Review

Unraveling the Connection Between Ion Channels and Pancreatic Stellate Cell Activation

Julie Auwercx[a]   Mathilde Fourgeaud[a]   Alexis Lalot[a]   Mathieu Gautier[a]

[a]UR-UPJV 4667, UFR Sciences, Université de Picardie Jules Verne, Amiens, France

Key Words

Ion channels • Pancreatic cancer cells • Desmoplasia • Pancreatitis • Pancreatic adenocarcinoma

Abstract

Quiescent pancreatic stellate cells (PSCs) represent only a very low proportion of the pancreatic tissue, but their activation leads to stroma remodeling and fibrosis associated with pathologies such as chronic pancreatitis and pancreatic ductal adenocarcinoma (PDAC). PSC activation can be induced by various stresses, including acidosis, growth factors (PDGF, TGFβ), hypoxia, high pressure, or intercellular communication with pancreatic cancer cells. Activated PSC targeting represents a promising therapeutic strategy, but little is known regarding the molecular mechanisms underlying the activation of PSCs. Identification of new biomarkers of PSC activation associated with desmoplasia in chronic pancreatitis and PDAC could lead to new therapeutic targets for exocrine pancreatic disease treatments. Ion channels and transporters are transmembrane proteins involved in numerous physiological and pathological processes, including PDAC. They are well known to act as biosensors of the tissue microenvironment, and they can be easily accessible for drugs. However, their role in PSC activation is not fully understood. In this review, we briefly discuss the role of activated PSCs in pancreas inflammation and pathological fibrosis (associated with chronic pancreatitis and PDAC), and we describe the role of specific ion channels and transporters (Ca^{2+}, K^+, Na^+ and Cl^-) in these processes in the light of recent literature.

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Introduction

The pancreas is a digestive gland with two distinct physiological functions. The endocrine portion of the pancreas plays a pivotal role in maintaining optimal blood glucose levels through the production of pancreatic hormones, including insulin and glucagon, which are released into the bloodstream. The exocrine portion of the pancreas is responsible for the production and secretion of digestive enzymes and bicarbonate ions, which are transported through the pancreatic ducts to the duodenum, where they facilitate the completion of the

Prof. Mathieu GAUTIER

UFR Sciences, Université de Picardie Jules Verne,
33, rue Saint-Leu, Amiens, 80039 cedex, France
E-Mail: mathieu.gautier@u-picardie.fr

digestive process. The exocrine part of the pancreatic tissue consists of acinar and ductal epithelial cells supported by a stroma containing blood vessels, cells and extracellular matrix (ECM). One of the distinctive characteristics of the pancreas, which it shares with the liver, is the presence of stellate cells within its stroma. Pancreatic stellate cells (PSCs) represent 4-7% of the healthy organ and are mainly involved in the regulation of tissue homeostasis by maintaining ECM turnover, but they also initiate pathological fibrosis when activated [1-4].

The pancreas is exposed to several stresses leading to tissue injury and acini degradation. Despite these injuries, pancreatic tissue can regenerate due to the plasticity of both epithelial and stellate cells. Acinar cells can adapt to their environment and response to stresses by transforming into duct or duct-like cells, a process called acinar-to-ductal metaplasia (ADM) [5, 6]. Metaplastic ductal-like cells have a proliferative phenotype which allows acinar repair and pancreatic tissue regeneration, avoiding self-digestion. ADM is under the control of RAS signaling, and it is also suggested as the first step of pancreatic carcinogenesis [7, 8]. Alongside ADM occurring in epithelial tissue, PSCs respond to injuries by activating. PSC activation leads to excess production of ECM inducing fibrosis. Both ADM and PSC activation are reversible, allowing pancreatic repair. However, chronic exposure to environmental stress can lead to pathological pancreatic remodeling and ultimately to neoplasia when the accumulation of mutations renders the remodeling irreversible [8]. The most common exocrine pancreatic diseases are pancreatitis and pancreatic ductal adenocarcinoma (PDAC, representing almost 90% of pancreatic cancers [8]). Chronic pancreatitis is defined as a pathologic fibro-inflammatory syndrome of the pancreas leading to progressive destruction of functional tissues [9]. The incidence of pancreatitis is generally low (4 to 14 cases for 100, 000 per year worldwide) but it is largely underestimated due to a lack of epidemiological studies [10]. Thus, recent studies suggest an increase in the incidence of chronic pancreatitis over the last 10 years [10]. Moreover, chronic pancreatitis increases risk of PDAC [11]. PDAC is the third-leading cause of mortality by cancer in men and women combined in the U.S., the seventh worldwide [8, 12], and it is expected to become the second one by 2040 [8, 13]. PDAC has a dramatically low 5-year overall survival rate of almost 10% [8, 14]. This poor outcome is explained by the fact that most patients are asymptomatic at early stages and present non-specific symptoms at advanced stages [8, 14, 15]. Consequently, PDAC is often diagnosed too late when the tumor is spread and unresectable. Moreover, PDAC is characterized by the formation of a fibrotic stroma with poor vascularization, which impedes the delivery of therapeutic molecules [8, 16]. This desmoplastic reaction is the primary cause of chemoresistance and therapeutic failure because the desmoplastic stroma establishes a barrier that prevents access to the drugs. Moreover, the desmoplastic stroma contains transformed cells (activated PSCs, cancer associated fibroblasts (CAFs), ...) which communicate with pancreatic cancer cells by releasing tumor-promoting soluble factors (including growth factors) which stimulate chemoresistance as well as properties to form distant metastasis [1, 2, 4, 8, 17, 18]. The activated PSCs are known to be the initiators of both pancreatitis and PDAC desmoplasia [2-4]. The targeting of activated PSCs represents a promising therapeutic strategy that has attracted the attention of numerous research teams [1-3]. Thus, there is an urgent need to better understand the molecular mechanisms underlying the activation of PSCs leading to the desmoplastic reaction in order to propose new biomarkers and therapeutic targets of PDAC. Ion channels are plasma membrane proteins which are well known to act as biosensors of the tissue microenvironment. Ion channels are involved in cancer cell fates [19, 20]. Importantly, ion channels are located at the plasma membrane, and they can be easily accessible for drugs. Moreover, since numerous ion channel blockers have been already used for treating nervous and cardiovascular diseases, these drugs could be repurposed to selectively target ion channels in cancer [21]. Although the role of ion channels in cancer cells has been extensively documented, there is a paucity of research examining the significance of these proteins in PSC activation.

