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Role of the tumor microenvironment in pancreatic adenocarcinoma

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1. ABSTRACT

Pancreatic cancer is a devastating disease with proclivity for early metastasis, which accounts for its poor prognosis. The clinical problem of pancreatic cancer is its resistance to conventional therapies, such as chemotherapy or radiation. Based upon these challenges, the focus of research on pancreatic cancer has shifted gradually towards the tumor microenvironment. The cancer microenvironment consists of various components, including fibroblasts, endothelial cells, immune cells, and endocrine cells, that interact with each other, and with the cancer cells in a complex fashion. Evidence is accumulating that the cancer microenvironment plays an active role in disease progression, and efforts are being made to target this interplay between cancer cells and host cells, to improve the prognosis of the disease. In the present review, we describe the cellular microenvironment of pancreatic ductal adenocarcinoma (PDA), the major type of pancreatic cancer. Our hope is that a better understanding of the cellular microenvironment of PDA will eventually lead to better treatments for this disease.

2. INTRODUCTION

Recent studies have reported significant advances in the treatment for many types of tumors, including melanoma, lung cancer, and colorectal cancer, based on the rational design of targeted therapies directed at molecular alterations arising in the cancer cells (1). Unfortunately, similar success has not been achieved for pancreatic ductal adenocarcinoma (PDA). Of all the solid tumors, pancreatic cancer has one of the worst prognoses, with a median overall survival duration of approximately 6 months following diagnosis, and an overall survival rate at 5 years of less than 5% (2). The reasons include tumor resistance to chemotherapy and radiotherapy, lack of specific early symptoms resulting in advanced disease upon diagnosis, and the ability of pancreatic cancer cells to metastasize early in disease development (3). Indeed, for the approximately 15%–20% of patients with seemingly operable disease at presentation, micrometastases have usually already occurred (4), and 85% of these patients will eventually experience relapse and subsequent cancer-related death (5). However, the majority of patients are diagnosed at a late stage in disease development, with approximately 30% and 50% having locally, advanced, or unresectable and metastatic disease, respectively, upon presentation (6).

Since gemcitabine was established in 1997 as the standard of care for advanced pancreatic cancer (7), there has been limited progress in the development of systemic treatments for PDA. The mainstream treatment remains using chemotherapy, including gemcitabine,

