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REVIEW

Role of tumor associated macrophages in regulating pancreatic cancer progression

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Abstract

Pancreatic cancer has an overall 5-year survival rate of less than 5%. Unfortunately, patient survival has not substantially improved in the last couple of decades despite advances in treatment modalities that have been successful in other cancer types. The poor response of pancreatic cancer to therapy is a major obstacle faced by clinicians. Increasing attention is being paid to how tumor cells and non-tumor cells influence each other in the pancreatic tumor microenvironment. Tumor-associated macrophages (TAMs) are a highlight in this field because of their vast presence in the tumor microenvironment. TAMs promote angiogenesis, metastasis, and suppress the anti-tumor immune response. Here we review the current understanding of the role of TAMs in regulating the progression of pancreatic cancer.

Key words: Pancreatic cancer; Tumor-associated macrophages; Tumor microenvironment; Macrophages

Core tip: Pancreatic cancer remains one of the most deadly cancers with dismal 5-year survival rates. Increasing importance is being given to the role of macrophages in pancreatic cancer. Tumor-associated promote angiogenesis, metastasis, and suppress the anti-tumor immune response. Targeting macrophages within the tumor microenvironment is an attractive novel therapeutic approach. Here we review the current understanding of the role of tumor-associated macrophages in the progression of pancreatic cancer.

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PANCREATIC CANCER

Pancreatic cancer is the eighth leading cause of death from cancer in men and the ninth leading cause of

death from cancer in women worldwide and is lethal in more than 95% of cases[1]. The incidence of pancreatic cancer ranges from 1 to 10 cases per 100000 people, is generally higher in developed countries, and has remained stable for the past 30 years relative to the incidence of other common solid tumors[2]. It is more common in the elderly and less than 20% of patients present with localized, potentially curable tumors[3]. The overall 5-year survival rate among patients with pancreatic cancer is less than 5%[4].

The causes of pancreatic cancer are not yet fully understood. Environmental factors have been implicated, yet evidence of a causative role only exists for tobacco use. The risk of pancreatic cancer in those that smoke is 2.5 to 3.6 times that in nonsmoking individuals[5]. Several medical conditions are associated with an increased risk of pancreatic cancer, including diabetes, chronic pancreatitis, chronic cirrhosis, a high-fat diet, and a high-cholesterol diet[3]. Additionally, it is estimated that 5% to 10% of cases are inherited, however currently there is no effective screening tool[6].

Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic cancer. The cancer arises in the ductal epithelium and evolves from premalignant lesions to fully invasive cancer. The lesion called pancreatic intraepithelial neoplasia (PanIN) is the best characterized histologic precursor of pancreatic cancer[3]. The progression from dysplasia to invasive carcinoma is paralleled by the accumulation of mutations that include activation of the KRAS2 oncogene, inactivation of the tumor-suppressor gene CDKN2A, and inactivation of the tumor-suppressor genes TP53 and DPC4[7].

In the past two decades, almost no progress has been made in the clinical management or outcomes of patients with pancreatic cancer[1]. Approximately 70% of patients diagnosed with pancreatic cancer die from extensive metastatic disease while 30% present with limited metastasis, yet the majority of these patients have bulky primary tumors[8]. The poor response of pancreatic cancer to therapy is a major obstacle faced by clinicians. Patient survival has not substantially improved despite advances in treatment modalities that have proven successful in other cancers (*i.e.*, breast, lung, colorectal, and melanoma)[9-11]. Novel biologic therapies such as cancer vaccines and methodologies using therapeutic gene transfer have also been either ineffective or shown limited promise[12]. The current standard chemotoxic drug, gemcitabine, has resulted in only a modest improvement in survival, and newer therapies show only marginal improvement[13]. Surgical resection is ultimately the most effective for pancreatic cancer. However, only 15% to 20% of patients are considered candidates for surgical resection[6] and outcomes of surgery alone are poor as less than 15% of resected patients are alive 5 years post-operatively[14]. Therefore, the development of new treatment strategies for the vast majority of patients afflicted with pancreatic cancer is vital.

