

# Research of immunotherapy in pancreatic cancer

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**Abstract:** Pancreatic cancer has a low incidence but remains one of the deadliest cancers, and its complex microenvironment is easy to coordinate metabolic changes and allow tumor cells to properly escape immunity. This article focuses on the immune microenvironment of pancreatic cancer, the current common immunotherapy methods and the state of clinical immunotherapy for pancreatic cancer and its outlook in the future. This article not only reviews the microenvironmental mechanisms studied by scientists, but also goes into more detail about recent developments in immunotechnology that have expanded our knowledge of how complex pancreatic cancer is. It is hoped that through the review of this article, readers can have a more detailed understanding of pancreatic cancer, which will help improve the survival rate of this too low disease through mechanism studies and clinical trials in the future.

## 1. Introduction

In 2018, 458918 cases of pancreatic cancer were detected and 432242 deaths were reported. Pancreatic cancer is a malignancy characterized by a particularly high mortality rate and a dismal prognosis on a global scale [1]. Patients diagnosed with the disease often face a grim prognosis, as the 5-year survival rates for this disease typically fall below 5% [2, 3]. Pancreatic ductal adenocarcinoma (PDAC) is the commonly observed histological subtype of pancreatic cancer, and adenocarcinoma represents approximately 85% of the total cases of pancreatic cancer, while pancreatic endocrine tumors constitute less than 5% of the overall incidence [1, 3, 4]. The timely detection of pancreatic cancer is challenging, and more patients are found to be in an advanced stage, which brings great difficulty to treatment.

According to recent studies, the development of pancreatic cancer is believed to be influenced by a range of factors, including congenital inheritance, terrible lifestyle habits, etc. [5, 6].

Advanced pancreatic cancer often loses the opportunity of surgery, and is not sensitive to chemotherapy or radiotherapy, and patients are at high risk of experiencing recurrence or metastasis. The postoperative five-year survival rate ranges from 15% to 25% [7]. Therefore, finding more effective treatment options in the clinic is of great value to pancreatic cancer patients. In recent years, immunotherapy has shown promising results in the clinical implementation of tumor treatment, and its clinical application in vaccine therapy has received more and more attention. Examples of dendritic cell vaccines, peptide vaccines, and DNA vaccines. They deliver tumor antigens directly to the immune system and induce tumor antigen-specific CTL activation, thereby exerting anti-tumor immunity [8]. On

the other hand, adoptive cell transplantation is also important. It collects the patient's own tumor antigen-specific T cells, proliferates them outside the body, and injects them into the patient. This can improve the body's immunity. This method has been shown to have good efficacy in a variety of tumor animal experiments [9].

This article briefly introduces the commonly used immunotherapy methods for pancreatic cancer, and explores the interaction and influence between cells in the immune microenvironment of pancreatic cancer. Finally, the current status and prospects of clinical immunotherapy for pancreatic cancer are discussed, including the immune side effects shown in clinical trials that prolong survival failure in patients, and comprehensive immunotherapy regimens that try to improve the survival rate of pancreatic cancer with a very poor prognosis. [10, 11]

## 2. Pancreatic cancer immune microenvironment

### 2.1 Pancreatic cancer cells

There are many types of pancreatic cancer cells, among which ductal adenocarcinoma is the most common, accounting for more than eighty percent of pancreatic cancer cases. Ductal adenocarcinoma consists mainly of differentiated ductal glands with abundant fibrointerstitium. The development of pancreatic cancer cells is usually accompanied by multiple gene mutations, and the most common subtype of oncogenic mutation is KRAS, according to the detailed genetic profile of PDAC that has been provided. KRAS mutations were found in approximately 95% of patients [12-15]. In addition, loss-of-function mutations in p53 often result in accumulation of intracellular genetic damage in pancreatic cancer. This

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phenomenon ultimately culminates in the onset and progression of malignant neoplastic diseases. In the later stages of cancer occurrence and development, approximately 75% of patients carry p53 mutations [16, 17]. Currently, the sole conventional biomarker employed for the management of PDAC is serum glucose antigen 19-9 (CA19-9), and in subsequent times the sensitivity of pancreatic cancer detection can be improved by measuring antigens on individual proteins or combining them with other markers.

