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TOPIC REVIEW

Medulloblastoma epigenetics and the path to clinical innovation

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Abstract

Introduction In the last decade, a number of genomic and pharmacological studies have demonstrated the importance of epigenetic dysregulation in medulloblastoma initiation and progression. High throughput approaches including gene expression array, next-generation sequencing (NGS), and methylation profiling have now clearly identified at least four molecular subgroups within medulloblastoma, each with distinct clinical and prognostic characteristics. These studies have clearly shown that despite the overall paucity of mutations, clinically relevant events do occur within the cellular epigenetic machinery. Thus, this review aims to provide an overview of our current understanding of the spectrum of epi-oncogenetic perturbations in medulloblastoma.

Methods Comprehensive review of epigenetic profiles of different subgroups of medulloblastoma in the context of molecular features.

Summary Epigenetic regulation is mediated mainly by DNA methylation, histone modifications and microRNAs (miRNA). Importantly, epigenetic mis-events are reversible and have immense therapeutic potential.

Conclusion The widespread epigenetic alterations present in these tumors has generated intense interest in their use as therapeutic targets. We provide an assessment of the progress that has been made towards the development of molecular subtypes-targeted therapies and the current status of clinical trials that have leveraged these recent advances.

Keywords Medulloblastoma · Epigenetics · DNA methylation · Histone modifications · MicroRNA · Therapeutics

Introduction

Medulloblastoma (MB), a malignant embryonal tumor of childhood, accounts for 20% of all brain tumors in pediatrics [1]. Current multimodal treatment is associated with potential lifelong morbidities and a high risk for relapse [2]. Previous classification was based upon histopathological designations of classic, desmoplastic nodular, MB with extensive nodularity (MBEN), and large cell/anaplastic [2]. However, significant heterogeneity in outcomes exists among patients treated uniformly based on histopathological and clinicoradiographical findings, underscoring the need to understand tumor biology as means to impact a patient's clinical course. Thus, work from several groups has led to the molecular stratification of MB into four major subgroups: WNT, SHH, Group 3, and Group 4 [3]. Current World Health Organization (WHO) classification is based upon integration of these two methods of classification, with the WNT, SHH, Group 3, and Group 4 tumors further sub-divided based on histopathology (Fig. 1).

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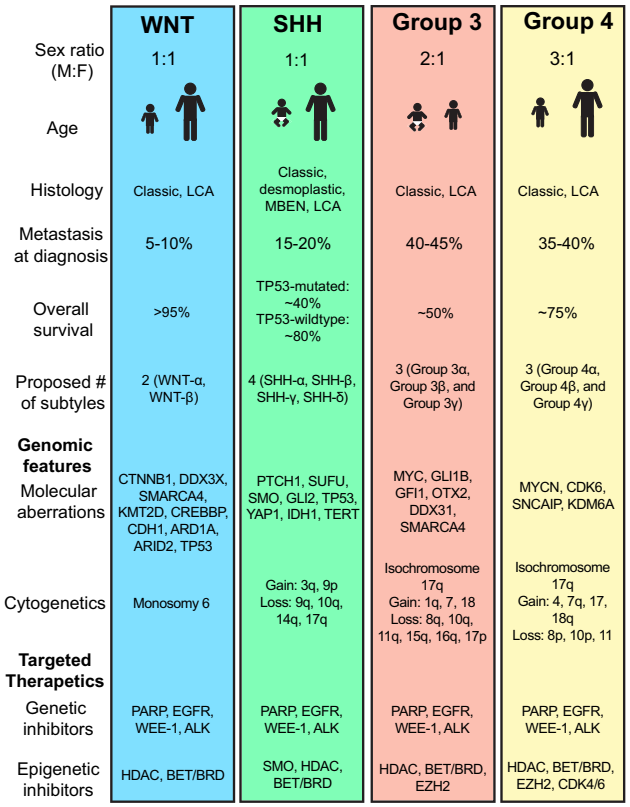

Fig. 1 Characteristics of the different subgroups of medulloblastoma. Age at diagnosis, histological features, subtypes, frequency of metastasis, molecular abnormalities, and targeted therapies are summarized

Historically, prognosis and therefore treatment was determined by a limited number of factors including age, extent of resection, and metastatic disease [4]. However, recent advances in tumor profiling have important prognostic implications [2], leading to a therapeutic shift with a greater emphasis on molecularly based risk adapted therapy and targeted therapy. Here, we provide an overview of our current understanding of the molecular landscape of MBs and the clinical implications.