PANCREATIC TUMOR MICROENVIRONMENT

The development of PDAC is marked by increasing desmoplasia, which results in a vast stroma that often exceeds the epithelial component of the tumor. Unlike most adenocarcinomas whose volume is comprised primarily of transformed cells, a pancreatic tumor is comprised of fibro-inflammatory stromal elements and islands of neoplastic epithelium[15,16]. Recent evidence suggests that far from being a passive observer, pancreatic tumor stroma affects both cancer progression and clinical outcome. In PDAC, activated pancreatic stellate cells have been shown to support tumor growth and immune dysfunction[17]. In particular, by releasing nutrient growth factors, such as insulin-like growth factor 2 and PDGF, into the tumor microenvironment, the stromal component of pancreatic cancer has been closely linked to both tumor growth and invasiveness[18-20]. In addition, chemotherapy resistance has been correlated with the extent of tumor desmoplasia as the stroma is thought to be a physical barrier to cytotoxic agents reaching the neoplastic epithelial cells[21,22]. Consequently, increasing attention is being paid to how tumor cells and non-tumor cells influence each other in the tumor microenvironment. Tumor-associated macrophages (TAMs) are a highlight in this field. Here we review the recent evidence for the role TAMs possess in promoting pancreatic cancer progression.

MACROPHAGE POLARIZATION

The immune system plays a critical role in the response to infection and elimination of foreign pathogens. In the context of cancer, the immune system recognizes antigens produced by tumor cells; therefore the cancer cell is deemed a foreign pathogen. Histopathological analyses of human tumors have provided evidence that variable numbers of infiltrating immune cells, such as macrophages, mast cells, granulocytes and myeloid-derived suppressor cells (MDSCs), are found in most cases infiltrating or surrounding tumor beds both in the core and at the invasive front of the tumor[23].

Macrophages play an important role in the innate immune system. They are essential in removing dead or dying cells and debris *via* phagocytosis, and activate the adaptive immune response[24]. After tissue damage, macrophages organize immune defenses and coordinate the tissue repair process. Normally, this process is self-limiting, yet if it doesn't resolve it leads to chronic inflammation characterized by an alteration in the immune cell types involved, including an increase in infiltrating macrophages[25].

Macrophages are activated in response to environmental signals, including microbial products and cytokines. Analogous to the dichotomous differentiation of T helper cells giving rise to T helper type 1 (Th1) and T helper type 2 (Th2) T cells with distinct cytokine

expression patterns and immunological functions, two fundamental macrophage phenotypes have been delineated. Activated macrophages are functionally divided into two subtypes: M1 (classical activated) and M2 (alternative activated)[26]. Th1-related cytokines such as Interferon gamma (IFN-γ), and lipopolysaccharide (LPS), polarize macrophages to M1[24]. M1 macrophages are characterized by IL-12^{hi}, IL-23^{hi}, tumor necrosis factor alpha (TNFα)^{hi}, IL-10^{low}, CXCL9^{hi}, CXCL10^{hi}, ROI^{hi}, RNI^{hi}, COX1^{low}, COX2^{hi} and iron uptake phenotype[24,27]. M1 macrophages preferentially induce anti-tumor Th1 cells, whereas Th2 cytokines such as IL-4 and IL-13 induce M2 macrophages[28]. These macrophages express IL-12^{low}, TNFα^{low}, IL-10^{hi}, IL-1decoyR^{hi}, IL-1RA^{hi}, Arginase1^{hi}, CCL17^{hi}, CCL18^{hi}, CCL22^{hi}, CCL24^{hi}, COX1^{hi}, COX2^{low}, iron release, and increased phagocytic activity[24]. M2 macrophages initiate pro-tumorigenic actions by promoting angiogenesis, tissue repair, and inducing immune suppression *via* induction of Th2 cells[27]. It is worth noting that M1 and M2 macrophage designations are extreme ends of a fluid scale. In fact, there is ample literature describing the plasticity of macrophages. Macrophages receive signals from the microenvironment in which they reside[27] and it is the integration of these signals that ultimately determines the macrophage subtypes.

MACROPHAGE RECRUITMENT

The development and progression of pancreatic cancer has been linked to inflammation[29-31], with chronic inflammation being a risk factor for the development of PDAC[32-35]. The inflammatory microenvironment that is characteristic of PDAC supports tumorigenesis through paracrine crosstalk between tumor cells and immune cells[36]. Importantly, inflammatory conditions are not only prominent in the tumor microenvironment but also present in the peripheral blood of PDAC patients, thus highlighting a role for peripheral immune cells in disease progression[37]. Once established, PDAC is characterized by marked leukocyte infiltration.

