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Clinical Progress of Targeted KRAS Drugs Combined with Immune Checkpoint Inhibitors in the Treatment of Pancreatic Cancer

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Abstract. Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) is one of the important drivers of pancreatic ductal adenocarcinoma. Although there has been progress in the development of targeted KRAS drugs, single-targeted therapy has limited effects due to the complexity of mutations. Immune checkpoint inhibitors have poor efficacy in common pancreatic cancer patients. Therefore, the combined treatment strategy of the two has attracted attention. By means of the targeted drugs to inhibit the tumor signaling pathway and the immune inhibitors to synergistically enhance the anti-cancer ability of the immune system, it is expected to improve the therapeutic effect. However, it faces challenges such as drug resistance and increased toxic and side effects, which urgently need to be studied and solved. Through analyzing the recent research progress, this study found that the microenvironment of pancreatic cancer is complex and immunosuppressive, and KRAS mutations will exacerbate this characteristic. By improving the function of antigen-presenting cells and reducing the influence of immunosuppressive cells, etc., the microenvironment can be improved. The combined use of KRAS inhibitors and immune checkpoint inhibitors can reverse immunosuppression, increase the infiltration of effector T cells, and improve the clinical efficacy. In the future, the combined treatment strategies developed based on relevant research are expected to bring more hope for refractory tumors.

Keywords: Pancreatic cancer; KRAS mutation; Targeted therapy; Immune checkpoint inhibitor; Combined treatment strategy.

1. Introduction

Pancreatic cancer is a highly aggressive malignant tumor characterized by early Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) gene mutations . KRAS mutations not only play a key role in the pathogenesis of pancreatic cancer, but are also closely related to drug resistance and treatment difficulty of the disease. Although drugs targeting this gene mutation are actively being developed, no effective monotherapy for KRAS has been developed to date . However, recent studies have explored strategies to combine drugs targeting KRAS with immune checkpoint inhibitors in an attempt to open up new avenues for pancreatic cancer treatment.

Immune checkpoint inhibitors (ICI) relieve immunosuppression by blocking CTLA-4, PD-1/PD-L1 signals and enhance anti-tumor immunity, but have toxic side effects and limited efficacy against pancreatic cancer . Studies have found synergy between drugs targeting KRAS (such as MEK inhibitors) and ICI: KRAS inhibitors reduce tumor immune escape by modulating signaling pathways, ICI restores T cell function, and both inhibit tumor growth and reshape the immune microenvironment. This strategy aims to break through the bottleneck of ICI single-drug resistance in pancreatic cancer and needs clinical verification of synergistic mechanism and safety.

This article focuses on pancreatic cancer treatment, expounds the research status, combination therapy strategy and synergistic mechanism of KRAS targeting drugs and immune checkpoint inhibitors, analyzes the challenges and solutions faced by combination therapy, and introduces the development prospects of new drugs and the potential of innovative strategies such as personalized therapy. In the future, pancreatic cancer treatment can improve the effect of combination therapy with targeted KRAS drugs and immune checkpoint inhibitors through in-depth research on combination therapy optimization, continuous research and development of new drugs, promotion of personalized

therapy, exploration of innovative strategies and multi-center collaborative research, providing stronger support for clinical application.

