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Barriers and opportunities in pancreatic cancer immunotherapy

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Pancreatic ductal adenocarcinoma (PDAC) presents a fatal clinical challenge characterized by a dismal 5-year overall survival rate, primarily due to the lack of early diagnosis and limited therapeutic efficacy. Immunotherapy, a proven success in multiple cancers, has yet to demonstrate significant benefits in PDAC. Recent studies have revealed the immunosuppressive characteristics of the PDAC tumor microenvironment (TME), including immune cells with suppressive properties, desmoplastic stroma, microbiome influences, and PDAC-specific signaling pathways. In this article, we review recent advances in understanding the immunosuppressive TME of PDAC, TME differences among various mouse models of pancreatic cancer, and the mechanisms underlying resistance to immunotherapeutic interventions. Furthermore, we discuss the potential of targeting cancer cell-intrinsic pathways and TME components to sensitize PDAC to immune therapies, providing insights into strategies and future perspectives to break through the barriers in improving pancreatic cancer treatment.

Pancreatic ductal adenocarcinoma (PDAC), accounting for 90% of pancreatic tumors, remains a formidable malignancy with a dismal 5-year survival rate of merely 12%[1]. More than 80% of patients are diagnosed at an advanced stage, either locally advanced or metastatic disease, rendering curative surgical intervention futile[2,3]. Although gemcitabine in combination with albumin-bound paclitaxel or modified FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) has been established as the standard first-line chemotherapeutic protocol for metastatic cases[2], the clinical median survival still falls short of 1 year[4,5].

Cancer immunotherapeutic approaches, including immune checkpoint blockade (ICB), chimeric antigen receptor (CAR) T-cell therapies, and cancer vaccines, have achieved significant advancements in treating various cancers[6–8], such as melanoma, lung cancer, renal cell carcinoma, and lymphoma[9–12]. However, their effectiveness in PDAC remains disappointing[6]. Clinical studies utilizing immune checkpoint inhibitors (ICIs), including anti-programmed death ligand-1 (anti-PD-L1) or anti-cytotoxic T-lymphocyte-associated protein-4 (anti-CTLA-4) monoimmunotherapy and combination therapy, have not been successful in treating pancreatic cancer[13–15]. In a recent phase 2 trial of metastatic PDAC, combining ICIs (durvalumab and tremelimumab) with chemotherapy (gemcitabine and nab-paclitaxel) did not improve survival compared with chemotherapy alone[16].

The immunosuppressive tumor microenvironment (TME) in PDAC, a major factor contributing to immunotherapy resistance, includes tumor-infiltrating immune-suppressive cells, stromal cells, the microbiome, and the extracellular matrix (ECM). The immune infiltration in PDAC is characterized by an abundance of suppressive cells, a deficiency of anti-tumor immune cells, and immune dysfunction[17–19]. Exploring combination strategies involving immunotherapy and agents tailored to target these TME characteristics has emerged as a prominent area of research in pancreatic cancer.

In this article, we review recent advances in understanding the immunosuppressive TME of PDAC, describe TME differences among various animal models, discuss the mechanisms of immune resistance induced by TME and tumor cells, and summarize strategies aimed at improving the efficacy of immunotherapy in pancreatic cancer.

Highly immunosuppressive tumor microenvironment in PDAC

The TME of PDAC consists of various immune-suppressive cells, including immunosuppressive myeloid cells, M2 macrophages, N2

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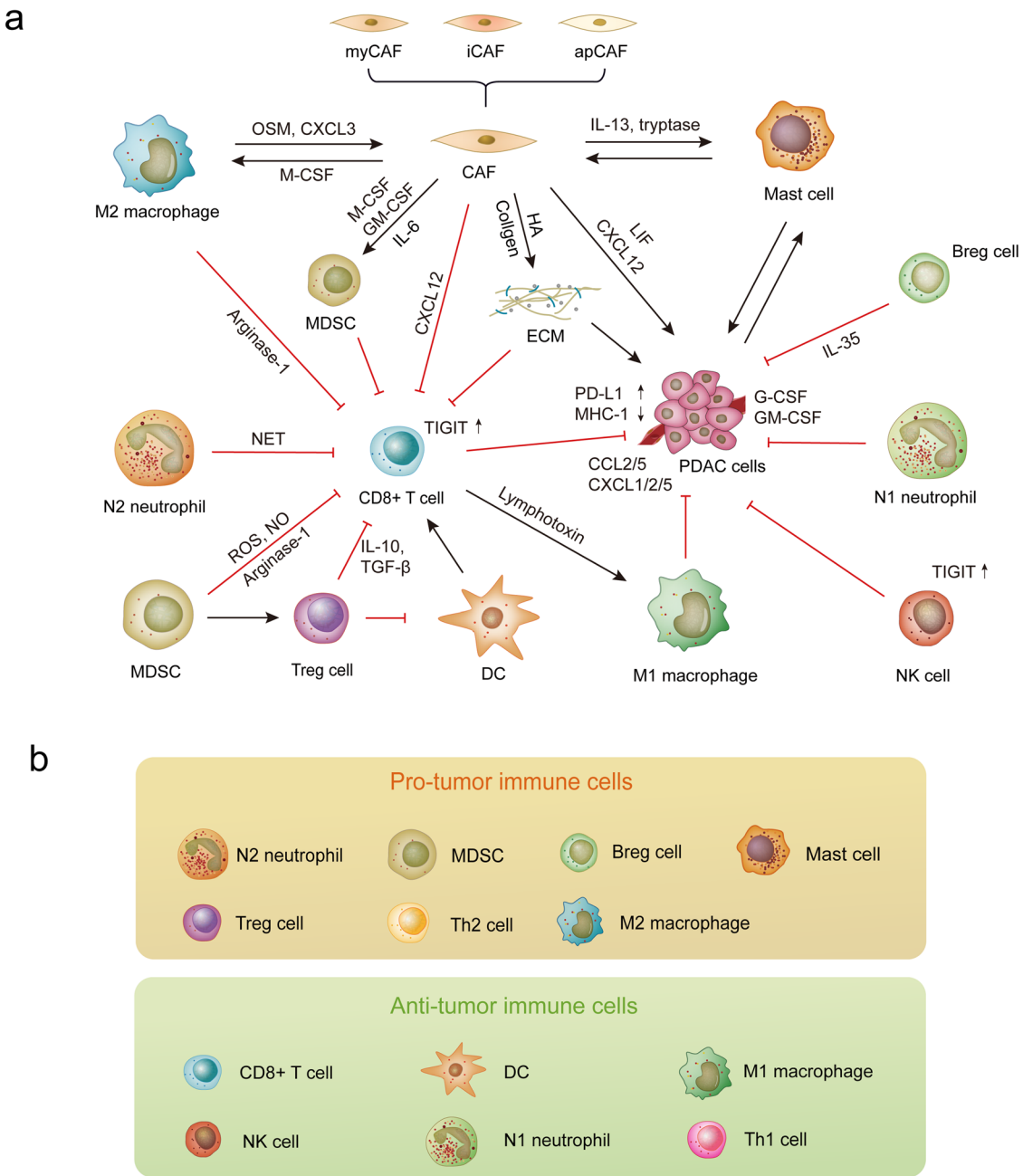

Fig. 1 | The immunosuppressive TME in PDAC. a Schematic representation of the interplay among tumor cells, tumor-infiltrating immune cells, and cancer-associated fibroblasts (CAFs) in the PDAC TME. Tumor cells and CAFs secrete chemokines and growth factors, such as granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), CXCL2/5, and CXCL12 to recruit suppressive immune cells to tumor tissues. Pro-tumor immune cells contribute to the exhaustion of effector T cells and the activation of CAFs. Activated CAFs, in turn, support tumor growth through desmoplasia and inflammatory cytokines such as IL-6; in addition, they may cooperate with mast cells to promote tumor cell proliferation and metastasis. Upregulation of immune checkpoint molecules (e.g., PD-L1 and TIGIT) on tumor cells and immune cells, as well as downregulation of MHC-I, contribute to T-cell dysfunction. **b** Pro-tumor cells include myeloid-derived suppressor cells (MDSCs), M2 macrophages, N2 neutrophils, regulatory T cells, regulatory B cells, mast cells, and Th2 cells. Anti-tumor immune cells include CD8 + T cells, dendritic cells (DC), M1 macrophages, natural killer (NK) cells, N1 neutrophils, and Th1 cells.

neutrophils, mast cells, Th2 cells, regulatory T cells, and regulatory B cells (Fig. 1 and Table 1). On the other hand, there is notable dysfunction and deficiency of anti-tumor immune cells, including CD8 + T cells, conventional dendritic cells, natural killer cells, M1 macrophages, N1 neutrophils, and Th1 cells (Fig. 1 and Table 2). The suppressive immune cells impede the cytotoxic T-cell-mediated tumor ablation effect, either directly or indirectly through inhibition of dendritic cells. In addition, the microbiome, stromal cells, and ECM modulate immune cell infiltration and function, contributing to the establishment of an immunosuppressive TME.

