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DIPG-75. PHARMACOLOGICAL INHIBITION OF LSD1/KDM1A IN DIFFUSE MIDLINE GLIOMA MODELS AND IMPACT ON KINASE SIGNALING

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BACKGROUND: High grade gliomas (HGGs) in both adults and children confer poor prognosis, with median survival rates under two years post-diagnosis. Diffuse midline gliomas (DMG) are a subset of HGG characterized by histone mutations, typically occurring in children. Genetic alterations in chromatin modifiers and receptor tyrosine kinases (RTKs) are seen in both adult and pediatric glioblastoma, however the interplay between these pathways requires further investigation to design therapeutic strategies. Our past work has evaluated KDM1A/LSD1 (Lysine-Specific Demethylase 1) inhibition through gene silencing and small molecules; here we assessed crosstalk between LSD1 and kinase signaling networks to uncover potential compensatory resistance mechanisms using clinically relevant pharmacological inhibitors of LSD1. METHODS: RNA-Seq and GSEA in high grade glioma cells bearing LSD1 knockdown were evaluated for kinase signaling pathway enrichment. A panel of DMG lines (SU-DIPGIV (MDM4, ACVR1), SU-DIPGV (TP53), VUMC-DIPG10 (NFI, MYCN), and SU-DIPGXIII and DMG data sets were probed for LSD1 expression, activity and kinase expression and treated with pharmacological inhibitors of LSD1 in vitro and in vivo. RESULTS: Pharmacological inhibition of LSD1 using clinically relevant agents revealed IC50s in the micromolar range across DMG lines. DMG lines varied with respect to LSD1 expression and baseline activation of ERK and AKT pathways. With LSD1 inhibition at subtoxic doses, increased phospho-ERK/ERK and phospho-AKT/AKT was noted in several DMG models and co-inhibition of these pathways suggests improved efficacy. CONCLUSIONS: Our data reveals that LSD1 inhibition causes an increase in kinase signaling at subtoxic doses which may alter drug response. These results urge the assessment of combination treatments with kinase inhibitors and additional in vivo analysis, which are currently underway.