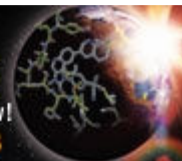


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Cancer Therapy: Preclinical

Targeted Inhibition of Cyclic AMP Phosphodiesterase-4 Promotes Brain Tumor Regression

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Purpose: As favorable outcomes from malignant brain tumors remain limited by poor survival and treatment-related toxicity, novel approaches to cure are essential. Previously, we identified the cyclic AMP phosphodiesterase-4 (PDE4) inhibitor Rolipram as a potent antitumor agent. Here, we investigate the role of PDE4 in brain tumors and examine the utility of PDE4 as a therapeutic target.

Experimental Design: Immunohistochemistry was used to evaluate the expression pattern of a subfamily of PDE4, PDE4A, in multiple brain tumor types. To evaluate the effect of PDE4A on growth, a brain-specific isoform, PDE4A1 was overexpressed in xenografts of Daoy

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medulloblastoma and U87 glioblastoma cells. To determine therapeutic potential of PDE4 inhibition, Rolipram, temozolomide, and radiation were tested alone and in combination on mice bearing intracranial U87 xenografts.

Results: We found that PDE4A is expressed in medulloblastoma, glioblastoma, oligodendroglioma, ependymoma, and meningioma. Moreover, when PDE4A1 was overexpressed in Daoy medulloblastoma and U87 glioblastoma cells, *in vivo* doubling times were significantly shorter for PDE4A1-overexpressing xenografts compared with controls. In long-term survival and bioluminescence studies, Rolipram in combination with first-line therapy for malignant gliomas (temozolomide and conformal radiation therapy) enhanced the survival of mice bearing intracranial xenografts of U87 glioblastoma cells. Bioluminescence imaging indicated that whereas temozolomide and radiation therapy arrested intracranial tumor growth, the addition of Rolipram to this regimen resulted in tumor regression.

Conclusions: This study shows that PDE4 is widely expressed in brain tumors and promotes their growth and that inhibition with Rolipram overcomes tumor resistance and mediates tumor regression.

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