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Broadening the impact of immunotherapy to pancreatic cancer: Challenges and opportunities

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is projected to become the second deadliest cancer in the US by 2025 ¹, with 5-year survival at less than 10% ². In other recalcitrant cancers, immunotherapy has shown unprecedented response rates, including durable remissions after drug discontinuation. However, responses to immunotherapy in PDAC are rare. Accumulating evidence in mice and humans suggests that this remarkable resistance is linked to the complex, dueling role of the immune system in simultaneously promoting and restraining PDAC. In this review, we highlight the rationale that supports pursuing immunotherapy in PDAC, outline the key barriers that limit immunotherapy efficacy, and summarize the primary preclinical and clinical efforts to sensitize PDAC to immunotherapy.

Keywords

PDAC; immunity; clinical trials; immunotherapy; pancreatic cancer

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1. Introduction

The most successful immunotherapies to date have leveraged the fundamental ability of T cells to recognize and kill tumor cells based on their aberrant expression of unique antigens. Immunotherapies harness this central tenant through multiple strategies, including boosting endogenous anti-tumor T cell activity with adoptive transfer of endogenous or genetically modified tumor-specific T cells, disrupting immune suppressive mechanisms restraining productive T cell immunosurveillance, and enhancing tumor antigen delivery with vaccines. Despite these varied approaches, PDAC has remained almost completely resistant to immunotherapy.

2. Barriers to immunotherapy in PDAC

A hallmark of the PDAC tumor microenvironment (TME) in both mice and humans is an abundance of non-cancer cell components in the tumor mass, collectively designated as the stroma. In PDAC, stroma can account for up to 50% of the total tumor mass and has been shown to inhibit both spontaneous and therapeutically induced anti-tumor immunity. Stromal barriers to immunotherapy in PDAC include both cellular and molecular suppressive components (Figure 1).

Cellular components of immunosuppression in PDAC

Myeloid cells—A widespread strategy of immune escape used by cancer cells is induction of an altered state of myelopoiesis via secretion of metabolites, cytokines, and chemokines. These factors promote the accumulation of suppressive myeloid cells in the TME that are capable of inhibiting anti-tumor T cell responses^{3,4}. Intratumoral suppressive myeloid cells are broadly classified as (i) myeloid-derived suppressor cells (MDSCs; defined as CD11b⁺ Gr-1⁺ in mice and CD11b⁺CD33⁺ in humans), which are comprised of myeloid progenitors and immature mononuclear cells, and (ii) tumor-associated macrophages (TAMs; defined as CD11b^{Low} F4/80⁺ Gr-1⁻ in mice and HLA-DR⁺ CD68⁺ in humans) that in contrast are mature and can be derived from either embryonic- or hematologic-origins⁵⁻⁷.

In mice, intratumoral myeloid cells are the most common suppressive cells and therefore are an important therapeutic target. In both genetically-engineered mouse models (GEMM) and orthotopic mouse models of PDAC, TAMs account for roughly 15–20% of the total cellular tumor mass, both in primary tumors and metastatic sites, while MDSCs account for 5–10%^{8,9}. Tumor cell-derived secreted factors, namely GM-CSF and CCL2 for MDSCs^{8,9} and CSF1⁸ and BAG3¹⁰ for TAMs, are critical determinants of the recruitment, polarization, and induction of intratumoral myeloid cell suppressive function. GM-CSF production has been shown to be dependent on oncogenic Kras, thereby directly linking oncogenic driver-dependency to myeloid cell suppression¹¹. GM-CSF can also be produced by cancer-associated mesenchymal cells to drive macrophage polarization within tumors and to support tumor growth, invasion, and metastatic potential¹². Both MDSCs and TAMs have been shown to directly induce T cell suppression through secreted factors, as well as indirectly by inducing tumor cell-specific PDL1 expression to inhibit spontaneous anti-tumor immunity¹³.

While myeloid cells have demonstrated clear suppressive potential within tumors, their role in regulating immune suppression in PDAC may not be restricted to the tumor microenvironment. In support of this, depletion of macrophages residing outside of tumors has been shown to promote CD4⁺ T cell infiltration and, in combination with immunotherapy, to induce CD8⁺ T cell-dependent immune responses¹⁴. As selective depletion of macrophages within tumors is technically challenging, it remains unclear from preclinical modeling whether myeloid cells disrupt productive T cell immunosurveillance in PDAC through suppressive mechanisms that are solely active within tumors, within secondary lymphoid organs, or both. Nonetheless, preclinical findings support the notion that targeted myeloid cell depletion can unmask endogenous T cell immunity^{8, 15}. Additionally, myeloid cell depletion has been shown to sensitize tumors to systemic therapies, including chemotherapy⁸, radiation¹⁶, checkpoint blockade¹⁷, and chemoimmunotherapy¹⁴.

Comparable roles for myeloid cells in PDAC tumor biology have been implicated in humans. In PDAC patients, mobilization of bone marrow (BM) derived inflammatory monocytes is increased, with lower inflammatory monocyte frequencies detected in the BM and greater frequencies observed in the periphery as compared to healthy controls¹⁸. Furthermore, both CD66b⁺ MDSCs and CD68⁺ TAMs infiltrate human tumors similar to what is seen in mice, and the intratumoral density of both cell types correlates with poor survival¹⁹. Similar to murine data, GM-CSF is also implicated as a key driver of tumor cell-derived altered myelopoiesis in humans. For instance, GM-CSF induces monocyte differentiation into MDSCs, thereby inhibiting T cell function *in vitro*²⁰. Collectively, these data demonstrate that altered myelopoiesis and myeloid cell-derived immunosuppression are key immune regulatory pathways operative in PDAC.

