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REVIEW ARTICLE

Title: The Advanced Research Progress of Tumor Immunotherapy

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Abstract: The mechanism of tumor formation is extremely complex. Traditional radiotherapy and chemotherapy for tumors have caused irreversible damage to normal tissues and cells when they kill cancer cells in a large area. Therefore, with the research on tumors and tumor microenvironment (TME), immunotherapy and targeted therapy have become the current research hotspots and the future development direction. Immunotherapy for tumors is a treatment strategy that relies on the function of the body's immune system to specifically kill tumor cells or inhibit tumor growth mechanisms. Numerous studies and clinical trials have confirmed the feasibility and effectiveness of this approach, which can alleviate the suffering of cancer patients compared to chemotherapy and radiation therapy. The current clinical treatment of tumors often combines a variety of tumor immunotherapies to form a unified and orderly mechanism to inhibit tumor growth, thereby destroying the hallmark of the tumor to avoid immune destruction.

Keywords: Immunotherapy; Tumor immune microenvironment; Immune checkpoint; CAR-T therapy; Cancer vaccine

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1. Introduction

Tumor, also known as vegetation because it always presents as occupying block like protrusions, refers to a new organism formed by local tissue cells under the action of all kind of oncogenic factors. Cancer is one of the leading causes of death in the world today. With the innovation of science and technology, people's life span has been extended, and the incidence of cancer is getting higher and higher. Moreover, due to people's bad living habits such as drinking, staying up late, huge pressure of life, and other reasons, the incidence of cancer is increasingly getting younger [1]. A model called "tumor microenvironment (TME)" has been constructed to study the complexity of tumor. The TME has a physiological persistence of low oxygen, low pH, and high interstitial fluid pressure, and contains various stromal cell regulatory factors and protein alcohols, which plays a role in the occurrence, development, metastasis, and immune response of tumors [2]. It contains various cells: cancer stem cell (CSC), cancer cell (CC), immune inflammatory cells (ICs), invasive cancer cell, pericyte (PC), endothelial cell (EC), cancer-associated fibroblast (CAF) [3]. There are different types of immune cells in the tumor microenvironment, but even among different tumor sites in the same patient, their functional immune phenotypes, localization, molecular patterns, cytokine characteristics, density, and metabolic status also differ, and these differences have been considered to be related to tumor progression, recurrence, and the promotion or suppression of successful responses to immunotherapy. There are different phenotypes of cells with different genomes in tumor lesions. We call this phenomenon tumor heterogeneity, which is one of the hallmarks of tumor. Tumor heterogeneity can be divided into intertumoural and intratumoural heterogeneity [4]. The difference in tumors of the same pathological type among different patients is referred to as Intertumoural, while the appearance of cell subgroups with different genomes in different locations of a tumor lesion of the same patient is referred to as intratumoural. This heterogeneity poses a challenge to tumor immunotherapy, as these immunotherapeutic methods are difficult to target all cell subtypes effectively. In the past long period of time, many researchers have spent a lot of time on the study of tumor immunotherapy, which promotes the formation of tumor immunotherapy. Under normal circumstances, the immune system can eliminate cancer cells through immune surveillance to prevent tumor development. However, tumors will avoid being killed by different strategies of immune evasion to ensure their safe growth, invasion and metastasis. Therefore, studying the mechanism of the interaction between immune cells and cancer cells is of great significance for the

