ABSTRACT

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Immune Checkpoint Inhibition in GBM Primed with Radiation by Engineered Extracellular Vesicles.

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The lack of safe and effective delivery across the blood-brain barrier and the profound immune suppressive microenvironment are two main hurdles to glioblastoma (GBM) therapies. Extracellular vesicles (EVs) have been used as therapeutic delivery vehicles to GBM but with limited efficacy. We hypothesized that EV delivery to GBM can be enhanced by (i) modifying the EV surface with a brain-tumor-targeting cyclic RGDyK peptide (RGD-EV) and (ii) using bursts of radiation for enhanced accumulation. In addition, EVs were loaded with small interfering RNA (siRNA) against programmed cell death ligand-1 (PD-L1) for immune checkpoint blockade. We show that this EV-based strategy dramatically enhanced the targeting efficiency of RGD-EV to murine GBM, while the loaded siRNA reversed radiation-stimulated PD-L1 expression on tumor cells and recruited tumor-associated myeloid cells, offering a synergistic effect. The combined therapy significantly increased CD8+ cytotoxic T cells activity, halting tumor growth and prolonging animal survival. The selected cell source for EVs isolation and the presented functionalization strategy are suitable for large-scale production. These results provide an EV-based therapeutic strategy for GBM immune checkpoint therapy which can be translated to clinical applications.

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