Pancreatic stellate cells: Key players in pancreatic health and diseases (Review)

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Abstract. As a pluripotent cell, activated pancreatic stellate cells (PSCs) can differentiate into various pancreatic parenchymal cells and participate in the secretion of extracellular matrix and the repair of pancreatic damage. Additionally, PSCs characteristics allow them to contribute to pancreatic inflammation and carcinogenesis. Moreover, a detailed study of the pathogenesis of activated PSCs in pancreatic disease can offer promise for the development of innovative therapeutic strategies and improved patient prognoses. Therefore, the present study review aimed to examine the involvement of activated PSCs in pancreatic diseases and elucidate the underlying mechanisms to provide a viable therapeutic strategy for the management of pancreas-related diseases.

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Abbreviations: PSCs, pancreatic stellate cells; IL, interleukin; TNF-α, tumor necrosis factor-α; TGFβ1, transforming growth factor β1; PC, pancreatic cancer; α-SMA, α-smooth muscle actin; ATRA, all trans-retinoic acid; CP, chronic pancreatitis; ACP, alcoholic CP; CTGF, connective tissue growth factor; Arl4c, ADP-ribosylation factor like-4c; SHH, Sonic Hedgehog; MMP, matrix metalloproteinase; NGF, nerve growth factor; EMT, epithelial-mesenchymal transition; HIF, hypoxia-inducible factor; PDGF, platelet derived growth factor; EGCG, epigallocatechin-3-gallate; ERK, extracellular regulated kinases; ROS, reactive oxygen species; FMOD, fibromodulin; PI3K, phosphatidylinositol-3-kinase; AKT, protein kinase B; PAC, pancreatic acinic cell; MAPK, mitogen-activated protein kinase; PPAR, peroxisome proliferator-activated receptor; NF-κB, nuclear factor κB; CoQ10, coenzyme Q10; SSd, Saikosaponin d; CO, carbon monoxide; Hsp90, heat shock protein; JAK, Janus kinase; STAT, signal transducers and activators of transcription; CAF, cancer-associated fibroblasts; JNK, c-Jun N-terminal kinase; RB, retinoblastoma; S100A4, S100 calcium binding protein A4; CnP, Conophylline; Hic-5, hydrogen peroxide-inducible clone 5; TnC, tenascin C; NDRG1, N-myc downstream-regulated gene-1; DpC, di-2-pyridylketone-4-cyclohexyl-4-methyl-3-thiosemicarbazone

Key words: PSCs, fibrosis, pancreatitis, cancer, treatment

Contents

1. Introduction

Pancreatic fibrosis is an important pathological feature of pancreas-related diseases and a key component of pancreatic injury repair, in which pancreatic stellate cells (PSCs) play a major regulatory role (1). As mesenchymal-like cells of non-endocrine nature in the pancreas, PSCs usually accumulate in the basal part of the pancreas and the lobules of the pancreas, accounting for about 4-7% of the total number of pancreatic cells (2). PSCs exist in two distinct states, namely resting and active states (3). Resting PSCs maintain their quiescent state by secreting nestin, glial fibers, acidic proteins, and waveform proteins, which play a prominent role in maintaining the normal function of the follicles and stabilizing the pancreatic pressure. However, when stimulated by various damaging factors, including trauma, inflammation, viral infection and cancer invasion, PSCs in the resting state will be converted into activated state, the myofibroblast-like phenotype. Subsequently, a significant increase in the cell volume accompanied by active proliferation, and secretion of various extracellular matrix (ECM) components, including collagen, fibronectin and laminin, is frequently observed. Moreover, various cytokines, including interleukin (IL)-1, IL-6, tumor necrosis factor-α (TNF-α), and transforming growth factor β1 (TGFβ1), chemokines and adhesion molecules are produced, promoting the chemotaxis, aggregation and adhesion of inflammatory cells, and ultimately participating in the repair

and remodeling of the pancreas and pancreas-related diseases' progression (4-6). In addition, PSCs also possess stem cell characteristics and participate in the process of pancreatic tissue regeneration (7). However, persistent over-activation of PSCs will continue to synthesize and produce a large number of ECM components, thus disturbing the dynamic balance of collagen metabolism and inducing pancreatic fibrosis, destroying the structure and function of normal tissues, and ultimately leads to the development of chronic pancreatitis (CP) and pancreatic cancer (PC). The mechanism of action of targeted activated PSCs in pancreatitis and PC is expected to provide a new choice for the diagnosis and treatment of pancreatic diseases. Therefore, the present review focused on the activation mode of PSCs, including different signal transduction pathways and key molecules inside and outside cells, and systematically summarized the important role of activated PSCs in pancreatic injury repair and pancreatic diseases.

2. Regulation of PSCs' activation

Resting PSCs are often used as a sign of normal pancreatic tissue function. Once stimulated by various pathogenic factors, PSCs transform into activated myofibroblast-like cells, accompanied by changes in function and morphology (8,9). The transition from resting to activated states involves regulating various intracellular and extracellular signaling pathways, which have been comprehensively elucidated in the present review. The differences between the resting and active PSCs are summarized in Table I.

Extracellular signaling. Several studies have revealed that extracellular signaling contributes to PSCs' activation and is involved in the process of pancreatic fibrosis, including TGF-β, IL-10, oxidative stress, intracellular stress and ion channel conduction (5,6).

Cytokines. TGF-β. The TGF-β is the first identified member of the TGF-β family, which regulates the conduction of various intracellular and extracellular signals, including proliferation, apoptosis and differentiation. Additionally, it is involved in the development of inflammation, autoimmune diseases, cancer and other diseases, especially in the gastrointestinal tract (10-12). The occurrence and development of pancreatic diseases requires the participation of pancreatic fibrosis, which is inseparable from the continuous activation of PSCs, with exogenous TGF-β playing a role in this mechanism. Upon receiving effective stimulation of TGF-β, PSCs undergo activation of the myofibroblast marker α-smooth muscle actin (α-SMA). This activation triggers a continuous secretion of fibronectin and type I collagen by PSCs, thereby facilitating the deposition of ECM (13,14). Additionally, activated PSCs are overexpressed and secreted extracellularly by TGF-β1, positively regulating their activation state (15,16). TGF-β is not initially discovered in an activated form within the ECM. Instead, it is stored as a latent TGF-β binding protein and subsequently released by a mechanism involving cells. This process can be inhibited by all trans-retinoic acid (ATRA), restoring the resting state of PSCs and reducing ECM synthesis and PC progression (17). Moreover, the researchers discovered that PSCs play a key role in the fibrosis of alcoholic CP (ACP). Furthermore, the activation of PSCs is dependent on the regulation of TGF-β1. By establishing a rat ACP model, it was observed that the levels of IL-6 and TGF-β1 in the pancreas were significantly higher in the ACP group compared with the healthy control group. This increase was accompanied by the α-SMA and Col1 production. The change of TGF-β1 expression was positively correlated with IL-6 levels, and further experiments revealed that the activation of PSCs was achieved by upregulating the TGF-β1/Smad2/3 pathway, which confirmed that the activation of PSCs depends on the effective play of TGF-β (18). The efficient inhibition of PSC activation and the prevention of pancreatic disorders can be achieved through targeted intervention of TGF-β.

Connective tissue growth factor (CTGF). The CTGF, a peptide characterized by its high cysteine content, is strongly associated with the modulation of several cellular processes, including cell differentiation, cycle and apoptosis, and adhesion. Moreover, CTGF is implicated in processes such as wound healing, tissue fibrosis and tumor progression (19,20). Previously, several studies have revealed that CTGF can promote the activation and proliferation of PSCs as well as the aggregation of ECM. These findings have garnered significant interest within the academic community. Especially in pancreatic disease, CTGF expression is associated with the severity of acute pancreatitis (AP) and CP (21,22). In PC, changes in CTGF levels directly affect the tumor stroma development (23). The aforementioned process is linked to the activation of PSCs. In necrotic tissue of pancreatic injury, activated PSCs auto-secrete CTGF and subsequently induce TGF-β and type I collagen production, which relies on the mediation of integrin α5β1 on PSCs. As a participant activated by PSCs, CTGF is continuously transmitted to other PSCs, induces their activation, and causes pancreatic fibrosis by promoting the synthesis of ECM components, ultimately leading to pancreatitis or PC (24,25). Tamura *et al* (26) investigated the pathogenesis of phosphatidylinositol-3-kinase (PI3K) and Hippo signaling in regulating the pathogenesis of CP. It was identified that knockdown of CEBPA in mouse CP models induced metaplasia from pancreatic acinar to duct and activation of PSCs, and this process could be mitigated by inhibiting CTGF, confirming that PI3K and Hippo signal-induced CP was achieved through the CEBPA/CTGF axis. As a member of the family of ADP-ribosylation factor-like protein 4A (ARL4), ARL4C is a small GTP-binding protein highly expressed in various types of cancer and has an important regulatory effect on tumor proliferation and drug resistance. In pancreatic tumors, cancer cells highly express ARL4C and promote paracrine CTGF, which subsequently causes activation of PSCs and promotes the progression of PC. Moreover, the aforementioned process can be reversed by silencing yes1 associated transcriptional regulator (YAP). Therefore, targeting the ARL4C-YAP-CTGF axis can prevent the progression of PC, however the in-depth regulatory mechanism remains unexplored (27).

