

Molecular Cancer Therapeutics



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Research Articles: Therapeutics, Targets, and Development

Targeting multiple pathways in gliomas with stem cell and viral delivered S-TRAIL and Temozolomide

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Abstract

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) selectively kills tumor cells. However, its short half-life, poor delivery, and TRAIL-resistant tumor cells have diminished its clinical efficacy. In this study, we explored whether novel delivery methods will represent new and effective ways to treat gliomas and if adjuvant therapy with the chemotherapeutic agent temozolomide would enhance the cytotoxic properties of TRAIL in glioma lines resistant to TRAIL monotherapy. We have engineered adeno-associated virus (AAV) vectors encoding recombinant secreted TRAIL (S-TRAIL) and bioluminescent-fluorescent marker fusion proteins and show that AAV-delivered S-TRAIL leads to varying degrees of killing in multiple glioma lines, which

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correspond with caspase-3/7 activation. *In vivo*, dual bioluminescent imaging revealed efficient delivery of therapeutic AAV vectors directly into the tumor mass, which induced marked attenuation of tumor progression. Treatment of glioma cells with the chemotherapeutic agent temozolomide alone lead to a significant accumulation of cells in G₂-M phase, activated the cell cycle checkpoint protein Chk1, and increased death receptor expression in a time-dependent manner. Furthermore, combined treatment with AAV-S-TRAIL or neural stem cell-S-TRAIL and temozolomide induced cell killing and markedly up-regulated proapoptotic proteins in glioma cells least sensitive to TRAIL. This study elucidates novel means of delivering S-TRAIL to gliomas and suggests combination of clinically relevant temozolomide and S-TRAIL may represent a new therapeutic option with increased potency for glioblastoma patients. [Mol Cancer Ther 2008;7(11):3575–85]

Footnotes

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