Chromatin remodeling defects in pediatric brain tumors

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Abstract: Brain tumors are regarded as the most prevalent solid neoplasms in children and the principal reason of death in this population. Even though surgical resection, radiotherapy and chemotherapy have improved outcome, a significant number of patients die in 6–12 months after diagnosis while those who survive, frequently experience side effects and relapses. Several studies suggest that many types of cancer including pediatric brain tumors are characterized by alterations in epigenetic profiles with deregulated chromatin remodeling and posttranslational covalent histone modifications playing a prominent role. Moreover, interplay of genetic and epigenetic changes has been associated to tumor growth and invasion as well as to modulation of patient's response to current treatment. Therefore, detection of tumor-specific histone changes and elucidation of the underlying gene defects will allow successful tailoring of personalized treatment. The goal of this review is to provide an update of genetic and epigenetic alterations that characterize pediatric brain tumors focusing on histone modifications, aiming at directing future molecular and epigenetic therapeutic targeting.

Keywords: Histones; methyltransferases; epigenetic; gliomas; medulloblastoma (MB); ependymoma (EPN)

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Introduction

Pediatric brain tumors are regarded as the most prevalent solid neoplasms and the principal reason of death in childhood. High grade gliomas (HGGs) are rare (8%), but account for the most lethal brain cancer in children (1). Despite the aggressive treatments which include combination of neurosurgery, chemotherapy and radiation therapy in most cases the outcome is poor (2). The 2-year survival for children with diffuse intrinsic pontine gliomas (DIPGs) is less than 10% and for those with supratentorial (ST) HGGs doesn't exceed 30% (3).

Low grade gliomas (LGGs) are the most frequent tumors of the central nervous system (CNS) that appear in childhood. LGGs are very heterogeneous, formed within the brainstem, brain, and spinal cord, with distinctive characteristics, occurrence patterns, treatment options and responses and variable survival rates (4). Current treatment includes surgery, chemotherapy, radiation and their combination (4). Patients' survival can vary with a 5-year overall survival in pilocytic astrocytomas (PAs) being described as high as 100%, while this percentage appears to be lower than 50% in diffuse fibrillary astrocytomas (DA) (5).

The most prevalent malignant pediatric brain tumor is medulloblastoma (MB) appertain to embryonal tumors. MB is a brain tumor with great heterogeneity and the second-most frequent brain cancer in children following PAs (6).

Ependymoma (EPN) also displays clinical and genetic heterogeneity with most EPs being infratentorial tumors, arising in or around the fourth ventricle and constituting

approximately 6% to 10% of all pediatric brain tumors (7). Surgical resection is the first line treatment, since EPs are rarely metastatic at diagnosis or recurrence.

Recently, efforts have been made to elucidate the genetic and epigenetic mechanisms of pediatric brain neoplasms (8). Deregulation of epigenetic mechanisms may provoke aberrant gene expression, contributing to tumor formation (9). The elucidation of these alterations is crucial for prognosis and the possibility to revert these changes has been valuable for drug development and for improvement of current tumor-specific therapeutic strategies (8).

Epigenetic mechanisms in tumor development

Epigenetics refer to studies of mitotically heritable modifications in gene expression that do not involve changes in DNA sequence, presenting a link between genotype and phenotype. In DNA replication the paternal epigenetic information is translated by enzymes known as "readers" which lead to the recruitment of other proteins termed as "writers", or "erasers" and preserve this information in the daughter strands (10). The main epigenetic mechanisms are DNA methylation, histone modifications and small non-coding RNAs (miRNAs).

The most well-studied epigenetic mechanism is DNA methylation, being essential for the expression of critical genes as well as for chromatin remodeling (8). DNA methylation involves addition of a methyl group at the 5' position of the pyrimidine ring of cytosine in cytosine-phosphate-guanine (CpG) dinucleotides and is commonly related to transcriptional silencing (8). CpG nucleotides are frequently found at the 5' end of the gene promoter and/or the first exon region as big clusters, termed CpG islands (8). The CpG nucleotides inside CpG islands are usually unmethylated, but more than 80% of those traced outside of CpG islands are commonly found methylated (10). DNA methyltransferases (DNMTs) are catalyzing the reaction of methylation and can be distinguished into two subgroups: maintenance methylation and *de novo* methylation (10). The maintenance methyltransferase DNMT1 is responsible for restoration of the parental DNA methylation pattern. *De novo* methylation is essential during embryogenesis and cell development, being mediated by DNMT3a and DNMT3b functions (10).

