Delivering Drug-Loaded Liposomes to Glioblastoma Stem Cells

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ABSTRACT

Due to the infiltrative capacity of glioblastoma (GBM) cells complete eradication is most of the time impossible to achieve. To control tumor growth, and ultimately cure patients, it is essential to develop treatment strategies to kill therapy refractory cells and to mount robust immunosurveillance to prevent disease recurrence. The radio- and chemo- resistance of Glioma Stem-like Cells (GSCs) together with their innate tumor-initiating aptitude and invasiveness, make this cell population a crucial target for effective therapies. However targeting GSCs is hardly difficult and complex, due to the presence of the blood brain barrier (BBB).

To overcome GBM hurdles, we encapsulate doxorubicin (DOXO), as paradigm of cytotoxic drug triggering immune cell death, into liposomes (LIPs) functionalized with an ApoE-derived peptide (mApoE). mApoE confers GSC specificity through the engagement of the Low-Density Lipoprotein Receptor (LDLR).

mApoE-DOXO-LIPs chronic administration to Patient-Derived Xenograft triggers GSC apoptosis resulting in a remarkable reduction of tumor growth and invasion. Apoptotic GSCs prompts microglia/macrophage phagocytic activity coupled to the activation of the antigen-presenting machinery propaedeutic to T cell priming. Importantly, the concomitant administration of radiation (2Gy) enhances the anti-tumor effects by altering BBB permeability and promoting the expression of LDLR on both BBB and GSCs.

Our results advocate for radiotherapy and adjuvant administration of drug-loaded targeted nanovectors as an effective strategy to deliver cytotoxic molecules circumventing BBB hurdles and targeting GSCs at the tumor burden, the forefront of GBM recurrence (*Pizzocri et al. Neurooncol Adv, 2021 Jun 18;3(1*), *doi: 10.1093/noajnl/vdab076*).