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REVIEW

Receptor-mediated cascade targeting strategies for the application to medical diagnoses and therapeutics of glioma

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Abstract Glioma is the most frequent tumor of the central nervous system with high morbidity and mortality. Despite the great progress to exploit diagnostic and therapeutic tools, the treatment of glioma remains a huge challenge. The special anatomical structure of the brain, in particular, the blood–brain barrier (BBB) and the blood–brain tumor barrier (BBTB), limits the drug delivery efficacy and causes the diagnosis and treatment failure of various drugs. This encourages researchers to develop some novel therapeutic strategies to address these problems. Currently, receptor-mediated cascade targeting (RMCT) strategies, with targeting ligands targeting BBB and BBTB simultaneously, have been developed to overcome the barriers and are expected to accurately deliver drugs to glioma for diagnosis and therapy. In this review, we summarize the receptors and targeting ligands used in glioma, the categories of RMCT strategies, and the nanoplatforms used in RMCT strategies. We believe that the RMCT strategies will provide a reference for glioma treatment in the clinic and improve the life quality of patients with glioma.

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Keywords Glioma · Blood–brain barrier · Blood–brain tumor barrier · Receptor-mediated cascade targeting · Diagnosis and therapy · Brain research · Nanoplatform

Introduction

Glioma, which is derived from glial cells, accounts for ~ 80% of primary central nervous system (CNS) tumors and is one of the most common and aggressive tumors (Bi et al. 2020). According to the growing speed and aggressiveness, the World Health Organization (WHO) classified glioma into four grades: low grade (WHO grade I/II), such as astrocytes, oligodendrocytes, and ependymal cells, and high grade (WHO III/IV), such as oligodendroglioma, ependymoma, and glioblastoma multiforme. The median survival of patients bearing glioma is 14.6 months and the 5-year survival rate is 5% (Lu et al. 2017; Kim et al. 2017). Accurate diagnosis plays a key role in cancer treatment, which could present important information about the histological type, classification, grade, potential aggressiveness, and so on. The imaging techniques such as magnetic resonance imaging (MRI), computed tomography (CT), positron-emission tomography (PET), and fluorescence imaging (FI) are widely used in glioma diagnosis, which could help doctors determine the best therapeutic schedule. Current treatments of glioma rely on surgical resection, but the therapeutic

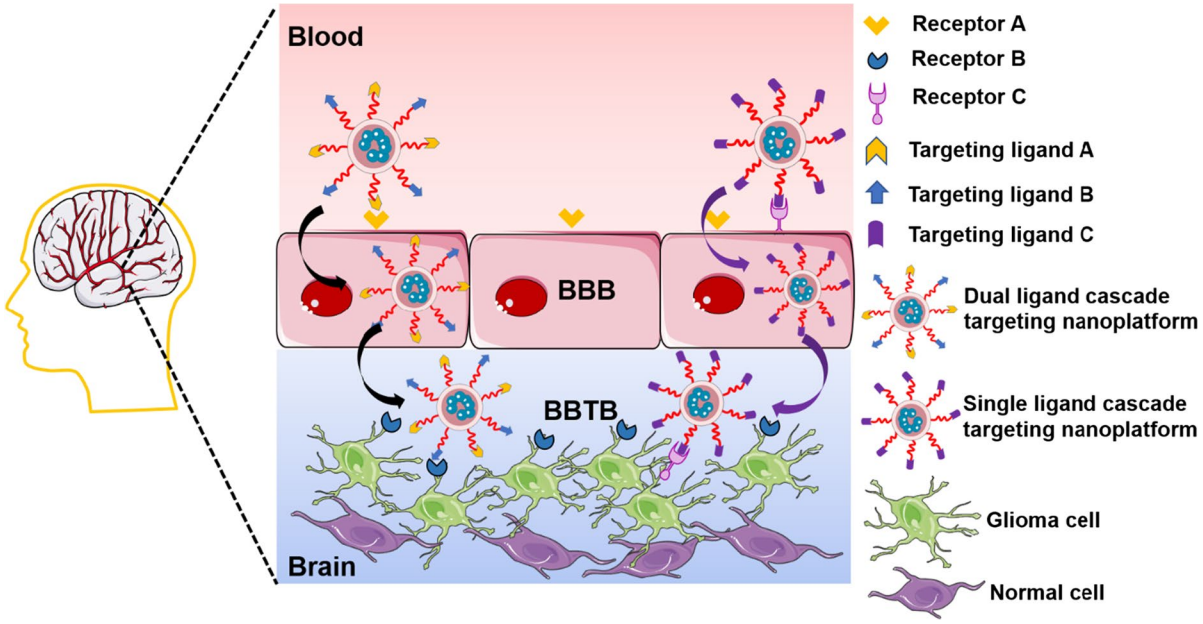

Fig. 1 Schematic illustration of RMCT strategies for GBM therapy

outcomes are limited due to the lack of a sharp border between glioma and normal tissues (Xie et al. 2021). The remaining invasive glioma cells can rapidly penetrate and destroy normal tissue structures. Therefore, malignant gliomas can rarely be cured by surgery alone. In 2013, Scholtyssek et al. found that the combination of chemotherapy with radiotherapy significantly prolonged the survival of patients, underlining the therapeutic potentials of chemotherapy for treating glioma. The mechanism of these chemotherapy agents includes directly killing of tumor cells, anti-angiogenesis, and inhibition of tumor invasion (Cooney et al. 2020). Besides, immunotherapy (Qi et al. 2020; Wang et al. 2020; Carpenter et al. 2021), gene therapy (Altshuler et al. 2020; Peng et al. 2018; Banerjee et al. 2021), and phototherapy (Li et al. 2020; Yang et al. 2020a; Liu et al. 2018a) are emerging as promising therapeutic methods for glioma. Although these above treatments can improve the quality of patients' life, 98% of small molecule drugs and nearly 100% of macromolecular drugs are difficult to penetrate into brain tissue due to the complicated blood–brain barrier (BBB) combined with the blood–brain tumor barrier (BBTB). Therefore, developing an effective strategy that can penetrate the BBB, and specifically enter the tumor area, is highly required.

