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The pancreatic cancer microenvironment: A True Double Agent

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Abstract

The tumor microenvironment in pancreatic cancer is a complex balance of pro- and anti-tumor components. The dense desmoplasia consists of immune cells, extracellular matrix, growth factors, cytokines, and cancer associated fibroblasts (CAF) or pancreatic stellate cells (PSC). There are a multitude of targets including hyaluronan, angiogenesis, focal adhesion kinase (FAK), connective tissue growth factor (CTGF), CD40, chemokine (C-X-C motif) receptor 4 (CXCR-4), immunotherapy and Vitamin D. The developing clinical therapeutics will be reviewed.

Keywords

tumor microenvironment; immunotherapy; hedgehog inhibitors; hyaluronan; vitamin D; Focal Adhesion Kinase

Introduction: Pancreas Cancer

Despite significant advances in the understanding of pancreatic cancer genetics, biology and clinical behavior, little has been accomplished in context of extending survival. The American Cancer Society estimates the incidence of pancreatic cancer to be 53,670 in 2017, with a concomitant mortality of 43,090.¹ The five-year survival has been lengthened to a mere 8%.¹ By 2030, the number of deaths from pancreatic cancer will surpass breast, prostate and colon cancer and become the second leading cause of death by cancer in the US². In 2016, data from the ESPAC-4 trial was released comparing gemcitabine alone to gemcitabine plus capecitabine in the adjuvant post-resection setting, improving survival from 25.5 months to 28 months.³ Unfortunately, 80% of patients present with locally advanced (unresectable) or metastatic disease. The standard of care first line systemic therapy options for metastatic disease include gemcitabine alone, gemcitabine with *nab*-paclitaxel or FOLFIRINOX with a respective median survival of 6 months, 8 months and

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11.1 months. The choice of regimen is dictated by the patients' performance status.^{4,5} The majority of patients both treated with resection and chemotherapy or chemotherapy alone eventually succumb to the disease. There remains a great deal to be accomplished in improving outcomes.

There are inherent unique characteristics of pancreatic ductal adenocarcinoma (PDAC) that have made it particularly challenging to treat. Limitations in the management of PDAC include: 1) the lack of early detection modalities; 2) the occult nature of progression where patients at presentation have disseminated disease and 3) the presence of an exacerbated desmoplastic response that severely compromises tumor blood perfusion and drug delivery while imposing pressure for selection, further enabling the emergence of drug-resistant malignant clones⁶⁻⁹.

The desmoplastic microenvironment within the tumor is comprised of a complex dynamic milieu that both enables and contains the tumor. As more work is being done on this complex tumor-stroma relationship, the biology of PDAC is being further elucidated. The content of this review will focus on delineating these critical stromal components and how they may be utilized as therapeutic targets.

The unique microenvironment of pancreatic cancer

The microenvironment in pancreatic cancer is comprised of acellular stroma, cancer associated fibroblasts (CAF, also known as pancreas stellate cells (PSC)), immune cells and soluble factors such as cytokines, chemokines, growth and pro-angiogenic factors. The interaction of the stroma and tumor cells has best been studied extensively in the context of the molecular and cellular evolution of PDAC. The eventual development of PDAC is thought to stem from acinar ductal metaplasia (ADM), and subsequent morphologic changes of pancreatic intra-epithelial neoplasia (PanIN 1-3) that are in part regulated by oncogenic inflammation.¹⁰⁻¹² The mutational changes in this progression include the presence of an activating mutation in the *K-ras*-oncogene as a critical event in greater than 90% of PDAC.¹³ Additional subsequent somatic mutations in tumor suppressor genes include *p16*, *p53*, and *DPC/SMAD4* which cumulatively lead to progressive epithelial transformation from PanIN1-3 and ultimately PDAC capable of metastasizing to lymph nodes and distant organs.¹⁴⁻¹⁶ Along this continuum there is progressive evolution of the tumor microenvironment accompanied by an intense desmoplastic response characterized by deposition of extracellular matrix proteins and proteases accounting for up to 80% of tumor volume^{9,17-19}

