Distinct Brain Lineage and Stromal Gene Expression Patterns in WNT, SHH, Group 3 and Group 4 Molecular Subgroups of Pediatric Medulloblastoma

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Introduction

Medulloblastomas are the most common malignant brain tumors in children. In this study, brain lineage-specific expression patterns and stromal immune signatures were compared across medulloblastoma molecular subgroups.

Methods

Gene expression data on N=105 pediatric medulloblastomas (Gene Expression Omnibus) were analyzed against data from the brain transcriptome database and Cancer Genome Atlas adult glioblastoma cohort (N=426). Centroid-based molecular subtypes were assigned in each patient. Significance Analysis of Microarrays was used to identify enriched genes (fold change>1.5, false discovery rate<5%) and develop custom gene sets of isolated CNS cell types (GSE9566) and human immune cells (GSE3982). Single-sample Gene Set Enrichment Analysis was used to compare custom gene set enrichment across patients.

Results

There were N=34 SHH (32.4%), N=8 WNT (7.6%), N=28 (26.7%) Group 3 and N=35 (33.3%) Group 4. Brain lineage-specific gene enrichment analysis indicated WNT and SHH molecular subtypes were astrocytic and astroglial, similar to adult mesenchymal/classical glioblastoma. Group 4 was neuronal and oligodendrocytic, similar to adult proneural/neural glioblastoma. Interestingly Group 3 medulloblastoma, unlike all the other adult and pediatric brain tumors, demonstrated no enrichment for any major brain lineage, potentially suggesting a distinct etiology may exist for this subset of tumors. Analysis of immune cell-specific gene signatures indicated significant enrichment of microglia/macrophage-specific gene signatures in WNT and SHH tumors, with profiles characteristic of an M2-polarization and no associated M1-specific signatures. Adult glioblastoma instead enriched in both M1 and M2 stromal immune signatures. While myeloid enrichment in adult glioblastoma was associated with worse prognosis and poor survival, the opposite was true in pediatric medulloblastoma, with improved outcomes in children having robust immune responses.

Conclusions

Medulloblastoma subtypes display distinct brain lineage enrichment and greater similarity to distinct adult glioblastoma subtypes than to other medulloblastoma subtypes. Innate immune responses are distinct between subtypes, and, in contrast to adult brain tumors, are associated with improved outcomes in children.

Learning Objectives

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1) Pediatric medulloblastoma molecular subtypes

2) Custom gene set development from isolated cell subsets

3) Custom single-sample gene set enrichment analyses (GSEA) in brain tumors

4) Distinct neural lineage patterns by molecular subtype in medulloblastoma

5) Distinct stromal immune response by molecular subtype in medulloblastoma

6) Clinical implications for immunotherapy trials and targeted therapy development

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