Receptor-mediated cascade targeting (RMCT) strategies have proven to be a viable approach for overcoming the abovementioned two obstacles (Fig. 1), in which the first phase targeting ligands circumvent the BBB barrier, and the second-phase targeting ligands deliver drugs selectively against glioma cells (Fu et al. 2019a; Cui et al. 2020). The RMCT strategies have been extensively employed in glioma targeting research, whose mechanism is based on the interaction between the targeting ligands and the receptors expressed in the brain. The receptors involve in transferrin receptor (TFR) (Luo et al. 2019; Choudhury et al. 2018; Kang et al. 2020), low-density lipoprotein receptor–related protein receptor (LRPR) (Zong et al. 2019; Han et al. 2018), insulin receptor (IR) (Bonnin et al. 2017), nicotinic acetylcholine receptor (NAR) (Clarke et al. 2021; Pucci et al. 2021), etc. To achieve RMCT strategies, two methods have been adopted. One method is to fabricate the drug delivery system modified with only one kind of ligand, the corresponding receptor of which is overexpressed on both BBB and glioma cells. The second method is to construct the drug delivery system modified with two kinds of ligands, one targeting BBB, and the other targeting glioma cells (Jang et al. 2016).

The integrated nanoplatforms are increasingly applied in RMCT strategies as the drug delivery

system (Ho et al. 2017; Tammam et al. 2017). The integrated nanoplatforms mainly include organic nanoplatform, inorganic nanoplatform, and cell-based nanoplatform. The nano-sized agents could preferentially target the tumor tissue passively due to the enhanced permeation and retention effect (EPR) (Byeon et al. 2016). It is evidenced that the EPR effects could offer 20–30% increases in tumor site targeting (Kobayashi et al. 2013). In addition, targeting ligands can be linked to nanoplatforms for active targeting. Therefore, combining RMCT strategies with nanoplatforms can further improve therapeutic efficacy and reduce toxic side effects.

In the current review, we summarize the receptor and targeting ligands used in glioma, the categories of RMCT strategies, and nanoplatforms used in RMCT strategies. We believe the RMCT strategies would have a revolutionary impact on glioma diagnosis and therapy.

Receptor-mediated cascade targeting strategies for the therapy of glioma

The tight BBB prevents therapeutic agents from entering the brain, functioning as the first barrier for glioma therapy (Dai et al. 2018; Chen et al. 2019). The nonspecific accumulation of drugs in the brain after crossing the BBB is the second barrier for glioma. To overcome these two obstacles, RMCT delivery systems modified with the active ligands for bypassing the BBB and BBTB respectively are being developed (Cui et al. 2016; Chen et al. 2017). The selection of targeting ligands for efficient BBB penetration and the subsequent BBTB targeting would be crucial for RMCT strategies. According to the modification of targeting ligands, there are two types of RMCT strategies: single ligand-modified RMCT strategy and dual ligand-modified RMCT strategy. Herein, we summarize the commonly utilized targeting ligands and the categories of RMCT strategies.

Receptor-mediated endocytosis

Receptor-mediated endocytosis (RME) is one of the most important pathways for drug delivery to the brain, which have been extensively employed in glioma targeting research. There are many receptors that are overexpressed on the BBB or glioma cells (Table 1 and Table 2), which can promote the drug targeting delivery via receptor-mediated endocytosis (Gao 2016).

Receptor-based on transferrin

Receptor based on transferrin (TFR), as a type of transmembrane protein, is overexpressed in brain capillary endothelium and glioma cell. Besides, TFR in gliomas can promote iron accumulation and promote tumor progression, which indicated that it is a promising target for achieving gliomas targeting therapy. TF, a serum glycoprotein of 80 kDa, with a high binding affinity to TFR, has been widely used to enhance the cellular uptake of drug-loaded delivery systems (Gu et al. 2017; Zhang et al. 2014). Despite some promising preclinical results, the application of TF is limited by the endogenous TF and high molecular weight of the protein. TF showed high concentrations in the blood and it could competitively inhibit the binding of TF-modified carrier to TFR. Besides, TF with relatively high molar weight is difficult to construct the drug delivery systems. Alternative ligands for TFR have been extensively evaluated. Recently, a novel targeting ligand, HAIYPRH (T7) peptide, was identified by a phage display system (Fu et al. 2019a; Han et al. 2011). This ligand showed a robust binding affinity for TFR. The binding site of T7 to TFR is different from that of TF to TFR. Thus, endogenous TF will not competitively inhibit the binding of TF-modified carrier to TFR. Surprisingly, research showed that the endogenous TF in vivo can conversely promote the uptake of T7. T7, thus, can be developed as a more advantageous targeting ligand for TFR as

Table 1 The receptor on BBB, glioma cells, and both BBB and glioma cells

The receptor on BBB	The receptor on glioma cells	The receptor on both BBB and glioma cells
Mannose receptor	IL-13 receptor	TFR
TGN receptor	Integrin	LRPR
	Nucleolin	N-Acetylglucosamine
		LR
		LDLR
		LRPR
		FR
		IR

Table 2 Targeting ligands used in RMCT strategies

Receptor	Targeting ligand	Modal drug	Reference
TFR	TF	DOX, RES, siRNA, TMZ/JQ1	Luo et al. 2019; Jhaveri et al. 2018; Liu et al. 2018b; Lam et al. 2018)
	T7	MiRNA, VC, siRNA, CED /PTX	
	CRT	PTX, fluorescent probe	Sukumar et al. 2019; Liang et al. 2018; Wei et al. 2016; Yu et al. 2019)
			Kang et al. 2015; Ni et al. 2020)
LRPR	Angiopep-2	DOX, ATO, DTX	Xu et al. 2016; Xu et al. 2021; Kadari et al. 2018)
IR	8314MAb	ETP	Kuo and Lee 2016)
LFR	LF	DOX, IONP, CUR, SHK	Zhang et al. 2021; Tomitaka et al. 2015; Xu et al. 2017; Li et al. 2018a)
TGNR	TGN	DTX	Gao et al. 2014)
IL-6R	I_6P_8 peptide	DOX	Shi et al. 2017)
Integrin $\alpha_v\beta_3$	RGD	PTX, DOX/siRNA, DTX	Fu et al. 2019b; Huang et al. 2018; Sonali et al. 2016)
FAR	FA	PTX, DOX, TMZ	Li et al. 2018b; Niu et al. 2020; Minaei et al. 2019)

