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T cells in pancreatic cancer stroma

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is a highly devastating disease with a dismal 5-year survival rate. PDAC has a complex tumour microenvironment; characterised by a robust desmoplastic stroma, extensive infiltration of immune-suppressive cells such as immature myeloid cells, tumour-associated macrophages, neutrophils and regulatory T cells, and the presence of exhausted and senescent T cells. The cross-talk between cells in this fibrotic tumour establishes an immune-privileged microenvironment that supports tumour cell escape from immune-surveillance, disease progression and spread to distant organs. PDAC tumours, considered to be non-immunogenic or cold, express low mutation burden, low infiltration of CD8⁺ cytotoxic lymphocytes that are localised along the invasive margin of the tumour border in the surrounding fibrotic tissue, and often display an exhausted phenotype. Here, we review the role of T cells in pancreatic cancer, examine the complex interactions of these crucial effector units within pancreatic cancer stroma and shed light on the increasingly attractive use of T cells as therapy.

Key Words: Immunosuppression; T cell exhaustion; Tumour microenvironment; Pancreatic ductal adenocarcinoma; Pancreatic cancer stroma

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Core Tip: Pancreatic ductal adenocarcinoma (PDAC) is a highly devastating disease with a dismal 5-year survival of less than 5% in patients with metastatic disease, and is predicted to become the second cause of cancer-related death by 2030. Here, we discuss the complexity of the PDAC immunosuppressive tumour microenvironment, the mechanisms involved in T cell dysfunction, and potential immunotherapeutic strategies for treating PDAC.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a highly devastating disease with a dismal 5-year survival of less than 5% in patients with metastatic disease[1], and is predicted to become the second cause of cancer-related death by 2030[2]. Late detection and incredibly aggressive biology are significant challenges determining therapeutic failure[3,4]. PDAC has a complex tumour microenvironment (TME) characterised by a robust desmoplastic stroma[5], and an expanded pool of immunosuppressive immune cells shielding the malignant cells harbouring aberrant expression of oncogenic pathways. The interplay between various cell types in this fibrotic TME supports tumour cell escape from immunosurveillance, disease progression and spread to distant organs [6,7], highlighting this cancer's ability to evade immune recognition and its extra-ordinary metastatic potential. In this review, we discuss the interactions between T cells and the other components of the PDAC TME and highlight the impact of these interactions on the phenotype and function of T cells. Emerging immune-therapeutic strategies employed in overcoming T cell dysfunction and improve patient survival are also discussed.

PDAC IMMUNE LANDSCAPE

PDAC carcinogenesis is characterised by an abundant fibro-inflammatory reaction and subsequent oncogene activation on epithelial cells, resulting in a pro-tumorigenic microenvironment[8]. At early stages of cancer development, oncogenic *KRAS* expression in pancreatic cells results in the formation of pancreatic intraepithelial neoplasia (PanIN), and drives an inflammatory reaction that modulates the recruitment and infiltration of immunosuppressive myeloid and lymphoid cell subsets. *KRAS*-mutated pancreatic cells regulate the maintenance of immunoregulatory microenvironment by inducing the release of interleukin (IL)-6, IL-10 and transforming growth factor (TGF- β) cytokines. In the setting of sustained chronic inflammation, PanIN progression to malignant lesion is accompanied by mutations in genes such as TP53, CDKN2A and SMAD4 frequently, which further contribute to shape the immune microenvironment. For example, the mutant tumour suppressor gene TP53 are implicated in sustaining the tissue damage and chronic inflammation by enhancing the expression of NF- κ B, secretion of vascular endothelial growth factor (VEGF) and activation of fibroblasts. Decreased infiltration of T and B cells and elevated numbers of Tregs were significantly correlated with CDKN2A mutations while SMAD4 mutations are involved with enhanced invasion, metastasis and immunosuppressive effects of TGF- β on immune response[9].

