

Nanoparticle Drug Delivery System for Glioma and Its Efficacy Improvement Strategies: A Comprehensive Review

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Jie Li¹⁻⁴
Jiaqian Zhao²⁻⁵
Tiantian Tan²⁻⁴
Mengmeng Liu²⁻⁴
Zhaowu Zeng²⁻⁴
Yiying Zeng²⁻⁴
Lele Zhang⁶
Chaomei Fu¹
Dajing Chen²⁻⁴
Tian Xie²⁻⁴

¹College of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, People's Republic of China;

²Holistic Integrative Pharmacy Institutes, Hangzhou Normal University, Hangzhou, Zhejiang, People's Republic of China; ³Key Laboratory of Elemene Class Anti-Cancer Chinese Medicine of Zhejiang Province, Hangzhou, Zhejiang, People's Republic of China; ⁴Engineering Laboratory of Development and Application of Traditional Chinese Medicine from Zhejiang Province, Hangzhou, Zhejiang, People's Republic of China; ⁵College of Pharmacy, Shanghai University of Traditional Chinese Medicine, Shanghai, People's Republic of China;

⁶School of Medicine, Chengdu University, Chengdu, People's Republic of China

Abstract: Gliomas are the most common tumor of the central nervous system. However, the presence of the brain barrier blocks the effective delivery of drugs and leads to the treatment failure of various drugs. The development of a nanoparticle drug delivery system (NDDS) can solve this problem. In this review, we summarized the brain barrier (including blood-brain barrier (BBB), blood-brain tumor barriers (BBTB), brain-cerebrospinal fluid barrier (BCB), and nose-to-brain barrier), NDDS of glioma (such as passive targeting systems, active targeting systems, and environmental responsive targeting systems), and NDDS efficacy improvement strategies and deficiencies. The research prospect of drug-targeted delivery systems for glioma is also discussed.

Keywords: glioma, brain barrier, nanoparticle drug delivery system, efficacy improvement strategies, deficiencies of NDDS

Introduction

Cancer remains the most threatening disease to human life and health. The cancer mortality rate remains alarming despite recent advances.¹ In 2016, there were 330,000 new cases and 227,000 deaths from central nervous system (CNS) tumors.² Glioma is the most common CNS tumor (40–50%) with an annual incidence of 3–8 cases/100,000 people.³ The World Health Organization (WHO) classifies glioma into four grades: WHO grade I and II tumors are low-grade gliomas including astrocytomas, oligodendrogliomas, dysembryoplastic neuroepithelial tumor, gangliogliomas, and mixed glioma. WHO III and IV are high-grade gliomas (malignant gliomas, MG) including anaplastic astrocytoma, oligodendroglioma, ependymoma, glioblastoma, and gliosarcoma. MG is more aggressive and worse prognosis. The 5-year survival rate in grade IV patients was less than 5%.^{4,5} Three conventional methods are usually used in clinical treatment: surgical treatment, radiotherapy, and chemotherapy.⁶ However, it is difficult to carry out an accurate resection due to the infiltrative growth of glioma.^{7,8} Furthermore, radiotherapy and chemotherapy greatly and negatively impact the quality of life.⁹⁻¹¹

Nano-targeted agents are drug delivery systems that integrate drugs into different nanocarriers to concentrate them in targeted tissues/organs.¹² This strategy is also called a nanoparticle drug delivery system (NDDS) and offers high drug stability, sustained release potential, and low drug toxicity to solve these issues.¹²⁻¹⁵ NDDS can increase the blood-drug concentration, prolong the half-life, and reduce the drug

Correspondence: Tian Xie; Zhaowu Zeng
Holistic Integrative Pharmacy Institutes,
Hangzhou Normal University, 1378
Wenyixi Road, Hangzhou, Zhejiang
311121, People's Republic of China
Tel +86 5 712 886 8269
Email xbs@dljg.sina.net;
artgreenking@126.com

delivery frequency by improving solubility, stability, and bioavailability of hydrophobic drugs. Thus, NDDS is an active area of research. However, the diagnosis and treatment of glioma remain difficult because the brain barrier restricts drug transport to the brain.

In this review, we summarize the biological characteristics of various brain barriers and other neural barriers that limit the delivery of brain-targeted drugs as well as the shortcomings of existing work. The latest progress in targeted drug delivery in glioma was discussed (Figure 1). The characteristics and advantages of NDDS are introduced, and strategies for enhancing brain targeting drug delivery are summarized. Finally, possible development directions are predicted.

Research Difficulties or Challenges Brain Barriers

Brain barriers are structures that prevent certain harmful substances from entering the brain. They are composed of

blood–brain barrier (BBB), blood–cerebrospinal fluid barrier, and brain–cerebrospinal fluid barrier (BCB).¹⁶ In addition, there are blood-brain tumor barriers (BBTB) in brain tumor tissues.¹⁷

BBB

Ehrlich¹⁸ first identified BBB in 1885 when he discovered that intravenous dyes could stain most organs except the brain. The BBB excludes almost all macromolecular drugs and more than 98% of small molecules.^{18,19} The BBB is mainly composed of brain capillary endothelial cells (BCECs), which can differentiate into pericytes, astrocytes, and neurons.²⁰ Most importantly, the BCECs prevent cross-cell transport of compounds from blood to brain, which greatly restricts the passive diffusion of compounds.^{21,22} Therefore, many studies have worked to develop targeted-NPs that can overcome BBB to improve the treatment and diagnosis of glioma—examples include liposomes, nanomicelles, microspheres, or nanoemulsions.²³ The structure and drug transport route of the BBB is shown in Figure 2.

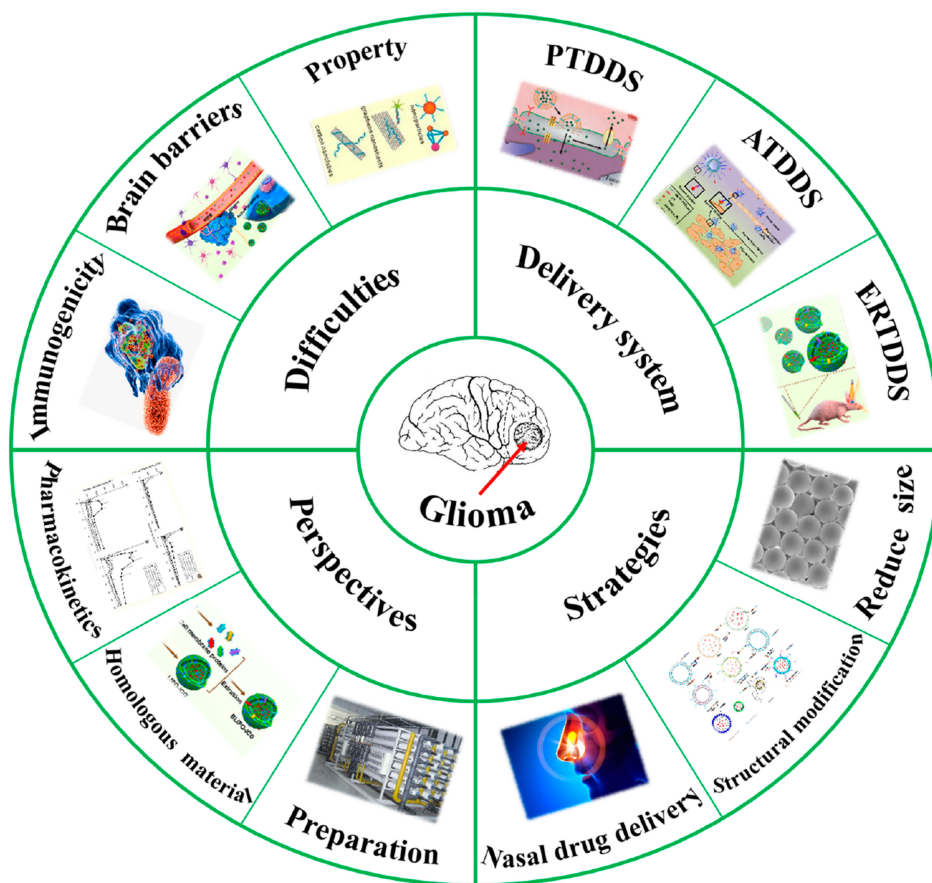


Figure 1 Schematic diagram of this review.