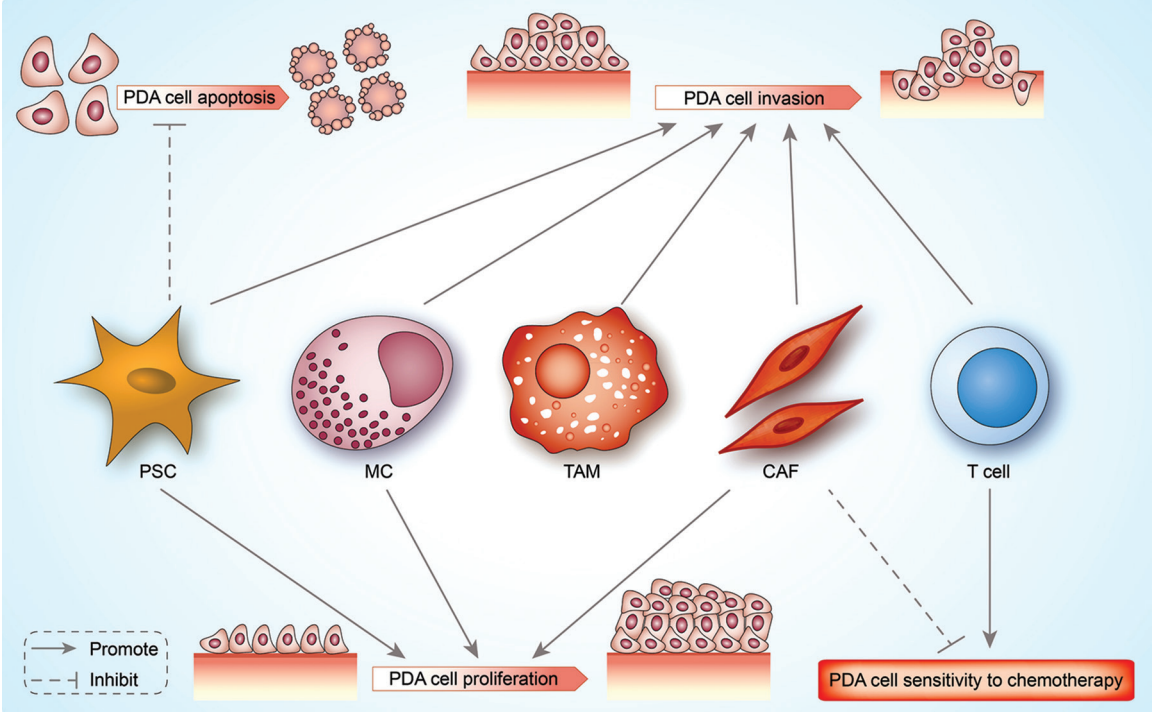

Figure 1. The tumor microenvironment cellular components in PDA include PSC, CAF, TAM, MC and T cell. The tumor microenvironment cellular components in PDA have different role in the progression of cancer by release of various proteins, growth factors and cytokines. PSC, MC and CAF promote pancreatic cancer cell proliferation; PSC inhibit cancer cell apoptosis; PSC, CAF, TAM, MC and T cell promote pancreatic cancer cell invasion and metastasis; T cell promote PDA cell sensitivity to chemotherapy, CAF inhibit cancer cell sensitivity to chemotherapy.

FOLFIRINOX, and nab-paclitaxel. Erlotinib is the only approved biological therapy. However, current therapies are usually ineffective in controlling the disease course. Pancreatic cancer tumors are highly heterogeneous, which may partially explain the resistance of pancreatic cancer to both chemotherapy, and to targeted therapies to specific tumor mutations (i.e., tumor suppressor genes such as *KRAS, CDKN2A, BRCA2, TP53, and SMAD4*) (8). Because of the continued lack of early diagnosis and treatment options for pancreatic cancer, and because the tumor microenvironment may play an active role in disease progression (9), further investigation of this microenvironment should be performed.

3. THE PDA TUMOR MICROENVIRONMENT

The tumor microenvironment is the internal environment in the progression from preneoplastic to invasive PDA. PDA is a type of cancer rich in stroma, which in some cases can make up to 80% of the tumor mass (10). It consists of various cellular and acellular components. The cellular components include pancreatic stellate cells, fibroblasts, immune cells, macrophages, and mast cells, and the acellular components include blood vessels, extracellular matrix (ECM), and soluble proteins such as cytokines and growth factors (11). The tumor microenvironment tumor microenvironment is not a static entity rather, it is constantly changing in composition, especially in the progression from preneoplastic pancreatic intraepithelial neoplasia to invasive PDA (12) (Figure 1).

4. TUMOR-ASSOCIATED PANCREATIC STELLATE CELLS

Using density centrifugation, pancreatic stellate cells (PSCs) were identified in 1998 as a rare stromal cell type in the healthy pancreas (13). A similar method to isolate human PSCs from histologically normal human pancreas was later reported by the same group (14). Bachem *et al.* (15,16) reported isolation of human PSCs from fibrotic pancreatic tissue of patients with chronic pancreatitis and pancreatic cancer using an explant technique. Their periacinar star-shaped morphology, characteristic marker protein expression, and storage of fat droplets rich in vitamin A resembled hepatic stellate cells and inspired the name.

With the availability of methods to isolate and culture PSCs, researchers have been able to make significant advances in the understanding PSC biology. Under homeostatic conditions, PaSCs are quiescent, but their physiological role has yet to be identified. Acute and chronic inflammatory conditions cause activation of PaSCs, which were characterized by morphologic changes, increased proliferation, deposition

of ECM, and expression of alpha-smooth muscle actin (α-SMA), as well as the loss of fat droplets (17,18). PSCs synthesized ECM proteins such as collagen, fibronectin, and laminin. They also expressed the matrix metalloproteinases (MMPs), MMP2, MMP 9, and MMP13, that degraded ECM, and expressed the tissue inhibitors of metalloproteinases (TIMPs), TIMP 1 and TIMP 2, that inhibited the activity of MMPs (19). PSCs are therefore thought to play an important role in maintaining a balance between ECM synthesis and degradation, in the maintenance of normal pancreatic architecture (18). Recent evidence suggested that in addition to synthesizing ECM proteins, PSCs may function as progenitor cells (20). When injected into hepatectomized recipient rats, they were able to migrate to the liver and were able to reconstitute large parts of the liver by differentiating into hepatocytes and cholangiocytes. This observation differentiated them from muscle fibroblasts, which did not show any such transformations (21). The stellate cells in normal and diseased tissues have some differences, with multiple genes found to be differentially expressed. Validation studies confirmed that MMP3 was upregulated 32.2.5-fold, collagen type α1 (a basement membrane component) was downregulated 2.2.5-fold, and syndecan-2 (a transmembrane heparan sulphate proteoglycan that plays a role in cell binding, cytoskeletal organization, migration, and invasion) was downregulated 2.0.4-fold (22). These three genes are postulated to be involved in ECM remodeling function and motility of PSCs (22).