Chemotactic factors associated with the recruitment of dysfunctional bone marrow-derived myeloid cells include granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte-colony-stimulating factor (G-CSF), IL-3, VEGF, and the interaction of the C-X-C chemokine ligand 12 (CXCL12)/C-X-C chemokine receptor 4 (CXCR4) or C-C chemokine ligand 2 (CCL2)/C-C chemokine receptor 2 (CCR2), amongst others [10]. Stromal-associated fibroblasts produce C-X-C chemokine ligand 13 (CXCL13), which recruits IL-35-producing regulatory B cells (Breg) into the TME, further contributing to PDAC progression through IL35-mediated stimulation of tumour cell proliferation[10]. Copious infiltration of immature myeloid cells, tumour-associated

macrophages (TAMs), neutrophils and regulatory immune cells ultimately establishes an immune-privileged microenvironment that protects the malignant cells from T cell immunosurveillance and sustains tumour growth[11].

Therefore, pancreatic cancer evolves to establish a complex and heterogeneous immune microenvironment, characterised by high numbers of strongly suppressive immune cells, and a modest infiltration of lymphocytes with anti-tumour properties [12-14]. As such, PDAC tumours are considered to be non-immunogenic or cold, displaying low infiltration of CD8⁺ cytotoxic lymphocytes (CTLs) that are localised along the invasive margin of the tumour border or trapped in the surrounding fibrotic tissue but are not present within the tumour core. Moreover, infiltrated CD8⁺ T cells in PDAC tumours often display minimal signs of activation[11,15,16]. T cell exclusion from TME has been demonstrated both in genetically engineered KPC (KRas^{LSL-G12D/+}, Trp53^{LSL-R172H/+}, Pdx1-Cre) mouse models[16] and PDAC patients[17].

Macrophages compose the most abundant immune cells in PDAC[11]. They play a critical role in the exclusion of T cells from tumours, maintenance of fibrosis through the secretion of pro-fibrotic cytokines[18] and induction of angiogenesis by secreting VEGF[19]. Increases in TAMs correlate with poor prognosis[20,21]. Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immunosuppressive cells, including immature monocytes, granulocytes and dendritic cells (DCs). These cells show potent ability to inhibit proliferation and induce apoptosis of both CD4⁺ and CD8⁺ T cells, secrete elevated amounts of immunosuppressive cytokines IL-10 and TGF- β , which collaborate to the recruitment of regulatory CD4⁺ T cells (Tregs), and decrease the infiltration of natural killer (NK) and NKT cells into the tumour[22]. MDSCs accumulation has been described in the spleen, tumours and metastatic lesions in KPC models of PDAC, and its accumulation negatively correlated with CD8⁺ T cells infiltration[19].

Likewise, Tregs upregulate the expression of CTL-associated antigen 4 (CTLA-4) [23], interact with DCs suppressing the expression of the co-stimulatory ligands, such as CD80 and CD86, necessary for T cell activation, secrete immunosuppressive cytokines, and directly suppress CD8⁺ T cells anti-tumour immunity[24]. Infiltration of Tregs occurs at early stages of PDAC formation, and increased numbers of both circulating and intra-tumoural. Tregs have been observed in pancreatic cancer patients [19]. Additionally, the presence of tumour-infiltrating IL-17-producing CD4⁺ T cells and $\gamma\delta$ T cells also contribute to tumour immune evasion and progression[11,25].

Similar to PDAC, in inflammatory conditions of the pancreas, such as pancreatitis, the inflammatory reaction leads to the infiltration of myeloid cells, such as monocytes and neutrophils. Although macrophages comprise a significant population within the inflamed pancreas, T cells are also present, and infiltration of CD4⁺ T cells has been implicated in the progression of acute pancreatitis in mice. As pancreatitis progresses, the ratio of CD4⁺ and CD8⁺ T cell increases, with increased numbers of immunosuppressive Tregs observed in patients with chronic pancreatitis.

T CELL INTERACTIONS AND IMMUNE DYSFUNCTION IN PANCREATIC CANCER

T cell infiltration is observed in patients with surgically-resected PDAC and correlates with improved outcomes suggesting the anti-tumour potential of tumour-infiltrating CD4⁺ and CD8⁺ T cells[26]. However, as PDAC progresses, tumour-infiltrating T cell composition shifts to a decrease in CD8⁺ T cells and elevated percentage of Tregs within the CD4⁺ T cell subset[27]. While CD4⁺ Tregs are a prominent feature of the immune infiltrate, CD8⁺ T cells are rare in the PDAC microenvironment[24]. Consequently, PDAC is considered to be a poorly immune responsive cancer, with T cells present within the tumour microenvironment often showing lack of activation, or an exhausted phenotype[28-30]. This observation demonstrates that infiltrated CD8⁺ T cell may recognise and mount a response against these tumours, but the unfavourable TME halts optimal cytotoxic function.

