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Development of bioactive materials for glioblastoma therapy

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ABSTRACT

Glioblastoma is the most common and deadly human brain cancers. Unique barriers hinder the drug delivering pathway due to the individual position of glioblastoma, including blood-brain barrier and blood-brain tumor barrier. Numerous bioactive materials have been exploited and applied as the transvascular delivery carriers of therapeutic drugs. They promote site-specific accumulation and long term release of the encapsulated drugs at the tumor sites and reduce side effects with systemic delivery. And the delivery systems exhibit a certain extent of anti-glioblastoma effect and extend the median survival time. However, few of them step into the clinical trials. In this review, we will investigate the recent studies of bioactive materials for glioblastoma chemotherapy, including the inorganic materials, lipids and polymers. These bioactive materials construct diverse delivery vehicles to trigger tumor sites in brain intravenously. Herein, we exploit their functionality in drug delivery and discuss the deficiency for the featured tumors, to provide guidance for establishing optimized therapeutic drug formulation for anti-glioblastoma therapy and pave the way for clinical application.

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Abbreviations: ALA, α-lipoic acid; BAG3, Bcl-2 associated athanogene 3; BBB, blood-brain barrier; BTB, blood-brain tumor barrier; CNS, central nervous system; CPT, camptothecin; cRGD, cyclic Arg-Gly-Asp; DACHPt, dichloro-(1,2-diaminocyclohexane)platinum (II); DCs, dendritic cells; DHA, dehydroascorbic acid; DOX, doxorubicin; DPPC, 1,2-dihexadecanoyl-rac-glycero-3-phosphocholine; FA, folate; GCV, ganciclovir; GLUT1, glucose transporter isoform 1; IL, interleukin; MMPs, matrix metalloproteinases; PTX, paclitaxel; ROS, reactive oxygen species; SN38, 7-ethyl-10-hydroxy-camptothecin; TAT, transactivator of transcription; TEG, tetra(ethylene glycol); TfR, transferrin receptor; TMZ, temozolomide; TNF, tumor necrosis factor.

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1. Introduction

Glioblastoma is the most common and malignant primary brain tumors. The median survival time of the patients is only 14.6 months after diagnosis, and the 5-year survival rate is less than 10% [1,2]. Glioblastoma cells rarely metastasize to other body organs, but they exhibit high aggressiveness and infiltration in brain tissues [3]. With these features, surgical resection cannot completely eliminate the tumor, and unavoidably leads to recurrence [4].

Numerous therapeutic agents, including chemical drugs, proteins and gene drugs, have emerged to show great potential to treat glioblastoma [5–7]. Like temozolomide (TMZ), a derivative of the alkylating agent dacarbazine, has been approved by oral administration for treating the newly diagnosed and recurrent malignant glioma [8–10]. However, the oral route offers insufficient drug concentration, and high daily doses leads to tumor resistance to the alkylating agents [11]. Due to the characteristics of the anti-tumor drugs, they always have poor solubility, short circulation and quick clearance. Most importantly, unlike other tumors, the intracranial tumors set up unique barriers to hinder effective therapy due to their individual position [12]. One is the blood-brain barrier (BBB), which is composed of brain endothelial cells, pericytes and astrocytic endfeet. It undertakes the responsibility to strictly regulate the transportation of large and small molecules between the blood and the brain parenchyma [13]. This structure is very essential to protect the healthy brain and prevent toxic transportation from blood [14]. However, it also impairs drug delivery into the lesion in the brain for effective therapy. The other one is the blood-brain tumor barrier (BTB), which refers to the transport obstacles between the blood vessels and brain tumor cells [15,16]. The blood vessels around the glioblastoma had the similar features with vessels in other tumor microenvironment, like permeability for drug entry. And the brain tumor cells also express transport protein for drug efflux. Due to these barriers in brain tumors, it is generally difficult for the free drugs to get appropriate targeting and suitable delivery penetrating into the glioma parenchyma. These all result in poor therapeutic responses against the tumor and severe side-effects to normal tissues. Herein, a more efficient strategy is urgently needed for glioblastoma therapy.

Recently, a variety of biomaterials has been exploited and applied as agents and delivery vehicles [17], including inorganic materials, lipids and polymers. They are widely used to overcome the problems including drug solubility and stability, and long circulation. They could be easily modified and manufactured to construct a more suitable and efficient delivery system for glioblastoma. With the development of nanotechnology, the drug delivery system could trigger these drugs to the tumor sites with minimal adverse effects. There had some reviews reported about the glioblastoma therapy. For example, Buddy D. Ratner's group detailed the intracranial tumor therapy by a localized application of polymeric microspheres with encapsulated drugs [18]. GLIADEL® wafer was the only FDA approved product for locally intracranial tumor therapy at the site of tumor resection, and its application for treatment of glioblastoma had been reported by Scott D. Wait et al. [19]. The therapeutic strategies and drug delivery process with nanoparticles against brain cancers had also covered in previous reports [20,21]. However, these reviews didn't exploit the structures and functionality of the applied bioactive materials for glioblastoma therapy *via* intravenous injection (*i.v.*). Here, in this review, we will focus on the bioactive materials applied in the treatment of glioblastoma, exploit their functionality in drug delivery and deficiency and discuss the influence of material structures on the transvascular transportation for drug delivery to brain tumors, to provide guidance for development of rational delivery vectors for effective anti-glioblastoma therapy.

