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Molecular mechanisms and therapeutic targets in pediatric brain tumors

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Brain tumors are among the leading causes of cancer-related deaths in children. Although surgery, aggressive radiation, and chemotherapy have improved outcomes, many patients still die of their disease. Moreover, those who survive often suffer devastating long-term side effects from the therapies. A greater understanding of the molecular underpinnings of these diseases will drive the development of new therapeutic approaches. Advances in genomics and epigenomics have provided unprecedented insight into the molecular diversity of these diseases and, in several cases, have revealed key genes and signaling pathways that drive tumor growth. These not only serve as potential therapeutic targets but also have facilitated the creation of animal models that faithfully recapitulate the human disease for preclinical studies. In this Review, we discuss recent progress in understanding the molecular basis of the three most common malignant pediatric brain tumors—medulloblastoma, ependymoma, and high-grade glioma—and the implications for development of safer and more effective therapies.

Introduction

The last several decades have seen major advances in the treatment and care of children with cancer (1). Among children younger than 15 years, 5-year survival rates for tumors of the central nervous system (CNS) have increased from 57% in 1977 to 75% in 2007 (1, 2). Nonetheless, CNS tumors remain the leading cause of cancer-related morbidity and mortality in children, due to therapeutic resistance and severe side effects. Consequently, risk stratification and reduction of side effects have become important goals in current clinical trials (3). Integrated genomic analyses have provided unprecedented insight into the etiology of CNS tumors and have begun to pave the way toward targeted therapy. In this Review, we highlight recent advances in genetics, epigenetics, animal models, and potential therapeutics for pediatric brain tumors, focusing on medulloblastoma, ependymoma (EPN), and high-grade glioma (HGG).

Medulloblastoma

Medulloblastoma (MB) is a highly malignant tumor of the cerebellum (4). With surgery, radiotherapy, and high-dose chemotherapy, the 5-year survival rate for MB is reaching 75 to 85% (5). However, although survival has improved significantly, the effects of therapy on neurocognitive and neuroendocrine function are devastating (6). Therefore, more effective and less toxic therapies are urgently needed for this disease.

Historically, MB has been classified on the basis of histology and clinical characteristics. In this scheme, patients with large cell or anaplastic tumors, those who are less than 3 years old at the time of diagnosis, and those who have had incomplete resection or exhibit leptomeningeal metastasis are considered to be at high risk (5, 7). However, recent studies have suggested that MB can also be divided into

molecular subgroups—WNT, Sonic hedgehog (SHH), group 3, and group 4—each characterized by distinct genetic alterations, clinical features, and outcomes (Table 1) (8, 9). These molecular subgroups appear to be more powerful predictors of patient outcome than histology (9, 10). For example, almost all patients with WNT tumors survive after current therapy, whereas those with group 3 tumors are much more likely to relapse and die of their disease. In addition, because each molecular subgroup is associated with distinct oncogenic drivers (Fig. 1), it is likely that subgroup identity will dictate responsiveness to therapy. For these reasons, many investigators view MB subgroups as distinct diseases that should be studied and treated as such. Recent advances in our understanding of these subgroups are discussed below.

WNT subgroup

WNT-associated MB (WNT-MB) occurs most frequently in children >3 years of age and is equally common among males and females (9). More than 95% of WNT-MB patients will survive for more than 5 years (5, 9), making this the subgroup with the most favorable prognosis. However, the survival rate of adults with WNT-MB is worse than that of children with this disease (11), suggesting that additional therapeutic approaches may still be necessary. WNT-MB is rarely metastatic (8, 9) and is the only subgroup in which metastasis is not prognostic (10). Cytogenetically, WNT-MB lacks focal somatic copy number aberrations (SCNAs) and frequently harbors monosomy of chromosome 6 (9, 12). Because of the favorable outcomes associated with WNT-MB, β -catenin status and monosomy 6 have been used as biomarkers of favorable prognosis across all subgroups of MB (10, 13–15). In addition, although somatic *Trp53* mutations are found most frequently in WNT-MB, they have little prognostic significance in this subgroup. Therefore, subgroup identity remains the major predictor of prognosis for WNT-MB (16).

The notion that some MBs result from activation of WNT signaling was initially based on the recognition that individuals with Turcot syndrome [a hereditary disorder associated with mutations in the adenomatous polyposis coli (*APC*) gene, a negative regulator of WNT signaling] had an increased incidence of MB (17). Subsequently, it was discovered that a subset of sporadic MBs harbored mutations in components of the WNT pathway, particularly *CTNNB1* (encoding β -catenin) (13, 14, 18–24). β -Catenin promotes transcription of WNT target genes by recruiting multiple chromatin modifiers, including histone acetyltransferases,

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CREBBP, and *SMARCA4*. Notably, mutations in these genes are also found in WNT-MB (24). Furthermore, whole-genome sequencing (WGS) has revealed that *CTNNB1* mutations often co-occur with mis-sense mutations in the DEAD-box RNA helicase *DDX3X* (24, 25).

WNT-MB is believed to originate from progenitor cells in the lower rhombic lip, with the resulting tumors often developing adjacent to the cerebellum in the dorsal brainstem (26). Consistent with this, preoperative magnetic resonance imaging in patients reveals

Table 1. MB molecular subgroups. Summary of key features of the four subgroups of MB, defined on the basis of gene expression and DNA methylation. LCA, large cell/anaplastic; DNMB, desmoplastic/nodular medulloblastoma; SVZ, subventricular zone; NSC, neural stem cell; RT, radiotherapy.

	WNT	SHH	Group 3	Group 4
Demographics				
Percentage of cases	~10%	~30%	~25%	~35%
Age distribution				
Gender Ratio				
Clinical features				
Histology	Classic; rarely LCA	Classic; DNMB; LCA; MBEN	Classic; LCA	Classic; rarely LCA
Incidence of metastasis	5–10%	10–15%	40–45% (50% in infants)	35–40%
Prognosis/5-year survival	Very good/>95% (80% in adults)	Intermediate/~75%	Poor/50%	Intermediate/~70% (20% in adults)
Diagnostics	Nuclear β -catenin; <i>CTNNB1</i> mut; monosomy 6; <i>DKK</i> exp	<i>SFRP1</i> , <i>YAP1</i> exp; 9q loss; <i>GLI2</i> amp	<i>NPR3</i> exp; <i>MYC</i> amp	<i>KCNA1</i> exp
Risk stratification biomarkers	monosomy 6 (subgroup-driven)	<i>GLI2</i> amplification; 14q loss; metastatic status	<i>MYC</i> amplification; Iso17q; metastatic status; <i>FSTL5</i> exp	11 loss or 17 gain; metastatic status; <i>FSTL5</i> exp
Genomic features				
Cytogenetics	chr 6 loss	chr 3q, 9p gain; 9q, 10q, 14q, 17p loss	chr 1q, 7, 17q, 18 gain; 8, 10q, 11, 16q, 17p loss; iso17q	chr 4, 7, 17q, 18 gain; 8, 10, 11, 17p, X loss; iso17q
Mutations (SNVs or indels)	<i>CTNNB1</i> , <i>DDX3X</i> , <i>SMARCA4</i> , <i>TP53</i> , <i>KMT2D</i> , <i>CNSK2B</i> , <i>CREBBP</i> , <i>MLL2</i>	<i>PTCH1</i> , <i>SMO</i> , <i>SUFU</i> , <i>MLL2</i> , <i>DDX3X</i> , <i>KMT2D</i> , <i>TP53</i> , <i>BCOR</i> , <i>LDB1</i> , <i>NCOR2</i> , <i>TCF4</i> , <i>GABRG1</i>	<i>SMARCA4</i> , <i>MLL2</i> , <i>SPTB</i> , <i>CTDNEP1</i> , <i>LRP1B</i> , <i>TNXB</i> , <i>GPS2</i>	<i>KDM6A</i> , <i>MML3</i> , <i>HDAC2</i> , <i>ZMYM3</i> , <i>CBFA2T2</i> , <i>CTDNEP1</i>
Somatic copy number alterations	No recurrent alteration	<i>GLI1/2</i> , <i>MYCN</i> , <i>CCND2</i> amplification; <i>PTCH1</i> , <i>TP53</i> deletion	<i>MYC</i> , <i>OTX2</i> amplification; <i>PVT1-MYC</i> fusion	<i>SNCAIP</i> duplication; <i>MYCN</i> , <i>CDK6</i> , <i>OTX2</i> amplification
Pathways	WNT signaling	SHH signaling	Photoreceptor/GABAergic; <i>MYC</i> and <i>TGFβ</i> signaling	Neuronal; glutamatergic; <i>NFκB</i> signaling
Biology				
Cell of origin	Lower rhombic lip progenitors; mossy-fiber neuron precursors	Cerebellar GNP of EGL; NSC in SVZ; brainstem progenitors	Prominin 1 ⁺ Lineage ⁻ NSCs; cerebellar GNP	Not yet determined
Mouse models	1. <i>Blbp-Cre:: Ctnnb1(ex3)^{Flx/+} Trp53^{Flx/Flx} Ptk3ca^{E545K}</i>	1. <i>Ptch^{+/-}</i> 2. <i>Ptch^{+/-}; Trp53^{+/-}</i> 3. ND2-Smoa1 4. Atoh1/GFAP/Nestin-Cre; <i>Ptch1^{flx/flx}</i> 5. Atoh1-SB11; <i>T2Onc; Ptch1^{+/-}</i>	1. <i>Myc^{T58A}/Dnp53</i> (MP)-transformed NSCs; cerebellar transplant 2. <i>Myc</i> -transformed <i>Trp53^{-/-}</i> GNP; cerebellar transplant 3. <i>Myc^{T58A}/Gfi1</i> or <i>Gfi1b</i> (MG)-transformed NSCs; cerebellar transplant 4. <i>Glit-tTA::TRE-Mycn; Luc</i> (GTML)	None
Therapeutics				
Targeted agents	1. De-escalation of therapy (reduced RT/chemotherapy) 2. WNT antagonists	1. SMOis 2. <i>GLI1/2</i> inhibitors 3. Bromodomain inhibitors 4. <i>MYCN</i> destabilizing agents 5. <i>PI3K</i> inhibitors 6. Aurora and Polo-like kinase inhibitors	1. Pemetrexed and gemcitabine combination 2. Bromodomain inhibitors 3. <i>HDAC</i> inhibitors and <i>PI3K</i> inhibitors	1. <i>MYCN</i> inhibitors 2. <i>CDK</i> inhibitors 3. Bromodomain inhibitors 4. Epigenetic modulators