Sonic hedgehog (SHH). HH signaling is a protein ligand secreted by cells to regulate the proliferation and differentiation of neighboring cells. This signaling pathway has been implicated in the genesis and spread of tumors (28). Particularly in the case of highly aggressive PC cells, the secretion of the SHH protein by these cells elicits a response in the quiescent PSCs, leading to their activation. This activation, in turn, influences

Table I. Summary of the differences between the resting and active PSCs.

Characteristic	Resting PSCs	Activated PSCs
Fat drops rich in vitamin A	Positive	Negative
α-SMA	Positive	Positive
Laminin, fibronectin, type I and III collagen	Positive	Positive
MMPs, TIMPs	Normal secretion	Hypersecretion
Cytokines, chemokines, growth factors	Normal secretion	Hypersecretion
Ability to proliferate and migrate	Weak	Strong
Metabolic change	Basically unchanged	Glucose metabolism, lipid metabolism, and amino acid metabolism increased

PSCs, pancreatic stellate cells; α-SMA, α-smooth muscle actin; MMP, matrix metalloproteinase; TIMP, metallopeptidase inhibitor 1.

the behavior of PC cells in a reciprocal manner, establishing a detrimental feedback loop. Consequently, this process contributes to a significantly unfavorable prognosis and renders patients with PC resistant to chemotherapy (29-31). The SHH overexpressed in PC activates the Hh pathway in PSCs through paracrine pathways and subsequently promotes matrix metalloproteinase (MMP)-2, MMP-9, and nerve growth factor (NGF) in PSCs and proliferation of PSCs. Activated PSCs act as signaling stations for interactions between cancer cells and nerves, promoting tumor growth, metastasis and perineural invasion (32). The activation of PSCs plays a crucial role in the matrix response of PC. In the PC matrix, the level of Gremlin 1 expression increases, which is closely related to the degree of PSC activation. Cyclopamine and siGli-1 inhibit the activation of PSCs and the proliferation, invasion and epithelial-mesenchymal transition (EMT) of cancer cells. Further studies have revealed that PC cells promote their progression by secreting SHH to induce the activation of PSCs and increase the expression content of Gremlin 1 (33). The degree of proliferation of PSCs is an important manifestation of their activation level. Hwang *et al* (34) revealed that PC has high Hh ligand expression and low levels of Smoothened receptors, while PSCs have opposite performance. The co-cultivation of cancer cells with PSCs results in an increased rate of proliferation for both cell types. However, the administration of Hh antagonist AZD8542 effectively impedes this enhanced proliferation. In the PC model, AZD8542 inhibits tumor growth only in the presence of PSCs, confirming that cancer cells activate PSCs by secreting SHH signals to accelerate their growth. These studies suggested that PSCs promote self-activation by receiving paracrine SHH signals.

Hypoxia-inducible factor 1α (HIF-1α). As a typical feature of the tumor microenvironment, hypoxia induces the proliferation and invasion of numerous malignant tumors, causing great obstacles to antitumor treatment. The transcription factor HIF-1α, which is widely present in hypoxic environments, is also closely related to the malignant phenotype of tumors (35,36). Previous studies have revealed that in pancreatic diseases, particularly pancreatitis and pancreatic tumors, hypoxia drives malignant progression, and an important factor is that hypoxia promotes the activation of PSCs and pancreatic fibrosis, which causes the aforementioned results (37,38). When Masamune *et al* (39) explored the role of hypoxia in PSCs, it was revealed that PSCs were activated by HIF-1α under hypoxic conditions, which promoted their proliferation and migration. Additionally, the activation of HIF-1α has been revealed to induce the synthesis of type I collagen and various angiogenic regulators, such as vascular endothelial growth factor, basic fibroblast growth factor, IL-8 and platelet-derived growth factor (PDGF). These molecular changes ultimately contribute to the development of pancreatic fibrosis and facilitate the metastasis of PC (39). In addition, a recent study demonstrated that hypoxia induces activation pf PSCs and produces IL-6, VEGFA, as well as stromal cell-derived factor 1 through HIF-1α to promote PC EMT. Furthermore, it inhibits apoptosis, and its efficacy was shown in a murine model of pancreatic carcinoma. However, the administration of resveratrol has the potential to reverse this outcome (40). These results demonstrated that HIF-1α in a hypoxic environment is an important source of PSCs activation, and its inhibition may be effective in alleviating pancreatic fibrosis or cancer progression.

PDGF. The PDGF, first discovered in platelets, has attracted marked attention for its ability to quickly activate the immune system at the trauma site and accelerate tissue wounds. Furthermore, PDGF has the functions of promoting angiogenesis and participating in cell division (41). Nevertheless, previous studies have revealed that PDGF is involved in the activation of PSCs and mediates the occurrence of pancreatic fibrosis. Hu *et al* (42) explored the pathogenesis of alcoholic pancreatitis, and it was revealed that the proliferation capacity of PDGF-treated PSCs was enhanced, and the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in cells was also increased. This finding provides confirmation that the activation and proliferation of PSCs are induced by PDGF through the stimulation of NADPH oxidase activity in quiescent PSCs. Consequently, this process leads to an accelerated production of ECM components and the promotion of pancreatic fibrosis. The effect of alcohol accelerated-process was aforementioned (42). Curcumin, as a polyphenolic compound, has powerful anti-inflammatory and antifibrotic properties. Several studies have revealed that using curcumin inhibited the expression of PDGF, IL-1β, α-SMA and collagen genes closely related to PSCs' activation, providing a new direction for treating pancreatic fibrosis and inflammation (43-45). The polyphenols in green tea extract,

including epigallocatechin-3-gallate (EGCG), are the main components of natural antioxidants and have important advantages in preventing oxidative stress diseases, including cancer, cardiovascular disease and degenerative diseases. The activation and proliferation of PSCs are the key to pancreatic fibrosis, and PDGF is an important regulatory point for this process. It has been previously reported that EGCG ultimately prevents PSCs proliferation and the process of pancreatic fibrosis by inhibiting PDGF-mediated signaling. The process is achieved by inhibiting tyrosine phosphorylation of PDGF receptors and activation of extracellular regulated kinases (ERK) and PI3K/protein kinase B (AKT) pathways (46). These studies provide new insights into the development of pancreatic fibrosis and may reveal that PDGF becomes a new target for treating pancreatic fibrosis.

IL-10. The IL-10 is a cell-derived cytokine involved in a wide range of anti-inflammatory and immune responses in the body and is closely related to infection damage, tumors and cardiovascular diseases (47). Furthermore, IL-10 is secreted by T helper type 2 cells, contributes to pancreatic fibrosis and significantly lowers TGF-β1 expression in pancreatic acinar cells (PACs) (48-50). Demols *et al* (50) revealed that IL-10 knockout (KO) mice had more severe pancreatic tissue lesions and worsened fibrosis than the control group by establishing an AP mouse model of IL-10 KO. The reverse transcription-quantitative PCR and immunohistochemistry detected significantly elevated expression levels of TGF-β1 and activated PSCs in pancreatic ducts and mesenchymal cells in the IL-10 KO group. These findings revealed that IL-10 inhibits pancreatic collagen synthesis by reducing the activation degree of PSCs and TGF-β1 levels, thereby limiting pancreatic fibrosis and gland atrophy caused by AP. However, an additional study reported that IL-10 activation of PSCs only affected the rate of PSCs collagen synthesis but had no obvious effect on α-SMA expression or cell proliferation. However, there is no doubt that exogenous IL-10 can significantly reduce the severity of AP (51). Previous studies have demonstrated confirmed that IL-10 may be an effective target for inhibiting PSC activation.

Other inflammatory factors. It is very well established that inflammation is essential for PSCs activation, and activated PSCs secrete a series of cytokines, including IL-1β, IL-6 and TNF-α, to amplify the inflammatory response and self-activation, and further aggravate the disease (52). In numerous cell and animal models, releasing these inflammatory cytokines promoted activation of PSCs. After becoming highly activated, PSCs release cytokines including CTGF, MMP1 and others in an autocrine or paracrine manner. This vicious cycle results in significant ECM deposition and accelerates the development of pancreatic fibrosis (53-55). Additionally, these inflammatory cytokines are secreted by damaged PSCs and even cancer cells, facilitating damage repair or cancer development (56,57).