Because children have not lived long enough to acquire spontaneous mutations, they tend to develop tumors with low mutational burden [5]. Indeed, several studies over the last decade have highlighted aberrations in developmental programs such as lineage specification, which are governed by spatial and temporal changes in epigenetic processes, as a hallmark of MB tumors [6]. Several lines of evidence suggest that epigenetic mechanisms play significant roles in subtype specific MB tumorigenesis, which in turn has engendered an active focus on targeting these processes for therapeutic purposes either alone or in combination with standard of care [7]. Broadly speaking, epigenetics refers to any heritable phenotypic changes in the absence of changes in nucleotide sequence. Here, we will discuss DNA methylation, post-translation modification of histones, and non-coding RNAs, specifically microRNAs (miRs) as effectors of epigenetic changes in MB cells.

DNA methylation

In mammals, DNA methylation occurs almost exclusively within the context of CpG dinucleotides and an estimated 80% of all CpG sites are methylated. CpG islands (CGI) are clusters of CpG dinucleotides that are often located near the 5′ end (promoter region) of genes. Methylation of promoter CGIs is rare in normal tissues, but frequent in cancers, and is usually associated with a closed chromatin structure and transcriptional silencing of the gene [8, 9]. However, the genome-wide DNA hypomethylation seen in parallel contributes to genomic instability and carcinogenesis [10, 11].

Methylation status has been utilized to classify multiple tumor types, including MB, and for the identification of biomarkers [12–17]. DNA methylation analysis is considered a method of choice for molecular tumor diagnosis, which may help further clinical stratification of patients with MB [18–23]. As mentioned above, MB has been historically classified into four major histopathological groups: classic, nodular/desmoplastic (ND), MBEN and large cell/anaplastic (LCA). Of these forms, LCA tumors have been associated with the worst prognosis, and ND tumors have more favorable outcomes [24]. With recent advances in genomics, gene expression profiling, and DNA methylation analysis, MB has more recently been divided into the four major subgroups; WNT, SHH, Group 3, and Group 4, each with distinct molecular and clinical characteristics [25–28]. The recent development of advanced algorithms for integrative genomics has provided a deeper understanding of the heterogeneity within these subgroups, subdividing these four major subgroups into 7 to 12 subtypes [22, 29, 30]. In one of the largest of these analyses, Cavalli et al. used 763 samples to define 12 subtypes of MBs using the similarity network fusion method to successfully integrate gene expression and DNA methylation data [29].

First described by Toyota et al., CGI methylator phenotype (CIMP) is characterized by a high degree of concordant CGI methylation in a subset of colorectal tumors [31]. In MBs, CDKN2A, CASP8, HIC1, CDH1, RASSF1 (tumor suppressor genes) [32–35], MGMT (DNA repair gene) [36], PTCH1 (the negative regulator of SHH signaling) [37], the SFRP family (inhibitors of the WNT signaling pathway) [38], DRD4 (brain development) [39], and ZIC2 (the transcriptional repressor) [40] are silenced by promoter CGI methylation. Initially, Lindsey et al. suggested that the CIMP did not exist in MB [32]. MB showed slightly higher CGI methylation than normal cerebellum, but without evidence for a CIMP. The gene silencing by promoter

