Matching mice to malignancy: molecular subgroups and models of medulloblastoma

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Abstract
Introduction Medulloblastoma, the largest group of embryonal brain tumors, has historically been classified into five variants based on histopathology. More recently, epigenetic and transcriptional analyses of primary tumors have subclassified medulloblastoma into four to six subgroups, most of which are incongruous with histopathological classification.
Discussion Improved stratification is required for prognosis and development of targeted treatment strategies, to maximize cure and minimize adverse effects. Several mouse models of medulloblastoma have contributed both to an improved understanding of progression and to developmental therapeutics. In this review, we summarize the classification of human medulloblastoma subtypes based on histopathology and molecular features. We describe existing genetically engineered mouse models, compare these to human disease, and discuss the utility of mouse models for developmental therapeutics. Just as accurate knowledge of the correct molecular subtype of medulloblastoma is critical to the development of targeted therapy in patients, we propose that accurate modeling of each subtype of medulloblastoma in mice will be necessary for preclinical evaluation and optimization of those targeted therapies.

Keywords Medulloblastoma · Mouse models · Molecular subgroups · Targeted therapies · Preclinical testing

Introduction

Medulloblastoma, a highly aggressive WHO-grade IV embryonal tumor of the cerebellum [1, 2], is the most common malignant brain tumor in children. Medulloblastoma accounts for 20% of pediatric central nervous system tumors [3], and the incidence is 0.6 per 100,000 children in patients 0–19 years
[4–6], decreasing with age. Seventy percent of cases occur in children younger than 10 years of age [6].

Leptomeningeal dissemination occurs in 30% of cases at presentation and is the strongest predictor of poor prognosis [7, 8]. The extent of surgical resection, which is affected by involvement of the brainstem, and the degree of tumor dissemination are also highly predictive of outcome [7, 9]. Multimodal surgical resection, radiation, and chemotherapy have led to modest improvements in overall survival over the last decade. Five-year survival rates are now as high as 70–80% in standard-risk patients [10–12], but survival is often achieved at the cost of treatment-induced morbidity [13–16]. Moreover, survivors suffer the continued risk of secondary tumors, relapse, and metastasis [17]. Despite the improved outcomes for standard-risk patients, the prognosis for high-risk patients (younger than 3 years old, or significant residual post-operative tumor, or leptomeningeal dissemination at presentation) remains dismal at only 25–40% 5-year event-free survival [18, 19].

Classification of medulloblastoma

Medulloblastoma arises in the posterior fossa [20]. Medulloblastoma tumor cells can invade the cerebellar cortex and white matter and spread, via the cerebrospinal fluid, to the leptomeningeal membranes that cover the CNS as well as to the spinal cord. Medulloblastoma cells typically appear undifferentiated, reminiscent of stem or progenitor cells. The WHO separates medulloblastoma into five variants based on histopathological features: (a) classic, (b) desmoplastic/nodular, (c) medulloblastoma with extensive nodularity, (d) large cell medulloblastoma, and (e) anaplastic medulloblastoma [21].

Biomarkers and molecular profiling

Several biomarkers with prognostic significance (some of which have been validated in clinical trials) have been identified for specific subtypes of medulloblastoma. The Sonic Hedgehog (SHH) signaling pathway, which is required for normal cerebellar development [21], was first implicated in medulloblastoma when patients with Gorlin’s syndrome, who develop nevoid basal cell carcinoma [22, 23] and sporadic medulloblastoma [24–27], were found to have germ line inactivating mutations of Patched1 (PTCH1). Subsequently, mutations in downstream SHH pathway components, such as Smoothed (SMO) and suppressor of fused (SUFU), and amplification of GLI1 and GLI2 and the miR17–92 complex were also identified in sporadic medulloblastomas [28–32]. SHH-dysregulated medulloblastomas comprise ~25% of all cases and may show desmoplastic or classic histopathology; desmoplastic tumors in particular have been associated with better prognoses [21, 33].

The canonical WNT pathway was first implicated in medulloblastoma based on observations that a subset of patients with germline mutations in the tumor suppressor APC (i.e., patients with Turcot syndrome) develops medulloblastoma [34, 35]. Subsequently, 5–10% of patients with sporadic medulloblastoma were also shown to harbor activating point mutations in the β-catenin gene CTNNB1, resulting in aberrantly activated WNT signaling [36, 37]. Other abnormalities found in WNT tumors include promoter methylation (hence gene silencing) of the secreted frizzled-related protein 1 family of WNT inhibitors and monosomy of chromosome 6 [4, 38]. WNT-associated tumors account for ~18–25% of all cases and are usually of classic histology [37, 39].

