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Current Status and Perspectives of Pancreatic Cancer Tumor Microenvironment and Therapy

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Abstract: *Pancreatic ductal adenocarcinoma (PDAC) is commonly known as the "king of cancers" because of its exceptionally aggressive nature and poor prognosis for patients. Moreover, the pancreas, being a retroperitoneal organ, presents a lack of specific markers, making early identification difficult. The tumor microenvironment (TME) consists of tumor cells, stromal cells, immune cells and cytokines, etc. together. Antitumor medications cannot penetrate PDAC due to its high mesenchymal component content, which also restricts immune cells to infiltrate the tumor tissue. At the same time, the TME of PDAC lacks anti-tumor immune cell infiltration and has strong immunosuppressive properties, and the components of TME play an important role in tumor growth, angiogenesis, immunosuppression, and resistance to chemotherapy and targeted drugs. In this paper, we provide an overview of the composition, biological properties and research progress of immunotherapy of TME in PDAC, in the hope of bringing new ideas for the treatment of PDAC.*

Keywords: *Pancreatic cancer, tumor microenvironment, immune cells, stromal cells, immunotherapy*

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most prevalent pathogenic kind of pancreatic cancer, making up around 90% of all primary malignant tumors in the pancreas. The occurrence is predominantly localized in the pancreatic head. PDAC occurs frequently in prosperous Western countries and is the fourth leading cause of cancer-related deaths globally. The occurrence of PDAC is rising by 1% due to the aging population and advancements in diagnostic methods [1]. By 2025, PDAC is forecasted to rank as the third most significant contributor to cancer-related fatalities [2].

Many poor lifestyle habits, such as smoking, heavy drinking, obesity, diabetes, pancreatitis, and exposure to carcinogens can increase the risk of PDAC, while genetic factors also play an important role in the development of PDAC. Familial PDAC patients can increase the risk of PDAC in the first degree of relatives 6.79 times, The incidence of PDAC is exponentially growing in correlation with the number of first-degree relatives[3]. People with harmful mutations in genes such as BRCA2, PALB2, BRCA1, ATM, CDKN2A, and others are more likely to suffer PDAC. The occurrence of PDAC in patients with BRCA2 mutations is approximately 3% [4].

Despite the rapid development of medical technology, the 5-year survival rate of PDAC is about 10%. Due to the retroperitoneal location of the pancreas and the insidious onset of symptoms in PADC, approximately 80% of those diagnosed are detected with advanced tumors, which eliminates the possibility of surgical resection [4]. Although neoadjuvant therapy has improved the surgical rate of PDAC, and patients with resectable cancers have a 5-year overall survival rate of approximately 27% [5]. For patients with advanced stages of the disease, treatment is based on chemotherapy. The FOLFIRINOX (calcium folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan) and the AG (gemcitabine and albumin-bound paclitaxel) are the first-line chemotherapy regimens for PDAC. Regarding the impact of the two treatment plans on the survival of patients with PDAC, several studies have determined that there is no discernible disparity in the extension of overall survival (OS) between the two regimens [6], but it has been suggested that FFX prolongs OS in PDAC patients more than GnP in others [7]. The results of a meta-analysis of 7030 PDAC patients, which included 21 publications, showed that there was no difference between the two regimens in terms of increasing OS and that FFX improved PFS, and that for drug-related adverse effects, patients on FFX had a greater incidence of anemia, and those on GnP were more likely to have diarrhea, while No notable discrepancy was

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detected in the prevalence of neutropenia and thrombocytopenia [8]. In summary, the efficacy of FFX and GnP is still very limited and the median survival is still less than 1 year. Many patients with malignant tumors now have a boost of optimism as a result of the development of targeted medications, yet PDAC patients have not seen much improvement in their condition. PDAC with high mutational microsatellite instability (MSI) responds better to PD-L1 inhibitors, but in less than 1% of patients, and even with high MSI/dMMR PDAC response rates to immune checkpoint inhibitors are still lower than in other types of tumors [9].