In this review, we briefly discuss the role of activated PSCs in pancreas inflammation and pathological fibrosis (associated with chronic pancreatitis and PDAC), and we describe the role of specific ion channels and transporters (Ca^{2+}, K^+, Na^+ and Cl^-) in these processes in the light of the literature.

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Role of activated pancreatic stellate cells in pancreas inflammation and diseases

PSCs were first observed in mouse pancreas in 1982 [22]. They represent 4-7% of the healthy pancreas and are present in both endocrine (surrounding Langerhans islets) and exocrine (mainly surrounding the basolateral side of acinar cells but also surrounding small ducts) tissues. They are characterized by the presence of lipid droplets storing vitamin A in their cytosol and by the expression of markers such as desmin, glial fibrillary acidic protein (GFAP), nestin, neural cell adhesion molecule (NCAM), nerve growth factor (NGF), and synemin [23-25]. Despite the expression of neuroendocrine tissue-specific markers, a number of pieces of evidence support the hypothesis of mesenchymal, bone marrow cell and monocyte origins [3]. PSCs are classified into two distinct categories, quiescent and activated. Quiescent PSCs are important for pancreas regulation by maintaining ECM turnover, immune function, cell differentiation (such as hepatocytes, bile ductal and epithelial cells), and acetylcholine synthesis and secretion [4]. Upon activation, PSCs are no longer capable of storing vitamin A and undergo a loss of lipid droplets. They acquire a myofibroblast-like phenotype characterized by enhanced cell proliferation, migration and secretion. Activated PSCs express alpha smooth muscle actin (αSMA), fibroblast activation protein alpha (FAP-α), fibroblast specific protein-1 (FSP-1) and fibrinogen [18]. PSCs can be activated by different types of stress including ethanol and its metabolites, hypoxia, oxidative stress, pro-inflammatory cytokines (e.g., IL-1, IL-6, TNFα) and growth factors (platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β)) [18]. PSC activation is reversible and treatment with molecules such as troglitazone (a ligand of peroxisome proliferator activated receptor γ (PPAR-γ)), vitamin D analogues, and vitamin A (retinol) or its metabolites like all trans-retinoic acid (ATRA) can reprogram activated PSCs into a quiescent state [4]. Activated PSCs synthetize excessive ECM proteins as well as metalloproteases leading to a dense fibrotic stroma called desmoplasia [1, 4, 18]. Desmoplasia leads to fibrosis and pancreatitis. Importantly, the desmoplastic reaction gives rise to the formation of a hypovascularized, hypoxic, stiffer microenvironment which provides an optimal milieu for tumor development. In PDAC, the desmoplastic stroma accounts for 50 to 80% of the tumor and is correlated with a poor outcome [1, 8]. Moreover, activated PSCs are present in the desmoplastic stroma, but they are also the source of some of the CAFs, particularly myofibroblast-like (myCAFs) and inflammatory/secretory CAFs (iCAFs) [26]. However, a recent study suggests that PSC-derived CAFs represent only a minority of the CAF population in PDAC [27]. Given that PSC activation represents a key event in the initiation of the desmoplastic reaction, reprogramming activated PSCs into quiescent ones has been proposed as a promising strategy for combating PDAC. To date, the only clinical trial based on activated PSC reprograming is a phase I trial repurposing ATRA in combination with chemotherapy for PDAC treatment [28]. Recent advances have identified promising activated PSC targets including multiple ion channels and transporters. These latter could be exploited to develop new therapeutic strategies against PDAC.

Role of Ca^{2+} channels and transporters

Cytosolic calcium cation (Ca^{2+}) is a ubiquitous second messenger involved in many physiological and pathological processes. The roles of Ca^{2+} in the physiology and the pathology of the exocrine pancreas have been extensively reviewed [29-31]. Notably, quiescent PSCs are sensitive to bradykinin (BK), a proinflammatory vasoactive nonapeptide which serum level increases during pancreatitis [29-33]. Physiological concentrations of BK (~50pM to 1nM) induces a biphasic Ca^{2+} response in rat PSCs through activation of the B2 receptors [31, 33]. The biphasic Ca^{2+} response is composed of a transient rise followed by a sustained phase of $[Ca^{2+}]_i$ increase [31, 33]. The initial transient Ca^{2+} response to BK is due to G protein coupled receptor (GPCR)/phospholipase C (PLC) signaling cascade, leading to

