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N-CoR pathway targeting induces glioblastoma derived cancer stem cell differentiation.

Park DM, Li J, Okamoto H, Akeju O, Kim SH, Lubensky I, Vortmeyer A, Dambrosia J, Weil RJ, Oldfield EH, Park JK, Zhuang Z.

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Nuclear receptor corepressor (N-CoR) is a critical regulator of neural stem cell differentiation. Nuclear localization of N-CoR is a feature of undifferentiated neural stem cells and cytoplasmic translocation of N-CoR leads to astrocytic differentiation. Comparative proteomic analysis of microdissected glioblastoma multiforme (GBM) specimens and matched normal glial tissue reveals increased expression of N-CoR in GBM. In GBM primary cell cultures, tumor cells with nuclear localization of N-CoR demonstrate an undifferentiated phenotype, but are subject to astroglial differentiation upon exposure to agents promoting phosphorylation of N-CoR and its subsequent translocation to the cytoplasm. Treatment of glioma cell lines with a combination of retinoic acid and low-dose okadaic acid decreases the corepressor effect of N-CoR and has a striking synergistic effect on growth inhibition. The identification of N-CoR in GBM provides insights into the tumorigenesis process and supports the development of differentiation-based therapeutic strategies.

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