The tumor microenvironment (TME) primarily consists of biological constituents, such as tumor cells, stromal cells, immune cells, the extracellular matrix (ECM), and dissolvable constituents, and the communication between tumor cells and other constituents within TME construct an ecosystem that suppresses anti-tumor immunity and promotes tumorigenesis and development. According to the invasion of T cells into tumor tissues, TME is classified as immune desert, immune rejection, and immune inflammation, and tumors with immune desert and immune rejection TME are commonly known as "cold tumors", while tumors that exhibit immunological inflammation in the TME commonly refer to "hot tumors". CD8 T-cells are not present in the immune-depleted TME, and they exhibit minimal response to immune checkpoint inhibitors; large numbers of immune cells are present in immune-rejected TME, but are confined to the stroma surrounding the tumor and rarely infiltrate the tumor parenchyma; and large numbers of immune cells are present in immunoinflammatory TME, which infiltrate the tumor interior and are the most responsive to PDL1/PD1 blocking agents [10]. PDAC is called a "cold tumor", with a dense, hypoxic, highly fibrotic stroma, this can account for as much as 90% of the tumor and is crucial in chemoresistance [11]. The specific TME of PDAC limits the efficacy of existing drugs in PDAC. To expedite the progress of pioneering therapeutic strategies or precise treatments in the future, it is imperative to fully comprehend the role of immune cells in the TME and the underlying reasons for the existing shortcomings of therapy. This paper will provide a comprehensive examination of the involvement of immune cells in the pathogenesis of PDAC, along with an analysis of the current status of treatment and research in this field.

2. Immune cells

2.1. T cells

The arrangement and geographical dispersion of T cells within tumor tissue have a tendency to correspond with the prognosis of patients diagnosed with PDAC. $CD8^+$ T cells infiltrated in tumor tissue and Th1 cells converted by $CD4^+$ T cells tend to predict longer survival, whereas Th2 cells converted by $CD4^+$ T cells are linked with tumor progression [12]. The TME of PDAC demonstrated a deficiency of $CD8^+$ T cells, and even when those were present, $CD8^+$ T cells predominantly expressed minimal amounts of activation markers, such as granzyme B (GZMB) and interferon gamma (IFNG) [10]. In the specimens from patients with advanced PDAC, $CD8^+$ T cells predominantly express depletion markers, further illustrating the suppression of immune function [13]. Infiltration of regulatory T cells (Tregs), commonly known as $CD4^{++}CD25^+Foxp3^+$ T cells, can be observed in precancerous lesions and increases with neoplastic advancement, which is closely linked to unfavorable prognosis in PDAC [14]. In expressing KRAS and P53 mutations in mouse models, Tregs can inhibit tumor growth mediated by $CD8^+$ T cells [15]. However, additional studies have shown that Tregs have the same inhibitory effect on tumor growth. In the PDAC mouse model, depletion of Tregs promotes increased infiltration of immune cells and induces a pancreatic inflammatory response, while when KRAS mutations are present, both synergistically promote pancreatic intraepithelial neoplasia (PanIN) that is the progression of abnormal cell growth in the pancreas. Depletion of Tregs leads to increased infiltration of myeloid-derived suppressor cells (MDSCs) and modulates TGFβ to inhibit differentiation of SMA^+ fibroblasts (myCAFs) and promotes tumor growth [16]. Neoadjuvant chemotherapy has expanded the likelihood for surgical removal in individuals with PDAC, resulting in a surgical procedure for approximately 30–40% of patients diagnosed with locally progressed and resectable PDAC. Multiple research have provided evidence that neoadjuvant chemotherapy can improve the density of $CD4^+$ T cells and $CD8^+$ T cells in the tumor and reduce the percentage of immunosuppressive cells such as Tregs, as well as promote the shift of Th2 cells with anti-inflammatory phenotype to Th1 cells with pro-inflammatory phenotype [17]. Hence, recent research indicates that Tregs have a dual function in the TME. Additional research is necessary to analyze the potential of targeting Tregs to enhance their anti-tumor activities and alleviate their inhibition of anti-tumor cells.