Immunosuppressive myeloid cells

Suppressive myeloid cells in the TME can be broadly categorized into myeloid-derived suppressor cells (MDSCs) comprising granulocytic MDSCs and monocytic MDSCs, tumor-associated macrophages (TAMs) derived from either the bone marrow or resident tissue macrophages[6,20],

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Table 1 | Pro-tumor immune cells in the PDAC TME

Cell type	Associated cells	Function/description	Molecule/signal	Reference	PMID
Myeloid-derived suppressor cell (MDSC)	T cell	Inhibiting T-cell's anti-tumor activity and promoting immune evasion	PD-L1	Myeloid cells are required for PD-1/PD-L1 checkpoint activation and the establishment of an immunosuppressive environment in pancreatic cancer	27402485
			Arginase-1, xc-transporter	Immunologic Strategies in Pancreatic Cancer: Making Cold Tumors Hot & Myeloid-derived suppressor cells inhibit T-cell activation by depleting cystine and cysteine	35839445 20028852
			ROS, NO	Coordinated regulation of myeloid cells by tumors	22437938
Tumor-associated macrophage (M2 macrophage)	T cell	Inhibiting T-cell response and supporting tumor growth	PD-L1, arginase-1	Immunologic Strategies in Pancreatic Cancer: Making Cold Tumors Hot	35839445
			TGF-β1, PD-L1	Tumor-associated macrophages promote PD-L1 expression in tumor cells by regulating PKM2 nuclear translocation in pancreatic ductal adenocarcinoma	34862460
			Dectin-1, galectin-9	Dectin-1 Activation on Macrophages by Galectin-9 Promotes Pancreatic Carcinoma and Peritumoral Immune-Tolerance	28394331
			Receptor-interacting serine/threonine protein kinase 1 (RIP1)	RIP1 Kinase Drives Macrophage-Mediated Adaptive Immune Tolerance in Pancreatic Cancer	30423296
	Cancer-associated fibroblast (CAF)	Inducing a pro-tumorigenic environment and fostering tumor cell survival and migration	Oncostatin M (OSM)	Heterocellular OSM-OSMR signaling reprograms fibroblasts to promote pancreatic cancer growth and metastasis	34921158
			IL-33, CXCL3	Inflammatory cell-derived CXCL3 promotes pancreatic cancer metastasis through a novel myofibroblast-hijacked cancer escape mechanism	33568427
	Tumor cell	Promoting tumor growth and metastasis	OSM, LOXL2	Macrophages direct cancer cells through a LOXL2-mediated metastatic cascade in pancreatic ductal adenocarcinoma	35428659
			TGF-β	(1) Macrophage-expressed CD51 promotes cancer stem cell properties via the TGF-β1/smad2/3 axis in pancreatic cancer (2) Tumor Microenvironment Remodeling Enables Bypass of Oncogenic KRAS Dependency in Pancreatic Cancer	31199988 32341020
	Lactobacillus, CD8+ T cell	Suppressing T-cell response and inducing tumor growth	AhR	Tryptophan-derived microbial metabolites activate the aryl hydrocarbon receptor in tumor-associated macrophages to suppress anti-tumor immunity	35139353
Tumor-associated neutrophil (N2 neutrophil)	T cell	Inducing neutrophil extracellular traps and excluding cytotoxic CD8+ T cells from tumors	IL17	Interleukin-17-induced neutrophil extracellular traps mediate resistance to checkpoint blockade in pancreatic cancer	32860704
		Effecting T-cell infiltration and promoting tumor metastasis	CXCR2	(1) CXCR2-Dependent Accumulation of Tumor-Associated Neutrophils Regulates T-cell Immunity in Pancreatic Ductal Adenocarcinoma (2) CXCR2 Inhibition Profoundly Suppresses Metastases and Augments Immunotherapy in Pancreatic Ductal Adenocarcinoma	27737879 27265504
Mast cell	CAF	Stimulating CAF proliferation and contributing to tumor development	IL-13, tryptase	Dynamic mast cell-stromal cell interactions promote growth of pancreatic cancer	20371681
	Tumor cell	Inducing cancer cell proliferation, migration, and invasion	Matrix metalloproteinase (MMP)	Crosstalk between mast cells and pancreatic cancer cells contributes to pancreatic tumor progression	20371681
Treg cell	Tumor cell	Migrating into the TME and exerting immunosuppressive effect via CCR5 signaling	CCR5	Disruption of CCR5-dependent homing of regulatory T cells inhibits tumor growth in a murine model of pancreatic cancer	19155524
	T cell	Inhibiting CD8+ T-cell response and eliciting T-cell exhaustion	CTLA-4, PD-1, TIGIT	Mechanisms of T-Cell Exhaustion in Pancreatic Cancer	32823814
			IL-10, TGF-β	Mechanisms of T-Cell Exhaustion in Pancreatic Cancer	32823814

Table 1 (continued) | Pro-tumor immune cells in the PDAC TME

Cell type	Associated cells	Function/description	Molecule/signal	Reference	PMID
Th2 cell	Tumor cell	Promoting tumor progression and decreasing survival	TH2 cytokines	(1) A circulating TH2 cytokines profile predicts survival in patients with resectable pancreatic adenocarcinoma (2) Intratumor T Helper type 2 cell infiltrate correlates with cancer-associated fibroblast thymic stromal lymphopoietin production and reduced survival in pancreatic cancer	28932629 21339327
Breg cell	T cell, NK cell	Reducing the proliferation of NK cells and attenuating T cell- and NK cell-mediated anti-tumor responses	IL-18, IL-10, PD-1	Regulatory B cells induced by pancreatic cancer cell-derived interleukin-18 promote immune tolerance via the PD-1/PD-L1 pathway	29599908
			STING, IL-35	STING-induced regulatory B cells compromise NK function in cancer immunity	36198789
	T cell	Inhibiting T-cell infiltration and anti-tumor immunity	IL-35, BCL6	Balance between immunoregulatory B cells and plasma cells drives pancreatic tumor immunity	36099917
			B-cell receptor (BCR), protein kinase D2 (PKD2), IL-35	B Cell Receptor Signaling and Protein Kinase D2 Support Regulatory B Cell Function in Pancreatic Cancer	35046933
			IL-35, STAT3	B-cell-derived IL35 Drives STAT3-Dependent CD8+ T-cell Exclusion in Pancreatic Cancer	32024640
			IL-1β, IL-35, PD-L1	Interleukin-1β-induced pancreatitis promotes pancreatic ductal adenocarcinoma via B lymphocyte-mediated immune suppression	32393543
	TAMs, T cell	Inducing T(H)2-type macrophage programming and suppressing CD8+ T-cell-mediated cytotoxicity	Bruton tyrosine kinase (BTK)	(1) Bruton's Tyrosine Kinase (BTK)-dependent immune cell crosstalk drives pancreas cancer (2) BTK signaling drives CD1dhiCD5+ regulatory B-cell differentiation to promote pancreatic carcinogenesis	26715645 30635655

LOXL2 lysyl oxidase-like protein 2, *AhR* aryl hydrocarbon receptor, *TIGIT* T-cell immunoreceptor with Ig and ITIM domains, *STING* stimulator of interferon genes.

tumor-associated neutrophils (TANs), and mast cells. These myeloid cells are recruited to the TME by various factors and attenuate anti-tumor T-cell responses in PDAC[21,22].

MDSCs. MDSCs are a subset of anti-inflammatory, immunosuppressive cells, originating from immature myeloid cells under various pathological conditions such as chronic inflammation, cancer, and autoimmune disease[23]. In pancreatic cancer, MDSCs exert immunosuppressive functions and promote immune evasion through EGFR-MAPK-dependent upregulation of PD-L1 expression in tumor cells[24]. It has also been reported that MDSCs deplete nutrition through arginase-1 and the Xc^- transporter, resulting in the downregulation of the T-cell receptor (TCR) and restriction of T-cell activation[6,25]. In addition, MDSCs can promote regulatory T (Treg) cell induction in a cell-cell-dependent manner[26,27]. In an autochthonous PDAC model, depletion of granulocytic MDSCs elevated CD8 + T-cell infiltration and increased tumor cell apoptosis[28]. Moreover, reducing MDSCs through loss or inhibition of CXCR2 mitigated tumor metastasis and conferred sensitivity to anti-PD-1 therapy, thus prolonging survival in mice with pancreatic cancer[29]. Notably, a recent preclinical study by DePinho and colleagues[30] demonstrated that inhibition of chemokine receptors on MDSCs (by using a CXCR1/2 inhibitor) combined with modulation of T-cell immune checkpoints (by using a 41BB agonist and a LAG3 antagonist) could reprogram the highly suppressive tumor immune microenvironment of pancreatic cancer. This approach led to durable responses and survival benefits in a mouse model of PDAC, suggesting a potential clinical strategy.

TAMs. TAMs in the PDAC TME are characterized by an enrichment of pro-tumor M2-like phenotypes and a relatively low presence of anti-tumor M1-like phenotypes[19]. The immune suppression mediated by these pro-tumor TAMs stems from their ability to hamper the anti-tumor activity of CD8+ cytotoxic T lymphocytes by supporting PD-L1 expression in tumor cells and depleting nutrition in T cells[24,27,31]. Moreover, TAMs hinder adaptive immune responses through the dectin-1/galectin-9 axis[32] and facilitate the production of immunosuppressive factors in tumor cells, such as CXCL1 and CXCL5, through elevated expression of apolipoprotein E (ApoE)[33].

In PDAC models, reprogramming TAMs through the blockade of receptor-interacting serine/threonine protein kinase 1 (RIP1) leads to activation of cytotoxic T cells and differentiation of T helper (Th) cells into a mixed Th1/Th17 phenotype[34]. Previous studies have revealed the pro-tumor effects of Th2 cells and the anti-tumor effects of Th1 cells[34,35]. While the precise function of combined Th1/Th17 phenotypes remains to be defined in tumors, they appear to possess significant immunogenicity and are associated with the downregulation of FOXP3, a biomarker of Treg cells[34]. Interestingly, an exosome-based dual delivery biosystem, featuring electroporation-loaded galectin-9 siRNA and surface modification with an oxaliplatin prodrug, effectively reversed M2-like phenotypes of TAMs and enhanced anti-tumor immunity in mice[36]. In addition to their role in immune suppression, TAMs support cancer cells by secreting growth factors such as TGF-β[37,38] and producing cytokines and chemokines that accelerate tumor metastasis directly or indirectly[39–41].

