Abstracts

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MDB-13: GERMINE ELPI DEFICIENCY SENSITIZES CEREBELLAR GRANULE NEURON PROGENITORS TO SHH MALIGNANT TRANSFORMATION
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BACKGROUND: Germline loss-of-function (LOF) variants in elongator complex protein 1 (ELP1) are the most prevalent predisposing genetic events observed in medulloblastoma (MB), accounting for 30% of the Sonic Hedgehog 3 subtype (SHH-3). Molecurally, ELPI-associated SHH-MBs acquire somatic PTCH1 mutations in >80% of cases, and universal loss-of-heterozygosity of the wild-type ELPI and PTCH1 alleles through loss of chromosome-arm 9q, resulting in their biallelic inactivation. Notably, germline ELPI LOF occurs mutually exclusive with somatic/germline TP53 mutations in the SHH-3 subtype, suggesting that genetic perturbation of either ELPI or TP53 may promote similar tumorigenic consequences in cerebellar granule neuron progenitors (GNPs), the accepted cellular origin of SHH-MB. Despite these findings, the molecular, biochemical, and cellular mechanism(s) by which ELPI-deficiency provokes malignant pathogenesis remain unknown. In this study, we sought to close this knowledge gap and functionally determine why children harboring pathogenic ELPI germline variants are at an increased risk of developing SHH-MB. METHODS: Mice were genetically engineered to mimic heterozygous Elp1 LOF (Elp1Het). We studied the effect of Elp1 LOF in GNPs using a combination of molecular profiling, immunophenotyping, and cellular assays. RESULTS: GNPs from Elp1Het mice exhibited a spectrum of molecular and biochemical hallmarks of malignant transformation including increased DNA replication stress, DNA damage, accelerated cell cycle progression, and stalled replication forks. Orthotopic transplantation of Elp1Het GNPs engineered to harbor somatic Ptch1 inactivation yielded SHH-MB-like tumors with compromised p53 signaling, providing an explanation for the specificity of ELPI-associated tumors in SHH-3, and their exclusivity with TP53-mutant tumors. Conclusions: Collectively, our findings functionally substantiate the role of ELPI deficiency in predisposition to SHH-3 MB and nominate therapeutic strategies to overcome p53 inhibition as a rational treatment option.