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### Regulation of glioblastoma stem cells by retinoic acid: role for Notch pathway inhibition.

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#### Abstract

It is necessary to understand mechanisms by which differentiating agents influence tumor-initiating cancer stem cells. Toward this end, we investigated the cellular and molecular responses of glioblastoma stem-like cells (GBM-SCs) to all-trans retinoic acid (RA). GBM-SCs were grown as non-adherent neurospheres in growth factor supplemented serum-free medium. RA treatment rapidly induced morphology changes, induced growth arrest at G1/G0 to S transition, decreased cyclin D1 expression and increased p27 expression. Immunofluorescence and western blot analysis indicated that RA induced the expression of lineage-specific differentiation markers Tuj1 and GFAP and reduced the expression of neural stem cell markers such as CD133, Msi-1, nestin and Sox-2. RA treatment dramatically decreased neurosphere-forming capacity, inhibited the ability of neurospheres to form colonies in soft agar and inhibited their capacity to propagate subcutaneous and intracranial xenografts. Expression microarray analysis identified ~350 genes that were altered within 48 h of RA treatment. Affected pathways included retinoid signaling and metabolism, cell-cycle regulation, lineage determination, cell adhesion, cell-matrix interaction and cytoskeleton remodeling. Notch signaling was the most prominent of these RA-responsive pathways. Notch pathway downregulation was confirmed based on the downregulation of HES and HEY family members. Constitutive activation of Notch signaling with the Notch intracellular domain rescued GBM neurospheres from the RA-induced differentiation and stem cell depletion. Our findings identify mechanisms by which RA targets GBM-derived stem-like tumor-initiating cells and novel targets applicable to differentiation therapies for glioblastoma. *Oncogene* advance online publication, 7 March 2011; doi:10.1038/onc.2011.58.

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