REVIEW

Nanomedicine regulating PSC-mediated intercellular crosstalk: Mechanisms and therapeutic strategies

Hui Wang [a],[†], Liang Qi [a],[†], Han Han [b],[†], Xuena Li [c], Mengmeng Han [b], Lei Xing [b],[d], Ling Li [a],[e],[f],[*], Hulin Jiang [b],[c],[d],[*]

[a]Department of Endocrinology, Zhongda Hospital, School of Medicine, Southeast University, Nanjing 210009, China
[b]State Key Laboratory of Natural Medicines, Department of Pharmaceutics, China Pharmaceutical University, Nanjing 210009, China
[c]College of Pharmacy, Yanbian University, Yanji 133000, China
[d]Jiangsu Key Laboratory of Druggability of Biopharmaceuticals, China Pharmaceutical University, Nanjing 210009, China
[e]Institute of Glucose and Lipid Metabolism, Southeast University, Nanjing 210009, China
[f]Department of Clinical Science and Research, Zhongda Hospital, School of Medicine, Southeast University, Nanjing 210009, China

Abstract Pancreatic fibrosis (PF) is primarily distinguished by the stimulation of pancreatic stellate cells (PSCs) and excessive extracellular matrix deposition, which is the main barrier impeding drug delivery and distribution. Recently, nanomedicine, with efficient, targeted, and controllable drug release characteristics, has demonstrated enormous advantages in the regression of pancreas fibrotic diseases. Notably, paracrine signals from parenchymal and immune cells such as pancreatic acinar cells, islet cells, pancreatic cancer cells, and immune cells can directly or indirectly modulate PSC differentiation and activation. The intercellular crosstalk between PSCs and these cells has been a critical event involved in fibrogenesis. However, the connections between PSCs and other pancreatic cells during the progression of diseases have yet to be discussed. Herein, we summarize intercellular crosstalk in the activation of PSCs and its contribution to the development of common pancreatic diseases, including pancreatitis, pancreatic cancer, and diabetes. Then, we also examine the latest treatment strategies of nanomedicine and potential

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*Corresponding authors.
    E-mail addresses: lingli@seu.edu.cn (Ling Li), jianghulin3@163.com (Hulin Jiang).
    [†]These authors made equal contributions to this work.

targets for PSCs crosstalk in fibrosis, thereby offering innovative insights for the design of antifibrotic nanomedicine. Ultimately, the enhanced understanding of PF will facilitate the development of more precise intervention strategies and foster individually tailored therapeutic approaches for pancreatic diseases.

1. Introduction

The pancreas has both exocrine and endocrine functions and is the second largest digestive organ in the human body after the liver. Pancreatic parenchyma is structurally divided into exocrine and endocrine glands[1,2]. The exocrine pancreas primarily consists of pancreatic acinar cells (PACs), duct cells, and PSCs, which collectively account for over 95% of the pancreatic mass and are responsible for digestion. The endocrine gland refers to the islets, which predominantly consist of five distinct types of islet cells. The endocrine gland, known as the islets, encompasses five distinct islet cell types and plays a crucial role in modulating glucose homeostasis[1,2]. Both the exocrine and endocrine functions are impaired after the stimulation of pancreatic injury, thereby contributing to the progression of various pancreatic diseases, including pancreatitis, pancreatic cancer (PC), and diabetes[3−5]. Given the escalating incidence of pancreatic diseases over time, they pose a significant threat to human life and well-being.

Pancreatic fibrosis (PF) is the result of progressive inflammation and continuous wound healing and is the major pathological feature of pancreatitis, pancreatic cancer, and diabetes[4,6,7]. It is increasingly recognized as an important determinant of pancreatic disease etiology, treatment response, and progression[8]. In the absence of effective intervention, PF leads to dysfunction of the pancreas and an increased risk of cancer, failure to therapy, and recurrence[9]. Fibrosis is a dynamic pathological process under the control of various cells. PSCs are usually considered as the key cells of PF that promote extracellular matrix (ECM) deposition and form a pathological barrier to drug release and accumulation[4]. In addition to PSCs, multiple cells, including PACs, islet cells, pancreatic cancer cells (PCCs), and immune cells, actively participate in pancreatic fibrosis through modulating PSCs by cytokines, inflammatory mediators, and extracellular matrix components[9−11]. Intercellular crosstalk between PSCs and various cells has been an essential event involved in fibrogenesis that constantly persists and may impact the efficacy of treatment. Degradation of the deposited ECM and intervention of intercellular crosstalk will facilitate targeted drug delivery and promote PF reversal.

Recently, nanoparticles have emerged as targeted delivery platforms for therapeutic genes, peptides, and small molecules. These nanoparticles have been extensively studied for the therapy of fibrotic diseases due to their exceptional druggability, remarkable biodegradability, and excellent biocompatibility[12−14]. Li et al.[15] reported that a peptide nanoparticle anti-fibrosis agent (IGNP-JQ1) inhibited the proliferation of hepatic stellate cells (HSCs) and reduced collagen deposition, an integrated systemic strategy for the therapy of liver fibrosis. Additionally, Bai et al.[16] designed an inhalable and mucus-penetrative nanoparticle (NP) system incorporating siRNA against IL-11 (siIL11@PPGC NPs). This system has been shown to increase drug accumulation in the lung, significantly reducing fibrotic development and improving lung function in idiopathic pulmonary fibrosis. Recently, Han et al.[17] used a nano-system based on the "nanodrill" strategy (LA-PC) to target PSCs and enhance the accumulation of all-*trans* retinoic acid (ATRA). The drug delivery efficiency through LA-PC was more than five times higher than free ATRA, and the degree of pancreatic fibrosis was significantly reduced. The use of nanomedicines has revolutionized the field of precision medicine. Compared to conventional drugs, nanomedicines can significantly increase the duration of blood circulation, improve targeting capabilities, and enhance therapeutic effects.

Accumulating evidence suggests that intercellular crosstalk between PSCs and other pancreatic cells significantly contributes to PSC activation and fibrogenesis[18,19]. However, the interactions occurring during disease progression have yet to be discussed. Hence, this review further summarizes fibrosis in the pathogenesis of three prevalent pancreatic disorders, namely pancreatitis, pancreatic cancer, and diabetes, along with an analysis of the intricate cellular interactions within the fibrotic microenvironment (Fig. 1). Meanwhile, we investigate potential therapeutic strategies utilizing nanomedicine and identify promising targets for mitigating fibrosis associated with pancreatic diseases.

2. The relationship between PSCs and pancreatic diseases

2.1. The role of PSCs in pancreatic fibrosis

In 1998, Bachem et al.[20] first isolated pancreatic stromal cells from human and rat pancreatic stroma that specifically express ECM components such as collagen types I (Col I), Col III and fibronectin (FN). These cells are named PSCs for their similarity to HSCs, which are enriched in vitamin A lipid droplets. PSCs are the stromal cells and account for about 4%−7% of the total number of pancreatic cells, mainly around the base of pancreatic acinar cells[20]. Pancreatic injury and inflammation activate PSCs, exhibiting myofibroblast-like phenotypes, such as expressing α-smooth muscle actin (α-SMA), producing ECM, and increasing proliferation[19,21]. PSC activation involves various growth factors, cytokines, and environmental stressors. For instance, treatment with platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β) can activate downstream signaling pathways, leading to PSC activation[21]. PF is caused by the excessive deposits of ECM and collagen fibers during repeated necrosis to repair damaged pancreatic tissue.

2.2. PSC activation and pancreatic diseases

PF is a pathological feature of pancreatitis, pancreatic cancer, and diabetes. Currently, the pathogenesis of PF remains unclear, but it is believed to result from the activation of PSCs. This activation causes excessive ECM production and rapid proliferation, migration, and proliferation of PSCs, ultimately reducing pancreatic parenchymal cells and promoting fibrosis in exocrine
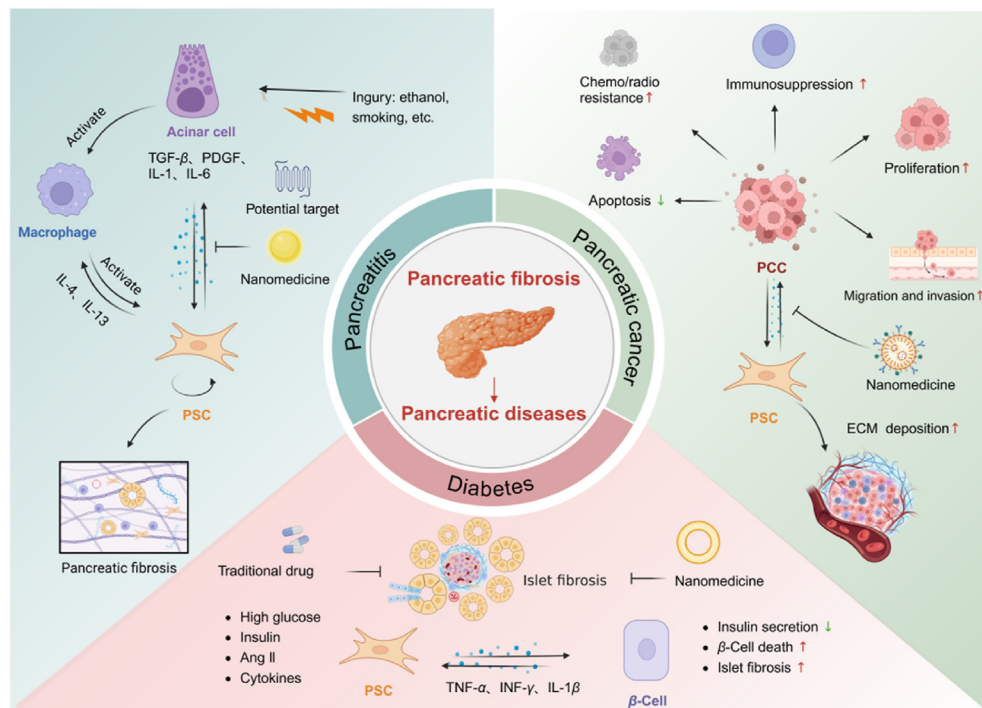
Figure 1 Intercellular crosstalk of PSCs and therapy in pancreatic diseases. Fibrosis is a dynamic pathological process involving multiple cells. There are different intercellular interactions in different diseases including pancreatitis, pancreatic cancer and diabetes. Paracrine signals from parenchymal and immune cells such as PACs, PCCs, islet cells, and macrophages can directly or indirectly modulate PSCs and participate in fibrosis. Nanomedicine and traditional therapy modulate intercellular crosstalk of PSCs and promote fibrosis regression.

glands and islets[22]. In summary, activated PSCs lead to pancreatic fibrosis, resulting in the loss of pancreatic function and potentially promoting the spread of pancreatic cancer cells, thus accelerating the development of pancreatic disease.

