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The dynamic interactions between the stroma, pancreatic stellate cells and pancreatic tumor development: Novel therapeutic targets

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ABSTRACT

The stroma is a main driver of metastasis and aggressiveness in pancreatic cancer (PC), one of the deadliest malignancies worldwide. Pancreatic stellate cells (PSCs) form approximately 50% of the pancreatic tumor stroma, causing desmoplasia, extracellular matrix (ECM) deposition, epithelial-to-mesenchymal transition (EMT) and metastatic spread. Furthermore, activated PSCs can remodel the pancreatic tumor microenvironment (TME) via dynamic and complex interactions and feedback loops with PC cells, thus facilitating tumor growth through various signalling and immune pathways. Hence, increased understanding of these cellular cross-talks and how they shape the TME in PC might guide the development of novel treatment approaches against this stubborn and deadly malignancy that has so far resisted therapeutic advances. In this review, we will explore the role of the stroma and PSCs in PC development, invasion and metastasis, examine their interaction with PC cells and discuss potential treatment approaches aimed at targeting PSCs in order to reprogram the pancreatic tumor environment.

1. Introduction

Pancreatic cancer (PC) remains an extremely lethal cancer worldwide and represents the seventh cause of tumor-associated mortality in both sexes [1]. The aggressive nature of this malignancy results from the unpalliated lack of appropriate detection methods and the fact that it is asymptomatic in its early stages. PC's dismal prognosis is further complicated by the frequent emergence of resistance to chemoradiotherapy, which limits the effectiveness of current stand-of-care regimens. Recent research has revealed a link between chemoresistance in PC and the presence of a compact and characteristic stromal tissue, which can constitute approximately 80% of the tumor microenvironment (TME) of PC [2]. This stromal mass consists of a heterogenous mix of various inflammatory and immune cells [3], forming a physical barrier that impedes successful delivery of chemotherapeutic drugs to cancerous cells and fuels chemoresistance. The most prominent component of this dense layer (up to 50% of its total mass) is pancreatic stellate cells (PSCs). PSCs act as crucial players in the pancreatic TME and have recently emerged as a potential target for tailoring novel therapies against PC. They can be described as exocrine and functional myofibroblasts modulated by both paracrine and autocrine stimulation [4]. Their sustained activity and dynamic interaction with tumor cells within the TME can enhance tumor progression and invasiveness and contribute to chemotherapeutic escape in PC through various signalling cascades [4,5]. Hence, improved understanding of the molecular mechanisms and intricate cross-talks that stromal components such as PSCs partake in will inform novel therapeutic approaches for targeted treatment of PC. These advances could potentially help in overcoming chemoresistance and enhancing therapeutic outcomes. In this review, we will delineate the biology of the stroma and PSCs, the molecular pathways that regulate their activity as well as their interactions with the various cellular types in the pancreatic TME. We will then explore possible future avenues of therapeutic treatment aimed at targeting the stroma in general and PSCs in particular in the pancreatic TME.

Abbreviations: Ang1, angiopoietin 1; aPSC, activated pancreatic cancer cells; aSMA, alpha smooth muscle actin; BMD cells, bone marrow derived cells; CAF, cancer associated fibroblasts; ECM, extracellular matrix; EMT, epithelial mesenchymal transition; FGF-2, fibroblast growth factor-2; HIF-1α, Hypoxia inducible factor 1-alpha; IGF1, insulin growth factor 1; IL-1, interleukin-1; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloproteinases; OS, overall survival; PC, pancreatic cancer; PCSCs, pancreatic cancer stem cells; PDGFR, platelet-derived growth factor receptors; PSC, pancreatic stellate cells; qPSCs, quiescent PSCs; SC, stellate cells; SHH, sonic hedgehog; TF, transcription factor; TGFβ1, tumor growth factor beta1; TME, tumor microenvironment; VDR, vitamin D receptor; VEGF, vascular endothelial growth factor

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2. The heterogeneous landscape of pancreatic tumors

2.1. Genetic aberrations in PC

PC is a complex disease that displays high intra and inter tumor heterogeneity in its genetic landscape, rendering it difficult to classify and stratify. The AJCC TNM staging system is currently employed by clinicians as a prognostic tool to predict survival following resection and inform treatment strategies [6]. However, this system is plagued by inaccuracy and fails at consistently estimating surgery outcomes [6]. Hence, newer PC classification approaches, based on genomic and molecular criteria, have been advanced to improve prognostic stratification [6,7]. The identification of molecular modifications involved in PC development has permitted the characterization of specific PC subtypes associated with particular molecular alterations and/or pathways, leading to the development of novel prognostic signatures [6,8–10]. These advances can guide the design of novel diagnostic methods and refined treatment strategies based on particular downstream PC targets.

As these various studies have revealed, PC is initiated by a limited number of key driver mutations affecting TP53, KRAS, SMAD4 and CDKNA2, detected in various combinations in the majority of PCs. For instance, KRAS undergoes mutations in approximately 90% of PCs [7]. However, even PCs harboring wild-type versions of KRAS are affected by somatic mutations that upregulate the KRAS/MAPK pathway modulated by KRAS, highlighting the crucial role of this axis in PC growth regardless of KRAS mutation status [11]. Inactivating TP53 mutations represent the second most frequent genomic modification observed in PC (up to 70%) [12,13]. Furthermore, alterations in SMAD4 occur in 50% of PCs and might promote a tumor driving microenvironment correlated with metastasis in all stages of PC [7,14]. Finally, CDKNA2 mutations are associated with the high neoplastic group and are caused by both epigenetic and genetic modifications [11]. Subsequent studies have identified driving mutations in additional genes including GATA6, TGFBR2, ARID1A and SF3B1 as well as alterations in the DNA repair gene ATM, ARID2 and EPC1 genes, implicated in chromatin alteration, and MAP2K4, ZIM2, MAGEA6, SLC16A4 and NALCN [6], highlighting the genetic heterogeneity of this stubborn disease.

2.2. Signalling aberrations in PC

Studies have shown that chemokines and cytokines are upregulated in PC. In fact, the analysis of PC serum has revealed that it is enriched with higher IL-6-, 8-, 10- and 1RA levels in comparison with healthy serum [15]. IL-6 is a key signalling molecule in PC, secreted by both cancer and stromal cells. Its overexpression is associated with weight loss and dismal prognosis [16]. Furthermore, research has uncovered the role of constitutive STAT3 activation in pancreatic tumorigenesis, establishing its close correlation with IL6 upregulation [17]. Another aberrantly expressed signalling factor in PC is IL-8, which can mediate tumor migration in cooperation with MMP-2 and SDF-1a [17]. IL-8 upregulation is linked to increased release of VEGF and metastatic spread under hypoxic conditions through MAPK/ERK cascades [18]. IL-8 is also associated with CXCR1 upregulation in patient tissue [19], which is predictive of poorer patient survival.

The NF-κB cascade is one of the most frequently dysregulated pathways in PC due to TNFα overexpression, as evidenced by its increased levels in patient samples with advanced disease [18]. Elevated TNFα expression also correlates with the upregulation of ADAM17, an enzyme that processes TNFα and contributes to PC invasiveness [20]. Another potentially prognostic molecule detected in PC patient serum is TGFβ, which coincides with poor OS [18]. Moreover, higher levels of the chemokine GRO1 are associated with dismal prognosis in metastatic PC [20]. Despite the critical role played by these various individual chemokines and cytokines in PC progression, large scale clinical studies also indicate that the general PC inflammatory blueprint consisting of combined inflammation markers correlates with increased mortality in PC patients [21]. Hence, targeting this inflammatory network could be a rational approach for combating PC.