TAMs are the main population of inflammatory cells found in the tumor microenvironment of solid tumors[38]. TAMs develop in response to tumor-induced cytokines, chemokines, and vascular endothelial growth factor (VEGF)[26,39,40]. Additionally, it is also well documented that granulocyte macrophage colony-stimulating factor (GM-CSF), released from the tumor microenvironment, regulates TAM recruitment, maturation, and differentiation. The matricellular glycoprotein secreted protein acidic and rich in cysteine (SPARC), an intracellular matrix protein, may influence macrophage infiltration and distribution in murine pancreatic tumors. Murine macrophages expressing F4/80 are more plentiful in tumors from wild-type SPARC mice and are distributed at the tumor margins[41]. Additionally, monocyte chemoattractants, such as the alarmins, may also play a role in the recruitment of monocytes and other macrophage precursors[42]. A factor released by dying tumor cells, the high mobility group box protein 1, is found in areas where TAMs reside[43].

TAMS CAN PROMOTE TUMOR PROGRESSION

The role that TAMs play in the tumor microenvironment remains controversial. For instance, in colorectal tumors, TAMs are pro-inflammatory, and are anti-tumor, which has been associated with a good prognosis[44]. However, in most tumors, the protumoral role of TAMs is supported by clinical studies that have reported a correlation between high macrophage content and poor prognosis[45-49]. Epidemiological data suggests that a tumor microenvironment that is rich in macrophages will lead to a more aggressive tumor with the potential for metastasis[50].

In pancreas cancer, there is evidence that TAMs infiltrate early lesions or PanINs and persist through invasive cancer[35]. It is well documented that early and advanced lesions have significant increases in macrophage infiltration, compared to normal pancreatic tissue. Moreover, evidence suggests that TAMs may regulate PanIN development. TAMs produce IL-6 in PanIN lesions of Kras^{G12D}-expressing mice, therefore inducing STAT3 signaling and promoting cancer progression[51]. Additionally, pancreatic cancer cell proliferation *via* sonic hedgehog production has been linked to NFκB-activated monocytes[52]. Liou *et al*[33] identified the macrophage-secreted inflammatory cytokines RANTES and TNF as mediators of acinar cell dedifferentiation and tumor initiation. These cytokines act *via* the activation of NFκB and its target genes involved in regulating survival, proliferation, and degradation of extracellular matrix. Furthermore, the authors identified matrix metalloproteinases (MMPs) as targets that drive dedifferentiation and show that MMP inhibitors may be efficiently applied to block inflammation-induced dedifferentiation[33]. Helm *et al*[53] conducted studies on the functional impact of TAMs from human PDAC tissues on premalignant and malignant pancreatic ductal epithelial cells. Both cell types acquired an elongated cell shape along with an increased expression of vimentin and a reduced expression of epithelial E-cadherin when indirectly cocultured with TAMs from PDAC tissues[53]. When the cells were cocultured in the presence of polarized M1- and M2-macrophages, to elucidate whether pro- or anti-inflammatory properties account for these effects, similar to TAMs, both macrophage subsets induced epithelial-mesenchymal transition alterations and even greater invasiveness in the malignant epithelial cells[53]. Similar findings have been reported by others, further elucidating the impact of pancreatic cancer cell interaction with macrophages on the differentiation and function of macrophages and behaviors of pancreatic cancer cells[54]. Tumor growth inhibition following clodronate depletion of macrophages further clarifies the

pivotal role macrophages have in tumor progression[55].

M2 macrophages

Macrophages often express an M2-phenotype at the tumor site[56]. During the early stages of pancreas tumor initiation and development, M1-macrophages are more abundant[57,58] and as the cancer progresses, macrophages switch to an M2-like phenotype[27,59-61]. In human patients, more M2-macrophages were detected in the context of pancreatic cancer than in chronic pancreatitis[62]. Furthermore, in pancreatic cancer patients a higher number of M2-macrophages was linked to larger tumor size, early liver recurrence, local recurrence, and reduced survival[62]. Similar results have been reported by others[63-65]. A higher percentage of M1-macrophages has been associated with longer survival[66].