Amplification of MYC genes (c-MYC and MYCN, a myelocytomatosis viral-related oncogene) correlates with poor prognosis and is often found in tumors with large cell anaplastic histopathology [40]. Amplification of c-MYC has been reported in 5–15% of medulloblastoma overall, while amplification of MYCN has been found in ~10% of cases [40–42]. TP53 loss or mutation contributes to 10–15% of cases, and Li–Fraumeni patients with germline mutations in TP53 have increased risk of cancers, including medulloblastoma [43–45]. In addition, loss of the tumor suppressor ARF due to homozygous deletion or promoter hypermethylation (with wild-type TP53) occurs in ~10% of tumors [44]. Analysis of a small subset of human tumors has found TP53 mutations and methylation and deletion of ARF in aggressive LCA tumors, demonstrating the importance of the ARF/TP53 pathway in promoting malignancy [44]. Curiously, the highest frequency of TP53 mutations is found in WNT medulloblastomas, which have the best relative prognosis [46].

Isochromosome 17q, the most frequent chromosomal aberration in medulloblastoma, is present in 30–50% of tumors [11, 38], and together with copy number abnormalities in chromosome 17, including 17q gains, and 17p deletions, is associated with poor prognosis [40]. Two candidate tumor suppressors, hypermethylated in cancer 1 (HIC1), a POZ domain transcriptional repressor, and RENKCTD11, an E3 ubiquitin ligase component that works with Cullin3 to deacetylate GLI1 and GLI2 [47–49], localize to this region. In medulloblastomas, HIC1 is frequently silenced in tumors due to promoter hypermethylation [50–52], while loss of RENKCTD11 during 17p deletion enhances SHH signaling [53].

Hypermethylation of promoters for tumor suppressor genes leads to gene silencing and may contribute to development of medulloblastoma. Implicated genes include ras association domain family protein 1, isoform A (RASSF1A) [54–56], serine protease inhibitor kunitz-type 2 (SPINT2), a
tumor suppressor gene that inhibits HGF/MET signaling [57], and Kruppel-like factor 4 (KLF4) [58]. Finally, the NOTCH and phosphatidylinositol 3′-kinase (PI3K) signaling pathways may also contribute to medulloblastoma. Activation of the NOTCH pathway may occur as a result of overexpression or amplification of NOTCH1, NOTCH2, and downstream targets HES1 and HES5 [59, 60] or silencing of miR199b-5p, a negative regulator of NOTCH signaling [61]. The PI3K pathway has also been shown to contain aberrations in medulloblastoma; mutations in the catalytic subunit PIK3CA are found in ~5% of cases [62], while deletions or mutations in PTEN (a negative regulator of PI3K) occur in 30–35% of cases [63].

Several transcriptome analyses of human medulloblastoma samples have sub-classified this disease [38, 64–66]. Two subclasses of tumors, with dysregulated WNT or SHH signaling, have been consistently identified [38, 64–66], suggesting that these tumors arise and develop differently from other subtypes. Independent groups have classified non-WNT, non-SHH tumors into two to four subgroups; expression of neuronal and photoreceptor markers determines the precise number of subgroups. These subgroups may be best represented as a spectrum of tumor types, with one end of the spectrum expressing a “neuronal/glutamatergic” signature, while the other end is characterized by expression of a photoreceptor/GABAergic signature. Importantly, a subset of tumors on the “photoreceptor/GABAergic” end of the spectrum also exhibits a MYC activation signature; these MYC-associated tumors are the most aggressive and display the worst prognosis.

A comparison of the broad histopathological WHO classification of classic, desmoplastic, and large cell/anaplastic tumors with the molecular/transcriptional subtypes indicates some correlation but also highlights inconsistencies in these subclassification schemes. The common classic tumors and the rare LCA tumors span all molecular subtypes, while true desmoplastic tumors are almost entirely restricted to the SHH subgroup.

Mouse models of medulloblastoma

Medulloblastoma cell lines generally lack cellular heterogeneity and components of the microenvironment, and acute transplantation of tumor cells into mice does not recapitulate the malignancy and alterations in the microenvironment that develop in situ in patients. The use of genetically engineered mouse (GEM) models provides physiologically relevant insights into human tumor settings, albeit with limitations. The first models of medulloblastoma were derived by inoculating viral agents such as adenoviruses and polyoma viruses into rodents early during postnatal cerebellar development. Among the early successes were studies using Simian adenovirus SA7 [67, 68], the JC human polyoma virus [69, 70], or the JC virus T antigen (viral early regulatory protein). Since then, GEM models of medulloblastoma have been developed using two main strategies: germline modifications via transgenes (genetic knock-ins or knock-outs) and somatic cell gene transfer by viral transduction (Fig. 1).

