Lysine Demethylase 4B: A Novel Epigenetic Target in Atypical Teratoid/Rhabdoid Tumor.

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Purpose of study: Atypical teratoid/rhabdoid tumor (ATRT) is a highly aggressive childhood brain tumor. Current treatment options often create therapy-related toxicity that is especially critical in this young patient population. Previous studies reported the loss of SMARCB1, a member of SWI/SNF chromatin remodeling complex, as a molecular feature of ATRT, creating an overall epigenetic dysregulation of the genome. This marks a potential avenue in the search for novel targeted therapy.

Methods: We utilized an unbiased epigenome-wide RNAi screen and identified lysine demethylase 4B (KDM4B) as a top epigenetic regulator critical for ATRT growth. Cell lines and patient tumor samples were used to validate the screen through both genetic perturbation and pharmacologic inhibition.

Summary of Results: Genetic depletion of KDM4B in ATRT has decreased cell viability by 79% and impaired the ability of tumor cells to form colonies. The suppression of KDM4B leads to a global increase in protein expression H3K9Me3, which has been shown to promote compaction in promotor regions. This suggests a hinderance of overall transcriptional activation which is currently being explored using integrated ChIP and RNA-sequencing. Importantly, KDM4B protein is highly expressed in ATRT cell lines and patient tumor samples, with minimal expression in normal cerebellum tissue. Small molecule inhibition of KDM4B shows preferential suppression of ATRT cells in comparison to normal human astrocytes.

Conclusions: We anticipate a promising translatable potential of KDM4B as a new target with a favorable therapeutic window. It additionally furthers our understanding of ATRT epigenetic biology and is a starting point to develop better, clinically translatable targeted therapies.