Interestingly, Tjomsland *et al*[67] found evidence that high gene expression levels of CD68 (general macrophage marker) might be associated with poor prognosis and thus decreased survival following tumor resection, whereas a CD163-dominating M2-macrophage phenotype conferred a survival advantage[67]. Helm *et al*[68] have shown that human PDAC-associated TAMs concomitantly exhibit characteristics of pro-inflammatory M1-macrophages (*e.g*., HLA-DR, IL-1B, TNF-α) and anti-inflammatory M2-macrophages (*e.g*., CD163, IL-10). The authors also found HLA-DR and CD163 double positive cells by immunohistochemistry staining in pancreatic tissue of PDAC and chronic pancreatitis[68], thus confirming that macrophages with a mixed phenotype sharing pro- and anti-inflammatory properties are abundant in PDAC and are already present in the setting of chronic pancreatitis. These findings challenge the dichotomous concept of M1- and M2-macrophages. Importantly, their location in the tumor and the tumor stage might affect their ability to contribute to tumor promotion[27], which may explain conflicting findings.

Given the aforementioned findings, reprogramming TAMs towards a more anti-tumorigenic phenotype may prove promising. An agonist monoclonal antibody against CD40, a co-stimulatory protein found on professional antigen-presenting cells, has demonstrated efficacy in mouse models of PDAC[69]. By reprogramming M2 TAMs into M1 TAMs using a CD40 agonist, tumor immune surveillance was restored[69]. This increased the therapeutic efficacy of gemcitabine. These results show that tumor immunosurveillance can at times be governed strictly by innate immunity under the regulation of the CD40 pathway. A CD40 agonist has also demonstrated efficacy in human patients with PDAC[70] when delivered in combination with the chemotherapeutic agent gemcitabine, ostensibly *via* the anti-tumor activities of macrophages[71]. Low-dose tumor irradiation may enable recruitment of antitumor T cells[72]. Using a mouse model, Klug *et al*[72] have shown that irradiation triggers the polarization of M2-macrophages toward M1-macrophages that express iNOS. They further show that iNOS activity was responsible for vascular normalization and activation, T cell recruitment, and tumor rejection. The authors also obtained similar results when transferring irradiated macrophages and T cells, thus representing a promising adjuvant therapeutic strategy[72]. These results hold great promises in the treatment of pancreatic cancer.

Immune suppressive activities of TAMs

Tumor immunosuppression is a recognized mechanism for regulating tumor growth and when it succeeds, tumor progression continues mostly unchecked. TAMs have been described as key players of the tumor microenvironment contributing to immunosuppression by secreting TGF-β, IL-10, and arginase 1[73-75]. TGF-β promotes TAM polarization to an M2-phenotype, further promoting TGF-β release and immunosuppression[56]. Additionally, TGF-β promotes Th2 cell differentiation, resulting in an inefficient antitumor response[76]. Interestingly, Zhang *et al*[77] provide a novel model to explain the paradoxical role of TGF-β in the development of PDAC. Although TGF-β receptor signaling may inhibit cancer cell growth in the early stages of PDAC, its promoting role in angiogenesis may improve the long-term survival and progress of PDAC, thus it appears to be tumorigenesis-enhancing in the later stages of tumor progression[77]. TAM-derived IL-10 suppresses IL-12 expression[78], prevents in situ DC maturation[74,79], and suppresses IFN-γ release[80]. However, IL-10 may have a role in the antitumor immune response due to immunostimulating properties[81-83]. Arginase 1, a marker for M2-macrophages that is expressed in tumors, causes dysregulation of the T cell receptor (TCR) signal resulting in a deficient $CD8^+$ T cell response[75,84]. Using a murine lung carcinoma model, Rodriguez *et al*[85] demonstrate that a subpopulation of mature tumor-associated myeloid cells express high levels of arginase 1. The authors also show that depletion of extracellular L-Arginine by tumor-associated myeloid cells blocked the expression of the TCR CD3ζ and inhibited antigen-specific T cell proliferation[85].

In human hepatocellular and ovarian carcinoma, $CD14^+$ myeloid cells suppress autologous T cell proliferation and IFN-γ expression *in vitro* and nullify anti-tumor T cell activity during *in vivo* adoptive transfer experiments[86,87]. In pancreatic cancer, TAMs have a significant immunosuppressive role. CCR2 or CSF1R blockade with gemcitabine reduced TAM numbers, increased cytotoxic T cells, and decreased $FOXP3^+$ Treg infiltration compared to gemcitabine alone[88]. These findings suggest that a reduction in macrophage infiltration at the tumor site resulted in an improved anti-tumor response in pancreatic cancer. More recently, using a retrospective cohort of patients with PDAC, Di Caro *et al*[89] report that the density of macrophages is a critical determinant of patient responsiveness to postsurgical conventional chemotherapy. *In vitro*, chemotherapy prevents the tumor-protective role of TAMs and reinstates their antitumor function, by a T-cell

independent mechanism[89]. Targeting TAMs may be beneficial to tumor prognosis and in some cases be sufficient to ignite an effective antitumor action.

