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Review

How to overcome the side effects of tumor immunotherapy

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ABSTRACT

The incidence of cancer is increasing year by year. Cancer has become one of the health threats of modern people. Simply relying on the surgery, chemotherapy or radiotherapy, not only the survival rate is not high, but also the quality of life of patients is not much better. Fortunately, the emergence and rapid development of cancer immunotherapy have brought more and more exciting results. However, when scientists think it is possible to overcome cancer, they find that not all cancer patients can benefit from immunotherapy, that is to say, the overall efficiency of immunotherapy is not high. Drug resistance and side effects of immunotherapy cannot be ignored. In order to overcome these difficulties, scientists continue to improve the strategy of immunotherapy and find that combination therapy can effectively reduce the incidence of drug resistance. They also found that by reprogramming tumor blood vessels, activating ferroptosis, utilizing thioredoxin, FATP2 and other substances, the therapeutic effect can be improved and side effects can be alleviated. This article reviews the principles of immunotherapy, new strategies to overcome drug resistance of cancer immunotherapy, and how to improve the efficacy of immunotherapy and reduce side effects.

1. Introduction

The normal immune system can recognize and remove malignant cells, thus inhibiting the occurrence of tumors, but some mutated tumor cells survive the "clearance" effect of immune editing. These cancer cells are less antigenic, so they are not easily recognized and cleared by the immune system [1]. When the accumulation effect of gene mutation reaches a certain level, the tumor cells enter the stage of immune escape. Tumor cells change the microenvironment of tumors by self-modification and metabolic changes and release some immunosuppressive molecules, which can inhibit other immune cells and lead to immune tolerance of the immune system to tumors [2]. At this stage, the anti-tumor mechanisms of the immune system completely collapses, the growth of tumors is completely out of control, and the metastasis is widespread [3–6]. The mechanisms of immune escape may be due to the lack of antigen expression or the establishment of immune tolerance environment [7,8]. Immunotherapy can improve the tumor microenvironment(TME) and make the immune system play an anti-cancer role again in the tumor microenvironment, so as to control or even eliminate cancer cells. Chen et al. believes that this effect is

Abbreviations: CAR-T, chimeric antigen receptor T; VEGFA, vascular endothelial growth factor; ANGTA2, immunoglobulin targeted angiopoietin 2; FATP2, fatty acid transporter 2; FMT, fecal microbiota transplantation; MDR1, multidrug resistance protein 1; PD-L1, programmed death ligand 1; TIL, tumor-infiltrating lymphocytes; TNP-1, copper-palladium alloy tetrapod nanoparticle.

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based on the three principles of cancer immunotherapy, namely, immune normalization, the use of tumor microenvironment, and the reconstruction of the immune response [9].

1.1. Normalization of immunity

Immunonormalization emphasizes the importance of identifying specific deficiencies or dysfunctions of the immune response in the progress of tumors [10]. Therefore, it is not to enhance the immune response, but to correct these defects and restore the body's natural anti-tumor immunity. This immunity, which the patient should have, is weakened in the growth of the tumor [11,12]. Although the ultimate outcome of normalization strategies may lead to an increase in immune responses, these responses generally do not exceed the upper limit of their own immune regulation. In theory, it does not cause permanent damage to normal organs or tissues [13].

1.2. Using the tumor microenvironment

The microenvironment transformed by tumor cells is the "soil" that nourishes tumor cells [14]. Under its influence, the number of tumor-specific T cells, macrophages and other immune cells, as well as immune factors decreased and their functions were impaired. Immunotherapy can selectively deliver therapeutic drugs to tumor microenvironment, improve tumor microenvironment and reduce the waste of a large number of drugs in other unrelated places [15–17].

1.3. Reconstruction of the immune response

Immunotherapy can transform the tumor microenvironment from a lazy state full of inhibiting molecules and cells to an environment with an extremely active immune system. This alteration of a molecule, which causes a chain reaction, is called reconstruction of the immune response [18–20].