2. Organization of the Text

2.1. Current status of KRAS targeting drugs in pancreatic cancer treatment

2.1.1. Mechanism of KRAS as a Key Driver of Pancreatic Cancer

KRAS downstream signaling pathways include PI3K/AKT and MEK/ERK signaling pathways. PI 3K (phosphatidylinositol 3 phosphokinase) is a major effector molecule of RAS signaling. Class I PI 3K is widely studied and has a great impact on cancer. It consists of regulatory subunits and catalytic subunits. Mutations in the oncogene KRAS are often accompanied by mutations in PIK3CA. PIK3K can be activated by many factors. After activation, it can convert PIP2 (phosphatidylglycerol) to PIP3 (phosphatidylinositol 3 phosphate), activate AKT (protein kinase B), and then activate mTORC1 (mammalian rapamycin target protein complex 1). This pathway regulates cell growth, survival and metabolism [1]. AKT has three isoforms, which are activated by binding to PDK1, PIP3 and phosphorylation at two sites, affecting TSC1/TSC2 and mTORC1. mTOR has two complexes, mTORC1 and mTORC2, mTORC1 can promote cell growth, mTORC2 can activate AKT, etc., and their interaction makes the PI3K/AKT/mTOR signaling pathway more complex [2]. MEK/ERK pathway is also critical for cell survival. Activated KRAS can activate ERK (extracellular regulated protein kinase) through Ras-Raf- MEK - ERK pathway. ERK is involved in various physiological processes. RAF-MEK- ERK pathway can drive the formation of PanINs and PDAC. It is reasonable to target this pathway for pancreatic cancer treatment [3].

PI3K/AKT and MEK/ERK signaling pathways are not simple linear conduction, and there is a cross dialogue between them. For example, ERK activation can activate mTOR, PI3K can regulate ERK signaling through AKT, and inhibition of one pathway alone will cause compensation activation of the other pathway, thus weakening the anti-tumor effect. Therefore, combination therapy targeting multiple KRAS downstream signaling pathways has become an effective strategy to inhibit KRAS signaling in pancreatic cancer. Combined application of MEK (mitogen-activated protein kinase) inhibitors and PI3K inhibitors can reduce phosphorylation of related proteins, increase apoptosis, and synergistically inhibit tumor growth. However, the clinical trial of PI3K inhibitor combined with MEK inhibitor in advanced pancreatic cancer has limited effect and obvious adverse reactions. In order to overcome acquired drug resistance and adverse reactions after combined application, targeted gene therapy with stronger specificity may be an effective solution .

2.1.2. KRAS inhibition methods

The high affinity of KRAS for GTP long hindered inhibitor development until it was discovered that the G12C mutation could be covalently targeted, leading to irreversible inhibitors such as sotorasib and adagrasib. These drugs have been approved for non-small cell lung cancer and have shown partial efficacy in pancreatic cancer, but resistance issues have led to combination therapy strategies [4]. Allele-specific inhibitors against other common mutations, such as KRAS G12D, have been difficult to develop, but preclinical studies have shown that the non-covalent inhibitor MRTX1133 has the advantage of high selectivity and low toxicity . To break through the limitations of "off" inhibitors, novel "on" inhibitors (such as RMC-6236, which entered clinical trials) directly target GTP-bound activated KRAS and exhibit broad spectrum resistance to G12 subtype mutations, potentially reducing resistance caused by upstream signal activation .

Significant progress has been made in the development of RAS signaling pathway co-inhibitors: clinical studies targeting upstream regulatory proteins SOS1 (inhibitor BI-1701963) and SHP2 (inhibitor RMC-4630) have shown synergistic inhibition of tumor activity in combination with KRAS inhibitors. Downstream nodal inhibitor development has been limited by signal redundancy (e.g., RAF/MEK inhibition elicits ERK compensatory activation) and toxicity issues, but novel dual RAF

inhibitor combination protocols have been optimized through mathematical models and have entered clinical trial validation [5].

Autophagy is also closely associated with pancreatic cancer therapy. Autophagy exhibits dual regulation in cancer: autophagy inhibitor (hydroxychloroquine) in combination with MEK inhibitor in KRAS/LKB1 co-mutant NSCLC (Trametinib) specifically inhibits KL tumor growth by inducing iron death (KP null), LKB1 deletion is a key biomarker; in KRASG 12D mutant PDAC, autophagy-dependent iron death mediates exosomes release of KRASG 12D, activation of STAT3-FAO axis drives M2 polarization after uptake by macrophages via AGER receptor, which can be blocked by targeted autophagy or AGER; Meanwhile, autophagy maintains PDAC survival through KRAS-dependent metabolic support (lysosomal activation) and chemotherapy resistance, but existing drugs (such as hydroxychloroquine) limit clinical efficacy due to non-specificity. In the future, it is necessary to develop precise autophagy target drugs (such as ULK1 inhibitors), combine MEK/STAT3 inhibition or immunotherapy, and optimize individualized strategies in combination with biomarkers such as LKB1/KRAS mutations [6~8].

