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The nanocarrier strategy for crossing the blood-brain barrier in glioma therapy

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ABSTRACT

Glioma is the most common malignant tumor of the brain. The postoperative recurrence rate was high, and the 2-year survival rate only increased by 20%–25%. The reason is the blood-brain barrier (BBB). BBB is a physical barrier that stabilizes the physiological environment of brain tissue and protects the central nervous system from the invasion of harmful substances. Drug delivery based on nanotechnology and nanocarriers has attracted much attention due to its biological safety, continuous drug release time, increasing solubility, biological drug activity, and enhanced BBB permeability. By modifying different substances on the surface of nanocarriers, the BBB is bypassed by receptor-mediated and cell endocytosis and exocytosis. In addition, the purpose of bypassing BBB-targeted drug delivery can also be achieved by intranasal administration and local administration. This paper reviews different target transport mechanisms, mainly in invasive and non-invasive strategies, the nanocarriers that have made progress and the nanocarrier strategy of bypassing BBB are listed.

1. Introduction

The incidence of primary ventral tumors has increased, and the number of chondromas occupies 77% to 80% of the total incidence and is the most common intracranial malignancy [1]. Poor postoperative chemotherapy is one of the reasons for the high recurrence rate [2]. Brain tissue is an extraordinary organ. After hundreds of thousands of years of evolution, brain tissue has established a complete defense mechanism to prevent other non-nutrients from entering. The working unit of this protective mechanism is the blood-brain barrier (BBB) [3,4].

The BBB consists of basal cells of brain capillary endothelial cells, astrocytes, and peripheral cells, it is shown in Fig. S1 (Supporting information). The endothelial cells of the central nervous system are tightly connected [5]. BBB only allows free diffusion of lipophilic nutrients and drugs with relative molecular weight less than 200–600 D [6]. The exact protective effect of BBB is to maintain the stability of the internal environment and protect the brain from toxins, bacteria, and other harmful substances. On the other hand, it also limits the entry of drugs into the brain [7].

Overcoming the BBB has always been an essential topic in the research of applied drug delivery systems. So far, drug delivery in brain tissue can be divided into several aspects. It can be divided into invasive and non-invasive. The invasive approach involves breaking the BBB after entry or direct injection of drugs into the central nervous system [8]. Direct injection administration includes intracerebral, intraventricular, or intravenous injection. However, patients who receive injections through these routes will suffer from many adverse reactions, including bacterial infections, pain, allergic reactions, and some surgical complications [9-11]. The non-invasive strategy does not destroy the BBB. Intranasal administration is a noninvasive delivery technique, that by passing the BBB through the olfactory nerves [12-14]. However, the main limitation is the small number of molecules able to diffuse through the olfactory epithelial cells.

Although there are still some challenges to achieving drug delivery across the BBB, the use of nanoparticles as carriers to encapsulate drugs and modify different receptors on the surface can achieve non-invasive crossing of the BBB to reach the tumor and achieve targeted drug delivery [15-20]. The ideal drug carrier has

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the characteristics of good biocompatibility, high drug loading and appropriate active groups on the surface of the carrier for further functional modification [21-23]. For example, polymer nanoparticles have been widely synthesized and used in clinical practice because of their stability, easy preparation, and combination with other small molecules or drugs [24-26]. The characteristics of nanomaterials may affect the transport capacity across the BBB, which provides a broad space for researchers to develop more promising BBB crossover strategies based on nanomaterials. In this review, we will provide the latest progress in nanomaterial-based BBB crossing strategies.

2. BBB disruption

2.1. Drug-based strategies

Due to the physiological structure of BBB, direct destruction of BBB structure is an important research direction of invasive drug delivery strategy. Drugs such as mannitol, fructose [27], lactamide, urea, and glycerol may produce high osmotic pressure. Changes in osmotic pressure lead to vasodilation and contraction of cerebrovascular endothelial cells [28], leading to the temporary opening of the BBB. It can promote the transmission of water-soluble and high molecular weight substances in the central nervous system for the treatment of brain tumors or other central nervous system diseases. RMP-7 is a synthetic analog of slow excitation peptides, which causes similar changes, but the half-life is longer, and that reversibly destroys the BBB by structural changes closely associated with the endothelial B2 receptor. However, related research has stalled, and the dose has become a major obstacle to research. Dose, time, and method are the potential reasons for this difference. Future research using different procedures may get better results, but at present, there is no pending experiment registered to study this problem [15].

2.2. Ultrasound disruption

Magnetic resonance (MR) guided focused ultrasound (MRgFUS) is a blood-brain barrier disruption (BBBD) strategy based on non-invasive ultrasound [29-31]; MRgFUS is an accurate BBBD that can directly visualize real-time improvement rather than relying on delay evaluation. However, treatment may require a certain dose of ultrasound or repeated ultrasound, which increases the risk of complications. Moderate-density high-intensity focused ultrasound (HIFU) is an alternative to traditional techniques that overcome this limitation of joints [32,33]. However, the amount of dissolution is limited. The non-focused ultrasound. It can lead to a large opening of the BBB, which is conducive to the treatment of diffuse diseases. To this end, the transducer is embedded in the skull to provide a controlled ultrasound energy distribution and reduce the energy passing through the skull [34]. Non-focused ultrasound has a huge potential, and non-focused ultrasound is mainly used for diagnosis and imaging. However, if a sensor is inserted into the brain, the safety of the human body will be threatened [35].

2.3. Magnetic disruption

Most drug delivery targeted at the brain will enter the brain through BBB. The system cross-links magnetic particles with chemotherapy drugs into magnetic fluids so that magnetic particles are loaded with chemotherapy drugs under the action of an external magnetic field to gather in the target area [36]. When the magnetic nanoparticles are exposed to an alternating magnetic field, heat is generated, which causes local damage to the BBB. It has the advantages of carrying more chemotherapeutic drugs, good drug distribution kinetics, significantly reducing the burden of metabolic organs, and ensuring the targeted killing of chemotherapeutic drugs on tumors [37].

3. Local injection

Injecting the brain can provide the most direct way to treat tumors in the brain and the surrounding cranial cavity, thereby reducing the possible negative effects on the surrounding tissues. In addition, biodegradable chemotherapy-impregnated tablets (such as carmustine implants) can be implanted into the tumor resection cavity. Both rely on diffusion to transport drugs to the brain parenchyma. However, this technique has limitations due to the exponential attenuation of brain diffusion with distance. To achieve the maximum target of drugs on tumors, it is necessary to accurately determine the injection or transplantation site [38].

Convective-enhanced drug delivery (CED) is a strategy proposed by Boboetal in 1994 [39]. Chemotherapeutic drugs can be delivered directly and continuously into the tumor through positive pressure micro-perfusion of implanted catheters [40]. Various antitumor drugs, including immunotoxins, are being studied [41,42]. Another approach is transporting chemotherapy drugs through CED nanoparticles [43,44]. Although this study has proved effective *in vivo*, more work needs to be done to study the long-term effects of nanoparticle accumulation in the brain. CED can be used to treat postoperative tumors, tumors, or non-operative tumors. The main disadvantages of CED are operational risk and backflow limiting drug distribution [45,46].

