Narrative Review Article

Functionalized Lipid Nanoparticles Show Efficacy in Glioma Animal Models

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ABSTRACT

Gliomas, particularly glioblastomas, are brain tumors characterized by aggressive growth, high recurrence rates, and a median 5-year survival rate of ~5%. Treatment of brain tissue is highly restricted due to the blood-brain barrier's (BBB) selective permeability, which makes gliomas incredibly difficult to target. In recent years, there have been many developments in the use of lipid nanoparticles (LNPs) as drug delivery systems. Specifically, functionalized LNPs have shown promise in treating gliomas due to their ability to cross the blood-brain barrier. This review presents the surface-modified LNPs designed for glioma treatment that have demonstrated efficacy in in vivo animal studies. Presented here are LNPs loaded with chemotherapy and functionalized with transferrin, lactoferrin, Angiopep-2, ApoE, and cell-penetrating peptides that demonstrate a promising ability to treat gliomas.

Keywords: Lipid Nanoparticle; Blood-Brain Barrier; Glioma; Glioblastoma; Brain Cancer

INTRODUCTION

Gliomas are notoriously challenging to treat, resulting in high mortality and morbidity rates (1). Glioblastoma (GBM), the most aggressive and common form of glioma, has an incidence rate of 3 - 4 per 100,000 individuals in the US per year (2). GBM patients have a poor prognosis with a median survival time of ~10 months, a 1-year survival rate of 37.2% and a 5-year survival rate of 5.1% (3). Standard treatments for gliomas, which typically include surgery, followed by radiation therapy and chemotherapy, have limited impact (4). Much of the restriction in treating these tumors is due to the difficulty in administering chemotherapies past the blood-brain barrier (BBB) to reach the glioma. The BBB, which protects the brain from harmful substances, restricts the entry of hydrophilic, large, or highly charged particles into the brain and prevents conventional therapeutics from entering the brain through passive transport. As a result, they often fail to reach the brain tissue to treat gliomas effectively (5). Recently, studies have shown that functionalized lipid nanoparticles have the ability to deliver chemotherapy payloads across the BBB (6). This review investigates functionalized LNP's that have demonstrated efficacy in delivering chemotherapies to gliomas in animal models. Here, the *in vivo* functionalized LNP studies are synthesized.

BLOOD-BRAIN BARRIER BACKGROUND

Due to the tight junctions, only small particles (~9 Å) can penetrate the BBB (5). This barrier makes it impossible for LNPs to enter the brain through

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paracellular transport. Nano carriers must traverse the BBB through three mechanisms: carrier-mediated transcytosis (CMT), receptor-mediated transcytosis (RMT), and adsorptive-mediated transcytosis (AMT).

CMT is a transport mechanism used by the BBB to allow entry of small molecules such as glucose, amines, amino acids, and nutrients from the bloodstream into the brain (7). It relies on specialized molecular carriers on both the apical and basolateral side of the BBB (8).

RMT is the process by which highly expressed receptors on the capillary endothelial cells facilitate the transport of essential macromolecules through the BBB. Once the macromolecules have entered the luminal side of the cell, they are further transported through the cell and exocytosed on the abluminal side, where they are released into the brain parenchyma (9). RMT is effective in delivering nanoparticles to the brain. Ligands are attached to nanoparticles, which allows for high-affinity bonding to specific receptors (10).

AMT is a way for delivering large molecules into the brain that is distinct from CMT and RMT. Unlike RMT and CMT, which rely on specific receptors, AMT works through electrostatic interactions. Positively charged molecules/nanoparticles are attracted to the negatively charged BBB. This process causes the cell membrane to form vesicles that engulf the particles and transport them through the cell (11). Many cell-penetrating peptides have been developed to utilize AMT for delivery, such as Penetratin and Mastoparan (12).

LIPID NANOPARTICLES BACKGROUND

Lipid nanoparticles (LNPs) are composed of amphiphilic lipid molecules, which, under certain environmental conditions, can self-assemble into highly stable colloids. These include liposomes, cubosomes, hexosomes, solid lipid nanoparticles, and nanostructured lipid carriers (13). LNPs offer flexibility in particle size, surface properties, and shape, making them suitable for various drug delivery systems (14). Moreover, their surfaces can be modified with ligands and antibodies to improve BBB targeting (Figure 1) (15).

