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REVIEW

This paper is dedicated to the 70th anniversary of the founding of Physiologia Bohemoslovaca (currently Physiological Research)

Pancreatic Stellate Cells - Rising Stars in Pancreatic Pathologies

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Summary

Pluripotent pancreatic stellate cells (PSCs) receive growing interest in past decades. Two types of PSCs are recognized – vitamin A accumulating quiescent PSCs and activated PSCs- the main producents of extracellular matrix in pancreatic tissue. PSCs plays important role in pathogenesis of pancreatic fibrosis in pancreatic cancer and chronic pancreatitis. PSCs are intensively studied as potential therapeutical target because of their important role in developing desmoplastic stroma in pancreatic cancer. There also exists evidence that PSC are involved in other pathologies like type-2 diabetes mellitus. This article brings brief characteristics of PSCs and recent advances in research of these cells.

Key words

Pancreatic stellate cells • Pancreatic cancer • Diabetes mellitus • Chronic pancreatitis • Tumor microenvironment

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Introduction

Stellate cells in humans were for the first time described by the great German pathologist von Kupffer in 1876. Kupffer described black stained "Sternzellen" in his letter to a famous German anatomist Wilhelm Waldeyer as the star-shaped cells localized in perisinusoidal spaces in the liver tissue revealed by gold chloride method. At that time, von Kupffer (1876) (who formerly described resident macrophages in liver (recently known as Kupffer cells) was uncertain about the role of hepatic stellate cells and considered them to be liver macrophages. After several decades Ito *et al.* (1952) proved vitamin A storing ability of these perisinusoidally localised cells and later Wake *et al.* (1999) described differences between Ito´s stellate cells and Kupffer cells in the liver. These findings were followed by increased interest in hepatic stellate cell´s (HSC´s) functions and further characterisation of these cells. Nowadays it is clarified that HSC have a crucial role e.g., in liver regeneration, tissue repair, production of extracellular matrix and immunomodulation.

Surprisingly, not the same attention was aimed at pancreatic stellate stells (PSCs). Unlike other pancreatic cells e.g. pancreatic islet cells, acinar or ductal cells, existence of PSCs was unrecognized until 1982 (106 years after Kupffer´s discovery of HSC), when Watari *et al.* (1982) found vitamin A accumulating cells in pancreatic tissue. In 1998 PSCs were successfully isolated from rat and human pancreas, which enabled further research of PSCs physiology in vitro. Apte *et al.* (1998) developed a technique for isolation of PSC based on lower density of PSCs caused by high amount of lipid vacuoles. It is supposed that it is possible to use density gradient based centrifugation of pancreatic cells suspension to isolate PSC. Since that time PSC received growing interest of researchers focused on pancreas and

their research enabled deeper insight into PSCs role in pancreatic (patho)physiology. In this brief review, we would like to introduce recent knowledge about the relationship between PSCs and distinct pancreatic pathologies.

Biology of PSC

Origin of PSCs

Pancreatic stellate cells comprise about 7 % of pancreatic cells and are found both in exocrine and exocrine parts of the pancreatic tissue. The origin of PSCs remains unclear. Despite the expression of neuroendocrine tissue specific markers, PSCs are supposed to be of mesenchymal origin as demonstrated by Asahina *et al.* (2009).

Existing evidence suggests that PSCs originate from mesenchymal cells, bone marrow cells (Sparmann *et al.* 2010) and certain type (CCR^{2+}) of monocytes (Ino *et al.* 2014).

Characteristics of PSCs

PSCs surround small pancreatic ducts and blood vessels and are mostly present in the basolateral part of pancreatic acinar cells. They can be identified by using immunohistochemical analysis because PSCs present some specific markers such as vimentin, desmin, glial fibrillary acidic protein (GFAP), neural growth factor (NGF), neural cell adhesion molecule (NCAM), synemin and nestin (Apte *et al.* 1998).

Presence of various intracellular filaments shows a broad spectrum of possible functions of PSCs (Uyama *et al.* 2006, Omary *et al.* 2004).

PSCs typically exhibit blue-green fluorescence based on vitamin-A accumulation in intracellular lipid vacuoles when exposed to 328nm UV light (Watari *et al.* 1999).

Features of PSC varies depending on their location and state. Recent systematic work of Zha *et al.* (2014) revealed that PSC are present in pancreatic islets as well. These cells are characterized by lower concentration of vit. A containing droplets and are rapidly activated in comparison to parenchymal PSC. After activation, islet-localized- PSCs produce lower amount of activation specific protein SMA-alfa compared to PSC in pancreatic parenchyma. After activation, islet PSCs exhibit lower proliferative and migrative potential. Recently, several works were published, where the authors propose islet PSCs as possible stem cells of beta cells of Langerhans´s islets (Zhou *et al.* 2019, Zha *et al.* 2014).

PSCs and vitamin A

The ability of PSCs to store retionoids seems to be important for pancreatic tissue homeostasis as retinoids are vital for differentiantion of pancreatic duct cells and regulating cells death in pancreatic tissue. (Tulachan *et al.* 2003)

The presence of vitamin A molecules – retinoids containing lipid droplets seems to be the main characteristic of quiescent PSC. The PSCs are the only vitamin-A storing cells in pancreatic tissue, but play just a minor role in retinoid storing system of the human organism, as quitescent hepatic stellate cells contain 50-80 % of total body vitamin A. (Blaner *et al.* 2009) Retionoids, especially ATRA (all trans-retinoic acid) are involved in regulation of gene trascription, where ATRA controls expression of hundreds of genes (Balmer *et al.* 2002). Mechanism of their accumulation in quitescent phase and loss during activation of PSCs remains unclear, but it seems that retinoids stored in lipid rich droplets are important for maintaining quiescent phase of PSCs e.g. by their possible interaction with peroxisome proliferator-activated receptor beta/delta (PPARβ/δ) (Berry *et al.* 2009).

Bleul *et al.* reported markedly reduced levels of all-*trans*-retinoic acid and all-*trans*-retinol in PDAC tissue obtained from human and mouse pancreata. This suggests, together with work of Colvin, the importance of retinoid signalling in PDAC pathophysiology (Bleul *et al.* 2015, Colvin *et al.* 2011).