4. Intranasal administration

Compared with intravenous administration and direct lateral ventricle injection, it is a non-invasive brain drug administration route. In addition, due to the unique structure of the nasal mucosa, there is a large specific surface area, a large contact area with drugs and preparations, and vascular distribution is very dense so that drugs can be rapidly absorbed. Drugs introduced *via* the nasal route do not undergo primary metabolism in the liver, so small doses of the drug can be effectively treated while also reducing side effects [47-49]. Nasal administration of drugs may also produce systemic effects. Drugs are absorbed from the nasal respiratory area through the olfactory nasal epithelium. In addition, the nasal route of administration is relatively easy, and the patient can operate their own [50].

In the olfactory area of the nose, the drug moves to the brain through an extracellular and intracellular transport mechanism through a particular pathway and moves along the neural channels of olfactory cells. Finally, the drug reaches the spine and enters the posterior region and cerebrospinal fluid. Once the drug reaches the spinal cord, it will be mixed with the spinal fluid and distributed to the brain and the entire central nervous system (CNS) [51].

Despite the lack of understanding of the exact mechanisms behind nasal drug delivery. However, there is much evidence that there is a nerve relation between the nasal mucosa and the brain, it was shown in Fig. 1 [50]. The first channel is the olfactory channel and consists of a natural layer of the olfactory epithelium and olfactory bulb. Neurons in the olfactory epithelium ancestral cell and support cells. All these are closely connected. Nerve cells start from the back of the CNS to the epithelium of the nose. Basal cells and neurons alternately move in continuous motion, making nasal mucosa infiltrate. This enhanced the transport of drugs to the brain. The second channel is the trigeminal nerve channel which plays an important role in drug transportation. The trigeminal nerve is mainly the nasal cavity. The trigeminal nerve is the fifth nerve (V), and the maxillary nerve. The optic nerve and the maxillary nerve control the nasal mucosa and transmit the information necessary for the nasal cavity to the central nervous sys-

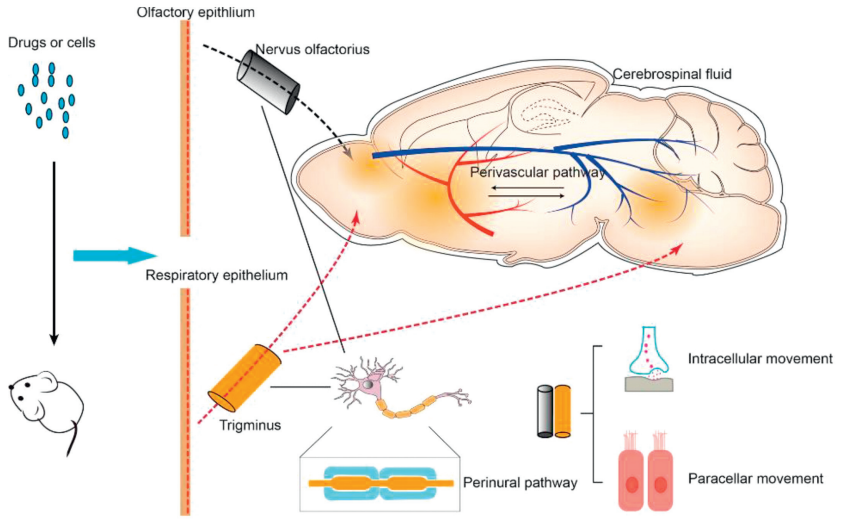

Fig. 1. Possible brain pathways for intranasal administration in rodents. Copied with permission [50]. Copyright 2021, Springer Nature Limited.

tem [52,53]. The drug delivery system delivers drugs to two brain branches, the nasal cavity. The trigeminal nerve enters the brain stem through the pons and reaches the whole brain through the spine. To promote the drug to enter the brain's tail and nostrils. Compared with the two methods, the olfactory pathway delivers drugs to the forebrain. The trigeminal nerve function also acts on the tail lobe of the brain as well as the frontal lobe. This makes it difficult to distinguish whether drugs are transported to coastal areas through smell or trigeminal nerve [54,55].

5. Nanocarriers for targeted transport

Over the past few decades, the field of drug and gene delivery has increasingly focused on nanomaterials, apart from widely used drugs like paclitaxel and doxorubicin (DOX), we have also compiled a list of currently approved drugs or drugs in clinical trials, as shown in Table S1 (Supporting information). Such materials, including inorganic nanoparticles, polymer nanoparticles, micelles, liposomes, and nanofibers, are extensively used in drug transport due to their high drug-loading capacity, controllable release, excellent active and passive targeting, stability, biodegradability, biocompatibility, and low toxicity. Nanomaterials are also specifically utilized in drug delivery systems targeting brain diseases, enabling effective transportation of drugs to the central nervous system [22,56]. Fig. 2 summarizes some nanocarriers for the treatment of gliomas [57].

5.1. Polymer nanocarriers

Over the past few decades, polymer nanoparticles have been widely synthesized and applied in drug delivery due to their stability, ease of preparation, and ability to bind with other small molecules or drugs, Fig. S2 (Supporting information) shows the current biomedical polymer materials [58].

5.1.1. Natural polymer nanocarriers

Natural polymer nanoparticles have been widely used in drug delivery due to their non-toxicity, biocompatibility, and controllable drug release [59,60]. Chitosan polymer has the advantages of low toxicity, invasiveness, biocompatibility, and adhesion. At present, chitosan nanoparticles have been widely used in the treatment of brain diseases, including glioma, Parkinson's disease, and Alzheimer's disease [61-63]. Chitosan is a cationic linear polysaccharide obtained by the reaction of partial *n*-deacetylation of chitin in a hot alkaline medium. The characteristics of polycationic amino groups enable chitosan nanoparticles to establish ion interactions with anions on the cell surface or mucosa, increasing the residence time at the target site [64]. Alginate is an anionic biopolymer, which is widely used in tissue engineering, drug delivery, wound healing, and other fields. Alginate is a non-branched linear polymer extracted from brown alga [65]. There are a large number of carboxyl and hydroxyl groups on the surface of alginate, which can be used to bind drugs, ligands, and other functional materials. In addition, these groups are also convenient for modification to further improve biocompatibility and targeted delivery [66,67]. In addition, Zhang *et al.* synthesized poly ferulic acid (PFA) using ferulic acid from natural ingredients and encapsulated DOX, demonstrating significant potential as a stable nano-carrier in the treatment of leukemia. They utilized a simple and convenient nano-precipitation method for aggregation, providing a new approach for the treatment of gliomas [68].

5.1.2. Synthesis of polymer nanocarriers

Due to the difficulty in controlling the composition, structure, and degradation behavior of natural biopolymers, as well as their generally short degradation periods, people's primary interest has shifted to the research direction of synthetic polymer materials [69]. Compared to naturally biodegradable polymers, artificially synthesized biopolymers exhibit better biocompatibility, and the mechanical properties of synthetic polymers can be easily modified through chemical and physical methods. By controlling factors such as monomer ratio and temperature during the synthesis process, different products with distinct physical properties can be obtained [70].