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that WNT-MBs are almost always in contact with the brainstem and the fourth ventricle (27, 28). Activation of *Ctnnb1* in granule neuron precursors (GNPs) does not lead to tumorigenesis in mice; in contrast, *Ctnnb1* activation in *Blbp*-expressing cells in the dorsal brainstem of mice interrupts cell migration and, in conjunction with deletion of *Trp53*, results in tumors that resemble human WNT-MB (26, 29). Incorporation of a mutation in *Pik3ca*, which encodes the catalytic subunit of phosphoinositide 3-kinase (PI3K), increases tumor penetrance and decreases latency (24, 30), resulting in a model that is potentially useful for preclinical studies.

In light of the favorable prognosis of WNT-MBs, current clinical trials are focused on de-escalation of radiation or chemotherapy in the hope of lessening long-term side effects (31). Notably, it has been suggested that WNT signaling itself might contribute to the remarkable response of WNT-MB to standard therapy (32). Moreover, a recent study suggests that secretion of soluble WNT antagonists by these tu-

mors may impair the blood-brain barrier, rendering tumors more susceptible to chemotherapy (33). If this is the case, activating similar pathways in non-WNT tumors could sensitize them to therapy as well.

SHH subgroup

SHH-MB patients have a 5-year survival rate of 75%, worse than WNT patients but more favorable than patients from group 3. Similar to WNT-MB, the gender distribution for SHH-MB is roughly even. However, in contrast to WNT-MB, most SHH-MB patients are infants or adults; relatively few children present with this tumor subtype. Cytogenetically, the genome of SHH-MB contains significantly more SCNAs than WNT-MB.

The role of SHH signaling in MB was first recognized in the context of Gorlin syndrome, a hereditary disease characterized by basal cell carcinomas of the skin, craniofacial abnormalities, and an increased incidence of MB (34). Gorlin patients harbor germline mutations in

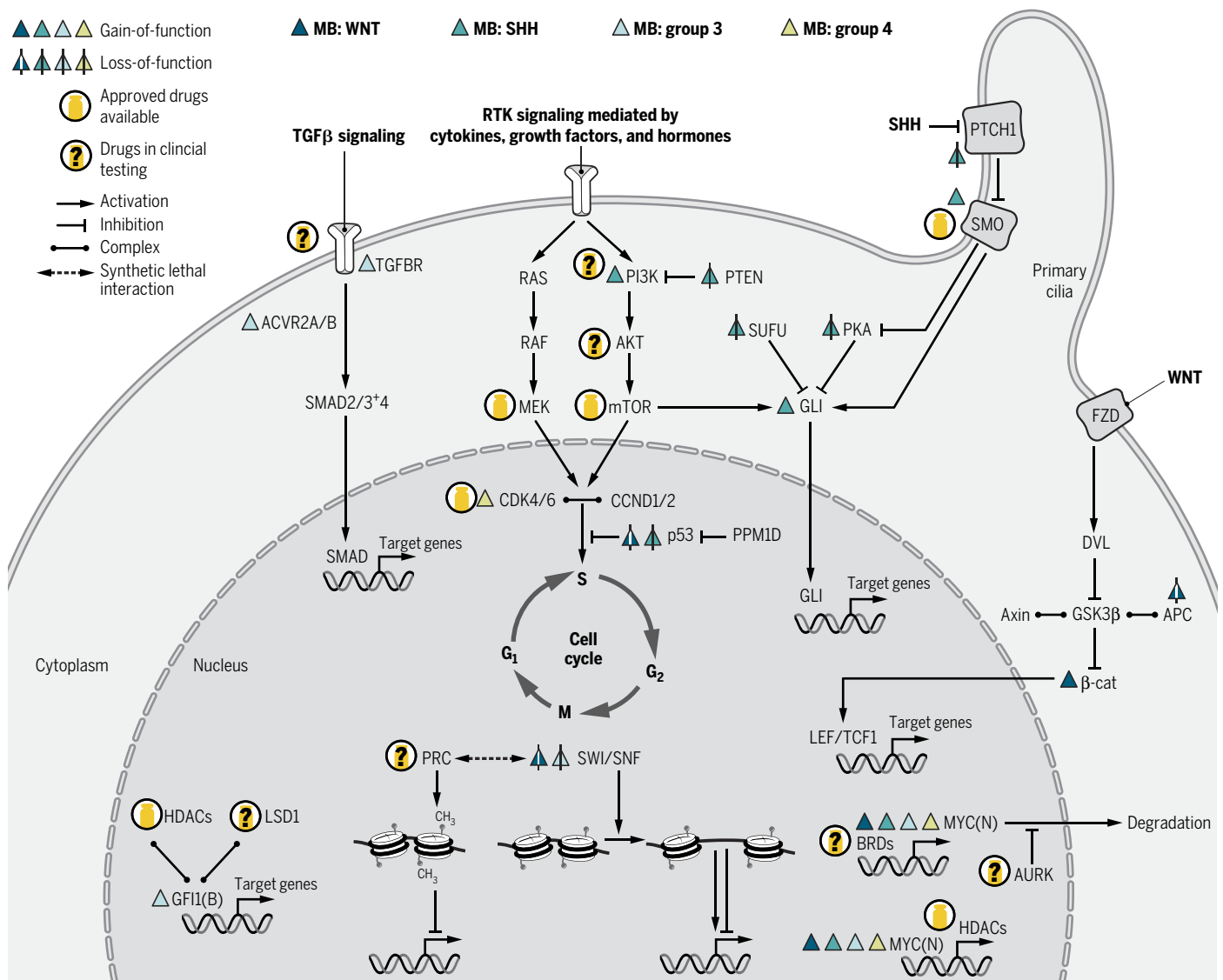


Fig. 1. Synopsis of signaling pathway alterations and potential drug targets in molecular subgroups of pediatric MB. Gain- or loss-of-function aberrations in pathway components that have been identified within distinct molecular subgroups of MB. Candidates for targeted therapy are indicated, including information on the current developmental stage of potential drugs.

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PTCH1, a negative regulator of the SHH pathway (34, 35). Germline mutations in the gene encoding Suppressor of Fused (*SUFU*), another negative regulator of the pathway, also predispose to SHH-MB (36–38). In addition, sporadic MBs in the SHH subgroup exhibit loss-of-function mutations in *PTCH1* (39, 40) and *SUFU* (38), activating mutations in Smoothed (*SMO*) (41) and amplifications of *SHH*, *GLI2*, and *MYCN* (42). Mutations in SHH pathway genes are usually mutually exclusive and are found in an age-dependent manner: *PTCH1* mutations occur across all age groups, *SUFU* mutations are found mostly in infants, *SMO* mutations are mainly found in adults, and *MYCN* and *GLI2* amplifications are mainly found in children >3 years old (42). Mice with mutations in *Ptch1*, *Smo*, *Sufu*, and *Gli2* are also predisposed to MB, supporting the role of these genes as drivers of tumorigenesis (43–49).

