Published in final edited form as:

Mol Cell Neurosci. 2018 March ; 87: 65–76. doi:10.1016/j.mcn.2017.09.003.

Epigenetic Regulation in Medulloblastoma

Jiaqing Yi¹ and Jiang Wu^{1,*}

¹Department of Physiology, University of Texas Southwestern Medical Center, Dallas, TX 75390-9040, USA

Abstract

Medulloblastoma is the most common malignant childhood brain tumor. The heterogeneous tumors are classified into four subgroups based on transcription profiles. Recent developments in genome-wide sequencing techniques have rapidly advanced the understanding of these tumors. The high percentages of somatic alterations of genes encoding chromatin regulators in all subgroups suggest that epigenetic deregulation is a major driver of medulloblastoma. In this report, we review the current understanding of epigenetic regulation in medulloblastoma with a focus on the functional studies of chromatin regulators in the initiation and progression of specific subgroups of medulloblastoma. We also discuss the potential usage of epigenetic inhibitors for medulloblastoma treatment.

Medulloblastoma subgroups

Medulloblastoma of the cerebellum accounts for 20% of malignant childhood brain tumors. These tumors mainly occur during infancy and childhood, but a small percentage occur in adulthood. The overall survival of medulloblastoma patients is relatively high due to efficacy of traditional radiation therapy and chemotherapy; however, the long-term effects of these treatments on development and cognition are debilitating (Gajjar et al., 2006; Northcott et al., 2012b; Rutkowski et al., 2010). Recent genomic studies of medulloblastoma have dramatically improved our understanding of the genetic causes and molecular programs underlying progression of medulloblastoma (Gajjar et al., 2015; Holgado et al., 2017; Northcott et al., 2015). The disease is heterogeneous and tumors are classified into four subgroups based on distinctive transcription profiles. These subgroups are referred to as WNT, SHH, Group 3, and Group 4 (Jones et al., 2012; Northcott et al., 2012c; Parsons et al., 2011; Pugh et al., 2012; Robinson et al., 2012). Subgroups differ in age and gender distributions and clinical outcomes. At the molecular level, the tumors from the different subgroups are characterized by specific mutations, rely on distinct signaling pathways, and possibly have different cell origins (Kool et al., 2012; Northcott et al., 2012a; Taylor et al.,

CORRESPONDENCE: Jiang Wu, jiang9.wu@utsouthwestern.edu, Department of Physiology, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas TX 75390-9040, Phone: 214-648-1824.

Conflict of interest: The authors declare no conflict of interests.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

2012a). Recently, a more detailed classification based on gene transcription profile, DNA copy number alterations, and DNA methylation pattern has been proposed that further divides medulloblastoma into 12 subgroups (two WNT, four SHH, three Group 3, and three Group 4 subgroups) (Cavalli et al., 2017). However, more detailed molecular basis of each subgroup is still under intensive investigation. The improved understanding of medulloblastoma tumor biology may enable personalized targeted therapy, preventing the overtreatment of some medulloblastoma patients and developing new treatment for the more aggressive subgroups.

WNT subgroup

The WNT subgroup accounts for about 10% of medulloblastoma patients (Taylor et al., 2012a). The WNT α type tumors mainly occur in children, whereas WNT β occurs in adults (Cavalli et al., 2017). These tumors appear to arise from the lower rhombic lip and often develop in a central location (Gibson et al., 2010). Most WNT medulloblastomas contain activating *CTNNB1* mutations and display activated WNT signaling. *DDX3X*, which encodes an ATP-dependent RNA helicase, has mutations enriched in but not exclusive to the WNT subtype (Jones et al., 2012; Northcott et al., 2012c; Parsons et al., 2011; Pugh et al., 2012; Robinson et al., 2012). *TP53* mutations are identified in approximately 15% of WNT medulloblastomas but are not associated with poor prognosis (Zhukova et al., 2013). It remains unclear how *DDX3X* and *TP53* mutations function in tumorigenesis in this subtype. Patients with WNT medulloblastoma have the best prognosis and survival among the four main subgroups (Ellison et al., 2005).