(1) Poly(lactic acid glycolic acid)

Poly(lactic-*co*-glycolic acid) (PLGA) is an environmentally friendly produced by fermenting lactic acid and glycolic acid from sugar. PLGA's degradation products are lactic acid and glycolic acid, both natural compounds that can be metabolized and eliminated by the human body [71,72]. However, due to problems such as hydrophilicity and electricity, it can be connected to ligands that target receptors on the surface of BBB endothelial cells (such as transferrin (Tf), insulin, and lipoprotein receptors) to provide targeted brain delivery and improve brain uptake of nanoparticles [73,74]. Ramalho uses PLGA to encapsulate anticancer drugs bortezomib (BTZ) and temozolomide (TMZ), and further couple Tf to achieve targeted drug delivery. *In vitro* cell experiments, interesting phenomena have emerged. Compared with Tf-conjugated

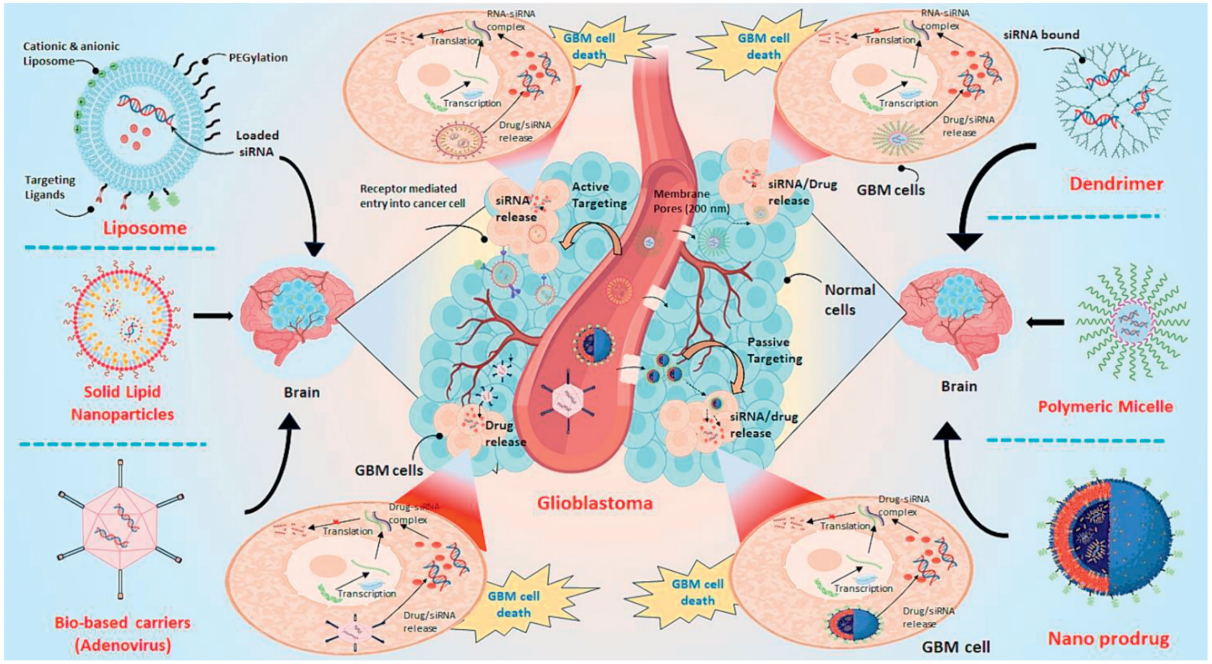

Fig. 2. Nanocarriers for drug delivery in the treatment of brain gliomas. Copied with permission [57]. Copyright 2024, Elsevier.

nanoparticles, Tf-unconjugated nanoparticles more effectively inhibit tumor cell growth, possibly because the release rate is faster and can enhance intracellular drug accumulation [75]. Kaya *et al.* constructed an *in vitro* model of BBB and used PLGA to encapsulate etanercept and modify the NH_2-GGGGSGCLRVGGRrRrRrRr-COOH (DAS) peptide. Because of the affinity of the DAS peptide to nicotinic acetylcholine receptors (nAChR), it helps to transport the loaded nanoparticles to BBB through by receptor-mediated transcytosis (RMT). In the new *in vitro* BBB model of human immortalized cells constructed by Kaya, PLGA nanoparticles have become an ideal carrier for transporting large hydrophilic molecules across BBB [76].

(2) Polyamidoamine dendrimers (PAMAM)

PAMAM are branched nano molecules. Many dendrimers are synthesized and have potential applications [77-79]. PAMAM have a large cavity that can be loaded with a variety of chemotherapeutic drugs and can therefore be used to treat various cancers and other organ diseases [80,81]. Many researchers prefer to attach drug covalent bonds to the PAMAM dendrimer surface by hydrolyzing amide or ester bonds rather than cavity loading. One of the reasons may be that the release rate of capsule drugs is faster than that of covalent. It also uses a combination of cavity loading and surface modification. Table S2 (Supporting information) summarizes the use of some dendritic polymers in brain tumors. Song *et al.* developed a new type of PAMAM multifunctional nanocarrier, showing good resistance to protein adsorption, penetration of BBB, and targeting glioma cells *in vitro*. After loading copper ions, it can also be used for MR imaging of *in situ* glioma after intravenous injection [82]. Wiwatchaitawee *et al.* incorporated two different positively charged surface modifiers PAMAM and polyethyleneimine (PEI) into different nanoparticles. *In vitro* and *in vivo* experiments showed that the surface of nanoparticles modified with PAMAM significantly improved their ability to accumulate in healthy mice [83].

In addition, we also discussed the application prospects of several other synthetic high molecular weight polymers, including polylactic acid (PCL), polyethylene glycol (PEG), polycaprolactone (PCL), polydopamine (PDA), and polyamino acids. Specific information is provided in Supporting information.

5.1.3. Polymer blend nanoparticles

It can be seen from the above that various types of polymers have their advantages as carriers, but there are also shortcomings [84,85]. For example, the drug loading of chitosan nanoparticles is low, and clinical experiments on PAMAM are almost not carried out. With the progress of research, more and more blended polymers are used for drug delivery [86].

Tian *et al.* prepared PEG/PEI-encapsulated DOX-SPIONs superparamagnetic nanoparticles. Experiments show that the drug loading is significantly improved and the targeting is stronger. *In vitro* animal experiments showed that the survival time of rats treated with PEG/PEI nanoparticles was longer and the number and size of tumors were significantly reduced [87]. In addition, Das *et al.* used PLGA as the core, coated with a layer of PEG, and loaded with carmustine (BCNU). Experiments showed that while the drug loading increased, 55% of the drug was still in the tissue after 15 days [88]. In addition, PEGylated PAMAM nanocarriers are also superior to PAMAM in half-life, bioavailability, and cycle time [89].

