Published in final edited form as:
Curr Opin Pediatr. 2012 February ; 24(1): 33–39. doi:10.1097/MOP.0b013e32834ec106.

The Molecular Classification of Medulloblastoma: Driving the next generation clinical trials

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Abstract

Purpose of Review—Most children diagnosed with cancer today are expected to be cured. Medulloblastoma, the most common pediatric malignant brain tumor, is an example of a disease that has benefitted from advances in diagnostic imaging, surgical techniques, radiation therapy and combination chemotherapy over the past decades. An incurable disease 50 years ago, approximately 70% of children with medulloblastoma are now cured of their disease. However, the pace of increasing the cure rate has slowed over the past two decades, and we have likely reached the maximal benefit that can be achieved with cytotoxic therapy and clinical risk stratification. Long-term toxicity of therapy also remains significant. To increase cure rates and decrease long-term toxicity, there is great interest in incorporating biologic "targeted" therapy into treatment of medulloblastoma, but this will require a paradigm shift in how we classify and study disease.

Recent Findings—Using genome-based high-throughput analytic techniques, several groups have independently reported methods of molecular classification of medulloblastoma within the past year. This has resulted in a working consensus to view medulloblastoma as four molecular subtypes including WNT pathway subtype, SHH pathway subtype, and two less well-defined subtypes, Group C and Group D.

Summary—Novel classification and risk stratification based on biologic subtypes of disease will form the basis of further study in medulloblastoma, and identify specific subtypes which warrant greater research focus.

Keywords

Medulloblastoma; Brain Tumor; Gene Expression Profiling

INTRODUCTION

Brain tumors are the most common tumors in children, and medulloblastoma is the most common malignant pediatric brain tumor. Approximately 400 cases are diagnosed in the US each year.[1] The World Health Organization (WHO) pathologic classification of brain tumors includes five subtypes of medulloblastoma: classic, anaplastic, large cell, nodular desmoplastic, and medulloblastoma with extensive nodularity.[2] Recent updates to WHO classification included separation of large cell subtype from anaplastic subtype and

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separation of medulloblastoma with extensive nodularity from the nodular desmoplastic subtype. Risk stratification in medulloblastoma is currently based on age, metastatic status, extent of surgical resection, and histological presence or absence of diffuse anaplasia. Standard risk patients are over the age of three with localized disease and without anaplastic subtype. All other patients are considered high risk.[3] Other embryonal brain tumors including atypical/teratoid rhabdoid tumor (ATRT) and primitive neuroectodermal tumors (PNET) arising outside the cerebellum may be treated similarly to medulloblastoma, but represent biologically distinct diseases[4] that are not within the scope of this review.

Medulloblastoma therapy, including craniospinal radiation and multiagent chemotherapy, results in significant long term toxicity for many disease survivors, including neurocognitive impairment, neuropathy, endocrinopathy, impaired bone growth, impaired motor function, hearing loss, and secondary malignancy. These side effects are most closely related to dose of radiation therapy and age at diagnosis as well as factors at presentation such as hydrocephalus and shunting.[5, 6] Patients with medulloblastoma who relapse after standard therapy have a dismal prognosis, with few long-term survivors.[7, 8]

The treatment strategy for standard risk medulloblastoma patients has aimed to reduce the dose of craniospinal radiation therapy. The initial standard dose of 36 Gy has successfully been reduced to 23.4 Gy with the use of adjuvant maintenance chemotherapy while preserving a five-year survival rate of greater than 80%.[9, 10] Ongoing studies for standard risk medulloblastoma patients are evaluating further radiation dose reduction with the aim of reducing radiation-associated toxicity.[11–15]

Children with high-risk medulloblastoma over the age of three continue to have a lower five-year survival of 70% even with full-dose 36 Gy of craniospinal radiation therapy,[10] and dose reduction to 24 Gy resulted in survival under 40% for patients with metastatic disease inappropriately treated with standard risk regimens.[9] Therefore, current strategies for high risk patients include further therapy intensification or introduction of new agents such as isotretinoin (13-cis retinoic acid) based on pre-clinical studies showing apoptosis of medulloblastoma cells treated with isotretinoin.[16]

Because craniospinal radiation therapy is particularly devastating to the neurocognitive development of children under the age of three,[5] this youngest age group is currently treated with strategies using upfront chemotherapy with the intent of delaying or avoiding radiation therapy.[17–20] Intensity of therapy, including high-dose chemotherapy with stem cell rescue, appears to improve outcome for this group of patients.[19–21] Several studies are ongoing to incorporate children who are four or five years old into this strategy.[20]

