increased proton leak thorough the mitochondrial membrane. In addition, eEF2K inactivation results in increased Group 3 MB cell death under ND and doubles survival of MB bearing mice fed with calorie restricted diets ($p< 0.05$). Control of mRNA translation elongation by eEF2K is critical for mitochondrial ETC complex assembly and efficient OXPHOS in MYC-overexpressing MB, likely representing an adaptive response by which MYC-driven MB cells cope with acute metabolic stress. Future therapeutic studies will aim to combine eEF2K inhibition with caloric restriction mimetic drugs as eEF2K activity appears critical under metabolic stress conditions.

MEDB-20. THE OUTCOME OF MEDULLOBLASTOMA PATIENTS IN THE 2010-2018 PERIOD IN CHILDREN'S HOSPITAL ZAGREB

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This study aims to present the key characteristics of the medulloblastoma patients treated in Children's Hospital Zagreb and the University Hospital Center Zagreb in Croatia between 2010-2018 period. Croatia has around 145 newly diagnosed pediatric oncology patients annually, including approximately 30 neurooncology patients. We have conducted the retrospective analysis of the hospital records and have collected data on 32 medulloblastoma patients (9 females, 23 males). At the time of diagnosis, the median age was 5,62 (range 0.85-15.86). Before the treatment commencement, we determined conventional risk factors and stratified our patients into standard and high-risk groups (17 standard risk patients, 15 high risk). Qualification for high-risk included metastatic disease, postoperative local residual disease greater than 1.5 cm2, confirmed myc/nmyc amplification in the tumor tissue, and the large cell/anaplastic tumor subtype (p53 positive). The methods of molecular diagnostics were not available at the time. The patients that received solely postoperative chemotherapy were younger than three years. Children younger than five suffering from desmoplastic tumor subtype also received intraventricular methotrexate (Ommaya). High-dosage chemotherapy with autologous stem cell transplantation failed to treat metastatic infant medulloblastoma (2 patients with a lethal outcome). The rest of the patients received craniospinal irradiation, followed by adjuvant chemotherapy. According to the Kaplan-Meier survival analysis, the 5-year overall survival is 65,6 % (40% in the high-risk group and 88% in the standard-risk group). In addition, 5-year event-free survival is 59,4 % (33% in the high-risk group and 82,4% in the standard-risk group). None of the patients developed a secondary malignant disease during the follow-up. Conventional characteristics that determine standard-risk group affiliation are reliable, leading to a satisfactory treatment outcome. The results of the high-risk group treatment are poor necessitating modification treatment approach within clinical trials.

MEDB-21. SOX2$^+$ CELLS: THE PERPETRATORS OF MEDULLOBLASTOMA RELAPSE

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Pediatric brain tumors are the number one cause of cancer-related death in children, with medulloblastoma being the most common type. While survival in patients with medulloblastoma has dramatically improved since chemotherapy was added to standard of care protocols, still 30% of tumors will recur. As recurrent disease in medulloblastoma patients in considered uniformly lethal, it is key to identify the cells allowing tumor relapse, and their targetable regulators. By analyzing single cell transcriptomic data, we uncovered a population of SOX2 labeled astrocyte like cells resistant to SMO inhibitors in clinical trials. Using SOX2-enriched medulloblastoma cultures, we observed that SOX2$^+$ cells rely on non-canonical GLI signaling to propagate medulloblastoma. Therefore, *in vivo* inhibition of SHH signaling using functionally different GLI inhibitors depleted the SOX2$^+$ cell pool, what led to less aggressive tumors that lacked the ability to further engraft. Stressing the translational relevance of our findings, a clinically relevant GLI inhibitor not only exhausted SOX2$^+$ cells driving tumor relapse, but increased overall survival in mice harboring medulloblastoma. Our results emphasize the importance of using targeted therapies that deplete SOX2$^+$ cells to prevent medulloblastoma recurrence.