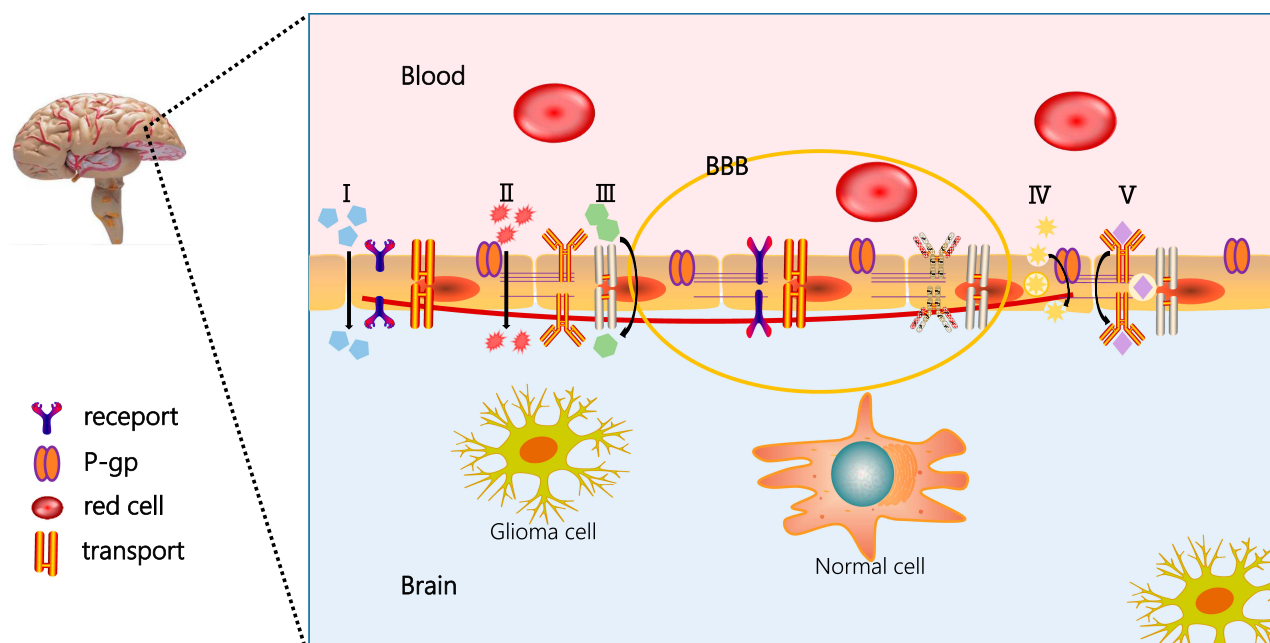


Figure 2 Structure and drug transport route of BBB. (I) penetrating through the tight junctions; (II) passive diffusion across the endothelial cells; (III) carrier-mediated transport; (IV) adsorption-mediated transcytosis or endocytosis; and (V) receptor-mediated transcytosis.

BBTB

The vascular permeability increased when the BBB was destroyed,²⁴ but some nourishing blood vessels of the tumor retained the characteristics of the BBB, which forms the BBTB.^{17,25} Similar to the BBB, the BBTB is composed of specific endothelial cells located between tumor cells and tumor blood vessels.²⁶ Some receptors are highly expressed in the blood vessels of brain tumors and thus facilitate ligand-dependent drug transport to provide convenience for targeting drugs in tumor tissues.^{16,17,24} The BBTB contains three distinct microvascular groups: continuous, nonporous capillaries (similar to normal blood vessels), continuous, porous capillaries, and capillaries with gaps between endothelial cells.¹⁷ Although the BBTB is more permeable than the BBB, its presence still prevents the use of drugs in cancer therapy.²⁷ Therefore, finding a way to facilitate drugs to cross the BBTB is crucial for drug treatment of glioma.

BCB

In the ventricular system, a ventricular tube separates the cerebral spinal fluid and brain tissue. The BCB²⁸ is composed of ependymal epithelial cells and astrocytes, and its high permeability makes it easy for substances in cerebrospinal fluid to enter brain tissue through ependymal. Therefore, drugs that do not easily cross the BBB can be injected

directly into the cerebrospinal fluid in clinical practice so that it can enter the brain tissue quickly.²⁹ After intrathecal injection, drugs can pass through the subarachnoid space and reach the cerebrospinal fluid to directly reach the brain tissue without passing the BBB. It has rapid effects and is suitable for the prevention and treatment of meningopathy or malignant tumor metastasis.³⁰

Nose to Brain Barrier

Nasal administration can also allow more drugs to reach the brain than peripheral intravenous administration. There are two parts of the nasal cavity (the breathing area and the olfactory area)—these are responsible for absorbing drugs into the brain or blood.³¹ Some drugs are absorbed into blood circulation through the mucous membrane of the respiratory department and then enter the brain tissue through the BBB. Other drugs bypass the BBB and enter the brain tissue directly through the olfactory mucous membrane or nerve. Of these pathways, the olfactory mucous pathway is the fastest and main route—the drugs travel from the nasal cavity to the brain. Indeed, humans only receive tiny amounts of drugs (25–200 μL) from the 3–10% mucous membrane, which limits the concentration of drugs delivered to the brain. Moreover, the clearance of nasal cilia can shorten the drug absorption time. Drug metabolism and secretion can also inhibit drug access to

the brain. Furthermore, long-term nasal administration can produce toxic and side effects on the nasal mucosa and cilia.³²

Security Issues

Anti-tumor drugs can have off-target effects including neurotoxicity to normal tissues due to low selectivity. Furthermore, drug resistance and dose toxicity after long-term chemotherapeutic drug use are also serious problems.¹⁰ Second, drug carriers generally have poor biodegradability and long-term safety concerns.³³ Peptides and antibodies are exogenous substances used for targeting but are often not selective to the brain and are highly unstable and immunogenic. Third, carrier-mediated active targeting and endocytosis are highly dependent on the corresponding receptor expression density of glioma cells. Individual differences are common among patients. Thus, it is quite likely to activate the rejection mechanism of the immune system (reticuloendothelial system and mononuclear phagocytic system).^{16,22,34}

Molecular Weight of Drug Carriers

PEG or other polymers are commonly used as drug carriers in NDDS. However, the molecular weights (MW) of polymers range from a few thousand to tens of thousands. Polymers with appropriate MW can reduce the adsorption of serum protein and the recognition ability of the immune system. PEG₂₀₀₀, PEG₃₀₀₀, and PEG₃₄₀₀ are often used, but there are few studies that carefully evaluate the most appropriate MW in glioma therapy. Different MW polymers should be used for NPs with different targeted functions. For the passive targeting drug delivery system (PTDDS) and the environmental responsive targeting drug delivery systems (ERTDDS), polymers with a large MW can lead to sufficient residence time to act on the EPR effect and promote NPs to enter the target site. For the active targeting drug delivery systems (ATDDS), polymers with a small MW can minimize interference between BBB-targeted ligands and BBB interactions—this is more conducive to vector-mediated endocytosis.³⁵

Properties of NPs

In addition, the size and morphology of NPs can greatly impact the efficiency of glioma treatment. The size only influences the tumor retention and penetration and also affects the BBB targeting and penetrating efficiency. Size changes are an enhancement strategy for glioma therapy and have been described in detail in “Reduction of the particle size of drug delivery system”. The shape of

nanoparticles also affects endocytosis between BBB and cell membranes. Rod/chain-like targeted NPs have higher brain accumulation than spherical NPs.³⁶ Other NP features include surface charge, ligand density, ratio of dual-targeting systems, and water solubility.