TFR transferrin receptor; *LRPR* low-density lipoprotein receptor–related protein receptor; *LFR* lactoferrin receptor; *TGNR* TGNYKALHPHNG peptide receptor; *IL-6R* interleukin-6 receptor; *FAR* folate receptor; *TF* transferrin; *LR* lactoferrin receptor; *T7* HAIYPRH peptide; *CRT* CRTIGPSVC peptide; *8314mAb* 8314 monoclonal antibody; *LF* lactoferrin; *TGN* TGNYKALHPHNG peptide; I_6P_8 LSLITRL; *RGD* Arg-gly-asp peptide; *FA* folic acid; *DOX* doxorubicin; *RES* resveratrol; *siRNA* small interfering RNA; *TMZ* temozolomide; *miRNA* micro RNA; *VC* vincristine; *CED/PTX* cediranib/paclitaxel; *ATO* arsenic trioxide; *ETP* etoposide; *IONPs* iron oxide nanoparticles; *CUR* curcuminoid; *SHK* shikonin; *DTX* docetaxel

compared to TF. Besides T7, another peptide, e.g., the cycle nine amino-peptide CRTIGPSVC (CRT), has also been developed to improve the binding between TF and TFR (Kang et al. 2015). It is noted that the CRT is able to functionally "mimic" iron via binding to a complex of TF and TFR, inducing an allosteric conformational shift to apo-TF that leads to transport (Kang et al. 2015).

Receptor based on low-density lipoprotein receptor–related protein

LRP, a member of the low-density lipoprotein receptor family, is not only highly expressed on the blood–brain barrier but also on glioma cells (Xu et al. 2016; Jiang et al. 2018; Du et al. 2020). LRP can interact with a variety of secreted proteins and molecules on the surface of cells (Shi et al. 2018a). Angiopep-2 (TFFYGGSRGKRNNFKTEEY, molecular weight 2.4 kDa), a high-efficiency ligand of LRP receptor, can be used for modifying nanoplatforms as RMCT delivery systems to deliver chemotherapy molecules to glioma (Zhu et al. 2018; Tian et al. 2018). Fan et al. (Tian et al. 2018) developed angiopep-2-modified biocompatible framework nucleic acid (FNA)–based imaging probe (ANG-TDNs) for brain tumor targeting. This probe exhibited high binding efficiency with low-density lipoprotein receptor–related protein-1 (LRP-1) of BBB and glioma. They found that ANG-TDNs stayed intact for at least 12 h in serum, and that enhanced cellular uptake of tetrahedral DNA nanostructures in brain capillary endothelial cells and Uppsala 87 malignant glioma (U87MG) cells. Remarkably, studies in both in vitro and in vivo models revealed that ANG-TDNs could cross the BBB. Especially, in vivo imaging showed strong fluorescent signals in U87MG human glioblastoma xenograft in nude mice.

Receptor based on insulin

IR, a transmembrane glycosylated protein, which consists of two α and two β chains linked by disulfide bonds, could mediate the transport of blood-borne insulin into the brain parenchyma, having been extensively studied as a part of the RMCT delivery system (Hampton 2015; Newton 2006). The insulin molecular pocket formed by two α subunits results in an increase in tyrosine phosphorylation of the β subunit, and induces a conformational change of the IR to form a channel. This special conformational change could allow transmembrane transport of drug molecules (Fang et al. 2017). The 8314 monoclonal antibody (8314 mAb), a kind

of peptidomimetic antibody, could recognize the α-subunit of IR expressed on human brain microvascular endothelial cells (HBMECs) which can be used for the first targeting.

Other related receptors

In addition to the several receptors above, there are also some receptors highly expressed on both glioma cells and angiogenesis including interleukin-4 receptor (IL-4R) with specific binding to CRKRLDRNC peptide (AP-1) (Sun et al. 2017), heparan sulfate proteogly receptor (HSPG) with specific binding to CGKRK peptide (Lv et al. 2020), TGNYKALHPHNG receptor (TGN) with specific binding to TGN peptide (Gao et al. 2014; Yang et al. 2020b), and interleukin-6 receptor (IL-6R) with specific binding to I_6P_8 peptide (Shi et al. 2017) that can be applied in RMCT strategies.

Categories of receptor-mediated cascade targeting strategies

According to the modification of targeting ligands, there are two types of RMCT strategies: single ligand-modified RMCT strategy and dual ligand-modified RMCT strategy (Table 3). Both of them show their advantages and disadvantages (Table 4).

Single ligand-modified receptor-mediated cascade targeting strategy

The single ligand-modified RMCT strategy is linked with one ligand, which could not only target BBB but also can target glioma cells. Specifically, it was found that a large number of receptors are richly expressed on brain capillary endothelial cells, such as TFR, LRPR, LFR, and IR. Among them, TFR, LRPR, and LDLR, etc. are highly expressed in glioma cells.

Table 3 An overview of two RMCT strategies

RMCT strategies	BBB	GBM cells	Reference
Single ligand-modified RMCT delivery system	TF ligand	TF ligand	Lam et al. 2018; Ramalho et al. 2022)
	WGA	WGA	Xiao et al. 2018)
	LF	LF	Xiong et al. 2020)
	LRP ligand	LRP ligand	Liu et al. 2021a; Polidoro et al. 2021; Jiao et al. 2019)
Dual ligand-modified RMCT delivery system	83–14 mAb	Anti-EGF receptor	Kuo and Lee 2016)
	LRP ligand	Anti-CD133 mAb	Kim et al. 2018)
	TF ligand	FA	Gao et al. 2013)
	TGN peptide	AS1411 aptamer	Gao et al. 2014)

TF transferrin; *WGA* wheat germ agglutinin; *LF* lactoferrin; *LRP* low-density lipoprotein receptor–related protein; *FA* folate; *TGN* TGNYKALHPHNG

Table 4 Advantages and disadvantages of the two RMCT drug delivery systems

RMCT strategies	Advantages	Disadvantages
Single ligand-modified RMCT strategy	1. Easy for preparation 2. Easy for production	1. Low specificity 2. Fewer targeting ligands to choose from
Dual ligand-modified RMCT strategy	1. High specificity 2. High affinity 3. High accumulation in tumor site	1. Complex preparation process 2. High production cost 3. Interference between the two molecules

These ligands could serve as dual-targeting to achieve cascade delivery. Xiao et al. (Su et al. 2014) prepared LF-modified DOX-loaded bovine serum albumin nanoparticles, which enhanced blood–brain barrier (BBB) penetration and improved cellular uptake in the glioma cells of the drug. Jiang et al. (Pang et al. 2011) used TF to modify doxorubicin-loaded poly(ethylene glycol)-poly(caprolactone) (PEG-PCL) vesicles, which overcame BBB, promoted drug accumulation in the brain, and enhanced the cellular uptake in the glioma cells of the drug. Jiang et al. (Bi et al. 2016) prepared T7 peptide-conjugated, carmustine-loaded micelles via the emulsion-solvent evaporation method, which could target the TFR expressed on BBB endothelium and glioma cells.