3. Genetic and molecular classifications of PC

3.1. Collisson's classification of PC

The first genetic classification of pancreatic tumors was proposed in 2011 by Collisson et al. [10] and demarcated three tumor subtypes: 1) classical, 2) quasi-mesenchymal and 3) exocrine-like tumors, associated with distinct therapeutic responses and clinical outcomes. The classical subtype displayed better survival rates and was characterized by the upregulation of adhesion and epithelial genes and GATA6, which codes for a TF mediating pancreatic development [22]. In contrast, quasi-mesenchymal tumors correlated with the poorest survival rates of all three classes and exhibited increased levels of mesenchymal genes, including CAV1, HK2 and TWIST1 [6,7]. Finally, the exocrine-like tumors were characterized by the overexpression of genes coding for digestive enzymes and linked to exocrine pancreas function [6,7]. Furthermore, the classical subtype displayed higher sensitivity to erlotinib whereas quasi-mesenchymal tumors showed higher sensitivity to gemcitabine [6,7]. This indicates that molecular classification can guide therapeutic decisions.

3.2. Moffitt's classification of PC

A second classification system was developed in 2015 using microarray data analysis from metastatic versus primary tumors compared to normal tissues [6,7]. Based on the observation that the PC stroma induces chemoresistance by obstructing drug access, Moffitt et al. [9] segregated the stromal milieu from the 'malignant' and epithelial component using microdissection, thus identifying distinct PC subtypes. Gene analysis revealed two different stromal PC subtypes, i.e. the 'normal' versus the 'activated' group, which displayed poorer prognosis (1 year survival: 60%) than normal tumors (1 year survival: 82%) [9]. Similarly, data analysis revealed two 'malignant' subgroups, namely "classical" and "basal-like" tumors. Patients diagnosed with basal-like tumors exhibited the lowest survival rates, independent of stroma type [9]. Additionally, the best prognostic outcome was associated with classical tumors harboring normal stromal subtypes whereas the worst outcomes were observed in basal-like PCs characterized by activated stromal milieus. Gene analysis showed that the activated stroma subgroup overexpressed genes involved in fibroblastic activity, the WNT pathway (WNT 2 and 5A), chemokine signaling (CCL13 and 18) and macrophages (ITGAM) [9]. In contrast, the normal stroma was characterized by markers of PSCs (DES, VIM and ACTA2) [9]. Hence, Moffitt's system offered a more refined classification of the PC milieu by taking into account its various components and degrees of complexity.

3.3. Bailey's classification of PC

A more recent classification, advanced by Bailey et al. [8], identified 4 PC subtypes associated with various molecular pathways and termed 1) squamous, 2) PC progenitor, 3) immunogenic and 4) aberrantly differentiated endocrine exocrine subtypes. This classification was informed by the differential patterns of expression of downstream effectors and transcription molecules involved in lineage differentiation during PC development [6,7]. Bailey's squamous subgroup, which overlaps with Collisson's quasi-mesenchymal subtype, is characterized by increased mutations in KDM6A and TP53 and in genes implicated in metabolic reprogramming, inflammation, TGFβ signalling, hypoxia, autophagy, MYC activation and upregulation of TP63delataN and its associated target genes [6,7]. This subtype displays the worst OS. The pancreatic progenitor tumors, on the other hand, overlap with

Collisson's classical subtype and harbor molecular networks enriched with TFs mediating early PC development (MNX1, PDX1, HNF4A, HNF4G, HNF1A and B, HES1 and FOXA2 and 3) [6,7]. Thirdly, the ADEX group overlaps with Bailey's exocrine-like tumors and features genetic networks implicated in modulating the advanced phases of exocrine and endocrine PC differentiation and development (KRAS, MIST1, NR5A2, NEUROD1, INS, RBPJL, and MAFA) [6,7]. Finally, the immunogenic tumors are characterized by immune infiltration and upregulated immune networks associated with antigen presentation, B and T-cell signaling, CD4+ and 8 + T cells, and TLR cascades [6,7]. Hence, this classification can link differential signalling and immune signatures involved in PC development to prognostic rates.

3.4. TGCA classification of PC

Integrated genomic analysis profiling of PCs by the TGCA confirmed and corroborated the existence of only two PC subtypes, namely the basal-like/squamous and PC progenitor/classical subgroups across the three previously described platforms (Collisson, Moffitt, Bailey) [11]. Moreover, the analysis revealed that classical subtype tumors were enriched with GNAS mutations, whereas the basal-like tumors were characterized by TP53 mutations. Additionally, the two subgroups were segregated by differential patterns of gene expression modulated by DNA methylation and miRNA levels. In contrast, the immunogenic and ADEX tumors showed low neoplastic cellularity in this cohort, suggesting that the stroma or TME could have influenced the molecular and genetic blueprint of these tumors [11]. Another interesting finding from this study was the detection of distinct subclonal KRAS mutations within the same tumor samples, a heterogeneity that could explain the propensity of certain pancreatic tumors for developing drug resistance [11]. These various analyses and classification systems highlight the heterogenous nature of pancreatic malignancies, indicating that the integration of various molecular analyses will improve patient stratification and provide roadmaps for genetically informed treatment options and future clinical trials. The development of a diagnostic and prognostic molecular signature or blueprint could thus enhance the early detection and management of this stubborn disease.

4. Morphology of PC

As these classification systems illustrate, PC development is influence by the intricate interplay between pancreatic tumor cells and host cells in the surrounding TME. The influence of each individual component on the other, however, remains to be elucidated to uncover the critical interactions at the TME-tumor interface and their effects on PC progression and dissemination. Interestingly, aggressive PCs are characterized by dissociative growing coupled to increased numbers of migrating cancer cells at invasive sites, known as 'tumor buds', which function as an independent prognostic factor in PC [23,24]. Tumor budding shares important genetic similarities with EMT, suggesting an EMT-like landscape [25,26]. For instance, tumor buds overexpress the key EMT biomarkers (Snail, N-cadherin and ZEB1 and 2) but have reduced levels of E-cadherin and β-catenin [7,27]. Additionally, tumor buds lack markers of proliferation and apoptosis [28], indicating that proliferation versus migration represent mutually exclusive phenomena.

Studies have also shown that miRNA dysregulation can influence bud formation [29]. In fact, the bud phenotype exhibits reduced levels of miR-200b and 200c, which are inversely correlated with the upregulation of ZEB1 and 2 in PCs with increased budding [29,30]. Since the miR-200 family inhibits migration, tumor growth and metastasis, the downregulation of these key tumor suppressors is thought to contribute to tumor bud formation [7]. Furthermore, the inverse relationship between the miR-200 family and ZEB proteins enables the stabilization of the epithelial or mesenchymal states in EMT [31]. More importantly, evidence also suggests that TME components such as stromal cells could mediate tumor budding by upregulating E-cadherin inhibitors and supporting miRNA dysregulation [7]. This finding highlights the potential contribution of the stroma to the formation of a compromised cancerous environment conductive of tumor budding. Recent research also suggests that tumor buds might arise from subpopulations of migratory CSCs, indicating that the TME could aggravate EMT-like phenotypes [32]. Hence, increased understanding of the interaction between tumor buds and the TME could improve PC classification and guide the development of novel therapeutic strategies.

