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Current Status of Immunotherapy for Pancreatic Cancer

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Abstract:

Pancreatic ductal adenocarcinoma remains an awfully fatal malignancy whose five-year survival rate was merely 11%. Its immunosuppressive tumor microenvironment, characterized by immune cell dysfunction, limits the efficacy of conventional therapies. Immunotherapy has become the fifth major strategy of cancer therapy after chemotherapy, surgery, targeted therapy and radiotherapy, showing revolutionary therapeutic effects in a variety of solid tumors. Understanding the immune-related mechanisms of pancreatic cancer and developing targeted immunotherapy strategies have become the top priorities of current research. Recent advances show promise through strategies such as engineered chimeric antigen receptor-modified T(CAR-T) cells secreting cytokines like Chemokine (C-C motif) ligand 19(CCL19) and interleukin-7(IL-7), which enhance T-cell persistence and tumor clearance. Immune checkpoint blockade (ICB), though ineffective alone, benefits from combinations with metabolic modulators, β-blockers, or microbiome metabolites like trimethylamine N-oxide(TMAO). Oncolytic virotherapy combined with chemotherapy or immunomodulators can degrade stroma and stimulate antitumor immunity. Despite progress, challenges remain due to TME immunosuppression and low immunogenicity for pure immunotherapy. Future efforts should focus on combination therapies and microenvironment reprogramming to improve outcomes.

Keywords: Pancreatic ductal adenocarcinoma; Combination therapy; CAR-T cell therapy, Immune checkpoint inhibitors; Oncolytic virotherapy

1. Introduction

Pancreatic cancer, also known as pancreatic ductal adenocarcinoma (PDAC), is an awfully fatal adenocarcinoma of digestive system. It is hard to diagnose since its symptoms are initially vague. As a result, it remains an awfully fatal disease, whose five-year survival rate was only 11% in 2022 [1]. By 2030, PDAC

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is therefore predicted to rank second in the major causes of cancer-associated death in America [2]. Similar to other solid tumors, PDAC is caused by the accumulation of genetic mutations that lead to uncontrolled cell proliferation. During this process, reactions like pancreatic intraepithelial neoplasia (PanIN) and a mesenchymal transition of the surrounding stroma also sculpt a tumor microenvironment (TME) that actively promotes the growth of tumor, playing a crucial role in the development and treatment of PDAC [3].

The normal approaches of PDAC therapy, cytotoxic chemotherapy and radiotherapy, have a relatively low effect on PDAC, only extending overall survival (OS) of the patients by a few months [3]. However, immunotherapy has performed well in many different treatments of many kinds of solid tumors. Strategies such as chimeric antigen receptor (CAR) T cell therapy, included in adoptive cell transfer therapy; immune checkpoint-oriented immunotherapy, including immune checkpoint blockade (ICB) and oncolytic virotherapy have yielded clinical benefits in multiple cancers between 2010 and 2024, which can last for a relatively long period [3]. For example, it is reported that strategies like immune checkpoint blockade have achieved great success in leukemia and melanoma [4]. CAR-T also performed well in malignancies of blood system [5].

Yet, as is mentioned above, in PDAC, these successes have been significantly rare. The unique TME of pancreatic cancer, which is absolutely poor in immune-stimulatory stromal elements while rich in immunosuppressive cell subsets, physically and biochemically blocks the cytotoxic effect of cytotoxic T lymphocytes (CTLs). What is more, PDAC cells frequently upregulate programmed death-ligands 1 and 2 (PD-L1/PD-L2) to escape from immune surveillance of the immune system. But there still exist studies mentioning that through combining chemotherapy, surgery, cytotoxic agents or other complementary therapies with immunotherapy maybe can partially overcome these barriers and improve clinical outcomes of the treatment [3].

As a result, this article summarizes the progress in immunotherapy of pancreatic cancer in recent years, reviewing the mechanisms happening in pancreatic cancer and systematically clarifies the roles of important cellular components within the tumor microenvironment. Then the article focuses on the key immunotherapeutic approaches for PDAC: adoptive cell transfer therapy, immune checkpoint-oriented immunotherapy, and oncolytic virotherapy — highlighting recent progress in each area. Finally, it discusses the current limitations of immunotherapy in pancreatic cancer, hoping to provide insights and directions for future research.