T cells—PDAC has been classically described as a “cold tumor” in both mice and humans, as it is characterized by a relative paucity of intratumoral CD8⁺ T cells. However, emerging evidence has now shown significant heterogeneity in intratumoral T cell infiltrates detected in both mice²¹ and humans^{19, 22}, with the clear association between intratumoral effector T cell densities and improved outcomes bolstering the rationale to pursue immunotherapy in PDAC. Despite this, the majority of PDAC tumors show T cell populations skewed toward suppressive CD4⁺ T cell lineages. In GEMM of PDAC, CD4⁺ T cells account for <5% of all intratumoral cells²³. Foxp3⁺ regulatory T cells (Tregs) are recruited early during PDAC development and account for approximately 25% of all CD4⁺ T cells in both pancreatic intraepithelial neoplasia (PanIN) as well as invasive PDAC²³. In orthotopic models of PDAC, Treg depletion elicits effective CD8⁺ T cell-dependent anti-tumor immunity²⁴. However, Treg depletion in spontaneously arising PDAC induces only a modest infiltration of conventional CD4⁺ T cells without impacting CD8⁺ T cell recruitment and, as such, is insufficient to restore productive T cell immunosurveillance²⁵. Thus, while these data suggest a role for Tregs in shaping the immune response to PDAC, they also imply that additional immunoregulatory mechanisms exist to inhibit productive immunosurveillance.

In treatment-naïve stage I-III human PDAC, Tregs are expanded nearly two-fold in the peripheral blood, accounting for 13% of all CD4⁺ T cells²⁶. Similarly, Tregs accumulate in neoplastic pancreatic tissue as compared to both inflammatory and non-inflammatory

pancreatic tissues^{19, 27}, ultimately comprising nearly 20% of intratumoral CD4⁺ T cells²⁶. Intratumoral Tregs secrete suppressive cytokines, including TGF β and IL-10, and can suppress CD8⁺ T cell proliferation and IFN γ production. Moreover, intratumoral Treg density correlates with lymph node metastases and poor survival^{19, 27}.

Other T cell lineages have also been detected in PDAC, with predominantly protumorigenic effects. Gamma delta T cells can inhibit classical CD3⁺ alpha-beta T cells through secreted and ligand-dependent mechanisms^{28, 29}. Th17 cells have been shown to have the potential for both pro- and anti-tumorigenic effects, differences which are likely model-dependent. Th17 cell infiltration into subcutaneous murine PDAC tumors (Pan02) was associated with delayed tumor growth and survival in the setting of tumor-derived IL-6³⁰. In contrast, oncogenic Kras has been shown to induce Th17 cell infiltration into PanIN lesions and promote PDAC progression in an IL17-dependent manner²⁸. IL17-dependent PDAC progression has similarly been reported in other preclinical studies³¹, and pharmacologic blockade of IL17 has demonstrated anti-tumor activity^{28, 31}. Together, these findings illustrate the remarkable ability of PDAC to orchestrate a microenvironment enriched in suppressive T cell populations, with few effector T cells.

B cells—B cells are a more recently studied cell type in PDAC and have been linked to the suppressive cellular PDAC TME. CD19⁺ B cells account for nearly 20% of CD45⁺ immune cells in PanINs³² and 7% in PDAC³³. B cell recruitment to PDAC tumors is dependent on tumor cell production of CXCL13³⁴ as well as the B cell and myeloid cell-specific kinase Bruton's Tyrosine Kinase (BTK)³³. Pancreatic ductal cell-specific production of the hypoxia-inducible factor (HIF) 1 α can restrict B cell infiltration into tumors³². Functionally, studies using genetic and pharmacologic depletion^{33, 34} and augmentation³² have shown that B cells promote PDAC tumorigenesis. Similar to mice, human PDAC tumors can also be infiltrated by B cells²². However, the clinical significance of B cells in human PDAC remains ill-defined.

Stromal cells—PDAC is characterized by dense desmoplasia, which stems from activated pancreatic stellate cells (PSCs) that produce collagens, laminin, and fibronectin. These desmoplastic components of the stroma are classically thought to be immunosuppressive. For instance, PSCs can promote MDSC differentiation in humans³⁵. Consistent with this, Fibroblast Activation Protein- α (FAP) expressing stromal cells were found to inhibit immune-dependent PDAC growth in a subcutaneous model³⁶. PSCs were subsequently shown to induce CD8⁺ T cell sequestration in a CXCL12-dependent manner^{37, 38}. Interrupting the CXCL12-CXCR4 axis results in greater intratumoral densities of CD8⁺ T cells and rapid treatment responses in combination with immune checkpoint blockade³⁷. However, elements of the stroma may also act to restrain, rather than support PDAC growth³⁹. Depletion of α -SMA⁺ myofibroblasts in GEMM mice decreases effector T cell frequency while increasing regulatory T cell frequency. This finding suggests that myofibroblasts may have some immunostimulatory capacity⁴⁰. However, paradoxically, myofibroblast depletion was reported to sensitize GEMM mice to CTLA-4 blockade⁴⁰. These studies demonstrate that the immunomodulatory effects of stromal cells in the PDAC

TME are complex, with cell-type and context-specific biology. Understanding these cellular networks remains an active area of investigation.

Molecular components of immunosuppression in PDAC

Beyond cellular immunosuppression, tumor cell-derived molecular factors have also been shown to suppress spontaneous anti-tumor immunity. Human PDAC cells can hyperactivate Focal Adhesion Kinase (FAK), a non-receptor tyrosine kinase whose activation is correlated with higher fibrosis and poor CD8⁺ T cell infiltration ⁴¹. In GEMM mice, inhibition of FAK activation reduces intratumoral fibrosis, decreases the accumulation of intratumoral myeloid suppressive cells, limits tumor progression, and sensitizes PDAC to PD-1 inhibition ⁴¹. Additional networks of tumor cell-derived, kinase-mediated suppression of adaptive immunity through macrophages have also been reported. For example, Receptor Interacting Protein (RIP)1 and RIP3 are key mediators of necroptosis, a form of caspase-8 independent, non-apoptotic, organized cellular necrosis seen in PDAC. Intact RIP1/RIP3 signaling can promote PDAC oncogenesis through CXCL1 ligation of its receptor, Mincle, which is expressed on tumor-infiltrating myeloid cells ⁴².

Extracellular matrix components such as hyaluronic acid can collapse intratumoral vasculature due to elevated interstitial fluid pressures, potentially creating a physical barrier to the delivery of chemotherapy and immunotherapeutics ^{43, 44}. It is notable, though, that monocytes and neutrophils effectively infiltrate pancreatic tumors. While some intratumoral myeloid cells are derived from local proliferation of embryonically derived macrophages, more than half are continually replenished from the circulation ⁷. Post-capillary venules, where immune cells can extravasate, tend to be located on the periphery of pancreatic tumors, suggesting that myeloid cells are capable of penetrating the tumor microenvironment and do so more effectively than lymphocytes ⁴⁵. T cell accumulation in pancreatic tumors is impeded by numerous factors, including extratumoral macrophages, expression of FASL on vascular endothelial cells, and TGFβ signaling ^{14, 46, 47}. T cell function and accumulation can also be augmented by angiotensin system inhibitors, which result in increased blood vessel diameter and improved perfusion of pancreatic tumors ^{48–50}. Increased perfusion likely increases oxygen and glucose availability to T cells in pancreatic tumors.