5. The TME and tumor interface in PC, a constantly shifting mosaic

5.1. PC stromal subtypes

The PC TME consists of a dense and desmoplastic stroma enriched with CAFs. A recent classification system by Puleo et al. [33] has delineated four different stromal subtypes: 1) structural vascularized, 2) activated, 3) inflammatory and 4) immune, in addition to the previously identified PC subgroups, thus highlighting the heterogeneity of the malignant pancreatic TME. The study reported that the activated stroma subtype, characterized by high levels of CAFs, and the basal-like subtypes harbor less immune infiltrates and have the worst prognosis compared with other subgroups [33]. These findings suggest that the complex interaction between stromal fibroblasts, immune cell infiltration and tumor cells might modulate tumor suppressing or promoting functions following the abrogation or upregulation of specific molecular networks and pathways in PC [7]. Increased understanding of this intricate interplay might inform the development of novel diagnostic, prognostic and therapeutic solutions for PC management.

5.2. The immune microenvironment in PC

Recent research indicates that the immune microenvironment of PC could function as a predictive and prognostic marker of PC development [7]. Traditionally, PC is defined as a 'non-immunogenic' malignancy that can adopt multiple strategies of immune circumvention and evasion. These measures include the production of immunosuppressing chemokines (stromal cell derived factor), the recruitment of regulative immune cells, and various cytokines (IL-1, 6 and 10 and TNFα), and the expression of PDL1, CTLA4 and CSF1R [34,35]. In fact, PDL-1 is frequently upregulated in PCs and correlates with worse prognosis [36]. Alternatively, CSF1R is predominantly located in myeloid cells and mediates the recruitment of macrophages, which constitute the major leucocyte population in the PC stroma and contribute to the squamous phenotype [37]. Increased levels of macrophages in PC are associated with dismal prognosis [7]. This group of tumors can be described as the 'immune escape PC phenotype', defined by the overexpression of pro-EMT factors, miRNA dysregulation and somatic mutations, leading to an aggressive malignancy with EMT-like tumor buds and poor prognosis [7]. In this neoplastic context, tumor budding cells could interact with the TME to generate a permissive niche that favors their survival. The clinical properties of this phenotype overlap with Bailey's squamous tumors and Collisson's quasi-mesenchymal group, characterized by molecular blueprints that enable EMT, cellular plasticity, immune evasion and the inhibition of immune infiltration into tumor sites [7,38].

Research also indicates that differential rates of immune recruitment could yield heterogenous immune landscapes in PC, leading to distinct immune phenotypes. For instance, the immune environment of many PCs is enriched with T reg infiltrates, TAMs displaying M2 polarization and myeloid-derived suppressing cells that inhibit CD4+ and 8 + T cells [39–41]. To further complicate this heterogenous landscape, immunoediting, which alters the immunogenicity of PC cells, can also result in immune-refractory clonal populations, further aggravating prognosis [35]. In sharp contrast, a different subclass of immunogenic

PCs possesses a TME rich in CD4+ and 8 + T cells and devoid of immunosuppressive cells, thus correlating with improved survival outcomes [41,42]. Additionally, a subgroup of these tumors is enriched with peritumoral B lymphocytes, and CD20+ and 30+ stromal immune infiltrates that lead to tertiary lymphoid tissue (TLT), which induces a potent anti-tumor activity resulting in favorable survival rates [42,43]. This group of tumors is termed 'immune-rich PC phenotype' and shows reduced tumor budding and improved survival [7]. PCs with cytotoxic TMEs display immunogenic characteristics [38], i.e. higher neoantigen loads and mutations in genes implicated in interferon signalling and DNA damage responses.

As the previous sections show, PC is a highly heterogenous disease that can be divided into distinct tumor subgroups characterized by differential genetic signatures and microenvironment conditions, leading to divergent neoplastic phenotypes and prognostic outcomes. These primary subgroups can be further subdivided into varying subgroups characterized by distinctive molecular mechanisms that can alter the interplay between cancerous and immune cells, thus generating different "permissive" contexts of tumor growth and diversification underlying the heterogeneity of immune responses detected in PC [7]. These subgroups depict fluctuating landscapes of host and tumor interactions that enable distinctive mechanisms of immune evasion impacting phenotype and clinical outcomes. Hence, integrated classification tools could enable a more accurate differentiation between these various immune subtypes according to their immune landscapes and inform the development of novel targeted and immune therapies. It could also enhance the selection of specific subgroups of patients for clinical testing based on their molecular signatures, thus excluding non-responders.

6. The role of the ECM in shaping the PC stroma

One of the prevalent and dynamic components of the PC stroma is the ECM. The ECM's main function is to ensure tissue integrity by depositing a biochemical and structural matrix that supports cells [44]. This matrix is constantly being reshuffled and remodeled by TIMPs and MMPs, thus altering its abundance and composition [44]. In PC, tumor and stromal cells can interact to reshape the ECM by secreting enzymes and structural components, thus affecting tumor development and motility [45,46]. The ECM's predominant component is collagen I, which mediates proliferation, attachment and migration through $\alpha_2\beta_1$ integrins, thus hampering adhesion in cells [47,48]. Collagen I has been found to decrease E-cadherin expression in PC cells by upregulating FAK and Smad-interacting protein I, thus disrupting β-catenin/E-cadherin complexes and driving neoplastic cells into a precipitated cell cycle [49,50]. Furthermore, collagen I can upregulate N-cadherin, mediate NF-κB translocation through DDR2 and upregulate LEF-1 and SNAIL. These combined mechanisms drive EMT and tumor motility in PC [51]. Another ECM component that exerts its action through $\alpha_2\beta_1$ is Collagen V, which accelerates the proliferation of PSCs and stimulates angiogenesis in the TME to enable PC metastasis [51]. Hence, the crosstalk between tumor cells and stromal cells ensures the constant reshuffling of the ECM to assist the proliferation requirements of the tumor.

Laminins represent another important building block of the ECM and promote cellular differentiation and adhesion through integrins [52]. Fibronectin, on the other hand, is produced by PSCs and binds to collagen and integrins to induce migration [44]. Aberrant fibronectin signalling can induce IL-8 secretion, thus stimulating invasiveness [44,53]. Other components of the ECM include proteoglycans, which can also bind to ECM components and are expressed by both PSCs and malignant cells [44]. The proteoglycan Glypican-1 is overexpressed in PC cells and induces tumorigenicity whereas SPOCK-1 is upregulated in stromal cells by the SHH pathway, thus remodeling the ECM and promoting invasiveness in PC cells [54–56]. The dense stroma of PC compresses the blood vessels [57], resulting in poor vascularization, nutrient depletion and hypoxia, which causes PC cells to undergo adaptative modifications that promote survival.

7. The role of the vasculature in modelling the PC stroma

Angiogenesis in PC is modulated by growth factors, cytokines and hypoxia, most of which are produced in the TME [44]. This creates a feedback loop that causes tumor cells, immune cells and PSCs to release angiogenic factors in response to hypoxia, thus further promoting the hypoxic milieu [58]. Moreover, PSCs secrete VEGF and other pro-angiogenic molecules such as β-FGF to sustain ECM production and limit vascularization, further promoting tumorigenesis [59]. Interestingly, PSCs exert a heterogenous angiogenic effect in tumors, resulting in an asymmetric vascularization of the pan versus juxtatumoral stromal compartments [44]. The juxtatumoral stromal region resides in proximity with PC cells, while the pan-stromal section encompasses the remainder of the stromal environment [60]. The juxtatumoral section is hypovascularized whereas the pan-stroma is irrigated with blood vessels and corresponds to the invasive tumor front [60]. Hence, PSCs shape the stromal milieu into two distinctive portions through differential vascularization to support invasiveness.