hypermethylation was not a prominent feature, and many differentially methylated promoters were at genes that were not expressed even in unmethylated samples [17]. However, in adult patients with gliomas, IDH1 mutations represent a hallmark genetic event that exhibits a distinct hypermethylation phenotype which is referred to as G (glioma)-CIMP [41–43]. Somatic mutation of the IDH1 gene was also found to establish CIMP in IDH-mutant astrocytomas and oligodendrogliomas, as well as secondary glioblastomas arising from these tumors [41]. In MB, a recent study revealed that their five IDH1 mutated SHH-MB samples were CIMP positive [30], suggesting that IDH1 mutations are the molecular basis of CIMP in MB tumorigenesis. However, El-Ayadi et al. could not confirm the CIMP in their single IDH1-mutated SHH-MB case [44]. This discrepancy may be due to low sample size of IDH1-mutated tumors in both studies. Further studies are needed to understand the wider role of DNA methylation patterns in MB, along with their clinical impact (Table 1).

Large genomic domains that are devoid of DNA methylation, which are termed as DNA methylation valleys, DMVs [45], or canyons [46], are generally hypomethylated in normal tissues. DMVs have been reported to contain CGIs that are particularly prone to silencing by hypermethylation in cancer [45, 47, 48]. In addition to these epigenetic gene down-regulations occurring in MB, highly prevalent regions of hypomethylation (linked to transcription factor binding sites) correlating with increased gene expression have also been detected, which may cause the differential transcriptional networks between MB subgroups [17]. At the same time, an MB subgroup-specific gain of DNA methylation in DMVs was also linked to reactivation of repressed genes due to densely packed chromatin [17, 49]. Moreover, partially methylated domains affecting up to one-third of the genome showed increased mutation rates and gene silencing in an MB subgroup-specific manner [17].

Further, and most importantly, DNA methylation analysis can point to possible therapies using epigenetic drugs. For example, tumors that exhibit a CIMP may be responsive to drugs that inhibit DNA methylation [50]. Some of the first epigenetic drugs proposed as anti-cancer therapeutics were DNA methylation inhibitors such as 5-azacytidine (5-aza-CR) and 5-aza-2′-deoxycytidine (5-aza-CdR) when it was realized that they can cause tumor cells to differentiate in culture. These nucleoside analogs incorporate into DNA and trap DNA methyltransferases onto DNA by preventing their release from the cytosine analog after adding the methyl group. This mechanism depletes their availability in the cell, preventing their activity and restoring expression of tumor suppressor genes [51].

Histone modifications

Histone modifications are crucial for spatial and temporal control of gene expression during development and for adult cell homeostasis. In eukaryotic cells, the amino-terminal tails of histones in nucleosomes are subject to covalent chemical modifications that cooperate to govern chromatin state and gene expression. At least ten different types of histone modifications on more than 50 residues of histone tails have been described [52, 53]. Acetylation, methylation, phosphorylation, and ubiquitylation are the best studied modifications, although, sumoylation, GlcNAcylation, citrullination, butyrylation, crotonylation, and isomerization are also known to occur [52–55]. Dynamic regulation of these modifications by families of enzymes that add (writers), remove (erasers), or read (readers) are key for functional translation and serve to turn “on” or “off” gene expression by modulating active and repressive chromatin states [56, 57]. Several lines of evidence support a role for aberrations in chromatin remodelers in MB development

Table 1 Aberrant histone modification in medulloblastoma

Genes	Histone modification	Expression	Pathways affected	Sample type	References
hMOF/KAT8	H416ac	Decreased	DNA damage	Patient tumors	[63]
PCAF/KAT2B	H3K9Ac	Decreased	Proliferation, apoptosis	Cell lines	[64]
HDAC2	Histones (H2A, H2B, H3 and H4)	Increased	Proliferation	Patient tumors, cell lines	[69]
HDAC5	Not defined	Increased	Proliferation, differentiation	Patient tumors, cell lines	[70]
HDAC9	Not defined	Increased	Proliferation, differentiation	Patient tumors, cell lines	[70]
SIRT1	H4K16, H3K9	Increased	Cell cycle, apoptosis	Patient tumors, cell lines	[79]
EZH2	H3K27me3	Increased	Proliferation, differentiation	Patient tumors, cell lines	[91]
UTX/KDM6A	H3K27	Increased	Proliferation, differentiation	Mouse model, cell lines	[94]
JMJD3/KDM6B	H3K27	Increased	Proliferation, differentiation	Mouse model, cell lines	[94]
JMJD2B/KDM4B	H3K9, H3K36	Increased	Not defined	Patient tumors	[89]
JMJD2C/KDM4C	H3K9, H3K36	Increased	Not defined	Patient tumors	[89]