Several metabolic pathways can also impede T cell function in tumors. For example, intratumoral myeloid cells produce the enzyme IDO, which converts tryptophan to kynurenine ⁵¹. Tryptophan is an essential amino acid for T cell function, whereas kynurenine supports immunosuppression. Similarly, extracellular ATP derived from dying cells is converted by CD39 and CD73 to adenosine, which is supportive of the immune suppressive activity of Tregs and can inhibit effector T cell function ⁵². Overall, there are likely multiple metabolic networks mediating suppression of adaptive immunity in PDAC ⁵³.

3. T cell antigens in pancreatic cancer

A priority in the field of PDAC immunotherapy is to develop strategies for unleashing the anti-tumor potential of endogenous effector T cells. These strategies rely on the presence of immunogenic tumor antigens. Tumor antigens capable of eliciting spontaneous, cancer-

specific T cell responses ideally are selectively expressed in cancer cells, with relatively little expression in normal cells. Here, we focus on two major categories of antigens: shared antigens derived from differential cancer cell-specific expression and antigens resulting from mutations or rearrangements in gene-coding sequences (mutational neoantigens).

The study of tumor-specific T cells in PDAC using preclinical modeling has relied on multiple immunocompetent mouse models, of which the most broadly studied is the KPC GEMM of PDAC. In KPC mice, Cre-Lox technology is used to induce pancreatic neoplasia via conditional expression of mutant *Kras* and *Trp53* (*Pdx-1-Cre;LSL-Kras^{G12D/+};LSL-Trp53^{R172H/+}*)⁵⁴. KPC mice develop spontaneous, stepwise, pre-invasive to invasive PDAC that recapitulates both histologic and immunologic features of human PDAC⁵⁵. Cell lines derived from KPC mice have been used for development of orthotopic, subcutaneous, and metastatic models of PDAC⁵⁶. In most cases, the cell lines used in these transplantation models reproduce many of the elements of the stromal architecture and immune infiltration that is seen in spontaneously arising tumors. However, differences can exist as illustrated by the capacity of some forms of immunotherapy to induce T cell-dependent tumor responses in implantation models but not in the spontaneous KPC model¹⁴. Thus, interpretation of preclinical findings investigating the immunobiology of PDAC needs to consider the model in which the findings were observed. However, both models have significant similarities to the immunobiology observed in humans, and no clear superior model with greater relevance to humans has emerged.

In the KPC model, the intratumoral T cell infiltrate has been shown to be significantly heterogeneous^{57–60}. KPC cancer cells harbor a low mutational burden, with a nearly complete absence of predicted neoepitopes^{21, 61}. Neoantigens are therefore unlikely endogenous T cell targets in KPC mice, suggesting the presence of non-mutational tumor antigens²¹. Consistent with this, spontaneous T cell responses to shared antigens in KPC mice have been reported³⁷. CD8⁺ T cells from KPC mice respond to tumors arising spontaneously in other KPC mice³⁷, demonstrating the presence of a spontaneous anti-tumor T cell response to shared antigens.

Multiple shared antigens have been studied in pancreatic cancer, including telomerase, Muc1, enolase, WT1, Kras, mesothelin, and others. Telomerase and Muc1 responses have both been demonstrated in pancreatic cancer, which may also be signs of early transformation across epithelial cell types^{62, 63}. DNA vaccination against enolase in mice can induce a polyfunctional adaptive immune response capable of preventing tumor formation⁶⁴. WT1 is also overexpressed in human PDAC,⁶⁵ and WT1-specific T cells have been shown to kill PDAC cell lines *in vitro*⁶⁶. In a phase-I clinical trial, WT1-peptide vaccination was shown to be safe and associated with disease stability in some patients⁶⁷. Similarly, endogenous mesothelin-specific CD4⁺ and CD8⁺ T cells have been detected in PDAC patients,^{68, 69} and these cell populations can be subsequently boosted in the setting of therapeutic vaccination^{70–72}. Immunotherapeutic targeting of mesothelin can also delay tumor outgrowth in KPC mice⁷³. Cancer germline antigen expression has also been detected in PDAC, with both antibody and T cell responses to cancer germline antigens detected in PDAC patients^{74, 75}. Overall, it is likely that multiple shared antigens may be targets for T cell immune responses in PDAC. However, whether a dominant shared antigen(s) directs the

heterogeneous endogenous T cell infiltrate remains unclear. It is, however, recognized from PDAC orthotopic tumor models that T cell exclusion in tumors arising in the pancreas can be overcome by introducing a strongly immunogenic antigen (e.g., ovalbumin), which effectively restricts successful engraftment of KPC tumors in a T cell-dependent manner⁶¹. However, the consequences of conditional expression of a highly immunogenic antigen on T cell immunosurveillance in an established tumor in PDAC remains unknown.

Although self-antigens are more universal T cell targets for human PDAC, neoantigens remain important. The prevailing belief is that neoantigen formation is a stochastic process⁷⁶, and therefore tumors with higher mutational loads generate more neoantigens. Extending this logic, early reports posited that neoantigens were unlikely to be T cell antigens in human PDAC, owing to a relatively low somatic mutational prevalence⁷⁶. However, these estimates have been confounded by stromal contamination, as more recent sequencing efforts utilizing techniques to maximize tumor DNA capture have identified a higher burden of somatic mutations^{77, 78}. Moreover, while some reports show no clear associations between putative neoantigen load, activated T cell infiltrates, and survival in human PDAC^{79, 80}, recent findings demonstrate substantial heterogeneity in intratumoral T cell infiltrates, with neoantigens possibly serving as T cell targets in select subgroups²². To this end, PDACs harboring double-strand break repair and mismatch repair mutational signatures show increased expression of markers of adaptive immune activation and are correlated with a higher neoantigen frequency⁸¹. Neoantigens have also been identified as T cell targets in rare long-term PDAC survivors²². Tumors from long-term PDAC survivors show a 12-fold greater density of cytolytic CD8⁺ T cells. Further, a neoantigen quality fitness model, integrating clonal genealogy, epitope homology, and T cell receptor affinity, was prognostic of survival in two independent PDAC datasets²². Hence, spontaneous T cell responses in mouse models and human PDAC show substantial heterogeneity, although the presence of neoantigens serving as T cell targets in PDAC patient subsets remains an important distinction between the autochthonous mouse model and humans.