development of new targeted therapies for tumors in the future. Based on the above facts, the immune system to kill tumor cells were designed: enabling T-lymphocytes to reidentify tumor cells or using inhibitors to break down the barrier between immune cells and tumor cells. The aim of tumor immunotherapy is to assist or enhance the body's own immune system to kill tumor cells, reduce the inhibition of cancer cells on the killing mechanism, and achieve the treatment goal. The advantages of tumor immunotherapy lie in its wide application, as some treatment strategies can be applied to multiple cancer cells. In addition, immunotherapy has a higher level of biological safety [5]. Furthermore, its durability has been confirmed, as the human body can maintain the function of clearing cancer cells for a long time after initiating an immune response [6]. With the continuous deepening of research and clinical trials, the technology of tumor immunotherapy is becoming more and more diversified and mature, which makes more and more tumor patients see the hope of being cured. In fact, it is very necessary for us to spend more efforts to explore more mysteries of tumors, and make the greatest efforts to find all possible approaches to eradicate tumors as well as the symptoms and sequelae caused by the occurrence of tumors. In this review, I combined the research reports and review articles of the past few years and sorted out five methods of tumor immunotherapy, including immune checkpoint blocking therapy, regulatory role of immune cells in the tumor microenvironment, tumor vaccines, small molecule inhibitors and immune system modulators (Figure 1). This article also introduces the tumor immune microenvironment (TIME), hoping that the modulators acting on the microenvironment can provide new ideas for the immunotherapy of cancer cells.

2. The development of tumor immunotherapy

In 1863, Rudolf Virchow first discovered that there were a large number of immune cells around tumors, so he put forward the hypothesis that tumors originated from chronic inflammation. By 1898, Dr. William Coley of New York, United States, treated cancer by injecting lipopolysaccharide, and the development of tumor immunotherapy also began. In 1957, Australian immunologist Frank Macfarlane Burnet proposed and confirmed the theory of immune surveillance, which provided a strong basis for the later development of tumor immunology and tumor immunotherapy [7]. In 1980, Morales published a paper that used the Bacillus Calmette-Guerin Vaccine to treat superficial bladder cancer [8]. In November 1984, a female melanoma patient received a high dose of IL-2 injection, and the patient was successfully cured, she also became the first patient in history to be successfully cured by tumor immunotherapy, and IL-2 also became the first tumor immunotherapy drug approved by the FDA [9]. At a later stage, more immune checkpoints were discovered, and more immunotherapy methods were created, all the way to the current boom. Nowadays, tumor immunotherapy is still a hot topic, and I believe that more researchers will devote more time and finance to the research of tumor immunotherapy.

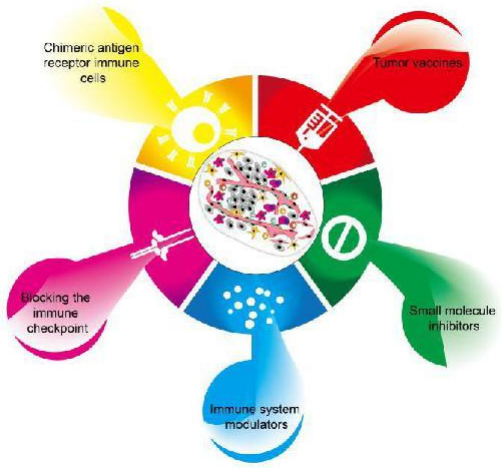

Fig. (1). Five methods of tumor immunotherapy.

3. Tumor immune microenvironment

There are many different types of cells present in tumor microenvironment, including cancer cell populations (cancer cells, cancer stem cells, invasive cancer cells), functional cells, and various immune cells that infiltrate or are recruited by the tumor [3, 10]. According to the tumor's immune environment, TME can be divided into three types: immune-inflamed phenotype, immune-excluded phenotype, and immune-desert phenotype. The characteristic of immune-inflamed phenotype is the presence of CD4 and CD8-expressing T cells close to tumor cells in the tumor stroma; the characteristic of immune -excluded phenotype is the presence of a large number of immune cells surrounding tumor cells in the stroma; and the characteristic of immune-desert phenotype is the lack of T cells in the tumor stroma or matrix [11]. Various immune cells play a crucial role in the development of tumors and the composition of the tumor microenvironment. For example, tumor-associated fibroblasts can transform the TME into an immune-excluded phenotype through the TGF-β signaling pathway. Xiang et al.'s review points out that tumor-associated macrophages contribute to establishing a pro-inflammatory microenvironment, and the close relationship between inflammation and tumor development can increase the risk of tumors; at the same time, they can produce mediators that remodel the tumor-supportive TME and promote tumor development. In addition, they can express cell surface proteins or release soluble factors with immune-suppressive functions to reduce the activity of T cells and NK cells or evade immune surveillance by recruiting immunosuppressive cells [12]. The ten biological hallmarks of tumor, such as inducing or accessing