SHH pathway models

Because the SHH pathway has been shown to be important in normal cerebellar development and implicated in Gorlin’s syndrome, many models have been developed to manipulate components of this pathway. These manipulations include deletion of PtcH1, activation of Smo, and deletion of Sufi. While homozygous deletion of PtcH1 results in early embryonic lethality due to cardiac and neural tube defects, heterozygous mice are viable. Medulloblastoma develops in 14–19% of these mice by 10 months of age, with peak occurrence at 16–25 weeks [71–73] (systemic heterozygosity of PtcH1 also results in other tumors, notably sarcomas). Some groups have observed the retention of wild-type PtcH1 allele in these PtcH1+/− tumors [71, 73], while others report loss of heterozygosity or mutation of the remaining PtcH1 allele [74, 75]. Loss of PtcH2 (which has 73% amino acid similarity to PtcH1) can cooperate with PtcH1 heterozygosity to promote medulloblastoma progression [76], and complete loss of p53 in PtcH1+/− mice has also been shown to increase the incidence of tumors (95–100%) and reduce the latency to 4–16 weeks [77, 78]. Loss of PtcH1 results in increased activity of downstream genes Gli1 and Cyclin D1 in cerebellar granule neuronal precursors (CGNPs) and accordingly, complete loss of Gli1 or CyclinD1 in PtcH1+/− mice results in reduced tumor incidence, demonstrating that these genes contribute significantly to SHH-driven medulloblastoma [79, 80]. In addition, PtcH1+/− mice crossed into an Igf2-null background fail to develop tumors, demonstrating that IGF2 is essential for SHH-driven medulloblastoma [81, 82].

Transgenic mouse models have also been generated using activated SMO, either with the mutation W535L (SmoM2) in human SMO or the corresponding mutation W539L in mouse SMO (SmoA1). The mutation resides in the transmembrane domain of SMO and results in SHH ligand-independent activation of downstream signaling. The SmoM2 mouse model uses a ubiquitously expressed CreER transgene to allow for tamoxifen-mediated activation of mutant SmoM2 and induction of downstream SHH signaling [83]. Sporadic leakiness of Cre activity results in 27% of mice developing medulloblastoma, and acute activation of SmoM2 at postnatal day 10 increases medulloblastoma incidence to 40%. The SmoA1 mouse model uses the NeuroD2 (ND2) promoter to drive SmoA1 expression in CGNPs
Hemizygous mice develop medulloblastoma at a median age of 26 weeks with 48% incidence, while 94% of homozygous mice develop tumors at 8 weeks of age.

Both the Ptc1 and SmoM2 models have been further engineered to restrict activated SHH signaling to cerebellar neural stem cells or CGNPs. When hGFAP-Cre or Math1-Cre drivers were used to delete Ptc1 conditionally, tumors developed in 100% of mice by 1–3 months of age [85]. Similarly, Schüller et al. expressed activated SmoM2 using hGFAP-, Math1-, Olig2-, and Tlx3-Cre drivers [86], where
Olig2-Cre and Tlx3-Cre are specifically expressed in neuronal progenitors in the posterior EGL and remain expressed in the IGL. Medulloblastoma developed in 100% of mice using all four drivers, with an average survival of about 1–2 months. The authors also targeted SmoM2 using the Gli1 promoter. However, incidence of tumors was only 40%, and the animals displayed prolonged survival, suggesting that driving tumors using promoters of genes downstream from SHH less potently promotes oncogenesis [86]. Finally, a model targeting downstream Sufu has also been reported, in which Sufu$^{+/−}$; p53$^{+/−}$ mice develop medulloblastomas with an incidence of 58% and rhabdomyosarcomas at 9% incidence by 10 months [87].

The other main strategy for generating GEM models of medulloblastoma is somatic cell gene transfer. Early studies used SHH-expressing Moloney murine leukemia viruses injected in utero into embryonic day 13.5 mouse cerebellum. Medulloblastoma arose in 76% of animals by P14–21, suggesting that direct overexpression of SHH alone is sufficient to initiate tumors [88, 89]. SHH-expressing retroviruses have also been introduced in the cerebellum of Gli1$^{+/−}$ mice. Medulloblastoma still formed, indicating that Gli1 is not critical in this model [87]. Gli2 was shown to be expressed in the tumors, suggesting that Gli2 may compensate for Gli1 loss.