Cancer Associated Fibroblasts (CAF)/Pancreatic Stellate Cells (PSC)

In the normal pancreas, there exist resident fibroblasts and pancreatic stellate cells that function to maintain normal gland connective tissue architecture. In response to injury or tissue damage (e.g. chronic pancreatitis) there is local production of inflammatory cytokines and pro-angiogenic growth factors that increases recruitment of both adaptive and innate immune cells, promoting angiogenesis and PSC/CAF mediated-deposition of extracellular matrix (ECM).^{20,21} In the context of carcinogenesis, PSCs/CAFs acquire a myofibroblast-like phenotype accompanied by excessive secretion of ECM proteins including laminins, fibronectins, and collagens.^{21,22} *In vitro* and *in vivo* studies have demonstrated that PSC

transformation is induced by signaling through growth factors and cytokines such as PEDF (pigment epithelium derived factor), ET-1 (endothelin 1), IGF-1 (insulin-like growth factor), TFF2 (trefoil factor 1) and PDGF (platelet derived growth factor).^{23–28} Subsequently, intense signaling crosstalk between tumor cells and transformed α -SMA (alpha smooth muscle actin)-expressing PSCs leads to enhanced tumor cell proliferation and apoptosis resistance, facilitating migration and invasion of malignant cells.^{29,30}

In a somewhat reciprocal fashion, PSCs supports PDAC cell proliferation via secretion of TGF β (transforming growth factor beta), FGF2 (fibroblast growth factor 2), PDGF, epidermal growth factor (EGF), connective tissue growth factor (CTGF), AM (adrenomedullin) and Galectin-1.^{29,31–33} PSCs also stimulate invasion and migration of PDAC cells by the production of SDF-1 (stroma cell-derived factor-1), SPARC (secreted protein acidic and rich in cysteine), MMPs (matrix metalloproteinases).^{29,34–36} PSCs contribute to PDAC chemoresistance in part via release of NO (nitric oxide), IL-1 β (interleukin-1 β), periostin and type 1 collagen signaling.^{23,37–39}

With the activation of PSCs, there is this perpetual propagation of fibrosis, which is a major limiting factor in the delivery of therapeutics and will be further addressed as a therapeutic target below.²⁰ In addition, PSCs also control ECM turnover via production of tissue inhibitor proteases.⁴⁰ Excessive deposition of ECM components leads to distortion of normal parenchyma, vascular compression and subsequent hypoxia. This hypoxia induces a host of changes including activation of PSCs leading to not only further ECM deposition and but neoangiogenesis as well.⁴¹

Tumor immune infiltrate

Changes in the composition of the immune infiltrate occur alongside the increase in mutational burden and progressive fibrosis during the transition from normal pancreas to pancreatic cancer.⁴² A small proportion of patients with chronic pancreatitis (4–6%), where there is persistent inflammation involving continuous activation of tissue damage and repair responses, will ultimately develop PDAC anywhere from 10–20 years from disease onset.⁴³ Inflammatory mediators such as interleukin 1b (IL-1b), IL-6, and TNF released by altered acinar cells promote chronic inflammation due to persistent activation of an immune response.⁴⁴ Chronic inflammation leads to profound changes in transcriptional programs in pre-neoplastic cells and quiescent PSCs within the injured tissue niche, ultimately promoting transformation into malignant phenotypes and myofibroblast-like cells, respectively.^{45–47} Chronic inflammation also leads to a significant shift in the immune cell infiltrate towards an immunosuppressive phenotype, further facilitating immune evasion of transformed cells and tumor establishment/progression.⁴⁸ Specifically, there is a significant increase in the tumor-infiltrating population of tumor-associated macrophages (TAMs), with an M2 phenotype, neutrophils with an N2 phenotype, regulatory T cells (Treg) cells as well as a Th1/Th2 cell shift.⁴⁹