The relationship of vitamin A and pancreas was recently reviewed in detail by Zhou *et al.* (2021).

Phenotypes of PSCs: Activated vs. quiescent PSCs

Quiescent PSCs

There exist basically two phenotypes of PSC based on the presence of various features (Table 1). Relatively little is known about quiescent PSCs (qPSCs). In healthy pancreas, qPSCs contain abundant vitamin A containing lipid droplets, characteristically express desmin, glial fibrillary acidic protein (GFAP) - which is specific for pancreatic stellate cells (Ding *et al.* 2008), nestin and vimentin. These quiescent PSC are “resting” cells. Their ability to proliferate, migrate or produce

Table 1. Main differences between quiescent and activated PSCs

Quiescent PSCs	Activated PSCs
Rich in vitamin A droplets	Loss of vitamin A containing droplets
Alpha SMA negativity	Alpha SMA positivity
Low ability to proliferate and migrate	High migration and proliferation activity
Balanced ECM turnover (low MMP, higher TIMPs)	High ECM production (high MMP, low TIMPs)

Abbreviations: PSCs – pancreatic stellate cells; SMA – smooth muscle actin; ECM – extracellular matrix; MMP – matrix metalloproteinases, TIMP – tissue inhibitor of metalloproteinases. Modified from: Wu Y et al. (2021) and Jin G *et al.* (2020).

extracellular matrix is rather limited compared to activated PSC.

qPSCs create a network adjacent to capillary and ductal structures of pancreas, but are present in pancreatic islets as well (Zha *et al.* 2014). In quiescent state PSCs produce limited amount of MMP and TIMPs to maintain homeostasis of the extracellular matrix (Phillips *et al.* 2003).

Activated PSCs

After activation the appearence of PSCs changes dramaticaly into myofibrobalst like phenotype. Activated PSCs express various proteins such desmin and α-SMA (which differentiates them from fibroblasts), collagen I and III, various metaloproteinasas and their inhibitors, fibronectin, ICAM – 1 (Masamune *et al.* 2002), cadherine 11 (Row *et al.* 2016) and lose vitamin A containting lipid droplets.

Activated spindle-shaped PSCs exhibit several functions which are involved in pancreatic tissue repair. This is done mainly by production of ECM, which replaces destroyed parenchymal cells. This process is under normal circumstances limited to damaged area. Under patological circumstances e.g. chronic pancreatitis or pancreatic cancer this process continues and results in pancreatic fibrosis with loss of endocrine and exocrine pancreatic function. Activated PSCs also produce a variety of cytokines, which further serve as an auto-activators of PSC.

There exists evidence of the role of activated PSCs in phagocytosis in inflammed areas of pancreas (Shimizu *et al.* 2005).

Molecular mechanism of PSCs activation

Activation of PCSs seems to be one of the key points of generating pathological microenvironment leading to progression of such deteriorating conditions as chronic pancreatitis and pancreatic cancer. This microenvironment, characterized by excessive production of fibrous extracellular matrix, is responsible for chemoresistance of PDAC, promotes tumor growth and metastasing. The activation can be provided by both autocrine and paracrine mechanisms. There exist several mechanisms of extracellular signalling involved in activation of PSCs, such as cytokines, non-coding RNAs, oxidative stress, hyperglycemia and ion channels signalling (Jin *et al.* 2020).

PSCs activation and cytokines

Most of the cytokines are produced by activated PSCs as well, which fact ephasises the crucial role of vicious circle of PSCs autoactivation while once stimulated. This process is a possible mechanism of fibrogenesis in certain pancreatic pathologies – mainly chronic pancreatitis.

Transforming growth factor beta 1 (TGF-β1) is a strong fibrosis inducing agent in pancreatic tissue. It activates MAPK pathway (Xu *et al.* 2018), which leads to change of PSCs phenotype by increased mRNA expression of extracellular signal-regulated kinases (ERK) and C-Jun amino terminal kinase (JNK) (Fitzner *et al.* 2004). It has been proved that PSCs produce TGF-β1, which suggests, that this "auto-activation" by TGF-β1 followed by increased production of ECM by PSCs is one of the possible mechanisms of excessive fibrosis in chronic pancreatitis. This production of TGF-β1 by PSC can be hampered by ATRA. ATRA prevent PCSs to mechanically release TGF-β1 *via* downregulation of organizing of inactive complex with latent TGF-β binding protein and thus liberating TGF-β1. (Sarper *et al.* 2016). TGF-β1 induced hydrogen peroxide-inducible clone-5 (Hic-5) deficiency inhibits activation of PSCs in CP model as well as iSMAD interferes with TGF-β signalling pathway, which emphasises the role of TGF-β/SMAD pathway in PSCs activation

(Lin *et al.* 2021).

Recent findings emphasise the role of interplay between various cytokines – mainly PDGF, TGF-β1 and Yes-associated protein 1 (YAP). YAP modulates cell proliferation and development as well as apoptosis in various tissues. YAP is also involved in cancer cell growth. Besides other pathways, YAP interacts with SMAD pathway, and plays a role in sustaining of activated state of PSCs, partialy by interacting with PDGF. (Hu *et al.* 2019)

The main source of PDGF in pancreatic tissue are macrophages and cancer cells. While activated, PCSs are another important source of PDGF. PDGF was shown to be a potent mitogen and co-cultivation of PSC and PDGF led to increased production of ECM by those cells. (Luttenberger *et al.* 2000) PDGF is also overexpressed in chronic pancreatitis (Ebert *et al.* 1998).

Another source of PDGF and TGF-β1 in pancreas could be platelets. In pancreatitis event, as demostrated by Gress *et al.* (1994), platelets accumulating in inflammed areas of pancreatic tissue are source of PDGF, which further stimulates fibrogenesis by activatating PSC (Luttenberger *et al.* 2000).