2. How to improve the efficacy of immunotherapy and reduce side effects

Immunotherapy is one of the most promising developmental direction in the field of tumor therapy, and its breakthrough effect has become a new hope for many tumor patients. However, the effective rate of tumor immunotherapy is only 10 %–30 %, and its side effects cannot be overlooked [21–24]. The reason for the low efficacy of tumor immunotherapy is related to some substances in the tumor microenvironment, such as thioredoxin, fatty acid transporter 2, vascular endothelial growth factor, etc. These substances in the tumor microenvironment, by destroying the lymphocyte, or by stimulating the neovascularization in the tumor, result in reduced T-cell infiltration, reduced tumor immunogenicity, and decreased antigen presentation. These factors make tumor cells can easily escape the attack of immune cells, resulting in immune escape, so that the effectiveness of immunotherapy is reduced. The causes of side effects after treatment with checkpoint inhibitors are still in the exploratory phase. The potential mechanisms of immune-related adverse events are T-cell repertoire diversification, shared tumor and organ-specific neoantigen, shared tumor and self-antigens, etc.. There are still many problems to be solved on the way of tumor immunotherapy. How to improve the efficacy of immunotherapy and alleviate side effects has also been paid more and more attention.

2.1. Thioredoxin

The tumor microenvironment is rich in toxic reactive oxygen species (ROS), which can destroy lymphocyte and lead to a sharp decrease in lymphocyte life. So even though checkpoint inhibitors remove the cancer's ability to suppress immune cells, patients still have too few immune cells, and their resistance to cancer is still limited. Antioxidants antagonize active oxygen molecules, and thioredoxin is a natural antioxidant. It not only neutralizes ROS on the surface of lymphocyte, but also reprograms lymphocyte to enhance the ability of lymphocyte to compete with tumor cells for nutrients, thus improving the efficacy of immunotherapy. In addition, ROS enhances the responsiveness of donor cells to healthy cells after hematopoietic stem cell transplantation, leading to GVHD. The antioxidation of thioredoxin can reduce the toxic ROS in donor T-cells. Then T-cells become less responsive to the patient's healthy tissue, preventing the development of GVHD [25,26].

2.2. Reprogramming tumor blood vessels

Tumor vessels provide oxygen and nutrients to tumor cells. Tumors produce vascular endothelial growth factor (VEGFA) and immunoglobulin targeted angiopoietin 2 (ANGPT2), proteins that stimulate the growth of new blood vessels and thus promote tumor growth. With VEGFA and ANGPT2, tumor blood vessels block T-cell invasion, so patients with tumors who received anti VEGFA therapy quickly developed drug resistance, and the efficacy of immunotherapy was limited. A2V is an antibody that inhibits VEGFA and ANGPT2. Reprogramming tumor blood vessels with A2V can lead to the degeneration of many tumor blood vessels, and can also reverse the structure of blood vessels to normalize them, making it easier for anti-tumor T-cells to pass through. It enhances the efficacy of immunotherapy [27]. Some anti-angiogenic drugs not only target blood vessels, but also assist in initiating an anti-tumor immune response [28,29], which can be used to enhance the efficacy of immune checkpoint inhibitors (Fig. 1).

2.3. Fatty acid transporter 2

Veglia et al. [30] found that fatty acid transporter 2 (FATP2) promotes arachidonic acid utilization and prostaglandin E2 synthesis in polymorphonuclear-myeloid derived suppressor cells (PMN-MDSCs), mediating immune suppression, and inhibiting FATP2 can improve the efficiency of tumor treatment. Specific inhibition of fatp2 can also make the drug specifically act on the tumor tissue with high expression of fatp2, without causing damage to other parts of the body, and effectively reduce the side effects.

