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# Notch Pathway Blockade Depletes CD133-Positive Glioblastoma Cells and Inhibits Growth of Tumor Neurospheres and Xenografts.

Fan X, Khaki L, Zhu TS, Soules ME, Talsma CE, Gul N, Koh C, Zhang J, Li YM, Maciaczyk J, Nikkhah G, Dimeco F, Piccirillo S, Vescovi AL, Eberhart CG.

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Cancer stem cells (CSCs) are thought to be critical for the engraftment and long-term growth of many tumors, including glioblastoma (GBM). They are at least partially spared by traditional chemo- and radiation-therapies, and finding new treatments which can target CSC may be critical for improving patient survival. It has been shown that the Notch signaling pathway regulates normal stem cells in the brain, and that GBM contain stem-like cells with higher Notch activity. We therefore used low-passage and established GBM-derived neurosphere cultures to examine the overall requirement for Notch activity, and also examined the effects on tumor cells expressing stem cell markers. Notch blockade by gamma-secretase inhibitors (GSIs) reduced neurosphere growth and clonogenicity in vitro, while expression of an active form of Notch2 increased tumor growth. The putative CSC markers CD133, Nestin, Bmi1, and Olig2 were reduced following Notch blockade. When equal numbers of viable cells pretreated with either vehicle (DMSO) or GSI were injected subcutaneously into nude mice, the former always formed tumors, whereas the latter did not. In vivo delivery of GSI by implantation of drug-impregnated polymer beads also effectively blocked tumor growth, and significantly prolonged survival, albeit in a relatively small cohort of animals. We found that Notch pathway inhibition appears to deplete stem-like cancer cells through reduced proliferation and increased apoptosis associated with decreased Akt and STAT3 phosphorylation. In summary, we demonstrate that Notch pathway blockade depletes stem-like cells in GBMs, suggesting that GSIs may be useful as chemotherapeutic reagents to target CSCs in malignant gliomas.

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