A subset of SHH-MB patients—particularly older children and teenagers—exhibits extensive shattering of one or more chromosomes known as “chromothripsis” (50). Using WGS, Rausch *et al.* (50) found that these patients usually carry somatic or germline *TP53* mutations, the latter being associated with Li-Fraumeni syndrome (LFS). Chromothripsis can result in amplification of SHH pathway genes such as *GLI2* and *MYCN*, which increase the expression of SHH target genes and drive aggressive tumor growth (50). Because patients with LFS are thought to be at increased risk for radiation-induced malignancies (51, 52), it is important to take into account *TP53* status—and consider avoiding radiotherapy—when planning treatment for patients with SHH-MB (42).

The cell of origin for SHH-MB was debated for years, but most recent studies suggest that these tumors arise from GNP. In support of this notion, *Ptch1* mutant mice develop preneoplastic lesions in the external granule layer (EGL), where GNPs arise (53, 54). Moreover, deletion of *Ptch1* or activation of *Smo* in GNPs (using an *Atoh1*-driven Cre recombinase) results in MB in mice (44, 45). Notably, activation of the pathway in multipotent stem cells also causes tumors, but only after the targeted cells have committed to the granule lineage. Other cells that have been shown to give rise to SHH-MB in mice include *Atoh1*-expressing cells in the cochlear nuclei of the brainstem (55) and *Nestin*-expressing progenitors in the neonatal cerebellum, which are distinct from conventional GNPs but also give rise to granule neurons and are highly susceptible to transformation after SHH pathway activation (56).

The advent of small-molecule antagonists of the SHH pathway has opened up new opportunities for treatment of this subgroup of tumors (57, 58). In particular, SMO inhibitors (SMOis), such as NVP-LDE225 (erismodegib) and GDC-0449 (vismodegib), have been associated with significant (albeit often transient) responses in MB patients in clinical trials (59–61). In some cases, failure to exert long-term therapeutic effects is attributable to mutations in *SMO* itself (62, 63); in other cases, mutations in downstream elements of the SHH pathway (for example, *GLI2* or *MYCN* amplifications) or in other pathways may render tumor cells insensitive to these drugs (42, 63, 64). These genetic alterations may be present before treatment or may emerge after SMOi exposure (63). In either case, drugs with distinct mechanisms of action must be considered. These include agents that act on other regions of the *SMO* molecule, on downstream elements of the SHH pathway, or on other pathways that contribute to disease. Examples of second-site SMOis include the antifungal agent itraconazole and the cyclopamine derivative IPI-926 (saridegib), both of which have shown promise in preclinical studies (65, 66). Inhibitors of downstream components of the SHH pathway include arsenic trioxide, which can promote *GLI2* degradation (65); bromodomain inhibitors, which not only reduce expression and transcriptional activity of the SHH target *MYCN* (67) but

also impair the function of *GLI1* and *GLI2* (68); and Aurora kinase A inhibitors, some of which can impair cell cycle progression as well as destabilize *MYCN* (69–71). The observation of increased PI3K pathway activity in tumors that develop resistance to SMOis (63, 64), along with reports of recurrent mutations affecting this pathway (12, 42), has suggested that PI3K inhibition may be an important strategy for preventing or overcoming resistance of SHH-MB. Finally, preclinical studies have suggested that Polo-like kinase inhibitors may be particularly effective in SHH-MB (71, 72). The heterogeneity of driver mutations and resistance mechanisms even within the SHH-MB subgroup suggests that careful patient selection and a diversity of therapeutic approaches will be necessary to effectively target this disease.

Group 3

Group 3 MB (G3-MB) accounts for ~25% of MBs and has the worst prognosis among the subgroups. Nearly half of G3-MB patients have metastases at the time of diagnosis, the highest among all subgroups. G3-MB occurs more frequently in males than in females and includes a higher proportion of infants and young children than adults (8, 9). Most G3 (and G4) MBs grow in the midline in proximity to the fourth ventricle or in contact with the brainstem (27, 28); it is possible that this location facilitates access to cerebrospinal fluid and contributes to increased metastasis.

Unlike WNT-MB and SHH-MB, there are no known germline mutations that predispose to G3-MB. However, these tumors frequently exhibit SCNAs. The most prominent of these is amplification of the *MYC* oncogene, which occurs in 17% of G3-MB patients (12, 20, 21). Among *MYC*-amplified tumors, about 60% harbor a fusion between *MYC* and plasmacytoma variant translocation 1 (*PVT1*), a long non-coding RNA cluster on chromosome 8. Although the functional significance of the *PVT1*-*MYC* fusion transcript remains unclear, the *PVT1* RNA has been suggested to help stabilize the *MYC* protein (12, 73). Gain of both *MYC* and *PVT1* occurs in more than 98% of *MYC*-amplified tumors across all cancer types. Thus, targeting *PVT1* may represent an alternative or additional strategy to targeting *MYC* itself (73), which is notoriously challenging to target. G3- and G4-MBs also frequently exhibit amplification of *OTX2* (*orthodenticle homeobox 2*); this is mutually exclusive with *MYC* amplification and has been suggested to promote tumor formation by up-regulating *MYC* expression (74). Finally, amplifications and deletions that dysregulate the transforming growth factor- β (TGF β) signaling pathway are found in 20% of G3-MBs (12), suggesting that this pathway might be a promising target for therapy.

G3-MBs rarely show recurrent somatic single-nucleotide variants (SNVs) or small insertions/deletions (indels) (25, 75); rather, most exhibit chromosomal instability, characterized by abundant SCNAs. This suggested the possibility of a catastrophic genomic event mimicking the chromothripsis seen in SHH-MB, but to date, the only such events reported have been restricted to the *MYC* locus, leading to *PVT1*-*MYC* fusions (24, 25, 50, 75). While investigating genome-wide somatic mutation allele frequencies, Jones *et al.* showed that G3- and G4-MB frequently acquire tetraploid genomes at early stages of tumor development, leading to chromosomal instability (75) and possibly rendering cancer cells resistant to chemotherapeutic agents (76). On the basis of these findings, it may be worth considering therapies that target the vulnerabilities of tetraploid cells, such as inhibitors of mitotic checkpoint kinases or kinesins (75).

The genomic instability in G3-MB is also associated with gains and losses of chromosomes. One common event in both G3- and G4-MB is concurrent loss of 17p and gain of 17q (termed “isochromosome” 17q

or i17q) (24, 25, 75). MB patients with i17q fare worse than those without the aberration, and i17q is one of the most powerful prognostic biomarkers for G3-MB patients (9, 10). Early studies suggested that i17q resulted in loss of a tumor suppressor gene [such as *TP53* or the C-terminal domain nuclear envelope phosphatase 1 (*CTDNEP1* or *DULLARD*)] on 17p (75, 77) and gain of an oncogene (such as *WIP1*) on 17q (78). In addition, various chromatin remodeling genes on chromosome 17 have also been implicated in i17q MBs (24, 25). Whether i17q represents a driver event in tumorigenesis and which oncogenes and tumor suppressors are targeted by this alteration clearly warrant further investigation. MBs with i17q have significantly lower *TP53* expression than can be explained by the 17p loss alone, suggesting that the i17q target genes may converge on dampening *TP53* signaling (79).

In addition to chromosome 17, a recent study identified structural variants (SVs) including deletions, inversions, tandem duplications, amplifications, and other complex rearrangements on chromosome 9 (80). These events lead to juxtaposition of the growth factor independence 1B (*GFI1B*) gene with highly active enhancer elements (“super-enhancers”), resulting in increased expression of the *GFI1B* gene. Likewise, the gene encoding *GFI1*, a paralog of *GFI1B*, exhibits SVs that result in its activation in a subset of tumors (mutually exclusive with those exhibiting activated *GFI1B*). Together, *GFI1/1B* are activated in at least one-third of G3-MBs (80). In mouse models of acute lymphoblastic leukemia, *Gfi1* restricts p53 activity by repressing its proapoptotic targets (81, 82). In hematopoietic cells, *Gfi1/1b* recruit the corepressor CoREST, the histone demethylase LSD1, and histone deacetylases (HDACs) 1 and 2 to target promoters involved in lineage differentiation (83). Further studies will be necessary to identify the mechanisms by which *GFI1/1B* promote MB and to determine whether HDACs or LSD1 represent therapeutic targets in patients with *GFI1/1B* activation.

Genetically engineered mouse models (GEMMs) of G3-MB have recently been generated by orthotopic transplantation of cerebellar progenitors expressing *Myc* and a dominant-negative form of *Trp53* (*DNp53*) (hereafter called MP) (84) or by transplantation of *Trp53*^{-/-}/*Cdkn2c*^{-/-} progenitors that have been engineered to overexpress *Myc* (85). Combined *MYC* and *TP53* defects have been found in patients with relapsed MB (70), and thus, these mouse models may represent valuable tools for studying recurrent tumors. Because *TP53* aberrations have not been found in newly diagnosed G3-MBs, the search has begun for alternative “second hits” that can cooperate with *Myc* to drive tumorigenesis in mice. To date, the only genes known to do so are *Gfi1* and *Gfi1b* (80). Progenitors overexpressing *Myc* and *Gfi1* or *Gfi1b* can also give rise to tumors that resemble G3-MB (80), and these may be useful for studying the pathogenesis and therapeutic responsiveness of this subgroup of tumors.

