

Research Progress of Cancer Immunotherapy

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Keywords: Cancer, Immunotherapy, Cell therapy, Immune checkpoint therapy, Molecular therapy, Immune system regulator

Abstract: Clinical results show that tumor immunotherapy has shown exciting long-term efficacy in various cancer patients. At present, it is believed that the tumor's immune surveillance is divided into three stages: the early elimination stage, followed by equilibrium stage, in which the selective variation of immune system can protect the tumor from attack, and the third stage is the immune escape stage of tumor cell variation. The concept of immunotherapy is to indirectly kill cancer cells by stimulating or enhancing the ability of the body's immune system to specifically recognize and kill cancer cells, which is a cancer therapy mode of "using force to fight". Unfortunately, immunotherapy can only make a few cancer patients produce curative effect response. Therefore, the biggest problem faced by immunotherapy is not how to maintain long-term effect, but how to enable patients produce curative effect response at the beginning of treatment. This article will review the clinical progress of molecular therapy, cell therapy, immune checkpoint therapy and immune system regulator for cancer immunotherapy.

1. Introduction

Cancer is a major disease that threatens human life and health. According to the global cancer data survey, the number of liver cancer cases in China accounts for 50% of the world [1], and hepatocellular carcinoma accounts for 70% ~ 90% of primary liver cancer [2]. In our country, the incidence rate of renal cancer is second only to bladder cancer and second to urinary system tumors. In recent years, it has shown an upward trend, seriously threatening people's lives, health and safety. Immunotherapy, as a kind of tumor biotherapy, aims to improve the responsiveness of the human immune system to tumors and the immunogenicity of tumors. With the rapid development of tumor immunology, a series of tumor-related antigens have been identified one after another. Immunotherapy against these antigens has achieved certain effects in removing small residual lesions. Therefore, appropriate immunotherapy should be adopted for different types of tumor microenvironment to achieve the best therapeutic effect. In addition, the combination therapy for multiple components in the tumor microenvironment can prevent tumor cells from obtaining the necessary conditions for survival through a compensatory approach and achieve better therapeutic effects. This article will summarize the research on immunotherapy applied to tumor immunotherapy in recent years.

2. Molecular Therapy

Early animal experiments have shown that reducing leukocytes before stroke can improve blood flow in ischemic foci. This experimental result supports the view that reducing leukocyte migration and endothelial cell adhesion after ischemia can prevent hypoperfusion in ischemic sites [3]. Its dynamic balance with cell proliferation is a basic process necessary to maintain growth and development, internal environment stability and immune regulation. The initiation and implementation of apoptosis process involves a series of complex biochemical reactions and is regulated by various molecules. With the publication of the first human genome sequencing map and

other subsequent biological genome sequencing maps, molecular diagnostics has entered a new era with unprecedented opportunities and challenges. The tumor tissue contains tumor stem cells and tumor cells at different differentiation levels, showing a high degree of heterogeneity. These cells have different positions, perform different functions, and can exchange information and support each other. These effects are achieved through cell-to-cell interactions and/or soluble factors (including CTLA-4, LTA10 and TGF- β). However, the interaction between targeted drugs and immunotherapy is complex, and the time, dose and sequence of administration may affect the overall anti-tumor effect and toxicity characteristics of combined therapy.