Several studies have demonstrated that pancreatic fibrosis is a characteristic of pancreatitis and plays an active role in the development of CP. Recent evidence suggests that gene-associated pancreatitis or alcohol-induced CP can be characterized by progressive parenchymal fibrosis[23]. PSC activation is considered the core event in the development of pancreatic fibrosis. The activated PSCs further secrete more inflammatory factors, which regulate immune cells and fibrosis[24]. During tumorigenesis, stroma cells and pancreatic cancer cells will secret a variety of stimulating factors to activate PSCs. Then, active PSCs can create a suitable microenvironment and facilitate cancer progression[25]. There has been plenty of evidence that confirms the importance of PSCs in pancreatic cancer development. Jin et al.[18] demonstrated that the cell supernatant of activated PSCs induced cancer cell proliferation and migration mediated by PDGF. Pothula et al.[6] discovered that PSCs can induce tumor-promoting paracrine effects. Furthermore, CP poses a high risk for PC development, indicating the role of the fibrotic microenvironment in PC progression. Different degrees of fibrosis exist in the islet areas in diabetes patients and animal models[26]. Changes in the local microenvironment of the islet, high glucose and hyperinsulinemic, oxidative stress and inflammatory factors can induce PSC activation[27]. Activated PSCs secreted various products, interleukin 1 (IL-1), IL-6 and tumor necrosis factor-α (TNF-α), which lead to local inflammatory response in islets, induce apoptosis of β cells and promote diabetes progression[7]. Therefore, PSC activation may be a central link between islet fibrosis and islet β-cell dysfunction.

3. Intercellular crosstalk of PSCs and therapeutic strategies in pancreatitis

Pancreatitis is a common gastrointestinal disorder that, depending on its progression, can be categorized as either acute pancreatitis (AP) or chronic pancreatitis (CP). It is generally accepted that there is a continuum of AP, recurrent AP and CP[4]. About 20% of patients who receive an initial diagnosis of AP later have a relapse, and about 35% of relapsed AP cases progress to CP[28]. CP is a disorder featured by recurrent inflammation of the pancreas, resulting in the development of fibroinflammatory histology. Pathologic changes include acinar atrophy, chronic inflammation, extensive interstitial fibrosis, and exocrine and endocrine dysfunction[29]. Irreversible fibrosis, which has a profound effect on the physiological function of the pancreas, is one of the most prominent pathological features of CP.

3.1. Intercellular crosstalk of PSCs in chronic pancreatitis

As the pancreatic-specific mesenchymal stromal cells, PSCs tend to aggregate in the vicinity of blood vessels and conduits within pancreatic tissue and the basal portion of glandular follicles. PSCs constitute only approximately 4% of the total number of pancreatic cells when quiescent, and their cytoplasm is entirely of vitamin A lipid droplets[20]. The presence of desmin (+), glial fibrillary acidic protein (GFAP) (+), and the lack of α-SMA (−) serve as indicators for the cells[30]. In response to pancreatic tissue injury and stress, PSCs undergo a process of activation and transition into a myofibroblast phenotype. This change is marked by the vanishing of lipid droplets in the cytoplasm containing vitamin A and the activation of α-SMA expression. Additionally, activated

PSCs exhibit an enhanced capacity for ECM synthesis and secretion of various cytokines[31]. The development of single-cell RNA sequencing technology has facilitated the discovery of more subtypes of fibroblasts. Yang et al.[11] showcased the diversity of PSCs in CP and identified a specific group of PSCs that express the very low-density lipoprotein receptor (VLDLR) and have a heightened lipid metabolism. These cells have the potential to facilitate immunological responses and stimulate PF. Further elucidation is required to determine if distinct subcategories of PSCs are present at various phases of pancreatitis, as well as the governing mechanisms that ensue upon the activation of specific fibroblast subtypes.

The activation of PSCs is essential for developing a pathological microenvironment characterized by excessive fibrous extracellular matrix. Various factors, including cytokines, non-coding RNAs, oxidative stress, hyperglycemia, and ion channel signaling trigger PSC activation[32]. When the PACs are exposed to harmful stimuli, the macrophages and neutrophils become active and release inflammatory cytokines such as TGF-β, TNF-α, IL-1/6, and PDGF[33,34]. Inflammatory cytokines can activate PSCs, which in turn secrete additional inflammatory factors such as connective tissue growth factor (CTGF), chemotactic protein 1, IL-1/6, PDGF, C-X3-C Motif Chemokine Ligand 1 (CX3CL1), and endothelin-1 (ET-1)[35]. It suggests that PSCs can induce their activation or the activation of neighbouring cells, hence facilitating the progression of pancreatic fibrosis. When the pancreas is exposed to endogenous or exogenous stimuli, abnormal activation of trypsinogen in acinar cells leads to acinar cell necrosis, necrotic acinar cells release damage-associated molecular patterns (DAMPs), which promote PSC activation and macrophage infiltration and polarization. Polarized macrophages secrete inflammatory cytokines to activate PSCs further[36]. Activated PSCs secrete pro-fibrotic cytokines, which eventually induce massive extracellular matrix deposition, contributing to the formation of pancreatic fibrosis (Fig. 2).

3.1.1. The injury of pancreatic acinar cells triggers PSC activation

PACs are the predominant cells found in the pancreas. Damage to these cells is the primary cause of pancreatitis and fibrosis. Research has shown that crucial elements involved in the stimulation of PSCs, such as TGF-β and CTGF, were elevated in acinar cells located in

regions of PF in individuals with CP[37,38]. The necrosis of PACs is ultimately caused by the abnormal activation of trypsinogen, which is induced by either endogenous or external stimuli. The release of DAMPs from PACs enhances the activation of PSCs and the infiltration and polarisation of macrophages, thus enhancing pancreatic fibrosis[39,40]. PACs modulate the microenvironment and recruit immune cells to influence PSC activation and play a subsidiary role in fibrosis. After co-cultured with PSCs, pancreatic acinar cells exhibited significant morphological changes and became insensitive to post-stimulation secretion. Co-culture promoted the migratory activity and expression of ECM protein in PSCs[41]. In their study, Wang et al.[42] discovered that PACs regulate PSCs by producing exosomal miR-130a-3p and targeting peroxisome proliferator-activated receptor gamma (PPAR-γ). The authors observed that suppressing miR-130a-3p resulted in a substantial amelioration of PF. Meanwhile, The PAC-derived trypsinogen serves as a means of interaction between PACs and PSCs. It can be internalized by PSCs and has an impact on the activation of PSCs and the progression of CP[43]. PSCs underwent apoptosis after phagocytosis of necrotic acinar cells, whereas surviving PSCs were activated and continued to proliferate[6]. Recently, Wang et al.[44] have elucidated the intricate mechanism through which PACs activate PSCs during the process of pancreatic fibrogenesis in CP. A significant increase of sphingosine kinase 1 (SPHK1) and sphingosine 1-phosphate (S1P) was observed in acinar cells in animal models of CP caused by cerulein injection or pancreatic duct ligation. PAC-derived SPHK1 catalyzes the conversion of sphingosine to S1P, which subsequently binds to S1PR2 receptors located on the surface of PSCs. This interaction promotes the activation of PSCs by inducing autophagic flux *via* the AMPK-mTOR pathway. The deposition of ECM further contributes to pancreatic fibrosis and local hypoxia, exacerbating PAC injury. Consequently, crosstalk is established between PAC and PSCs mediated by the hypoxia/SPHK1/S1P pathway, playing a pivotal role in both the onset and the progression of CP.

3.1.2. Immune cells promote PSC activation by releasing inflammatory factors

In addition to PACs and PSCs, immune cells such as macrophages, lymphocytes, and neutrophils are also involved in the progression of pancreatic fibrosis. Macrophages have garnered significant attention among these immune cell types due to their pivotal
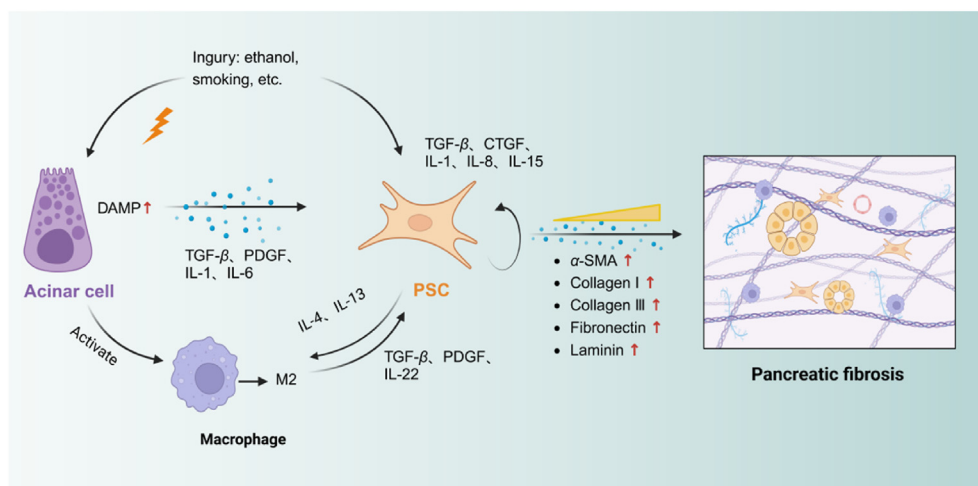

Figure 2 Intercellular crosstalk of PSCs in chronic pancreatitis. Injured PACs release DAMPs, which promote the activation of PSCs and the infiltration and polarisation of macrophages. Figure created with Biorender.com.

involvement. Macrophages, derived from monocytes, can be stimulated and polarized into specific subtypes to exert targeted effects. These special monocytes are crucial in inflammatory, immunological and oncological processes[45,46]. Typically, M1 macrophages primarily participate in the immune response, engaging in phagocytosis and promoting inflammation development. Conversely, M2 macrophages are mainly associated with suppressing inflammation while facilitating wound healing and fibrosis[47]. In physiological conditions, there are relatively few resident macrophages in the pancreas. Following the fragmentation of damaged local PACs, chemokines are produced, attracting monocytes that traverse the vascular endothelium and differentiate into macrophages within the injured tissue[18]. Various models of chronic pancreatitis have demonstrated an increase in pancreatic macrophages. The initial stages of chronic pancreatitis are characterized by local inflammation, and M1 macrophages activate PSCs *via* secreting TNF-α and IL-6[48]. Xue et al.[49] explored the correlation between macrophages and PF. Co-culturing normal mouse bone marrow-derived macrophages (BMDM) with isolated PSCs from CP mice revealed heightened secretion of IL-4, IL-5, TGF-β, IL-10, IL-13, and other cytokines associated with Th2 cells. The alteration in M1 and M2 markers signifies the ability of activated PSCs to induce polarization of macrophages towards the M2 phenotype. Following the blockade of IL-4/IL-13, there was a notable reduction in the expression levels of α-SMA, which significantly alleviated PF[49]. These essays emphasize the pivotal function of macrophages in promoting the advancement of PF. The communication between macrophages and PSCs within the local microenvironment potentially drives a vicious cycle of CP and fibrosis.