Posttranslational modifications are targeting the amino-terminal of histones in a dynamic and reversible manner under the control of "histone code" which regulates the various combinations of histone modifications that modulate the genetic information of the transcript (10). Histone methylation is a covalent chemical modification that involves the addition of a methyl group on a lysine or arginine residue catalyzed by histone methyltransferases (HMTs). Several histone methylations have been identified, including the lysine (K) residues of histone H3 (K4, K9, K27, K36 and K79) and histone H4 (K20), and the arginine (R) residues of histone H3 (R2, R17 and R26) and histone H4 (R3) (10). Methylations of H3K4, H3K36, and H3K79 are linked to transcriptional activation, whereas methylations of H3K9, H3K27, and H4K20 are accompanied by gene repression (10). Another critical histone modification is acetylation which involves the relocation of an acetyl group from acetyl-CoA to the lysine ε-amino groups on the N-terminal of histone tails by histone acetyltransferases (HATs) (10). Histone acetylation is responsible for the interaction between the negatively charged DNA and histones, as a result of an increase in negative charge (8). This modification is commonly associated with the open state of chromatin, the accessibility of DNA to the binding proteins, and increased transcriptional activity. The reverse reaction, deacetylation, is triggered by histone deacetylases (HDACs) which remove the acetyl groups from histones contributing to chromatin condensation and transcriptional repression (10). HDACs are implicated in several signaling pathways and they are responsible for repressive chromatin complexes. Several HDAC inhibitors that result in chromatin decompression and gene activation have been identified and investigated for their therapeutic value in neurodegenerative disorders and cancer (10).

RNA-based mechanisms consist of small non-coding oligonucleotides, microRNAs (miRNAs) and short interfering RNAs (siRNAs) that contribute to gene silencing (10). By contrast to messenger RNAs (mRNAs), miRNAs are biologically stable and are not easily decomposed by RNAses due to their incorporation into the miRNA-containing RNA-induced silencing complex (RISC) (10). This contributes in RNA silencing and post-transcriptional regulation of gene expression through translational repression or mRNA cleavage, by guiding RISC to detect messenger RNAs (10). MicroRNAs are able to regulate the translation and mRNA transcripts in the cytoplasm through binding to the 3' untranslated region (10). MicroRNA expression can be modulated by promoter methylation or acetylation of histones (10). Short interfering RNAs are acting both in the cytoplasm and nucleus, mediating chromatin-dependent and

posttranscriptional gene silencing (10). The contribution of miRNA in tumorigenesis has been revealed recently with their expression being associated with apoptosis and cell cycle arrest (11). Furthermore, miRNAs implicated in metastasis and invasion have been found upregulated in tumors (11). Recent progress in the elucidation of mechanisms by which miRNAs and siRNAs regulate gene expression have endorsed the design and synthesis of therapeutically effective molecules that induce silencing of target genes *in vivo* (10).

The epigenetic marks are generated on genomic DNA during development and differentiation (10). These modifications establish active and repressive chromatin structures and operate as molecular switches turning gene expression either "on" or "off", or by altering overall gene expression levels (8).

Genetic landscape of gliomas

The majority of pediatric LGGs (pLGGs) present alterations in the RAS/MAP kinase pathway. The most frequent change is a fusion of *B-Raf proto-oncogene (BRAF)* with *KIAA1549*, which induces constant activation of BRAF kinase domain resulting in the enhancement of mitogen-activated protein kinase (MAPK) pathway (12). In a small percentage of pLGGs, a missense mutation of *BRAFV600E* has been identified (13). Another important contributor to the development of pLGGs involves mutations on the phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway, affecting cell proliferation and growth (14,15). Several components of this pathway are overexpressed in pLGGs and have been linked to poor prognosis (16). Other frequently altered genes include *fibroblast growth factor receptor 1* (*FGFR1*), *tumor Protein p53* (*TP53*) and *neurofibromatosis 1* (*NF1*), and they were detected in 17.6% (22/125), 5.6% (7/125) and 8.8% (11/125) of cases, respectively (17). Mutations on *NF1* cause activation of platelet-activating factor (PAF) pathway that leads to tumorigenesis (18).