Oxidative stress. The imbalance between oxidative and non-oxidative balance induces the production of large amounts of oxidative active substances, including reactive oxygen species (ROS) and reactive nitrogen species, which ultimately lead to the aging of the body and disease development (58). Pancreatic fibrosis development is also inseparable from activation of PSCs induced by oxidative stress. Aging pancreatic β cells can induce type 2 diabetes, partly due to islet fibrosis caused by activated PSCs. In order to validate these findings, Ryu *et al* (59) conducted an isolation procedure on numerous resting PSCs derived from Sprague Dawley rats. Upon exposure to elevated sugar levels, the PSCs underwent a transformation into myofibroblasts and exhibited a significant increase in proliferation. Therefore, high sugar levels promote the activation of these cells by increasing oxidative stress of PSCs, consequently exacerbating the extent of islet fibrosis. To inhibit the progression of pancreatic fibrosis and prevent β cell dysfunction, Zhang *et al* (60) employed glutathione as a means to mitigate ROS generation in pancreatic tissue. Consequently, this intervention led to a reduction in the population of PSCs and a decrease in the severity of pancreatic fibrosis. These effects were achieved by modulation of the ROS/TGF-β/SMAD signaling pathway. The expression of fibromodulin (FMOD) and α-SMA by establishing a rat CP model has been previously determined; it was discovered that it is closely related to the degree of pancreatic fibrosis. Further experiments confirmed that FMOD upregulation increased collagen I expression and α-SMA and the proliferation and migration of PSCs, while the co-culture of pro-oxidant MND and PSCs increased FMOD levels, subsequently promoting PSCs activation (61). Therefore, reducing the production of exogenous ROS has also become the main contributor to pancreatic fibrosis.

Extracellular pressure. Mechanical stimulation plays an important role in cell growth and differentiation. It actively contributes to several cellular processes, including participating in the cell cycle, autophagy, and other processes influencing organismal homeostasis. Moreover, mechanical stimulation has been implicated in developing several pathological conditions, including heart disease, autoimmune diseases and cancer (62). Pancreatic lesions, increased tissue pressure and massive fibrosis often accompany the development of CP. To further understand the effect of extracellular hypertension on pancreatic fibrosis, the researchers induced a decrease in superoxide dismutase activity and increased ROS production in PSCs by adding compressed helium to the pressure loading device and applying pressure to PSCs, ultimately causing PSCs to produce a large amount of ECM and α-SMA, and the elimination of stress prevented the aforementioned outcome (63). Radoslavova *et al* (64) revealed that Ca^{2+} channels on the PSCs' membrane mediated the occurrence of the aforementioned behaviors. In addition to pancreatitis, the hypoxic microenvironment in which pancreatic tumors are located is a high-pressure environment, and the proliferation of tumor-associated fibroblasts is closely related to it (65). However, there are few studies on the link between extracellular hypertension and PSCs activation, and the pathway of hypertension-induced PSCs activation needs further exploration.

Calcium signaling. Previous studies have shown that the mechanical properties of the PC microenvironment can greatly promote activation of PSCs. These mechanical features include increased tissue pressure, as well as other elements previously discussed. It is plausible that this activation process is associated with the activation of relevant ion

signals (66). These ion channels mainly convert mechanical forces into intracellular biological signals, acting as sensors in which calcium ions' conduction plays a key role. This process then triggers a cascade of cellular reactions, encompassing cell proliferation, migration and the secretion of relevant proteins (67). Radoslavova *et al* (64) revealed that extracellular high-pressure mechanical forces increase Ca^{2+} inflow into mouse PSCs through TRPC1 activation, whereas TRPC1 KO leads to inactivation of ERK1/2 and SMAD2 pathways and decreased Ca^{2+} inflow in PSCs. Finally, the proliferation and migration ability of PSCs deteriorated. The activation of PSC under hypoxia is related to the regulation of TRPC6 signaling, and calcium ion signaling appears to be involved in this activity (68). Additionally, as a free radical messenger mediating inflammation and vasodilation, NO production is closely related to the activation of calcium ion signal in PSC. Blocking the interaction between calcium ions can inhibit NO production to protect PSC and PAC from necrosis, a potential target for anti-inflammatory therapy (69). Moreover, pancreatic fibrosis induced by AMP, ADP and ATP-induced signaling depends on increased calcium ion concentration in PSC, and macrophages are involved in the important process (70). Further studies are needed to clarify the relationship between calcium ion related signals and the active state of PSC.

Intracellular signaling. The activation of PSCs is also inseparable from the conduction of intracellular signals, including PI3K/AKT, mitogen-activated protein kinase (MAPK), Smad, proliferator-activated receptor-g, and nuclear factor κB (NF-κB). A deeper understanding of these mechanisms affecting activation of PSCs is expected to provide new avenues for reversing pancreatic fibrosis-related diseases.

PI3K/AKT. The PI3K/AKT pathway is important in carcinogenesis, inflammation and other related diseases. Furthermore, it is essential for the activation of PSCs (71,72). Coenzyme Q10 (CoQ10), a coenzyme with a powerful antioxidant function, participates in electron transport in mitochondria, and regulates the inflammatory response. The CoQ10 has been shown to effectively inhibit activation of PSCs and stop the progression of pancreatic fibrosis. Simultaneously, the PI3K/AKT/mTOR signaling axis participates in this reaction, and this result can be implemented by establishing a C57BL/6 mouse model (73). Cui *et al* (74) additionally identified the involvement of the PI3K/AKT pathway in the activation of PSCs. In their study, they induced a rat model of CP and observed increased activation of PSCs, along with significant secretion of collagen. After the infusion of different doses of Saikosaponin d (SSd) into the aforementioned model, the utilization of SSd was documented for subsequent histological and molecular biological investigations. The findings revealed that the use of SSd inhibited PSCs activation and ECMs production, consequently mitigating pancreatic damage induced caused by inflammation. It was further reported that this phenomenon is achieved by crosstalk in the PI3K/Akt/mTOR and TGF-β1/Smads pathways. Carbon monoxide (CO) inhibits various cells as an endogenous gaseous signaling transmitter. It has been revealed that CO released by the CO-releasing molecule-2 can inhibit protein synthesis by mediating eukaryotic elongation factor 2 phosphorylation and 4E-binding protein 1 inactivation. Consequently, this leads to the downregulation of PSCs cyclin D1 and cyclin E and the arrest of the cell cycle, preventing activation of PSCs. The occurrence of these cellular activities is closely related to inhibition of PI3K/Akt/mTOR signaling (75). The PI3K/Akt/mTOR pathway is expected to provide an effective target for treating pancreatic fibrosis.

MAPK. As a key hub for communication between cells and beyond, the MAPK pathway involves physiological processes, including cell proliferation, differentiation and cycling. Moreover, it regulates the pathogenesis of several diseases, including cancer, inflammation and autoimmune diseases (76,77). Highly aggressive PDAC has a dense fibrotic matrix that acts as a barrier to immunosuppression. The formation of this matrix is primarily influenced by the interaction of PSCs with cancer-associated fibroblasts (CAF). This interaction leads to sustained activation of inflammatory signals in the tumor microenvironment (TME) through the production of inflammatory and chemokines, ultimately promoting the malignant progression of cancer. As a chaperone protein, heat shock protein (Hsp90) regulates various cellular activities between immune cells and tumors in TME. The use of Hsp90 inhibitors has been revealed to reduce PSCs' activation and α-SMA expression through Janus kinase (JAK)/signal transducers and activators of transcription (STAT) and MAPK/ERK signaling, limit PSCs/CAF growth and enhance sensitivity to PD-1 blockade (78). Oxidative stress can also use the MAPK/AP-1 signaling axis to promote FMOD overexpression in PSCs, subsequently causing upregulation of collagen I and α-SMA and proliferation and migration of PSCs, while the use of ERK and Jun N terminal kinase (JNK) inhibitors reverses the aforementioned results (61). During alcohol-induced pancreatic fibrosis, activation of PSCs is always accompanied by the loss of cytoplasmic retinol. Additionally, previous studies have confirmed that ethanol can mediate PSCs' activation through the MAPK pathway. Consequently, the question is if retinol supplementation prevents ethanol-induced PSCs' activation. This problem is explained by McCarroll *et al* (79), who co-cultured retinol and its metabolites ATRA and 9-RA with ethanol-treated PSCs and revealed a significant decrease in α-SMA, collagen I, fibronectin and laminin in the medium, accompanied by a decrease in activation of MAPKs (EKR1/2, p38 kinase and c-JNK). Finally, activation of PSCs was inhibited (76). The MAPK signaling pathway has also become an effective way to inhibit PSCs' activation, requiring further comprehensive investigation.

