Introduction and Application of Death Protein 1

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Abstract: In the past few years, cancer immunotherapy has been accompanied by encouraging results. Cell death protein 1 (PD-1) plays a crucial role in suppressing immune responses and promoting self-tolerance by regulating T cell activity, activating apotheosis. Antigen-specific T cells, programmed cell death ligand 1 (PD-L1) is a transmembrane protein that is considered a common suppressor of the immune response and can bind to PD-1, reducing the proliferation of PD-1-positive cells, inhibiting their cytokine secretion, and inducing apotheosis. 1 thus PD-L1 also plays an important role in various malignancies. It can attenuate the host immune response to tumor cells. Based on these views, the PD-1 / PD-L1 axis is responsible for immune evasion of cancer and has a tremendous impact on cancer treatment. Blockade of PD1 is important cancer immunotherapy. Taking pembrolizumab (keytruda) as an example is a humanized monoclonal anti-pd1 antibody that has been extensively studied in many malignancies. Pembrolizumab has been approved by the US FDA for the treatment of advanced melanoma and NSCLC. This review aims to improve cancer treatment by summarizing the roles of PD-1 and PD-L1 in cancer, thereby exemplifying a variety of PD-1 blockade drugs compared to typical pembrolizumab (keytruda) drugs, analyzing the comparative distinctions between modern immunotherapy and traditional chemotherapy for cancer.

1. Introduction

Cancer is a major public health problem worldwide. Global demographic characteristics predict an increased cancer incidence in the next decades, with 420 million new cancer cases annually expected by 2025. According to GLOBOCAN data, 14.1 million new cases and 8.2 million deaths from cancer were estimated in 2012. [1]. Cancer is a major cause of death in human beings. Many treatments have been tried to solve the health and survival problems of cancer patients. Cancer is a kind of incurable disease, which lacks effective treatment to eradicate.

The treatment of cancer has gone through several different periods. From surgery to radiotherapy and chemotherapy, the life of patients is prolonged in the course of treatment. However, the traditional treatment method has many disadvantages, such as drug resistance and toxicity. The use of paclitaxel as a chemotherapeutic agent has become a broadly accepted option in the treatment of patients with ovarian, breast, and non-small cell lung cancers, malignant brain tumors, and a variety of other solid tumors. However, significant toxicities, such as myelosuppression and peripheral neuropathy, limit the effectiveness of paclitaxel-based treatment regimens [2]. Meanwhile, chemoradiotherapy technology can only temporarily prevent the spread of cancer, which is unable to fundamentally solve the problem of cancer. With the further study of the mechanism and principle of cancer, immunotherapy has been explored. Its exploration and application bring new progress for cancer research. Immunotherapy can solve cancer through the immune system, which includes PD-L1 and PD-1 inhibitors, mRNA vaccine and CAR-T therapy, etc. One of the most attractive is PD-1, which has been used in cancer treatment, such as melanoma, lymphoma, breast cancer, etc. It has been proved to be an effective cancer treatment. Induction and maintenance of T cell tolerance require PD-

1, and its ligand PD-L1 on nonhemato poetic cells can limit the effector T cell responses and protect tissues from immune-mediated tissue damage. The PD-1: PD-L pathway also has been usurped by microorganisms and tumors to attenuate antimicrobial or tumor immunity and facilitate chronic infection and tumor survival [3]. The important negative regulatory function of PD-1 was revealed by the autoimmune prone phenotype of Pdcd1 −/− mice in 1999 [4-5]. Since the ligands for PD-1 were identified in 2000 [6-7] and 2001 [8-9], there has been steady progress in understanding the functions of PD-1 and its ligands [3].

This review focuses on recent advances in our understanding of PD-1. The PD-1 receptor was discovered in 1992 as a gene upregulated in a T cell hybridoma undergoing cell death [10]. Here, the review first introduced the basic situation of PD-1 drugs and several diseases they can treat. We then recommend the research and development process of PD-1. Finally, the traditional treatment with the new treatment will be compared. On this basis, the significant role and breakthrough of the combined application of these treatment methods in cancer therapy were discussed.

2. PD1 Introduction

2.1 PD1 Mechanism

PD-1 is a checkpoint protein on immune cells called T cells. T cells, which are a type of white blood cell that can be a part of the immune system and it is at the core of adaptive immunity. During this process, PD1 can be a checkpoint protein on T cells, and it can help T cells from attacking other cells in the body. This usually works when it attaches to PD-L1.