[6] (Table 2). Mutations, deletions, or amplifications in genes encoding epigenetic modifiers are seen across all four molecular subgroups [58–61]. These contribute to abnormal acetylation and methylation of lysine (K) in MB tumors [7].

Histone acetylation decompacts DNA, most commonly to upregulate gene expression [52]. The enzymes that catalyze the addition of acetyl (Ac) groups to histone lysine residues are called histone acetyltransferases (HATs), and are divided into three major families: the Gcn5-related *N*-acetyltransferase family (GNAT), the MYST family (MOZ, Ybf2, Sas2, TIP60), and the orphan family (CBP/EP300 and nuclear receptors) [62]. Human MOF (hMOF), a HAT for H4K16 acetylation, is downregulated in MB tumors and is associated with poor outcomes for patients [63]. Downregulation of PCAF, a HAT, reduces H3K9Ac on SHH target gene promoters (*Ptch1* and *Gli1*) and decreases proliferation and increases apoptosis of tumor cells [64]. The HATs, CBP and p300, which catalyze H3K27Ac, a marker for active enhancers, are mutated in MB tumors. Genome-wide studies to assess H3K27Ac and recognition of the mark by BRD4 revealed a consequent widespread disruption of enhancer and super-enhancer activity in medulloblastomas [65, 66]. Additionally, p300 can also acetylate Gli2 to modulate SHH pathway activity [67].

The opposing process of deacetylation is catalyzed by histone deacetylases (HDACs), which causes chromatin compaction and transcriptional repression. There are four distinct families of HDACs: Class I, II, and IV are Zn^{2+}-dependent, whereas the Class III/Sirtuins are NAD-dependent [62, 68]. Several HDACs are implicated in MBs [69, 70]. HDAC2 expression is higher in the SHH, Group 3, and Group 4 MBs compared to normal brain and WNT-driven tumors [69]. HDAC2 depletion promotes MB cell death and pre-clinical studies showed that MYC-amplified group 3 MB cell lines exhibit sensitivity to class I HDAC inhibitors [69]. Upregulation of HDAC5 and HDAC9 expression in MB samples has been shown to be associated with poor overall survival [70]. Consistent with their role in cell cycle regulation and differentiation, HDAC5 and HDAC9 loss promotes a reduction in tumor cell viability [70–72]. MBs exhibit recurrent somatic mutations in N-CoR-HDAC corepressor complexes [65]. Elevated expression of transcriptional repressors that HDACs associate with has also been shown, suggesting that their activity could be perturbed independent of expression changes. For example, expression of the *RE1* silencing transcription factor (REST) is elevated in SHH and Group 4 MBs, and is associated with poor prognosis [73–76]. HDACs 1 and 2 are required for REST-mediated silencing of neuronal differentiation genes and inhibition of their activity blocks MB growth in vitro and in vivo [76, 77]. Similarly, HDACs 1 and 3 interact with the transcriptional repressor insulinoma-associated 1 (INSM1) to regulate the expression of NeuroD/Beta2, a gene involved in neuronal differentiation [78]. Finally, expression of SIRT1, a class III HDAC, is upregulated in MBs and its knockdown or inhibition caused G1 arrest and apoptosis in tumor cells [79].