To identify novel therapies for G3-MB, Morfouace *et al.* performed a high-throughput screen on neurospheres generated from their model of G3-MB (85, 86). This study identified two U.S. Food and Drug Administration–approved drugs—pemetrexed and gemcitabine—that suppress growth of murine and human G3-MB. Although these drugs prolonged survival of tumor-bearing mice, animals eventually succumbed, in part because of changes in the microenvironment that rendered tumors insensitive to the drugs (86). The MP mouse model has also been used for high-throughput drug screening (87). These studies demonstrated that the pan-HDAC inhibitor panobinostat was highly effective against G3-MB and cooperated with a PI3K inhibitor, BKM-120 (buparlisib), to block growth of murine and human G3-MB cells in vitro and in vivo. Other strategies for treating G3-MB have focused on the *MYC* proteins that are overexpressed in these tumors. Although *MYC* itself is often considered “undruggable,” recent studies have sug-

gested that its expression and transcriptional activity can be targeted with inhibitors of bromodomain proteins, which function as “readers” of acetylated lysines on open chromatin (88). Treatment of *MYC*-amplified human and mouse MBs with the bromodomain inhibitor JQ1 arrested cell cycle at the G₁ stage, induced apoptosis, and prolonged survival of tumor-bearing mice (67). Bromodomain inhibitors are currently in trials for other cancers and, based on their activity in preclinical models of both SHH-MB and G3-MB (67, 68, 89), are being considered for treatment of MB as well.

Group 4

G4-MB is the most prevalent MB subgroup, accounting for more than a third of all cases, with about threefold more male than female patients. Metastasis is almost as common in this subgroup as in G3, with 35 to 40% of patients showing metastasis at the time of diagnosis. Pediatric G4-MB patients have an intermediate survival rate, whereas adult patients often show a poor prognosis (11). Like G3-MB, G4-MBs are usually found adjacent to the fourth ventricle (27).

G4-MB is the least understood of the MB subgroups; because the most common molecular aberrations are found in only a small fraction of cases, little is known about the critical genetic driver events (90). However, there are some important similarities between G3- and G4-MB. Rather than *MYC* amplification, a subset G4-MBs harbor amplicons of *MYCN* (8). Likewise, i17q aberrations are even more common in G4-MB than in G3-MB. Most of the G4-MBs also exhibit chromosomal instability that causes prevalent SCNAs, which might result from tetraploidization (91). Some of the genes that are recurrently mutated or altered in copy number in G4-MBs overlap with those in G3-MBs (21, 91).

In addition to these shared events, there are some genetic alterations that are more specific to G4-MB. The most frequent SCNA found in G4-MB (and not in G3-MB) is a tandem duplication resulting in a gain of the *SNCAIP* gene, which encodes Synphilin 1, a protein important in promoting Lewy body formation in patients with Parkinson’s disease (92). This alteration defines a subtype within G4-MB, group 4 α (G4 α -MB), that exhibits a relatively balanced genome. G4 α -MBs frequently harbor i17q but no other SCNAs, whereas G4 β -MBs more commonly exhibit amplification of *MYCN* or *CDK6* (12). G4-MBs also have mutations in *KDM6A*, *MLL3*, *ZMYM3*, *CBFA2T2*, and *CTDNEP1*; however, almost all of these aberrations are found in <10% of all G4-MB cases (12, 24, 25, 75, 93, 94). G4-MBs have been reported to exhibit SCNAs affecting nuclear factor κ B (NF- κ B) signaling, suggesting that this pathway might represent a potential therapeutic target for G4-MB (12).

Although the cell of origin for G4-MB is unknown, genomic and epigenomic data provide some clues. G4 tumors have a gene signature resembling that of glutamate-secreting neurons (20), suggesting that they may arise from glutamatergic progenitors. Moreover, recent analysis of gene expression, histone acetylation, and DNA methylation indicates that the transcription factors *LMX1A*, *EOMES*, and *LHX2* are highly expressed in G4-MB and may function as master regulators in these tumors (95). During development, these factors are restricted to the nuclear transitory zone (NTZ), which generates glutamatergic projection neurons in the deep cerebellar nuclei. These studies suggest that the NTZ may represent the origin of G4-MB.

To date, there is no confirmed animal model for G4-MB. Targeted expression of human *MYCN* in glutamate transporter 1 (*Glt1*)–expressing cells generated tumors that were initially suggested to model G4-MB (96, 97), but subsequent genomic analysis has suggested that these tumors may more closely resemble G3-MB (70). Because G4-MBs have few recurrent SNVs and indels and frequently harbor i17q

or other chromosomal changes (12, 91), it is likely that multiple genetic driver events are necessary for initiation of this disease. This presents a challenge for investigators attempting to model the disease using conventional genetic approaches. However, newer genome-editing technologies may facilitate development of animal models that recapitulate the genetic aberrations seen in human G4-MB.

In the absence of clear driver mutations, there are few candidate therapeutics for G4-MB. For the subset of tumors that exhibit amplification of *CDK6* and *MYCN*, cyclin-dependent kinase (CDK) inhibitors, bromodomain inhibitors (67), and *MYC/MYCN*-destabilizing Aurora kinase A inhibitors (69) may be worth exploring. In addition, because multiple aberrations affecting histone modifiers have been found in these tumors (98), drugs that target epigenetic regulators could also represent a viable option. Consistent with this, HDAC inhibitors have shown some efficacy in G4-MB patient-derived xenograft (PDX) lines (87). Although the absence of a faithful animal model that mimics human G4-MB has hindered the development of therapeutic strategies against tumors of this subgroup, the finding that G3- and G4-MBs share overlapping genetic alterations suggests that drugs targeting G3-MB might also represent candidate therapeutics for at least a subset of G4-MBs.

Epigenetic regulation in MB

With recent advances in technologies to interrogate the epigenome, it has become clear that epigenetic changes are common in MB and may constitute an important class of drivers for the disease (12, 24, 25, 75, 94, 99). Among the most frequent mutations in MB are those that affect genes that alter histone methylation. Examples are those that result in generation of trimethylated histone 3 lysine 4 (H3K4me3), such as truncating mutations in the methyltransferases *MLL2* and *MLL3* (94, 100); those that cause hypomethylation of histone 3 lysine 9 (H3K9) such as the acetyltransferase *MYST3*, the methyltransferases *EHMT1* and *SMYD4*, the demethylases *JMJD2B* and *JMJD2C*, and several polycomb group (PcG) genes (101); and those leading to accumulation of trimethylated histone 3 lysine 27 (H3K27me3), such as mutations in trithorax group genes, *KDM6A* (also known as *UTX*) and *KDM6B*, which are found mostly in G4-MB (24, 94, 102). Overexpression of the PcG protein EZH2 is also commonly seen in G3- and G4-MBs (24) and is thought to promote stem cell maintenance by repressing lineage differentiation genes (103).

Although the mechanisms by which these histone modifications mediate pathogenesis of MB remain largely elusive, some evidence suggests that their net effect is to shift the balance between H3K27 and H3K4 methylation, resulting in silencing of genes responsible for progenitor cell differentiation (98, 100, 102). Suppressing H3K27me3 by silencing the homeobox gene *OTX2* leads to a differentiated phenotype in MBs (104, 105). Whether the presence of “repressive” heterochromatin (high H3K27me3 and low H3K4me3) in G3- and G4-MBs reflects the epigenetic status of the tumor-initiating/propagating cells that generate these tumors, or whether it is a consequence of mutations in the genes that regulate these modifications, requires further investigation.

In addition to histone modifications, MBs contain unique changes in DNA methylation. Hovestadt *et al.* (99) reported that in WNT- and G3-MBs, partially methylated domains (PMDs) correlate with decreased gene expression, and the presence of the repressive histone marks H3K9me3 and H3K27me3 (101, 102). PMDs are also associated with increased mutation rates that might result in driver mutations early in tumorigenesis. Smaller, more localized, hypomethylated regions called

DNA methylation valleys (DMVs) are prevalent in all subgroups. In some cases, DMVs show a positive correlation with gene expression, for example, the region around the *FOXG1* gene, which is frequently gained in G3- and G4-MBs (106). In other cases, there is a negative correlation, such as the region around *OTX2*, which is strongly hypomethylated and overexpressed in WNT-, G3-, and G4-MBs (12, 74). Analysis of localized hypomethylated regions further revealed an interesting link between these regions and binding of transcription factors that might be responsible for subgroup-specific signature gene expression and tumorigenesis (99). Methylation analysis not only has provided insight into the mechanisms of altered gene expression in MB but also has become an important tool for subgrouping and risk stratification (107), complementing the widely used genetic profiling approaches (8). Further studies will be necessary to understand the interplay between epigenetic and genetic events, and the functional significance of these alterations in tumorigenesis (95).