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inositol trisphosphate receptor (IP_3R) opening and Ca^{2+} release from endoplasmic reticular (ER) stores [31, 33]. The sustained phase of $[Ca^{2+}]_i$ increase is dependent on extracellular Ca^{2+} influx through store-operated Ca^{2+} entry (SOCE) channels [31, 33]. SOCE represents a physiological process that serves to replenish Ca^{2+} supplies within ER lumen. Decrease of Ca^{2+} levels within ER lumen are sensed by the EF-hands of stromal interaction molecule 1 (STIM1) which activates, oligomerizes and translocates at junctions between ER and plasma membranes. At these junctions or puncta, STIM1 clusters bind and activate SOCE channels, leading to sustained Ca^{2+} influx [34]. SOCE channels have been identified as Ca^{2+} release-activated Ca^{2+} or CRAC channels, which main representatives are the Orai1 protein [35]. Both Orai1, Orai2 and STIM1 are expressed in mouse PSCs [36] and Orai1 inhibitor GSK-7975A prevents the plateau phase of $[Ca^{2+}]_i$ rise but not the initial transient [33]. This increase of intracellular Ca^{2+} ($[Ca^{2+}]_i$) induced by BK leads to nitric oxide (NO) production by PSCs through Ca^{2+}-sensitive enzyme nitric oxide synthase (NOS) [33]. However, the physiological role of BK-induced NO production by PSCs is not yet fully understood [29]. There is a considerable heterogeneity of Ca^{2+} response between the different types of pancreatic cells (e.g., acinar, neuron, macrophage and stellate) [29, 31]. PSC Ca^{2+} responses are not sensitive to membrane depolarization and PSCs do not seem to form functional synapses with pancreatic neurons, suggesting an absence of voltage-gated ion channels in normal PSCs [29].

As mentioned above, Ca^{2+} entry in PSCs is due to activation of SOCE channels after stimulation of GPCR, PLC signaling and Ca^{2+}-release from ER stores. Radoslavova *et al.* showed that Orai1 channels contribute to SOCE in PS-1 pre-activated human PSCs and regulate cell proliferation and TGF-β secretion through Ca^{2+}-dependent AKT signaling pathway [37]. Moreover, treatment of PS-1 cells with TGF-β stimulates Orai1 expression, SOCE, as well as Orai1-dependent cell proliferation and secretion suggesting a role of Orai1 in PSC activation induced by a TGF-β-dependent positive feedback autocrine loop [37]. Finally, collagen deposition from PS-1 cells stimulated by TGF-β and/or vitamin C is regulated by Orai1 modulation [38].

The superfamily of Transient Receptor Potential (TRP) channels is composed of various ion channels essential for cation fluxes and particularly for Ca^{2+} entries in non-excitable cells while they are also permeant to Na^+, K^+, Mg^{2+} and other metal ions such as Zn^{2+} [39-41]. TRP channels are involved in numerous physiological and pathological processes, and are considered as promising drug targets [42]. TRP channels are classified as ankyrin (TRPA), classical or canonical (TRPC), melastatin (TRPM), mucolipin (TRPML), NO-mechano-potential or NOMP (TRPN), polycystin (TRPP), and vanilloid (TRPV) based on their primary sequence [39-41]. TRP channels are activated by different stimuli including osmolarity, mechanical stretch, pH, temperature, ... [39, 41]. As cellular sensors, TRP channels have been studied in PSCs because of the many environmental stresses to which the pancreas is subjected during the development of pathologies. For example, Fels *et al.* hypothesize that desmoplasia occurring during pancreatic carcinogenesis induces stroma rigidity and increased stiffness that could be sensed by PSCs through mechanosensitive ion channels [43]. They identify TRPC1, a Ca^{2+} permeable channel [44], as a part of the mechanism involved in PSC activation induced by elevated pressure in mice. It has been demonstrated that exposure to high pressure (100 mmHg, 24h) results in an increase of PSC migration and in an increase of constitutive cation entry which are both strongly attenuated in TRPC1 KO mice [43]. Furthermore, this has been confirmed by Radoslavova *et al.* by showing that TRPC1 regulates α-SMA expression and IL-6 secretion through the activation of the small and mothers against decapentaplegic homolog 2 (SMAD2) and the extracellular signal-regulated kinase (ERK1/2) pathways in human PSCs [45]. Moreover, Schwab's group highlights another mechanism of Ca^{2+}-regulated PSC migration involving the complex formed by Ca^{2+}-activated K^+ (K_{Ca}) and TRPC3 channels which mediate Ca^{2+} entry and calpain activation [46]. K^+ channel opening induces membrane hyperpolarization, leading to enhanced electrochemical gradient for Ca^{2+} influx [47] through Ca^{2+} permeable channels such as TRPC3 [48]. By using data mining of published microarray analyses of microdissected patient tissue samples, Storck *et al.* showed that TRPC3 is mainly overexpressed in the stromal compartment of PDAC [46]. Moreover, they observed that almost two-thirds of TRPC3 are colocalized with