The bromodomain (BRD) and bromodomain extraterminal (BET) family proteins recognize and bind acetylated histone lysine residues to regulate the transcription of oncogenic transcription factor drivers. BET/BRD inhibition downregulates MYC, an important driver of Group 3 MB [66, 80]. In MB samples, targeting BRD4 decreased cell survival in pre-clinical models, suggesting an important role for this reader in MB growth [49, 81–83]. Interestingly, DNA methylation is seen to inversely correlate with distribution of activating enhancer-associated H3K27ac and BRD4 on chromatin in MBs [49]. Hovestadt et al. have shown that increased DNA methylation was associated with gain of

Table 2 Alterations of miRs in medulloblastoma

miR	Expression in tumor	Targeted genes	Pathways affected by targeted genes	References
miR-9	Decreased	REST/TrkC	Proliferation, apoptosis, differentiation	[137, 138]
miR-17	Increased	TOPORS, BAMBI		[139]
miR-17-92 cluster	Increased	–		[121, 122]
mIR-34a	–	c-Met	Cell proliferation, survival, metastasis	[140]
miR100	Increased	BTG2		[139]
miR106b	Increased	–		[139]
miR124	Decreased	CDK6, REST/NRSF, SLC16A	Proliferation, apoptosis, differentiation	[138, 141–143]
miR-125a	Decreased	TrkC	Apoptosis	[137]
mIR-128a	Decreased	BMI1	Self-renewal, cell proliferation, senescence	[116]
mIR-199-5p	Decreased	HES1	Self-renewal, cell proliferation, differentiation	[144]
miR218	Decreased	EGFR, CTNND2	Cell proliferation	[139]
miR-125b miR-326 miR-324-p	Decreased	SMO, GLI1	Cell proliferation	[119]

H3K4me3, loss of H3K27me3, and increased gene expression in DMVs [17].

Histone methylation, which can occur on lysine or arginine residues, does not alter histone charge, but directly impacts chromatin structure and regulates gene transcription. Changes in mono-, di-, or tri-methylated lysines of histones are seen in MB tumors [33–35]. Lysine methylation can occur on histone H3 (K4, K9, K27, K36, and K79) and histone H4 (K20) [84]. Whereas methylation of H3K4, H3K36, and H3K79 is associated with gene activity, that of H3K9, H3K27 and H4K20 mostly results in gene silencing. The coordinated activities of methyltransferases (writers) and histone lysine demethylases (KDMs) (erasers) control the state of methylation marks to turn transcription on and off [85]. Most histone lysine methyltransferases (HMTs), except Dot1L, contain a SET domain (Su(var)3–9, enhancer of zeste and trithorax) [86]. HMTs MLL1-5, SET1A, SET1B, SETD7, and PRDM9 modify H3K4; G9a, GLP, SUV39H1, SUV39H2 and SETDB1 methylate H3K9; SETD2, NSD1-3, ASH1L, and SYMD2, target H3K36; EZH1and EZH2 methylate H3K27; DOT1L targets H3K79; and finally, SET 8, SUV420H1, and SUV420H2 methylate H4K20 [87]. Genomic sequencing has identified inactivating mutations of MLL2/KMT2D and MLL3/KMT2C and deletions of histone lysine methyltransferases (EHMT1 and SMYD4) and Polycomb group (L3MBTL2 and L3MBTL3) genes in human MBs [88, 89]. Since MLL2 and MLL3 can catalyze monomethylation of histone H3K4 on enhancers, changes in their activity affect the enhancer landscape in tumors [88, 90]. Elevated expression of EZH2, EED and SUZ12, components of the PRC2 complex in MBs, together with the demonstration of high H3K27me3 in Groups 3 and 4 MBs supports an oncogenic role for these remodelers in MB genesis [59, 66, 91].