2. Inorganic material-based nanoparticles

Many inorganic biomaterials were exploited as delivery platforms to deliver therapeutic drugs [22–24]. They could regulate the size of nanoparticles to overcome the limitation of unique structures of brain tumors. For example, Maciej S. Lesniak et al. exploited a blood-brain barrier permeable platform with ultra-small gold nanoparticles (5 nm) to deliver anticancer drug doxorubicin (DOX) to brain tumor tissues (Fig. 1) [25]. The pH-sensitive Au nanoparticles modified with a transactivator of transcription (TAT)

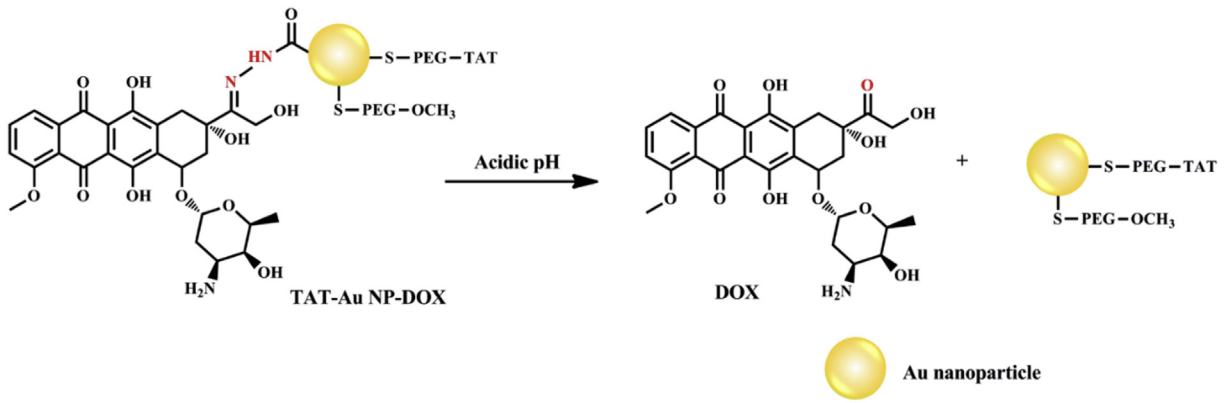

Fig. 1. The chemical structure of TAT-Au NP-DOX, and the release process under acidic conditions. Reprinted and modified with the permission from Ref. [25].

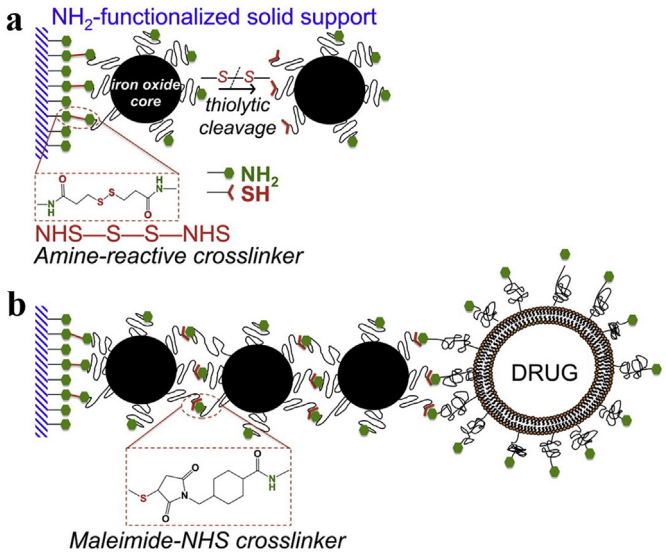

Fig. 2. Illustration of the controlled assembly of multicomponent nanochain by using solid-phase chemistry. Firstly, janus-faced iron oxide nanospheres with two functional groups were synthesized (a). Secondly, the unique faces on the nanospheres conjugated together and chemically linked with a DOX-loading liposome (b). Reprinted with permission from Ref. [37].

peptide, and brought the drug penetrate through BBB and reach the tumor. Comparing with free drug group (37.5 days), the median survival of TAT-Au NP-DOX treated group was 44 days after a single administration by *i.v.* injection in an intracranial U87 mouse model.

Ultra-small sized metal nanoparticles could be easily prepared. This provided better condition for this sized nanoparticles getting into the brain [26]. However, this nanoparticles also facilitate entry into normal organs, like liver and kidney, without a suitable guidance [27]. Moreover, these metal-based nanoparticles are mostly non-biodegradable, which might induce metabolic problem and side-toxicity to human body [26,28]. Herein, the proper target and optimized clearance are the important parameters for the design and application of inorganic material-based system for glioblastoma therapy.

3. Liposomes

Liposomes were promising delivery vesicles composed of lipid bilayers [29]. They had spherical structures, and formed a hydrophilic cavity with the lipid bilayers. The size of the liposomes could be varied from nanometers to micrometers. The first liposomal drug, Doxil (doxorubicin•HCl liposome injection), was approved by FDA to treat ovarian cancer, AIDS-related Kaposi's sarcoma, and multiple myeloma [30]. From then on, the delivery of therapeutic drugs with liposome had attracted intensive attentions for anticancer application [31–33]. For example, Efstathios Karathanasis's group developed a multicomponent nanochain carrier to access the brain and accumulate at the glioma sites [34]. This nanochain was composed of a DOX-loading DSPE-PEG/DPPC/cholesterol liposome and three iron oxide nanospheres by using a two-step solid-phase chemistry (Fig. 2) [35–37]. The hydrodynamic diameter of the liposome was 35 nm, and the iron oxide nanospheres was 27 nm, with the iron oxide core only 10 nm. The unique linear assembly modified with a c(RGDfC) peptide as a targeting ligand for $\alpha_v\beta_3$ integrin receptor, which resulted in 18.6-fold increase of drug accumulation in brain tumors. With the assistant of a radio-frequency field, the encapsulated drug could quickly release by the oscillation the iron oxide. And the survival time of the nanochain treated group extended to 25 ± 3 days, 2.5-fold increase in