5.2. Liposomes

Liposomes are tiny vesicles composed of phospholipid bilayers, with sizes ranging from 20 nm to 200 nm. They possess excellent biocompatibility and biodegradability, making them suitable for carrying drugs, genes, or other therapeutic substances. Due to the superior performance of liposomes, they have been applied in the treatment of chronic wounds in diabetic patients [90]. In the treatment of gliomas, liposomes can traverse the BBB to precisely deliver drugs to the tumor site. Due to their nanoscale size and unique surface properties, liposomes can enhance the bioavailability and therapeutic efficacy of drugs in the body. Additionally, liposomes can provide a protective enclosure, reducing drug side effects and prolonging circulation time in the body. Another significant advantage is the tunability of liposomes. By adjusting their composition, size, and surface properties, targeted and controlled drug release can be achieved, thereby improving the precision and efficiency of treatment [91,92].

Furthermore, liposomes can be actively directed towards particular cells by altering their surface with ligands that adhere to

receptors on these cells, a process referred to as active targeting. Active targeting liposomes are capable of identifying and binding to target cells *via* interactions between ligands and receptors. Upon internalization (endocytosis), these liposomes discharge their cargo within the cells, leading to diminished off-target effects in contrast to passive targeting mechanisms [93].

Cen and others developed a liposomal nanocarrier modified with SS31 peptide for the targeted delivery of the anticancer drug DOX to gliomas. The incorporation of the SS31 peptide significantly increased the transport across the BBB and uptake by brain microvascular endothelial cells and glioma cells of the liposomal nanoparticles. Both *in vitro* and *in vivo* experiments showed that the liposomes could effectively penetrate the BBB and target glioma cells, significantly inhibiting glioma *in situ* in mice. Due to the encapsulation by the liposomes, the toxicity of DOX could be effectively reduced, enhancing its therapeutic effect [94]. To achieve efficient brain delivery of liposomes, Kato and others first discovered among eight BBB penetrating peptides that ApoEdp could accumulate more effectively in the brain, leading to the development of ApoEdp-modified PEGylated liposomes. *In vitro* experiments showed that these liposomes could be observed to accumulate more significantly in the brain [95].

5.3. Nano lipid carriers

The lipid-based nanoparticle system with a solid matrix mainly comes from the oil in water lotion that replaces oil or liquid lipid with solid lipid to make it carry solid in body temperature. Lipid nanoparticles can overcome the limitations of lipophilic drug encapsulation due to their unique advantages. Solid lipid nanoparticles (SLN) are the first generation of lipid nanoparticles developed in the early 1990s for solid lipids [96]. Nano lipid carriers (NLC) are the second generation of fat nanoparticles, consisting of one or more mixtures of solid and liquid fats. Compared with first-generation fat nanoparticles such as SLN, NLC has significant advantages. Highly purified solid lipids form perfect crystals, which limits the loading capacity of SLN, and active substances may also be discharged during storage. On the other hand, geological mixtures with different structures tend to form amorphous clusters or distorted perfect crystal structures. This defect creates a gap in the control of active ingredients, thereby increasing the dosage. Meanwhile, this incomplete NLC matrix improves the stability of the nanocarrier system by preventing the release of encapsulated particles [97].

Farshbaf *et al.* designed a targeted delivery system based on two proteolytically stable D-peptide D8 and RI-VAP (dual NLCs) modified NLCs. D8 has a high affinity for nAChRs. It can effectively penetrate the BBB. RI-VAP is a specific ligand on the surface of GRP78 cells and a specific marker for angiogenesis and cancer cell surface, which can avoid BBTB with characteristics of high glioma recurrence, it has excellent glioma homing characteristics and can bypass the BBB. Both *in vivo* and *in vitro* imaging of animals have confirmed the excellent targeting ability of dual NLCs for gliomas [98].

5.4. Micelle

Micelles consist of an amphiphilic block copolymer that aggregates stable spherical nanostructures having hydrophobic and hydrophilic surfaces in an aqueous solution and mixing efficiency and controlled release rate of chemotherapeutic drugs. The unique core-shell structure and particle size of 10–100 nm are effective for protecting micellar particles from micelle removal. The hydrophobic core of the adhesive can package hydrophobic or insoluble drugs to increase the stability of drugs [99]. The hydrophilic part of the micelles helps to reduce the phagocytosis of the endothelial system. Therefore, the micelle drug delivery system is also used in studying brain drug delivery. Polymer micelle drug delivery systems can effectively improve the delivery efficiency of hydrophobic or insoluble drugs *in vivo*, which is crucial for selecting polymer micelle materials [100,101].

Polyamino acid derivatives or polycool chain segments with good biocompatibility are commonly used as the hydrophobic core of micelles. Among them, PLA, PCL, and polyglycolic acid (PGA) are the Food and Drug Administration (FDA)-certified polyesters suitable for biomedical applications in the human body due to their biocompatibility and biodegradability. The hydrophilic shell of micelles separates the hydrophobic segments of hydrophobic drugs from the external aqueous phase, ensuring the stability of micelles and minimizing protein adsorption onto micelles and cell adhesion, thereby affecting the pharmacokinetic parameters of drugs. PEG, polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), PEI, chitosan, and others are common hydrophilic polymers that can serve as the hydrophilic shell of micelles [102,103].

Lu *et al.* developed a polymer micelle for chemotherapy and photodynamic therapy, consisting initially of a polymer composed of camptothecin (CPT) and PEG, further modified with internalizing arginine-glycine-aspartic acid (iRGD) peptide. This polymer can self-assemble into polymer micelles with a diameter of around 100 nm, then loaded with the photosensitizer IR780. The micelles exhibit good stability and controlled drug release. Both *in vitro* and *in vivo* studies have shown that this micelle system can effectively cross the BBB to reach glioma sites, significantly enhancing the anti-tumor effect upon laser irradiation [101]. Li *et al.* used a hydrophobic O^6-benzyl guanine (BG) analog as the hydrophobic core to encapsulate the anti-tumor drug carmustine (BCNU). Hyaluronic acid (HA) was chosen as the hydrophilic shell to prolong the circulation time of the nanodrug in the blood. Amino groups on BG were covalently linked to carboxyl groups on HA, allowing self-assembly into nano micelles in an aqueous solution. Tween 80 was then coated on the hydrophilic shell to enhance BBB penetration ability. Through an *in vitro* BBB model, these micelles demonstrated higher BBB permeability and specific targeting of brain glioma cells [104].

5.5. Gold nanoparticles

Because of their unique optical and thermal properties and easy surface functionalization, gold nanoparticles (AuNPs) enable targeted gene/protein/drug delivery and various biological analysis, AuNPs have made some progress in imaging in the near-infrared II regions [105]. They have received extensive attention in bionanotechnology and related fields. It has adjustable size, large specific surface area and volume ratio, easy to carry out various surface modifications, and high biocompatibility, making an appropriate vector for transporting drugs and brain tumors *via* BBB. The size of gold nanoparticles plays a crucial role in their penetration into brain microvessels. Drugs encapsulated inside gold nanoparticles have various advantages. Due to biocompatibility and drug-binding ability, it is easy to denature. Gold nanoparticles play an important role in the treatment of intracellular infection [106].

Due to the therapeutic effects of resveratrol (Rsv) on glioblastoma, Liu *et al.* utilized AuNPs to couple with resveratrol, obtaining Rsv-AuNPs. *In vitro* experiments revealed that after treatment with gold nanoparticles, the proliferation, migration, and invasion of U87 cells were significantly inhibited. Next, Rsv-AuNPs will undergo further animal and clinical studies for application in the clinical treatment of glioblastoma [107].