2.4. Flora transplantation

The intestinal flora composed of Bifidobacterium and Lactobacillus plays a non-specific immune function by occupying space and producing bacteriocin, organic acid, hydrogen peroxide and other substances. Intestinal flora can also be used as antigen to stimulate and promote the development and maturation of the immune system, so that the body can obtain the resistance to many pathogenic bacteria and toxins, and play a specific immune effect. If the patients used broad-spectrum antibiotics before and after immunotherapy, the intestinal flora will be disordered, and the therapeutic effect is worse than that of patients who have not used broad-spectrum antibiotics. Flora transplantation (FMT) is to transplant healthy bacteria into the intestinal tract of patients, improve the intestinal flora and enhance the anti-tumor ability of T-cells, help the human body form a strong immune system barrier, and realize the treatment of diseases inside and outside the intestine. The transplanted flora can repair the missing microbiota in the intestinal tract of patients, regulate the imbalance of flora, and reconstruct the intestinal microbial system. Lida and Viaud have found that intestinal flora can regulate the immune response to drugs. Bifidobacterium improves the anti-cancer immune effect in vivo in an antigen independent manner. This study shows that one of the reasons for the difference of immunotherapy efficacy among individuals is the composition of intestinal flora, which can be improved by changing the intestinal flora. Narula et al. [31] successfully treated the first case of colitis associated with immune checkpoint inhibitors (ICI) through FMT. FMT can