According to Sturm *et al.* there are six subgroups of HGG based on DNA methylation patterns, gene-expression profiles and mutation profiles, isocitrate dehydrogenase (IDH) mutations, platelet-derived growth factor receptor alpha amplification (PDGFRA), receptor tyrosine kinase I, II (RTK I, II), lysine 27 (K27), glycine 34 (G34), and mesenchymal [very few copy number alterations (CNAs) or point mutations] (19).

PDGFRA amplifications are frequently detected in a proportion of pHGGs and possess a key role in tumor development by contrast to mutations in IDH that are absent on pediatric gliomas (20). A large amount of pediatric HGG is characterized by mutations in genes that encode histone 3, in particularly *H3 Histone family member 3A* (*H3F3A*) or H3.1 genes *Histone cluster 1 H3 family member B* (*HIST1H3B*). These missense mutations result in amino acid substitutions that generate two mutants: K27M mutant, where lysine of position 27 is replaced by methionine, and G34R or G34V mutant, where either arginine or valine substitutes glycine at position 34 (21,22).

H3.3K27M is spreading throughout the midline and pons, and occurs in 63% of DIPG and in 59.7% of non-brainstem midline tumors. In all locations, these mutations were associated with a considerably shorter survival period (overall median 11 months, 2-year overall survival 4.7%). H3.1/3.2K27M was highly specific to the pons (21.4%) representative of a younger age group (median 5.0 years) with a significantly longer overall survival (median 15.0 months) than H3.3K27M (23).

Moreover, these mutations affect other mutations, for example the mutation H3.3K27M observed in the pons is correlated with *TP53* loss of function mutations (60%) and PDGFRA gain-of-function mutations or amplifications (40%) (21,24), while the H3.1K27M mutations in the pons are associated with recurrent gain of function somatic mutations in the *activin A receptor type 1* (*ACVR1*; 20%) (25,26). As for the CNAs the most frequent chromosomal changes found in children are chromosome 1q gain (20%), loss of 16q (18%), and loss of 4q (15%) (27). Common large-scale chromosomal alterations include chromosome 17 and 9. More specifically the loss of 17p is targeting *TP53* and is linked to shorter survival independently of the subgroup or the tumor location. The gain of 9q34 has been associated with shorter overall survival in pHGGs and DIPGs (23).

Epigenetic histone modifications in gliomas

In pHGGs, there are two mutations implicated in regulatory posttranslational modifications, G34V/R and K27M (21). The role of histone lysine methylation is crucial for gene expression and the state of chromatin (28).

G34V/R mutation occurs in H3.3 histone tail and is reported to correlate with reduced H3K36 methylation through loss of function mutations in the N-methyltransferase SET domain-containing 2 (SETD2) (29). This reduction is associated with enhancement of gene expression. Mutations

in SETD2 methyltransferase are taking place solely in hemispheric HGGs, and are more frequently observed in pediatric patients (15% of tumors) than adults (8% of tumors) (29). These missense mutations were not detected in LGGs or midline structures. SETD2 encodes the histone H3K36 tri-methyltransferase in humans and affects the function of histone H3.3. The location of tumor origin in gliomas may be affected by these mutations (30). Additionally, the oncogene *MYCN* was upregulated by G34R/V mutation and led to transcriptional upregulation through altered genomic binding of methylated H3K36 to specific gene loci (31,32). *MYCN* was found to be implicated in many cancers including glioblastoma in mouse (31,33).