Neutrophil granulocytes are frequently considered as a reference marker for pancreatic inflammation[50]. Neutrophils release reactive oxygen species (ROS), proteases, and antimicrobial peptides to eliminate infections. Neutrophils are the primary generator of reactive ROS during pancreatitis[51]. They can cause oxidative damage to acinar cells and increase trypsinogen activation[50,51]. The secretion of proteases facilitates acinar cell dissociation and tissue degradation. These findings suggest a clear relationship between neutrophils and disease severity[52]. It was verified by using anti-neutrophils serum to deplete neutrophils, which decreased pancreatic damage and protease activation[51].

3.2. Therapeutic strategies related to crosstalk of PSCs in pancreatitis

Multiple cells interact with PSCs to promote activation and influence the development of CP. Regulating the communication between PSCs and other cells in the pancreas may be an effective therapeutic strategy (Fig. 3).

3.2.1. Targeting pancreatic acinar cells and PSCs for CP

The precise mechanisms underlying acinar cell injury contributing to CP and pancreatic fibrosis remain unclear. Meanwhile, specific pharmacological interventions for treatment still need to be improved. Dysregulation of various signaling proteins, transcription factors, kinases, and cytokines secreted by acinar cells presents potential targets for intervention in pancreatic fibrosis. Activating the SPHK1/S1P pathway in PACs triggers autophagy and activates PSCs, thereby promoting fibrogenesis of chronic pancreatitis. SPHK1 and S1PR2 represent promising therapeutic targets for clinical treatment and inhibitors targeting SPHK1 and S1PR2 effectively mitigate CP and fibrosis progression[44,53].

Parathyroid hormone-related protein (PTHrP), released by PACs, influences the function of acinar cells by regulating the production of inflammatory cytokines and stimulating PSCs in paracrine. Several animal models of CP exhibit elevated levels of PTHrP. The disruption of the PTHrP gene in PACs protects by decreasing histological harm and fibrosis[54]. Vacuole membrane protein 1 (VMP1), an endocytoplasmic reticulum (ER) membrane protein, has been found to have a vital function in autophagosome production. In particular, VMP1 is down-regulated in AP and CP. The absence of pancreatic VMP1 leads to a decrease in the ability to break down cellular components through autophagy, causing stress in the endoplasmic reticulum and triggering the activation of the nuclear factor, erythroid 2 like 2 (NFE2L2/NRF2) pathway. The elimination of VMP1 in the acinar cells of the pancreas induces inflammation, the transformation of acinar cells into ductal cells, and the development of fibrosis in mice[55].

The research group has designed and synthesised lipid nanoparticles termed AT-CC, loaded with dual drugs ATRA and ammonium tetrathiomolybdate (TM). These nanoparticles are decorated with collagen-binding peptide (CBP) and collagenase I. This enables effective transport of ATRA and TM into the pancreas. The delivered ATRA efficiently decreases excessive collagen synthesis by preventing the activation of PSCs. TM inhibits lysyl oxidase activation, resulting in a decrease in collagen cross-linking. The synergistic action of ATRA and TM suppresses PSC activation and collagen synthesis and promotes the discovery of PACs function. These results demonstrate that AT-CC is a secure and effective collagen-targeting drug delivery technology for alleviating PF. These innovative nanoparticles represent a novel approach to targeted therapy for pancreatic fibrosis, demonstrating improved precision and efficacy[56].

3.2.2. Targeting macrophages and PSCs for CP

Inhibition of the interaction between macrophages and PSCs or reduced macrophage infiltration within the pancreatic tissue has demonstrated improved therapeutic outcomes. Targeting macrophages presents a promising avenue for the treatment of CP and fibrosis. Dasatinib, a second-generation multiple tyrosine kinase receptor inhibitor, was found to inhibit the promotion of M2 macrophage polarization by PSCs in a study investigating their crosstalk. Zeng et al.[57] demonstrated that dasatinib led to an amelioration of fibrosis severity in cerulein-induced CP mice models and exerted notable antifibrotic and anti-inflammatory effects through the glycogen synthase kinase-3β/TKs/β-linker pathway. Sulindac, a non-steroidal anti-inflammatory medicine, effectively decreases the levels of pro-inflammatory cytokines, specifically TNF-α and monocyte chemotactic protein-1 (MCP-1), and the production of TGF-α and PDGF-β in chronic pancreatic tissue. Furthermore, sulindac demonstrates notable effectiveness in diminishing the intensity of chronic pancreatitis by decreasing the loss of acinar cells, infiltration of inflammatory cells, and fibrosis of the stroma[58]. Berberine (BR), as an AMPK activator, inhibits TGF-β signaling and modulates M2 macrophage polarisation. In the animals with CP, berberine significantly reduced PSC activation, inflammatory cell infiltration and collagen deposition[59]. Isoliquiritigenin (ILG), a chalcone-type flavonoid isolated from liquorice roots, has recently been reported to attenuate inflammation and PF by inhibiting PSC activation and macrophage infiltration into the pancreas[60].

In addition to the promising therapeutic agents mentioned above, Khurana et al.[61] found that cerium oxide (NC) nanoparticles effectively inhibited the activity of pro-inflammatory cytokines and
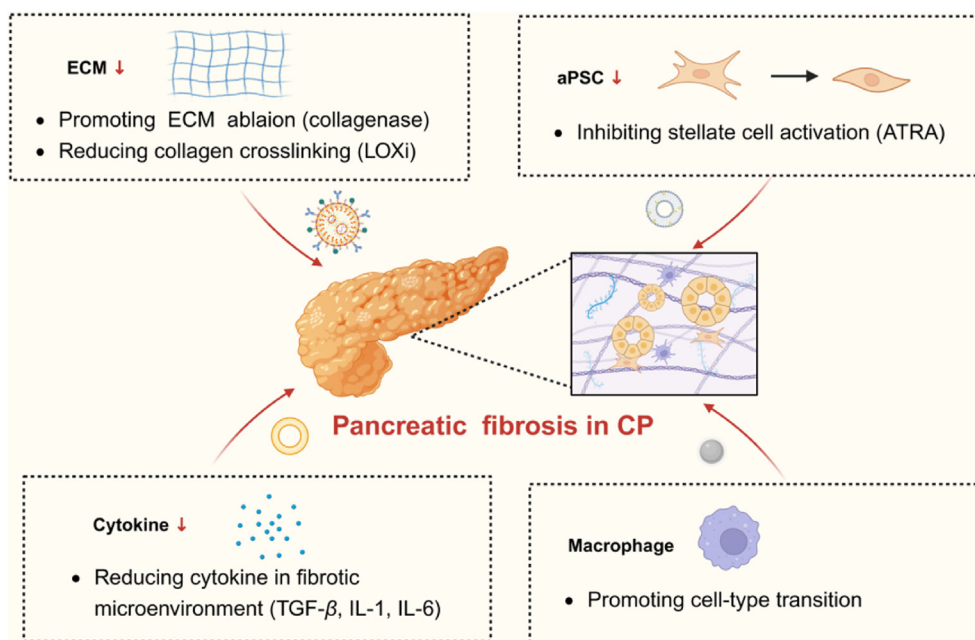
Figure 3 Antifibrotic therapy of nanomedicine in chronic pancreatitis. Nanomedicine therapeutic strategies in CP include targeting PSC, macrophage, cytokine and ECM. Figure created with Biorender.com.

chemokines *via* disrupting macrophage signaling. In addition, NC showed a remarkable ability to attenuate fibrogenesis through inhibition of TGF-β signaling, endoplasmic reticulum stress and epithelial-to-mesenchymal transition. A nanotechnology-based CO-bound haemoglobin vesicle (CO-HbV) was developed by Nagao et al.[62] Treatment with CO-HbV resulted in polarization of macrophages towards an M2-like phenotype and inhibition of pancreatic neutrophil infiltration. Cell membrane coating technology opened an avenue for nanoparticles. Wang et al.[63] developed a biohybrid nanosystem to treat CP. It comprises a polymer nanoparticle loaded with Somatostatin (SST) and a macrophage membrane surface. The nanoparticle reduced PF and showcased the benefits of combining the synthetic polymer with biological membranes in the development of nanoplatforms for sophisticated and efficient peptide delivery. We have summarized more detailed information on examples of nanomedicine treatment of pancreatitis and fibrosis in Table 1 [15,56,61−64].

4. Intercellular crosstalk of PSCs and therapeutic strategies in pancreatic cancer

Pancreatic cancer is a common and aggressive malignancy that affects the digestive system, ranking 14th and 4th among all malignant tumors in terms of new cases and deaths worldwide in 2020, respectively, according to GLOBOCAN statistics[65]. Pancreatic ductal adenocarcinoma (PDAC), arising from glandular epithelium, accounts for approximately 90% of pancreatic cancers. PDAC is one of the most stroma-rich cancers due to its unique interstitial fibrosis feature compared to other tumors[66,67]. The cancer cells are surrounded by an abundance of dense fibrous stromal components, with the stroma constituting around 80%−90% of the tumor mass. The ECM of pancreatic cancer hinders the adequate transportation of chemotherapeutic medicines to cancer cells and sustains their growth[68]. Moreover, this stromal mass comprises various cells, such as PSCs, fibroblasts, myofibroblasts, immune cells and vascular endothelial cells. PSCs are the most prominent component, which is up to 50% of its total mass, and perform a crucial role in the tumor microenvironment (TME) of PC[68,69]. Their continuous activity and active contact with tumor cells in the TME might enhance tumor growth and spread, leading to resistance to chemotherapy in PC through many signaling pathways. Tumor heterogeneity, interstitial fibrosis, and an immunosuppressive microenvironment collectively contribute to the elevated fatality rate observed in pancreatic cancer.