Spatial localisation of the immune cells in these tumours reflect the challenging biology of PDAC TME. Tumour-infiltrating CD8⁺ T cells are localised at the periphery, within the surrounding fibrotic stroma in PDAC tissues[6,21,31,32]. CD8⁺ T cells migrate away from the juxta-tumoural compartment by favouring their movement towards CXCL12-rich stroma laid by activated pancreatic stellate cells (PSCs)[6]. The proximity of intra-tumoral CD8⁺ T cells to tumour cells correlates with patient survival [32].

PSCs play a central role in shaping the architecture of PDAC by modulating the ECM components and producing a physical barrier that limits T cell infiltration, migration and direct interaction with neoplastic cells[33]. These cells can also act as non-professional antigen-presenting cells (APCs) and secrete cytokines and growth factors that boost the recruitment of immunosuppressive cells and inhibit T cell responses, resulting in increased disease aggressiveness and decreased overall survival[34]. Therefore, in conjunction with the immunosuppressive cells, PSCs are crucial players in the orchestration of an immuno-privileged PDAC microenvironment by combination of secreted cytokines, chemokines and extra-cellular matrix proteins as well as direct cell-cell contact.

Cancer cell-intrinsic factors also impact T cell function. Overexpression of immune checkpoint mediators like programmed death-1 receptor (PD-1)-ligand (PD-L1) is one mechanism by which cancers suppress T cell immunity. PD-L1 is overexpressed in PDAC cells, and this overexpression correlates with worse prognosis[20]. Pancreatic cancer cells can also downregulate Fas, a cell surface receptor associated with the induction of Fas-mediated apoptosis in tumour cells. CD8⁺ T cells use the Fas-FasL and perforin-granzyme pathways as major effector mechanisms of cytotoxicity, and loss of Fas expression in PDAC tumours result in cancer immune evasion[7,35]. Spatial localisation and T cell interactions within the PDAC tumour microenvironment are shown in Figure 1.

PDAC has a low mutation burden, resulting in low neoantigen burden and the scarcity of tumour-infiltrating effector T cells. Only a few PDAC tumour antigens capable of inducing an anti-tumour immune response have been identified. Low mutation burden with minimal expression of neoantigens, and consequently marginal T cell infiltration is a classical feature in KPC models[36], and in PDAC patients[29, 37]. In a recent study aimed to identify T cell neoantigens in long-term survival patients, it appears that the total neoantigen burden does not correlate with increased survival, but the presence of high-quality neoantigens played an essential role in the immunosurveillance of long-term survival patients. This study also highlighted the correlation of prolonged survival with granzyme B⁺ CD8⁺ T cells[26]. In keeping with this hypothesis, the total number of infiltrated CD8⁺ T cells after vaccine immunotherapy did not show correlation with survival, but the subset of granzyme B⁺ CD8⁺ T cells was associated with long-term survivors[38]. These findings suggested that T cell quality may be more important than the total number of T cells for adequate anti-tumour immunity[39].

Identification of multiple dense lymphocyte aggregates, known as tertiary lymphoid structures (TLS) has also been observed in PDAC[38]. Importantly, detection of TLS in tumour tissue of PDAC patients was an independent prognostic factor for prolonged survival[40-42]. Although TLS can occur intra-tumoral or at the tumour periphery, only the presence of intra-tumoral TLS correlates with survival[41]. TLS aggregates contain T- and B-cell areas co-localised with myeloid and follicular DCs, and high-endothelial venules, displaying similar organisation to secondary lymphoid organs. They comprise ectopic lymphoid sites where T-cell activation and proliferation takes place[41]. Nevertheless, PDAC immune microenvironment is enriched with both exhausted and senescent T cells, and a diverse pool of highly immunosuppressive cells [43].

