EDITORIAL

Utilizing natural compounds in glioma immunotherapy

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ABSTRACT

The increasing focus on glioma immunotherapy stems from the recognition of the crucial role played by the immune system in inhibiting tumor growth. Clinical trials are already underway to assess various immunotherapy approaches, such As Immune Checkpoint Inhibitors (ICIs), vaccines, chimeric antigen receptor T-cell (CAR-T cell) therapy, and virus-based treatments. However, the practical application of these immunotherapies is hampered by their significant side effects and limited effectiveness due to factors like glioma heterogeneity, antigen evasion, and the presence of a Glioma Immunosuppressive Microenvironment (GIME).

In light of these challenges, natural products have emerged as a promising and safe strategy for treating glioma. Many of these natural compounds exhibit potent anti-tumor properties and the ability to regulate the immune system, thereby counteracting the effects of the GIME. This review provides an overview of the current status of immunotherapy strategies for glioma, including the obstacles they face. Additionally, it delves into recent developments in the use of natural products for glioma immunotherapy.

Key Words: *Natural products; Immunotherapy; Glioma; Tumor Immunosuppressive microenvironment; Natural medicine*

INTRODUCTION

Current treatment approaches for glioma encompass surgical resection, radiotherapy, and chemotherapy. Despite employing a combination of these methods, the disease progresses rapidly, with an average recurrence period of 9 months post-diagnosis and an average survival duration of merely 15 months.

Cancer immunotherapy leverages the body's immune system to prevent, control, and eliminate cancer. In the context of glioma immunotherapy, a critical objective is to reverse the tumor's immunosuppressive microenvironment and trigger effective immune responses. Gliomas have been characterized as "cold" tumors from an immunological standpoint. For decades, it was believed that they exhibited immune evasion mechanisms that allowed them to evade surveillance by immune cells, including microglia, T cells, Natural Killer cells (NK cells), and macrophages.

Although the pathways for antigens from the brain to the deep cervical lymph nodes were initially identified in the 1980s, it was not until 2015 that a direct drainage route for cerebrospinal fluid containing immune cells from the cervical lymph nodes was discovered, primarily due to the identification of functional lymphatic vessels in the meninges. This discovery laid the foundation for the development of glioma immunotherapy.

Historically, the central nervous system has been regarded as immune-privileged, primarily due to the absence of a conventional lymphatic system, which results in only minimal immune responses. However, as the concept of "immune privilege" in the central nervous system has been debunked and the presence of a brain lymphatic system has been established, the field of central nervous system immunology has gained prominence. Various immune cells within the central nervous system, such as microglia and monocyte-derived macrophages, now play pivotal roles in immune responses.

Nevertheless, in the context of glioma, the immune system within the brain is suppressed. Resident immune cells in the brain, known as microglia, do not effectively eliminate tumor cells; instead, they transform into tumor-associated microglia/macrophages (TAMs) in gliomas, typically adopting an anti-inflammatory M2 phenotype. These TAMs release cytokines like epidermal growth factor and vascular endothelial growth factor to facilitate tumor growth. Furthermore, glioma cells secrete molecules like C-C motif chemokine 2 (CCL2), Colony Stimulating Factor 1 (CSF-1), CX3CL1, and EGF, which attract TAMs, promote their M2-type polarization, and contribute to an immunosuppressive tumor microenvironment that further fuels glioma cell proliferation. Simultaneously, glioma cells release indoleamine-2,3-dioxygenase depleting tryptophan to inhibit T cell activation.

Natural products possess a range of diverse biological activities while typically exhibiting lower toxicity levels. Their significance in the treatment of glioma is noteworthy. Furthermore, many natural products display notable immunomodulatory properties. These natural compounds employ various mechanisms to modulate the immune system and reshape the glioma microenvironment, all in the

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context of glioma immunotherapy.

This article offers an account of present strategies and notable challenges in glioma immunotherapy, with a particular focus on the role played by natural products in this context. The aim is to offer a more effective approach to glioma therapy.

PRESENT STATE OF GLIOMA IMMUNOTHERAPY

Ongoing clinical trials of immunotherapeutic approaches for glioma, encompassing Immune Checkpoint Inhibitors (ICIs), vaccines, CAR-T cell therapies, and viral studies, have yielded numerous encouraging clinical outcomes. Particularly noteworthy is the ability of ICIs to substantially enhance immune cell infiltration and significantly extend survival, rendering them a highly promising therapeutic avenue in the field of glioma immunotherapy. Nevertheless, it remains crucial to recognize that the immunosuppressive microenvironment continues to pose a significant obstacle to the success of glioma immunotherapy.

Immune checkpoints

Immune checkpoints represent a significant hurdle in the context of glioma immunotherapy. These checkpoints, operating through signaling pathways like PD1/PDL1, are responsible for deactivating and, in some cases, even eliminating activated T cells. Consequently, by obstructing these signaling molecules, it becomes possible to maintain the continuous activation of T cells.

In recent years, the advent of Immune Checkpoint Inhibitors (ICIs) has marked a pivotal moment in the realm of glioma immunotherapy, infusing hope into the lives of glioma patients. An illustrative clinical study involving neoadjuvant PD1 blockade with pembrolizumab therapy for recurrent glioblastoma has demonstrated significant enhancements in overall survival and progression-free survival. Patients who received neoadjuvant pembrolizumab, followed by continued adjuvant therapy after surgery, experienced a substantial improvement compared to those assigned to receive adjuvant PD-1 blockade alone. Specifically, the median overall survival in the neoadjuvant group was extended by 189 days in comparison to the pembrolizumab-alone group, while the median progression-free survival was prolonged by 27 days.