4.1. Intercellular crosstalk of PSCs in microenvironment

PSCs are the main cellular components responsible for developing the desmoplastic reaction in PC. During the development of tumors, these cells experience a gradual process of activation and secrete collagen fibers that surround and protect cancer cells. The presence of collagen in the surrounding tissue plays a vital role in the development of tumors, as cell interactions are essential at all stages of tumor formation, including the beginning, advancement, and spread to other parts of the body. Besides, multiple interactions between PSCs and PCCs, endothelial cell, neurons, other immune cells play different roles in pancreatic cancer (Fig. 4).

4.1.1. The interactions between PSCs and PCCs mediate the progression of cancer

There is strong evidence of an interaction between PSCs and PCCs, as shown in laboratory experiments involving co-cultures or exposure to conditioned media. PSCs display heightened proliferation, migration, and ECM formation when exposed to PCCs. Conversely, PCCs exhibit heightened cell division but decreased programmed cell death when exposed to secretions from PSCs[70,71]. Cancer cells stimulate the activation of PSCs by utilizing signaling pathways such as the phosphoinositide 3-kinase (PI3K)/Akt, the Janus kinase (JAK)-signal transducer and activator of transcription (STAT), and Hedgehog. Additionally, they employ inflammatory cytokines and ROS components.

Table 1   Therapeutic strategies related to intercellular crosstalk of PSCs in CP.

| Nanomedicine	Targeting therapeutic agent	Mechanisms of action	Pancreatitis model	Preclinical/ clinical	Ref.
LA-PC	All-*trans* retinoic acid (ATRA)	Inhibiting of PSCs activation by ATRA and reducing the level of PDGF-BB by a down-regulated ERK pathway.	Mice with CP induced by caerulein	Preclinical	17
AT-CC	ATRA and ammonium tetrathiomolybdate (TM)	Inhibition of PSCs activation and reduction of collagen cross-linking by lipid nanoparticles loaded with ATRA and TM.	Mice with CP induced by caerulein	Preclinical	56
NC	Cerium oxide	Nanoparticles of cerium oxide (NC) effectively suppressed inflammatory cytokines and chemokines through the disruption of macrophage signaling.	Mice with CP induced by caerulein and rats with CP induced by L-arginine	Preclinical	61
CO-HbV	Carbon monoxide (CO)	CO-bound haemoglobin vesicles (CO-HbV) polarised macrophages and suppressed neutrophil invasion into the pancreas.	Mice with severe acute pancreatitis induced by CDE diet	Preclinical	62
MP-SST	Somatostatin (SST) peptide	The nanoparticles loaded with SST and camouflaged with macrophage membrane (MP-SST) resulted in the suppression of factors associated with CP and mitigated the histological damage of the pancreas.	Mice with CP induced by the diethyldithiocarbamate (DDC)	Preclinical	63
NY	Yttrium oxide	Yttrium oxide nanoparticles (NY) reduced pancreatic oxidative-nitrosative stress and inflammatory cytokines and chemokines resulting in the inhibition of fibrosis signaling.	Rats with CP induced by L-arginine	Preclinical	64
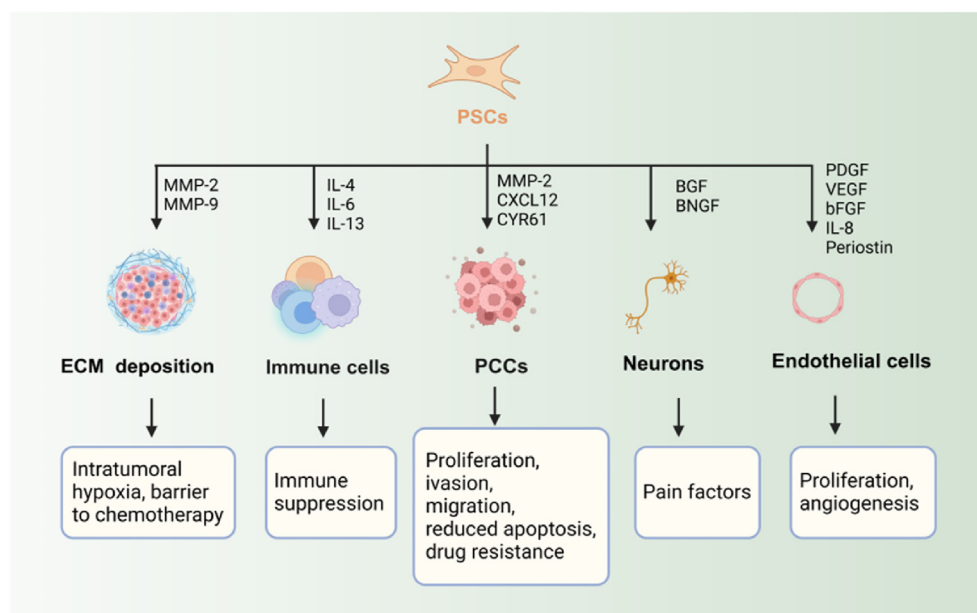
Figure 4   Role of activated PSCs in pancreatic cancer. Activated PSCs produce abundant ECM proteins and remodel the ECM. PDGF, platelet-derived growth factor; CTGF, connective tissue growth factor; IL-4,-6,-8,-13, interleukin-1,-4,-6,-8,-13; bFGF, basal fibroblast growth factor; VEGF, vascular endothelial growth factor; CYR61, cysteine-rich angiogenic inducer 61; MMP-2, matrix metalloproteinase-2; CXCL12, C-X-C motif chemokine ligand 12; BGF, bone growth factor; BNGF, beta-nerve growth factor. Figure created with Biorender.com.

Furthermore, PCCs stimulate autophagy in PSCs, resulting in releasing alanine, which serves as a substitute carbon source for mitochondrial oxidative pathway utilization by cancer cells under nutrient-limited conditions[71]. Knockdown of autophagy proteins in PSC resulted in a decrease in ECM and IL-6 production. Additionally, when these PSCs were combined with PCCs and administered to nude mice, they formed smaller tumors and fewer metastases[31]. Moreover, PSCs have been shown to stimulate cancer cell migration or epithelial-mesenchymal transition (EMT). The study revealed that the presence of PSC in co-culture with PCC resulted in the suppression of epithelial cell markers (E-cadherin, β-catenin) and the stimulation of mesenchymal cell markers (Vimentin). It indicates that PSC plays a crucial role in the initiation of EMT in PCCs[72]. Activation of TGF-β, Notch pathway, and Wnt/β-Catenin pathway drives target gene transcription and up-regulates mesenchymal marker expression. The epithelial cells lose polarity and intercellular adhesion and are transformed into a mesenchymal phenotype[73,74]. By activating PSCs, an optimal tumor microenvironment is established that facilitates the proliferation of PCCs and ultimately contributes to PC progression.

4.1.2. The crosstalk of PSCs and immune cells promotes immunosuppressive TME

Tumor-associated macrophages (TAMs) The TME consists of a wide range of immune cells, such as macrophages, neutrophils, dendritic cells, natural killer cells, effector T cells, regulatory T cells, and B cells[75]. TAMs infiltrate tumors and are the predominant immune cells in regions densely populated by PSCs[76]. Multiple studies have shown that PSCs promote the attraction and specialization of monocytes into pro-tumor M2 macrophage subsets using diverse regulatory molecules. This process impairs effector T-cell responses and induces immunosuppression of the TME[77,78]. Mace et al.[79] observed that cancer-associated fibroblast (CAF)-derived macrophage colony-stimulating factor 1 (M-CSF1), IL-6, and C−C motif chemokine ligand 2 (CCL2) play an essential role in attracting monocytes to PC and causing a subsequent rise in the M2/M1 macrophage ratio. The study also showed the importance of fibroblast activation protein (FAP), a marker for PSCs, in facilitating communication between PSCs and TAMs. It revealed that FAP played a role in the interaction between PSCs and TAMs primarily through the cleavage of type I collagen and the subsequent increase in macrophage adhesion. In turn, TAMs also modulate the activation and progression of PSCs. Confirmed that PSCs promote TAMs, M2 macrophages can also enhance EMT progress by secretion of factors including IL-6 and stromal cell-derived factor-1 (SDF-1) to stimulate PSC activation[80]. Activated M2-like macrophages contribute to ECM remodelling through the secretion of matrix metalloproteinases (MMPs), which negatively impact ECM. Tissue-resident macrophages, the predominant subset in TME, express prolactin receptors, and it has been reported that prolactin contributes to TME fibrosis[81]. Recent research has examined the impact of PSCs on TAMs, but the reciprocal influence of macrophages on PSCs has yet to be thoroughly explored and elucidated.

Other immune cells The nuclear factor-kappaB (NF-κB) activity in PSCs promotes tumor growth by increasing the expression of C-X-C chemokine ligand 12 (CXCL12), which prevents CD8$^+$ T cells from infiltrating the tumor and killing cancer cells. Blocking CXCL12 in pancreatic tumor cells might promote antitumor immunity[82]. TGF-β promotes tumor immune evasion through activation of PSCs, and combined inhibition of TGF-β and PDL1 synergistically increases CD8+ T cell infiltration and cytotoxicity to exert antitumor immunity[83]. PSCs also trigger differentiation in myeloid-derived suppressor cells (MDSCs) by releasing inflammatory cytokines such as IL-16. PSCs stimulate the migration of MDSCs to pancreatic tumors by secreting IL-16[79]. IL-6 secretion by PSCs promotes immunosuppression, and PSCs treated with a heat shock protein 90 inhibitor reduce IL-6 secretion[84]. It has been reported that PSCs can activate mast cells, which produce IL-13 and tryptase, thereby stimulating the proliferation of cancer cells and PSCs[85]. The C-X-C motif chemokine receptor 2 (CXCR2) is expressed in leukocytes, including neutrophils, natural killer cells (NK cells), monocytes, macrophages, and T cells. Its function is to regulate the migration of neutrophils to inflammatory sites by binding to IL-8[86].

