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REVIEW

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The role of innate immune cells as modulators of the tumor microenvironment in the metastasis and treatment of pancreatic cancer

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Abstract

Pancreatic cancer is a highly aggressive disease, which is often diagnosed late. Consequently, metastasis is common among newly diagnosed patients, leading to a poor prognosis and high mortality rates. The tumor microenvironment of pancreatic cancer, which comprises pancreatic cancer cells, stromal cells, and immune cells, as well as a multitude of extracellular components, plays a pivotal role in cancer progression and metastasis. Conventional immunotherapies focused on targeting the adaptive immune response have achieved suboptimal outcomes in patients with pancreatic cancer. Thus, the focus has shifted toward targeting innate immune cells, which can infiltrate the pancreatic tumor and contribute to the development and maintenance of the immunosuppressive microenvironment to promote tumor growth and metastasis. This review focuses on the roles of innate immune cells and their interactions in the shaping of an immunosuppressive tumor microenvironment to promote the metastasis of pancreatic cancer. In addition, we review strategies that target innate immune cells to remodel the immunosuppressive tumor microenvironment and improve the prognosis of pancreatic cancer.

Keywords Pancreatic cancer, Tumor microenvironment, Immune cells, Metastasis

Background

Despite decades of research, pancreatic cancer remains one of the most lethal cancers. In the U.S., the 5-year survival rate for pancreatic cancer is only 10%, which is primarily attributed to its aggressive nature and the late stage of diagnosis [1]. Pancreatic ductal adenocarcinoma (PDAC), the most common type of pancreatic cancer, is frequently diagnosed at the advanced stage after has metastasis occurred, which contributes to the high motility rates observed. PDAC is characterized by a highly immunosuppressive tumor microenvironment (TME), which lowers the efficacy of currently available immunotherapies. Thus, there is an urgent need to investigate how the TME contributes to PDAC development and metastasis,this information will help in the identification of potential targets to improve the outcomes of patients with PDAC.

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Immune cells play indispensable roles in tumor recognition and eradication. However, tumors often develop mechanisms to evade immune surveillance and re-educate immune cells to form an immunosuppressive TME, which is beneficial to tumor survival and progression. While residing in tissues, innate immune cells can be activated to participate in either tumoricidal or tumorigenic processes. Among these cells, neutrophils, macrophages, and dendritic cells (DCs), have been extensively studied due to their high heterogeneity and plasticity in the TME.

The TME of PDAC consists of tumor cells, stromal cells, immune cells, and extracellular components (Fig. 1). Tumor cells, stromal cells, and immune cells, which include tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), tumor-associated neutrophils (TANs), regulatory T cells (Tregs), and DCs, secrete extracellular components. These extracellular components, such as the extracellular matrix (ECM), growth factors, and chemokines, are essential for maintaining an immunosuppressive TME, which facilitates tumor progression and metastasis.

PDAC forms 'cold tumors', which are characterized by low effector T cell infiltration and immunogenicity. Thus, PDAC tumors respond poorly to currently available immunotherapies, which primarily focus on the action of adaptive immune cells such as T cells. Consequently, research focus is shifting toward the therapeutic potential of innate immune cells, which are considerably more abundant in the PDAC TME than adaptive immune cells [2]. This review briefly summarizes the roles of various innate immune cells in the PDAC TME. Specifically, we describe the mechanisms used by innate immune cells to contribute to PDAC metastasis and how they interact in

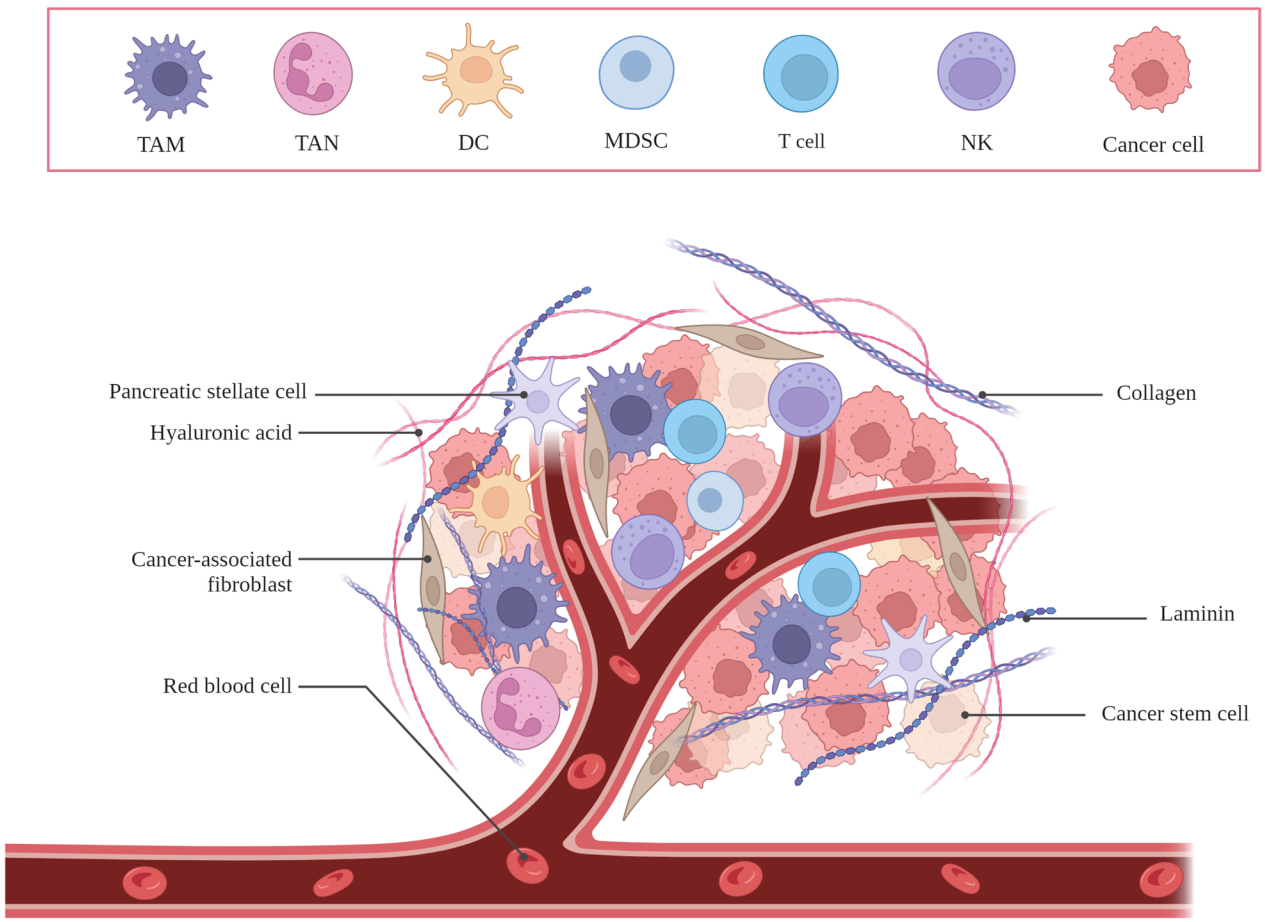

Fig. 1 The tumor microenvironment of PDAC. The PDAC tumor microenvironment (TME) is characterized by desmoplasia and immunosuppression. Extracellular matrix proteins, including collagen and laminin, are secreted by pancreatic stellate cells (PSCs). In addition, the PDAC TME contains immunosuppressive cells such as tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), myeloid-derived suppressor cells (MDSCs), dendritic cells (DCs), natural killer (NK) cells, cancer stem cells (CSCs), and cancer-associated fibroblasts (CAFs). Figure generated using Biorender

the TME, before discussing the potential clinical implications of targeting these immune cells.