Dual ligand-modified receptor-mediated cascade targeting strategy

The double ligand-modified RMCT strategy is conjugated with two specific ligands. These two ligands cooperate with each other, where one ligand targets to BBB and promotes penetration into the brain tissue, while the other targets glioma cells and promotes cellular uptake. Recently, the combination of various ligands has been widely studied. Gao et al. (Cui et al. 2020) used DWSW and NGR peptide ligands to modify PLGA nanoparticles that coated with erythrocyte membranes, which could penetrate the BBB and BBTB. Mei et al. (Zhang et al. 2017) developed T7 and DA7R dual peptide-modified liposomes to co-deliver doxorubicin (DOX) and vincristine (VCR) to glioma. The T7 could bind to TFR expressed on the BBB and glioma cells, while the DA7R has a high affinity to endothelial growth factor receptor 2 (VEGFR 2) highly expressed on angiogenesis.

Nanoplatform-based receptor-mediated cascade targeting delivery system

Nowadays, nanoplatforms are increasingly applied in cancer therapy and diagnosis (Woodman et al. 2021; Pavitra et al. 2021; Ali et al. 2021). The nano-sized agents could preferentially target the tumor tissue passively due to the enhanced permeation and retention effect (EPR) (Byeon et al. 2016). In addition, targeting ligands can be linked to nanoplatforms for RMCT drug delivery. Therefore, combining dual-targeting strategies with nanoplatform can further improve efficacy and reduce toxic side effects. The most widely used nanoplatforms to deliver drugs to glioma include organic nanoplatform (polymeric nanoparticles, liposomes, dendrimer nanoparticles, etc.), inorganic nanoplatform (metal nanoparticles, mesoporous silica, carbon nanotubes, etc.), and cell-based nanoplatform (circulating erythrocytes, stem cells, immune cells, etc.) (Fig. 2).

Organic nanoparticles

Liposomes are small lipid vesicles mainly made from naturally derived biocompatible and biodegradable phospholipids and clinically used as a drug delivery system by modulating the pharmacokinetics, biodistribution, or drug solubility (Large et al. 2021; Sonju et al. 2021; Wang and Grainger 2019; Zahednezhad et al. 2019). Liposomes have also been extensively used to increase the transport of drugs across the BBB via the binding effect between the specific endogenous transporters localized on the BBB and the specific ligands modified on the surface of the delivery system (Zhan and Wang 2018; Shi et al. 2018b; Zong et al. 2014). P-Aminophenyl-α-D-manno-pyranoside (MAN) is a kind of mannose analog that has a specific affinity to the glucose transporter (Singh et al. 2015). Ying et al. (Ying et al. 2010) developed the daunorubicin-loaded MAN and TF co-modified dual-targeting liposomes for glioma treatment. The dual-targeting effects were evaluated on the BBB model in vitro, C6 glioma cells in vitro, avascular C6 glioma tumor spheroids in vitro, and C6 glioma-bearing rats in vivo, respectively. After applying dual-targeting daunorubicin liposomes, the transport ratio across the BBB model was significantly increased up to 24.9%. The most significant uptake by C6 glioma was evidenced by flow cytometry and confocal microscope. The C6 glioma spheroid volume ratio was significantly lowered to 54.7%. HIV-1 transactivating protein (TAT), one of the cell-penetrating peptides (CPPs), can facilitate the intracellular delivery of drugs with various sizes and physicochemical properties (Torchilin 2008a, 2008b). Liposomes modified with TAT can deliver the cargoes into cells with high efficiency via an unsaturated and receptor/transporter independent pathway. Zong et al. (Zong et al. 2014) prepared dual-targeting doxorubicin liposomes modified with cell-penetrating peptide (TAT) and