4.1. PSCs promote pancreatic cancer cell proliferation and inhibit cell apoptosis

Cocultures of PSCs and PDA cells have generally shown an enhancement of pancreatic cancer cell proliferation and migration, caused by release of growth factors and cytokines (23). Studies using neutralizing antibodies have indicated that cancer cell-induced PSC proliferation and migration were mediated by platelet derived growth factor (PDGF), while the increase in synthesis of collagen and fibronectin was modulated by the profibrogenic factor, basic fibroblast growth factor-2 (FGF-2,) and transforming growth factor-β1 (TGF-β1) from cancer cells (24,25). *In vivo* studies confirmed these findings, revealing that the coinjection of PaSCs with tumor cells in orthotopic models of PDA increased tumor size and caused a higher incidence of metastasis, and at the same time, inhibited cancer cell apoptosis (25).

4.2. PSCs promote pancreatic cancer cell invasion and metastasis

Vonlaufen *et al.* (25) reported that mice injected with a mixture of pancreatic cancer cells and human pancreatic stellate cells (hPSCs) into the tail of the pancreas exhibited significantly larger tumors within the gland, compared with mice injected with cancer cells alone. No tumors were found in mice injected with hPSCs alone, suggesting that PSCs themselves did not have tumorigenic potential. Importantly, the incidence of distant metastasis (liver nodules) was significantly higher in mice injected with both MiaPaCa-2 cells and hPSCs (50%) compared with those injected with MiaPaCa-2 alone (10%). Xu *et al.* (26) used a gender mismatch approach, showing that male PSCs from primary tumors were able to (1) intravasate into blood vessels, (2) be transported in the circulation, and (3) extravasate from blood vessels at the metastatic sites. These results were supported by an *in vitro* study showing that PSCs migrated through an endothelial cell monolayer *in vitro,* which was upregulated by PDGF from cancer cells.

It has long been known that PDA is characterized by an extremely high frequency of perineural invasion (PNI) (27), and PSCs may play a regulatory role in the interaction between cancer cells and nerves. PSCs can directly induce proliferation, migration, and invasion of pancreatic cancer cells, by release of stimulation factors, and provide an appropriate microenvironment. PSCs can also regulate the expression of pancreatic cancer peripheral nerve metastasis-associated molecules such as nerve growth factor, and PSCs can induce neural remodeling, making the nerve more vulnerable to invasion (28). In addition, PSCs have been reported to increase the stem cell characteristics of cancer cells, by inducing the expression of cancer stem cell-related genes *ABCG2*, *Nestin,* and *LIN28 (*29). Together, the results have suggested that these surviving cancer stem cells may be important factors in pancreatic cancer recurrence (30,31).

5. TUMOR-ASSOCIATED FIBROBLASTS

One characteristic feature of PDA is an extensive desmoplastic stromal reaction, mainly comprised of morphological fibroblast-like cells. Knowledge of the origin and biology of these cancer-associated fibroblasts (CAFs) is still limited. Researchers have provided evidence for several possible CAF origins, including pancreatic stellate cells, local or bone marrow-derived mesenchymal stem cells, and cancer cells that have undergone epithelial-mesenchymal transition (EMT). By secretion of paracrine factors and extracellular matrix components that support cancer cell proliferation, EMT, and resistance to therapy and metastasis, CAFs can significantly contribute to the malignant traits of cancer (10,32).

CAFs consist of both fibroblasts and myofibroblasts Bronsert *et al.* (33) confirmed that zinc finger E-box binding homeobox 1 (ZEB1) expression in cancer cells and in stromal fibroblasts were strong prognostic factors in PDAC, and therapies targeting ZEB1 and its downstream pathways could target both cancer cells and supporting cancer-associated fibroblasts. Ozdemir *et al.* (34) reported that specific depletion of myofibroblasts, using compound genetic mouse models