A study comparing immune infiltrates in pancreatic cancer and melanoma identified VISTA (V-domain immunoglobulin suppressor of T-cell activation) as a potential immune checkpoint primarily expressed on CD68+ macrophages in PDAC[42]. Targeting VISTA-positive macrophages holds promise as a strategy to augment CD8 + T-cell responses and treat pancreatic cancer. Furthermore, a recent preclinical study demonstrated that dual antagonism of CCR2 and CCR5 (CCR2/5i), when combined with radiation therapy and an anti-PD-1 antibody, resulted in a reduction in tumor infiltration by Tregs, M2-like TAMs, and MDSCs[43]. Notably, this combination treatment increased intratumoral effector and memory T cells, supporting the clinical development of CCR2/5i in combination with radiation therapy and ICB for the treatment of PDAC.

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Table 2 | Anti-tumor immune cells in the PDAC TME

Cell types	Associated cells	Function/Description	Molecular/signal	Reference	PMID
NK cell	Tumor cell	NK cell killing function is inhibited by oncoprotein signaling	SKI, ligand for cytotoxicity receptor (NKG2D-L)	The oncoprotein SKI acts as a suppressor of NK cell-mediated immunosurveillance in PDAC	33023028
			Unknown	Defective NK cell expansion, cytotoxicity, and lack of ability to differentiate tumors from a pancreatic cancer patient in a long-term follow-up: implication in the progression of cancer	34559307
		Polysaccharide activates NK cells by upregulating NKG2D	Polysaccharide, TLR4/MAPKs/NF-κB	Polysaccharide enhanced NK cell cytotoxicity against pancreatic cancer via TLR4/MAPKs/NF-κB pathway in vitro/vivo	31521276
CD8+ T cell	Macrophage	Producing lymphotoxin that reprograms macrophages to be tumoricidal	Lymphotoxin	cIAP1/2 antagonism eliminates MHC class I-negative tumors through T-cell-dependent reprogramming of mononuclear phagocytes	34011631
Th1 cell	CD8+T cell	Inducing cytotoxic CD8+ T cells through T-bet and IFN-γ	T-bet, IFN-γ	Combination of gemcitabine and anti-PD-1 antibody enhances the anticancer effect of M1 macrophages and the Th1 response in a murine model of pancreatic cancer liver metastasis	33188035
Dendritic cell	T cell	Critical for T-cell priming while exhibiting paucity and dysregulation in PDAC	MHC-2, CD80/86, CD40, FLT3	(1) Type 1 conventional dendritic cells are systemically dysregulated early in pancreatic carcinogenesis (2) Dendritic Cell Paucity Leads to Dysfunctional Immune Surveillance in Pancreatic Cancer (3) Paucity of dendritic cells in pancreatic cancer (4) Cooperative induction of a tolerogenic dendritic cell phenotype by cytokines secreted by pancreatic carcinoma cells	32453421 32183949 11854690 16920987
M1 macrophage (tumoricidal macrophage)	Tumor cell	Activating tumoricidal M1 macrophages and altering tumor stroma	CD40	CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans	21436454
N1 neutrophil	CD8+ T cell, Treg cell	Enhancing CD8+ T-cell infiltration and inhibiting Treg cells	Unknown	Prognostic value of tumor-associated N1/N2 neutrophil plasticity in patients following radical resection of pancreas ductal adenocarcinoma	36600557
	Tumor cell	Inhibiting tumor growth and metastasis	Neutrophil elastase	Neutrophil elastase selectively kills cancer cells and attenuates tumorigenesis	33964209

FLT3 fms-like tyrosine kinase 3.

TANs. Neutrophils are major players in innate immunity. A single-cell RNA-seq (scRNA-seq) analysis uncovered a terminally differentiated subpopulation of TANs exhibiting hyperactivated glycolysis and pro-tumor functions in PDAC, which is associated with unfavorable prognosis in patients[44]. Pro-tumor neutrophils secrete immunosuppressive cytokines and chemokines, thereby inhibiting the activity of cytotoxic CD8 + T cells[45]. Moreover, neutrophil extracellular traps (NETs) have been reported to contribute to immunotherapy resistance induced by TANs. One of the inducers of NETs, IL17, which is upregulated in PDAC, recruits neutrophils while excluding cytotoxic CD8 + T cells from tumors[46]. In preclinical mouse models, targeting TANs with lorlatinib has been shown to enhance the response to PD-1 blockade, highlighting the potential of modulating pro-tumor neutrophils in the TME as a treatment strategy for PDAC[47].

Aside from primary tolerance, the replenishment of TANs is a contributing factor to therapy resistance in pancreatic cancer. Targeting CCR2+ macrophages led to a compensatory influx of CXCR2+ TANs, a phenomenon associated with poor outcomes in PDAC patients; interestingly, dual inhibition of CCR2+ TAMs and CXCR2+ TANs significantly improved anti-tumor immunity and chemotherapeutic responses in orthotopic models of PDAC[48]. Similar to the plasticity of TAMs, recent studies have revealed the plasticity of TANs—the presence of both N1 and N2 phenotypes in the TME of PDAC patients. The N1/N2 ratios positively correlated with CD8 + T-cell infiltration, median overall survival (OS), and recurrence-free survival, and inversely correlated with the abundance of tumor-infiltrating Tregs[49]. In mouse models of PDAC, blockade of the TGF-β1 receptor promoted the polarization of neutrophils into an anti-tumor N1 phenotype, thus enhancing the response of tumors to the combination treatment with irreversible electroporation (which ablates tumors by inducing irreversible membrane destruction of cells) and anti-PD-1[50].

Mast cells. Mast cells, like neutrophils and macrophages, originate from myeloid progenitor cells. Compared with normal tissues, PDAC tissues exhibit a significant increase in infiltration by mast cells, which promote the proliferation and invasion of pancreatic cancer cells and contribute to chemotherapy resistance[51–54]. The exact role and mechanisms by which mast cells regulate tumor immunity in PDAC are not fully understood. Nevertheless, it is worth noting that in preclinical models of melanoma, combining anti-PD-1 therapy with the depletion of mast cells resulted in tumor regression[55], suggesting that mast cells may suppress the immune response and limit the efficacy of immunotherapies.

Treg cells

Treg cells are a specialized subset of T cells that modulate effector T cells. The abundance of FOXP3+ Treg cells within pancreatic tumors increases during PDAC progression and correlates with poor survival[56–58]. The immunomodulatory effect of Treg cells has been studied in different models[59,60]. Bar-Sagi and colleagues[61] reported that Treg cells inhibit the function of dendritic cells through direct contact, leading to the down-regulation of dendritic cell-derived costimulatory ligands that are crucial for CD8 + T-cell activation in PDAC. This study also demonstrated that the elimination of Treg cells induced an effective anti-tumor immune response in mice bearing orthotopic pancreatic tumors derived from a KPC model (expressing mutant forms of Kras and Trp53)[61]. On the other hand, however, Pasca di Magliano and colleagues[62] reported that the removal of Treg cells accelerated tumor progression by reprogramming cancer-associated fibroblasts in genetically engineered mouse models of PDAC. The conflicting results from orthotopic and autochthonous models indicate context-dependent crosstalk between Tregs and other cell types in pancreatic cancer TME.

B cells

Plasma cells, a subtype of terminally differentiated B cells, play an essential role in amplifying anti-tumor immune responses through antibody production. However, in PDAC patients and tumor-bearing mice, cancer can induce differentiation of naïve B cells into regulatory B cells (as opposed to plasma cells) through Bruton tyrosine kinase (BTK) signaling, which results in a reduction in tumor-infiltrating cytotoxic T cells, thereby contributing to immune evasion[63,64]. In addition, BTK induces the programming of T(H)2-type macrophages and diminishes CD8 + T-cell cytotoxicity by facilitating the communication between B cells and TAMs in PDAC[65]. Furthermore, extensive research has advanced the understanding of the mechanisms of immunosuppression induced by B cells and IL-35[63,66–69]. Targeting B cells through molecular blockade has shown promise in reducing tumor growth and disease progression, presenting a therapeutic strategy for treating PDAC in combination with immunotherapy[63–65,68–71].

Stromal cells and extracellular matrix (ECM)

PDAC is characterized by extensive desmoplasia, where fibroblasts are the major cell type[72]. A subset of fibroblasts (myofibroblasts), along with tumor cells and macrophages, can produce a dense fibrotic matrix composed of ECM proteins, thereby influencing the progression of PDAC and its response to treatment[73–75]. The excessive desmoplastic stroma limits the penetration of tumors by drugs and cytotoxic CD8 + T cells[76]. Addressing this challenge, enzymatic degradation of hyaluronic acid (HA) has been shown to alleviate desmoplastic pressure. This approach not only expands the microvasculature but also contributes to a 2-fold increase in overall survival in mouse models when combined with chemotherapy[77,78]. In human PDAC tissues, elevated focal adhesion kinase (FAK) activity correlates with increased fibrosis and poor CD8 + T-cell infiltration[79]. Treatment with a FAK inhibitor led to a reduction in fibrosis and tumor-associated immunosuppressive cells, sensitizing the p48-Cre;LSL-$Kras^{G12D/+}$;$Trp53^{flox/+}$ mouse model of PDAC to T-cell immunotherapy and immune checkpoint inhibitors[79]. Furthermore, combining HA degradation with FAK inhibition promoted the survival of PDAC-bearing mice treated with an anti-PD-1 antibody[80]; notably, this combination treatment enhanced T-cell infiltration while concurrently reducing MDSCs.