Tumor-Associated Macrophages (TAM)

TAMs reside within the TME in PDAC and are thought to serve as a potential therapeutic target in several solid tumors.⁵⁰ There was a recent Phase II trial in PDAC targeting TAMs

with the cytotoxic agent trabectedin (NCT01339754).^{45,51} Trabectedin targets mononuclear phagocytes selectively via caspase-8 dependent apoptosis and via differential expression of signaling and decoy TRAIL receptors in macrophages. TAMs have also had a role in PDAC progression via production of IL-6 and activation of the STAT3 pathway.^{10,52} Upon recruitment and activation, TAMs release IL-6 and thus activate the STAT3/SOCS pathway. This accelerates PDAC generation.

Myeloid cell infiltration and Polymorphonuclear neutrophils (PMN)

There is mounting evidence that infiltrating immune cells in the PDAC microenvironment are pro-tumorigenic.⁵³ These cells are found early in the development of PDAC and can be found surrounding early PanIN I lesions.⁴² Local tumor derived production of granulocyte macrophage colony-stimulating factor (GM-CSF) recruits myeloid progenitor cells and induces subsequent differentiation of these into myeloid-derived suppressor cells (MDSCs).⁵⁴ MDSCs in turn function to mitigate the CD8+ killer T cell immune surveillance functions. This prevents tumor-specific cytotoxic T cells from clearing transformed pancreatic ductal cells.⁵⁵ Targeted depletion of granulocytic MDSC (Gr-MDSC) activates an endogenous antitumor T cell response indicating perhaps Gr-MDSC may be a promising therapeutic target in PDAC.⁵⁶

In PDAC, the presence of TANs is associated with poor clinical outcome.⁵⁷ PMN infiltrates can be observed near tumor cells or in the stroma and are associated with poor differentiation.⁵⁸ Neutrophils in PDAC have been further characterized in solid tumors as anti-tumor N1 TAN (Tumor Associated Neutrophils) or pro-tumor N2 TANs.⁵⁹ This polarization or phenotype has been attributed to the local concentration of TGF- β , whereby pro tumor N2 TANS are associated with higher concentrations of this cytokine.^{60,61} The release of neutrophil serine proteases (e.g. cathepsin), metalloproteases (e.g. MMP8 and 9) and reactive oxygen species (ROS) also greatly contributes to this immunosuppressive milieu by promoting tumor matrix remodeling and cell mobility.^{62,63} Current strategies to target tumor-infiltrating neutrophils and MDSCs in pancreatic cancer in the preclinical setting involve the use of CXCR2 (C-X-C motif chemokine receptor 2, also known as interleukin-8 receptor beta) inhibitors or RNA interference against the immunosuppressive molecule indoleamine 2,3-dioxygenase 1 (IDO).^{64–66} Overexpression of CXCR2 and IDO are independent markers of poor prognosis in pancreatic cancer, playing key roles in supporting immune evasion and establishment of metastatic processes.^{67–70}

Tumor infiltrating T cells

Upon examination of established PDAC there is an abundance of CD4+ T cells and a paucity of CD8+ T cells in the TME.⁴² Recent work has demonstrated that CD4+ T cells function to promote PanIN formation by intercepting antitumor immune responses by CD8+ T cells.^{71,72} The ratio for GATA3+ (Th2)/Tbet+ (Th1) tumor infiltrating lymphocytes was an independent predictive marker for survival after surgery in patients with (stage IIB/III) pancreatic cancer.^{73,74} T-cell-dependent antitumor immunity is thought to be in part via activation of the TNF receptor superfamily member CD40. Activation of CD40 via an agonist CD40 monoclonal antibody was adequate to overcome tumor induced immune suppression and induce macrophage and T cell dependent antitumor immunity in pancreatic

