RESEARCH PROGRESS ON IMMUNOLOGICAL CHARACTERISTICS AND IMMUNOTHERAPY OF BRAIN GLIOMAS

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ABSTRACT

Objective*: Glioma is one of the most common invasive tumors in the central nervous system, which can not significantly prolong the survival time of patients after treatment. As a new tumor therapy, immunotherapy can specifically treat gliomas, but its clinical application is still less. To investigate the immunological characteristics and immunoteerapy of gliomas reported so far, and to summarize the application experience.*

Methods: *By consulting the relevant literature on the treatment of glioma at home and abroad, I briefly describe the immunological characteristics of glioma and the existing immunotherapy methods of brain therapy.*

Results: *We found that the incidence of glioma was high, and the effects of existing surgery, radiotherapy and temozolomide therapy were not good. The researchers found that the immune escape pathway of glioma can be intervened through the immune response deficiency of glioma cells, and the effective immunotherapy for glioma can be carried out. This gives rise to new therapies, immunotherapies.*

Conclusion: *Through the unremitting efforts of medical researchers, active immunotherapy, passive immunotherapy and other immunotherapy have achieved good results in inhibiting tumor proliferation and promoting tumor cell apoptosis.*

Keywords: *Glioma, blood-brain barrier, immunotherapy, vaccine.*

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Introduction

Gliomas are the neurointerstitial cells of the brain neuroectoderm with a high incidence rate, and the incidence rate of gliomas in males is higher than that in females. The incidence rate of glioblastoma multiforme(GBM) can account for half of the total number of gliomas[(1)], while gliomas account for about 80% of the incidence of malignant tumors[(2)]. The survival time of tumor patients treated with surgery, radiotherapy and temozolomide after GBM, was only about 14.6 months, and the 5-year survival rate was only 5.1%[(3)]. Faced with this situation, glioma patients are eager for new treatments to improve the therapeutic effect of GBM.

In recent years, it has been found that tumor patients have achieved good results after targeted therapy, and the attention of immunotherapy has begun to shift to the direction of malignant gliomas. Experiments have confirmed that immune cells can enter brain tissue, and the blood-brain barrier is not hindering the entry of fully activated T cells[(4)]. At the same time, immune cells act on the parenchyma of the brain due to the changes in the brain capillaries of GBM patients[(5)]. All these provide new ideas for immunotherapy of glioma.

Immunological characteristics of glioma

The incidence of glioma is high and it shows diffuse and invasive growth. There is no clear boundary between the focus of infection and the surrounding healthy brain tissue, so it is very difficult to remove all malignant tumors[6]. At the same time, the invasive growth of malignant tumors restricts the effectiveness of local treatment, and the blood-brain barrier reduces the tumor's response to external apoptotic signals. The special microenvironment of glioma makes its immune response different from tumors of other organs, resulting in poor postoperative effect of malignant gliomas. Some experts analyze that the presence of human glioma-derived factors can cause T lymphocyte function failure, resulting in a weak anti-tumor immune response.

However, some studies have shown that effective anti-glioma immune response also exists in glioma patients, and the immune response can be activated by vaccination.

As an immune special area, the central nervous system of the human body also has a part of the immune response foundation[7-8]:

• The cerebrospinal fluid has a certain connection with the brain lymphatic system;

• A variety of immune cells can exert immune effect through the blood-brain barrier;

• There are very few antigen presenting cells in the central system;

• Macrophage markers, this means that the immune escape pathway of glioma can be intervened through the immune response defect of glioma cells[9], and the effective immunotherapy of glioma can be carried out.

Immunotherapy of glioma

William B. Coley found a patient with lymphosarcoma was infected with streptococci, and his tumor was relieved, and then he treated the tumor with bacterial toxins, which began the road of tumor immunotherapy[10]. A Meta analysis[11] showed that people with specific diseases such as allergies and asthma have a lower rate of gliomas than normal people. This shows that the immune status of the body may affect the occurrence and development of gliomas, and provides a theoretical basis for immunotherapy of gliomas.

In recent years, immunotherapy has achieved remarkable results in the direction of tumors, which brings hope for the treatment of gliomas. The National Cancer Institute(NCI) defines immunotherapy as a biological therapy, which shows specific tumor killing effect by regulating the immune system, reducing the proliferation rate of tumor cells and inducing their apoptosis.

There are three kinds of immunotherapy methods including active immunity, passive immunity and other immunotherapy.

Active immunotherapy

In the process of vaccination in patients with gliomas, it is necessary to overcome a mechanism that exists in the patient's body, which is the tumor escape mechanism, although there are more difficulties in the process of overcoming. But in many clinical trials, it has shown positive and gratifying results.

Dendritic cell vaccine

In the process of immunotherapy of tumor cells, the key to activate specific T cells is that stress cells should first receive tumor antigen and then produce targeted immune response.

