degeneration and an increased DNA damage response. These mice are currently being evaluated for their capacity to recapitulate *ELP1*-associated SHH-MB. Additional analyses carried out on SHH-MB patient-derived xenografts showed that *ELP1*-mutant tumor cells specifically exhibit defects in tRNA biogenesis. Therefore, the function of ELP1 as a translational regulator is severely impaired in *ELP1*-mutant SHH-MBs. Our ongoing molecular and functional studies will provide important insights into the most common MB predisposition gene and will lay the foundation for future preclinical studies.

MBRS-26. CDK7 MEDIATED TRANSCRIPTIONAL PROCESSIVITY OF DNA REPAIR NETWORKS REGULATES SENSITIVITY TO RADIATION IN MYC DRIVEN MEDULLOBLASTOMA

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Myc-driven Medulloblastoma remains a major therapeutic challenge due to frequent metastasis and a poor 5-year survival rate. Myc overexpression results in transcriptional dysregulation, proliferation, and survival of malignant cells. To identify therapeutic targets in Myc-amplified medulloblastoma we performed a CRISPR-Cas9 essentiality screen targeting 1140 genes annotated as the druggable genome. The cyclin-dependent kinase, CDK7, was identified as a top candidate. CDK7 phosphorylates the c-terminal domain of RNA Pol II facilitating transcriptional initiation and elongation. We subjected Myc-amplified cells treated with CDK7 inhibitors to whole transcriptomic analysis. The resultant data revealed gene networks mediating DNA repair were functionally repressed. Consistent with this data, ChIP-sequencing showed the most significant reduction in RNA Pol II and Myc promoter occupancy within a subset of DNA repair genes including BRCA2 and RAD51 but not across the whole genome. These data suggest that inhibition of CDK7 mechanistically limits Myc driven transcriptional processivity of DNA repair networks. Further, evaluation of genes mediating DNA repair show a muted response to DNA damage and increased cell death with CDK7 inhibition. We next evaluated Myc-amplified MB cell response to ionizing radiation *in vitro* and *in vivo* with CDK7 inhibition. Inhibition of CDK7 enhanced radiation sensitivity of Myc MB cells by potentiating DNA damage. Further, cotreatment produced decreased MRI T2 tumor volumes and enhanced survival benefit in orthotopic PDX xenografted mice compared to radiation alone. Our studies establish a mechanism for selective inhibition of Myc-driven MB by CDK7 inhibition combined with radiation as a viable therapeutic strategy for Myc-amplified medulloblastoma.

MBRS-27. EXOSOMES CARRY DISTINCT MIRNAS THAT DRIVE MEDULLOBLASTOMA PROGRESSION

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INTRODUCTION: Extracellular vesicles (EVs) represent an ideal source of functional biomarkers due to their role in intercellular communication and their ability to protect cargo, including RNA, from degradation. The most investigated EV's are exosomes, nanovesicles secreted by all cell types and able to cross the blood-brain-barrier. Here we characterised the RNA of exosomes isolated from medulloblastoma cell lines, with the aim of investigating exosomal RNA cargo as potential functional biomarkers for medulloblastoma. METHODS: Exosomes derived from a panel of matched (original tumour and metastasis) medulloblastoma cell lines were isolated and characterised by NanoSight, electron microscopy, western blotting and Nanoscale flow cytometry. Exosomal miRNA and mRNA from our matched cell lines and foetal neuronal stem cells, which were used as a normal control, were analysed by RNA-sequencing technology. RESULTS: Based on hierarchical clustering, malignant derived exosomes were distinctly separated from normal control exosomes. miRNA profiling revealed several established oncomiRs identified in our malignant derived exosomes compared to control samples. Using interaction pathway analysis, we identified that our malignant exosomes carry numerous miRNAs implicated in migration, proliferation, cellular adhesion and tumour growth. Several previously identified oncomiRs were also identified to be present at higher levels in metastatic exosomes compared to primary and normal, including hsa-miR-455-3p and hsa-miR-92a-3p. CONCLUSION: This study shows that exosomes from MB cells carry a distinct miRNA cargo which could enhance medulloblastoma progression. The use of circulating exosomes as markers of metastatic disease could be an innovative and powerful non-invasive tool.

