Valproic acid enhances anti-tumor effect of mesenchymal stem cell mediated HSV-TK gene therapy in intracranial glioma.

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Abstract
Suicide gene therapy of glioma based on herpes simplex virus type I thymidine kinase (HSV-TK) and prodrug ganciclovir (GCV) suffers from the lack of efficacy in clinical trials, which is mostly due to low transduction efficacy and absence of bystander effect in tumor cells. Recently, stem cells as cellular delivery vehicles of prodrug converting gene has emerged as a new treatment strategy for malignant glioma. In this study, we evaluated the anti-glioma effect of suicide gene therapy using human bone marrow mesenchymal stem cells expressing HSV-TK (MSCs-TK) combined with valproic acid (VPA), which can upregulate the gap junction proteins and may enhance the bystander effect of suicide gene therapy. Expression of HSV-TK in MSCs was confirmed by RT-PCR analysis and the sensitivity of MSCs-TK to GCV was assessed. A bystander effect was observed in co-cultures of MSCs-TK and U87 glioma cells by GCV in a dose-dependent manner. VPA induced the expression of the gap junction proteins connexin (Cx) 43 and 26 in glioma cell and thereby enhanced the bystander effect in co-culture experiment. The enhanced bystander effect was inhibited by the gap junction inhibitor 18-β-glycyrrhetinic acid (18-GA). Moreover, the combined treatment with VPA and MSCs-TK synergistically enhanced apoptosis in glioma cells by caspase activation. In vivo efficacy experiments showed that combination treatment of MSCs-TK and VPA significantly inhibited tumor growth and prolonged the survival of glioma-bearing mice compared with single-treatment groups. In addition, TUNEL staining also demonstrated a significant increase in the number of apoptotic cells in the combination treated group compared with single-treatment groups. Taken together, these results provide the rational for designing novel experimental protocols to increase bystander killing effect against intracranial gliomas using MSCs-TK and VPA.

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