At the same time, the development of molecular therapy has benefited from the emergence of in vitro DNA recombination technology and lymphocyte hybridoma technology. Tumor necrosis factor-related apoptosis-inducing ligand can induce apoptosis of various tumor cells. Zhang et al [4] recently reported that IL-1ra has a significant neuroprotective effect around ischemic foci. When normal cells become cancerous, the immune system discovers and initiates the response in the first place, thus nipping the occurrence of cancer in the bud. Only the tumor can secrete compounds that activate biological “immune checkpoints” to kill those protective cells, thus defending the tumor itself. Therefore, the activation of T cells must be strictly and finely regulated in order to start the activation process when external pathogens invade and tissues in the body become cancerous. In order to produce anti-tumor immunity, it is also injected into lateral ventricle with IL-1 antibody and IL-1 β blocker protoporphyrin zinc, which can block IL-1 β activity, reduce the volume of cerebral infarction and reduce the number of leukocyte infiltration [5]. Antisense nucleic acid targeting bcl-2 and bcl-xL homologous regions can simultaneously reduce the expression of both genes and induce apoptosis. Combined with the patient's general condition and molecular biological behavior, chemotherapy drugs and biological agents are systematically applied in combination for treatment.

IL-8 is induced and produced by TNF- α and IL-1 β , which not only plays a key role in the leukocyte chemotaxis, but IL-8-related chemotactic polypeptides can also rapidly activate the connecting molecules of integrin α and β chains within a few minutes, increasing the adhesion between leukocytes and endothelial cells. It is highly expressed in some common malignant tumors, but hardly expressed in most normal tissues. Although the therapeutic effect on solid tumors is not ideal, it has a good therapeutic effect in clinical trials for lymphoma and B-cell leukemia. Therefore, T cell activation must be strictly and finely regulated to prove that activation procedures can be initiated when external pathogens invade and tissues in the body become cancerous, so as to realize effective monitoring and strong killing. If the combination therapy for checkpoint inhibition can become a clinical tumor treatment strategy, it will just bring a good market opportunity for the development of small molecule inhibitors. At present, P53 (such as AV-P53), DC (such as AAV-BA46-DC) and TIL(IL-2, TNF- α) have been used in clinical research in various stages.

3. Cell Therapy

Infiltration of effector cells is a necessary but not sufficient condition for effective immunotherapy. Many stromal cells in tumor microenvironment and their regulatory factors will inhibit the effect of effector cells and help tumor growth and development. In addition to killing tumor cells, targeted therapy can also directly regulate the immune response, such as increasing the presentation of tumor antigen by dendritic cells (DC) and increasing the activation of tumor-specific cytotoxic T lymphocytes (CTL), thus increasing the sensitivity of tumor cells to immune regulation and killing [6]. However, in addition to the significant effect of CAR-T therapy on blood tumors, CAR-T therapy also has some problems, such as miss target effect, cytokine storm, insertion mutation, etc., and has not yet achieved significant curative effect on solid tumors. At present, many preclinical and clinical trials have proved the effectiveness and safety of gene therapy in the treatment of ischemic heart disease. The purpose of treating diseases is to promote angiogenesis, anti-oxidation and inhibit apoptosis by introducing specific genes. There are two main reasons for the poor effect of CAR-T cells: First, the low specificity of tumor antigens (limited difference from normal cells) limits the use

of CAR-T cells; Another reason is that the activation effect of CAR-T cells is limited, and the killing ability of cancer cells is insufficient.

Up to now, clinical trials of immunotherapy mainly evaluate a single drug and target a single process of anti-tumor immunity. In fact, several immune processes may be involved in producing an effective anti-tumor response. The experiment of combining blocking CTLA-4 or PD-1 with active immunity or active immunity plus pre-lymphocyte depletion has just begun. The composition of tumor stromal cells is complex. At present, the reported tumor stromal cells include fibroblasts, immune inflammatory cells, adipocytes, vascular endothelial cells, etc. [7]. In the first generation CAR structure, CD3 ζ intracellular segment of the TCR complex is commonly used as the intracellular signal region. Later, in order to increase cytotoxicity, proliferative activity and prolong the survival time of effector cells [8]. The function of the transmembrane region is to transfer extracellular information into cells. Now the most common transmembrane sequence is CD3 ζ . HLA-A2 and CD8 are also increasingly used as transmembrane sequences [9].