Dendritic cell vaccine is effectve because the collected tumor antigens are transported to T lymphocytes tha have not undergone sensitization, so that their natural immune response is stimulated; At the same time, CD_4^+ and CD_8^+ T cells are transformed into helper T cells and toxic T cells, regulating humoral and cellular immunity; It can also interact with macrophages and natural killer T cells (NKT) to regulate the body's immune response[12]. The current dendritic cell vaccine is produced by antigen loading method and generated in vitro, and further sensitized by small molecular peptide or RNA of gravity, and finally acted on human bod by subcutaneous injection. A number of phase II clinical trials of dendritic cell vaccines are currently underway.

Immune checkpoint inhibitor

Immune regulation depends on the balance between activation and inhibition signals. Immune checkpoints are molecules that play a protective role in the body's immune system, which inhibits the inflammatory damage caused by excessive stress on T cells. The immune checkpoint inhibitor antigen developed has the effect of "brake", enhances the immune efficacy, and achieves the purpose of anti-tumor[13-14]. Checkpoints such as apoptosis protein 1 and cytotoxic T lymphocyte-associated antigen 4 are the focus of research at this stage, and some clin-

ical trials have been carried out in a variety of solid tumors and achieved significant results[15]. However, there are still many difficulties in the use of immune checkpoint inhibitors in the treatment of gliomas. Not only the biomarker components have not been identified, but also more research is currently focuses on combination therapy. For example, immune checkpoint inhibitors are used in conjunction with surgery, chemotherapy, radiotherapy, chlorogenic acid and molecular targeted drugs.

Although it is faced with the complexity and difficulty of tumor treatment, medical researchers are constantly exploring the way of combined treatment, striving to get the best dose of drugs and the optimal combination of combination treatment as soon as possible, so that the purpose of the treatment more clear, the side effects are smaller, and the curative effect is more significant.

Passive immunotherapy

Chimeric antigen receptor T-cell (CAR-T) immunotherapy

The artificial fusion protein CAR consists of extracellular antigen binding region, intracellular signal transduction region and transmembrane region, and can specifically recognize tumor-associated antigens through the antigen binding region of CAR. The principle of CAR-T in the treatment of tumor is to take the normal T cell gene sequence as the target gene, and at the same time use a suitable vector to carry the target antigen receptor gene and introduce it into T cells. The T cell obtained after the encoding process is obtained and enhanced Its role in killing tumor cells[16]. The application of CAR-T therapy in the treatment of some solid tumors and hematological tumors[17-19] has shown a good curative effect[20-23].

This also aroused the research enthusiasm of medical researchers, and strive to make a breakthrough in treatment as soon as possible.

Other immunotherapy

Oncolytic virus

In the course of treatment of gliomas in recent years, researchers have found that oncolytic viruses have achieved good results in the treatment of gliomas. The oncolytic virus has the ability of replication, and its mechanism of killing tumors is to induce their death by over-replication in tumor cells, or to stimulate the body's anti-tumor immune system to achieve the purpose of eliminating tumor cells. In the current transformation of oncolytic virus, oncolytic viruses such as oncolytic adenovirus and Newcastle disease virus have initially achieved the purpose of transformation. Examples of the use of genetically modified herpes simplex virus to eliminate malignant gliomas has been published by Martuza R L[24].

Although in the process of using oncolytic viruses to eliminate gliomas, there are still many problems in the effectiveness, safety and side effects that need to be improved and overcome, but the use of oncolytic viruses in the treatment of GBM has shown Good application perspective. At the same time, there are experimental reports[25] that the combination of oncolytic virus and radiotherapy can significantly improve the tumor suppressive effect on glioma.

Chlorogenic acid (CHA)

CHA is a small molecular immunotherapeutic agent with little toxic side effects, it is one of the compound polyphenols, which can be extracted from green tea and other plants. In recent years, the oncology community has begun to pay attention to the use of CHA to carry out tumor suppression research[26].

The results of phase I clinical trial on the use of CHA injection in the treatment of advanced malignant gliomas[27] confirmed that CHA has lower side effects, and also has a better efficacy. In the process of immunotherapy with CHA, the researchers found that the brain lesions of some patients became smaller or even disappeared, making the clinical treatment benefit rate of GBM increased to more than 50%.

In the course of research and treatment, it was found that temozolomide can play a synergistic role with CHA, and can reverse the resistance of temozolomide to enhance its efficacy, thereby providing a good choice for the treatment of GBM. CHA may inhibit tumor by regulating its immune function or inhibiting tumor angiogenesis, so as to inhibit tumor proliferation and promote tumor cell apoptosis, and then achieve better therapeutic effect.

Conclusion and perspective

After the unremitting efforts of medical researchers, immunotherapy in glioma has achieved some good results. Even though it seems that these therapies have various problems and shortcomings at present, it is hoped that in the near future, various immunotherapy methods will be reasonably linked together, and then the remarkable results of tumor immunotherapy will be achieved. We firmly believe that with the continuous advancement of medical sci-

ence and technology, researchers continue to deepen their research on tumor immunology, and more unknown immunosuppressive mechanisms will be discovered. In the future, glioma may not be in the medical world puzzles.

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