on CP and pancreatic cancer have appeared in the literature over the recent years. Experimental studies (both *in vivo* and *in vitro*) that have targeted the profibrogenic function of PSCs have shown favorable results; however these results have not yet been satisfactorily reproduced in human CP. Table 2 summarizes the drugs and their effects in experimental studies of CP^[169-218].

In the context of pancreatic cancer, where conventional chemotherapy has shown dismal results, the current concept is to target the stroma along with conventional chemotherapy. Since the pancreatic cancer stroma has been shown to be associated with tumour hypoxia, metastasis, drug resistance, it is expected that prior stromal degradation could result in chemosensitivity of the tumour even with the conventional chemotherapeutic drugs. Table 3 shows the

Table 2. Therapeutic agents that have been used in experimental studies for inhibition of Pancreatic stellate cells in chronic pancreatitis

| Ref. | Agent | Class/type of agent | In vivo/in vitro (study) model | Outcome of the study |
|--------------------------------------------------|---------------------------------|------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nakamura <i>et al</i> ^[166] 2000 | FOY-007 | Synthetic serine protease inhibitor | Cytokine stimulated human periacinar fibroblast like cells | Both attenuated proliferation and procollagen type I C-terminal peptide (PIP) FOY-007 also inhibited collagen synthesis |
| Xie <i>et al</i> ^[170] 2002 | IS-741 | Carboxamide derivative | Wistar Bonn/Kobori rats | Suppressed the expression of IL-6 and CINC and pancreatic acute phase proteins (PAP and p8) |
| Kuno <i>et al</i> ^[171] 2003 | Lisinopril | Angiotensin-converting enzyme (ACE) inhibitor | Wistar Bonn/Kobori rats | Increased pancreatic weight and decreased pancreatic MPO and serum ACE activity was observed Decrease in serum MCP-1 levels, intra-pancreatic hydroxyproline content was identified TGF-β1 mRNA overexpression was suppressed |
| Yamada <i>et al</i> ^[172] 2003 | Candesartan | Angiotensin II receptor antagonist | Wistar Bonn/Kobori rats | Increased pancreatic weight and expression of angiotensinogen and angiotensin II receptor type 2 mRNA Decreased pancreatic MPO and serum ACE activity and hydroxyl proline content Suppressed TGF-β1 mRNA overexpression |
| Masamune <i>et al</i> ^[173] 2003 | Y-27632 and HA-1077 | Rho kinase inhibitors | Isolated PSCs from male Wistar rats | Inhibited α-SMA expression, proliferation, type I collagen production and chemotaxis |
| Nagashio <i>et al</i> ^[174] 2004 | AdTb-ExR | Adenoviral vector system expressing TGF-β receptor | Caerulein induced CP in BALB/c mice | Reduced the activated PSCs, number of apoptotic acinar cells and fibrosis Weight of the pancreas increased |
| Zhao <i>et al</i> ^[175] 2005 | Mutant MCP-1 | ... | DBTC induced CP in Lewis rats | Decreased MCP-1, fibrosis and hydroxyproline levels Reduced IL6, TGF-β, IL-1β, MCP-1 and PDGF expression |
| Gibo <i>et al</i> ^[176] 2005 | Camostat mesilate | Oral protease inhibitor | In vivo: DBTC induced CP in Lewis rat In vitro: Culture activated PSCs | In vitro: Inflammation, fibrosis and cytokines expression was inhibited In vitro: PSC proliferation and MCP-1 production was reduced |
| Yamada <i>et al</i> ^[177] 2005 | Lisinopril and candesartan | Angiotensin-converting enzyme inhibitor and angiotensin II type 1 receptor blocker | Wistar Bonn/Kobori rats | Reduced MPO activity, hydroxyproline content, inflammation and fibrosis in combination therapy Suppressed mRNA expression of TGF-β1, PDGF-β and TNF-α |
