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Application of nanomaterials for the treatment of glioblastoma

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Abstract. Glioblastoma, as the most severe type of primary brain tumor, presents great difficulties in treatment due to its fast-growing nature, recurrence, and resistance to typical treatment methods. A particularly hard challenge is the blood-brain barrier (BBB), which makes it difficult for many drugs to reach tumor regions in enough amounts for the treatment to work well. Nanomaterials may provide one possibility for enhancing immunotherapy in glioblastoma by improving the delivery of drugs, helping them cross the BBB, and adjusting immune responses. This research looks at recent progress in using nanomaterials for glioblastoma treatment, focusing on types of organic and inorganic nanoparticles. Organic nanomaterials like lipid-based or polymer nanoparticles have the potential to deliver drugs directly to the tumor, with longer-lasting effects. Inorganic nanomaterials, such as magnetic nanoparticles, iron oxide ones, or gold nanoparticles, have been shown to be helpful for hyperthermia and photothermal therapy, as well as improving radiotherapy. These nanomaterials can be used alone or as vaccine adjuvants, providing practical options for getting through the BBB and delivering therapeutic agents to the tumor site. The integration of nanomaterials into glioblastoma treatments holds a certain potential to create better treatment plans for glioblastoma cases.

Keywords: Glioblastoma; Nanomaterials; Blood-brain barrier; Drug delivery.

1. Introduction

Brain tumors are abnormal cells that grow in the brain and spread to other healthy tissues in the body. It mainly separates into benign and malignant. Glioblastoma is the most common and aggressive primary malignant brain tumor that happens in adults. This kind of cancer spreads very quickly to health tissues, which presses the brain or spinal cord to cause health problems that seriously reduce the quality of life of patients. The symptoms of glioblastoma include memory problems, vision problems, cognition problems, mood and behavior changes. Glioblastoma patients usually suffer from headaches, fatigue, and depression. Although there is a lot of research about glioblastoma, there is no treatment method that can cure this brain tumor currently. Glioblastoma can recur even with adequate treatment. The survival rate of glioblastoma patients is low. Patients who receive treatment can live longer, but there is no method or example of a complete cure for glioblastoma.

Current treatment of glioblastoma includes surgical tumor resection, radiation, and chemotherapy. Less aggressive brain tumors are easier to remove, but glioblastoma cannot be cured by surgery alone because almost all glioblastomas are recurrent. It is difficult to remove the tumor with surgical intervention completely. Radiotherapy is usually the next step after surgery. It is used to kill any remaining tumor cells and slow down the growth of tumors that cannot be removed with surgery. After surgical diagnosis, chemotherapy was combined with adjuvant therapy. Existing chemotherapy drugs or treatments for glioblastoma include temozolomide, lomustine, carmustine, nitrosoureas, and bevacizumab. However, these adjuvant therapies cause severe lymphopenia, which is not conducive to the immune system to compete with cancer cells. Additionally, tumors can maintain an immunosuppressive environment that promotes tumor growth by neuroprotective anti-inflammatory mechanisms.

Therapeutic vaccines can be used to treat glioblastoma. There are several types of therapeutic vaccines developing for glioblastoma, including peptide vaccines, dendritic cell vaccines, neoantigen

vaccines, and CAR T cell vaccines [1]. The goal of the vaccine is to increase antigen presentation to induce a sufficient immune response to fight the tumor. However, the isolation of the blood-brain barrier (BBB) is one of the main problems that vaccines and anticancer drugs are facing, which leads to resistance to immune responses against tumors caused by the infiltration of immunosuppressive cells. The BBB blocks immune cells and macromolecules to prevent inflammation, which leads to low activation of immune responses and lack of infiltration of lymphocytes into tumors, making them insufficient to fight tumors. Glioblastoma also has the ability to inhibit the whole-body immune response, which makes it more challenging to induce enough immune response to eliminate the brain tumor. The obstruction of BBB also prevents many anticancer drugs from reaching concentrations in the brain that effectively kill tumors. It is crucial to enable vaccines and drugs to penetrate BBB to reach the tumor area effectively.

Using nanomaterials as a mediator for drug delivery is a successful and a kind of non-invasive treatment strategy. Using nanomaterials as vaccine adjuvants can solve the problem of vaccine delivery and has development value in the treatment of glioblastoma. Nanomaterials as carriers can be used for targeted delivery at specific locations in the affected body area. It can improve the ability of medications to be absorbed quickly, decrease release duration, prevent drug agglomeration, and improve solubility [2]. Due to their diverse properties, nanomaterials have practical applications in many fields, include nanomedicine and drug delivery. This research focuses on the mechanism, development prospects, and advantages of different nanomaterials.