T CELL PHENOTYPE AND FUNCTIONS

Mature T cells can be classified as CD8⁺ T cells (CTLs) and CD4⁺ helper T cells (Th), which further differentiate into Th1, Th2, Th17 and Tregs[17]. CD4⁺ Th1 cells secrete the pro-inflammatory cytokine interferon- γ (IFN- γ) which activates and supports CTLs cytotoxicity, while CD4⁺ Th2 cells exhibit tumour-promoting functions by producing a plethora of cytokines, sustaining fibrosis through ECM and collagen deposition, and contributing to the differentiation of macrophages into a M2-immunosuppressive phenotype[44]. Polarisation towards Th2 cell subset is a common trait in pancreatic cancer, and this shift from Th1 to Th2 cells is correlated with decreased patient survival[45]. In PDAC patients, CD4⁺ Th17 cells functions are mediated by the secretion of IL-17 cytokine. Although not very well understood, infiltration of this population has been associated with immune tolerance and reduced survival in murine models[46]. Tregs are an essential component of the T cell population. PDAC patients have increased numbers of Tregs that are inversely associated with CD8⁺ T cells, therefore, they are often used as a negative prognostic biomarker in PDAC[45]. These cells can be identified by the expression of CD4⁺CD25⁺FOXP3⁺ phenotype[24]