4. Key insights from preclinical models

Pancreatic cancer is an immunologic outlier

Clinicians have long appreciated the unusual difficulties posed by pancreatic cancer, and many of these same challenges exist in the KPC GEMM⁵⁶. Unfortunately, many immunotherapy approaches that are promising in other cancer types have shown little effect in PDAC⁸². These agents include: IL-2, oncolytic viruses, checkpoint blockade, TGF β inhibitors, neoantigen vaccines, Treg depletion, and CD47 blockade⁸³. While it is possible that these agents can be incorporated into combination therapies, their failures as single agents reinforce the idea that multiple immunologic barriers regulate productive immunosurveillance in PDAC. Even agents with moderate efficacy, such as single chemokine receptor antagonists, stimulate the emergence of compensatory mechanisms^{84, 85}, reinforcing the notion that successful immunotherapy in PDAC will need to target multiple pathways.

Chronic inflammation drives tumor progression

Although epidemiologic studies in humans suggest a link between pancreatitis and PDAC, the mechanistic underpinnings by which chronic inflammation promotes tumor growth have been elucidated largely from mouse models. Indeed, pancreatitis is a critical determinant of PDAC development in mice genetically modified to conditionally express mutant *Kras* in the pancreas during adulthood^{86, 87}. From KPC mice, we have also learned that components of chronic inflammation, including IL-6, innate immune cells, and regulatory B cells, drive early tumorigenesis^{32, 34, 88, 89}. IL-13 converts inflammatory macrophages into tumor-promoting macrophages⁹⁰. CD4⁺ T cell production of IL-17 serves as a direct growth factor for IL-17R⁺ tumor cells²⁸. Further, CD4⁺ T cells contribute to early suppression of CD8⁺ T cell responses during tumor initiation,⁹¹ and exclusion of T cells is maintained during later tumor stages by extratumoral F4/80⁺ macrophages¹⁴.

Malignant cells play an active role in immune suppression

Kras activation in malignant cells drives malignant transformation and orchestrates immunosuppression in PDAC. In mice with inducible Kras targeted to the pancreas, myeloid-rich microenvironments form and neoplastic lesions develop in the setting of inflammation. However, silencing Kras expression induces regression of both the tumor and the microenvironment, implying that the microenvironment is dependent on sustained cues received from malignant cells^{87, 92}. To this end, pancreatic tumor cells can secrete cytokines and chemokines, including GM-CSF, CCL2, CXCL1, CXCL2, CXCL5, and others, which have established roles in the recruitment and differentiation of immunosuppressive myeloid cells. Of these, CXCL1 has recently been shown to be produced by tumor cells in preclinical models and to coordinate the recruitment of myeloid cells and the exclusion of T cells within tumors²¹. In addition, the IRE-1/XBP-1 axis is important in regulating Major Histocompatibility Complex (MHC) expression and latency in micrometastatic lesions and can control T cell infiltration into metastatic lesions⁹³. Thus, malignant cells are, not surprisingly, master orchestrators of immune suppression.

T cell responses can be elicited by *in situ* vaccination

The goal of vaccination is to elicit priming of tumor-specific T cells, and perhaps the simplest and most effective vaccination strategies involve direct delivery of immune stimulatory agents into the tumor microenvironment to produce “*in situ*” vaccines^{94, 95}. Successful *in situ* vaccination requires both induction of tumor cell death and the presence of an adjuvant. Presumably, spontaneous induction of this vaccination process explains the tumor antigen-specific responses that are seen in a rare subset of PDAC patients with microsatellite instability high (MSI-high) tumors that are responsive to PD-1 blockade⁹⁶ and the generation of tumor-specific T cells detected in resected tumors from long-term PDAC survivors²². However, the extent to which standard of care gemcitabine/nab-paclitaxel or FOLFIRINOX can elicit tumor antigen release and prime tumor-specific cell responses in PDAC remains ill-defined.

Local delivery of adjuvants, such as stimulator of interferon genes (STING) agonists and toll-like receptor (TLR) ligands, can potentially activate dendritic cells, leading to both dendritic cell maturation and production of type I and type II IFNs⁹⁷. However, the choice

of adjuvants may be critical, as some adjuvants that can stimulate T cell priming have also been associated with PDAC development in preclinical models^{98,99}. As such, manipulating the immune reaction induced by an adjuvant may be critical to unleashing its tumor-suppressive potential. Pancreatic tumor cells often have innate inflammatory pathways activated at baseline due to expression of TLR7 and chromosomal damage that lead to STING pathway activation, and both of which promote tumor cell survival through increased NF- κ B signaling^{98,100,101}. TGF β blockade can enhance the efficacy of PD-1 therapy to invoke T cell-dependent anti-tumor responses in non-pancreatic tumor models^{47,102} and synergizes with radiation in other tumor types^{103,104}. However, blockade of TGF β signaling in pancreatic tumors can inhibit systemic immunity induced by anti-CD40 and radiation¹⁰⁵. Thus, manipulating elements of the tumor microenvironment may be a favorable approach for harnessing tumor-specific T cells in some settings, but this also may depend on the adjuvant, tumor type, or both.

Radiation has emerged as an immunostimulatory strategy for cancer therapy and is being combined with immunotherapy in PDAC (Table 1). In mouse models of PDAC, although radiation depletes CD8⁺ T cells and recruits tumor-promoting myeloid cells¹⁰⁶ via increased CCL2, blocking CSF1 released by malignant cells responding to radiation therapy inhibits radiation-induced myeloid suppression and invokes T cell-mediated anti-tumor responses¹⁶. Radiation has also been shown to induce an increase in MHC class I expression on tumor cells and to synergize with anti-CD40, anti-PD1, and anti-CTLA4^{107,108}. Several studies have shown that radiation can also broaden the oligoclonality of the T cell response to cancer, presumably by inducing T cell responses against a wider array of tumor antigens^{108,109}. Thus, strategies that combine radiation with immune-stimulating interventions hold promise.