2. Nanomaterials-based drug delivery

Nanomaterials can be used as effective carriers of antibodies, nucleic acids, or chemotherapeutic medications. They have a high loading capacity and shielding effects and increase solubility, stability, and bioavailability. Nanomaterials have been developed that can pass through the BBB and reach the brain include both organic and inorganic. Size, shape, electrical properties, and surface modification are all important factors affecting nanomaterial effects. For targeted brain drug delivery, the shapes of nanoparticles include spheres, rods, porous rods, ribbons, disks, cubes, flowers, tubes, and stars [3]. Nanomaterials range in size from 1 to 100 nanometers and have distinct optical, magnetic, and electrical characteristics that can be changed to improve medication release and distribution in the tumor microenvironment. Nanomaterials can be used alone or as vaccine adjuvants to enhance immunotherapy of glioblastoma by regulating antigen release, enhancing immune response, and improving treatment efficiency. Nanoparticles can enhance penetration by interacting with endothelial cells of BBB, surfactant coating or ligand binding, and using magnetic fields to guide metal-based nanoparticles to target locations.

3. Application of organic nanomaterials for glioblastoma treatment

3.1. Liposomes

Liposomes are synthetic spherical vesicles of nanometer to micrometer size. They are made up of an aqueous spherical core with a hydrophilic head and a hydrophobic tail, encased in a phospholipid bilayer. They are biocompatible and have low toxicity. Biomimetic liposomes using cell membranes from M1 and M2 macrophages were used to deliver anti-carcinogenic drugs, which effectively inhibited the growth of glioblastoma cells. These nanocarriers demonstrated immune escape potential, with M2 macrophage-derived liposomes showing higher uptake and greater effectiveness in killing glioblastoma cells [4]. Microfluidics-derived docosahexaenoic acid (DHA) lipids, which is an ω3-PUFA that can induce the death of glioblastoma cells through apoptosis and autophagy processes, were used to create liposomes that effectively crossed the BBB and significantly reduced glioblastoma cell metabolic activity [5]. The developed functionalized liposomes that incorporate the NFL-TBS.40–63 (NFL) peptide are known for targeting glioblastoma cells. The vitro experiments showed that the NFL peptide not only promoted the liposomes' passage through the BBB and the

blood-brain tumor barrier (BBTB) under pathological conditions but also improved their internalization in glioblastoma cells [6].

3.2. Nano-structured lipid carriers (NLCs)

By combining many liquid lipids with solid lipids to cause the solid lipid core's structure to become less ordered, NLCs are able to overcome the drawbacks of solid lipid nanoparticles (SLNs) and enhance drug payload, release duration, and stability. The anticancer medication docetaxel (DTX) is prone to P-gp efflux at the blood-brain barrier and is unable to build up in the brain to levels high enough to eradicate tumors. Functionalized docetaxel-loaded nanostructured lipid carriers (DTX-NLCs) using polyunsaturated fatty acids (PUFAs), Gamma-linolenic acid (GLA), and Alpha-linolenic acid (ALA), can be used to enhance brain-targeted treatment of glioblastoma. These NLCs improved BBB permeability, cellular internalization, and selective uptake by glioblastoma cells, with ALA-DTX-NLCs showing greater efficacy and toxicity against glioblastoma cells compared to GLA-DTX-NLCs [7]. Lactoferrin conjugated temozolomide (TMZ) and resveratrol co-loaded nanostructured lipid carriers (LTR-NLCs) can be used for glioblastoma treatment through intranasal administration, where this approach overcomes the BBB and uses lactoferrin to achieve cancer cell targeting [8]. LTR-NLCs improved drug permeability, prolonged the duration of action, and showed a synergistic anticancer effect [8].

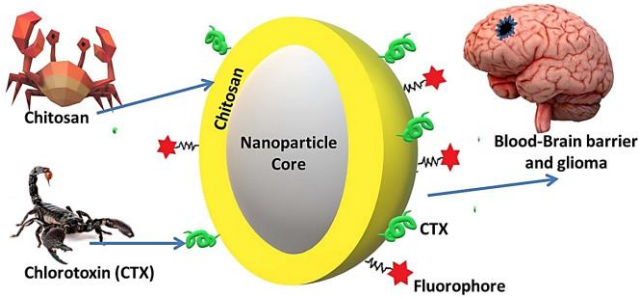

Figure 1. Functionalization of chitosan-based nanoparticles [9].

