plication. Five patients had febrile neutropenia and two developed sepsis. One patient required dose reduction for prolonged thrombocytopenia. Peripheral blood stem cell collection was achieved in all patients for whom it was attempted. This re-induction regimen is generally well-tolerated and effective in inducing responses for children with recurrent medulloblastoma.

MEDB-87. TRANSCRIPTOME-DRIVEN DRUG REPURPOSING IN GROUP 3 MEDULLOBLASTOMA

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Across the molecular spectrum of medulloblastoma (MB), group 3 (G3) tumors are the most aggressive with <50% five-year survival, the lowest of all MB subgroups. G3 MB tumors are characterized by frequent metastases at diagnosis, unique methylation profiles, MYC amplification, and i17q, but these unique molecular features have yet to be exploited for therapeutic purposes despite their contribution to the disease process. As such, we sought to address this gap in survivorship by identifying FDA-approved compounds with the potential to inhibit cellular processes critical to G3 MB tumor proliferation and metastasis, aiming to exploit the unique molecular pathogenesis of G3 tumors. Guided by analysis of RNA-sequencing data from locally obtained, patient-derived MB samples against the LINCS chemical perturbagens database, we identified nortriptyline (NT), a tricyclic antidepressant, as a candidate MB therapeutic due to: 1) its ability to revert the transcriptomic signature of G3 MB to a normal cerebellum-like state and 2) its ability to cross the blood-brain barrier. We first identified the IC_{50} of NT in D425 and HDMB03 cells as 28μM and 20μM, respectively. Then, we observed that NT increased apoptosis of HDMB03 cells 3-fold by flow cytometry and confirmed our observations with Western blotting of apoptotic markers. Additionally, NT treatment resulted in abrogation of colony formation, impairment of wound healing, and inhibition of cell migration and invasion in vitro in HDMB03 cells. In all, transcriptome-driven drug repurposing holds great promise, as identifying novel uses for compounds with a known safety profile can deliver effective treatments into the hands of both patients and physicians in an expedited manner when compared to traditional means.

MEDB-88. BAF60C/SMARCD3-MEDIATED NOVEL NEURODEVELOPMENTAL EPIGENOMIC PROGRAM PROMOTES METASTATIC DISSEMINATION IN MEDULLOBLASTOMA

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Normal brain development relies on precise genetic and epigenetic spatiotemporal regulation of gene expression. How dysregulation of neurodevelopment relates to medulloblastoma, the most common pediatric brain tumor, remains elusive. Here, we uncovered a novel neurodevelopmental epigenomic program that regulates Purkinje cell migration in developing cerebellum is hijacked to induce tumor metastatic dissemination in medulloblastoma. Integrating publicly available datasets with our in-house data, unsupervised analyses revealed that BAF60C/SMARCD3, a subunit of SWI/SNF chromatin remodeling complex, promotes tumor cell migration in vitro and metastasis in vivo. Based on analyzing the single-cell RNAseq data of cerebellum developmental trajectory in mice and humans, aligning with the medulloblastoma patients' datasets, we found that BAF60C/SMARCD3 regulated DAB1-mediated Reelin signaling is involved in Purkinje cell positioning during cerebellum development and medulloblastoma metastasis by orchestrating the cis-regulatory elements (CREs) at the DAB1 gene locus. Analysis of spatiotemporal gene expression and chromatin architecture in the human and mouse cerebellum demonstrated that transcription activity of the BAF60C/SMARCD3-DAB1 circuit is downregulated in a mature state of cerebellar development, however, is upregulated in metastatic medulloblastoma. We further identified that a core set of transcription factors, enhancer of zeste homolog 2 (EZH2) and nuclear factor I X (NFIX), bi-directionally control BAF60C/SMARCD3 transcriptional regulation by coordinating with the CREs at the BAF60C/SMARCD3 gene locus to form a chromatin hub during developing cerebellar development and medulloblastoma metastatic dissemination. Highly expressed BAF60C/SMARCD3 activates the Reelin/DAB1 signaling pathway downstream Src kinase, which was validated in the pair-wised primary and metastatic tumors from medulloblastoma patients. Preclinical medulloblastoma mouse models revealed that inhibiting Src activity reduces tumor cell migration and metastatic dissemination at a lower and safe dose. Together, these data deepen our understanding of how the developmental program influences disease progression and provide an opportunity for the development of therapeutics for this devastating brain cancer in children.