of PDAC, led to aggressive tumors with diminished animal survival. In addition, detailed studies showed that loss of myofibroblasts decreased the ability of the immune system to control cancer associated with the persistence of regulatory T cells. Myofibroblast depletion did not improve the effectiveness of gemcitabine, but immunotherapy to revive the immune attack prolonged the survival of mice. This study demonstrated a protective role of myofibroblasts, and suggested that targeting carcinoma-associated fibroblasts in pancreatic cancer should be approached with caution. Hu *et al.* (35) suggested that activated fibroblasts extracted from the inflamed synovium of a rheumatoid arthritis patient, when injected along with human breast cancer cells into a recipient mouse, promoted carcinoma growth by elevating the expression of cyclooxygenase-2 (COX-2) by carcinoma cells, an enzyme responsible for inflammation-associated tumorigenesis. Previous studies demonstrated that patients with carcinomas exhibited a greater myofibroblastic stromal reaction, resulting in a so-called “desmoplastic stroma”, and usually developed higher grade malignancies associated with poor prognostic outcomes (36).

Collectively, CAF secreted various cytokines and growth factors that promoted neoangiogenesis and tumor cell invasion (37). Further research is therefore required to fully understand the molecular mechanisms underlying the potential role of CAFs in promoting invasion and metastasis. It is also necessary to investigate how CAFs retain their ability to promote carcinoma growth in a cell autonomous fashion, and if particular somatic genetic alteration is not only responsible for the maintenance of this stable phenotype, but also capable of mediating the differentiation of cells into myofibroblasts.

6. TUMOR-ASSOCIATED MACROPHAGES

Macrophages belong to the myeloid cell lineage, and are derived from myeloid progenitor cells. These precursor cells are located in the bone marrow, and upon maturation, monocytes are released into the bloodstream. Circulating blood monocytes migrate into tissues where they differentiate into resident tissue macrophages. Macrophages are then activated in response to environmental signals, including microbial products and cytokines. Activated macrophages can be divided into M1 (classical activated) and M2 (alternative activated) phenotypes (38). The macrophages in tumors were usually named “tumor-associated macrophages” (TAMs), and often expressed the M2 phenotype (39). However, recent evidence suggested that the phenotype of TAMs varied with the stage of tumor progression. M1 macrophages were usually abundant in chronic inflammatory sites, where tumors were initiated and started to develop (40,41). During cancer progression, macrophages switched to an M2-like phenotype, as the tumor began to invade, vascularize, and develop (42-44). In agreement with these findings, analysis of human samples using CD68 as a pan-macrophage marker and the macrophage scavenger receptor CD204 as an M2 macrophage marker revealed that more M2-converted macrophages were found in patients with pancreatic cancer compared with patients with chronic pancreatitis (45). High numbers of M2 macrophages were also associated with larger tumor size, early recurrence in the liver, local recurrence, and shortened survival in patients with pancreatic cancer (45).

TAMs play a critical role in the immunosuppressive capacity of PDA. Reduction of TAM numbers in the pancreatic tumor microenvironment, by the use of CCR2 or CSF1R inhibitors in combination with gemcitabine, significantly increased numbers of $CD8^+$ T cells, and reduced FOXP3+ Treg infiltration and tumor progression, compared with treatment only with gemcitabine, suggesting an elevated anti-tumor immune response in pancreatic cancer due to reduced macrophage numbers (46). Besides macrophages, the immune suppressive capacity of myeloid-derived suppressor cells (MDSCs) was recently reported to play a significant role in pancreatic cancer progression (47). Because MDSCs and tumor-exposed macrophages both have the capacity to suppress a cytotoxic T-lymphocyte (CTL) immune response, it raises the possibility that immune suppressive TAMs are descendants of MDSCs. Although the relationship of these two cell populations is not fully understood, in the presence of tumor-derived factors, MDSCs could differentiate either *in vitro*, or after adoptive transfer into tumor-bearing mice, into immune suppressive macrophages (48,49).

TAMs secreted proangiogenic factors, including endothelial growth factors and extracellular matrix remodelling proteases (50,51). However, in pancreatic cancer, macrophages can also regulate tumor vascularization. Inhibition of macrophage recruitment to the tumor microenvironment by targeting adhesion molecule integrin $\alpha 4\beta 1$ or myeloid PI3Kγ resulted in a marked decrease of blood vessel formation in pancreatic cancer models, as well as reduced tumor burden (52,53). In contrast, conversion of macrophages to a more pronounced proangiogenic phenotype by depleting histidine rich glycoprotein (HRG) resulted in increased pancreatic tumor growth. Accelerated tumor formation in HRG deficient mice was in part associated with increased infiltration of M2 marker expressing macrophages and their increased proangiogenic gene expression profile, resulting in additional stimulation of tumor angiogenesis (54)

TAMs promoted metastasis at the primary tumor site by providing factors that enhanced the invasion of malignant cells into ectopic tissues, and by secreting ECM remodelling proteases and cathepsins (55). In human pancreatic cancer, the macrophage inflammatory protein-3

alpha (MIP-3a) has been implicated as a regulator of tumor cell invasion. MIP-3a is expressed by pancreatic cancer cells, as well as tumor-associated macrophages. It induced MMP9 expression of pancreatic cells through its CCR6 receptor, and consequently increased pancreatic cancer cell invasion in collagen Type IV (56,57).

