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ATRX loss in pediatric glioma results in epigenetic dysregulation of G2/M checkpoint maintenance and sensitivity to ATM inhibition

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ATRX loss in pediatric glioma results in epigenetic dysregulation of G2/M checkpoint maintenance and sensitivity to ATM inhibition

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ABSTRACT:

ATRX is a histone chaperone protein recurrently mutated in pediatric glioma. The mechanism which mediates the proliferative advantage of ATRX loss in pediatric glioma remains unexplained. Recent data revealed a distinct pattern of DNA binding sites of the ATRX protein using ChIP-seq in mouse neuronal precursor cells (mNPCs). Using the ATRX peaks identified in $p53^{-/-}$ mNPCs, we confirmed that ATRX binding sites were significantly enriched in gene promoters ($p < 0.0001$) and CpG islands ($p < 0.0001$) compared with random regions. Gene set enrichment (GSE) analysis identified that cell cycle and regulation of cell cycle were among the most significantly enriched gene sets (p=2.52e-16 and 1.61e-9, respectively). We found that ATRX loss resulted in dysfunction of G2/M checkpoint maintenance: (1) ATRX-deficient pediatric glioblastoma (GBM) cells exhibited a seven-fold increase in mitotic index at 16 hours after sub-lethal radiation, and (2) murine GBM cells with ATRX knockdown demonstrated impaired pChk1 signaling on western blot at multiple time points after radiation compared to

controls (p=0.0187). Notably, the ATM signaling (pChk2) remained intact in those cells, suggesting a potential therapeutic target. ATRX-deficient mouse cells were uniquely sensitive to ATM inhibitors at 1 uM alongside 8 Gy radiation compared to controls with intact ATRX (AZD0156: p=0.0027 and AZD01390: p=0.0436). Mice intra-cranially implanted with ATRX-deficient GBM cells showed improved survival (n=10, p=0.0018) when treated with AZD0156 combined with radiation. Our findings suggest that ATRX loss in glioma results in unique sensitivity to ATM inhibition via epigenetic dysregulation of G2/M checkpoint maintenance.