Donor NK cells are co-cultured with K562 cells (K562-mb15-41BB1) capable of expressing IL-15 and 41BB ligands, and specific amplification of NK cells can be realized under stimulation of IL-15 and 41BB ligands. CD19 receptor is modified on the surface of the amplified NK cells to obtain car-NK cells, which are then transfused into patients (fig. 1).

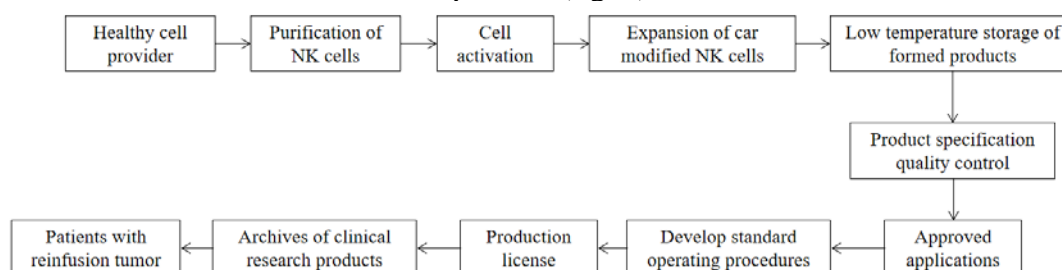


Fig.1 Car-Nk Clinical Trial Technical Process

The antigen-binding region and the transmembrane region are basically the same in CAR-NK and car-t. The antigen binding region can be tightly bound to tumor-related antigens expressed on the surface of tumor cells. Immunoinflammatory cells in the tumor microenvironment can also be divided into lymphocytes, bone marrow-derived macrophages, myeloid suppressor cells, etc. High concentration of NY-ESO-1- specific IgG will form immune complexes with NY-ESO-1 released by apoptotic or necrotic tumor tissues, after which these immune complexes will be effectively ingested by dendritic cells. Monoclonal antibody promotes DC to absorb tumor antigen and is helpful for activation and amplification of tumor specific CD4+and CD8+T cells. In 2010, CAR-T cells targeting the specific antigen CD19 of B-cell lymphoma were successfully developed with strong specificity, but the killing effect is still limited. For example, CD28, OX-40 and 4-1BB, etc., thus the second generation and the third generation CAR are derived, and the CAR structure that introduces cytokines and costimulatory ligands is called the fourth generation CAR [10]. In addition, the cost of treatment with antibody drugs alone is relatively high, while the combination of small molecule drugs and antibody drugs is an economical treatment option.

The specific killing of CAR-NK depends on the interaction of antigen binding region, transmembrane region and intracellular signal domain. Zhou [11] Fusion expression of tumor-associated antigen EGFR ligand TGF- α and granulose enzyme in NK cells. After artificial activation of NK cells, the released GrB-TGF- α fusion protein can target and kill EGFR-positive tumor cells. Xu et al. It is believe that the efficacy of CAR-T cell therapy in rescuing patients from the brink of death is enough to cheer up the majority of scientific researchers without fear of setbacks and tenacious progress [12]; Shortly after the success of this drug, scientists used antibodies to block PD-1 expressed on immune cells, or its corresponding inhibitory gene PD-L1 (present on tumors and some immune cells), and achieved gratifying results one after another. Therefore, blocking PD-R can eliminate the number of Treg in cancer tissue or inhibit its cell activity to enhance anti-cancer ability.

However, cells isolated from peripheral blood need to detect the contents of T cells and B cells to prevent GVHD and EB virus-related malignant lymphoproliferative diseases.

