

Medulloblastoma: advances and challenges

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Abstract

Medulloblastoma, a cancer of the posterior fossa, is the most common malignant brain tumor in children. Although 80% of patients with average-risk medulloblastoma are cured, their quality of life is often compromised by treatment-related side effects. Recently, molecular and genomic studies have shown medulloblastoma to be a heterogeneous disease made up of distinct disease subtypes. The importance of this finding is that response to therapy appears to be subtype-specific. Nevertheless, most patients are still treated according to risk stratification methods based on the clinically defined presence or absence of disseminated disease, which take no account of these newly defined subtypes. The potential, however, to vastly reduce therapy-mediated toxicity to patients with tumor subtypes that have good outcomes, while improving therapy through targeting for the poor responders, is now palpable. Critical to this effort will be the ongoing refinement of our understanding of medulloblastoma subgroups at the molecular level and the development of mouse models that faithfully recapitulate tumor subtypes.

Introduction and context

Each year, around 1,000 children (mostly between the ages of 3 and 7 years old) worldwide will develop medulloblastoma [1]. Although advances in neurosurgery, radiation oncology, and chemotherapy have led to dramatic increases in survival rates, 20% percent will die. For those that survive, current treatments have significant morbidity. Surgery carries a high risk of the development of postoperative cerebellar mutism [2]. Radiation therapy leads to a broad spectrum of cognitive and endocrine impairments [3]. Chemotherapy at the current doses designated to treat medulloblastoma frequently results in hearing loss, infertility, and neuropathies [4].

Not surprisingly, treatment failures have been noted to be higher in children whose cancer has metastasized at diagnosis [4,6]. Risk stratification is used to attempt to identify the severity of the disease and hence how intense the therapy should be, and consequently, clinical trials apply higher intensity treatment to the patients with disseminated disease than those without. Nevertheless,

metastasis is not the only feature associated with outcome. Medulloblastomas have also long been recognized by pathologists to have differing histologic characteristics and there are five variants recognized in the 2007 World Health Organization classification of central nervous system tumors [7]. Most of these variants can be categorized into three major pathologic groups: the classic, the nodular desmoplastic, and the large-cell anaplastic [5,7]. When outcome is measured accordingly, the large-cell anaplastic medulloblastomas fare the worst and the desmoplastics the best. Furthermore, if one uses immunohistochemical staining to identify those tumors that localize beta-catenin (CTNNB1) to the nucleus, another subgroup of classic histology emerges. These patients, with nucleopositive CTNNB1 tumors, have near complete survival on current therapy and, therefore, carry the most favorable prognosis [8,9]. Curiously, these tumors have been found to occur in older children and adolescents. Nodular desmoplastic tumors, on the other hand, generally occur in younger children [8,9]. The sum of these findings suggests that there are subtypes

of medulloblastoma that have inherent differences on the cellular level. Unfortunately, the histologic diagnosis of medulloblastoma is complicated by individual pathologists interpreting the histology differently and difficulties in defining subtle features like anaplasia. Improvements in technology have allowed research to delve into tumors at the molecular level, in order to find a more incontrovertible system for diagnosing medulloblastoma.

Molecular characterization

What has emerged is a series of studies that identify four to six subgroups of medulloblastoma on the basis of molecular differences [10-12]. Despite the disparity in the number of subtypes, there is a lot of common ground among the studies. All describe a subtype with aberrant Sonic Hedgehog pathway signaling (often *PTCH1* mutations), which has a high incidence amongst desmoplastic tumors [10-12]. Another subtype has aberrant signaling in the Wingless (WNT) pathway (frequently *CTNNB1* mutations), a classic histology that commonly affects older children [5,10-12]. Additionally, a less favorable subtype emerged from the latest studies [12], which associates *MYC* overexpression and amplification with poor prognostic features (i.e., high prevalence of metastatic disease and large-cell anaplastic histology).