PSCs activation and hypoxia

Hypoxia is another factor leading to PSCs activation (Estaras *et al.* 2020). Increased fibrogenesis by PSCs is often accompanied by hypoxemic environment, which results in increased proliferation of PSC. Hypoxia-inducible factor-1 (which level rises in hypoxic condition e.g. in cancer stroma) influences the fibrogenesis by PSCs *via* upregulating hepatoma-derived growth factor (HDGF) (Ide *et al.* 2006).

Besides impairment of pancreatic exocrine function, hypoxia mediated activation of PCSs leads to death of beta cells of pancreatic islets (Kim *et al.* 2020).

Inflammation of pancreatic tissue accompanied by oedema of adjacent structures as well as obstruction of pancreatic duct are conditions which increase pressure in pancreatic parenchyma. A study of Asaumi *et al.* (2007) showed that externally applied pressure increase reactive oxygen species (ROS) synthesis as well as synthesis of ECM by PSCs. This finding supports routine praxis of reducing of intraductal pressure in pancreatic parenchyma by drainage, stone removal, or surgery.

PSCs activation and miRNA

ncRNA accounts for about 70 % of human genetic information and as such is involved in many biological processes. (Storz G 2002). ncRNA is usually divided into following groups: small interfering RNA, microRNA and long ncRNA.

MicroRNAs (miRNA) are relatively small RNA molecules which have important role in regulating many cell functions - like differentiation, proliferation, or carcinogenesis.

There have been described various changes of miRNA profile in conditions such as PDAC and chronic pancreatitis (Chhatriya *et al.* 2019, Xin *et al.* 2017). miRNA can have both inhibitory and promoting function on PSCs.

PSCs´s miRNA has different profile before and after activation of PSCs This study revealed that some of more expressed miRNAs interact with signalling pathways, cellular development and cell activation, e.g. upregulated miR-31 (Masamune *et al.* 2014).

Histone deacetylase inhibitors reduce acetylation in histones, which is followed by increased expression of miR-15 and miR-16 which further leads to repression of TGF-β1/SMAD pathway. This results in reduction of fibrogenesis by PSCs and increased apoptosis of PSCs in chronic pancreatitis (Ji *et al.* 2020).

Other structures involved in activation of PSCs are exosomes – the carriers of miRNA. Exosomal miR-130a-3p participates on PSCs activation by affecting the cellular peroxisome proliferator-activated receptor gamma PPAR-γ (Wang *et al.* 2021).

MiRNA is also important in PCSs and tumor cells crosstalk: Recent study revealed that hypoxia-induced activated PSCs are source of exosomes which *via* phosphatase and tensin homolog (PTEN) activate protein kinase B pathway in PDAC cells which increase proliferation and invasion of these cells (Cao *et al.* 2021). The role of PSCs derived exosomes in PDAC cells proliferation was observed in several studies (Masamune *et al.* 2017).

Long ncRNA has length about 200 to 100,000 bp. These molecules involved in regulating of gene expressions were studied in connection with pancreatic cancer (Zhou *et al.* 2020), but little is known about their role in pancreatic fibrosis. Wang et al shows that certain lncRNAs e.g., STX12 lncRNA involves through miR-130b and miR-148a target mRNAs (SMAD5 and IL6ST) and have promoting effect of PSCs activation (Wang *et al.* 2016). On the contrary expression of miRNA 200a inhibits PSCs activation (Xu *et al.* 2017).

MiRNA let-7d through inhibiting expression of

thrombospondin 1 reduces activation of PSCs and reduced miRNA let-7d is a potential serum biomarker of PDAC (Suzuki *et al.* 2017).

PSCs activation and oxidative stress

Oxidative stress leading to production of ROS (e.g., nitric oxide) is associated with pancreatitis. There exists a well described link between calcium mediated activation of pancreatic enzymes and oxidative stress which is one of the mechanisms of acute pancreatitis onset (Petersen *et al.* 2006).

There has been proved (in rat PSCs) activity of nitric oxide synthase-2 (NOS2) following exposition of PSCs to pathogen associated molecular pattern (PAMP) (Jakubowska *et al.* 2016).

Coenzyme Q10 as potent antioxidant ameliorates pancreatic fibrosis and activation of PSCs *via* PI3K/AKT/mTOR signalling pathway (Xue *et al.* 2019).

Activation of PSCs and alcohol and smoking

Alcohol-induced chronic pancreatitis is a burden for healthcare system in last decades and as a chronic inflammatory condition bears an increased risk of PDAC development. Alcohol activates PSCs by several mechanisms mainly due to its metabolism to acetaldehyde (PSCs exhibit alcoholdehydrogenase) and generating oxidative stress by inducing inflammatory changes in pancreas. (Apte *et al.* 2000) Endotoxin lipopolysaccharide has been recognised as a trigger of alcoholic chronic pancreatitis. TGF beta1 -SMAD 2,3 pathway is the main axis of activation of PSCs in alcoholic chronic pancreatitis (Sun *et al.* 2018). There were observed increased levels of IL-6 in alcohol-induced-chronic pancreatitis (Pedersen *et al.* 2004). IL-6 promotes TGF -beta1 secretion by PSCs and *via* ERK pathway directly activates PSCs (Aoki *et al.* 2006).

MAPK kinase pathway is activated during exposure of PSCs to ethanol and acetaldehyde (McCarroll *et al.* 2003).

The relationship between PSC and alcohol intake seems to be even more complex, since alcohol increases gut permeability which can lead to release of endotoxins and lipopolysaccharides which activates PCSs probably *via* Toll-like receptor 4 (TLR-4) and CD-14 (Vomlaufen *et al.* 2007).

There seems to be links between environmental factors as alcohol and high caloric intake resulting in obesity which have impact on PSCs metabolism and thus increasing risk of pancreatic cancer. Obesity associated type 2 diabetes mellitus is associated with increased levels of lipopolysaccharides and TNF alpha (adipose tissue derived) which have effect on PSCs activation (Pandol *et al.* 2012).

Calcium signalling is a universal mechanism of regulating many biological processes. In pancreatic tissue, calcium signalling pathways contribute to regulation of secretion of pancreatic enzymes. Besides acinar cells, Ca^{2+} signalling is an important signalling pathway in PSCs.