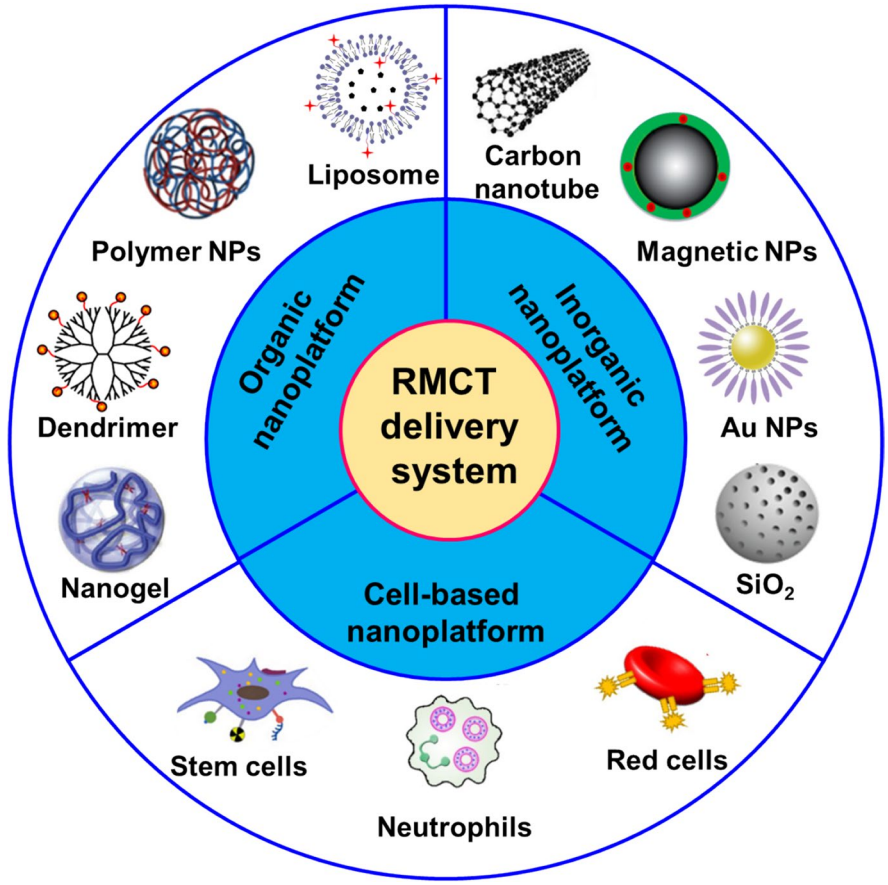

Fig. 2 Summary of nanoplatforms for the application to medical diagnoses and therapeutics of glioma

transferrin (T7) (DOX-T7-TAT-LIP) for targeting brain glioma (Fig. 3). In vitro cellular uptake and three-dimensional tumor spheroid penetration studies demonstrated that the system could not only target endothelial and tumor monolayer cells but also penetrate the tumor to reach the core of the tumor spheroids. In vivo imaging demonstrated that T7-TAT-LIP provided the highest tumor distribution.

Dendrimers are synthetic macromolecules with hyperbranched nanostructure, high degree of functionality, and low polydispersity, which are widely used in the field of drug delivery system. Poly(amidoamine) (PAMAM) is the first dendrimer with a three-dimensional spherical structure, and it was prepared by the classical Michael addition reaction and ester aminolysis reaction by the gradual divergence method (Araujo et al. 2018). Its properties change with the change of its generation (Li et al. 2018c). PAMAM can deliver drugs/genes through chemical bond coupling, physical encapsulation, and electrostatic interaction. Besides, PAMAM is acid-sensitive, and its size and structure would change with the change of pH. Because of the acidic microenvironment of tumor tissues, the drugs loaded in PAMAM may be released rapidly in the tumor site (Leng et al. 2013; Patil et al. 2018). Piao et al. (Shi et al. 2020) developed TGN and RGD dual peptide-modified PAMAM dendrimer that loaded arsenic trioxide to treat glioma. TGN can help transport PAMAM dendrimer into the brain, and RGD can enhance cellular uptake of PAMAM dendrimer, which showed great potential in targeted glioma therapy (Fig. 4).

Nanogels are formed by physical or chemical cross-linked polymeric networks (Liang et al. 2021; Hashimoto et al. 2018; Grimaudo et al. 2019). They can encapsulate both small molecules and macromolecule drugs through their cross-linked networks (Wang et al. 2018, 2021; Ekkelenkamp et al. 2018; Hajebi et al. 2019). Besides, the high biocompatibility of the polymers used, the high

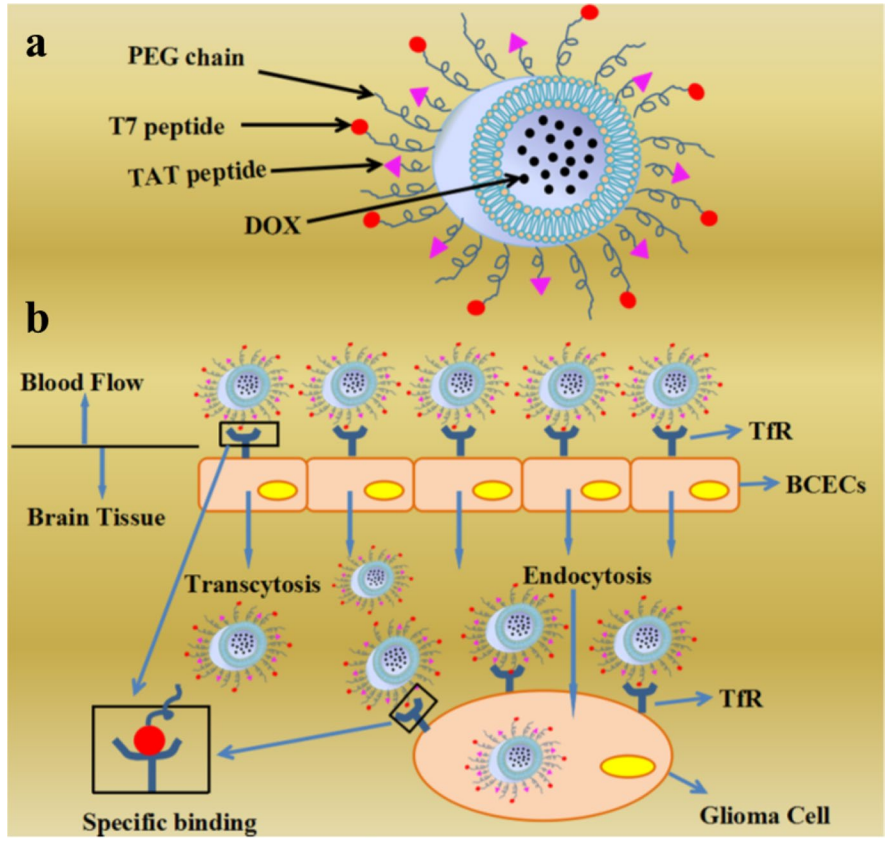

Fig. 3 Scheme of T7 and TAT modified DOX-loaded liposomes (DOX-T7-TAT-LIP). **a** The structure of DOX-T7-TAT-LIP. **b** DOX-T7-TAT-LIP could specifically bind to transferrin receptors expressed on BCECs, transport across the BBB, then effectively accumulate in the glioma. Reproduced with permission from Ref. (Zong et al. 2014), Copyright © 2014 American Chemical Society.