Augmenting T cell priming is important

T cells express both co-inhibitory and co-stimulatory receptors, and augmentation of the latter represents an important avenue for pancreatic cancer, where boosting co-stimulation may compensate for deficits in antigen quality or quantity¹¹⁰. Most co-stimulatory receptors are members of the TNF receptor superfamily and signal via NF- κ B. Augmentation of canonical or non-canonical NF- κ B signaling in immune cells can potently augment anti-tumor immunity^{111,112}. Agonistic antibodies to co-stimulatory receptors have also been developed, and of these anti-CD40 has shown promise in pancreatic cancer¹¹³. CD40 is a TNF receptor family member expressed on professional antigen presenting cells. When engaged by CD40L or by an agonistic antibody, CD40 signaling induces expression of co-stimulatory ligands, such as B7-1 and B7-2, production of IL-12 and other cytokines, enhanced antigen presentation, and, in the case of dendritic cells, upregulation of CCR7 and trafficking to draining lymph nodes. Agonistic antibodies to CD40 as monotherapy generate limited responses in both mice and humans with pancreatic tumors. In mice, combining CD40 agonists with chemotherapy can enhance T cell priming, producing T cell-dependent anti-tumor responses, and in other cases modulate the activation of myeloid cells to condition tumors for increased sensitivity to cytotoxic therapies^{114–117}. Together, these data imply that restoring productive immunosurveillance in cancer may require immune stimulation and not just disrupting elements of immune suppression.

Generating T cells is not enough

Adoptive cell therapy obviates the need for endogenous T cell responses and allows for a setting to study the anti-tumor potential of tumor-reactive T cells. In acute lymphoblastic leukemia, CAR-T cells that target CD19 produce remarkable clinical responses. However for patients with PDAC, significant clinical activity with CAR-T cells has not yet been appreciated¹¹⁸. Nonetheless, in mouse models, CAR-T cells directed against CEA, Her2/neu, and CD24 induce clearance of cognate antigen-positive tumor cells, with increased activity seen when Her2/neu and CD24 CAR-T cells are delivered in sequence^{119, 120}. Intratumoral delivery of a cytokine-armed oncolytic adenovirus can also enhance the efficacy of CAR T cells in implantation models of PDAC¹²¹. Consistent with a role for the microenvironment in defining T cell fate, activated tumor-reactive T cells expressing a mesothelin-specific T cell receptor were found to effectively infiltrate PDAC tumors in the KPC GEMM. However, within tumors, T cells demonstrate poor persistence and rapidly upregulate several co-inhibitory receptors⁷³. As these therapeutic approaches are limited by the quality and uniform expression of antigenic targets, the potential for adoptive cell therapy in PDAC may ultimately be dependent on the capacity to generate productive polyfunctional endogenous T cell responses¹²². Nonetheless, data from both mouse and human trials suggest that transferring tumor-specific T cells alone will be inadequate for inciting deep and durable remissions.

Myeloid and stromal immunosuppression is both targetable and interconnected with T cells

Embryonically derived, tissue-resident macrophages can expand in pancreatic cancer⁷, complementing a population of short-lived myeloid cells that are sustained by continual recruitment from the circulation¹²³. CCR2 and CXCR2 are major chemokine receptors expressed by monocytes and neutrophils, respectively, and are responsible for their trafficking into tissues. Blocking each receptor has demonstrated efficacy in mouse models, and there is preliminary evidence of activity in human clinical trials^{18, 124, 125}. However, derailing the recruitment of CCR2⁺ myeloid cells produces compensatory infiltration of CXCR2⁺ neutrophils into tumors and vice versa, such that blockade of both chemokine receptors is more effective than either alone⁸⁴.

The phenotype and maintenance of tumor-infiltrating myeloid cells are determined by cues received within the tumor microenvironment. For instance, CSF1/CSF-1R is an important survival signal for resident macrophages. Blocking CSF-1R *in vivo* can produce a loss of intratumoral macrophages in PDAC leading to improved anti-tumor responses with immune checkpoint inhibitors (e.g., anti-CTLA-4 and anti-PD-1)¹⁷. This finding suggests that effective T cell responses in PDAC may be generally curtailed by immunosuppressive myeloid cells, a finding that has now been seen in several preclinical settings^{13, 41, 84, 110}.

Cytokines are potent immune modulators

Cytokines generally act in an autocrine or paracrine fashion and demonstrate short half-lives necessitating local or sustained delivery¹²⁶. In PDAC models, exogenous application of IL-12 or IFN γ can reprogram myeloid cells, induce T cell responses, and lead to tumor regression^{44, 127}. Other Th1 family cytokines and chemokines can have similar effects, and

strategies to deliver or induce these responses *in vivo* are under active investigation. On the other hand, cytokines can also be potentially immunosuppressive. For example, IL-6, TGF β , and IL-10 have all been implicated in PDAC progression⁸⁹. Of these, IL-6 may be the most problematic given its ability to activate fibroblasts and induce production of extracellular matrix¹²⁸. Indeed, blockade of IL-6 in KPC mice has shown therapeutic benefit when combined with gemcitabine,¹²⁹ and in BRCA-deficient KPC mice when combined PD-1 blockade¹³⁰.

Cancer associated fibroblasts (CAFs) regulate tumor-infiltrating T cells. CAFs secrete several factors that can negatively impact the immune microenvironment in tumors, including myeloid-recruiting chemokines and inflammatory cytokines, notably IL-6¹³¹. CAF-derived extracellular matrix can be a physical barrier to drug delivery in PDAC^{43, 132}, but its role in PDAC progression has been debated. Stromal targeting agents, such as PEGylated hyaluronidase combined with gemcitabine, may reduce MDSC populations and increase CD8⁺ T cell infiltrates in KPC mice. Inhibition of FAK has also been found to reduce collagen and other extracellular matrix components in mouse models of PDAC. By suppressing tumor-derived chemokine production, FAK inhibitors can reduce myeloid cell accumulation, leading to T cell-dependent tumor regression in the setting of chemotherapy and checkpoint blockade⁴¹. Together, these studies highlight the interconnected nature of stroma, myeloid cells, and T cells, and demonstrate that each component may be a critical determinant of therapeutic efficacy.

