

activation mechanisms by matched genome sequencing and DNA methylation profiling, respectively. Our findings will be applied to deconvolute bulk RNA sequencing data, thus identifying therapeutically relevant signaling networks in larger cohorts of medulloblastoma patients. Eventually, candidate targets will be validated on patient-derived cell models and xenografts by overexpression and inhibition studies. Together, here we aim at identifying tumor-driving receptor/ligand interactions in medulloblastoma, with the goal to define targets susceptible to precision oncology approaches.

MEDB-83. A NOVEL EPIGENETIC NANOTHERAPEUTIC STRATEGY TO INDUCE MEDULLOBLASTOMA DIFFERENTIATION

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The histone-lysine N-methyltransferase EZH2 is the catalytic component of the PRC2 complex and is overexpressed in several medulloblastoma subtypes. However, its role in medulloblastoma tumorigenesis has been shown to be context-dependent using genetic approaches. Furthermore, pharmacological approaches have been limited by the very poor blood-brain barrier (BBB) penetration of current EZH2 inhibitors in use. Using laser capture microdissection and RNA-Seq analysis of human nodular/desmoplastic SHH medulloblastoma FPPE tissue, we provide data for the spatial epigenetic heterogeneity of primitive/proliferative regions compared to nodular/mature regions. Bioinformatic analysis identifies ~120 differentially expressed genes between primitive and mature regions with enrichment for genes regulated by H3K4me3 and H3K27me3 or SUZ12. ChIP-Seq analysis shows striking differences in H3K27me3 enrichment between primitive and mature medulloblastoma cells including at the EZH2 locus. Utilizing a genetically-engineered mouse model of SHH medulloblastoma, we show that conditional EZH2 genetic ablation within medulloblastoma cells results in wide-spread tumor cell differentiation (n=31 mice; *p=2e-07). Conversely, conditional EZH2 (Y641F) activation in this GEM model prevents tumor cell differentiation. Notably, we have found that the CDNK2A (p16) locus is an important EZH2 target that regulates tumor cell differentiation. qRT-PCR analysis of SHH medulloblastoma in wild-type and Ezh2 knockout settings show significant reduction in Gli1 and CCND1 and increase p15 and p16 expression in Ezh2 knockout mice compared to Ezh2 wildtype mice (*p<0.05). Importantly, genetic ablation of p16 conditionally in SHH MB EZH2 double knockout mice rescues the widespread tumor cell differentiation (n=9 mice; *p=3e-06) seen in Ezh2 single knockout SHH medulloblastoma mice. Finally, we developed a novel fucoidan-based nanoparticle strategy to deliver the EZH2 inhibitor (EPZ-6438) across the intact BBB of this GEM model to achieve significant extension of mouse survival (median 70 days compared to 19 days in control mice; *p=0.01, Mantel-Cox) with potential utility for other pediatric brain tumors.

MEDB-84. THE FRENCH EXPERIENCE OF ELP1-RELATED MEDULLOBLASTOMAS

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Medulloblastoma (MB), the most frequent embryonic tumor of the cerebellum is classified into four molecular subgroups (WNT group, SHH group, group 3 and group 4). Although the vast majority of MB are sporadic, predisposing genetic diseases have been described in rare WNT MB and more frequently in the SHH group. In a recent pediatric series of SHH-MB, germline alterations of the ELP1 gene have been described in 14% of cases, making this gene the most frequent genetic predisposition in MB. We have

investigated the potential interest of ELP1 immunostaining on a large cohort of 132 MB. A complete loss of ELP1 staining was observed in 12 SHH MB (among 57 total SHH MB: 21%). The loss of ELP1 immunostaining was well correlated with the presence of a bi-allelic alteration of the gene except for one case for which the MB had a loss of ELP1 protein expression demonstrated by immunohistochemistry (IHC) and confirmed by whole proteome analysis, although no obvious genetic alteration in the coding sequence of ELP1 could be found. Molecular analysis of a large “molecular” cohort of 266 MB from French centers for which somatic ELP1 was sequenced allows to identify 12 additional MB with bi-allelic ELP1 genetic alterations. Our results demonstrate the benefit of the ELP1 IHC as an accurate and reliable tool to screen ELP1-deficient MB. This new immunohistochemical tool will now be advantageously used to screen SHH MB upfront for genetic alteration in ELP1, and will subsequently help orientating these patients towards genetic counseling.

MEDB-85. TRANSCRIPTIONAL COMPLEXES AS RESISTANCE DRIVERS TO BET INHIBITION

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BET-bromodomain inhibition (BETi) is a promising therapeutic strategy to target MYC-driven cancers, including Group 3 medulloblastoma, a deadly childhood brain tumor. We have shown that BET inhibitors exhibit preclinical efficacy against MYC-amplified medulloblastoma, providing motivation to evaluate this drug class in early phase clinical trials. However, our work has also found that MYC-amplified medulloblastoma cells can acquire resistance to BETi, suggesting that curative responses for this disease will require combination therapy. To guide the development of such combination therapies, we have focused our efforts on elucidating the mechanisms through which medulloblastoma cells acquire resistance to BETi. We found that medulloblastoma cells can develop tolerance to BETi by reinstating the expression of cell-essential “rescue genes,” which include bHLH transcription factors, cell-cycle regulators, and anti-apoptosis genes. This transition to the resistant cell state is mediated through changes in chromatin structure including the upregulation of H3K4me3 promoters. Our preliminary results suggest that BETi-resistant cells maintain mRNA transcription and protein translation of important mediators of resistance. Importantly, we observe that BETi-resistant medulloblastoma cells are more dependent on specific protein complexes involved in transcriptional regulation. This project explores the mechanisms through which these transcriptional regulators help maintain transcription of rescue genes that drive BETi resistance and evaluates the potential of targeting these drivers of BETi resistance. These results will help guide the development of combination approaches to improve the efficacy of BETi for the treatment of MYC-driven medulloblastoma.

MEDB-86. A RE-INDUCTION REGIMEN FOR CHILDREN WITH RECURRENT MEDULLOBLASTOMA

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Medulloblastoma is the most common malignant brain tumor of childhood. Despite multi-modal therapies, ~30% of patients experience disease recurrence, which portends a poor prognosis. At initial recurrence, intensive chemotherapy may be effective prior to various consolidation therapies including high dose chemotherapy with autologous stem cell rescue or irradiation. We report outcomes for nine children treated at two institutions with the following regimen: cyclophosphamide 1500mg/m²/dose days 1,2; irinotecan 125mg/m²/dose days 1,8; temozolomide 150mg/m²/dose days 1-5, and oral etoposide 50mg/m²/dose days 1-7. Patients received 2-4 cycles based upon disease response and physician preference. The mean time from initial diagnosis to first recurrence was 19 months. After receiving two cycles of therapy, two patients had complete response (CR) and proceeded to consolidation. Of the remaining seven patients, five had partial response (PR) and two had stable disease (SD). Overall response rate was 78% after 2 cycles. Two patients with PR proceeded directly to consolidation with irradiation. Five patients (3 PR, 2 SD) received 2 additional cycles. After four cycles there was one CR, two with minimal residual disease, one SD and one progressive disease (PD). Four patients (44%) are alive with no evidence of disease (NED). One patient died of consolidation-related toxicity but had NED at time of death 28 months from initial recurrence. Five patients developed PD. Two patients died of disease, two are alive with disease, and one is alive with NED after PD and additional therapy. There were no treatment-related deaths. Infection was the most common com-