Unlike pancreatic acinar cells, PSCs do not respond to acetylcholine or cholecystokinin stimuli by Ca^{2+} increase in cystosole. On the contrary bradykinin elicits Ca signals from PSCs (Gryschenko *et al.* 2016).

As a consequence of alcohol-induced pancreatic injury inflammatory mediators e.g., kallikrein, are released, which increases levels of bradykinin. Bradykinin is involved in Ca^{2+} signalling playing an important role in activation of PSCs as PSCs express bradykinin receptor type 2 (Apte *et al.* 2003).

Ion channels in general seem to be crucial in PCSs metabolism regulation. One study revealed that inhibition of KCa3.1 is followed by reduced migration and chemotaxis of PSCs (Storck *et al.* 2017).

Smoking is another important environmental factor contributing to PSC activation *via* nicotinic acetylcholine receptors (nAChRs), which are expressed by PSCs (Lee *et al.* 2015) and by upregulation of IL-22 (Li *et al.* 2020).

PSCs in pancreatic pathologies

PSC and DM2

It is widely recognized, that DM2 is a risk factor of pancreatic cancer (De Souza *et al.* 2016). PSCs respond to glucose levels as they express glucose transporters GLUT 1-3 (Kiss *et al.* 2015).

DM 2 is a condition accompanied by chronic hyperglycemia, which leads to activation and proliferation of PSCs (Hong *et al.* 2007).

The relationship between PSCs and type 2 diabetes mellitus seems to be bilateral. Firstly, in diabetes, hyperglycemia can induce PSCs activation *via* renin-angiotensin system (RAS) system, promoting fibrosis in pancreatic islets (Ko *et al.* 2006). Hyperglycemia stimulates *via* RAS TGF beta synthesis which is one of key mediators of PSCs activation. Moreover, in pancreatic islets unlike in rest of pancreatic tissue, PCSs are in case of DM 2 exposed to high levels

of glucose and insulin. Combination of these two factors, initializing through ERK1/2 phosphorylation activation and proliferation of PSCs can cause islet specific fibrosis, which was observed on mouse models. Especially involvement of RAS system can be a promising therapeutic target in DM 2 therapy (Yang *et al.* 2020).

Chronic hyperglycemia leads to differentiation into myofibroblast-like phenotype of PSCs *via* p38 pathway. In chronic hyperglycemic condition PSCs produce more mRNA CXCL12, which can have influence on PDAC cells proliferation (Kiss *et al.* 2015). GLP-1 - an enzyme involved in glucose homeostasis possibly involves activation of PSC (Yand Y *et al.* 2013).

Hypoxia can occur within pancreatic islets – probably due to high oxygen consumption by insulin producing beta cells. (Sato *et al.* 2011). Hypoxia in pancreatic islets can activate PSCs resulting in islet fibrosis and further damage of beta cells (Kim *et al.* 2008).

Interestingly, vitamin A deficiency leads to activation of PSCs and islet fibrosis which is followed by dysfunction of pancreatic islet. This can be reversed by vitamin A supplementation (Zhou *et al.* 2020). The relationship between PSCs and DM2 is summarized in Fig. 1.

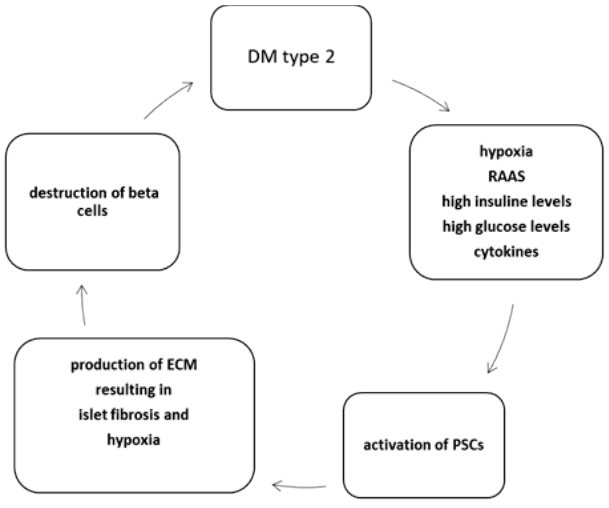

Fig. 1. Relationship between DM2 and PSCs. DM2 is a condition accompanied by environment rich in insulin and glucose within the pancreatic islets. High oxygen consumption by insulin producing beta cells results in hypoxia and oxidative stress. This, in combination with activation of angiotensin II pathway, leads to activation of PSCs. PSCs produce ECM and cytokines which results both directly and indirectly due to islet fibrosis in beta cells destruction. DM type 2 – Type 2 diabetes mellitus, PSCs – pancreatic stellate cells; RAAS – renin- angiotensin- aldosterone system; ECM – extracellular matrix. Modified from Kim *et al.* (2008).

PSC and PDAC

Pancreatic stellate cells comprise about 5 % of normal pancreas but they form about 50 % of desmoplastic stroma of PDAC, which comprise about 90 % of tumor mass (Farran *et al.* 2019). PDAC is characteristic by massive desmoplastic reaction, where multiple cells, including stellate cells, are involved. Research in last few decades shows emerging role of PSCs in modulation of PDAC microenvironment. Understanding PDAC cells and PSCs crosstalk is important for searching for therapeutical target of pancreatic cancer.

Interactions between tumor cells and PSCs were studied both in vivo and in vitro. Activated PSCs involve many processes within tumor stroma e.g., angiogenesis, ECM production, tumor growth, invasion, and proliferation as well as drug resistance. PSCs potentiate migration, proliferation, and differentiation of PDAC cells, and *vice versa* PDAC cells promote activation of PSC and their migration and proliferation as well as production of ECM.