Innate immune cells in the PDAC TME

The unsatisfactory response of PDAC to immunotherapy can be attributed to the PDAC TME, which is characterized by immunosuppression and desmoplasia (the excessive deposition of connective tissue). Tumor cells activate PSCs to promote fibrosis of the tissue surrounding the tumor. This creates a mechanical barrier around the tumor, limiting the infiltration of immune cells or exposure to chemotherapeutic drugs [3, 4]. Cytokines, such as tumor growth factor-β (TGF-β) and fibroblast growth factor 2 secreted in the ECM, can differentiate fibroblasts into cancer-associated fibroblasts (CAFs), promoting desmoplasia in the PDAC TME [5]. In addition to PSCs, immune cells are crucial components of the immunosuppressive PDAC TME,their roles are discussed in the following sections. The interactions between innate immune cells and tumor cells are summarized in Fig. 2.

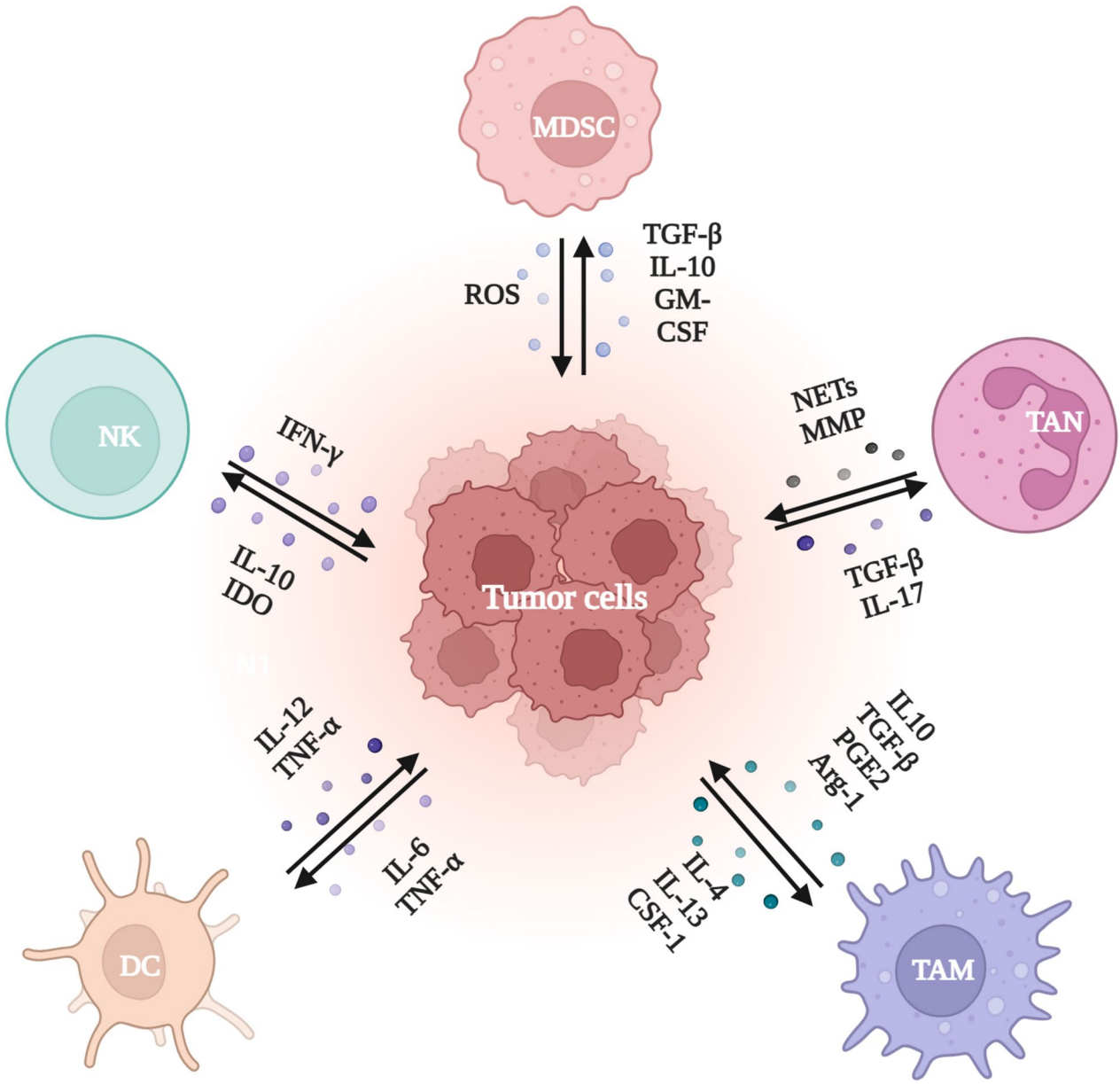

Fig. 2 Interaction between tumor and innate immune cells in the PDAC microenvironment. Interactions between tumor and tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), myeloid-derived suppressor cells (MDSCs), dendritic cells (DCs), and natural killer (NK) cells are depicted. Arrows depict interactions between tumor cells and each immune cell type. Image generated using Biorender

TAMs

Macrophages are innate phagocytic cells, which have broad functions in the process of inflammation; they exist as a heterogeneous population with distinct functional characteristics [6]. Macrophages are commonly classified as either the pro-inflammatory M1 type or the anti-inflammatory M2 type, which represent opposing extremes of a continuous functional spectrum [7]. Colony stimulating factor 1 (CSF-1), interleukin (IL)-4, and IL-13, which are abundant in the TME, promote the recruitment of monocytes and polarize TAMs toward the M2 type [8]. Thus, in solid tumors, including PDAC, TAMs have similar functions and characteristics to M2-type macrophages and their accumulation is associated with a poor prognosis [9–11]. However, the roles of TAMs appear to be more complex than initially thought. Several single-cell RNA-sequencing (scRNA-seq) studies have demonstrated that TAMs express a mixture of M1 and M2 markers in colorectal [12], liver [13], and renal [14] cancers. Another scRNA-seq study discovered that TAMs in PDAC could be subdivided into two groups: the $SPP1^{+}$TAMs and the $C1QC^{+}$TAMs [15]. The $SPP1^{+}$TAMs are enriched in genes involved in epithelial-mesenchymal transition (EMT), glucose metabolism, and hypoxia, whereas the $C1QC^{+}$TAMs are enriched in genes associated with the interferon (IFN) response and antigen presentation. Intriguingly, both the $SPP1^{+}$ TAMs and $C1QC^{+}$ TAMs also have an M2-like signature, which prevents them from being classified into the M1 or M2 categories [15].

