**BIOL-10. DISTRIBUTION AND VULNERABILITY OF TRANSCRIPTIONAL OUTPUTS ACROSS THE GENOME IN MYC-AMPLIFIED MEDULLOBLASTOMA CELLS**

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Group 4 medulloblastoma is the most common medulloblastoma subgroup with an intermediate prognosis and a high incidence of metastasis and late-onset relapse cases. Despite several comprehensive genomic studies in medulloblastoma, Group 4 medulloblastomas lack a unifying oncogenic driver and treatment targets. This subgroup is characterized by recurrent genetic alterations in chromatin modifiers, amplification of stemness genes, and reduced expression of tumor-suppressing events. 17% of Group 4 medulloblastoma cases are characterized by enhancer hijacking through tandem duplication of SNCAIP, resulting in high expression of PRDM6, a putative transcriptional repressor and histone methyltransferase. PRDM6 amplified medulloblastoma cell lines show additional hallmark characteristics, such as KDM6A, KMT2C, and ZMYM3, and high MYCN expression. In this project, we investigate the impact and oncogenic potential of sustained PRDM6 expression in early neural stem cell populations and the developing mouse cerebellum. We drive expression of PRDM6 in human iPSC-derived neuroepithelial stem cells (NECs) with and without high MYCN expression to study its implications in tumorigenesis. To test for tumor growth in vivo and changes in tumor progression as a function of PRDM6 activity, NECs are injected into the cerebellum of adult mice. In order to elucidate impact of PRDM6 activity during embryonic cerebellar development, we also introduce PRDM6 expression into mouse embryonic stem cells (ESCs) for analysis via a new, CRISPR-based system. Together, our findings reveal a real time action of Myc as a transcriptional factor in tumor cells, gain new insight into the pathogenic mechanism underlying Myc-driven tumorigenesis, and support IMPDHs as a therapeutic vulnerability in MB cells empowered by a high level of Myc oncoprotein.

**EMBRYONAL TUMORS**

**EMBR-01. CLASS I HDAC INHIBITORS AND PLK1 INHIBITORS SYNERGIZE IN MYC-AMPLIFIED MEDULLOBLASTOMA**

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Myc plays a central role in tumorigenesis by orchestrating the expression of genes essential to numerous cellular processes. While it is well established that Myc functions by binding to its target genes to regulate their transcription, the distribution of the transcriptional output across human genome in Myc-amplified cancer cells, and the susceptibility of such transcriptional outputs to therapeutic interferences remain to be fully elucidated. Here, we analyze the distribution of transcriptional outputs in Myc-amplified medulloblastoma (MB) cells by profiling nascent total RNAs within a temporal context. This profiling reveals a major portion of transcriptional action in these cells was directed at the genes fundamental to cellular infrastructures, including rRNAs and particularly those in the mitochondrial genome (mtDNA). Notably, even when Myc protein was depleted by as much as 80%, the impact on transcriptional outputs across the genome was limited, with notable reduction mostly in genes of involved in ribosomal biosynthesis, genes residing in mtDNA or encoding mitochondria-localized proteins, and those encoding histones. In contrast to the limited direct impact of Myc depletion, we found that the global transcriptional outputs were highly sensitive to the activity of Inosine Monophosphate Dehydrogenases (IMPDHs), rate limiting enzymes for de novo guanine nucleotide synthesis and whose expression in tumor cells is positively correlated with Myc expression. Blockage of the IMPDH pathway in the global transcriptional outputs with and without strong inhibitory effect on the aforementioned infrastructure genes, which was accompanied by the abrogation of MB cell's proliferation in vitro and in vivo. Together, our findings reveal a real time action of Myc as transcriptional factor in tumor cells, gain new insight into the pathogenic mechanism underlying Myc-driven tumorigenesis, and support IMPDHs as a therapeutic vulnerability in MB cells empowered by a high level of Myc oncoprotein.

**EMBR-02. OLIG2 REPRESENTS A PROGNOSTIC MARKER AND THERAPEUTIC TARGET IN MYC-AMPLIFIED MEDULLOBLASTOMA RELAPSE AND METASTASIS**

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Medulloblastoma (MB) is one of the most common pediatric CNS tumors. Patients with Group 3 MBs harboring MYC amplification exhibit low survival rates. Surviving patients suffer from therapy-induced sequelae, which call for new targeted therapy strategies. We and others have previously shown the sensitivity of MYC-amplified MB to class I histone deacetylase (HDAC) inhibition. After demonstrating that the MYC target gene PLK1 is significantly downregulated upon class I HDAC treatment, we hypothesized that inhibition of both HDACs and PLK1 could have synergistic effects. Methods: Cell metabolic activity changes upon HDAC and PLK1 inhibition were assessed in MYC-amplified and non-amplified MB cell lines, as well as in an additional MYC-inducible cell line. The interaction effect of both inhibitors was determined by combination index (CI) using the Chou-Talalay method. Results: We successfully evaluated cell viability, cell cycle and apoptosis induction. Transcription profile changes after combination treatment were evaluated. Results: MYC-amplified MB cell lines were more sensitive than non-amplified cell lines to PLK1i treatment, showing IC50 in clinically achievable concentrations. Inhibition of both HDACs and PLK1 synergistically reduced cell metabolic activity in lower concentrations in MYC-amplified compared to non-amplified MB cell lines. We also observed a significant loss of viability and cells in G1 phase, as well as induction of apoptosis after combination treatment in MYC-amplified cells. Non-amplified cell lines showed an IC50 2-3 fold lower with no significant loss of viability or apoptosis. After demonstrating the sensitivity of MYC-amplified MB cell lines to combination treatment, we aim to translate this novel combination to in vivo models. Our data suggest that MYC-amplification is a predictive marker for PLK1i treatment in MB. The combination of HDACi and PLK1i could be a candidate therapy for future clinical trials for MYC-amplified group 3 MB.