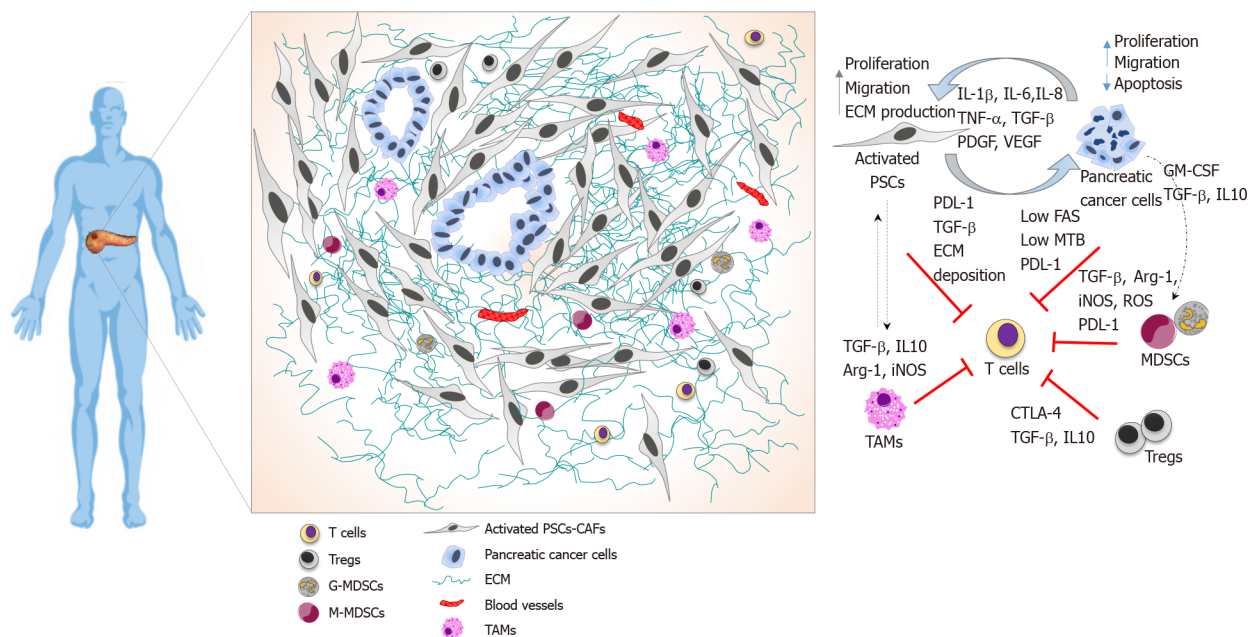


Figure 1 Pancreatic ductal adenocarcinoma immune landscape and T cell immunosuppression. Illustrative image showing spatial localisation of T cells in the pancreatic ductal adenocarcinoma tumour microenvironment and cellular interactions that collectively prevent T cell infiltration and function. T cells are localised at the periphery of tumours preventing direct contact with cancer cells. Pancreatic stellate cells produce elevated amounts of extracellular matrix driving a fibrotic tissue that entraps infiltrated T cells, alongside with immunosuppressive cytokine to and expression of programmed death-ligand 1 (PDL-1). Pancreatic cancer cells avoid T cell killing by downregulating Fas, exhibiting low tumour mutational burden, expressing PDL-1 and secreting growth factors and cytokines that recruits immunosuppressive cells. Myeloid-derived-suppressor cells express PDL-1 and suppress T cells functions by several mechanisms, including depleting of arginase 1, the release of reactive oxygen species, and secretion of cytokines. Tregs directly suppress T cells, express cytotoxic T-lymphocyte-associated protein 4 and secrete cytokines. TAMs play a role in sequestering T cells at the periphery and secrete immunosuppressive cytokines. PSC: Pancreatic stellate cells; TAMs: Tumour-associated macrophages; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; GM-CSF: Granulocyte-macrophage colony-stimulating factor; Arg-1: Arginase 1; PDL-1: Programmed death-ligand 1; iNOS: Inducible nitric oxide; MDSC: Myeloid-derived-suppressor cells; ROS: Reactive oxygen species; ECM: Extracellular matrix; TBM: Tumour mutational burden.

(Table 1).

CTLs are the preferred immune cells for targeting tumours. For durable and efficient immune responses, naïve T cells are primed in the lymph nodes with tumour antigens through interactions with APCs. Upon activation, they rapidly proliferate, differentiate into antigen-specific CTLs and migrate to tumour sites to perform their cytotoxic functions[47]. Elimination of tumour cells by CTLs occurs *via* the release of cytotoxic granzymes, IFN- γ and tumour necrosis factor α (TNF- α), or by induction of FasL-mediated apoptosis[48]. Following a cytotoxic immune response, the majority of CTLs will undergo apoptosis while a small fraction of them will further differentiate into diverse subsets of multipotent, long-lived memory CD8⁺ T cells endowed with self-renewal ability[47]. The integration of three coordinated signals regulates T cells activation, expansion, survival, and memory formation: T cell receptor (TCR) stimulation by antigens, engagement of co-stimulatory molecules (CD28, CD27, 4-1BB, and OX40) expressed by CD8⁺ T cells, and the release of inflammatory cytokines. In the absence of co-stimulatory signals, antigenic stimulation induces tolerance or clonal deletion in peripheral lymphoid organs[49]. The pro-inflammatory cytokines IL-12, IL-2 and IFN- γ , are crucial for satisfactory naïve CD8⁺ T cell activation, expansion and differentiation whereas IL-7 and IL-15 are predominantly required for formation maintenance of memory CD8⁺ T cells. In pancreatic cancer patients, both number and functions are altered within the CD8⁺ T cell population. These patients show a decrease in circulating CD8⁺ T cells and a decrease in perforin expression within these cells compared to healthy subjects. Moreover, intra-tumoural CD8⁺ T infiltrates often display abnormal exhausted phenotype[44].

Memory CD8⁺ T cells immediately proliferate upon antigen stimulation, execute cytotoxic functions, secrete effector cytokines, persist in greater numbers and exist in different metabolic, transcriptional, and epigenetic states[50]. Importantly, while the correlation between the numbers of memory CD8⁺ T cells and the efficacy of T cell immunity is firmly established, the quality (or functional ability) of memory CD8⁺ T cells also determines the degree of protection[47,48,50]. While memory T cell population are heterogeneous and consist of multiple subsets, the central memory T cells (T_{CM}) and effector memory T cell (T_{EM}) subsets have been best characterised. T_{CM}

Table 1 T cell phenotype and functions

T cell phenotype	Surface markers	Immune response	Effector functions
Cytotoxic T cell			
CTLs	CD8	Tumour killing	IFN- γ , TNF- α cytokines, granzymes, FasL
Helper T cell			
Th1	CD4 STAT4 T-bet	Tumour killing	IFN- γ , IL-2 cytokines, increase CTL activity
Th2	CD4 STAT6 GATA3	Tumour tolerance	IL-4, IL-5, IL-13 cytokines, decrease CTL activity
Th17	STAT3 ROR γ t	Tumour tolerance	IL-17 cytokine
$\gamma\delta$ T cells	TCR γ / δ	Tumour tolerance	IL-4, IL-10, TGF- β cytokines and CTL activity
Regulatory T cell			
Tregs	CD4 CD25 FOXP3	Tumour tolerance	IL-10, TGF- β cytokines, CTLA-4