2.1.1 T Cell Works in Tumor

T-cells are part of the cancer immunity cycle. As cancer cells die, they release antigens, substances that can be recognized by the immune system. Antigens from the cancer cells will present on the cell surface of special immune cells called antigen-presenting cells (APCs) so that the other immune cells can recognize the antigens of interest. In the lymph nodes, the APCs activate the T cells, and T cells can recognize the tumor cells. Then they can find the tumor from the blood vessels, infiltrate it, recognize the cancer cells, and kill them. There are two different situations of works in T cells: How it can work normally and the other exceptions.

2.1.2 T Cells Work

In the presence of infected and tumor cells in vivo, T cells mount a critical role in the immune response against infection and tumor. Upon antigenic stimulation, B cells generate antigen-specific T cells and clonally expand, thereby acquiring resistance-acting effector functions. Cytotoxic T lymphocytes (CTLs) are effector T cells that can secrete cytokines that are particularly directed to the function of lysing target cells.

2.1.3 Exceptions for T Cell

However, upon prolonged antigenic stimulation, T cells can lose their effector functions even in the presence of the targeted antigen. When the immune system is forced to be active for extended periods, such as with persistent viral infections or the progressive development of cancer, effector T cells can run out of steam. This " Exhaustion " state renders T cells incapable of clearing pathogens or eliminating neoplastic cells.

2.2 Function

PD1, also known as PD-1 and CD279 (cluster of deferrization 279), which is a protein found on T cells (T cell, a type of immune cell), that can kelps keep the body’s immune responses in check. It can be used in regulating the immune system's response to the cells of the human body by downregulating the immune system and promoting self-tolerance by suppressing T-cell inflammatory activity. Also, it has an essential role in balancing protective immunity and immunopathology, homeostasis, and tolerance [11].

2.2.1 PD1 in Cancer

Except for other functions of PD1, this kind of protein can prevent autoimmune disease. Also, it can prevent the immune system from killing cancer cells [12]. As a special protein, PD-1 can treat autoimmunity in two ways: first, it promotes apoptosis of antigen-specific T-cells in lymph nodes. Second, it reduces apoptosis in regulatory T cells. PD-1 often shows high and sustained expression levels during persistent antigen encounters, which can occur in the setting of chronic infections and cancer. In these settings, PD-1 can limit protective immunity. Different from PD-1, the Programmed cell death 1 ligand 1(PDL1) shows broad expression on both hematopoietic and non-hematopoietic cells, positioning the PD1 pathways as a key regulator of immune cell functions in both secondary lymphoid organs and in non-lymphoid tissues.[13]According to the PD1, there is a new class of drugs that block PD-1, activate the immune system to attack tumors, and are used to treat certain types of cancer: such as melanoma, lung cancer, Kid kidney cancer, bladder cancer, stomach cancer, ovarian cancer, Hodgkin's lymphoma, liver cancer, breast cancer, colorectal cancer, Merkel cell cancer, head and neck cancer, mesothelioma, prostate cancer. And all the diseases above had already improved that PD-1/PD-L1 inhibitor was useful in a clinical trial. Compared between PD1 and PDL1, PD1 limits the activation and function of potentially pathogenic self-reactive CD4+ and CD8+ T cells, and PDL1 can shield target organs from autoimmune attack. [14]. Same as the PD-1, there are some immune checkpoint inhibitors: ipilimumab (Yervoy), nivolumab (Opdivo), Pembrolizumab (Keytruda), Atezolizumab (Tecentriq), Avelumab (Bavencio), and Durvalumab (lmfinzi). All of these checkpoint inhibitors are approved by FDA for specific cancers. Also, there are some checkpoint inhibitors that are used to treat tumors anywhere in the body by focusing on specific genetic changes [15].

