Dual-targeted antitumor effects against brainstem glioma by intravenous delivery of tumor necrosis factor-related, apoptosis-inducing, ligand-engineered human mesenchymal stem cells.


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OBJECTIVE: We sought to explore the dual-targeted antitumor effects of membrane-spanned, tumor necrosis factor-related, apoptosis-inducing ligand (TRAIL)-engineered human mesenchymal stem cells (hMSCs) against brainstem gliomas. METHODS: The migration capacity of hMSCs toward gliomas was studied by the Transwell system in vitro and by intravenous injection of hMSCs in glioma-bearing mice in vivo. MSCs were engineered with native full-length human TRAIL (hTRAIL) by a recombinant adeno-associated virus (rAAV) vector (rAAV-hTRAIL). The targeted antiglioma effect was analyzed by coculture of hTRAIL-engineered MSCs with glioma in vitro and by systematic delivery of hTRAIL-engineered MSCs to established human brainstem glioma xenografts. RESULTS: We demonstrated systematically that transplanted MSCs migrated to a brainstem glioma with a high specificity. MSCs penetrated the vessels surrounding the tumor, then streamed in a chain pattern toward the glioma, eventually surrounding the tumor. Membrane-spanned, TRAIL-engineered MSCs not only expressed full-length TRAIL in MSC surface, but secreted some soluble TRAIL in medium. After being infected with rAAV-hTRAIL, hMSCs showed no increase in apoptosis. After coculture of hTRAIL-engineered MSCs and U87MG cells, the apoptosis of U87MG cells significantly increased more than soluble TRAIL-treated U87MG cells. Systematic delivery of hTRAIL-engineered MSCs to established human brainstem glioma xenografts resulted in the potent induction of apoptosis in gliomas, but not in normal brain and prolonged survival to 38.0 +/- 10.46 days compared with phosphate-buffered saline (16.0 +/- 0.66 days), soluble TRAIL (19.0 +/- 1.65 days), and hMSC-LacZ (14.0 +/- 0.59 days) treated groups. CONCLUSION: Systematically transplanted MSCs migrated to gliomas with a high specificity. Systematic delivery of MSC-hTRAIL can prolong the survival of brainstem glioma-bearing mice, presumably through a dual-targeted effect of membrane-spanned, TRAIL-engineered MSCs in the tumor microenvironment. MSCs may be an effective vehicle for the targeted delivery of therapeutic agents to brainstem gliomas.

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