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2.2. B cells

PDAC cells can secrete C-X-C motif chemokine ligand 13 (CXCL13) and express C-X-C motif chemokine receptor 5 (CXCR5) to attract B cells to infiltrate tumor tissues, tumor-infiltrating B cells (TIL-B) can secrete interleukin 35 (IL35), which promotes tumor growth through a paracrine mode, and IL35 specifically expressed by B cells in mouse specimens and human PanIN lesions, and IL35-secreting $CD24^{+}CD38^{+}$ B cells are major contributors to the progression of PDAC [18]. Within tertiary lymphoid structures (TLS), B cells differentiate into memory cells and plasma cells, which release IgG1 antibodies in response to activation by tumor-associated antigens. IgG1 stimulates the antibody-dependent cytotoxicity of NK cells and the phagocytosis performed by macrophages. Additionally, It possesses the capability to display tumor-related antigens to T cells. However, TIL-B distributed in the tumor stroma has an immunosuppressive role [19]. BCL6 is critical for maintaining Breg/plasma cell homeostasis. IL35 can stimulate signal transducer and activator of transcription 3(STAT3)- paired box gene 5(PAX5) complex formation thereby upregulating the transcriptional regulator B-cell lymphoma 6 (BCL6) in naïve B cells leading to B cell malfunction while inhibiting plasma cell infiltration in tumors [20]. Bregs, as a class of subpopulations of B cells, suppress autoimmunity and contribute to the maintenance of self-tolerance. A high circulating level of Bregs correlates with lower survival in PDAC [21]. Bregs have the ability to produce anti-inflammatory cytokines, including IL10. Additionally, Bregs can express immune checkpoint molecules, specifically PD-1 and PD-L1, which function to inhibit the activity of $CD4^{+}$, $CD8^{+}$ T cells, and NK cells. Meanwhile, Breg cells can impede the entry of $CD8^{+}$ T cells by suppressing the activity of C-X-C motif chemokine receptor 3 (CXCR3) and C-C chemokine receptor 5 (CCR5) through the release of IL35, and promote Tregs and tumor-associated macrophages (TAMs) infiltration [21]. Protein kinase D2 (PKD2) has a vital function in controlling the expression of IL-35 in a specific type of B cells known as $CD19^{+}CD1d^{hi}CD21^{hi}CD5^{+}$ Bregs. Treatment of a PDAC mouse model with protein kinase D1/2 (PKD1/2) inhibitor (CRT0066101) reduced PDAC tumor volume [22]. Targeting cytokines and Bregs may provide novel approaches for the treatment of PDAC.

2.3. Neutrophils

Cancer is often characterized as a chronic injury that fails to heal, and neutrophils are the first responders to remove pathogenic factors. Neutrophil infiltration is tightly linked to cancer progression and is associated with tumorigenesis, angiogenesis, immunosuppression, and metastasis. Neutrophil penetration is higher in PDAC than in non-cancerous tissues, which may be associated with the release of chemokines such as C-X-C motif chemokine ligand 1(CXCL1), granulocyte/macrophage colony-stimulating factor (GM-CSF) and C-X-C motif chemokine ligand 6(CXCL16) by tumor cells to induce neutrophil migration [23]. The neutrophil-to-lymphocyte ratio (NLR) is linked to the progression of tumors and resistance to chemotherapy; the higher the NLR, the higher the probability of chemotherapy resistance and the lower the survival rate of patients [24]. Additionally, an elevated NLR is indicative of increased amounts of tumor-associated neutrophils (TANs), which possess a high degree of adaptability and can be directed towards either a N1 phenotype characterized by pro-inflammatory properties or a N2 phenotype characterized by anti-inflammatory properties. TANs can be induced to present as the N1 subpopulation by interferon-β (IFN-β) in TME, and can exert anti-tumor effects by releasing active substances such as peroxidase or through antibody-dependent cellular cytotoxicity (ADCC) [25]. TGF-β has the ability to stimulate the differentiation of TANs into the N2 subpopulation, which can promote tumor growth and inhibit T cell recruitment and maturation [26]. Unfortunately, there is a lack of specific markers to identify N1 and N2 subpopulations. Neutrophil extracellular capture (NET) is a meshwork that kills invading microorganisms and is expelled extracellularly by dying neutrophils; its main components are decondensed chromatin and intracellular granular proteins. However, an ever-growing number of studies have shown that NET can promote tumor metastasis [27]. Discoidin domain receptor tyrosine kinase 1(DDR1), a collagen receptor, on PDAC cells interacts with collagen and attracts TANs, whilst collagen, through the DDR1/PKCθ/SYK/NF-κB pathway, stimulates PDAC cells to produce C-X-C motif chemokine ligand 5(CXCL5), which induces the formation of NET [27]. NET can remodel the tumor stroma, promote tumor cell motility, and induce apoptosis of cytotoxic T cells. Hence, directing efforts towards inhibiting TAN or obstructing particular pathways that facilitate the development of tumors in NET could serve as a novel therapeutic strategy for PDAC.