4.1.3. The crosstalk of PSCs and endothelial cells

Activated PSCs express a variety of proangiogenic factors, such as VEGF, bFGF, IL-8, PDGF, and periostin. Additionally, MMP-9 is produced by PSCs to degrade the basement membrane and aids in the development of blood vessels[87]. VEGF stimulates angiogenesis by enhancing endothelial cell viability, proliferation, and permeability[88]. Hepatocyte growth factor (HGF) produced by PSCs is the ligand for the c-Met expressed on cancer cells as well as endothelial cells. HGF/cellular mesenchymal-epithelial transition (c-MET) pathway plays a vital role in PSC-induced tube formation of endothelial cells[89]. Another study has shown that activated PSCs promote tumor cell proliferation and endothelial cell tube formation through the therapeutic miRNAs 199a-3p and 214-3p[90].

4.1.4. The crosstalk of PSCs and neurons

PSCs may be involved in neural invasion as pancreatic cancer progresses. The study showed that PSCs can induce neuron outgrowth. It was demonstrated by incubating dorsal root ganglia with the conditioned medium collected from PSCs derived from human pancreatic cancer[91]. Li et al.[92] reported that activated PSCs promote neurite outgrowth towards pancreatic cancer cells and facilitate neural invasion by cancer cells. More recently, it has been demonstrated that PSCs cause pain in pancreatic cancer by stimulating the release of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (BGF), which causes the dorsal root ganglia to secrete pain factors[93].

4.2. Therapeutic strategies related to crosstalk of PSCs in pancreatic cancer

The phenomenon of cancer-associated desmoplasia and fibrotic response is a multifaceted and intricate entity that has extensive ramifications. The interconnection of various cells in the TME is crucial for the progression and spread of solid pancreatic cancers. Introducing intercellular crosstalk as an intervention provides a new approach to hinder the advancement of PCs effectively (Fig. 5).

4.2.1. Targeting PCCs and PSCs for PC

Due to the pivotal role of PSCs in the development of PC, medicines that modulate their activation hold great potential as therapeutic candidates. Several anticancer agents have been shown to influence PSC function and ECM production, thereby suppressing tumor growth. In the context of PC, Extensive research has been conducted on medication delivery methods that utilize polymers and nanocarriers. ATRA is the biologically active form of vitamin A. It controls the state of PSC inactivity by controlling the
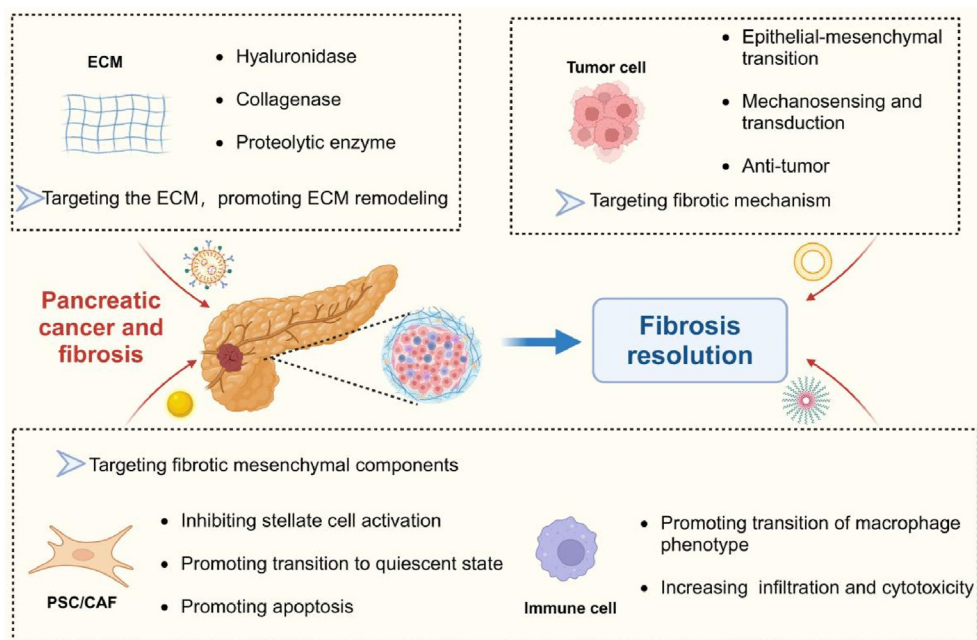
Figure 5 Nanomedicine therapeutic strategies in pancreatic cancer. Nanomedicine therapeutic strategies in pancreatic cancer including (1) Targeting ECM and promoting ECM remodeling; (2) Targeting fibrotic mechanism; (3) Targeting fibrotic mesenchymal components. Figure created with Biorender.com.

transcription of specific genes when it binds to corresponding nuclear receptors[94,95]. The nanosystem Au@PP/RA/siHSP47, *via* AuNP nanocarriers, simultaneously delivered all-trans retinoic acid, which induces the restoration of PSC to the resting state, and siRNA targeting heat shock protein. The drug delivery and penetration were significantly improved in the model. The progression of invasive pancreatic tumors was inhibited considerably[96]. A composite of magnetic nanoparticles, co-modified with gemcitabine (GEM) and pH (low) insertion peptide (pHLIP), was created and labeled as GEM-MNP-pHLIP. The intelligent nanocarrier consisted of a pH-responsive transmembrane unit and a controlled release unit, in addition to Fe_3O_4 nanoparticles that enable the tracking of targeted drug delivery using magnetic resonance imaging (MRI). In the animal trials, we administered metformin (MET) through intraperitoneal injection to deplete the thick stromal barrier of PDAC. It was done before injecting the aforementioned nano agents in order to enhance the efficient delivery of GEM[97].

Gemcitabine resistance in cancer cells can be induced by PSCs through both direct and indirect coculture systems. The secretion of FN by PSCs within the ECM has been identified as a pivotal contributor to gemcitabine resistance *via e*xtracellular signal-related kinases 1 and 2 (ERK1/2) activation[98]. The arsenic trioxide (ATO)-loaded nanoparticles were synthesized through self-assembly utilizing poly(D,L-lactide) and poly(ethylene glycol) (PEG-PDLLA) and subsequently modified with the single-chain antibody of FAP-α (scAbFAP-α) to form scAb-ATO-NPs. ATO nanoparticles significantly prevent the activation of the PI3K/AKT/galectin-1 pathway, resulting in a decrease in stromal secretion and a reduction in the tumor-promoting potential of PSCs. In addition, this method increases the responsiveness of cancer cells to GEM, thereby offering a new viewpoint on the treatment of pancreatic cancer[99]. The integration of photothermal therapy (PTT) with the purpose of depleting the stroma locally, increasing the permeability of GEM, and synthesizing C-G NPs

has shown significant promise in suppressing the activation of PSCs, deposition of collagen fibers, and production of TGF-β. These findings offer vital insights into the development of resistance to gemcitabine in PC and propose promising therapeutic options to inhibit the progression of PC[100]. Consequently, these results hold significant promise for future clinical translation. A highly efficient MMP-9-cleavable linker was developed to selectively remove a PEG shield from a polymeric nanocarrier (Magh@PNPs-PEG-RegaCP-PEG) based on PLGA-*b*-PEG. This linker was evaluated in the mouse model of pancreatic cancer, which is clinically relevant. The heightened tumor-specific presence and functionality of MMP-9 can be utilized to provide an MMP-9-activatable nanoparticle, thereby diminishing liver metastasis and significantly reducing the average size of colonies[101]. MMPs can be utilised as ECM-based targets or stimulants for the treatment of PDAC in order to optimize therapeutic strategies.

4.2.2. Potential tumor associated macrophage (TAM) targeting strategies

Typically, these therapy strategies focus on addressing different aspects of TAMs, such as their ability to survive, change their features, attract other cells, engulf foreign particles, and promote the growth of new blood vessels. Recently, the utilization of nanotechnology has been evaluated as a strategy for explicitly targeting macrophage polarization. Numerous types of nanoparticles have been assessed for their ability to target TAMs[102,103]. Iron oxides have shown the ability to transform M2 into the M1 macrophages, while also increasing the production of ROS and triggering death in cancer cells. Zhao et al.[104] fabricated tumor-derived antigenic microparticles (T-MPs) incorporating nano-iron oxide. The surface of T-MPs was modified by including adjuvant CPG to develop a Fe_3O_4/T-MPs-CpG/Lipo vaccine. Following the implementation of combination vaccination in TME, a phenomenon called repolarization was observed, wherein

M2-like macrophages underwent a conversion into an M1-like phenotype. Another approach to regulate the polarization of macrophages in the TME of PC is to interfere with the galectin-9/dectin axis. Previous studies have demonstrated that this axis plays a role in promoting the conversion of macrophages into M2. The delivery mechanism comprises exosomes obtained from bone marrow mesenchymal stem cells (BM-MSCs), which are filled with galectin-9 siRNA and coated with an oxaliplatin (OXA) prodrug. The purpose of this alteration is to stimulate immunogenic cell death. Utilizing biomaterials, particularly BM-MSC exosomes, can significantly improve the effectiveness of targeting tumors, leading to a higher concentration of drugs at the tumor location. The siRNA-EXO-OXA (iEXO-OXA) combination therapy elicits anti-tumor immunity by polarizing tumor-suppressive macrophages, attracting cytotoxic T cells, and suppressing Tregs[105]. It has demonstrated significant therapeutic efficacy in cancer treatment. Finally, we have summarized more detailed information on examples of nanomedicine for the treatment of pancreatic cancer in Table 2 [83,96,97,99−101,104,105].