vasculature, avoiding immune destruction, resisting cell death, etc., are all involved in the immune system and immune cells in the microenvironment [13]. The behavior of tumor cells such as Epithelial-Mesenchymal Transition (EMT), invasion and metastasis is affected by the surrounding immune cells, so we call it the tumor immune microenvironment [10]. In the process of tumor metastasis, malignant cells undergo diversified changes, so that different tumors have different microenvironments. Therefore, we say that tumors have heterogeneity. Tumors may be infiltrated by the immune system, including many cytokines, immune cells, cytotoxic factors, and immunosuppressive small molecules, and even tumor cells produce some small molecules to recruit immune cells [3]. A tumor composed of different cells is like an organ, and we can even say that the tumor "parasitises" within the body, like a parasite that exploits the host's conditions to satisfy its own survival. It can be said that the tumor immune microenvironment is very complex, in such an environment, the tumor and the immune system interact with each other, and even can be said to be symbiotic. However, the tumor immune microenvironment is more like a double -edged sword for tumors, such a centralized environment, coupled with the immune surveillance ability of the body itself, also promotes anti-tumor immunity. Based on the existence of the immune microenvironment, we can more clearly explore the mechanism of the interaction between the immune system and tumor cells.

4. Immune checkpoints blocking therapy

Immune Checkpoints (ICPs) are programmed death receptors and their ligands. Immune checkpoint targeted blocking therapy refers to the targeted inhibition of the binding of programmed death receptors and ligands to block the immune checkpoint signaling pathway, so as to up-regulate the immune system's ability to kill cancer cells. So far, the targeted blocking therapy of immune checkpoint has achieved remarkable results in the application of melanoma, gastric cancer, non-small cell lung cancer and other tumors [14]. According to common immune checkpoints such as CTLA-4, PD-1/ PD-L1, IDO1, etc., researchers have designed immune checkpoint inhibitors (ICIs) to block the ligand expressed on the surface of tumor cells and myeloid-derived suppressor cells from binding to the programmed death receptor expressed on the surface of immune cells T cells, thereby preventing T cells from failing to kill cancer cells because of their exhaustion. Up to now, FDA has approved antibodies blocking two of the immune checkpoint receptors: PD-1/PD-L1 and CTLA-4 [15].

4.1 Targeted immunotherapy of the PD-1/ PD-L1 pathway

Programmed death receptor (PD-1), also known as CD279 belongs to immunoglobulins superfamily, is one of the membrane protein with 288 amino acid residues as well as an important immunosuppressive molecule in the CD28 / CTLA-4 receptor family [16]. Tumor cells use these inhibitory pathways to escape host immune surveillance through overexpression of PD-L1. Antibodies to PD-1/PD-L1 can activate T cells in the tumor microenvironment to restore their ability of immune killing [17]. At present, the research of targeted immunotherapy for PD-1/ PD-L1 pathway has made unprecedented success. Tumor cells can express PD-L1 which can specifically bind to PD-1 expressed on T cells which can inhibit the production of T cell factor and induce the death of Treg cells [18]. Zhang et al. found that after cells were infected with viruses, mitochondrial CPT1A was down-regulated and inhibited, while epigenetic perturbations induced them to maintain the IFN-I response activated by double-stranded RNA. Targeting epigenetic regulators enhances anti-PD-1 immunotherapy, which focuses on activation of the IFN-I response, mimicking how cells respond to viral infections. The study found that CPT1A is a stabilizer of MAVS activation, and its association with epigenetic perturbations could be used in cancer immunotherapy [19].