SHH subgroup

Approximately 25% of medulloblastoma occurrences are SHH subgroup tumors. The cells of origin for SHH medulloblastoma are cerebellar granule neuron precursors (CGNPs) (Gibson et al., 2010). SHH signaling is required for normal CGNP proliferation during development. Mutations causing constitutively active SHH signaling and increased downstream target gene expression are drivers of SHH medulloblastoma (Barakat et al., 2010; Kool et al., 2014). Most SHH medulloblastomas contain mutations or deletions of SHH pathway genes such as *PTCH1*, *SMO*, or *SUFU* or amplifications of downstream transcription activators *GLI1* or *GLI2* (Kool et al., 2014). SHH medulloblastomas are grouped into four subcategories that occur in infants (<4 years, SHH β and SHH γ), children (4 to 17 years, SHH α), and adults (>17 years, SHH δ) (Cavalli et al., 2017; Kool et al., 2014). Infant SHH γ medulloblastoma patients have excellent prognosis when treated with chemotherapy alone, whereas infant patients with SHH β tumors often suffer metastases and have poor prognosis. About half of the SHH α childhood medulloblastomas contain *TP53* mutations. These patients have the worst outcome. Patients with adult or childhood SHH medulloblastoma with wild-type *TP53* have intermediate prognosis (Kool et al., 2014; Kool et al., 2012). Interestingly, mutations in *TERT* (telomerase reverse transcriptase) promoters are highly enriched in SHH δ medulloblastoma, and these mutations are associated with better treatment outcomes within this group (Cavalli et al., 2017; Lindsey et al., 2014; Remke et al., 2013).

Group 3

Group 3 represents roughly 25% of medulloblastoma occurrences. It occurs more commonly in males than females and is found in infants and children. The most frequently mutated gene is *SMARCA4* (11%), which encodes a chromatin remodeling factor. Almost half of Group 3 patients are in Group 3 α . The amplification of a homeobox gene *OTX2* and enhancer hijacking for *GFI1/GFI1B*, which juxtapose *GFI1* or *GFI1B* coding sequences proximal to active enhancer elements, are enriched in Group 3 β medulloblastoma (Cavalli et al., 2017; Northcott et al., 2014). *MYC* amplification is highly associated with Group 3 γ medulloblastoma. Group 3 γ medulloblastoma patients have high rates of metastasis and poor treatment outcomes with less than 50% 5-year survival rates, whereas other Group 3 patients have intermediate survival rates (Cavalli et al., 2017; Taylor et al., 2012a).

Group 4

Group 4 tumors account for more than 35% of all occurrences and are the most prevalent among all medulloblastoma subgroups. The molecular pathogenesis of Group 4 medulloblastoma remains unclear. These tumors share some similarities with Group 3 medulloblastoma but with few *MYC* amplifications. Some Group 4 medulloblastomas also harbor *OTX2* amplifications and enhancer hijacking of *GFI1/GFI1B* albeit with lower percentages than Group 3 medulloblastoma (Cavalli et al., 2017; Northcott et al., 2014). One prominent feature of Group 4 medulloblastoma is that approximately 80% of these patients have isochromosome 17q (Shih et al., 2014). *KCNA1* has been suggested as an immunohistochemical marker for Group 4 tumors, and genes involved in neuronal differentiation and development are overrepresented in Group 4 medulloblastoma transcription profiles (Taylor et al., 2012a). Group 4 α tumors are enriched for *MYCN* amplifications, and Group 4 β are strongly enriched for *SNCAIP* duplications. Groups 4 α and 4 γ are enriched for focal *CDK6* amplifications (Cavalli et al., 2017). One of the frequently mutated genes in Group 4 tumors encodes the H3K27me3 demethylase KDM6A/UTX (Dubuc et al., 2013). Group 4 medulloblastoma occurs most often in children between 6 and 8 years old and with a high male preponderance. Female patients with Group 4 medulloblastoma have high incidence of X chromosome loss in tumor tissues (Shih et al., 2014). The overall therapeutic outcomes of patients with Group 4 medulloblastoma are intermediate.