TGF-β/Smad. The TGF-β is an important regulator of fibrotic disease occurrence, which can regulate the transformation of fibroblasts to myofibroblasts. Through interaction with the downstream cytoplasmic transcription factor Smads, TGF-β induces the collagen synthesis, and is widely involved in physiological and pathological processes, including tissue fibrosis and tumor occurrence and development (80-82). Especially in pancreatic diseases, TGF-β/SMAD is crucial for pancreatic wound healing, cell growth, cell cycle regulation, angiogenesis and immune regulation (83-85). Derived from hormone-like muscle factors produced by skeletal muscle motor response, irisin is involved in various body activities, including systemic inflammation, bone balance maintenance, metabolic

regulation and cancer proliferation (86). Irisin has attracted marked attention for its ability to alleviate the process of tissue fibrosis, including heart, liver and kidney fibrosis (87-89). This antifibrotic effect was also demonstrated in the mouse CP model. Continuous stimulation of inflammation causes pancreatic damage and extensive fibrosis while increasing irisin, a protective factor, significantly reduces the degree of apoptosis and necrosis of pancreatic cells. Furthermore, the immunohistochemistry results of pancreatic tissue showed a significant reduction in ECM deposition, which correlated with the oxidation-reduction and ER stress in pancreatic cells from CP mice. *In vitro* experiments also confirmed that these effects are mediated by downregulating kindlin-2 and inhibiting the SMAD2/3 pathway (90). Berberine (BR), extracted from the root and rhizome of various Ayurvedic and Chinese medicinal plants, has numerous pharmacological effects, including anti-inflammatory and fibrotic. In the cerulein-reduced pancreatitis model, it was revealed that BR intervention inhibited collagen deposition in pancreatic tissue, the infiltration of inflammatory cells, pancreatic vacuolization and pancreatic cell atrophy through histopathological analysis, and improved the degree of pancreatic damage. At this time, the markers of PSCs activation markers, including α-SMA, Collagen1a, collagen3a and fibronectin, were significantly downregulated, and further experiments confirmed that BP alleviated the fibrosis process of CP by activating the AMPK pathway by inhibiting TGF-β1/Smad signaling (91). In addition, Choi *et al* (92) confirmed that piperine, derived from black pepper, improves the degree of pancreatic fibrosis in a dose-dependent manner. The mechanism involves piperine inhibiting TGF-β-induced pSMAD2/3 activation, followed by a reduction in the expression of fibrotic mediators in PSCs, including α-SMA, collagen and fibronectin1, ultimately achieving the therapeutic purpose of CP. The targeted intervention combined with traditional Chinese medicine may be effective in stopping the process of pancreatic fibrosis.

Peroxisome proliferator-activated receptor (PPAR). Peroxisome proliferators are widely known for their involvement in various intracellular metabolic processes, belonging to ligand-induced nuclear receptors. These receptors include three subtypes, namely PPAR-α, PPAR-β/δ, and PPAR-γ (93). Previous studies have confirmed that in addition to regulating whole-body energy homeostasis, PPAR, especially PPAR-γ, plays a key role in blocking PSCs' activation (94). Wang *et al* (95) used taurocholate (TLC) to treat AR42J cells to establish a CP model. They subsequently extracted exosomes secreted by acinar cells and manipulated the expression of miR-130a-3p by overexpression or knockdown techniques. Finally, they incubated PSCs with the aforementioned exosomes. In the miR-130a-3p overexpression group, expression levels of activation markers α-SMA protein and fibrotic markers collagen I and collagen III in PSCs were significantly elevated at the RNA and protein levels. The knockdown of exosome miR-130a-3p significantly inhibited PSCs' activation and fibrosis. Further experiments have confirmed that exosome-derived miR-130a-3p promotes pancreatic fibrosis by inhibiting PPAR-γ expression in PSCs, ultimately exacerbating the severity of CP. Albumin is a plasma protein primarily synthesized by liver cells. Its primary function is to support to maintain the nutrient metabolism of body and facilitate the maintenance of the internal environmental conditions necessary for tumor growth. However, PSCs extracted from the rat pancreas exhibit a significant ability to detect and regulate high levels of albumin in order to sustain their quiescent condition. However, when albumin content decreases after PSCs' activation, PPAR-γ and C/EBP-α expression levels decrease. The albumin content is increased by overexpressing PPAR-γ and C/EBP-α, whereas activated PSCs undergo a transition toward a resting state. Albumin-mediated PPAR-γ or C/EBP-α-induced phenotypic changes in PSCs provide a new strategy for treating pancreatic fibrosis (96). Cyclic AMP-response element-binding protein-binding protein (CBP)/β-catenin signaling also plays an important role in organ fibrosis. The use of CBP-β catenin antagonists has been revealed to inhibit PSCs' activation, downregulate 'activation' markers [α-SMA/actin alpha 2, collagen alpha1, Prolyl 4-hydroxylase, and Survivin], and reduce their proliferation. Notably, the observed effects can be counteracted by inhibiting PPAR-γ expression. Moreover, CBP/β-catenin antagonism impedes the migration of PSCs-induced PC cells, presenting a promising therapeutic approach for managing pancreatic fibrosis (97).

NF-κB. Aberrant NF-κB signaling, functioning as a multifunctional transcription factor, has been implicated in the pathogenesis of chronic inflammation, autoimmune diseases and malignancies (98). Previous studies have shown that knocking out NF-κB p65 in PACs can promote fibrosis in rain frog-induced mouse models of CP induced by rain frogs, for which the activity of NF-κB is closely related to activation of PSCs (99). Wu *et al* (100) conducted an in-depth discussion of this phenomenon. It was hypothesized that in pancreatic inflammation, overexpressed TGF-β1 binds to receptors on PSCs to induce TAK1 phosphorylation and activation of the NF-κB signaling pathway. The NF-κB activation further promotes MMP-1/TIMP-1 imbalance, subsequently increasing ECM production and aggravating pancreatic fibrosis. Furthermore, NF-κB activation induces PSCs to produce a large amount of MCP-1, recruiting distant macrophages to aggravate the inflammatory infiltration of pancreatic tissue. Hydrogen peroxide-induced cloning-5 (Hic-5), a LIM (Lin-11, Isl-1 and Mec-3) containing adherent scaffold proteins, is involved in various physiological activities *in vivo*, including cell proliferation, differentiation, aging, apoptosis and signal transduction. Previous studies have reported that Hic-5 plays an important role in fibrotic diseases, including liver fibrosis, intestinal fibrosis and glomerulosclerosis. The researchers established a mouse model of CP to confirm whether it has similar functions in pancreatic fibrosis. Compared with the untreated group, the pancreas size and weight of Hic-5 knockout mice were significantly increased. Additionally, there was a significant decrease in pancreatic tissue necrosis and inflammatory infiltrates, as well as a reduction in the extent of fibrosis. These observed effects can be attributed to inhibiting downstream NF-κB/p65/IL-6 signaling. As a diterpenoid epoxide with immunosuppressive activity, triptolide can reduce the activation ability of PSCs by inhibiting the transcriptional activity of NF-κB/p65, thereby reducing the fibrosis process of CP mice. These findings hold promise for developing novel therapeutic

