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Noninvasive nanoparticle strategies for brain tumor targeting

Chunmeng Sun[a,b,1], Yang Ding[a,1], Li Zhou[c], Di Shi[d], Linlin Sun[d], Thomas J. Webster, PhD[d,*], Yan Shen[a,b,d,*]

[a]*Center for Research Development and Evaluation of Pharmaceutical Excipients and Generic Drugs, China Pharmaceutical University, Nanjing, China*
[b]*State Key Laboratory of Nature Medicines, Department of Pharmaceutics, China Pharmaceutical University, Nanjing, China*
[c]*Department of Pharmacology and Pharmaceutical Sciences, University of Southern California School of Pharmacy, Los Angeles, CA*
[d]*Department of Chemical Engineering, Northeastern University, Boston, MA, USA*

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Abstract

The blood–brain barrier (BBB) maintains the integrity and homeostasis of the central nervous system (CNS) yet represents an intimidating hurdle for efficient drug delivery to brain tumors. This up-to-date review summarizes strategies that have been employed to cross the BBB with a focus on non-invasive nanoparticles that could pass the BBB after systemic administration. Recent advances in liposomes, polymeric nanoparticles, micelles, and inorganic nanoparticles are scrutinized mechanistically with an emphasis on design principles. As highlighted in this review, effective drug delivery to brain tumors may be achieved by rationally engineering nanoparticles to possess appropriate sizes, surface properties, and ligands.

Key words: Blood–brain barrier; Brain tumors; Drug delivery; Brain penetration; Nanoparticles

Malignant brain tumors are a devastating disease which attracts enormous attention due to poor prognosis and high recurrence.[1] With an incidence rate of about 10 in 100,000,[2] having a malignant brain tumor is fatal with a low average survival rate of only 34.4%. In particular, glioblastoma multiforme (GBM), the most prevalent primary malignant brain tumor, has a five-year relative survival rate of only 5.1%.[3] Brain and central nervous system (CNS) tumors are categorized based on the presumed tissue of origin, *i.e.*, neuroepithelial-originated; cranial and paraspinal nerves-originated; meninges, lymphoma germ cell-originated; tumors of the sellar region; and metastatic brain tumors.[4] Within the scope of this review, the main focus will be on neuroepithelial originated gliomas, which can further be classified into grades I to IV based on their clinical manifestations and malignancies (Table 1).[4] It is worth noting that all gliomas will eventually develop into a fatal tumor with time except for grade I pilocytic astrocytomas. Diffusely infiltrating gliomas (grade II) mostly affect younger adults and are characterized by a high degree of cellular differentiation and slow growth. Over time, these tumors evolve into anaplastic astrocytomas or oligodendrogliomas (grade III) or into glioblastomas. Grade IV astrocytoma or GBM represents the most malignant type of brain tumors in adults and are also the most frequently occurring primary brain tumor.[5] With currently a-18 months from the time of diagnosis.

Malignant gliomas differ from other solid tumors concerning its invasion into the surrounding normal brain tissue.[6] The current standard treatment for GBM consists of surgical resection to the extent feasible followed by radiotherapy and adjuvant chemotherapy with temozolomide (TMZ).[7] Although surgery

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* Corresponding authors.
E-mail addresses: th.webster@neu.edu (T.J. Webster), shenyan@cpu.edu.cn (Y. Shen).
[1] These authors contribute equally to this work.

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Table 1
World Health Organization (WHO) tumor grading system[7].

Grade I tumor	• Benign = non-cancerous • Slow growing • Long-term survival
Grade II tumor	• Relatively slow growing • Sometimes comes back as a higher grade tumor
Grade III tumor	• Malignant = cancerous • Tumor spreads into nearby normal parts of the brain • Tends to come back, often as a higher grade tumor
Grade IV tumor	• Most malignant and grows very fast • Easily spreads into nearby normal parts of the brain • Tumor forms new blood vessels to maintain rapid growth

remains one of the most effective treatments of gliomas, wide surgical margins that are preferable for other solid tumors are unfortunately impractical in the brain, since damage to the surrounding eloquent cortex or brainstem structures as a result of excess removal might cause unacceptable neurological disability. Therefore, complete removal of the glioma by conventional surgery is usually impossible. Radiation therapy (RT) and chemotherapy are often required in combination with surgical removal for the further elimination of residual tumors, and retrospective studies confirmed that improved survival rates correlate with a decreased volume of the residual tumor.[8,9] Unfortunately, both treatments still have their limitations and are not curative by any means. For example, microscopic foci of tumor cells can sometimes be found beyond the reach of radiation therapy. As a consequence, glioma patients face a high risk of recurrence caused by the residual tumor. Additionally, severe damage to the CNS can be induced by radiation therapy as a high dose of at least 60 Gy of radiation is required to treat malignant gliomas.[10]