4.2 Targeted immunotherapy of the CTLA-4 pathway

Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), also known as CD152 is a kind of cluster of differentiation as well as a transmembrane receptor on the surface of T cells. CTLA-4 is a key negative regulator of T cell response which may prevent T cell activation by inhibiting signaling, and the available evidence now points to an important role of CTLA-4 in the inhibitory function of regulatory T cells. CD28 is a protein expressed by T lymphocytes that can specifically bind to B7 molecules on the plasma membrane of APC to mediate the costimulation of T cells to promote the production of cytokines, survival and proliferation. At present, there is evidence that CTLA-4 competitively binds ligands with CD28 and can recruit CD80 to down-regulate the interaction between CTLA-4 and CD28 [20]. Zhao et al. found that PD-L1 heterodimerizes with CD80 to selectively weaken CD80:CTLA-4 interaction but not CD80: CD28 interaction which implicates that PD-1 is able to repress CTLA-4 pathway [21].

4.3 Clinical trial

Cercek et al. found that for some rectal cancer patients caused by mismatch repair deficiency, the use of PD-1 blockade therapy can bring certain clinical benefits. They conducted a prospective phase II study, using a single PD-1 inhibitor - dostarlimab as a treatment for locally advanced rectal cancer. Patients received treatment every 3 weeks, followed by standard radiotherapy and chemotherapy for 6 months, and then surgery. The results showed that all 12 patients treated achieved clinical complete remission without tumor progression. This indicates the significant therapeutic effect of PD-1 inhibitors [22]. Patient resistance to inhibitors has always been a barrier to immunotherapy, which has also prompted researchers to find more ways to overcome this resistance. However, Davar combined fecal microbiota transplantation (FMT) from responders of melanoma patients who were resistant

to PD-1 antibody therapy with PD-1 antibody therapy, conducting a clinical trial on 15 patients, of which 6 patients experienced clinical benefits. This suggests that combining anti -PD-1 therapy with FMT from responders can overcome resistance in PD-1-resistant melanoma patients [23]. Although we generally believe that the effectiveness of immunotherapy for non-solid tumors is significantly greater than for solid tumors, researchers are also working to enhance the effectiveness of immunotherapy for solid tumors. Ma et al. conducted a phase I clinical trial of a novel bispecific antibody KN046 targeting PD-L1 and CTLA-4 for late-stage solid tumors, recruiting a total of 100 patients including nasopharyngeal carcinoma and non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) mutations. The trial results showed that KN046 demonstrated good tolerability, safety, and promising antitumor effects in patients, especially showing good efficacy in nasopharyngeal carcinoma patients. Immunohistochemical analysis also revealed that patients with high CD8 and PD-L1 expression had longer overall survival periods [24].

5. Regulatory role of immune cells in the tumor microenvironment

Cells such as T cells and natural killer (NK) cells that possess cytotoxicity can recognize and eliminate alien cells. We can utilize these cells to kill tumor cells, thereby achieving the goal of eliminating residual cells after surgical removal. However, in normal human body, the presence of cytotoxic cells that can specifically recognize and kill tumor cells is minimal. Therefore, we can artificially modify and engineer these cells to trigger immune killing effects against tumors. In the following, I will introduce several popular immune cell therapies.

5.1 CAR-T immunotherapy

Chimeric antigen receptor T-Cell (CAR-T) immunotherapy is a precise targeted therapy method that involves genetically modifying T lymphocytes by equipping them with tumor-specific chimeric antigen receptors. These modified cells are then artificially cultured in vitro to proliferate in large quantities and subsequently infused into the patient's body to specifically target and attack tumor cells [25-26]. T cells are activated after specific binding with the antigen on the surface of tumor cells, and can release granzyme, perforin, etc. to directly kill tumor cells, and at the same time can release cytokines to recruit other immune cells in the body that can kill tumor cells to jointly carry out tumor immunotherapy
[27]. These T cells can also form memory T cells to obtain long-lasting anti-tumor mechanisms. A large number of clinical trials and mouse experiments have shown that CAR-T immunotherapy has achieved great success and become a hot research direction at present. Fan et al. synthesized lipid-modified FITC and made it taken up by tumor cells as an artificial ligand, so that different phenotypic solid tumors can display the same FITC, which can perfectly avoid the limitations brought by tumor heterogeneity in tumor immunotherapy [28]. However, the FDA recently announced that some CAR-T therapy drugs have a serious risk of inducing T cell lymphoma, so the adverse reactions of CAR-T therapy still need to invest time to find ways to improve.