PDAC cells influence production of ECM, activation and proliferation of PSCs. Both PDAC cells and PSCs produce cocktail of various cytokines, which stimulate activity and proliferation of both cell lines. Activation of PSCs is stimulated by cytokines like IL-1, IL-6, colony-stimulating factor 1 (CSF1), platelet-derived growth factor BB (PDGF-BB), TGF-β1, fibroblast-growth factor (FGF) (Carter *et al.* 2021). FGF, located in several tissues, is part of signalling cascade regulating cell proliferation and differentiation (Kang *et al.* 2019). FGF-1 and -2 are present in PDAC in higher amount than in healthy pancreas and their levels are possibly linked to oxidative stress accompanying PDAC microenvironment. On the contrary, some studies show positive effect of FGF 1 and 2 to cell adhesion and differentiation in PDAC (El-Hariry *et al.* 2001).

FGF released by PSCs stimulates production of TGF-β1 by PDAC cells, which reversely stimulates further proliferation of PSCs. TGF-β1, secreted by PSCs as well, downregulates levels of L1 cell adhesion molecule L1CAM which promotes aggressive stem-like phenotype of PDAC cells (Cave *et al.* 2020).

Surprisingly, it seems, that the role of TGF-β1 is rather conflicting as in early stages of PDAC TGF-beta plays inhibitory role, but in advanced stages of PDAC it is involved in epithelial- mesenchymal transformation of PDAC cells (Morrison *et al.* 2013).

Besides TGF beta1/SMAD axis, other pathways

are linked to regulation of PDAC cells invasion e.g., stromal cell-derived factor-1/CXCR4 axis or c-Met/PI3K/Akt signalling pathway (Xu *et al.* 2020, Gao *et al.* 2010). Galectin-1 / NF-kB axis promotes PDAC metastasing (Erkan *et al.* 2009). Interplay between PSCs and PDAC cells is depicted in Fig. 2.

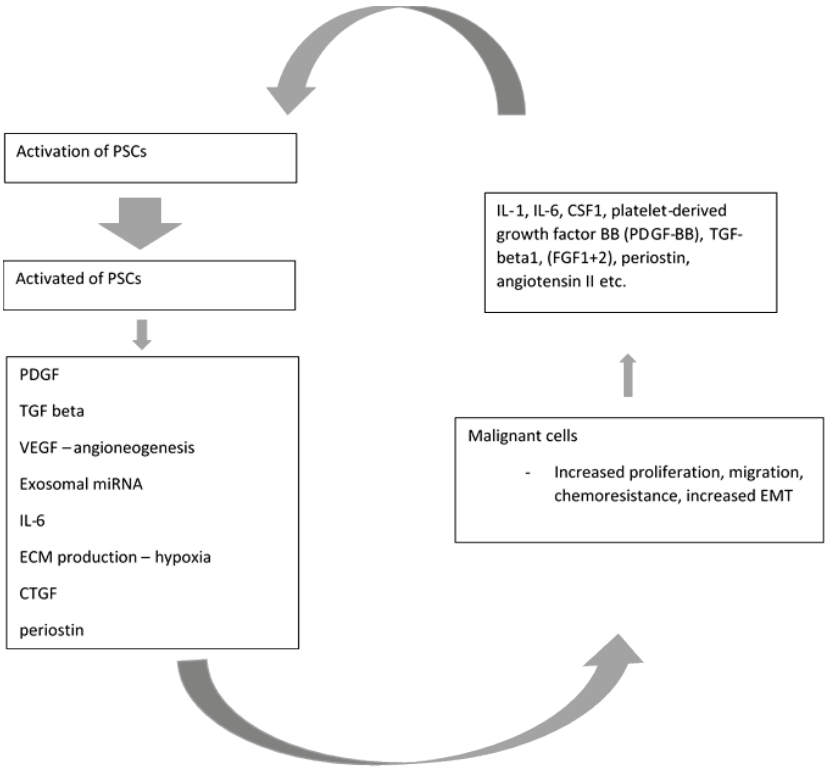

Fig. 2. Paracrine signalling *via* cytokines produced by malignant cells leads to PCSs activation. While activated, PSCs secrete factors, which increase ability of malignant cells to proliferate and migrate, increase metastatic potential and resistance to chemotherapeutics. Both malignant cells and activated PSCs produce factors which further activate PSCs. PDGF : platelet derived growth factor, VEGF – vascular endotelial growth factor, TGF – tumor growth factor; miRNA – microRNA; ECM - extracellular matrix; CTGF – connective tissue growth factor; EMT – epitelial-mesenchymal transformation; CSF1 – colony-stimulating factor 1; FGF – fibroblast growth factor. Modified from: Carter *et al.* (2021)

MiRNA pathways are also involved in PDAC PSCs crosstalk. Exosomal miRNA is utilized by PDAC cells and contributes to migration and proliferation of PDAC cells. Exosomal PSCs derived miRNA 21 is internalized by PDAC cells and high levels of this miRNA result in increased PDAC cells migration and EMT. (Ma *et al.* 2020) MiR-4459/KIAA0513 axis involving pancreatic cancer growth and metastasing was described by Shao *et al.* (2020) Exosomes are also involved in chemoresistance of PDAC treated by gemcitabine (Richards *et al.* 2017).

In vitro studies shows that co-cultivation of PSCs – and PDAC leads to transition of PDAC cells into fibroblast–like phenotype, reduction of e-cadherin and membrane associated beta catenin expression as well as increase of migration of co-cultured PDAC in comparison with monocultured PDAC cells (Kikuta *et al.* 2010). PDAC cells co-cultivated with activated PSCs seem to have decreased apoptotic response to gemcitabine treatment (Liu *et al.* 2018).

Epitelial-mesenchymal transformation (EMT), a process of cellular changes resulting in transition of polarised epithelial cells to mesenchymal-like cellular phenotype characterized by increased proliferative and migration potential as well as invasiveness and increased resistance to apoptosis (Kalluri *et al.* 2010) is an important process in development of PDAC and is also influenced by activated PSCs.

