The Progress and Development Prospects of Targeted Therapy for Pancreatic Carcinoma

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Abstract. Pancreatic cancer is a malignant tumor with extremely high malignancy and poor prognosis. At present, targeted therapy is the latest progress in the treatment of pancreatic cancer; The development of receptors for drugs targeting pancreatic cancer has also made great progress, and specific drugs targeting some receptors have also been approved for marketing. However, the clinical effect of targeted therapy for pancreatic cancer has not reached a stable state, and the side effects of some targeted drugs have not been effectively solved. This article reviews the research on therapeutic targets for pancreatic cancer such as TROP2, PI3K and CIP2A in recent years and the development of Claudin 18.2, a new target. It is found that the research on Trop2 and CAPA is relatively complete and has achieved effective results. Both of them are effective targets for targeted treatment of pancreatic cancer. However, the research on PI3K and Claudin 18.2 is less, and their effects and mechanisms are not effectively supported by theory. In addition, this article summarized the research on EGFR, Her, CAR-T, GRPR and other receptors related to targeted treatment of pancreatic cancer and their related drugs and therapies. It was found that the research on EGFR, Her and CAR-T had achieved significant research results in the clinical stage, and their related drugs and therapies were approved for marketing; However, there are still deficiencies in the research on the influencing factors, stable clinical efficacy, and side effects of drugs targeting the aforementioned receptors. Future research can focus on overcoming tumor microenvironment, avoiding side effects of targeted drugs for pancreatic cancer, and new targets for targeted treatment of pancreatic cancer.

Keywords: Targeted therapy for pancreatic cancer; EGFR; CAR-T; GRPR.

1. Introduction

Pancreatic carcinoma (PC) is a common malignant tumor of the digestive tract, originating from pancreatic tissue, and is known as the "king of cancer" in the field of tumors. According to The Lancet, the five-year survival rate for PC after diagnosis is about 10%, making it one of the malignancies with the worst prognosis. Because the pancreas is located deep in the human body, it is often difficult to detect in the early stage of PC, and it usually has no obvious symptoms in the early stage, and as the disease progresses, symptoms such as abdominal pain, jaundice, and weight loss may occur. Compared with other gastrointestinal cancers, PC has a low incidence of only 15 per 100,000, and if PC is detected at an early stage and no other organ transplants have occurred, it can usually be completely removed by surgery, with a cure rate of 90%. However, because the symptoms of PC are relatively insidious and atypical, it is difficult to detect in the early stage of cancer, and the cancer cells metastasize relatively quickly, usually found to be in the middle and advanced stages, the disease has been more serious, and the chance of radical cure has basically been lost, so the mortality rate of PC is relatively high, about 50% to 90%, and the incidence of pancreatic cancer is on the rise worldwide [1]. PC is difficult to treat, and even if pancreatic cancer is diagnosed with clinical symptoms, surgery is more difficult, and the risk is very high. In addition, PC cells tend to be malignant, prone to spread and metastasize, and are less sensitive to radiotherapy and chemotherapy, resulting in a very poor prognosis.

The main treatments for PC include surgery, chemotherapy, radiotherapy, interventional therapy, and supportive care. Supportive care is a subset of drug therapy that helps patients undergo subsequent surgery, radiotherapy, and chemotherapy, but there is no absolute most effective drug due to large individual patient variations. Patients with advanced PC or before or after surgery are given chemotherapy, but PC is not sensitive to chemotherapy. Therefore, the combination of radiotherapy

and chemotherapy is the first choice and important treatment for locally advanced PC, but the value of radiotherapy after PC is still controversial due to the high resistance to radiotherapy and the poor tolerance of radiation to adjacent organs. Surgical resection is currently the only effective way for PC patients to achieve cure and long-term survival, and patients need to undergo a number of related examinations regularly after surgery, but more than 80% of patients lose the chance of radical cure due to late diagnosis. Interventional therapy and TCM treatment can play a role in assisting and relieving pain in other PC treatments.