4. Immune Checkpoint Therapy

Programmed death receptor -1(PD-1) is a member of the CD28 /CTLA-4 family costimulatory receptor, originally from apoptotic mouse T cell hybridoma 2B4. Under pathological conditions, the PD-1 receptor on T cell surface interacts with its ligands PD-L1, PD-L2, which can inhibit T cell proliferation and activation, thus allowing tumor immune escape. Pearce et al. [13] assumed that the only colorectal cancer patients in KEYNOTE-028 who achieved partial remission are due to its important genetic characteristics, and completed a phase II clinical trial to screen patients with tumor genetic characteristics and evaluate anti-PD-1 efficacy. The PD-1 intracellular segment has two key functional domains, the N-terminal immunoreceptor tyrosine inhibitory motif and the C-terminal immunoreceptor tyrosinase converting motif. The tumor microenvironment can induce tumor cells to express PD-L1 highly. PD-L1 negatively regulates T cell function, inhibits T cell proliferation and inhibits the activity of cytotoxic T lymphocytes by combining with PD-1. In tumors, the interaction between PD-1 and PD-L1 can prevent the activation of T cells in the tumor microenvironment and lead to immunosuppression, thus weakening the anti-tumor effect.

PD-1 has two ligands, PD-L1 and PD-L2. PD-L1 is mainly expressed on the surface of antigen presenting cells, activated T cells, B cells, placental trophoblast cells, cardiac endothelial cells and thymic cortical epithelial cells. Immune checkpoint receptor, such as PD-1, is an important endogenous signal molecule that leads to the damage of anti-tumor immune system. PD-1 can negatively regulate the activation of normal T cells to inhibit normal immune response. Therefore, by blocking the combination of PD-1 and PD-L1, the immune killing effect of T lymphocytes in tumor body can be restored, thus inhibiting the recurrence and metastasis of malignant tumor. Down-regulating T cell activation to improve immune tolerance is also used by tumor cells to induce anti-immune state, so that tumor cells can grow and develop without being cleared by the immune system. At the American Gastrointestinal Tumor Symposium, researchers reported a phase I clinical trial of anti-PD-1 antibody combined with stereotactic radiotherapy [14]. Under physiological conditions, PD-1 has low expression on the surface of various types of immune cells. Only when T cells are stimulated by double signals can the expression of PD-1 be upregulated.. For example, PD-1/PD-L1 interaction can promote CD4+T cells to differentiate into FOXP3+Treg, further inhibit the immune system, and aggravate the peripheral immune tolerance of cancer patients.

At present, there are many clinical studies on the role of PD-1 / PD-L1 in the treatment of liver cancer through blockers. In 2010, Harvard Sharpe research group applied for a patent to protect mPD-1/mPD-L2 blockers of sulfamethoxypyrimidine or sulfaimidazole structural type [15]. The representative structure is shown in Figure 2. The expression of PD-1 on CD8+ cytotoxic T lymphocytes in the mouse model with AML progression increased. The dynamic balance of the costimulatory signal and the costimulatory signal can reduce damage to normal tissues caused by overreaction of immune response to the greatest extent under normal physiological conditions, realize immune tolerance and avoid occurrence of autoimmune inflammation. Abiko et al [16] studied the expression of PD-L1 on the surface of ovarian cancer cells. CD8+T cells were co-cultured with ovarian cancer cells with high PD-L1 expression and cells with low PD-L1 expression. However, the expression of PD-L1 is closely related to anti-PD-1 and anti-PD-L1 treatments. Some studies have shown that patients with high PD-L1 expression are significantly better than patients with low PD-L1 expression when using immune checkpoint inhibitors. CTLA-4 and PD-1 play different roles in inhibiting immune responses, including anti-tumor response. At present, there is evidence that MSI-H colorectal cancer can be recommended as a suitable patient for anti-PD-1/PD-L1 immunotherapy, while the remaining indicators are not yet clear. However, when inflammation or tumor occurs, the expression of PD-L1 on the surface of tissue cells will be up-regulated under the stimulation of cytokines.