RNA interference (RNAi) technology has opened up new avenues for pancreatic cancer treatment, showing therapeutic potential by targeting and silencing oncogenes. For example, earlier studies demonstrated that silencing KRAS G12V can inhibit tumor activity in xenograft models, while current RNAi delivery systems based on engineered vesicles or biodegradable implants have entered clinical trials, with some results showing an increase in progression-free survival for patients. Focusing on MUC4, a mucin protein with specific high expression in pancreatic cancer, the study found that after silencing this gene by RNAi technology (such as highly effective shRNA-A141), the proliferation and migration ability of BxPC-3 cells was significantly reduced, and the tumor volume in nude mice was only 1/10 of that in the control group. It was confirmed for the first time that MUC4 directly promoted tumor progression by driving malignant phenotype [9].

Immunological approaches also play an important role in pancreatic cancer treatment. T-cell therapy with tumor-infiltrating lymphocytes (TILs) has been used in other solid tumors, and pancreatic cancer is also actively explored, but faces the problem of immune escape. CAR-T therapy has not been effective in pancreatic cancer clinical trials;mRNA vaccines can induce specific immune responses, and multiple mRNA vaccines are being tested in combination with immune checkpoint inhibitors; immune checkpoint inhibitors are ineffective as monotherapy for pancreatic cancer, while combination with drugs that directly inhibit KRAS has shown better efficacy in mouse models, and exploration of such combination therapy strategies is ongoing [10,11].

2.2. Application of immune checkpoint inhibitors in the treatment of pancreatic cancer

ICIs activate T cells by blocking molecules such as PD-1/PD-L1 and CTLA-4, enhancing anti-tumor immunity. They have shown significant efficacy in cancers such as melanoma and lung cancer. However, their effectiveness in pancreatic cancer is limited, mainly due to the highly immunosuppressive tumor microenvironment (TME) (fibrotic stroma, enrichment of regulatory T cells [Tregs] and myeloid-derived suppressor cells [MDSC]), low tumor mutational burden (TMB) (fewer neoantigens), and insufficient infiltration of immune cells. Pancreatic cancer cells evade immune surveillance by upregulating PD-L1, and the inhibitory signals of CTLA-4 and the enrichment of Tregs further weaken the efficacy of ICIs. Studies have shown that the combination of ICIs with other therapies (such as chemotherapy and targeted therapy) can improve the immunosuppression of the TME, increase antigen exposure or immune cell infiltration, offering new hope for the treatment of pancreatic cancer .3. Synergistic Mechanism of KRAS Targeting Drugs and Immune Checkpoint Inhibitors

Targeted therapy enhances anti-cancer efficacy through a dual mechanism: 1) direct killing of tumor cells and reduction of tumor burden, while inducing immunogenic cell death to enhance anti-tumor immunity;2) some targeted drugs enhance immune recognition by restoring antigen presenting molecule expression, or reshape tumor microenvironment (inhibition of angiogenesis, reduction of

immunosuppressive cell infiltration) to synergize immunotherapy. However, it is important to note that inhibitors of specific pathways, such as VEGF/VEGFR blockers, may inhibit T cell activity and increase immunosuppressive cell infiltration [12,13].

The interaction of cellular signaling pathways plays a crucial role in the synergistic mechanism of KRAS targeting drugs and immune checkpoint inhibitors. Mutations in the KRAS gene are the most common drivers of pancreatic cancer, and these mutations lead to sustained cell proliferation and anti-apoptotic signaling. KRAS mutations activate a series of downstream signaling pathways, including MAPK, PI3K-AKT, etc., and the interaction of these signaling pathways forms a complex signaling network that supports tumor cell growth and survival. Similarly, immune checkpoints such as PD-1/PD-L1 signaling pathways control immune responses by regulating T cell activity, while KRAS signaling may indirectly affect the efficacy of immune checkpoint inhibitors by affecting immune cell activity in the immune microenvironment .