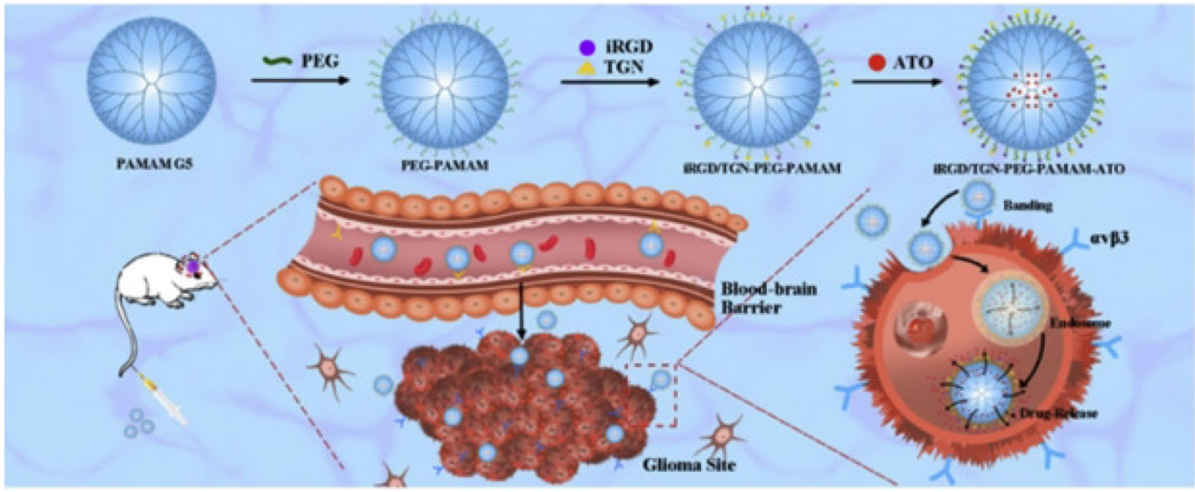

Fig. 4 Scheme of TGN and iRGD co-modified PAMAM-based nanoplatform. Reproduced with permission from Ref. (Shi et al. 2020), Copyright © 2020 Published by Elsevier Inc.

stability, the softness, and the swelling properties allow for achieving a controlled drug release at the target site, which allows them to be applied in cancer therapy and diagnosis. Zhao et al. (Song et al. 2021) developed a DOX-loaded dual-sensitive nanogel (CMCSN) that was modified with targeting

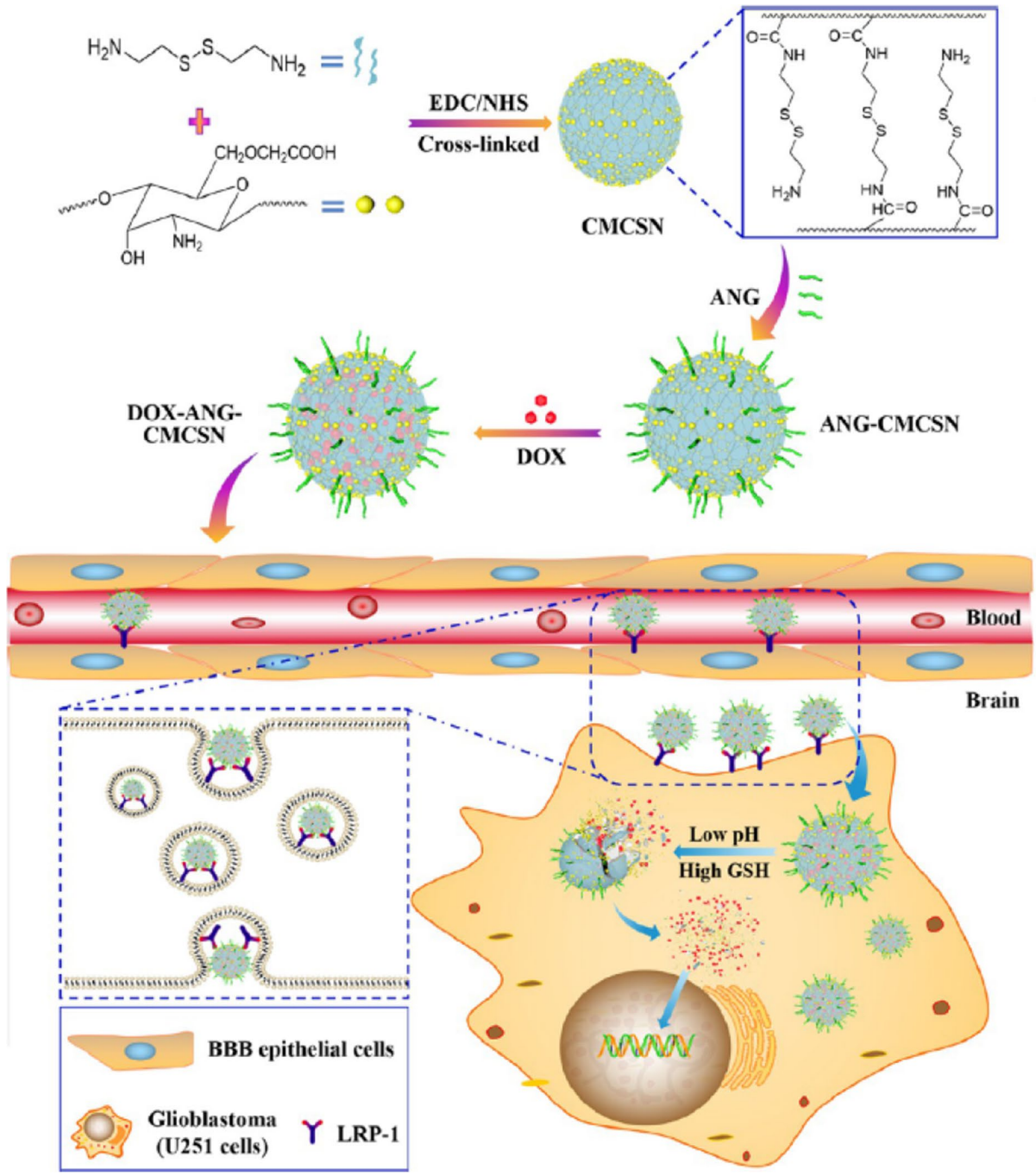

Fig. 5 Scheme of the AGN-modified DOX-loaded nanogels for GBM targeting therapy. Reproduced with permission from Ref. (Song et al. 2021), Copyright © 2021 American Chemical Society

ligand ANG peptide, which was named DOX-ANG-CMCSN. DOX-ANG-CMCSN exhibited pH and redox sensitivity, and significantly enhanced BBB penetration and glioma cells targeting ability. Compared with the nanogel without modification of targeting ligand, DOX-ANG-CMCSN significantly improved the antitumor efficacy of DOX (Fig. 5).