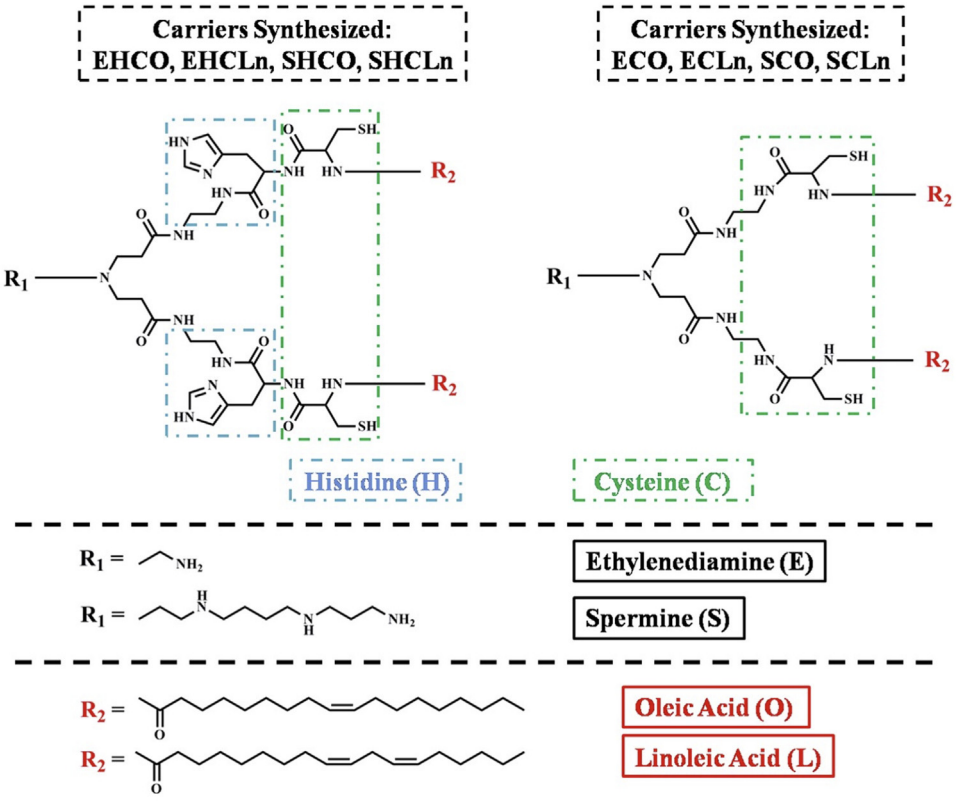

Fig. 3. The chemical structures of the synthesized cationic lipids. Reprinted with permission from Ref. [39].

comparison with the DOX treated group in highly invasive CNS-1 (central nervous system-1) model.

In order to trigger site-specific release and enhance drug accumulation in tumor sites, many stimuli-sensitive lipids were designed and constructed to form multifunctional formulations. Thomas L Andresen et al. designed a matrix metalloproteinases (MMPs)-sensitive lipid nanoparticle, which could be cleaved in the tumor microenvironment [38]. The PEGylated cleavable lipid nanoparticles decorated with angiopep ligand on the surfaces, which targeted to the low-density lipoprotein receptor-related protein-1 expressed on the blood-brain barrier. The hydrodynamic diameter of the nanoparticles was around 100–200 nm after angiopep functionalization. The siRNA delivery system induced 10-fold higher uptake than non-targeted nanoparticles, and comparable gene knockdown with the commercial agent RNAiMAX, which was used as standard for *in vitro* siRNA delivery.

Recently, Zheng-Rong Lu et al. developed a series of pH-sensitive, amphiphilic cationic lipids as nucleic acid carriers [39]. The lipids possessed three structural domains: a protonable amine-based head group (R_1), a hydrophobic tail containing two long-chain unsaturated fatty acids (R_2) and cysteine-based linker group (Fig. 3). The unique characteristic of the carrier endowed the formed nanoparticles with multifunctional properties, such as electrostatic binding, pH-sensitive and reducible-sensitive. The lead cationic carrier, ECO ((1-aminoethyl) iminobis[N-(oleicylcysteinyl-1-amino-ethyl)-propionamide]), was emerged for siRNA delivery into U87 glioblastoma cells [40]. The particle diameter of ECO/siRNA nanoparticles decreased while their zeta potential increased as the N/P ratio increased. The nanoparticles could readily escaped from endosomes, and exhibited potential and sustained gene silencing *in vitro*. However, liposomes were prone to liver accumulation without a direction [41,42]. Herein, selective targeting should be required to cross the brain barriers and transport drug into glioblastoma for further studies [43].

Though the liposomes make huge studies to investigate the application in human diseases, there still have some problems need to solve, including the *in vivo* instability, poor reproducibility in formulation and relatively higher cost to production [29,44]. These all hinder the clinical application of liposomes. Moreover, for glioblastoma therapy, there have other aspects need to consider as liposomes. Due to the individual position of the brain tumor, the diameter and stability of the liposomes should be optimized to cross the BBB and facilitate to localize at the tumor sites with sufficient drug concentration.