TAMs contribute to the immunosuppressive TME by secreting cytokines, chemokines, and enzymes, such as TGF-β, IL-10, prostaglandin E2 (PGE2), and arginase-1 (Arg-1) [16]. For instance, the secretion of C–C chemokine ligand 5 (CCL5) and tumor necrosis factor-α (TNF-α) by TAMs induces pancreatic acinar-to-ductal metaplasia through NF-κB pathway activation [17]. TAMs polarized by tumor-secreted granulocyte macrophage (GM)-CSF, inhibited $CD8^{+}$ T cells in a pancreatic mouse model [18]. Moreover, TAMs have been shown to express high levels of C-X-C motif chemokine receptor 2 (CXCR2,these $CXCR2^{+}$TAMs trafficked to the PDAC tumor site in response to the tumor-derived C-X-C motif ligand 8 (CXCL8), impairing the efficacy of anti-PD1 therapy [19]. The galectin-9-mediated activation of dectin-1 on TAM also leads to tolerogenic T cell program induction in PDAC [20].

MDSCs

Although their distribution and functions are still under debate, MDSCs are an important component of the PDAC TME [21]. MDSCs are a heterogeneous population of immature myeloid cells, which can be classified into two subtypes: granulocytic or polymorphonuclear (PMN-MDSCs) and monocytic (M-MDSCs) MDSCs. PMN-MDSCs are phenotypically and morphologically similar to neutrophils, with $CD11b^{+}Gr\text{-}1^{+}Ly6G^{high}Ly6C^{low}$ and $HLA\text{-}DR^{-}CD33^{+}CD11b^{+}CD15^{+}CD14^{-}$ signatures in mice and humans, respectively. Meanwhile, M-MDSCs are related to monocytes and have a $CD11b^{+}Gr\text{-}1^{+}Ly6G^{low}Ly6C^{high}$ signature in mice and a $HLA\text{-}DR^{low}CD11b^{+}CD15^{-}CD14^{+}$ signature in humans [22–24].

MDSCs help shape the immunosuppressive TME by suppressing $CD4^{+}$ and $CD8^{+}$ T cells, stimulating Tregs expansion, and promoting M2 phenotype polarization [25, 26]. Moreover, the TGF-β and IL-10 in the TME cause MDSCs to release reactive oxygen species (ROS), which promote oxidative stress and further impair T cell function [8, 27]. Interactions between MDSCs and activated T cells lead to STAT3 activation in MDSCs and an increase in PD-1 expression in T cells, resulting in the suppression of T-cell activation [28]. MDSCs can be recruited to the tumor sites via chemokines and cytokines, such as CXCL12, CCL2, and IL-6 [29, 30]. Inflammatory CAFs use the FAP-STAT3 signaling pathway to release CCL2, which recruits MDSCs and ultimately dampens the activity of $CD8^{+}$ T cells in the TME; these events further promote tumor progression [31, 32]. The expression of CXCL12 by CAFs facilitates the migration of MDSCs, which can be suppressed by using the poly ADP ribose polymerase inhibitor olaparib (R. [30]. Direct physical interactions between MDSCs and Tregs were observed in both the murine PDAC model and the tissues of PDAC patients, whereby MDSCs induced Treg proliferation [33].

TANs

Similar to TAMs, TANs can be divided into the pro-inflammatory N1 and the anti-inflammatory N2 types [34]. The TME can influence the polarization of TANs. For instance, IFN-γ and TGF-β in the TME polarize TANs toward the N1 or N2 types, respectively [34, 35]. N2 neutrophils have a strong immunosuppressive function. They recruit Tregs and macrophages to the TME and secrete factors such as matrix metalloproteinases (MMPs), hepatocyte growth factor (HGF), and neutrophil elastase (NE) [26, 36]. scRNA-seq analysis has revealed that TANs can be classified into four subpopulations: a terminally differentiated pro-tumor subtype (TAN-1), an inflammatory subpopulation (TAN-2), a transitional stage population (TAN-3), and a subtype that preferentially expresses IFN-γ-associated genes (TAN-4) [37]. The infiltration of TANs into the PDAC TME is associated with a poor prognosis [38]. Moreover, in clinical studies of PDAC patients, the neutrophil

to lymphocyte ratio was suggested as a predictor of prognosis [39–41]. After being recruited to the tumor site by adipocyte-secreted IL-1β, TANs induce the activation of PSCs, which leads to further IL-1β section and contributes to PDAC progression [42]. Mutations in genes such as *SETD2* and *TP53* promote the recruitment of TANs, and consequently, PDAC tumorigenesis [43, 44]. SETD2-deficient PDAC tumor cells recruit neutrophils to the tumor site and reprogram them toward the N2 type,this causes the neutrophils to upregulate genes such as *IL10* and *MRC1* via the activation of AKT signaling [43]. The gain-of-function $TP53^{R172H}$ mutation promotes TAN infiltration into the tumor in response to tumor-cell-derived chemokines; these TANs subsequently render the tumor resistant to chemotherapy and CD40 combination immunotherapy [44]. scRNA-seq analysis has shown that, in liver cancer, $CCL4^{+}$TANs and PD-$L1^{+}$ TANs recruit TAMs to the tumor site and suppress T cell cytotoxicity, respectively [45].

Neutrophil extracellular traps (NETs) were first discovered in the context of inflammation. NETs are web-like structures composed of DNA, histones, and various proteins, which are extruded by neutrophils in a process termed NETosis [46]. In the TME, NETs promote tumor cell proliferation and metastasis, as well as inducing hypercoagulation [47]. Moreover, IL-17 production in the PDAC TME leads to the recruitment of neutrophils and triggers NET formation [48]. A recent study reported that the binding of TIMP1 (an MMP inhibitor) to its receptor CD63 induced NET formation in neutrophils via ERK signaling [49]. Moreover, KDM6A depletion from PDAC cells induced neutrophil recruitment to the tumor site and NET formation via the CXCL1-CXCR2 axis [50]. Emerging evidence suggests that NETs directly or indirectly foster tumor proliferation, shield tumor cells from cytotoxic lymphocytes, and promote tumor angiogenesis [51].

TANs and MDSCs have common origins and share a differentiation pathway, which raises questions about whether they are indeed distinct cell types. Moreover, there is currently no standardized nomenclature or methods for accurately differentiating these cells. MDSCs were named on the basis of their immunosuppressive function, whereas TANs described a group of neutrophils modulated by the tumor. Although TANs and MDSCs express similar surface markers (e.g., $CD66b^{+}$, $CD11b^{+}$, and HLA-DR^{-}), unlike MDSCs, TANs exhibit high chemokine secretion and low ROS production, suggesting that TANs and MDSCs are different types of cells [52]. In addition, despite some sample processing limitations, neutrophils and MDSCs can be separated by gradient centrifugation [53]. However, Shaul et al. suggested that MDSCs are a subset of neutrophils with a unique activation state rather than a separate cellular entity. Furthermore, the existence of MDSCs as a population of myeloid cells with an entirely immunosuppressive function contradicts the typical plasticity and dynamics of myeloid cells [54]. Given the challenges of differentiating between these myeloid cell types, TANs and MDSCs will be discussed alongside each other in this review,however, we prefer the term TANs over MDSCs as it better describes the plasticity of these cells and their interplay with various other cell types.