$K_{Ca}3.1$ channels at the plasma membrane of RLT-PSCs, a human PSC model isolated from a chronic pancreatitis [46]. Finally, TRPC3 silencing abolishes PDGF-stimulated migration of RLT-PSCs and the Ca^{2+} response with no additional effect when combined with TRAM-34 $K_{Ca}3.1$ blocker, suggesting a functional interaction between the two channels [46]. The same group also studied the effects of hypoxia, another important feature of desmoplasia, on TRPC channel expression and PSC migration [49]. They identified TRPC6 as a regulator of 3D migration and constitutive cation entries stimulated by hypoxia (1% O_2, 24h) in mouse PSCs [49]. Moreover, TRPC6 also regulates hypoxia-dependent secretions of cytokines that are involved in autocrine stimulation of PSCs [49]. Interestingly, both TRPC3 and TRPC6 are receptor-operated channels (ROC) which are activated following GPCR stimulation. These results suggest that ROC channels play an important role in the activation of PSCs mediated by soluble factors. TRPM7 is a dual function protein comprising a non-selective cation channel and an atypical kinase domain [50, 51]. TRPM7 is expressed ubiquitously but upregulated in PDAC [52, 53]. TRPM7 expression has been studied in hepatic stellate cells, where it regulates cell proliferation [54]. In human PSCs, we showed that TRPM7 expression depends on the state of activation [55]. TRPM7 expression is strongly decreased following treatment by ATRA while it increases in PSCs "educated" with media of pancreatic cancer cells, and also in RLT-PSCs [55]. TRPM7 regulates PSC proliferation through the stabilization of p53 via the PI3K/Akt pathway [55]. Moreover, data mining analysis shows that TRPM7 is upregulated in CAFs compared to fibroblasts from normal pancreas [55]. TRPV1, a thermosensitive channel activated by heat, mediates Ca^{2+} influx induced by hyperthermia [56] leading to heat shock factor 1 (HSF1) nuclear translocation and cell adaptation to stress [57]. Indeed, TRPV1 blockade enhances thermo-immunotherapy (use of local hyperthermia in combination with potent immunomodulator for treating neoplasia) by inhibition of TGFβ pathway leading to activation of immune response and notably reduced fibrosis in PDAC [57]. However, the role of TRPV1 in PSC activation is not yet fully understood.

Piezo channels have been identified as the main mechanoreceptors of cell membranes, as they allow cation (mostly Ca^{2+}) entry following mechanical stimuli [58]. Interestingly, Romac *et al.* showed that Piezo1 is the main mechanosensitive ion channel expressed in the pancreas and its activation initiates pancreatitis in mice [59]. Mechanistically, Piezo1 activation is responsible for the initial Ca^{2+} rise which in turn activates TRPV4 leading to sustained Ca^{2+} increase, Ca^{2+} overload and trypsin release by acinar cells [60]. In a similar way, Swain *et al.* show that Piezo1 channels are expressed in PSCs and are responsible for pressure-induced fibrosis [61]. Mice where *Piezo1* was deleted specifically in PSCs were protected against fibrosis induced by pancreatic duct ligation and intraductal elevated pressure [61]. Piezo1 activation by Yoda1 or by shear stress induces $[Ca^{2+}]_i$ rise as well as fibrogenic response evaluated by fibronectin and collagen type I expression [61]. Finally, neither Yoda1 nor shear stress were able to induce sustained $[Ca^{2+}]_i$ rise in PSCs isolated cells from TRPV4-KO mice, suggesting that TRPV4 opening is required to maintain Ca^{2+} overload induced by Piezo1 activation in PSCs exposed to high pressure [61]. Piezo1 channels are also involved in PSC migration, as demonstrated by Kuntze *et al.* [62]. More recently, Budde *et al.* showed that mechanosensitive channels including Piezo1, TRPV4 and TRPC1 are involved in PSC durotaxis which represents the directional cell migration along stiffness gradient of ECM [63]. In particular, they show that Piezo1 is essential for durotaxis but in interaction with TRPV4 or TRPC1 to allow an optimal PSC migration along stiffness gradient [63].

Nicotine, the major component of tobacco, is an independent risk factor of pancreatic fibrosis [64]. Li *et al.* showed that nicotine treatment (1μM, 48h) activates human PSCs leading to enhanced cell proliferation, reduced apoptosis, overexpression of α-SMA, secretion of ECM, and autophagy [64]. This work also shows that nicotine induced the overexpression of the α7 nicotinic acetylcholine receptor (α7nAChR), a ligand gated Ca^{2+} channel, in PSCs [64]. Use of the specific α7nAChR antagonist α-bungarotoxin (α-BTX, 0.1μM) inhibited the α7nAChR-mediated JAK2/STAT3 signaling pathway and prevented PSC activation induced by nicotine [64]. These results were confirmed in a rat model of chronic pancreatitis [65]. Interestingly, Wei *et al.* also demonstrated that nicotine induces fibrosis in rats and activates PSCs [66]. They further show that nicotine induces the production of reactive oxygen species

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(ROS) in the mitochondria as well as mitochondrial Ca^{2+} overload through upregulated mitochondrial Ca^{2+} uniporter (MCU) expression [66].