4. Polymer nanoparticles

Due to their potential of diversified structures and feasible functionality, polymer carriers are promising vectors to overcome the brain barriers for therapeutic drugs delivery. Many bioactive materials have caught the attentions of the researchers, including poly(lactic-co-glycolic acid) (PLGA) [45], poly(ethylene glycol)-poly(lactic acid) (PEG-PLA) [46], polyethylene imine (PEI) [47], poly(β-amino ester)s (PBAEs) [48] and so on. They could generally protect the free therapeutic drugs during the transportation and provide long circulation. Moreover, they could be modified with specific targets in brain tumor cells and tumor microenvironment for targeting delivery. For instances, the brain vascular endothelial cells and glioblastoma cells overexpressed many receptors, including low-density lipoprotein receptor [49,50], IL-13 receptor [51,52], transferrin receptor [53,54] and nicotine acetylcholine receptor [55], which could be acted as targets for drug delivery to the brain [43,56]. However, the anti-tumor efficiency and median survival time varied due to the structures of polymers and constitutes of nanoparticles. The deeper comprehension of influence on the efficiency should help us design more effective bioactive materials and develop novel approaches applied for glioblastoma therapy.

4.1. Poly(lactic-co-glycolic acid) (PLGA)

PLGA was a copolymer prepared by ring-opening polymerization of cyclic dimers of lactic acid and glycolic acid. It had been used in FDA approved therapeutic devices due to its biocompatibility and biodegradability. It had been applied in many delivery systems against various diseases, including tumors. Also, the PLGA nanoparticles prepared by nano-emulsion could be played as efficient carriers across the blood-brain barrier [45,57,58]. For example, a cyclic nine amino peptide, CRTIGPSVG (CRT), was introduced into poly(ethylene glycol)-poly(D, L-lactic-*co*-glycolic acid) (PEG-PLGA) [59], with a final diameter of 118.8 nm. The CRT peptide was able to bind to a complex of transferrin-transferrin receptor (Tf-TfR) by functionally mimic iron and facilitate deep penetration into the C6 glioma spheroids, with 2.8-fold as that of non-target nanoparticles. The enhanced penetration prolonged survival of mice bearing C6 glioma. The median survival time of the treated groups (CRT-NP-PTX) extended to 46 days, with 214% over the control group. While the median survival time of non-target group (NP-PTX) was 33 days, reaching 153% over that of the control group.

The PLGA nanoparticles exhibited long circulation and deeper penetration in glioma spheroids. However, for the *in vivo* distribution, higher concentration of the injected nanoparticles accumulated in liver and spleen [57]. This greatly reduced the sufficient drug entry into brain tumor. Considering the position and characteristics of glioblastoma, proper guide and optimized size might promote the drug concentration in glioblastoma tissues.

4.2. Poly(lactic acid) (PLA)

Lactic acid was a compound emerging in the process of metabolism. The formed polymer, poly(lactic acid) (PLA), was a biodegradable and hydrophobic polymer, which could be used as a carrier for hydrophobic chemical drugs. And it had been applied in clinical trials for anti-tumor research. For example, monomethoxy poly(ethylene glycol)-block-poly(D, L-lactide) (mPEG-PDLLA) loaded with paclitaxel formed the Genexol®-PM [60]. The formulation got into clinical trials and had commercially available for treatment of non-small cell lung cancer (NSCLC), ovarian cancer and breast cancer [61,62].

Recently, Jun Chen et al. used the poly(ethylene glycol)-poly(lactic acid) (PEG-PLA) as paclitaxel (PTX) delivery carriers [46]. The nanoparticles were functionalized with tLyp-1 peptide, which had good affinity with neuropilin and facilitated to target both glioma cells and endothelial cells. After modification, the diameter of the nanoparticle slightly increased from 105.32 nm to 111.30 nm. The tLyp-1-conjugated nanoparticles (tLyp-1-NP) exhibited greater penetration into the C6 glioma spheroids, with 1.32 folds deeper than that of unmodified nanoparticles. This capability enhanced the drug accessing into the solid tumors and prolonged the medium survival time to 37 days in intracranial C6 glioma mice, while those treated with the saline, Taxol® and unmodified NP-PTX were only 18, 23 and 28 days, respectively.

However, the structure of PLA belonged to polyester family, which was sensitive to esterase. And the degradation by esterase was not the specific response in glioblastoma. This might result in instability of the PLA formulated delivery systems and drug leakage during the transportation to the brain tumor. Herein, smart structural design and modification are required for proper degradation rate of these bioactive materials.

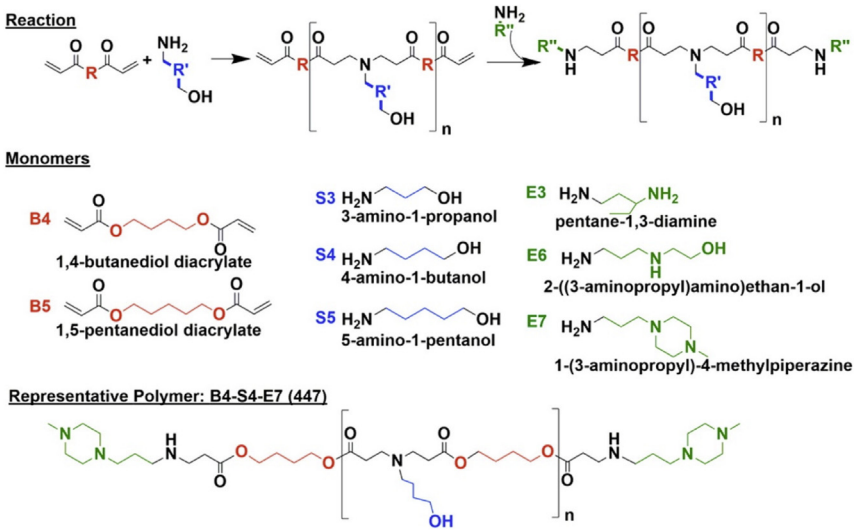

Fig. 4. The structures of monomers and synthesis of poly(β-amino ester)s (PBAEs). B: base monomer; S: side chain monomer; E: end-capping monomer. Reprinted with permission from Ref. [48].

