Advances in Targeted Nanomedicines in Glioma Therapy

Haoyang Tan, Junshu Wang, Xinyue Feng*
Soochow University, Suzhou 215123, Jiangsu, China
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Abstract: Objective. This article explores the classification, characteristics, and challenges in the treatment of gliomas, and assesses the use of targeted nanomedicines in therapy and their research progress. Methods. A literature review was conducted to compare and analyse conventional treatments with nanomedicine delivery systems, focusing on the use of polymer-based, biomimetic, and inorganic nanoparticles in the treatment of gliomas. Results. Nanotargeted drugs significantly enhance drug bioavailability, duration of action, and reduce side effects compared to conventional formulations. Polymeric nanoparticles increase the concentration of tumour drugs through a targeting mechanism. Biomimetic nanoparticles enhance drug biocompatibility and targeting. Inorganic-type nanoparticles, on the other hand, exploit their physicochemical properties and show their potential in tumour imaging and therapy. Conclusion. Targeted nanomedicines have great potential in glioma therapy, but challenges such as target specificity, penetration efficiency and BBB damage need to be overcome. Future studies should focus on personalised therapeutic strategies to improve treatment efficacy and safety.
***Keywords*:** glioma; targeted nanomedicines; therapy; research progress

1. Introduction

1.1 Classification, characteristics and therapeutic challenges of gliomas

In recent years, the incidence of tumours has been increasing year by year and has become one of the major threats to human life and health. Among the many refractory tumours, intracranial gliomas (GBM) are among the most difficult to cure. Gliomas originate from glial cells in the brain or spinal cord and are a group of malignant tumours occurring in the central nervous system (CNS). Among the most malignant and aggressive are: glioblastomas, which account for 46.1% of primary CNS malignancies[1].

1.2 Limitations of conventional treatments

Due to the infiltrative growth of the tumour, complete resection by surgery may cause damage to normal brain tissue and affect the integrity of the patient's postoperative neurological function, so the traditional treatment of surgical resection can only delay the further deterioration of the tumour. In addition, the protective function of the blood-brain barrier (BBB), in addition to warding off foreign harmful substances, also takes effect against chemotherapeutic drugs, making them significantly less effective. Together, the tumour microenvironment and the immune microenvironment in the host body make the treatment of glioma more complicated, and despite the rapid medical development in recent years, there are still many challenges in the treatment of glioma.

1.3 Classification, characteristics and therapeutic principles of targeted nanomedicines

At present, with the research on the biological characteristics of glioma in today's medicine, targeted nanomedicine comes into being. Compared with ordinary preparations, passive targeted drugs can reach the target organs related to them with the help of reticuloendothelial system; active targeted drugs can reach the target organs directly through specific binding with the receptors on the tumour surface. On the one hand, nano drug delivery system makes use of different materials (e.g. dendrimer, polymer micelle, phospholipid bilayer, etc.) to encapsulate the drug inside, which effectively reduces the degradation of the drug by metabolism enzymes in vivo, improves the bioavailability of the drug, and prolongs the duration of the drug's action. Therefore, it occupies an important position in the innovative therapies for the clinical treatment of glioma.

2. Advances in nanotargeted drug delivery systems in gliomas

Compared with traditional formulations, targeted nanodrugs carried by nanoparticles (NPs) are safer and more effective. Currently, based on the chemical structure and composition, the targeted drug delivery systems used for the treatment of gliomas in the clinic can be classified into the following categories: polymer-based, biomimetic, and inorganic, which will

be highlighted in the following section from the perspective of the structure and function of these three types of targeted drug delivery systems.