Besides producing dense ECM, CAFs interact with immune cells and induce immune suppression through secreted factors such as IL-6, CXCL12, granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage colony-stimulating factor (M-CSF)[81,82]. The removal of CAFs expressing fibroblast activation protein (FAP) has been shown to inhibit tumor growth and enhance the efficacy of anti-CTLA-4 and anti-PD-L1 antibodies in mouse models of PDAC[83]. On the other hand, however, depletion of alpha smooth muscle actin (αSMA)-positive CAFs hampers immune surveillance, leading to an increase in Treg cells and shorter survival in mice with PDAC[84]. Taken together with other studies[73,74,85–87], these findings underscore the functional heterogeneity of CAFs. CAFs can be classified into inflammatory CAFs (iCAFs), αSMA + myofibroblasts (myCAFs), and antigen-presenting CAFs (apCAFs), with a small subset of CAFs being derived from pancreatic stellate cells[74,87,88]. While apCAFs support immune evasion by inducing expansion of Treg cells[89], the pro-tumor role of iCAFs is associated with the cytokine IL-6, which suppresses anti-tumor immunity by eliciting metabolic stress and dendritic cell apoptosis[90,91]. Moreover, induction of iCAFs by IL-17A-producing CD8 + T cells promotes PDAC progression and is associated with a poor prognosis[92]. myCAFs are the major source of type I collagen in the PDAC stroma, and depletion of type I collagen leads to upregulation of Cxcl5 in tumor cells, which promotes the recruitment of MDSCs and dysfunction of CD8 + T cells, thereby accelerating pancreatic cancer progression and decreasing survival[93]. Intriguingly, whereas intact type I collagen triggers degradation of discoidin domain receptor 1 (DDR1) and impedes PDAC, matrix-metalloprotease-cleaved type I collagen promotes PDAC growth by activating the DDR1–NF-κB–NRF2 axis[94].

Stroma-modulating drugs have shown the potential to enhance the efficacy of ICB therapy in preclinical models of PDAC. For instance, combination treatment with the sonic hedgehog inhibitor cyclopamine and the chemotherapeutic drug paclitaxel increased the infiltration of CD8 + T cells into tumors. A synergistic effect of this combination with anti-PD-1 therapy was observed in both orthotopic and genetically

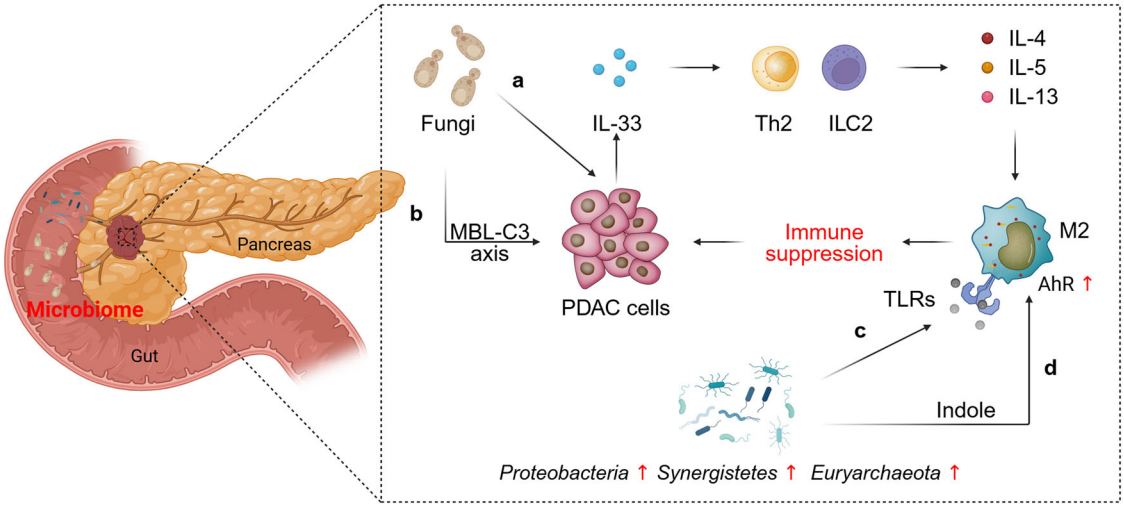

Fig. 2 | The microbiome associated with immune suppression in PDAC TME. **a** Intratumoral fungus-mediated IL-33 secretion by PDAC cells recruits and activates Th2 cells and innate lymphoid cells 2 (ILC2), which stimulate tumor growth by secreting pro-tumorigenic cytokines such as IL-4, IL-5, and IL-13. **b** Pathogenic fungi promote PDAC progression by driving the complement cascade via a mannose-binding lectin (MBL)–C3 axis. **c** *Proteobacteria*, *Synergistetes*, and *Euryarchaeota* are enriched in PDAC patients, reprogramming TAM toward a pro-tumor M2-like phenotype through Toll-like receptors (TLRs). (**d**) *Lactobacillus*-derived indole fosters TAM polarization toward an immune-suppressive phenotype through the aryl hydrocarbon receptor (AhR). Figure created with BioRender.com.

engineered mouse models of PDAC[76]. More recently, the combination of MEK inhibitor (MEKi) with STAT3 inhibitor (STAT3i) demonstrated promising results in mitigating the polarization of iCAFs and enriching CAFs with mesenchymal stem cell-like features. The resulting stroma remodeling facilitated the M2-to-M1 reprogramming of TAMs, improved the trafficking of CD8 + T cells, and impeded the infiltration of myeloid cells[95]. When the MEKi + STAT3i combination was added to anti-PD-1 treatment, prolonged survival was observed in PDAC-bearing mice compared with anti-PD-1 treatment alone. These findings suggest that targeting the stromal components holds promise as a strategy to overcome immunotherapy resistance in PDAC. The exploration of stroma-modulating drugs in combination with immunotherapies may pave the way for improved treatment outcomes.

Microbiome

Recent studies have implicated the microbiome in the pathogenesis and immune suppression in PDAC[96,97]. The gut microbiome can translocate into pancreatic cancer tissues, modulating the tumor microbiome and altering the immune landscape of TME[97,98] (Fig. 2). Ablation of the gut microbiome by oral antibiotics has been shown to reverse the immunosuppressive TME. This reversal is characterized by an increase in anti-tumor interferon-γ-producing T cells, Th1 cells, and M1 macrophages, as well as a decrease in pro-tumor IL-17a- and IL-10-producing T cells and MDSCs, thereby enhancing the efficacy of ICB therapy[97,99]. Moreover, fungus-dependent IL-33 secretion by PDAC cells plays a role in recruiting and activating Th2 cells and innate lymphoid cells 2 (ILC2)[100]; these cells, in turn, contribute to immune suppression by secreting pro-tumorigenic cytokines. In addition, pathogenic fungi can promote PDAC progression via a mannose-binding lectin (MBL)–C3 axis[96]. It has also been reported that compared with healthy individuals, *Proteobacteria*, *Synergistetes*, and *Euryarchaeota* are enriched in PDAC patients, reprograming TAMs toward a pro-tumor M2-like phenotype through Toll-like receptor (TLR) signaling[97]. Intriguingly, *Lactobacillus* metabolization of dietary tryptophan fosters TAM polarization toward an immune-suppressive phenotype through the aryl hydrocarbon receptor, accelerating PDAC progression[101].

Collectively, these findings highlight the complex relationship between the microbiome and the immune response in PDAC, opening up potential avenues for therapeutic interventions. For instance, the delivery of gut microbiome-derived metabolite trimethylamine *N*-oxide (TMAO) has been shown to enhance anti-tumor immunity and restrain tumor growth in orthotopic models of PDAC. When combined with anti-PD-1 therapy, TMAO delivery led to a significant reduction in tumor burden and prolonged survival compared with treatment with TMAO or ICB alone[102]. In a study led by McAllister and colleagues[98], analysis of the tumor microbiome in PDAC patients by using 16S rRNA gene sequencing revealed higher microbial diversity in patients with longer survival. Notably, human-to-mice fecal microbiota transplants from control, long-term survival, or short-term survival donors differentially modulated the tumor microbiome, tumor growth, and tumor immune infiltration[98]. Furthermore, a metagenomic analysis uncovered specific microbiome species associated with PDAC, including enrichment of *Streptococcus* and *Veillonella spp* and depletion of *Faecalibacterium prausnitzii*[103]. This study suggests that microorganisms could serve as potential sources of biomarkers for pancreatic cancer. It should be noted that recent re-analyses of previously reported pan-cancer microbial composition data have identified significant pitfalls, including contamination, false positive classifications, problematic handling of batch effects, and limitations in the machine learning approaches used[104], which warrant corrections and future improvement.

Immune features of PDAC metastases

The liver and lung are the common sites of metastasis in patients with PDAC[105,106]. In general, patients with liver metastases have a poorer prognosis compared with those with lung metastases, indicating inherent disparities between these metastatic sites[105,106]. In mouse models of metastatic PDAC, significant differences were observed in the TME between the liver and the lung: whereas the liver exhibited immunosuppressive characteristics, the lung TME showed high levels of immune infiltration and activated immune signaling[105]. Using cytometry by time-of-flight, Jaffee, Fertig, and colleagues analyzed a mouse model of metastatic PDAC and found a reduction in dendritic cells, NK cells, cytotoxic T cells, and Th cells in the TME of liver metastases relative to those present in lung metastases[105]. Moreover, significant enrichment of PD-L1 and LAG3 was observed in the hepatic TME, along with higher levels of pro-tumorigenic chemokines such as CCL5, CCL22, and CXCL12 relative to the lung. In contrast, immune-activating chemokines, such as CXCL9 and CXCL10, were found to be enriched in lung metastases relative to liver metastases[105].