DCs

Dendritic cells bridge the gap between innate and adaptive immunity. Generally, DCs can be classified into three populations: conventional DCs (cDCs), plasmacytoid DCs (pDCs), and monocyte-derived DCs (moDCs) [55]. cDCs can be further divided into two subsets: the $CD8\alpha^{+}$ and/or $CD103^{+}$ cDC1 subset, which presents antigens and recruits cytotoxic T cells, and the $CD103^{+}$ cDC2 subset, which activates $CD4^{+}$ T cells such as T helper type 17 (Th17) cells. pDCs are less adept at antigen presentation than cDCs and instead play a dominant role in IFN-γ secretion during viral infection. moDCs are mainly generated under inflammatory conditions and are involved in Treg generation during cancer pathogenesis [55, 56].

The tumor nests of pancreatic cancer contain fewer cDCs than those of lung cancer; moreover, these cDCs exhibit reduced antigen presentation capacity [57]. Moreover, the level of cDC infiltration into PDAC tumors is correlated with increased patient survival [58]. The recruitment of cDCs into early pancreatic lesions leads to a decrease in the number of immunosuppressive Th17 cells and an increase in that of cytotoxic $CD8^{+}$ T cells. This remodeling of the TME activates the antitumor Th1 response and promotes tumor eradication [57]. DCs lacking heat shock proteins 70 (Hsp70) express higher TNF-α and MHC-II levels and are more effective at reducing the tumor burden than wildtype DCs in KPC mice models [59]. Moreover, the stimulator of IFN genes (STING) agonist induced DC activation and maturation both in vivo and in vitro, which also increased the DC-mediated secretion of the proinflammatory cytokines IL-6 and TNF-α [60]. Collectively, these findings suggest that DCs are promising targets in the treatment of pancreatic cancer.

Innate lymphoid cells (ILCs)

Despite representing a small population of immune cells, ILCs are crucial players in the progression and prognosis of cancers. ILCs are divided into five subsets: natural killer (NK) cells, ILC1, ILC2, NCR^{+}ILC3, and

NCR$^-$ILC3, based on their lineage-specific progenitor populations [61].

NK cells, which have similar functions to CD8$^+$ cytotoxic T cells, have been the most extensively investigated of all the ILCs in the tumor. The function of NK cells is impaired by the accumulation of tumor-derived factors such as TGF-β, IL-10, indoleamine 2,3-dioxygenase (IDO), in the TME; moreover, the characteristics of NK cells are influenced by the tumor type [62]. For instance, in PDAC, NK cells exhibit impaired cytotoxicity, while expressing low levels of IFN-γ and high levels of IL-10 [63]. The cytotoxicity of NK cells can also be impaired by the overexpression of UQCRC1, a key component of mitochondrial complex III, in response to elevated extracellular ATP concentrations [64]. The roles of other ILCs in PDAC remain unclear, largely due to their low frequencies in the PDAC TME. While the IL-33-mediated activation of ILC2s, which led to the recruitment of CD103$^+$ DCs into the PDAC TME and subsequently CD8$^+$ T cell activation, was associated with better PDAC prognosis in one study, it was associated with poor prognosis in another [65, 66].

Compared with other immune cells, our understanding of ILCs remains limited, especially considering the complexity of the TME and the low ILC frequencies. Therefore, strategies such as scRNA-seq will be instrumental in investigating ILC function in PDAC.

Role of innate immune cells in PDAC metastasis

Approximately 80% of PDAC patients present with unresectable or metastatic cancer; thus, metastasis is a leading cause of death among newly diagnosed PDAC patients [1]. Common PDAC metastatic pathways are local invasion and lymphatic metastasis, with distal metastasis typically occurring in the liver, lung, and bone. Metastasis involves several sequential steps: angiogenesis, lymphangiogenesis, EMT, migration, invasion of surrounding tissues, formation of the pre-metastatic niche, and growth at the metastasis site. The crosstalk between tumor cells and stromal cells, which contributes to PDAC metastasis, is outlined in Fig. 3.

TAMs

Interplay among TAMs, tumor cells, and stromal cells through various pathways is pivotal in PDAC metastasis. A recent study has shown that TAM numbers are positively correlated with the microvessel density of PDAC tissues and that exosomes derived from TAMs promote