Except from G34V/R, another frequent posttranslational histone modification is the methylation or acetylation of lysine 27 (K27) in all histone 3 variants (24). The histone N-methyltransferase, enhancer of zeste homologue 2 (EZH2) catalyzes the mono-, di-, or trimethylation of K27 and induces gene silencing. On the other hand, acetylation of K27 leads to activation of gene transcription and gene expression (34). Sometimes due to K27M mutation, there is a reduction of H3K27me2/3 which causes transcriptional activation. However, K27 mutation may also increase H3K27me3 leading to silencing of tumor suppressor gene expression (35).

The polycomb repressive complex 1 (PRC1) and polycomb repressive complex 2 (PRC2) compose the polycomb-group of proteins (PcG). PRC2 complex acts as a HMT through its subunits EZH1 and EZH2 and trimethylates histone H3 on lysine 27 (H3K27me3) resulting in gene silencing (36). A study by Lewis *et al.* reported the inhibition of PRC2 as a result of abnormal binding of K27M to EZH2 (37). This aberrant remodeling of EZH2 is causing reduction of H3K27 methylation and is leading to gene activation and DNA hypomethylation (37,38). The result of DNA hypomethylation is gene activation and cell differentiation due to CpG hypomethylator phenotype (39). Although, there is a decrease of H3K27 methylation in K27M mutated gliomas, another study reported enhancement of HMTs EZH2 and H3K27 methylation at defined gene loci (40).

Genetic landscape of MBs

In 2012, four MB subgroups were established with distinct clinical, pathological and molecular features, namely Wingless (Wnt), sonic hedgehog (SHH), group 3 and group 4. However, more recent publications propose a different classification encompassing more subgroups and a biological overlap between group 3 and 4 (41).

Wnt tumors may be the rarest (11%) subgroup of MB but it is well-studied with really good prognosis. Wnt subgroup is named after the predominant activation of Wingless signaling pathway (Wnt) that involves a family of growth factor receptors with function during embryonic development (42). Molecular analysis of Wnt MBs shows that the most frequent mutations occur on the gene encoding for β-catenin (43). These somatic *catenin beta 1* (*CTNNB1*) mutations were found in 85% of the patients. Another characteristic alteration found on patient with Wnt MB is monosomy 6 (83%) (44).

SHH tumors account for almost the 30% of all MBs (45). They have an intermediate prognosis ranking between good prognosis of Wnt tumors and decreased prognosis of group 3 tumors. They have been correlated with mutations in *Patched 1* (*PTCH1*), but also in *smoothened* (*SMO*) and *suppressor of fused (SUFU)* genes leading to over activation of the sonic hedgehog signaling (SHH) pathway (43). Additionally, SHH tumors exhibit increased *N-myc proto-oncogene* (*MYCN*) expression levels (46).

Group 3 MB is characterized as classic MBs with dismal prognosis and frequently metastatic, harboring elevated *MYC* expression (46).

Group 4 are the most frequent MBs (34%) and even though they are often metastatic, they are correlated with an intermediate prognosis, similar to SHH tumors. The majority of this group harbors an isochromosome *17q*. Group 4 MBs are also associated with *MYCN* and *cyclin dependent kinase 6* (*CDK6*) amplification but minimal *MYC* over-expression (43).

Epigenetic histone modifications in MBs

In MBs, most common mutations affect genes that target histone methylation (47). More specifically, molecular screening of MBs revealed truncating mutations in histone lysine methyltransferases MLL3/KMT2C and MLL2/KMT2D that are responsible for the histone methylation H3K4me2/3, associated with "open" chromatin and gene expression (48). These mutations are suppressing tumor formation and are found in 16% of MB as well as in SHH and group 4 (48). Moreover, mutations in genes encoding for methyltransferases SET and MYND domain containing 4 (SMYD4) and euchromatic histone lysine methyltransferase 1 (EHMT1), acetyltransferase MYST3, demethylases JMJD2B and JMJD2C and several PcG

have been associated with hypomethylation of H3K9 (49). Furthermore, mutations in trithorax group genes, *lysine demethylase 6A* (*KDM6A*) and *lysine demethylase 6B* (*KDM6B*), *KDM6A* (*UTX*) encoded by lysine demethylases (KDM) result in elevation of H3K27me3 and are commonly found in G4-MB (47) along with overexpression of the PcG protein, EZH2 which is involved in stem cell maintenance by repressing lineage differentiation genes (47).

