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Notch pathway blockade targets medulloblastoma-initiating cancer stem cells

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Many tumors, like normal organs, contain stem-like cells capable of long-term self renewal critical for neoplastic initiation and growth. We investigated whether Notch activity, which is required in non-neoplastic neural stem cells, might also regulate cancer stem cells in malignant brain tumors such as medulloblastoma. Constitutive Notch2 activation in medulloblastoma cultures increased side population, a marker of cancer stem cells, over three-fold, while Notch pathway blockade using a gamma-secretase inhibitor reduced side population from 1.9% to 0.01%. The cell fraction expressing other stem cell markers such as CD133 and nestin was also significantly reduced by pharmacological Notch inhibition. Both forced differentiation and Akt-dependant apoptosis caused depletion of stem-like tumor cells. A large viable cell population remained after gamma-secretase inhibitor therapy, but did not efficiently initiate tumor xenografts, while equal numbers of vehicle-treated cells always did. Our data suggest that Notch signaling is critical in brain tumor stem cells, and that gamma-secretase inhibitors preferentially target this tumor-initiating cell fraction, leaving behind a population of viable cells with significantly reduced malignant potential.

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