During pancreatic lesions associated with both pancreatitis and PDAC, ATP is released in stroma following acinar cell death [29]. It has been shown that extracellular ATP induces $[Ca^{2+}]_i$ increase in mouse activated PSCs [67]. ATP regulates $[Ca^{2+}]_i$ by binding to plasma membrane purinergic receptors such as P2X (ligand-gated Ca^{2+} channels) and P2Y (G-protein coupled receptors). Several P2X (P2X1, P2X4, P2X5, and P2X7) and P2Y (P2Y1, P2Y2, and P2Y6) receptors are expressed in PSCs [67-70]. Haanes *et al.* showed that P2X7 regulates mouse PSC proliferation in low serum conditions as well as $[Ca^{2+}]_i$ [71]. Giannuzzo *et al.* showed also that PSCs isolated from P2X7$^{-/-}$ mice were unable to stimulate pancreatic cancer cell migration [72]. Moreover, treatment of orthotopic PancTu-1 Luc pancreatic tumor mouse model with the P2X7 inhibitor AZ10606120 reduces PSC activity and fibrosis [72]. In human RLT-PSCs, P2X7 stimulation by BzATP (an ATP analog which is 10-fold more potent than ATP to activate P2X7) induced $[Ca^{2+}]_i$ increase, collagen secretion, and IL-6 release leading to stimulated pancreatic cancer cell migration through STAT3 pathway [73]. Interestingly, P2X7 variant polymorphisms with opposite roles have been described in PDAC tissues [74]. While the Gly150Arg variant expression has a protective effect on $[Ca^{2+}]_i$ overload and cell migration, the Arg276His promotes $[Ca^{2+}]_i$ increase and inflammatory cytokine release (IL-6, IL-1β, IL-8, TNF-α) as for the wild-type [74].

Intracellular Ca^{2+} can also be regulated by secondary active transport mechanisms such as the Na^+/Ca^{2+} eXchanger (NCX) which allows Ca^{2+} extrusion (forward mode) or entry (reverse mode) depending on Na^+ electrochemical gradient [75]. NCX1 is expressed in both murine and human PSCs [76]. In physiological conditions (pH_e 7.4), NCX1 works in forward mode, prevents cellular Ca^{2+} accumulation, and slows down PSC migration [76]. Nevertheless, the role of NCX1 on PSC migration is dependent of tumoral microenvironment because NCX1 inhibition enhances PSC migration at pH_e 7.4 while decreasing it at pH_e 6.6 [76].

Taken together, these data show that PSC activation is highly regulated by Ca^{2+} toolkit depending on the environmental stimuli. The main results discussed in this section are summarized in Fig. 1.
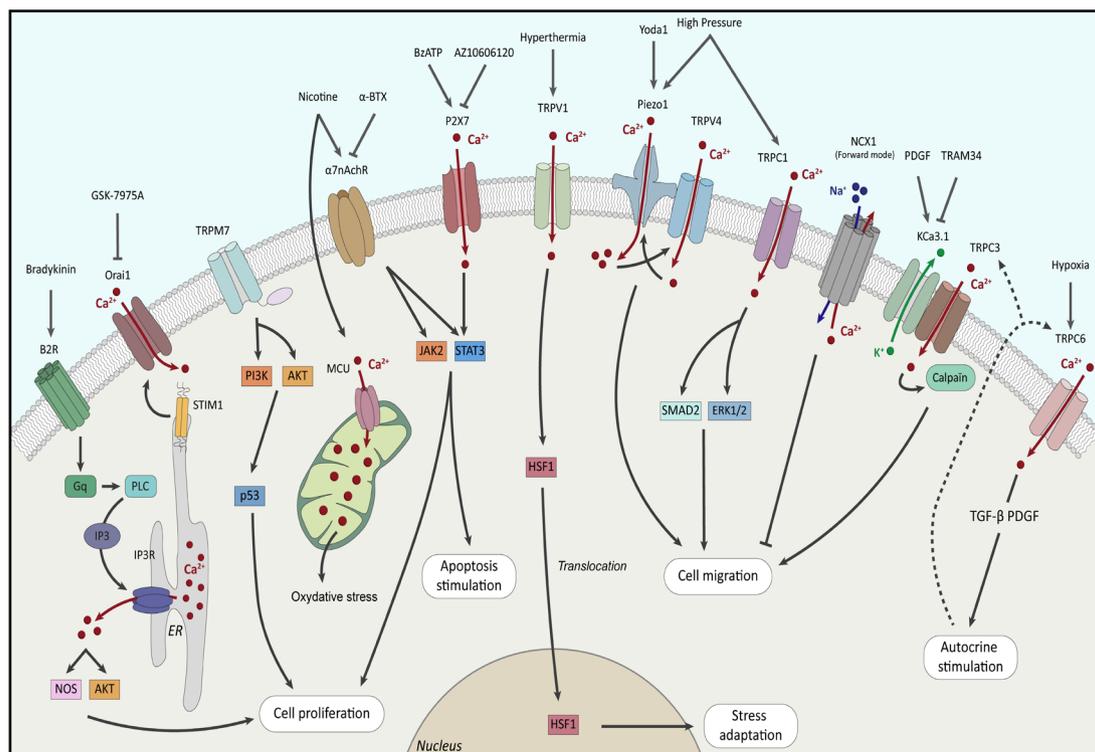

Fig. 1. Roles of Ca^{2+} channels and transporters in PSC fates.