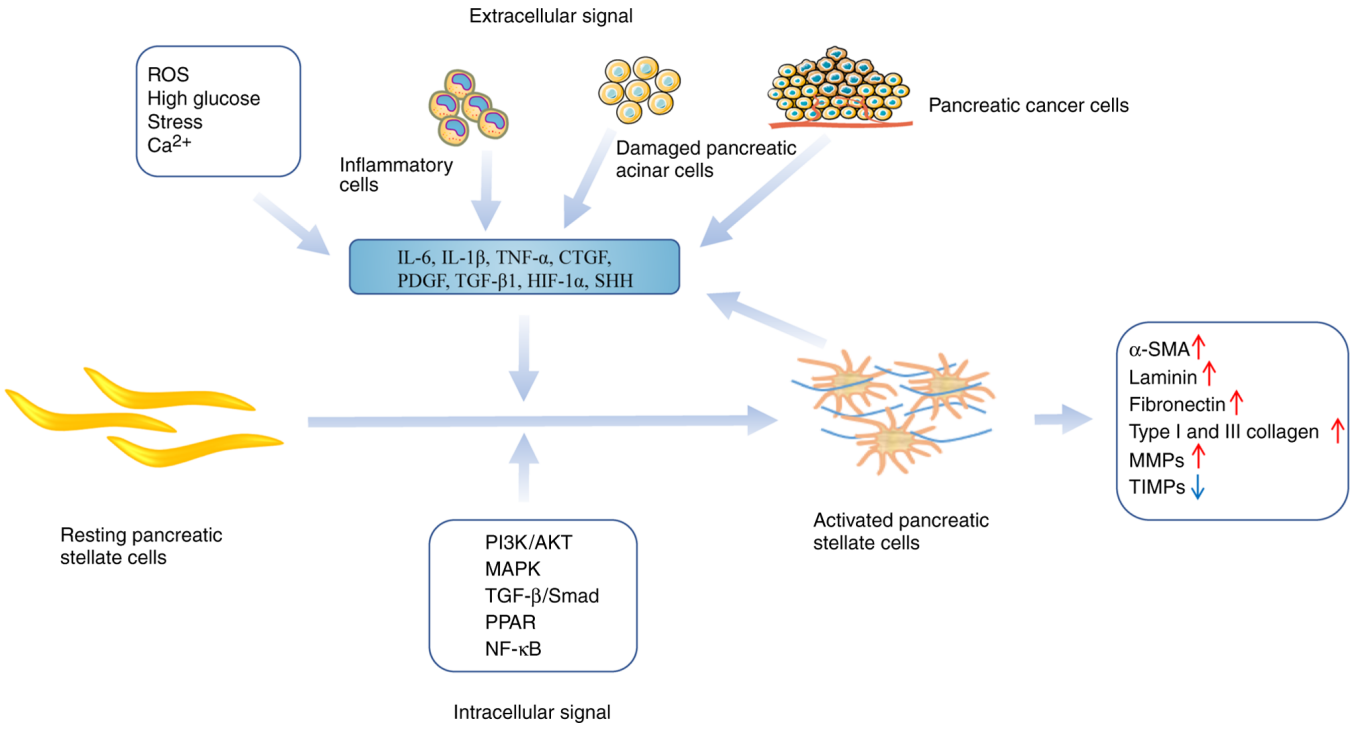

Figure 1. The molecules and signaling pathways are related to converting PSCs from resting to active states. The figure describes the main intracellular and extracellular signals transforming PSCs from resting to active states, including high glucose, stress, oxidative stress, inflammatory factors, and the MAPK and PI3K/AKT signaling pathways. Upon activating PSCs, there is an observed increase in the secretion of α-SMA, laminin, fibronectin, and type I and III collagen associated with ECM. Additionally, there is an alteration in the equilibrium between MMPs and TIMPs, indicating an imbalance in their regulation. PSCs, pancreatic stellate cells; α-SMA, α-smooth muscle actin; ECM, extracellular matrix; MMP, matrix metalloproteinase; TIMP, metallopeptidase inhibitor 1.

approaches for managing clinical CP patients (101). As a mediator of cell activation, Retinoblastoma (RB) also acts as a signal receiver to exert anti-inflammatory and antitumor effects, especially in the superphosphate state (102). Massively releasing pro-inflammatory mediators activate PSCs in pancreatic injury, which subsequently induces pancreatic fibrosis and systemic inflammation. As previously mentioned, the sequence of actions is closely connected to the involvement of hydrogen sulfide, which plays a regulatory role in the development of proteins associated with the inflammatory response through the activation of NF-κB (103). Growing evidence suggest that the RB state regulates hydrogen sulfide production, especially during RB super-phosphorylation. The large production of hydrogen sulfide induced a large increase in serum amylase, inflammatory factor TNF-α, pancreatic edema and lung injury in mice. Super-phosphorylation of RB depends on the extensive infiltration of CDK4/6. The utilization of CDK4/6 inhibitor palbociclib decreased the level of RB phosphorylation, downregulation of hydrogen sulfide production and NF-κB activation, and the reversal of pancreatic inflammation and fibrosis (104). Targeting NF-κB may effectively reduce the process of pancreatic fibrosis. However, more investigation is necessary to elucidate its efficacy fully. The molecules and signaling pathways related to converting PSCs from resting to active states are demonstrated in Fig. 1.

3. The key role of PSCs' activation in damage repair

As one of the most important parenchymal organs in the human body, it is extremely difficult for the adult pancreas to repair itself due to slow cell renewal and low regeneration ability. Therefore, in addition to exogenous damage, pancreatic damage caused by AP, CP and PC is difficult to recover, which is closely associated with the inherent characteristics of PSCs. This section summarized the mechanism of action of PSCs and their activation in repairing pancreatic injury.

PSCs' activation promotes the secretion of ECM. The ECM is a dynamic structure outside the cell, which is essential for regulating the proliferation, migration, differentiation and other aspects of cells, and its existence provides an effective barrier for the structural and functional integrity of tissues (105,106). However, remodeling of ECM (composition, abundance and hardness) contributes to progression of diseases, including fibrosis and cancer (107,108). Concurrently, repairing pancreatic injury is strongly connected to the involvement of ECM since the creation and deposition of ECM promote fibrosis formation, which afterwards facilitates the restoration of tissue defects (109). A previous study revealed that pancreatic injury-induced activation of PSCs was followed by increased production of laminin, fibronectin, and type I and III collagen, compared with resting PSCs, which are important manifestations of ECM accumulation. Compared with normal pancreatic tissue, excessive ECM secretion and remodeling are beneficial for post-injury repair (13). Additionally, activated PSCs secrete cytokines, chemokines and growth factors, and induce an imbalance between MMP and TIMP, further promoting fibrosis (110). Therefore, activating targeted PSCs to inhibit excessive ECM secretion can effectively hinder the pancreatic fibrosis process.

Activation of PSCs enhances the EMT pathway. EMT is a complex biological process characterized by a series of sequential steps. During EMT, epithelial cells undergo a phenotypic transformation, acquiring characteristics similar to the interstitial phenotype. Several modifications, including disruption of the ECM, reconstruction of the cytoskeleton and production of ECM proteins, accompany this transformation significantly contributes to embryonic development, chronic inflammation, cancer and several fibrotic diseases (111,112). The EMT is divided into three types, of which type 2 EMT can transform epithelial cells into fibroblasts, promote the secretion of tissue ECM, and is closely related to injury repair and organ fibrosis (113). It was revealed that the activation of PSCs shared morphological and functional changes with the EMT process. After PSCs' activation, the classical regulatory molecules of EMT process, including E-cadherin, N-cadherin and vimentin can change accordingly. Furthermore, bone morphogenetic protein 7 and S100 calcium-binding protein A4 (S100A4) experienced significant protein content. The BMP signaling inhibits the progression of EMT, ultimately affecting tissue fibrosis and cancer progression. Additionally, S100A4 expression increased significantly in fibroblasts when the PSCs remained fully activated, implying an enhancement of the type 2 EMT process (114-117). Xu *et al* (118) also confirmed that the enhancement of EMT accompanies the activation of PSCs. It was revealed that TGF-β1 is strongly associated with pancreatic fibrosis, a result achieved by triggering activation of PSCs and promoting EMT through the PI3K-Akt signaling axis. Therefore, PSCs are considered to be essential in repairing damaged pancreatic tissue through EMT. The activation of PSCs involves transitioning from a resting state to a fibroblast-like phenotype, resembling an EMT-like process.

Crosstalk between PSC activation and mononuclear macrophages in the pancreatic microenvironment. Pancreatic injury repair is inseparable from the interaction of numerous microenvironment components (119,120). Particularly, PSCs' activation can regulate other cell functions, ultimately affecting the regeneration of pancreas (121). Infiltration of monocytes in the body is characteristic of several fibrotic diseases. Furthermore, macrophages can differentiate into different phenotypes by stimulating the microenvironment within the receptor, mainly including the M1 and M2 types, called macrophage polarization, mainly including the M1 and M2 types, which are called macrophage polarization. Among them, the M1 type is mainly manifested as pro-inflammatory, and M2 macrophages are selectively activated macrophages, which have anti-inflammatory and pro-fibrotic effects and can be directly activated by cytokines including IL-4 and IL-13 (122). Pancreatic injury can induce macrophage differentiation to M2 type by activating PSCs' production of IL-4 and other factors, further promoting the secretion of ECM in pancreatic tissues and accelerating injury healing (123). Michalski *et al* (124) established a monocyte and PSC co-culture system and revealed that infiltrated monocyte macrophages can promote PSCs' activation and improve autocrine capacity of PSCs, which may lead to persistent chronic inflammatory states. Another study has reported that lipopolysaccharide-stimulating macrophage activation promoted PSCs over-secretion of ECM and pancreatic fibrosis, an effect achieved by TGF-β (125). Furthermore, when the static PSC was co-cultured with macrophages, TGF-β1, fibroblast growth factor-2, TGF-α and PDGF, and tumor necrosis factor (IL-1 and IL-6) deactivate PSCs and transform them into myofibroblasts (126). Gerasimenko *et al* (127) revealed that a special pathway between PSC and macrophages, in which PSC secretes IL-18 in response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptor activation. Subsequently, IL-18 stimulates macrophages to induce the production of numerous calcium ion signals and inflammatory factors. This mechanism plays a significant role in AP outbreak and fibrosis. Further exploring the interaction between activated PSCs and macrophages may be crucial for repairing pancreatic damage.