2. Mechanisms in Pancreatic Cancer

2.1 Immune Mechanisms in Pancreatic Cancer

Within the PDAC microenvironment, immune cells are not passive bystanders, instead they are significantly important to the development and progression of tumors. Its composition and relative abundance are also an unneglectable factor of pancreatic cancer. Meanwhile, the percentage of the different cells influences the efficacy of treatment, namely the regression of tumors after therapy too. Among these immune cells, there are some kinds of cells which weight more, such as T cells, macrophages and natural killer (NK) cells.

Among T cells, CTLs are the major participants of tumor cell killing. Their intra-tumoral density correlates positively with patient prognosis. The T-cell receptors (TCRs) of CTLs can recognize the tumor-associated antigens through the reaction with MHC class I molecules, triggering the recognition and cytotoxicity related with perforin and granzyme to destroy the carcinoma cells. However, the role of helper T (TH) cells, another kind of T cells, is less well defined. Although TH1 has been associated with a prolonged survival, other TH cells present a contradictory outcome between experiments in murine and human. At the same time, regulatory T cells (Tregs) accumulated in PDAC are related with poor prognosis. They can use method such as cytokine secretion, metabolic re-programming and direct cell–cell contact, to disrupt the activity of T effector cells and boost the depletion of T lymphocytes. Then comes the NK cells. They are related with the surveillance tumor immunosurveillance and growth resistance. However, for the tumor cells, up-regulating Igγ-1 chain C region (IGHG1) and down-modulating CXCR2 are the method frequently observed to the evade the NK cells immunity. What is more, circulating monocytes will also be recruited into the TME and differentiate into tumor-associated macrophages (TAMs) because of the elements like the stimulation promoted by cytokines. Although classically activated M1 macrophages exert anti-tumor activities, most TAMs are still related with poor prognosis to some extent. This may be because M2 macrophages, which are also part of TAMs, secrete anti-inflammatory signals leading to the progression of pancreatic cancer [3].

2.2 Non-immune Mechanisms in Pancreatic Cancer

Beyond immune cells, non-immune constituents of the TME, including pancreatic cancer stem cells (PCSCs), pancreatic stellate cells (PSCs), cancer-associated fibroblasts (CAFs) and mesenchymal stem cells (MSCs),

equally play important parts during the whole process of cancer development.

The PCSCs, which cannot be forgotten as the main part of cancer, are endowed with self-renewal and tumor-initiating capacities. They can enhance the drug resistance of pancreatic cancer cells and promote their metastasis through irregular signal transduction of pathways like Hedgehog, Notch and JAK-STAT. At the same time, specific subsets of CSC marked by CD133 and CXCR4 can also enhance tumor metastasis of human pancreatic cancer.

MSCs will be transformed into tumor associated MSCs (TA-MSCs) by TME. TA-MSCs can recruit immune cells such as neutrophils through CCL2 and CCl7 and release substances such as CXCL9, CXCL10, CXCL11 to suppress effector T cells. In addition, it also produces a large amount of factors that promote metastasis and tumor, promotes tumor angiogenesis through VEGF, and increases tumor chemotherapy resistance through NO.

Meanwhile, CAFs, originating from diverse cell sources like adipocytes, pericytes, and bone marrow-derived macrophages, which directly interact with cancer cells via paracrine signaling and cell-cell pathways, are influenced by TGF - β, forming a mechanical barrier and producing cytokines and chemokines such as IL-6 to boost cancer proliferation. CAFs are also nonnegligible in the formation of immunosuppressive microenvironment in PDAC. In addition to controlling immunosuppressive cells, CAFs promote the expression of immunosuppressive checkpoints.

What's more, PSCs also have a promoting effect on immune suppression. PSCs can release basal fibroblast growth factor (bFGF), insulin-like growth factor 1 (IGF-1), platelet-derived growth factor (PDFF) to amplify pancreatic tumor aggressiveness [3].