MOLECULAR SUBTYPING OF MEDULLOBLASTOMA

Although nearly all medulloblastoma occurs sporadically, there are three known inherited syndromes associated with medulloblastoma, Gorlin syndrome which is associated with mutation in the PTCH1,[22, 23] PTCH2[24] or SUFU[25] genes resulting in deregulation of the Sonic Hedgehog (SHH) pathway; Turcot syndrome which is characterized by mutation in APC gene resulting in deregulation of the WNT/beta-catenin pathway; and Li Fraumeni syndrome characterized by p53 mutations resulting in familial cancer predisposition.[26] An understanding of these pathways has allowed for creation of transgenic mouse models of medulloblastoma representing SHH,[27, 28] and more recently WNT pathways.[29]

The most common recurring gene amplifications in medulloblastoma include C-MYC or N-MYC genes, and each occur rarely in only 5% of medulloblastoma cases.[30, 31] Increased gene or protein expression occurs more frequently even without amplification, in 20–40% of medulloblastoma[32, 33]. Both amplification[34–37] and increased expression[32, 38–41]

of MYC are associated with aggressive tumors and poor outcome, and MYC status has been proposed but not yet prospectively implemented as a marker to improve clinical risk stratification.[42, 43]

High-throughput technology has facilitated the rapid study of the cancer genome in cohorts of patient tumor samples. These include RNA-based expression analysis and DNA-based copy number analysis as well as whole-genome sequencing studies. Nearly a decade ago, Pomeroy et al. used gene expression analysis to show that medulloblastoma was molecularly distinct from other embryonal brain tumors including atypical teratoid/rhabdoid tumor (AT/RT) and supratentorial primitive neuroectodermal tumor (sPNET). In addition, a gene expression signature was identified, consisting of only eight differentially expressed genes, which could predict patient survival more accurately than clinical risk stratification.[4]

Thompson et al. used gene expression analysis to demonstrate that medulloblastoma comprises five molecularly distinct subgroups, and that specific known genetic aberrations including PTCH1 and beta-catenin mutations were found exclusively within specific subtypes (referred to as SHH subtype and WNT subtype, respectively).[44] Kool et al. integrated gene expression and copy number analysis to further describe the association between five expression-based subtypes and specific genomic aberrations, including monosomy of chromosome 6 in WNT subtype and loss of 9q in SHH subtype. In addition, a strong association was observed between patient age, metastatic status and expression-based subtype. Kool et al. also re-analyzed the data produced by Thompson et al., which demonstrated reproducibility across independent datasets as well as minor but key differences which can be created by the bioinformatics process.[45]

Within the last year, the results of four separate international collaborative genome-based studies of medulloblastoma have been published. Parsons et al. performed whole genome sequencing;[46] Northcott et al.[47] and Cho et al.[48] performed gene expression and copy number analysis; and Remke et al.[49] performed similar gene expression and copy number analysis to characterize a cohort of adult medulloblastoma patients. The sheer volume of this data dwarfs previous studies in medulloblastoma. The potential for further study using these now publicly available datasets is nearly unlimited. One thing is clear: the time has come to clinically view medulloblastoma as a group of molecularly distinct subtypes (summarized in Table).[44, 45, 47–50]

WNT Subtype

Activating mutations in beta-catenin in approximately 10% of medulloblastoma represent the WNT subtype.[44, 46, 51, 52] The identification of nuclear beta-catenin has been demonstrated to be nearly 100% specific and sensitive for the presence of mutation and makes it possible to reliably identify WNT pathway tumors using routine immunohistochemistry.[51, 52] Monosomy of chromosome 6 is also present in nearly all WNT subtype medulloblastoma.[44, 47, 48] Pathologically, WNT tumors are almost exclusively of classic histology with rare anaplastic tumors reported.[48]

Although medulloblastoma as a whole has a male predominance, WNT tumors occur at equal rates in males and females[47, 49] or perhaps even with a slight female predominance.[48] The long-term survival of patients with WNT tumors is excellent, exceeding 90%.[48] Also, WNT tumors arise exclusively in an older age group of children over the age of three years.[45, 48]

In the past few decades, the ability to create genetically engineered mouse models of disease has facilitated the detailed study of a large variety of cancers as well as insight into developmental pathways.[53] Gibson et al. recently reported the first genetically engineered

mouse model representing the WNT subtype of medulloblastoma, and in doing so suggested that WNT subtype tumors actually arise outside the cerebellum from cells in the dorsal brainstem, and not the cerebellar granule neuron precursor thought to be the cell of origin for medulloblastoma. This finding explains the midline location of WNT subtype tumors, distinct from the lateral cerebellar position of SHH subtype tumors, and emphasizes that not only molecular but specific cellular origins distinguish medulloblastoma subtypes.[29]

