EDITORIAL

Advances in pediatric neuro-oncology

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The field of pediatric neuro-oncology research has undergone succession of rapid advances in the past ten years at an incredible pace. Most of these advances were driven by genomic and epigenomic characterizations of large cohort of samples assembled through international collaboration. As a result of these efforts, robust molecular markers of several types of pediatric brain tumors have been developed for diagnostic and prognostic applications. The impact of all these recent work is evident in the 2016 WHO Classification of Brain Tumors eliminating primitive neuroectodermal tumor (PNET) as a separate entity[1]. In addition, the new classification of brain tumors based on integration of histologic and molecular analysis is best illustrated by several major types of pediatric brain tumors including medulloblastoma, the most common form of malignant brain tumor in children. Some of these mutations are also actionable targets which leads to remarkable modifications of strategies in the management of these diseases.

Current basis for clinical prognostication and stratification for medulloblastoma include clinical factors as well as histological subgrouping. Recent consensus suggested multiple distinct molecular subgroups that differ in their demographics, transcriptomic profiles, somatic genetic events, and clinical outcomes[2]. Four subtypes based on histology and genetic aberrations are associated with unique prognosis. The first subtype is characterized by loss of chromosome 6q and exon 3 mutation in the beta catenin gene leading to activation of the WNT pathway as shown by expression profiling. They are typically found in the midline of the cerebellum of older children and carries the best prognosis (~90% overall survival rate). This excellent prognosis is most likely due to partial breakdown of the blood brain barrier secondary to paracrine signals driven by mutant beta-catenin inducing an aberrant fenestrated vasculature which allows the accumulation of high levels of intra-tumoral chemotherapy[3]. Current treatment strategies for WNT subtype include an overall goal to reduce therapy potentially leading to a reduction in late effects of therapy.

The second subtype of medulloblastoma is characterized by activation of the sonic hedgehog pathway (SHH-MB) as a result of mutation in one of the members of the pathway such as PTCH, SMOH, SUFU, etc. This subtype is rather heterogeneous and carries an intermediate prognosis similar to Group 4. TP53 mutated SHH-MB patients however have a very poor prognosis and new treatment options are needed especially if the TP53 mutation is germline. Availability of SMOH inhibitors (e.g. Vismogedib) may also be effective, albeit temporary, treatment options for these tumors[4].

The remaining two subtypes, Groups 3 and 4 have the worst prognosis with Group 3 having high levels of MYC expression, whereas Group 4 have relatively low expression of both MYC and MYCN. No dominant driver pathway has been identified yet for either group and therefore no specific targeted therapy is currently available.

Ependymomas currently are treated mainly with
surgery and radiation with an overall cure rate of 60%. The two major subtypes are based on anatomical location, supratentorial (ST) and posterior fossa (PF) as well as histologic grade, well differentiated (WHO Grade II) and anaplastic (WHO Grade III). There have been no recurrent mutations identified until the recent finding that ~70% of ST ependymomas carry a recurrent translocation involving the NFKB member RELA (fusion partner is C11orf95), which may serve as a potential therapeutic target. The two major subtypes of PF ependymoma are differentiated by pattern of CpG island methylation; group A (PFA-CIMP+) found predominantly in infants and associated with poor prognosis while group B (PFB-CIMP-) which occurs in older children and adults is associated with a very good prognosis. Treatment of PFA-CIMP+ cultures with the DNA-demethylating agent 5-aza-2'-deoxycytidine (decitabine or DAC) resulted in suppression of tumor growth lending this agent for repurposing in clinical trials for PFA-CIMP+ patients.

Pediatric high grade gliomas (HGG) are molecularly and genetically distinct from adult tumors with associated recurrent somatic driver mutations in histone 3 variants (H3.3 and H3.1). These histone mutations lead to amino acid substitutions at key residues and are tightly correlated with a distinct global DNA methylation pattern, neuroanatomical and age specificities, and specific associated genetic alterations. These mutations most likely cause significant changes in the epigenome in the vulnerable cell population during various windows of neurodevelopment and thus correlate well with the age of diagnosis. These distinct origins are also reflected in the anatomical distribution of tumors carrying the mutations, with H3.3 K27M distributed throughout the midline structures, H3.3 G34R/V found exclusively in the cerebral hemispheres, and H3.1 K27M restricted to the pons. In addition to H3 mutations, 20-32% of diffuse intrinsic pontine gliomas (DIPG) harbored somatic missense mutations in ACVR1, also known as ALK2. BRAF (V600E) mutations have also been detected but may be secondary to HGG arising from malignant transformation of a low-grade lesion and tend to have a more favorable outcome compared with other HGGs.

Low grade gliomas (LGGs) are associated with BRAF mutations including V600E and gene rearrangements (BRAF/KIAA1549). Other genetic alterations include FGFR1 in pilocytic astrocytoma which also points to the activation of the MAPK pathway as an actionable target.

Combination of a BRAF V600E inhibitor (e.g. dabrafenib) with a MEK inhibitor may mitigate the toxicity of each drug alone. MTOR inhibitors (e.g. everolimus) have also demonstrated promise in the treatment of pediatric LGG based on evidence of PI3K/AKT pathway activation and mTOR overexpression. As discussed in this issue’s article, Sema5A and Sema3E expression is upregulated in pilocytic astrocytomas thus promoting endothelial cell migration and angiogenic tumor growth. Anti-angiogenesis drugs (e.g bevacizumab) may be treatment options in these tumors.

Intracranial Germ Cell Tumors (GCT)

Intracranial Germ Cell Tumors (IGCT) have been traditionally classified histologically into germinomas and non-germinomatous germ cell tumors (NGGCT) but molecular classification is emerging following the first publication in 2014 reporting several recurrent somatic mutations with c-KIT being the most frequent (26%), followed by KRAS which is mutually exclusive from KIT, as well as AKT amplification and sporadic mutations in BCOR, CBL, mTOR, and NF1. These findings were validated by two subsequent reports lending support to the use of c-KIT inhibitors especially those that are active against mutations in exon 17. In addition, a more recent report from the Japanese IGCT consortium also shows striking global DNA hypomethylation in germinomas implicating primordial germ cell (PGC) as the cell of origin. In the study by Wang et al, a germline mutation in the JMJ1C gene was also identified in the Japanese population which is associated with an odds ratio of 4.8 for IGCT. JMJ1C is a member of the Jumanji domain gene family and encodes for a H3K9 histone demethylase. Although the function of JMJ1C in IGCT is yet to be elucidated, it is recently shown to be involved in the maintenance of male PGCs in mice.

The genomic, transcriptomic and epigenomic analysis of childhood brain tumors have led to the identification of many clinically relevant biomarkers and therapeutic targets. With the future addition of proteomic profiling when robust proteomic platforms become available, it is anticipated that the biological studies of these tumors will be more comprehensive and provide even more insightful understanding of these tumors. With the accumulation of molecular characterization of pediatric brain tumors at a breath-taking pace, we have reasons to be optimistic.
that the classification and treatment of these diseases will continue to be refined, ultimately leading to better outcome for the patients in the near future.

**Conflict of interest**

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

**References**


