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Emerging Role of Vaccines in Glioblastoma Treatment

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Abstract. Glioblastoma is the most common primary intracranial malignant tumor, classified by the World Health Organization as a grade IV glioma of the central nervous system due to its high mortality, recurrence rate, and morbidity. This disease has difficulty to treat. Currently commonly used therapies, such as surgery, chemotherapy and radiotherapy, have poor prognosis. Therefore, new treatments are needed to control tumor progression and improve patient outcomes. After years of development, cancer vaccines have gradually become an important part of tumor immunotherapy, and they have shown a more rapid development trend in the current era. Cancer vaccines introduce tumor antigens, genes encoding tumor antigens, immune cells, and molecules into the body. Cancer vaccines activate specific immune responses that control tumor growth and ultimately clean it. In recent years, a number of research groups at home and abroad have explored the safety and feasibility of different types of therapeutic vaccines for the treatment of GBM according to the characteristics of GBM. This review introduces results, mechanism, safety and efficacy of virus-like particles (VLPs) vaccine, mRNA vaccine and dendritic cells (DC) vaccine. The feasibility of using these vaccines to treat GBM was discussed to provide reference for further research.

Keywords: Glioblastoma; VLPs vaccine; mRNA vaccine; dendritic cells vaccine.

1. Introduction

Glioblastoma (GBM) is the deadliest and most common primary malignant brain tumor in adults. Despite receiving therapies such as surgical resection, chemoradiotherapy and tumor electric field therapy, most patients still have a poor prognosis with a 2-year survival rate of only 43% [1]. With the in-depth study, some new immunotherapies have emerged, such as immune checkpoint inhibitors, chimeric antigen receptor T cells (CAR T cells), vaccines and so on. By stimulating the adaptive immune system in the body which specifically targets tumor-specific antigens, therapeutic cancer vaccines enhance and maintain specific T cell responses, promoting immune system to dominate in its competition with tumors, thereby controlling tumor growth and ultimately eliminating it [2]. Some trials have shown that tumor vaccines can prolong patient life span [3]. Among these immunotherapies, vaccines mainly have two advantages. First, immune vaccine have specialty. Unlike other traditional therapy, immune vaccines typically target on several kinds of proteins which only tumor cells have. Vaccines need to accurately find tumor cells and kill them. Therefore, there is lower risk for vaccines to kill normal cells. As a result, humans can reduce side effects by using immune vaccine therapy. Secondly, vaccines are highly efficient. Compared with traditional therapy such as chemo immune, vaccine therapy require smaller doses to have curative effects. According to the characteristics of GBM, researchers have explored different types of therapeutic vaccines: virus-like particless (VLP) vaccines, messenger RNA (mRNA) vaccines, dentric cells (dentric cells). DC vaccines, etc. This review introduces the current progress of GBM vaccine treatment at home and abroad in recent years, including above treatments.

2. Virus-like Particles Vaccine

Virus-like particles (VLP) is a nanoscale multi-protein structure that mimics viruses. Its particles are able to self-assemble without a genome, so VLP do not infect host cells to produce new viruses [4]. Compared with polymer micelles and liposomes, VLP has a more uniform structure and relatively cheap production process. Furthermore, it is also biodegradable and able to interact with DC cells with a lower risk of cytotoxicity. In addition, various types of ligands, such as antibodies, transferrin, and oligopeptides, can be displayed on the VLP surface to achieve specific tumor cell targeting [5].

Some researchers have tried to pair HSV1-TK with ganciclovir (GCV). Through alpha-herpesvirus thymidine kinase, VLPs vector (TK-VLP) of TK delivers the antiviral drug GCV into GBM cells and activates the expression of TK to transform the prodrug GCV into cytotoxic monophosphate derivatives and triphosphate derivatives, thus inhibiting the growth and proliferation of GBM. Human polyomavirus 2 (JCPyV) has also been used as a VLPs [6]. DEL and other researchershave shown that JCPyV can cause a variety of brain tumors [7]. Moreover, JCPyV can be used as a carrier to deliver TK for the treatment of glioblastoma, and can also improve the therapeutic effect by inducing apoptosis of GBM cells and activating immune cells.