Histone lysine demethylases KDMs are divided into the lysine demethylase 1 (KDM1) and the jumonji C (JmjC) containing protein families [87]. KDM1 family includes only two members, LSD1 (lysin-specific demethylase 1, KDM1A) and LSD2 (KDM1B). The Jumonji C (JmjC) containing protein family represents the larger KDM class, and include about 30 enzymes grouped into KDM2-7 subfamilies in humans [92]. UTX/KDM6A and ZMYM3 (zinc finger MYM-type3) control H3K27 and H3K4 methylation. UTX/KDM6A has a tumor suppressive function, and mutations and homozygous deletions in the gene are enriched in Group 4 MBs [66]. Since UTX/KDM6A is also a subunit of MLL2/3 complexes and its K3K27 demethylating activity is coordinated with H3K4 methyltransferase activity of MLL2/3, mutations in these genes are mutually exclusive in MBs [59, 93]. Loss of SHH-dependent cerebellar granule neuron progenitor (CGNP) proliferation following JMJD3/KDM6B inhibition suggest a role for the enzymes in Group 4 and SHH medulloblastoma tumorigenesis [59, 94]. Finally, recurrent focal amplifications in JMJD2C and JMJD2B, genes involved in controlling histone H3K9 methylation, are described in human MBs [89]. Homozygous deletion of EHMT1, a H3K9 demethylase, is seen in MB, and global decreases in H3K9me2 levels are reported in nearly 40% of MB tumors compared to normal samples [61, 89].

Integrative deep-sequencing analysis has clearly identified recurrent mutations in SMARCA4, a key component of the SWI/SNF chromatin-remodeling complex, in WNT-activated and Group 3 tumors [58]. Pre-clinical studies on histone phosphorylation and ubiquitination are restricted to a few examples in MBs. Inhibition of WEE1, a tyrosine kinase and a regulator of the S/G2 checkpoint, impairs MB cell growth [95, 96]. WEE1 phosphorylates H2B at Tyr37 and inhibits transcription of multiple histone genes. The resultant change in DNA/histone ratio affects mitotic entry [97, 98]. Reduced expression and allelic deletion of REN (KSCTD11), a component of the Cullin3 E3 ubiquitin ligase, is seen in SHH-MBs [99]. It ubiquitinates and promotes degradation of HDAC1, resulting in suppression of SHH signaling and MB growth [99].

MicroRNA (miRNA)

miRNAs are short sequences about 19–25 nucleotides long that negatively regulate the expression of target oncogenic or tumor suppressive genes and drive cancer progression. Several reviews have covered the specific roles of miRNAs in MB and other pediatric brain tumors, which are summarized in Table 2 [100–110]. As discussed below, small RNA signature changes correlate with initial transformation in the different medulloblastoma subtypes and may have potential application in risk stratification [111–116]. MBs are thought to arise from perturbations in normal brain development and neural lineage specification [117, 118]. From this perspective, the analyses by Ferretti et al. using proliferating and differentiating CGNPs, the proposed cell of origin for SHH medulloblastoma, provides an excellent view of changes in miR levels during normal neurogenesis and their alteration during tumorigenesis [119]. These authors defined a signature of 34 murine miRNAs whose expression is also seen in human SHH medulloblastoma samples. Work by two separate groups showed the importance of the miR-17/92 cluster in driving SHH-medulloblastoma progression in mice [120–122]. Gokhale et al. identified overexpression of miR-193a, miR-224/miR-452 cluster, miR-182/miR-183/miR-96 cluster, and miR-148a in WNT-driven medulloblastomas [123]. Ectopic expression of miR-193a and miR-224 could inhibit proliferation and increase the radio-sensitivity of medulloblastoma cells in culture [123]. Non-WNT, non-SHH medulloblastomas with downregulated miR-592 or overexpressing miR-182 were associated with poor survival

[124]. miR148a targets *Nrp1*, a gene involved in the control of invasion, metastasis and angiogenesis, and its upregulated expression in WNT-medulloblastomas confers a survival advantage [125]. Two complementary studies highlighted the link between miR-183-96-182 cluster and upregulation and activation of PI3K/AKT/mTOR pathway activation in MYC amplified Group 3 tumors [120, 126].

Finally, the expression of miRNAs can be inactivated by aberrant DNA hypermethylation, highlighting cross-talk between the two epigenetic regulatory pathways [127].