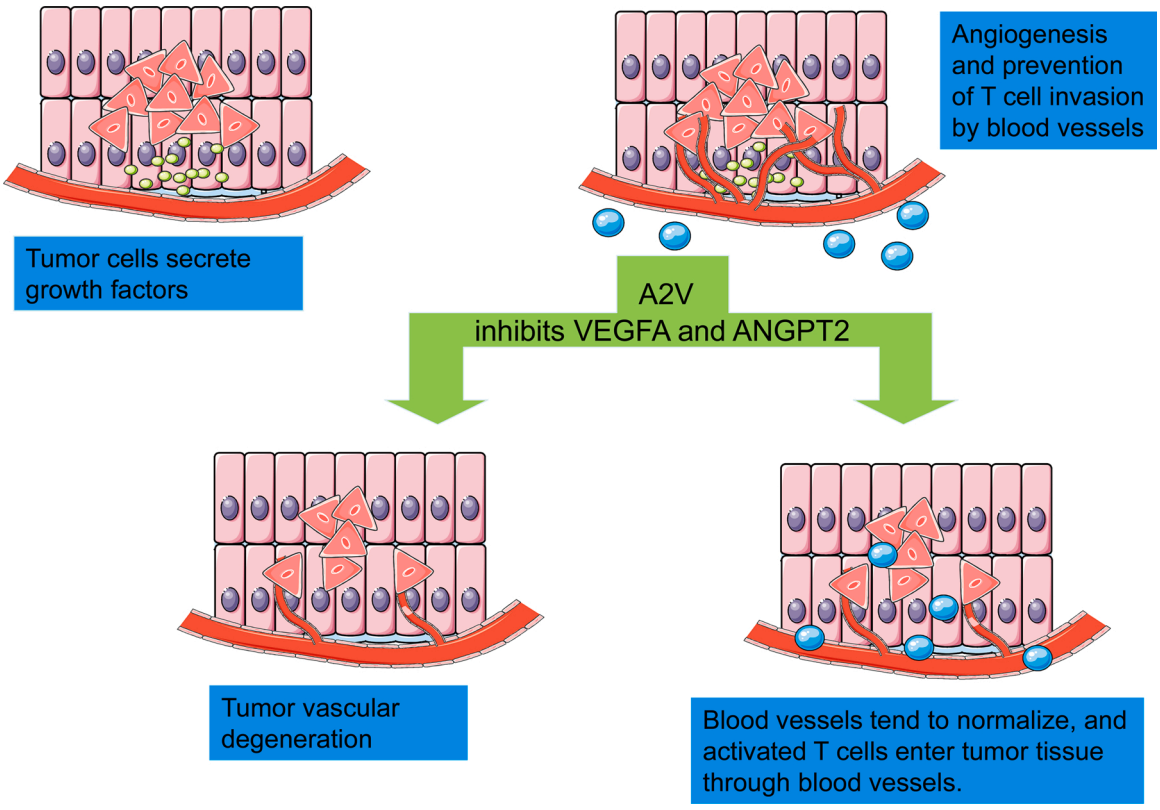

Fig. 1. The existence of a tumor induced angiogenesis, which provides nutrients for tumor cells growth and promotes tumor growth. Under the influence of VEGFA and ANGPT2, tumor blood vessels will form structures that can prevent T cells from invading. A2V is an antibody that can inhibit VEGFA and ANGPT2. It can not only cause tumor vascular degeneration, but also reverse the structure of blood vessels. Blood vessels tend to be normalized, which is beneficial for activated T-cells to enter tumor tissue through blood vessels, improve tumor microenvironment, weaken immunosuppression, and then promote more tumor vascular normalization.

improve the therapeutic effect, alleviate the toxic and side effects of tumor treatment, inhibit the growth of tumor cells, and reshape the immune microcirculation.

2.5. Ferroptosis

In order to meet the growth needs, tumor cells need more iron than ordinary non tumor cells. This iron dependent oxidative damage leads to cell death mode, i.e. ***Ferroptosis***. This pattern is morphologically

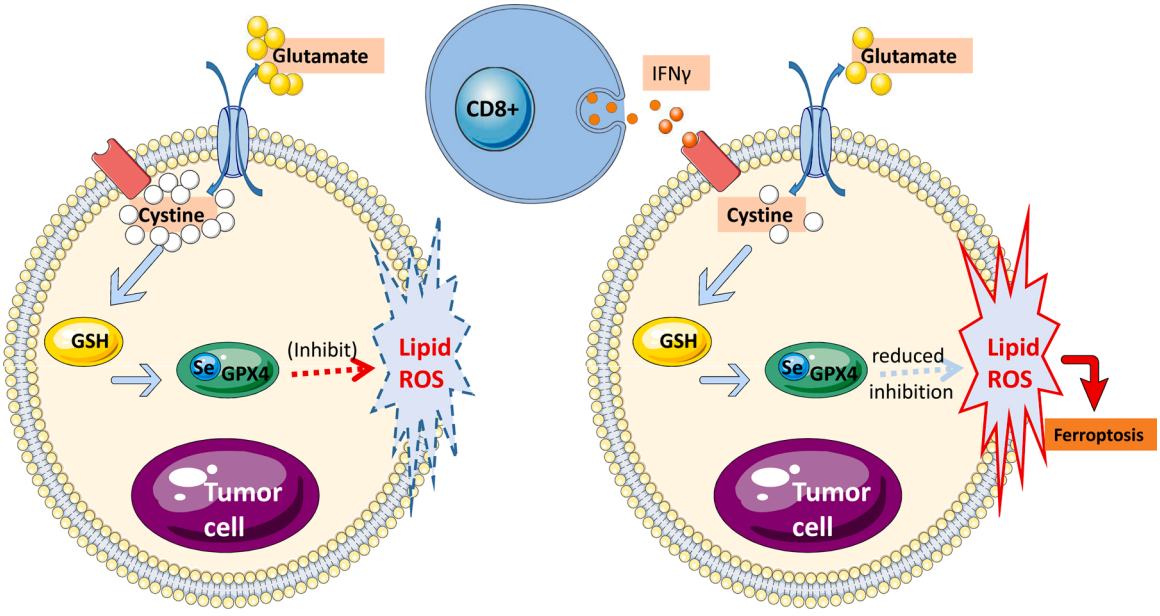

Fig. 2. Activated CD8+ T-cells enhanced specific lipid peroxidation of ferroptosis in tumor cells. IFNγ released by CD8+ T-cells will down-regulate the expression of cystine transporter on the surface of tumor cells, thereby inhibiting the uptake of cystine by tumor cells, thereby enhancing lipid peroxidation and ferroptosis of tumor cells.