Research on the treatment of pancreatic cancer has been carried out for many years, and finding suitable therapeutic targets will bring new hope for improving the prognosis of this disease. Despite the diversity of PDAC mutations between and within tumors, more than 95% of patients demonstrate activating mutations in the KRAS gene [14, 18, 19].

## 2.2 Cell matrix components

The cell matrix provides sufficient nutrients and metabolic components for the growth and proliferation of tumor cells, and scientists have conducted extensive research on the cell matrix, hoping to regulate the main substances in the cell matrix, and then as an innovative idea for intervention in pancreatic cancer. The PDAC matrix primarily comprises the extracellular matrix (ECM) and cancer-associated fibroblasts (CAF) [20]. Among them, CAF can produce a variety of paracrine molecules, such as transforming growth factor- $\beta$  (TGF- $\beta$ ) and platelet-derived growth factor (PDGF), which contribute to local tumor invasion and metastasis. One study showed that loss of E-cadherin, increased wave protein expression, and activation of CAF in tumor buds coincided with epithelial-mesenchymal transformation (EMT) in cancer cells and was associated with an increased probability of highly aggressive tumors requiring prompt resection.

ECM is a component of the three-dimensional framework of tumors that is not made up of cells. It is produced and released by cells in the tumor microenvironment to provide physical and chemical help to the tumor. The characteristic of connective tissue hyperplasia also lies in the continuous remodeling of ECM, which refers to the ongoing breakdown and accumulation of ECM molecules (like collagen) in the tumor microenvironment. The excessive accumulation of collagen in the tumor microenvironment leads to an increase in tumor density, which in turn affects its mechanical characteristics. Research has shown that collagen is the most prominent proteome in the matrix during the development of PDAC and long-term inflammation of the pancreas. More than 90% of the proteins in ECM are made up of collagen.

## 2.3 Immune cells

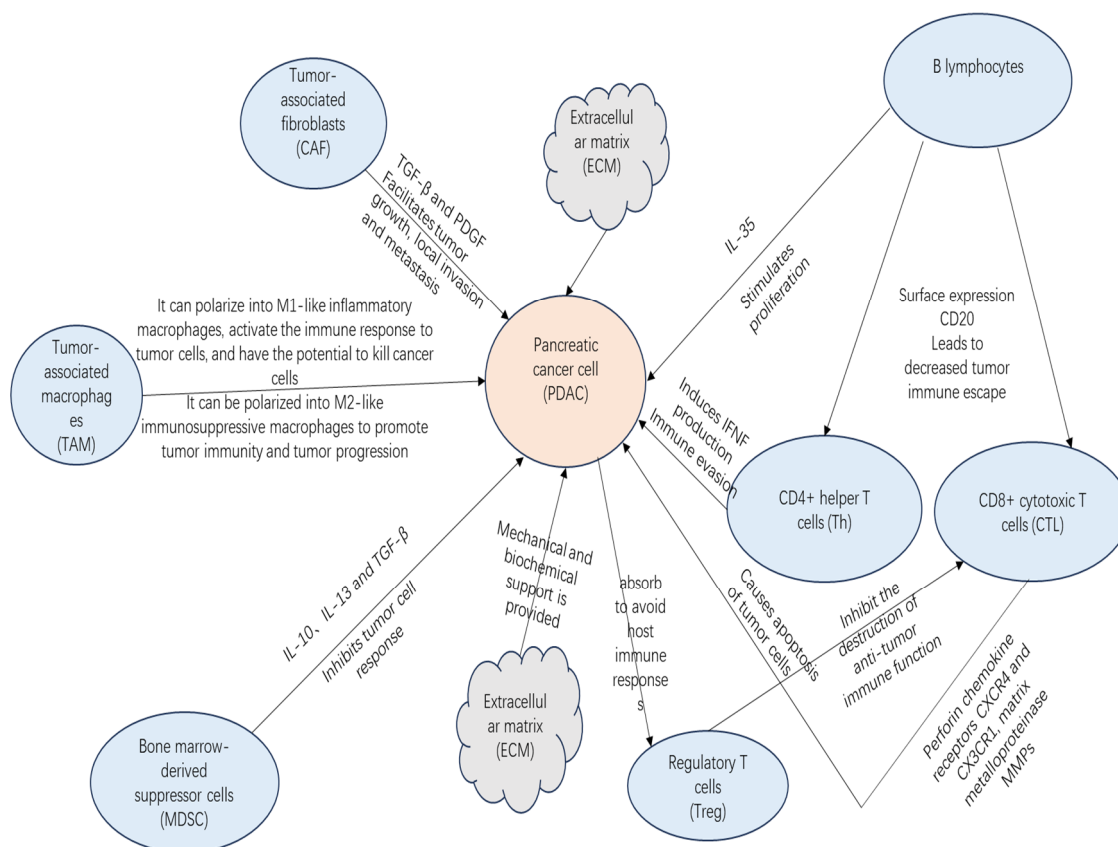
Pancreatic cancer immune cells rely on immunosuppressive cells to function. These immunosuppressor cells can be divided into three main types: myeloid-derived suppressor cells (MDSCs),

