CBIO-26. MITOGEN-ACTIVATED PROTEIN KINASE PHOSPHATASE 1 EXERTS AN ANTI-PROLIFERATIVE AND PRO-APOPTOTIC BIAS IN GBM
Bradley Mills, Jeanne Hansen, and Marc Halterman; University of Rochester Medical Center, Rochester, NY, USA

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, DUSP1's role 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 GBM tumors from the Rochester Brain Bank. DUSP1 regulation was also studied in vitro to define the response to hypoxia and chemotherapeutic exposure using qPCR and to explore effects of manipulating DUSP1 expression on proliferation and apoptosis by imaging flow cytometry. RESULTS: In silico analyses of GBM cases revealed marked variation in DUSP1 mRNA with levels below control specimens in up to 25% of cases. DUSP1 mRNA is also increased by disease-relevant factors including hypoxia, dexamethasone, and camptothecin in vitro. Enforced expression of DUSP1 increased levels of the pro-apoptotic factor BCL2-like 1 and exerted both anti-proliferative and pro-death effects, while DUSP1 knockdown enhanced cellular proliferation and survival. CONCLUSIONS: DUSP1 exerts an anti-proliferative and pro-death bias in GBM. While part of the observed variability in DUSP1 expression in vivo appears related to stimulatory effects of tumor ischemia and/or chemotherapeutic exposure, acquired loss of function mutations involving DUSP1 expression may be involved. Our findings argue that strategies geared towards increasing DUSP1 activity in situ could augment existing chemotherapeutic approaches.