MEDB-22. IPSC-DERIVED CEREBELLAR ORGANOID MODEL FOR HEREDITARY GENETIC PREDISPOSITION IN SHH-MEDULLOBLASTOMA

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Medulloblastoma is one of the most common malignant embryonal brain tumors in children. Medulloblastomas of the Sonic Hedgehog (SHH) group arise from excessive proliferation of granule neuron progenitor (GNP) cells during cerebellar development. Genetic predisposition accounts for nearly 40% of all pediatric SHH-medulloblastomas. Recently, *ELP1*, a novel predisposition gene, was shown to be germline mutated in 15% of SHH-medulloblastoma patients. *ELP1* encodes the scaffolding member of the Elongator complex and is required for efficient translation. Heterozygous mutations in *ELP1* have been associated with the neural disorder Familial Dysautonomia, but not cancer. *ELP1*-associated medulloblastomas frequently harbor somatic *PTCH1* co-mutations. It remains unclear how *ELP1* affects the GNP lineage during normal cerebellar development and tumorigenesis in pediatric SHH-medulloblastoma patients. To characterize *ELP1* mutations in the GNP lineage in vitro, we established a cerebellar organoid model from human induced pluripotent stem cells (iPSCs). We genetically inserted an EGFP reporter downstream of the endogenous GNP-specific *ATOH1* locus in control iPSCs and generated cerebellar organoids according to published protocols. Marker gene and protein expression levels confirmed the cerebellar identity of the 3D model. Furthermore, activation of the EGFP reporter in single cells within the organoid highlighted the specification of putative GNPs. Next, we will determine the specific cell state of putative iGNPs and compare to human GNPs identified in our scRNAseq cerebellum atlas. To analyze tumorigenesis through *ELP1* loss, we will introduce patient-specific *ELP1*mutations into *ATOH1-EGFP* iPSCs. Cerebellar organoids derived from *ELP1*-, *PTCH1*-deficient and control iPSCs will serve as models to study GNP proliferation, differentiation, apoptosis and tumor formation. Combining genome editing, in vitro 3D differentiation and functional studies, we will characterize the novel predisposition gene *ELP1*in GNPs during cerebellar development. In addition, we will determine the interplay of *ELP1*and *PTCH1* co-mutations, predisposing SHH-medulloblastoma formation.

MEDB-23. TARGETING EPIGENETIC DYSREGULATION IN MEDULLOBLASTOMA WITH POOR PROGNOSIS

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Medulloblastoma (MB) is the most common paediatric malignant brain tumour and is classified into four distinct molecular subgroups (WNT, SHH, G3 and G4), each of them further subdivided into subtypes with different prognosis and responses to therapy. Deregulation of chromatin modifier genes play an essential role in MB, particularly in the G4 subgroup. A BMI1^{High};CHD7^{Low} molecular signature identifies patients with poor survival within this subgroup. We show that BMI1^{High};CHD7^{Low} sustains MB growth through regulation of MAPK/ERK signalling and via a novel epigenetic regulation of inositol metabolism in both G4 MB cells and patients. These tumours display over-activation of MAPK/ERK signalling, sustaining tumour proliferation, and of AKT/mTOR pathway which leads to energetic rewiring characterised by enhanced glycolytic capacity and reduced mitochondrial function. We demonstrate that inositol administration counteracts this metabolic alteration, impairs proliferation and significantly extends survival in a pre-clinical model. Moreover, inositol synergises with cisplatin, a chemotherapy agent currently used in MB treatment, enhancing its therapeutic effect *in vivo*. Additionally, we identify a synergistic vulnerability of BMI1^{High};CHD7^{Low} MB to a combination treatment with BMI1 and MAPK/ERK inhibitors that overcomes acquired resistance to single-drug therapy. Mechanistically, we observe a CHD7-dependent binding of BMI1 to MAPK-regulated genes underpinning the CHD7-BMI1-MAPK regulatory axis that is critical for the anti-tumour effect of the inhibitors *in vitro* and in a pre-clinical model. Moreover, we demonstrate that the BMI1^{High};CHD7^{Low} molecular signature defines G4 MB patients with an enhanced ERK1-ERK2 phosphorylation activity. Importantly, cerebellar neural stem cells modelling the BMI1^{High};CHD7^{Low} signature are not affected by BMI1 and MAPK/ERK inhibitors and do not show metabolic adaptation hence are resistant to the proposed treatments. In summary, we have identified two actionable vulnerabilities in a pre-clinical setting modelling a molecularly defined group of MB patients, paving the way for the design of signature-matched clinical trials.