5. Intercellular crosstalk of PSCs and therapeutic strategies in diabetes

Diabetes is a metabolic disorder characterized by chronic hyperglycaemia and glucose intolerance due to impaired insulin action or deficiency. Worldwide, 537 million adults (aged 20−79 years) are living with diabetes, according to the IDF Diabetes Atlas 2021. These figures are projected to rise to 643 million by 2030 and 783 million by 2045. Diabetes causes life-threatening, disabling and costly complications and reduces life expectancy, making it one of the most severe and common chronic diseases of our time[106,107]. In related studies, fibrosis is another essential pathogenic factor in pancreatic islet dysfunction. β-Cell dysfunction plays a critical role in the pathogenesis of diabetes, with multiple factors contributing to the loss of β-cell mass and function. These factors include glucose lipotoxicity, chronic inflammation, endoplasmic reticulum stress and epigenetic modifications[108]. Pathological studies have revealed varying degrees of fibrosis in pancreatic islets and peri-islet regions in both diabetes patients and animal models, alongside exocrine pancreatic fibrosis. Immunohistochemical staining has detected ECM deposits, primarily composed of Col I, Col III, and FN, and have been detected in the fibrotic areas of DM pancreatic islets. In contrast to fibrosis of pancreatic exocrine tissue, pancreatic fibrosis in diabetes is mainly confined to the pancreatic islets, which suggests that islet fibrosis in diabetes is associated with different activation pathways in pancreatic exocrine disease[109,110]. However, the specific pathogenesis needs to be further clarified.

5.1. Intercellular crosstalk between PSCs and β-cells

The association between PSCs and diabetes seems to be reciprocal. Within the realm of diabetes, elevated blood sugar levels, known as hyperglycemia, can initiate the activation of PSCs through the renin-angiotensin system (RAS)[111]. Matrix deposition led to the development of islet-specific fibrosis in mice models. In pancreatic islets, the cells responsible for insulin secretion experience higher levels of glucose and insulin in cases of diabetes, unlike the rest of the pancreatic tissue. The simultaneous occurrence of ERK1/2 phosphorylation activation and proliferation of PSCs can result in a decrease in insulin secretion and an elevation in β-cell mortality caused by TNF-α, INF-γ, and IL-1β[112] (Fig. 6). Significantly,

directing efforts towards the RAS system shows potential as a viable treatment strategy for treating diabetes.

5.1.1. Hyperglycemia contributes to the activation of PSCs and islet fibrosis

Diabetes is a condition characterized by persistent high levels of blood glucose. The presence of hyperglycemia and hyperinsulinemia triggers the RAS, which is renowned for its conventional role in regulating blood pressure, fluid balance, and electrolyte homeostasis through its effects on vascular smooth muscle cells and aldosterone secretion. Angiotensin II (Ang II) acts as the main active peptide in the signaling pathway of the RAS, mainly exerting its effects through Ang II receptor type 1 (AT1R). Furthermore, Ang II functions as a growth factor that promotes the multiplication of cells and the inflammation of tissues, which is essential in the development of fibrosis and impaired function in different organs associated with diseases[112,113]. In individuals with diabetes, increased glucose levels trigger the synthesis of Ang II and the activation of AT1R, resulting in an increase in the production of TGF-β through the interaction of Ang II with AT1R. TGF-β is a pivotal mediator in the activation of PSCs. Islet fibrosis is further exacerbated by the activation and proliferation of PSCs and the increased production of ECM proteins, which is produced by the signaling of ATII and TGF[114,115]. Remarkably, in the OLETF rat model, the activation of PSCs and the development of fibrosis are mainly confined to the islets, even though hyperglycemic circumstances impact the entire pancreas. Glucose and insulin can stimulate the proliferation of PSCs and the phosphorylation of ERK 1/2. In turn, it leads to the production of the CTGF gene and the activation of PSCs[116]. Consequently, hyperglycemia and hyperinsulinemia are critical mitogenic factors that drive PSC activation and proliferation, potentially elucidating islet-specific fibrosis in diabetes.

Advanced glycation end products (AGEs), metabolites involved in diabetes, also activate PSCs. AGEs are formed through non-enzymatic glycation and oxidation of proteins, lipids, and glucose[117,118]. The production of AGEs is significantly augmented in diabetic patients due to elevated blood glucose levels, playing crucial roles in the development and progression of vascular complications related to diabetes[119,120]. Studies have demonstrated that AGEs can induce endothelial-to-mesenchymal transition (EndMT) in islet endothelial cells and contribute to islet fibrosis in diabetic mice. It suggests that EndMT induced by AGEs may contribute to the pathogenesis of islet fibrosis associated with diabetes[121]. However, the comprehensive molecular mechanisms underlying this phenomenon during the diabetic condition remain unclear.

5.1.2. Activated PSCs induced β-cells injury and diabetes progression

It has been suggested that activated PSCs induce apoptosis of pancreatic islet β-cells. Activated PSCs secrete various products, including IL-1, IL-6, TNF-α, MCP-1, and galectin-1 (Gal-1), leading to local inflammatory reactions in pancreatic islets and promoting the generation of ROS. Consequently, this process induces apoptosis of islet β-cells and accelerates the progression of diabetes[7]. Among these factors, IL-1β plays a critical role in inhibiting β-cell apoptosis. It can upregulate Fas expression in β-cells along with interferon (IFN) γ and TNF-α; however, IL-1β exhibits the most significant impact. Furthermore, IL-1β binds to the IL-1 receptor on β-cell membranes to activate the NF-κB signaling pathway, mitogen-activated protein kinases (MAP)/

Table 2 Therapeutic strategies related to intercellular crosstalk of PSCs in PC.

Nanomedicine	Targeting therapeutic agent	Mechanism of action	Combination therapy	Cancer model	Preclinical/clinical	Ref.
LYiClustersiPD-L1	TGF-β receptor inhibitors (LY2157299) and siRNA targeting PD-L1 (siPD-L1)	LY2157299 can effectively inhibit the activation of PSCs and result in a reduction in type I collagen. SiPD-L1 silenced PD-L1 gene expression in tumor cells, increased tumor infiltrating CD8$^+$ T cells and provoked antitumor immunity.	Immunotherapy	A subcutaneous pancreatic tumor model induced by Panc02 cells	Preclinical	83
Au@PP/RA/siHSP47	ATRA and siHSP	By utilizing AuNP nanocarriers, we can transport both ATRA, which triggers the restoration of PSC to its resting state, and siRNA that specifically targets heat shock protein.	N/A	Panc-1/PSC co-inoculated subcutaneous xenograft tumor model	Preclinical	96
GEM-MNP-pHLIP	GEM	The composite magnetic nanoparticles, consisting of pH-responsive transmembrane unit and controlled release unit, were formed by combining GEM and pH (low) insertion peptide (pHLIP) with Fe$_3$O$_4$ nanoparticles (MNPs).	N/A	A tumor subcutaneous xenograft tumor model	Preclinical	97
scAb-ATO-NPs	Arsenic trioxide (ATO)	Targeting the AP4/AKT/PI3K galectin-1 pathway using ATO nanoparticles effectively inhibits its activation, leading to a reduction in stromal secretion and attenuation of the tumor-promoting capability of PSCs.	N/A	MIA Panc-2/PSC co-inoculated subcutaneous xenograft tumor model	Preclinical	99
C-G NPs	Gemcitabine	C-G nanoparticles (NPs) are created by incorporating acid-responsive photothermal molecules with gemcitabine. These NPs are used to study the combined effects of chemophotothermal therapy and the interaction between photothermal therapy (PTT) and the TGF-β pathway in pancreatic ductal adenocarcinoma.	Photothermal therapy (PTT)	Metastatic xenograft PDAC tumor mouse model	Preclinical	100
Magh@PNPs-PEG-RegaCP-PEG	MMP-9	A highly efficient MMP-9-cleavable linker was developed to selectively remove a PEG shield from a polymeric nanocarrier (Magh@PNPs-PEG-RegaCP-PEG) based on PLGA-b-PEG. This linker was tested in a mouse model of pancreatic cancer, which is therapeutically relevant.	N/A	Liver metastasis induced by injection of the well-established L-CI.5s experimental liver metastasis model	Preclinical	101

Fe$_3$O$_4$/T-MPs-CpG/Lipo	Tumor-derived antigenic microparticles (T-MPs)	Reversal of infiltrating TAMs to a tumor-suppressive M1 phenotype and modulating the tumor immunosuppressive network.	Immunotherapy	Tumor mouse model induced by injection of cells	Preclinical	104
iEXO-OXA	OXA	The delivery mechanism comprises exosomes obtained from bone marrow mesenchymal stem cells (BM-MSCs), which are filled with siRNA that specifically targets galectin-9 and are externally modified with oxaliplatin (OXA). The nanoparticles induce the formation of anti-tumor immunity by promoting the polarization of tumor-suppressive macrophages.	Immunotherapy	Orthotopic PANC-02 pancreatic tumor models	Preclinical	105

stress-activated protein kinases (SAPK) pathway, and protein kinase C (PKC) pathway. In contrast, IFN-γ binds to the IFN-γ receptor on β-cell membranes, triggering signaling and activation of transcription factor-1 (STAT-1), which regulates caspase expression. TNF-α induces apoptosis in a time- and dose-dependent manner in β-cells[122−124]. Additionally, islets co-cultured with PSCs in a hypoxia-conditioned medium exhibited a reduction in cellular viability and an elevation in apoptotic events. PSCs are activated in hypoxia and promote β-cell apoptosis and death through exosomal miR-23a-3p. The addition of N-acetyl-L-cysteine, an antioxidant, mitigated the activation of PSCs in islets[125,126]. In conclusion, these studies support that PSC activation within the islets increases β-cell death and contributes to the progression of diabetes.

5.2. Therapeutic strategies related to fibrosis in diabetes

The therapies of diabetes-associated fibrosis include traditional drugs and nanomedicine. Some antidiabetic agents on the market have been reported to have anti-fibrotic effects, but more explicit evidence of efficacy is still needed. Meanwhile, the discovery of new targets provides another way for anti-fibrotic therapy in diabetes (Fig. 7).

5.2.1. Antidiabetic therapy

Some antidiabetic agents have demonstrated efficacy in lowering blood sugar levels and exhibiting therapeutic potential as anti-fibrotic agents in diabetes. (1) Administration of the glucagon like peptide-1 (GLP-1) analogue exendin-4 has demonstrated the ability to inhibit the onset of diabetes in a rat model of type 2 diabetes following partial pancreas removal. This treatment has led to a significant 40% increase in the mass of β-cells[127]. In addition, exendin-4 demonstrates anti-inflammatory properties and functions as an antifibrotic agent in mesangial cells. Exendin-4 efficiently decreases the synthesis of Ang II and TGF-β1 by decreasing the creation of ROS while not influencing the phosphorylation of ERK[128,129]. (2) Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new oral medication for lowering blood sugar levels. They work independently of insulin and successfully reduce blood glucose levels by increasing the amount of glucose excreted in urine[130]. The precise mechanisms behind the protective effects of SGLT2 inhibitors luseogliflozin on islet β-cells remain incompletely comprehended. Mice treated with luseogliflozin showed a notable decrease in the expression levels of genes associated with fibrosis, such as TGF-β, FN, Col I, and Col III[131]. These compelling findings suggest that SGLT2 inhibitors are promising therapeutic agents for safeguarding β-cells against islet fibrosis.

