

esis. Among them, mutations in chromatin modifiers are frequently detected in medulloblastoma, suggesting the importance of alterations in the epigenome in tumor development. However, it remains unclear how epigenomic changes are involved in tumorigenesis. Here, we have used the SHH-group medulloblastoma (MB-SHH) mouse model to understand the epigenomic changes during tumor development and identify new therapeutic targets for medulloblastoma. To this end, we utilized an Atoh1-EGFP:Ptch1^{+/+} mice that specifically label cerebellar granule cell progenitors (GNPs) that are known to be the cellular origin of MB-SHH, preneoplastic (PNCs) and tumor cells with EGFP during MB-SHH formation. Following FACS-based collection of EGFP-positive cells, comparative ATAC-seq analysis revealed that the open chromatin regions dynamically changed during transformation of GNPs into PNCs with enrichment of nuclear factor I (NFI) binding motifs. Cut & Tag analysis on these cells showed that NFI proteins bound chromatin regions that become more accessible during tumorigenesis, suggesting that NFI could play an important role in tumorigenesis after the epigenomic changes. Indeed, CRISPR-engineered *in vivo* somatic deletion of Nfia and/or Nfib prevented hyperplasia formation, confirming their essential role in tumor initiation. Knockdown of either NFIA or NFIB in patient-derived xenograft models also attenuated tumor growth. Thus, our study has uncovered a novel oncogenic mechanism that contributes to the development of MB-SHH tumors via alterations of accessible chromatin and aberrant DNA binding of NFI transcription factors.

MEDB-16. PERSISTENT RADIOLOGICAL LESIONS AT THE END OF PRIMARY THERAPY IN CHILDHOOD MEDULLOBLASTOMA: RESIDUAL LESION OR ACTIVE RESIDUAL TUMOR?

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BACKGROUND: Magnetic resonance imaging (MRI) of patients with medulloblastoma (MB) often shows persistent residual findings after primary treatment. Criteria for characterizing these lesions and consensus on further therapeutic approaches are not established. **MATERIAL AND METHODS:** Eighty-four patients ≥ 4 years with centrally reviewed residual lesions on MRI at the end of primary therapy with initial surgery between 2000 and 2018 were identified. Data were extracted from the German HIT-MED database. **RESULTS:** Median age at initial diagnosis was 9.3 (4.0-20.8) years. 91.7% were histologically classified as CMB, 7.1% as LC/AMB and 1.2% as DMB. The majority (65.5%) of the evaluated cohort was assigned to molecular subgroup 4, 24.1% to group 3, 6.8% to WNT, 3.4% to SHH. Median follow-up for survivors was 5.96 (1.41-16.67) years. Univariate analysis revealed that patients showing an overall partial response (PR) to primary therapy have a significantly lower risk of progression of residual lesions compared to patients with stable disease (SD) (5-year PFS [PR]: 62.5 \pm 7.0; 5-year PFS [SD]: 35.9 \pm 12.8; 5-year OS [PR]: 85.6 \pm 5.1; 5-year OS [SD]: 54.1 \pm 13.7; $p=0.02$ [PFS], $p=0.04$ [OS]). Additionally, patients with multiple residual lesions (M+ and R+) were at higher risk of progression (5-year PFS [R+ only]: 72.4 \pm 12.0, 5-year PFS [R+/M+]: 22.9 \pm 17.9; $p=0.02$ [PFS]). Further procedures after the end of primary therapy (additional resections, chemotherapy, radiotherapy) did not impact on PFS and OS. These results were confirmed by multivariate Cox regression. For molecular or histological type no significant effect was found, presumably due to small cohort. **CONCLUSION:** PFS in patients with residual lesions at the end of primary treatment depends on the overall response to primary therapy. Additional procedures do not seem to be superior compared to watch-and-wait strategies. Decisions regarding further therapies should be scrutinized on a case-by-case basis. Further identification of biomarkers is warranted.

