EPEN-44. EXTRACELLULAR VESICLES OF SUPRATENTORIAL EPENDYMOMA RELA MEDIATE INTERACTIONS WITH CELLS OF THE TUMOR MICROENVIRONMENT

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Ependymal tumors (EPNs) account for ~10% of all pediatric brain tumors. Supratentorial EPN characterized by RELA fusions (ST-EPN-RELA) and posterior fossa EPN group A (PF-EPN-A) form the two most frequent molecular groups, both of which are associated with poor prognosis and for which only limited therapeutic options are available. Since pediatric EPNs have a relatively low mutational burden, identification and characterization of tumor-associated pathways and molecular processes is of critical importance to inform potential therapeutic targets. Previous transcriptional studies implicated aberrant vesicular pathways in ST-EPN-RELA, prompting further investigation into their putative role in EPN pathogenesis. To this aim, we isolated extracellular vesicles (EVs) of ST-EPN-RELA patient derived cell lines and performed protein mass spectrometry. The specific ST-EPN-RELA EV protein content resembles the parental cells as well as primary tumors. Promising candidates to be transferred by ST-EPN-RELA EVs but not control EVs were associated with unfolded protein response and endoplasmic reticulum stress. When uptaken by recipient cells of the tumor microenvironment, brain endothelial cells or microglia, ST-EPN-RELA EVs induced proliferation and had a chemoattractant effect towards the tumor. ST-EPN-RELA EVs stimulated angiogenesis of brain endothelial cells potentially by the transfer of ER stress proteins. Uptake of ST-EPN-RELA EVs by microglia changed their activation status indicating a tumor promoting function through EV transfer. Therefore, we hypothesize that vesicular pathways play an important role in the pathogenesis of pediatric ST-EPN-RELAs and that an improved understanding may promote new therapeutic opportunities.

EPEN-45. NORMALIZING AND FACILITATING GENOMIC TESTING AT DIAGNOSIS IN PEDIATRIC EPENDYMOMA

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The current consensus is that diagnosis and treatment of ependymoma should be based upon clinical and molecular classification. As we move into this paradigm, it is important all ependymoma cases undergo tumor collection, preservation, and molecular profiling at diagnosis. Our group of 6 sites gathered data on a cohort of 72 ependymoma cases. Sites were asked to report known molecular findings; 60/68 eligible cases (88%) did not include genetic findings. The low number of cases with molecular findings was surprising and since cases were diagnosed from as early as 2004, we asked collaborators to share their current practice in profiling (e.g., how frequently; in what setting were ependymomas sent for testing) to try and better understand current practice at sites. Since the publication of ependymoma molecular data, sites with a neuro-oncology program report sending almost all newly diagnosed ependymomas for molecular testing, whereas current practices at sites without dedicated neuro-oncology were less consistent. Profiling in the setting of relapse was more frequently reported at all centers. The implementation of molecular testing at diagnosis may need support at sites without dedicated neuro-oncology. Lead investigators for upcoming ependymoma clinical trials will need to think carefully about the logistics of profiling at centers where this is not standard practice at diagnosis.

EPEN-46. DNA METHYLATION LANDSCAPE OF RECURRENT PEDIATRIC EPENDYMOMA IDENTIFIES KEY DRIVER EVENTS

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Pediatric ependymoma has a propensity of developing late and multiple relapses over many years. About 50% of patients will experience relapses and eventually succumb to their disease. Our study is aimed to understand the mechanism of resistance and drivers associated with pediatric ependymoma relapse. We developed 10 sets of patient-derived orthotopic xenograft (PDOX) models of recurrent pediatric ependymoma from both RELA and PFA tumors. Time from primary tumor to last recurrence ranges from 2.75 – 13 years. Number of recurrences per patient ranges from 1 – 7 times. We performed Reduced Representation Bisulfite Sequencing (RRBS) and Whole Genome Bisulfite Sequencing (WGBS) to map the DNA methylation landscape of total of 30 samples of matched primary and recurrent tumors. Molecular subtypes and DNA methylation profiles were maintained, and RELA/PFA signature genes showed similar expression pattern during serial relapses. RELA- and PFA-specific Differentially Methylated CpGs (DMCs) are identified from primary tumors. During the recurrent process, individual patients displayed consistent changes of DMCs and shared DMCs among patients became convergent. We then identified shared common specific DMCs in recurrent RELA and PFA tumors that emerged as the driver signatures. We found that these recurrent DNA methylation signatures could be identified from primary tumors. Our analysis of the PDOX models showed that they can mostly recapitulate humor tumors' DNA methylation and we were able to identify shared recurrent specific DMCs associated genes in PDOX models. Our comprehensive data is the first of its kind aimed to investigate the epigenetic mechanisms during pediatric ependymoma recurrence.

EPEN-47. PEDS: PEDIATRIC EPENDYMOMA DISCOVERY STUDY

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The prognosis for pediatric ependymoma remains unaffected by recent discovery. Upfront therapy is maximal surgical resection followed by radiation and the utility of histologic diagnosis remains unreliable. Nine molecular subgroups and possible genetic drivers of ependymoma have been identified, but the implementation of these findings into targeted therapy and stratified clinical trials has not occurred. It is imperative that researchers work collaboratively to move discovery towards clinical testing. Heterogeneity of ependymoma requires that we collect a large amount of data; progress in the field is dependent on deep analysis of this information. As we further subclassify ependymoma, it will be important to have a large patient population for enrollment onto clinical trials, which will maximize data collection and the amount of materials available for experimentation and analysis. Researchers in the United States, Europe, and Japan propose an international ependymoma research collaborative which aims to synthesize research across sites, foster drug discovery, and prove strategies to integrate clinical and molecular diagnostics into biology-based therapy. Our goal is to maximize information and materials from existing bio and data repositories and not to 're-create the wheel'. We envision PEDS as an open science platform and present this concept at ISPNO to invite our colleagues to harmonize efforts towards pediatric ependymoma discovery.

EPEN-49. RESPONSE OF RECURRENT EPENDYMOMA TO MEMMAT BASED METRONOMIC ANTIANGIOGENIC COMBINATION THERAPY UTILIZING TAPERED BEVACIZUMAB AND MAINTENANCE THERAPY WITH CELECOXIB AND FENOFIBRATE

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Recurrent ependymomas have a dismal prognosis (2 year survival rates 29% OS and 23% EFS) and are relatively resistant to conventional chemotherapy. We previously reported five relapsed ependymoma patients treated with a MEMMAT based metronomic antiangiogenic combination therapy. All patients are currently alive, including four patients who were multiply relapsed with at least three recurrences. These four patients received between 44–52 weeks of therapy with minimal toxicity. Three had recurrent disease within an average of 44 months (median 42 months) after discontinuation of therapy. One patient who received the following tapering bevacizumab schedule: q3 weeks x 3, q4 weeks x 4 and q5 weeks x 5 followed by maintenance therapy with fenofibrate and celecoxib is in complete remission 12 months post treatment. This regimen was well tolerated with good quality of life in this patient population. Our results suggest that the chosen anti-angiogenic drug combination prolonged the time to progression in these multiply relapsed patients and thus may be particularly beneficial for patients with recurrent ependymoma. Tapered bevacizumab and maintenance therapy with celecoxib and fenofibrate may be modifications worth further investigation for prolonged disease free survival in relapsed ependymoma patients.