MBRS-51. MUTATIONS IN BRPF1 FOUND IN SHH MEDULLOBLASTOMA PREVENT INTERACTION WITH TP53 AND LEADS TO RADIORESISTANCE IN VITRO

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Medulloblastoma (MB) is one of the most common pediatric tumors in children. Among them, SHH subgroups of MB (MB_{SHH}) is characterized by constitutive activation of SHH pathway. Somatic mutations in *BRPF1*, a chromatin modifier, is found in more than 5% of MB_{SHH} and accounts for almost 20% of adult MB_{SHH} but its potential role in MB_{SHH} pathophysiology is still unknown. In this study, we first examined the function of Brpf1 on pro-tumorigenic features of MB_{SHH} and evaluated molecular pathways regulated by Brpf1 using Brpf1floxed::Atoh1-*Cre* conditional knockout mice, in which *Brpf1* is conditionally deleted in cerebellar granule neuron progenitors (GNPs). While RNA-seq analysis on GNPs from *Brpf1* WT and KO mice showed significant differences in the pathways related with cell cycle and cell death, deletion of *Brpf1* did not cause acceleration of tumorigenesis in the *Ptch1* heterozygous tumor-prone BACKGROUND**:** Co-immunoprecipitation followed by mass spectrometry analysis identified interaction partners of BRPF1 including MOZ, MORF and ING5, known partners of BRPF1. Gene ontology analysis also depicted pathways important for cell cycle progression, cell death and response to DNA damage. Consistent with these observations, TP53 was identified as a novel co-factor of BRPF1. Of note, some of MB_{SHH}-relevant *BRPF1* mutations prevented interaction with TP53. According to the previous finding that cytosolic TP53 is required for apoptotic cell death, GNPs expressing the *BRPF1*-R600X mutant gene exhibited the resistance to irradiation-induced cell death. In conclusion, our data revealed that BRPF1 mutants found in MB_{SHH} could prevent the complex formation with TP53, leading to enhanced resistance to cell apoptosis.

MBRS-53. CONTROL OF MEDULLOBLASTOMA VASCULATURE BY A REGULATOR OF NEUROGENESIS

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Medulloblastomas are characterized by poor neuronal lineage specification. Expression of the RE1 Silencing Transcription Factor (*REST*), a regulator of neurogenesis, is aberrantly elevated in human sonic hedgehog (SHH) medulloblastomas. Using a novel transgenic mouse (*RESTTG*) model, we demonstrated that REST is a driver of medulloblastoma genesis and promotes tumor progression in mice with loss of an allele of *Ptch1* (*Ptch+/–).* Tumor formation in *Ptch+/–/RESTTG* mice occurred with 100% penetrance and a latency of 10–90 days in contrast to *Ptch+/–* mice, which developed tumors at a frequency of 15–20% at 6–9 months of age. Histopathological analyses showed leptomeningeal dissemination of tumors in *Ptch+/–/RESTTG* mice, in addition to a significant increase in tumor vasculature compared to tumors in *Ptch+/–* mice. These findings were recapitulated in xenografted tumors of isogenic low and high-REST medulloblastomas in mice. Proteome profiler human angiogenesis array analyses revealed a REST-dependent increase in vascular endothelial growth factor (VEGF) and placental growth factor (PLGF). Surprisingly, REST elevation also caused co-localization of tumor cells with tumor vasculature, specifically endothelial cells, and was associated with upregulated expression of a number of pro-angiogenic genes, including receptor VEGFR1 and the positive regulator of endothelial differentiation, E26 transformation specific-1 (*ETS1*), in tumor cells. In addition, expression of several anti-angiogenic molecules was downregulated. Knockdown of *ETS1* reversed the above findings. Thus, our data demonstrate that REST elevation not only blocks neurogenesis in medulloblastoma cells, but also modulates the tumor microenvironment by mechanisms that likely involve vascular mimicry.