Activated PSCs differentiate into parenchymal cells. Pancreatic parenchymal cell proliferation is important in repairing the damaged pancreas. Several studies have revealed that pancreatic stem cells exist in pancreatic acinar and islet tissues, which can control acute inflammatory response by antagonizing the release of inflammatory mediators, reducing immune response, and differentiating into PACs and endothelial cells to repair damaged pancreas (128,129). It has been established that various pancreatic mesenchymal cells have been established to have stem cell functions, including nestin-positive cells and side population cells (130,131). Moreover, it has been previously revealed that activated PSCs have biological phenotypes of pancreatic stem cells, including common markers (nestin, CK-19 and ATP-binding cassette superfamily G member 2) (132). Several studies isolated part of PSCs from pancreatic tissues of rats and measured their expression of various stem/progenitor cell markers, including CD133 and paired-like homeodomain 2 (133). Additionally, as the signaling pathways necessary for stem cell maintenance and development, β-catenin-dependent Wnt and Notch signaling participate in the cellular regulation of PSCs, indicating that PSCs have a characteristic expression profile of stem cells, clonal cell growth, long-term survival transplantation ability and regeneration process (134). The source of pancreatic stem cells is still debated. However, according to the aforementioned research analysis, the function of PSCs is limited to the secretion of ECM, and as a cell with differentiation potential, by differentiating into cells with pancreatic endocrine function and then supplementing and repairing pancreatic necrotic tissue from the cellular level when pancreatic damage, but more studies are needed to confirm it in the future. The mechanisms of action of activated PSCs in pancreatic injury repair are presented in Fig. 2.

4. PSCs in pancreatic disease

Type 2 diabetes. Type 2 diabetes is a chronic metabolic disorder characterized by fundamental pathophysiological features, including islet β cell dysfunction and insulin resistance (135). The functional status of pancreatic islets β cells is crucial for the progression of type 2 diabetes. Especially when the body develops insulin resistance, pancreatic islets β cells exhibit a heightened ability to adapt and respond to elevated metabolic demands. However, the dysfunction of pancreatic islet β cells means this glucose cannot be converted and

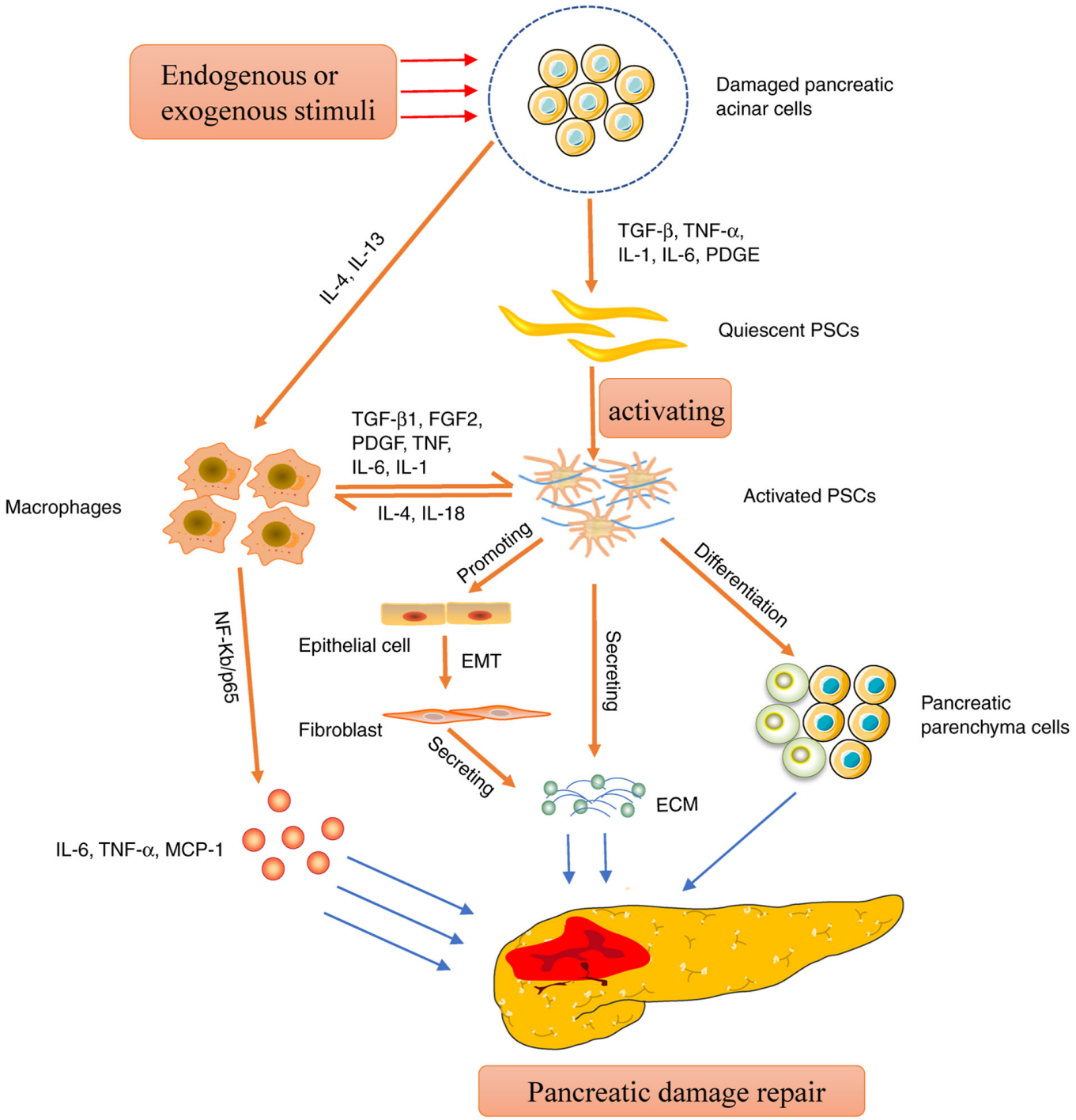

Figure 2. Mechanism of action of activated PSCs in pancreatic injury repair. This figure mainly describes the self-secretion of ECM when resting PSCs are activated, and the secretion of ECM through the EMT pathway to promote pancreatic fibrosis. Additionally, activated PSCs promote pancreatic injury repair by recruiting monocytes for macrophage infiltration and inducing macrophages to polarize to M2 type, followed by the secretion of IL-6, TNF-α and other factors. Activated PSCs have characteristics resembling those of pancreatic stem cells, which can be guided toward differentiation into pancreatic endocrine cells, hence facilitating pancreatic repair. PSCs, pancreatic stellate cells; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition.

utilized, eventually leading to a continuous increase in blood sugar (136). The causes of secretory dysfunction of pancreatic islet β cells include chronic inflammation, endoplasmic reticulum stress, glucolipid toxicity and oxidative stress (137). Furthermore, the fibrosis of islets causes irreversible damage to the β cells of islets, ultimately promoting the progression of diabetes. In this process, activated PSCs play a crucial role (138,139). Previous studies have revealed islet fibrosis obvious in rat models with type 2 diabetes. Additionally, a substantial presence of α-SMA-positive cell infiltration is observed in and around pancreatic islets, confirming that activated PSCs are closely related to islet fibrosis in type 2 diabetes. The investigation of oxidative stress as a potential contributor to the progression of islet fibrosis through the activation of PSCs deserves additional examination, given its significance as a key determinant (140). Ryu *et al* (59)

revealed that the use of antioxidants reduced islet fibrosis by establishing an animal model of type 2 diabetes and measured that the degree of PSCs activation was reduced at this time. High-glucose feeding reversed the aforementioned results, and ROS, α-SMA, fibronectin, collagen and cytokines production in PSCs increased, confirming that high sugar increased the oxidative stress of PSCs, induced its activation and ultimately promoted islet fibrosis. Conophylline (CnP), as a natural compound, is effective in promoting the proliferation of pancreatic islet β cells and exerts antifibrotic effects. To further understand the mechanism, the researchers revealed that the medium added to CnP when PSCs were cultured *in vitro* decreased collagen production. The activation of PSCs was also reduced by establishing a rat model of type 2 diabetes mellitus and obtaining pancreatic pathology sections. After immunohistochemistry analysis, it was revealed that the infiltration level of pancreatic CD68-positive macrophages and PSCs in rats fed with CnP was significantly reduced. Additionally, there was a significant improvement in islet fibrosis. These findings confirmed that CnP could inhibit islet fibrosis and promote the regeneration of islet β cells by affecting the activation of PSCs (141). Targeted activation of PSCs may become an effective treatment for type 2 diabetes.