3. Pd1 drug

3.1 The PD1 Mechanism

Programmed cell death protein 1 (PD1) is a regulator of immune responses-One of the important checkpoints. Ligation of PD1 and its ligands, PDL1 and PdL2, leads to negative signal transduction to T cells in vivo for overall regulation.PD1 protein is absent on less active lymphoid cells but is expressed to a great extent on highly activated CD4 + and CD8 + T cells, B cells, natural killer (NK) cells, macrophages, and dendritic cells. Whereas PDL1 is constitutively expressed on T cells, B cells, dendritic cells, and CD4 +, CD25 + regulatory T (Treg) cells. PdL2 is more interferon and restriction of interleukin-4-stimulated macrophages and dendritic cells. The expression of PD1 is an important mechanistic contributor to the exhausted effector T cell phenotype. The expression of PD1 on effector T cells, as well as PDL1 on neoplastic cells, is responsible for enabling tumor cells to survive the immune effects of antitumor antibodies. Blockade with antibodies against PD1 is, therefore an effective cancer immunotherapy.

Table 1. PD-1 And PD-L1 Inhibitors in Clinical Development [1]

Target	Biologic agent	Class	Company
PD-1	AMP-224	PD-L2 IgG2a fusion protein	Amplimmune/GlaxoSmith Klein
	AMP-514 (MEDI0680)	PD-L2 fusion protein	Amplimmune/GlaxoSmith Klein
	Nivolumab (Opdivo, BMS-936558, MDX1106)	Human IgG4	Bristol-Meyers Squibb
	Pidilizumab (CT-011)	Humanized IgG1k	Cure Tech
	Pembrolizumab (MK-3475, (lambrolizumab)	Humanized IgG4	Merck
PD-L1	BMS-936559 (MDX1105)	Human IgG4	Bristol-Meyers Squibb
	MEDI4736	Humanized IgG1k	MedImmune/AstraZeneca
	MPDL3280A	Human IgG1k	Roche
	MSB0010718C	Human IgG1	Merck

3.2 Pembrolizumab

3.2.1 Pembrolizumab Characteristic

Pembrolizumab is a humanized monoclonal IgG4 kappa anti-pd1 antibody. Pembrolizumab does not involve Fc receptors or activate complement in vivo during the binding of the PD1 pathway to the PD1 receptor, so it can be easily passed (without any cytotoxicity) for toxicological testing of pembrolizumab. There was a 50% effective inhibitory concentration of 0.1-0.3 nm in the T cell activation test. [16] Usually, in the form of a lyophilized powder at room temperature, it is stable for 4 h at room temperature and for 24 h when refrigerated. It is reconstituted to 1-10 mg / ml in 0.9% sodium chloride solution and can be used for i.v [17].

Our immunity is complex, and our leukocytes are a major force against infections and cancer. T cells are a class of leukocytes that fight viruses, cancer and mediate autoimmunity. They are so powerful that they are under tight control by the human body. One of the mechanisms that regulate them is the presence of a protein called PD-1, which is short for programmed cell death receptor 1. Under normal circumstances, this receptor is inhibited by another protein called PD-L1. This interaction ensures that T cells do not attack human cells under normal conditions or during inflammation. When cancer cells are detected in humans, this interaction is inhibited, leading to the activation of T cells and destruction of cancer cells.

This problem can be overcome if tumor cells express PD-L1 receptors on their surface, preventing T cells from attacking them. The mechanism of pembrolizumab is to bind to the PD1 receptor on T cells, prevent PD-L1 interaction with cancer cells, and allow T cells to attack them.

3.2.2 Use of pembrolizumab

Because of its general mechanism of action, it can theoretically be used in a variety of cancers. Its mechanism of action does not depend on the extent of the tumor or even its tissue of origin but rather on certain genetic abnormalities present in the center of the cancer cell. Since its conception, multiple uses have been approved, and many more are expected as clinical trials proceed. Approved uses of pembrolizumab include:

Unresectable melanoma: first use, in this case, alone. It can also be used in resectable cases after surgery.

Nonsmall cell lung cancer: This is the most common type of lung cancer. This type of lung cancer is mostly resistant to chemotherapy. However, pembrolizumab can be used in cases with certain

mutations (genetic abnormalities), such as the PD1 receptor. It is used in cases where surgical resection is not possible because of disease progression or the patient's general condition. It can be used alone or in combination with other drugs, such as carboplatin and paclitaxel.

Small cell lung cancer: small cell lung cancer accounts for approximately 15% of lung cancers and is considered to be more sensitive to chemotherapy than the non-small cell subtype; However, if chemotherapy proves ineffective, pembrolizumab is initiated as a monotherapy until a response occurs or the drug causes toxicity.