3.3. Chitosan-based nanomaterials

Chitosan is a natural polymer commonly used in brain treatment that has good biocompatibility and biodegradability. As shown in Figure 1, chitosan-modified nanoparticles can improve their properties, such as hydrophilicity and stability, and promoting coating adsorption through charge interactions [9]. Chitosan coatings and chitosan-modified nanoparticles and hydrogels have shown significant effects in delivering therapeutic agents and imaging agents to gliomas, showing broad application prospects [9]. Nasal-brain drug delivery provides an effective alternative to bypass the BBB, and chitosan nanoparticles (CS NPs) show potential due to their good mucosal adhesion [10]. Transferrin (Tf) was used as a targeting ligand to modify CS NPs to achieve specific drug delivery. These nanoparticles can be internalized by specific cells through transferrin receptor-mediated endocytosis [10]. A new type of selenium nanoparticles (Se NPs) that functionalized with chitosan and sialic acid (SA) was designed, and its antitumor effect on human glioblastoma cell lines was analyzed. After optimizing the synthesis conditions, Se NPs@Cs with a diameter of about 23 nanometers were obtained and modified with sialic acid to form Se NPs@Cs-SA [11]. These nanoparticles can be stably stored at 4 °C for about 60 days and show dose and time-dependent inhibitory effects on glioblastoma cells, while sialic acid improves their stability and biocompatibility [11].

3.4. Poly (lactic-co-glycolic acid) (PLGA) nanoparticles

PLGA nanoparticles exhibit excellent properties in drug delivery, including good bioavailability, high safety, complete degradation, and non-toxic metabolism. These particles can achieve controlled and prolonged release while shielding medications from premature breakdown, thereby reducing the required drug dose and improving safety. The good interaction of PLGA nanoparticles with the

immune system makes them ideal immunotherapy carriers that can be designed to target specific cell types or be effectively absorbed, modulate immune responses by delivering immunosuppressants or stimulants, improve disease conditions, and enhance therapeutic effects in cancer immunotherapy [12]. Kuźmińska's study investigated the synergistic antitumor activity of etoricoxib (ETO) and cannabidiol (CBD) in glioblastoma cell lines and developed PLGA-based nanoparticles loaded with both drugs. In T98G and U-138 MG cell lines, the combination of ETO and CBD decreased cell viability and induced apoptosis in a dose-dependent way [13]. The combination of ETO and CBD may become an effective adjuvant therapy for the treatment of glioblastoma, and the development has the potential for further applications [13]. Younis's research evaluated the effect of poly (lactic-co-glycolic acid) nanoparticles (AMR-PLGA-NPs) loaded with amorubicin (AMR) in combating TMZ-resistant glioblastoma. AMR-PLGA-NPs induced apoptosis and inhibited proliferation of TMZ-resistant glioblastoma cells while upregulating PTEN expression and inhibiting the PI3K/AKT signaling pathway [14]. In addition, AMR-PLGA-NPs can deliver drugs in vivo and accumulate in the brain, effectively inhibiting tumor growth, reducing systemic side effects, and providing sustained drug release [14].

4. Application of inorganic nanomaterials for glioblastoma treatment

4.1. Magnetic nanoparticles (MNPs)

MNPs have a wide range of surface areas and magnetic properties, which facilitate drug delivery, precise targeting, and therapeutic applications such as magnetic hyperthermia and resonance imaging. Coating MNPs with other materials can enhance their stability and modulate their pharmacokinetics and pharmacodynamics. The heat transfer produced by MNP injection is more influenced by frequency than by electric field intensity. Increasing frequency will rapidly increase the temperature, while uniformly distributed MNPs contribute to a more uniform distribution of heat, encouraging the destruction of the tumor while reducing harm to healthy tissue [15]. An MNP-based ferroptosis catalytic nanoreactor loading cisplatin (CMNP-Cis-Arg) was prepared. The formulation exhibited peroxidase (POD)-like enzyme activity, produced additional ROS to induce ferroptosis in glioblastoma cells, and promoted GSH depletion through nitric oxide (NO) generation [16]. Through systemic administration, CMNP-Cis-Arg significantly inhibited glioblastoma progression in an orthotopic mouse model, demonstrating its potential as an effective glioblastoma treatment strategy [16].