Pancreatitis

AP. This condition is defined by the self-digestion of the pancreas and its surrounding tissues, which is triggered by the excessive release of excess intracellular calcium (142). However, PSC is not only activated in PC or PC, and numerous calcium ion signals can be generated even in the normal microenvironment, which is an important pathophysiological mechanism of AP (143). Previous studies have revealed that elevated bradykinin levels in AP are associated with calcium signaling. First, bradykinin induces calcium signal storage in PSC inositol triphosphate through the B2 receptor and then releases the CRAC channel into pancreatic acinar cells under the action of the inositol triphosphate receptor. Using B2 receptor or CRAC channel inhibitors can reduce PAC necrosis induced by pancreatitis (144). However, in the experimental model of alcohol-related, bradykinin production is initially mediated by PACs. The initial injury of acinar cells includes the entry of kallikreins and other substances into the interstitial fluid, leading to an increase in bradykinin concentration, which promotes the activation of calcium ion signals in PSC and the subsequent release of a large amount of NO. This could accelerate the deterioration of acinar cells and aggravate the progression of pancreatitis. Pharmacological inhibition of NO synthase can provide a highly effective anti-necrosis effect, which was also confirmed by Gryshchenko *et al* (145) and Jakubowska *et al* (69). Unlike alcoholic pancreatitis, bile acid-induced AP has a lower degree of fibrosis, mainly due to bile acid-dependent calcium signal and NA-bile acid cotransporter-mediated eliminating effect on PSCs. Targeting NA-dependent bile acid transport provides the pharmacological basis for intervention in the acute phase of biliary pancreatitis (146). In addition to releasing bradykinin, ATP, ADP and other substances are released to activate purinergic receptors on the surface of macrophages, producing numerous calcium signals and secreting numerous inflammatory factors to aggravate pancreatic inflammatory storms. Relevant experiments showed that suramin blocking ATP can significantly reduce the levels of cytokines in AP plasma, including IL-6 and the degree of pancreatic injury (147). Furthermore, inhibition of the SARS-CoV-2 receptor to block calcium signal production of calcium signals in macrophages is expected to reduce the degree of inflammation in AP (123).

CP. When pancreatic inflammation occurs repeatedly, CP is formed by prolonged stimulation, accompanied by progressive destruction of the pancreatic acinar and massive fibrosis, eventually leading to the loss of pancreatic function, a process that currently has no means of reverse (148). Previous studies have shown that the activation of PSCs plays a crucial role in the fibrotic process of CP. The hydrogen peroxide-inducible clone 5 (Hic-5) acts as an adherent plaque scaffold protein that controls the cytoskeleton and influences vascular remodeling and disease fibrosis (149). Gao *et al* (150) evaluated the expression of Hic-5 in normal pancreatic tissues and CP tissues by immunohistochemistry and immunofluorescence, and it was revealed that it was highly expressed in activated PSCs in human CP tissues. When Hic-5 was knocked out in cerulein-induced CP fibrosis mice, the expression of pancreatic fibrosis-related factors, including Col1a1 and Col3:1 was significantly reduced, and the degree of PAC destruction and fibrosis was significantly reduced, confirming that Hic-5 contributes to the progression of CP fibrosis. Further research study has revealed that Hic-5 regulates the activation of PSCs and the production of ECM through the TGF-β/Smad signal axis, ultimately affecting the fibrosis process of CP. Autophagy is a dynamic process by which cells selectively eliminate dysfunctional cellular components through lysosomes. This process facilitates the timely screening of damaged organelles and other components to maintain intracellular metabolism, nutrient and energy balance (151). The aforementioned study identified that the activation of PSCs depends on autophagy and ultimately affects the CP fibrosis process. In this process, Lnc-PFAR is essential and its inhibition affects the expression of α-SMA, collagen I, collagen III and fibronectin in PSCs, which is caused by regulating the maturation of miR-141-5p. The Lnc-PFAR facilitates autophagy and exacerbates pancreatic fibrosis by reducing pre-miR-141 maturation in CP. The miR-141-5p induces dephosphorylation of Unc-51 like autophagy activating kinase 1 by binding to RB1 inducible Coiled-Coil 1, which ultimately inhibits autophagy and PSCs' activation. Furthermore, *in vivo* experiments also validate the accuracy of these findings. Therefore, the high expression of Lnc-PFAR reflects the severity of CP fibrosis and has also become a biomarker for early detection of CP (152). Moreover, the disorder of lipoprotein metabolism in PSCs is an important contributor to CP progression. Particularly, very low-density lipoprotein receptor overexpression promotes the accumulation of intracellular lipids, which subsequently causes the excessive release of IL-33 by PSCs. Conversely, PSCs-derived IL-33 inversely promotes the activation of PSCs, eventually causing PSCs to secrete ECM, leading to fibrosis during CP (153). Briefly, targeting the correlated factors of PSCs activation may effectively reverse the process of fibrosis during CP.

PC. PC, a malignancy mostly affecting the digestive tract, exhibits notable features, including delayed detection, heightened aggressiveness and poor prognosis, with a survival rate of <10%. PC is expected to be the second leading cause of global

cancer-related death by 2030 (154,155). Tumor-interstitial interactions are considered to contribute to the progression of PC cancer progression significantly. The infiltrated collagen matrix is produced by activated PSCs, which are closely related to cancer cells and components in the microenvironment, including immune cells, endothelial cells and microorganisms, and participate in malignant biological behaviors such as tumor growth and metastasis invasion (156). As a bridge between cancer cells and the microenvironment, exosomes mediate the crosstalk of components between PSCs cells and PC cells to regulate tumor proliferation. It has been revealed that miR-5703 in PSC secreted exosomes can promote PC cells' proliferation. A previous study has demonstrated that miR-5703 ultimately promotes the progression of PC by binding to CKLF-like MARVEL transmembrane domain containing 4 and inducing its expression downregulation, which is achieved by the PAK4/PI3K/AKT signal axis. These results were verified in animal experiments, confirming that PSCs-derived exosomes mediate the malignant process of PC (157). As a member of the neurotrophic factor family, the NGF is closely related to PC proliferation, apoptosis and metastasis. Jiang *et al* (158) revealed a high expression of NGF by isolating PSCs in pancreatic tissues and then co-culturing PSCs with PC cells; it was revealed that PC cells' invasion and proliferation ability was significantly enhanced. This promotion is achieved by overexpressing NGF, which further binds to TrkA on the PC cell membrane and activates the PI3K/AKT/GSK signaling axis, which then promotes the secretion of MMP9, vimentin and E-cadherin, and ultimately enhances the proliferation and invasion ability of PC cells. The Wnt and tenascin C (TnC) are key regulatory mediators during PC cell interaction with PSCs, which promote tumor proliferation and metastasis by activating oncogenic β-catenin and YAP/TAZ signaling pathways in PC cells in a paracrine manner. Targeting of N-myc downstream-regulated gene-1 (NDRG1) by di-2-pyridylketone-4-cyclohexyl-4-methyl-3-thiosemicarbazone (DpC) inhibited PSCs secretion of Wnt and TnC, while weakening the activation of Wnt/β-catenin and YAP/TAZ signaling in PC cells, hindering the connection between PSCs and PC cells and PC progression. Moreover, NDRG1 inhibition affects PSCs activation mediated by PC cells through TGF-β. Furthermore, *in vivo* experiments have confirmed that NDRG1 and DpC inhibit Wnt/TnC-mediated interactions between PC cells and PSCs (159).

Dense fibrotic stroma is characteristic of pancreatic tumors, achieved through the interaction between PC cells and stromal cells, including PSC (5). Activation of PSC enhances malignant processes of PC, including EMT and stem expression of tumor cells (160,161). The fibrous matrix created by PSC provides the PC cells with hypoxia, nutrient deficiency, oxidative stress and an acidic environment. Cancer cells and PSCs are under constant pressure to adapt to their surroundings, and they do so by altering the expression of signaling molecules, transporters and metabolic enzymes (161). Previous studies have shown that PC tissues are significantly hypoxic compared with neighboring normal tissues, accompanied by HIF-1 activation. Hypoxia-induced upregulation of HIF-1 can promote the expression of transcription factor TWIST and enhance EMT in cancer cells (162). Additionally, HIF-1 can mediate CTCF production to protect PC from hypoxic-induced apoptosis and enhance gemcitabine resistance (163,164). Moreover, HIF-1 recruits macrophages by inducing PC cells to secrete large amounts of chemokines, including CCL2. Numerous tumor-associated macrophages promote the expression of miR-4465 and miR-616-3p in PSC, leading to increased proliferation, migration and invasion of PC (165). The hypoxia of tumor is accompanied by the mass production of superoxide anion, hydroxyl radical, hydrogen peroxide and oxidative stress reaction. To prevent excessive oxidative stress from damaging cancer cells, tumors upregulate the expression of NRF2, a transcription factor that recognizes elements of the antioxidant response in target genes (166). Increased NRF2 promotes chemotherapy resistance, EMT and metabolic remodeling of PC cells (167,168). *In vivo* animal models confirm that oxidative stress activates PSCs, and activated PSCs can secrete IL-6 and matter-derived factor-1α, which in turn activate PC cells to express NRF2. This results in increased cancer cell proliferation and reduced oxidative stress response, which has been confirmed *in vivo* in animal models (169,170). Several NRF2 inhibitors have been applied in preclinical studies, including NSC84167 and fluofuranone (171,172), and are expected to enter clinical trials for further validation. Targeting the signal axis between PSCs and PC may play an irreplaceable role in treating PC, and it is worth further exploration in the future. The role and mechanism of PSCs' activation-related factors in pancreatic diseases are summarized in Table II.