Application of NDDS

NDDS can be classified into passive targeting systems, active targeting systems, and environmental responsive targeting systems according to their different modes of action.^{37,38} Part of the glioma drug delivery system and the relative mechanisms are shown in Figure 3 and Table 1. Nano-carriers are mainly used in passive targeting systems to encapsulate drugs such as nanoparticles, liposomes, and microspheres.³⁹ Drug-containing nano-carriers are naturally engulfed through the physiological process of cell endocytosis to achieve targeted drug distribution. Besides, various targeted molecules act as “missiles” to modify drug-carrying nano-carriers such as proteins, antibodies, small molecules, or nucleic acid aptamers. These are common in active-targeting systems and deliver drugs through a directional role to target sites.⁴⁰ Moreover, the physicochemical targeting system could realize the targeted distribution of drug-carrying nanocarriers in the body through physical and chemical effects such as magnetism, heat, sound, light, electricity, and pH.⁴¹

Passive Targeting Drug Delivery System

The PTDDS mainly delivers drugs to tumor tissues based on the “enhanced permeability and retention effect” (EPR effect) in tumor tissues instead of normal tissues.⁴² Interestingly, in the late stage of brain tumors, passive targeting nanoparticles can even enter the brain tumors through gaps in the endothelium due to the weak difference of EPR effect between tumor tissues and peripheral tissues. The most common passive-targeting drug delivery systems include liposomes, microemulsions, and nanoparticles.

Liposomes

Liposomes are spherical vesicles formed by phospholipid bilayer membranes that have attracted wide interest in biocompatibility and targeting with BBB. They are a common carrier for glioma PTDDS.

The elemene liposome (EL) injection was approved by the China Food and Drug Administration (CFDA) in 1994. More than 20 years of clinical studies have shown that EL is a non-cytotoxic anti-cancer drug with a high content of anti-cancer active ingredients (β -elemene, 85%).^{43,44} It can

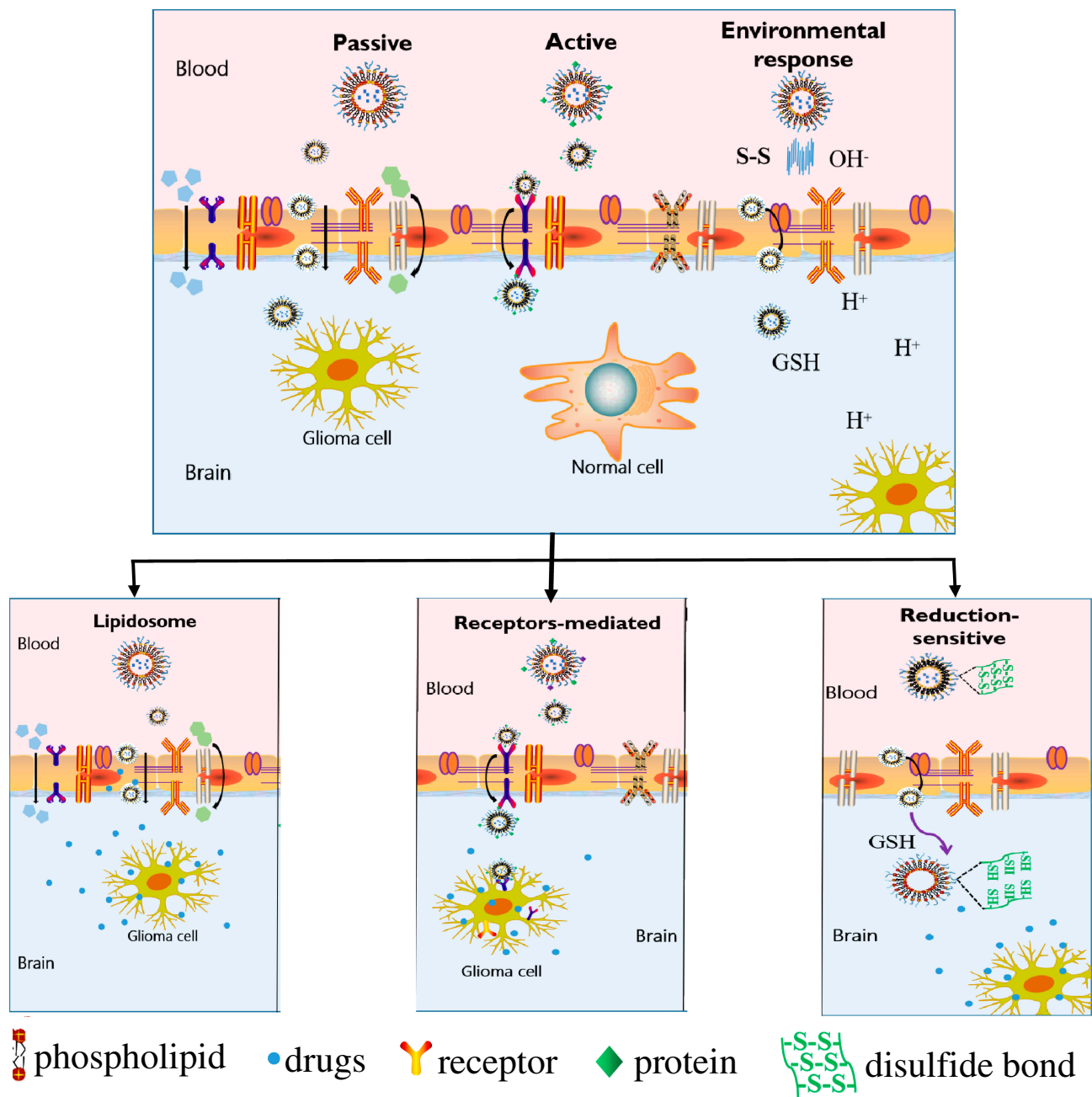


Figure 3 Schematic diagram of the classification and transport mechanism of a targeted drug delivery system.

suppress varieties of cancer cells and improve the immune system. It has obvious effects on improving patients' quality of life, prolonging the survival period, resisting metastasis and recurrence, and reversing multiple-drug resistance (MDR), etc. EL has benefited more than 7.07 million cancer patients in southeast Asia, Hong Kong, Japan, Korea, Europe, and the US.⁴⁵ Zhu et al⁴⁶ found that EL (48 h) significantly accelerated the apoptosis initiation time of C6 glioma cells versus the normal elemene group (72 h). Moreover, Gao et al⁴⁷ formulated the temozolomide-

liposome (TL) that could be distributed in the brain. The $t_{1/2}$, mean residence time (MRT), C_{max} , and AUC values of TL were several-fold higher than the solution, which showed that TL could improve the therapeutic effect of the brain, reduce heart-lung toxicity, and prolong the circulation time of TZM in vivo.

Microemulsions

Microemulsions are drug delivery systems formed spontaneously in the water phase and oil phase with surfactant

Table 1 Application and Mechanism of Glioma Drug Delivery Systems

NDDS	Types	Mechanisms	Ref.
PTDDS			
Liposomes	Phospholipid bilayer	EPR effect/across the endothelial cells of BBB	46,47
Microemulsions	P-gp/endocytosis	EPR effect/inhibition of P-gp efflux/across the endothelial cells of BBB	49,51
Niosome	P-gp	EPR effect/inhibition of P-gp efflux	87,88
Nanoparticles	Endothelial cells	EPR effect/transcytosis or endocytosis	57,59
ATDDS			
Receptor-mediated	Insulin	Endocytosis/insulin receptor	89
	Transferrin	Endocytosis/transferrin receptor	71
	Lactoferrin	Endocytosis/lactoferrin receptor	73,74
	Endothelial growth factors	Endocytosis/endothelial growth factors receptor	90
	Amino acids	Endocytosis/amino acids receptor	91
	Apolipoproteins/ angiop-2	Endocytosis/low density lipoprotein receptor	92,93
	H-ferritin	Endocytosis/HFn receptor (transferrin receptor I)	72
Peptide-mediated	iRGD	Endocytosis/ $\alpha v \beta 3 / \alpha v \beta 5$	78
	RDP	Endocytosis/nerve-penetrating properties	82,83
	Chlorotoxin	Endocytosis/ matrix metalloproteinase-2	54
	T7	Endocytosis/transferrin receptor	94
	CDX peptide	Nicotinic acetylcholine receptors	95
	F3	Bind to nucleolin	96
	CendR motif	Neuropilin-1/across the endothelial cells	97
Small molecule-mediated	Folic acid	Folate receptor	85
Apt-mediated	AS1411/FB4	Recognize proteins/phospholipids/ nucleic acids	98,99
Cytokine-mediated	Interleukin-13	IL-13R $\alpha 2$ receptor	100
Matrix metalloproteinases-mediated	MMP-9	Key modulators of tumor invasion/ metastasis	101
Cell-mediated	Mesenchymal stem cells	Endocytosis/across the endothelial cells of BBB	102
	Macrophages	Endocytosis/across the endothelial cells of BBB	103
Dual targeting-mediated	Transferrin-folic acid	Promote drug across BBB/targeting tumor cells	66
	Ang-2-VEGF receptors	Endothelial growth factors receptor/low density lipoprotein receptor	104
	T7- Δ A7R-LS	Transferrin receptor/VEGF receptor 2	105
	Thermosensitive-PINS	Winding-contraction phase transition /nerve-penetrating properties	106
	Transferrin-pH	Promote drug across BBB/pH difference	107
	pH-reduction	pH difference and glutathione/dithiothreitol	108
ERTDDS			

(Continued)

Table I (Continued).