different from other known programmed cell death. Through this death process, the cell cytoplasm and lipid reactive oxygen species increased, mitochondria became smaller, and the density of mitochondrial membrane increased [32,33]. Wang et al. [33] found that ferroptosis occurs in tumor cells and plays a role in cancer immunity. Activated CD8+ T-cells enhanced specific lipid peroxidation of ferroptosis in tumor cells. IFNγ released by CD8+ T-cells will down-regulate the expression of cystine transporter on the surface of tumor cells, thereby inhibiting the uptake of cystine by tumor cells, thereby enhancing lipid peroxidation and ferroptosis of tumor cells (Fig. 2).

2.6. Necroptosis

Necroptosis refers to the use of the immune system to attack and destroy the body's own cells. In one study, scientists found that injecting cells that were undergoing programmed necrosis into mouse tumors induced killer T-cells to attack malignant tumors and slow their growth [34]. In addition, studies have shown that if tumor cells produce enzymes that induce programmed necrosis, they can also start a process that prevents tumor growth [35,36]. The strategy may improve the effectiveness of existing immunotherapies.

3. New strategies for overcoming cancer immunotherapy resistance

With the development of immunotherapy, the efficacy of immunotherapy is gradually verified in clinical practice, and many defects are exposed one by one. For example, most patients have no response to the treatment of immune checkpoint inhibitors, a small number of patients develop drug resistance soon after the response [37], and even some patients with good initial response have relapsed due to acquired drug resistance. At present, there are mainly four strategies for the treatment of immunotherapy resistance, among which new nano-drugs belong to the frontier technology of tumor immunotherapy resistance treatment.

3.1. Combination therapy strategy

By taking immunotherapy as the cornerstone and combining with other treatment methods, the goal of overcoming various kinds of immune resistance is achieved, including immunotherapy combined with anti-angiogenesis therapy [38,39], chemotherapy [40], radiotherapy [41,42], targeted therapy (limited to IO combined with BRAF TKI in malignant melanoma [43]), epigenetic modification agents [44,45], etc., all of which have made certain progress.

Researchers found that patients with stage 4 melanoma who received a combination of the BRAF inhibitor Dabrafenib, the MEK inhibitor Trametinib, and the PD-1 blocker Pertuzumab had a controlled adverse reaction compared to monotherapy, and that some patients produced a sustained response [46–49]. The researchers found no adverse effects of triple therapy on the appearance of an immune response in the tumor. This study suggests that this triple therapy may benefit patients with metastatic melanoma with BRAF mutations by increasing the frequency of long-term anti-tumor responses [50,51]. Studies have found that multiple ABCB1 transcription fusions are responsible for resistance to ovarian cancer and breast cancer. ABCB1 induces drug resistance by encoding multidrug resistance protein 1 (MDR1), and the addition of MDR1 inhibitors can sensitize fusion-positive cell lines to paclitaxel [52].

3.2. Crowd selection strategy

Different tumor patients have different mutation load, so the response to immunotherapy is different. It has been found that patients with positive or high expression of PD-L1 are more likely to benefit from immunotherapy. The efficacy of cisplatin in patients with low expression of PD-L1 is not as effective as chemotherapy. Therefore, FDA has removed patients with low expression of PD-L1 from the indications of cisplatin treatment. Patients with PD-L1 $\geq$ 25 % expressed on the surface of tumor cells or lymphocytes can obtain the best clinical results. Therefore, PD-L1 can be used as a biomarker for screening immunotherapy beneficiaries. In addition, tumor infiltrating lymphocytes, T cell receptor cloning, mutation load, DNA damage response (DDR) gene and microsatellite instability (MSI) can be used as biomarkers for screening immunotherapy benefit groups. Through continuous screening and development of immunotherapy related biomarkers, including those of the dominant group and those of the disadvantaged group, the incidence of resistance to immunotherapy can be reduced and its efficiency can be improved [53,54].