A recent investigation of patient samples revealed significant immune heterogeneity in PDAC recurrences across various sites including the liver, lung, peritoneum, and local areas[106]. This study demonstrated low immunogenicity, stemness, and innate immune responses in patients with liver

and/or peritoneal recurrences, contrasting with notable interferon-γ signaling and mixed adaptive and innate immune responses in PDACs with local and/or lung recurrences. In addition, accumulation of P2RX1-negative neutrophils was found in PDAC liver metastases, alongside various suppressive cells such as macrophages and fibroblasts, which promote metastatic progression in the liver[107–109]. Furthermore, JAK-STAT–dependent macrophage-fibroblast crosstalk was reported to facilitate liver metastatic outgrowth in PDAC. Notably, pharmacological inhibition of STAT3 or myofibroblastic metastasis-associated fibroblast (myMAF)-specific genetic depletion of STAT3 restored anti-tumor immunity and reduced liver metastases[109].

TME differences among various mouse models of pancreatic cancer

Patient-derived xenograft (PDX) models, syngeneic mouse models, and genetically engineered mouse models (GEMMs) are widely used in pancreatic cancer research and preclinical drug testing[110]. It is important to recognize that these models exhibit distinct TMEs, necessitating careful selection based on the specific experimental objectives in preclinical studies. Moreover, there is a critical need to emphasize comparative validation across multiple models to ensure the robustness and reproducibility of findings.

Cell line-derived xenograft and PDX models of pancreatic cancer are widely used for gene function studies and evaluation of therapeutic approaches[111]. These models are categorized based on the implantation site into orthotopic and subcutaneous models. Subcutaneous models facilitate non-surgical implantation of tumor cells or tissue fragments, whereas orthotopic models, despite being more technically challenging to establish, better recapitulate tumor growth in the natural tissue microenvironment compared with subcutaneous models. It is important to note that PDX models require immunodeficient mice (typically nude mice, SCID mice, or NOD-SCID mice) to prevent immune rejection of human-derived xenografts. However, this immunodeficiency limits their utility for studying the immune cell composition of tumors or evaluating immunotherapy efficacy. Addressing this limitation, humanized mouse models have been developed for immunotherapy studies. For example, Chang and colleagues[112] isolated $CD34^+$ hematopoietic stem cells from human umbilical cord blood and injected them into 3- to 4-week-old NSG mice to establish a humanized model. Treatment with siRNA nanoparticles targeting PD-L1 upregulated interferon-γ-positive CD8 + T cells and inhibited pancreatic tumor growth in this model, underscoring the potential of humanized PDAC PDX models for advancing immunotherapy research.

Syngeneic mouse models of PDAC involve implanting immunologically compatible cancer cells or tissues into mice with an intact immune system, which distinguishes them from xenograft models. These models can also be established through subcutaneous or orthotopic implantation[110]. Orthotopic tumors actively interact with the tissue microenvironment, providing a more physiologically relevant model. However, due to the technical challenges associated with orthotopic models, subcutaneous models remain commonly used in preclinical drug trials. It should be noted that cell line- or model-dependent effects are often observed. For example, in a study investigating the potential of a CD47 monoclonal antibody to enhance the response of PDAC to ICIs, combination therapy targeting CD47 and PD-L1 showed synergistic inhibition of tumor growth in the Panc02 but not in the MPC-83 syngeneic mouse model[113]. This indicates that treatment responses may vary between models derived from different PDAC cell lines. scRNA-seq analysis revealed that anti-CD47 treatment reshaped the intratumoral lymphocyte and macrophage populations in Panc02 tumor-bearing mice, resulting in increased intratumoral CD8 + T cells, more active T-cell clusters, enhanced anti-tumor pro-inflammatory macrophages, and reduced anti-inflammatory macrophages[113]. These findings underscore the suitability of specific syngeneic models with intact immune systems for investigating the intratumoral immune microenvironment and conducting preclinical trials of immunotherapy.

GEMMs allow immunocompetent mice to spontaneously develop pancreatic cancer, eliminating the need for exogenous implantation methods. They have become indispensable for evaluating various therapeutic strategies[111]. Among these models, the LSL-$Kras^{G12D/+}$;$Trp53^{flox/flox}$;Pdx-1-Cre (KPC) model is a commonly used GEMM capable of generating spontaneous pancreatic tumors that closely mimic human PDAC, with features including prominent connective tissue hyperplasia, abnormal vascular distribution, and high metastatic potential. These tumors also exhibit extensive infiltration of immunosuppressive macrophages and low numbers of effector T cells[110]. Studies on KPC mice have demonstrated that CD40 activation induces tumor regression through a T-cell-independent mechanism. This finding aligns with histological analyses of human tumors treated with a combination of CD40 agonists and gemcitabine. However, these results differ from those observed in the implantable KPC model[114,115], suggesting that GEMMs may be more similar to humans in terms of the TME and the mechanisms of immunotherapy response. This highlights the importance of model selection.

In conclusion, various PDAC mouse models exhibit significant differences in TME and response to immunotherapy. For preclinical experiments, selecting models with intact immune function, tumor pathological features, and microenvironments similar to those of humans is important for studying pancreatic carcinogenesis, metastasis, and immunotherapeutic strategies.

Pancreatic cancer cell-intrinsic factors contributing to immunotherapy resistance

In addition to the immunosuppressive TME of PDAC cells, tumor-intrinsic features also contribute to immune evasion (Fig. 3). KRAS mutations are present in more than 95% of PDAC[116], among which the major mutations are G12D (40%), G12V (33%), and G12R (15%)[117] (Fig. 3a). Downstream signaling pathways and metabolic networks in mutant KRAS (mKRAS)-driven tumors play a pivotal role in immune suppression and tumor progression[116,117]. For instance, mKRAS leads to upregulation of CXCL1, CXCL5, and GM-CSF through NF-κB, PI-3K, or MAPK pathways, fostering the proliferation, maturation, and recruitment of immunosuppressive myeloid cells[33,118,119]. Moreover, mKRAS boosts PD-L1 expression on tumor cells through p38 and MAPK pathways, thereby activating the PD-1/PD-L1 checkpoint and causing T-cell exhaustion[24,120]. In addition, mKRAS modulates the tumor cell metabolism, increasing glucose uptake, and aerobic glycolysis, as well as the production of reactive oxygen species (ROS)[121,122]. ROS, in turn, mediates mKRAS-induced PD-L1 expression through FGFR1 signaling[122]. It has also been shown that mKRAS recruits immunosuppressive IL-17-producing T cells[35] and promotes the formation and maintenance of fibro-inflammatory stroma[123].

Activation of WNT signaling is often observed in pancreatic cancer[124,125] (Fig. 3b). In PDAC, WNT pathway activation is associated with the aberrant expression of WNT ligands. Moreover, a subset of PDAC tumors carry mutations in *RNF43*, which encodes ring finger 43, a ubiquitin ligase that inhibits WNT signaling by ubiquitinating FZD receptors and LRP5/6 co-receptors, leading to their internalization and lysosomal degradation[126,127]. The loss of RNF43 in a genetically engineered mouse model of PDAC accelerated tumor progression and upregulated regulatory T-cell immune checkpoint molecules, which could be a potential mechanism of immune evasion[128]. In addition, lncRNA-mediated inhibition of β-catenin degradation has been observed in pancreatic cancer cells[129,130]. Although current evidence indicates that WNT pathway activation is immunosuppressive in PDAC, the role of WNT–β-catenin signaling in regulating cancer immunosurveillance may be cancer-type-dependent[131].

In addition to KRAS mutation and RNF43 loss, downregulation of major histocompatibility complex class I (MHC-I) contributes to immune evasion and immunotherapy resistance due to impaired antigen presentation. Kimmelman and colleagues[132] demonstrated that in pancreatic cancer cells, an autophagy-dependent mechanism, involving the autophagy cargo receptor NBR1, targets MHC-I molecules for lysosomal degradation. A subsequent study revealed that progranulin from tumor cells (not macrophages) correlates with poor overall survival in PDAC. Inhibition of progranulin effectively halted autophagy-dependent degradation of MHC-I and

