MINI REVIEW

Natural remedies for glioma immunotherapy

Andrew Tesera

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ABSTRACT

Since the immune system is essential in preventing tumour progression, glioma immunotherapy has gained more and more interest. Clinical trials are already testing immunotherapy approaches including Immune Checkpoint Inhibitors (ICIs), vaccinations, and Chimeric Antigen Receptor T-Cells (CAR-T).

Treatment using viruses and cells. However, due to their severe adverse effects and minimal efficacy brought on by glioma heterogeneity, antigen escape, and the presence of Glioma Immunosuppressive Microenvironment (GIME), the clinical applicability of these immunotherapies is restricted. Since most natural compounds have excellent anticancer effects and immunoregulatory qualities via reversing GIME, they have emerged as a potential and secure option for glioma therapy. The status of contemporary immunotherapy approaches for glioma, as well as their challenges, are summarised in this review.

Key Words: *Natural products; Immunotherapy; Glioma; Integrative medicine*

INTRODUCTION

Glioma can now be treated clinically with chemotherapy, radiation, and surgical resection. Despite the fact that the tumour is treated with a variety of techniques, the disease advances quickly, with an average recurrence occurring 8–9 months after diagnosis and an average survival time of only 15 months .Cancer immunotherapy makes use of the immune system to stop, control, and eventually eradicate cancer [1]. Reversing the tumor's immunosuppressive milieu and inducing efficient immune responses are crucial to glioma immunotherapy. Immunologically "cold" tumours are what gliomas are known as [1]. It was once thought that they could resist immune cell surveillance by microglia, T cells, and Natural Killer Cells (NK cells), and that they had an immunological escape phenomena from typical immune responses. Because they do not have a conventional lymphatic system, which will only trigger a very mild immune response, central nerve systems have generally been thought of as immune privileged [2]. The immunology of the central nervous system has started to increase, nonetheless, as a result of the elimination of the idea of "immunity privilege" in the central nervous system and the confirmation of the lymphatic system in the brain [2]. The immune response is greatly influenced by certain immune cells found in the central nervous system, such as microglia and monocyte-derived macrophages [3]. The immune system of the brain is, however, inhibited in gliomas. The microglia, which are immune cells that are naturally present in the brain, develop into Tumor-Associated Microglia/Macrophages (TAMs) in the presence of tumour cells. Epidermal Growth Factor (EGF) and Vascular Endothelial Growth Factor (VEGF) are released by gliomas to stimulate tumour growth, and these cytokines are typically anti-inflammatory M2-types [3]. In addition, glioma cells can secrete C-C Motif Chemokine 2 (CCL2), Colony-Stimulating Factor 1 (CSF-1), CX3CL1, and EGF, which can encourage the attraction of TAMs, encourage M2-type transformation, and create an immunosuppressive tumour microenvironment, all of which can promote the growth of glioma cells. Natural products exhibit a variety of biological behaviours, although they are less harmful [4]. They make a significant contribution to glioma treatment.

Additionally, several organic substances have positive immunomodulatory effects [4]. Natural products can alter the glioma microenvironment and modulate the immune system in a number of ways to support glioblastoma immunotherapy. This study highlights the present strategies and significant challenges in glioma immunotherapy with a focus on the function of natural products in glioma immunotherapy in an effort to improve glioma therapy.

CURRENT STATUS OF IMMUNOTHERAPY FOR GLIOMA

Numerous encouraging clinical outcomes have been observed in recent glioma immunotherapy trials using ICIs, vaccinations, CAR-T cells, and virus investigations. It is interesting that ICIs have the potential to both considerably increase immune cell infiltration and significantly extend longevity, making them a promising treatment strategy for glioma immunotherapy. In spite of this, the immunosuppressive microenvironment continues to be a significant factor in the failure of glioma immunotherapy.