4.3. Polyethylene imine (PEI)

With many amino residues, PEI was exploited for gene drug delivery in 1995 [63]. The buffer capability of PEI over a wide range of acidic environment facilitated the endosomal escape and released gene into cytosol [64]. This character enhanced effective gene delivery into tumor cells. For instance, Xin-Tao Shuai and Ying Peng's group designed a PEGylated hyperbranched-polyethylene imine (PEI) with a cell specific targeting molecule folate (FA-PEG-PEI) for combination of enzyme (cytosine deaminase)/prodrug (5-fluorocytosine) therapy and immunotherapy (TNF-related apoptosis-inducing ligand genes) against rat C6 glioma [65]. Animal studies showed that the average tumor size of the combined therapy was significantly diminished compared with the controls, with 53.13 mm^3 *vs* 172.52 mm^3, and demonstrated a longer survival time course.

Combining with anticancer drug, the gene therapy would result in enhanced antitumor efficacy for treating with glioblastoma cells. Weiyue Lu et al. prepared a cyclic RGD peptide (c(RGDyK), cyclic arginine-glycine-aspartic acid-D-tyrosine-lysine)-poly(ethylene glycol)-polyethylene imine (RGD-PEG-PEI) as a gene carrier for the plasmid encoding tumor necrosis factor-related apoptosis-inducing ligand (pORF-hTRAIL). The c(RGDyK) peptide had a high affinity binding to integrin $\alpha_v\beta_3$, which overexpressed on neovasculature and U87 glioblastoma cells. Co-delivery of paclitaxel loaded poly(ethylene glycol)-block-poly(lactic acid) (CDX-PEG-PLA-PTX) micelles, the median survival prolonged to 33.5 days when treated with the intracranial glioblastoma [66]. While the CDX-PEG-PLA-PTX and RGD-PEG-PEI/pORF-hTRAIL single treated groups only survived for 25.5 and 24.5 days, respectively.

These studies demonstrated that PEI exhibited good gene binding ability and endosomal escape due to the protonation of amines. This promoted enhanced effects for the gene drugs. And the PEI nanoparticles exhibited synergistic effect when combing with other therapeutic methods. However, due to the great number of amine groups, the balance between gene binding and toxicity of PEI should be considered for further studies [67].

4.4. Poly(β-amino ester)s (PBAEs)

Poly(β-amino ester)s (PBAEs) are a class of biodegradable polymer that has been exploited for gene delivery vectors [68]. These polymers could degrade quickly under weak acidic condition by hydrolytically cleaving the β-amino ester bonds. The unique characteristic enable effective gene transportation and release for *in vitro* and *in vivo* studies [69].

Seven poly(β-amino ester)s (PBAEs) were reported by Jordan J. Green and Betty Tyler et al. (Fig. 4). They were evaluated as carriers for DNA delivery of herpes simplex virus type 1 thymidine kinase (HSVtk) in a malignant glioma model [48]. The optimized nanoparticle formulation (poly(1,4-butanediol diacrylate-*co*-4-amino-1-butanol) end-modified with 1-(3-aminopropyl)-4-

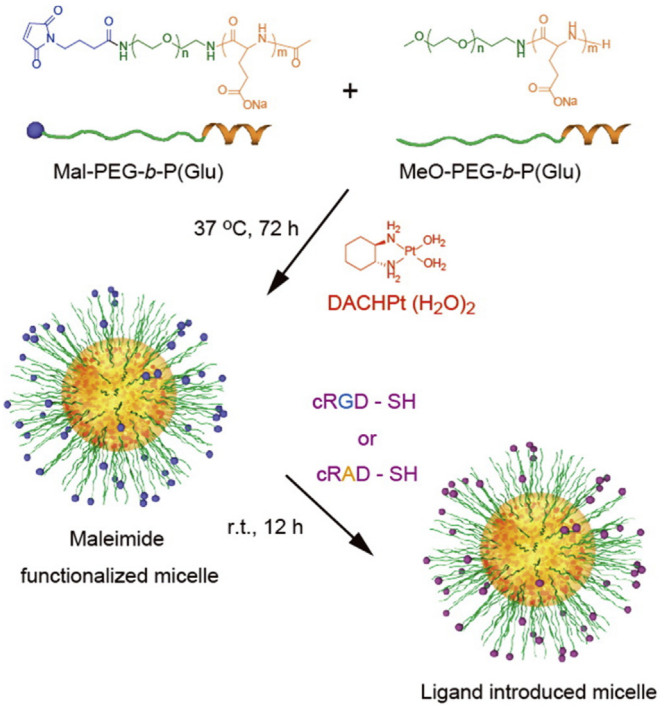

Fig. 5. The structures of PEG-P(Glu), and the synthetic route for the ligand introduced micelle (cRGD/m). Reprinted with permission from Ref. [76]. Copyright (2013) American Chemical Society.