Clinical implications

The establishment of a clear role for epigenetics in MB tumorigenesis has allowed the development of novel diagnostic and therapeutic tools (Table 3). Methylation profiling of MBs has revealed additional subgroups within the designated subtypes of MBs, therefore providing diagnostic information [7, 23, 25]. Though hypomethylating agents 5-azacytidine and decitabine have been extensively evaluated in other pediatric tumors, their clinical application in brain tumors is surprisingly lacking, especially given the hypermethylation of tumor suppressor genes in SHH- and WNT-MBs [33, 40, 128, 129]. A study is evaluating gemcitabine, a DNA synthesis inhibitor, in combination with the CDK4/6 inhibitor ribociclib, in the setting of recurrent or refractory MBs in children [130]. Ribociclib is also being evaluated in combination with trametinib (MEK inhibitor) or sonidegib (a SMO inhibitor) in Group 3/Group 4, WNT/SHH-activated and SHH-activated tumors, respectively (NCT03434262). A phase I trial using a combination of prexasertib (a small molecule CDK inhibitor, mainly active against CHEK1, with minor activity against CHEK2) and cyclophosphamide in participants with recurrent/refractory Group 3 and Group 4 medulloblastoma and recurrent/refractory Sonic Hedgehog (SHH) medulloblastoma is also ongoing (NCT04023669). CDK4/6 inhibitors are also being studied in combination with everolimus (mTOR inhibitor) as well as with irinotecan and temozolomide (NCT03387020, NCT03709680).

Histone modifiers have also been examined clinically in pediatric MB. The Children's Oncology Group (COG) recently completed a phase I study of suberanilohydroxamic acid (SAHA)/vorinostat, an HDAC inhibitor in combination with temozolomide, in 19 children with relapsed/refractory CNS disease (NCT1076530) [131, 132]. This study using 5 days of vorinostat along with temozolomide demonstrated safety and tolerability, with three patients exhibiting stable disease and one partial response [132]. A study combining vorinostat with the proteasome inhibitor bortezomib, has also been completed in children with recurrent/refractory solid tumors including CNS malignancies, but results have not yet been published (NCT01132911). Vorinostat was also investigated in combination with isotretinoin in a feasibility study, enrolling 33 participants (NCT00867178). And lastly, a phase I trial to study fimepinostat, a HDAC/PI3Kinase inhibitor, in children and adolescents with brain tumors is currently active and recruiting patients (NCT03893487).

EZH2 inhibitors are under investigation in several CNS tumors, including relapsed or progressive MBs (NCT03213665). Similarly, BRD/BET inhibitors are being assessed in children with recurrent cancers including MBs (NCT03904862). Drugs targeting EHMT1/EHMT2 and LSD1 have shown efficacy in vitro and in pre-clinical investigations, but remain to be explored in the clinical context [73, 133].

In SHH MBs, early phase studies targeting the SHH pathway using Smoothened (SMO) inhibitors vismodegib (GDC-0449) and sonidegib (LED-255) as single agents revealed initial clinical response in some patients; however, the quick development of tumor progression prompted their evaluation in combination with traditional chemotherapeutic regimens [134] (NCT01125800, NCT01708174, NCT01878617). Since several SHH-pathway components including SMO and GLI oncogenes are subject to epigenetic modulation, the combination of SMO inhibitors in combination with epigenetic modifiers is attractive clinically. In recurrent/refractory MB, a molecularly based group-specific targeted therapy utilizing ribociclib with sonidegib is currently being evaluated (NCT03434262) [134–136].

Conclusions

Medulloblastoma is a complex and heterogeneous disease entity, with each subgroup exhibiting its own distinct genetic profile and clinical treatment course. Despite advances in the molecular classification of these subgroups, treatment has historically been defined by histopathological and clinicoradiological findings. Mutational targets are being investigated in this population but are limited by the relatively quiescent mutational landscape, particularly in Group 3, which shows the lowest overall survival. Our more recent understanding of epigenetics has elucidated several possible targetable aberrations in each subgroup, some of which are already being investigated in clinical trials. As these discoveries continue, their integration into the classification and therapeutic implications of these tumors provides hope for improved outcomes with decreased sequelae for this vulnerable population.