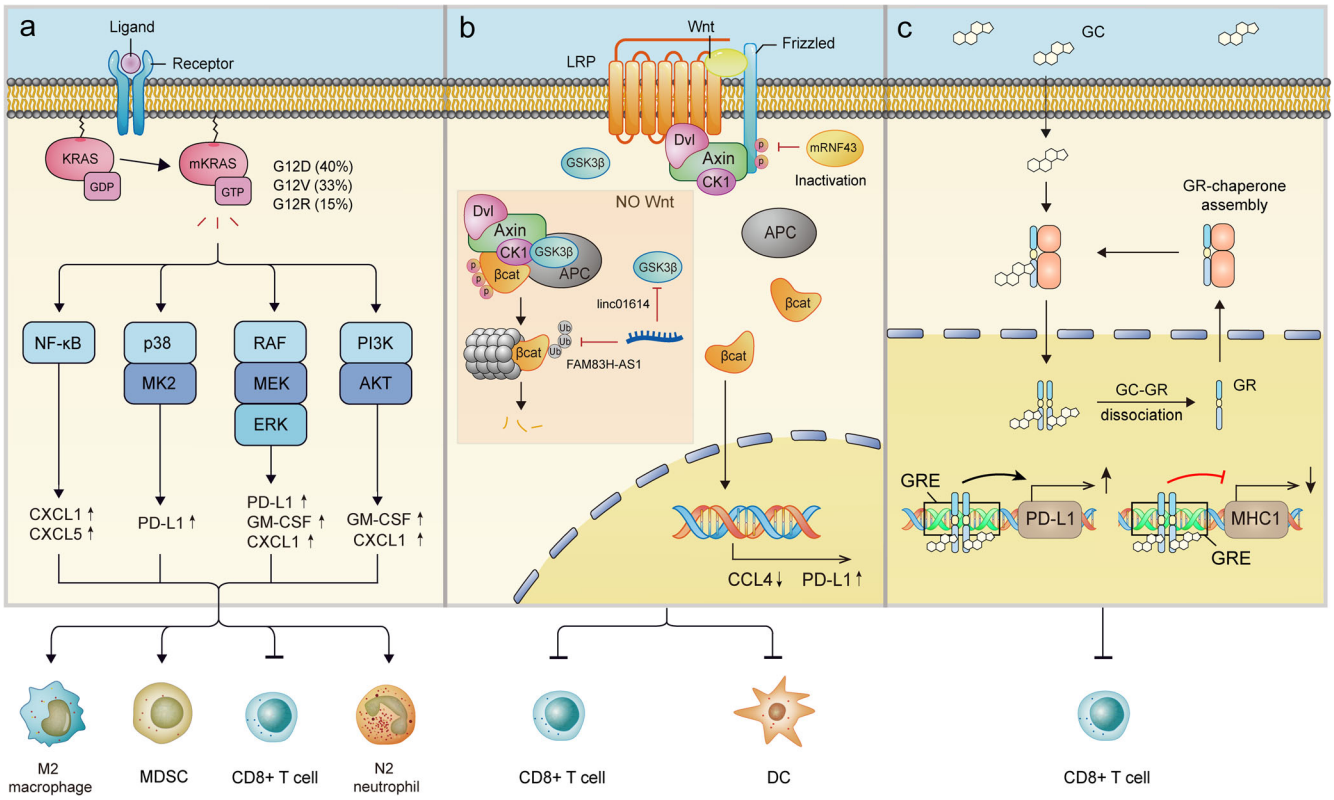

Fig. 3 | Tumor-intrinsic signaling pathways associated with immune evasion in PDAC. a Mutated KRAS (mKRAS), which is permanently bound to GTP, constitutively activates downstream signaling pathways, resulting in PD-L1 overexpression and the recruitment of immunosuppressive cells to pancreatic tumors. **b** Aberrant activation of the WNT–β-catenin pathway, which can be caused by mutation of RNF43 or lncRNA-mediated inhibition of β-catenin degradation, reduces dendritic cell recruitment by downregulating CCL4 and upregulating PD-L1 expression. **c** Lipophilic glucocorticoids (GCs) diffuse through the cell membrane and bind to the glucocorticoid receptor (GR) in the cytoplasm of PDAC cells. This binding induces a change in the chaperone complex bound to GR, leading to its translocation into the nucleus. Once in the nucleus, GR activates PD-L1 expression and represses MHC-1 expression by binding to glucocorticoid response elements (GREs), ultimately leading to the reduction in the abundance and effector function of tumor-infiltrating CD8 + T cells.

restored MHC-I expression in pancreatic cancer cells. Moreover, antibody-based progranulin blockade in a mouse model of PDAC impeded the initiation and progression of tumors[133]. Glucocorticoid receptor (GR) signaling was thought to suppress immunity by acting on immune cells[134]. In a recent study, our laboratory uncovered a new role of GR as a transcriptional activator of PD-L1 and a transcriptional repressor of MHC-I in pancreatic cancer cells[135] (Fig. 3c). In preclinical models, either genetic depletion or pharmacological inhibition of GR promoted the infiltration and effector function of cytotoxic T cells, leading to enhanced immune surveillance and sensitization of pancreatic tumors to ICIs[135]. These findings highlight GR signaling in pancreatic cancer cells as a tumor-intrinsic mechanism of immune suppression and suggest that therapeutic intervention targeting GR holds promise for improving the responsiveness of pancreatic cancer to immunotherapy. Furthermore, it should be noted that p53, which is frequently altered in PDAC, has been shown to promote antigen processing and MHC-1 surface expression[136,137]. Both aspects of antigen presentation are downregulated in p53-null and p53-mutant cancer cells[136,137].

Metabolic enzymes have crucial roles in multiple aspects of cancer, including tumorigenesis, progression, metastasis, and therapy resistance. Recently, Sherman and colleagues[138] reported that pancreatic cancer cell-intrinsic glutamic-oxaloacetic transaminase 2 (GOT2), a key player in the malate-aspartate shuttle, remodels TME to suppress anticancer immunity[138]. Mechanistically, GOT2 promotes the transcriptional activity of nuclear receptor peroxisome proliferator-activated receptor delta (PPARδ) to restrict CD4+ and CD8 + T-cell infiltration of the TME, revealing a non-canonical function for this metabolic enzyme[138]. Moreover, Zhang and colleagues[139] showed that deficiency in quinoid dihydropteridine reductase orchestrates a series of events culminating in the recruitment of MDSCs, which ultimately induce immunosuppression in PDAC. In addition, pancreatic cancer cells can impair NK cell activity by competitively depleting vitamin B6, thereby compromising anti-tumor immunity[140]. Interestingly, metabolism-focused CRISPR screens have identified genes linked to immune evasion in PDAC, including *Tap1*, *Tapbp*, and the autophagy gene *Atg7*[141]. Furthermore, tumor cell-intrinsic deficiency in the epigenetic regulator SETD2 has been shown to promote tumor progression through two mechanisms: 1) by enhancing mitochondrial oxidative phosphorylation through interactions with a subset of lipid-rich CAFs[142], and 2) by boosting recruitment of immunosuppressive neutrophils through activation of the PI3K-AKT pathway[143].

Reprogramming cancer microbiome has been linked to immune evasion, particularly in PDAC. The collagen I (Col1) homotrimer produced by pancreatic cancer cells fosters oncogenic signaling by binding to α3β1 integrin, resulting in the development of a tumor microbiome abundant in anaerobic Bacteroidales in hypoxic and immunosuppressive TME[144]. Deleting Col1 homotrimers in a mouse model of PDAC yielded significant benefits, including increased overall survival, enhanced T-cell infiltration, and improved responsiveness to anti-PD-1 immunotherapy[144].

Therapeutic strategies and clinical trials of pancreatic cancer immunotherapies

Despite a number of breakthroughs in immunotherapies for multiple cancer types, their clinical utility in PDAC, whether administered as monotherapy or in combination with other therapies, has been insufficient. Nevertheless, extensive preclinical studies and clinical trials have provided valuable insights. In this section, we discuss three types of immunotherapeutic strategies for pancreatic cancer treatment (Table 3): (i) targeting myeloid

Table 3 | Clinical trials targeting immune cells or stroma in PDAC

Target	Targeted therapy	Immunotherapy	Chemotherapy or radiotherapy	Phase	NCT Number	Patient population	Status/results
Myeloid cell	GB1275 (CD11b)	Pembrolizumab (PD-1)	Gemcitabine, nab-paclitaxel	1	NCT04060342	Untreated advanced or metastatic cancers including PDAC	Terminated for no clear benefit of GB1275
	IMC-CS4 (CSF-1R)	Pembrolizumab (PD-1), GVAX	Cyclophosphamide	1	NCT03153410	Previously treated borderline resectable or locally advanced PDAC	Completed. Awaiting results
	Pexidartinib (CSF-1R)	Durvalumab (PD-L1)	N/A	1	NCT02777710	Metastatic/ advanced pancreatic or colorectal cancers	Completed. Awaiting results
	Cabiralizumab (CSF-1R)	Nivolumab (PD-1)	N/A	1	NCT02526017	Advanced or metastatic cancers including PDAC	ORR 6.0%, mOS 5.6 months, mPFS 1.7 months
		Nivolumab (PD-1)	Gemcitabine, nab-paclitaxel, FOLFOX	2	NCT03336216	Previously treated advanced or metastatic PDAC	No increase in PFS
	PF-04136309 (CCR2)	N/A	FOLFIRINOX	1/2	NCT01413022	Locally advanced or borderline resectable PDAC	49% ORR and 97% DCR compared with 0% ORR and 80% DCR in the FOLFIRINOX alone group
		N/A	Gemcitabine, nab-paclitaxel	2	NCT02732938	Untreated metastatic PDAC	Terminated
	BMS-813160 (CCR2/5)	Nivolumab (PD-1), GVAX	SBRT	1/2	NCT03767582	Untreated unresectable, locally advanced PDAC	Recruiting
		Nivolumab (PD-1)	Gemcitabine, nab-paclitaxel	1/2	NCT03496662	Locally advanced PDAC	Active. Not recruiting
		Nivolumab (PD-1)	FOLFIRI, gemcitabine, nab-paclitaxel	1/2	NCT03184870	Advanced or metastatic cancers including PDAC	Completed. Awaiting results
	AZD5069 (CXCR2)	MEDI4736 (PD-L1)	N/A	1/2	NCT02583477	Metastatic PDAC	ORR 5.6%, OS 2.8 months, PFS 1.6 months
	SX-682 (CXCR1/2)	Nivolumab (PD-1)	N/A	1	NCT04477343	Metastatic PDAC	Recruiting
Dendritic cell	Mitazalimab (CD40)	MesoPher	N/A	1	NCT05650918	Previously treated metastatic PDAC	Completed. Awaiting results
	CDX-30 (FLT3), CDX-1140 (CD40)	N/A	N/A	2	NCT04536077	Resectable PDAC	Terminated
		Pembrolizumab (PD-1)	Gemcitabine, nab-paclitaxel	1	NCT03329950	Locally advanced or metastatic cancers including PDAC	Completed. Awaiting results
Macrophage	CP-870,893 (CD40)	N/A	Gemcitabine	1	NCT00711191	Untreated advanced PDAC	mOS 8.4 months, mPFS 5.3 months
	APX005M (CD40)	Nivolumab (PD-1)	Gemcitabine, nab-paclitaxel	1/2	NCT03214250	Untreated metastatic PDAC	1-year OS was met for nivo/chemo but was not met for sotiga/chemo or sotiga/nivo/chemo
	NG-350A (CD40)	Ipilimumab (CTLA-4)	Gemcitabine, nab-paclitaxel	1	NCT04787991	Untreated metastatic PDAC	Active. Not recruiting
	ASTX660 (cIAP1/2)	Pembrolizumab (PD-1)	N/A	1	NCT05082259	Advanced solid tumors including PDAC	Recruiting
	SGN-CD47M (CD47)	N/A	N/A	1	NCT03957096	Solid tumors including pancreatic cancer	Terminated
	PT886 (CD47 and claudin 18.2)	N/A	N/A	1	NCT05482893	Unresectable or metastatic PDAC	Recruiting
B cell	Ibrutinib (BTK)	N/A	Gemcitabine, nab-paclitaxel	1/2	NCT02562898	Metastatic PDAC	mOS 246 days, mPFS 128 days
		N/A	Gemcitabine, nab-paclitaxel	3	NCT02436668	Untreated metastatic PDAC	No improvement in mOS (9.7 vs 10.8 months; P = 0.3225); reduced PFS (5.3 vs 6.0 months; P = 0.0001) and ORR (29% vs 42%; P = 0.0058) compared with standard chemotherapy