Epigenetic alterations associated with human medulloblastoma subgroups

Epigenetic regulation plays important roles in cancer development with alterations identified in many cancers with high frequency (Feinberg et al., 2016; Jones et al., 2016). One of the most intriguing discoveries from the genomic studies of medulloblastoma is the high rate of alterations of epigenetic regulators across all four subgroups (Table 1). More than 30% of medulloblastoma samples harbor mutations, deletions, or amplifications of genes encoding epigenetic regulators. Each medulloblastoma subtype also displays common and distinct epigenetic properties (Batora et al., 2014; Dubuc et al., 2013; Jones et al., 2013). This finding suggests that epigenetic alterations may be important drivers of medulloblastoma. Although the functions of epigenetic factors are not restricted to transcription regulation, it is speculated that in cancer these factors regulate expression of genes that drive cancer

progression. The generation and the maintenance of the transcription programs specifically required for each medulloblastoma subtype may require different sets of chromatin remodelers and histone modifiers. In this review, we will mainly focus on three types of epigenetic regulation in medulloblastoma: DNA methylation, histone modifications, and ATP-dependent chromatin remodeling. One common feature of these epigenetic regulators is their diverse and context-dependent functions in cancers. Epigenetic regulators can function as tumor suppressors or oncogenes, possibly depending on the gene program regulated by these factors and the gene programs required for tumor growth. The possibility of inhibiting enzymatic activities of epigenetic regulators has put these factors in the spotlight as candidate drug targets for treatment of medulloblastoma. Due to the highly context-dependent and subgroup-specific functions of epigenetic regulators, treatments will need to be personalized.

DNA methylation

Alteration of DNA methylation is a common feature of tumorigenesis (Jones and Baylin, 2007). Repression of candidate tumor suppressors by promoter CpG island hypermethylation was studied in medulloblastoma before the genome era. Using several assays for methylated DNA, including bisulfite sequencing of specific regions, a number of candidate tumor suppressors were identified that are silenced in medulloblastoma by promoter hypermethylation; these include *PTCH1* and *ZIC2* (Diede et al., 2010; Pfister et al., 2007). Treatment of medulloblastoma cancer cell lines with DNA methylation inhibitors also resulted in identification of genes with expression increased by the inhibitors (reviewed in (Batora et al., 2014)). In these studies, however, the tumor samples used were not subgroup classified, and some studies were not properly controlled, using cells of origin for specific medulloblastomas.

Recent genome-wide studies of DNA methylation patterns in subgroup classified medulloblastoma has provided new insights into the tumor molecular pathogenesis. Using DNA methylation microarrays, DNA methylation status at 1505 loci in 807 genes was analyzed in 230 medulloblastoma samples previously classified with transcription profiles. The four subgroups identified based on DNA methylation are highly related to their transcriptome counterparts, suggesting that each medulloblastoma subgroup has a specific DNA methylation pattern which can be used as a robust subclassification standard (Schwalbe et al., 2013). By comparing DNA methylation in both mouse and human medulloblastoma, an oncogene *VAV1* was found hypomethylated with elevated expression in most human SHH medulloblastoma and mouse SHH medulloblastoma models. Manipulation of *VAV1* levels in medulloblastoma models showed that *VAV1* is important for tumor maintenance (Lindsey et al., 2015).