Vaccine

Vaccines have recently gained popularity in immunotherapy and are

Editorial Office, Current Research : Integrative Medicine , UK

Correspondence: Andrew Tesera, Editorial Office, Current Research : Integrative Medicine, Belgium e-mail: integrativemedicine.p@outlook.com

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an excellent addition to glioma treatment plans. In order to trigger immune responses that are particular to tumour cells, vaccine immunotherapy is based on the personalised properties of tumours [5]. It can increase a patient's quality of life and increase their chance of survival. Peptide vaccines and dendritic cell vaccines are the two primary types of glioma tumour vaccines; they stimulate immune responses by enhancing the recruitment of T cells specific for the antigen. Wen et al. found that with the dendritic cell vaccine ICT-107, newly diagnosed glioblastoma patients experienced a 2.2 month increase in progression-free survival (PFS) while maintaining their quality of life. In this research, an increase in responders treated with ICT-107 (50%) relative to controls (33%) was seen in the IFN immune response test [5].

CAR-T cell therapy

One of the most promising methods for T cell treatment is Chimeric Antigen Receptor (CAR) technology. The therapy and management of haematological malignancies have undergone a radical change since it acquired the first batch of FDA approval in 2017 [6]. A bispecific CAR molecule (TanCAR) was created by Hegde et al. to precisely recognise the glioma-related antigens HER2 and IL-13R2.

TanCAR T cells can increase anticancer effects, boost antigen-resistance, and increase the survival rate of orthotopic glioblastoma transplantation in mice. According to a study, IL-12 therapy combined with CAR-T cells not only increased their cytotoxicity but also altered TMEs, encouraged pro-inflammatory CD4+ T cell infiltration, and decreased the amount of Treg cells [7].

Virus Therapy

Viruses are used in oncolytic virus therapy to infect and kill tumour cells. New infectious virus particles are released, further destroying the remaining tumour cells while destroying the infected cancer cells. The immune system is then stimulated by the virus therapy, encouraging the immune cells to attack the tumour. In order to break immunological tolerance, oncolytic virus therapy might boost immune cell infiltration and cause inflammation within the TME. In 2015, the FDA approved Talimogene Laherparepvec (T-VEC) for the use of genetically altered Herpes Simplex Viruses (HSVs) in the treatment of metastatic melanoma [8].

MAJOR OBSTACLES IN IMMUNOTHERAPY OF GLIOMA

Despite the fact that immunotherapy has given the treatment of gliomas hope, there are still many obstacles facing glioma immunotherapeutics today.

Glioma heterogeneity

Glioma is a heterogeneous tumour with varying levels of proliferative potential, invasiveness, histological grade, and clinical behaviour. According to research [8], glioma heterogeneity is a significant contributor to drug resistance, recurrence, and is a significant barrier to immunotherapy. 82% of patients who received the EGFRvIII peptide vaccine showed EGFRvIII expression decrease when the tumour returned, according to Sampson et al.'s research [9].

In order to combat the inherent heterogeneity of gliomas, future possibilities in vaccination therapy may necessitate targeting several epitopes.

Glioma antigen escape

Loss or downregulation of an antigen is considered antigen escape. The ability of glioblastoma to quickly adapt through antigen escape continues to be a significant barrier to vaccination therapy and CAR-T cell therapy. Antigen escape can have an impact on vaccination therapy, resulting in reduced vaccine immunogenicity and an inadequate antitumor immune response [9]. There are various difficulties with CART cell therapy, including as the potential for tumour resistance to single antigen-targeted designs.

Glioma immunosuppressive microenvironment

The inflammatory response has a significant impact on the tumour microenvironment during the process of oncogenesis. The development and spread of gliomas are significantly influenced by immune cells. Apart from glioma cells, there are two other types of immune cells in this microenvironment: immune effector cells including T cells and NK cells, as well as immunosuppressive cells like Myeloid-Derived Suppressor Cells (MDSCs), M2-type TAMs, and Tregs. In addition to maintaining an immunosuppressed state, M2-type TAMs, MDSCs, and Tregs encourage glioma development, invasion, and metastasis.