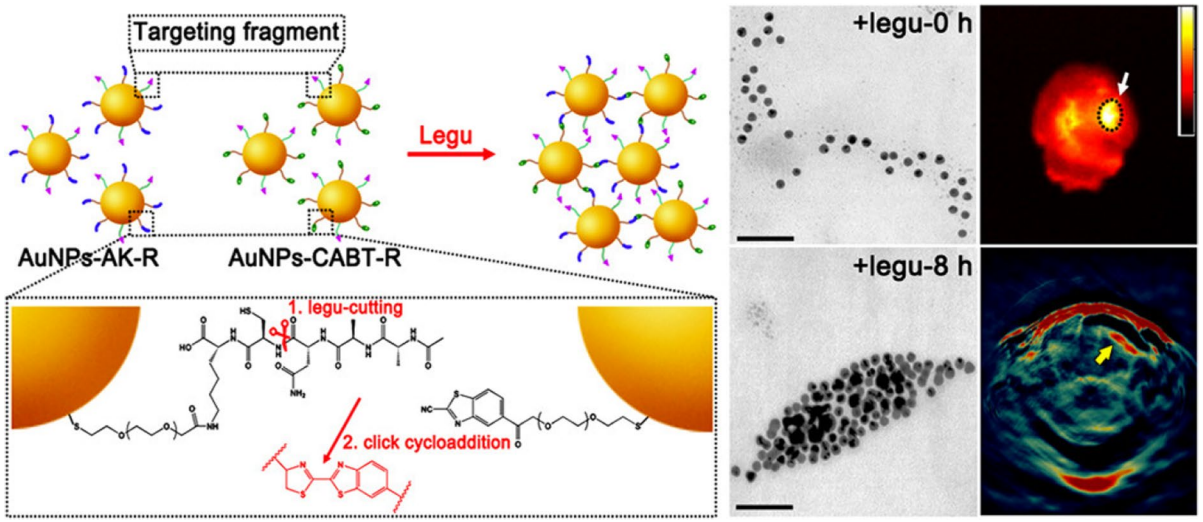

Fig. 6 Scheme of the AGN-modified DOX-loaded nanogels for glioma targeting therapy. Reproduced with permission from Ref. (Ruan et al. 2017), Copyright © 2017 American Chemical Society

Inorganic nanoparticles

Nowadays, carbon nanotubes (CNTs) have received great attention on drug delivery systems because of their unique physicochemical properties (Ren et al. 2012; Santos et al. 2014). With the unique one-dimensional structure, CNTs showed good transmissibility passing cell membrane, which makes it easier to deliver therapeutic drugs or diagnostic molecules to the tumor (Santos et al. 2014; Yaghoubi and Ramazani 2020). Moreover, CNTs have an ultrahigh surface area that permits efficient loading of multiple molecules alongside the nanotube wall. In addition, supramolecular binding of aromatic molecules can be easily achieved by the p-p stacking of those molecules onto the polyaromatic surface of nanotubes. In order to make it suitable for biomedical applications, improve its biocompatibility, and reduce its toxicity, appropriate pre-treatment, surface chemical modification, or modification are needed (Loh et al. 2018; Zhuang et al. 2019; Hassan et al. 2019). The bond for surface modification includes covalent or a non-covalent bond. For covalent bond, it is necessary to design a reaction of the molecules on the surface of the tube wall with the modifier chemically. The surface can also be modified with non-covalent bonding such as some amphiphilic polymers, the hydrophobic segments of the polymer can be attached to the surface of CNTs by p-p stacking, and the hydrophilic segments play an increasing role of water solubility (Xiang et al. 2020; Raphey et al. 2019; Kuche et al. 2018). Ren et al. (Ren et al. 2012) constructed the RMCT delivery system using angiopep-2-modified oxidized multi-walled carbon nanotubes (O-MWNTs) to load DOX as a drug delivery system for treatment of glioma. The effects of brain targeting and glioma targeting were testified by fluorescence image, illustrating that the angiopep-2-modified carbon nanotube is a prospective RMCT drug delivery system for glioma therapy.

Au nanoparticles (Au NPs) including nanospheres, nanorods, nanoshells, and nanocages are widely studied as inorganic nanoplatform (Sharifi et al. 2019; Luther et al. 2020). They have attracted great attention in the therapy of glioma due to their favorable properties including high penetration to the brain microvasculature, easy modification with various ligands, high stability, and low toxicity (Mignani et al. 2021). Besides, Au NPs have the ability to generate heat, which can directly kill the tumor cells via photothermal therapy (Chen et al. 2020; Christie et al. 2015). Gao et al. (Ruan et al. 2017) developed dual peptide-modified Au NPs (AuNP-A&C-R), which could target the integrin αvβ3 receptor on the BBB, cross BBB via receptor-mediated endocytosis, then target to the glioma cells. Besides, these dual-functional Au NPs

improved the chemotherapeutic effect on glioma-bearing mice (Fig. 6).

Cell-based nanoplatform

Cell-based nanoplatform such as circulating erythrocytes (Cui et al. 2020; Chai et al. 2017), stem cells (Wu et al. 2019; Su et al. 2015), and immune cells (Wu et al. 2019; Majumder et al. 2019) have been a new field of cancer therapy. This delivery system shows various advantages including long circulation in the bloodstream, abundant surface ligands, low immunogenicity, and high penetration to BBB as well as minimizing side effects (Suryaprakash et al. 2019; Dong et al. 2021). Because of these unique features, cell-based nanoplatform has received great attention in glioma therapy (Suryaprakash et al. 2019). Zhang et al. (Xue et al. 2017) obtained the neutrophil (NE)-based delivery vehicles (PTX-CL/NEs) by co-incubating NEs with liposomes that contain paclitaxel (PTX). PTX-CL/NEs retained the original activity of NEs during the preparation process, and its chemotactic effect on inflammatory factors was similar to that of natural NEs. After surgical resection of glioma, a large number of inflammatory factors (IL-8 and TNF-α) were released. Due to the targeted penetration of NEs, PTX-CL/NEs can effectively penetrate the BBB and reach the tumor site, thus preventing postoperative recurrence of glioma. Liu et al. (Liu et al. 2021b) labeled harvested live neutrophils with a lipid-decorated molecular photoacoustic contrast agent TFML, which showed strong photoacoustic signal and excellent brain tumor-targeting ability. Besides, the original activity of NEs during the preparation process and its chemotactic effect on inflammatory factors were not affected. These results indicated that TFML-labeled neutrophils have great potential for glioma detection (Fig. 7).

