upregulating antioxidant production. METHODS/STUDY POPULATION: Highly aggressive tumors tend to exhibit increased oxidative metabolism, and thus rely on a mechanism to eliminate reactive oxygen species (ROS) in order for cells to evade autophagy and cell death. We propose that recurrent GBM cells achieve this is by promoting methionine metabolism, upregulating glutathione production and preventing ROS accumulation. We investigated the expression of AHCY and MAT2A, two key enzymes in the methionine pathway, at the gene and protein level in both GBM and non-GBM tissues. We probed for markers of cell death following pharmacological inhibition and siRNA knockdown, and performed metabolite-mediated rescue experiments. Finally, we evaluated changes in cellular respiration using the Seahorse XFe96 real-time mitochondrial stress test following inhibitor treatment. RESULTS/ANTICIPATED RESULTS: The selective AHCY inhibitor markedly reduced cell viability in different cancer cell types, but significantly reduced cell viability in recurrent GBM cells compared to newly diagnosed GBM (p=.009; MD: -0.828, 95% CI -1.350 to -0.306) and normal astrocytes (p=.073; MD: -0.609, 95% CI -1.305 to 0.085). AHCY and MAT2a protein expression appeared to be higher in GBM cells compared to normal astrocytes, medulloblastoma cells and other cancer cell lines. Genetic knockdown of AHCY and MAT2A demonstrated reduced cell viability, increased Caspase, SOD2, LC3-II and Transferrin receptor expression. Acute treatment with the AHCY inhibitor induced cell death, markedly reduced oxygen consumption rate and ablated spare respiratory capacity in recurrent GBM cells compared to newly diagnosed GBM cells. DISCUSSION/SIGNIFICANCE: Oxidative damage was induced following interference with key methionine pathway enzymes by pharmacological inhibition, while a similar concentration of drug largely preserved normal astrocyte viability. These results point to a novel targetable mechanism of disease progression and expand the realm of treatment options for recurrent GBM.

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Harnessing the potential of transcriptional adaptation as a mechanism for rare Amyotrophic lateral sclerosis

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OBJECTIVES/GOALS: Transcriptional adaptation is a phenomenon in which a mutation in one gene leads to the genetic compensation of another homogenous gene. Understanding the mechanism of transcriptional adaptation may contribute to an explanation for variation in clinical manifestations of rare Amyotrophic lateral sclerosis patient phenotypes. METHODS/STUDY POPULATION: The presence of a premature termination codon triggers transcriptional activation. Therefore, we utilized CRISPR-Cas9 tool to generate a premature termination codon in CHCHD10 gene in multiple types of cells, including induced pluripotent stem cells derived from patient samples with known CHCHD10 mutations causative for Amyotrophic lateral sclerosis. CRISPR-Cas9 tool was delivered via ribonucleoprotein electroporation and transfect cell's DNA was sequenced to validate gene editing. To confirm transcriptional adaption, changes in levels of protein and gene expression will be measured via immunoblot and quantification of CHCHD10 and CHCHCD2 from whole cells lysates of the edited cells. RESULTS/ANTICIPATED RESULTS: We anticipate that CHCHD2 transcriptional adaptation can functionally compensate for the locus loss of function of CHCHD10. This mechanism of transcriptional adaptation may contribute to an explanation for variation in clinical manifestations of patient phenotypes. DISCUSSION/SIGNIFICANCE: Our approach would advance discovery science towards by exploring transcriptional adaptation mechanism in humans, which can lead to novel therapies for rare Amyotrophic lateral sclerosis, such as CHCHD10.

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A Machine Learning Approach to Predicting High-Risk Irritability Trajectories Across the Transition to Adolescence*

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OBJECTIVES/GOALS: Irritability, a proneness to anger and frustration, is a transdiagnostic symptom associated with poor mental health outcomes. Levels of irritability vary across development and high-risk trajectories have been observed. This study aims to use machine learning to predict irritability trajectories across the transition to adolescence. METHODS/STUDY POPULATION: Data were from the Adolescent Brain Cognitive Development (ABCD) Study, which is a 10-year longitudinal study that tracks the brain development, cognitive skills, physical health, and psychosocial functioning of a large, national sample starting from preadolescence. The baseline sample consisted of 11,861 9-10-year-old preadolescent youth. Irritability was parent-rated at baseline, 1-year, 2-year, 3-year, and 4-year follow-ups on the Child Behavior Checklist (CBCL) irritability index. Latent class growth analysis (LCGA) was used to determine developmental trajectories of irritability. Two machine learning approaches were applied to develop predictive models of youth irritability developmental trajectories. We used baseline (preadolescent) variables that spanned a wide range of domains. RESULTS/ANTICIPATED RESULTS: Preliminary results fromthe LCGA indicated best support for a four-class model that differentiated growth trajectories in irritability across the transition to adolescence: 1) persistent low irritability (n = 8691, 73.27%), 2) moderate irritability and decreasing (n = 1257, 10.60%), 3) low to moderate irritability and increasing (n = 1295, 10.92%), and 4) chronic high irritability (n = 618, 5.21%). We expect the machine learning analyses to generate predictive models with acceptable accuracy. We hypothesize that the most important predictors in the models will originate from the youth mental health domain, including baseline youth irritability, externalizing symptoms, internalizing symptoms, and oppositional behaviors, and the parent psychopathology domain, particularly parent irritability. DISCUSSION/SIGNIFICANCE: The present study elucidates unique developmental trajectories of irritability and generates predictive models to classify high-risk irritability trajectories using machine learning approaches. Clinicians can use these predictive models to identify at-risk youth and provide early intervention to preadolescents at high risk.

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