Histone demethylase KDM4B: a novel epigenetic target in atypical teratoid/rhabdoid tumor (ATRT)

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

Methods used: We utilized an unbiased epigenome-wide RNAi screen and identified one of the top hits, histone lysine demethylase 4B (KDM4B), as a novel epigenetic regulator that is critical for ATRT growth. ATRT cell lines and patient tumor samples were used as models to validate the screen through both genetic perturbation and pharmacologic small molecule inhibition. We further performed chromatin immunoprecipitation sequencing to understand the epigenetic remodeling after KDM4B perturbation.

Summary of results: Suppressing KDM4B in ATRT has decreased cell viability by an average of 79.34% and prevented colony formation of tumor cells. Moreover, KDM4B suppression resulted in increased protein expression of histone H3K9Me3, which is known to be associated with the hinderance of overall transcriptional activation by promoting compaction in promoter regions. Importantly, KDM4B is highly expressed in ATRT tumor cell lines and patient tumor samples but has minimal expression in normal human astrocyte cells and normal cerebellum tissue.

Conclusions: We anticipate this finding to implicate 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 targeted therapies that can be translated to the clinic.