5. Therapeutic applications targeting PSCs

Targeting PSCs' activation. The activation of PSCs is a double-edged sword, and regulation of the transition from the resting state to the active state of PSCs depends on the state of the organ or tissue itself. When the pancreas is damaged, PSCs can be activated and produce numerous ECM components, including fibrin, to reduce body damage. Therefore, factors related to the activation of PSCs will become targets for the repair of pancreatic damage, including IL-10 and TGF-β (173). However, when pancreatic diseases occur, the activation of PSCs forms a vicious cycle. Therefore, inhibition of the activation of PSCs becomes the key to treating pancreatic diseases, and the aforementioned inhibitors of PSCs activation-related molecular targets are an effective choice. Additionally, traditional Chinese medicine plays an important role. For example, Resveratrol can inhibit intracellular ROS and reduce the fibrosis of CP by inhibiting the expression of miR-21 and the activation of PSCs (174). Rhein can mediate NF-κB and STAT3 signaling pathways to reduce the activation of PSCs in pancreatic fibrosis (175). Additionally, radiotherapy resistance against pancreatic malignancies is closely related to the massive activation of PSCs after radiation irradiation (176). The potential of combining activation inhibitors of PSCs with radiation as a means to sensitize PC requires further investigation.

Targeting proliferation of PSCs. It is well known that when PSC is activated, it will proliferate, accompanied by cell migration, increased ECM deposition and cytokine secretion. Therefore, when the activation of PSCs is uncontrolled,

Table II. Summary of the role and mechanism of PSCs activation-related factors in pancreatic diseases

Related factors	Patient	Mechanism of action	*In vitro/ in vivo*	(Refs.)
High glucose	Type 2 diabetes	Promotes oxidative stress in PSC and increases the expression of ROS, α-SMA, fibronectin, collagen, and cytokines.	*In vitro*	(140)
CnP	Type 2 diabetes	Reduces PSC activation, inhibits collagen synthesis and CD68-positive macrophage infiltration, and promotes islet β cell proliferation.	Both	(59)
Bradykinin	AP	Binding to the B2 receptor on PSC induces calcium ion signal production and NO release.	Both	(143)
ADP, ATP	AP	Activates purinergic receptors on the surface of macrophages and promotes PSC activation	Both	(144)
SARS-CoV-2	AP	Activating PSC to secrete IL-18 promotes macrophages to produce numerous calcium ion signals and inflammatory factors.	Both	(126)
Hic-5	CP	Activation of TGF-β/Smad promotes PSC activation and proliferation and increases Col1a1 and Col3:1 expression.	Both	(148)
Lnc-PFAR	CP	ULK1 dephosphorylation is induced by mediating the miR-141-5p/RB1CC1 axis, inhibiting autophagy and fibrosis.	Both	(151)
VLDLR	CP	Promotes lipoprotein accumulation and PSC secretion of IL-33.	*In vitro*	(152)
miR-5703	PC	Binds to CMTM and Promotes cancer progression through the PAK4/PI3K/AKT signaling axis.	Both	(156)
NGF	PC	Binds to TrkA and activates PI3K/AKT/GSK to promote MMP9, vimentin and E-cadherin secretion.	*In vitro*	(157)
Wnt/TnC	PC	Promotes tumor proliferation and metastasis by activating β-catenin and YAP/TAZ signaling axes.	Both	(158)
HIF-1	PC	Inducing the secretion of CCL2 by cancer cells recruited macrophages to promote the expression of miR-4465 and miR-616-3p by PSC.	*In vitro*	(164)
NRF2	PC	Activated PSC promotes NFR2 expression in cancer cells and reduces oxidative stress.	Both	(168,169)

PSCs, pancreatic stellate cells; ROS, reactive oxygen species; α-SMA, α-smooth muscle actin; AP, acute pancreatitis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CP, chronic pancreatitis; Col3:1, collagen type IX alpha 3 chain; ULK1, Unc-51 like autophagy activating kinase 1; RB1CC1, RB1 inducible coiled-coil 1; VLDLR, very low density lipoprotein receptor; miR, microRNA; PC, pancreatic cancer; PAK4, P21 (RAC1) activated kinase 4; NGF, nerve growth factor; TrkA, neurotrophic receptor tyrosine kinase; MMP, matrix metalloproteinase; TnC, tenascin c; YAP, yes1 associated transcriptional regulator; TAZ, WW domain containing transcription regulator 1; HIF, hypoxia-inducible factor; CCL2, C-C motif chemokine ligand 2; NRF2, NFE2 like BZIP transcription factor 2.

inhibition of PSC proliferation activity can also regulate the fibrosis process of the disease. Melatonin extracted from the pineal gland has been widely studied for its role in regulating inflammation and tumors. It is involved in regulating cell cycle and differentiation. With the participation of melatonin, the signaling pathway involved in the proliferation of PSCs (PI3K/Akt/mTOR and MAPK) is inhibited. Furthermore, mitochondrial function in PSCs is inhibited, energy generation is blocked, and proliferation of PSCs is ultimately inhibited (177). In conclusion, glucose metabolism, as the main way of energy production, will also become the direction of exploration for regulating PSCs' proliferation. Moreover, with the rise of pancreatic malignant tumors, tumor metabolism has become a focus of future research and the exploration of metabolic crosstalk between PSCs and cancer cells will be the focus of tumor treatment in the future.

Targeting of ECM. Excessive secretion of ECM is an important reason for the deterioration of pancreatic diseases. Especially for PC, the ECM is a barrier to protecting cancer cells from invasion, leading to poor therapeutic effects of molecular target drugs and chemotherapy drugs. However, tumor cells can secrete MMP to dissolve ECM to facilitate cancer cell migration and invasion. This adaptive regulation of tumors makes treatment more difficult. Moreover, under the influence of an anoxic microenvironment, the ECM structure secreted by PSCs can be remodeled to adapt to the migration of cancer cells (178). However, fibronectin in ECM can increase the resistance of PC cells to gemcitabine

by activating the ERK1/2 signaling pathway, resulting in worse clinical prognosis for patients (179). Hyaluronan, one of the main components of the gelatinous matrix of tumor ECM, has been revealed to hydrolyze the important structure of the hyaluronidase skeleton of the ECM, improve the absorption of drugs at the tumor site, and recruit more T lymphocytes for antitumor effects (180). Simultaneously, if Hyaluronan is combined with an immune checkpoint, including PD-1/PD-L1, inhibitors may provide favorable results, further preclinical or clinical trials may be warranted. This provides a new option for treating pancreatic diseases, particularly PC.

6. Summary and prospect

Recently, as the function of PSCs has been gradually revealed, it is increasingly understood that PSCs play an important role in the normal repair of pancreatic injury and are also closely related to pancreatic diseases. In the present review, it was revealed that multiple intracellular and extracellular signals are closely associated with PSCs' activation, which contributes to the understanding of the critical role that activated PSCs play in pancreatic disease development and injury repair. Targeted regulation of these signals is conducive to restoring or inhibiting the activation of PSCs, and becomes an important strategy for pancreatic injury repair and treatment of pancreatic-related diseases.

Nevertheless, there are still numerous questions that have not been elucidated clearly, including how PSCs differentiate into stem cells with differentiation ability to participate in pancreatic injury repair and whether other components in the progression of pancreatic inflammation are also involved in the regulation between PSCs and acinar cells, including endothelial cells and microbiota, and how exogenous stimuli such as radiation affect the activation and proliferation of PSCs. Moreover, the activation of PSCs in chronic inflammation of the pancreas or in progressive cancer blocks the targeted penetration of drugs, leading to the occurrence of therapeutic resistance, especially in PC. Elucidating the crosstalk between stromal heterogeneity and tumor cells is an important way to address drug resistance. In addition, the development of inhibitors against key molecular targets where PSCs play a role through multi-omics technology, combined therapy such as immunotherapy, radiation therapy or the development of precision drug delivery systems will be the future direction for PC cure. Moreover, PSCs have a wide range of subgroups and functional heterogeneity due to differences in cell surface markers and functional differences. Reversing the activation of PSCs in specific subgroups can block the secretion of ECM, which is crucial for severing the link between PSCs and pancreatic diseases. In addition, the exosome-mediated information transfer and substance exchange of PSCs reshape the microenvironment of pancreatic disease development, therefore it is of great significance to further explore the key role pathways of specific exosomes and develop corresponding targeted blocking drugs for the treatment of related pancreatic diseases. In conclusion, targeting the pathways associated with PSCs activation may provide new insight for the treatment of pancreatic diseases and pancreatic injury.

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Authors' contributions

ZW wrote, visualized and prepared the original draft. SD wrote, reviewed and supervised the editing process. WZ wrote and prepared the original draft, supervised and administrated this project and acquired funding. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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