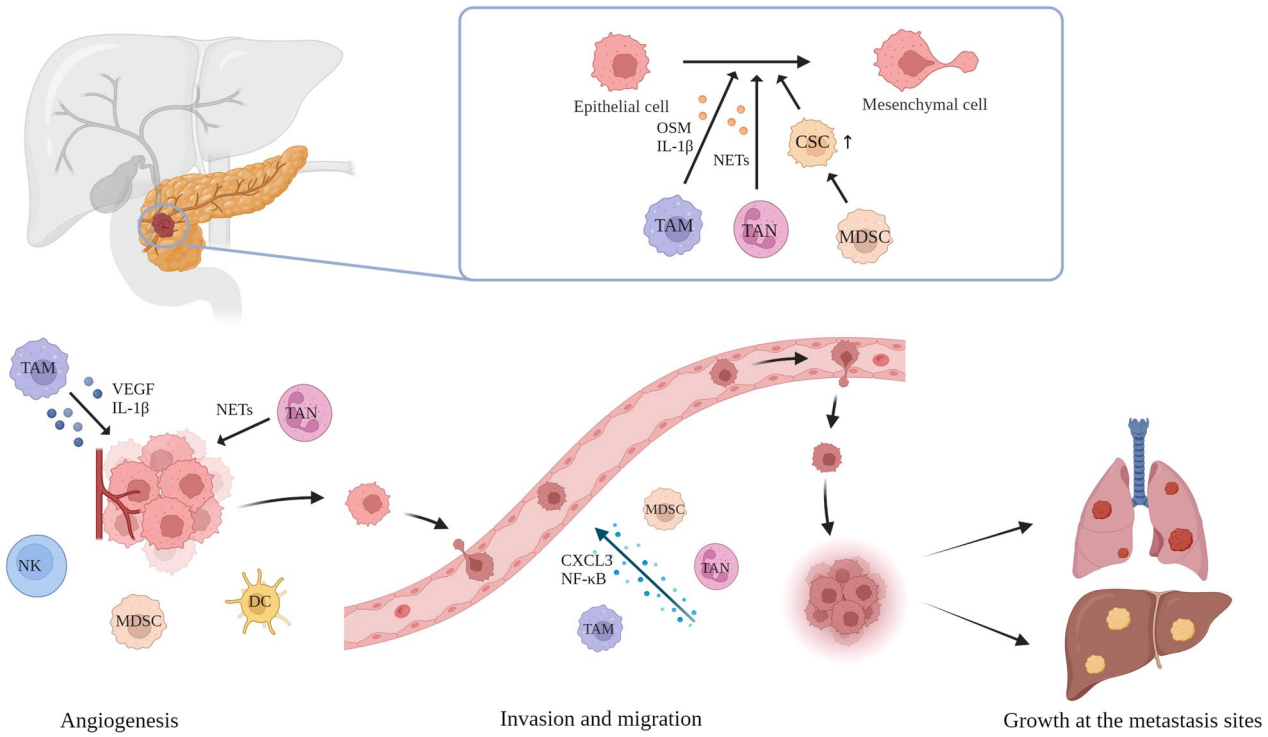

Fig. 3 Innate immune cells participate in PDAC metastasis. Innate immune cells participate in multiple steps of PDAC metastasis. Cytokines, such as vascular endothelial growth factor (VEGF), IL-1β, and CCL5, secreted by innate immune cells promote angiogenesis and tumor cell proliferation. Meanwhile, signaling pathways such as NF-κB induce the invasion and migration of tumor cells. Exosomes and cytokines derived from TAMs and TANs promote EMT and growth of PDAC tumors at metastatic sites. Image generated using Biorender

the angiogenesis of endothelial cells in vitro [67]. TAMs are involved in angiogenesis and lymphangiogenesis through the direct secretion of vascular endothelial growth factor (VEGF) [68] or the activation of several signaling pathways. Moreover, ANXA-1, contained in the extracellular vesicles of PDAC cells, regulates M2 phenotype polarization, which in turn activates endothelial cells and fibroblasts and contributes to angiogenesis and ECM degradation [69]. In addition, the frequency of M2-polarized TAMs in the regional lymph nodes of PDAC patients is strongly associated with nodal lymphatic vessel density, suggesting that TAMs are capable of lymphangiogenesis [70].

Several other PDAC metastasis mechanisms implicating TAMs have been described. For instance, the exosomal microRNA-301a-3p expressed by hypoxic pancreatic cancer cells induced M2 polarization of macrophages via the PTEN-PI3Kγ signaling axis, promoting PDAC cell migration, invasion, and EMT [71]. Notch signaling triggered by microRNA-124 in PDAC cells promoted M2 polarization, leading to STAT3 pathway activation, which facilitated tumor cell EMT and invasion [72]. EMT is also triggered when TAM-secreted oncostatin M (OSM) activates the LOXL2-mediated metastatic cascade [73]. In addition, debris and IgG derived from PDAC cells can induce IL-1β secretion from TAMs via the TLR4/TRIF/NF-κB signaling pathway, resulting in EMT, and consequently, PDAC metastasis [74]. Moreover, blocking, growth-arrest-specific 6 (GAS6), which is produced by TAMs and CAFs in the PDAC TME, partially reversed EMT and supported NK activation [75]. TAMs can also enhance PDAC cell migration by inducing EMT via the TGF-β/SMAD/SNAIL signaling axis [76].

TAM-derived exosomal micro-RNA-501-3p activates the TGF-β signaling pathway, promoting PDAC cell migration and invasion by inhibiting the tumor suppressor gene *TGFBR3* [77]. The STAT3/NF-κB pathway is activated by PDAC-derived exosomal FDG5-AS1, polarizing the formation of M2 macrophages, which in turn stimulates PDAC cell proliferation and metastasis [78]. The expression of TNFSF9, an immune checkpoint marker originally shown to be expressed on antigen-presenting cells, on PDAC cells was associated with a poor prognosis [79]. A recent study revealed that TNFSF9 promoted the metastasis of PDAC by inducing M2 polarization via Src/FAK/p-Akt/IL-1β signaling [79]. TAMs can also contribute to liver fibrosis and sustain the growth of tumor cells by secreting granulin to activate resident hepatic stellate cells; these events contribute to the development of PDAC liver metastases [80].

Besides tumor cells, TAMs interact with CAFs to promote PDAC metastasis. The binding of OSM secreted by TAMs to its receptor (OSMR) on CAFs induces inflammatory gene expression in CAFs. Thus, OSM depletion creates a more immunogenic environment, in which CAFs exhibit reduced inflammation gene expression, M2-like TAM numbers decline, and T cell function increases (evidenced by elevated CD44 and CD127 expression) [81]. Crosstalk between PDAC cells, TAMs, and CAFs is mediated via the IL-33/ST2/CXCL3/CXCR2 signaling pathway. The activation of the IL-33/ST2 pathway in TAMs induces them to express CXCL3, which in turn converts CAFs into myoblast CAFs,because these myoblast CAFs express the cell surface matrix protein collagen III, they can form clusters with PDAC cells to promote PDAC metastasis [82].

MDSCs and TANs

An increasing number of studies have revealed that TANs and their NETs are involved in the progression and metastasis of PDAC via diverse signaling pathways. GAS6 expressed by TANs activates the AXL receptor on PDAC cells, enabling their regrowth after chemotherapy [83]. Gap junction protein beta 3 (GJB3), a protein which forms gap junctions (channels for the transportation of small molecules between adjacent cells), was found to facilitate PDAC liver metastasis by promoting neutrophil accumulation and N2 polarization by transferring cAMP [84], GJB3 depletion consequently suppressed PDAC liver metastasis in vivo. It was also observed that circulating tumor cells (CTCs were surrounded by neutrophils in tumor-adjacent vessels of PDAC tumors [85],thus, TANs may assist in distant metastasis formation through their direct interaction with CTCs. A population of immunosuppressive P2RX-1^{-} neutrophils, which promoted metastatic tumor growth by upregulating PD-L1 expression on tumor cells, was identified in a murine PDAC liver metastasis model and in clinical PDAC samples [86]. NRF2, a ROS-sensitive transcription factor, may promote PDAC liver metastasis by increasing PD-L1 expression on PDAC cells after boosting intracellular ROS production by P2RX-1^{-} neutrophils [86].

NETs also contribute to PDAC metastasis via a variety of signaling pathways. The peptidylarginine deiminase 4 (PAD4)-mediated release of DNA from NETs was shown to activate PSCs by interacting with receptors for advanced glycation end products (RAGE) and promoting the proliferation and metastasis of PDAC cells [87]. In addition, PDAC cells express collagen-induced discoid domain receptor (DDR1). In response NF-κB signaling, DDR1 stimulates CXCL5 production from tumor cells, leading to TAN recruitment, NET formation, and eventually, the invasion and metastasis of PDAC cells [88]. In PDAC, NETs facilitate EMT, as well as tumor cell migration and invasion, via the IL-1β/EGFR/ERK pathway

[89]. NETs can also promote PDAC liver metastasis by enhancing the migration of hepatic stellate cells [90].

Although less investigated, the interactions among MDSCs and other cells in the PDAC TME may also have important roles in the metastatic process. For instance, MDSCs significantly increased CSC numbers in a mouse model of PDAC, which was accompanied by a significant upregulation of genes related to EMT in tumor cells [91].