NDDS	Types	Mechanisms	Ref.
Photo-sensitive	Photosensitizer/ photothermal agent	ROS/singlet oxygen/local hyperthermia	109–111
pH-sensitive	Acidic microenvironment	pH difference	112
Reduction-sensitive	Disulfide bond	Glutathione/dithiothreitol	113,114
Magnetic sensitive	Magnetic resonance	The magnetic field	115
Ultrasonic sensitive	Ultrasonic	Ultrasonic cavitation effect	116
Thermo-sensitive	Hydrogen bonding	Winding-contraction phase transition	106

and cosurfactants. Oil phase components can increase the affinity of drugs to BBB endothelial cells, and surfactants/cosurfactants can inhibit or reduce P-gp efflux.^{45,48}

Li et al⁴⁹ constructed a microemulsion containing linoleic acid conjugated with paclitaxel (CLA-PTX) against brain tumors. The CLA-PTX microemulsion had a lower IC₅₀ and a higher tumor inhibition rate than CLA-PTX solution and free PTX, which is possibly because of the higher affinity of CLA-PTX to BBB endothelial cells and the enhanced permeability and retention effect for passive targeting. Xie et al^{50,51} prepared a hyaluronic acid chitosan-based microemulsion (HAC-ME), which significantly increased the BBB permeability of glioma cells after 0.25 h of administration. The material down-regulated the expression level of the tight junction protein claudin-5. Carboplatin combined with HAC-ME can promote the apoptosis of glioma cells versus free carboplatin.

Nanoparticles

Nanoparticles are widely used in the treatment of glioma.^{52–54} An et al⁵⁵ designed realgar nanoparticles (RN) that could significantly increase the proportion of C6 cells in S and G2/M phases. This decreased the proportion of C6 cells in the G0/G1 phase, downregulated Bcl-2 expression, and substantially upregulated Bax expression versus free realgar and control. Jain et al⁵⁶ fabricated surface-modified PLA nanoparticles loaded with TMZ. Such PLA-NP nanoparticles can significantly increase the accumulation of the macromolecular dye coumarin-6 in the brain and reduce the accumulation in other organs. These results indicated that the nanoparticles could enhance the permeability of drug transport across the BBB into the brain. Thus, nanoparticles have potential value in glioma treatment and may reduce drug toxicity to other organs.

Many other nanomaterials have been used to treat glioma including chitosan that can effectively prolong the time of drug action and increase circulation.⁵⁷ Dendritic polymers can improve drug release and biocompatibility.⁵⁸ Macromolecular block copolymer micelles have a long cycle capacity and high stability.⁵⁹

Active Targeting Drug Delivery Systems

However, the PTDDS has unfortunately not shown clinical value due to a lack of selectivity and affinity—this can lead to toxicity and side effects in normal tissues.^{34,40,60} Therefore, many researchers are working on ATDDS to achieve selective treatment of glioma.⁶¹ ATDDS are designed to exploit differences in receptors or antigen expression on the surface of tumor cells and normal cells. By virtue of the high affinity between ligand and receptors, ATDDS can achieve higher cross-BBB transport ability or tumor penetration. These features promote selective drug targeting with anti-tumor activity. Common active targeting vectors include small molecules, proteins, peptides, and aptamers; examples include folic acid, transferrin, and the RGD peptide.^{62–69}

Receptors-Mediated ATDDS

Many receptors are expressed in the BBB including receptors of insulin, transferrin, endothelial growth factors, and amino acids. Receptor-mediated endocytosis is one of the main mechanisms by which drugs cross the BBB into the brain.⁷⁰ Herein, researchers have modified nano-carriers with proteins to improve the ability of transporting across BBB and to improve the effectiveness of glioma drugs.

Sun et al⁷¹ fabricated TMZ/transferrin (Tf)-nanoparticles (PAMAM-PEG-Tf/TMZ) that successfully crossed the BBB and killed glioma tumor cells. These particles lead to

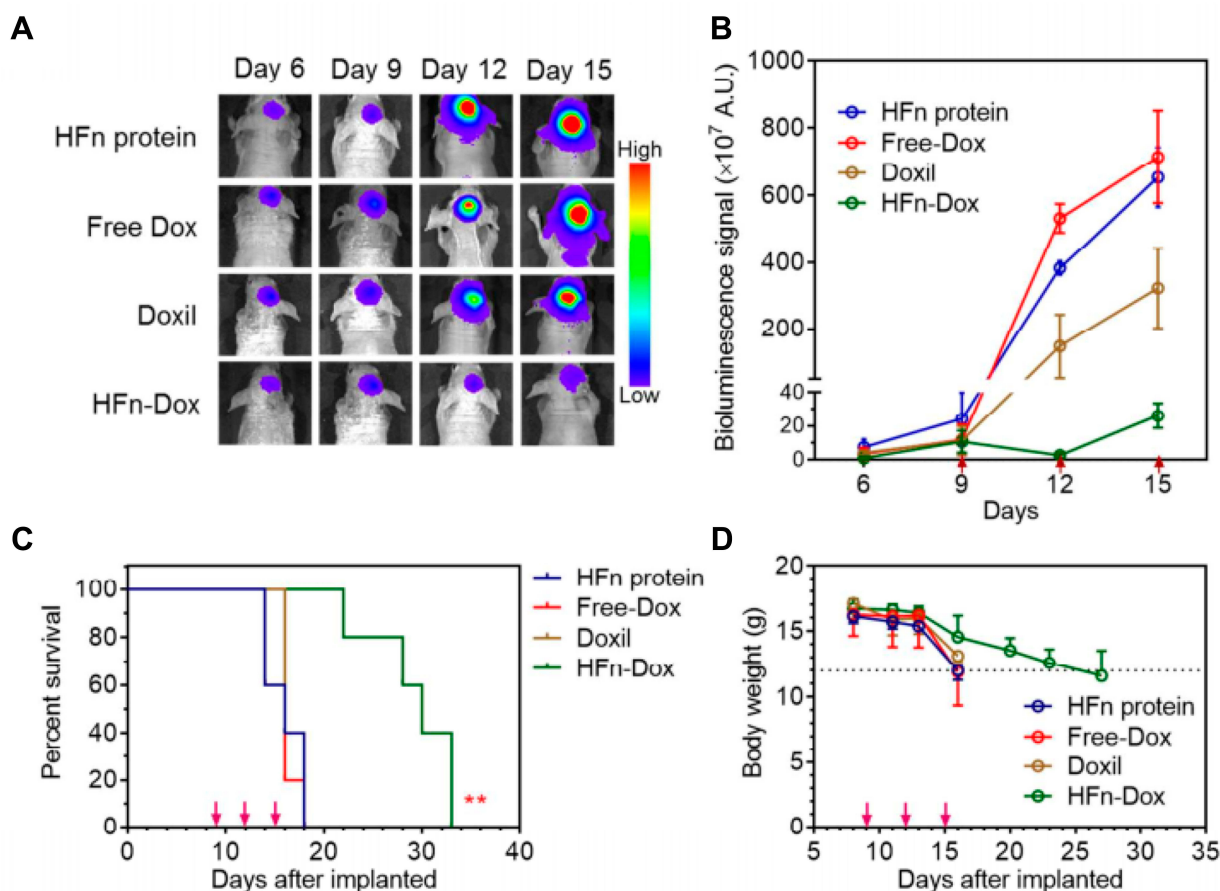


Figure 4 HFn-encapsulated Dox effectively improves anti-glioma tumor activity. **(A)** In vivo BLI images of GBM tumor cells in orthotopic mice that were intravenously injected with different formulations, ie, HFn-Dox, Doxil, free Dox, and HFn protein. **(B)** Quantitative analysis ($n=5$) of the BLI signals of **(A)**. The red arrows indicate the time points of administration. **(C)** Animal survival curves in different groups. Asterisks indicate that the difference between HFn-Dox and free Dox or Doxil was statistically significant (Kaplan–Meier, $p=0.0019$ and 0.0023 , respectively). **(D)** The effect of different treatments on mouse body weight (mean \pm SD, $n=5$). Reprinted with permission from Fan K, X Jia, M Zhou, et al Ferritin Nanocarrier Traverses the Blood Brain Barrier and Kills Glioma. *ACS Nano*. 2018; 12(5): 4105–4115. Copyright (2018) American Chemical Society.⁷²