Enhanced changes of PDAC cells typical for EMT transition were described in an in-vitro study where they were co-cultivated with PSCs. Interestingly, these changes were markedly more evident in the presence of high glucose environment (Karnevi *et al.* 2016) which emphasises the role of type-two diabetes as risk factor of PDAC development. Wu *et al.* (2017) reported promoting EMT of PDAC cells by IL-6 secreted by PSCs and involving Stat3/Nrf2 pathway. Production of IL-6 by PSCs is also induced by interaction with distinct immune cells. Gamma-delta T-cells promote secretion of IL-6 by PSCs. IL-6 levels correlate with tumor size and moreover has a role in PanIN -> PDAC transition (Seifert *et al.* 2020). Another cytokine- IL-13 – produced by mastocytes increases proliferation of PSCs (Ma *et al.* 2013).

ECM produced by PSCs is essential for PDAC cells survival and metabolism. For example, collagen produced by activated PSCs as the main component of ECM, serves as nutrient reservoir for cancer cells (Olivares *et al.* 2017) which is important even more as collagen seems to have suppressive effect on neovascularization in PDAC stroma (Berchtold *et al.* 2014). PSCs play a role in PDAC metabolism also by regulating branched- chain amino acid metabolism (Jiang *et al.* 2021).

Hypoxia usually accompanying hypovascular PDAC stroma activates PSCs, which produce metalloproteinases. Among these, MMP-10 and MMP-3 seem to promote invasive growth of PDAC (Liu *et al.* 2020). Under hypoxic condition PSCs secrete connective tissue growth factor (CTGF) which enhances PDAC cells invasion. (Eguchi *et al.* 2013) Excessive production of ECM further promotes hypoxic microenvironment which is followed by further activation of PSCs. Hypoxic condition leads to expression PSCs derived exosomal miRNA (miR-4465 and miR-616-3p), which promotes PDAC cells proliferation by influencing the PTEN/AKT pathway (Cao *et al.* 2021).

Moreover, some product released by activated PSCs – e.g. periostin-increase resistance of PDAC cells to hypoxia (Liu *et al.* 2015). The overall effect of periostin on PDAC invasiveness is probably multiple and perhaps concentration-dependent (Kanno *et al.* 2008).

Angiogenesis is essential for tumor nutrition and growth. Cancer cells use several factors, like vascular endothelial growth factor (VEGF), to induce angiogenesis in tumor stroma to obtain adequate supply of oxygen and nutrients (Yancopoulos *et al.* 2000). It was well described that PSC produce many proangiogenic molecules such as basic fibroblast growth factor, periostin and PDGF. As potential therapeutical target miRNA-199a-3p and miRNA-214-3p were described as these miRNAs regulate formation of capillary tubes induced by activated PSCs. (Kuninty *et al.* 2016) In vitro study of Patel *et al.* showed that PSCs enhance *via* HGF/c-MET pathway formation of neovessels by human microvascular endothelial cells (Patel *et al.* 2014).

It is probably the excessive production of ECM, which – despite strong proangiogenic potential of some products of PSCs – leads to compression of neovessels and hypoxia. It is also worth to mention the reactive defensive regression of neovessels as part of host response on tumor growth (Yancopoulos *et al.* 2000).

Interesting crosstalk between PSCs and PDAC was described *in vitro* by Erkan *et al.* (2009). Although PSCs are under hypoxic condition producents of endothelial growth stimulating VEGF, they stimulate PDAC cells to produce endostatin, which on the contrary supresses angiogenesis. PSCs are also stimulated by PDAC cells to produce metalloproteinases, which cleave endostatin (produced by PDAC) from its precursor.

Perineural invasion, another vicious feature of PDAC is also influenced by PSCs. Nerve growth factor (NGF) was proven to be involved in PDAC growth, perineural invasion and proliferation of PDAC cells. NGF and its receptor TrkA,B,C were found in PDAC tissues (Miknyoczki *et al.* 1999).

PI3K/AKT pathway was activated by NGF/TrkA which promoted invasion and proliferation in PDAC cells in co-culture with PSCs (Jiang *et al.* 2020).

Nan *et al.* showed that HGF/c-Met is essential for perineural invasion of PDAC – it increased production of NGF and MMP – 9 (cellular marker of EMT) and promoted invasion of PDAC in dorsal root ganglia in in-vitro study (Nan *et al.* 2019).

Interesting is the role of PSCs and PDAC cellular interaction in modulating pancreatic pain which usually accompanies pancreatic cancer. Sonic hedgehog (sHH) secreted by PDAC cells triggers sHH pathway in PSCs. PSCs in reaction secrete several neurotropic factors which are involved in generating pain in pancreatic tissue (Han *et al.* 2016).

PSCs are able to co-migrate with PDAC cells to distant organs where they can create microenvironment suitable for further growth and spreading of metastatic process. (Suetsugu *et al.* 2015) PSCs exhibit the ability to in/extravasate cross the endothelial barrier and stimulate angiogenesis in mouse models (Xu *et al.* 2010).

PSCs seem to be partially responsible for chemoresistance of PDAC. There exist several mechanisms of protecting PDAC cells from effect of chemotherapeutic agents. Massive production of ECM by activated stellate cells generates hypoxic microenvironment of PDAC further facilitating PDAC growth and resulting in worse outcome of chemotherapy. Besides that, PSCs are able to produce molecules which directly promote chemoresistance of PDAC cells e.g., deoxycytidine – deoxynucleoside produced by PSCs reduce effect of nucleoside analogue gemcitabine (Dalin *et al.* 2019). PSCs also seems to be unaffected by certain regimens of PDAC targeted therapy (Carbera *et al.* 2014). PSCs / PDAC crosstalk is briefly summarized in Fig. 3.