5.2 Tumor immunotherapy with NK cells

There is more evidence that CAR-NK therapy has several other advantages over CAR-T therapy, including higher biosafety and more cytotoxic activation mechanisms. As CAR-T therapies have matured and been successful in various ways, researchers have taken a greater interest in the engineering of chimeric antigen receptors in NK cells [29]. Liu et al. demonstrated that the modified NK cells which can express an anti-CD19 CAR have the ability to overcome the problem that CAR-T immmunotherapy may induce substancial toxic effects [30].

5.3 Clinical trial

Zhang et al. developed a non -viral vector and gene-specific targeted CAR-T cells using CRISPR-Cas9 technology. They infused CAR-T cells into eight patients and observed a complete remission rate of up to 87.5% with long-lasting therapeutic responses, demonstrating their safety and effectiveness in treating relapsed/refractory aggressive B-cell non-Hodgkin lymphoma [31].

6. Tumor vaccines

Through Hanahan's landmark review article, we have learned that one of the ten biological capabilities of tumors includes the ability to induce or access vasculature [13]. The mechanisms of tumor vaccine include enhancing immunity, overcoming tumor immunosuppression, and inhibiting tumor angiogenesis. At present, different kinds of vaccines have been developed such as DNA vaccine, mRNA vaccine, adenovirus vaccine, whole cell vaccine to cope with different degrees of anti-tumor immune response [32-35]. With the continuous development of nanotechnology, making tumor vaccines with nanocarriers has become a hot topic. For example, Baharom et al. developed an individualized cancer vaccine based on self-assembled nanoparticles, which induces T cell immune responses by linking tumor-specific neoantigen (neoAg) peptide segments with TLR7/8 agonists (SNP-7/8a) [36]. Many clinical studies have shown that tumor vaccines can not only prevent and slow down the development of tumors, but also prevent tumor growth, invasion, metastasis and angiogenesis [37]. Therefore, the development of new tumor vaccines and the improvement of existing results is a good news for tumor patients, that is, it can reduce the pain caused by chemotherapy, but also can prevent the

occurrence of tumors, which will be the direction of many researchers to explore and the expectation of the public. Some cancer vaccines work indirectly. For example, human papillomavirus (HPV) vaccine can prevent human papillomavirus infection, infection with this virus will show condyloma acumen, etc., and high -risk patients will show cervical cancer, anal canal cancer, oral cancer, nasal cancer, esophageal cancer, etc. There are also cases of skin bowen disease, basal cell carcinoma, Pajer's disease, squamous cell carcinoma and other epithelial tumors are also related to such viral infection. The FDA has approved two cancer vaccines, targeting HPV and the targeting hepatitis B virus (HBV) for preventive purposes as these two viruses can induce the occurrence of corresponding cancers. Cafri et al. developed a process using tumor-infiltrating lymphocytes to identify specific immunogenic mutations expressed by patients' tumors. They concatenated neoantigens, neoepitopes and mutations of driver genes into a single mRNA construct to vaccinate patients with metastatic gastrointestinal cancer. They found that this method was safe which can be in combination with checkpoint inhibitors or adoptive T cell therapy [38]. Ding et al. conducted a study to investigate the feasibility of a personalized neoantigen peptide-pulsed autologous DC vaccine in the treatment of advanced lung cancer patients and found that it can elicit T cell responses and induce antitumor immunity [39]. At present, the research and development of tumor vaccine is still in an immature stage, and we can see broad development prospects in this filed.

7. Small molecule inhibitors

Even though the tumor's ability to grow is so strong that it can even compete with the immune system, there are still mechanisms in our body that try to kill the tumor to ensure that the internal environment is stable. In the tumor microenvironment, there are many immunosuppressive small molecules, which can inhibit tumor growth. In the past period of time, we have paid attention to these immunosuppressive molecules, hoping to improve the tumor immune microenvironment by changing their structure or regulating and improving their function, so as to achieve the purpose of better tumor immunotherapy.