In addition to bona fide macrophages, there is extensive literature on abnormal accumulation of immature myeloid cells, known as MDSCs, which accumulate in the spleen and tumors as a consequence of tumor-associated changes in myelopoiesis and play a critical role in immunosuppression[90]. MDSCs represent a heterogeneous population of cells and are Gr-1$^+$CD11b$^+$[91]. Moreover, *in vitro*, Gr-1$^+$CD11b$^+$ MDSCs have the ability to impair T cell responses[92]. Although the relationship between MDSCs and TAMs is not yet entirely clear, in the context of tumor-derived factors, it has been suggested that MDSCs have the ability to differentiate *in vitro* into macrophages with immunosuppressive characteristics[93].

In pancreatic cancer, MDSCs may play a significant role in tumor progression. Using a murine model of PDAC, Bayne *et al*[94] demonstrate that GM-CSF, derived from the tumor, recruits Gr-1$^+$CD11b$^+$ myeloid cells that leads to the suppression of antitumor T cell response. *In vivo* abrogation of GM-CSF prevented the infiltration of MDSCs at the tumor site and blocked tumor progression[94]. Similar findings have been recently reported[95]. Interestingly, Pylayeva-Gupta *et al*[96] demonstrate that upregulation of GM-CSF in mouse pancreatic ductal epithelial cells is oncogenic Kras^{G12D}-dependent. Mutational activation of Kras triggers the production of GM-CSF, promoting the expansion of immunosuppressive Gr-1$^+$CD11b$^+$ myeloid cells and leading to the evasion of CD8$^+$ T cell-driven antitumor immunity. The suppression of GM-CSF production, in turn, inhibits the *in vivo* growth of Kras^{G12D} tumors[96]. These findings provide insights into the challenges for designing effective therapeutic modalities targeting pancreatic cancer.

Strategies to reduce the effects of myeloid cell populations within the tumor microenvironment may offer great therapeutic potential. Using a mouse model of PDAC, Zhu *et al*[97] demonstrate that CSF1R blockade may enhance macrophage antigen presentation and T cell responses. CSF1R blockade upregulated the T cell checkpoint molecules PDL1 and CTLA4[97]. When PD1 and CTLA4 antagonists were combined with CSF1R blockade, this resulted in tumor regression. These findings provide a rationale to reprogram immunosuppressive myeloid cell populations in the tumor microenvironment under conditions that can significantly empower the therapeutic effects of checkpoint-based immunotherapeutics[97].

TAMs promote angiogenesis

Angiogenesis is a requirement for tumor growth and spread. TAMs have the capacity to regulate the vascular programming of tumors[27]. Upon activation, TAMs release multiple factors such as VEGF, PDGF, and TGF-β[98], all of which can promote angiogenesis. Vascular endothelial growth factor A (VEGFA) produced by TAMs is critical for angiogenesis and reverses the effects of macrophage depletion[99], whereas loss of VEGFA leads to vascular normalization[100].

However, while increased vascularization during tumor progression is recognized as an important step for the majority of solid tumors, in the context of pancreatic cancer this is unclear. Hypovascularized regions are characteristic of PDAC and has served as a diagnostic tool[101]. Moreover, this conflicts with the understanding that an angiogenic switch is required for tumor growth to occur[102]. Interestingly, in several animal models Sunitinib, an anti-angiogenic drug that targets VEGF and PDGF receptor signaling, showed progressive blockade of tumor growth but did not inhibit PDAC progression in a murine model[103]. In a murine model of pancreatic tumor of endocrine origin, which is highly vascularized and accounts for approximately 1% of pancreatic cancers in humans, Sunitinib reduced tumor formation[104]. Schmid *et al*[105,106] suggest that tumor vascularization may be promoted by circulating macrophages. The authors have shown that the chemoattractants SDF-1α and IL-1β collaborate with myeloid cell integrin-α4β1 to promote macrophage recruitment and adhesion to vascular endothelium resulting in tumor inflammation and growth. Inhibition of these molecules markedly decreased angiogenesis in pancreatic cancer models thus reducing tumor burden[105,106].