Furthermore, lack of vascularization in the proximal PC stroma provokes oxygen and nutrient depletion in the TME, leading to metabolic stress [44]. This alters the metabolism of PC cells, causing them to harness alternative nutrient sources. These mechanisms include the uptake of proline derived from collagen I and V in the ECM for TCA cycle entry or glutamine synthesis [61]. Alternative routes include micropinocytosis or the uptake of lipids and extracellular proteins by scavenging [61]. Nutrient depletion can induce autophagy in both PC cells and PSCs. Autophagy in PSCs provides PC cells with non-essential amino acids including alanine, thus preventing the loss of their migratory capacity [62,63]. Finally, hypoxia in PC is mediated by HIF-1a, leading to tumor stemness and invasion [44]. Downstream targets of HIF-1a comprise CX3CR1, CypA and Fascins, which contribute to PC migration [64,65]. Moreover, hypoxia mediates chemoresistance through several mechanisms, including ERK1/2 signalling, NF-κB stimulation, upregulation of the Hh pathway and depletion of chemotherapy-associated ROS [44]. The lack of vascularization in the stroma further hampers drug delivery and reinforces chemoresistance [44]. Hence, the interplay between PC cell signalling and the composition of the stroma promotes survival and the emergence of radiochemoresistance.

8. Pancreatic stellate cells in the PC stroma

Human stellate cells (HSCs) were originally described by the German researcher Carl von Kupffer in 1876, who identified them in the lung and kidneys [66]. However, it wasn't until 1982 that Japanese scientists observed HSC-like cells enriched with vitamin A in mouse pancreatic tissue [67]. A decade later, in 1998, two studies reported the isolation, culture and expression of this novel pancreatic cell type, which was subsequently named as PSC [68,69]. PSCs can be described as star-shaped cells present at basolateral sides in acinar cells or in the periductal and perivascular sites of the normal pancreas [70]. They can be classified as either quiescent or activated. In the healthy physiological state, PSCs remain quiescent and characteristically express desmin, vimentin, GFAP and nestin [5]. Quiescent PSCs (qPSCs) participate in storing of retinoids, namely vitamin A-enriched droplets, endocrine and exocrine secretion, immunity, phagocytosis and the preservation of normal pancreatic stromal architecture and composition [71]. Reported biomarkers of qPSCs in the healthy pancreas comprise adipohilin and cytoglobin [72]. Tumorigenic progression is characterized by a transition from quiescent to activated PSCs, which engage in various tumor-promoting activities in the PC stroma. PSCs biomarkers related with PC growth, metastasis and suppression were summarized in Table 1.

Table 1
PSCs biomarkers related with pancreatic cancer (PC) growth, metastasis and suppression.

Biomarkers	Function	Ref.
CD10	$CD10^+$ PSCs increase the growth of PC.	[73]
CD271	$CD271^+$ PSCs subpopulation associates with prognosis of PC and is controlled by interaction with malignant cells.	[74]
P2 × 7R (receptor P2 × 7)	It expressed in PC cells as well PSCs. P2 × 7R also associated with PSCs number or activity and collagen deposition.	[75]
HGF	It exhibits the functional heterogeneity in PC derived PSCs, which concerned the mitogenic signalling and migration in PC.	[76]
Cadherin-11	It is an important signaling molecule for PC migration and overexpressed on surface of PSCs.	[77]
Kindlin-2	It expressed in PSCs and induces the growth of PC.	[78]
PAK1 (p21-activatedkinase1)	Suppression of PAK1 inhibits PSCs activation and prolongs survival of mice with PC.	[79]
Galectin-1	It is overexpressed in aPSCs and is essential for the activation of PSCs.	[80]

8.1. Activation of PSCs in PC

Various mechanisms can lead to the activation of quiescent PSCs, including chronic inflammation, chronic smoking and environmental stress (e.g., oxidative stress, hypoxia and hypoperfusion), increased secretion of IL-1 and -6, HIF1α and TGF-β as well as the upregulation of key pathways, i.e. PI3K and Wnt and β-catenin cascades [81]. PSCs stimulation is accompanied by numerous morphological modifications that enable their differentiation into activated PSCs (aPSCs), particularly vitamin A loss and upregulation of a α-smooth muscle actin (α-SMA), an independent prognostic marker of PDAC [81,82]. aPSCs display a migratory phenotype that renders them invasive by promoting the synthesis and deposition of ECM components, namely fibronectin, hyaluronic acid, collagen and laminin and the unbalanced production of tissue inhibitors of metalloproteinases (TIMPs) and matrix metalloproteases (MMPs) as described above, thus profoundly altering the architecture of the TME [70,81]. Furthermore, aPSCs can upregulate the expression of critical cytokines (IL-1,-6,-8, and -10) and key growth factors, such as IGF1, VEGF, PDGF, FGF, CTGF, and CXCL12 (Fig. 1) [70,82]. These growth factors and cytokines enhance angiogenesis and invasiveness of epithelial cancer cells, leading to tumor metastasis [70,81,83]. Interestingly, PSCs-secreted factors, i.e. IL-6, are implicated in the transition of noninvasive PC into an invasive tumor phenotype and can contribute to MDSCs accumulation through the STAT-3 pathway, thus fueling immunosuppression within the TME [84,85]. Hence, aPSCs play a crucial role in forging and configuring the tumorigenic stromal milieu, ensured by sustained communication with PC cells.

8.2. Origins of PSCs

The secretory profile of PSCs is mirrored by that of cancerous cells, which can also secrete upregulated levels of cytokines (IL-1 and -6, TGF-β1, TNF-α and PDGF-B) [86]. This reciprocal cross-talk between aPSCs and tumor cells fuels PC progression and metastasis. Moreover, PC cells can elicit autophagy in PSCs, resulting in the secretion of alanine, which sustains the metabolic needs of PC cells and their survival in the nutrient-depleted microenvironment of the pancreas [86]. In addition to their dynamic role in PC invasiveness, PSCs can additionally promote drug escape by sequestering gemcitabine, thus greatly limiting its therapeutic effects against PC cells [87]. As this interactive, complex and constantly changing landscape reveals, reciprocal communication and intricate cross-talk between PSCs and PC cells significantly stimulates PC progression and aggressiveness, thus contributing to its dismal prognosis. Although PSCs express both neurotrophic factors and mesenchymal markers, their exact origin remains unknow [5]. Research indicates that the bone marrow might constitute a major source of PSCs [88]. Additionally, the remarkable heterogeneity of pancreatic SCs might be explained by the fact that some PSCs originate in hematopoietic cells while others are derived from the mesodermal cells [5]. A greater understanding of the origin of PSCs will thus shed light on their function and clinical significance, guiding the development of effective therapeutic approaches.

8.3. The role of PSCs in PC pathophysiology

PC originates from various pancreatic precursor lesions, including:

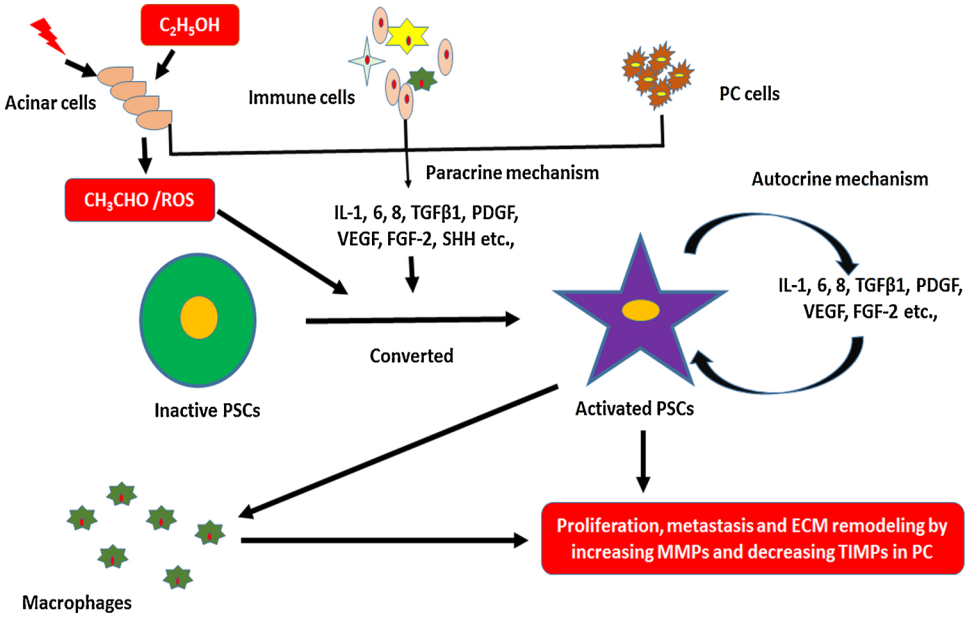

Fig. 1. Mechanisms of activation of pancreatic stellate cells (PSCs): PSCs can be activate through three distinct mechanisms. 1- Infection or ethanol (C_2H_5OH) induces reactive oxygen species (ROS) production and acetaldehyde (CH_3CHO) release through acinar cells, leading to the activation of inactive PSCs. 2- Immune cells can induce the production of various cytokines and growth factors through paracrine mechanism, leading to PSC activation. 3- Pancreatic cancer (PC) cells can also activate PSCs through paracrine mechanisms. The activation of PSCs results in further self-activation through autocrine release of various cytokines and growth factors. This leads to proliferation, metastasis and the deposition and remodeling of the extracellular matrix (ECM) by increasing matrix metalloproteinases (MMPs), Hypoxia inducible factor 1-alpha (HIF-1α) and macrophage infiltration. IL-1, interleukin-1, VEGF, vascular endothelial growth factor; TGFβ1, tumor growth factor beta1; PDGF, platelet-derived growth factor; FGF-2, fibroblast growth factor-2; SHH, sonic hedgehog.

1) intraepithelial neoplasia (PanIN), 2) intraductal papillary mucinous neoplasm (IPMN), and 3) mucinous cystic neoplasm (MCN) [4]. Most invasive PCs sprout from PanIN lesions. Interestingly, staining of α-SMA reveals a population of activated PSCs surrounding PanIN lesions [4]. Furthermore, studies examining PC progression have demonstrated that the IL-6 produced by aPSCs can stimulate the STAT3 cascade in non-invasive PanIN cells, inducing colony formation and cell invasiveness [85]. Accordingly, inhibiting IL-6 and STAT3 successfully attenuated the aPSC -induced STAT3 tumorigenic pathway, suggesting that aPSCs actively drive the transformation of precursor pancreatic cells to invasive PC [85]. Further research will be necessary for elucidating the dynamic role of PSCs in PC development. The aggressive phenotype of PC can be attributed to many factors including the repression of tumor immunity, the proliferative capacities of cancerous cells, chemoresistance due to the impaired penetration of chemotherapeutic drugs into the stromal TME and the suppression of apoptosis [89]. aPSCs seem to be implicated in the various facets of PC tumorigenesis, either through indirect interaction with the stroma or direct physical interaction [4]. Understanding this intricate web of cross-talk between aPSCs, the stroma and the TME in PC is thus necessary for devising new and effective strategies against this malignancy.

8.4. aPSCs enhance ECM production in PC

aPSCs aggravate PC invasiveness by impairing the activity of therapeutic drugs and inducing chemoresistance through desmoplasia. The desmoplastic reaction is characterized by aPSC-induced secretion of ECM proteins leading to hypoxia and fibrosis (Fig. 2) [89]. These disruptions provoke genomic instability in PC cells, EMT, increased tumor aggressiveness and chemoresistance [89]. Furthermore, the complex network of tumor-cell and stroma interactions is associated with peritoneal dissemination as well as perivascular invasion, histological grade and lymph node metastasis [90]. In fact, aPSCs have been observed in metastatic nodules, indicating that they can both intravasate and/or extravasate in or out of the blood vessels, travel in the circulation and spread into distant organs [91]. aPSCs fuel PC aggressiveness through the excessive production of ECM molecules such as laminin, fibronection, and collagens, which can modulate the phenotype of PC cells [52]. For instance, the upregulation of collagen in PDAC can enhance the adhesion, survival, migratory and metastatic capacities of pancreatic tumor cells through the FAK/β1 integrin pathway [52]. Additionally, the deposition of a thick layer of ECM creates a barrier that obstructs the penetration of drugs through blood vessels, thereby hindering the delivery of drugs to PC cells [60]. aPSCs-induced chemoresistance could arise through another mechanism (Fig. 2). According to this novel scenario, TGF-β- stimulated PSCs produce CYR61 (cysteine rich angiogenic inducer 61), a matricellular molecule that modulates hCNT3 and hENT1, two nucleoside transporters responsible for gemcitabine uptake [92]. This depletes gemcitabine in PC cells, leading to chemoresistance and subsequent therapy failure.

8.5. aPSCs reprogram the pancreatic TME

The ECM secreted by aPSCs weaves a dense stroma that provokes elevated interstitial pressure [93]. This increased stromal pressure causes hypoperfusion, nutrient depletion, vascular collapse and amplified delivery of oxygen to tumor tissue [4]. Since the upregulation of the glucose metabolism through the Warburg effect, due to mitochondrial disruption, or the reverse Warburg effect, is not sufficient to counterbalance tumor progression, the nutritional requirements of tumorigenesis are supported by metabolic rewiring between the stroma and PC cells [4]. Interestingly, previous findings suggest that aPSCs are significantly involved in PC reprogramming, which enables its progression in a nutrient-depleted environment [94]. The mutual and crucial crosstalk between aPSCs and PC cells results from genetic alterations and paracrine signalling [4]. In fact, KRAS mutations have been found to upregulate glucose uptake and enhance aerobic glutamine metabolism as well as aerobic glycolysis through various pathways [94]. Alterations in oncogenic KRAS augment the secretion of sonic hedgehog (SHH) in PC cells, leading to the activation of PSCs. This in turn stimulates downstream signalling pathways such the PI3K cascade and respiratory activity in the mitochondria and enhances the availability of oxygen for PC cells in hypoxic niches [95]. Additionally, KRAS mutations enable micropinocytosis, leading to the repurposing of extracellular proteins for lysosomal-mediated catabolism. This phenomenon ensures the recycling of amino acids, thus fueling tumor growth [4]. Moreover, exosomes derived from aPSCs are enriched in miRNA, mRNA and various cellular metabolites such as amino acids, stearate, lactate and palmitate, which drive the TCA cycle in PC, further stimulating tumor growth [96]. Interestingly, PC cells can upregulate autophagy in aPSCs, thus inducing the production of alanine as an alternative source of carbon to glutamine or glucose, which compensates for the nutritional needs of PC cells through NEAA, lipid or Ser/Gly biosynthesis [63]. Hence, the metabolic interaction between PC cells and activated PSCs mediates the progression of PC in the hypoxic and nutrient-depleted pancreatic milieu, further aggravating PC phenotype and amplifying its invasive capacities.