Effector activity by other immune cell types may be leveraged

Loss or downregulation of MHC class I molecules on malignant cells renders them invisible to CD8⁺ T cells and is a common explanation for acquired resistance to immunotherapy^{133, 134}. In contrast, NK cells recognize and destroy MHC-negative cells. However, NK cell abundance in pancreatic cancer is low and recruitment may be antagonized by malignant cell expression of the NK inhibitory ligand CD155¹³⁵. Nonetheless, NK cells have been implicated in the prevention of tumor recurrence after R0 resection in PDAC¹³⁶.

Other lymphocytes recruited to the PDAC TME are gamma delta T cells, which are activated by nonclassical MHC molecules. Gamma delta T cells infiltrate human PDAC, and their depletion in orthotopic mouse models of PDAC results in smaller tumor size and delayed tumor progression²⁹. Although these innate lymphocytes appear to be tumor-promoting, their baseline abundance and ability to secrete inflammatory cytokines raises the possibility that they might be repurposed for therapeutic benefit.

Myeloid cells can be directly tumoricidal¹¹⁴. Macrophages can also acquire anti-fibrotic properties and, as a result, condition tumors with enhanced sensitivity to chemotherapy¹¹⁶. Neutrophils, eosinophils, and mast cells produce reactive oxygen species and proteases that are effective at destroying tissue, yet it is unclear how best to harness this destructive prowess for control of tumor growth. One potential avenue may involve Tuft cells, which are chemosensory DCLK1⁺ cells. In the intestine, DCLK1⁺ Tuft cells proliferate in response to parasites, secrete IL-25, and initiate Th2 responses via IL-13 production from ILC2 cells¹³⁷. In pancreatic cancer, IL-17R⁺ DCLK1⁺ cells have been found in early PanIN lesions and

may have a role in early establishment of the malignant microenvironment^{138–140}. Whether these Tuft cells could be repurposed for therapeutic benefit is unknown.

5. Current status of I/O in human PDAC

For most patients with PDAC, immunotherapy has not demonstrated significant clinical activity⁶⁰. Early clinical studies investigating PD-1/PDL1 antagonists showed no activity in patients with PDAC, despite remarkable efficacy seen across a wide range of malignancies¹⁴¹. Similar findings have been reported with CTLA-4 antagonists¹⁴² and most recently with combining PD1 blockade with a small molecule inhibitor of indoleamine 2,3-deoxygenase (IDO)¹⁴³. The apparent lack of efficacy observed with checkpoint blockade in PDAC has now led to combination studies with chemotherapy under the premise that chemotherapy can be immunogenic^{144, 145}. However, to date, efforts to combine immune checkpoint blockade (i.e., anti-PD1 and anti-CTLA-4) with chemotherapy have not produced remarkable clinical activity in human PDAC beyond what would be expected with chemotherapy alone^{146–148}.

The lack of efficacy seen with checkpoint blockade as monotherapy in PDAC has suggested the need to incorporate vaccine strategies to prime and activate tumor-specific T cells. To this end, numerous vaccine strategies have been evaluated, but unfortunately no vaccine approach by itself has demonstrated significant clinical benefit⁶⁰. This includes vaccines incorporating irradiated autologous tumor cells (e.g., GVAX, algenpantucel), live attenuated bacteria expressing mesothelin (CRS-207), and peptide-based vaccine approaches^{149–151}. Despite this, correlative studies have shown that vaccines can stimulate tumor-specific T cells and significantly alter immune biology in resected tumors of some but not all patients. Specifically, it has been shown that GVAX, a GM-CSF gene-transfected, irradiated, allogeneic whole tumor cell vaccine, stimulates the formation of tertiary lymphoid aggregates in tumor tissue which correlate with improved outcomes for patients with surgically resected disease⁷¹. GVAX vaccination can also impact the immune microenvironment of PDAC by stimulating an increase in T cell infiltrates and myeloid cell activation⁵⁷. To potentiate the activity of GVAX, cyclophosphamide (Cy) has been incorporated. At low doses (e.g., 250 mg/m²), Cy inhibits Tregs, and in preclinical models, pretreatment with low-dose Cy enhances anti-tumor activity induced by vaccination¹⁵². In patients with unresectable PDAC, inclusion of Cy with GVAX also appears to augment the generation of tumor-specific T cells detected in the peripheral blood¹⁵³. Expansion of a diverse repertoire of mesothelin-specific T cells in the peripheral blood has been detected in some patients responding to Cy/GVAX/CRS-207⁷². These T cell immune responses correlate with improved outcomes. Together, findings from these translational studies form the impetus for current investigations (Table 1) evaluating vaccines in combination with immune checkpoint blockade, which seek to prime T cells while also disrupting immunoregulatory mechanisms that may limit T cell effector activity.

The success of cancer immunotherapy in PDAC will rely on restoring multiple key steps involved in immune activation, as described in the cancer immunity cycle¹⁵⁴. Recent advances in synthetic biology offer the opportunity to engineer autologous T cells with tumor reactivity and, in doing so, restore steps of the cancer immunity cycle related to T cell

priming and activation¹¹⁸. This approach has been investigated in PDAC using autologous T cells engineered with a chimeric antigen receptor (CAR) that recognizes mesothelin, a self-antigen overexpressed on malignant cells¹⁵⁵. Whereas mesothelin-specific CAR T cells demonstrate potent anti-tumor activity *in vitro* against autologous tumor cells¹⁵⁶, infusion of CAR T cells into patients has shown limited clinical benefit¹⁵⁵. This lack of clinical efficacy implies that additional immunoregulatory barriers beyond antigen release and T cell priming will need to be addressed to realize the potential of immunotherapy in PDAC¹⁵⁷. It is noteworthy, though, that mesothelin-specific CAR T cells were observed to produce some anti-tumor activity in one patient¹⁵⁵. Specifically, in this patient there was a loss of FDG-uptake detected in liver lesions but not the primary lesion. This mixed treatment response suggests that distinct mechanisms of immune evasion may be present depending on the location of disease. In addition, these findings imply there is significant biological heterogeneity between lesions even in the same patient. Consistent with this hypothesis, remarkable treatment response heterogeneity has also been reported based on FDG-PET/CT imaging in newly diagnosed metastatic PDAC patients treated with chemotherapy and a CD40 agonist¹¹⁵. Together, these observations imply that immunotherapy may need to be tailored based on the uniformity of treatment responses to accommodate intralesional heterogeneity. In this regard, a treatment would not be considered a failure if some lesions respond. Rather, mixed responses would signal a need to incorporate additional treatment regimens to capture non-responsive lesions rather than abandoning the initial therapeutic approach for lack of efficacy.