On the other hand, SUFFIAN et al. proposed that VLPs nanoparticles could be used as a new nanomedical carrier, holding the opinion that the combination of actively targeting VLP encapsulated drugs in cancer therapy can increase the drug cycle half-life of systemic administration and drug uptake by targeted cells [5]. In 2016, a study conducted by the Department of Chemistry at the University of California, Berkeley, and Lawrence Berkeley National Laboratory evaluated nanoscale VLPs targeting GBM, including the 27 nm spheroidal MS2 and the 18 nm tobacco mosaic virus disk [8]. TMV. The two vectors have their own characteristics: the 2 nm surface on MS2 VLPs allows for internal capsid changes and drug release, while the TMV virus-like particles of the nanodisk composed of tobacco [9]. Mosaic virus can maintain structural characteristics under all biological conditions that can simulate the patient's condition due to double arginine mutants.

3. mRNA vaccines

Cancer mRNA vaccines operation mechanism is introduced here: First, package mRNA encoding tumor-related or tumor-specific antigens through delivery systems such as lipid nanoparticles. Then, deliver it into human cytoplasm, or directly introduce it into the body without delivery system. After translation and modification, fully functional proteins are produced and expressed on the cell surface. Activate humoral and cellular immunity and generate immune protection, thereby inducing or enhancing anti-tumor immunity [10,11]. Cancer mRNA vaccines mainly have three advantages. ① mRNA is characterized with high body safety. RNA-like nucleic acids can be degraded naturally within 2 to 3 days after entering the human body. Moreover, they are safer than DNA-based vaccines, because they do not enter the nucleus and do not integrate with the human genome, avoiding the risk of insertion mutations. In addition, appropriate purification and incorporation modification techniques can reduce the inflammatory response caused by the mRNA delivery system. Thus, these techniques further enhance the safety of mRNA vaccines [12]. ② Production of mRNA vaccines is more convenient. In contrast to many other current vaccination strategies (such as DNA vaccines, etc.), the manufacture of RNA vaccines does not require cell culture and avoids the risk of contamination [13,14].Secondly, production of mRNA vaccine is more convenient. In contrast to many other current vaccination strategies (such as DNA vaccines, etc.), the manufacture of RNA vaccines does not require cell culture. Therefore, it avoids the risk of contamination [14]. ③ mRNA vaccine combined with ICIs can play a role in reversing the drug resistance pathway. It is also expected to become a powerful auxiliary of ICIs, which is more conducive to the implementation of precision and individualized treatment for patients [15].

The feasibility of cancer mRNA vaccines was first demonstrated in vitro and in vivo in the mid-1990s [10]. Since then, clinical studies related to cancer mRNA vaccines have emerged. At present, the number of clinical studies has accounted for a quarter of the total research on mRNA vaccines. However, the current clinical trials of cancer mRNA vaccines are still basically stuck in phase I or phase II with a slow development rate [12,13].

The KEYNOTE-942 trial registered in ClinicalTrials.gov (NCT03897881), phase Ⅱ clinical study shows that pembrolizumab, a PD-1 inhibitor, is used as adjuvant therapy in patients with advanced melanoma who are at high risk of recurrence after surgery. The study has yielded promising results. The data shows that patients who received the mRNA vaccine combined with pabolizumab have a 44% lower risk of disease recurrence compared with patients who received pabolizumab alone. For its significant curative effect, the mRNA vaccine in combination with PD-1 inhibitors was approved by the Food and Drug Administration (FDA) as a new adjuvant treatment for melanoma at high risk of recurrence in February 2023. This is the first cancer mRNA vaccine in the world to receive this certification. It makes a qualitative breakthrough in the field of anti-tumor mRNA vaccines.

mRNA vaccine also have limitations: first, the transportation and storage conditions are harsh. RNA itself is an unstable molecule because of the presence of hydroxyl groups on ribose, which allows biological nucleases in the environment to split it easily. The second limitation is about low anti-tumor effect of single use due to poor stability, strong tumor-specific antigen immune tolerance and tumor cell heterogeneity. the anti-tumor effect of cancer mRNA vaccine itself is difficult to improve qualitatively. This also leads to slow development of clinical research and difficult rapid promotion. In addition, the immune microenvironment of advanced tumors often has a highly immunosuppressive effect, which may also be one of the reasons for the poor effect of mRNA vaccine alone [14].