Chemotherapy is generally regarded as one of the less invasive therapies compared to surgery. However, it only plays an adjuvant role in the management of glioma patients due to various limitations. For instance, glioma shares some common properties with peripheral tumors, such as elevated interstitial pressure,[11] low pH ,[12] low pO_2,[13] and infiltrated growth,[14] all of which present great challenges to effective drug penetration. In addition, the unique microenvironments of glioma, *i.e.* extreme low permeability and high heterogeneity of the blood–brain barrier (BBB) and the blood–brain tumor barrier (BBTB), make it even more difficult to achieve a therapeutically relevant dose or a homogenous coverage of all infiltrated glioma. Although TMZ, the most commonly used therapeutic in GBM treatment, is able to cross the BBB, it is 10,000-100,000 times less potent than other common cancer drugs with limited BBB-crossing ability, including paclitaxel, doxorubicin, vincristine and vinblastine,[15] thereby requiring much higher doses, which can lead to significant peripheral toxicity. In this sense, brain delivery systems for highly potent chemotherapeutics that can achieve better efficacy as well as safer pharmacokinetic profiles are urgently needed, and non-invasive nanoparticulated chemotherapy may prove to be one of the most promising strategies.

With the advances in nanotechnology, engineering nanomaterials by modulating size, morphology, surface properties and epitope ratios have shown great potential in various biomedical applications.[16–28] Nanoparticles hold unique advantages over conventional drug delivery systems, such as oral solid preparations,[29] in brain-targeted drug delivery due to their precision targeting abilities and ameliorated systematic toxicities (Table 2). Among all nanoparticulate systems, polymeric nanoparticles receive the most attention due to their superior stabilities and ease of surface modification.[30] In addition, therapeutic cargos can be loaded *via* various mechanisms, such as electrostatic interactions, covalent conjugation, physical entrapment in the core of nanoparticles, *etc.*[31] It has also been reported that nanocarriers can concentrate preferentially at tumor sites, inflammatory sites, and antigen sampling sites by virtue of the enhanced permeability and retention (EPR) effect of the vasculature. Once concentrated at the diseased site, *e.g.*, solid tumors, hydrophobic biodegradable polymeric nanoparticles can serve as a local drug reservoir providing a source for the continuous release of encapsulated therapeutic compounds.[32,33]

Toward this end, nanoparticles, such as polymeric nanoparticles, liposomes, lipid micro-spheres, niosomes, and solid lipid nanoparticles, have all shown promise in the treatment of brain tumors.[34] Successful delivery of nanoparticles to the brain, however, also depends on the ability of the nanoparticles to cross the BBB, a restrictive barrier that separates the circulating blood from the brain extracellular fluid. It has been successfully demonstrated in the literature that only a few lipophilic drugs that are below the 400-500 Da threshold can passively diffuse across the BBB[35,36] and even those that can pass quite often suffer from active efflux mediated by P-gp. Therefore, a high initial dose is required to achieve a therapeutic dose in the CNS, which usually leads to off-target toxicities. In contrast to small molecular drugs, nanoparticles can penetrate the BBB and deliver both hydrophilic and lipophilic drugs to the brain tumor without prereleasing drugs into circulation by precisely engineering the core and the surface coating.

In this review, we will introduce the numerous challenges in brain drug delivery, and more importantly, current strategies to overcome these hurdles with a focus on nanoparticulated drug delivery systems.

BBB and strategies for the improved delivery of pharmaceutics into the brain

Physiology and pharmacology of the BBB

The brain functions in a well-controlled yet dynamic environment and is separated from the peripheral circulation by three barriers: the blood–brain barrier (BBB), the blood–cerebrospinal fluid barrier (BCSFB), and the ependymal barrier.[37] These barriers selectively impede the invasion of toxins while allowing free passage of essential nutrients and neurotransmitters. More specifically, the BBB, formed mainly by endothelial cells, restricts the free diffusion of substances from the peripheral circulating blood to the brain parenchyma; the BCSFB established by the choroid plexus epithelium in the ventricles restrains free diffusion from circulating blood to the cerebrospinal fluid (CSF); while the ependymal that consists of epithelial cells in the ventricles regulates diffusion from the CSF to the brain.[37,38] Acting together, these three barriers limit free