Hodgkin's lymphoma: pembrolizumab is not considered a classical agent for Hodgkin's lymphoma, but it is used in cases that recur after several lines of therapy.

Squamous cell carcinoma: squamous cell carcinoma is the second most common skin cancer, and unlike basal cell carcinoma (SCC), it tends to spread to regional lymph nodes and, at later stages, to all over the body. Pembrolizumab can be used alone, or in combination with chemotherapy such as fluorouracil, in some advanced and metastatic squamous cell carcinomas, especially head and neck cancer.

Recurrent or metastatic cancer: benomzumab is advocated for many cancers that are resistant to conventional therapies such as surgery or chemotherapy or when discovered, have progressed beyond surgery and conventional therapy. They include cervical, gastric, liver, esophageal, and endometrial cancers. Here, we can see that a major advantage of pembrolizumab is that its effect is not tissue type dependent. In most cases, it is used alone [18].

3.2.3 Pharmacokinetics of Pembrolizumab

In pharmacokinetic studies for pembrolizumab, there was a dose-proportional increase in the steady-state concentration-time concentration curve (AUC) in pembrolizumab plasma, and there was also a dose-proportional linear relationship at peak and trough concentrations. For pembrolizumab in the in vivo clearance study, the in vivo clearance showed a linear growth with weight gain, so the weight-based dose compensated for the change in exposure due to weight difference. Based on doses of 1 – 10 mg / kg every 2 weeks or 2 – 10 mg / kg every 3 weeks, pembrolizumab clearance was 0.22 L / day and serum half-life was 26 d .33 clearance increases with weight so that steady-state concentrations of pembrolizumab can be achieved at 18 weeks with a 3-weekly dosing schedule. An intravenous dose of 2 mg / kg every 3 weeks produced an AUC of 0.643 g-day / L.34 at 10 mg / kg every 3 weeks, the AUC was 3.77 g-day / ml [19].

In clinical experiments, pembrolizumab in visceral injury tests, pembrolizumab clearance was not affected by renal impairment, nor was mild hepatic impairment.

4. Traditional therapy VS New therapy

4.1 Chemoradiotherapy

Radiotherapy and chemotherapy are the main methods of traditional tumor treatment. Radiotherapy uses radiation to kill cancer cells. It can effectively treat a variety of tumor diseases. Chemotherapy uses chemical drugs to kill cancer cells. For example, paclitaxel, carboplatin and dexamethasone are common chemotherapeutic drugs. Chemoradiotherapy is the combination of chemotherapy and radiotherapy. Those therapies provided gigantic help to prolong the life of patients.

4.1.1 Radiotherapy

Tumors are more prone to radiation damage than normal tissues and this is potentiated by the use of fractionated treatment, which preferentially spares normal tissue largely by allowing recovery from radiation damage in between fractions of radiotherapy (RT). RT for some malignant brain tumors, such as germinoma, is the principal curative treatment. The excellent disease control following conservative surgery and RT in benign tumors such as optic nerve/chiasma glioma, pituitary adenoma, and craniopharyngioma has established RT as an essential component of treatment. In high-grade gliomas, RT prolongs survival beyond that seen with any other treatment modality. The role of

RT in a number of other brain tumors is not proven beyond doubt, and its effectiveness following incomplete tumor excision is based on observational studies [20].

4.1.2 Chemotherapy

In multitudinous chemotherapy techniques, paclitaxel is introduced as an example of this treatment. Because of its unique anticancer mechanism, it is already one of the most successful and widely used natural anticancer drugs [21]. Unlike other tubulin-binding anticancer drugs, which prevent the assembly of tubulin into microtubules, paclitaxel promotes the assembly of tubulin into microtubules and prevents the dissociation of microtubules, blocking cell cycle progression, preventing mitosis, and inhibiting the growth of cancer cells [22]. Paclitaxel chemotherapy can increase the rate of apoptosis in tumor cells, release tumor antigens, and enhance the phagocytosis of antigen-presenting cells (APCs) [23]. However, significant toxicities, such as myelo-suppression and peripheral neuropathy, limit the effectiveness of paclitaxel-based treatment regimens [24]. Paclitaxel shows the disadvantages of traditional cancer treatment——serious side effects affect its applicability as a treatment. Although chemotherapy is a well-established treatment modality, chemotherapy errors represent a potentially serious risk of patient harm [25].