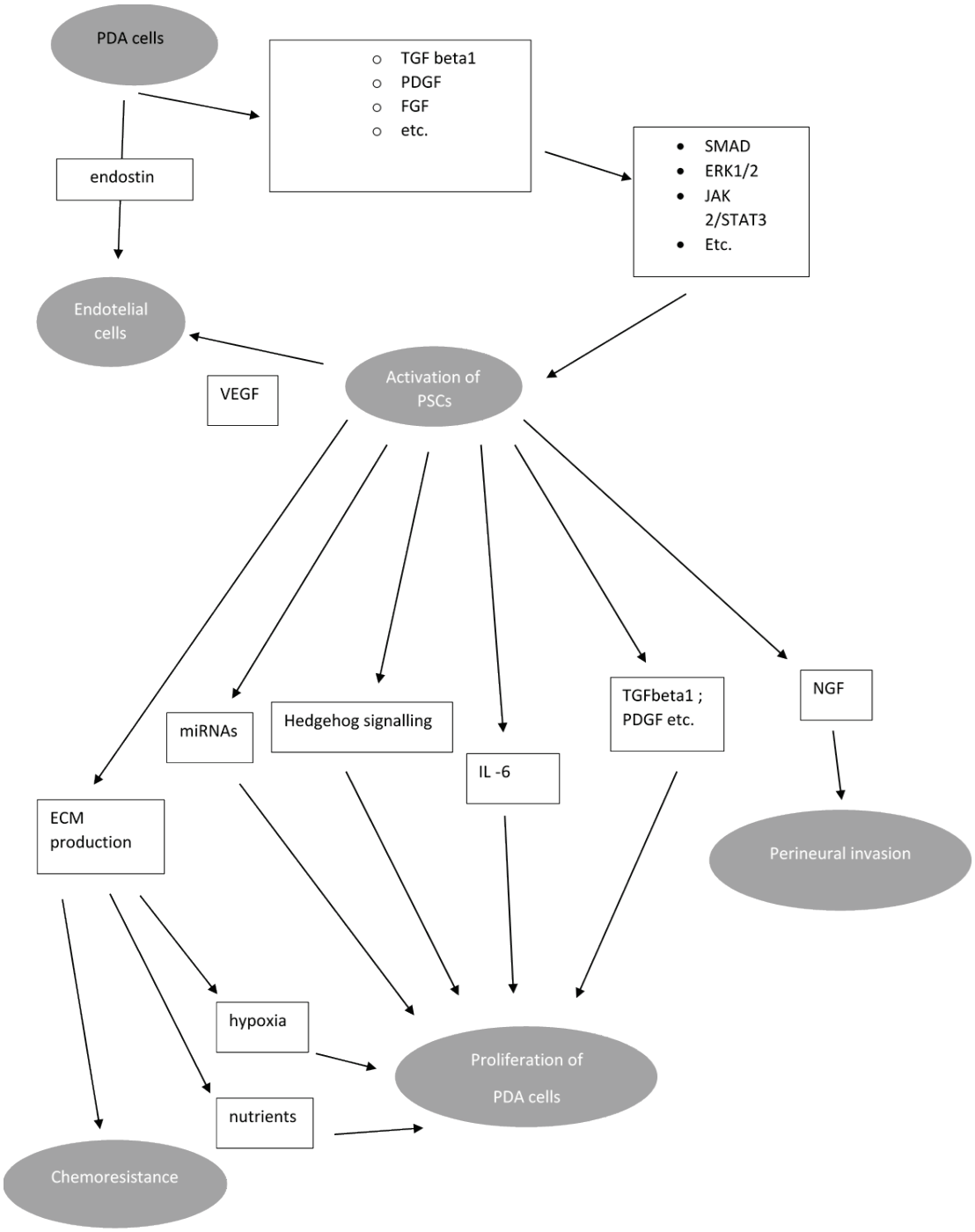

Fig. 3. Crosstalk between malignant cells and PSCs. Factors produced by PSCs increase *via* several signalling pathways proliferation of malignant cells, perineural invasion, metastasing and chemoresistance. Both PSCs and malignant cells regulates angioneogenesis. Proliferation of malignant cells and hypoxia due to low blood supply increases activation of PSCs. Abbreviations: PDGF : platelet derived growth factor, VEGF – vascular endotelial growth factor, TGF – tumour growth factor; miRNA – microRNA; ECM – extracellular matrix; FGF – fibroblast growth factor; NGF – nerve growth factor; ERK extracellular signal-regulated kinases; JAK- Janus kinase; PDA – pancreatic ductal adenocarcinoma. Modified from: Bynigeri *et al.* (2017)

PSCs and chronic pancreatitis

Chronic pancreatitis (CP) is a chronic disease characterised by replacement of functional parenchyma of pancreas by fibrous tissue which in advanced stages results in exocrine and endocrine pancreatic insufficiency. CP is a condition leading to increased risk of pancreatic cancer (Kirkegård *et al.* 2017). Excessive and persistent activation of PSCs as a result of repeated injury and/or autocrine signalization is the key point of remodelling pancreatic tissue in CP (Jin *et al.* 2020).

Activation of PSCs is a process accompanying inflammatory reaction in pancreatic tissue and is

responsible for production of fibrotic stroma typical for PC. There exist several mechanism of PSCs activation in CP. Alcohol – a common cause of CP in western countries- was proved to activate MAPK pathway in PSCs. (McCarroll *et al.* 2003) Upregulated connective tissue growth factor (CCN2) - exosomal miRNA21 levels forming positive feedback loop responsible for transition of PSCs into myofibroblast-like phenotype was described in mouse models of alcoholic chronic pancreatitis (Charrier *et al.* 2014).

Smoking was proved as a potential activator of PSCs as PSCs exprime nACH receptors and respond to nicotine-derived nitrosamine ketone – content of cigarette smoke. Cigarette smoke also stimulate T-lymphocytes *via* aryl-hydrocarbon receptor, which leads to increased levels of IL-22. This cytokine activates PSCs *via* IL22RA1 (Lee *et al.* 2015, Xue *et al.* 2016). The damaged pancreatic acinar cells release various cytokines enhancing activation of PSCs, oxidative stress activates PSCs as well.

In CP, M2 macrophages (unlike in the acute pancreatitis where M1 macrophages dominates (Hu *et al.* 2020)), play a pivotal role in the pathogenesis of inflammation. The crosstalk between PSCs and macrophages seems to be a crucial mechanism of fibrogenesis in CP. Liu et al revealed in his work – where he studied interaction between co-cultivated PSCs and macrophages - that M2 macrophages produce various cytokines, which have the ability to enhance activation of PSCs e.g., TGF beta 1 and PDGFbeta (Liu *et al.* 2018). TGF beta 1 also increased procollagen I gene transcription on PSCs and TGF beta signalling in activated PSCs induced a mechanism which inhibits protease-inhibitory function of RECK - membrane-anchored MMP inhibitor (Lee *et al.* 2008).