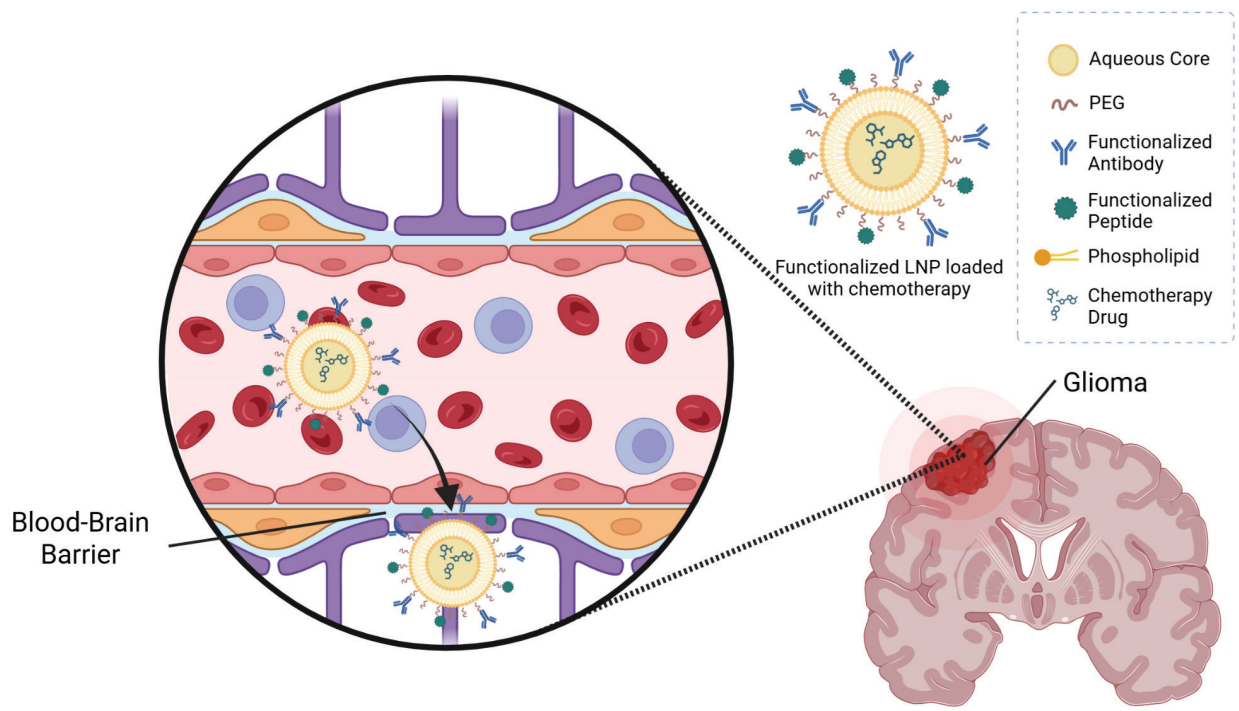

Figure 1. Schematic of functionalized LNP bypassing the BBB and delivering chemotherapy to the glioma. LNPs loaded with chemotherapy are modified with PEG-linked ligands such as peptides, proteins, and antibodies to utilize active transport across the BBB. These ligands bind to receptors on brain endothelial cells and allow for the LNPs transported to the brain tissue where it can release its chemotherapy payload and effectively target gliomas.

Liposomes are assembled from amphiphilic lipid particles such as phospholipids. When placed in aqueous environments, these lipids will spontaneously arrange themselves into a colloidal sphere (16). A lipid bilayer is formed, with the hydrophobic tails in the interior, and the hydrophilic heads exposed to the aqueous phases (17).

Solid Lipid Nanoparticles (SLNs) are formed from a solid lipid matrix along with stabilizers. The lipids typically consist of long-chain saturated fatty acids, like palmitic and stearic acids (18). SLNs have spherical geometries with diameters ranging from 50 to 1000 nm (19). The drug release rates by SLNs can be modified by altering the chain length of the fatty acids, with longer saturated chains having slower release rates. Polymer and lipid coatings can provide a protective barrier and a site for ligand attachment, facilitating the targeting of specific cells and tissues (20).