MBRS-28. EXOSOMES DRIVE MEDULLOBLASTOMA METASTASIS IN A MMP2 AND EMMPRIN DEPENDENT MANNER

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INTRODUCTION: Recurrent/metastatic medulloblastoma (MB) is a devastating disease with an abysmal prognosis of less than 10% 5-year survival. The secretion of extracellular vesicles (EVs) has emerged as a pivotal mediator for communication in the tumour microenvironment during metastasis. The most investigated EV's are exosomes, nanovesicles secreted by all cell types and able to cross the blood-brain-barrier. Matrix metalloproteinases (MMPs) are enzymes secreted by tumour cells that can potentiate their dissemination by modification of the extracellular matrix. We hypothesise that exosomal MMP2 and its inducer EMMPRIN could enhance metastasis of MB. METHODS: Proliferation, invasion and migration assays were used to evaluate the phenotypic behaviour of primary cell lines pre-treated with metastatic tumour cell-derived exosomes. Gelatin zymography and western blotting were performed to confirm MMP2 functional activity in cell lines and exosomes. Nanoscale flow cytometry was used to measure surface exosomal EMMPRIN levels. Exosomal MMP2 and EMMPRIN were modulated at the RNA level. RESULTS: Number of exosomes is directly related to the migratory behaviour of parental MB cell lines ($p<0.01$). Notably, functional exosomal MMP2 and EMMPRIN levels also correlate with this. Furthermore, exosomes from metastatic cell lines conferred enhanced migration and invasion on their matched isogenic primary (non-metastatic) cell line pair by ~3.8-fold ($p<0.01$). Exosomes from metastatic cell lines also conferred increased migration on poorly migratory foetal neuronal stem cells. CONCLUSION: Together this data suggests that exosomal MMP2 and EMMPRIN may promote medulloblastoma metastasis and supports analysis of exosomal MMP2 and EMMPRIN levels in patient cerebral spinal fluid samples.

MBRS-29. PROSPECTIVE MOLECULAR PROFILING IN PEDIATRIC MEDULLOBLASTOMA PATIENTS ENROLLED ON THE "HEAD START 4" PROTOCOL

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Medulloblastoma is the most common malignant embryonal brain tumor in children with only modest improvements in outcomes achieved over the last 20 years. The implementation of irradiation-avoiding strategies, including trials by the "Head Start" consortium, have demonstrated improved cure rates along with enhanced quality of life. Simultaneously, the classification of medulloblastomas has undergone a dramatic shift as molecular testing has made it possible to divide these tumors into distinctive subtypes. Currently, the WHO recognizes four medulloblastoma molecular subgroups; however it remains unclear how patients within these subgroups respond to modern irradiation-avoiding therapies. This study aims to demonstrate the feasibility of prospective molecular profiling in medulloblastoma patients enrolled on the "Head Start 4" trial. Whole-exome sequencing (SureSelect Human All Exon *V6+COSMIC)* and DNA methylation (Illumina EPIC Array) profiling were performed on 10 paired tumor/blood samples and 4 tumor samples, respectively. High-quality mutational and copy number data were produced for each of the 10 subjects demonstrating well-described gene mutations (SUFU) and chromosomal losses (9q and 10q). Four subjects had methylation profiling which successfully separated them into the WHO subgroups (two SHH and two Group 3). These data showed the feasibility of prospective high-dimensional mutational and DNA methylation analysis using "Head Start 4" patients. Future work will focus on finalizing these profiling efforts, enabling the development of models that predict response to irradiation-avoiding treatment and, in general, a better understanding of the molecular mechanisms underlying treatment resistance and tumor progression, leading to more personalized approaches to treating children with medulloblastoma.

MBRS-31. COMBINING IRRADIATION AND ANTI-CD47 TO ENHANCE THE TREATMENT OF GROUP 3 MEDULLOBLASTOMA

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Medulloblastoma (MB) is the most common malignant primary pediatric brain tumor. The Group 3 molecular subgroup of Medulloblastoma