In another whole-genome bisulfite sequencing analysis, Hovestadt et al. compared 34 human and five mouse medulloblastoma samples plus proper human and mouse normal controls. The bisulfite sequencing analysis together with matched RNA-seq and ChIP-seq data provided a comprehensive view of the DNA methylation landscape and gene expression profiles (Hovestadt et al., 2014). The authors found that the classical notion of gene silencing through promoter hypermethylation was not a prominent feature in

medulloblastoma. Instead, there is a high incident of hypomethylation of the region downstream of promoters extending tens of kilobases into the gene body, and this correlates with increased gene expression. Focal regions of low methylation are linked to transcription factor binding sites that may specify different transcription networks in different medulloblastoma subgroups. Differential methylation around the *LIN28B* gene suggested use of an alternate promoter in Group 3 and Group 4 tumors, which may result in higher levels of *LIN28B* and more aggressive tumor growth (Hovestadt et al., 2014). Notably, DNA methylation in tumors can be inherited from their cell-of-origin neural lineages but also can be generated *de novo* in tumors. It is not clear how these cancer-specific DNA methylation alterations are regulated by changes of the activities of DNA methyltransferases and/or enzymes that remove the methyl groups.

Histone modifications

Histone modifications such as acetylation, methylation, phosphorylation, and ubiquitination may either alter local chromatin structures or, more importantly, recruit proteins (readers) that recognize the modifications and regulate gene transcription. Multiple genes encoding histone modification enzymes or readers are altered in medulloblastoma, most with specific subgroup bias. An early study of DNA copy number alterations provided strong evidence that many epigenetic regulators are affected in medulloblastoma (Northcott et al., 2009). Recurrent focal amplifications and homozygous deletions in genes targeting histone lysine methylation, particularly that of H3K9, were identified. These include genes encoding the methyltransferases EHMT1 and SMYD4, polycomb proteins L3MBTL3, L3MBTL2, and SCML2, and histone demethylases JMJD2C and JMJD2B. Consistent with this finding, approximately 40% of medulloblastoma samples display lower than normal global H3K9me3. A recent more comprehensive study analyzing more than 1000 medulloblastoma samples confirmed the importance of the copy number changes of histone modification enzymes in medulloblastoma (Northcott et al., 2012c). However, it remains largely unclear how these epigenetic changes impact medulloblastoma development.

Dysregulated chromatin regulation pathways identified through genome-wide sequencing of medulloblastoma involve H3K4 and H3K27 methylation. The genes encoding H3K4 methyltransferases MLL2/KMT2D and MLL3/KMT2C are mutated in about 8% and 3% of medulloblastomas independent of subgroups. MLL2/3 complexes are required to maintain levels of H3K4me1, which marks enhancers (Rao and Dou, 2015; Sze and Shilatifard, 2016). MLL2/3 may activate gene expression through modulating enhancer activities during development and in cancer. *UTX/KDM6A* mutations and homozygous deletions are identified in 4% of medulloblastoma and are enriched in Group 4 tumors. In addition, Group 4 medulloblastoma patients are generally male, and tumors in female patients have often lost one X chromosome, where *UTX* is located (Dubuc et al., 2013; Jones et al., 2013). *UTX* activates genes by demethylating the repressive H3K27me3 mark. Interestingly, *UTX* interacts tightly with MLL2/3 complexes and is considered a subunit of these complexes (Cho et al., 2007; Lee et al., 2007). Together they may activate genes by methylating H3K4 and removing H3K27me3. Therefore, *MLL2/3* and *UTX* mutations are largely mutually exclusive in medulloblastoma (Dubuc et al., 2013); however, the pan-medulloblastoma mutation pattern of *MLL2/3* indicates its additional role in non-Group 4 medulloblastoma.