The limited clinical activity seen with immunotherapy in PDAC has produced a generalized belief that PDAC is immunologically “cold”. However, correlates from vaccine strategies suggest that the poor immunogenicity of pancreatic cancer may be reversible⁷¹. Moreover, the notion that PDAC is unlikely to respond to immunotherapy is beginning to evolve. A new perspective is emerging based on findings in PDAC patients with microsatellite instable tumors, where responsiveness to PD-1/PDL1 antagonists can be observed¹⁵⁸. This also suggests that the promise of immunotherapy in PDAC may rely on precise patient selection. However, even some chemotherapy-refractory PDAC patients with microsatellite stable disease have demonstrated responses to PD-1 blockade when combined with CSF1R antibodies designed to deplete a subset of myeloid cells with immunosuppressive properties^{159, 160}. Thus, targeting elements of the tumor microenvironment may shift PDAC from an immunologically-resistant to immunologically-sensitive phenotype. Overall, these findings underscore the genetic and biological variability that exists in PDAC and indicate that non-cytotoxic therapies designed to harness the immune system may provide clinical benefit to at least a subset of patients. However, thus far this patient subset appears to be rare, representing less than 2% of all PDAC patients¹⁶¹.

Efforts to broaden the impact of immunotherapy in PDAC are focusing on two major approaches. First, multi-targeted strategies are being examined to stimulate anti-tumor T cell responses. For example, an ongoing clinical study is evaluating a four-drug regimen involving chemotherapy (i.e., gemcitabine plus nab-paclitaxel) with an immune agonist targeting CD40 and an immune checkpoint inhibitor (i.e., anti-PD1) (Table 1). Other strategies are addressing roles for PD-1/PD-L1 blockade when combined with drugs that inhibit immunosuppressive mechanisms mediated by fibroblasts (e.g., FAK), matrix proteins

(e.g., hyaluronidase), and myeloid cells (e.g., CSF1R, BTK CCR2, CXCR2) (Table 1). A second approach is examining immune-based strategies to condition tumors for enhanced responsiveness to chemotherapy. For example, disrupting the immune cell recruitment to tumors (e.g., CCR2 inhibitor) that occurs in the setting of cytotoxic stress has demonstrated promising activity in patients with locally advanced PDAC¹²⁴. In general, these two strategic approaches to applying immunotherapy in PDAC are being pursued in combination with chemotherapy as a therapeutic backbone.

While most studies applying immunotherapy to PDAC are currently building on chemotherapy, there remains little understanding around the immunogenicity and mechanisms of anti-tumor activity induced with chemotherapy in PDAC. A recent phase-II study evaluating gemcitabine plus nab-paclitaxel in combination with indoximod revealed that responders to treatment demonstrate increased CD8⁺ T cell density in on-treatment tumor biopsies¹⁶². Moreover, all patients (both responders and non-responders) showed increases in the CD8⁺ effector to Foxp3⁺ regulatory T cell ratio in on-treatment biopsies (compared to baseline). These findings imply that chemotherapy may alter the immune microenvironment of PDAC and that these alterations may be important for therapeutic efficacy.

It remains unclear at this point, though, whether concurrent chemotherapy and immunotherapy will be the best therapeutic approach despite elegant studies in preclinical models demonstrating the potential of chemotherapy to be immunogenic^{14, 144, 145, 163, 164}. In this regard, unlike in most preclinical studies, chemotherapy is administered repeatedly to patients over the course of multiple cycles of therapy, raising the possibility that chemotherapy may ultimately attenuate the maintenance of any anti-tumor immune response by ablating proliferating immune cells and inducing T cell senescence¹⁶⁵. Chemotherapy can also be myelosuppressive, and thus while chemotherapy has the potential to ablate suppressive myeloid cells, it may also impact the efficacy of immunotherapeutic approaches designed to redirect myeloid cells with anti-tumor activity^{116, 166, 167}. An alternative approach to concurrent chemo-immunotherapy involves treatment sequencing as recently reported in non-small cell lung cancer where immunotherapy is initiated after chemotherapy induction¹⁶⁸. Such an approach is also now being evaluated in PDAC, wherein patients without progression on first-line platinum-based chemotherapy are switched to maintenance therapy with a PARP inhibitor and checkpoint immunotherapy (anti-CTLA-4 or anti-PD1) (Table 1). This approach to sequencing therapies represents a shift in the current treatment paradigm, which has historically been grounded on continuing treatment until progression (Figure 2).

With so many combinations of immunotherapies possible, there is a clear need for a framework for advancing immunotherapy in PDAC. It is likely that most attempts to stimulate productive anti-tumor immunity will be unsuccessful. Further, incorporation of immunotherapy into the treatment of PDAC has the potential to unveil an array of inflammatory-based side effects,¹⁶⁹ which can complicate management. For example, determining the etiology of colitis or hepatitis in the setting of immunotherapy is not straightforward and could reflect disease progression or infection in addition to immune activation induced by immunotherapy^{170, 171}. As inflammation is a key driver of PDAC, it

also remains possible that immunotherapy may accelerate disease progression in some instances as has been recently suggested for a subset of patients with non-small cell lung cancer treated with PD-1 antagonists¹⁷². Thus, it will be critical for studies which do not produce benefit or worsen outcomes to fail rapidly. However, it will be equally vital to learn from these efforts by including correlatives beyond safety assessments and pharmacokinetic assays¹⁷³ (Figure 3). Specifically, incorporating appropriate translational correlatives to inform both treatment responses and failures will be important. Well-designed clinical studies that are unsuccessful despite effective triggering of immune activity can provide key insights into compensatory mechanisms of resistance. For immunotherapy, these correlatives will need to address at a minimum the capacity of the investigational agent to target the biological pathway of interest. For example, this might entail demonstration that a small molecule inhibitor blocks *in vivo* phosphorylation of the target protein of interest. However, additional pharmacodynamic assays probing immune activation and immune complexity within and outside of tumors will also be beneficial to understanding changes in immune and tumor biology that may inform appropriate treatment combinations, sequencing, or both. Fundamentally, there is strong value in learning from every patient and understanding their immune status to guide the design of subsequent clinical trials in a strategic manner.