The epigenome is controlled by enzymatic processes that represent potential targets for therapeutic intervention. Strategies to modulate the epigenetic dysregulation associated with cancer have been a major focus for drug development in the past few years. Among the best examples of drugs that can reprogram the epigenome are HDAC inhibitors, which have shown activity in a number of different cancers. Recent studies have revealed that G3-MB may be particularly sensitive to these drugs (87), particularly to small molecules that target class I HDACs (HDACs 1, 2, 3, and 8) (108, 109). In addition to HDAC inhibitors, therapeutic agents targeting histone methylation have also been developed. For example, inhibition of the polycomb repressive complex 2 (PRC2) protein EZH2 has been shown to decrease global H3K27me3 and has shown some promise in preclinical models of MB (110, 111). These are just the first epigenetic modulators to be evaluated in MB; as additional drugs become available and as our understanding of the epigenome of MB increases, we can expect to see increased interest in this approach to therapy.

Ependymoma

EPN is a tumor of the CNS that occurs in both children and adults (112). About 40% of cases remain incurable due to the paucity of effective treatment options (112–115). EPN can arise almost anywhere along the neuraxis, including the supratentorial region (cerebral hemispheres), the posterior fossa (cerebellum and brainstem), and the spinal cord (116). In children, 90% of EPNs occur intracranially, with two-thirds located in the posterior fossa (117). The clinical behavior of EPN is highly variable, with some patients experiencing a rapidly fatal clinical course and others harboring relatively slow-growing variants that may recur years after primary treatment (112, 118, 119). Especially in younger children, local tumor progression is one of the most important clinical problems, probably owing to both the anatomic location and the exclusion of young children from protocols involving adjuvant radiotherapy (112, 120–122). Ten-year overall survival is 64% in pediatric patients and ranges from 70 to 89% in adult patients (113). Tumors in infancy are associated with a particularly poor 5-year survival rate (42 to 55%) (123). Surgery and radiation are the current mainstays of treatment because standard chemotherapies are ineffective in most patients (114, 117). Notably, application of high-dose conformal radiotherapy after surgery, even in children <3 years of age, significantly improved event-free survival with tolerable toxicity, although long-term follow-up is still pending (114). Accurate histopathological diagnosis and tumor grading according to the World Health Organization (WHO) classification for CNS tumors are often challenging for ependymal tumors and

may produce divergent results if performed by different neuropathologists (124, 125). Furthermore, immunohistochemistry has thus far proved inadequate as a diagnostic tool to reliably distinguish between histological grades and subgroups of EPN.

Despite histopathological similarities among tumors, EPN molecular biology is heterogeneous, with diverse expression profiles and distinct genetic alterations (Fig. 2) (112, 126–130). A cross-species *in vivo* screen recently identified oncogenes and tumor suppressor genes located within recurrent copy number alterations in intracranial EPN. A number of these converged on dysregulation of trafficking of the growth factor receptors, FGFR (fibroblast growth factor receptor) and EGFR (epidermal growth factor receptor) (ERBB1), which are oncogenic in EPN (131). Unfortunately, a targeted therapeutic approach including lapatinib, a selective small-molecule inhibitor of ERBB1/ERBB2, recently proved to be ineffective in children with recurrent EPN (132). The lack of identified druggable targets, reasonable molecular tumor classification, and cell lines, xenografts, and animal models of the disease have so far hindered efforts to develop targeted therapies for EPN, in contrast to the situation for other intracranial neoplasms. A recent study based on DNA methylation profiles of 500 ependymal tumors across all age groups and histopathological grades identified nine molecular subgroups, three in each anatomical compartment of the CNS: spine (SP), posterior fossa (PF), and supratentorial (ST) (133). Analysis of clinical and demographic data revealed that the most high-risk patients are children restricted to just two of the subgroups, one within the posterior fossa (PF-EPN-A) and one in the supratentorial compartment (ST-EPN-RELA) (Table 2).

Posterior fossa EPN

Previous studies consistently identified two biologically distinct forms of primary EPN occurring in the posterior fossa, designated PF-EPN-A and PF-EPN-B (posterior fossa EPN groups A and B), which show a clear disparity in molecular characteristics, patient demographics, and clinical outcomes (120). PF-EPN-A patients are younger and more likely to die of their disease than PF-EPN-B patients. Their tumors are typically laterally located with a balanced genome and are more likely to recur and exhibit metastatic dissemination at recurrence. WGS and whole-exome sequencing of hindbrain EPNs revealed a very low mutation rate with no significant recurrent somatic SNVs (134, 135). Transcriptional silencing in PF-EPN-A tumors driven by CpG methylation converges on targets of the PRC2 complex, which repress the expression of genes involved in differentiation through trimethylation of the H3K27 histone mark. This spurred the hypothesis that PRC2 complex hyperactivity with subsequent gene silencing by DNA CpG hypermethylation causes tumor suppressor gene silencing and contributes to PF-EPN-A tumor pathogenesis (134). Mack *et al.* also used short-term, patient-derived primary cultures from PF-EPN-A EPNs to show that these tumors do respond to 3-deazaneplanocin A (DZNep), which causes PRC2 complex degradation, and to GSK343, a selective small-molecule inhibitor of EZH2 that competes with *S*-adenosyl-*L*-methionine binding (134, 136, 137). Treatment with the DNA methyltransferase inhibitor 5-*aza*-2'-deoxycytidine (decitabine) significantly reduced cell survival, accompanied by marked derepression of gene sets enriched for EZH2 targets and known DNA-hypermethylated genes in other solid cancers (134).

Supratentorial EPN

Parker *et al.* recently demonstrated that more than two-thirds of pediatric supratentorial EPNs harbor fusions between the gene encoding the principal effector of canonical NF- κ B signaling, *RELA*, and a previously

uncharacterized gene, *C11orf95*, resulting from chromothripsis (135). Novel EPN classification approaches based on genome-wide methylation analysis can reliably detect this important subgroup, termed ST-EPN-RELA, which is associated with a dismal prognosis (133). This suggests that a specific precursor cell population in the brain at a distinct time point during development might be particularly susceptible to this oncogenic insult. In contrast to wild-type *RELA*, the fusion protein translocates spontaneously to the nucleus where it activates L1CAM and other targets associated with NF- κ B signaling, which are known to drive aberrant cell-cell adhesion and invasion in tumor cells (135, 138). Parker *et al.* showed that *RELA* fusion proteins alone are sufficient to transform neural stem cells, which rapidly form tumors in mice after transduction with retroviruses containing the fusion construct.

Although the mechanisms by which *RELA* fusion proteins exert their oncogenic potential are not yet completely understood, it is clear that NF- κ B signaling represents a promising new therapeutic target for supratentorial pediatric EPNs. Milde *et al.* successfully established a human high-risk EPN stem cell model (DKFZ-EPINS) of the ST-EPN-RELA subgroup by *in vivo* transplantation of primary tumor cells into nonobese diabetic/severe combined immunodeficient mice (139). Cells derived from this model are intrinsically resistant to temozolomide, vincristine, and cisplatin, thus mimicking the broad chemoresistance of primary ependymal tumors. In clear contrast, EPINS cells are susceptible to a panel of HDAC inhibitors including panobinostat, entinostat, valproic acid, and vorinostat. Application of vorinostat at therapeutically achievable concentrations significantly impaired EPINS proliferation and self-renewal capacity and induced cell cycle arrest and neuronal differentiation (139). An integrated *in vitro* and *in vivo* high-throughput drug screen using another model of ST-EPN, deriving from murine neural stem cells with *Cdkn2a* deletion and overexpression of *Ephb2*, demonstrated that the chemotherapeutic agent 5-fluorouracil has selective toxicity against this model (127, 140). However, an early clinical study of 5-fluorouracil in a molecularly unselected cohort of children and young adults with recurrent EPN only reported limited response to the drug in these patients (141).

Most of the ST-EPNs that lack *RELA* fusions represent a separate molecular subgroup, termed ST-EPN-YAP1, which is characterized by a stable genome without chromothripsis and recurrent fusions to the gene encoding the main effector of the Hippo signaling pathway, *YAP1* (133, 135). Preliminary evidence from small retrospective cohorts indicates that these patients have an excellent prognosis. Although the exact function of these fusions remains to be investigated, it is highly likely that *YAP1* fusions comprise the oncogenic drivers in this distinct subgroup of ST-EPN. Ongoing efforts using mouse models of ST-EPN-RELA and ST-EPN-YAP1 to evaluate potential drugs hold promise for the development of targeted therapies for tumors with *RELA* or *YAP1* fusion proteins.

High-Grade Gliomas

Pediatric HGGs traditionally comprise glioblastoma [glioblastoma multiforme (GBM)], anaplastic astrocytoma, and diffuse intrinsic pontine glioma (DIPG). Collectively, HGGs are the most common malignant brain tumors in children and are estimated to occur in 0.8 per 100,000 children per year (113). GBM is classified as grade IV in the WHO classification scheme and characteristically displays high mitotic activity, extensive neovascularization, and intratumoral necrosis (116). In contrast to adults, the stepwise transformation from less-malignant (*IDH*-mutated) gliomas into GBM is very rare in children (142, 143).