All these subtypes have correlations with the histologic variants (i.e., the Sonic Hedgehog subtype are largely desmoplastic tumors and the *MYC* subtype are frequently large-cell anaplastic tumors), so the molecular profiling of these tumors should reduce the inconsistencies between different pathologists' interpretations. Signaling pathways that promote growth (e.g., Sonic Hedgehog, WNT, Notch, Hippo, and IGF/PI3K) or suppress proliferation (e.g., BMP2, BMP4, and BMP7) can now be analyzed by subtype [13,14]. Furthermore it is likely that tumor suppressors, oncogenes, microRNAs, and epigenetic mediators will be identified as we continue to analyze the molecular profile and conduct next generation sequencing on an increasing number of tumors. Such molecular analysis of tumors should ultimately allow us to use targeted therapies directed at the defective pathway.

The cellular origin of medulloblastoma subgroups

Recent studies have suggested that medulloblastomas arise from neuronal stem/progenitor cells in the cerebellum as a result of defects in genes that regulate normal growth and differentiation [5]. As such, identifying the cell of origin of these embryonal tumors is also an intense ongoing area of investigation. For example, granule neuron progenitors (GNPs), a type of progenitor

cell in the brain, rely on the mitogen Sonic Hedgehog binding with the transmembrane receptor *PTCH* for their expansion [15], and it was recently demonstrated that the subgroup of medulloblastomas with mutations that lead to constitutive activation of this pathway originate from GNPs [16]. Similarly, albeit in a mouse model, medulloblastomas with mutated *Cttnb1*, which resemble the human WNT subgroup [17], were shown to arise from a distinct germinal zone of the hindbrain called the lower rhombic lip that develops into structures within the brainstem [17]. The finding that the two best-known subgroups originate from different developmental zones of the hindbrain further supports the hypothesis that different subgroups of medulloblastoma arise from different progenitors. In addition, these progenitors differ from each other as they appear to be uniquely susceptible to disruption by different mutations. Unfortunately, despite great strides into the molecular analysis of the disease, it is still unclear from which cells the other subgroups of medulloblastomas arise.

Targeted therapies

Our increasing understanding of Sonic Hedgehog signaling has led to the discovery and development of multiple mouse models with mutations that disrupt this pathway. These models, in turn, have led to the discovery of drugs that inhibit proteins activated by this pathway. Because these compounds have worked remarkably well to suppress medulloblastomas in mouse models [18], they have recently entered clinical trials [19]. Early results are promising even in highly aggressive relapsed tumors [19]. Unfortunately, these effects are not all permanent and even highly responsive tumors appear to be able to generate resistance when the compounds are given as monotherapy [20]. Like most chemotherapy, remission may only become sustainable when given as a part of multiregimen treatment plan.

Future directions

The information we gain from the molecular analysis of medulloblastomas should enable physicians to better target therapies [21,22]. Currently, one can envision how early identification of the WNT subgroup at diagnosis could be used to stratify these patients to a less aggressive treatment arm, thus lessening the negative secondary effects of treatment. Also, if proven safe, it will not be long before inhibitors of Sonic Hedgehog signaling can be given to patients with Sonic Hedgehog-subtype tumors as part of their therapy. We remain, however, desperate to find better therapy for all patients, especially those who are succumbing to high risk aggressive tumors. This improvement in therapy can only come from an improved understanding of the disease itself and every effort needs to be made to increase our knowledge

of medulloblastoma at the molecular level. Understandably, the molecular defect in all the medulloblastoma subtypes will enable us to develop new and improved mouse models that recapitulate the human disease, which in turn will lead to targeted treatment with the potential to cure all the forms of this once devastating disease.

Abbreviations

BMP2, bone morphogenetic protein 2; CTNBN1, catenin (cadherin-associated protein) beta 1; IGF/PI3K, insulin-like growth factor/phosphatidylinositol 3-kinase; GNP, granule neuron progenitor; PTCH1, patched 1; WNT, wingless.

Competing interests

The authors declare that they have no competing interests.

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