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hMSC-mediated Concurrent Delivery of Endostatin and Carboxylesterase to Mouse Xenografts Suppresses Glioma Initiation and Recurrence.

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Abstract

Glioma stem cells (GSCs) are known to be maintained within a "vascular niche"; thereby, disruption of this microenvironment using antiangiogenesis agents is a promising therapeutic modality. However, this regimen leads to treatment failure and tumor recurrence in patients with glioblastoma multiforme (GBM). Therefore, more effective therapeutic approaches that can eradicate GSCs and the bulk tumors are needed. Toward this goal, we examined the antitumor effects of an antiangiogenesis approach combined with conventional chemotherapy on suppressing glioma xenograft growth. We established three genetically engineered mesenchymal stem cell (MSC) lines (GE-AF-MSCs) by stably transducing the gene encoding endostatin (an antiangiogenesis factor), the gene encoding secretable form of carboxylesterase 2 (sCE2, a prodrug-activating enzyme), or a mixture of both genes. Among the three GE-AF-MSC cell lines, injection of amniotic fluid (AF)-MSCs-endostatin-sCE2 cells into U87MG-EGFRvIII-driven orthotopic brain tumor and postsurgery tumor recurrence models, and subsequent CPT11 treatment yielded the strongest antitumor responses, including diminished angiogenesis, increased cell death, and a reduced Nestin-positive GSC population. Therefore, our antitumor strategy provides a novel basis for designing stem cell-mediated therapeutic approaches to target and eradicate GSCs and the bulk tumors.

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