| van Westerloo <i>et al</i> ^[178] 2005 | Troglitazone | PPAR-γ ligand | Caerulein induced experimental CP in female C57BL/6 mice | Intrapancreatic fibrosis and hydroxy proline contents were reduced Attenuated increase in MPO content and TGF-β1 levels |
| Reding <i>et al</i> ^[179] 2006 | Rofecoxib | COX-2 inhibitor | Wistar Bonn/Kobori rats | Reduced TGF-β, collagen synthesis, inflammation and macrophage infiltration |
| Asaumi <i>et al</i> ^[180] 2006 | Epigallocatechin-3-gallate EGCG | Antioxidant of polyphenols | Ethanol stimulated PSCs isolated from Wistar rats | Inhibited lipid peroxidation, SOD activity and p38 phosphorylation Decreased TGF-β1 and collagen secretion |
| Baumert <i>et al</i> ^[181] 2005 | IFN-γ | Antifibrotic cytokine | Culture activated PSCs, isolated from LEW:1W rats and pancreatic stellate cell lines | Diminished PSC proliferation and collagen synthesis Inhibited α-SMA expression |
| Fitzner <i>et al</i> ^[182] 2006 | | | | Induction of quiescent phenotype mediated through activated STAT1 |
| Ohashi <i>et al</i> ^[183] 2006 | Thioredoxin-1 (TRX-1) | Redox-regulating protein with antioxidative activity | Caerulein induced CP in wild type C57BL/6 mice and transgenic mice overexpressing TRX-1 | Attenuated PSC activation and fibrosis TGF-β1 and PDGF expression was reduced Lower levels of MCP-1 in serum and acinar cells |
| McCarroll <i>et al</i> ^[184] 2006 | Retinol and its metabolites | Vitamins of vitamin A | Ethanol stimulated culture activated rat PSCs | Inhibited PSC activation, proliferation, expression of collagen I. All MAP kinases were activated |
| Tasci <i>et al</i> ^[185] 2007 | Allopurinol | Xanthine oxidase inhibitor | Trinitrobenzene sulfonic acid (TNBS) induced CP in Sprague-Dawley rats | PSC activation was inhibited <i>in vitro</i> |
| Lu <i>et al</i> ^[186] 2007 | Ascorbic acid | Antioxidant | DBTC induced CP in Sprague-Dawley rats | Lower collagen deposition and lobular and sub-lobular atrophy was observed Decreased malondialdehyde (MDA), hyaluronic acid, laminin concentrations and pancreatic injury Increased superoxide dismutase activity |
| Shirahige <i>et al</i> ^[187] 2007 | Taurine | Amino sulfonic acid | DBTC induced pancreatic fibrosis in Wistar rats | Improved pancreatic fibrosis in rats. Increased IL-6 and decreased IL-2 were observed in pancreatic tissue homogenates |
| Rickmann <i>et al</i> ^[188] 2007 | Tocotrienols | Vitamin E family members | Culture activated PSCs from Wistar rats Culture activated PSCs isolated from Wistar rats | PSC culture supernatants showed decreased type I collagen, MMP-2 and TGF-β1 Reduced viability of activated PSCs by apoptosis and autophagy |

| | | | | |
|-------------------------------------------------|------------------------------------------------|-----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Michalski CW <i>et al</i> ^[189] 2008 | Canabinoid WIN 55,212-2 | Aminoalkylindole derivative | Human PSCs from CP tissues | Reduced fibronectin, collagen1 and α -SMA levels Decreased IL-6, MCP-1 and MMP-2 secretion and invasiveness by PSCs Increased n-3 PUFA tissue levels Decreased PSC activation |
| Weylandt <i>et al</i> ^[190] 2008 | Omega-3 polyunsaturated fatty acids (n-3 PUFA) | Polyunsaturated fats. | Caerulein-induced CP in fat-1 transgenic mice | Less pancreatic fibrosis and collagen content Lower serum amylase, lipase, hyaluronic acid, nitric oxide levels and tissue hydroxyproline levels Pancreatic inflammation and acinar cell atrophy was reduced |