To enable cell-type specific infection, the RCAS/tv-a system is now commonly used [90, 91]. The avian retrovirus RCAS (replication competent ASLV long terminal repeat with splice acceptor) only infects murine cells that are engineered to express the avian RCAS receptor tumor virus-A (tv-a), which is not normally expressed in mammalian cells [91]. RCAS-SHH retroviruses injected into Nestin promoter driving tv-a (Ntv-a) mice induce medulloblastoma at 9–39% incidence within 3 months [92–96]. Several genes of the IGF2/Pi3K pathways were each introduced with SHH, including (a) IGF2, (b) an activated transforming form of AKT (Akt-Myr-Δ11-60), and (c) a stabilized, non-degradable T58A mutant NMYC [94, 95]. Additionally, RCAS-SHH system was combined with RCAS-Cre; PTEN-floxed mice to delete PTEN [97]. Viruses encoding the anti-apoptotic protein BCL-2 were also combined with SHH to block cell death mechanisms without affecting cell proliferation [93]. Combinations with all genes tested showed at least a doubling in incidence of tumors. Of note, viruses encoding IGF2, activated AKT, wild-type or mutant NMYC, and BCL-2 were not able to drive medulloblastoma in the absence of SHH, and combining NMYC with GLI1, AKT, IGF2, or BCL-2 was also insufficient to drive tumor formation. Together, these experiments suggest that the pro-tumorigenic effect of SHH is not solely mediated via NMYC and that other downstream effectors of SHH cooperate with IGF2/Pi3K signaling to drive tumorigenesis.

Hepatocyte growth factor (HGF) has been shown to regulate expression of c-MYC and can cooperate with c-MYC to drive cell proliferation and apoptosis [98, 99]. High levels of HGF/c-MET receptor and amplification of c-MYC in human medulloblastoma are independently associated with LCA tumors and poor prognosis [99]. When expressed together with SHH using the RCAS/Ntv-a system, c-MYC and HGF each cooperated with SHH to increase penetrance, aggressiveness, and regional desmoplasia [92, 96]. However, it is not clear that this combination of genes mirrors cooperative expression in human tumors [38, 98, 99].

Other models with upregulated SHH signaling include deletion of cell cycle-associated genes Rb [100, 101] and cyclin-dependent kinase inhibitor Ink4e [102]; deletion of DNA repair enzymes Lig4 [103], Xrcc4 [104], KU80 [103], Brea2 [105], and Parp1 [106]; and candidate gene on chromosome 17 Hic1 [49]. The pathology of tumors in all of these SHH-associated models is mostly classic. Only the SHH/PTEN loss and SHH + HGF RCAS/Ntv-a models show some desmoplastic pathology, a feature characteristic of many SHH-driven human medulloblastoma tumors.

Non-SHH models

A limited number of non-SHH mouse models have also been developed. A model for WNT tumors was initiated from Blbp-expressing cells in the lower rhombic lip/dorsal brainstem, via activated β-catenin combined with p53 loss [107]. Classic tumors formed in 10 months, at 4% or 15% incidence dependent on partial or complete loss of p53. Tumors formed due to accumulation of Zic1-positive post-mitotic mossy-fiber neuron precursors that failed to migrate from the dorsal brainstem to form pontine gray nuclei in the ventral brainstem. The MRIs, location, and transcriptome of the murine tumors mirrored human WNT medulloblastoma, providing evidence that the WNT subclass of tumors likely originates from the lower rhombic lip/dorsal brainstem region, distinct from SHH tumors that originate from the CGNPs in the upper rhombic lip/EGL region.

In another model, the glutamate transporter (Glt1) promoter and a bidirectional Tet-operator were used to drive bidirectional and simultaneous expression of human MYCN and luciferase in the cerebellum (GTML), resulting in primarily SHH-independent tumors with classic or LCA histopathology [108]. These MYCN-driven tumors demonstrated recurrent genomic aberrations, suggesting that additional events cooperate with MYCN. Notably, a rare number of mice showed spinal metastases, consistent with leptomeningeal spread of the malignant primary brain tumor. MYC/MYCN amplification is correlated with poor prognosis and aggressive LCA subtype in human tumors [40], thus supporting the use of this model in pursuing investigations of high-risk patients with poor prognosis.
Current and future use of medulloblastoma models

The early implication of SHH pathway in medulloblastoma and the vast efforts of SHH tumor modeling have facilitated the preclinical testing of a number of SHH inhibitors, often using allografted tumors from variants of the Ptch1+/− model (Table 1). Cyclopamine is a steroidal alkaloid isolated from the corn lily Veratum californicurn that was discovered to inhibit tissue response to SHH signaling [109, 110] and was effective in blocking growth of SHH-driven medulloblastoma cells [74, 111]. Cyclopamine acts by binding directly to SMO, inhibiting activation of downstream SHH signaling [112, 113]. Treatment of mice with subcutaneous allograft tumors (derived from Ptch1+/−; p53+/− murine tumors) with cyclopamine led to decreased tumor mass and decreased proliferation [74].

