EPENDYMOMA

EPEN-01. RESPONSE ASSESSMENT IN PEDIATRIC INTRACRANIAL EPENDYMOMA: RECOMMENDATIONS FROM THE RESPONSE ASSESSMENT IN PEDIATRIC NEURO-ONCOLOGY (RAPNO) WORKING GROUP

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INTRODUCTION: Ependymomas remain a major cause of cancer-related death in childhood and adolescence, with recurrence occurring in up to 50% of patients. Despite exciting molecular advances in understanding ependymoma tumorigenesis and recurrence, MRI remains the mainstay for assessing objective response to therapy and duration of disease stability. Standardized response assessment criteria for clinical trials studying pediatric intracranial ependymoma are critically needed in order to accurately compare results between studies. METHODS: To generate these standardized response criteria in pediatric intracranial ependymoma, a multidisciplinary team of pediatric neuro-oncologists, neuroradiologists, neurosurgeons, radiation oncologists, and molecular biologists formed the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. The expert members reviewed relevant published literature, assessed current clinical practices, and engaged in iterative discussions to provide consensus recommendations for objective response assessment in pediatric intracranial ependymoma for use in prospective clinical trials. RECOMMENDATIONS AND CONCLUSIONS: The primary sequences for detecting and measuring disease and assessing radiologic response to therapy should be the contrast-enhanced T1-weighted sequence or T2-weighted sequence (T2 or T2-FLAIR) depending on which sequence the tumor is best visualized. When metastatic disease is present, only the three largest lesions will be followed in addition to any residual disease at the primary tumor focus. Importantly, the RAPNO working group notes that radiologic response to therapy is of limited value in clinical trials of patients with ependymoma, since most patients enroll on clinical trials with either no evidence of disease or only minimal disease. In recurrent or progressive disease that cannot be resected, true radiologic disease response to therapy is less clinically meaningful as a study endpoint than event-free and/or overall survival (representing prolonged stable disease) but may provide a signal of efficacy worthy of future exploration in patients with complete to near complete resections.

EPEN-02. ADAPTIVE CONVERGENCE OF METHYLOMES REVEALS EPIGENETIC DRIVERS AND BOOSTERS OF REPEATED RELAPSES IN PATIENT-MATCHED CHILDHOOD EPENDYMOMAS AND IDENTIFIES TARGETS FOR ANTI-RECURRENCE THERAPIES

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Ependymoma (EPN) is the third most common brain tumor in children and frequently recurs. Here, we report an integrated longitudinal analysis of epigenetic, genetic and tumorigenic changes in 30 patient-matched repeated relapses obtained from 10 pediatric patients to understand the mechanism of recurrences. Genome-wide DNA methylation analysis revealed stable molecular subtypes and convergent epigenetic reprogramming during serial relapses of the 5 RELA and 5 PFA EPNs that paralleled with elevated patient-derived orthotopic xenograft (PDOX) (13/27) formation in the late relapses. Differentially methylated CpGs (DMCs) preexisted in the primary tumors and persisted in the relapses (driver DMCs) were detected, ranging from 51 hypo-methylated in RELA to 148 hyper-methylated DMCs in PFA tumors; while newly acquired DMCs sustained in all the relapses but was absent in the primary tumors (booster DMCs) ranged from 38- 323 hyper-methylated DMCs in RELA and PFA EPNs, respectively. Integrated analysis of these DMC associated DNA methylation regions (DMRs) and RNAseq in both patient and PDOX tumors identified a small fraction of the differentially expressed genes (4.6±4.4% in RELA and 4.5±1.1% in PFA) as regulated by driver DMRs (e.g., up-regulated CACNA1H, SLC12A7, RARA in RELA and HSPB8, GMPR, ITGB4 in PFA) and booster DMRs (including the sole upregulated PLEKHG1 in RELA and NOTCH, EPHA2, SUFU, FOXJ1 in PFA tumors). Most these genes were novel to EPN relapses. Seven DMCs in RELA and 22 in PFA tumors were also identified as potential relapse predictors. Finally, integrating DNA methylation with histone modification identified LSD1 as a relapse driver gene. Combined treatment of a novel inhibitor SYC-836 with radiation significantly prolonged survival times in two PDOX models of recurrent PFA. This high-resolution epigenetic and genetic roadmap of EPN relapse and our 13 new PDOX models should significantly facilitate biological and preclinical studies of pediatric EPN recurrences.

EPEN-03. USP7 IS AN INTERACTION PARTNER OF EZHIP AND POTENTIAL DRUGGABLE TARGET IN PFA EPENDYMOMAS

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Ependymomas (EPN) arise in the supratentorial brain (ST-EPN), posterior fossa (PF-EPN), or the spinal cord (SP-EPN), in children and adults. Molecular profiling has identified distinct subgroups in each location. Among the three molecular subgroups of PF-EPN, PFAs are characterized by young median age at diagnosis, an overall balanced genome and bad clinical outcome (56 % 10-year OS). Therapy involves tumor resection and radiotherapy, but the role of chemo- or targeted therapies remains to be defined. Recently, we and others identified enhancer of zeste inhibiting protein (EZHIP) as potential driver of PFAs. By inhibiting EZH2, catalytic subunit of the polycomb repressive complex 2 (PRC2), EZHIP prevents the distribution of the epigenetic repressor mark H3K27me3. However, since EZHIP does not possess any known enzymatic functions, it does not seem to be the druggable target urgently searched for in PFA. We therefore focused on essential and potentially druggable interactions. Here, we present ubiquitin-specific protease 7 (USP7), a known cancer regulator with multiple inhibitors available, which has been shown to interact with EZHIP in non-PFA cells. We confirmed this interaction in PFA cells by co-immunoprecipitation and mass spectrometry, and showed that the EZHIP-USP7 interaction is independent of EZH2, a separate interactor of both. Functionally, we show that USP7 de-ubiquitinates EZHIP, preventing its degradation and thus stabilizing it. As EZHIP is essential for PFA cell survival, we aim to target EZHIP indirectly by affecting its stability regulation via USP7. Knockdown experiments showed a susceptibility of PFA cells to a USP7 loss, focusing on proliferation, apoptosis, and expressional changes induced by altered USP7 levels. Moreover, USP7 inhibitors highly affected the survival of different PFA cell lines at a low micromolar IC50 in vitro and in vivo treatments of PFA patient-derived xenografts with USP7 inhibitors are ongoing, hopefully helping to improve targeted therapies for PFA ependymoma patients.

EPEN-04. REFINEMENT OF MOLECULAR AND CLINICAL CHARACTERISTICS IN A COHORT OF 1,801 EPENDYMOMAS

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DNA methylation profiling led to the definition of ten molecular types of ependymomas with distinct biological and clinical features. The largest published reference cohort consists of 500 ependymomas encompassing nine molecular types that were known at this point. Our study aimed to confirm and refine molecular and clinical characteristics of ependymoma types and subtypes based on a considerably larger, well-annotated cohort of ependymal tumors. Here, we analyzed previously published and newly generated DNA methylation profiles, generated on the Illumina 450k and EPIC arrays, from a total of n=1,801 ependymomas. We looked at both global