4.2. Iron oxide nanoparticles (IOMNPs)

IONPs can kill cancer cells at the tumor site through hyperthermia and immune enhancement and become a highly effective anticancer tool by inducing reactive oxygen species formation. Yao's research developed chlorin e6 (Ce_6)-conjugated iron oxide (Fe_3O_4-Ce_6) nanoparticles for in vitro ablation of glioblastoma cells by combining photothermal therapy (PTT) and photodynamic therapy (PDT). Fe_3O_4-Ce_6 nanoparticles combined with laser irradiation significantly decreased the viability and destroyed cancer cells, and ROS generation in cancer cells was confirmed by fluorescence imaging [17]. This suggests that Fe_3O_4-Ce_6 nanoparticles may be used for combined cancer therapy guided by fluorescence imaging [17]. The existing study investigated whether combining superparamagnetic ferrite nanoparticles (USIO NPs) and magnetic resonance-guided focused ultrasound (MRgFUS) could enhance the magnetic resonance (MR) imaging of glioblastoma. Through MRgFUS technology combined with microbubbles, BBB can be opened non-invasively, thereby facilitating the delivery of USIO NPs-1,3-PS in glioblastoma [18]. The experimental results showed that the modified USIO NPs-1,3-PS performed well in MR imaging, cytocompatibility, and biosafety, especially after MRgFUS-mediated BBB opening, which significantly increased the accumulation of nanoparticles in the tumor area [18]. MM-camouflaged gossypol-crosslinked USIO NCs (G-USIO@MM NCs) exhibited excellent stability and glioma specificity under physiological

conditions, and they effectively induced tumor cell apoptosis and necrosis by promoting intracellular ROS generation and GSH consumption [19].

4.3. Gold nanoparticles (AuNPs)

AuNPs induce apoptosis mainly through oxidative stress due to their controllability, biocompatibility, and low toxicity, and their cytotoxicity increases with penetration depth. AuNPs have been shown to be one of the safest and most effective delivery systems for treating glioblastoma because they are easy to synthesize, highly modifiable, and safely penetrate the BBB. They exhibit significant effects when combined with photothermal therapy, showing great potential to improve glioblastoma treatment outcomes [20]. Folate receptor (FR)-targeted gold nanoparticles (IND/Au-GSH-FA NPs) are effective in treating glioblastoma in 2D and 3D cultures. These nanoparticles increased toxicity to FR+glioblastoma cells while reducing potential cytotoxic effects on healthy cells [21]. Fluorescent ultrasmall AuNPs (AuTio-Dox NPs) successfully crossed the BBB and effectively delivered doxorubicin into normal and glioblastoma organoids, leading to a higher rate of glioblastoma cell killing compared to free drug [22]. AuNPs have also shown great potential in experiments related to radiotherapy. AuNPs as radiosensitizers enhanced the immunogenic cell death effect of radiotherapy on glioblastoma cells, promoting better tumor cell death and immune response [23]. Chemically and nuclear reactor-synthesized radioactive AuNPs exhibited superior therapeutic efficacy against glioblastoma xenografts when combined with TMZ [24]. In addition, Au@DTDTPA(Gd) nanoparticles with X-ray radiation can significantly reduce tumor cell invasion and viability in a glioblastoma model [25].

5. Conclusion

Nanomaterials represent a breakthrough method to deal with the difficulties of glioblastoma treatment, especially concerning the BBB and targeted drug administration. Organic nanoparticles, for example, lipid nanoparticles and polymer nanoparticles, provide considerable benefits in treating glioblastoma because they show good compatibility with biological systems and capability to encapsulate and release drugs in a controllable way. Inorganic nanomaterials, such as MNPs and AuNPs, have been shown to have wide use in improving treatments like hyperthermia, photothermal therapy, and radiation therapy, which may grow into multimodal therapeutic strategies. These particles are capable of crossing the BBB and delivering drugs directly to glioblastoma cells, improving their treatment potential. Although progress has been made, more research is necessary to refine their effectiveness, safety, and long-term impact in clinical use. As nanoparticle development continues, it could offer new directions in glioblastoma therapy, increasing survival chances for patients and giving new hope in this difficult disease.

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