CTL: Cytotoxic lymphocyte; IFN- γ : Interferon- γ ; TNF- α : Tumour necrosis factor α ; IL: Interleukin; TGF- β : Transforming growth factor β .

cells express high levels of CD62L and CCR7 and efficiently home to lymph nodes, whereas T_{EM} cells lack these molecules and reside mainly in non-lymphoid peripheral tissues but are able to migrate rapidly in response to cytokine gradient. T_{CM} and T_{EM} subsets can also be identified along with a terminally differentiated $CD8^+$ T subset that expresses CD45RA (T_{EMRA}). This way, the T_{CM} subset is classified as $CD45RA^- CD27^{high}$ CCR7 $^+$ cells and T_{EM} subset as $CD45RA^- CD27^{low}$ CCR7 $^-$ cells. In contrast, T_{EMRA} subset can be identified as $CD45RA^+ CD27^{lo}$ CCR7 $^-$ cells, and naïve T cells as $CD45RA^+ CD27^{high}$ CCR7 $^+$ cells, but there are other methods of differentiating these sub-types[47,50].

A handful of other markers have been described to differentiate T cell populations during the effector-to-memory transition states. Increased expression of IL-7Ra (CD127) is functionally required for long-term survival and can be used to identify memory precursor $CD8^+$ T cells. Other proteins co-expressing with CD127 $^+$ $CD8^+$ T cells include Bcl-2, CD27, CXCR3, and CD28. Cells expressing these set of markers have the most remarkable capacity to develop into central memory $CD8^+$ T cells (T_{CM}), showing elevated ability to proliferate upon antigen stimulation, increased IL-2 secretion, and self-renewal. Conversely, $CD8^+$ T cells with increased expression of KLRG1, CD57 and decreased expression CD127, CD27, CXCR3, and CD28 are associated with effector or memory $CD8^+$ T cells that display cytotoxicity, elevated IFN- γ production and short-life span. Therefore, KLRG1 $^+$ CD127 $^-$ $CD8^+$ T cells can be considered effector memory $CD8^+$ T cells (T_{EM}), at least in murine models, though human equivalent data is awaited[47,50].

Transcriptional factors promote the development and function of T_{EM} and T_{CM} cells. Expression of T-bet, Blimp1, ID2, and STAT4 is associated with T_{EM} cells, while high expression of TCF1, BCL-6, ID3, and STAT3 is linked to the formation of T_{CM} cells[49, 50]. Interesting, in B cells, Blimp-1 and BCL-6 are essential for the development of germinal centre B cells and long-lived plasma cell through reciprocally antagonising each other[51], suggesting that this set of transcription factors acts in a similar fashion, in the regulation of effector- memory T-cell transition. Moreover, Tcf7 and Lef1 transcription factors are found in self-renewing multipotent $CD8^+$ T cells known as memory stem cells[52].

T CELL EXHAUSTION

Exhausted T cells differ from other dysfunctional T cells, including anergic T cells and senescent T cells. Anergic T cells are induced by suboptimal stimulation showing cells with low proliferative capacity and minimal effector function. Senescent T cells initiate from repeated stimulation, resulting in cells with low proliferative capacity, low expression of inhibitory receptors but show high effector functions despite shortened telomeres. Differently, exhausted T cells result from persistent antigenic stimulation causing T cells with low proliferative capacity, low to moderate effector functions and elevated expression of multiple inhibitory receptors[53].

In cancers such as PDAC, T cells that go through the activation process will later differentiate into memory-like cells and will ultimately become terminally differen-

tiated exhausted T cells. Exhausted T cells result from persistent antigen exposure featuring cells with low proliferative capacity, increased apoptosis, loss of their cytotoxic function, and elevated expression of multiple inhibitory receptors also known as immune checkpoints such as PD-1, CTLA-4, T cell immunoglobulin and mucin-domain containing-3 (TIM-3), lymphocyte activation gene 3 (LAG-3), or T cell immunoreceptor with Ig and ITIM domains (TIGIT)[43,53]. Each inhibitory receptor binds to its ligand, typically expressed by APCs and tumour cells in the TME.