| Karatas <i>et al</i> ^[191] 2008 | Halofuginone | Synthetic halogenated derivative of febrifugine | Complete pancreatic duct obstruction and caerulein hyperstimulation in female Wistar rats | Inhibited PSC proliferation and collagen synthesis Reduced the expression of ET-1, α -SMA and CIGF PSC proliferation was inhibited through p38/HO-1 pathway activation |
| Fitzner <i>et al</i> ^[192] 2008 | Bosentan | ET-1-receptor antagonist | Culture activated rat PSCs | Decreased MPO activity and inflammatory cell infiltration Reduction in collagen I and fibronectin mRNA levels |
| Schwer <i>et al</i> ^[193] 2010 | Carbon monoxide-releasing molecules-2 (CORMs) | Metal carbonyl compounds delivering carbon monoxide | Culture activated PSCs isolated from Wistar rats | Reduced amylase, hydroxyproline and TGF- β 1 levels were observed Diminished α -SMA, fibronectin and collagen expression was identified <i>In vivo</i> : Reduced inflammatory cell infiltration and expression of α -SMA, collagen I and TGF- β 1 <i>In vitro</i> : PSC proliferation and activation was inhibited |
| Nathan <i>et al</i> ^[194] 2010 | Pancreatic secretory trypsin inhibitor (PSTI) | Protein | Caerulein induced CP in C57BL/6 PSII transgenic mice | Inhibited PSC proliferation, migration and reduced collagen I and fibronectin Increased MMP/TIMP ratio and promoted fibrolysis |
| González <i>et al</i> ^[195] 2011 | Palm oil tocotrienol-rich fraction | Vitamin E family members | Arginine induced chronic like pancreatitis in Wistar rats | Decreased serum amylase mRNA expression of TNF- α , IL-1 β and COX-2 were reduced and IL-10 was increased |
| Long <i>et al</i> ^[196] 2011 | Octreotide | Analog of somatostatin | <i>In vivo</i> : PSC induced Pancreas Graft Fibrosis in Rats (Sprague Dawley rats as donors and Wistar rats as recipients) <i>In vitro</i> : PSCs isolated from Sprague Dawley rats | Attenuated fibrosis and mRNA levels of TNF- α and TGF- β 1 and increased IL-10 expression Exocrine secretion was improved |
| Li <i>et al</i> ^[197] 2011 | Pancreatic stone protein/ regenerating protein | Secretory stress proteins family | Culture activated PSCs from human CP tissue obtained by outgrowth method | SOD activity was increased Reduced fibrosis and enhanced survival rate Pancreatic weight was increased in CP model |
| Tang <i>et al</i> ^[198] 2011 | Simisan | Chinese herb | TNBS induced CP in Sprague-Dawley rats | mRNA levels of α -SMA, COX-2, IL-6, MIP-3 α and TNF- α were decreased and PAP was increased |
| Wei <i>et al</i> ^[199] 2011 | Pravastatin | Competitive inhibitor of HMG-CoA | Pancreatic ductal hypertension induced CP in Wistar rats | Inhibited acinar cell apoptosis |
| Li <i>et al</i> ^[200] 2011 | α -Tocopherol | Vitamin E family member | TNBS induced CP in Sprague-Dawley rats | Suppressed PSC proliferation and ECM synthesis Reduced fibrosis, acinar cell loss and inflammatory cell infiltration TNF- α and MCP-1 levels were decreased Expression of TGF- β , PDGF- β , SHH and Gli was reduced PSC proliferation was inhibited synergistically |
| Monteiro <i>et al</i> ^[201] 2012 | Vitamin E supplementation | Vitamin E family member | Ethanol induced (alcoholic) CP in Wistar rats | Decreased α -SMA, TIMP-1, IL-1 β TGF- β 1 expression and hydroxyproline levels and increased MMP-2 levels |
| Matsushita <i>et al</i> ^[202] 2012 | Taurine | Amino sulfonic acid | <i>In vivo</i> : DBTC induced CP in Wistar rats <i>In vitro</i> : AR42J acinar cells | |
| Yang <i>et al</i> ^[203] 2012 | L-Cysteine | Amino acid | <i>In vivo</i> : TNBS induced CP in Sprague-Dawley rats | |