Role of K$^+$ channels and transporters

K$^+$ is the most abundant cation in the cell. As mentioned above, PSCs express K$_{Ca}$ channels [46] which are opened by intracellular Ca^{2+} increase and promote Ca^{2+} influx through Ca^{2+} channels (Orai or TRP channels) by hyperpolarizing the plasma membrane leading to a large electrochemical gradient for Ca^{2+} entry [29]. The K$^+$ intermediate conductance Ca^{2+}-activated K$_{Ca}$3.1 (also identified as KCNN4, IK1 or SK4) channels are expressed and functional at the plasma membrane of RLT-PSCs [46]. These channels are required for stimulated PSC migration through calpain activity and Ca^{2+} signaling by interacting with TRPC3 channels [46]. One of the major roles of PSCs in PDAC is the intercellular communication with cancer cells, leading to chemoresistance and metastasis. Interestingly, Rapetti-Mauss *et al.* described that the K$^+$ small conductance Ca^{2+}-activated SK2 channels expressed in the plasma membrane of pancreatic cancer cells are activated by the secretome of CAFs [77]. Importantly, SK2 is a part of a signaling complex, including Sigma1R (Sig-1R) chaperone, β1-integrin, EGFR and AKT, which can be targeted by Sig-1R ligand leading to delayed tumor progression and extended overall survival in an endogenous PDAC mice model [77]. While such mechanism has not been yet described in PSCs, it is tempting to speculate that K$_{Ca}$ channels could also interact with other signaling proteins to regulate PSC activation and pancreatic fibrosis. Recently, K$_{2P}$2.1 channels have been identified in murine PSCs where they regulate resting membrane potential and cell migration modulated by acidic extracellular pH (pH$_e$ 6.6) and high pressure (+100 mmHg) mimicking PDAC microenvironment [78].

The H$^+$, K$^+$-ATPase is expressed in normal pancreatic ductal cells where it regulates the intracellular K$^+$ homeostasis, participates in the secretin-stimulated secretion, and in both intracellular (pH$_i$) and extracellular pH (pH$_e$) regulation by inducing active influx of K$^+$ and outflow of H$^+$ [79]. One of the hallmarks of PDAC is its acidic microenvironment which promotes fibrosis, resistance and metastasis [79, 80]. Tozzi *et al.* demonstrated that H$^+$, K$^+$-ATPases are expressed in RLT-PSCs at the leading edge of migrating cells [81]. Moreover, inhibition of these pumps by using selective blockers such as pantoprazole decreased PSC proliferation and collagen I secretion [81]. The main results discussed in this section are summarized in Fig. 2.
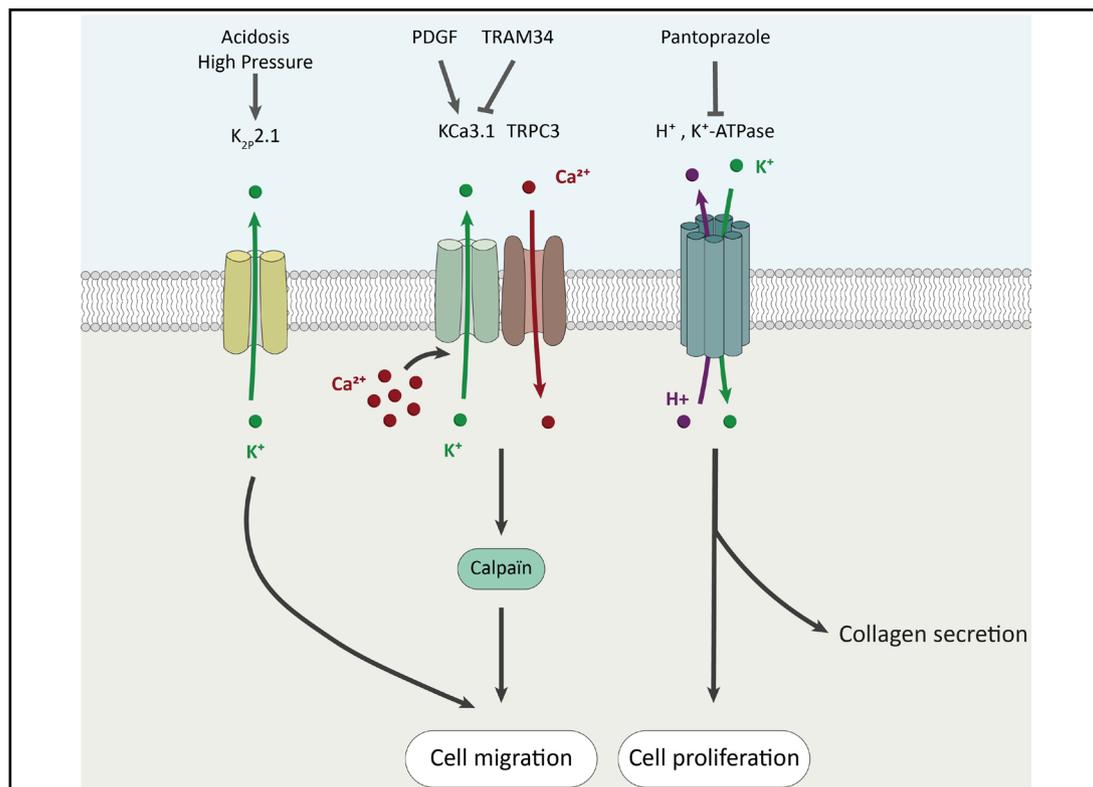

Fig. 2. Roles of K$^+$ channels and transporters in PSC fates.