cancer both in mice and in humans.⁷⁵ CD4+ T cells can be categorized as regulatory T cells (Treg) or T helper 17 (TH17), and both were found in the PDAC TME in a *Kras* dependent fashion. CD4+ T cells and IL-17 are required for oncogenic *Kras*-driven pancreas cancer development. During *Kras*-driven PanIN development, CD4+ T cells suppress the antitumor activity of CD8+ T cells via secretion of IL-17.⁷⁵ Additionally TH17 cells secrete IL-17A which via IL-17RA induces acinar-ductal metaplasia and PanINs, thus inducing tumor initiation and progression.⁷² CD4+T cells and their cytokine signaling has been an additional target of PDAC however, this will not be further addressed in this review.

Clinical targets: success and failure

Hyaluronan (HA)

HA is a glycosaminoglycan that is found in abundance in the PDAC TME. The fibrotic collagens and HA contribute to the ECM component of PDAC thus creating the desmoplasia that is so characteristic of these tumors.⁹ The desmoplasia and elevated interstitial fluid pressure (IFP) contribute to the barriers in the delivery of systemic therapies to this tumor by compressing/collapsing the tumor blood vessels.⁷⁶ HA contributes to this IFP and functions as a core polymer whereby multiple hydrophilic matrix proteoglycans are formed. This allows for a gel like matrix that supports tumor growth and retains growth factors and cytokines.⁷⁷

Functionally HA also binds to the CD44 and RHAMM cell surface receptors. This activates signaling pathways that contribute to cell invasion, migration, proliferation, adhesion and survival.⁷⁸ Based on these roles, HA has been identified as a target to enhance delivery of therapeutics.^{79,80} PEGPH20 is a PEGylated recombinant hyaluronidase that degrades HA and has been found in both animal and human studies to transiently enhance penetration of systemic chemotherapy. In a Phase I/II clinical trial, gemcitabine when combined with PEGPH20 improved both overall survival and progression-free survival in advanced PDAC (NCT01453153). These findings were even more pronounced with patients that had high levels of HA expression. The limitations of this therapy include thromboembolic events and therefore anticoagulation is now administered in conjunction with PEGPH20 in active clinical trials (combination of PEGPH20/ gemcitabine/*nab*-paclitaxel-NCT02715804 and PEGPH20 and FOLFIRINOX-NCT01959139).

Hedgehog inhibitors

Targeting the stromal components has not always been a success. The Hedgehog pathway is hyperactivated in PDAC and is known to stimulate PSC's to regulate stromal production.⁸¹ PDAC cells produce Hh ligand which binds to its receptor Patched2 located on PSCs. This results in signaling that removes the inhibitory effects of smoothened (Smo) and allows for Gli1 transcription factor translocation into the nucleus and the production of a host of genes including ECM proteins.⁸² There have been several strategies to interrupt Hh signaling and thereby create stromal depletion. IPI-926 is a small molecule inhibitor that inhibits the Hh pathway (Smo inhibitor) and in pre-clinical studies was shown to improve gemcitabine perfusion and survival.⁸¹ Unfortunately, clinical trials targeting this pathway were subject to early termination secondary to progression. There have been several proposed explanations

for this lack of success. First, as predicted, depletion of the pro-stromal Shh pathway leads to fewer myofibroblasts and tumor stroma. However, there were more frequent ADM and PanIN lesions during early carcinogenesis and established tumors were undifferentiated, more likely to metastasize and with a higher proliferative index compared to littermates.⁸³ Second, there is increased tumor vasculature and reduced autophagy.⁴⁵ Lastly it has been postulated that with regards to gemcitabine chemotherapy, there is a transporter hENT1 and an activating enzyme deoxycytidine kinase that are associated with improved survival.^{84,85} This suggests that gemcitabine metabolism rather than biophysical delivery may matter more. Perhaps the stroma is contributing to some tumor control and therefore permanent stroma depletion leads to more aggressive disease.