Improved SMO antagonists [114, 115] include the benzimidazole derivative HhAntag-691 (HhAntag) [115], the semisynthetic cyclopamine analog IPI-926 [116], and the biphenyl carboxamide compound NVP-LDE225 [117, 118]. HhAntag treatment in young mice was reported to have permanent bone growth defects (presumably due to inhibition of Indian hedgehog signaling in the developing bone), calling into question the safety of using of this drug in young patients [119]. Although NVP-LDE225 treatment in mice showed initial success, extended analyses showed that tumors developed resistance to the drug and regrew [118].

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### Table 1 Use of SHH-associated medulloblastoma models for testing of targeted therapy

<table>
<thead>
<tr>
<th>GEM</th>
<th>Drug</th>
<th>Target</th>
<th>GEM study outcome</th>
<th>Status in human clinical trials</th>
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<tr>
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<td>Cyclopamine</td>
<td>SMO</td>
<td>Tumor regression</td>
<td>Preclinical only</td>
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<td>SMO</td>
<td>Tumor inhibition, prolonged survival</td>
<td>Preclinical only</td>
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<td>SMO</td>
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<td>Phase I</td>
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<tr>
<td>Ptch1+/−; p53+/−Ptch1+/−; Hic1+/− allografts</td>
<td>NVP-LDE225</td>
<td>SMO</td>
<td>Tumor regression, regrowth</td>
<td>Phase I</td>
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<tr>
<td>Ptch1+/−; p53+/−</td>
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<td>SMO</td>
<td>Tumor regression</td>
<td>Phase II</td>
</tr>
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<td>Ptch1+/−; p53+/−</td>
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<td>SMO</td>
<td>Tumor regression; regression of GDC-0449 resistant tumors</td>
<td>Preclinical</td>
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<td>Histone deacetylase</td>
<td>Increased apoptosis</td>
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<td>DNA methylating agent</td>
<td>Prevented tumors, prolonged survival when combined with VPA</td>
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<td>Preclinical</td>
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<td>HGF</td>
<td>Prolonged survival</td>
<td>Preclinical</td>
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histone deacetylase inhibitors suberoylanilide hydroxamic acid [127] and valproic acid [128]. Lastly, other classes of compounds not targeting the SHH pathway have been reported to be effective in treating SHH-associated tumors. In a model driven by Ptch1 and p53 mutations, IGF signaling was found to be upregulated, and accordingly, picropodophyllin, an inhibitor of IGF1R tyrosine phosphorylation, effectively inhibited proliferation of tumor cells isolated from the murine tumors [129]. In the SmoAl mouse model, tumors were found to concurrently upregulate the NOTCH pathway along with the SHH pathway. Inhibition of NOTCH signaling using soluble Delta ligand or gamma-secretase inhibitors could decrease proliferation and induce apoptosis in vitro, suggesting that SHH tumors that exhibit concurrent NOTCH activation may be effectively treated by targeting the NOTCH pathway [60]. Lastly, in the RCAS/tv-a SHH + HGF model, HGF neutralizing antibody L2G7 was more effective than SHH antagonists in increasing median survival time, suggesting potential use of HGF-targeted therapy for patients with elevated HGF levels [92, 130].

Conclusion

The development and use of relevant mouse models that closely reflect human medulloblastoma is critical to understand malignant progression in this disease and to test developmental therapeutics. Extensive progress has been made in modeling SHH tumors, with inhibitors of SHH signaling now entering clinical trials. Follow-up studies are critical to examine the mechanisms of resistance to these drugs, so that newer, more effective drugs can be developed. As WNT antagonists become available, it will be important to test the efficacy of these drugs in animal models of WNT-associated medulloblastoma. Finally, additional studies are needed to identify the drivers of non-SHH and non-WNT tumors (which comprise approximately half of all cases), so that models can be developed for these tumors as well. With robust animal models for each subtype of medulloblastoma, it should be possible to develop appropriate targeted therapies that eradicate tumor cells while sparing patients the devastating side effects of conventional radiation and chemotherapy.

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