Long-term diabetes causes several significant organ damage and dysfunctions, as seen in both diabetic individuals and animal models. The development of fibrosis, which primarily involves the deposition of ECM, is one pathological reaction to tissue injury. It has been proposed that fibrosis has a role in the pathophysiology of diabetic nephropathy, neuropathy, cardiomyopathy, and retinopathy. Individuals who have diabetes for an extended period frequently have large fibrotic lesions in their liver, kidney, heart, etc. Currently, there are no approved antifibrotic treatments available. Insulin replacement therapy is an important anti-glycemic agent approach to diabetes[132]. Due to gastrointestinal effects, insulin and other macromolecular agents must be injected subcutaneously, which can be inconvenient and painful, leading to poor patient compliance[133]. Nanotechnology is being applied to
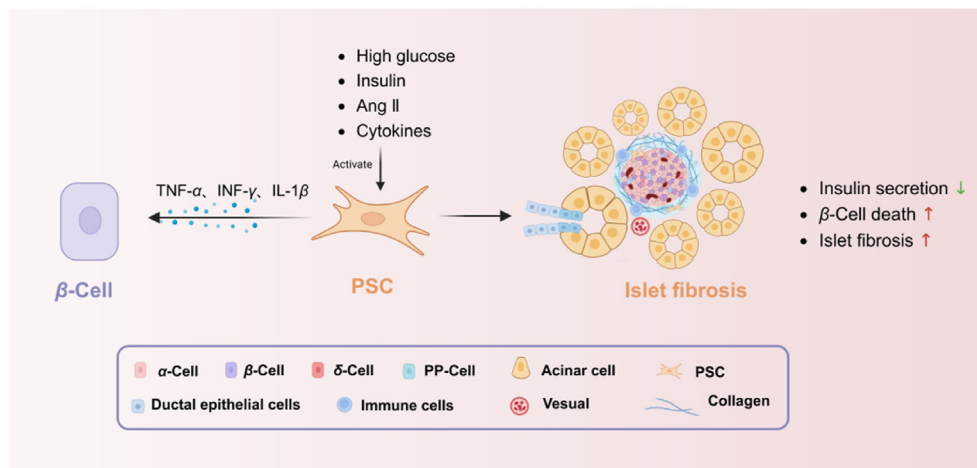
Figure 6 Intercellular crosstalk between PSCs and β-cells in islet fibrosis. High-glucose levels, insulin and angiotensin II (Ang II), and a release of pro-inflammatory cytokines induce PSC activation. Activated PSCs cause decrease of insulin secretion and increase of β-cell death by TNFα、INFγ、IL1β. Pancreatic fibrosis arises with extracellular matrix production. Figure created with Biorender.com.

improve insulin replacement therapy's simplicity, efficacy and safety. Hunt et al.[134] recently applied a silver sulfide quantum dots platform to insulin with a pH- and enzyme-sensitive encapsulating polymer. The formulation is insoluble in acidic environments and sensitive to glucosidase enzymes that trigger insulin release. As a responsive oral insulin nanoformulation, it shows the potential to control blood glucose without hypoglycemia orally. Cheng et al.[135] developed insulin-loaded nanoparticles decorated with folic acid to target intestinal cells. Folate is transported through a proton-coupled folate transporter (PCFT), which was upregulated in the intestinal epithelial cells of diabetic rats. Folate-modified

nanoparticles loaded with insulin have a higher oral insulin bioavailability than subcutaneous insulin injection.

5.2.2. Antifibrotic therapy
RAS blockers, including angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), have shown promise in efficiently avoiding or reducing islet fibrosis in persons with high blood sugar levels by directly inhibiting PSCs. Ramipril has demonstrated efficacy in mitigating pancreatic islet fibrosis over an extended period of treatment[136]. Candesartan and ramipril have proven effective in attenuating the increased expression of
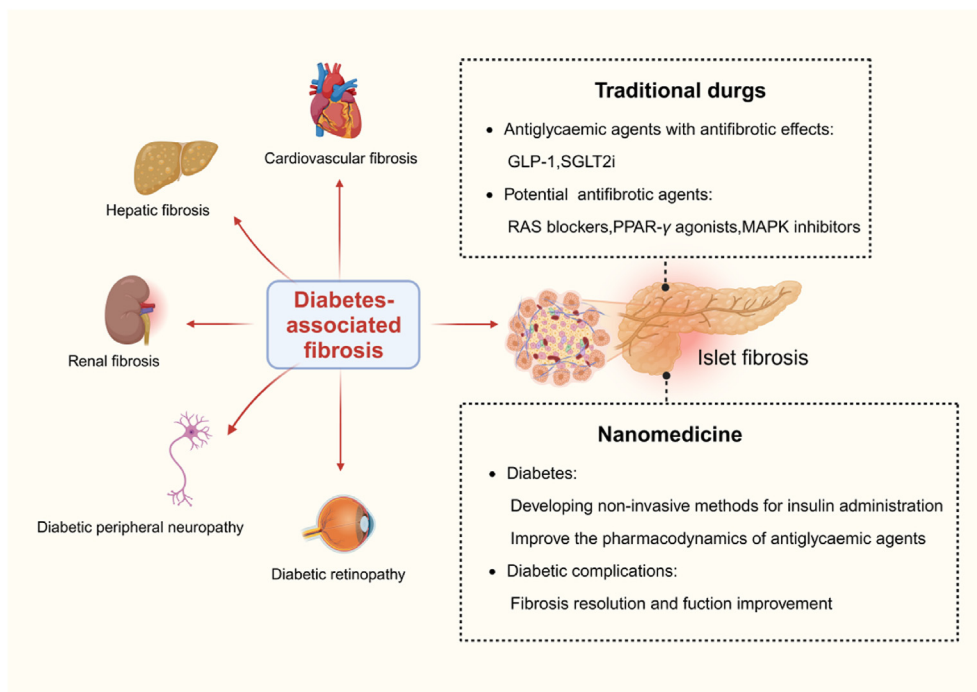

Figure 7 Diabetes-associated fibrosis and therapeutic strategies. In addition to islet, fibrosis has a role in the pathophysiology of diabetic nephropathy, neuropathy, cardiomyopathy, and retinopathy. The therapies of diabetes-associated fibrosis include traditional drugs and nanomedicine. Figure created with Biorender.com.

TGF-β following elevated levels of Ang II. The significant elevation observed in CTGF and type IV collagen proteins was effectively reduced by candesartan and ramipril[111]. Furthermore, troglitazone, a PPAR-γ agonist, has demonstrated inhibitory effects on the profibrogenic activity of PSCs[137]. Taurine and tempol are both potent antioxidants with notable antifibrotic properties. They reduced the activation of PSCs and the development of fibrosis in the islets of OLETF rats in response to high glucose[138,139]. Prior studies have shown that mitogen-activated protein kinase inhibitors can effectively decrease the phosphorylation of ERK 1/2 and the proliferation of pancreatic stellate cells triggered by both glucose and insulin[140]. However, additional inquiries are required to ascertain their precise impacts. Furthermore, a recent study on the antifibrotic drug pirfenidone showed a decrease in the expression of α-SMA and a restriction of islet fibrosis in the pancreas of OLETF rats. However, this therapy did not increase glucose tolerance or insulin secretion[116]. Despite these limitations, targeting PSCs directly could be considered a focused strategy, either alone or in combination with other drugs.

Ahangarpour et al.[141] have prepared solid lipid nanoparticle (SLN) of myricitrin. In a mouse model of diabetic nephropathy (DN), moderate and low doses of SLN were found to be more effective in reducing TGF-β gene expression and ameliorate fibrosis of kidney compared to a diabetes group. Hussein et al.[142] designed a type of Zinc oxide nanocrystals (ZnO-NPs) using hydroxyethylcellulose as a stabiliser and directing agent. It was showed that levels of C-reactive and cytokines (IL-1 and IL-6) decreased and NO level increased in the diabetic group. ZnO-NPs can effectively attenuate vascular diseases as a promising agent for diabetic vascular diseases and hyperglycaemia. More detailed information of nanomedicine for the treatment of diabetes and fibrosis can be found in Table 3[134,135,141,142].

6. Conclusions and future perspectives

Pancreatic fibrosis is a long-term and ongoing process that ultimately results in pancreatic endocrine and exocrine insufficiency. This dynamic pathological process exhibits varying compositions and roles across different diseases, necessitating a comprehensive understanding of fibrosis within the unique microenvironment associated with each disease. Firstly, CP, PC and diabetes are interrelated and may act as risk factors for one another. CP is characterized by persistent and permanent damage in pancreatic tissue. The injury results in the gradual loss of the exocrine to endocrine compartments of the pancreas, which are replaced by atrophy or fibrosis[78]. The development of CP leads to organ dysfunction and increases the risk of developing PC. Pancreatic fibrosis is also a typical feature of PC, which promotes the activation and recruitment of CAFs[8]. Pancreatic fibrosis can be used as a diagnostic marker of PC. Type 2 diabetes, particularly when accompanied by obesity, is a known risk factor for the development of PC. Meanwhile, CP and PC are the most common cause of pancreatogenic diabetes, also known as type 3c diabetes[145]. In addition, fibrosis is found in the endocrine pancreas[55]. However, the mechanism underlying PSC activation in the islet still needs to be discovered, and the relationship between fibrosis and diabetes warrants further attention.

