

malignant pediatric brain tumour. Current molecular Nsubgroups of MB recognize distinct disease entities of which activated Wnt signaling (monosomy 6, exon 3 mutations in CTNNB1, and Wnt gene signature) is associated with a distinct subgroup and the best overall outcome. In contrast, only non-Wnt MBs are characterized by metastatic disease, increased rate of recurrence, and poor overall survivorship. Given the excellent clinical outcome in patients with Wnt-driven MB, we aimed to convert treatment-resistant MB subgroups into an ostensibly benign tumour through selective targeting by small molecule Wnt agonists (Wnt3A), GSK3 inhibitors (CHIR99021), and transgenic lines containing a stabilized beta-catenin mutant. Activated Wnt signaling resulted in decreased in vitro self-renewal and promoted differentiation within primary human MB stem cells. The clinical relevance of these findings were demonstrated with an in vivo survival advantage in mice containing orthotopic injections of cells containing a stabilized beta-catenin mutant representative of constitutively active Wnt signaling. Xenografts generated from Wnt-activated tumours were much smaller in size, maintained a much lower rate of proliferation, and reduction in key MB stem cell self-renewal genes (Bmi1, Sox2, Msi1, FoxG1). Our work establishes activated Wnt signaling as a novel treatment paradigm in childhood MB, while providing evidence for the context-specific tumour suppressive function of the canonical Wnt pathway.

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Inhibition of eEF2K as a Novel Therapeutic Strategy in Neuroblastoma and Medulloblastoma

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Medulloblastoma and neuroblastoma are aggressive solid pediatric tumors, with 5 year survival rates lower than 50-60%. In addition, more than 80% of the survivors develop permanent neurological impairments. Hence, there is a dire need to identify and validate novel, more effective and less toxic therapeutic approaches. Tumors are continually exposed to acute changes in the micro-environment, including nutrient availability. We previously showed that eukaryotic Elongation Factor-2 Kinase (eEF2K) is a

critical regulator of cellular adaptation to acute metabolic stress. Based on those findings, we hypothesize that eEF2K is a marker of outcome and mediates medulloblastoma and neuroblastoma adaptation to acute stress. METHODS – Proprietary gene expression datasets (for medulloblastoma) and the R2 genomic analysis platform (for neuroblastoma) were analyzed for links between eEF2K expression and outcome. Effects of eEF2K knockdown on cell survival were evaluated in BE(2)C neuroblastoma cells. Immunoblotting and immunohistochemistry were performed on neuroblastoma cell lines and tissue microarrays (TMAs) for key molecules in the pathway. Similar studies are underway in medulloblastoma cell lines and TMAs. RESULTS - Low eEF2K mRNA expression is predictive of improved survival in medulloblastoma and neuroblastoma. Low p-eEF2 protein expression, indicative of low eEF2K activity, improves survival in human neuroblastoma. Neuroblastoma cell lines with eEF2K knockdown are more sensitive than controls to nutrient deprivation. CONCLUSIONS - eEF2K may represent a critical mechanism for adaptation to acute metabolic stress in neuroblastoma and medulloblastoma, and is therefore a promising therapeutic target. We are currently exploring the pharmacological inhibition of eEF2K in xenograft tumor models.

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Gliomas in Young Adults: Presence of Mutations in Histone Genes

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A point mutation resulting in a specific amino acid change(K27M) in either one of the genes encoding histone H3, H3F3A (H3.3) or HIST1H3B/C/I (H3.1) is present in most pediatric intrinsic pontine gliomas, and has been described in other midline locations. The objective of the present study was to determine the frequency and location of this mutation in diffuse infiltrating gliomas in young adults. The study group consisted of 22 consecutive diffuse gliomas in patients under the age of 40 treated at St. Michael's Hospital, an adult hospital in the University of Toronto system. Ultra-sensitive digital droplet PCR, a method capable of highly sensitive and specific mutation detection affecting either H3.3 or H3.1, was performed on sample DNA to determine H3K27M status. The H3K27M mutation was detected in the gliomas of five patients, aged 17 to 34 years. The male: female ratio was 3:2. The allele frequency ranged from 26% to 44%, reflecting the infiltrating character of the tumors. Three of the tumors were located in the thalamus, one in the medulla, and one was intraventricular. In terms of grading, one tumor was considered WHO grade II, two III, and two IV. In contrast, most tumors in patients with gliomas lacking the K27M mutation (17 subjects, age 19 to 39 years) were located in the lobes of the cerebral hemispheres, with the following exceptions: 1 in the thalamus, 1 in the hypothalamus, 1 in the cerebellum, and 1 periventricular. WHO grades were 1 II, 9 III, 7 IV. Correlation with patient outcome is ongoing. We conclude that the H3K27M is common in thalamic gliomas in young adult patients, and rare or absent in lobar hemispheric gliomas.