Vaccine

Vaccines have gained significant prominence in recent years as a focal point in immunotherapy, offering a valuable complement to glioma treatment strategies. Vaccine-based immunotherapy capitalizes on the individualized characteristics of tumors to elicit specific immune responses against tumor cells. This approach holds the potential to extend patients' survival and enhance their quality of life.

Glioma heterogeneity

Glioma is a highly heterogeneous tumor characterized by variations in proliferative potential, invasiveness, histological grade, and clinical behavior. This heterogeneity has been recognized as a significant contributor to drug resistance, recurrence, and a formidable challenge in the field of immunotherapy. For instance, Sampson et al. found that 82% of patients treated with the EGFRvIII peptide vaccine experienced a loss of EGFRvIII expression when their tumors recurred. To address this issue, the future of vaccine therapy may involve targeting multiple epitopes to counteract the inherent diversity within gliomas.

Moreover, a clinical study involving biopsies from multiple regions within a tumor from a patient treated with EGFRvIII CAR-T cells revealed significant variation in the degree of EGFRvIII expression across different tumor areas. This observation underscores the fact that CAR-T cell efficacy varies at different locations within the tumor. The heterogeneity of gliomas poses a substantial challenge to the success of immunotherapy, reducing its overall effectiveness. Therefore, targeting tumor heterogeneity will be a pivotal focus in glioma immunotherapy. Tailored treatments based on each tumor's specificity or the exploration of synergistic therapies may offer viable solutions to address this challenge.

NATURAL PRODUCTS IN GLIOMA IMMUNOTHERAPY

As contemporary immunotherapy for gliomas continues to face unmet challenges, researchers have turned their attention to natural products as a means to enhance therapeutic efficacy while prioritizing drug safety. In contrast to conventional chemotherapeutic agents, natural products exert their pharmacological effects through a mode of action that involves multiple components, channels, and targets. Importantly, they are associated with fewer side effects. Natural products demonstrate the ability to regulate the immune system, playing a significant role in glioma immunotherapy through several mechanisms:

1. Modifying Tumor Associated Microglia/Macrophages (TAMs)
2. Suppressing Myeloid Derived Suppressor Cells (MDSCs) and Regulatory T Cells (Tregs)
3. Revitalizing Immune Effector Cells, including T Cells and Natural Killer (NK) Cells
4. Modulating Immune-Related Signaling Pathways within Glioma Cells

These mechanisms collectively contribute to the promising role of natural products in the immunotherapy of glioma.

Chlorogenic acid

Chlorogenic acid (also known as 3-O-caffeoylquinic acid) is a phenolic compound characterized by its relatively small molecular weight, found abundantly in various plants like *Lonicera*, *Eucommia*, and *Crataegus*. Previous research has highlighted CHA's diverse pharmacological benefits, including antibacterial, anti-inflammatory, antioxidant, and antitumor properties. Of particular note are its antitumor and immune-regulation functions, which have garnered increasing attention in cancer immunotherapy, particularly for glioma.

Curcumin

Curcumin (often abbreviated as CC) is a polyphenolic compound derived from the rhizome of *Curcuma longa*. It has garnered significant public attention due to its remarkable pharmacological properties, which make it a valuable agent in the treatment of various conditions, including neurodegenerative diseases, inflammatory disorders, and a broad spectrum of tumors, including glioma .

Ginsenoside Rg3

Ginsenoside Rg3, one of the primary anti-tumor components found in Panax ginseng C.A. Meyer, demonstrates notable effectiveness in inhibiting tumor infiltration, proliferation, and metastasis. This compound has shown potent immune regulatory properties in reversing the Glioma Immunosuppressive Micro Environment (GIME).

In a study by Zhu, a liposome system was developed to co-deliver ginsenoside Rg3 and the anticancer drug paclitaxel (referred to as Rg3-PTX-LPs) to achieve synergistic anti-glioma effect. Their research revealed that Rg3-PTX-LPs exhibited greater antitumor efficacy

compared to paclitaxel-loaded cholesterol liposomes. Furthermore, this formulation extended the survival time of mice with intracranial C6 cell transplants by reactivating the immunosuppressive microenvironment within gliomas.

Apigenin

Apigenin is a flavonoid derived from the Brazilian plant *Croton betulaster*. It exhibits anti-glioma effects by inhibiting cell proliferation, promoting differentiation, and altering the inflammatory characteristics of glioma cells. Apigenin's immunoregulatory properties involve the modulation of cytokine immune profiles, including IL-10 and TNF.

CONCLUSIONS

The impacts of natural products on the immune system are intricate and diverse, with different natural products affecting various immune cells in distinct ways. Natural products encompass a broad spectrum of chemical components, including alkaloids, polysaccharides, glycosides, flavonoids, and more. These constituents exhibit a multitude of biological functions and have a wide-ranging influence on the immune system.

Traditional Chinese Medicine (TCM), for instance, has the capacity to reshape the tumor microenvironment and modulate the immune system. It can reduce the population of M2-type Tumor Associated Macrophages (TAMs) and regulatory T cells (Tregs) while enhancing the activation of T cells. In China, TCM has a rich history of clinical applications, and the immune-boosting properties of certain traditional Chinese medicines offer a promising avenue for glioma treatment.

In fact, nano-drug delivery systems have already played a crucial role in glioma treatment. These systems facilitate the penetration of natural products through the blood-brain barrier, allowing them to be released precisely at the glioma site. This targeted approach enables direct interaction between natural products and glioma cells. Moreover, with their slow-release capabilities, nano-drug delivery systems can enhance the bioavailability of natural products, further optimizing their therapeutic potential.

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