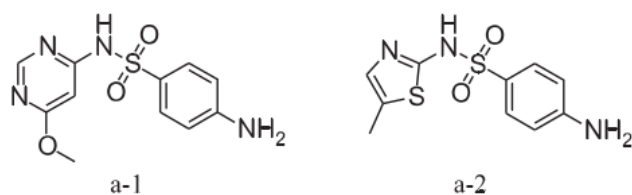


Fig.2 Molecular Structure of Pd-1/Pd-L2 Blocker in W02011082400

In solid tumors, the main mechanism of PD-1/PD-L1 pathway mediated inhibitory immune effect of effector T cells is PD-1 receptor recruitment and activation of intracellular phosphatase such as SHP-2 to inhibit T cell receptor signals. This provides an important matrix microenvironment for tumor growth. RS cells are often highly expressed on the surface of PD- L1. When they combine with PD-1 receptor, they can suppress normal immune responses and promote the growth of RS cells. Ribas et al [17] further studied the effect of PD-L1 expression on tumor cell surface using ovarian cancer mouse model. In the ongoing clinical trials of anti-CTLA-4 plus anti-PD-1 or anti-PD-L1 in other tumor types, the initial result data also indicate the hope of combined therapy, which emphasizes that this innovative combination can be provided to tumor patients as an immunotherapy strategy. Immunohistochemical assay showed that all regulatory T cells were FOXP3+. Regulatory T lymphocytes inhibit the activation of other cells by consuming IL-2, thus leading to the weakening of the anti-tumor ability of the body.

5. Immune System Regulator

In vitro test results show that AS-101 can stimulate the proliferation of normal lymphocytes and stimulate the production of IL-2 and CSF. Generally speaking, anti-reflux induced CGMP level increase in target cells, while immunosuppressive agents induced CAMP level increase in target cells. Some specific or non-specific cellular immune function of donor lymphocytes can be transferred to the receptor to improve and trigger the immune defense function of the body and improve the immune state of the body. Li et al [18] reported that glycoprotein extracted from *Klebsiella pneumoniae* was used as an immunopotentiator to treat RRI patients. The results showed that the number of infections, course of disease and blood immune index in the treatment group were significantly different from those in the control group without side effects. Zhang [19] took BALB/C mice as the research object, and divided them into different groups with cyclophosphamide, cyclophosphamide and LBP, respectively, to measure the killing activity of NK cells and the number of leukocytes. The results showed that LBP could promote the recovery of NK cells induced by cyclophosphamide. Researchers attributed the anti-tumor effect of AS-101 to the immune promotion effect of AS-101. It can also inhibit the response and phagocytosis of macrophages to chemokines and block the clearance of foreign bodies by reticuloendothelial-system. It has similar effect to transfer factor, has no obvious side effect, is more easily accepted by children, and can effectively treat RRTI of children.

Transfer factor (TF) is a small molecular peptide extracted from healthy human leukocytes, which can transfer cellular immune activity to the receptor to improve the cellular immune function of the receptor. Scholars at home and abroad have confirmed that Epimedium Polysaccharides can enhance the proliferation and differentiation of T and B lymphocytes in spleen and thymus, promote phagocytic activity of macrophages, and induce the production of various cytokines such as IFN, IL-1 and IL-2 [20]. T cells are activated through the cross presentation and capture of TAA in APC, or TAA specific T cells are directly activated, thus triggering an acquired immune response. Although PD-1 inhibitor is the most mature immunotherapeutic drug, several research and development companies are also developing other immune checkpoint inhibitors. Recent studies show that cetuximab activates NK cells and DC cooperation to trigger tumor antigen-specific T cell immunity in patients with head and neck tumors. Tumor-specific antibodies from patients are expected to become drugs for initiating comprehensive tumor-specific immune responses and combine with multiple treatment methods to prevent cancer.