MEDB-17. RE-IRRADIATION FOR RECURRENT MEDULLOBLASTOMA IN A MATCHED COHORT: ADVANTAGEOUS ESPECIALLY IN PATIENTS WITHOUT RESECTION

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INTRODUCTION: Radiotherapy with craniospinal irradiation (CSI) is an important part of initial treatment for medulloblastoma in most children. Radiotherapy after recurrence is currently not widely used. This analysis aims to evaluate whether re-irradiation (RT2) may show survival benefits. **METHODS:** Data for patients with recurrent medulloblastomas from the German HIT-REZ studies was gathered. Patients with RT2 at 1st recurrence were matched by propensity score to an equal number of patients without radiotherapy. Matching variables were sex, initial therapy, time to recurrence, metastatic stage and therapy at 1st recurrence and radiotherapy at subsequent recurrences. The matched cohort was analysed regarding PFS and OS after 1st recurrence. **RESULTS:** From a cohort of 240 pre-irradiated patients, 106 patients were matched. Patients with RT2 showed improved median PFS [21.0 months (95%-CI: 17.5 – 27.6)] and OS [37.5 months (CI: 30.0 – 59.4)] compared to control patients [PFS: 12.0 months (CI: 8.1 – 17.7) / OS: 20.1 months (CI: 14.5 – 44.8)]. When stratifying by resection at recurrence (36.8% resected), a survival advantage for RT2 was found in patients without resection in PFS [19.6 (CI: 14.9 – 31.5) vs. 8.0 months (CI: 5.4 – 14.4)] and OS [41.9 (CI: 30.0 – 59.4) vs. 13.3 months (CI: 8.1 – 36.7)]. However, no advantage was found after resection [PFS: 22.5 (CI: 17.5 – 50.4) vs. 19.1 months (CI: 14.1 – 34.3) / OS: 32.3 (CI: 27.6 – NA) vs. 48 months (CI: 23.4 – NA)]. CSI was used in 6 patients without differences in survival to focal RT2. Median PFS after first irradiation was 32.5 months, after RT2 20.9 months. No patients with RT2 were alive past 10 years after 1st recurrence. **CONCLUSION:** Patients with recurrent medulloblastoma show benefits from RT2 in median PFS and OS. However, no advantage for RT2 was found when resection was also applied at recurrence. Cure after treatment with RT2 was not found in our cohort.

MEDB-18. ELONGATION CONTROL OF MRNA TRANSLATION SUPPORTS GROUP 3 MEDULLOBLASTOMA ADAPTATION TO NUTRIENT DEPRIVATION

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Group 3 affiliation and MYC genetic amplification are associated with poor life expectancy and substantial morbidity in children suffering from medulloblastoma (MB). However, the high metabolic demand induced by MYC-driven transformation sensitizes MYC-overexpressing MB to cell death under conditions of nutrient deprivation (ND). Additionally, MYC-driven transformation is known to promote mitochondrial oxidative phosphorylation (OXPHOS). We previously reported that eukaryotic Elongation Factor Kinase 2 (eEF2K), the master regulator of mRNA translation elongation, promotes survival of MYC-overexpressing tumors under ND. Interestingly, eEF2K is overexpressed in MYC-driven MB and our preliminary proteomics data highlight large-scale alterations in OXPHOS components affecting eEF2K deficient MB cells. We therefore hypothesized that eEF2K activity is required for the selective translation of mRNAs needed for efficient OXPHOS, and for the progression of MYC-driven MB. We performed Multiplexed enhanced Protein Dynamic Mass Spectrometry in eEF2K knockdown MYC-overexpressing D425 MB cells to identify mRNAs selectively translated upon eEF2K activation. Messenger RNAs encoding multiple (9 out of 10 detected) components of the mitochondrial OXPHOS pathway are selectively translated upon eEF2K activation. Inactivation of eEF2K by genetic KO leads to the disassembly of electron transport chain (ETC) complexes I-IV without affecting mRNA levels of their respective components. Consistently, eEF2K KO MB cells display decreased mitochondrial membrane potential and 20%