In line with the mutations of *UTX* in Group 4 medulloblastoma, *EZH2*, *EED*, and *SUZ12* subunits of the H3K27 methyltransferase PRC2 complex, are highly expressed, and the genes encoding these factors are often amplified in medulloblastoma (Bunt et al., 2013; Dubuc et al., 2013). In many cancers, PRC2 subunits function as oncogenes. Overexpression and gain-of-function mutations of PRC2 were observed in many cancers, which may result in a high level of H3K27me3 (Greer and Shi, 2012; Hock, 2012; Martinez-Garcia and Licht, 2010). PRC2 may repress specific tumor suppressor genes and facilitate cancer development. Notably, however, some cancers are associated with PRC2 loss-of-function mutations and low levels of H3K27me3 (Hock, 2012; Simon and Lange, 2008), which drives the expression of specific oncogenes (Chan et al., 2013; Lewis et al., 2013; Schwartzenuber et al., 2012; Wu et al., 2012a). Group 3 and Group 4 medulloblastoma have relatively high global H3K27me3 levels (Robinson et al., 2012). Within Group 3 and Group 4 tumors, a global high H3K4me3 and low H3K27me3 status is associated with better prognosis than low levels of both H3K4me3 and H3K27me3 (Dubuc et al., 2013). However, a recent genetic study indicated a tumor suppressor function of *EZH2* in a mouse Group 3 medulloblastoma model (discussed further below) (Vo et al., 2017). The tumor suppressor functions of *MLL2/3* and *UTX* have not yet been verified in mouse models or human medulloblastoma xenografts.

In addition to histone methylation modifiers, histone acetyltransferases (HATs) and deacetylases (HDACs) also play important and context-dependent roles in medulloblastoma. hMOF, a HAT for H4K16, has been shown to be down regulated in many medulloblastoma samples, and this down regulation is associated with low rates of survival (Pfister et al., 2008). The HAT genes that are mutated in some medulloblastoma patients are *CREBBP* and *EP300* (Jones et al., 2012; Pugh et al., 2012; Robinson et al., 2012); these genes encode CBP and p300, respectively, enzymes that catalyze H3K27Ac. H3K27Ac is a marker for active enhancers, and the HATs CBP and p300 activate the expression of many genes important for development and cancer progression (Jin et al., 2011; Ong and Corces, 2011). Although the target genes of CBP and p300 remain unclear in medulloblastoma, a genome-wide enhancer and super-enhancer study using H3K27Ac ChIP-seq revealed subgroup specific cis-regulatory element landscapes (Lin et al., 2016). Importantly, the analyses of super-enhancer regulated transcription factors suggest *LMX1a* as a master regulator in both cerebellum upper rhombic lip and in Group 4 medulloblastoma. The neural precursors derived from upper rhombic lip are putative cells of origin for Group 4 tumors. In general, HDACs likely support medulloblastoma growth, and HDAC inhibitors are being tested in clinical trials for treatment of medulloblastoma (see below). In SHH medulloblastoma, however, genes encoding several members of a nuclear receptor corepressor (N-CoR) complex, which is associated with HDACs to repress gene expression, were found to be mutated (Pugh et al., 2012), suggesting an inhibiting role of this complex in SHH medulloblastoma.

ATP-dependent chromatin remodeling

ATP-dependent chromatin remodeling complexes regulate chromatin structure using energy derived from ATP hydrolysis. The prototypical complex, the SWI/SNF-like BAF complex, containing 10–12 tightly associated subunits, can function as a transcription repressor and activator and is important for many developmental processes (Hargreaves and Crabtree,