Role of Na⁺ channels and transporters

Na^+ is the most abundant cation of the extracellular fluids. In mouse and human PSCs, bile acid salts induce $[Ca^{2+}]_i$ oscillations and necrosis which are dependent on extracellular Na^+ [82]. The effect of bile acid salts on PSCs could be explained at least in part by the presence of the sodium–taurocholate cotransporting polypeptide (NTP) coding by the *slc10A1* gene in both mouse and human PSCs [82]. As mentioned before, the Na^+/Ca^{2+} eXchanger 1 (NCX1) regulates differently the PSC migration according to the tumor microenvironment, and particularly depending on the pH context [76]. Pancreatitis and PDAC development are accompanied by dramatic alterations of pH [79]. Several Na^+ channels/transporters including Acid-Sensing Ion Channels (ASIC) and Na^+/H^+ Exchangers (NHE) are regulated by pH. ASIC1 channels have been detected in PSCs and their expression is upregulated by acidosis [83] but also by the co-culture with pancreatic cancer cells leading to PSC activation [84]. Interestingly, ASIC1 silencing in PSCs inhibited both cell viability and migration stimulated by conditioned media from pancreatic cancer cells [84]. Mechanistically, pancreatic cancer cells stimulate PSC viability and migration through ASIC1 and ERK signaling, but the role of Na^+ influx and/or membrane depolarization still needs to be deciphered [84]. Moreover, Wang *et al.* showed that acidosis-induced PSC activation and autophagy, depend on ASIC1a channel activity and expression [83]. However, outside-out and whole-cell patch-clamp experiments in oocytes expressing ASIC1 showed that acidic pHe rapidly inactivates ASIC1 channels and the pHe must be returned to pHe 7.4 to reactivate the channels [85]. This suggests that ASIC1 activation by acidic pH_e is probably transient, or there may be other factors present in the tumor microenvironment capable of permanently activating these channels. Pethő *et al.* described the role of NHE in PSC activation into a myofibroblast-like phenotype *in vitro* and in PDAC-associated fibrosis *in vivo* [86]. PSCs exposed to alkaline pH_e (7.4 instead of 6.6) express myofibroblast-like markers, suggesting that the disruption of intermittent acidosis in the stroma induces PSC activation. These data support the hypothesis that PSCs are intermittently exposed to acidosis due to secretions of bicarbonates (HCO_3^-) in the pancreatic ducts (at the apical side of the plasma membrane) which are associated to a secretion of H^+ in the stroma during the digestive processes [79, 86]. Thus, intermittent acidosis maintains the PSCs in a quiescent state. NHE1 encoded by the *SLC9A1* gene is overexpressed in PSCs cultivated at pH_e 7.4 and in PDAC-derived CAFs [86]. Moreover, NHE1 is mainly located at the plasma membrane and acts as a H^+ extruder induced by Na^+ influx in PSCs and PDAC-derived CAFs [86]. Finally, NHE1 activity maintains myofibroblast-like phenotype in PSCs exposed to acidic tumor microenvironment and NHE1 inhibition by cariporide can be used as a neoadjuvant drug in combination with gemcitabine to reduce fibrosis and improve the immune response [86]. The main results discussed in this section are summarized in Fig. 3.

Role of Cl⁻ channels

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) is a chloride (Cl^-) channel essential for fluid and electrolyte secretions in respiratory and digestive tracts. In the pancreas, CFTR is expressed in the apical membrane of centroacinar and proximal ductal cells, where it regulates ductal bicarbonate secretion. The mutation of the *CFTR* gene is associated with cystic fibrosis (CF) which can lead to abnormal function of the pancreas resulting in diabetes for almost half of the CF patients [87]. Moreover, *CFTR* mutation associated with mutations of other genes are frequently found in chronic pancreatitis [88]. In CFTR knockout animal models, it has been shown that CF is associated with activation of PSCs [87]. Moreover, the development of fibrosis in CFTR$^{-/-}$ sheep during gestation is accompanied by an enrichment of the stellate cell population in the pancreas [89]. However, while PSC abundance and activation were dependent on CFTR expression, a possible link between CFTR activity, Cl^- flows and PSC activation has not yet been demonstrated. Moreover,
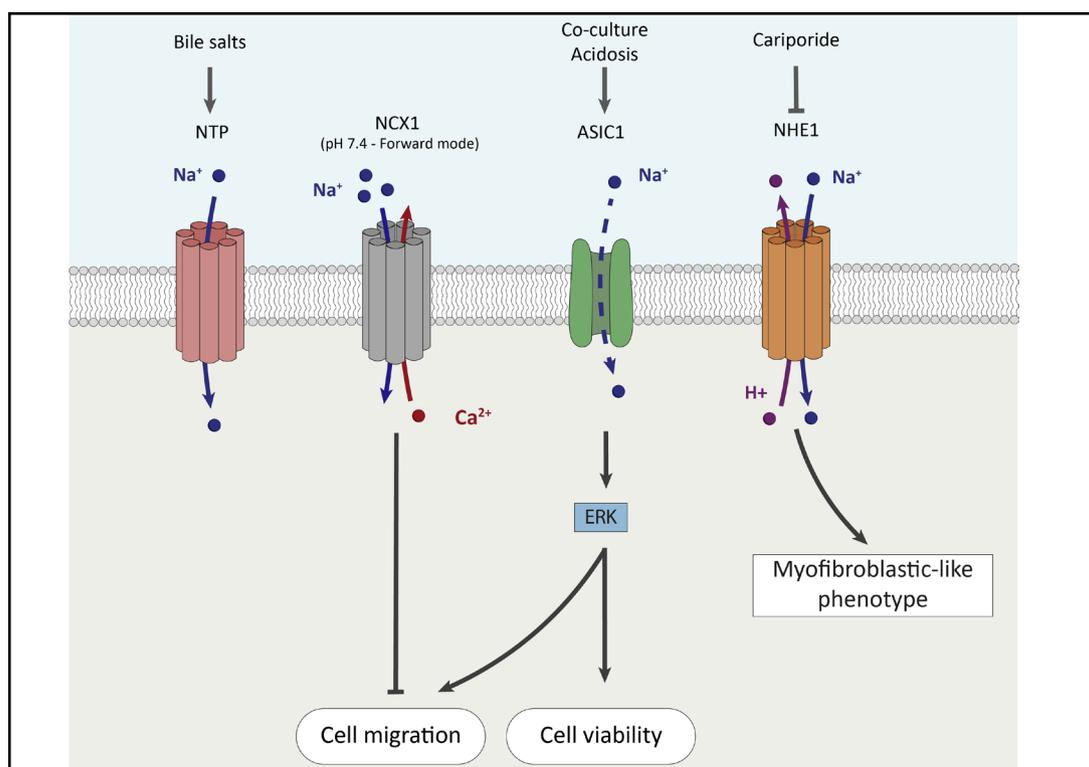
Fig. 3. Roles of Na⁺ channels and transporters in PSC fates.