| Bai <i>et al</i> ^[204] 2012 | Sulindac | Non-steroidal anti-inflammatory drug | <i>In vitro</i> : Culture activated PSCs Caerulein induced CP in C57BL/6 mice | |
| Lee <i>et al</i> ^[205] 2012 | Simvastatin and Troglitazone | HMG-CoA reductase inhibitor and PPAR agonists | Culture activated PSCs isolated from Sprague-Dawley rats | |

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|----------------------------------------------|---------------------------------------|--------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Shen <i>et al.</i> ^[206] 2013 | rCXCL9 | Chemokine | <i>In vivo</i> : TNBS induced CP in Sprague-Dawley rats <i>In vitro</i> : Culture activated PSCs from Sprague-Dawley rats | <i>In vitro</i> : protein expression of collagen 1 α 1 and TGF- β 1 decreased |
| Gao <i>et al.</i> ^[207] 2013 | Bone morphogenetic proteins | TGF- β superfamily members, | <i>In vivo</i> : Caerulein induced CP in female Swiss Webster mice <i>In vitro</i> : PSCs isolated from female Swiss Webster mice and human pancreatic tissue | <i>In vitro</i> : BMP2 protein levels were increased <i>In vitro</i> : PSC pre-treatment with BMP2 attenuated TGF- β 1, α -SMA, fibronectin and collagen type Ia expression |
| Zhou <i>et al.</i> ^[208] 2013 | Eedaravone | Free radical scavenger | DBTC induced CP in Sprague-Dawley rats | Rats body weight was improved and reduced the fibrosis SOD activity was increased and MDA levels were decreased TGF- β , TNF- α and IL-6 levels were downregulated NF- κ B and PSC activation was inhibited |
| Niina <i>et al.</i> ^[209] 2014 | ONO-1301 | Prostacyclin agonist, | DBTC induced CP in Lewis rats | Reduced interstitial fibrosis and inflammatory cell infiltration Increased HGF and decreased IL-1 β , TNF- α , TGF- β , MCP-1 and collagen mRNA expression was observed |
| Mrazek <i>et al.</i> ^[210] 2015 | Apigenin | Hydroxyflavone | <i>In vivo</i> : Caerulein induced pancreatitis in C57/BL6 mice <i>In vitro</i> : PSCs isolated from human pancreatic tissues | <i>In vivo</i> : Reduced pancreatic fibrosis and retained acinar cell morphology <i>In vitro</i> : Induced PSC apoptosis and death Downregulated the parathyroid hormone related protein induced fibronectin, collagen 1 α 1, PCNA, TGF- β and IL-6 expression |
| Tsang <i>et al.</i> ^[211] 2015 | <i>Trans</i> -resveratrol | Natural stilbenoid | Rat pancreatic stellate cell line LTC-14 | Collagen type I, α -SMA and fibronectin was downregulated both at mRNA and protein level NF- κ B activation was decreased |
| Lin <i>et al.</i> ^[212] 2015 | Rhein, Emodin, and Curcumin | Phenolic compounds | Rat pancreatic stellate cell line LTC-14 | Collagen type I, α -SMA and fibronectin expression was decreased |
| Gundewar <i>et al.</i> ^[213] 2015 | L49H37 | Curcumin analog | Immortalized human pancreatic stellate cell line | Inhibited PSC proliferation and promoted apoptosis Decreased the phosphorylation of ERK1/2 |
| Tsang <i>et al.</i> ^[214] 2015 | Eruberin A | Flavanol glycoside | Rat PSC line LTC-14 | Inhibited expression of α -SMA Collagen type I and fibronectin Reduced the activation of NF- κ B and phosphorylation PI3K/AKT |
| Bläuer <i>et al.</i> ^[215] 2015 | 1,25-dihydroxyvitamin D3 | Vitamin D metabolite | PSCs isolated from C57BL/6J OlaHsd mouse | Antiproliferative and antifibrotic effects were observed |
| Xiao <i>et al.</i> ^[216] 2015 | Retinoic acid | Vitamin A Metabolite | <i>In vivo</i> : Caerulein induced CP in Balb/c mice <i>In vitro</i> : Culture activated PSCs | Decreased expression of TGF- β RII, collagen 1 α 1 PDGF-R β and β -catenin Nuclear translation of β -catenin was decreased Wnt 2 and β -catenin protein expression was downregulated Inhibited PSC proliferation and induced apoptosis Both drugs inhibited PSC proliferation |