KRAS mutant pancreatic cancer presents immunosuppressive microenvironment: immunosuppressive cells (Tggs/MDSC) account for 50% of tumor tissues, while CTL is almost absent. KRAS mutation activates PI3K/AKT pathway by secreting IL-6, TGF-β and other factors, remodels macrophage and T cell function, and forms immune escape barrier [14]. The study proposes a sequential strategy of combined targeting of KRAS signals (such as MEK inhibitors) and immune checkpoint blockade (PD-1 inhibitors): short-term PD-1 monoclonal antibody "priming" immune response followed by MEK inhibitors can not only reduce the risk of toxicity superposition, but also synergistically enhance CTL activity and break the balance of immunosuppression. This protocol achieves synergistic antitumor effect by blocking KRAS pathway at multiple levels and optimizing T cell function, and clinical trials are needed to verify efficacy .

The tumor microenvironment (TME) of pancreatic cancer has highly immunosuppressive characteristics. KRAS mutations not only drive tumor proliferation but also reshape the TME (such as increasing myeloid-derived suppressor cells [MDSC] and regulatory T cells [Tregs], and reducing the function of dendritic cells [DC]), thus weakening the efficacy of drugs targeting KRAS and immune checkpoint inhibitors (ICI). Strategies for reversing the immunosuppression of the TME include enhancing the functions of antigen-presenting cells (DC and macrophages), reducing the infiltration of MDSC/Tregs, enhancing the activity of effector T cells, regulating the cytokine network, and combining KRAS inhibitors with ICI. Experiments have shown that combination therapies can reverse the immunosuppression of the TME, increase the infiltration of effector T cells, and significantly improve the clinical efficacy.

Tumor cells evade immune clearance by reducing antigen presentation through mechanisms such as low tumor mutational burden (TMB), diminished immune infiltration, loss or mutation of MHC/β2-microglobulin (β2-M), and mutations in the T-cell receptor (TCR) binding domain. At the immune cell level, inhibitory checkpoint molecules like TIM-3 (T-cell immunoglobulin and mucin-domain containing-3) and LAG-3 (lymphocyte-activation gene 3), in addition to CTLA-4, suppress T cell function. Further impairment of antitumor immunity arises from insufficient co-stimulatory signals, inadequate cytokine secretion, and increased infiltration of immunosuppressive cells such as regulatory T cells (Tregs). Within the tumor microenvironment (TME), factors like vascular endothelial growth factor (VEGF) hinder cytotoxic T cell migration while recruiting Tregs. Concurrently, immune checkpoint molecules (e.g., PD-1/PD-L1, LAG-3) inhibit immune activity and promote tumor proliferation.

Preclinical and clinical studies in pancreatic cancer models can elucidate the interplay between KRAS signaling and the TME, guiding the development of combination therapies . Potential strategies include targeting stromal remodeling, modulating cytokine networks, and restoring immune-mediated tumor killing functions. These approaches may overcome drug resistance and improve therapeutic outcomes for refractory cancers like pancreatic cancer, offering new directions for treatment.

3. Summary

This article mainly analyzes the KRAS targeting drugs combined with immune checkpoint inhibitors in the treatment of pancreatic cancer. In the aspect of therapeutic strategy, the research progress of KRAS and KRAS was reviewed, including the mechanism of action, inhibition methods and application of immune checkpoint inhibitors. The mechanism of combination therapy analyzed potential mechanisms such as cellular signaling pathway interactions, microenvironmental changes, and enhanced immune response. Challenges and solutions discuss challenges such as drug resistance and toxic side effects, and suggest ways to improve efficacy. The results show that combination therapy has the potential to enhance immune response and improve efficacy, and provide insight into the mechanisms involved. The significance of this study is that it provides new therapeutic strategies and helps to understand tumor mechanisms. However, there are limitations such as drug resistance and clinical application limitations. Future prospects include personalized therapy and the development of novel drugs to improve treatment outcomes.

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