tumor-associated macrophages (TAMs), and regulatory T cells (Tregs). The occurrence of pancreatic cancer is closely related to immune dysfunction. Certain types of pancreatic cancers are caused by the enlistment of cells that suppress the immune system, such as MDSC and TAM. These cells are enlisted to the tumor microenvironment and have the ability to suppress the activity of T cells. The MDSCs have the ability to release indoleamine 2,3- $\beta$  Dioxygenase, arginase- $\beta$  I, reactive oxygen species (ROS), and various inhibitory cytokines (IL-10, IL-13, and TGF- $\beta$ ) to inhibit immune responses against tumors. TAM and myofibroblasts play a vital role in cancer progression and are closely related to drug resistance in PDAC. Tumor-associated macrophages (TAMs) and myofibroblasts played a direct role in promoting chemoresistance in pancreatic cancer cells by secreting insulin-like growth factors (IGF) 1 and 2. Treg cells exert their influence on tumor growth through direct interactions with cancer cells or by suppressing the activity of effector immune cells. These Treg cells, which belong to the CD4<sup>+</sup> T cell subset, play a significant role as constituents of tumor-infiltrating lymphocytes. Their unique function involves facilitating tumor progression and invasion by dampening the host's immune response and pro-inflammatory reactions.

B lymphocytes, an indispensable part of the acquired immune system, having a significant impact on facilitating anti-tumor responses. This is achieved by participating in the presentation of antigens, activation of T cells, and production of antibodies against tumors. Studies have shown that B cells can hinder the immune response to tumors by inhibiting the function of anti-tumor cytotoxic T lymphocytes and Th1 cytokine responses. Studies have shown that the CD40 molecule expressed by B lymphocytes may contribute to this inhibitory process.

