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Design of Bio-Responsive Hyaluronic Acid–Doxorubicin Conjugates for the Local Treatment of Glioblastoma

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Abstract: Glioblastoma is an unmet clinical need. Local treatment strategies offer advantages, such as the possibility to bypass the blood–brain barrier, achieving high drug concentrations at the glioblastoma site, and consequently reducing systemic toxicity. In this study, we evaluated the feasibility of using hyaluronic acid (HA) for the local treatment of glioblastoma. HA was conjugated to doxorubicin (DOX) with distinct bio-responsive linkers (direct amide conjugation HA-NH-DOX), direct hydrazone conjugation (HA-Hz-DOX), and adipic hydrazone (HA-AdpHz-DOX). All HA-DOX conjugates displayed a small size (less than 30 nm), suitable for brain diffusion. HA-Hz-DOX showed the best performance in killing GBM cells in both 2D and 3D in vitro models and displayed superior activity in a subcutaneous GL261 tumor model in vivo compared to free DOX and other HA-DOX conjugates. Altogether, these results demonstrate the feasibility of HA as a polymeric platform for the local treatment of glioblastoma and the importance of rationally designing conjugates.

Keywords: glioblastoma; local treatment; hyaluronic acid; polymer–drug conjugates; bio-responsive linkers

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1. Introduction

Glioblastoma (GBM) is the most common malignant primary central nervous system tumor in adults, representing approximately 57% of all gliomas and 48% of all primary brain cancers [1]. Furthermore, the associated morbidity, with a progressive decline in neurologic function and quality of life, can have a devastating impact on patients, caregivers, and families [2]. The current standard of care to tackle GBM has remained almost unchanged since 2005 and consists of a multimodal approach that involves surgery, radiotherapy, and systemic therapy (temozolomide). Despite recent advances in drug discovery and delivery, the overall prognosis remains poor, and long-term survival is rare, making GBM a significant unmet clinical need [3,4]. The minimal improvement in outcomes for GBM patients is due to several factors, including (1) the high propensity of GBM to migrate and invade surrounding healthy brain parenchyma; (2) GBM is located in the brain, which is shielded by the blood–brain barrier (BBB), the major obstacle for the systemic delivery of drugs in the brain, inhibiting the efficacy of the majority of treatments; (3) intrinsic resistance to current therapies due to high inter- and intra-patient heterogenicity, making it difficult to target and efficiently treat the entire GBM [5].

Localized strategies for delivering therapeutics and nanomedicines to the GBM (including intratumoral injection, convention-enhanced delivery, and filling the resection cavity) are an exciting approach that allows us to circumvent the BBB and achieve high drug doses in the brain while minimizing both local and systemic toxicity in order to overcome tumor resistance [6–8]. An example of a local treatment is Gliadel, a wafer loaded with carmustine, locally implanted in the brain after tumor resection, that was approved by the U.S. Food and Drug Administration in 1996 for the treatment of recurrent GBM [9].