Table 3 Epigenetic modifiers in clinical trials in medulloblastoma

Targeted agent	MB subgroup	Disease status	Target	Patients known or estimated	Outcome	Reference
Vismodegib (GDC-0449)	SHH	Recurrent or progressive	Smoothened inhibitor	12	PFS 1.41 months	NCT01239316 PMID 26169613
Vismodegib (GDC-0449)	All subgroups	Recurrent or progressive	Smoothened inhibitor	34	Results not available	NCT0822458
Sonidegib (LDE225)	All subgroups	Recurrent or progressive	Smoothened inhibitor	60	Objective response rate 3.3%	NCT01125800
Sonidegib (LDE225)	SHH	Recurrent or progressive	Smoothened inhibitor	2 Pediatric patients	PFS 1.6 months	NCT01708174
Vismodegib + maintenance chemotherapy + CSI	SHH	Upfront	Smoothened inhibitor	625	Trial ongoing	NCT01878617
Gemcitabine + pemetrexed + maintenance chemotherapy + CSI	Non-WNT/non-SHH intermediate and high risk	Upfront	DNA synthesis inhibitor + inhibition of folate metabolism			
Vorinostat + temozolomide	All subgroups	Recurrent or refractory	HDAC inhibitor	19	3 Stable disease and 1 partial response	NCT01076530 PMID 23554030
Vorinostat + isotretinoin + maintenance chemotherapy + irradiation	All subgroups	Upfront	HDAC inhibitor	33	Results not available	NCT00867178
Fimepinostat (CUDC-907)	All subgroups	Recurrent or progressive	HDAC/PI3K inhibitor	30	Trial ongoing	NCT03893487
Prexasertib + gemcitabine	Group 3/Group 4	Recurrent or refractory	CHK 1/2 inhibitor + DNA synthesis inhibitor	100	Trial ongoing	NCT04023669
CX-4945	SHH	Recurrent or progressive	Casein kinase 2 inhibitor	60	Trial ongoing	NCT03904862
BMS-986,158	All subgroups	Recurrent or refractory	BET/BRD inhibitor	34	Trial ongoing	NCT03936465
Tazemetostat	EZH2, SMARCB1/SMARCA4 mutated tumors	Recurrent or refractory	EZH2 mutation or loss of function mutation SMARCB1/SMARCA4	49	Trial ongoing	NCT03213665
Ribociclib + gemcitabine	Group 3 and Group 4	Recurrent or progressive	CDK4/6 inhibitor + DNA synthesis inhibitor	108	Trial ongoing	NCT03434262
Ribociclib + trametinib	WNT-activated/SHH-activated		CDK4/6 inhibitor + MEK inhibitor			
Ribociclib + sonidegib	SHH-activated		CDK4/6 inhibitor + Smoothened inhibitor			
Palbociclib + irinotecan + temozolomide	All subgroups	Recurrent or refractory	CDK4/6 inhibitor	100	Trial ongoing	NCT03709680
Ribociclib + everolimus	All subgroups	Recurrent or refractory	CDK4/6 inhibitor + mTOR inhibitor	45	Trial ongoing	NCT03387020
Palbociclib	All subgroups	Recurrent or refractory	CDK4/6 inhibitor	49	Trial ongoing	NCT03526250
Palbociclib + temozolomide + irinotecan	All subgroups	Recurrent or refractory	CDK4/6 inhibitor	100	Trial ongoing	NCT03709680
Abemaciclib	All subgroups	Recurrent or refractory	CDK4/6 inhibitor	60	Trial ongoing	NCT02644460
Abemacicilib + temozolomide + irinotecan	All subgroups	Recurrent or refractory	CDK4/6 inhibitor	60	Trial ongoing	NCT04238819

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Compliance with ethical standards

Conflict of interest None of the authors have any conflict of interest or disclosure relevant to this publication.

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