This explanation has yet to be clearly elucidated but the disappointing findings of trials targeting the Hh pathway indicate that clearly the stroma may have a tumor insulating role.

Connective Tissue Growth Factor (CTGF)

CTGF is a pro-fibrotic mediator that is found in abundance in the stroma of PDAC and is the target of an ongoing trial (NCT02606136).⁸⁶ Over expression of CTGF is regulated by chemokine signaling through CXC proteins which bind integrins and growth factors to promote fibrosis and collagen deposition, and subsequently cancer progression and metastasis.^{87,88} In preclinical models the monoclonal antibody FG-3019 resulted in higher rates of tumor cell apoptosis when combined with gemcitabine. Interestingly, the gross appearance of the cellular and acellular tumor stroma was unchanged. In contrast, there was significant molecular down regulation of pro-survival and anti-apoptotic proteins such as hypoxia inducible factor-1alpha (HIF1- α), Psen1, Ubqln2, Birc6, X-linked inhibitor of apoptosis (XIAP).⁴⁵ In a recent Phase I trial, the human monoclonal antibody against CTGF (FG-3019) was tested with gemcitabine and erlotinib in Stage 3 or 4 pancreatic adenocarcinoma. Results were that with a high exposure (at least 15 days of treatment) and low baseline CTGF plasma levels there was improved PFS and OS. Currently there is an ongoing Phase I/II trial of gemcitabine and *nab*-paclitaxel with or without FG-3019 (pamrevilumab) in the neoadjuvant setting for locally advanced pancreatic cancer (NCT02210559).

Angiotensin Inhibitors

There is currently a clinical trial investigating the combination of losartan (angiotensin inhibitor) and FOLFIRINOX assessing if this inhibitor sensitizes pancreatic cancer to standard chemotherapy (NCT01821729). Angiotensin II may play a role in promoting tumor desmoplasia. Ang II is thought to promote PSC activation via inducing the protein kinase C and EGF-ERK pathways.^{89,90} However, there are some conflicting data whereby in mice with AT2 receptor deficiency in pancreatic fibroblasts, tumors grow significantly larger than controls in a syngeneic orthotopic model.⁹¹ Additionally, there are studies demonstrating that angiotensin inhibitors have stromal effects by targeting TGF- β signaling.^{92,93}

Nearly 55% of PDACs have the tumor suppressor gene SMAD4 (DPC4) inactivated.⁹⁴ SMAD4 is the primary transcriptional mediator of TGF- β effects on cell proliferation and morphology. Loss of SMAD4 leads to not only the loss of a tumor suppressor and but also

no mitigation of TGF- β ligand abundance. This contributes to desmoplasia due to the downstream effects of TGF- β over-expression.^{95–97}

Pirfenidone

Similar to the downstream impact of angiotensin inhibitors, pirfenidone is a compound that mitigates the expression several mediators of fibrosis such as TGF- β and collagen. Treatment with pirfenidone inhibited PSC growth, migration, invasion, and ECM production. In preclinical studies pirfenidone has demonstrated some promising effects in combination with gemcitabine, with β -cyclodextrin MMP2 responsive liposome and with the antioxidant *N*-acetyl cysteine.^{98–100} This compound has yet to be evaluated in human trials.

Angiogenesis

In the PDAC TME there is angiogenesis in response to chronic hypoxia, however the vessels appear compressed secondary in part to the abundance of extracellular matrix proteins. There has been work in designing a hypoxia-activated prodrug TH-302 that improved progression free survival of mice and is currently in Phase II/III clinical trials in advanced PDAC patients (NCT-01746979). Additionally the most well studied inhibitor of angiogenesis (Bevacizumab; anti-VEGF antibody) when studied in pancreatic cancer patients did not translate into significant benefits in survival.¹⁰¹ Unlike its common use in metastatic colorectal cancer, bevacizumab has not materialized as the standard of care for PDAC.