Immune checkpoints are often used by tumor cells to realize immune escape, among which CTLA-4, PD-1 and PD-L1 are studied most and deeply. Tumor antigen may be expressed in thymus, and tumor-specific T cell lines with high affinity to tumor antigen may be eliminated in thymus. NK cells activated by cetuximab can promote DC cell maturation and CD8⁺T cell activation, and increase EGFR- specific CTL in patients. At present, besides PD-1/PD-L1, many inhibitors for immune checkpoints have been researched and developed, and it is believed that a series of experiments will eventually be conducted to explore how tumors evade the attack of the immune system, just as a series of gene tests are now conducted to examine the mutation map of tumors. Almost everything on the surface of T cells is now a potential target for activating immune response. Can reduce residual cancer cells and cancer recurrence, and also provides conceptual evidence for targeted delivery of cells, small molecules or biological agents.

PG is a powerful local immunomodulator. PGE can inhibit T cell proliferation, IL-2 production by normal peripheral blood lymphocytes and lymphatic factor production by lymphocytes. In vitro JAK2 inhibitor increases DC expression on MHC- II class II molecules, CD40 and CD86. Regulatory T cells in tumor microenvironment block local T cell function or block formation of tumor-specific T cells. It can prevent CAR-T cells reaching tumor tissues from being inhibited, obtain more lasting effects and achieve remarkable anti-tumor effects. The combination of immune checkpoint inhibitors and targeted therapy can also obtain better therapeutic effects. It provides continuous autocrine-like stimulation signals to cells, avoids the rapid decline of the activity and function of transferred T cells, and enhances ACT's anti-lymphoma effect. Objectively speaking, immunotherapy is only an important supplement to cancer treatment programs, and there is no evidence that it can fundamentally solve the huge problem of cancer. In some cases, chemotherapy is either the only choice or the optimal solution in a few unsatisfactory schemes, but it can already replace chemotherapy in many cases.

Monoclonal antibodies at immune test points are easy to destroy the self-balance of the immune system due to the activation of the immune system in the application process, and often lead to inflammation of multiple organs or multiple tissues, which is called immune-related adverse reactions. Therefore, it is only applied clinically as an adjuvant therapy at present, and some patients benefit from it. The second is the high cost. T cells must avoid negative regulatory signals (called immune checkpoints, which inhibit their activation or induce immune tolerance processes), leading to their incompetence or depletion. Finally, soluble factors, such as IL-10 and TGF- β , may be produced in tumor environment or promote the production of bone marrow-derived suppressor cells. Local factors inhibit the function of effector T cells. Studies have shown that blocking IDO can produce strong synergistic effect with CTLA-4 and PD-1/PD-L1 antibodies and enhance the activity of CD8⁺T cells in tumor. Endorphine bark and enkephalin bark can also protect immune system from glucocorticoid-induced inhibition, and can restore normal function to immune dysfunction induced by endocrine disorder caused by nervous system disorder. Changing physiological environment of colon (lowering pH value) affects metabolic activity of intestinal microflora, and changing cholic acid activity causes quantitative and qualitative changes in degradation of bacteria by cholic acid. Strengthen the host's immune system.

6. Summary

As a “fertile soil” for the growth of tumor cells, the tumor microenvironment has an important influence on the occurrence and development of the whole tumor. In general, immune checkpoint blocking is a non-specific strategy to eliminate immunosuppression to achieve cancer cell killing, with poor targeting and a “double-edged sword” effect. Nanotechnology can greatly improve the efficacy of tumor vaccines, improve the curative effect of immunotherapy, realize combined therapy, overcome the shortcomings of immunotherapy itself, and reduce side effects. Similarly, immunotherapy based on anti-tumor immune mechanisms can obviously prolong the survival time of patients, suggesting the advent of immunotherapy era. In a word, immunotherapy has provided a powerful new weapon for oncologists and opened up a new biological field to be explored urgently.

