

PubMed

U.S. National Library of Medicine
National Institutes of Health



Display Settings: Abstract

[J Neurosurg..](#) [Epub ahead of print]

The effect of a PP2A inhibitor on the nuclear receptor corepressor pathway in glioma.

Lu J, Zhuang Z, Song DK, Mehta GU, Ikejiri B, Mushlin H, Park DM, Lonser RR.

Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland; and.

Object Nuclear receptor corepressor (N-CoR) forms a complex that maintains neural stem cells in an undifferentiated state through transcriptional repression. Recently, it has been shown that N-CoR is overexpressed in glioblastoma multiforme (GBM) tumor stem cells and has a putative role in maintaining these cells in an undifferentiated immortal state. To determine the effects of disruption of N-CoR complex function by serine/threonine protein phosphatase 2A (PP2A) inhibition on GBM tumor cell differentiation and proliferation, the authors developed and investigated a competitive small molecule inhibitor (LB1) of PP2A in GBM. Methods The authors investigated the effects of LB1 on GBM proliferation and molecular differentiation pathways using in vitro and in vivo studies. Results The LB1 inhibited PP2A, leading to increased levels of phosphorylated Akt kinase and decreased NCoR expression, as well as dose-dependent antiproliferative activity in cultured U87 and U251 malignant glioma cells (dose range 1-10 μ M). Systemic LB1 treatment (1.5 mg/kg/day for 21 days) had significant tumor antiproliferative effects in mice harboring U87 glioma xenografts (73% mean reduction in tumor volume compared with controls; $p < 0.001$). Moreover, a reduction in PP2A expression and activity after LB1 treatment in vivo correlated with increased Akt phosphorylation, reduced nuclear N-CoR expression and N-CoR cytoplasmic translocation, and increased accumulation of acetylated core histones, which coincided with the appearance of glial fibrillary acidic protein-expressing tumor cells. Conclusions These findings indicate that PP2A inhibition effectively disrupts N-CoR complex function/expression and leads to cytoplasmic translocation of N-CoR with subsequent tumor cell differentiation and/or death. Therapeutic paradigms that target N-CoR function in the cancer stem cell component of malignant gliomas may have treatment utility.

PMID: 20001590 [PubMed - as supplied by publisher]

[LinkOut - more resources](#)