DIPGs are high-grade tumors that histologically resemble malignant gliomas arising in other locations but show a diffusely infiltrative growth pattern within the brainstem (144–146). Patients with HGGs have a very dismal prognosis, with a 5-year survival of <5% for GBM patients and a median survival of <1 year for patients with DIPG, pointing to an urgent need for alternative therapeutic approaches (147, 148).

Even in cases where gross total surgical resection of newly diagnosed GBM is possible, its highly invasive nature means that microscopic residual lesions usually remain. Therefore, current standard treatment combines adjuvant radiotherapy together with chemotherapy (147–149). Methylation of the O⁶-methylguanine-DNA methyltransferase (MGMT) promoter is found in about 45% of GBMs occurring in adult patients, causing impaired DNA repair in response to alkylating agents such as temozolomide (150–157). MGMT promoter methylation is therefore used as a biomarker to predict responsiveness to temozolomide (153, 154, 157, 158). However, both the frequency and the predictive value of MGMT silencing in pediatric HGGs remain controversial, even after collectively more than 1000 children with HGG have been treated with temozolomide in multicenter trials (159–162). Temozolomide treatment itself has been linked with induction of inactivating mutations in DNA mismatch repair genes (such as *MSH6*), leading to a GBM hypermutator phenotype that may be linked to acquired treatment resistance (163–165). Surgery (other than stereotactic biopsy for diagnostic purposes and for the identification of potential molecular drug targets) is not an option for DIPGs because of their location within the brainstem, and, at present, radiotherapy represents the only current treatment showing a clear clinical benefit (166, 167).

To date, no targeted therapy or chemotherapy has provided a survival benefit for HGG patients when administered alone or in combination with other drugs (148, 168). However, these novel therapeutic approaches were almost exclusively tested in unselected GBM cohorts with no attempt at matching targets with drugs, which might have resulted in the rejection of drugs because trials failed to recruit adequate numbers of rationally selected, treatment-sensitive patients. Comprehensive molecular profiling

studies conducted in recent years have greatly extended our understanding of the underlying alterations associated with gliomagenesis (Fig. 3). Recurrent genomic and/or epigenomic aberrations in combination with distinct patient characteristics have allowed the identification of meaningful biological and clinical glioblastoma subgroups, indistinguishable by their histology, across the entire patient age continuum (169). Integrated genomic analyses by The Cancer Genome Atlas (TCGA) network have delineated four distinct adult GBM subtypes (proneural, neural, classical, and mesenchymal) that are associated with distinct gene expression patterns and genetic aberrations (170). Genome-wide DNA methylation profiling has further refined this classification to subdivide proneural GBMs into those having or lacking the glioma CpG island methylator phenotype (G-CIMP) (171). Sturm *et al.* recently identified six biological subgroups based on global DNA methylation patterns in a cohort comprising GBMs from adult and pediatric HGGs, designated (the overlap with TCGA methylation subclass affiliation is given in parentheses) “IDH” (G-CIMP), “K27,” “G34,” “Receptor Tyrosine Kinase I (RTKI)” (M6), “Mesenchymal” (M1 or M2), and “RTKII” (M3 or M4) (150, 169, 171, 172). Whereas tumors in children and adolescents belonged predominantly to the K27 and G34 subgroups, tumors in the RTKI, IDH, and mesenchymal subgroups showed a more widespread age distribution, and the RTKII subgroup only occurred in elderly patients. Placing these epigenetic subgroups into the context of molecular GBM classification schemes based on gene expression profiling reveals overexpression of mesenchymal genes within the mesenchymal subgroup and a correlation of proneural patterns with IDH, K27, and RTKI clusters, whereas the G34 and the RTKII subgroups comprise mixed and classical gene expression signatures, respectively (173). Here, we focus on the K27, G34, and IDH subgroups as well as on pediatric HGGs without IDH or H3 mutations, hereafter referred to as H3–/IDH–wild-type tumors.

K27 and G34 tumor subgroups

The K27 and G34 HGG subgroups are characterized by mutually exclusive heterozygous mutations in *H3F3A* (one of the genes encoding histone 3.3) or *HIST1H3B/C* (H3.1). These mutations result in amino acid substitutions either at position K27 (K27M mutant) or G34 (G34R or G34V mutant) (145, 169, 174, 175). Mutations that lead to amino acid changes at K27 are present in about 80% of midline GBMs (including in the thalamus, cerebellum, and spine) or DIPGs in younger children and can be seen in H3.3 or H3.1 (169). These different H3K27 alterations are associated with distinct oncogenic programs resulting in specific potential therapeutic targets (176). Furthermore, H3.1 and H3.3 K27M tumors also display differences in age at diagnosis. H3.1-mutant tumors arise earlier and have a better prognosis than H3.3-mutant tumors, although it is currently not clear whether these two observations are themselves directly linked (176). H3.1-mutant DIPGs are also more closely linked with recurrent and clonal activating mutations of activin A receptor type 1 (*ACVR1*, previously known as *ALK2*) that have been identified in 20 to 32% of DIPGs (175, 177–179). Notably, identical *ACVR1* mutations, when occurring in the germline, give rise to the

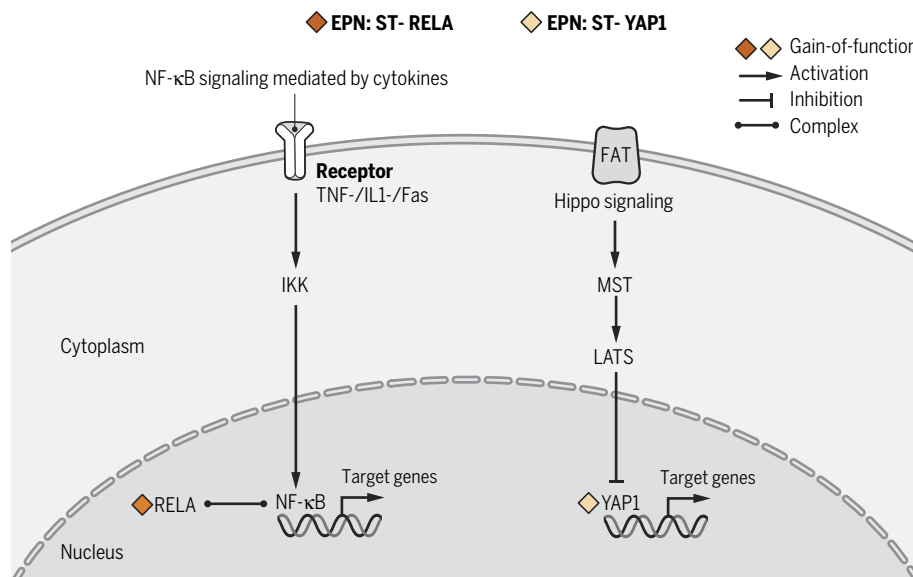


Fig. 2. Synopsis of signaling pathway alterations and potential drug targets in molecular subgroups of pediatric EPN. Gain- or loss-of-function aberrations in pathway components that have been identified within distinct molecular subgroups of EPN. Candidates for targeted therapy are indicated, including information on the current developmental stage of potential drugs.

Table 2. Molecular and clinical characteristics of ependymal tumor subgroups. Summary of key molecular and clinical findings in the nine molecular subgroups of ependymal tumors as identified by methylation profiling. CIN, chromosomal instability. I, infant; C, children; A, adults; M, male; F, female.

Anatomic compartment	SPINE (SP-)			Posterior Fossa (PF-)			Supratentorial (ST-)		
Molecular subgroup	SE	MPE	EPN	SE	EPN-A	EPN-B	SE	EPN-YAP1	EPN-RELA
Histopathology	subependymoma (WHO I)	myxopapillary ependymoma (WHO I)	(anaplastic) ependymoma (WHO II/III)	subependymoma (WHO I)	(anaplastic) ependymoma (WHO II/III)	(anaplastic) ependymoma (WHO II/III)	subependymoma (WHO I)	(anaplastic) ependymoma (WHO II/III)	(anaplastic) ependymoma (WHO II/III)
Genetics	6q deletion	CIN	CIN; <i>NF2</i> mutation	balanced	balanced	CIN	balanced	focal aberrations Chr. 11q; YAP1-fusion	aberrations Chr. 11; chromothripsis; <i>RELA</i> -fusion
Age distribution (I=Infant; C=Children; A=Adults)									
Gender Ratio (M=Male; F=Female)									
Prognosis	good	good	good	good	poor	intermediate	good	good	poor

congenital malformation syndrome fibrodysplasia ossificans progressiva (FOP) (180). Thus, repurposing drugs that target the ACVR1 receptor in FOP patients may represent a potential therapeutic approach for a subset of patients with DIPG.