Apart of lysine methyltransferases, lysine acetyltransferases (HATs) are also involved in brain development and they are linked to poor survival such as the downregulation of H4K16 HAT, hMOF (50). SHH tumors are overexpressing somatic modifications that target HATs (44). In contrast, HDACs are associated with gene silencing and some of them (HDAC5 and HDAC9) are upregulated in MB leading to deregulated cell cycle (51).

In group 3 and 4 modifications in histone demethylases have been detected that induce aberrant histone methylation of H3K4 and H3K27 (48). Bromodomain (BRD) and extra-terminal (BET)-containing proteins (BET/BRD) are binding in acetylated histones and are responsible to manage MYC levels in group 3 MB (52). In recent preclinical studies BET inhibitor (JQ1) is evaluated for its therapeutic role in MBs (53).

Although elucidation of the mechanism that histone modifications mediate pathogenesis of MB is still missing, 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 (54-56). Suppressing H3K27me3 by silencing the home box gene *Orthodenticle Homeobox 2* (*OTX2*) leads to a differentiated phenotype in MBs (57,58). Whether the presence of "repressive" heterochromatin (high H3K27me3 and low H3K4me3) in group 3 and group 4 MBs reflects the epigenetic status of the tumor-initiating/propagating cells that generate these tumors, or whether it is a consequence of mutations in genes that regulate these modifications, requires further investigation (47).

Genetic landscape of EPNs

In 2016, the World Health Organization (WHO) classified ependymal tumors into five main subtypes: subependymoma, myxopapillary EPN, EPN, RELA fusion-positive, and anaplastic EPN (7).

The majority of pediatric ST EPNs exhibits gene fusions involving *RELA*. Chromosome 11 open reading frame 95 (C11orf95-RELA) fusion is associated with constitutive induction of the nuclear factor-kappa B (NF-κB) pathway by an increase in a RELA-encoded transcription factor p65 (59).

Another molecular subgroup for ST EPN is characterized by the fusion of yes-associated protein 1 (YAP1), a transcriptional regulator involved in proliferation, with other genes such as *mastermind like domain containing 1* (*MAMLD1*) and *family with sequence similarity 118 member B* (*FAM118B*) (59).

Epigenetic histone modifications in EPNs

Recent studies unraveling the epigenetic pattern of EPN with particular emphasis on histone modifications identified a decrease in H3K27me3 in ~80% of posterior fossa (PF) EPN (60). PF-ve EPN are not characterized by recurrent genetic mutations by contrast to H3K27M gliomas (59,61). Several studies suggest that there is a positive association between unmethylated CpG islands and PRC2 recruitment which depends on DNA methylation (62,63). By contrast, in PF EPN, as a result of the increased CpGi methylation, H3K27me3 is reduced due to incapability of PRC2 to access chromatin (60). Additionally, Bayliss *et al.* reported that the PF radial glia displayed reduced H3K27me3 through early development, reflecting which tumor formation is going to be developed (60).

Finally, H3K27M gliomas and PF-ve/PFA EPN share many similarities such as tumor location and patient age, and perhaps this chromatin state defined by DNA and H3K27 hypomethylation could have a crucial role in transformation and/or growth of tumor (60). The elucidation of these regulators that share this chromatin state may be critical in understanding the biology of PF EPN.

Biomarker potential of histone alterations in pediatric brain neoplasms

The last decade has seen major advances in pediatric neuro-oncology. Genomic and epigenomic analyses have underlined the heterogeneity of HGG, MB and EPN, and recognized some of the key molecular alterations associated with each tumor subtype (47).

Huse *et al.* applied whole-exome and next-generation sequencing in order to analyze the molecular profile of MBs and HGGs (64). MBs have been classified into four subtypes based on their molecular differences. Wnt tumors which comprise the first category are frequently harboring

CTNNB1 mutations. These mutations are affecting Wnt signaling pathway and are correlated with a prognostic and diagnostic role and favorable survival of patients. SHH tumors are frequently characterized by *PCTCH1* mutations and are responsible for the activation of SHH pathway, with a potential diagnostic role (65). Additionally, other genetic aberrations are also found indicating 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 (47). MYCN amplification may also have a prognostic significance, often correlated with poor survival (65).