| Witteck <i>et al.</i> ^[217] 2015 | Trametinib and dactolisib | MEK inhibitor and PI3kinase/mTOR inhibitor | Culture activated PSCs isolated from Lewis rats | Trametinib suppressed the expression of IL-6 and TGF- β 1 Dactolisib decreased the levels of α -SMA and Collagen type Ia1 |
| Ulmasov <i>et al.</i> ^[218] 2016 | CWHM-12 (RGD peptidomimetic compound) | Integrin inhibitor | <i>In vivo</i> : Caerulein induced pancreatitis in C57/BL6 mice <i>In vitro</i> : Rat PSC line LTC-14 | Pancreatic fibrosis, acinar cell atrophy and loss was reduced Decreased the expression of TGF- β regulated genes and PSC activation |

CINC: Cytokine-induced neutrophil chemoattractant-1; MCP-1: Monocyte chemoattractant protein-1; DBTC: Dibutyltin dichloride; MPO: Myeloperoxidase; PSC: Pancreatic stellate cell; CP: Chronic pancreatitis; α -SMA: α -smooth muscle actin; PDGF: Platelet derived growth factor; TGF- β : Transforming growth factor- β ; COX-2: Cyclooxygenase-2; MAP: Mitogen activated protein; CTGF: Connective tissue growth factor; SOD: Superoxide dismutase; TNBS: Trinitrobenzene sulfonic acid; MMP: Matrix metalloproteinase; MDA: Malondialdehyde; HMG-CoA: 3-hydroxy-3-methylglutaryl-L-coenzyme A reductase; TNF- α : Tumor necrosis factor- α ; IL: Interleukin; SHH: Sonic hedgehog; MIP: Macrophage inflammatory protein-3; NF- κ B: Nuclear factor- κ B; HGF: Hepatocyte growth factor; PCNA: Proliferating cell nuclear antigen.

Table 3 Therapeutic agents that have been evaluated in experimental/pre-clinical studies targeting pancreatic stellate cells and cancer stroma in pancreatic ductal adenocarcinoma

| Ref. | Agent | Class/type of agent | <i>In vivo/in vitro</i> (study) model | Outcome of the study |
|----------------------------------------------------------|---------------------------------------|-------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Feldmann <i>et al</i> ^[219] 2007 | Cyclopamine | Steroidal alkaloid | Orthotopic xenograft model | Inhibited cancer cell invasion and metastasis by suppressing hedgehog |
| Diep <i>et al</i> ^[220] 2011 | Erlotinib RDEA119 and AZD6244 | EGFR tyrosine Kinase and MAP kinase inhibitors | <i>In vitro</i> : Pancreatic cancer cell lines <i>In vivo</i> : BxPC-3 and MIA PaCa-2 mice xenograft model | Inhibited cancer cell proliferation, EGF receptor signaling and induced apoptosis Suppressed tumour growth |
| Froeling <i>et al</i> ^[221] 2011 | ATRA, 9-cis-RA and 13-cis-RA | Metabolites of vitamin A | <i>In vivo</i> : <i>LSL-KrasG12D/+;LSL- Trp53R172H/+;Pdx-1-Cre</i> mice <i>In vitro</i> : AsPc1 and Capan1 pancreatic cancer cell lines, PS1 and other PSC cell lines | Retinoic acid induced PSC quiescence and decreased migration Decreased and induced proliferation and apoptosis of cancer cells |
| Chauhan <i>et al</i> ^[222] 2013 | Losartan | Angiotensin inhibitor | Orthotopic mice model | Reduced stromal collagen production, expression of TGF-β1, CCN2 and ET-1 Improved drug and oxygen delivery to tumour Inhibited proliferation and promoted apoptosis Cancer cell invasion and migration was decreased |
| Sun <i>et al</i> ^[223] 2013 | Curcumin | Phenolic compound | TGF-β1 stimulated PANC-1 cell line | Inhibited proliferation and promoted apoptosis Cancer cell invasion and migration was decreased |
| Edderkaoui <i>et al</i> ^[224] 2013 | Ellagic acid Embelenin | Polyphenolic and benzoquinone phytochemical | Pancreatic cancer cells and PSCs | Induced apoptosis and inhibited proliferation NF-κB activity was decreased |