a significantly longer MST in mice with gliomas. Fan et al⁷² prepared a human H-ferritin (HFn) nanocarrier. The main entry point is HFn receptor 1, which is overexpressed in BCECs and glioma cells. In contrast, when specifically targeted and loaded into glioma cells, nearly all HFn accumulates in lysosomes leading to the death of glioma tumor cells—the surrounding healthy brain tissues do not have HFn aggregation. Such anti-glioma tumor activity is shown in Figure 4.

Similarly, Chen and Li et al^{73,74} used a lactoferrin-modified PEG-poly(D,L-lactide-co-glycolide) (PLGA) nanoparticles loaded with shikonin and procationic liposomes loaded with doxorubicin (DOX) for glioma therapy. The drug delivery system modified by lactoferrin can promote the drug-carrying nanoparticles across BBB so that the drugs can be enriched in the brain and achieve better efficacy.

Peptides-Mediated ATDDS

Polypeptides are small molecules composed of 2–50 amino acids with non-advanced structure. When ligand peptides bind to receptors, nano-carriers linked to peptides generally enter cells through receptor-mediated endocytosis. For example, RGD peptide including cyclic RGD peptide (cRGD) or internalizing RGD peptide (iRGD).^{75–78} Cell-penetrating peptides (CPPs) such as rabies-derived peptide (RDP) are also of interest because they can transport exogenous molecules to tumor tissues.^{79–81}

Gu et al⁷⁸ modified PEG-PLA nanoparticles containing PTX with MT1-AF7p peptide (MT1-NP-PTX). This material has obvious anti-proliferation activity on C6 glioma cells with IC₅₀ values of 2.81- and 2.47-fold lower than free PTX and NP-PTX, respectively. The percentage apoptosis of MT1-NP-PTX was the highest versus PTX and

NP-PTX, which suggested more PTXs were delivered when combined with iRGD (high-affinity for cancer-related integrins such as $\alpha v\beta 3$ and $\alpha v\beta 5$). Zhao et al⁸² established RDP-conjugated curcumin-coated nanoliposomes (RCL). Expectedly, the growth inhibition efficiency of RCL was 3.33-fold higher than curcumin liposomes (CL) in U251MG. The results of anti-glioma activity showed the survival time of glioma model mouse in the RCL group was longer than model and CL. In addition, RDP-p53 could efficiently and selectively enter and inhibit SH-SY5Y cells; the total percentage of apoptotic cells of RDP-p53 significantly improved versus the PBS and p53.⁸³ All of the above showed that RDP-mediated nano-carriers were promising options for glioma therapy.

Small Molecule-Mediated ATDDS

Small molecules, such as folic acid (FA), biotin, and bisphosphate, are often used as targeted ligands in ATDDS for tumors. They offer good safety, no immunogenicity, and easy modification. FA is the most widely used because the folate receptor (FR) is highly expressed on many cancers but not in normal tissues.⁸⁴

Xu and Li et al^{85,86} proposed a nano-targeted delivery of DOX for glioma based on PAMAM G5 dendrimer. The therapeutic effect of glioma was significantly improved after FA modification. The tumor growth inhibition of FA-PAMAM/DOX was increased up to 57.44%, while free DOX was 17.70% only. Meanwhile, FA-PAMAM/DOX could significantly reduce tumor volume in mice. Moreover, the data show that FA-PAMAM/DOX could significantly prolong the half-life time and improve DOX accumulation in brain tumor versus DOX. The MST of xenograft rats of FA-PAMAM/DOX was obviously longer than free DOX. This novel strategy of targeting nano-carriers modified with FA offers a promising way to increase the accumulation of drugs at tumor sites.

Aptamer-Mediated ATDDS

Aptamers (Apt) are oligonucleotides that can be synthesized chemically to promote targeted drug delivery. Compared with other targeted molecules, Apt attracted more and more attention due to their specific binding ability, high affinity, and low immunogenicity. Apt could easily penetrate tumor tissues because they can specifically identify target molecules such as proteins, phospholipids, sugars, and nucleic acids.¹¹⁷ Of these, AS1411 has extensive application value and potential development ability in clinical treatment of tumor—it could inhibit the growth of a variety of tumor cells without affecting normal cells.^{118,119}

Luo et al⁹⁸ established a nanoparticle with AS1411-functionalized poly (L- γ -glutamyl-glutamine)-PTX (AS1411-PGG-PTX). The percentage of apoptosis of S1411-PGG-PTX was significantly increased versus PGG-PTX. In addition, the MST of mice in the AS1411-PGG-PTX group was significantly longer than the PTX group and the saline group. This might be due to the good stability in blood, long circulation time, and more accumulation of PTX in glioblastoma tissues. Mu et al⁹⁹ combined FB4—a segment of RNA that can specifically bind to transferrin receptor—with micelles loaded with flurbiprofen and conducted in vitro experiments with bEND5 cells (brain microvascular endothelial cells) in mice. Compared with untargeted micelles, the drug concentration in the micelles with FB4 ligand increased by 1.67-fold.

Cytokine-Mediated ATDDS

Human interleukin-13 (IL-13) is a cytokine secreted by activated T cells and has two receptors (IL-13/4R and IL-13R $\alpha 2$). It can induce pro-inflammatory and anti-inflammatory immune responses.^{120,121} IL-13/4R is present in normal cells and binds to IL-4, whereas IL-13R $\alpha 2$ is associated with glioblastoma but not expressed in normal tissues. A recent study showed that IL-13R $\alpha 2$ receptor is overexpressed in the most common hair cell astrocytomas in children.^{121–123} Therefore, it is a promising target for cytotoxic drugs in various brain tumors.

For example, Madhankumar et al^{124,125} prepared a DOX liposome modified with IL-13 to guide the liposome to the tumor site by binding to the over-expressed IL-13R $\alpha 2$ receptor in glioblastoma. Compared with free DOX, liposomes modified with IL-13 enhanced cytotoxicity and increased the accumulation/retention of DOX in glioma cells. After 7 weeks of i.v. injection, the average tumor volume in IL-13-modified DOX liposome group had a 5-fold reduction compared with the non-targeted DOX liposome group. These data show that IL-13 targeted nanovesicles are a viable option for the treatment of brain tumors.

Stem Cell-Mediated ATDDS

Recent studies showed that the application of cell-modified nanoparticles for drug delivery system is an effective method to encourage the drugs to pass through for drug delivery. These drugs have an affinity for brain tumors and can be used as a drug carrier for the treatment of glioma such as mesenchymal stem cells (MSCs).^{126–128}

Wang et al¹⁰² manufactured MSCs loaded with PTX-encapsulated PLGA NPs to demonstrate the therapy for orthotopic glioma in rats. The PTX-migration rate of

MSC-loaded PTX-PLGA NPs increased by $44.4 \pm 5.4\%$, and MSC-loaded PTX-PLGA NPs had enhanced sustained PTX release to induce glioma cell death compared with PTX-PLGA NPs. Survival was significantly longer in control MSC-loaded PTX-PLGA NPs than those injected with PTX-PLGA NPs alone. These data suggest that MSC-loaded PTX-PLGA NPs are effective for glioma treatment and are a promising strategy for tumor-targeted therapy.