3.3. Individualized immunotherapy strategies

Individualized immunotherapy has the potential to cure cancer. According to the patient's tumor genomic variation information, identify the tumor specific mutations produced by tumor mutant proteins that can be used to identify individual neoantigen. With these unique mutations, screening and preparation of new antigens, the development of individualized neoantigen cancer vaccine. Clinical and experimental studies have shown that there is a significant correlation between the load of cancer neoantigen and the clinical prognosis of patients. Other studies have found that if the tumor has a high level of new antigen, often accompanied by a strong T cell response, patients will have better clinical results. In addition to cancer vaccines, oncolytic viruses and adoptive immunotherapy (including CAR-T [55], PD-L1 [56,57], TIL [58], TCR-T [59], CAR-NK [60], etc.) are also immunotherapies based on the characteristics of individual immune microenvironment.

3.4. New nanoscale drugs, the leading edge of tumor immunotherapy

Due to their unique physical and chemical properties such as size, structure and surface properties, nanomaterials can avoid tumor immune tolerance. At the same time, due to the enhanced permeability and retention (EPR) effect, nanomaterials can be effectively enriched in the tumor site [61]. In addition, nanomaterials have immunomodulatory function, which can stimulate macrophage polarization and strengthen killer immune cells. Moreover, the photothermal or Magnetocaloric Properties of nanomaterials can enhance the immune response of tumor cells when they respond to external stimuli such as near-infrared light and magnetic field. Therefore, nanomaterials have great potential in tumor immunotherapy [16]. Wallat et al. found that simple self-assembled nanoparticles of low molecular weight fluorinated copolymers can show special passive targeting in a variety of tumor models. This is due to the high fluorine content of the copolymer. In the aqueous phase, the redox copolymer forms stable micelles [15]. By regulating the composition and morphology of the nanomaterials, the researchers developed a copper-palladium alloy tetrapod nanoparticle (TNP-1). The photo aggregation at the tip of the particle enables the nanoparticles to have excellent near-infrared conversion efficiency and initiate protective autophagy in tumor cells [62]. Autophagy inhibitors greatly improve the photothermal killing effect of TNP-1 on tumor cells, which has been well verified in the patient-derived drug-resistant breast tumor model [63]. At present, nano materials are widely used as carriers to transport photosensitizers, chemicals, plasmids, proteins to tumor or immune cells, so as to achieve high loading, targeted delivery, controlled release and other functions, and enhance the anti-tumor immune response more safely and efficiently. The designed composite nano formulation shows higher efficacy than monotherapy and reduces the disadvantages of single therapy [64–66].

4. Conclusions and perspectives

Tumor immunotherapy is a method to control and remove tumors by restarting and maintaining the recognition and killing of tumor cells by

the immune system and restoring the normal anti-tumor immune response of the body [67]. This therapy has attracted a lot of attention for its amazing efficacy. However, immunotherapy is not perfect. There are still many limitations to be solved. In order to reduce adverse reactions and increase the number of beneficiaries, according to the results of many studies, future immunotherapy should be combined with other therapies, rather than a single application. In addition, more and more breakthroughs have been found to improve the efficacy of immunotherapy and alleviate side effects, such as thioredoxin, bacterial flora transplantation and ferroptosis. As for the problem of drug resistance, besides combination therapy, it is also a solution to select the appropriate population for immunotherapy and to implement individualized treatment for patients. With the increasing application of nanomaterials in the field of cancer combined immunotherapy, drug resistance has been further solved. It is believed that it is only a matter of time to conquer cancer. Through human unremitting efforts, we will be able to rekindle the hope of life for cancer patients as soon as possible.

Author's contribution

XZ and LC conceived the review and provided project funding; SL drafted the manuscript. ZZ and WL discussed and were involved in editing and reviewing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Declaration of Competing Interest

The authors report no declarations of interest.

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