Additional targets of angiogenesis in pancreas cancer have been the hepatocyte growth factor (HGF)-c-MET pathway. In the TME, PSC's secrete HGF which binds to cMET on pancreatic cancer cells. This binding leads to cMET receptor phosphorylation and downstream signaling, inducing PDAC cell growth and migration. Blockage of HGF has been found to decrease angiogenesis. This may be a target of future investigation.

Immunotherapy and the Tumor Microenvironment

It is clear that the complex interaction between pancreatic cancer cells and the tumor microenvironment is heavily dependent on interactions with immune cell populations. Unlike some other solid tumors, such as lung cancer, melanoma and renal cell carcinoma, pancreatic cancer has not been able to gain advances in progression-free and overall survival with current immunotherapy even though following immunophenotyping of clinical specimens, tumors appear to be amenable to immunotherapy.^{102,103} However, the interdependent relationship between inflammation and tumor progression remains an area of intense interest and study.

There is progressive evidence that PSCs/CAFs not only modulate the stromal environment in PDAC but also play a significant role in mediating local immunosuppression and thus facilitate tumor progression and metastases.^{45,104–107} The chemokine ligand CXCL12 is secreted by CAFs and binds to PDAC cells and leads to the depletion of CD8+ T cells. Depletion of CAFs that express fibroblast activation protein (FAP) and delivery of a CXCL-12 competitive blocker increased the accumulation of cytotoxic T cells in the TME

and diminished PDAC tumor growth.¹⁰⁸ Additional work evaluating a CXCR4 inhibitor (CXCR4 is the receptor for CXCL12 ligand) plerixafor induced a rapid T cell response and acted in synergy with PD-L1 antibody to inhibit tumor growth in KPC mice.¹⁰⁸ This approach in combining a CXCR4 inhibitor with an immune checkpoint inhibitor is a current clinical trial (NCT02301130).

CD40 is an additional target that has been evaluated as it may have a role in T cell dependent and independent immune mediated mechanisms of tumor regression. CD40 is cell surface molecule and as a member of the TNF receptor family, partakes in immune regulation, and tumor apoptosis.¹⁰⁹ CD40 was initially thought to be crucial in T cell dependent anti-tumor immunity, however, more recently it is thought that CD40 mediated tumor regression is more dependent on macrophages that facilitate stroma depletion. In a phase I trial, patients with advanced PDAC were treated with a monoclonal antibody that is a CD40 agonist (CP-870).¹¹⁰ Of the 22 patients, four (18%) achieved a partial response and in those tumors, there was a significant population of macrophages and minimal tumor infiltrating lymphocytes.

Both programmed cell death-1 receptor (PD-1) and PD-1 ligand expression are associated with poor prognosis. The expression of these, suppresses T cell activity and allows for immune escape in the TME. However, early clinical trials targeting either PD-1 or PD-L1 did not demonstrate a significant response as monotherapy for PDAC.^{111,112} There are currently several trials underway utilizing combination therapies with targeted therapies to PD-1 or PD-1 ligands.

Secreted protein acid and rich in cysteine (SPARC)

SPARC is over expressed in the PDAC TME and is associated with promoting tumor invasion and inhibiting angiogenesis.¹¹³ An additional strategy to better deliver therapeutics to PDAC is to modify chemotherapeutic agents such that the affinity for endogenous stromal receptors is increased. With this in mind, paclitaxel was conjugated with albumin-nanoparticles (nab-paclitaxel) with the hopes of better efficacy via albumin mediated absorption and binding by SPARC. However, the levels of SPARC expression did not appear to correlate with response to treatment.^{114,115} Additionally, there is work citing that the efficacy of nab-paclitaxel is actually dependent upon drug internalization by TAMs via macropinocytosis.¹¹⁶ Therefore, targeting the optimization of macropinocytosis may be an additional option to improving nab-paclitaxel efficacy. A Phase 3 clinical trial demonstrated a modest increase in overall survival when combined with gemcitabine. At present, the combination of gemcitabine and nab-paclitaxel is one of 2 regimens deemed as standard of care for metastatic PDAC.⁴

