

granule neuron precursors (CGNPs) undergo proliferation. Analysis of pre-symptomatic mutant mice showed proliferative defects and retained cells in the EGL, suggesting that the tumors may arise from CGNPs. However, targeting a subset of CGNPs using *Math1-creER^{T2}* did not lead to MB development, suggesting that an earlier EGL precursor may be required for tumorigenesis. Analysis of tumor transcriptome and MB subtype-specific genes and markers show that Dicer tumors most resemble extremely high risk p53-mutated SHH MB. Small RNA and mRNA sequencing analyses showed downregulation of microRNAs and dysregulation of its targets such as N-Myc. These studies demonstrate a role for microRNAs in MB development and show a fully penetrant genetic mouse model of highly metastatic MB.

OMICS

OMIC-01. THE LANDSCAPE OF EXTRACHROMOSOMAL CIRCULAR DNA IN MEDULLOBLASTOMA SUBGROUPS

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Extrachromosomal circular DNA (ecDNA) is an important driver of particularly aggressive human cancers. However, the prevalence of ecDNA, and its role in tumor development and progression in the different molecular subgroups of medulloblastoma (MB), remain unknown. To answer these questions, we have assembled a multi-institutional retrospective cohort of 472 MB patients with available whole genome sequencing (WGS) data, drawing from three cancer genomic data repositories and covering all MB subgroups (WNT, SHH, Group 3 and Group 4). Using recent computational methods to detect and reconstruct ecDNA, we find ecDNA in 66 patients (14%) and observe that the presence of ecDNA is associated with significantly poorer outcomes. By subgroup, ecDNA was found in 0/24 WNT (0%), 22/109 SHH (20%), 15/107 Group 3 (14%) and 20/181 Group 4 (11%) patients. Affected genomic loci harbor up to hundredfold amplification of oncogenes including MYC, MYCN, TERT, and other novel putative oncogenes. We further analyzed 24 patient-derived xenograft (PDX) and four cell line models of MB tumors. ecDNA was substantially more frequent in patient-derived models (17 of 29, 59%) than in our patient cohort. To elucidate the functional regulatory landscapes of ecDNAs in MB, we generated transcriptional (RNA-seq), accessible chromatin (ATAC-seq), and chromatin interaction (Hi-C) profiles of 6 MB tumor samples. In each case, we identify regulatory interactions that cross fusion breakpoints on the ecDNA, representing potential “enhancer rewiring” events which may contribute to transcriptional activation of co-amplified oncogenes. To test this hypothesis, we are currently conducting in-vitro CRISPRi screens targeting regulatory regions on the ecDNA of a MB cell line to determine whether these enhancers promote proliferation. In summary, our study analyzes the frequency, diversity and functional relevance of ecDNA across MB subgroups and provides strong justification for continued mechanistic studies of ecDNA in MB with the potential to uncover new therapeutic approaches.

OMIC-02. COGNITIVE DEFICITS AND ALTERED FUNCTIONAL BRAIN NETWORK ORGANIZATION IN PEDIATRIC BRAIN TUMOR PATIENTS

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Pediatric brain tumor survivors experience significant cognitive sequelae from their diagnosis and treatment. The exact mechanisms of cognitive injury are poorly understood, and validated predictors of long-term cognitive outcome are lacking. Large-scale, distributed brain systems provide a window into brain organization and function that may yield insight into these mechanisms and outcomes. We evaluated functional network architecture, cognitive performance, and brain-behavior relationships in pediatric brain tumor patients. Patients ages 8–18 years old with diagnosis of a brain tumor underwent awake resting state functional Magnetic Resonance Imaging during regularly scheduled clinical visits and were tested with the National Institutes of Health Toolbox Cognition Battery. Age- and sex-matched typically developing children were used as controls. We observed that functional network organization was significantly altered in patients compared to controls ($p < 0.001$), with the integrity of the dorsal attention network particularly affected ($p < 0.0001$). Moreover, patients demonstrated significant impairments in multiple domains of cognitive performance, including attention

($p < 0.0001$). Finally, a significant amount of variance (R squared = 0.52, $F = 3.2$, $p < 0.05$) of age-adjusted total composite scores from the Toolbox was explained by changes in segregation between the dorsal attention and default mode networks. Our results suggest that changes in functional network organization may provide insight into long-term changes in cognitive function in pediatric brain tumor patients.