Nanostructured Lipid Carriers (NLCs) differ from SLNs in that they have both a solid lipid and a liquid lipid component, which makes the structure less ordered and more flexible. Recently, SLNs have been employed in the delivery of COVID-19 mRNA vaccines (21). These SLNs use ionizable amine-containing lipids that bear a positive charge to facilitate the loading of negatively charged RNA molecules. These LNPs are typically composed of four main components: a polyethylene glycol (PEG) lipid for steric stabilization and size control, a neutral phospholipid for structural support, an ionizable lipid that provides a positive charge at low pH to improve attraction to mRNA (21), and cholesterol for membrane rigidity. These particles typically range from 60 - 100 nm and have a structure with a central core surrounded by a surface layer (22). This streamlined composition has been adopted by many modern efforts to utilize SLNs for molecular delivery, including those being studied for enhanced BBB transport and brain disease treatment.

IN VIVO TESTED FUNCTIONALIZED LNP

The potential of functionalized LNPs to overcome the BBB has been demonstrated through *in vivo* models that evaluate their efficacy in delivering chemotherapeutics to gliomas. This section reviews the most promising ligand-LNP systems that have been tested in animal models, organized by the primary targeting ligand used for functionalization (Table 1).

Table 1. *In vivo* efficacy of functionalized LNP for glioma therapy

Ligands Targeting	Nanostructure	Drug/ bioactive	*In vivo* models	*In vivo* results	Refs
Angiopep-2	SLNs	Docetaxel	GL261-bearing mice	Mean survival time increased significantly from 24 days to 39 days compared to control	(27)
Angiopep-2	Liposomes	Calcium arsenite	U87-bearing mice	Decreased glioma size and increased survival from 17 days to 21 days when compared to non-functionalized control	(24)
Angiopep-2, CD133 antibody	Liposomes	Temozolomide	U87-bearing mice	Decreased glioma size and increased survival from from 23 days to 29 days when compared to control	(28)
Transferrin	Liposomes	Temozolomide and the bromodomain inhibitor JQ1	U87/GL261-bearing mice	Decreased tumor burden 1.5 fold and increased survival time compared to free drug	(30)
Transferrin, p-aminophenyl-α-D-manno-pyranoside	Liposomes	Daunorubicin	C6 glioma-bearing rats	Increased survival time up from 17 days to 22 days compared to other controls	(31)
Transferrin and Penetratin	Liposomes	Doxorubicin and Erlotinib	U87-bearing mice	Showed high tumor regression with an increase in survival time from 30 to 36 when compared to only Tf functionalized liposome	(32)

Continued Table 1. *In vivo* efficacy of functionalized LNP for glioma therapy

Ligands Targeting	Nanostructure	Drug/ bioactive	*In vivo* models	*In vivo* results	Refs
Transferrin and Octa-arginine (R8)	Liposomes	Doxorubicin	U87-bearing mice	Increased survival time from 22 days to 25 days compared to free DOX control	(33)
Lactoferrin and Arginine-Glycine-Aspartic acid	Liposomes	Temozolomide and Vincristine	U87 MG cell-bearing mice	Dual ligand showed slowest tumor growth when compared to control and single ligand groups	(34)
ApoE	Liposomes	Temozolomide	U251-TR-bearing mice	Demonstrated CNS tumor penetration, reduced U251-TR glioma burden, and extended survival time	(35)
dNP2 peptide and Folic acid	Liposomes	Paclitaxel	Orthotopic gliomas (luc-C6) bearing mice	Strong tumor growth inhibition and increased survival time	(36)
p-aminophenyl-α-D-mannopyranoside	Liposomes	Curcumin and Quinacrine	glioma stem cells bearing mice	Increased survival time from 27 days to 34 days compared to control.	(37)

LNP's are functionalized with various ligands to allow for active transport across the BBB to deliver chemotherapy payloads to gliomas. These are the current LNP functionalizations and their given chemotherapy payload that have been tested in animal glioma models. The results and references to these studies are also presented.