References

- [1] Lu Ping, Hao Sha, Yuan Weiping, et al. Chimeric Antigen Receptor--A New Hope for Cancer Immunotherapy. *Chinese Medical Journal*, vol.095, no.004, pp.311-314, 2015.
- [2] Chen Yunfan, Hong Juan, Shen Junjie, et al. New clinical progress in cancer immunotherapy. *Advances in Biochemistry and Biophysics*, vol.044, no.008, pp.709-716, 2017.
- [3] Ping Lu, Sha Hao, Weiping Yuan, et al. Chimeric antigen receptor--a new hope for cancer immunotherapy. *Zhonghua yi xue za zhi*, vol.95, no.4, pp.311-314, 2015.
- [4] Zhang Nisi, Zhou Mingming, Dai Zhifei. Research progress of using nanotechnology to improve the effect of cancer immunotherapy. *Science Bulletin*, vol.063, no.005, pp.535-546, 2018.
- [5] Sabado R L, Bhardwaj N. Cancer immunotherapy: Dendritic-cell vaccines on the move. *Nature*, vol.519, no.7543, pp.300-301, 2015.
- [6] Vanamee, éva S, Faustman D L. TNFR2: A Novel Target for Cancer Immunotherapy. *Trends in Molecular Medicine*, 2017:S1471491417301697.
- [7] Nishimura Y, Tomita Y, Yuno A, et al. Cancer immunotherapy using novel tumor-associated antigenic peptides identified by genome-wide cDNA microarray analyses. *Cancer Science*, vol.106, no.5, pp.505-511, 2015.
- [8] Yu Lu, Jin Gang, Li Qinghai, et al. Attenuated Salmonella as a new tumor vaccine delivery vehicle-a new hope for cancer immunotherapy. *International Journal of Immunology*, vol.039, no.003, pp.267-270, 2016.
- [9] Xue Runtao. Methods and research progress of cancer immunotherapy. *Chemical Intermediates*, vol.000, no.001, pp.177-179, 2019.
- [10] Sha Lun (excerpt). High-fiber diet can improve the response of cancer immunotherapy. *China Medical Information Herald*, vol.2019, no.6, pp.13-13, 2019.
- [11] Zhou Hai. What are the advantages of cancer immunotherapy in cancer treatment entering the "immune era". *Self-care*, vol.2019, no.10, pp.12-12, 2019.
- [12] Xu Bing, Zhou Zumu. The 15th Annual Meeting of the Cancer Immunotherapy Association. *International Journal of Biological Products*, vol.41, no.2, pp.101-103, 2018.
- [13] Pearce O M T, Heinz L. Cancer Immunotherapy. *Glycobiology* vol.9, no.9, pp.11, 2012.
- [14] Schumacher T N, Schreiber R D. Neoantigens in cancer immunotherapy. *Science*, vol.348, no.6230, pp.69-74, 2015.
- [15] Gall C M L, Weiden J, Eggermont L J, et al. Dendritic cells in cancer immunotherapy. *Nature Materials*, vol.17, no.6, pp.474-475, 2018.
- [16] Fesnak A D, June C H, Levine B L. Engineered T cells: the promise and challenges of cancer immunotherapy. *Nature Reviews Cancer*, vol.16, no.9, pp.566-581, 2016.
- [17] Ribas A, Wolchok J D. Cancer immunotherapy using checkpoint blockade. *ence*, vol.359, no.6382, pp.1350-1355, 2018.
- [18] Li Zhong, Sun Yan, Qian Qijun. Precise targeting of local tumor immunotherapy may become a key strategy for curing cancer. *Chinese Journal of Cancer Biotherapy*, vol.26, no.01, pp. 13-2, 2019.
- [19] Zhang Keming. Subversion of cancer treatment revolution--A brief introduction to new progress of immunotherapy. *Bachu Medicine*, vol.1, no.04, pp.7-13, 2018.
- [20] Li Shuwao, Gao Xiaoping, Chen Qianqi, et al. Influencing factors of immunotherapy related liver adverse events in patients with malignant tumors. *Chinese Journal of Oncology*, vol.42, no.01, pp.50-54, 2020.