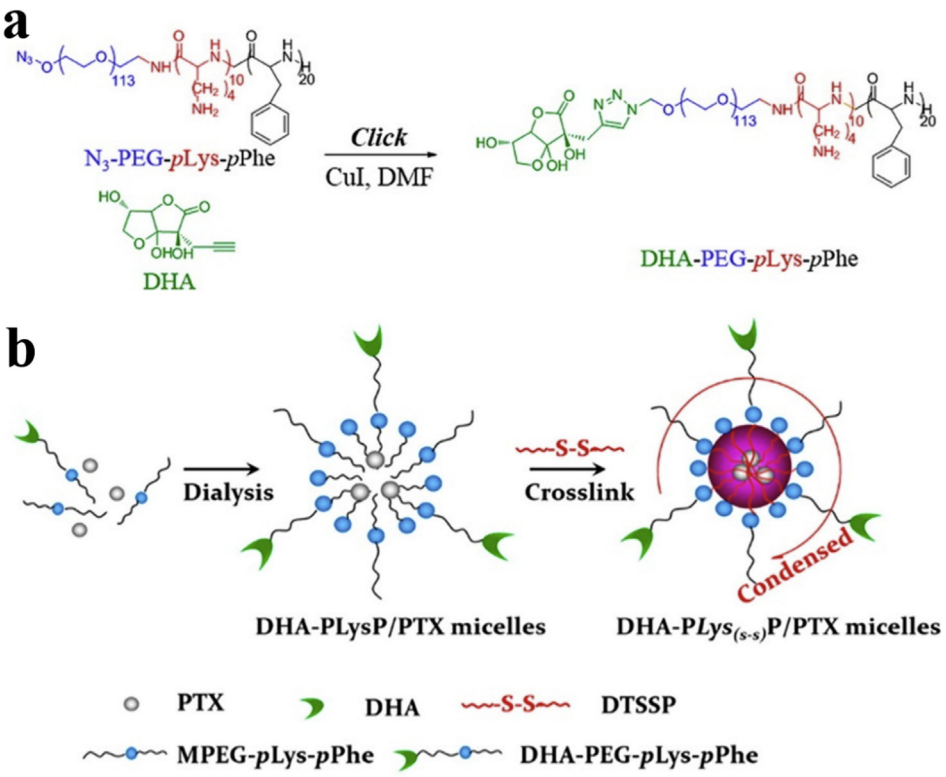

Fig. 6. The synthetic route of DHA-PEG-pLys-pPhe (a), and DHA-PLys$_{(s\text{-}s)}$P/PTX micelles (b). Reprinted and adapted with permission from Ref. [78]. Copyright (2014) American Chemical Society.

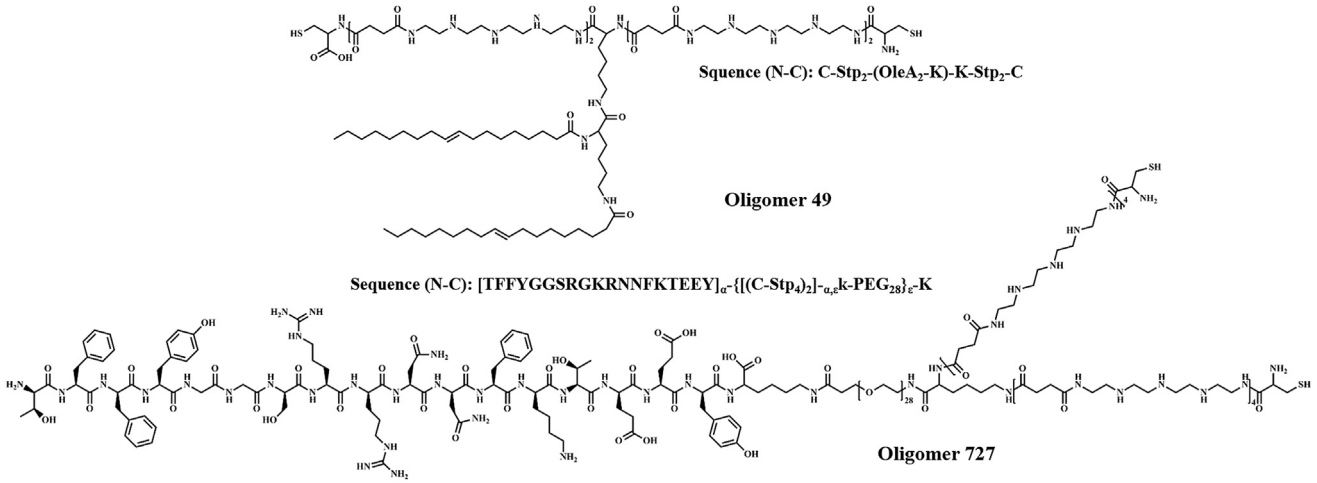

Fig. 7. The chemical structures and sequences of oligomer 49 and oligomer 727. Reprinted and modified with permission from Ref. [79].

methypiperazine formed nanoparticle with HSVtk DNA, for short: NP-HSVtk) initiated 106 ± 3% cell death of 9Ls and 96 ± 7% cell death of F98s when administrated with the prodrug ganciclovir (GCV). And the systemic administration led to a significant prolonged survival compared with that of the untreated control group ($p = 0.0012$) in a 9L glioma model.