6. Conclusions

The incidence of PDAC is rising – this, coupled with a >90% mortality despite our best current treatments, accentuates the urgent need to find effective therapies. Long-term remissions with current standard treatments of chemotherapy, surgery, and targeted therapies remain rare, underscoring the need for novel approaches. Immunotherapy is a promising new therapeutic strategy for PDAC given the remarkable and durable outcomes observed in many other treatment-refractory cancers, including in patients that have failed multiple standard treatments. Burgeoning evidence has now confirmed in humans that despite lower T cell density in PDAC tumors compared to more immunogenic counterparts, T cell recognition of tumors is associated with improved survival. Moreover, checkpoint blockade has demonstrated efficacy in some PDAC patients with microsatellite instability. Together, these clinical observations are the best testaments to the potential of immune-based therapies in PDAC and argue against organ site-specific resistance to immunotherapy in the pancreas, while also providing proof-of-concept for PDAC treatment with immunotherapy. However, it is clear that PDAC is uniquely characterized by multiple redundant barriers to immunotherapy, and effective therapies likely will require combination approaches with current standard agents, many of which are currently in clinical testing. These clinical trials are expected to uncover fundamental concepts critical to the development of new therapies for PDAC, with preclinical models providing key insights into the mechanistic underpinnings underlying these observations, and thus are essential for propelling the much-needed progress in PDAC treatment. Through concerted and coordinated efforts between scientists, clinicians, and patients to identify the most efficacious strategies, we anticipate immunotherapy to become a key component of future PDAC therapies.

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Biography

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Figure 1. The pancreatic tumor microenvironment is highly immunosuppressive Malignant cells (purple), fibroblasts, and myeloid cells in the tumor microenvironment secrete a variety of immunosuppressive cytokines and chemokines (pink) that prevent effective anti-tumor CD8 T cell responses. TAM, tumor-associated macrophage; Treg, Foxp3⁺ regulatory T cell; MoMDSC, monocytic myeloid-derived suppressor cell; GrMDSC, granulocytic myeloid-derived suppressor cell; iCAF, inflammatory cancer-associated fibroblast; myCAF, myofibroblastic cancer-associated fibroblasts.

Figure 2. Therapeutic sequencing versus treat-to-progression for PDAC

(A) Conceptual model showing treatment-naïve PDAC responding initially to first-line (1L) chemotherapy but then acquiring resistance on continued (cont'd) chemotherapy and ultimately manifesting as tumor progression. (B) Conceptual model showing treatment-naïve PDAC responding initially to 1L chemotherapy; chemotherapy is then discontinued prior to tumor progression. A series of sequential treatments (i.e., A, B, and C) are then initiated to coax the tumor into remission. Each treatment is designed to anticipate mechanisms of acquired resistance that emerge from the prior treatment.

Figure 3. Workflow for advancing therapeutic strategies in PDAC

Patients enrolled in a clinical study are monitored with repeat liquid and tissue biopsies beginning at baseline prior to treatment and at defined time points on-treatment. Responders (partial or complete response) and non-responders (stable or progressive disease) are defined early after treatment (within 2–4 cycles) based on radiologic imaging (CT, MRI, or PET/CT). Sample biopsies are interrogated in the laboratory to assess pre-defined biomarkers of biological response and their relationship to clinical response. Pharmacodynamic markers in blood and tissue that are defined a priori are used to understand mechanisms of response and resistance to therapy. Findings are then used to inform development of new preclinical data and scientific rationale for the conduct of subsequent clinical studies.

Table 1.

Select immunotherapy trials in PDAC

Treatment category	Immunotherapy targets	ClinicalTrials.gov Identifier
Radiation plus immunotherapy	PD1, CTLA-4, radiotherapy	NCT02639026
	Cyclophosphamide, PD1, GVAX, radiotherapy	NCT02648282 , NCT0316379
	PD1, radiotherapy	NCT03245541
Vaccines plus immune checkpoint inhibitors	CRS-207, PD1, CTLA-4, GVAX	NCT03190265
	Cyclophosphamide, GVAX, PD1	NCT02451982
	Cyclophosphamide, GVAX, PD1, CSF1R	NCT03153410
	Cyclophosphamide, GVAX, CRS-207, PD1, IDO	NCT03006302
Chemotherapy plus immune agonists and antagonists	Chemotherapy, CD40 agonist, anti- PD1	NCT03214250
Anti-stromal drugs plus immunotherapy	FAK, PD1	NCT02758587
	FAK, PD1, Gemcitabine	NCT02546531
Matrix-targeted drugs plus immunotherapy	PEGPH20, PD1	NCT03481920 , NCT03193190 , NCT03634332
Myeloid inhibitors plus immunotherapy	PDL1, CFS1R	NCT02777710
	PD1, CSF1R	NCT02526017
	Cyclophosphamide, GVAX, PD1, CSF1R	NCT03153410
	Nab-paclitaxel, gemcitabine, BTK	NCT02436668
	Nab-paclitaxel, gemcitabine, CCR2/5, PD1	NCT03496662
PARP inhibitor plus immunotherapy	PARP, PD1, CTLA-4	NCT03404960

BTK: Bruton's Tyrosine Kinase; CRS-207: live attenuated listeria-encoding human mesothelin vaccine; CSF-1R: Colony Stimulating Factor 1 Receptor; CTLA-4: Cytotoxic T-lymphocyte-associated Antigen 4; CCR2/5: Chemokine (C-C motif) Receptor 2 and 5; FAK: Focal Adhesion Kinase; GVAX: GM-CSF transduced allogeneic whole tumor cell vaccine; IDO: Indoleamine 2,3-dioxygenase; PARP: poly ADP ribose polymerase; PD-1 : Programmed Cell Death Protein 1; PD-L1 : Programmed Death-Ligand 1; PEGPH20: pegvorhyaluronidase alfa.