2.1 Polymer-based NPs

Polymeric NPs are compounds in which the drug is directly bound to polymers and water-soluble macromolecular substances in the form of covalent bonds. Common ones are: polyethylene glycol PEG, polyamide-amine PAMAM, and polylactic acid PLA. Compared to normal tissues, tumour tissues are characterized by rapid vascular growth, large vascular endothelial cell gaps, and defective lymphatic reflux system, which leads to enhanced permeability of tumour cells to macromolecules, and thus local drug concentration can be increased with the help of polymer NPs. The nanomaterials can encapsulate the therapeutic drug inside the polymer, which effectively reduces the degradation of the drug by various types of cellular enzymes in the BBB, significantly prolongs the circulation time of the drug in the body, and improves the pharmacokinetic properties. At the same time, the encapsulated materials used (PEG, PAMAM) mostly have excellent biocompatibility, effectively reducing the cytotoxicity of the drug. Polyethylene glycol (PEG) is an electrically neutral, non-toxic and hydrophilic polymer with unique physicochemical properties and good biocompatibility. The hydration layer formed by its molecular chains on the surface of nanoparticles not only reduces non-specific interactions with plasma proteins, but also effectively circumvents the clearance by the reticuloendothelial system and prolongs the residence time of the drug in the circulatory system. In addition, the non-immunogenicity of PEG reduces the immune recognition of the nanoparticles, thereby reducing the inflammatory response and immune-related clearance. This property is critical for prolonging drug bioavailability in vivo. By adjusting the molecular weight and surface density of PEG, drug release kinetics and nanoparticle biodistribution can be finely tuned. However, with further studies, it was found that polyethylene glycolisation (i.e. PEGylation, an excessively slippery surface of the drug carrier) allows for prolonged nanoparticle cycling time in organisms, but at the same time, may also reduce the interaction with tumour cells. In the presence of the tumour microenvironment, PEGylated nanoparticles are difficult to bind to the lysosomal membrane, and therefore may hinder the release of some nucleic acid and gene-based drugs. These are referred to as the "polyethylene glycol dilemma". Research in this area has been very active in order to improve the efficacy of polyethylene glycol NPs. [6-8] Polyamide-amine (PAMAM) dendritic macromolecules are important in the treatment of gliomas due to their unique physicochemical properties and have been hailed as "artificial proteins". 1985 Tomalia et al. synthesised the first highly branched, symmetric, radiolucent PAMAM materials, which they named starbursts. tree macromolecules. [9] PAMAM has a huge internal water-transport space and a high density of surface functional group hydrophobic space. It is first coupled with molecules or ligands with solubilising effect, and then combined with insoluble drugs to better increase the aqueous solubility of insoluble drugs, and to achieve the purpose of controlling the release of drugs and mediating the targeted delivery of drugs.

2.2 Bionic NPs

Bionic NPs are nanoscale carriers designed to mimic the structure and function of biological systems, and they can mimic the properties of cell membranes, proteins, peptides, or other biomolecules, allowing them to avoid being recognised by the body's immune system as an exogenous substance in the course of glioma treatment, thereby avoiding a series of subsequent immune responses and effectively reducing the drug'sliver and kidney clearance. Biomimetic nanoparticles are of interest for their excellent biocompatibility, targeting and environmental responsiveness. The common ones are: polysaccharide-based materials, natural vesicles, and biomimetic proteins. Chitosan (CS) is a polysaccharide-like material consisting of N-acetyl-D-glucosamine and D-glucosamine linked by β-1,4-glycosidic bonding, which has good biocompatibility. Meanwhile, CS is extremely responsive to pH and temperature, a feature that makes it potentially applicable in microenvironmental targeting of gliomas. In addition, by modifying the structure of CS, it is possible to construct CS nanogels camouflaged by macrophage membranes, thereby avoiding the rapid clearance of the drug from the body by the mononuclear phagocytosis system captured during blood circulation and implementing specific cell-targeting functions, and for the precise diagnosis of in situ gliomas by T1 MR imaging. [11] Liposomes are small vesicles composed of lipid materials such as phospholipids and cholesterol, usually presenting a spherical or elliptical structure. Liposomes have a phospholipid bilayer structure, which is key to improving biocompatibility as well as targeting. Through the use of liposome carrier system, the pharmacological distribution of some traditional chemotherapeutic drugs (e.g. , adriamycin) can be changed, the damage to normal tissue cells can be reduced, and the cardiotoxicity can be effectively reduced, which is of strong clinical application value. At the same time, the modification of its surface with the help of specific functional proteins or peptides can help to further improve the therapeutic effect with the help of active targeting. For example, modification with cell-penetrating peptides (CPPs) can directly cross the BBB through direct penetration and endocytosis, and unlike CPPs, brain capillaries express transferrin receptors on their surfaces, and tumour neovascularisation is significantly increased in comparison to normal tissues, so

modification of liposome surfaces with the corresponding ligands can further increase the concentration of the drug in the tumour site. [12]