In pHGGs, research findings detected chromatin remodeling defects, mainly mutations in histone H3F3A with the replacement of lysine 27 with methionine (K27M) to be found in 78% of DIPGs whereas one-third of non-brainstem HGGs carries K27M or G34V/R mutations (38). These mutations are correlated with poor outcome therefore can be used for prognosis. TP53 and *ATRX* mutations are commonly found in HGGs but their prognostic value remains unclear (66). PDGFRA mutations which are correlated with poor survival are frequently observed in HGGs and may also have a prognostic role (67).

On the contrary to HGGs, LGGs are mainly characterized by activation of *BRAF* oncogene. The fusion gene *KIAA1549*:*BRAF* is found in 50–70% of PAs and is generated by tandem duplication at 7q34 deregulating the MAPK signaling pathway, affecting cell proliferation, differentiation and apoptosis (65).

Some studies showed that this fusion gene could improve patients' survival but it is still uncertain if it useful in prognosis. Furthermore, the frequent *BRAF* modifications in PAs may have a diagnostic role in differentiating PAs from grade II gliomas. However, *BRAF V600E* mutations are found both in LGGs and in HGGs with partial diagnostic and predictive value (65).

In EPN, several genes such as JHDMD1, ASAH1 GNAO1, IMMT, IPO7 and CISD3 are found implicated in cell proliferation, signaling pathways, methylation and tumor development. These genes could have a potent prognostic role in EPN because they are participating in deregulation of cell cycle, in tumor formation, cell migration and possibly in metastasis (68).

Except of the molecular profiling of pediatric brain neoplasms, epigenetic changes are also critical during their development and constitute a distinct set of biomarkers that characterize tumor subgroups (69). For instance, pediatric EPNs exhibit a CpG island methylator phenotype (CIMP). Such DNA hypermethylation is mediated by the polycomb group of proteins and targets differentiation genes that are transcriptionally controlled by H3K27 marks. Pharmacological compounds against these alterations proved to be efficacious *in vitro* and *in vivo* (61). Finally, vascular endothelial growth factor (VEGF) is an alternative noninvasive biomarker in children with brain tumors that reflects enhanced tumor angiogenesis (70). Sobol-Milejska *et al.* reported significantly elevated VEGF expression in blood samples of 106 children diagnosed with brain tumors in comparison to the control group. VEGF expression has also been found upregulated in UW402 MB cells upon hypoxia. In accordance, strong expression of VEGFR has been correlated with gadolinium enhancement in MRI of pediatric patients with MB, a feature with prognostic significance (70).

Molecular therapeutic targeting of pediatric brain tumors

Recent studies on pediatric brain tumors treatment based on their specific genetic background have revealed several efficient molecular targets (*Table 1*). For example, in tuberous sclerosis-associated subependymal giant cell tumors, the mTOR pathway inhibitor everolimus has been tested with beneficial treatment outcome (79) and is currently further evaluated in LGGs (80). Other molecular targets including *BRAF V600E* and MEK inhibitors such as vemurafenib, dabrafenib and trametinib may enable the management of brain tumors. These inhibitors appear to have improved brain penetration and they could result in shrinkage of brain tumors (80). However, the study of Sievert *et al.* showed that BRAF inhibitors like Dabrafenib and PLX4720, can cause paradoxical stimulation of MAPK signaling in other BRAF mutations, like the fusion *BRAF/KIAA1549* gene (81). Selumetinib, an efficient inhibitor of MAP kinase pathway (MEK inhibitors) could be an additional option for patients with LGG (82).

