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Precise glioma targeting of and penetration by aptamer and peptide dual-functioned nanoparticles

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ABSTRACT

The treatment of a brain glioma is still one of the most difficult challenges in oncology. To effectively treat brain glioma and reduce the side effects, drugs must be transported across the blood brain barrier (BBB) and then targeted to the brain cancer cells because most anti-tumor drugs are highly toxic to the normal brain tissue. A cascade delivery strategy was developed to perform these two aims and to achieve enhanced and precisely targeted delivery. Herein, we utilize a phage-displayed TGN peptide and an AS1411 aptamer, which are specific targeting ligands of the BBB and cancer cells, respectively and we conjugate them with nanoparticles to establish the brain glioma cascade delivery system (AsTNP). *In vitro* cell uptake and three-dimensional tumor spheroid penetration studies demonstrated that the system could not only target endothelial and tumor cells but also penetrate the endothelial monolayers and tumor cells to reach the core of the tumor spheroids, which was extremely important but mostly ignored in glioma therapy. *In vivo* imaging further demonstrated that the AsTNP provided the highest tumor distribution and tumor/normal brain ratio. The distribution was also reconfirmed by fluorescent images of the brain slides. As a result, the docetaxel-loaded AsTNP presents the best anti-glioma effect with improved glioma bearing survival. In conclusion, the AsTNP could precisely target to the brain glioma, which was a valuable target for glioma imaging and therapy.

1. Introduction

Although brain glioma remains a serious threat and is widely incurable, despite anti-tumor battle has achieved much in terms of outcomes for other types of tumors. The 5-year survival rate of patients with brain cancer is only 33.3% and this rate was still decreasing, although that of most of the other cancers is increasing [1]. The average length of survival for patients with malignant glioma is even worse and ranges between 15 and 22 months [2]. Radiotherapy or chemotherapy followed by a surgical resection is the standard treatment [3]. However, due to the infiltrate growth of gliomas, it is hard to completely remove the tumor [4,5]; simultaneously, the important function of the brain leads to conservative resections. Noninvasive treatment to improve the glioma bearing survival is a promising direction. However, most chemotherapy has failed because of the rare blood brain barrier (BBB) penetration and poor glioma targeting of the chemotherapeutics [6]. Therefore, it is patently clear that there is a dire need for effective brain glioma targeting systems with a high BBB penetration and specific glioma targeting abilities.

As a disease of the whole brain, effective treatment for brain glioma needs to conquer two barriers: BBB and the brain-glioma barrier [7]. Traditional targeted delivery has focused only on how to transport across the BBB [8–10]. The selected distribution to the diseased region and the penetration into cancer cells after the drugs enter into the brain was more important for glioma therapy to achieve a better efficiency with lower side effects. The cascade targeting strategy is considered to be a promising resolution for this dilemma [11]. In the cascade targeting delivery system, the nanoparticle is conjugated to a BBB targeting ligand and a glioma targeting ligand, which may achieve high and precise brain glioma targeting.

Targeting ligands were a crucial component of the targeting delivery system, because of the immunogenicity and competitive nature of endogenous ligands, exogenous ligands gained much attention. Phage display was a method that could select tissue specific ligands from a random sequence library. A 12-amino acid

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