PSCs are source of IL-4 which in autocrine ways further activates PSCs and macrophages. Besides that, IL-4 works as a potent growth factor for PDAC cells (Prokopchuk *et al.* 2005). As mentioned previously, activated PSCs produce metalloproteinases and their inhibitors e.g. TIMP-1, TIMP-2, MMP-2, MT1-MMP, which have direct impact on collagen turnover in ECM (Shek *et al.* 2002).

NF-κB, depending on the site of production, has impact on the progression of CP associated fibrosis. NF-κB pathway seems to be activated *via* TGF beta 1 in PSCs. NF-κB pathway activation in PSCs leads to an imbalance between MMP and TIMPs (in favor of TIMPs) resulting in fibrogenesis. This pathway also increase secretion of MCP -1 with attracts macrophages to the damaged region. This possibly contributes to the vicious circle of persistent fibrogenesis in CP (Prokopchuk *et al.* 2005).

Conclusion and future directions

The progress of knowledge about tight relationship between pathologies of pancreas and PSCs and lack of efficient therapy of such debilitating diseases like PDAC and CP necessarily lead to increased interest into PSCs as potent therapeutic target. Commonly used therapy with nab-paclitaxel or FOLFIRINOX does not offer satisfying effectivity. The crosstalk between PDAC and PSCs reveals promising therapeutical targets. In recent years some promising therapeutical strategies were tested, mainly as combination with standard chemotherapy. Targeting pathways involved in PDAC/PSCs crosstalk offer promising strategy of influencing both cancer cells and the stromal component of PDAC mass. The therapy can be focused on reprogramming PSCs to maintain their quiescence, targeting PDAC crosstalk or directly influence production of ECM.

Several studies were focused on influencing different PSCs-associated signalling pathways.

PSCs associated hepatocyte growth factor pathway HGF/c-MET seems to be a promising target of therapy as well as targeting FGF signalling by selective tyrosine-kinase inhibitor (Pothula *et al.* 2017).

Pancreatic fibrosis, a typical feature of chronic pancreatitis, can be ameliorated by coenzyme Q10, a potent antioxidant, *via* inhibition PI3K/AKT/mTOR signalling pathway (Xue *et al.* 2019, Xue *et al.* 2017).

IL-6 produced in PDAC stroma mainly by PSCs is essential for progression of PDAC (Zhang *et al.* 2013). Blockade of this cytokine in combination with blockade of programmed death-1-ligand 1 (PD-L1) leads to decreased tumor progression in murine model of pancreatic cancer (Mace *et al.* 2018). Similar effect was achieved by the use of HSP-90 inhibitor (Zhang *et al.* 2021).

In *in-vitro* model, metformin reduces viability and activation of PSCs *via* angiotensin-II receptor 1 (AT1)/TGF-beta /STAT3 signalling pathway. Furthermore, metformin seems to reduce MMP-9 levels which has beneficial effect on ECM (Incio *et al.* 2015). Reducing of angiotensin signalling by losartan also reduces the activation of PSCs and combination of losartan with chemotherapy increased survival of mouse

models of PDAC in comparison with chemotherapy alone (Cauhan *et al.* 2013). Angiotensin II induced by hyperglycemia increases TGF beta levels, so using renin-angiotensin blockers seems to have beneficial effect for patients with DM 2 (Yang *et al.* 2020).

ATRA is a promising molecule in PDAC involvement as it targets PSCs. It restores mechanical quiescence of PSC *via* retinoic acid receptor beta (RAR-β)/ actomyosin (MLC-2) pathway. Downregulation of MLC-2 contractility reduces mechanosensing-dependent ECM remodelling which has an effect on cancer cells invasion (Chronopoulos *et al.* 2016).

It was proved in *in-vitro* cultures of PSCs by Jaster *et al.* (2003) that cultures treated by ATRA showed lower proliferation rate and produced less collagen. McCarroll *et al.* (2005) extended these findings by revealing that cultures of ATRA-treated rat PSCs decreased expression of alpha smooth muscle actin (alpha-SMA) and fibronectin (typical for activated stellate cells) and decreased activation of mitogen activated protein kinase (MAPK) signalling pathways.

Froeling *et al.* (2011) proved that retinoic acids reduced motility and activation of PSCs and led to increased apoptosis of adjacent cancer cells.

Delivery of ATRA and heat shock protein 47 targeting siRNA by gold-coated nanoparticles which can cross the barrier of ECM induced PSCs quiescence (Han *et al.* 2018). Combination of gemcitabine and ATRA in in-vitro model shows better effect than gemcitabine alone (Carapuça *et al.* 2016). Unlike most of other agents, which were tested mainly *in-vitro*, ATRA as a stromal targeting drug in combination with gemcitabine-nab-paclitaxel was recently tested in phase Ib of clinical trial performed by Kocher *et al.* (2020). Antidiabetics can also have effect on PSCs, while suppression of activation of PSCs can be achieved by combination of N-acetyl cysteine and pioglitazone (Feng *et al.* 2021).

Because of high expression of vit D receptors (VDR) in PSCs, targeting those receptors by VDR ligand calcipotriol leads to reduced inflammation and fibrosis in murine pancreatitis model (Sherman *et al.* 2014).

These findings show the importance of ECM for proper delivery of chemotherapeutics to PDAC cells. Complex stroma-PDAC interaction highlights the need of sophisticated in vitro models e.g., tumor organoids and 3D models (Norberg *et al.* 2020). Another goal would be novel strategies of drug delivery to target cells (Huang *et al.* 2019). In summary, combination therapy targeting both stromal and cancer cells would be optimal strategy to achieve better outcome.

Nevertheless, despite advances in understanding the complex relationship between PSCs and the rest of pancreatic tissue, many studies mentioned were performed on animal models or in-vitro cultures. Thus, further research aimed on in-vivo studies in human pancreas is urgently needed.

Conflict of Interest

There is no conflict of interest.

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