In a normal pancreas, the gland is divided into many indistinct lobules by the connective tissue of the capsule. The pancreatic tissue exhibits few fibrous components. However, the tissue of CP is characterized by complete atrophy of the acinar cells and progressive fibrotic destruction of the pancreatic secretory parenchyma[143]. The fibrotic component of pancreatitis is primarily located in the interlobular or perilobular area. The incomplete obstruction of the pancreatic duct and the presence of cells expressing α-SMA, a marker of myofibroblasts, are significant factors in interlobular fibrosis[143]. The most common type of PC is ductal adenocarcinoma. During tumor progression, fibrosis progresses due to duct obstruction and the proliferation of interlobular myofibroblasts. The tissue of PC has a dense fibrous stroma with excessive connective tissue hyperplasia and fibrosis[144]. Different from pancreatitis and pancreatic cancer, where fibrosis occurs in the exocrine division, the fibrosis of diabetes appears in the capillaries, intra-islet and peri-islet of the endocrine gland[110] as shown in Table 4[110,143,144]. Although the characteristics of fibrotic tissue and the triggers for PSC activation vary in different disease contexts, PSCs are vital mediators of fibrosis. They are activated to produce large amounts of ECM deposited between tissues[8]. Hence, targeted inhibition of PSCs is a universal therapeutic strategy for antifibrotic treatment of different diseases. Interventions targeting PSCs include changing cells from activated to resting states and promoting apoptosis, with the ultimate goal of reducing the production of extracellular matrix proteins.

PF is a dynamic, cell-mediated pathological process in which activation of PSCs is generally recognized as the central event. In response to intracellular and extracellular microenvironmental stimuli, activated PSCs interact with other pancreatic cells, including PACs, islet cells, PCCs and immune cells. Notably, these cells play essential roles in activating PSCs in various diseases through different molecular and cellular signaling mechanisms. Firstly, PSCs are activated by paracrine profibrogenic chemo and molecular signals. Besides, pancreatic cells inhibit the activation of PSCs and eliminate activated PSCs through the induction of death and senescence. In order to gain new insights into therapeutic interventions for PF, it is essential to unravel the specific cellular mechanisms underlying cellular interactions in PSC activation. Further investigations should prioritize identifying of the pivotal elements that govern the activation of PSCs by these specific pancreatic cells. It will aid in the determination of precise approaches for intervening in PF. Additionally, the intercellular crosstalk in the regression of PF still needs to be better understood. In particular, which factor plays a leading role in regulating PSC activation during this process has yet to be discovered. A better understanding of this critical process would facilitate the development of more effective strategies to promote the regression of fibrosis and delay the progression of pancreatic disease.

Currently, numerous studies have provided the limitations of conventional drug delivery systems. To date, numerous studies have provided evidence of the limitations of conventional clinical drug delivery systems. They are mostly related to lack of potency and reduced efficacy or altered effects for several reasons: (1) restricted route of administration, (2) inappropriate or ineffective dosage, (3) low biological half-life, (4) lack of target specificity, and (5) side effects of the agents. Therefore, developing novel nanocarrier formations to improve bioavailability, efficacy and safety is expected to improve traditional drug delivery systems in fibrosis therapy. Recent research in the development of various nanocarriers such as polymeric NPs, liposomes and micelles has progressed phenomenally and shown promising advances in the treatment of antifibrosis and pancreatic diseases. In nanomedicine design, the aspects of material selection shall be considered including better biocompatibility and biodegradability, low immunogenicity, and accessibility. Due to interaction with organs, tissues and cells, nanoparticles are exposed in humans and induce

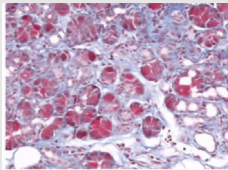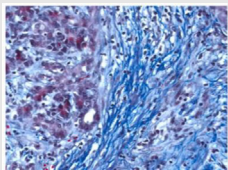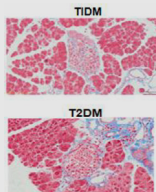**Table 3** Antifibrotic treatment strategies in diabetes mellitus.

Nanomedicine	Targeting therapeutic agent	Mechanism of action	Diabetes model	Preclinical/ clinical	Ref.
QD-INS-CS/GS	Insulin	Silver sulfide (Ag_2S) quantum dots (QDs) are orally bioavailable and increase the rate of absorption. Insulin release is mediated by enzymatic cleavage of polymerization chitosan and glucose copolymer.	NOD/ShiLtJ mice	Preclinical	134
Ins/PBCA NPs	Insulin	Folate is actively transported through proton-coupled folate transporter (PCFT). Due to increasing intracellular trafficking, folate-modified nanoparticles loaded with insulin have a high oral bioavailability.	Diabetic rats induced by alloxan	Preclinical	135
SLN	Myricitrin	Myricitrin targeted into kidney cell with solid lipid nanoparticle (SLN) to inhibit the expression of TGF-β and reduce oxidative stress and cytotoxicity.	Diabetic mice induced by streptozotocin-nicotinamide (STZ-NA)	Preclinical	141
ZnO-NPs	ZnO	Zinc oxide nanocrystals (ZnO-NPs) decrease levels of C-reactive and cytokines (IL-1 and IL-6) and increase NO level.	Diabetic rats induced by STZ	Preclinical	142

side effects and toxicity. We shall further emphasize the long-term safety of nanomedicine.

As mentioned above, the crosstalk between PSCs and other pancreatic cells plays a crucial role in pathological conditions of PF. Some nanomedicines have been developed to treat PF and pancreatic diseases by targeting the crosstalk between PSCs and other cells. There still needs to be more understanding of the complex mechanisms that cause PSCs to become active and the molecular processes that lead to pancreatic fibrosis. Additional inquiry is necessary to understand and solve these intricacies and create inventive treatment approaches. Continued endeavors in researching PSCs and their interactions with other cellular constituents have immense promise for substantial advancements in

the management of pancreatic disorders. In addition, our team has examined the significant function of various cells in other fibrotic conditions and conducted therapeutic experiments with nanomedicine intervention. Mesenchymal stem cells (MSCs) are self-renewing pluripotent stem cells with multidirectional differentiation potential, and their application in organ transplantation and other aspects has been extensively explored[146]. We developed a platform (MSCs-Lip@NCAF) using MSCs, and liposomes modified with type I collagenase loaded with nintedanib. MSCs-Lip@NCAF can be migrated to fibrotic lungs because of the homing characteristic of MSCs and then Lip@NCAF was sensitively released. Subsequently, Lip@NCAF ablated collagen fibers, delivered nintedanib into fibroblasts, and inhibited fibroblast

Table 4 Differences of PSCs activation in CP, PC and diabetes.

| Comparison	CP	PC	Diabete
Fibrosis mechanism	PSCs are key mediators of fibrosis. PSCs are activated to produce large amounts of ECM deposited between tissues.		
The triggers for PSCs activation	Pancreatic acinar cells	Pancreatic cancer cells	β-Cells
Location of fibrosis	Exocrine gland	Exocrine gland	Endocrine gland
	Interlobular or perilobular area	Periductal and interlobular	Islet
Pathological features	The tissue is characterized by complete atrophy of the acinar cells and progressive fibrotic destruction of the pancreatic secretory parenchyma[143].	The tissue is characterized by a dense fibrous stroma with excessive connective tissue hyperplasia and highly fibrotic[144].	Capillaries, intra-islet and peri-islet wrapped in fibrous tissue[110].
Masson of tissue			
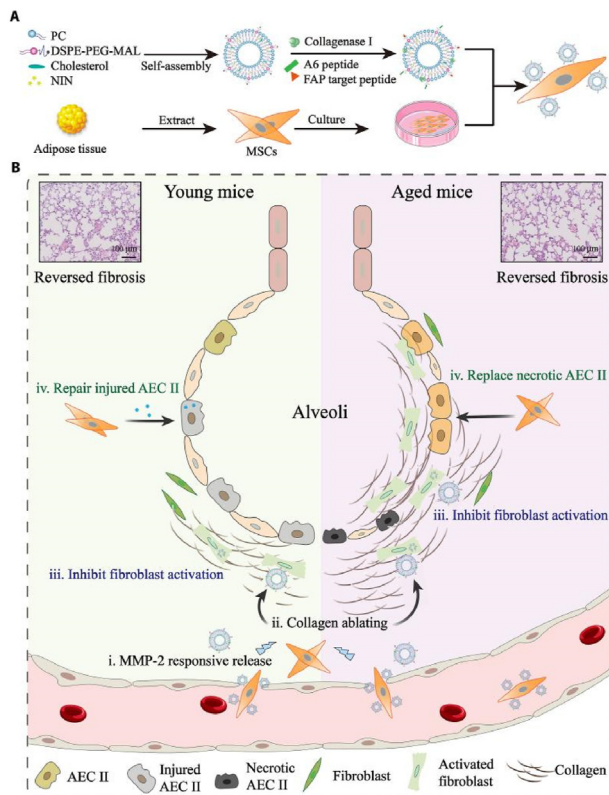
Figure 8 Illustration of lung-targeting nanoengineered MSCs-Lip@NCAF designed to reverse PF in young and aged mice. (A) Preparation of MSCs-Lip@NCAF. PC, phosphatidylcholine. (B) MSCs-Lip@NCAF migrated to injured lungs because of their homing ability, and Lip@NCAF was released in response to MMP-2. Then, Lip@NCAF degraded collagen fibers and inhibited fibroblast overactivation. Moreover, MSCs repaired injured AEC IIs in young mice and differentiated into AEC IIs to participate in alveolar reestablishment in aged mice. Reprinted with the permission from Ref. 147. Copyright © 2023 American Association for the Advancement of Science.

overactivation. MSCs differentiated into AECIIs to repair the alveolar structure and ultimately promote the regeneration of damaged lungs in aged mice. MSCs-Lip@NCAF was designed for the treatment of severe fibrosis and exhibited exceptional efficacy in treating fibrosis in elderly mice[147] (Fig. 8). MSCs have unique anti-inflammatory and immunomodulatory effects, which will be a potential therapeutic to reduce the inflammatory response, inhibit fibrosis, and rescue pancreatic function. Ultimately, it is crucial to understand, regulate, or take advantage of the abnormal microenvironment to maximize drug effectiveness. This task presents numerous obstacles and possibilities that require urgent consideration. There will be increased research attention on regulating the intercellular crosstalk in the future. Progress in this area will significantly contribute to the field of precision medicine.

Acknowledgments

Author contributions

Hui Wang: Writing − original draft, Conceptualization. Liang Qi: Writing − original draft. Han Han: Writing − original draft. Xuena Li: Data curation, Investigation. Mengmeng Han: Data curation, Resources. Lei Xing: Supervision. Ling Li: Writing − review & editing. Hulin Jiang: Conceptualization, Writing − review & editing.

Conflicts of interest

The authors have no conflicts of interest to declare.

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