8.6. aPSCs support resistance to chemoradiotherapy in PC

As these previous sections illustrate, the intricate crosstalk between aPSCS and PC cells remodels the architecture of the TME and hijacks its

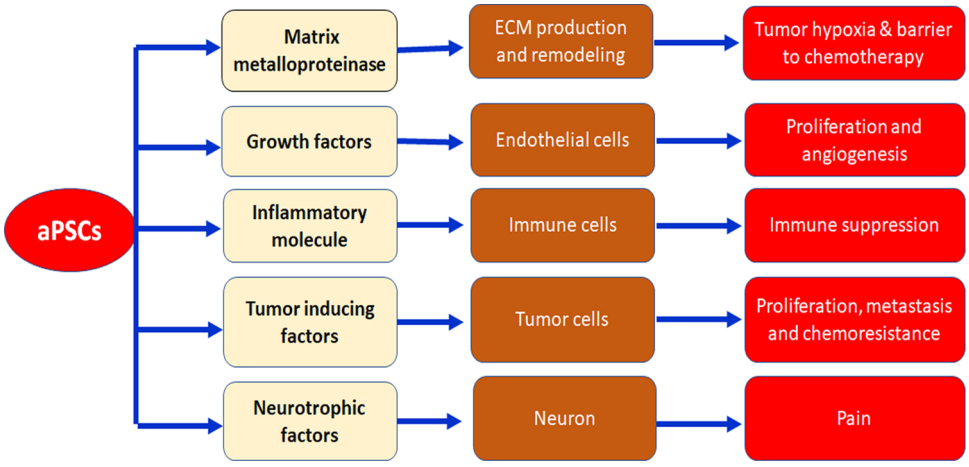

Fig. 2. Biological behavior of activated pancreatic stellate cells (aPSCs) in pancreatic cancer.

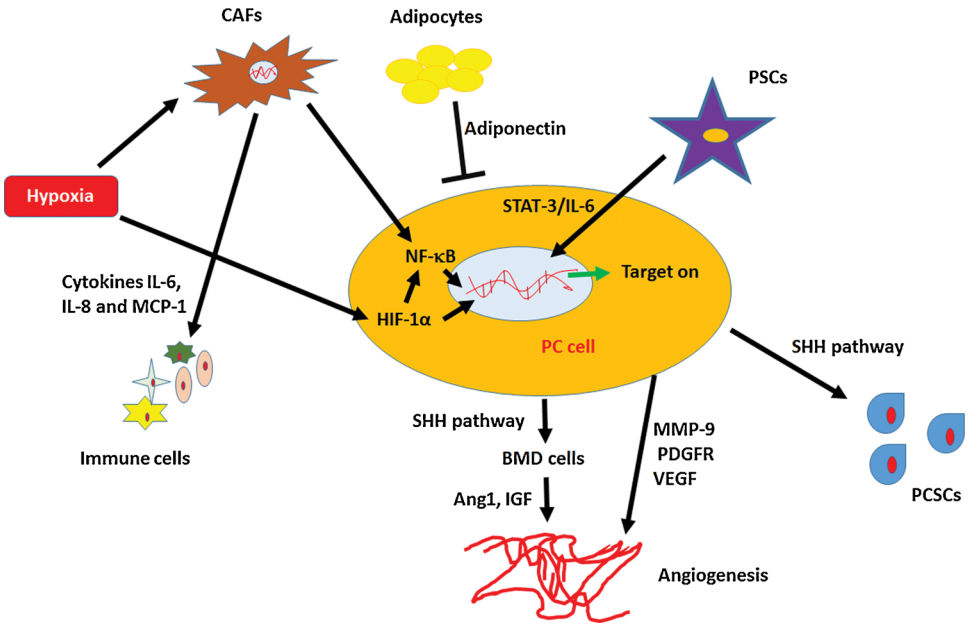

Fig. 3. The network of interactions between the stroma and PC cells in pancreatic tumor development: Hypoxia induces nuclear factor kappa light chain enhancer of activated B cells (NF-κB) activity in pancreatic cancer (PC) cells through cancer-associated fibroblasts (CAFs) and Hypoxia inducible factor 1-alpha (HIF-1α), which stimulates the transcription of oncogenic pathways in PC cells. Pancreatic stellate cells (PSCs) in the stroma trigger oncogenic signalling through Signal transducer and activator of transcription-3/ Interleukin 6 (STAT-3/IL-6) pathways. Furthermore, they induce the sonic hedgehog (SHH) pathway to activate pancreatic cancer stem cell markers. These various interactions upregulate angiogenesis by further stimulating the release of cytokines, growth factors and proteases. In contrast, adipocytes produce adiponectin to inhibit PC cell growth. PCSCs, pancreatic cancer stem cells; MCP-1, monocyte chemoattractant protein-1; BMD cells, bone marrow derived cells; IGF1, insulin growth factor 1; Ang1, angiopoietin 1; MMP-9, matrix metalloproteinase -9; PDGFR, platelet-derived growth factor receptors; VEGF, vascular endothelial growth factor.

various metabolic, molecular and physiological processes to support tumor development and survival (Fig. 2). This total reconfiguration of cellular activity towards malignant growth by aberrant activity in multiple signalling cascades, involves a wide array of key oncogenic molecules. For instance, PSCs produce a wide variety of exosomes, miRNAs, cytokines as well as chemokines into the stromal milieu [4]. These molecules exert autocrine activity leading to the stimulation of PSCs or to paracrine signals in epithelial cells, thus enhancing migration/ invasion of PC cells. Furthermore, aPSCs-secreted paracrine factors help tumor cells evade apoptosis and chemoradiotherapy [97], further supporting their survival and spread. In fact, research has shown that aPSCs can increase the production of nitric oxide, leading to paracrine-induced IL-1b expression in PC cells [4]. Autocrine IL-1b signalling in PC cells is associated with the development of chemoresistance (Fig. 2). Other factors secreted by aPSCs include periostin, which sustains aPSCs activity, increases the chemoresistance of PC cells and promotes their metastasis through the EGFR/AKT and the ERK/c-MYC pathways, thus aggravating PC prognosis [98]. Interestingly, periostin inhibition resulted in the abrogation of gemcitabine resistance in PC cells and mouse models, indicating that this protein plays a crucial role in chemoresistance [99]. Additionally, the CXCR4/SDF1 pathway has emerged as a crucial modulator of stromal-tumor interactions [100]. In fact, SDF1 is produced by PSCs, while CXCR4 is released by PC cells. Recent findings have revealed that PSCs elicit chemoresistance to GEM in PC cells through the paracrine CXCR4/SDF-1α-associated activation of ERK1/2 and FAK/AKT pathways, followed by an autocrine IL-6 loop [101]. Furthermore, fibronectin released by PSCs has been found to contribute to GEM resistance in PC cells through the ERK1/2 pathway [102]. Finally, it should be noted that immune cells in the TME can induce chemoresistance by activating PSCs, further enhancing the effect of PSCs on chemoresistance.

On the other hand, radio-resistance in PC has been attributed to the FAK/integrinβ1 pathways, as evidenced by the fact that suppressing this cascade can significantly reduce the protective effect of PSCs against radiation in PC cells [4]. As these various findings reveal, chemoresistance and radiotherapy escape are mediated by several aPSC-associated mechanisms, indicating that the simultaneous inhibition of these signalling axes in the dense PC stroma is necessary to successfully overcome chemo-radio-resistance.