Endoneurial macrophages can facilitate the invasion of pancreatic cancer cells along the nerves. Compared with normal nerves, tissue analyzed from patients with PDA showed a significant increase in the number of endoneurial macrophages that were present around nerves invaded by cancer. These macrophages secreted high levels of glial-derived neurotrophic factor (GDNF), which induced the activation of the GDNF receptor α1 (GFRα1) and its co-receptor RET. In addition, phosphorylation of RET induced ERK activation and the migration of pancreatic cancer cells (58).

7. TUMOR-ASSOCIATED MAST CELLS

Mast cells (MCs) are derived from a unique bone marrow precursor, and mature in tissues. They are commonly known for their role in allergic and anaphylactic reactions, during which they secreted numerous vasoactive, chemoattractant, and inflammatory molecules, as well as growth factors (59). Increasing evidence has indicated that inflammation around tumors, including infiltration by mast cells, facilitated cancer growth, especially that of PDA (60). Theoharides *et al.* (61) reported that pancreatic cancer cells secreted chemoattractants that recruited mast cells to their vicinity. Mast cells were then activated either by direct contact or by cancer cell-derived triggers, to selectively release “procancer” mediators. These mediators induced angiogenesis, promoted tumor proliferation, inhibited immune responses, and digested the surrounding stroma to permit metastases. Soucek *et al.* (62) reported that the activation of the Myc oncogene protein in mice induced rapid development of pancreatic islet tumors that were dependent on the recruitment of mast cells. Myc is a pleiotropic transcriptional factor that contributes to tumor angiogenesis, tumor growth, tumor proliferation, and stromal remodeling. Myc activation led to rapid mast cell recruitment through CC chemokine ligand 2 (CCL2), and mast cells were required for the angiogenesis and growth of pancreatic tumors. Furthermore, inhibition of mast cell activation was sufficient to result in tumor death (63).

MCs are involved in neovascularization in experimentally-induced tumors, accumulate near tumor cells before the angiogenesis onset, and participate in the metastatic spreading of primary tumors. MCs also intervened in angiogenic processes, releasing classical proangiogenic factors, such as vascular endothelial growth factor (VEGF), thymidine phosphorylase (TP), fibroblast growth factor-2 (FGF-2), and the nonclassical proangiogenic factor, with tryptase stored in their secretory granules (59,63-66). Recent studies have shown that the MC density is correlated with angiogenesis and progression of patients with pancreatic cancer (67,68). Ammendola *et al.* (69) reported on MCs and angiogenesis in primary tumor tissue from patients with PDA, as well as MCs positive for tryptase (MCDPT). Areas occupied by MCs positive for tryptase (MCAPT), microvascular density (MVD), and endothelial area (EA) were related to each other, and to the main clinical pathological features. The results suggested that MCs positive for tryptase may play a role in PDA angiogenesis, and that they could be further evaluated both as a novel tumor biomarker and as a target of antiangiogenic therapy.

8. TUMOR-ASSOCIATED LYMPHOCYTES

The role of the immune system during PDA progression has long been debated. PDA expresses a variety of cancer-associated antigens that can potentially be recognized by T cells. Among infiltrating T lymphocytes, $CD8^+$ T cells were rare, whereas $CD4^+$ T cells were abundant (70). Recent studies reported that functionally competent $CD4^+$ and $CD8^+$ T cells with specificity for cancer antigens were spontaneously induced in the bone marrow of all PDA patients (71,72).