OMIC-03. TRANSLATIONAL CONTROL IN MYC AND MYCN MEDULLOBLASTOMA

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Medulloblastoma has been extensively characterized at the genomic and transcriptional levels, but little is known about how alterations in translational control underlie tumor development. Myc and Mycn are often deregulated in medulloblastoma and play important roles in tumor initiation, maintenance and progression. Although both proteins have similar structures and are functionally redundant in hindbrain development, their amplification in cerebellar granule neural precursor cells leads to different medulloblastoma subtypes. In this project we are employing ribosome profiling on mouse medulloblastoma tumors generated from granule neural precursor cells with enforced expression of Myc or Mycn. Ribosome-protected mRNA sequencing allows us to quantitatively assess the specific transcripts regulated at the level of translation, identify translation regulatory sequences within the mammalian transcriptome, and understand genotype-to-phenotype processes. We discovered that Myc- and Mycn-driven tumors exhibit many more changes at the translational rather than at the transcriptional level. In particular, we found that Mycn-driven medulloblastoma upregulates the translation of Myc target genes, while mRNA levels of those genes show no difference between Myc- and Mycn-driven tumors. Furthermore, we find that the most significant translationally upregulated Myc target genes in the Mycn tumors are transcripts that encode ribosome biogenesis factors. We will further study the role of Myc and Mycn on translational regulation of the medulloblastoma transcriptome using our xenograft model of human iPSC-derived neuroepithelial stem cells overexpressing Myc or Mycn. Our goal is to understand the regulatory function of the translational landscape in Myc- and Mycn-driven medulloblastoma and to decipher the oncogenic signaling cascades leading to different medulloblastoma subtypes.

OMIC-04. IDENTIFICATION AND CHARACTERIZATION OF CIRCULATING RNAs (CODING AND NONCODING) AND METABOLITES IN CEREBROSPINAL FLUID IN MEDULLOBLASTOMA PATIENTS

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Medulloblastoma (MB) is the most common malignant brain tumor in children, and monitoring patients for treatment response and recurrence can be challenging with available current technologies in neuro-imaging and performing a biopsy to confirm response or recurrence carries risks, whereas cerebrospinal fluid (CSF) can be obtained with a little invasiveness. MB has altered cellular metabolism due to changes in gene expression, therefore, we hypothesized that any changes in MB cells lead to changes in cell-free transcripts and metabolites in CSF. To test this, we applied RNA-sequencing and mass spectrometry to analyze transcripts and metabolites including lipid in CSF from patients with different sub-groups of MB tumors (i.e., WNT, SHH, G3/4, G4, and unknown) and compared them to non-cancerous CSF. Tumor and sub-group specific transcriptomic and metabolic signatures were shown by unsupervised hierarchical clustering facilitating tumor type differentiation. By comparison with previously published tumor tissue RNA-seq data, we were able to identify a group of upregulated molecular signatures in both tumor tissue and CSF. We also identified a group of lipids that differentiate each MB sub-group from normal CSF, and Pathway analysis confirmed alterations in multiple metabolic pathways. Finally, we attempted to integrate RNA-seq data with lipidomics data, and results depict that the combinatorial analysis of CSF RNAs and metabolites can be useful in diagnosing and monitoring patients with MB tumors. (This research was conducted using samples made available by The Children's Brain Tumor Network.)

OMIC-05. PHOSPHOPROTEOMIC ANALYSIS IDENTIFIES SUBGROUP ENRICHED PATHWAYS AND KINASE SIGNATURES IN MEDULLOBLASTOMA

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