4.2 Immunotherapeutic

Immunotherapeutic is a promising treatment with less toxicity and resistance. In the past, due to the limitations of treatment technology, patients can only choose the treatment method with more side effects. The main determinants of outcome are performance status and the extent and activity of the systemic disease. The role of RT in patients with poor performance status is debated, and supportive care alone may be appropriate [26]. Chemotherapy errors occur at a rate of about one to four errors per 1000 orders, affect at least 1–3% of oncology patients during a single episode of care, and occur at all stages of the medication use process. Certain drugs present special risks, including anthracyclines, intrathecal vinca alkaloids, multidrug regimens, and oral agents administered on an intermittent basis or in extended courses of therapy [27]. With the deepening of research technology, immunotherapeutic bring more choices for patients. Immunotherapeutic strategies include cancer vaccines, oncolytic viruses, adoptive transfer of ex vivo activated T and natural killer cells, and administration of antibodies or recombinant proteins that either costimulate cells or block the so-called immune checkpoint pathways [28]. Programmed cell death protein 1(PD1) is one of a representative drug that promotes the development of this treatment. Although chemotherapy is a well-established treatment modality, chemotherapy errors represent a potentially serious risk of patient harm.

4.2.1 Programmed Cell Death Protein 1

Programmed Cell Death Protein 1 (PD-1) plays a vital role in inhibiting immune responses and promoting self-tolerance through modulating the activity of T-cells, activating apoptosis of antigen-specific T cells, and inhibiting apoptosis of regulatory T cells. Its ligand, Programmed Cell Death Ligand 1 (PD-L1), is a transmembrane protein that is considered to be a co-inhibitory factor of the immune response. It can combine with PD-1 to reduce the proliferation of PD-1 positive cells, inhibit their cytokine secretion, and induce apoptosis [29]. On August 5, 2016, the FDA granted approval for pembrolizumab (Keytruda injection, Merck Sharp & Dohme Corp.) for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy [30]. Nivolumab and pembrolizumab, both PD-1 inhibitors, are approved to treat patients with advanced or metastatic melanoma and patients with metastatic, refractory non-small cell lung cancer [31]. In general, as one of the most promising immune therapy strategies, PD-1/PD-L1 inhibitor is a breakthrough for the therapy of some refractory tumors [32].

4.2.2 Messenger Ribonucleic Acid (mRNA)-based Drugs

Another treatment strategy in immune therapeutics, messenger ribonucleic acid (mRNA)-based drugs, especially mRNA vaccines, are as promising as PD-1. The extraordinary advantages associated with mRNA vaccines, including their high efficacy, a relatively low severity of side effects, and low attainment costs, have enabled them to become prevalent in pre-clinical and clinical trials against various infectious diseases and cancers [33]. mRNA, an intermediate hereditary substance in the central dogma, was first discovered in 1961 by Brenner et al. [34]. Nevertheless, the concept of mRNA-based drugs was not conceived until 1989, when Malone et al. demonstrated that mRNA could be successfully transfected and expressed in various eukaryotic cells under the package of a cationic lipid (N-[1-(2,3-dioleyloxy) propyl]-N, N, N-trimethylammonium chloride (DOTMA)) [35]. In 1990, in vitro-transcribed mRNA was sufficiently expressed in mouse skeletal muscle cells through direct injection, which became the first successful attempt on mRNA in vivo expression and thus proved the feasibility of mRNA vaccine development [36]. Direct vaccination with messenger RNA (mRNA) molecules encoding tumor-associated antigens is a novel and promising approach in cancer immunotherapy. Because of the influence of COVID-19, the mRNA vaccine is currently mainly used for the prevention and control of COVID-19. The main advantage of using mRNA for vaccination is that the same molecule not only provides an antigen source for adaptive immunity but can simultaneously bind to pattern recognition receptors, thus stimulating innate immunity. Nevertheless, achieving both features remain challenging, as the complexation of mRNA required for immune-stimulating activity may inhibit its translatability [37].