8.1. $CD8^+$ cytotoxic T cells

Cytotoxic $CD8^+$ T lymphocytes are important components of tumor-specific cellular adaptive immunity, efficiently recognizing their tumor targets and attacking tumor cells presenting tumor-associated antigen peptides with the major histocompatibility complex class I on their surface. $CD8^+$ cytotoxic T cells were capable of eliminating tumor cells via IFN-γ-mediated direct effects on malignant cells, and via induction of macrophage tumoricidal activity (73-76). In human pancreatic cancer, $CD8^+$ T cells represented the predominant T cell subset, which was associated with favorable clinical outcomes and significantly prolonged survival (77-79). $CD8^+$ T cells ($CD8^+$ CD103) bearing markers analogous to gut intraepithelial lymphocytes ($CD8^+\alpha E\beta 7^+$) were found to be mainly located in the fibrous stroma distant from cancer cells (their potential effector domain) (77). These findings, together with the previously reported downregulation of the adhesion molecule ligand E-cadherin (80) on intercellular junctions, as well as the overexpression of TGF-β by pancreatic cancer cells,(81) has led to the possibility that pancreatic cancer cells may escape the cytolytic effect of cytotoxic T cells by promoting their aggregation in fibrous tissue. Moreover, downregulation of activation markers on cytotoxic $CD8^+$ $CD18^+$ T-lymphocytes may diminish their cytotoxic activity toward pancreatic cancer.

8.2. $CD4^+$ T cells and subtypes

8.2.1. Th1/Th17 and Th2 cells

In murine pancreatic cancer, an increase of Th17 cells in the tumor microenvironment retarded

pancreatic tumorigenesis and contributed to improved survival (82), whereas more recently in human pancreatic cancer, increased levels of Th17 cells and their related cytokines accounted for invasion and metastasis, thereby affecting the patient's prognosis (83,84). Th2 responses exhibited a tumor-promoting function in pancreatic cancer, thus accelerating disease progression and reducing survival (85). The exact pathomechanisms and signaling pathways responsible for these observations are not completely understood. However, various studies have reported a general Th2 shift in pancreatic cancer, and a predominance of Th2 cytokines (IL-5, IL-6, IL-10, and especially IL-13) were found in the plasma of pancreatic cancer patients (86,87).

8.2.2. T regulatory cells (Tregs)

Of all the different types of immune cells, Tregs have received the most attention in tumor immunology research. They are generally defined as CD4+CD25+FoxP3+ cells, and they are found in the tumor microenvironment in increased numbers. By expression of CTLA-4 and secretion of IL-10 and TGF-b, among others, Tregs suppressed exaggerated immune responses and were essential in the prevention of autoimmune diseases, however, in cancer, they produced a local immunosuppressive environment ideal for tumor growth (88,89). Patients with pancreatic cancer had increased numbers of Tregs, both in the circulation and at the tumor site. Moreover, the presence of Tregs at the tumor site correlated with a more advanced presentation of the disease, a lower chance of surgical resection, and a worse survival after resection (8), while low Treg percentages in the circulation 1 year after resection correlated with improved survival, as levels of Treg cells increased while levels of the CD8+ effector cells decreased (90-92). Hence the Treg compartment represents an attractive target for the treatment of pancreatic cancer.

9. SUMMARY AND FUTURE PERSPECTIVES

The influences of the microenvironment in pancreatic cancer are as numerous as its components, and the cellular components of the tumor microenvironment are significantly different than normal tissue, both in phenotype and function. This shift is determined by the characteristics of tumor cells and their special microenvironment. The various components of the matrix and cells in the PDA microenvironment are interrelated, and form a complex bidirectional regulation network which together supports tumor growth. Based upon our extensive studies on the interaction between the components of the matrix and the tumor microenvironment, to achieve long-lasting therapeutic responses, we anticipate that future therapies will be tailored to target several of the previously described components of the microenvironment.

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Abbreviations: PDA: pancreatic ductal adenocarcinoma; ECM: extracellular matrix; PSCs: pancreatic stellate cells; α-SMA: alpha-smooth muscle actin; MMPs: matrix metalloproteinases; TIMPs: tissue inhibitors of metalloproteinases; PDGF: platelet derived growth factor; FGF-2: fibroblast growth factor-2; TGF-β1: transforming growth factor-β1; hPSCs: human pancreatic stellate cells; PNI: perineural invasion; EMT: epithelial-mesenchymal transition; ZEB1: zinc finger E-box binding homeobox 1; COX-2: cyclooxygenase-2; TAMs: tumor-associated macrophages; CTL: cytotoxic T-lymphocyte; MIP-3a: macrophage inflammatory protein-3 alpha; GDNF: glial-derived neurotrophic factor; GFRα1: GDNF receptor α1; CCL2: CC chemokine ligand 2; VEGF: vascular endothelial growth factor; TP: thymidine phosphorylase; MCDPT: MCs positive for tryptase; MCAPT: MCs positive for tryptase; MVD: microvascular density; EA: endothelial area

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