Recent studies have demonstrated that mTOR pathway upregulation may be related with malignant pLGGs. Rapalog everolimus could be used for mTOR-driven tumors, since it has successfully treated SEGAs in children with tuberous sclerosis (83). Furthermore, several novel targeted approaches such as, BRAF V600E, Ras/Akt pathway and telomerase are under investigation (84). In MYC-driven MB models, JQ, which is a BET BRD inhibitor was shown to be efficient (53) and in SMO inhibitor-resistant SHH MB with potential efficiency

Table 1 Effects of chromatin remodeling inhibitors in pediatric brain tumors

Histone modification enzyme/ protein	Inhibitor	Type of pediatric brain tumor	Clinical observation
HDAC (71,72)	Vorinostat individually or in combination with 13-cis retinoic acid (isotretinoin)	Refractory solid tumors	Stable disease in one of seven patients with DIPGs
HDAC (73)	Vorinostat with the alkylating agent temozolomide	Relapsed or refractory primary CNS tumors	Stable disease in one of seven patients with HGGs
HDAC (74)	Vorinostat in combination with bortezomib	Recurrent or refractory solid tumors	No objective response in any of the patients
HDAC (75)	Valproic acid	Refractory solid or CNS tumors	A response was observed in 2/4 of patients with DIPGs
JMJD3 (H3K27demethylase) (76)	GSKJ4	High-grade gliomas	Reduction of tumor growth and extended survival
HDAC (77)	Panobinostat, with GSKJ4	H3.3K27M mutant DIPG cells	Decrease of cell viability
EZH2 (78)	Tazemetostat	H3K27M-positive glioma cells in presence of functional *p16INK4A*	Reduction of cell growth

HDACs, histone deacetylases; EZH2, enhancer of zeste homologue 2; CNS, central nervous system; DIPG, diffuse intrinsic pontine glioma; HGG, high grade gliomas.

in GFI1/1B-activated MBs (85,86). Another SMO inhibitor tested specifically in patients with MB is the vismodegib, as well as sonidegib (87).

High-throughput screening has revealed the potential effectiveness of pemetrexed and gemcitabine and HDAC/PI3K inhibitors for group 3 MBs with the worst prognosis, being currently under clinical trial and expected that PF-EPN-A and histone-mutant HGGs will be responsive to epigenetic regulators (88). To date, the only clinically validated therapies that have emerged from molecular analysis of pediatric brain neoplasms are SMO antagonists, which show activity in patients with SHH-MB resulting from mutations in *PTCH* or *SMO*. The efficacy of these approaches remains to be validated in patients, but this strategy—using animal models (including GEMMs and PDXs) to detect and examine therapies for distinct types of brain tumors—holds great promise. Genetic characterization of PF EPN and MB (groups 3 and 4) is highly demanded in order to improve patients' prognosis.

In another study, Taylor *et al.* reported that heterozygous somatic mutations in ACVR1 gene, which encodes the activin A type I receptor serine/threonine kinase ALK2 were found in 21% of pediatric DIPG (26). ACVR1 mutations were found to co-segregate with histone H3.1 K27M mutated DIPG (26). Previously, in patients with the autosomal dominant congenital childhood developmental disorder fibrodysplasia ossificans progressive (FOP), identical ACVR1 mutations have been suggested to constitutively activate the bone morphogenic protein (BMP)-dependent transforming growth factor-β pathway (89). This study proposes a role for BMP inhibitors to target one of the potential tumorigenic mechanisms in DIPG (26). Future trials would be of interest to see the efficacy of single BMP inhibitors or combined with epigenetic targeted therapies such as HDAC or EZH2 inhibitors.

Epigenetic targeting of histone modifications in HGGs using HDAC inhibitors

In many cancer types, HDACs are overexpressed. Therefore, using inhibitors to target them may contribute to the development of novel therapeutic schemes for pediatric brain tumors (*Table 1*). A phase I clinical trial performed by the Children's Oncology Group, investigated the pan-HDAC inhibitor vorinostat individually or in combination with isotretinoin in children with refractory solid tumors (71).

The clinical observations detected prolonged stable disease in one of seven patients with DIPGs (72). In the same trial, vorinostat was given in relapsed or refractory primary brain tumors along with the alkylating agent,

temozolomide and 1/7 patients with HGGs exhibited stable disease (73). Another phase I trial examined vorinostat in combination with bortezomib which is a ubiquitin-proteasome pathway blocker, in children with recurrent or refractory solid tumors. The results showed no objective response in any of the patients (74). In addition, the HDAC inhibitor valproic acid was explored in children with refractory solid or CNS tumors and a response was observed in 2/4 of patients with DIPGs (one partial and one minor) (75). Ongoing clinical trials evaluate event-free survival in children with newly diagnosed HGGs and brainstem gliomas after treatment with valproic acid and radiotherapy, followed by bevacizumab. An ongoing phase II/III trial in children with HGG, investigates the event-free survival using vorinostat, or temozolomide, or bevacizumab in combination with radiotherapy, followed by treatment with bevacizumab and temozolomide (28).