At present, the latest development in the treatment of PC is targeted therapy, that is, drugs that target specific organs or cells are used alone or in combination with chemotherapy drugs to produce a certain effect on PC. Most of the existing therapies for PC have certain limitations. Compared with traditional therapies, targeted therapeutics have the advantage of accurately reaching tumor cells or tissues and inhibiting or killing tumor cells. Currently, the existing targeted therapeutics for PC include vascular-targeted drugs, cell-targeted drugs and immune-targeted drugs [2]. The commonly used target drugs for PC include erlotinib, nituzumab, etc., but the efficacy is uncertain. The tumor microenvironment of PC, such as matrix barrier, immune microenvironment, and exosomes, plays an important role in promoting the proliferation, invasion, metastasis, and chemoradiotherapy resistance of PC cells [3]. At present, the main causes of PC treatment failure are the intensive fibrotic reaction in the stroma and the changes in the tumor immune environment. Therefore, the tumor microenvironment has a certain impact on the development and progression of PC and the targeted therapy of its immunity [4]. The study of potential targets related to the tumor microenvironment and its clinical therapeutic effects can provide new ideas for the treatment of PC.

Currently, the side effects of targeted drugs for PC, the efficacy of targeted therapy, and the differences between the treatment effects achieved by targeted therapy combined with other PC treatment methods such as chemotherapy and immunotherapy and the expected treatment effects are all in the stage of research exploration and clinical experimentation.

Based on the research progress of targeted therapy and efficacy of targeted drugs for PC in the past five years, this paper summarizes and compares the therapeutic effects and side effects of different targeted drugs for PC targeted at various organs or cells, in order to find the most effective targeted drugs suitable for people with different physical conditions and make a modest contribution to the future research on curing PC.

2. Related Target Research and the Development of New Targets

2.1. Research on Relevant Targets

Regarding the study of targeted therapy for PC, the important targets currently used for the treatment include: KRAS, BRCA1/2, hENT, etc., and the drug targets-immune drugs that have been approved for marketing include EGFR-erlotinib, mTOR-everolimus, etc [5]. This section will focus on the research progress of many researchers in the treatment of PC targeting TROP2, PI3K and CIP2A.

2.1.1 TROP2

TROP2, also known as tumor-associated calcium signal transduction protein 2, is a type I transmembrane cell surface glycoprotein that is highly expressed in a variety of malignant tumors through cell surface receptor signaling in the proliferation, migration, and adhesion of malignant tumor cells [6]. Qiu Jinrong et al. studied the relationship between the expression of Trop2 in human PC and its corresponding clinicopathological features by using RT-PCR detection, immunofluorescence detection and immunohistochemistry detection. After statistical analysis of the results, it was concluded that Trop2 protein was mainly expressed on cancer cell membranes in PC tissues, and its positive expression increased with the decrease in the degree of differentiation of human PC tissues, and its expression was independent of the age and sex of patients [7]. Zhou et al. used RT-PCR to detect and control the protein expression of Trop2-si RNA and human PC PANC-1

cells after 48 hours of culture and used CCK8 method and flow cytometry (FC) to inhibit the expression of Trop2 in PC tissues and its effect on the proliferation and apoptosis of PC cells. After summarizing the analysis, it was concluded that inhibiting the expression of TROP2 gene in PC tissues could significantly reduce the proliferation ability of tumor cells and promote apoptosis [8]. This article summarizes the results and conclusions of the two groups of studies and concludes that Trop2 can be used as an effective potential target for targeted therapy of PC and plays a role in the clinical detection of the malignancy of PC. In addition, the current Trop-2 targeted drugs have made phased progress in clinical trials, which provides great confidence and motivation for the study of the mechanism of Trop-2 in the treatment of PC and the improvement of patient outcomes.