Vitamin D

Vitamin D has been more recently recognized as a stromal reprogramming agent. Activation of the vitamin D receptor (VDR) has been shown to induce PSCs into engaging in more dormant and less pro tumorigenic behavior.¹¹⁷ VDR activation decreases fibrosis and pro-inflammatory markers and increases intratumoral gemcitabine levels.¹¹⁸ Treatment with all-trans retinoic acid (ATRA) induced quiescence in CAFs leading to decreased proliferation,

invasion and increased apoptosis. Vitamin D and several of its analogs have significant anti-inflammatory properties. Genetically engineered mouse models (GEMMS) of PDAC were treated with calcipotriol (Cal), a vitamin D analog in combination with gemcitabine. This treatment again induced stroma with less inflammation, enhanced drug delivery and improved survival of mice in a preclinical model.¹¹⁷ There are currently clinical trials in PDAC forthcoming utilizing vitamin D analogs as a stromal remodeling mechanism (NCT02930902, NCT02030860).

Focal Adhesion Kinase (FAK)

FAKs are non-receptor tyrosine kinases which include FAK1 and PYSK2 (FAK2). FAK1 has been implicated in cancer migration, proliferation and survival.^{119,120} Jiang et al demonstrated hyperactivated FAK activity in neoplastic PDAC cells as an important regulator of the fibrotic and immunosuppressive TME.¹²¹ FAK activity was elevated in human PDAC tissues and correlates with high levels of fibrosis and poor CD8+ cytotoxic T cell infiltration. Single agent FAK inhibition with VS-4718 limited tumor progress in a KPC mouse model of human PDAC.¹²¹ This correlated with reduced tumor fibrosis and decreased numbers of tumor infiltrating immunosuppressive cells. Additionally, the combination of FAK inhibition and PD-1 antagonists allowed for improved immune surveillance and a marked increase in survival in this preclinical model. Currently the clinical trial for VS-4718 is on hold (NCT02758587). However there are at least 2 other trials that are active targeting with FAK inhibition for PDAC (NCT02428270 and NCT025465310).

Conclusions

At present there are clearly multiple targets in PDAC. However, it has become clear that the TME plays a crucial role in both tumor containment and progression. The proper combinatorial approach in mitigating tumor desmoplasia and optimizing the systemic delivery of anti-cancer therapy to diminish the local tumor mediated immunosuppression will lead to success in this challenging disease.

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Synopsis

The tumor microenvironment in pancreatic cancer is thought to contribute to both carcinogenesis, tumor progression and immune evasion. Herein, we review the important components of the microenvironment and potential targets to overcome in treating this challenging disease.

Figure 1.

With progressive acquisition of somatic mutations, the TME in PDAC changes in a number of ways as summarized in part above.

Table 1

Selected Clinical Trials Targeting PDAC Stroma

TARGET	STRATEGY	TRIAL
Hyaluronan	PEGylated hyaluronidase	NCT02715804 NCT01959139
Connective Tissue Growth Factor	Monoclonal Ab to CTGF (pro-fibrotic mediator)	NCT02606136 NCT02210559
Angiotensin	Angiotensin Inhibitor losartan via preventing PKC and EGF-ERK pathway activation	NCT01821729
Angiogenesis	Hypoxia activated prodrug TH-302	NCT01746979
CXCR4 inhibitor	Combination of CXCR4 inhibition AND checkpoint inhibition	NCT02301130
Vitamin D analogs	Vitamin D receptor activation decreases fibrosis	NCT02930902 NCT02030860
Focal Adhesion Kinase (FAK) inhibition	FAK implicated in cancer migration, proliferation and survival	NCT02758587 NCT02428270 NCT025465310