ANGIOPEP-2 FUNCTIONALIZED LIPOSOMES

Angiopep-2 (Ang2) is a 19-amino acid peptide from the Kunitz domain of aprotinin (Apr). It binds to lipoprotein receptor-related protein-1 (LRP-1) receptors, overexpressed on BBB and glioma endothelial cells (23). Ang2-functionalized SLNs have shown promise in crossing the BBB. In *in vivo* pharmacokinetic and tissue distribution studies, an Ang2-functionalized SLN loaded with docetaxel (DTX) was revealed to be selective for brain tissue relative to non-functionalized SLNs (24). Furthermore, similar studies have also confirmed the increased BBB selectivity with Ang2-functionalized liposomes (25, 26).

Ang2 functionalized on pH-responsive liposomes loaded with calcium arsenite (Ang2-PEG-LP@CaAs) have been developed for enhanced BBB targeting efficiency (27). In an *in vitro* transwell BBB model, Ang2-PEG-LP@CaAs showed higher BBB penetration relative to non-functionalized LP. When tested in U87 cell-bearing nude mice, Ang2-PEG-LP@CaAs accumulated the most effectively at glioma sites and achieved the longest median survival at 21 days with the smallest tumor size relative to non-functionalized LP.

Kim *et al*. have developed temozolomide (TMZ) loaded dual-targeting liposomes functionalized with angiopoietin-2 (Ang2) and anti-CD133 monoclonal antibody (CD133 mAb), a known antibody treatment for glioma (28, 29). *In vitro* studies revealed that Ang2/CD133-conjugated liposomes had approximately double the BBB permeability of only CD133-conjugated liposomes. In orthotopic U87 MG cell-bearing BALB/c nude mice, treatment with dual-targeting liposomes resulted in an increase in median survival time compared to TMZ-loaded liposomes and free TMZ at 134.7% and 211.2%, respectively.

TRANSFERRIN FUNCTIONALIZED LIPOSOMES

Lam *et al*. synthesized transferrin (Tf)-functionalized liposomes loaded with potent chemotherapies temozolomide (TMZ) and thienotriazolodiazepine (JQ1) for glioma treatment (30). Intravital imaging revealed that Tf-liposomes significantly increased BBB penetration compared to non-functionalized liposomes for both human U87MG and murine GL261 intracranial glioma models. In GL261 tumor-bearing mice, Tf-liposomes carrying TMZ and JQ1 achieved a 99.3% reduction in tumor signal, outperforming free drug combinations

and dual drug-loaded PEG-liposomes. Additionally, Tf-liposome therapies significantly extended survival in both mouse groups beyond that of the controls.

Dual-targeting daunorubicin liposomes, conjugated with p-aminophenyl-alpha-D-manno-pyranoside (MAN) and transferrin (TF), were developed to transport drugs across the BBB and target gliomas (31). Evaluations across *in vitro* and *in vivo* models of C6 glioma cells showed improvements. *In vitro* results showed a 24.9% increase in transport across the BBB model and a 54.7% reduction in C6 glioma spheroid volume ratio. C6 glioma-bearing rats treated with dual-targeting daunorubicin liposomes exhibited a prolonged survival time of 22 days compared to 17 days for those receiving free daunorubicin.

Liposomes were modified with Transferrin (Tf), for RMT, and cell penetrating peptide penetratin (Pen), to enhance cell penetration. These Tf-Pen liposomes were loaded with doxorubicin and erlotinib for the treatment of glioblastomas (32). *In vitro* tests demonstrated high biocompatibility for *in vivo* administration, with high hemocompatibility and low cytotoxicity. Studies in mice revealed a 12-fold increase in doxorubicin and a 3.3-fold increase in erlotinib accumulation in the brain compared to free drugs. Furthermore, results showed ~90% tumor regression when compared to no treatment. Moreover, the use of Tf-Pen liposomes resulted in the highest survival time of 36 days, outcompeting Tf-liposomes, Pen-liposomes, and free drug, with survival times of 30, 27.5, and 25 days, respectively.

Transferrin (Tf) and cell-penetrating peptide octa-arginine (R8) co-modified liposomes (Tf-LPs) loaded with doxorubicin (DOX) were developed (33). Tf-LPs were spherical, uniform in size (128.64 nm), and had a ξ-potential of 6.81 mV. They remained stable in serum for up to 48 hours and were efficiently taken up by U87 and GL261 cells. Tf-LPs demonstrated sustained drug release with a 50% cumulative DOX release and high anti-glioma efficacy. Histology of major organs all showed low toxicity.