The feasibility of widespread reliable identification of WNT subtype medulloblastoma and the excellent outcome of children with this subtype treated with conventional therapy identify this group of patients as ideal candidates for trials of therapy reduction. Targeted therapy against the WNT pathway is also likely to be feasible in the future.[54]

SHH Subtype

SHH pathway activation appears to drive approximately 25–30% of sporadic medulloblastoma as identified by cluster analysis of gene expression array data.[44, 45, 47, 48] It is not yet clear how to best to identify the SHH subtype on an individual patient basis, and ongoing studies aim to identify conventional pathological markers which may reliably identify SHH tumors[47, 50]. Not all SHH subtype medulloblastoma may be identified by mutation status of known SHH pathway genes such as PTCH1 or SUFU.[45, 47, 48] 30–40% of SHH subtype medulloblastoma have 9q loss, which includes the location of the PTCH1 gene.[47, 48] 50% of SHH subtype medulloblastoma exhibit nodular desmoplastic histology, but classic and anaplastic types also exist within this group and rarely nodular desmoplastic types are reported outside the SHH subtype.[45, 47]

SHH subtype medulloblastoma occur in a bimodal age distribution with peaks within the infant (less than three year old) and adult populations. In these specific age groups, approximately 50% of medulloblastoma is of the SHH subtype.[47, 49] In the infant population, nodular desmoplastic subtype predicts survival, and these young patients represent a group in which radiation therapy may be successfully eliminated.[19, 20, 55, 56] Nodular desmoplastic histology has not been shown to confer a substantial survival advantage in adult patients,[49] and significant molecular differences exist between adult and infant tumors within the SHH subtype.[57]

Mouse models of medulloblastoma have been genetically engineered by inactivation of PTCH1[28] or activation of the PTCH1 ligand, smoothened.[27] These models have facilitated extensive preclinical study of this subtype. Several promising small molecule inhibitors of the smoothened protein have entered clinical trial in pediatric medulloblastoma patients.[58] However, these agents are likely to be effective for only a portion of patients with the SHH group. Additional agents may be needed to effectively target tumors with pathway activation downstream of the smoothened protein.

MYC Activated

As an entire group, the non-WNT, non-SHH subtypes of medulloblastoma predict the worst outcome in both pediatric[47, 48] and adult[49] populations. MYC protein activation, which characterizes a portion of one non-WNT non SHH subtype of medulloblastoma in pediatric patients[48] and appears to be notably absent from the adult population,[49] confers the worst prognosis of any single predictive factor with survival as low as 20% in this subset of patients.[48] MYC activation is associated with a higher prevalence of metastatic disease, but the association between MYC activation portends a poor outcome even in patients with localized disease, and is likely to represent a significant portion of patients classified as standard risk on current treatment protocols who are destined for treatment failure.[47, 48]

This finding supports the idea that metastatic status itself may be a marker for biologic subtype rather than temporal disease progression.

The MYC protein has been a notoriously difficult direct target for novel drug development,[59] although a variety of anticancer drugs on the market may function at least in part by decreasing activity of MYC.[60–62] Synthetic lethal screens that identify molecules that are uniquely effective in cells with elevated MYC provide one option for further drug development. Mouse models that are currently being generated will greatly accelerate preclinical work in this important area.

Other subtypes

The remaining patients, non-WNT, non-SHH subtypes without MYC amplification present a unique challenge, because the molecular drivers of these tumors are not yet known. While a number of mutations or copy number variants have been described, is remains unclear which of these drive the cancer and represent a point of vulnerability. The first unifying hypothesis suggests that deregulation of chromatin-modulation is responsible for induction of these tumors,[63] which is supported by the recent finding that MLL gene mutations occur across medulloblastoma subtypes.[46] It remains unclear whether a chromatin remodeling event that initiates tumors represents a vulnerable driver for established tumors. Histone deacetylase inhibitors, such as vorinostat (Zolinza), broadly affect chromatin remodeling and show pre-clinical activity against medulloblastoma as single agents and in combination therapy[16, 64], and are being evaluated in human clinical trials.[65]

Four subtypes of medulloblastoma

Gene expression analyses summarized here each independently described a WNT subtype, SHH subtype and two,[47] three,[44, 45] or four[48] additional subtypes. A commendable collaborative effort involving each of the international groups who performed these studies has resulted in a working consensus to attempt to incorporate a four-group model (WNT, SHH, “Group C”, and “Group D”) into future studies of medulloblastoma.

