ABSTRACT CITATION ID: NOAE064.070

DIPG-17. DYSREGULATED PURINE METABOLISM IN A LEthal CHILDHOOD BRAINSTEM TUMOR REVEALS NEW TREATMENT STRATEGIES WITH OLD DRUGS

Ian Mersch1,2, Sunny Congrove1,2, Matthew Horchar1, Roman Caceres1,2, Janki Desai1, Pankaj Desai1, Larry Sallans1, Julie Haines5, Ranjith Menon1, Charles Stevenson6, Peter de Blank1, Natasha Pillay-Smiley1, Trent Hummel1, Ali Tavassoli1, Angelo D’Alessandro1, Timothy Phoenix1, Biplob Dasgupta2, 1Division of Oncology, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, USA, 2Division of Biochemistry and Molecular Genetics, University of Colorado Anschutz Medical Campus, Aurora, CO, USA, 3Division of Pediatric Neurosurgery, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, USA, 4Chemical Biology, Diagnostics and Therapeutics, University of Southampton, Southampton, United Kingdom

The median survival of children with Diffuse Intrinsic Pontine Glioma (DIPG), an incurable brainstem cancer is less than 1 year. Radiation therapy is the only treatment that offers a transient benefit. The preclusion of surgery and biopsy due to the anatomical location of the tumor impeded our understanding of tumor biology for a long time. Genomic analysis during the past decade revealed that over 80% of DIPGs harbor an oncogenic histone H3K27M point mutation. However, the pathways altered by the mutation are still poorly understood. Metabolites serve as proxies to the state of biochemical pathways in a tissue. Given that unbiased a priori knowledge about metabolic alterations in DIPG is limited, we set out for the first time to identify metabolic dependencies intrinsic to DIPGs by leveraging untargeted and targeted metabolomics, transcriptomics, ChIP-Seq and ATAC-seq and integrating multi-omics datasets. We discovered that the mutant histone reprograms chromatin landscape causing aberrant misregulation of genes including a family of transcription factors that in turn causes misregulation of purine biosynthesis and folate metabolism. Specifically, the mutation alone is sufficient to upregulate a rate limiting bifunctional enzyme of de novo purine biosynthesis called ATIC, and the reduced folate carrier SLC19A1 to enhance purine synthesis and folate import, respectively, causing antifolate resistance. Genetic or pharmacological inhibition of ATIC greatly reduced tumor burden and extended survival in mice. Finally, folate removal from the microenvironment sensitized DIPGs to the antifolate methotrexate. Our studies identify ATIC as a novel target in DIPG and reveal a potential treatment strategy with antifolates in children with this lethal brain tumor.