Other innate immune cells

The roles of NK cells, DCs, and other innate immune cells in PDAC metastasis are not as well-studied as those of TAMs or TANs. An immunosuppressive DC subset was found to express PD-L2 in the metastatic site and induce the expansion of Tregs in vitro, suggesting that they played a role in shaping the immunosuppressive PDAC TME [92]. NK cells are the only innate immune cells with direct tumoricidal function. Moreover, NK-cell-derived exosomal miR-3607-3p inhibits the migration and invasion of PDAC cells in vitro by targeting IL-26 [93].

Crosstalk between innate immune cells

In the TME, innate immune cells communicate via the secretion of soluble factors (e.g., cytokines and chemokines) or interactions between surface molecule and their receptors, which regulate various signaling pathways (Fig. 4). The levels of cytokines such as IL-1β, IL-10, VEGF, and TNF were reported to be increased in

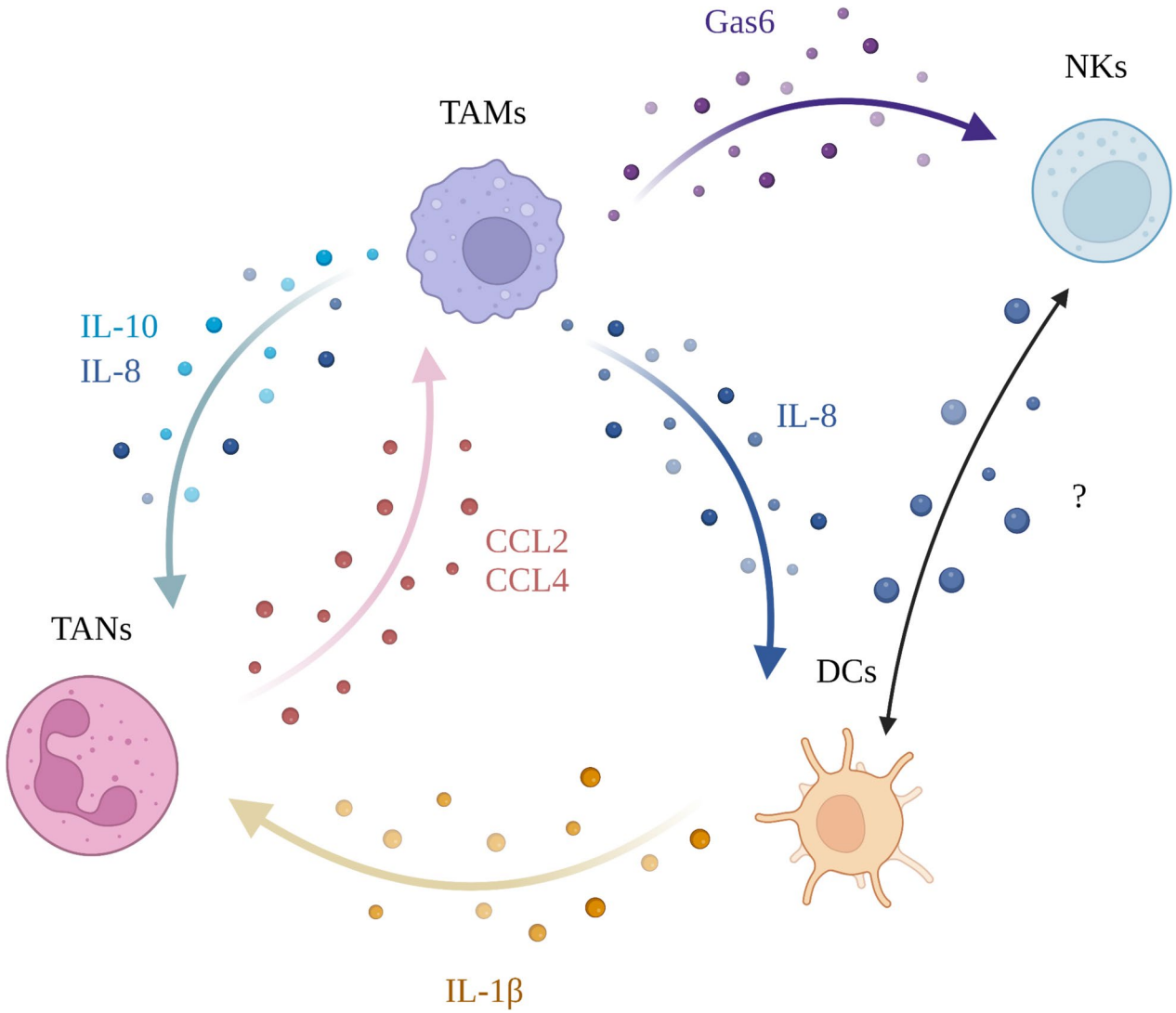

Fig. 4 Crosstalk between innate immune cells in the PDAC TME. Innate immune cells, such as tumor-associated macrophages, tumor-associated neutrophils, dendritic cells, and natural killer cells, secrete cytokines, chemokines, and molecules to interact with each other, forming an immunosuppressive microenvironment that promotes tumor progression and proliferation. Image generated using Biorender

patients with PDAC [94]. IL-10 is an anti-inflammatory cytokine secreted by most immune and tumor cells. A study of breast cancer revealed that macrophages were a major source of IL-10 and that DCs were responsive to this cytokine as they expressed high levels of the IL-10 receptor (IL-10R). Thus, high IL-10 levels reduced the capacity of DCs to produce IL-12, which in turn impaired the recruitment of cytotoxic T cells to the tumor site [95]. In addition, IL-1β, which promotes NETosis, can be secreted by TAMs, DCs, and tumor cells, suggesting possible interactions among these cell types [96, 97]. Moreover, TAMs release IL-8 in response to tumor cells, which leads to the recruitment of neutrophils and MDSCs to the tumor site [98]. In addition, innate immune cells may mutually recruit each other via the secretion of specific chemokines. For instance, scRNA-seq analysis predicted that $CCL4^{+}$TANs recruited macrophages via the CCL4/CCR5 axis; this result was validated in an in vitro chemotactic assay in which liver tumor cells were co-cultured with TANs [45]. In chronic pancreatitis, macrophages were recruited via the CCL2/CCR2 axis,however, the disruption of this axis inhibited not only macrophage but also neutrophil recruitment, implying that chemokines are important for crosstalk between macrophages and neutrophils [99]. Gas6 is a TAM receptor ligand, and binding of Gas6 to its receptor AXL causes phosphorylation and activation of AXL. Interestingly, blocking GAS6 binding to AXL activated NK cells and partially reverse the EMT of tumor cells [75]. In the PDAC TME, TAMs express high levels of apolipoprotein E (ApoE), which drives tumor cells to secrete CXCL1 and leads to the recruitment of more immunosuppressive myeloid cells [100].

Despite being well documented in the context of inflammation, the crosstalk between innate immune cells and tumor cells in cancer is not well characterized. The arrival of state-of-the-art technologies such as scRNA-seq and spatial transcriptomics, will enable a more comprehensive and detailed exploration of the intricate interactions among innate immune cells in the TME. A deeper understanding of the PDAC TME will pave the way for the development for promising therapeutic strategies.