The surface receptor PD-1 (CD279) is the primary receptor involved in T cell inhibitory signalling. PD-1 has two ligands: PD-L1 (CD274) and PD-L2 (CD273) can be found on the surface of antigen-presenting, MDSCs, TAMs and cancer cells. IFN- γ is the main trigger for PD-L1 and PD-L2 upregulation, while induction of PD-1 expression on T cells results from cell receptor (TCR) stimulation or secretion of the cytokines IL-2, IL-7, IL-15, IL-21, and TGF- β . Engagement of PD-L1 or PD-L2 with PD-1 receptor on T cells, inhibits dephosphorylation of TCR signalling components, specifically CD28, resulting in decreased IL-2, IFN- γ , and TNF- α cytokine production, survival, proliferation and effector functions[54].

CTLA-4 (CD152) is a B7/CD28 family member that is constitutively expressed by Tregs. CTLA-4-mediated immunosuppression occurs by limiting signalling through the co-stimulatory receptor CD28 during antigen-presentation, by either binding or deleting CD80 and CD86 from APCs[55]. Thus, indirectly reducing T cell activation and immune responses to tumour antigens. Other T cell subsets such as CD4⁺ T cells can also upregulate this receptor upon activation[56]. LAG-3 exerts inhibitory effects on T cells through MHCII binding, which results in decreased T cell activation and cytotoxicity, and increased suppressive function in Tregs. In PDAC, upregulation of this receptor is observed in association with upregulation of both PD-1 and CTL-4[57].

The inhibitory receptor TIGIT compete with CD226 to bind the ligands CD112 and CD155 while Tim-3 binds to Galectin-9 and CEACAM1 proteins to inhibit T cell function[58]. Of note, upregulation of Tim-3 in patients with PDAC is correlated with decreased patient survival[57]. Transcription factors involved in the formation of dysfunctional T cells include T-bet, Eomes, Foxo1, Blimp-1, NFAT and IRF-4[53].

A recent study using multiplex immunohistochemistry imaging combined with single-RNA sequencing to evaluate T cell landscape and function in patients with pancreatic cancer, demonstrated that infiltrated CD8⁺ T cells displayed a senescent phenotype, identified by the expression of CD57⁺CD27⁺CD28⁻ or CD45RA⁺ CD27^{-/Low} CD28^{-/Low} or an exhausted phenotype with elevated expression of TIGIT⁺ and CD39⁺ markers alongside PD-1^{low/intermediate} expression[30]. Senescent and exhausted T cells as well as Tregs were also identified within the CD4⁺ population. Additionally, intra-tumoural Tregs exhibit highly suppressive phenotypes, highlighted by the expression of multiple (TIGIT, ICOS, CD39) inhibitory markers[30].

IMMUNOTHERAPY AND PANCREATIC CANCER

Strategies aiming to leverage the activity of CTLs or the reversal of T cell dysfunction are widespread and have shown clinical success across a variety of cancer[27,29,59]. However, efforts to translate immunotherapy to PDAC, have been met with substantial challenges. The presence of tumour-infiltrating lymphocytes (TILs) with effector and memory functions within the tumour microenvironment and the positive correlation between CD8⁺ T effector memory cells and patient survival highlight the significance of the T cell immune infiltrate in limiting cancer progression[48]. Hence, the lack of efficacy in existing immunotherapies reflects the challenging non-immunogenic PDAC TME[11,38,48,60].

Chimeric antigen receptor (CAR) T cells or tumour vaccines alone have not demonstrated a survival benefit in PDAC tumours[11,35,48,61]. However, work is ongoing on demonstrating novel targetable antigens or switchable CAR T cells which get activated on reaching the tumour[62,63]. Although most infiltrated CD8⁺ T cells in the PDAC stroma display features of an exhausted phenotype, demonstrated by cell surface expression of multiple inhibitory receptors, immunotherapy with single-agent immune checkpoint blockade (ICB) has been disappointing. KPC mouse models did not show anti-tumour responses to either CTLA4, PD-1, PDL-1 monotherapy or CTL-4 combined with PD-1/PDL-1 blockade[19,64]. Similarly, human clinical trials using ICB demonstrated insufficient clinical activity and minimal improvement on prognosis, with clinical benefit observed in only highly selected patients[27,39]. Equally, monotherapy with CTLA-4 antibodies and in combination with chemotherapy has not shown ideal clinical activity[59]. Furthermore, exciting avenues for targeting novel

antigens such as CEACAM7 offers hope for CAR-T cell therapy[62,65,66].

