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Therapeutic approach of stem cell carrying retroviral replicating vectors in human glioma model.

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Toca 511, an improved retroviral replicating vectors (RRVs) expressing a codon-optimized cytosine deaminase, has shown highly promising evidence of therapeutic benefit in preclinical and clinical studies for gene therapy of glioma. In the present study, we engineered human mesenchymal stem cells (MSC) as tumor-homing cellular carriers that produce and release RRV, and evaluated the effect of this mode of virus delivery on the time course of intratumoral RRV dissemination. Human MSC isolates were engineered to produce RRV (MSC-RRV). Cytotoxicity assays confirmed efficient prodrug activator function in U-87 glioma cells transduced with vectors produced from MSC-RRV. To evaluate intratumoral migration activity and tumor-homing migration activity *in vivo*, individual MSC isolates were injected either directly into human glioma xenografts, or into the contralateral brain hemisphere. MSC-RRV isolates showing the highest levels of intratumoral migration activity were selected, and the efficiency of intratumoral dissemination and tumoricidal activity achieved by these isolates was compared against injection of RRV virus preparations in subcutaneous glioma models. Compared to virus injection, MSC-RRV achieved 1.6x-higher levels of tumor transduction ($p<0.05$), and 2x-reduced tumor growth ($p=0.018$) at earlier time points. In short-term survival studies using lower doses of MSC-RRV cells vs. RRV virus injected 14 days post-establishment of intracranial U-87 gliomas, a small but statistically significant prolongation of median survival was seen with intracranial tumors treated with MSC-RRV as compared to RRV (26 vs. 20 days, $p<0.05$) after only a single cycle of 5-FC prodrug. Thus, MSC can be employed as mobile tumor-homing RRV-producer cells, which release RRV as they migrate to tumor foci *in vivo* and actively penetrate into individual tumor masses, resulting in more rapid tumor transduction and earlier therapeutic efficacy, which may be advantageous particularly for multi-focal and metastatic disease. This study was funded by the California Institute for Regenerative Medicine (TR2-01791).

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