Gene Expression Data Points to a Role for Hypoxia in Medulloblastoma Pathogenesis

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Background: Medulloblastoma (MB) is the most common intracranial tumor in children. While molecular classification of MB is well-established, detailing cell origin, biological properties, and biomarkers, little research has been performed concerning the MB tumor microenvironment. Hypoxia is significantly associated with tumor spread, poor prognosis, malignant phenotype, and resistance to radiotherapy and chemotherapy in numerous cancer types. The aim of the present study was to assess a possible role for hypoxia in MB and the potential effect on clinical outcomes.

Methods: We, therefore, performed a systematic review examining the role of hypoxia in MB as well as pediatric brain tumors in general. In vitro studies have identified a role for HIF-1α in chemotherapy resistance, while patient samples suggest hypoxia-induced changes in gene expression as well as proteomic, metabolomic, and lipidomic profiles. Based on this literature review, 55 candidate hypoxia-related genes were identified. The PedcBioPortal for Integrated Childhood Cancer Genomics was used to assess expression differences in pediatric patient samples for these genes of interest.

Results: RNA expression was analyzed for correlation with survival, molecular group, and Chang stage. Expression of DDAH1, HYOU1, MYC, and RBX1 were significantly associated with survival. ANOVA and Ttest with a Bonferroni correction were used to assess for expression differences between groups and Chang stage. Multiple hypoxia candidate genes (ARNT2, BHLHE40, CYP3A5, DDAH1, DDIT4L, EGLN3, MT3, MYC, MYCN, TGFBR2, TP53, VEGFA) were significantly correlated with molecular group. Expression levels of TGFBR3 and GPR37 were associated with Chang stage.

Conclusion and Potential Impact: The results of our systematic review and gene expression analyses support a role for hypoxia in the pathogenesis and potentially the clinical outcomes of children with MB. Future studies comparing gene expression levels at normal oxygen tension (21%) and physiologic oxygen tension (1-3%) will allow us to assess the role of hypoxia in medulloblastoma pathogenesis.