MBRS-54. POOR SURVIVAL IN REPLICATION REPAIR DEFICIENT HYPERMUTANT MEDULLOBLASTOMA AND CNS EMBRYONAL TUMORS: A REPORT FROM THE INTERNATIONAL RRD CONSORTIUM

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BACKGROUND: Mutations in mismatch repair (MMR) and DNA-polymerase (POL) genes lead to DNA replication repair deficiency (RRD), resulting in a growing group of previously under-recognized childhood brain tumors. Medulloblastoma and embryonal tumors are rarely reported in RRD. Their biological and clinical significance is unknown. METHODS: We analyzed the clinical and genomic data of embryonal tumors registered in the International RRD Consortium. RESULTS: Twenty-six tumors were centrally reviewed to confirm medulloblastoma (n=18), embryonal-tumor, NOS (n=5), and three glioblastoma (excluded). Embryonal tumors were observed at a young age (median: 7-years, IQR: 5;11), and all but one exhibited clinical cues (café-au-lait macules/ family history) of germline RRD. Medulloblastomas with RRD exhibited high-risk features, including anaplastic histology (50%), and SHH-subgroup with TP53-mutation (50%). Importantly, 68% harbored POLE/POLD1 mutations, resulting in median tumor mutation burden of 164 mut/mb. POL-mutated tumors were significantly ultra-hypermutated (>100 mut/mb) than tumors with MMR-deficiency alone (p=0.015). Synchronous and metachronous tumors were observed in 40%. However 90% of the deaths were related to the diagnosis of embryonal CNS tumor. Median survival for the entire cohort was 17-months (95% CI: 10 to 23). Predicted 3-year survival was 37% for medulloblastoma, with no survivors among other embryonal tumors. CONCLUSIONS: This is the largest cohort of replication repair deficient medulloblastoma reported till date. The tumors are hypermutated, harbor somatic mutations in TP53 and/or POLE/POLD1, and have very poor survival with current chemo-irradiation based approaches. These biologically unique tumors expand the spectrum of high-risk TP53-mutant SHH-medulloblastoma, and need novel strategies for treatment.

MBRS-56. RE-EVALUATION OF LEPTOMENINGEAL METASTASIS IN MEDULLOBLASTOMA WITH MAGNETIC RESONANCE IMAGING, RELATED SYMPTOMS AND CEREBROSPINAL FLUID METABOLOMIC PROFILES

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BACKGROUND: Diagnosis of leptomeningeal metastasis (LM) in medulloblastoma is made by positive findings in either MRI or CSF cytology. We studied if CSF metabolomics profile can differentiate the discordant results between MRI and CSF cytology and reflect the sampling time related to treatment. MATERIALS AND METHODS: We prospectively collected 83 CSF samples from 45 medulloblastoma patients. A total of 6,527 low-mass ions (LMIs) were detected using liquid chromatography tandem mass spectrometry (LC-MS/MS). Discriminative low-mass ions (LMIs) between four different MRI and cytology results groups were evaluated and representative LMIs were identified. RESULTS: CSF cytology and MRI finding were both positive for LM in 8 samples and both negative for 47 samples. Tests were cytology (-) and MRI (+) in 20 samples, whereas cytology (+) and MRI (-) status were in the remaining 8 samples. The diagnostic accuracy by area under the curve (AUC) was 0.722 for cytology and 0.888 for MRI each. Based on the exclusiveness of LMI between groups, we verified 27 discriminative LMIs in MRI (+)/ cytology (+), 9 LMIs in MRI (+)/ cytology (-), and 12 LMIs in MRI (-) and cytology (+) group, separately. Metabolic pathways involved in MRI (+)/ cytology (+) group were linoleic acid, phenylalanine, TCA cycle, retinol, arginine-ornithine, nicotinate-nicotinamide, etc. Low-mass-ion discriminant equation (LOME), which could differentiate both different MRI and cytology results and the sampling time or presence of LM-related symptoms was found. CONCLUSION: Non-targeted MSanalysis CSF metabolite in medulloblastomas revealed significantly different profiles, and these results suggest LMI profiles might have a higher sensitivity for LM diagnosis than either MRI or cytology.