This nanoparticle is not only used as a carrier but also as a probe for observing tumors and is widely used in diagnostic imaging systems. Currently, magnetic resonance imaging (MRI), computed tomography (CT) scanning, positron emission tomogra-

phy (PET), and other imaging systems, including ultrasound and surface-enhanced Raman spectroscopy (SERS), are being used. For example, MRI generates 1 mm high-resolution soft tissue images under magnetic field intensity. This technology provides detailed anatomical information about structure and physiology, enabling diagnosis, prognosis, and monitoring of responses to precision treatment [108,109]. When using *in vivo* brain MRI, there may be resistance to exogenous contrast agents, so the best choice of contrast agent should be used. The optical performance mainly comes from local surface plasmon resonance (LSPR). Absorb light of various colors based on the size, shape, local refractive index, and aggregation state of nanoparticles. Photothermal therapy (PTT) can increase the aspect ratio of gold nanorods and absorb them from the visible light region to the infrared region to achieve higher oscillator strength. Multiple studies have developed gold nanoparticles targeting brain cancer molecules, as well as a BBB for treatment. Especially, the target of gold nanoparticles is very important for the degradation of PTT in brain tumors [110]. When it reaches the brain tumor area, the laser from the infrared region penetrates the skin and heats the tumor area. It mainly kills cancer while protecting healthy tissues. Ohta *et al*. investigated the optimal size for nanoparticles to enter the brain using ultrasound contrast agents and BBB opening techniques. The results showed that with the aid of ultrasound contrast agents, the permeability of 3 nm and 15 nm gold nanoparticles significantly increased in an *in vitro* BBB model, with smaller diameter particles exhibiting higher permeability. However, in transcranial ultrasound exposure experiments in mice, smaller particles did not necessarily penetrate the brain better. Among them, 15 nm gold nanoparticles had the highest delivery efficiency, accumulating the most at tumor sites [111].

5.6. Mesoporous silica nanoparticles (MSN)

MSN have shown good application prospects in cancer treatment due to their unique advantages, such as high loading, effective cellular uptake, and low cytotoxicity. Furthermore, their surfaces are easily modified and provide new functions to MSNs, such as targeted delivery and controlled release of drugs. Therefore, the multi-size of silica nanoparticles is designed to deliver chemotherapy drugs, genes, and proteins to treat cancer [112-114]. The properties of MSNs are determined by the synthesis method and reaction conditions; hence, particle size, shape, and pore size can be tailored for each specific application. Primarily, different types of surfactants (non-ionic or cationic) and their concentrations can dictate pore size and volume. Additionally, the silica precursor and reaction conditions (such as temperature, pH, reaction time, and catalyst concentration) can also control the morphology of the pores as well as their particle size and shape [115].

Zhang *et al*. successfully loaded temozolomide (TMZ) and chloroquine (CQ) into MSN, improved drug delivery efficiency, and enhanced anti-tumor effects by coating with PDA and connecting with arginine-glycine-aspartic (RGD), resulting in the preparation of TMZ/CQ@MSN-RGD. The study found that RGD-MSNs had higher accumulation in cell and tumor models [116]. Liu *et al*. used manganese-doped mesoporous silica nanoparticles to load paclitaxel through adsorption, which could bypass the BBB and accumulate in tumors. Additionally, the surface properties of the nanoparticles were modified to be electrically neutral and hydrophilic, to improve the absorption rate of orally administered drugs. This research provides new ideas and methods for the development of orally administered drugs and tumor treatment [117].

In addition, covalent organic frameworks (COFs) are emerging porous organic materials characterized by large surface area, high crystallinity, low density, and excellent stability. Additionally, COFs exhibit outstanding biocompatibility, demonstrating significant potential in biomedical applications. Wei *et al*. have utilized COFs to target glioma cells, demonstrating tremendous potential *in vitro* experiments [118].

5.7. Nanogel

Nanogels are a type of gel material with a microscopic structure, where the gel network is made up of nanoparticles. These particles are typically composed of polymers, inorganic materials, or biomaterials. Nanogels are notable for their highly controllable pore structure, large surface area, and adjustable physicochemical properties. They have a wide range of potential applications in drug delivery, biosensing, tissue engineering, and environmental protection [119].

Nanogels also hold potential applications in the treatment of glioma. One common use is as a drug delivery vehicle to transport anticancer drugs to the site of the glioma. This nanogel carrier can improve the stability of drugs and allow precise control of the release rate and location of the drugs, thereby reducing the damage to healthy tissues and enhancing the treatment effect. Additionally, nanogels can be designed to be targeted, capable of crossing the BBB and precisely targeting glioma cells [120]. This targeted nanogel can be achieved through surface functionalization or specific design, thereby increasing the local concentration of the drug and reducing adverse effects on surrounding healthy tissues. Nanogels can also be designed for image-guided therapy. For instance, by injecting fluorescently labeled nanogels into the glioma site, they can help surgeons accurately locate the tumor during surgery and guide tumor resection, improving the precision and safety of the surgery [121,122].

Li *et al*. developed a DOX-loaded nanogel, DOX@PNGs, which is coated with a platelet membrane to achieve redox/pH dual-responsive targeted delivery. The $CD6_2P$ expressed on the platelet membrane (PLTM) surface enables the targeting of tumors, while another component, CD_{47}, prevents the nanogel from being cleared by the innate immune system. According to *in vivo* tests, DOX@PNGs demonstrated excellent targeting effects and prolonged *in vivo* retention time [123].

5.8. Nanoemulsion

Nanoemulsion is a stable liquid dispersion system containing tiny oil droplets or water droplets, typically in the nanometer range. These tiny droplets are enveloped by surfactants or other stabilizers to prevent them from coalescing or merging. In terms of drug delivery, nanoemulsion can enhance the solubility, bioavailability, and stability of drugs while reducing their dosage and side effects. Hence, it holds potential therapeutic value in the treatment of glioblastoma [124,125]. Nanoemulsion can serve as a carrier to deliver anticancer drugs to the site of glioblastoma. Due to its nanoscale droplet size and high surface activity, nanoemulsion can increase the bioavailability of drugs and facilitate drug penetration through the BBB to reach glioblastoma cells. Additionally, some anticancer drugs may have limited solubility in water due to their chemical properties, which nanoemulsion can improve, thereby enhancing drug stability and bioavailability. Nanoemulsion also ensures that drugs are released to the site of glioblastoma in a more sustained and uniform manner, thereby enhancing therapeutic efficacy and prolonging the duration of drug action. Because it is more similar to the characteristics of liquid, nanoemulsion is more often used in the nasal administration pathway, rather than oral or injection [126].

5.9. Exosomes

Exosomes are the nanoscale cysts secreted from cells and can be separated from the conditioned cell medium or body fluid.