2011; Wu, 2012). Recent genomic studies showed that genes encoding BAF complex subunits were mutated in more than 20% of all cancers, making them among the most mutated genes in cancer (Kadoch et al., 2013; Wilson and Roberts, 2011; Wu, 2012). The functions of these ATP-dependent chromatin remodeling complexes in cancers appear to be highly context-dependent. Various signaling pathways and cancer-related genes were identified as targets of Brg1/SMARCA4, a BAF complex core ATPase subunit, in different cancers, which may contribute to its potential tumor suppressor functions. BAF complexes are abundant in the nucleus, but effects are dose sensitive. Heterozygous missense mutations as well as homozygous deletions in genes encoding BAF complex subunits are observed in different type of cancers (Kadoch et al., 2013). Different mechanisms may contribute to cancer growth, which are under intensive investigation. Interestingly, in certain cancers, genes encoding BAF subunits are not mutated and are even required for oncogenesis (Romero et al., 2014; Shi et al., 2013). In addition to chromatin remodeling activities, BAF complexes interact with many other chromatin regulators. BAF complexes functionally antagonize polycomb repressive complexes (PRC1 and PRC2) under specific conditions (Kadoch et al., 2017; Stanton et al., 2017). In atypical rhabdoid tumors (ATRTs), where mutations of BAF subunit genes are the main oncogenic cause, PRC2 activities are increased (Wilson et al., 2010). Inactivating PRC2 activities has been pursued as a treatment strategy for ATRT and other cancers with BAF subunit mutations (Kim et al., 2015), but currently there are no effective BAF inhibitors.

In medulloblastoma, mutations in genes encoding BAF subunits such as Brg1 and ARID1A are among the most frequently observed in WNT and Group 3 tumors, with 25% and 11% having these mutations, respectively (Jones et al., 2012; Parsons et al., 2011; Pugh et al., 2012; Robinson et al., 2012). The missense mutations of *Brg1* are mostly located in the ATPase domain and have been shown to affect the interaction with topoisomerase 1a (Dykhuizen et al., 2013). The expression of Brg1 with point mutations identified in medulloblastoma leads to anaphase bridge formation and a G₂/M phase block characteristic of the decatenation checkpoint. It remains unclear whether this defect contributes to medulloblastoma pathogenesis. In SHH and Group 4 medulloblastoma, *Brg1* is largely free of mutations, suggesting an essential function of Brg1 in tumorigenesis. Our study of Brg1 function in SHH medulloblastoma revealed a key function of Brg1 in coordinating a genetic and epigenetic network supporting SHH medulloblastoma proliferation and identity (discussed below) (Shi et al., 2016). Interestingly, although mutations in genes encoding other BAF subunits are rare in pediatric SHH medulloblastoma, they are present in adult SHH medulloblastoma (Kool et al., 2014). It is not clear how these mutations regulate adult tumor progression; they may contribute to the tumor heterogeneity between pediatric and adult medulloblastoma.

In addition to BAF subunits, mutations in *CHD7*, which encodes another chromatin remodeler, were identified in Group 3 and Group 4 medulloblastoma (Robinson et al., 2012). Germline mutations in *CHD7* cause CHARGE syndrome, a multiple anomaly condition with defects in the nervous system (Martin, 2015). Medulloblastoma has been reported in CHARGE syndrome patients (Gajjar et al., 2014). Similarly, germline mutations in several chromatin regulators cause multi-system developmental diseases. For example, *CREBBP* mutation is the genetic cause of Rubinstein-Taybi Syndrome (Petrij et al., 1995), and these

patients are predisposed to medulloblastoma (Bourdeaut et al., 2014; Skousen et al., 1996). Mutations in BAF subunits cause Coffin-Siris syndrome (Santen et al., 2012; Tsurusaki et al., 2012). *MLL2* or *UTX* mutations cause Kabuki syndrome (Miyake et al., 2013). It remains unclear whether Coffin-Siris and Kabuki patients are predisposed to medulloblastoma.

