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BCL-6 transcriptional corepressor (*BCOR*) is an epigenetic regulator that silences gene expression mainly via the polycomb repressive complex 1.1 (PRC1.1). *BCOR* genomic alterations are found in a variety of different tumors and recently central nervous system (CNS) tumors with *BCOR* internal tandem duplication (ITD) were classified as a distinct molecular subgroup. We established and characterized two cell models derived from *BCOR* altered CNS tumor patients. One model is characterized by a frameshift mutation in the *BCOR* gene resulting in the expression of a truncated protein lacking the C-terminal PUFD domain required for correct assembly of the PRC1.1. Additionally, this model harbors a translocation of the *BCOR* homologue *BCORL1*. The second model has a characteristic internal tandem duplication (ITD) within the *BCOR* gene. To study the effects of mutated *BCOR/BCORL1* on gene expression, we performed siRNA mediated knockdown of altered *BCOR/BCORL1* transcripts in both models and analyzed transcriptional changes by mRNA expression array. Differentially expressed genes in *BCOR/BCORL1* knockdown versus wild type conditions were enriched for signaling pathways involved in cell cycle progression, cell growth, DNA replication and cancer. This suggests that the alterations in *BCOR/BCORL1* might have pro-oncogenic effects and thereby contribute to the aggressive phenotype of this disease. Especially in the *BCOR* ITD model knockdown of *BCOR* led to transcriptional downregulation of genes associated with the development of brain tumors such as *FGF18*, *PDGFA* and *PDGFRA*. Our results indicate that specific *BCOR/BCORL1* alterations might impair its endogenous function as transcriptional repressor and deregulate the expression of multiple PRC1.1 target genes. An in depth characterization of epigenetic and transcriptional changes in *BCOR/BCORL1* altered CNS tumors could lead to the identification of critical downstream effectors and ultimately reveal new therapeutic vulnerabilities.

ETMR-12. NOVEL CELL MODELS OF CNS TUMORS WITH BCOR FUSION OR INTERNAL TANDEM DUPLICATION SUGGEST FGFR AND PDGFR AS PROMISING THERAPY TARGETS

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Central nervous system (CNS) tumors with *BCOR* internal tandem duplications (CNS-BCOR ITD) are aggressive malignancies recently included in the 2021 WHO Classification of CNS tumors. This entity is characterized by ITDs within the PUFD domain of *BCOR*, potentially interfering with protein-protein interactions and preventing non-canonical polycomb repressive complex 1.1 (ncPRC1.1) complex formation. Additionally, other *BCOR* alterations like frame shift mutations and gene fusions have been described. However, the underlying molecular mechanisms promoting tumor aggressiveness remain unknown. We established cell models from one patient harboring a *BCOR* frameshift mutation and another one with a concomitant *BCORL1*-fusion. Two additional models were derived from a patient with a CNS-BCOR ITD tumor. Multidrug screening uncovered high sensitivity against defined receptor tyrosine kinase (RTK) inhibitors (TKIs). In detail, ponatinib, nintedanib, and dovitinib reduced cell viability at half maximal inhibitory concentrations (IC50) in the low micro-molar range (<2.5 µM). Expression analyses of the respective TKI targets suggested fibroblast growth factor receptor 3 (FGFR3) and platelet derived growth factor receptor A (PDGFRA) as central players in this response. RTK inhibition resulted in strongly impaired downstream MAPK and Pi3K/AKT signaling. Vice versa, exposure to the RTK ligands bFGF and PDGFAA increased S6, Erk and Akt phosphorylation. Next, we treated two patients – one with a *BCOR* frame shift mutation/*BCORL1*-gene fusion and one with an ITD with nintedanib – within a multimodal treatment approach and achieving complete remission and disease stabilization, respectively. Ultimately, we analyzed respective RTK ligands in patient cerebral spinal fluid (CSF) and found FGF18 and PDGFA to correlate with tumor treatment response and progression. Summarizing, we uncover a central role of defined RTK signaling modules in the malignant phenotype of CNS-BCOR-ITD and tumors harboring *BCOR* alterations and elucidate their potential as therapeutic targets. Currently, we aim to dissect the interconnection between *BCOR/BCORL1* alterations and RTK hyperactivation.

ETMR-13. EMBRYONAL TUMOR WITH MULTILAYERED ROSETTES IN AN INFANT: CASE REPORT

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Embryonal tumor with multilayered rosettes (ETMR) is a highly malignant tumor (WHO grade 4) seen predominantly in infants. It includes morphologically distinct embryonal tumors namely, embryonal tumor with abundant neuropil and true rosettes, ependymoblastoma, and medulloepithelioma. The presence of multilayered rosettes and C19MC amplification at chromosome 19q13.42 confirms the diagnosis. The median overall survival is less than a year and the prognosis is generally poor. We report the case of a 1-year-old girl who presented with vomiting, lethargy, and increasing head circumference over a period of six months. On admission, she was drowsy and irritable. Verbal output was limited to moans and motor response was localizing. She was macrocephalic with a head circumference of 51 cm. MRI showed a large 5 x 5 x 6.5cm contrast-enhancing cerebellar vermian tumor with obstructive hydrocephalus. There was no evidence of leptomeningeal disease or spinal metastasis at this time. She underwent a right frontal ventriculoperitoneal shunt insertion, followed by suboccipital craniotomy and subtotal tumor resection one week later. Her shunt was ligated two days after tumor excision, due to development of bilateral subdural hygromas. The patient regained full consciousness, but still had spastic lower extremities and inability to swallow at the time of discharge. Histopathology and immunostains were consistent with an embryonal tumor, possibly ETMR, and the patient was for advised chemotherapy. Before initation of chemotherapy, the patient was admitted in another instution because of alteration in sensorium. Repeat imaging showed progression of the patient's subdural hygromas, requiring insertion of a subduroperitoneal shunt. The patient died seven weeks after tumor resection due to progression of her tumor residual. Management options for ETMR are limited, especially in low- and middle-income countries. International linkages may help facilitate the accurate diagnosis and early treatment of these patients with rare but aggressive brain tumors.

ETMR-14. THE SINGLE-CELL LANDSCAPE OF PINEOBLASTOMA IDENTIFIES DEVELOPMENTAL ORIGINS AND EXPOSES NOVEL THERAPEUTIC VULNERABILITIES.

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Pineoblastoma (PB) is a rare and aggressive childhood brain tumor with highly variable age and treatment-associated outcomes. Our recent bulk tumor analyses of DNA methylation and mutational landscapes uncovered four discrete PB molecular subgroups (PB-miRNA1, PB-miRNA2, PB-MYC/FOXR2, and PB-RB), providing a major advance in our understanding of biological and clinical heterogeneity. However, developmental origins of PB subgroup heterogeneity and mechanisms governing how specific genetic alterations promote malignancy remain unknown. To resolve the cellular origins of PB, we assembled a large single-nucleus RNA-sequencing cohort (n=32) of primary PB tumors, including representatives from each subgroup. Transcriptomic analysis identified subgroup-specific gene expression programs driving intra-tumoral heterogeneity. In addition, we discovered substantial differences in the expression of miRNA biogenesis genes between the PB-miRNA1 and PB-miRNA2 subgroups, providing mechanistic support for their distinct subgroup identities despite overlapping driver events. The MYC/FOXR2 subgroup was characterized by over-expression of the FOXR2 proto-oncogene in bulk RNA-seq, which we validated in single-nuclei and identified co-expressed downstream