When released from the cell, the outer secretion is fused with the membrane of another cell to transfer a secreted molecule from one cell to another. This property allows drug delivery to cells *in vitro* [127]. The mechanism of the intake of the exocrine is the protein action mediated by the grid protein. It can be fused to the limiting membrane of the nucleus, and the outer secretion can pass through the complete BBB. Exosomes are secreted by living cells and are natural delivery carriers. Compared with existing formulations, they have it has the advantages of non-toxicity, minimal immune response, and good stability of the circulatory system. Animal experiments have shown that the binding, transportation, and delivery of extracellular vesicles originating from the blood are induced by the dynamic internal circulation of the entire transporter receptor. During this process, transgender individuals are internalized by binding to receptors on the cell surface. Next, the transferrin receptor (TfR) releases products (exocrine and Tf), and then the receptor returns to the cell surface to begin the next cycle [128,129]

Wang *et al*. utilized the favorable BBB permeability of BV2 murine microglial cell-derived exosomes to deliver DOX for the treatment of glioblastoma. However, due to the limited efficiency of exosomes in crossing the BBB [130], they designed and synthesized three functional oligopeptides incorporated into the exosomes to enhance targeting. These peptides, containing disulfide bonds on cysteine residues, facilitated better encapsulation of DOX and, upon encountering the high concentration of glutathione (GSH) within the tumor, underwent disulfide bond cleavage, releasing DOX from the exosomes. Both *in vitro* and *in vivo* experiments demonstrated the excellent brain-targeting ability and antiglioblastoma activity of this exosome delivery system, with minimal observed biotoxicity [131].

5.10. Quantum dots (QDs)

QDs are an emerging technology with potential application prospects discovered by Ale in the research of nanolithography systems in 1980. These QDs are artificial nanosemiconductor materials with particle size and three-dimensional corona limitation. It has outstanding fluorescence properties, high optical stability, excitation capability, size-dependent emission, and electrochemical properties. It can be used for drug delivery, targeting, diagnosis, bioimaging, optical radiotherapy (PDT), and disease sensing. The application of QDs in biomedicine and medicine shows that it is of great significance in the pharmacokinetic study of the human system [132]. Complete information about QD pharmacokinetics still needs to be researched. QDs are widely administered through the gastrointestinal tract and inhalation routes and are also suitable for targeted therapy. QDs are absorbed at the cellular level through receptor-mediated endocytosis and may accumulate in targeted tissues. The distribution of QDs in the blood is performed by intravenous injection, and metabolism is essential because it contains toxic substances at the structure's core. The QD shell and any coating can generate decomposition products through photolysis and oxidative metabolism to prevent the release of core materials. The QDs are discharged by interacting with plasma proteins [133].

QDs mainly include the following types: Semiconductor QDs, composed of semiconductor materials such as cadmium sulfide (CdS), zinc sulfide (ZnS), lead selenide (PbSe); Metal QDs, consisting of metal atoms such as Au and Ag; Nanocrystal QDs, with core-shell structures typically composed of one semiconductor material as the core and another semiconductor material as the shell, such as CdSe/CdS, CdTe/CdS; Organic QDs, composed of organic molecules such as carbon dots, conjugated polymer nanoparticles; Magnetic QDs, introducing magnetic elements on the surface or structure of QDs to make them magnetic. Therefore, QDs can meet various needs for glioblastoma treatment such as drug delivery, bioimaging, and others [134,135].

Huang *et al*. designed neural stem cell (NSC) membrane-coated AgAuSe QDs, combined with rabies viral glycoprotein (RVG) peptide, to reduce the toxicity of AgAuSe QDs while enhancing their ability to cross the BBB and target neural cells. AgAuSe QDs can be used *in vivo* to monitor and assess the blood circulation, BBB crossing, and neural cell targeting process of nanomaterial formulations [136]. Lin *et al*. developed brain-targeted ZnO QDs nanocarriers capable of delivering therapeutic genes associated with Parkinson's disease across the BBB into the brain. It is believed that such QDs nanocarriers could also be applied in the treatment of glioblastoma in the future [137].

5.11. Polymersomes

Polymersomes are artificially synthesized nanostructures, resembling the shape and function of cell membranes. They are composed of polymer compounds, typically polymers such as PEI, PPA, or PLA. The structure of polymersomes can be utilized in various applications such as drug delivery, biosensing, and nanomedicine. Compared to traditional liposomes, they exhibit higher stability, stronger mechanical properties, and better chemical stability. Two-component copolymer organic solvent/water system or water medium [138]. Typical, two copolymers with a hydrophilicity of 25%–35% were polymerized into a polymer wrapped in an axial aqueous solution for drug packaging and delivery. Hydrophilicity, copolymer aggregation bilayer membrane can carry less hydrophobic drugs, and the polymer structure is similar to a liposome. The main difference is that the two outer layers consist of two copolymers with a molecular weight of 100 kDa [139]. Geological building blocks are natural phospholipids with a molecular weight of less than 1 kDa. Polymer membranes are thicker than liposomal membranes for high molecular weight building blocks, providing a more durable physical barrier to protect the blocked drug. When used for drug administration, the stronger the polymer membrane, the less leakage the membrane has, improving cycle times and preventing uncontrolled drug release. The polymer was functionalized into a nanocarrier with specific receptors for passing through the BBB [140].

6. Strategies for enhancing carrier penetration through the BBB

From the above content, it is easy to see that almost all nanocarrier systems include therapeutic drugs for glioblastoma, nano-carriers carrying drugs, targeting glioblastoma, and molecules to help bypass the BBB. Therefore, in this section, we will summarize strategies to target glioblastoma by bypassing the BBB, mainly introducing two strategies: receptor-mediated [141], adsorption-mediated [142], and carrier-mediated transport [143].

6.1. Receptor-mediated BBB crossing

Receptor-mediated transport (RMT) is a mechanism by which cells selectively internalize molecules from their external environment *via* interactions with specific receptors on the cell membrane. In this process, ligands or target molecules bind to receptors on the cell surface, triggering the formation of coated pits and subsequent endocytosis. Once internalized, the cargo can be transported across the cell and released into intracellular compartments or undergo recycling back to the cell surface. Because many molecules can be used as receptors, in this part, we will introduce the target of the receptor [144].

6.1.1. Transferrin receptor (TfR)

TfR has important applications in the treatment of glioblastoma. By utilizing the overexpression of TfR on the surface of glioblastoma cells, targeted drug delivery systems can be designed, coupling drugs with Tf to specifically deliver the drugs into glioblastoma cells. This approach can increase the local concentration of the drug within the tumor tissue while reducing the impact on surrounding healthy tissues, thereby enhancing the therapeutic efficacy and minimizing side effects [145].

Tf is a serum protein responsible for transporting iron ions in the body, and it interacts with TfR on the cell surface to facilitate iron uptake. Li *et al*. coupled Tf with carbon QDs, enabling the carbon QDs to bypass the BBB and deliver it to the central nervous system. In a zebrafish model, it was found that carbon QDs without Tf conjugation were unable to penetrate the BBB, while the conjugated carriers passed through the BBB *via* transferrin receptor-mediated delivery [146].

