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PLoS Biol. 2010 Feb 23;8(2):e1000319.

# Targeting A20 decreases glioma stem cell survival and tumor growth.

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Glioblastomas are deadly cancers that display a functional cellular hierarchy maintained by self-renewing glioblastoma stem cells (GSCs). GSCs are regulated by molecular pathways distinct from the bulk tumor that may be useful therapeutic targets. We determined that A20 (TNFAIP3), a regulator of cell survival and the NF-kappaB pathway, is overexpressed in GSCs relative to non-stem glioblastoma cells at both the mRNA and protein levels. To determine the functional significance of A20 in GSCs, we targeted A20 expression with lentiviral-mediated delivery of short hairpin RNA (shRNA). Inhibiting A20 expression decreased GSC growth and survival through mechanisms associated with decreased cell-cycle progression and decreased phosphorylation of p65/RelA. Elevated levels of A20 in GSCs contributed to apoptotic resistance: GSCs were less susceptible to TNFalpha-induced cell death than matched non-stem glioma cells, but A20 knockdown sensitized GSCs to TNFalpha-mediated apoptosis. The decreased survival of GSCs upon A20 knockdown contributed to the reduced ability of these cells to self-renew in primary and secondary neurosphere formation assays. The tumorigenic potential of GSCs was decreased with A20 targeting, resulting in increased survival of mice bearing human glioma xenografts. In silico analysis of a glioma patient genomic database indicates that A20 overexpression and amplification is inversely correlated with survival. Together these data indicate that A20 contributes to glioma maintenance through effects on the glioma stem cell subpopulation. Although inactivating mutations in A20 in lymphoma suggest A20 can act as a tumor suppressor, similar point mutations have not been identified through glioma genomic sequencing: in fact, our data suggest A20 may function as a tumor enhancer in glioma through promotion of GSC survival. A20 anticancer therapies should therefore be viewed with caution as effects will likely differ depending on the tumor type.

PMID: 20186265 [PubMed - in process]

PMCID: PMC2826371

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