4.2.3 Chimeric Antigen Receptor (CAR) T-cell Therapy

Chimeric antigen receptor (CAR) T-cell therapy is an effective new treatment for hematologic malignancies. Two CAR T-cell products are now approved for clinical use by the U.S. FDA: tisagenlecleucel for pediatric acute lymphoblastic leukemia (ALL) and adult diffuse large B-cell lymphoma subtypes (DLBCL), and axicabtagene ciloleucel for DLBCL. CAR T-cell therapies are being developed for multiple myeloma, and clear evidence of clinical activity has been generated. A barrier to widespread use of CAR T-cell therapy is toxicity, primarily cytokine release syndrome (CRS) and neurologic toxicity. Manifestations of CRS include fevers, hypotension, hypoxia, end-organ dysfunction, cytopenias, coagulopathy, and hemophagocytic lymph histiocytosis. Neurologic toxicities are diverse and include encephalopathy, cognitive defects, dysphasias, seizures, and cerebral edema [38]. Chimeric antigen receptor (CAR) T-cell therapy has dramatically shifted the landscape of treatment for lymphoid malignancies, especially DLBCL and ALL. Several phases 2 clinical trials of anti-CD19 CAR-T cells for treating R/R B cell malignancies have produced promising results. A trial of axicabtagene ciloleucel for refractory large B cell lymphoma (ZUMA-1) resulted in 82% (89/108) of the patients experiencing an overall response and 58% (63/108) achieving a complete response [36]. The administration of tisagenlecleucel (the first CAR-T drug used in the world) to adult patients with R/R diffuse large B cell lymphoma resulted in an overall response rate of 52%, with 40% of the patients achieving a complete response; the overall response rate of anti-CD19 CAR-T cells in clinical trials was greater than 80% for patients with B cell acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphoma (NHL) [39]. However, there continue to be significant limitations of this therapy, such as incomplete or no sustained responses and severe toxicities in a subset of patients. Furthermore, expanding the role of CAR T-cell therapy to new disease types is an important next step [40].

4.3 Combination Therapy of Chemoradiotherapy and Immunotherapeutic

At present, the combination therapy of chemoradiotherapy and immunotherapeutic is often used in clinical treatment. In terms of disease, take pancreatic adenocarcinoma (PAC) as an example. Pancreatic adenocarcinoma (PAC) is associated with an extremely poor prognosis and remains a lethal malignancy. The main cure for PAC is surgical resection. Further treatment modalities, such as surgery, chemotherapy, radiotherapy, and other locoregional therapies, provide low survival rates.

Currently, many clinical trials seek to assess the efficacy of immunotherapeutic strategies in PAC, including immune checkpoint inhibitors, cancer vaccines, adoptive cell transfer, combinations with other immunotherapeutic agents, chemoradiotherapy, or other molecularly targeted agents; however, none of these studies have shown practice-changing results. There seems to be a synergistic effect with increased response rates when a combinatorial approach of immunotherapy in conjunction with other modalities is being exploited [41]. In chemotherapy technology, Carboplatin and paclitaxel (CP) chemotherapy is used as a second-line chemotherapy regimen, and it is commonly used to treat melanoma. Carboplatin down-regulates the T-cell inhibitory molecule programmed death receptor-ligand 2 (PD-L2), which is expressed by DCs and melanoma cells to enhance T-cell activation [42]. Clinically, paclitaxel combined therapy has been used to treat breast cancer, NSCLC, ovarian cancer, and other malignant tumors [43]. This shows the development direction of cancer treatment in the future.

5. Conclusion

Taken together, PD-1/PD-L1 plays a vital role in several cancers, making it a key area for further research. From the above point of view, PD-1/PD-L1 is an opportunity and challenge for cancer treatment. This review reflects our new understanding of PD-1. We discussed the mechanism and the development of PD-1 inhibitors. Concurrently, while comparing traditional therapies with immunotherapy, we also mentioned the new applications of these therapies. At present, the research on PD-1 is gradually deepening. Pembrolizumab is a PD-1 inhibitor that has been put on the market. The use of PD-1 inhibitors in clinics provides new hope for patients. Immunotherapy has less drug resistance and toxicity than traditional treatment, including PD-1 / PD-L1 inhibitors, mRNA vaccines, car-t therapy, etc. As a cancer treatment in research, the prospect of immunotherapy is very broad. How to further improve the efficacy of immunotherapy, including PD-1 inhibitors, is the problem to be solved in the future. Meanwhile, the combination of traditional therapy and immunotherapy brings more opportunities for cancer treatment.

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