Epigenetic targeting of histone modifications in HGGs using histone demethylase inhibition

The constant knowledge of epigenetic changes underlying HGGs could be targeted and reversed leading to therapy of these tumors (76). Apart of HDAC inhibition Hashizume *et al.* investigated a therapeutic approach of histone demethylase inhibition using the H3K27 demethylase, JMJD3, with GSKJ4 in pHGGs (76). The increase of H3K27 methylation, is leading to gliomagenesis by inhibiting gene expression and blocking cell differentiation (90). In H3.3 K27M glioma cell lines, GSKJ4 treatment displayed a 50% reduction in growth, increased apoptosis, and inhibition of clonogenicity, while JMJD3-depleted glioma cells exhibited no significant decrease in proliferation (76). In athymic brainstem K27M glioma murine xenografts (nu/nu, BALB/c), GSKJ4 treatment reduced significantly tumor growth and prolonged survival (76). The pan-HDAC inhibitor panobinostat, was used with the histone demethylase inhibitor GSKJ4 in 14 patient-derived DIPG cell cultures (77). Cells expressing the H3.3 K27M mutation exhibited elevated H3 acetylation and H3K27 methylation after treatment, indicating a partial rescue of the H3.3 K27M-induced global hypomethylator phenotype CHOP. Additionally, in H3.3 K27M mutant DIPG cells, panobinostat was shown to act synergistically with GSKJ4 to decrease their viability (77), indicating histone methylation and acetylation targeting as an exciting treatment option for HGGs.

EZH2 inhibition is also an alternative mechanism to prevent abnormal histone methylation of target genes and could promote cell differentiation, while reducing cell proliferation in different tissues (91). Preclinical studies have tested pharmacological inhibition of EZH2 in pediatric rhabdomyosarcoma (92). EZH2 overexpression is reported in many malignancies including breast cancer, lymphoma, and prostate cancer (93,94). Clinical trials are currently investigating EZH2 inhibitors for the treatment of children with MB and EPN which display elevated PRC2 activity (56,61,95). Finally, tazemetostat, an EZH2 inhibitor, was shown to affect H3K27M-positive glioma cell growth in the presence of functional *p16INK4A* (78).

Conclusions

Experimental data over the last decade have changed entirely our view on the genomic and epigenetic landscape of pediatric brain neoplasms. Molecular and epigenetic biomarkers play a crucial role in tumor classification and novel therapeutic approaches. The identification of histone modifications that are correlated with the development of brain tumors in children has stimulated the investigation of epigenetic inhibitors such as histone demethylase and HDAC inhibitors in cancer treatment. However, the complex interaction between DNA methylation, histone modifications, gene expression, and chromatin organization presents a challenge for the design of rational trials (28). For instance, there are some restrictions in epigenetic targeting including elucidation of the underlying molecular mechanism or the effects of HDAC inhibitors on cellular signaling and pathways which are still unclear. Moreover, HGGs may be protected from damage due to intratumoral genetic heterogeneity, which could change the intracellular concentration and recruitment of the HDAC inhibitor. Furthermore, another limitation is the non-effective penetration of the blood-brain barrier of HDAC inhibitors such as vorinostat and panobinostat, hence they are failing to translate into efficient treatment (28,96). These reasons possibly explain the slow advance of clinical trials investigating HDAC inhibitors use in HGGs. The most important goal for the future will be to apply the molecular information of tumor's subgroups in the identification of subgroup-specific or patient-specific therapies. In the long run, it is likely to use genomic, transcriptomic, and epigenetic information not only to predict patient outcomes but also to guide selection of the most efficient with the least toxicity forms of therapy (28).

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Footnote

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