Table 3 (continued) | Clinical trials targeting immune cells or stroma in PDAC

Target	Targeted therapy	Immunotherapy	Chemotherapy or radiotherapy	Phase	NCT Number	Patient population	Status/results
Stroma	PEGPH20 (HA)	N/A	mFOLFIRINOX	1/2	NCT01959139	Untreated metastatic PDAC	Increased toxicity; OS 7.7 months compared with 14.4 months in the mFOLFIRINOX control arm
		N/A	Gemcitabine, nab-paclitaxel	2	NCT01839487	Untreated metastatic PDAC	No improvement in ORR and OS. Moderately improved PFS
		N/A	Gemcitabine, nab-paclitaxel	3	NCT02715804	Untreated HA-high metastatic PDAC	Terminated
		Pembrolizumab (PD-1)	N/A	2	NCT03634332	Previously treated HA-High metastatic PDAC	Unknown
Stroma	Defactinib (FAK)	Pembrolizumab (PD-1)	N/A	2	NCT03727880	Resectable PDAC	Recruiting
			N/A	1	NCT02546531	Advanced cancers including PDAC	No PR or CR observed. Increased T-cell infiltration
			N/A	1/2	NCT02758587	Advanced solid tumors including PDAC	Unknown
	Ruxolitinib (JAK-STAT)	N/A	Capecitabine	2	NCT01423604	Previously treated metastatic PDAC	Signficant improvement in OS (HR, 0.47, P = 0.011) in patients with systemic inflammation (C-reactive protein [CRP] >13mg/dL)
		N/A	Capecitabine	3	NCT02117479	Previously treated advanced or metastatic PDAC	Terminated early based on the results of the interim analysis
		N/A	Capecitabine	3	NCT02119663	Previously treated advanced or metastatic PDAC	Terminated based on a lack of efficacy in a similar trial
	Ruxolitinib (JAK-STAT), trametinib (MEK)	Retifanlimab (PD-1)	N/A	1	NCT05440942	Metastatic PDAC	Recruiting
	LY2510924 (CXCR4)	Durvalumab (PD-L1)	N/A	1	NCT02737072	Previously treated advanced cancers including PDAC	Terminated
	BMS-936564 (CXCR4)	Nivolumab (PD-1)	N/A	1/2	NCT02472977	Previously treated advanced cancers including PDAC	Terminated for lack of efficacy
	BL-8040 (CXCR4)	Pembrolizumab (PD-1)	Onivyde	2	NCT02826486	Previously treated metastatic unresectable PDAC	ORR 32%, DCR 77%, DOR 7.8 months
			N/A	2	NCT02907099	Previously treated metastatic PDAC	Completed. Awaiting results

FLT3 fms-like tyrosine kinase 3, *cIAP1/2* cellular inhibitor of apoptosis proteins 1 and 2, *BTK* bruton tyrosine kinase, *HA* hyaluronic acid, *FAK* focal adhesion kinase, *JAK-STAT* Janus kinase-signal transducer and activator of transcription, *FOLFIRINOX* 5-fluorouracil, leucovorin, irinotecan and oxaliplatin, *SBRT* stereotactic body radiation, *FOLFIRI* 5-fluorouracil, leucovorin and irinotecan, *MesoPher* autologous monocyte-derived dendritic cells loaded with tumor lysate, *mFOLFIRINOX* modified FOLFIRINOX, *N/A* not available, *ORR* objective response rate, *DCR* disease control rate, *OS* overall survival, *PFS* progression-free survival, *PR* partial response, *CR* complete response, *DOR* duration of response, *HR* hazard ratio.

cells, dendritic cells, or B cells to enhance T-cell trafficking and anti-tumor responses; (ii) reprogramming macrophages to be tumoricidal; and (iii) remodeling stroma cell and ECM.

Targeting myeloid cells

The reduction of immunosuppressive myeloid cells in the TME can be achieved by blocking the chemokine-receptor axis in these cells, resulting in diminished infiltration of myeloid cells. Targeting CD11b, CSF-1R, CCR2/5, and CXCR1/2 has emerged as therapeutic strategies.

CD11b is an integrin molecule expressed on myeloid cells, playing a role in chemotaxis and cellular functions. In preclinical studies, the administration of a small-molecule agonist of CD11b led to a reduction in suppressive myeloid cell infiltration and repolarization of TAMs toward an anti-tumor phenotype, thereby eliciting a T-cell response. This treatment also showed an enhancement in the therapeutic effects of an anti-PD-1 antibody[145]. However, a clinical trial (NCT04060342) investigating the combination of the CD11b agonist (GB1275) with gemcitabine, nab-paclitaxel, and pembrolizumab (an anti-PD-1 antibody) was terminated due to the lack of a clear benefit in PDAC patients when GB1275 was used either as a monotherapy or in combination with pembrolizumab[146].

In an orthotopic model of PDAC, blocking CSF-1R not only reduced TAM infiltration but also reprogrammed TAMs to enhance T-cell activation, resulting in increased efficacy of anti-PD-1 and anti-CTLA-4[147]. Unfortunately, clinical trials combining an anti-CSF-1R antibody with immunotherapy for PDAC treatment have not yielded satisfactory results thus far. For example, a phase 1a/b single-arm study combining the anti-CSF-1R antibody cabiralizumab with PD-1 blockade (nivolumab) demonstrated discouraging outcomes with an objective response rate (ORR) of 6.0%, a median overall survival (OS) of 5.6 months, and a median progression-free survival (PFS) of 1.7 months (NCT02526017)[148]. Moreover, a phase 2 clinical study evaluating cabiralizumab in combination with nivolumab and chemotherapy did not improve PFS in patients with advanced PDAC (NCT03336216)[6,149]. Currently, several ongoing trials are testing the combination of small-molecule CSF-1R inhibitors with immunotherapy in pancreatic cancer. One such trial is a dose escalation phase 1 study evaluating the safety and efficacy of a small-molecule CSF-1R inhibitor (pexidartinib) combined with an anti-PD-L1 antibody (durvalumab) in patients with metastatic/advanced pancreatic or colorectal cancer (NCT02777710)[150].

Chemokine receptors, CCR2/5 and CXCR2, play a crucial role in facilitating myeloid cell infiltration into the TME[43,48]. Blocking these pathways has emerged as a potential strategy to overcome immunosuppression. A phase 1b trial investigating the combination of the CCR2 inhibitor PF-04136309 with FOLFIRINOX not only demonstrated safety but also yielded an ORR of 49% and a disease control rate (DCR) of 97%, surpassing the 0% ORR and 80% DCR observed in the FOLFIRINOX alone group[151]. However, a phase 2 trial of PF-04136309 in combination with gemcitabine and nab-paclitaxel was terminated due to toxicity and a lack of superior efficacy compared with the gemcitabine plus nab-paclitaxel group[152]. Several early-phase clinical trials combining BMS-813160 (a CCR2/5 dual antagonist) with ICIs and chemotherapy or vaccines are underway (Table 3). Meanwhile, targeting CXCR2 with AZD5069 in combination with an anti-PD-L1 antibody in patients with metastatic PDAC resulted in disappointing results, with an ORR of 5.6%, OS of 2.8 months, and PFS of 1.6 months (NCT02583477)[153]. Currently, an early-phase clinical trial investigating a CXCR1/2 dual inhibitor (SX-682) plus an anti-PD-1 antibody (nivolumab) is recruiting patients with metastatic pancreatic cancer (NCT04477343)[154].

Targeting dendritic cells

Pancreatic cancer often exhibits a paucity and dysfunction of dendritic cells, which underlies poor infiltration and effector function of T cells[90,155,156]. Restoring dendritic cells in PDAC might enhance anti-tumor immunity. CD40, a member of the tumor necrosis factor (TNF) receptor superfamily, holds the capacity to license dendritic cells for promoting anti-tumor T-cell activation[157]. Several formulations of agonistic CD40 antibodies have undergone testing in preclinical and clinical settings, demonstrating tolerability and feasibility. DeNardo and colleagues[156] engineered a neoantigen-expressing mouse model of PDAC and showed that enhancing dendritic cell infiltration and activity using FLT3 ligand along with an agonistic CD40 antibody resulted in increased intratumoral CD8+ cells and prolonged survival when combined with radiation therapy. Currently, early-phase clinical trials are in progress, evaluating the combination of the agonistic CD40 antibody and FLT3 ligand with anti-PD-1, gemcitabine, and nab-paclitaxel for treating pancreatic cancer and other advanced cancers (e.g., NCT03329950)[158].