3. Immunotherapy of Pancreatic Cancer

In PDAC, immunotherapy refers to treatment strategies designed to activate or enhance one's own immune system so that it can identify and attack tumor cells. Common immunotherapies include adoptive cell transfer therapy, oncolytic virotherapy (OVT) and immune checkpoint–oriented immunotherapy. Yet, the effect of single-agent approaches can be limited, usually because pancreatic tumors create a profoundly immunosuppressive microenvironment. In this part, the concepts and strategies in pancreatic-cancer immunotherapy will be discussed, with particular emphasis on the mechanisms and impact of CAR-T, ICB and OVT.

3.1 Adoptive Cell Transfer Therapy

Adoptive cell transfer therapy is a method of treating cancer by obtaining, editing, and regenerating the cells got from the patients. One of the most well-known adoptive cell therapies is CAR-T cell therapy. One's T cells are collected and edited to produce CARs on the surface that can detect tumor antigens in this therapy. Recent studies have shown that combining cytokines with CAR-T cells can improve the curative effect of CAR-T in PDAC.

Related animal experiments have proven this idea. The study by Yang Zhao et al. showed that CAR-T cells can enhance their own mitochondrial fitness through MPC and restore mitochondrial oxidative phosphorylation by secreting IL-10, thereby resisting T cell exhaustion [6]. In their experiment, CD19 hCAR T cells expressing IL-10 performed better in treating PDAC than traditional CD19 hCAR T cells, with 100% of treated mice showing complete response, compared to only 40% of treated mice with traditional CD19 hCAR T cells [6].

Moreover, in human trials, some studies have also shown that further modifying CAR-T cells to secrete cytokines can significantly improve their therapeutic effects. In the study by Nengzhi Pang et al., a patient with advanced pancreatic cancer expressing MSLN, who had local lymph node metastasis, achieved complete remission after infusion of MSLN-7×19 CAR-T cells, a type of CAR-T cell that secretes human IL-7 and CCL19 [7].

Although ordinary CAR-T is highly effective in curing blood tumors, such as B-cell malignancies, its healing effect in solid tumors is not satisfactory. Ordinary CAR-T cells are usually exhausted and become dysfunctional in the microenvironment of solid tumors. Charly R. Good et al. validated through TCR sequencing and lineage tracing that the dysregulation of CARs is associated with the conversion from CD8+ T cells to NK-like T cells, a step that leads to the dysfunction in CAR-T cells [5]. A variety of NK receptors, including KIR2DL4, KLRB1, KLRC3, KLRD1, KLRC2, and KLRC1, can be upregulated on dysfunctional CAR-T cells. Meanwhile, they also identified crucial switch of CAR-T cell exhaustion: SOX4 and ID3. They demonstrated that genetically downregulating the expression of ID3 and SOX4 will improve the healing effect of CAR-T, reducing the conversion of NK-like T cells caused by long-term exposure to tumor antigens by about 50% [5].

3.2 Immune Checkpoint-oriented Immunotherapy

Immune checkpoint-oriented immunotherapy mainly refers to immune checkpoint blockade (ICB) therapy, and the drugs used in this therapy are called immune check-

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point inhibitors (ICIs). By inhibiting specific inhibitory immune checkpoints, it can restore T cells' abilities and prevent tumor cells from suppressing them. Common immune checkpoints include CTLA-4 and PD-1.

Lately, numerous studies have illustrated that ICB therapy combined with other drugs has an improved performance in treating tumors. Ji Liu et al. proved in 2024 that anti-PD1 ICB shows a better result when the patients are supplemented by tetrahydrobiopterin (BH4). While in human PDAC, patients with high quinone dihydropteridine reductase (QDPR) levels have a response rate of 53.8% to ICB, and those with low QDPR levels have only 7.7%, supplement of BH4 can enhance the scale of BH4 to dihydrobiopterin (BH2) in PDAC to confront the effect of low QDPR, almost fully inhibiting neoplasm proliferation and greatly extended the survival time in animal tests [8]. Anna-Maria Globig et al. also found that ICB used with β-blockers, which can block the ADRB1 and ADRB2, can increase the reaction of CD8+ T cells. This therapy can restore the cancer-controlling activity of T lymphocytes and promote the formation of memory T cells to form antitumor immunotherapy at the same time [9]. In addition, ICB can also interact with the metabolism of gut microbiota to improve the therapeutic effect. Gauri Mirji et al. found that trimethylamine N - oxide (TMAO), which is found as a gut-microbiota metabolite, can boost the type I interferon (IFN) pathway, improving the survival in tested PDAC subcutaneous murine model. About 75% ICB + TMAO treated examples survived more than 70 days, while only less than 50% ICB treated mice survived the same time [10].

