Cellular delivery of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) by mesenchymal stem cells inhibits tumor growth in an orthotopic glioma model

Abstract

PURPOSE: High-grade gliomas are highly infiltrative tumors with a bleak prognosis. Current treatments regimens, which include surgery followed by radiation and chemotherapy, do little to prevent recurrence and only increase patient survival by a few months. The extensive tropic capabilities of human mesenchymal stem cells (hMSCs) and relative ease of genetic manipulation make them an ideal candidate as a therapeutic delivery vehicle.

EXPERIMENTAL DESIGN: hMSCs were transduced with a secretable form of TNF-related apoptosis-inducing ligand (S-TRAIL) packaged in a lentiviral vector. The migratory ability and therapeutic efficacy of transduced hMSCs were studied both in vitro and in vivo using an orthotopic U87 glioma model. S-TRAIL was chosen as the therapeutic protein because of its potential to reduce tumor growth through selective and potent induction of apoptosis. RESULTS: The migratory capacity of hMSCs was shown by an in vitro migration assay and confirmed in vivo by fluorescent tracking of cells implanted into the contralateral hemisphere of nude mice. Production of S-TRAIL by transduced cells was confirmed by RT-PCR and quantitated using ELISA. Biological activity of S-TRAIL was demonstrated in vitro by cytotoxicity assay and kinetic studies. In vivo therapeutic efficacy studies in nude mice showed an 8l% reduction in tumor volume when S-TRAIL hMSCs were injected ipsilaterally to an established U87 tumor. Histological analysis confirmed the presence of hMSCs in the tumor site and the induction of apoptosis.

CONCLUSION: The results of these experiments demonstrate that S-TRAIL hMSCs can migrate to the site of glioma tumors and inhibit tumor growth.