Dendritic cell vaccination has emerged as a strategy to enhance anti-tumor immunity[159]. In a syngeneic Panc02 model of pancreatic cancer, combining dendritic cell-based vaccination with gemcitabine significantly improved the survival of tumor-bearing mice compared with vaccination or gemcitabine alone[160]. Moreover, the combination of an allogeneic tumor lysate-loaded dendritic cell vaccine with an agonistic CD40 antibody significantly increased survival in a mouse model of pancreatic cancer, which was accompanied by an increase in CD8 + T-cell infiltration[161]. A recent phase 1 clinical trial involving 10 patients with resected PDAC demonstrated the safety of an allogeneic tumor lysate-loaded autologous dendritic cell vaccine, with seven out of 10 patients showing no recurrence or progression at a median follow-up of 25 months[162]. An ongoing phase 1 clinical trial is evaluating the safety and efficacy of a tumor lysate-loaded dendritic cell vaccine in combination with an agonistic CD40 antibody in patients with metastatic PDAC following FOLFIRINOX chemotherapy (NCT05650918)[163].

Targeting B cells

BTK-dependent crosstalk between B cells and TAMs has been identified as a driver of PDAC growth. In mice bearing PDAC, the use of a BTK inhibitor (ibrutinib) led to the restoration of anti-tumor immunity, inhibition of pancreatic tumor growth, and enhanced responsiveness to standard-of-care chemotherapy[65]. However, a phase 3 clinical trial combining ibrutinib with gemcitabine and nab-paclitaxel failed to show improvements in PFS and overall survival in PDAC patients compared with the placebo plus gemcitabine/nab-paclitaxel cohort[164]. Meanwhile, the combined treatment with acalabrutinib (a second-generation BTK inhibitor) and pembrolizumab produced modest clinical benefits, with an ORR of 7.9% and a DCR of 21.1%, compared with the 0% ORR and 14.3% DCR observed in the acalabrutinib monotherapy group[165].

Reprogramming macrophages

Beyond its role in activating conventional dendritic cells, CD40 activation has been found to reprogram macrophages into tumoricidal TAMs in PDAC-bearing mice[115]. However, in a randomized phase 2 trial involving 105 patients with PDAC, sotigalimab, an agonistic CD40 antibody, did not demonstrate survival benefits when combined with chemotherapy (gemcitabine/nab-paclitaxel) and an anti-PD-1 antibody (nivolumab)[166]. Currently, a phase 1 clinical trial is recruiting patients with metastatic PDAC to assess the response to gemcitabine/nab-paclitaxel in combination with the anti-CTLA-4 antibody ipilimumab plus nivolumab, hydroxychloroquine, or NG350A (a CD40 agonist) (NCT04787991)[167]. In addition to CD40 agonism, the cellular inhibitor of apoptosis proteins 1 and 2 (cIAP1/2) antagonist has demonstrated the induction of T-cell-dependent reprogramming of TAMs to be tumoricidal, reducing tumor burdens by enhancing phagocytosis in orthotopic models of PDAC[168]. A phase 1 trial evaluating the combination of the cIAP1/2 antagonist ASTX660 with the anti-PD-1 antibody pembrolizumab is recruiting patients with pancreatic cancer or other solid tumors (NCT05082259)[169].

CD47 expressed on tumor cells acts as a “don’t eat me” signal by engaging signal-regulating protein alpha (SIRPα) expressed on macrophages, thereby blocking phagocytosis. This phagocytic checkpoint has gained attention as an attractive target for immunotherapy[170]. Given the substantial T-cell dysfunction and exhaustion observed in PDAC and other “cold” tumor types, macrophage-based therapeutic strategies have emerged

to address resistance to T-cell-based immunotherapy[21]. A phase1/2 clinical trial is currently recruiting patients to evaluate the safety and efficacy of PT886, a bispecific antibody targeting both CD47 and claudin 18.2—a tumor antigen that is overexpressed in PDAC (NCT05482893)[171].

Targeting stroma

Following encouraging preclinical studies, clinical trials focused on targeting PDAC stroma to enhance therapy responses have emerged. In preclinical models, the degradation of hyaluronan by PEGPH20 demonstrated a significant survival benefit when combined with gemcitabine[77,78]. In PDAC patients not selected for tumor hyaluronan status, the addition of PEGPH20 to FOLFIRINOX led to increased toxicity and a reduced median OS (7.7 months compared with 14.4 months in the FOLFIRINOX alone group)[172]. On the other hand, in a randomized phase 3 clinical trial involving patients with hyaluronan-high metastatic PDAC, the combination of PEGPH20 with gemcitabine/nab-paclitaxel improved the ORR but did not increase OS or PFS when compared with the placebo plus gemcitabine/nab-paclitaxel arm[173]. Currently, a phase 2 trial is evaluating the combination treatment with PEGPH20 and pembrolizumab in patients with hyaluronan-high metastatic PDAC (NCT03634332)[174].

In a genetically engineered mouse model of PDAC, the administration of an FAK inhibitor led to a reduction of fibrosis and increased sensitivity to immunotherapy (anti-PD-1 plus anti-CTLA-4)[79]. A phase 1 study demonstrated that the combination of defactinib (a small-molecule inhibitor of FAK) with PD-1 blockade plus gemcitabine resulted in stable disease in 11 out of 20 patients with metastatic PDAC[175]; this outcome was accompanied by an increase in CD8 + T cells and a decrease in Tregs, macrophages, and stromal cells. Currently, a phase 2 trial is underway to evaluate the efficacy of pembrolizumab plus defactinib following chemotherapy as a neoadjuvant and adjuvant treatment in patients with resectable PDAC (NCT03727880)[176].

CXCL12, produced by FAP+ CAFs, inhibits T-cell infiltration in pancreatic cancer. In a preclinical model of PDAC, pharmacological inhibition of CXCR4, the cognate receptor of CXCL12, enhanced the anti-tumor efficacy of PD-L1 blockade[83]. A phase 1 study investigated the safety and tolerability of the CXCR4 antagonist LY2510924 in combination with the anti-PD-L1 antibody durvalumab, revealing modest clinical benefits, with three out of eight patients achieving stable disease[177]. Of note, a recent phase 2 trial assessing the combination of BL-8040 (a CXCR4 antagonist), pembrolizumab, and Onivyde (topoisomerase I inhibitor) demonstrated encouraging results, including an ORR of 32%, a DCR of 77%, and duration of response (DOR) of 7.8 months in patients with metastatic chemotherapy-refractory PDAC[178].

The JAK-STAT pathway activates pancreatic stellate cells (PSCs) and induces inflammatory CAFs, contributing to immunosuppression in PDAC[81,87,179]. In a phase 2 study of ruxolitinib, a small-molecule JAK1/JAK2 inhibitor, in combination with the chemotherapeutic agent capecitabine, there was no observed benefit in OS generally, but a significant increase in OS was noted in patients with systemic inflammation compared with the placebo plus capecitabine group[180]. Unfortunately, two subsequent randomized phase 3 studies combining ruxolitinib and capecitabine for treating advanced/metastatic pancreatic cancer showed no improvement in OS or PFS[181]. Currently, a phase 1 clinical trial combining ruxolitinib, retifanlimab (an anti-PD-1 antibody), and trametinib (a MEK inhibitor) is recruiting patients with metastatic PDAC (NCT05440942)[182].

Discussion

Both pancreatic cancer cell-intrinsic signaling pathways and the TME play significant roles in immune suppression, contributing to the inherent resistance of pancreatic cancer to immunotherapy. Various therapeutic strategies, when combined with immunotherapy, have shown encouraging results in preclinical studies. However, the translation of these findings into clinical benefits has been challenging thus far. It is crucial to elucidate the mechanisms by which human PDAC evades immune surveillance and to devise approaches that effectively overcome immunotherapy resistance in patients. It should be noted that unrestricted cell death or tissue damage induced by chemotherapy might lead to an immunosuppressive TME[183]. In contrast, radiation therapy was reported to enhance the response to immunotherapy in patients with microsatellite-stable pancreatic cancer[184].

Improving pancreatic cancer immunotherapy involves exploring various strategies. Some key strategies and future perspectives include: (1) combination therapies: combining different immunotherapeutic agents, including inhibitors of established and newly discovered immune checkpoints, with targeted therapies or other immunomodulators, may enhance the overall anti-tumor response. (2) Stroma-targeted approaches: targeting the dense stroma in pancreatic cancer to reduce fibrosis holds promise for improving drug delivery and enhancing immune cell infiltration. (3) Vaccine development: developing personalized cancer vaccines based on individual tumor profiles has the potential to stimulate a specific and robust immune response against cancer cells. (4) Bispecific antibodies: designing antibodies that can simultaneously target multiple antigens is likely to enhance their specificity and efficacy in engaging immune cells against cancer. (5) Adoptive cell therapies: CAR T-cell therapies, which use genetically engineered T cells directed to specific cancer-associated antigens to elicit cytotoxic activity, represent a promising therapeutic modality, although significant challenges exist for CAR T-cells to infiltrate the immunosuppressive TME of pancreatic tumors. (6) Biomarker identification: identifying reliable biomarkers to predict the response to immunotherapy will allow for better patient stratification and treatment selection. (7) Clinical trial innovation: designing innovative clinical trials to test emerging therapies and combinations can ensure a rapid translation of promising preclinical findings into clinical benefits.

These strategies are active areas of research and development, with the potential to significantly impact the future of pancreatic cancer immunotherapy. In addition, investigating strategies for early detection of pancreatic cancer will enable timely intervention, potentially improving the success of immunotherapeutic approaches.

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Author contributions

Y.J. wrote the draft. D.X., Y.J., and M.L. made the figures and tables. Y.S., F.Y., and L.M. provided intellectual input. Y.S., W.B., F.Y., and L.M. edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Competing interests

The authors declare no competing interests. Figure 2 was created with BioRender.com.

Additional information

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