7.1 IDO inhibitors can prevent T cell proliferation from being inhibited

Indoleamine 2,3-dioxygenase (IDO) is a key player in enzymes that degrade tryptophan, which can also participate in immune regulation related to tryptamine metabolism [40]. It can change the tumor's inflammatory environme nt, turning a non-T cell inflammatory tumor to a T cell inflammatory tumor. IDO overexpression and Kyn accumulation in tumors inhibit the function of effector T cells and NK cells and promote tumor angiogenesis. In summary, IDO down -regulates the immune surveillance effect of tumors, is beneficial to tumor growth, and mediates tumor avoidance of immune destruction. Therefore, it is necessary to use IDO inhibitors to regulate this phenomenon. Inhibitor drugs for IDO, a potential target, can be roughly divided into two types. The first is to selectively or non-selectively directly inhibit the activity of IDO. The second is an IDO pathway inhibitor that stimulates mTORC1 downstream of the Kyn pathway [41]. Huang et al. found that the DNA/PEI nanoparticles (DNPs) that can rapidly release pro-inflammatory cytokines to promote anti-tumor immunity, are able to upregulated IDO enzyme activity in mouse lymphoid tissue to degrade the IDO in order to prevent the degradation of tryptophan by IDO and led to a rapid increase in serum IFNαβ and IFNγ levels (these are potent IDO inducers) [42].

7.2 Clinical trial

Zakharia and others organized a Phase II clinical trial targeting 131 patients with advanced melanoma, exploring the efficacy and safety of the combination therapy of IDO pathway inhibitor indoximod and one of the ICIs, pembrolizumab. The study found that the side effects of combination therapy were similar to monotherapy and well-tolerated [43].

8. Immune system modulators

Immune system modulators include cytokines, agonists and adjuvants, etc. This treatment method is mainly non-specific immunotherapy, which is a relatively old means, mainly used for the treatment of solid tumors, because these inhibitors cannot achieve precise regulation, but to widely regulate the inflammatory response of tumors to achieve the purpose of treatment. Another drawback is that the drug's effectiveness is low, averaging only about 10 percent. Perhaps in the future, combining immune system modulators with specific immunotherapies, or combining different modulators, could open up new ways to improve efficiency.

8.1 Targeted immunotherapy of the IL-4 axis

IL-4 is a typical cellular immunomodulator that plays an extremely important role in the response of effector T cells [44]. LaMarche et al. found that IL-4 can promote the production of immunosuppressive myeloid cells, which in turn can inhibit the immune response against NSCLC, which will provide favorable conditions for tumor immune evasion. However, the use of Dupilumab supplementation to suppress IL-4 is expected to achieve synergistic effect with the currently used lung cancer immunotherapy, and preliminary clinical trials have also demonstrated this view [45].

9. Conclusion and future vision

Some of the targets and methods introduced in this review are no longer new to people at the forefront of scientific research, but the new research on these methods

is still worth learning and criticizing. The methods of tumor immunotherapy are also constantly being innovated, and some existing immunotherapies are constantly being optimized to improve their effectiveness and reduce the harm caused by side effects. However, immunotherapy has some drawbacks, including the possibility of off-target and damaging side effects. And years of research have shown that a portion of tumors will develop resistance to immunotherapy, which brings great challenges to treatment. Meanwhile, due to the heterogeneity of tumors, the use of a single drug to treat various tumors seems to be a difficult way to achieve. More importantly for clinical patients, the cost of immunotherapy is very high compared to traditional chemotherapy and radiation, although this approach can lead to a deeper level of treatment. In any case, immunotherapy is very promising for tumor treatment, and in the future we can focus on how to improve tumor immunogenicity, increase tumor recruitment of NK cells and T cells, overcome tumor immune barriers, and combine multiple immunotherapies and multi-target inhibitors. Immunotherapy can be used in clinical practice as a first-line or adjuvant therapy, but the mechanism of drug resistance and the occurrence of side effects still need a lot of researchers to invest a lot of energy to explore.

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