8.7. aPSCs promote EMT in PC

The loop of interactions between aPSCs and PC cells also plays a critical role in the architectural reconfiguration of the stroma through ECM deposition initiated by paracrine activation of PSCs by tumor cells (Fig. 2) [81]. In PDAC for instance, PSCs can remodel the ECM through enhanced thickness and alignment of the collagen fibrils and matrix contraction [103–105]. ECM stiffness and remodeling is crucial for PC proliferation, PSCs activation, and the migratory capabilities of both aPSCs and PC cells [103–106]. This intricate web of events allows aPSCs to promote PC invasiveness and metastasis via EMT induction in malignant epithelial cells [4]. Previous findings have highlighted the involvement of a collagen-binding protein known as integrin a11 in modulating PSC-elicited PC cell migration [4]. The development of EMT traits that enable invasion is accompanied by decreased cell to cell physical contacts, enhanced migration, the loss of epithelial biomarkers including cytokeratin-19 and E-cadherin, as well as the upregulation of mesenchymal biomarkers such as vimentin and Snail [107]. These various alterations are pervasive at the invasive site of PC, characterized by exposure of PC cells to stromal signals [108]. Recent research has also revealed that galectin-1 related increase of SDF-1 (stromal derived factor) or CXCL12 within aPSCs is implicated in PC metastasis [109]. These various phenomena are complicated by the intricate network of cross-talks and feedback loop between aPSCs and PC cells. Hence, while aPSCs promote the metastatic spread of PC cells, these malignant cells, on the other hand, have been shown to secrete PDGF, a chemotactic factor that could modulate PSC activity in the metastatic milieu [4]. This constant interaction between PC and aPSCs orchestrates and fine-tunes PC progression and facilitates its survival and aggressiveness (Fig. 1).

8.8. aPSCs contribute to the emergence of CSC niches in PC

To add an additional layer of complexity, studies have revealed that cancer stem cells (CSCs) in PC exhibit a very metastatic and chemoresistant phenotype that supports disease recurrence, therapy escape and postoperative metastasis [110–113]. Interestingly, PSCs have been found to promote CSC-like traits in PC cells, as demonstrated by the expression of CSC-associated markers such as nestin, LIN28 and ABCG2, thus suggesting that aPSCs could contribute to the emergence of a CSC niche in the PC milieu (Fig. 3) [114]. As this overview demonstrates,

aPSCs are implicated in an intricate and extremely complex web of interactions that results in the physical remodeling of the stromal architecture, supporting EMT, invasion and subsequent metastatic spread and favoring tumor survival and therapeutic escape (Fig. 1). This aggressive phenotype is further aggravated by the PSC-associated stimulation of CSC-like properties in PC stroma. The interaction between aPSCs and PC cells, which oversees this reconfiguration, helps sustain metastatic tumor activity. Increased insights into the various mechanistic and signalling components of this interaction will thus aid in breaking it down into therapeutically targetable axes to ensure improved therapeutic efficacy.

8.9. aPSCs promote immune tolerance of PC cells

The PC milieu is characterized by significant alterations in immune signalling. For instance, aPSCs, mast cells, immunosuppressive MDSCs, cancer-infiltrating macrophages and T cells release high levels of immunosuppressive molecules such as TGF-β1 and IL-10, which suppress dendritic cells, inhibit immune responses and stimulate immune tolerance in PC (Fig. 2) [115]. Moreover, MDSC levels are elevated in the TME and are correlated with negative prognosis [116,117]. Research suggests that aPSCs might fuel the differentiation and expansion of MDSCs and could lead to an immunosuppressive TME through the IL-6/STAT-3 cascade, which drives resistance to immunotherapy (Fig. 3) [4,84]. In PC, obesity is linked with higher desmoplasia, which is driven by PSCs activated by TANs (tumor associated neutrophils) via IL-1β produced by adipocytes [118]. Furthermore, macrophages can recruit PSCs by secreting HIF-1α (Fig. 1) [119]. aPSCs can also aggravate invasive PC phenotypes through T cells. In fact, aPSCs regulate the survival of T cells, inhibit their activation, induce their death or retain them in an anergic mode in the tumor while also redirecting cytokine production towards a Th2 (T helper type 2) response through galectin-1 secretion [120]. Additionally, research [121] has demonstrated that aPSCs can impede CD8 + T cells migration to stromal juxtatumoral compartments, thus obstructing them from accessing PC cells. Furthermore, aPSCs can secrete IL-4 and -13, which convert macrophages into stimulated M2 macrophages that can subsequently activate other PSCs through PDGF and TGFβ signaling (Fig. 1) [122]. Hence, targeting the IL-1/13 pathway could shut down this feed-forward mechanism and represents a potential therapeutic strategy [4]. In summary, aPSCs hijack the immune response against PC by skewing the activity of immune cells, impairing the immune response and enhancing the immune tolerance of PC cells. Understanding these complex interactions is thus a prerequisite for reactivating the immune response against PC cells and devising novel immune therapeutic strategies.

8.10. aPSCs promote angiogenesis in PC

In addition to their pro-metastatic and anti-immune activities, aPSCS can also promote angiogenesis (Fig. 2) by secreting various proangiogenic molecules, such as IL-8, VEGF, PDGF, FGF and periostin as well as MMP-9, which promotes blood vessel development by disintegrating the basement membrane (Fig. 3) [108]. VEGF contributes to the growth and permeability of endothelial cells, thereby enhancing angiogenesis [108]. Periostin, alternatively, supports the growth of endothelial cells and the phenotype of PSCs [108]. Another angiogenic factor released by aPSCs is prokinectin (PK), which activates the PK/PKR pathway in endothelial cells, thus facilitating angiogenesis [108]. Recent reports also reveal that TGFβ stimulated PSCs can elicit cancer cell growth and the formation of endothelial cellular tubes through miRNA-214-3p and miRNA-199-3p [123]. Furthermore, PSCs can enhance tube formation through the cMET/HGF/uPA pathway. As these findings show, aPSCs can support malignant growth by activating the various hallmarks of tumorigenesis in the stromal milieu [124]. Successful strategies against aPSCs should thus address their multifaceted activities in order to effectively reverse their pro-metastatic capacity. The section below will explore some potential approaches against aPSCs and how they could be harnessed to improve therapeutic efficacy against PC.

9. Therapeutic strategies against aPSCs in PC

9.1. Conventional PC treatments

Unlike many other malignancies where significant breakthroughs have been achieved in targeted and immune therapies, no similar advances have been made in PC, thus limiting the arsenal of available treatment options to conventional chemotherapy. The current standard of care regimens for PC are 1) gemcitabine in combination with nab-paclitaxel and 2) leucovorin/5-fluorouacil with irinotecan and oxaliplatin (FOLFIRINOX) [125]. Statistical analysis indicates that quasi-mesenchymal tumors (Collisson) are the most sensitive to GEM, whereas basal-like, squamous and quasi-mesenchymal PCs respond to 5-FU and oxaliplatin [6]. The first approved targeted therapy for PC was erlotinib plus GEM for advanced PC, although this combination did not yield significant clinical benefits [125]. The classical PC subtype seems to display the greatest sensitivity to erlotinib [6]. The dismal outcomes of targeted and immune therapies in PC could result from the paucity of driving mutations, the non-immunogenic TME and the density of the stroma, which hinders drug access to cancerous cells. Taking into account these various underlying causes, new combinatorial regimens, based on GEM and FOLFIRINOX plus novel agents, are currently undergoing clinical investigation in the setting of advanced PC [125]. These novel strategies aim at targeting the TME, the stroma and CSCs to inhibit potential niches of chemoresistance and enhance the cytotoxic effects of traditional chemotherapies. Alternatively, the success of future clinical evaluations and trials will depend on the effective stratification of patients to determine subgroups candidates for specific therapeutic interventions based on molecular and genetic profiling [125]. As this overview indicates, there is an urgent need for developing more effective therapeutic strategies for PC that address its distinctive stromal component and drug resistant TME.

This endeavor constitutes a sword with a double edge, however. In fact, strategies aimed at reducing PSC numbers have been counterproductive and seem to enhance PC aggressiveness as opposed to improving therapeutic benefits [4]. Strategies aimed at reprogramming PSCs, however, appear to be more effective. Hence, anti-aPSCs approaches should be geared towards counteracting the stimulation of quiescent PSCS and preventing their transformation into CAFs, a phenomenon that would hinder stromal enhancement and tumorigenic effects. An alternative strategy consists in reversing aPSCs into quiescent PSCs in order to reverse or de-program the tumorigenic milieu [4]. This strategy could inhibit the action of secreted cytokines, growth factors or chemokines that mediate the interaction between aPSCs and PC cells. Recent advances in the field of stromal targeting will be summarized below.