Another widely used TfR-targeting molecule is the OX26 antibody. OX26 antibody is a monoclonal antibody targeting the transferrin receptor, thus it can be employed to design targeted delivery systems, delivering drugs or therapeutic payloads precisely to glioblastoma cells. Similar to utilizing transferrin receptors, this method involves the binding of drugs or therapeutic payloads with OX26 antibody to achieve targeted delivery, enhancing therapeutic efficacy while reducing side effects. Ashrafzadeh *et al*. designed a cisplatin-loaded polyethylene glycolylated liposome, utilizing the OX26 antibody targeting transferrin receptors to target *in vitro* expression of rat glioma C6 cells. They observed a significant increase in cytotoxicity after 72 h, but subsequent *in vivo* and clinical trials are still ongoing [147]. Additionally, RI7217 is a monoclonal antibody targeting TfR [148]. This antibody has been extensively researched and has shown potential in drug delivery and therapy. Dasgupta *et al*. used RI7217-modified non-spherical polyacrylonitrile-butadiene-styrene microbubbles for BBB ultrasound permeation. Both *in vivo* and *in vitro* experiments found that compared to spherical microbubbles, actively targeted non-spherical microbubbles had a much higher binding efficiency to endothelial cells. When combined with transcranial-focused ultrasound, they significantly enhanced BBB opening and the accumulation of model drugs in the brain [149].

In addition to using endogenous Tf or antibodies, some researchers have also developed short peptides that bind to the transferrin receptor. For example, peptides such as T7 (HAIYPRH) and T12 (THRPPMWSPVWP), were discovered by Lee *et al*., have been widely utilized [150]. Compared to Tf and antibodies, peptides are smaller, making them easier to penetrate the BBB and reach brain tissue more rapidly. Moreover, peptide synthesis and modification are typically simpler and more economical than antibodies, reducing preparation costs and accelerating drug development. Additionally, due to their relatively small size and simple structure, peptides generally exhibit lower immunogenicity compared to antibodies, reducing the risk of potential immune reactions and allergic responses. However, unfortunately, there are few studies on other short peptides [151].

6.1.2. Lactoferrin receptor (LfR)

LfR is a membrane protein typically found on the endothelial cells of the BBB. It serves as one of the key pathways for regulating the transport of iron into brain tissue *via* transferrin. In the context of gliomas, the lactoferrin receptor is often utilized as a target for drug delivery. By designing ligands with high affinity, such as peptides or antibodies, drugs can be targeted to the lactoferrin receptor, facilitating more efficient passage across the BBB and entry into glioma cells, thereby enhancing therapeutic efficacy [152,153].

The targeted delivery system of Lf-LfR helps reduce damage to normal brain tissue by increasing the concentration of drugs in tumor cells, leading to better therapeutic outcomes. Lf itself possesses the ability to transport across the BBB both *in vitro* and *in vivo*. Additionally, Lf exhibits anti-inflammatory, antioxidant, and anti-tumor effects, potentially providing additional benefits in the treatment of gliomas. Chen *et al*. utilized Lf-modified PCL liposomes loaded with DOX, demonstrating significantly higher absorption efficiency of C6 cells for Lf-PCL liposomes compared to PCL liposomes *in vitro* [154]. Furthermore, Li *et al*. employed Lf-modified PLGA-PEG nanoparticles to deliver the anti-glioma drug Shikonin (SHK), with *in vivo* studies showing higher brain concentrations of SHK, indicating a significant impact of Lf-coated NPs on brain targeting [155].

6.1.3. Folate receptor (FR)

FR is a glycoprotein receptor expressed on the surface of cells, primarily involved in the cellular uptake of folate (vitamin B9, FA) and related compounds. Folate is an essential nutrient for the human body, playing a crucial role in the synthesis of DNA, RNA, and proteins, and is vital for cell division and growth. There are several subtypes of FRs, including FRα, FRβ, and FRγ, each with different expression patterns and functions in various tissues [156]. Particularly, FRα is typically expressed at low levels in healthy tissues but significantly upregulated in certain tumors, such as brain and ovarian tumors. This characteristic makes FRα an attractive target in cancer therapy. By targeting the FR, drug concentrations in tumor tissues can be increased, reducing adverse effects on normal tissues and enhancing therapeutic efficacy [157]. Liu *et al*. utilized the overexpression of FRs in glioma cells, combining FA-modified exosome carriers with TMZ, achieving active targeting of glioma cells. Consequently, this approach improved the distribution of TMZ carrier exosomes in tumor tissues, thereby achieving targeted therapy. Through both *in vitro* cell experiments and *in vivo* glioma models, they demonstrated the impact of this nanomedicine system on glioma cells [158].

6.1.4. Insulin receptor

The insulin receptor is a receptor protein expressed on the cell membrane, primarily responsible for recognizing and binding insulin. Within the cell, the insulin receptor regulates various biological processes, such as glucose metabolism, cell growth, and proliferation, by activating internal signal transduction pathways. Some studies have utilized the overexpression of insulin receptors on tumor cells to design targeted treatment strategies, including using the insulin receptor as a channel for targeted drug delivery. Ulbrich *et al*. monoclonal antibody and insulin receptor antibody (29B4) were combined with human serum albumin (HSA) nanoparticles containing loperamide. In the ICR (CD-1) mice tail-flick test, HSA nanoparticles showed a significant anti-injury effect, indicating that coupling with HSA nanoparticles may help transport chloroaniline to the BBB [159].

6.1.5. Nicotinic acetylcholine receptor (nAChR)

nAChRs are a class of neurotransmitter receptors that primarily respond to the neurotransmitter acetylcholine and nicotine. In the treatment of brain gliomas, particularly in the glioblastoma research on nAChRs is relatively new. Some studies suggest that nAChRs may play a role in the development and progression of brain gliomas. For example, the expression of specific nAChR subtypes in glioma cells may be associated with tumor cell proliferation, migration, and anti-apoptotic (anti-death) mechanisms [160,161]. This implies that nAChRs could serve as potential therapeutic targets. RVG29 peptide refers to a specific peptide derived from the rabies virus glycoprotein. It is widely known for its ability to cross the BBB, making it a useful tool for delivering drugs or other therapeutic agents directly to the brain. This characteristic has sparked interest in its potential applications in treating various

neurological diseases and conditions by enabling more effective delivery of treatments to the central nervous system. RVG29 peptide selectively binds to the nAChR, which facilitates its transport across the BBB. This property has led to its investigation in targeted drug delivery systems, especially for treating brain tumors, neurodegenerative diseases, and other brain-related disorders. Ji *et al*. utilized RVG29-modified CD70 CAR-T cells (70R CAR-T cells), which can be effectively delivered to the brain *via* peripheral blood circulation, extending their circulation time. RVG29-modified CAR-T cells can better penetrate the BBB and remain in the bloodstream for an extended period, maximally enhancing their tumor-killing efficacy compared to control CAR-T cells [162].

6.1.6. The low-density lipoprotein receptor (LDLR)

The LDLR is a cell surface receptor primarily involved in the absorption and metabolism of LDL. In the study of gliomas (a common type of malignant brain tumor), LDLR has also shown potential application value. Research has found that many glioma cells exhibit overexpression of LDLR, which may be related to the tumor cells' increased uptake of LDL to meet their high metabolic demands [163]. Additionally, the expression level of LDLR could serve as a biomarker for gliomas, aiding in the diagnosis and prognosis assessment to determine the aggressiveness of the tumor and the response to treatment. Ye and others used apoptosis-inducing peptide KLA and targeting peptide LDL to functionalize drug-loaded extracellular vesicles. The modified LDL extracellular vesicles can promote membrane receptor-mediated internalization both *in vitro* and *in vivo*, enhancing the transport to the U87 glioma nanodelivery system. This represents a highly promising delivery system [164].