Conclusion and prospect

The diagnosis and therapy of glioma remains a huge challenge due to two major barriers BBB and BBTB.

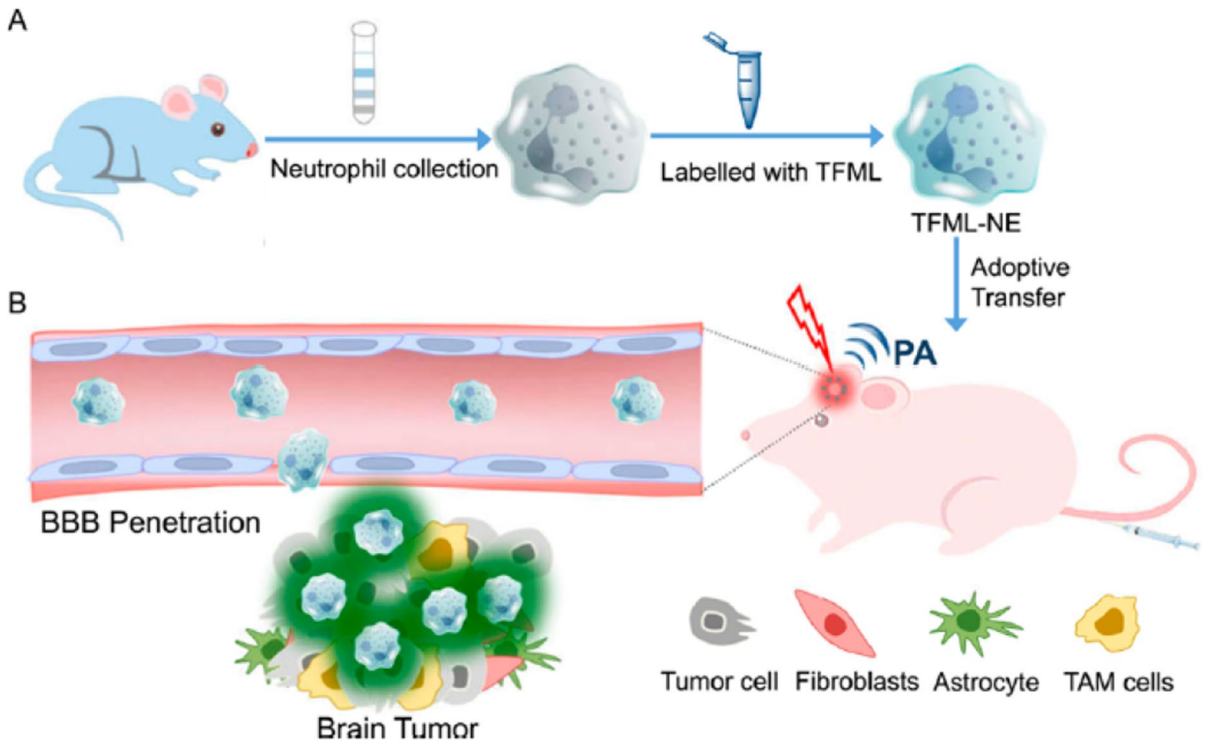

Fig. 7 Schematic illustration of NE-mediated drug delivery system for targeted GBM photoacoustic imaging therapy. Reproduced with permission from Ref. (Liu et al. 2021b), Copyright © 2021 American Chemical Society

In this context, great efforts have been made to facilitate drugs through the BBB and specifically reach the tumor cells. These approaches mainly include invasive techniques and noninvasive techniques. Intrathecal injection, a kind of invasive technique, consists in a direct injection of therapeutics into the cerebrospinal fluid (CSF), which show the advantages of high drug concentration in the brain, excellent therapeutic effect and low side effects. However, this strategy has certain disadvantages, including CSF infection, catheter obstruction, and inadequate drug distribution. The RMCT strategy, a kind of noninvasive technique, can regulate in vivo drug distribution in space, time, and dose due to its unique biological characteristics, which simultaneously overcome BBB and BBTB. The RMCT strategy consists of two important components: nanoplatforms and targeting ligands. The nanoplatforms not only can encapsulate and deliver drugs, but also can be modified with targeting ligands, which would be recognized by receptors highly expressed on the BBB or the glioma cell. In this review, a variety of receptors and targeting ligands used in glioma, such as transferrin, peptides, and aptamers were summarized. Besides, the categories of RMCT strategies, and nanoplatforms used in RMCT strategies, such as organic nanoplatform, inorganic nanoplatform, and cell-based nanoplatform were also summarized. More and more studies have shown that RMCT strategies can promote drug accumulation in the glioma and reduce the biodistribution of drugs in the normal brain site, thus improving the therapeutic effect and decreasing the toxic and side effects. Despite the great progress, the RMCT strategy is more complex compared with intrathecal injection, and many challenges still remain in the process of design, preparation, and release of RMCT strategy, which greatly limited their wide application.

To promote the application of RMCT strategy, we proposed several suggestions for the further research on RMCT strategy to treat glioma: (1) the proportion and density of targeting ligand, linker length, affinity between ligands and receptors, and preparation conditions should be fully studied, which can provide a reliable basis for in vivo application; (2) the in vitro and in vivo stability should be fully considered, which have a great effect on the targeting ability of targeting ligands; (3) to obtain homogenous nanoplatform and push up possible clinical translation, a simple and uniform preparation method should be developed; (4) for dual ligand-modified RMCT delivery system, the synergistic effect of dual ligand should be carefully investigated. Overall, great progress has been made in the treatment of glioma. With the in-depth study of nanoplatforms and glioma therapy, it is believed that RMCT strategy will be developed and applied in the clinic. This will fundamentally change the current defect of traditional clinical treatment, improving the quality of life of patients effectively.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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