Dual-Targeting-Mediated ATDDS

Compared with PTDDS, ATDDS enhances the efficacy of glioma treatment via the two following aspects: (1) They promote drug delivery systems for transport across the BBB; (2) They selectively target glioma cells while increasing the distribution of drugs in glioma and reduce their distribution in normal brain tissues.¹²⁹ Currently, most ATDDS have only one feature that allows drugs to be non-selectively distributed throughout the brain after passing through the BBB. This low selectivity can cause some serious neurological side effects. Thus, an ideal glioma TDDS should have the above two characteristics at the same time, ie, dual-targeting-mediated ATDDS. Dual-targeting-mediated ATDDS usually refers to the modification of two functional ligands on the PTDDS. One is targeted to the BBB to promote the cross-BBB transport of the drug delivery system, and the other is targeted to the glioma tissue and further concentrates the drug in the glioma. A ligand, targeting both BBB and glioma, is connected to the PTDDS—this can also be called a dual-targeting-mediated ATDDS.³²

Gao et al⁶⁶ prepared DOX liposomes modified by transferrin and folate (Tf/F-DOX-Lip). A near-infrared fluorescent probe showed that the fluorescence of DOX solution and DOX-Lip was mainly in the cardiac region, but Tf/F-DOX-Lip was mainly distributed in brain—these data illustrated that liposomes modified by transferrin and folate could promote the migration of liposome to the brain. The tumor inhibition rate of Tf/F-DOX-Lip was six-fold higher than DOX-Lip after i.v. administration. The data show that Tf/F-DOX-Lip could not only promote DOX for transport across the BBB but also increase the distribution of DOX in glioma.

Environmental Responsive Targeting Drug Delivery Systems

Traditional drug delivery systems are not ideal for maintaining system stability and promoting drug release at target sites.¹³⁰ Therefore, the design of ERTDDS has gradually become a research hotspot in the field of pharmacy.

To understand the physiological differences between tumors and normal tissues, ERTDDS¹³¹ can specifically respond to endogenous or exogenous stimuli including physical (such as photosensitivity^{109,132,133}), chemical (as pH sensitivity^{134–137} and reduction sensitivity^{113,138}), and biological (as matrix metalloproteinases¹³⁹) features. ERTDDS only responds to internal and external environmental conditions when it is close to the drug action site—these conditions then trigger the release of drugs in tumor tissues while remaining stable in other tissues. Thus, it can improve the anti-tumor efficacy and reduce the toxicity and side effects.

Photo-Sensitive TDDS

Photosensitive TDDS is a tumor therapy method based on photodynamic therapy (PDT) and photothermal therapy (PTT).^{109,140–142} It is based on light conditions reaching the photosensitive TDDS in the tumor site. Photosensitizer (PS) or photothermal agent (PA) will absorb the light, and reactive oxygen species (ROS), singlet oxygen, or local hyperthermia will be released. While preserving normal tissues, the nanoparticles selectively and efficiently produce cytotoxic activity and kill tumor cells.

Xu et al¹⁰⁹ constructed a therapeutic nano-platform (ICG-SFNPs) with silk fibroin (SF) to use indocyanine green (ICG) for PTT of glioblastoma. Meanwhile, the photothermal effect of ICG-SFNPs is more stable than free ICG under near-infrared radiation (NIR). After local NIR, the temperature of ICG-SFNPs rapidly increased by 33.9°C within 10 min and remained high for a long time to kill tumor cells. The growth of glioblastoma cells was completely inhibited by ICG-SFNPs.

Jia et al¹⁴² developed a biomimetic proteolipid nanoparticles (NPs) with ICG for phototherapy of orthotopic glioma in mice. Biomimetic ICG-loaded liposome (BLIPO-ICG) NPs were obtained by embedding the glioma cell membrane protein into NPs. Due to the good homologous targeting and immune escape characteristics, BLIPO-ICG NPs can pass through BBB and specifically bind to glioma cells and reach glioma in early stages. At 12 h post-injection, the signal-to-background ratio in the brain tumor reached 8.4 demonstrating good accumulation. In addition, after NIR (1 W/cm^2 , 5 min), the photothermal effect of BLIPO-ICG NPs effectively inhibited the proliferation of glioma cells with an inhibition rate of 94.2%. No photothermal damage of normal brain tissue or other side effects of treatment were observed. These results indicate that the bionic protein lipid NP is a promising

phototheranostic nanoplatform for brain tumor-specific treatment. The mechanism and anti-glioma tumor activity are shown in Figure 5.

pH-Sensitive TDDS

The normal pH of human blood and interstitial fluid is usually alkaline (pH 7.4), while the tumor microenvironment is acidic (approximately 5.6).^{143,144} The slightly acidic environment is mainly caused by the rapid proliferation of tumor cells and excessive accumulation of lactic acid. In addition, most tumor cells are characterized by insufficient blood supply and slow excretion, which further acidify the tumor microenvironment. Using pH differences between tumor tissues and normal tissues, numerous researchers have constructed drug delivery systems via pH-responsive materials.^{112,145-148} These delivery systems can change their physicochemical properties such as swelling and increasing solubility during the transition from weakly alkaline to slightly acidic environment. Thus, it can further trigger the release of drug molecules in the package and play a targeted role in tumor therapy.

Yin et al¹¹² developed a pH-sensitive prodrug (Lf-HA-DOX) by combining hyaluronic acid (HA) with DOX. The release of DOX in Lf-HA-DOX was 45%, 35%, and 12% at pH 5.0, 6.0, and 7.4 at 24 h, respectively. Furthermore, the geometric mean fluorescence intensity (GMFI) of

DOX in the free DOX group was almost unchanged when the concentration of DOX changed; it increased in the Lf-HA-DOX group. Similarly, Li et al¹⁰⁷ synthesized a pH-sensitive dual-targeting drug carrier (G4-DOX-PEG-Tf-TAM) with conjugated Tf and Tamoxifen (TAM) of the PAMAM dendrimers for enhancing the BBB transportation and improving the drug accumulation in the glioma cells. They found that the DOX release was 32% at pH 4.5 and 6% at pH 7.4 indicating that the drug release is relatively fast at weak acidic conditions and stable in normal physiological environments.

Reduction-Sensitive TDDS

Reduction-sensitive TDDS refers to the particle delivery system connected by a disulfide bond (S-S) between the carrier and the drug. These particles self-assemble in solvent to form a nanostructure.¹⁴⁹ Disulfide bonds are a special yet common chemical bond that is stable in normal physiology. However, they are broken in tumor tissues (reductive environment) with high expression of dithiothreitol and glutathione (GSH) to release the drug and achieve targeted release.^{113,150-153} Indeed, reduction-sensitive TDDS are reduction-sensitive and biodegradable and are an ideal platform for targeted tumor chemotherapy.

Zhu et al¹¹³ showed a biodegradable PEG-SS-PCL micelle functionalized by cRGD (cRGD/PEG-SS-PCL).