2.1.2 PI3K

PI3K is a lipid kinase that controls cell growth, proliferation, migration, survival and angiogenesis. Wu Song et al conducted a comparative review of the changes in the PI3K-mTOR signaling pathway and its mechanism of action over the years after multiple cancer cell lines. The conclusion is that because it is widely expressed in mammalian cells, activation of PI3K can promote the development of tumors, which can be used as a targeted target for the treatment of PC [9]. Zhang Tongjun et al used immunohistochemistry to detect the expression of PI3K and studied its expression and clinical significance. After analyzing the relationship between research and clinical pathological parameters, the conclusion is that the activation of the PI3K signaling pathway can promote the occurrence, invasion and metastasis of PC [10]. Wu Song's research suggests that there are mechanisms related to the participation of PI3K signal pathway in the process of PC, but the current relevant research defects lie in the fact that there are few studies on the development and research of PI3K inhibitors that can effectively inhibit PC in their clinical trials. In the future, relevant research can be developed in this area and provide new ways for it.

2.1.3 CIP2A

CIP2A, the protein phosphatase 2A cancer inhibitor, is a carcinogenic factor that is highly expressed in the cytoplasm of a variety of malignant tumor cells [11]. Fu Jingdong et al. detected CIP2A expression in 42 cases of PC and adjacent tissues by immunohistochemical method and studied its clinical significance. The detection results showed that the expression rate of CIP2A in PC and adjacent tissues was 71.4% and 7.7%, respectively, and the difference was statistically significant [12]. Zhang Tongjun et al. used the same method as Fu Jingdong et al. to detect CIP2A expression in 64 PC tissues and adjacent tissues, and conducted the same research as the former, but the detection results were slightly different, that is, the positive expression rate of CIP2A in PC tissues and adjacent tissues was 70.3% and 5.6% respectively [13]. Therefore, most recent studies focused on the expression rate of CIP2A in PC and adjacent tissues, and the focus of the studies and the examination methods used were the same, so the research results were reliable and convincing. In this paper, after summarizing the conclusions of recent studies, CIP2A has been confirmed to be involved in the malignant progression of PC, so it has become an effective targeted therapy gene for the treatment of PC, providing strong support for the research on the targeted therapy of PC.

2.2. Development of New Targets

At present, for targeted therapy for PC, in addition to further expanding research on already developed targets, the development of new targets is also crucial. In recent years, the development of Claudin 18.2 has attracted much attention. Claudin 18.2 is a protein that manifests itself on the cell surface, belonging to a subtype of the tight junction protein family, which is involved in cell-to-cell adhesion [14] and is also a backbone protein that makes up tight junction structures. It is aberrantly activated in various malignancies of the digestive system continues to be expressed after malignant transformation, and is involved in the proliferation, differentiation, and migration of tumor cells [15]. According to the latest information published on the Global Oncologist website, Claudin 18.2 has a positive rate of about 50% in PC, making it a very promising new target for the treatment of PC [16] and has received worldwide attention. Although no drug targeting claudin18.2 has been approved for

marketing worldwide, there have been successful phase III clinical trials of antibodies targeting the same target [17], which further strengthens people's confidence and motivation to develop drugs targeting it.

3. Comparison of the Role of Receptors in Targeted Therapy

Receptors are essential for physiological function, and they are associated with many diseases and provide great targets when treating diseases. Drug molecules work by interacting with receptors to deliver chemical signals to produce therapeutic effects, so understanding how druggable receptors work and how they target drugs is key to developing effective drugs, understanding diseases, and studying their treatment options. Targeting receptor-bound ligands by studying them can lead to the better development of drug molecules that can be more effective or potentially control the effects of receptors. The basic receptor pharmacology needs to be considered when developing and designing effective new drugs, i.e., how the receptor interacts with the drug (ligand) and causes various physiological effects, how the ligand causes receptor activation or inhibition, i.e., ligand function, and the relationship between the drug effect and the structural characteristics of the receptor. Understanding the above can help in the development of drugs that can safely and effectively treat diseases. Therefore, in order to develop targeted drugs that can effectively treat PC, it is necessary to rely on forward and reverse pharmacology to develop receptors with high affinity for specific drugs (ligands) to produce better drug efficacy. In summary, receptors are the key to the development of targeted drugs for PC in order to identify, develop, and improve drugs that can produce the desired effects. This article will compare and review the role of epidermal growth factor receptor (EGFR), especially human epidermal growth factor receptor (HER), chimeric antigen receptor T cells, and gastrin receptor in targeted therapy for PC.