NATURAL PRODUCTS FOR IMMUNOTHERAPY OF GLIOMA

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Natural products remodeling TAMS

Chlorogenic Acid:

A phenolic molecule with a tiny molecular weight known as chlorogenic acid (3-O-caffeoylquinic acid, or CHA) is found in many different plants, including honeysuckle, eucommia, and hawthorn. According to earlier research, CHA has a number of advantageous pharmacological properties, including antibacterial, anti-inflammatory, antioxidant, and anticancer actions [10]. Particularly for glioma, its anticancer and immune-regulation capabilities are gaining attention in cancer immunotherapy.

Curcumin:

Due to its excellent pharmacological action in the treatment of neurological diseases, inflammatory disorders, as well as a wide range of tumours, including glioma, Curcumin (CC), a polyphenolic component derived from the rhizome of *Curcuma longa L.*, is gaining popular interest.

Apigenin:

The Brazilian plant *Croton betulaster Müll.* yields a flavonoid called apigenin, which has antiglioma properties by preventing proliferation, promoting differentiation, and altering the inflammatory features of glioma cells. The immunological profiles of cytokines like IL-10 and TNF are modified by apigenin, which has

immunoregulatory effects.

Natural products inhibiting MDSCs and Tregs

Sulforaphane:

Sulforaphane is a natural substance found in broccoli sprouts that is prized for its ability to modulate the immune system. According to a study, sulforaphane can lessen the quantity of MDSCs, which shield glioma cells from immunosurveillance and promote tumour growth in glioma-conditioned medium in vitro. By blocking the conversion of healthy monocytes to MDSCs and simultaneously encouraging MDSC differentiation into a mature DC phenotype that encouraged T-cell proliferation, sulforaphane was able to reduce the amount of MDSCs.

Gamabufotalin:

One of the active bufadienolides formed from cinobufacini, a traditional Chinese medicine product, is gamabufotalin. This substance is derived from dried toad venom (Chan Su), which is obtained from the skin glands of *Bufo gargarizans* or *Bufo melanostictus*. Numerous malignancies, including hepatoma and lung cancer, have been studied in relation to the potential immunomodulatory effects of cinobufacini.

Natural products modulating immune-related signaling pathway in glioma cells

Paeoniflorin:

A monoterpene glycoside substance called paeoniflorin is produced from the ancient Chinese herb *Paeonia lactiflora Pall*. Previous research revealed that it exhibits a variety of pharmacological actions, the anticancer effects of which have been the subject of increased study [4]. In a preclinical investigation, paeoniflorin was specifically studied for glioma immunotherapy due to its immunoregulation effects and fast blood-brain barrier penetration

Diosmetin:

Diosmetin, a flavonoid that is derived from the *Dracocephalum peregrinum L.* plant used in traditional Kazakh medicine, has mostly been researched for its ability to fight cancer, reduce inflammation, and promote antioxidant activity. Additionally, it has been shown to be safe and capable of causing cancer cells to die without harming healthy cells. Diosmetin was demonstrated by Wu et al. to decrease the growth, proliferation, and migration of gliomas both in vivo and in vitro, most likely due to its suppression of the TGF- signalling pathway in glioma cells [5].

CONCLUSION

Natural products have a variety of complex impacts on the immune system, and they have diverse effects on different immune cells. Alkaloids, polysaccharides, glycosides, flavonoids, and other chemical compounds are among the numerous chemical components found in natural goods. These substances perform a variety of biological processes and have a wide range of immune-system-related effects. TCM can alter the tumour microenvironment to control the immune system, for instance, by reducing the proportion of M2 type TAMs and Treg cells and increasing the activation of T cells in macrophages. The enhancement of antiglioma immunity by various traditional Chinese medicines will offer a promising technique for the treatment of glioma. Traditional Chinese medicine has a long history of clinical applications in China. Natural products are still far from having the optimal therapeutic impact, even if they may be important in the immunotherapy of glioblastoma due to their distinct advantages.

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