| Macha <i>et al</i> ^[225] 2013 | Guggulsterone | Plant polyphenol | CD18/HPAF and Capan1 cell clones | Inhibited growth and colony formation Induced apoptosis and arrested cell cycle Decreased motility and invasion |
| Kozono <i>et al</i> ^[226] 2013 | Pirfenidone | Pyridone compound | <i>In vivo</i> : Orthotopic tumour mice Model <i>In vitro</i> : PSCs isolated from pancreatic tissue | <i>In vivo</i> : Reduced tumour growth, PSC proliferation and the deposition of collagen type I and periostin in tumours was decreased <i>In vitro</i> : Proliferation, invasiveness and migration of PSCs was inhibited |
| Guan <i>et al</i> ^[227] 2014 | Retinoic acid | Vitamin A derivative | Panc-1 and Asp-1 cell lines Cancer associated fibroblasts | Reduced α-SMA, FAP and IL-6 expression Inhibited cancer cell migration and EMT |
| Gonzalez-Villasana <i>et al</i> ^[228] 2014 | Bisphosphonates and nab-paclitaxel | Monocyte- macrophage lineage inhibitors | <i>In vitro</i> : Human PSCs and cancer cell line <i>In vivo</i> : Orthotopic mice model | <i>In vitro</i> : Inhibited PSC activation, proliferation MCP-1 release and collagen 1 expression and induced apoptosis <i>In vivo</i> : Reduced tumour size, fibrosis, proliferation and increased apoptosis |
| Pomianowska <i>et al</i> ^[229] 2014 | Prostaglandin E2 (PGE2) | Lipid compound | Human PSCs isolated from resected pancreatic tumour tissue | IL-1β and EGF induced COX-2 expression, TGF-β induced collagen synthesis and PDGF induced PSC proliferation was inhibited |
| Gong <i>et al</i> ^[230] 2014 | Nexrutine | Phytoceutical with COX-2 Inhibitor activity | <i>In vitro</i> : pancreatic cancer cell lines <i>In vivo</i> : BK5-COX-2 transgenic mice | <i>In vitro</i> : promoted cancer cell apoptosis and reduced their growth Suppressed COX-2 expression <i>In vivo</i> : NF-κB and Stat3 activity and fibrosis was decreased |
| Yan <i>et al</i> ^[231] 2014 | Crizotinib | c-MET/HGF receptor and ALK tyrosine kinases inhibitor | <i>In vitro</i> : Human pancreatic cancer cell lines AsPC-1, PANC-1, MIA PaCa-2 and Capan-1 <i>In vivo</i> : Mouse xenograft model | <i>In vitro</i> : Growth and proliferation was inhibited Induced apoptosis Inhibited ALK activity <i>In vivo</i> : Inhibited angiogenesis, tumour growth and ALK activity |
| Zhang <i>et al</i> ^[232] 2014 | 5-Azacytidine | Cytidine analogue | Bxpc-3 cancer cell line | Inhibited cancer cell proliferation by suppressing Wnt/ β-catenin signaling |
| Wang <i>et al</i> ^[233] 2014 | miR-216a | microRNA | <i>In vitro</i> : Capan-2 and PANC-1 pancreatic cancer cell lines <i>In vivo</i> : BALB/c nude mice | <i>In vitro</i> : Inhibited cell growth and induced apoptosis Down regulated survivin and XIAP expression <i>In vivo</i> : Inhibited xenograft tumour growth by suppressing JAK2/STAT3 signaling pathway |
| Kumar <i>et al</i> ^[234] 2015 | miR-let7b and GDC-0449 | microRNA and Hedgehog inhibitor | <i>In vitro</i> : Capan-1, HPAF-II, T3M4 and MIA PaCa-2 cell lines <i>In vivo</i> : Athymic nude mice bearing ectopic tumour | <i>In vitro</i> : Decreased cell proliferation and induced apoptosis <i>via</i> Gli dependent mechanism <i>In vivo</i> : Reduced tumour cell proliferation with increased apoptosis and tumour growth was inhibited |
| Petrova <i>et al</i> ^[235] 2015 | RU-SKI 43 | Hedgehog acyltransferase inhibitor | <i>In vitro</i> : Pancreatic cancer cell lines <i>In vivo</i> : Panc-1 xenograft mouse model | <i>In vitro</i> : Reduced cancer cell proliferation and Gli-1 activation through Smo independent signaling Decreased Akt and mTOR activity <i>In vivo</i> : Tumour growth decreased |
