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TRANSLATIONAL AND CLINICAL RESEARCH

Mesenchymal Stem Cells Effectively Deliver an Oncolytic Adenovirus to Intracranial Glioma

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Abstract

Gene therapy represents a promising treatment alternative for patients with malignant gliomas. Nevertheless, in the setting of these highly infiltrative tumors, transgene delivery remains a challenge. Indeed, viral vehicles tested in clinical trials often target tumor cells only adjacent to the injection site. In this study, we examined the feasibility of using human mesenchymal stem cells (hMSC) to deliver a replication competent oncolytic adenovirus (CRAd) in a model of intracranial malignant glioma. To do so, CRAds with a chimeric 5/3 fiber or RGD backbone ± CXCR4 promoter driving E1A were examined with respect to replication and toxicity in hMSC, human astrocytes, and human glioma cell line U87MG by qPCR and membrane integrity assay. CRAd delivery by virus-loaded hMSC was then evaluated *in vitro* and in an *in vivo* model of mice bearing intracranial U87MG xenografts. Our results show that hMSC are effectively infected by CRAds that utilize the CXCR4 promoter. CRAd-CXCR4-RGD had the highest replication, followed by CRAd-CXCR4-5/3, in hMSC, with comparable levels of toxicity. In U87MG tumor cells, CRAd-CXCR4-5/3 showed the highest replication and toxicity. Virus-loaded hMSC effectively migrated *in vitro* and released CRAds that infected U87MG glioma cells. When injected away from the tumor site *in vivo*, hMSC migrated to the tumor and delivered 46-fold more viral copies than injection of CRAd-CXCR4-5/3 alone. Taken together, these results indicate that hMSC migrate and deliver CRAd to distant glioma cells. This delivery strategy should be further explored as it could improve the outcome of oncolytic virotherapy for glioma.

Key Words. Glioma, stem cells, adenovirus, oncolytic virus, vector, migration, gene therapy

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