Mutations resulting in amino acid changes at G34 (restricted to H3.3) are mostly found in hemispheric tumors of various histologies (either classically GBM-like or more primitive neuroectodermal) in adolescents (169, 181). Mutations at G34 typically co-occur with mutations in *α*-thalassaemia/mental retardation syndrome X-linked (*ATRX*), which is thought to promote alternative lengthening of telomeres (ALT) (182). Notably, G-quadruplex ligands, which might impair telomere replication and mitotic progression, have recently been shown to effectively prevent tumor development in an orthotopic glioma mouse model with an alternative mechanism of telomere maintenance (183, 184). There is also evidence for synthetic lethality when additionally inhibiting the protein kinase ATR, a critical regulator of recombination, in ALT cells (185). In contrast, other alterations of the telomerase complex are rare in children, suggesting that pharmacologically inhibiting telomerase activity might not be effective in most pediatric HGGs (186, 187). Genome-wide mapping of histone marks in a cell line representative of the G34 subgroup demonstrated an increased signal of the H3K36me₃-activating mark at the *MYCN* locus, constituting a potential alternative mechanism for up-regulating *MYCN* in pediatric HGGs besides focal gene amplification (169, 188, 189). Both *MYCN* and *MYC* (amplified in ~8% of histone-mutated pediatric HGG) are epigenetically regulated by bromodomain and extraterminal (BET) domain proteins such as BRD4, which can be targeted by the novel class of small-molecule BET inhibitors that are currently under development or being tested in clinical trials in adult patients (173, 190, 191).

There is also evidence from studies of *Drosophila melanogaster* harboring the K27M mutation that nucleosomes contain increased levels of bromodomain-containing proteins, making BET inhibitors a potential target for this subgroup as well (192). K27M mutants inhibit the PRC2 complex by interfering with its catalytic subunit, EZH2, thereby leading to a reduction of H3K27me₃ histone marks with consequent transcriptional derepression at these loci (193–196). In a recent study, Hashizume *et al.* demonstrated that small-molecule inhibition of the

H3K27 demethylase, JMJD3, in patient-derived intrapontine xenografts of pediatric DIPGs harboring the H3K27M mutation leads to increased H3K27 methylation levels and prolonged survival (197). Thus, reestablishing H3K27 methylation or PRC2 complex functionality might represent therapeutic approaches for pediatric HGGs with mutations at K27. However, care must be taken when considering this approach, because H3K27 hypermethylation can drive initiation of other brain tumors, and the role of the PRC2 complex is context-dependent, with increased activity leading to more aggressive stages in other malignancies (198–201). A recently published chemical screen in patient-derived DIPG cultures identified a histone-modifying combination therapy comprising the multi-HDAC inhibitor panobinostat and the histone demethylase inhibitor GSK-J4 as being effective both in vitro and in DIPG orthotopic xenograft models (202), making this an interesting strategy for further validation.

IDH tumor subgroup

HGG patients in the IDH subgroup have a more favorable prognosis than patients in other subgroups (169, 171). IDH tumors mostly occur in young adults and are characterized by widespread DNA hypermethylation at promoters (the G-CIMP phenotype), lack of typical SCNAs, and mutations in the *IDH1* gene (169). In contrast with adult astrocytic IDH-mutant tumors, not all cases display *TP53* mutations, although it is still a common event. Mutant IDH proteins exhibit neomorphic enzymatic activity resulting in the production of the R enantiomer of 2-hydroxyglutarate (2-HG), a putative oncometabolite (203, 204). (R)-2-HG leads to a functional blockade of several 2-oxoglutarate-dependent dioxygenases such as the DNA demethylating enzymes of the TET or Jumonji domain families, explaining the hypermethylated phenotype of the IDH subgroup (205, 206). A selective R132H-IDH1 inhibitor (AGI-5198) was recently reported to inhibit the ability of the mutant IDH1 enzyme to produce (R)-2-HG (207). Blockade of mutant IDH1 impaired the growth of glioma cells harboring *IDH1* mutations compared with wild-type *IDH1* cells. The phenotypic effects, probably relying on induction of signaling pathways involved in differentiation, occurred without changing the genome-wide DNA methylation pattern. Notably, Schumacher *et al.* recently reported a mutation-specific anti-IDH1 (R132H) peptide-based

vaccination, which may represent an alternative novel therapeutic strategy for IDH1-mutated HGGs (208).

H3 or IDH wild-type subgroup

Most of the hemispheric HGGs in children, and a smaller proportion of midline and brainstem tumors, lack one of the hotspot H3 or IDH mutations. Initially, these were found to resemble the receptor tyrosine kinase I (RTKI) subgroup, which is enriched for genomic alterations of platelet-derived growth factor receptor α (PDGFRA), but there is growing evidence for the need of further molecular refinement (169, 172, 209). Alterations in this subgroup include amplification of wild-type PDGFRA, activating mutations, or intragenic rearrangements of this kinase that are age-specific, resulting in constitutively increased tyrosine kinase signaling and activation of downstream mitogen-activated protein kinase (MAPK) and PI3K pathways (210, 211). Inhibiting PDGFRA with imatinib, a small molecule that also targets BCR-ABL and c-KIT, showed only very limited effects in cohorts of adults with progressive

or recurrent high-grade malignant gliomas in past studies (212–214). Preliminary results using the second-generation tyrosine kinase inhibitors, tandutinib or dasatinib, which have a higher ability to cross the blood-brain barrier, also have not had a substantial effect against gliomas in adult patients (168), suggesting that careful stratification and improved methods of drug delivery may be important strategies for further consideration. A recent study demonstrated that Neuroligin 3 (NLGN3), secreted from active neurons, activates PI3K and promotes glioma proliferation, suggesting that neuron–glioma cell interactions may also be future targets for therapeutic intervention (215).

The BRAF^{V600E} mutation that activates the MAPK signaling pathway has been reported in about 10% of pediatric cortical HGGs but not in DIPGs (216). Note that in a recent series of 202 histologically diagnosed pediatric HGG patients, a subset displayed methylation profiles similar to those of pleomorphic xanthoastrocytomas (PXAs; $n = 40$, 20%) with roughly half of these molecularly PXA-like tumors being V600E mutant, whereas only very few true molecular HGGs (2%)