Targeting immune cells to remodel the PDAC TME

The PDAC TME comprises diverse interactions among cells, cytokines, chemokines, and other factors; this complex and dynamic nature of the TME poses challenges for the development of strategies aimed at targeting its specific components. The studies discussed above provide strong evidence that TAMs, TANs, MDSCs, and other innate immune cells play vital roles in PDAC metastasis. Targeting these cells can be a potential therapeutic strategy against PDAC. Here, we discuss present and potential future strategies related to the targeting of innate immune cells in PDAC TME. Among these strategies, the targeting of macrophages, neutrophils, and MDSCs has been most extensively investigated (Table 1); however, as most of the evidence has been gathered at the preclinical stage, the efficacy of these strategies will need to be validated in larger trials.

Targeting TAMs

Reprogramming TAMs is one of the most popular immunotherapeutic strategies being developed for PDAC. For instance, IFN-γ was reported to re-educate TAMs into M1-type macrophages, which released higher levels of the pro-inflammatory cytokine IL-12 and lower levels of the pro-tumorigenic factors IL-10, MMP9, and VEGF [101]. CD40 can also be targeted to reprogram TAMs. Treatment with an agonistic anti-CD40 antibody mAb CP-870,893 led to partial tumor regression in both mice and humans, via a mechanism in which the CD40-activated macrophages became tumoricidal and contributed to the degradation of the tumor stroma [102]. A phase Ib, multicenter study combining a monoclonal, agonistic anti-CD40 antibody with chemotherapy, showed that this combination had promising clinical activity and tolerable adverse effects [103]. The use of selicrelumab, another agonistic anti-CD40 antibody as a neoadjuvant therapy, activated T cells, increased the production of the inflammatory factors CXCL10 and CCL22 by several cell types, and decreased TAM numbers in the PDAC TME [104]. The PI3K-γ and CSF1-R signaling pathways have also been targeted to enhance the response of T cells to checkpoint immunotherapy and reprogram TAMs in pancreatic cancer mouse models (clinical trial number: NCT02777710) [105, 106]. Specifically, a PI3K-γ inhibitor and a CSF1-R-siRNA were simultaneously administered to PDAC model mice [105]. Increased numbers of M1 type macrophages and a reduction in the M2 type macrophages were observed in mouse tumors, which was associated with a significant decrease in tumor weight [105].

Macrophage depletion is another research direction being explored. Several studies [109, 110, 112, 129] have targeted the CCL2/CCR2 axis, which is vital in the recruitment of TAMs to the TME [130]. Using a CCR2 inhibitor in combination with FOLFIRINOX chemotherapy, achieved local tumor control with tolerable adverse effects [109]. CCL2 inhibition increased effector T cell responses, enhanced chemotherapeutic efficacy, and inhibited metastasis [110]. The specific depletion of TAMs with lurbinectedin increased the extent of gemcitabine-mediated DNA damage in a PDAC mouse model, thus improving the efficacy of gemcitabine therapy [111].

Table 1 Targeting innate immune cells to treat PDAC

References	Mechanism	Treatment	Stage
[101]	Macrophage reprogramming	IFN-γ	Preclinical
[102–104]		CD40 agonistic antibody	Phase I
[105, 106] NCT02777710		PI3K-γ and CSF1-R inhibition	Phase I
[107, 108]		CD47 antibody	Phase I
[109]	Macrophage depletion	CCR2 inhibitor	Preclinical
[110]		CCL2 inhibitor	Preclinical
[111]		Lurbinectedin	Preclinical
[35]	Neutrophil reprogramming	IFN-β	Preclinical
[112]	Neutrophil depletion	CXCR2 blockade	Preclinical
[113]		Lorlatinib	Preclinical
[87]	NETosis inhibition	DNase	Phase II
[114, 115]		Chloroquine	Phase II
[48]		IL-17/IL-17R blockade	Preclinical
[116]		PAD4 inhibition	Preclinical
[50]	Neutrophil depletion and NETosis inhibition	CXCL1 inhibition	Preclinical
[117] NCT03767582	MDSCs depletion	CCR5 antagonist CCR2/CCR5 dual antagonist	Preclinical Phase II
[118]	MDSC migration	CD11b/CD18 agonist	Preclinical
[119, 120]	Neutrophil and MDSC depletion	CXCR2 inhibition	Preclinical
[121–123]	DC maturation	CD40 agonist DC vaccines	Phase I
[124]	DC expansion	FLT3L	Preclinical
[123, 125–128]	Cytotoxicity of NK cells	CAR-NK	Phase II
NCT03841110	Allogenic NK cells	iPSC-derived NK	Phase I

This table summarizes the strategies developed to treat PDAC, focusing primarily on targeting innate immune cells

CD47 is a transmembrane glycoprotein, which binds to signal regulatory protein α (SIRPα) to send a "don't eat me" signal to macrophages, reducing their phagocytic ability [131]. Therefore, blocking the CD47/SIRPα interaction has emerged as a promising next-generation immune checkpoint disruption strategy [131]. Indeed, administering a blocking anti-CD47 antibody to PDAC model mice increased the numbers of $CD4^+$ and $CD8^+$ T cells in the tumor, while decreasing those of monocytes/macrophages [132]. A phase I trial of an anti-CD47 antibody has demonstrated that it is well tolerated and associated with objective responses in multiple tumor types [107, 108].

Targeting TANs and MDSCs

Similar to targeting TAMs, the reprogramming or depletion of TANs are potential PDAC strategies being investigated in clinical trials. The protumor N2-like TANs have the potential to transform into N1-like TANs via IFN signaling pathway activation. Indeed, β-glucan administered to a subcutaneous mouse model of melanoma activated the IFN signaling pathway and promoted neutrophils to exhibit long-term antitumor effects [133]. Endogenous IFN-β inhibits tumor angiogenesis through the repression of genes encoding VEGF, MMP9, and CXCR4 in TANs [35]. Blocking CXCR2 signaling on TANs improved antitumor immunity in a murine PDAC model by enhancing the chemotherapeutic efficacy [112]. Lorlatinib treatment inhibited PDAC progression in a PDAC mouse model by specifically targeting $Ly6G^+$ neutrophils and suppressing their development, mobilization, and infiltration, as well as improving the efficacy of immune checkpoint blockade [113].

The depletion of neutrophils or the inhibition of NETosis are valid strategies aimed at remodeling the PDAC TME. NETosis inhibition by DNase, chloroquine, IL-17/IL-17R blockade, or the PAD4 inhibitor have been reported [48, 87, 114–116]. DNase treatment of PDAC model mice inhibited tumor growth and stromal activation within the PDAC TME [87]. In a phase II clinical trial, the administration of chloroquine to preoperative patients with PDAC in combination with chemotherapy resulted in greater antitumor responses and autophagy inhibition [114]. IL-17 recruits neutrophils and triggers NET release. Accordingly, disrupting the IL-17/IL-17R interaction increased immune checkpoint blockade sensitivity in a PDAC model [48]. Thus, IL-17 and checkpoint blockade may be combined to enhance the

efficacy of existing PD-1-targeting therapies for the treatment of metastatic PDAC. Inhibiting PAD4, an enzyme with a central role in NET formation, reduced the NET forming capacity of both murine and human neutrophils,moreover, this PAD4 inhibitor can be used in combination with other therapeutic agents such as an IL-17 inhibitor [116]. CXCL1 inhibition significantly reduced TAN infiltration and NETosis, and ultimately attenuated the tumor growth in *KDM6A*-deficient PDAC mice model in vivo [50].