The unique structure of poly(β-amino ester)s promoted cellular uptake and endosomal escape of gene drugs for anti-tumor therapy [69]. But single formulation of gene nanoparticles was not sufficient to completely kill the malignant tumors. Suitable targets and combination strategy should be considered for effective therapy for glioblastoma.

4.5. Polypeptide

Self-assembled polypeptides were widely applied for improved antitumor drug delivery and studied in preclinical and clinical trials due to their excellent biodegradability and biocompatibility [70,71]. Like poly(ethylene glycol)-poly(L-glutamic acid) (PEG-P(Glu)), it had been used for delivery of cisplatin (the formulation name: NC-6004), dichloro-(1, 2-diaminocyclohexane)platinum (II) (DACHPt, the formulation name: NC-4016) and 7-ethyl-10-hydroxy-

camptothecin (SN38, the formulation name: NK012) in clinical trials [72–75]. When bound with the drug, the PEG-P(Glu) could form micelles in the aqueous phase, with the hydrophilic regions spread outside and hydrophobic regions aggregated in the center. After modified with cyclic Arg-Gly-Asp (cRGD) peptide ligand (Fig. 5) [76], a target for endothelial cells and glioblastoma cells (e.g. the U87MG cell line) [77], the micelle (cRGD/m) produced exhibited relatively small diameters, between 27 and 31 nm, with a narrow polydispersity. This feature made the micelle bypass the blood-tumor barriers and penetrate into glioblastoma *via* cRGD-mediated transvascular transport. The tumor of the treated group (cRGD/m) was observed 5-fold inhibition compared to those treated with oxaliplatin and non-targeting group (cRAD/m) in orthotropic U87MG glioblastoma model.

Recently, Chen Jiang et al. developed an amphiphilic polypeptide poly(ethylene glycol)-polylysine-polyphenylalanine (PEG-pLys-pPhe) for paclitaxel delivery (Fig. 6) [78]. The copolymer modified with dehydroascorbic acid (DHA), which was substrate of glucose transporter isoform 1 (GLUT1) and facilitated glioma-targeting. Moreover, the amino groups on pLys block were cross-linked to stabilize the micelle structures during blood circulation and trigger release in tumor cellular condition. The micelles had a diameter of 47 nm with a very narrow polydispersity. With this smart nanodevice (DHA-PLys$_{(s\text{-}s)}$P/PTX), the drug accumulation in tumor sites was 2.36-fold increased than non-targeting groups at 8 h. And the survival time was markedly prolonged to 46 days in intracranial U87 glioma-bearing mice, while free drug Taxol and non-cross-linked micelles DHA-PLysP/PTX had only 25.5 and 36.5 days, respectively.

Later, Chen Jiang and Ernst Wagner et al. developed a peptide-like oligomer, oligomer 49 (Fig. 7), as a siRNA carrier for gene silencing in U87 glioma cells [79]. This biomimetic polymer was combined with oligomer 727, modified with angiopep2 peptide, to exert effective targeting and accumulation. The formulation (angiopep-PEG/siRNA) suppressed 70% BAG3 (Bcl-2 associated athanogene 3) expression *in vivo*, while the control group (PEG/siRNA) only exhibited nearly 50% suppression.

These biomimic polypeptide-based nanoparticles exhibited good biocompatibility [80], and better performance against glioblastoma. Some of them have stepped into clinical trials [74]. But the ratio between the peptide segment and polymer segment should be optimized to accommodate drug delivery into brain cancer. Moreover, unlike other biomaterials, most of the polypeptide had the corresponding secondary structures. This property also played its role on the biological application as drug carriers, and should be put further comprehension on the relationship between the secondary structures and the properties of the polypeptide.

4.6. Prodrug-based nanoparticles

Nanoparticles composed with various polymers obtained impressive achievements in drug delivery for anticancer therapy. However, a great deal of inert materials was applied as drug carriers and markedly reduced the drug-loading of nanoparticles [81]. To resolve this problem, Youqing Shen et al. utilized a hydrophobic therapeutic drug as a component of drug carriers [82,83]. This strategy not only greatly promoted drug-loading, but also reduced inert materials in nanoparticles, which might cause side-effect to human body. Recently, John S. Yu's group prepared a reactive oxygen species (ROS)-responsive prodrug of camptothecin (CPT-TEG-ALA), and assembled into a nanoprodrug by spontaneous nanoemulsification with α-tocopherol (Fig. 8) [84]. The nanoprodrug exhibited a diameter of 220 nm, and inhibited 80% tumor growth in subcutaneous U87 glioma xenograft mice model. Moreover, the median survival time was significantly extended to 72.5 days against intracranial U87 tumor compared with irinotecan (41.0 days) and control groups (40.5 days).

Prodrug-based nanoparticles exhibited good performance against gliobalstoma as the therapeutic drug carriers. They greatly enhanced the drug-loading with less inert materials. Considering the unique feature of the tumor in brain, suitable targets should be introduced into the nanoparticles for better guidance [85,86]. Most of the targets, like cRGD and TAT peptide, had similar or larger molecular weight than the prodrugs. Herein, unlike other drug carriers, the influence on the functionality might be huge for the prodrug-based nanoparticles when conjugating with the targets.