9.2. Targeting the SHH pathway

The hedhog pathway can sustain the PC stroma through paracrine signalling originating from malignant to PC stromal cells. Blocking this pathway thus represents a promising strategy for targeting the PC stroma. A novel hedgehog inhibitor, namely IPI-926, was combined with gemcitabine in PC cells and found to increase both the intratumoral density and concentration of chemotherapeutic compounds, leading to disease stabilization [126]. Furthermore, SHH deletion in a PC mouse model decreased stromal components in tumors. Unfortunately, these tumors displayed increasingly aggressive phenotypes characterized by greater vascularization, undifferentiated histology and increased proliferation in comparison with controls [4]. This led to the suspension of a phase II investigation of the IPI-926 due to high mortality [127]. Negative outcomes were also observed in other trials

investigating stroma-reducing inhibitors. For instance, depleted α-SMA myofibroblasts in mice provoked undifferentiated and invasive tumors with increased EMT, hypoxia, CSCs and decreased survival [4]. The failure of stroma-depleting approaches might result from the complete abrogation of the fibrotic barrier that maintains PC cells in their place and stops their metastasis. Hence, these results highlight the antagonistic role of the TME, both oncogenic and tumor suppressive depending on the context. Accordingly, modulation rather than depletion of the PC stroma might be a more successful approach with beneficial outcomes.

9.3. Reprogramming aPSCs

Another promising strategy consists in reverting aPSCs back to their quiescent inactive state in order to inhibit aPSC tumor promoting effects [86]. One of the markers of PSC activation is the loss of vitamin A storing droplets. In fact, PC patients often suffer from vitamin A and D deficiencies, which further lead to PSC activation [128]. In this regard, aPSC treatment with all-trans retinoic acid or ATRA repressed PSC collagen synthesis and migration. Furthermore, it induced PSCs quiescence, thus diminishing PC proliferation and enhancing apoptosis [4,128]. A phase I investigation is currently assessing the combination of ATRA plus gemcitabine and paclitaxel for PDAC treatment [4]. Additionally, the combination of ATRA and HSP47 siRNA delivered using gold nanoparticles was tested *in vivo* [129]. The formulation successfully reprogrammed aPSCs and blocked ECM hyperplasia, which resulted in increased drug delivery to PC cells in a mouse model and improved gemcitabine efficacy [129]. Another potential strategy against aPSCs consists in targeting the vitamin D receptor or VDR, which exerts a crucial role in transcriptionally regulating reversal to a quiescent PSC state [130]. The VDR ligand calcipotriol combined with gemcitabine successfully elicited the reprogramming of the stroma in mouse models, enhanced drug buildup in PC cells, decreased tumor volume and improved survival in comparison to gemcitabine monotherapy [130]. Accordingly, these innovative and non-traditional approaches warrant further investigation in the clinical setting to evaluate their therapeutic efficacy and safety in PC patients.

9.4. Targeting the stromal milieu

As describe above, the deposition of a dense ECM in PC causes elevated interstitial pressure that results in capillary compression and perfusion impairment, decreasing drug delivery and increasing hypoxia [125]. Several attempts have been made to target stromal PSCs and connective tissue. Dovitinib, a SMI of VEGFR and FGFGR, is currently being investigated in combination with capecitabine and GEM for metastatic PC [125,131,132]. The connective tissue growth factor GTGF is another attractive target given its involvement in ECM production, migration and desmoplasia through its interactions with TGFβ and BMP4 [133]. The monoclonal antibody pamrevlumab suppresses CTGF, is currently undergoing investigation in combination with GEM and nab-plactitaxel for unresectable PC treatment and has been found to increase respectability [133]. An alternative strategy, which consists in targeting connective stromal tissue with MMP inhibitors, yielded no clinical benefits compared with GEM [125]. Recently, pegylated hyaluronidase formation, PEGPH20, has demonstrated promising outcomes. In fact, a phase I investigation evaluating PEGPH20 + GEM showed small improvements in OS and PFS in patients with high hyaluronan (HA) levels [134]. A phase II trial also reported enhanced PFS following treatment with GEM/PEGPH20/n-PC in patients with high HA [135]. In contrast, a phase I/IIb investigation of PEGPH2 with FOLFIRINOX in untreated patients diagnosed with metastatic PC had detrimental outcomes due to increased toxicity rates [136]. As these disappointing results indicate, developing successful targeted therapies for PC remains a challenge due to the density of the stroma and its intricate interconnection with the tumor cells. Hence, tailoring effective anti-PC therapeutics might require the combined targeting of PC cells and reprogramming of the stroma. This strategy could achieve more potent anti-tumor action by simultaneously suppressing multiple tumorigenic pathways.

9.5. Inhibiting angiogenesis

As mentioned above, VEGF is upregulated in PC, rendering it another promising anti-tumor target. Hence, a number of anti-VEGF compounds have been tested so far in PC, with little success. For instance, no improvements in survival were observed from bevacizumab/erlotinib/GEM [137] or bevacizumab/erlotinib [138]. Furthermore, the potent VEGF inhibitor, axitinib, did not yield significant survival benefits [139]. Similarly, the multikinase antagonist sorafenib failed to improve survival when incorporated with GEM regimens [140]. Finally, vatalanib, a poly-TKI inhibitor with high affinity for VEGF, yielded promising results as a monotherapy in resistant PC, eliciting a 29% improvement in six-month survival rates [141]. These disappointing outcomes highlight the necessity of developing new generation VEGF drugs that more effectively target angiogenesis in the complex cellular milieu of PC.

9.6. Additional approaches for targeting the stroma in PC

Among the arsenal of exciting therapeutic innovations that has emerged in recent years, targeting oncogenic or tumor suppressive miRNAs has generated wide interest and efforts. In the context of PC, restoring miR-29 expression within activated PSCs diminished stromal accumulation and tumor progression, and could represent an interesting therapeutic approach [107]. Research has also revealed that miR-214 and miR-199a were upregulated in aPSCs and could constitute novel therapeutic targets that warrant further investigation [123]. Another promising therapeutic approach for PC consists in targeting MMPs, although trials investigating MMP inhibitors in PC have so far failed [4]. Alternative strategies for aPSC reversal to quiescent phenotype consist in targeting galectin-1 [142], liopoxin A [143] and bromodomains [144]. Since these various approaches have not yet been thoroughly investigated, their evaluation in both the *in vitro* and clinical setting is required to assess their effectiveness and toxicity profiles in PC patients.

10. Conclusion

As this overview illustrates, stromal components such as aPSCs play a central and complex role in PC progression. For instance, the intricate interactions between aPSCs and PC cells, mediated by various cytokines, growth factors and chemokines, modulates the metastatic phenotype of PC cells, enhancing the various hallmarks of carcinogenesis. A greater understanding of these cross-talks and their underlying mechanisms will thus guide the design of innovative treatment regimens that target the dense stroma and TME of PC cells. Furthermore, the identification and characterization of CAF populations deriving from aPSCs and the elucidation of their role in PC progression could enhance the efficacy of conventional therapeutic regimens. Most importantly, current research indicates that the successful reprogramming of the stroma into a less invasive, quiescent phenotype might require the simultaneous targeting of various pathways trough combinatorial approaches. Clinical trials will eventually determine the feasibility and effectiveness of these therapeutic endeavors against PC.

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Declaration of Competing Interest

We report no conflicts of interest.

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