MEDB-89. ELUCIDATION OF THE ONCOGENIC ROLE OF NUCLEAR FACTOR I/B (NFIB) IN GROUP 3 MEDULLOBLASTOMA

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Amongst the 4 subgroups of medulloblastoma (MB), tumors falling into group 3 are the most aggressive and associated with increased incidence of aberrations on chromosome 17p, c-Myc amplification, metastases at diagnosis, and rapid tumor relapse. Thus, patients with group 3 tumors suffer the worst prognosis with a 5-year survival rate of <50%. We have prior identified a novel tumor-suppressive microRNA, miR-212, silenced on chromosome 17p and its deregulated oncoprotein target, Nuclear Factor I/B (NFIB). Here, we sought to identify the role of NFIB in group 3 MB pathophysiology. NFIB is a transcription factor that regulates chromosomal gene accessibility and expression of pro-metastatic genes in various cancers. Transcriptomic interrogation of group 3 tumors revealed deregulated expression of NFIB. Kaplan-Meier survival analysis confirmed poorer survival in NFIB high-expressing patients. Using inducible silencing of NFIB in a classic group 3 MB cell line, HDMB03, we observed downregulation of key driver genes (49 genes, Log2 fold change < -0.5, $p < 0.001$) associated with group 3 MB pathogenesis by RNA sequencing. NFIB expression knockdown ($NFIB^{KD}$) further reduced tumor cell growth and aggressiveness, as evidenced by reduced proliferation, colony formation, migration, and invasion. $NFIB^{KD}$ also affected group 3 MB stemness, with attenuation of medullospheres and a reduction in stem cell markers (Nanog, Oct4, Sox2, CD133). Moreover, $NFIB^{KD}$ destabilized c-Myc phosphorylation at serine-62, resulting in reduced total c-Myc levels and subsequent cellular apoptosis. Concurrently, $NFIB^{KD}$ decreased the expression of upstream activators of c-Myc such as p-Akt and p-Erk. Taken together, these results validate the oncogenic role of NFIB in group 3 medulloblastomas and provide a potential new therapeutic target.

MEDB-90. IRON IMBALANCE CAN POTENTIATE CISPLATIN RESPONSE IN PEDIATRIC MEDULLOBLASTOMA BY REGULATING FERROPTOSIS

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Medulloblastoma (MB), the most common malignant pediatric brain tumor, is a leading cause of childhood mortality. Of the four primary subgroups, patients with group 3 tumors have the poorest prognosis. Loss of chromosome 17p is a high-risk feature associated with poor outcomes in group 3 tumors. We recently elucidated the tumor suppressive properties of a novel miR, miR-1253, on the terminal end of 17p. In further exploring its anti-neoplastic effects, we discovered that miR-1253 can disrupt iron homeostasis, causing oxidative stress and inducing lipid peroxidation. These concurrent events are capable of triggering an iron-mediated form of cell death called ferroptosis. Notably, our in silico interrogation of ferroptosis regulator genes (FRGs) in group 3 tumors revealed high expression of genes associated with iron transport and glutathione metabolism. These included mitochondrial iron transporters and GPX4, a critical regulator of ferroptosis. Restoration of miR-1253 expression in group 3 cell lines resulted in specific downregulation of ABCB7, an iron-sulfur cluster exporter, and GPX4. Consequently, cytosolic and mitochondrial labile iron pools rose, glutathione levels declined, and mitochondrial oxidative stress and lipid peroxidation were induced. These events were recapitulated by ABCB7 knockdown and potentiated cell death. Treating miR-1253-expressing cancer cells with cisplatin, a group 3 MB chemotherapeutic agent with ferroptotic properties, further elevated oxidative stress, depleted glutathione levels, and augmented lipid peroxidation, with added inhibitory effects on cell viability and colony formation. Treatment with a ferroptosis inhibitor (ferrostatin-1) lead to recovery from the cytotoxic effects of this combination therapy. Our studies highlight a novel mechanism for group 3 MB pathogenesis via ferroptosis regulation and provide a proof-of-concept for exploiting group 3 MB tumor vulnerability to iron imbalance as a novel treatment strategy.