CCR5 and CXCR2, two chemokine receptors involved in the recruitment or maturation of neutrophils, are also potential targets for remodeling the PDAC TME [117, 119]. In other cancers, the inhibition of CCR5 reduced MDSC recruitment to the tumor and prevented tumor metastasis [117]. In PDAC, CXCR2 signaling is predominantly upregulated in TANs and MDSCs. Thus, treatment of a PDAC model mice with a CXCR2 inhibitor significantly decreased their intratumoral MDSC numbers, while increasing the infiltration of $CD8^+$T cell into the PDAC TME [120]. Moreover, CXCR2 blockade suppressed PDAC metastasis and, to some degree, inhibited tumorigenesis [119].

The CD11b/CD18 integrin heterodimer is expressed on the membranes of MDSCs, TANs, and TAMs, where it mediates myeloid adhesion, migration, tissue recruitment, phagocytosis, and survival. Given these functions, CD11b/CD18 blockade promises to reduce the infiltration of most myeloid subsets into the tumor [134]. Indeed, the CD11b modulator GB1275 reduced the tumor infiltration of $CD11b^+$ MDSCs and prolonged the survival of KPC model mice [118].

Targeting DCs

Emerging DC-targeting treatment methods have been developed. These include DC vaccines and the use of CD40 agonists to promote cDC1 maturation [121, 122]. A phase I clinical trial was conducted by injecting autologous, tumor-lysate-loaded moDCs into patients with resected PDAC. After a median follow-up of 25 months, seven out of ten patients did not experience PDAC recurrence or progression and had no vaccine-related serious adverse effects, suggesting the favorable safety and feasibility of this DC vaccine [121]. A clinical trial combining DC agonists with allogeneic tumor-lysate-loaded DCs is ongoing, with treatment safety and tolerability as the primary endpoints and the magnitude of the antitumor immune response as the secondary endpoint [122]. In the context of lung cancer, combining neoantigen-presenting DCs with an anti-CD38 antibody has been shown to reduce Treg infiltration, thereby reshaping the immunosuppressive TME [123].

As professional antigen-presenting cells, DCs prime and stimulate T cells to eliminate cancer cells. Hence, boosting DC function represents a promising immunotherapeutic strategy in cancer treatment. Growth factors, such as FMS-like tyrosine kinase 3 ligand (FLT3L) have attracted increasing attention due to their ability to expand and activate DCs [135]. Administration of FLT3L expanded cDC1s in both lymphoid and peripheral tissues, while also enhancing tumor-specific T cell responses in conditions such as breast cancer and melanoma [124, 136]. Notably, in the case of melanoma, the administration of FLT3L activates $CD103^+$ DC progenitors, thereby increasing the efficacy of BRAF and PD-L1 blockade [124].

Targeting NK cells

NK cells can be likened to the innate immune equivalent of T cells; as such, NK cells represent promising targets for the treatment of PDAC. Inspired by the successes of CAR-T cell therapy, CAR-NK cell therapy has emerged as a budding immunotherapy, with several notable advantages over CAR-T cells (e.g., a better safety profile) [137]. Treating a PDAC subcutaneous mouse model with CAR-NK cells engineered to target folate receptor alpha and death receptor 4, both highly expressed in tumor cells, increased NK infiltration into the tumor tissue and promoted tumor cell apoptosis [138]. CAR-NK cells displayed even greater antitumor efficacy when used in combination with a STING agonist, as evidenced by marked tumor growth inhibition in PDAC model mice and their prolonged survival [125]. Robo1-specific CAR-NK cell immunotherapy enhanced the efficacy of ^{125}I seed treatment. Higher greyscale values and a significant reduction in tumor size were observed in the orthotopic PDAC mouse model treated with the combination therapy compared with either monotherapy [126]. Given that NK cells are less likely to induce graft-versus-host disease than $CD8^+$ T cells, clinical trials of allogenic NK cells have also been carried out [127, 137]. Patients with stage III PDAC being treated with a combination of irreversible electroporation and allogenic NK cell immunotherapy had a higher median overall survival and progression-free survival than the control group, and few adverse events [127].

Induced pluripotent stem cells (iPSCs) provide an "off-the-shelf" supply of lymphocytes, which can be used a source of NK cells for immunotherapy. NK cells generated from human iPSCs, express NK-defining markers such as CD56, CD16, and death-inducing ligands, and exhibit cytotoxicity through cytokine secretion or antibody-dependent cell-mediated cytotoxicity [128]. The iPSC-derived NK cell product FT500 is being administrated in a phase I clinical trial to target solid tumors,

including pancreatic cancer (clinical trial number: NCT03841110). FT516 and FT576 are other allogeneic NK cells being trialed in the treatment of ovarian cancer and multiple myeloma, respectively (clinical trial number: NCT04630769, NCT05182073).

Conclusions and future perspectives

Despite the emergence of advanced therapies, pancreatic cancer remains one of the most lethal cancers, which is largely due to its complex immunosuppressive TME. Innate immune cells such as TAMs, TANs, and MDSCs play critical roles in shaping the immunosuppressive PDAC TME, which also impacts tumor progression and metastasis.

Despite our growing understanding of the PDAC TME and the development of many innovative TME remodeling strategies, various challenges still exist. Owing to the heterogeneity of tumors, the TME of orthotopic and metastatic sites may be different. This may explain the unsatisfactory response observed to currently available treatments. Moreover, innate immune cells, especially TAMs and TANs, exhibit considerable plasticity, which is greatly influenced by the TME. Thus, techniques such as spatial transcriptomics and multiplex phenotyping are needed to accurately characterize the subtypes of immunosuppressive cells in the TME. These cells can then either be eliminated or repolarized to attack tumor cells and enhance the efficacy of other immunotherapies. Given the complexity of the TME, interactions among its various components, especially among innate immune cells, are not fully understood. In addition, PDAC patients are usually diagnosed at a late stage after metastasis has occurred. Thus, finding more sensitive diagnostic biomarkers for PDAC remains a priority.

In light of these challenges, we believe that a deeper understanding of the PDAC TME is needed to successfully and safely target this cancer. For instance, recent studies have used scRNA-seq to explore the differences in the TME between orthotopic and liver metastasis in PDAC. However, the primary focus of these studies was on cancer cells, CAFs, and T cells, with less emphasis on innate immune cells such as TAMs and TANs [139]. Consequently, the specific roles and mechanisms through which innate immune cells, such as macrophages and neutrophils, may influence these TME differences are unclear. Moreover, the intricacies of interactions among innate immune cells in the PDAC TME remain a mystery. At present, the hunt for potential biomarkers and drug targets expressed by cells in the PDAC TME continues. What is evident, however, is that by gaining a deeper understanding of the PDAC TME, we are moving closer to developing more effective, targeted therapeutics for this aggressive cancer.

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Authors' contributions
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