T lymphocytes are the workhorse of immune cells. They are typically classified into two categories: CD4<sup>+</sup> helper T cells (Ths) and CD8<sup>+</sup> cytotoxic T cells (CTLs). Research has demonstrated that PC-soluble mediators directly target CD4<sup>+</sup> Ths. These mediators inhibit cell proliferation, impede their migration, promote the growth of CD69<sup>+</sup> subsets, and stimulate the production of interferon F (IFNF). These results indicate that pancreatic cancer is able to achieve immune evasion with the help of CD4<sup>+</sup> Ths. CD8<sup>+</sup> CTLs are essential in the body's immune defense against cancer. These cells identify class I MHC peptide complexes on the outer layer of cells and eliminate cancer cells through mechanisms such as membrane penetration, apoptosis induction, or activation of self-destruction pathways. Studies have shown that CD8<sup>+</sup> CTLs have the capability to trigger programmed cell death in cancerous cells through the release of perforin and granzyme. This mechanism effectively hinders the beginning and advancement of cancerous growths. Additionally, CTL possess enhanced migratory capacity and the ability to infiltrate the ECM of tumors. These cells express a diverse range of chemokine receptors, including CXCR4 and CX3CR1, as well as matrix metalloproteinase MMPs. These characteristics collectively contribute to the heightened resistance of CTL cells against pancreatic

tumors (figure 1). In summary, the rich functions of T cells make them the protagonists of cellular immunity.



**Figure 1.** Pancreatic cancer immune microenvironment

### 3. Methods of immunotherapy for pancreatic cancer

#### 3.1 Oncology vaccines

Therapeutic oncology vaccines are crucial in the field of tumor immunotherapy as they enhance the immune response against tumors in patients through active immunity. These vaccines encompass various types such as dendritic cell (DC) vaccines, DNA vaccines and peptide vaccines.

Dendritic cells are antigen-presenting cells (APCs). They have the ability to stimulate initial T cells and enhance the anti-tumor immune response. DC vaccines are generated by isolating DCs from patients and culturing them outside the body. These DCs are then matured and activated before being reintroduced into the patient. The DC vaccine presents antigens to T lymphocytes and secretes IL-15, IL-12, IFN- $\gamma$  and TNF, among others, thereby activating cytotoxic CD8 + CTLs to kill cancer cells. In addition, there is growing evidence that tumor antigen-based DC vaccines demonstrate effectiveness in inducing T cell-mediated, adaptive cellular lytic immune responses in PDAC.

Peptide vaccines offer several advantages, including simplicity, safety and stability. There is a wide range of peptide vaccines, including telomerase peptide vaccines. Telomerase, an enzyme responsible for preserving

cellular stability, is found in nearly all pancreatic cancer cells, accounting for approximately 85 to 90% of cases. A study investigating the effects of administering a telomerase peptide vaccine demonstrated a correlation between the vaccine's immunogenic response and prolonged survival, while also exhibiting good tolerability. However, the utilization of peptide vaccines is subject to certain limitations. These include the restricted availability of antigenic peptides and the potential influence of suppressor immune cells within the tumor microenvironment, both of which can impact the efficacy of the vaccine.

The DNA vaccine, also referred to as a nucleic acid vaccine or gene vaccine, involves the direct administration of a recombinant eukaryotic expression vector containing a protein antigen into an animal. This results in the expression of the foreign gene within the animal's body, leading to the production of the antigen. Consequently, the body's defense system against diseases is activated, leading to the formation of targeted humoral immunity and cellular immune response. DNA vaccines seek to introduce the naked DNA sequence of a specific component of a disease-causing microorganism directly into the host organism. This type of vaccine offers the benefits associated with attenuated vaccines. At the same time, there is no danger of reversal, so it is regarded as the third generation of vaccines after traditional vaccines and genetically engineered subunit vaccines.

### 3.2 Adoptive immune cell therapy

Adoptive immune cell therapy is increasingly being explored in solid tumors. Specifically, The use of genetically modified targeted T cells for adoptive transfer has become a reliable approach for treating PDAC.

Chimeric antigen receptor (CAR) T-cell therapy is a commonly employed modality of adoptive cell therapy in contemporary clinical contexts. The process entails the retrieval of T cells from patients via apheresis. These T cells are subsequently expanded and genetically altered to express a CAR, which enables them to identify and bind to tumor cells. In the end, the modified CAR-T cells are introduced into the patient's body with the aim of specifically and effectively attacking and eradicating the malignant cells. T cells in close proximity to the tumor exhibit distinct T cell receptors linked to PDAC, such as p53 or telomerase. These CTLs maintain their ability to target tumors and their existence is significantly correlated with enhanced patient survival.