The vast majority of trials targeted towards T cells in pancreatic cancer are centred around the use of immune inhibitory receptors against PD-1 and CTLA-4[67]. Most of these trials have enrolled patients with metastatic or borderline resectable pancreatic cancer and assessed the response to either single or double agent immunotherapy or combination therapy with chemotherapy/radiotherapy. The results regarding progression free survival or overall survival have been so far underwhelming[68]. In a meta-analysis on checkpoint inhibitors overall survival and progression-free survival showed no improvement in single agent therapy but a small number of studies on combination therapy have been more promising[69]. It is feasible that the limited tumor mutational burden of pancreatic cancer compared to immunotherapy responsive tumours, such as melanoma or non-small cell lung cancer, may be the key differentiating factor. The phase II KEYNOTE-185 study trying to assess the efficacy of pembrolizumab on patients with non-colorectal microsatellite unstable/mismatch repair deficient cancers enrolled 22 patients with pancreatic cancer, of which four patients showed response to treatment with increase in progression-free survival and median survival[70]. These results, although encouraging, demonstrate that there key barriers around identifying correct groups of patients that would benefit from T cell targeted therapies.

There are various explanations for ICB failure in PDAC tumours including low mutational burden and expression of neoantigens, minimal intra-tumoural infiltration of CD8⁺ T cells, expression of multiple inhibitory receptors in CD8⁺ T cells that infiltrate tumours, as well as decreased tumour and myeloid expression cell expression of PDL-1[31,57]. To improve PADC response to ICB, combined approaches have been investigated. Multi-agent immunotherapeutic protocols targeting multiple inhibitory receptors is a promising approach, and has proved more effective than single inhibitory receptor blockade in reversing dysfunctional CD8⁺ T cells PDAC[27,71]. In the same way, strategies with the goal to prime effector CD8⁺ T cells to increase their immunogenicity and responsiveness before the use of checkpoint inhibitor treatment represents an exciting opportunity in cancer immunotherapy[12,27,59,72,73]. Combinatory approaches utilising GM-CSF-secreting tumour cells vaccine (GVAX), to induce upregulation of PD-L1 expression into the PDAC TME, prior CTLA-4 and anti-PD-1/PDL-1 blockade has shown promising results in PDAC patients[57,72], and a dual blockade targeting CXCR4 and PD-1 demonstrated improvement in T cell infiltration with a decline in MDSCs[57].

Strategies with the co-stimulatory molecule agonist CD40 used to enhance APC capabilities of macrophages[74] combined with gemcitabine, PD-1 and CTL-4 ICB resulted in increased T-cell priming and infiltration in PDAC tumours[64,72]. Extraction and *in vitro* expansion of TILs from PDAC tumours also have been explored [40] and the results demonstrated autologous T cell killing activity[75,76].

CONCLUSION

The PDAC tumour microenvironment is characterised by complex fibrotic stroma with substantial infiltration of tumour-promoting immunosuppressive cells and pronounced T cell exhaustion, favouring immune evasion that results in immunotherapeutic failures and poor clinical outcome. Therefore, understanding the complexity of PDAC immune landscape and the mechanisms involved in T cell dysfunction may contribute to identifying new immunotherapeutic strategies for treating PDAC and monitoring such response with novel technologies such as ctDNA to assess tumour lysis[77]. As such, unsuccessful immunotherapies could be reversed using combined approaches targeting multiple pathways that obstruct T cell anti-tumour immunity along with other strategies to target stroma[78,79].

A variety of preclinical studies highlighting the influence of PDAC stromal components on T cell anti-tumour responses provided rationale for the development of clinical trials incorporating combined approaches to enhance T cell responses[80]. CXCL12 from cancer-associated fibroblasts synergizes with anti-PD-L1 blockade resulting in activation of T cells and tumour regression in mice[6,81]. Similarly, dual blockade of TGF- β and anti-PD1 resulted in increased T cell responses and tumour regression[82]. Moreover, targeting of myeloid cells with CSF1R in combination with PD-1 or CTLA-4 blockade[83] or focal adhesion kinases inhibitors has been shown to decrease infiltration of suppressive myeloid populations with concomitant activation of T cells, and improved survival in mice models[84].

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