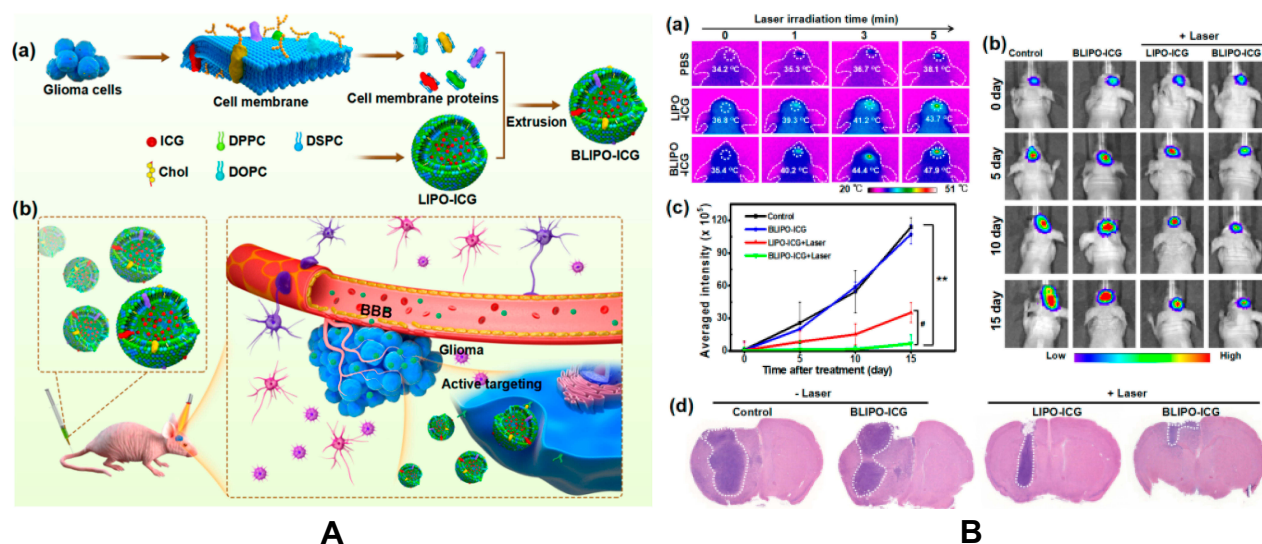


Figure 5 (A) Schematic illustration of biomimetic proteolipid BLIPO-ICG for crossing the BBB and active targeting delivery of orthotopic glioma. (a) Preparation process of BLIPO-ICG. (b) Schematic of BLIPO-ICG for crossing BBB and active targeting imaging. (c) Representative in vivo infrared thermal images of the brain region before and after 808 nm laser irradiation (1 W/cm², 5 min). CLIPO-ICG = CBLIPO-ICG = ICG 1 mg/kg. (d) Representative bioluminescent images of C6-Luc glioma-bearing mice in different groups. (e) Semi-quantitative bioluminescent signal intensity in the brain. ***p* < 0.01 versus control. #*p* < 0.05 versus LIPO-ICG+laser. (f) H&E staining of brain sections of orthotopic glioma-bearing mice in all groups. Scale bar = 200 μm. Reprinted with permission from Jia Y, X Wang, D Hu, et al Phototheranostics: Active Targeting of Orthotopic Glioma Using Biomimetic Proteolipid Nanoparticles. *ACS Nano*. 2019; 13(1): 386–398. Copyright (2019) American Chemical Society.¹⁴²

These materials can enhance DOX delivery in a reductive environment (10 mM GSH) to significantly improve tumor inhibition and decrease toxicity upon comparison with non-targeting agents and reduction-insensitive cRGD/PEG-PCL. Su et al¹⁵⁰ proposed a novel copolymer mPEG-PAsp (MEA)-CA. The DOX was only slightly released in the absence of GSH. However, there was 37% DOX released after only 2 h when 10 mM GSH was added indicating that GSH broke the S-S through a thiol-disulfide exchange reaction to promote the release of DOX.

ERTDDS are also thermosensitive,¹⁰⁶ magnetic sensitive,^{115,154} and ultrasonic sensitive.¹⁵⁵ They are a research focus in recent years and can also specifically target the treatment of glioma under different conditions without affecting normal tissues.

Strategies to Improve the Drug Targeting to Glioma

Reduce the Particle Size of the Drug Delivery System

A smaller (200–800 nm) particle can usually be easily endocytosed by phagocytes. However, when the particle size is less than 200 nm, the curvature of local areas on the surface of the carrier will also decrease as the particle size decreases. Therefore, the particles could avoid being adsorbed by receptors on the surface of the phagocytes—they can escape phagocytosis and be cleared by phagocytes.^{156,157}

Wan et al¹⁵⁸ placed tartaric acid vinorelbine liposomes with particle size of 200 nm and 800 nm in medium containing mouse mononuclear macrophage RAW264.7 and luciferin, respectively. After 12 h, the probability of devouring liposomes with particle size of 200 nm was 13%, while that of 800 nm was only 8%. Bi et al¹⁵⁹ injected curcumin nano-suspension with the size of 70 nm (A) and 200 nm (B) into the body. The $AUC_{0-60\text{min}}$ of A was 2.58 times higher than B in the brain. When the size of the curcumin decreased from 200 nm to 70 nm, the $AUC_{0-60\text{min}}$ of liver drug also decreased from $8491 \text{ ng}\cdot\text{min}\cdot\text{g}^{-1}$ to $2300 \text{ ng}\cdot\text{min}\cdot\text{g}^{-1}$. These results indicate that the size decrease can not only promote drug delivery to the brain but also reduce drug uptake by the liver. This is critical for the treatment of brain diseases and the reduction of drug toxicity and liver side effects.

Structural Modification

Studies have shown that small lipophilic drug molecules with a molecular weight of less than 500 Da can cross the BBB by

passive diffusion. Therefore, small-molecule drugs can have improved properties by modifying their polar groups such as esterification and alkylation of hydroxyl or carboxyl groups. Non-polar groups such as methyl and benzene rings can also be introduced to increase lipophilicity and improve BBB transmittance.^{160,161}

Chen et al¹⁶² designed and synthesized a series of novel derivatives to improve the anticancer efficacy of natural β -elemene. Most derivatives exhibited significant anti-proliferative activities against the three cancer cell lines (SGC-7901, HeLa, and U87) versus natural β -elemene. Interestingly, these compounds displayed excellent sensitivity to glioma cells. Moreover, further mechanistic studies revealed that 11a caused the G2 phase arrest of the cell cycle and induced apoptosis of glioma cells by preventing the activation of the PI3K/Akt pathway. In addition, 11a significantly suppressed the tumor growth in cancer xenograft mouse model, which was superior to β -elemene at the same condition. In conclusion, the remarkable biological properties of these new β -elemene derivatives may make them promising candidates for glioma treatment.

Combination with Resuscitative CHMs

Resuscitative CHMs^{163,164} are traditional Chinese medicines considered “orifice-opening” agents including musk, borneol, acorus gramineus, and benzoin. With spicy and fragrant attributes, Resuscitative CHMs can better enter the brain tissue through the BBB. The active ingredients have strong lipid solubility and minimal molecular weights. In addition, resuscitative CHMs can also induce other drugs upward into the brain, ie, they can increase the permeability of BBB, promote drugs to pass through the BBB, and improve the efficacy of drugs. The cell structure is basically complete after this action. Pharmacological studies have found that resuscitative CHMs can increase the content of Evans blue (EB) in the brain tissue of normal mice confirming that Resuscitative CHMs can open the BBB in normal mice.

Borneol

The mechanism of borneol passing through BBB may be inhibition of transporters to increase the vasodilatory neurotransmitters and inhibit active transport of ion channels.^{165,166} P-glycoprotein (P-gp) is an efferent protein on the BBB. It can easily bind with a variety of substrates and expel them from brain tissues to reduce the therapeutic drug effects. Borneol inhibited the expression of P-gp to allow drugs to enter brain tissue. For instance, tanshinol has been

used to treat epilepsy and other brain diseases, but it will be excreted by P-gp within a short time after entering the brain. When borneol was introduced into tanshinol to form an esterification complex, it could easily travel through the BBB into the brain for a longer retention time. Moreover, the inhibitory effect on P-gp of borneol made the higher concentration of tanshinol play a role in brain tissue.¹⁶⁷ The effect of borneol on aprotinase-modified nanoparticles can significantly increase the absorption of nanoparticles by capillary endothelial cells in the brain of Alzheimer's disease and can improve memory.¹⁶⁸ These data provide a new idea for targeted glioma drug delivery.¹⁶⁹

α -Asarone

Wu et al¹⁷⁰ evaluated the "orifice-opening" effect of α -asarone (a main active ingredient of *acorus gramineus*) on the improvement of brain delivery of Puerarin (PUE) and tetramethylpyrazine (TMP). They then investigated whether the enhancing effects were associated with adenosine receptors (ARs)-mediated trans-BBB pathway. Their results indicated that α -asarone significantly increased the accumulation of permeated PUE and TMP, and the enhancing effects could be counteracted by AR inhibitors. Indeed, α -asarone decreased the expression of ZO-1 (an important BBB junction protein) and increased the expression of A₁AR and A_{2A}AR. Pharmacokinetic studies showed that oral administration of α -asarone significantly increased AUC_{brain} 1.34-fold and 1.79-fold for PUE and TMP. These results suggested that α -asarone is an effective adjuvant agent for the delivery of PUE and TMP to the brain.

