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CANCER STEM CELLS

Brain Cancer Stem Cells Display Preferential Sensitivity to Akt Inhibition

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Abstract

Malignant brain tumors are among the most lethal cancers, and conventional therapies are largely limited to palliation. Novel therapies targeted against specific molecular pathways may offer improved efficacy and reduced toxicity compared to conventional therapies, but initial clinical trials of molecular targeted agents in brain cancer therapy have been frequently disappointing. In brain tumors and other cancers, subpopulations of tumor cells have recently been characterized by their ability to self-renew and initiate tumors. Although these cancer stem cells, or tumor initiating cells, are often only present in small numbers in human tumors, mounting evidence suggests that cancer stem cells contribute to tumor maintenance and therapeutic resistance. Thus, the development of therapies that target cancer stem cell signal transduction and biologies may improve brain tumor patient survival. We now demonstrate that populations enriched for cancer stem cells are preferentially sensitive to an inhibitor of Akt, a prominent cell survival and invasion signaling node. Treatment with an Akt inhibitor more potently reduced the numbers of viable brain cancer stem cells relative to matched non-stem cancer cells associated with a preferential induction of apoptosis and a suppression of neurosphere formation. Akt inhibition also reduced the motility and invasiveness of all tumor cells but had a greater impact on cancer stem cell behaviors. Furthermore, inhibition of Akt activity in cancer stem cells increased survival of immunocompromised mice bearing human glioma xenografts *in vivo*. Together, these results suggest that Akt inhibitors may function as effective anti-cancer stem cell therapies.

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