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2.4. Macrophages and TAMs

Macrophages are the primary component of immune cells within the TME. The expression of macrophage markers was much higher in mice PDAC tissues compared to normal pancreatic tissues, and there was an upward trend between the quantity of macrophages and the extent of fibrosis [28]. Macrophages are versatile and can change their characteristics. They can be categorized into two separate sorts: M1-like TAMs, which act as antigen presenters and have anti-tumor effects, and M2-like TAMs, which promote cancer growth and inhibit the immune system. TAMs in PDAC TME are classified as M2-like macrophages. C-C motif chemokine ligand 2(CCL2) released by tumor cells promotes the recruitment of circulating monocytes into tumor tissues, and tissue-infiltrating monocytes or tissue-resident macrophages can differentiate into TAMs, and studies have demonstrated a negative correlation between the quantity of circulating monocytes and the survival rate of individuals with PDAC [29]. Macrophages in many organs of the body have a mixed origin and macrophages of different developmental origins may have the same or different functions in the same tissue. A related study reported that suppression of tissue-resident macrophages greatly impeded the advancement of PDAC, whereas the elimination of monocyte-derived macrophages had a restricted impact on the advancement of the tumor, and that embryonic-derived TAMs have a unique fibrosis-regulating function and can expand with tumor progression [28]. Fibrosis is a characteristic feature of both PDAC and pancreatitis, and TAM secretes, directly deposits, and remodels ECM through the activation of fibroblasts. Chemotherapeutic drugs can induce tissue mismatch repair (MMR) in synergy with TAMs, and 5-fluorouracil, adriamycin, gemcitabine, paclitaxel, platinum compounds, and other chemotherapeutic agents, as well as resistance to anti-VEGF therapy are associated with TAMs [30]. Hence, the therapeutic strategy for targeting TAMs should prioritize inducing the conversion of M2-like TAMs to M1-like TAMs and inhibiting fibroblast activation.

2.5. MDSCs

MDSCs consist of myeloid progenitor cells, undeveloped macrophages, undeveloped granulocytes, and undeveloped dendritic cells. MDSCs can crosstalk with diverse immune cells. MDSCs affect macrophage and neutrophil polarisation and activation, interfere with macrophage and dendritic cell antigen-presenting functions, and inhibit NK cell cytocidal action [31]. All MDSC subpopulations are immunosuppressive, but the mechanism of suppression varies among subpopulations. PDAC cells release significant quantities of GM-CSF, a cytokine that induces the differentiation of myeloid progenitor cells in the bone marrow into MDSCs[32]. These MDSCs then accumulate within the tumor through the bloodstream. Multiple cytokines participate in triggering of the immunosuppressive characteristics of MDSCs. Chemotherapeutic drugs such as gemcitabine and fluorouracil upregulate GM-CSF while inducing tumor cell death, which is one of the reasons for the low responsiveness of PDAC to chemotherapy [33]. Gemcitabine-resistant PDAC cells would express higher levels of PD-L1 and produce more GM-CSF, thereby triggering aggregation of MDSCs and formation of immunosuppressive TME [33]. Recombinant telomerase-specific adenovirus lysosomal viruses have the ability to directly cause cell damage and suppress the production of GM-CSF by reducing the activity of the ERK, AKT, and NF-kB signaling pathways. These viruses can be utilized to inhibit the production of GM-CSF. When combined with PD-L1 blockers, they can effectively impede the growth of gemcitabine-resistant PDAC [34]. MDSCs can enhance EMT by modulating the CCL2-CCR4 axis and promote tissue fibrosis through the CCL5-CCR5 axis [35]. Using a mouse model that has been genetically modified to develop PDAC, by specifically targeting depleted MDSCs, there was an observed increase in the concentration of activated $CD8^+$ T cells within the tumor, induced apoptosis, and remodelled the tumor stroma. The integration of targeted treatments for MDSCs with chemotherapy or immunotherapy has the capacity to promote the growth of an anti-tumor TME that effectively eliminates tumor cells.