However, treatment with ICI alone does not benefit patients with pancreatic cancer. In the study by Richard E. Royal et al., according to the RECIST criteria, Ipilimumab, a kind of ICIs, which are used to inhibit CTLA-4, showed no therapeutic effect in 27 patients who were diagnosed with metastatic / locally advanced pancreatic cancer [11].

3.3 Oncolytic Virus Therapy

Oncolytic virotherapy (OVT) is a therapeutic approach that involves the injection of oncolytic viruses (OVs) to directly lyse tumor cells and elicit an immune response against the tumor within the body. Common oncolytic viruses include Talimogene laherparepvec (T-VEC), a Herpes simplex virus (HSV), and VCN-01, which selectively replicate in tumor cells rather than normal cells, thereby exhibiting specificity for tumor cells.

Recent studies have found that combining OVT with other therapies can effectively enhance therapeutic efficacy. VCN-01 can generate hyaluronidase while targeting tumor cells, as an oncolytic adenovirus. It is designed to reproduce in the cells whose RB1 pathway doesn't work. The VCN-01 can lead to more complete tumor regression in over 50% of cases when nab - paclitaxel and gemcitabine are used together. Research has shown that the hyaluronidase expressed can degrade the tumor stroma, consequently facilitating the delivery of other drugs and enhancing its antitumor effects when used in combination with chemotherapy [12]. Shiyu Liu et al. engineered herpes simplex virus - 1 (HSV-1)by inserting an OX40L fragment to construct the OV - mOX40L oncolytic virus, which can enhance T cell function and prolong the survival of PDAC - bearing mice. Versus the control cohort, OV - mOX40L can extend the median survival time of mice from 39 days to 61.5 days, an increase of approximately 58%, and its integration with anti - IL6 anti-body as well as anti-PD - 1 antibody can even lead to the cure of 62.5% of the PDAC - bearing mice [13]. In addition, in the study by Pooya Farhangnia et al., they combined OA targeting PD - L1 with T cells. Their work showed that the engineered oncolytic virus markedly lowered PD-L1 levels in tumor cells, raising the 60-day survival of humanized PSCA+ PDAC PDX model mice to 40 % [14].

However, OVT is not without its drawbacks. The systemic delivery methods more commonly used in clinical practice can prevent OVs from directly entering the tumor, resulting in a low rate of viral uptake. Additionally, it boosts immune-checkpoint ligands across tumor and immune-cell populations, blunting effector T-cell activity.

4. Conclusion

Pancreatic cancer is an awfully fatal neoplasm of the digestive system. During its initiation and progression, despite the tumor-suppressive roles of CTLs, NK cells and M1 macrophages, many kinds of immune and non-immune components can foster an immunosuppressive microenvironment by enhancing tumor drug resistance and up-regulating immune-checkpoint molecules, thereby exhausting immune cells and promoting tumor growth. Clinically, immunotherapeutic strategies-including CAR-T cells reprogrammed for cytokine release, ICB combined with other agents, and oncolytic viruses together with chemotherapy or cellular therapies—have been employed to prolong survival, remodel the immune microenvironment, and alleviate T-cell exhaustion. Nevertheless, immunotherapy still faces limitations: the immunosuppressive tumor microenvironment and low tumor immunogenicity may render single-modality immunotherapy ineffective. Future research should therefore focus on combination regimens that integrate immunotherapy with other modalities and on approaches that reverse the immunosuppres-

sive tumor microenvironment.

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