Tumor-suppressive potential of dual specificity phosphatase 1 in glioblastoma tumors.

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BACKGROUND: The dual specificity phosphatase 1 (*DUSP1, MKP-1*) is a stress-induced enzyme that provides feedback inhibition on MAP kinases. While associated with chemoresistance in other cancers, the role of *DUSP1* in glioblastoma remains unsettled.

METHODS: To investigate *DUSP1* expression in glioblastoma, we analyzed archived microarray data from the Repository for Molecular Brain Neoplasia Data (REMBRANDT) as well as a cohort of GB tumors from the Rochester Brain Bank. *DUSP1* regulation was studied *in vitro* to define the response to hypoxia, chemotherapy, and differentiation using qPCR. The effects of manipulating *DUSP1* expression on proliferation, apoptosis, and stemness were examined with flow cytometry.

RESULTS: *In silico*, *in vivo*, and *in vitro* analyses of GB samples/cells revealed marked variation in *DUSP1* mRNA with levels below control specimens in up to 25% of cases. *DUSP1* mRNA induction was observed *in vitro* upon introduction of disease-relevant factors including hypoxia and chemotherapy. Interestingly, *DUSP1* expression was also found to increase upon cellular differentiation, and enforced *DUSP1* expression induced maturation of GB tumor stem cells. *DUSP1* overexpression was also found to decrease GB tumor stem cell and cell line viability and proliferation.

CONCLUSIONS: While part of the observed variability in *DUSP1* expression *in vivo* appears related to stimulatory effects of tumor ischemia and/or chemotherapeutic exposure, acquired mutations of upstream regulators of *DUSP1* and/or *DUSP1* loss of function mutations may be involved. Our findings argue that strategies geared towards increasing *DUSP1* activity *in situ* could augment existing chemotherapeutic approaches.