LACTOFERRIN AND ARGININE-GLYCINE-ASPARTIC ACID FUNCTIONALIZED LIPOSOMES

Liposomes modified with lactoferrin (Lf) and arginine-glycine-aspartic acid have also shown promise in *in vivo* studies (34). NLCs modified with Lf and RGD were loaded with TMZ and vincristine (VCR) (Lf-RGD-T/V-NLCs), two chemotherapies known for their effectiveness in treating glioblastoma (GBM). When tested in U87 MG cell-bearing BALB/c nude mice, liposomes with both Lf and RGB released significantly higher TMZ and VCR in the tumors when compared to liposomes with just one or no ligand. Moreover, the mice treated with Lf-RGD-T/V-NLCs showed stronger inhibition of tumor growth when compared with single functionalized and non-functionalized nanoparticles, demonstrating the efficacy of BBB penetration when using both ligands in tandem.

APOE FUNCTIONALIZED LIPOSOMES

Ismail *et al*. developed ApoE-modified liposomes encapsulating TMZ within an artesunate phosphatidylcholine matrix (ApoE-ARTPC@TMZ) (35). *In vivo* studies in healthy Balb/c mice showed that these liposomes could efficiently cross the BBB, confirmed through immunofluorescence analysis. Further treatment with ApoE-ARTPC@TMZ significantly inhibited tumor growth and enhanced survival compared to non-ApoE-modified liposomes or liposomes without TMZ.

FOLIC ACID AND DNP2 PEPTIDE FUNCTIONALIZED LIPOSOMES

Paclitaxel (PTX) loaded liposomes dual-modified with a cell-penetrating peptide (dNP2) and folic acid (FA) (36). The FA was introduced to take advantage of FA receptors on both BBB and glioma cells to facilitate penetration. Moreover, an acid-cleavable cFd-Lip/PTX linker was engineered to cleave FA under mildly acidic conditions of the tumor cells, pH 6.8. *In vitro* studies demonstrated that FA-dNP2 dual-modified liposomes had enhanced BBB penetration over liposomes modified with FA or dNP2 alone. Under mildly acidic conditions, the FA is cleaved, exposing dNP2 and enhancing cellular uptake. In orthotopic glioma-bearing mice, cleavable dual-modified liposomes showed higher tumor accumulation and intratumoral penetration compared to non-cleavable FA-dNP2-liposomes or liposomes modified with just FA or dNP2.

CONCLUSION

Glioblastomas are a very aggressive form of brain tumors that are incredibly challenging to treat. The difficulty in treating these tumors is mainly due to their presence in the brain and the restrictiveness of

the BBB. The BBB's highly selective permeability prevents conventional therapeutic agents from entering the brain. Recent *in vivo* studies have demonstrated the ability of functionalized lipid nanoparticles to penetrate this barrier and facilitate targeted drug delivery to glioma cells. Various types of lipid nanoparticles, including liposomes, solid lipid nanoparticles, and nanostructured lipid carriers, can be surface modified with specific ligands that target receptors on the BBB to allow for transport to the brain tissue. So far, chemotherapy-loaded LNPs that have shown efficacy in *in vivo* animal studies have been functionalized with receptor-targeting proteins, such as transferrin, lactoferrin, Angiopep-2, and Apolipoprotein E, as well as cell penetrating peptides, penetratin and dNP2, enhancing brain uptake and tumor accumulation of drugs. Among the various lipid nanoparticles available, liposomes have been most widely used as a delivery vehicle for this task. Moreover, from these studies, it has been revealed that dual-functionalized liposomes often outperform single-ligand liposomes. For example, transferin is frequently paired with other ligands to reveal improved BBB penetration. It is unclear whether the dual ligand strategy displays significant synergy or if the presence of more receptor options allows for more effective transport across the BBB. While there have been LNP's used in clinical trials for glioma, none have moved past Phase II due to failure to show improvement over standard of care (37). With the promise of functionalized LNP's in the animal glioma models the future of this therapeutic strategy lies with advancing LNP-functionalized glioblastoma treatments to clinical trials.

CONFLICT OF INTERESTS

The author declares that there are no conflicts of interest regarding the publication of this article.

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