6.2. Absorptive-mediated transport (AMT)

AMT refers to a mechanism by which substances are absorbed into cells across biological membranes through interactions with specific receptors or transporters. This process involves the active uptake of molecules into cells, often through endocytosis or transcytosis, facilitated by receptors or transporters present on the cell membrane. AMT plays a crucial role in the absorption of nutrients, drugs, and other molecules in various biological systems, including the gastrointestinal tract and the BBB [165].

6.2.1. Cell-penetrating peptides (CPPs)

CPPs are a class of short peptides that can cross the BBB, intestinal wall, retina, neurons, and other biological barriers. CPPs can carry small molecule drugs into cells through endocytosis and direct penetration mechanisms to exert their efficacy. CPPs have the advantages of good biocompatibility, low toxicity, and degradability. In the past decade, CPPs have been widely used for tumor delivery in nano-drug carriers. The grafting or conjugation of CPPs into liposomes can promote the drug molecules loaded in liposomes to cross BBB [166-168]. One of the most studied cell-penetrating peptides currently is the TAT peptide (trans-activator of transcription peptide). This is a peptide produced by the HIV-1 virus and has been widely used to facilitate the intracellular delivery of drugs and biomolecules. TAT peptide primarily enters cells by binding to receptors on the cell membrane, such as glycoproteins, thereby achieving targeted drug delivery. In addition to the TAT peptides, other extensively studied cell-penetrating peptides include Penetratin and Arginine-rich peptides, such as R8. These peptides are also widely used in drug delivery. Shadmani *et al.* prepared around 50 nm MSN and utilized TAT peptide conjugated to MSN as a targeting ligand to deliver methotrexate (MTX) across the BBB to the brain. *In vitro* experiments demonstrated that compared to free MTX, the uptake rate of this nanocarrier system by brain tissue was increased by 31.13 times. The apoptosis rate induced in U87 cells was nine times higher than that of free MTX [169]. In addition, the CPPs and their sequences applied to glioma are listed in Table S3 (Supporting information).

6.2.2. Cationic proteins

Cationic proteins typically refer to proteins carrying positive charges, playing various crucial physiological and immunological roles within organisms. In the treatment of glioblastoma, some studies suggest that cationic proteins can serve as carriers for therapeutic drugs, delivering drugs directly to tumor tissues by crossing the BBB, thus enhancing treatment efficacy. These cationic proteins usually form complexes with drugs or other therapeutic molecules, leveraging their cationic properties to interact with negatively charged cell membranes for targeted delivery. Additionally, cationic proteins may also have direct anti-tumor effects, such as promoting tumor cell apoptosis or inhibiting proliferation [170,171].

6.2.3. Lectins

Lectins are a type of protein that can bind to specific sugar molecules, typically found in plants, animals, and microorganisms. They play various important physiological and immunological roles within organisms, including cell recognition, immune modulation, and pathogen clearance. Lectins can selectively bind to overexpressed glycosylated structures on the surface of tumor cells, thus enabling targeted tumor therapy. Additionally, lectins can be designed to improve the permeability of drugs across the BBB, facilitating the delivery of therapeutic drugs to tumor tissues [172].

6.3. Carrier-mediated transport (CMT)

CMT refers to the process whereby specific carrier proteins on the cell membrane facilitate the transfer of substances from the extracellular or intracellular environment across the cell membrane in a specialized manner. These carrier proteins are responsible for transporting specific substances, such as drugs, nutrients, or metabolites, across the cell membrane, typically through either active transport or passive diffusion [173,174]. Therefore, this transport pathway is only applicable to certain small molecular substances, such as glucose transporter 1 (GLUT1), large neutral amino acid carrier (LAT1), cationic amino acid carrier (CAT1), and others. 2-Deoxy-D-glucose (2-DG) is a glycolysis inhibitor that enters the cytoplasm through GLUT1 like glucose. Zhang *et al*. designed and prepared 2-DG-modified nanocapsules, which penetrate the BBB and target glioblastoma (GBM) by surface-loading 2-DG. Subsequently, these nanocapsules responsively release encapsulated drugs. They inhibit tumor angiogenesis and suppress aerobic glycolysis, and fatty acid oxidation, thereby disrupting tumor cell energy supply. These actions collectively inhibit GBM proliferation both *in vitro* and *in vivo* [175].

7. Conclusion and prospect

As a non-invasive method, nanomaterial-mediated BBB crossing has demonstrated safety, cost-effectiveness, and the advantage of applicability to almost all drugs. Clinical trials in neurology based on nanomaterials have been developed. For example, ultrasound experiments (NCT02253212, studies on convection-enhanced delivery used for treating glioblastoma, or surgical MRI composition imaging (NCT02022644). The BBB crossing ability of magnetic nanoparticles in a magnetic field (NC100150), along with some mentioned CPPs, has also progressed to the preclinical stage [176,177].

Although many nanomaterials have been approved by the FDA or entered clinical trials, most are still in the preclinical research

stage. The main reasons are the various issues associated with these materials, such as low drug loading efficiency, aggregation of hydrophobic nanoparticles in the bloodstream, susceptibility to clearance by the reticuloendothelial system, and low efficiency in crossing the BBB. Additionally, the amount of drug released after entering tumor cells is often lower than expected. Consequently, the research on various hybrid nanocarriers is gradually gaining attention. These carriers can possess characteristics of different carriers simultaneously and serve as high-quality carriers for targeting gliomas [178].

Additionally, there are few clinical applications for strategies targeting the crossing of the BBB using nanocarriers. For example, the clinical application of the most studied TAT peptide is still in its early stages [179]. Although its potential effects have been demonstrated in laboratory and animal models, its application in clinical therapy still faces several challenges. These challenges primarily include safety concerns; while the TAT peptide exhibits efficient cellular penetration, its binding to cell membranes may also lead to nonspecific cellular uptake, potentially causing toxic side effects. Secondly, immunogenicity is a concern: as an exogenous protein, the TAT peptide may be perceived as a foreign antigen, triggering immune responses. Lastly, delivery efficiency remains an issue; although the TAT peptide can facilitate the entry of drugs into cells, its delivery efficiency still needs further improvement, especially for certain cell and tissue types [180].

However, some new nanomaterial synthesis techniques have been developed, such as flash nanocomplexation [181]. This contributes to the discovery of more novel nanocarriers. Therefore, there is still great potential for nanocarrier drug delivery systems. Nasal administration combined with nanoparticles is also a research focus, offering broad prospects for curing gliomas in the future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Han Wu: Writing – review & editing, Writing – original draft, Conceptualization. **Yumei Wang:** Formal analysis. **Zekai Ren:** Data curation. **Hailin Cong:** Visualization. **Youqing Shen:** Visualization, Methodology. **Bing Yu:** Software, Resources, Project administration.

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Supplementary materials

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