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### Examination of the therapeutic potential of Delta-24-RGD in brain tumor stem cells: role of autophagic cell death.

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#### Abstract

The eradication of brain tumor stem cells is essential for long-term brain tumor remission after treatment. In this study, we examined the therapeutic potential of an oncolytic adenovirus, Delta-24-RGD, targeted to the abnormal p16INK4/Rb pathway in brain tumor stem cells. Four brain tumor stem cell lines from surgical glioblastoma specimens expressed high levels of adenoviral receptors and allowed for efficient viral infection, replication, and oncolysis in an Rb-dependent manner. Delta-24-RGD induced autophagic cell death, as indicated by accumulation of Atg5 and LC3-II protein and autophagic vacuoles. Treatment of xenografts derived from brain tumor stem cells with Delta-24-RGD statistically significantly improved the survival of glioma-bearing mice (means: 38.5 versus 66.3 days, difference = 27.8 days, 95% confidence interval = 19.5 to 35.9 days,  $P < .001$ ). Analyses of treated tumors showed that Atg5 expression colocalized with viral fiber protein and delineated a wave front of autophagic cells that circumscribed areas of virally induced necrosis. Our results show for the first time that brain tumor stem cells are susceptible to adenovirus-mediated cell death via autophagy in vitro and in vivo.

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