4. Dendritic Cells Vaccines

Dendritic cells (DC) are the most powerful antigen-presenting cells in the body, which can directly activate the body helper T cells (Th) and cytotoxic T lymphocytes (CTL) in the immune system. It also enable B cells to produce antibodies.

As an antigen-presenting cell, DC cells have attracted more and more attention in the biological immunotherapy of cancers [15,16]. DC sensitized by tumor antigen in vitro is obtained by isolation and purification of DC. That can activate T cells by stimulating MHC class I and MHC class II molecules at a high level. At the same time, it can induce the secretion of IFN-α, IFN-γ, IL-3, IL-12 and other factors to produce related immune responses. In addition, the anti-tumor immune response of DC can also be improved through genetic engineering [17]. Domestic and foreign animal experimental studies have confirmed that DC tumor vaccines can induce anti-tumor specific immunity in animals and significantly prolong the survival time of tumor animal models [18].

DC vaccines in GBM have already entered the clinical stage. The first is Pickling deantigen peptide vaccine. Non-specific tumor antigens acid-washed from tumor cells can effectively increase the ability of tumor surface peptides binding to MHC Class I molecules [19]. Yu et al. administered DC vaccine sensitized by 50~100 μg acid-washed tumor peptide to about 20 patients with GBM, three times every two weeks, with about 1×106 cells each time. [20] Results showed that vaccine-related autoimmune reactions or dose-related toxic reactions did not occurred in all patients; compared with the patients without CTL immune response, more than half of the patients produced tumor-specific T lymphocyte response in vivo, and the survival rate was significantly extended. In addition, half of the patients who underwent tumor removal after vaccination were found to have an infiltration of CD3+T cells in their tumors, consisting primarily of CD8+/CD45RO+ memory T cells. The second drug is tumor lysate antigen. In a phase III clinical trial on autologous tumor lysate sensitized DC vaccine in 2018, Liau et al. found that adding autologous tumor lysate sensitized DC vaccine to GBM standard treatment not only had the characteristics of feasibility and safety, but also extended the progression-free survival time and overall survival time of patients [21]. The third drug is tumor-specific antigen vaccine. EGFRvIII is an ideal immunotherapeutic target, caused by the loss of a subunit that produces a tumor-specific antigen, which is present in approximately 30% of GBM. At present, preclinical studies have shown that it has significant antitumor activity against intracranial tumors. A phase 1 dose escalation clinical study was conducted to treat EGFRvIII positive tumors with EGFRvIII peptide-sensitized DC [22]. In this study, patients with newly diagnosed GBM received 3 doses of the DC vaccine after maximum safe excisions and standard radiation therapy. With patients receiving up to 5.7×107DC, no dose-limiting toxicity or serious adverse effects were observed. The majority of patients showed EGFRvIII specific immune response after inoculation：83% of patients (10/12) had EGFRvIII specific T cell proliferation response in vitro; 56%(5/9) had EGFRvIII specific positive and negative, delayed type hypersensitive skin test; the median time to progression and overall survival from the date of diagnosis were 10.2 months and 22.8 months, respectively [22].

Although the DC vaccine was well tolerated, there was no significant improvement in median overall survival, median disease-free progression, disease-free progression rate, or overall survival with DC-based vaccination compared with the control intervention group. Some studies have shown that DC vaccine can increase the survival of newly diagnosed GBM, with a median survival of more than 2 or 3 years in some patients. However, DC-based vaccination showed no statistical difference in disease-free progression or median overall survival at 12 months between the control and vaccine groups [23]. Therefore, there are still major challenges for DC vaccines in the future.

5. Conclusion

In recent years, the remarkable research progress of immunotherapy in the field of cancer has brought the new ways of GBM treatment. mRNA vaccines can enable precise, safe and regulated treatment by selecting the right vector to carry the mRNA specific to the pathogen. Phase I clinical trials of the DC vaccine in patients with GBM show clear clinical advantages. For VLPS-type vaccines, studies on disc-shaped TMV have shown that low doses can achieve the expected efficacy. in the future, cancer vaccines can be combined with other therapies to develop new immunotherapy means, which will bring new ideas for GBM immunotherapy.

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