2.6. Dendritic cells (DCs)

DCs possess the most potent capability to deliver antigens and can activate memory T cells to set up immunological responses, which play a key role in the activation of cytotoxic T lymphocytes (CTLs). Elevated numbers of circulating DCs have been associated with improved survival rates in patients with PDAC, however, the cells are less frequent in the TME of PDAC and are mostly located in the margins of the tumor [36]. Various tumor-derived factors have been documented to impede DC aggregation and promote dysfunction [37]. The infiltration of DCs into the TME has the potential to reverse the immunological desert state observed in PDAC. Additional research is required to

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comprehend the precise factors that impede the penetration of DCs into the tumor. Regenerative islet-derived protein 3A (Reg3A) can be secreted by vesicular cells of pancreatitis and by PDAC cells, and is a marker of inflammatory pancreatic disease. PDAC cell-derived Reg3A upregulates the expression of STAT3/pSTAT3 and JAK2 in DCs to inhibit DC differentiation and maturation, while inhibiting the production of interleukin 12(IL12), which possesses antitumor effects, and increasing the secretion of pro-tumorogenic interleukin 23(IL23) to promote PDAC progression [38]. Tumor vaccines can overcome the tumor-induced immunosuppressive state, increase immunogenicity, and activate CTL cell activity. DC-based immunotherapy is undergoing clinical trials, and DC vaccines can now be prepared from tumor cells or their lysates, peptides, tumor RNA, mRNA, and viruses. DC vaccines can be prepared by isolating and culturing mononuclear cells from a patient's blood, stimulating their transformation into DCs, and stimulating them with tumor antigen peptides. The combination of a DC vaccine containing the nephroblastoma tumor gene 1 peptide (TLP0-001) and Tegio could offer advantages to patients with advanced or recurrent PDAC that is unresponsive or not well-tolerated by conventional treatment [39].

2.7. Mast cells (MCs)

MCs originate from bone marrow progenitor cells and are key effector cells in the process of anaphylaxis. An increased number of MCs infiltrating the TME correlates with an increase in pro-angiogenic factor expression and neovascularization, which frequently indicates that patients with PDAC have a poor prognosis [40]. TNF released by MCs stimulates the development and activity of DCs and triggers the activation of $CD8^+$ T cells, leading to the start of an adaptive immune response. This process ultimately results in the induction of anti-tumor actions [41]. However, MCs can also secrete vascular endothelial factor (VEGF), fibroblast factor 2 (FGF2), vascular-derived growth factor, and angiopoietin 1 expression, which promotes angiogenesis in tumors [42]. Differences in the function of MCs may be related to tissue heterogeneity and stage specificity. MCs may secrete bioactive substances by degranulation while affecting the function of other cells residing in the tissue. PDAC cells and pancreatic stellate cells (PSCs) can recruit and induce MC activation, MCs can stimulate PDAC proliferation and induce tumor cell resistance to gemcitabine, while MC-derived Interleukin 13(IL13) and trypsin-like enzymes promote PSC proliferation, and the connections between tumor cells, pancreatic stellate cells, and mast cells result in connective tissue proliferation in PDAC [43]. Investigators have been able to inhibit tumor growth in PDAC mouse with drugs that block MC migration and function [43]. Patients with PDAC have higher trypsin-like activity, and their levels correlate with the density of microvessels within the tumor [44]. Therefore, it has been suggested that inhibiting MC function can block tumor growth and relieve patients of drug resistance. A CXCR4 inhibitor that blocks the migration of MCs reduces tumor volume and inhibiting MCs migration in mice could increase survival [43].

3. Conclusions

PDAC is a very aggressive tumor with a very unfavorable prognosis, and surgery is the only way to eradicate PDAC, but the postoperative recurrence rate is nearly 90%, and about 50% of patients develop local recurrence and metastasis within 1 year after surgery[45]. Immune checkpoint inhibitors and T-cell immunotherapy demonstrate efficacy in only 2% of PDAC patients [4]. Current immunotherapy for PDAC focuses on relieving TME tolerance to immunotherapy and enhancing immune response against tumors in TME. The composition of immune cells, stromal cells, tumor cells and their stroma, blood vessels, and so on constitutes a special TME that leads to cellular growth, infiltration, and resistance to medication in PDAC. The functions of immune cells in the TME are not singular or static, and immune cells are heterogeneous, which can change their phenotypes through the interaction of various cells, and cytokines. They play the "double-edged sword" role, and with the deepening of the research, the subpopulations of cells performing different functions may be continuously refined. Nowadays, the correlation between TME and tumorigenesis and development and potential therapeutic targets are hotspots in PDAC research, and the treatment targeting TME may bring new benefits to PDAC patients. However, the composition and function of TME have complexity, and it is difficult to achieve the possibility of eradicating the tumor by single targeting of cells or stromal components, therefore, the combination of different targeted drugs or therapeutic strategies such as targeting drugs in combination with chemotherapy may play a more advantageous role. A comprehensive comprehension of the function of the TME, particularly immune cells, in PDAC, is crucial for the advancement of drug development and combination therapies.

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