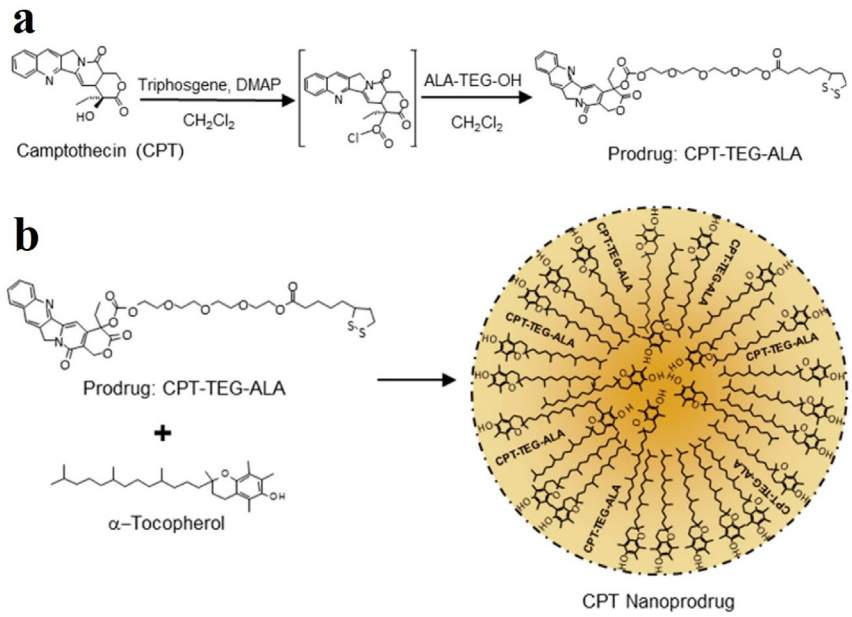

Fig. 8. Free camptothecin (CPT) is incorporated with α-lipoic acid (ALA) and tetra(ethylene glycol) (TEG) into prodrug CPT-TEG-ALA (a). CPT-TEG-ALA and α-tocopherol self-assembly to CPT nanoprodrug (b). Reprinted and adapted with permission from Ref. [84]. Copyright (2013) American Chemical Society.

5. Conclusion and perspective

Comparing with other tumors, glioblastoma possesses inherent barriers for therapeutic drugs due to its individual position. To overcome these obstacles, numerous bioactive materials are applied as delivery carriers and reported over the years. The drug formulation with these materials exhibits a certain extent of anti-glioblastoma effect and extends the median survival time compared with the free therapeutic drug. These bioactive materials self-assemble to nanoparticles with a wide range of diameters, and provide protection and long circulation of the chemotherapeutic drugs for *in vivo* transportation. The diverse structures of the materials ensure a controllable release by various tailoring, which is suitable for distinctive tumor environment. Moreover, these drug delivery systems greatly reduce toxicity to normal tissues in compare with free drugs. However, as we seen from the above-mentioned delivery systems, these materials need a proper guidance for more effective and accurate targeting to glioblastoma. The individual targets for the intracranial tumors have been summarized in other reviews [85,87]. Modified with the specific targets could promote the selective accumulation in brain and tumor cells. All these factors exert synergistic effect for glioblastoma therapy and make us step closer to clinical studies and application.

The route of drug crossing the brain barriers, delivering into tumor cells and performing their functions is a complicated physiological and biological process. And the tumor heterogeneity is a marked feature of glioblastoma. For example, some tumor regions are hypoxic and necrotic, while others exhibit more proliferative or vascularized [88]. These phenotypic features constructed a complicated tissue. The intratumor heterogeneity and inherent molecular complexity of glioblastoma urgently needed a rational combination therapy [89]. Pharmacodynamics failure in biodistribution in the brain tumor region due to BBB/BTB made the adequate drug delivery a critical challenge in glioblastoma treatment. Completely comprehension of the detail delivery pathway to glioblastoma will help us to construct rational delivery vectors for therapeutic drugs.

Another potential strategy to further improve the effect of glioblastoma therapy is to combine chemotherapy with immunotherapy. Immunotherapy has emerged as a potential and perspective treatment for brain cancer [90]. Recently, Jonathan Kipnis's group proved the existence of lymphatic vessels in the central nervous system [91]. This discovery provided theory foundation and new light on the immunotherapy for brain cancers. The immunotherapy could specifically kill the cancer cells in cellular level without damaging the normal brain tissue, and provide a long-term immune surveillance against the recurrence [92]. The recent achievement with immunotherapy in the treatment against glioblastoma sparks widespread interests and stimulates to develop various immunotherapeutic strategies [93]. For example, ex-vivo matured dendritic cells (DCs) pulsed with tumor lysates and glioma-associated antigens have been extensively studied and proceeded to clinical trials [94,95]. Later, a glioblastoma associated peptide vaccine, EGFR variant III (EGFRvIII) peptide, was reported to induce better progression-free survival and longer overall survival (26 months *vs* 15 months) comparing with the controls in patients with newly diagnosed glioblastoma [96]. The immunotherapy inspires the whole immune system and fights for glioblastoma cells. This is a completely different therapeutic route from the chemotherapy and a potential therapeutic treatment for the brain tumors.

Herein, from the above description, proper targeting and rational design of therapeutic drugs delivery systems should be very important for efficient chemotherapy. This needs us to get more comprehension with molecular biology of the progression and composition of glioblastoma, and the surrounding microenvironment. The more rational drug delivery formulation with biomaterials are designed with the deeper understanding of these processes. Moreover, combining the chemotherapy with immunotherapy, activating the immune response and immune surveillance against the tumor cells, will provide a promising strategy for clearing up the glioblastoma and inhibiting recurrence. This two-pronged strategy will get unexpected harvest against the glioblastoma.

Competing interests

The authors declare that they have no competing interests.

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