it is possible that other Cl⁻ channels are involved in PSC activation. For example, in human hepatic stellate cells, non-specific blockers (4, 40-diisothiocyanatostilbene-2, 20-disulfonic acid (DIDS), 5-nitro-2-(3-phenylpropyl-amino) benzoic acid (NPPB), and indanyloxyacetic acid (IAA-94)) of Cl⁻ channels inhibited cell activation induced by reactive oxygen species [90].

Roles of metals?

Auwercx *et al.* showed that TRPM7 regulates human PSC proliferation through PI3K/Akt/p53 signaling pathway in a Mg^{2+}-dependent manner [55]. Epidemiological studies show that low Mg^{2+} intake (<75% of recommendary daily allowance: ~219.43mg per day) is an independent risk factor of PDAC [91], and a low Mg^{2+} level is found in the serum of PDAC patients (0.72±0.13mM) compared to healthy controls (0.82±0.13mM) [92]. But the data published in cell and in animal models are often contradictory regarding the role of Mg^{2+} intake. Thus, low Mg^{2+} intake (from 1000 to 30mg/kg in diet) decreases lung cancer cell proliferation and primary tumor growth, while it promotes metastasis in mice [93]. Importantly, low Mg^{2+} (0.08mM) in the tumor microenvironment of pancreatic cancer cells potentiates allosteric inhibition of wild-type isocitrate dehydrogenase 1 (wtIDH1), improving survival in preclinical models [94]. Cellular Mg^{2+} homeostasis is complex and involves many channels and transporters [95]. To our knowledge, little is known about the regulation of Mg^{2+} in PSCs and further investigations are needed to better understand the role of Mg^{2+} in PSC activation and fibrosis.

There is growing evidence that trace metal exposure is associated with various pathologies, including cancer [96]. Recent data highlight an increase of toxic metal (i.e., As, Pb and Hg) concentrations in PDAC tissues compared to non-cancer adjacent ones [92]. However, the link between trace metal exposure and PSC activation has not yet been identified.

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Future directions

In this review, we summarized the recent findings on ion channels associated with PSC activation, fibrosis and desmoplasia. Activation of PSCs can be induced by many stimuli, leading to fibrosis and progression of pancreatic diseases such as chronic pancreatitis or PDAC. The present review highlights a variety of mechanisms modulating the properties of PSCs involving ion channels. This can be partly explained by differences in the cell models used. The studies presented use PSCs from mouse models or human cell lines isolated from pancreatitis (RLT-PSC) or healthy pancreas (PS-1). Given the anatomical differences between the mouse and human pancreas, it is possible that there are also differences in the stroma and nature of the PSCs [97]. Furthermore, there is anatomical heterogeneity within the human pancreas and also in the types of PSCs that are activated [98]. Activation of PSCs can lead to the presence of several subpopulations of CAFs in the tumor microenvironment, including myCAF and secretory iCAF subtypes [99, 100]. It is not yet fully understood whether these phenotypes are a consequence of the different stimuli to which PSCs are exposed, or whether they are due to the origin of the PSCs. PSCs can be derived from different cell types, in particular hematopoietic stem cells. It is possible that their origin determines their activation mechanisms, their role in desmoplasia and tumor development, and probably the nature of the ion channels they express. It is important to be able to standardize the cellular models used to study PSCs and to better understand the origin and heterogeneity of these cells. To the best of our knowledge, no studies have yet been conducted on the expression or activity of ion channels in patient-derived CAFs. A systematic study of the ion channels expressed in primary CAFs as a function of clinical parameters could prove invaluable in understanding their role in carcinogenesis and, in particular, intercellular communication with cancer cells. Indeed, one of the defining characteristics of PDAC is the interaction between CAFs and cancer cells, which promotes metastasis formation and resistance to treatment. It is established that ion channels are involved in the activation of PSCs and in the regulation of their proliferation and migration. However, it has yet to be fully established if certain ion channels are involved in the ability of CAFs to stimulate pancreatic cancer cells.

Conclusion

In conclusion, recent studies have underscored the significance of ion channels in activating PSCs and regulating their characteristics. These channels can, therefore, be regarded as biomarkers of desmoplasia and as potential therapeutic targets. However, the heterogeneity of the pancreas, the cell models employed, and the subtypes of activated PSCs and CAFs imply that a more profound comprehension of these cells and the intricacy of their interactions with cancer cells is imperative.

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