### 3.3 Immune checkpoint inhibitors

In general, immune cells produce small protein molecules that inhibit their own function, which tumor cells take advantage of mechanism inhibits immune cells to elude the immune response of the body's immune system and persist. Immune checkpoint inhibitors (ICI) can remove this inhibition and reactivate immune cells to destroy cancer cells. Currently, the immune checkpoints that are frequently utilized are cytotoxic T lymphocyte associated antigen-4 (CTLA-4), programmed death-1 (PD-1), and programmed death ligand-1 (PD-L1). PD-1 is found to be present on T lymphocytes, along with various other immune cells. Additionally, PD-L1 is one of the ligands associated with it. The interaction between these two molecules can result in the generation of inhibitory signals within T lymphocytes. Ipilimumab (MDX-010) and tremelimumab are human monoclonal, a member of the B-7 family whose binding to CTLA-4 blocks the conduction of immunosuppressive signals. One study has tested the tumor-killing effect of the anti-PD-L1 antibody Nivolumab. The report surveyed 207 patients diagnosed with various forms of advanced cancer. Objective response rate was 93.2%.

However, the efficacy of these antibodies in PDAC therapy remains uncertain due to the presence of many immunosuppressive mechanisms and the immunosuppressed nature of pancreatic cancer. It should be noted that simply blocking immune checkpoints does not guarantee complete suppression of the immunosuppressed environment. The concurrent administration of ICI and chemotherapy demonstrated favorable outcomes. A research study discovered that previously untreated patients who were administered a combination of pembrolizumab, gemcitabine, and albumin-bound paclitaxel exhibited a greater overall survival (OS) rate compared to those who received folfirinnox (a combination of oxaliplatin, irinotecan, and 5-Fluorouracil/folinic acid), as reported in terms of OS. These findings may suggest that adding immune

checkpoint inhibitors to standard PC therapy may be more effective (table 1).

**Table 1.** Common immune checkpoint inhibitors and targets

Immune checkpoint inhibitors	Monoclonal antibody targets
Ipilimab	CTLA-4
Trametinumab	CTLA-4
Pembrolizumab	PD-1
Nivolumab	PD-1
Pidilizumab	PD-1
Atezumab	PD-L1
Devaluzumab	PD-L1

## 4. Current status and prospect of pancreatic cancer immunotherapy

The initial stages of pancreatic cancer typically do not present with readily apparent clinical symptoms. Early diagnosis is challenging. In addition, the degree of malignancy of the disease is usually high, resulting in a poor prognosis. In the treatment of early-stage pancreatic cancer, it is frequently advised to administer adjuvant chemotherapy after surgical removal for patients with unresectable locally advanced tumors and distant metastases. Despite initial optimism surrounding the use of FOLFIRINOX (a combination of oxaliplatin, irinotecan, and 5-fluorouracil/folinic acid) and gemcitabine/albumin-bound paclitaxel, which have demonstrated the ability in enhancing the outcomes of patients with advanced pancreatic cancer. But the emergence of chemoresistance continues to contribute to unfavorable clinical outcomes. Immunotherapy has made significant progress and has become an important part of medical treatment. But monotherapy does not appear to be effective. In the field of oncology, the development of tumor vaccines and CAR-T has made significant progress, and the approach of altering the immune microenvironment to transform "non-responsive" tumors into "immunologically active" tumors has demonstrated favorable safety profiles and prognostic outcomes. The implementation of combination therapy is expected to significantly improve the prognosis of pancreatic cancer, thereby providing a positive outlook for the disease.