3.1. EGFR and HER

The EGFR family is a class of transmembrane glycoprotein tyrosine kinases composed of 1 186 amino acids, including four family members, namely human HER-1, HER-2, HER-3, and HER-4. These four classes of human EGFs have a relatively similar structure: they all exhibit ligand-specific specificity in the extracellular ligand-binding region and have a high degree of homology in the transmembrane region, and the two intracellular regions have tyrosine kinase activity, which allows them to autophosphorylate [18]. Its corresponding ligands, such as EGF, can bind to the extracellular region of EGFR, and then self-mediate EGFR dimerization to form homologous or heterodimers, thereby realizing receptor autophosphorylation in the dimer and activating receptor tyrosine kinase (RTK), which initiates the activation of a series of downstream signal transduction pathways, and finally acts on transcription factors in the nucleus, thereby inducing the proliferation, invasion, and metastasis of tumor cells, and inhibiting their apoptosis and tumor angiogenesis [19], so the development of anti-EGFR family molecularly targeted drugs is called the key to the treatment of PC. Gao Wei et al. pointed out that there are two types of targeted drugs at present, one is a monoclonal antibody that acts on the extracellular region, which inhibits the binding of the ligand to the receptor to inactivate the receptor through competition, thereby the growth of hollow bamboo tumor cells, and the other is a small molecule tyrosine kinase inhibitor that acts on the intracellular region, which interferes with adenosine triphosphate (ATP) to inhibit tyrosine kinase phosphorylation, thereby blocking the signal transduction process to inhibit the spread of tumor cells [20], and the more well-known erlotinib is such a drug. Huang Changshan et al. obtained a bispecific antibody CT-BiAb that can simultaneously target human HER-2 and EGFR molecules by gene synthesis and overlapping polymerase chain reaction EGFR molecules, and then measured its cancer cell binding ability by flow cytometry, the inhibition ability of MTT detector on cancer cell proliferation and calculated the apoptosis rate of cancer cells. It can effectively inhibit the proliferation of cancer cells in vitro and in vivo, providing a new idea for anti-tumor therapy [21]. Therefore, the use of anti-EGFR molecular targeted drugs or anti-EGFR and HER-2 bispecific antibodies in PC patients can effectively inhibit

or block the increase of EGFR phosphorylation and the enhancement of its activity, thereby accelerating the apoptosis of tumor cells in the relevant treatment process, and EGFR has become an effective therapeutic target for PC.

3.2. Antigen Receptor T Cells (CAR-T)

In recent years, CAR-T cells, as an emerging therapy in the field of tumor immunotherapy, have achieved satisfactory efficacy in tumor treatment, so it has also become a new direction for the treatment of PC. T cells are key effectors of tumor immune response, and they have strong immunogenicity for tumors growing in an immunodeficient environment, so solid tumors lacking T cell infiltration usually have a poor prognosis. CAR-T therapy cleverly uses this feature by chimerizing selected antigens onto T cells, thereby changing the pathways and uses of T cells, and changing their metabolic and biological effects, and finally achieving direct killing of tumor cell pairs. In addition, the therapy enhances T cell function or inhibits the growth of PC cells in vitro and in vivo by incorporating antigenic epitopes such as B7-H3, MSLN and PSCA that are highly expressed in PC tissues.