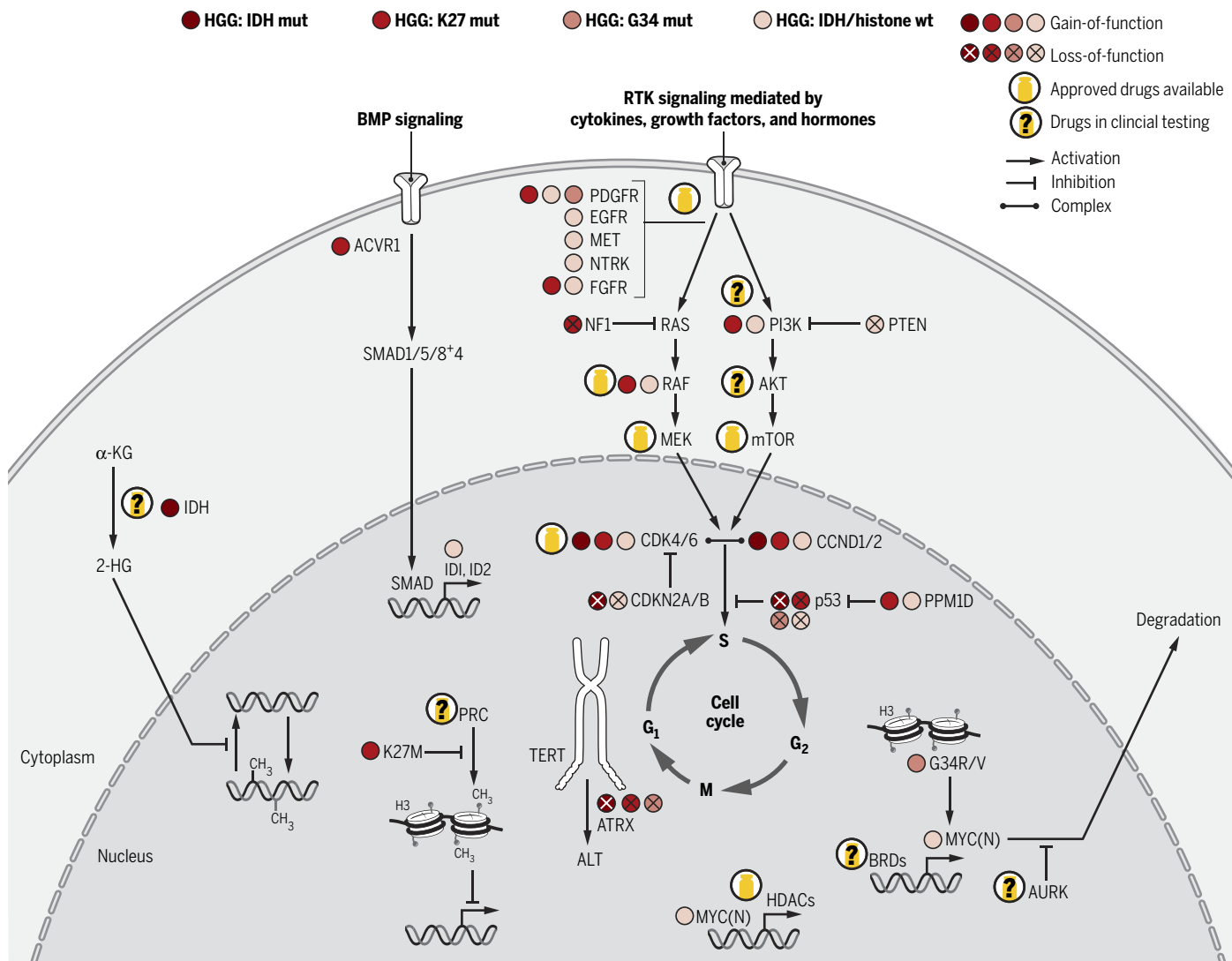


Fig. 3. Synopsis of signaling pathway alterations and potential drug targets in molecular subgroups of pediatric HGG. Gain- or loss-of-function aberrations in pathway components that have been identified within distinct molecular subgroups of HGG. Candidates for targeted therapy are indicated, including information on the current developmental stage of potential drugs.

harbored this alteration (172). *BRAF*^{V600E} and *CDKN2A* deletions were also found to constitute early events in lower-grade gliomas that ultimately undergo transformation to secondary HGG (217). Recent reports provide the first evidence that *BRAF* inhibition has important therapeutic potential in pediatric HGGs with activating *BRAF* mutations (218–220), making this an important population to study in more detail.

Apart from *PDGFRA*, H3–/IDH–wild-type pediatric HGGs are also enriched in alterations of other RTKs including *EGFR*, *FGFR*, and *MET* (Table 3) (172). Notably, Wu and colleagues identified recurrent oncogenic fusions involving the neurotrophin receptor genes *NTRK1*, *NTRK2*, and *NTRK3* in 40% of nonmidline infant HGGs (175). Using a mouse model, they showed that *NTRK*-activating fusions drive GBM formation and lead to MAPK and PI3K pathway activation; thus, *NTRK* family inhibitors, which are currently in early development, might represent a potential therapeutic option in a subset of HGGs in very young patients. More recent data suggest that enrichment for particular oncogene amplifications may also define additional subgroups within the H3–/IDH–wild-type tumors, with *EGFR*- and *MYCN*-amplified cases in addition to those with *PDGFRA* amplifications, each seeming to show distinct properties (Table 3). The *MYCN*-amplified cases (mostly supratentorially located) also commonly show coamplification of *ID2*, as described recently in a subset of DIPG cases (178).

In addition to these oncogene amplifications, key members of downstream signaling pathways are also often mutated across pediatric HGG patients. Activating alterations of the PI3K complex (*PIK3CA* in 8 to 20% and *PIK3R1* in 10 to 12%), for example, represent possible targets for inhibitors of PI3K itself or its downstream pathway members *AKT* or mammalian target of rapamycin (173). Disturbed cell cycle control resulting from alterations of the *TP53* and retinoblastoma (*RB*) pathways is another universal feature across pediatric HGG sub-

groups. Whereas mutually exclusive *TP53* and *PPM1D* mutations are the most frequent alteration of cell cycle regulation in the K27 and G34 subgroups, loss of the tumor suppressor *CDKN2A* and amplification of cyclin D genes (*CCND*) or CDKs are relatively more common in the wild-type subgroups (Table 3) (172, 221). CDK inhibitors, which are currently undergoing clinical development (including for pediatric HGG), may be a promising approach for targeting cancers with a deregulated *CDKN2A*-*CCND*/*CDK*-*RB* pathway (222).

Conclusions and Future Perspectives

The last decade has seen major advances in pediatric neurooncology. Genomic and epigenomic analyses have highlighted the heterogeneity of MB, EPN, and HGG and identified some of the key molecular alterations associated with each subtype of these diseases. This information has markedly enhanced our ability to predict patient outcomes, for example, identifying the relatively favorable prognosis associated with WNT-MB and the poor outcomes associated with G3-MB, SHH-MB with *TP53* mutation, and PF-EPN-A. Genomic studies have also shed light on some of the key oncogenic drivers associated with these diseases, and this, in turn, has led to the development of animal models that have been used to study the biology of these diseases. However, there are still major gaps in our understanding of the molecular basis of pediatric brain tumors. The drivers for G4-MB (the most prevalent form of the disease) and the molecular lesions responsible for PF-EPN-A and PF-EPN-B remain a mystery. Even for tumors in which candidate driver genes have been identified (including G3-MB, ST-EPN-RELA, and histone mutant HGG), the mechanisms by which these genes promote tumor formation are poorly understood. Thus, a major goal over the next few years will be to test candidate driver genes—and cooperating genes—and determine which of these are capable of promoting tumorigenesis.

Table 3. Clinicopathological features of pediatric HGG subgroups. Summary of major molecular and clinical characteristics of pediatric HGG subgroups as defined by a combination of DNA methylation profiles and genetic alterations. amp, amplification; del, deletion; mut, mutated; NA, as yet unclear; OS, overall survival; wt, wild type.

Methylation subgroup	IDH mut	K27 mut	G34 mut	Histone/IDH wt				
Further specification		H3.1 K27M	H3.3 K27M	H3.3 G34R/V	MYCN	PDGFRA	EGFR	Others
Location	Hemispheric, mostly frontal lobe	Almost exclusively pons (DIPG)	Midline (thalamus, cerebellum, spine) pons (DIPG)	Hemispheric	Hemispheric	Hemispheric	Hemispheric	Hemispheric
Average age	Teenage/young adult	~4.5 years	~7 years	Teenage/young adult	~8 years	~11 years	~10 years	NA
Prognosis	Intermediate median OS >5 years	Poor median OS ~15 months	Very poor median OS ~10 months	Poor median OS ~24 months	Poor median OS ~14 months	Poor median OS ~21 months	Intermediate median OS ~44 months	NA
Mutations	<i>IDH1</i> , <i>TP53</i> , <i>ATRX</i>	<i>HIST1H3A/B/C</i> , <i>TP53</i> , <i>PPM1D</i> , <i>ACVR1</i> , <i>PIK3R1</i> , <i>PIK3CA</i>	<i>H3F3A</i> , <i>TP53</i> , <i>PPM1D</i> , <i>ATRX</i> , <i>PI3KR1</i> , <i>PIK3CA</i> , <i>NF1</i> , <i>FGFR1</i> , <i>BRAF</i>	<i>H3F3A</i> , <i>TP53</i> , <i>ATRX</i> , <i>PDGFRA</i>	<i>TP53</i>	<i>TP53</i>	<i>TP53</i>	<i>TP53</i> , <i>PTEN</i> , <i>PIK3CA</i>
Copy number aberrations	<i>CCND</i> / <i>CDK</i> amp <i>CDKN2A/B</i> del		Various RTK amp <i>CCND</i> / <i>CDK</i> amp	<i>PDGFRA</i> amp	<i>MYCN</i> amp <i>ID2</i> amp <i>CDK4/6</i> amp Chr7 gain	<i>PDGFRA</i> amp	<i>EGFR</i> amp <i>CDKN2A/B</i> del 10q del	<i>MET</i> fusion/ amp <i>NTRK</i> fusion
Other features	<i>MGMT</i> methylation occasional hypermutation phenotype	Global H3 K27me3 loss	Global H3 K27me3 loss	<i>MGMT</i> methylation subtelomeric hypomethylation	NA	NA	NA	NA

Such “functional genomics” will not only provide insight into the mechanisms of tumor growth but also help create additional animal models that can be used to study tumor biology. Furthermore, efforts must be made to understand and tackle the extensive intratumoral heterogeneity seen in tumors such as HGG, where multiple targets can be altered in different tumor subclones (223, 224).

A critical goal for the future will be to use the information about subgroups to identify subgroup-specific or patient-specific therapies. To date, the only clinically validated therapies that have emerged from molecular analysis of pediatric brain tumors are SMO antagonists, which show activity in patients with SHH-MB resulting from mutations in *PTCH* or *SMO*. Additional candidate therapies (for example, pemetrexed/gemcitabine and HDAC/PI3K inhibitors) have been proposed on the basis of models of G3-MB, and it has been predicted that PF-EPN-A and histone-mutant HGGs will be responsive to epigenetic regulators. The efficacy of these approaches remains to be validated in patients, but this strategy—using animal models (including GEMMs and PDXs) to identify and test therapies for distinct types of brain tumors—holds great promise. In the long run, it may be possible to use genomic, transcriptomic, and epigenetic information not only to predict patient outcomes but also to guide selection of the most effective and least toxic forms of therapy.

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