Application of Physical Technology

During ultrasonic processing, liquids undergo a series of dynamic processes such as vibration, growth, and rupture under the action of sound waves. When physical effects are applied to the cell interface of the surrounding tissues, tight junctions between cells become loose and reversible pores appear. This improves cell endocytosis. In addition, ultrasonic vibration can improve the permeability of cell membrane and promote drug uptake.^{171,172}

EB can bind with plasma albumin to form an EB-albumin complex, which has a large molecular weight and cannot penetrate the complete BBB. The gap between BBB cells becomes larger under the action of ultrasound, which may promote the passage of the complex through the BBB. Based on this hypothesis, Chen et al¹⁷³ performed ultrasound treatment on the brains of rats successfully transplanted with tumor cells. The results showed that the compound could pass

through BBB after i.v. injection. After injection of lipid microbubble solution and saline, the brain tumor sites of the two groups of rats were first treated with ultrasound (1.0 MHz). The EB solution was injected immediately, and glioma tumor tissues were extracted after 72 h. Under confocal laser microscope, only sparse red spots of fluorescence were observed in the control group, while many areas of red fluorescence were observed in the experimental group. This confirms that ultrasound can promote EB through BBB into glioma tissue.

Currently, ultrasound-mediated targeted therapy¹⁷⁴ is still in the experimental stage. The appropriate ultrasound parameters for optimal drug delivery must be identified with studies for potential adverse reactions including bleeding, brain injury, and inflammation after the destruction of ultrasound BBB. Nevertheless, this technology is expected to lead to breakthroughs in targeted drug delivery to the brain and cancer therapy after the development of new ultrasound targeted therapy and continuous optimization of ultrasound parameters.

Alternative Routes of Administration

Nasal Drug Delivery

After nasal administration (NA), some drugs bypass the BBB and enter brain tissue directly through the olfactory mucosa or olfactory nerves. Compared with peripheral vein administration, NA allows increased delivery and faster transfer of drugs into the brain.¹⁷⁵ Zhang et al¹⁷⁶ administered a β -asarone microemulsion through the nose and tail vein injection on rats. The results showed that β -asarone microemulsion was absorbed into the blood and brain tissues quickly and could be detected at 2 min after NA. However, the ratio of AUC_{brain(0-2 min)}/AUC_{plasma(0-2 min)} was 1.49, and more drugs entered the brain with a nearly 50% higher amount of drug in brain tissues than in plasma. Meanwhile, a lower amount of drug could enter into the brain after caudal vein administration. Compared with NA, the concentration of β -asarone in the brain after i.v. administration was only 56.85% of the NA. This suggests that NA has unique advantages in promoting drug delivery to the brain and may be one of the pre-selected methods for glioma treatment.

Intrathecal Injection

Intrathecal injection (i.t.) refers to the injection of drugs into the spinal canal. The delivery of the cerebrospinal fluid plays a key role after delivery through the subarachnoid space. This approach is suitable for the prevention and/or treatment of meningeal lesions, malignant tumor metastasis, and other diseases.¹⁷⁷ The i.t. offers low dosages and targeted drug

Table 2 Strategies for Enhancing the Treatment of Glioma

Types	Strategies		Mechanisms	Enhancements	Ref.
	Before	Behind			
Use new drug delivery system	Free realgar	Realgar nanoparticles	EPR effect/endocytosis	C6 cells apoptosis rate was increased by 5.50 times	⁵⁵
	Free TMZ	PAMAM-PEG-Tf/TMZ	Endocytosis/Tf receptor	MST of mice bearing gliomas was extended by 22.9 days	⁷¹
	Free TMZ	TMZ-Lf/NPs	Endocytosis/Lf receptor	The concentration of TMZ in brain was higher 3 times; IST increased 1.4 times	¹⁷⁸
	Free DOX	Lf-HA-DOX	Endocytosis/pH difference/Lf receptor	The GMFI of DOX was increased 8.71 times	¹¹²
Reduce the particle size	200nm	70nm	Promote drug delivery to the brain; reduce drug uptake by the liver; avoid being adsorbed by receptors on the surface of phagocytes, escaping phagocytosis and clearance by phagocytes	After 5 minutes of administration, the concentration in the brain improved 2-fold; after 20 min of administration, the concentration in the brain improved 3-fold; AUC _{0-60 min} in the brain was 2.58 times	¹⁵⁹
Structural modification	β -elemene	Derivatives-I Ia	Caused the G2 phase arrest of the cell cycle; induced apoptosis of glioma cells by preventing the activation of the PI3K/Akt pathway	Tumor inhibitory ratio increased from 49.6% to 64.8%	¹⁶²
Combination with resuscitative CHMs	Tanshinol	Tanshinol-borneol esterification complex	Inhibit the expression of P-gp; reduce P-gp efflux	It was easy to travel through BBB to the brain with the higher concentration of tanshinol; had a longer retention time	¹⁶⁷
	PUE and TMP	Combination with α -asarone	Decrease expression of ZO-1, while increase the expression of A1AR and A2AAR	The accumulation of permeated PUE and TMP was increased; AUC _{brain} for PUE and TMP was increased 1.34-fold and 1.79-fold	¹⁷⁰
Application of physical technology	EB-albumin complex	Performed ultrasound treatment	The tight junctions between cells become loose and reversible pores appear; improved endocytosis of cells	Fluorescence intensity increased significantly	¹⁷³
Change route of administration	Oral/intravenous	Nasal drug delivery/intrathecal injection	Directly through the BCB without crossing BBB	i.v. administration was only 56.85% of the nasal administration/ prolong drug release time; enhanced healing and reduced drug toxicity	^{30,176}

delivery. It can be administered by a single puncture or multiple rounds of delivery after the sheath is implanted. After i.t., the drug can directly reach the target site through BCB without crossing the BBB for quick action.

Etmianet et al³⁰ used nimodipine microspheres for intrathecal injection, and the results showed that nimodipine microspheres could prolong drug release time, enhance healing effect, and reduce drug toxicity. While drugs act more directly when given i.t., they can cause more damage. Strategies for enhancing glioma treatment are shown in Table 2.

Perspectives

Due to the protective effect of the brain barrier on the brain, the clinical treatment of glioma still remains difficult. Brain-

targeted drug delivery has attracted wide attention because of its slow release and controllable and targeted safety. Regardless of the target, drug targeting is based on the interaction between the dosage form characteristics of the drug delivery system and the specific physiological/pathological structure of the body. The development of biomimetic drugs/materials with homologous binding and immune escape functions has been regarded as the most ideal alternative. These drugs/materials use autologous tissues/cells/proteins from the human body as carriers to quickly reach the target site after entering the human body.

For example, NPs wrapped in glioma cell membrane or glioma cell membrane proteins were loaded on NPs. Under certain conditions, tumor cells are killed by various mechanisms such as starvation therapy and photodynamic/

photothermal therapy.^{132,142} In addition, as endogenous substances, it is difficult for the immune system to recognize the drug-carrying system in membrane disguise. Thus, these systems can escape rejection by the immune system for long therapy cycles. The carriers are gradually degraded or absorbed without accumulation in the body. Such bionic materials can be applied independently without chemotherapy drugs. Thus, they do not cause serious adverse reactions and might be safer.

Accordingly, the following four suggestions are proposed for further research on targeted agents for glioma. (1) While studying the brain-targeted delivery of drugs, researchers should also pay attention to the latest progress in basic research including structural characteristics, composition, and permeability of BBB and glioma. It is important to improve the efficiency of brain-targeted delivery of drugs. (2) Researchers should identify and evaluate the factors that affect the behavior of the glioma NDDS in vivo, which is the basis of the effectiveness. (3) Considering the perspective of biosafety, biodegradable material without immunogenicity or biotoxicity that can be removed from the brain should be utilized in glioma NDDS. (4) A unified preparation method should be developed to make NPs more uniform, stable, and controllable—this will ensure clinical efficacy.

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Disclosure

The authors report no conflicts of interest in this work.

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