CAR-T cell therapy has now developed to the fourth generation, and many preclinical research results have confirmed the effectiveness of CAR-T cell therapy in the treatment of PC models, including human-derived xenograft models and human-derived tumor tissue xenograft models, but due to the complex tumor microenvironment of CAR-T, the internal hypoxia, acidic metabolites and continuously produced inhibitory molecules are not conducive to the survival and activation of T cells, affecting their proliferation. Currently known suppressive immune cells, such as regulatory T cells and M2 tumor-associated macrophages, have become the main obstacles to the therapeutic effect of CAR-T. The culture conditions of CAR-T may also inhibit its activity and therapeutic effect, so the tumor microenvironment in which CAR-T is located and the culture conditions before its reinfusion become the key factors determining the efficacy. In addition, targeting CAR-T cells to tumor-specific antigens in PC can minimize off-target effects of this treatment. At present, mesothelin-targeting CAR-T cells have been widely used in various preclinical malignancy models [22], and they are also the most experienced in the treatment of PC with CAR-T cells, making mesothelin one of the main targets for PC treatment at this stage. Based on the analysis above, it can be concluded that CAR-T cell therapy has achieved good clinical results, but the tumor microenvironment in which it is located and whether it targets specific targets have become the main difficulties faced by the therapy. However, although the heterogeneity of solid tumors and the complexity of the microenvironment can affect the efficacy of this therapy, the development of new technologies, the optimization of CAR structures, and the combination of various immune adjuvants make CAR-T cell therapies worthy of further investigation [22].

3.3. Gastrin-Releasing Peptide Receptor (GRPR)

GRPR belongs to the G protein-coupled receptor family, which is mainly distributed in the central nervous system, spinal cord and gastrointestinal tissues, and exerts biological effects by binding to its ligand GRP. Previous studies suggest that GRPR is involved in the regulation of many physiological functions in the human body and has important physiological functions in vivo. In addition, GRPR is highly expressed in PC and is involved in the occurrence and progression of cancer. The use of GRPR inhibitors and antisense oligonucleotide therapies targeting GRPR have been found to inhibit tumor growth [23]. This article summarizes the relevant studies and finds that GRPR can become a new hotspot in the research and treatment of PC in the future.

This article summarizes the relevant studies of the above three studies and finds that the current research on anti-EGFR targeted drugs has been relatively complete, and has been approved for marketing and has achieved good clinical efficacy, and further research can be carried out on the development of bispecific antibodies combining anti-EGFR and HER-2 in the future; Although there are still some obstacles to T therapy, with the development of each generation, more effective clinical efficacy has been achieved, and follow-up research will focus on reducing or overcoming the impact

of tumor microenvironment on its efficacy, while there are few studies focusing on the field of GRPR inhibitors, and there are not enough research results to support its efficacy and research problems and difficulties, and follow-up research can be developed in this field to provide new ideas for the development of new drugs for the effective treatment of PC.

4. Conclusions

This article summarized and elaborated the research methods and progress of TROP2, PI3K, CIP2A and other PC therapeutic targets and related targeted drugs, and made a prospect of Claudin 18.2 as a new target for future research direction; In addition, the research progress of EGFR, Her, CAR-T, GRPR and other receptors related to targeted treatment of PC, as well as related drugs and therapies, were summarized, and the research direction of receptors for targeted treatment of PC in the future was prospected. Targeted therapy for PC aims to solve the defects and limitations of radiotherapy, chemotherapy and other therapies for PC. However, in general, targeted therapy for PC is still in the research and development stage. Although some targeted drugs that have been approved to enter the market have obtained relatively complete research results, they cannot ensure their stable clinical efficacy; At the same time, the receptor therapy for PC targeted therapy that has been developed at present, like PC radiotherapy, will be affected by the tumor microenvironment of PC. In addition, this article also analyzes and elaborates the side effects of targeted treatment of PC on other cells or organs, such as skin and heart toxicity, allergic reactions, liver, kidney and immune suppression, as well as the research and development of related treatment methods and adjuvants. Therefore, the author believes that the targeted treatment of PC can also learn from the successful cases of targeted treatment of other cancers and targeted treatment of PC with significant effects and provide reliable theoretical support for the development of new targets for PC treatment and their targeted receptors in the future and the improvement of existing targeted drugs. In addition, we will focus on the impact of tumor microenvironment on targeted drugs for PC treatment and the side effects of marketed drug combinations, so as to strive for an early breakthrough. In the future, more targets and potential beneficiaries can be developed to provide the most effective personalized comprehensive treatment scheme for patients with PC in combination with other treatment methods and combination drugs for patients with different physical conditions, provide new ideas for prolonging the life cycle of PC patients and thoroughly and successfully curing PC, and enhance the confidence of researchers to benefit more patients.

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