Functions of epigenetic regulators in medulloblastoma

The high frequency of alterations of epigenetic regulators in medulloblastoma suggests the importance of chromatin regulation in tumor pathogenesis. To determine functions of proteins in medulloblastoma initiation and progression, loss-of-function and gain-of-function analyses are essential (Table 1, Figure 1). Since many medulloblastoma cell lines do not closely recapitulate tumor properties in culture, here we will focus on the studies using mouse models and patient-derived xenografts. Several genetically modified mouse lines develop medulloblastomas that resemble specific human subgroups. The *Blbp-cre Ctnnb1(ex3)^{Fl/+} TP53^{Fl/+}* mice express active β -catenin proteins in hindbrain germinal zones and develop medulloblastoma at the dorsal brainstem region. These tumors resemble WNT subtype (Gibson et al., 2010). A number of strains harboring mutations in SHH pathway genes such as *PTCH1*, *SMO* or *SUFU* produce medulloblastomas resembling SHH-type, albeit more similar to the adult subtype than the infant ones (Poschl et al., 2014). Recently, Group 3 mouse models were generated by overexpression of MYC in *TP53*-deficient CGNPs or cerebellum neural stem cells (Kawauchi et al., 2017; Kawauchi et al., 2012; Pei et al., 2012). No mouse model for Group 4 medulloblastoma has been generated. Several lines of patient-derived medulloblastoma xenografts have been generated that maintain the molecular fidelity of primary tumors and are useful for genetic or pharmacological studies of medulloblastoma (Dietl et al., 2016; Milde et al., 2012; Zhao et al., 2012). Notably, genetic mutations of most epigenetic regulators alone cause developmental defects but rarely produce tumors in mice. Therefore, these epigenetic regulators may need to cooperate with other cancer gene alterations to facilitate tumor development. The spatial and temporal manipulations of the epigenetic regulators also need to be well controlled in order to cause relevant context-dependent functions in tumor development.

Epigenetic regulation in SHH signaling and SHH medulloblastoma

SHH medulloblastoma is more extensively studied than other subgroups, mainly due to our good understanding of the SHH signaling pathway and the availability of several SHH medulloblastoma mouse models. SHH signaling regulates development and cancer by modulating the activities of GLI family transcription factors. SHH activation releases inhibition of SMO by PTCH1 to activate GLI1/2 transcription activators and downstream target gene expression (Briscoe and Therond, 2013; Fuccillo et al., 2006; Ingham and McMahon, 2001; Jiang and Hui, 2008). An active SHH signaling pathway is required for the proliferation of CGNPs, the cells of origin of SHH medulloblastoma (Gibson et al., 2010). Mutations that result in constitutively active SHH signaling cause over proliferation of CGNP and are the essential genetic causes of SHH medulloblastoma (Barakat et al., 2010; Kool et al., 2014).

GLI-mediated gene activation is the downstream executive step of SHH signaling and is an attractive treatment target for SHH medulloblastoma. In recent years, the epigenetic mechanism regulating GLI mediated gene transcription has begun to be characterized (Figure 1A). Our early work demonstrated that the chromatin remodeler Brg1 plays a dual role in SHH signaling by both repressing the GLI3R-mediated basal expression and activating GLI1/2-mediated target gene activation (Zhan et al., 2011). Conditional *Brg1* deletion in cerebellum leads to decreased expression of SHH/GLI target genes and reduced CGNP proliferation, resulting in smaller cerebellum (Moreno et al., 2014; Shi et al., 2016). In a SMO-induced medulloblastoma model, reducing *Brg1* dose or deleting *Brg1* in CGNPs impaired medulloblastoma initiation, and deleting *Brg1* after tumor formation significantly reduced tumor cell proliferation and growth (Shi et al., 2016).

Gene expression and Brg1 ChIP-seq analyses revealed a central role of Brg1 in regulating the key transcription pathways that control medulloblastoma proliferation and identity. In addition to the mitogenic SHH/GLI target genes, Brg1 also activates the target genes of ATOH1, a master regulator of CGNP and SHH medulloblastoma identity. Brg1 is also required for repression of a large number of neuronal genes that are targets of a master repressor REST/NRSF. By activating the GLI and ATOH1 oncogenic activities and repressing neuron differentiation, Brg1 coordinates a transcription network underlying SHH medulloblastoma proliferation and identity. In human SHH medulloblastoma, these transcription pathways are also over-represented and likely play key roles in tumor development (Shi et al., 2016).

