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HGG-53. MULTI-DIMENSIONAL INTEGRATIVE PROFILING IDENTIFIES BCL2L1 METHYLATION AS A PREDICTIVE BIOMARKER FOR MCL-1 ACTIVITY IN PEDIATRIC HIGH-GRADE GLIOMAS
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BACKGROUND: Pediatric high-grade gliomas (pHGGs) pose a significant challenge as the most aggressive central nervous system tumors in children. The lack of effective treatment and poor survival rates emphasize the critical need for innovative therapies to improve the prognosis of pediatric patients with pHGG. METHODS: We executed CRISPR-cas9 knockout (KO) screenings in 65 pediatric and 10 adult high-grade glioma (HGG) cell lines to explore unique functional dependencies associated with pHGGs. Drug assays were carried out to assess the targetability of a gene dependency of interest in pHGG cell lines. Subsequently, Random Forest machine learning algorithm was employed on ‘omics’ datasets to identify biomarkers indicative of drug response. Finally, biomarkers were confirmed through sequencing-based methods across various pediatric cancers. RESULTS: CRISPR-cas9 KO screens revealed 8 crucial genes essential for pHGG growth, namely MCL-1, ATIC, DHFR, EED, HDAC2, PARP1, PDK1, PIK3CA and TYMS. Among these, Myeloid Cell Leukemia (MCL-1) was further characterized as it emerged as the top differential genetic dependency in pHGGs. Consistent with this, MCL1 inhibitors exhibited potent anti-cancer activity on 43% of pHGG cell lines. Multi-feature prediction analysis identified 140 features correlated to response. Strikingly, a previously undescribed methylation site within the BCL2L1 locus, cg00300298, ranked in the top 3% of features. Tissue analysis revealed a wide range of other pediatric brain cancers that harbor the BCL2L1 cg00300298 methylation mark as compared to non-malignant brain tissue. Lastly, we validated the utility of BCL2L1 methylation as a predictive biomarker of MCL1 inhibitor sensitivity across a large panel of pediatric brain cancer cell lines. CONCLUSION: Using an integrated genomic approach, we identify MCL1 as a distinct therapeutic target in BCL2L1-methylated pediatric brain cancers. This offers a rational approach for stratifying patients who may benefit from MCL1 inhibitors.