| Massó-Vallés <i>et al</i> ^[236] 2015 | Ibrutinib | Tyrosine kinase inhibitor | Transgenic mouse and xenograft mice models | Reduced fibrosis and extended survival |
| Zhou <i>et al</i> ^[237] 2015 | Zileuton | 5-LOX inhibitor | Pancreatic cancer SW1990 cell line | Induced apoptosis, decreased proliferation and expression of 5-lipoxygenase |

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|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Lui <i>et al</i> ^[238] 2015 | Desferrioxamine, Di-2-pyridylketone-4,4-dimethyl-3-thiosemicarbazone and Di-2-pyridylketone 4-cyclohexyl-4-methyl-3-thiosemicarbazone | Thiosemicarbazones | <i>In vitro</i> : PANC-1 and MIAPaCa-2 <i>In vivo</i> : PANC-1 tumour xenograft mice | Activation of the non-receptor tyrosine kinase Src and cAbl was decreased <i>in vitro</i> and STAT3 activation was reduced in both <i>in vivo</i> and <i>in vitro</i> condition |
| Khan <i>et al</i> ^[239] 2015 | Ormeloxifene | Nonsteroidal drug | Pancreatic cancer cell lines and PDAC xenograft mice | Inhibited cell proliferation, tumour stroma through SHH pathway and stromal cell infiltration Decreased collagen I expression Restored the tumour-suppressor miR-132 expression Migration and EMT was inhibited by affecting Wnt/ β -catenin signal events |
| Liu <i>et al</i> ^[240] 2016 | Oridonin | Tetracycline diterpenoid compound | Aspc1, Bxpc3, Panc1 and SW1990 cell lines | Migration and EMT was inhibited by affecting Wnt/ β -catenin signal events |
| Haqq <i>et al</i> ^[241] 2016 | Gemcitabine with omega-3 polyunsaturated fatty acid emulsion, (Lipidem TM) | Nucleoside analog | <i>In vitro</i> studies using pancreatic cancer cell lines Capan-1 and Panc-1 and PSC cell line; RLT-PSC | Drugs showed antiproliferative and anti-invasive effects |
| Ji <i>et al</i> ^[242] 2016 | MMP-2 responsive liposome loaded with Pirfenidone and gemcitabine | --- | <i>In vivo</i> : BALB/c nude Orthotopic tumour mice model <i>In vitro</i> : Human PSCs isolated from surgical specimens of Pancreatic cancer | Pirfenidone inhibited collagen I and TGF- β expression in PSCs Gemcitabine killed pancreatic tumour cells |

PSC: Pancreatic stellate cell; TGF- β : Transforming growth factor- β ; CCN2: Connective tissue growth factor; NF- κ B: Nuclear factor- κ B; FAP: Fibroblast activation protein; EMT: Epithelial-mesenchymal transition; MCP-1: Monocyte chemoattractant protein-1; COX-2: Cyclooxygenase-2; PDAC: Pancreatic ductal adenocarcinoma; SHH: Sonic hedgehog; PDGF: Platelet derived growth factor; ALK: Anaplastic lymphoma kinase; MMP: Matrix metalloproteinase; XIAP: X-linked inhibitor of apoptosis protein; IL: Interleukin; HGF: Hepatocyte growth factor; mTOR: Mechanistic target of rapamycin.

recently tested drugs/biologics that targeted pancreatic cancer stroma in preclinical studies^[219-242]. Besides the preclinical studies, several SHH pathway inhibitors have also been tested in advanced or metastatic PDACs in phase I and II studies (both open labeled and randomized double-blind controlled trials). Few of these include Vismodegib (GDC-0449), Saridegib (IPI-926) and Erismodegib (LDE225), PDGFR inhibitor (TKI258), hyaluran (PEGPH20) and dasatinib, to name a few. These have been used along with gemcitabine and/or nab-Paclitaxel and FOLFIRINOX. Discussion of details of the study designs and results of these trials are out of the scope of this review and can be obtained from recent high quality reviews^[243,244].

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