TAMs and tumor metastasis

A hallmark determining the severity of cancer is tumor metastasis, which is the result of tumor cells traveling through blood and lymphatic vessels to form ectopic tumors. Pancreatic cancer commonly metastasizes to the liver, peritoneum, lungs, and bones[104]. It has been suggested that TAMs have a role in tumor-cell migration, invasion, and metastasis[107]. There is an abundance of evidence showing how TAMs influence tumor cell migration. Precursors of TAMs, blood monocytes, may also contribute to the formation of an invasive microenvironment in a manner dependent on the secretion of soluble mediators such as TNF[108]. Conversely, pancreatic cancer cells induce differentiation of pro-tumor macrophages. Tumor-educated macrophages may promote pancreatic cancer cell invasion *in vitro*[109], thus underscoring the crosstalk that occurs between tumor cells and TAMs resulting in disease progression. It has been suggested that EGF released by TAMs interacts with CSF-1 produced by tumor cells to induce tumor cell migration[43]. TAMs also influence the tumor microenvironment by providing factors that promote tumor cell invasion, including proteases[110]. Macrophage-derived microRNA have also been suggested to regulate tumor invasion[111]. In pancreatic cancer of human origin, the macrophage inflammatory protein-3α (MIP-3α) has been linked to tumor cell invasion[112,113]. Interactions between MIP-3α and CCR6, the receptor expressed by PDAC cells, have been shown to induce PDAC cell proliferation, migration, and invasion in type Ⅳ collagen[112,113].

Pharmacologic inhibition of macrophage infiltration at the tumor site using the CSF1R inhibitors decreased liver metastasis in pancreatic tumor mouse models[88]. Focal adhesion kinase (FAK), which is a known regulator of cell migration, proliferation, apoptosis, and survival, has been linked to macrophage infiltration[114]. Using an inhibitor of FAK (PF-562,271), Stokes *et al*[114] found diminished migration of tumor cells, cancer-associated fibroblasts, and macrophages. Treatment of mice with this inhibitor reduced tumor growth, invasion, and metastases[114].

TAMs and cancer stem cells

Cancer stem cells (CSC) or cancer initiating cells are a specific subpopulation of cells with distinct stem cell properties, such as self-renewal and differentiation, with the ability to initiate tumorigenesis within tumors[115,116]. The interaction between CSCs and TAMs promotes tumor growth, maintains the CSC population, and reduces therapeutic efficacy. Furthermore, the histological grade of the malignancy has been found to positively correlate with the number of infiltrating macrophages because TAMs have been found distributed around CSC populations[117,118]. Wu *et al*[119] have shown that CSCs in glioma tissue recruit macrophages with an M2-phenotype that secrete IL-10 and TGF-β. The authors also found enhanced capacity of macrophages to inhibit T cell proliferation and therefore induce immunosuppression. In another study, blockade of macrophage infiltration lead to a reduction in the expression of ALDH, a CSC marker on pancreatic cancer cells[88].

Recently, Hou *et al*[120] found elevated expression levels of the CSC markers CD44/CD133 and TAM marker CD204 in human PDAC tissues. High coexpression of CD44/CD133 and CD204 was associated with shorter overall survival and disease-free survival. These findings suggest that for patients with PDAC the coexpression of CD44/CD133 and CD204 may be useful for predicting survival[120].

CONCLUSION

Pancreatic cancer remains one of the most common and deadly cancers. The limited success of chemotherapy in patients with pancreatic cancer is partly due to the complexity of the tumor microenvironment. Increasing attention is being given to the interactions of tumor cells and non-tumor cells found in the tumor microenvironment. In the pancreatic tumor microenvironment, TAMs are the most common cell population encountered. Accumulating evidence suggests that TAMs infiltrate early cancer lesions, subsequently promoting angiogenesis, tumor growth, spread, and immunosuppression. Additionally, the interaction between CSCs and TAMs promotes tumorigenicity, metastasis, maintains the CSC population, and impedes therapeutic efficacy. The success of studies inhibiting macrophage recruitments to the tumor microenvironment and reactivats their cancer cell killing activities provide evidence of novel therapies for future tumor management. Altogether, these findings suggest that targeting TAMs with anticancer therapies may represent a novel strategy to treat pancreatic cancer.

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