2.3 Inorganic NPs

Inorganic NPs for drug delivery have very unique physicochemical and biological properties: on the one hand, they use their specific optical properties to provide enhanced signals or act as contrast agents for tumour detection; on the other hand, the surface of inorganic NPs is easy to be modified, which can further improve the targeting of the drug and avoid its damage to normal tissues. Currently, the common ones are: mesoporous silica nanoparticles, superparamagnetic iron oxide, nano gold Mesoporous silica nanoparticles (MSNs) are silica-based spherical nanomaterials with regularly arranged mesopores, which are loaded with hydrophobic anticancer drugs through ionic bonding, hydrogen bonding, and electrostatic interactions, and then their surfaces are modified to take advantage of the receptors or antigens abnormally expressed by the tumour cells, to achieve active targeting so that the drugs can directly reach the lesion site. In addition, it has been shown that MSNs can release loaded drugs in response to external stimuli (e.g. , pH changes, cellular metabolites, enzymes, light and heat, etc.), which in turn achieves localised drug release. [13] Superparamagnetic iron oxide (SPIO) mainly consists of Fe3O4 or γ-Fe2O3. Iron oxide nanoparticles exhibit superparamagnetism when their particle size is smaller than a certain critical value, and thus can be used for positive contrast enhancement in MRI to improve the clarity and diagnostic accuracy of glioma imaging. Under the action of an alternating magnetic field, superparamagnetic iron oxide nanomaterials (SPIONs) convert magnetic energy into thermal energy to kill tumour cells by local heating, and thus can be used for magnetothermal ablation of gliomas. Using the magnetic properties of SPIONs, the release of drugs from the nanocarriers is controlled by changes in the external magnetic field, enabling precise dose control. It has been shown that SPIONs also have oxidase-like catalytic properties to kill tumour cells by catalysing hydroxyl radicals in the tumour environment to produce highly reactive single-linear oxygen. [13] Gold nanoparticles (GNPs) are usually particles with spherical, rod-like, polyhedral or other morphologies. In addition to other features such as quantum size effect of nanocarrier systems and ease of surface modification, they also have the phenomenon of localised surface plasmon resonance (SPR), which is capable of absorbing and scattering light, especially in the visible to near-infrared region. At the same time, GNPs have a larger absorption cross-section than organic photothermal agents, absorbing infrared light and converting it into thermal energy, thus efficiently exothermic at the local level for therapeutic effects.

3. Summary and outlook

Glioma, as a tumour originating from glial cells, is the most common primary malignant tumour of the central nervous system and has been a hot research topic in recent years. Currently, the incomplete surgical resection and the toxic effects of radiotherapy on normal tissue cells have also become the biggest limitations in its treatment. With the development of molecular oncology and the deepening of nanomaterials research by researchers, nanoparticle (NPs)-based drug delivery systems have made significant progress in the field of drug delivery and are gradually moving towards clinical applications. Although brain-targeted nanoparticles have been gradually recognised for their innovativeness and technological advances over the past decades, they still face challenges in terms of targeting specificity, penetration efficiency, and potential damage that may be inflicted on the blood-brain barrier (BBB), which have limited the further popularity of nanoparticles in clinical applications. In addition, rare subgroups of GBM may have different targets and signalling pathways, and the physiological environments in different patients are also different, so further research is needed on how to achieve personalised medication, further increase the target concentration, and control the adverse effects of drugs.

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