Immunotherapy has limitations, and ICI therapy alone has not resulted in universal benefit for patients. In a study evaluating the efficacy of ipilimumab monotherapy in patients with advanced pancreatic adenocarcinoma, a total of 27 participants were enrolled. During the course of the trial, three instances 3,4 immune-mediated negative events were documented among the participants. Tragically, one case resulted in death. The combination of chemotherapy and immunotherapy has shown significant progress in the treatment of certain types of solid tumors. However, the development of effective treatment protocols for PDAC continues to be a challenge.

In recent years, immunotherapy for pancreatic cancer has given birth to many new strategies. Therapeutic oncology vaccines are crucial in the field of tumor immunotherapy as they enhance the patient's immune

response to tumors by activating active immunity. GVAX has the ability to generate granulocyte-macrophage colony-stimulating factor, which in turn stimulates T cell immunity against cancer antigens. Additionally, the combination of GVAX with low-dose cyclophosphamide (Cy) has the potential to suppress Tregs. *Listeria mesothelin* expresses *Listeria mesothelin* (CRS-207) attenuated live monocytogenes *Listeria* has the ability to stimulate innate and adaptive immune responses. Research has found that initial immunization with Cy/GVAX, followed by booster immunization with CRS-207 Nor, can significantly extend the survival of individuals with pancreatic cancer, while causing minimal adverse effects. Equally significant is the utilization of targeted matrix drugs in conjunction with immunotherapy. Focal Adhesion Kinase (FAK) is a kind of tyrosine kinase. Regulates various cellular functions, especially those related to tissue adhesion and migration. In experimental PDAC mouse models prior to clinical trials, the administration of pharmacological inhibitors targeting FAK has been shown to result significantly delay tumor progression and prolong overall survival. Furthermore, the effectiveness of FAK inhibition in suppressing tumor growth is further enhanced when combined with and gemcitabine, a commonly used chemotherapy drug. The concurrent administration of defactinib, pembrolizumab, and gemcitabine demonstrates favorable tolerability and safety profiles, exhibits encouraging initial efficacy. The aforementioned substance demonstrates biomarker activity within infiltrating T lymphocytes.

## 5. Problems with the existing treatment of pancreatic cancer

First of all, there are few obvious symptoms in the early stage of pancreatic cancer, and ordinary imaging tests such as abdominal ultrasound and ordinary CT usually do not detect early pancreatic tumors. To make matters worse, it lacks the ideal early screening tools. Secondly, surgical treatment has played a significant role but still faces challenges, pancreatectomy is still a difficult and high recurrence rate of surgery, and common complications include delayed gastric emptying, pancreatic fistula and infection. In today's day and age, the incidence after pancreatectomy is 40-50%. Finally, there is a lack of effective therapeutic drugs. Pancreatic cancer is not sensitive to chemoradiotherapy, and there is a lack of effective targeted drugs, and the latest PD1-PDL1 immune checkpoint inhibitors are also ineffective against pancreatic cancer.

## 6. Conclusion

This article focuses on the clinical research of pancreatic cancer immunotherapy, mainly including the immune microenvironment of pancreatic cancer, commonly used immunotherapy, and the current status and prospect of clinical immunotherapy. Unlike conventional therapies such as surgery, chemotherapy, radiotherapy, etc., immunotherapy mainly uses the own immune system to

fight tumors. This approach has yielded promising research findings and has been implemented in clinical settings. Combination therapies have become mainstream. The current state of research on pancreatic cancer is still limited, indicating that further research and exploration in this field is urgently needed. In the future, we should learn from the immune side effects shown in failed clinical trials that prolong patient survival, and the use of comprehensive immunotherapy regimens to try to improve survival for this disease with a very poor prognosis. It is hoped that through the elaboration of this article, readers will have a preliminary understanding of immunotherapy. It is anticipated that in the foreseeable future, human beings will achieve triumph over pancreatic cancer and achieve a comprehensive cure for the disease.

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