FUTURE DIRECTIONS AND URGENT CLINICAL NEEDS

As we begin the transition from clinical stratification to molecular stratification, it will be important in our opinion to re-join groups of patients that have historically been stratified based on clinical parameters. Even if nearly all children over age three are pooled as study subjects, randomized phase III trials are expected to take five to ten years to accrue sufficient numbers of patients. This is particularly true for those patient groups where modest improvements in outcome are possible or for efficacy equivalency studies, both of which require more patients to achieve statistically relevant endpoints.

Molecular classification of all medulloblastoma using a gene expression based approach will improve current clinical risk stratification, but require significant coordination and centralization of testing.[66, 67] Use of novel technology to measure gene expression using paraffin embedded tissue may significantly improve feasibility in national consortium clinical trials.[68] This approach will likely be coupled, at least initially, with reliable traditional pathological techniques including beta-catenin nuclear staining and fluorescent in situ hybridization to detect MYC amplification.[52] At a minimum, the practical application of this strategy in the next phase of clinical trial development would be to exclude patients with MYC amplified tumors from inclusion on trial arms studying therapy de-escalation such as the current standard risk trial.

There is a most urgent clinical need for further research into the biology of non-WNT, non-SHH medulloblastoma. Because driver mutations are not well understood, there are no

published transgenic mouse models of this disease. An alternative strategy for mouse model development is the patient-derived xenograft in which human tumor samples obtained at the time of therapeutic surgery are transplanted into animal models. This method, developed by the Li laboratory, provides resources for study and therapeutic evaluation for rare and incompletely understood subtypes of disease for which there are no transgenic models.[69] Pediatric tumor samples from the Children's Oncology Group brain tumor biology study (ACNS02B3) are now being utilized for this purpose and are available to any brain tumor investigators (contact: jolson@fhcrc.org).

An additional critical need is the biologic study of the supratentorial primitive neuroectodermal tumor (sPNET), a distinct disease still included on medulloblastoma trials which has not fully experienced the benefit of advancing cure rates that have been seen for medulloblastoma.[70–72] Not surprisingly, genome-based biology studies have indicated that sPNET also represent several clinically relevant biological subtypes of disease separate from medulloblastoma.[4, 73, 74]

CONCLUSION

The study of the medulloblastoma genome has led us to a turning point where this disease is recognized as a group of molecularly distinct subtypes. The majority of research to date has been performed on the subtypes representing patients with the best prognosis, and we are now impelled by clinical need to shift research focus towards the less well-understood subtypes, such as the MYC-amplified tumors. Key opportunities are provided by the wealth of genome-based data now available and novel pre-clinical patient-derived tumor models. The molecular classification of medulloblastoma represents a modern paradigm shift in the diagnosis and treatment of malignancy. Similar shifts towards biologic stratification are likely to apply to an increasing number of tumors, perhaps all cancers, in the future.

Acknowledgments

JO receives support from the following NIH NCI Grants related to medulloblastoma: R01CA112350 (bHLH factors in medulloblastoma genesis and maintenance) and R01CA114567 (Targeted therapy in ex vivo medulloblastoma/PNET). SL receives grant support from the Seattle Children's Center for Clinical and Translational Research Mentored Scholars Program. (Targeting pediatric brain tumors)

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KEY POINTS

- Recently published genome-based studies confirm that pediatric medulloblastoma is comprised of at least four biologically distinct disease subtypes.
- Incorporation of molecular factors will greatly improve risk stratification for pediatric patients with medulloblastoma.
- There is an urgent clinical need for additional research into non-WNT, non-SHH medulloblastoma subtypes.

Table

Summary description of molecular subtypes of medulloblastoma

Molecular Subtype	Approximate percent of patients	Typical patient age	Typical Histology	Cytogenetic markers	Molecular markers	Clinical strategy
WNT	10%	Older childhood	Classic	Monosomy 6	Beta-catenin	Reduction in therapy
SHH	25%	Infant and Adult	Desmoplastic or Classic	9q loss	SFRP1[47]or GAB1[50]	SHH pathway inhibitors
Group C	30%	Childhood	Classic or Anaplastic	Isochromosome 17q	MYC activation in 50% of this subtype	Intensified therapy, novel therapeutics
Group D	35%	Childhood	Classic or Anaplastic	Isochromosome 17q	Unknown	Research focus needed