In addition to the chromatin remodelers, histone modification enzymes also play important roles in regulating SHH/GLI-mediated target gene expression and SHH medulloblastoma. An examination of histone modifications of SHH target genes revealed that these genes all have H3K4me3/H3K27me3 bivalent chromatin domains at their regulatory regions (Shi et al., 2014). These bivalent domains keep the target genes at poised states under basal conditions. PRC2 complex is required to maintain the H3K27me3 levels and basal repression of target genes. SHH stimulation induces an exchange of epigenetic regulator complexes from the repressive PRC2 to a GLI1/2 interacting co-activator complex containing an H3K27me3 demethylase JMJD3/KDM6b, H3K4 methyltransferase MLL/SET complex, and BAF complexes (Figure 1A). In response to SHH activation, JMJD3 replaces PRC2, removes H3K27me3 repressive marks, and recruits other co-activators such as MLL complex. *JMJD3* deletion in mice led to impaired SHH-dependent developmental processes and resulted, for example, in smaller cerebella. Further, JMJD3 inhibition reduces proliferation and growth of SMO-induced medulloblastoma ((Shi et al., 2014) and Yi et al., unpublished data).

Interestingly, mouse and human SHH medulloblastomas have low global H3K27me3 levels and relatively high PRC2 levels (Gibson et al., 2010; Shi et al., 2014). This paradox indicates the presence of and possibly the requirement for high H3K27me3 demethylase activities in SHH medulloblastoma. In SMO-induced medulloblastoma, *Brg1* deletion impairs tumor growth, which correlates with increased global H3K27me3 and reduced JMJD3 binding to SHH target genes (Shi et al., 2016). Therefore, a complex epigenetic network comprising chromatin remodelers and histone modifiers function together with GLI

activators to produce specific transcription outcomes supporting SHH medulloblastoma growth (Figure 1A). GSK-J4, an inhibitor of H3K27me3 demethylases JMJD3 and UTX, inhibits cancer growth (Hashizume et al., 2014; Kruidenier et al., 2012; Ntziachristos et al., 2014). However, since it inhibits both JMJD3 and UTX and these factors may play opposite roles in medulloblastoma growth (Yi et al., unpublished data), it will be of interest to evaluate the effect of GSK-J4 on medulloblastoma development.

In an RNAi screen for HATs that affect SHH/GLI-induced gene activation, PCAF/KAT2B was identified (Malatesta et al., 2013). *PCAF* depletion impairs SHH activity and reduces expression of SHH target genes. PCAF downregulation in medulloblastoma and glioblastoma cells leads to decreased proliferation and increased apoptosis. PCAF interacts with GLI1 and possibly regulates gene expression by affecting local H3K9Ac levels. *PCAF* silencing reduces the glioma-forming potential of neural stem cells in a mouse xenograft model. However, in another study, PCAF was shown to be elevated by p53 and to represses SHH signaling in response to DNA damage by ubiquitinating and destabilizing GLI1 through its ubiquitin ligase activity (Mazza et al., 2013). DNA-damaging agents fail to inhibit GLI1 activity in the absence of either p53 or PCAF. Medulloblastoma samples from *TP53*-null mice display low levels of PCAF and upregulated GLI1. Therefore, inhibiting PCAF in SHH medulloblastoma may lead to complex consequences.

Class I HDACs such as HDAC1 have been shown to enhance GLI1/2 activities by deacetylating GLI1 and GLI2 (Canettieri et al., 2010; Coni et al., 2013). Activation of SHH signaling increases HDAC1 levels, leading to GLI1/2 deacetylation and activation. A ubiquitinase complex REN-CUL3 represses GLI activities by ubiquitinating and degrading HDAC1. HDAC1 inhibition impairs CGNP proliferation and the growth of medulloblastoma cell lines (Canettieri et al., 2010). Interestingly, we have shown that Brg1 facilitates class I HDAC2 binding to GLI target genes and functions in conjunction with HDACs to activate SHH target genes (Zhan et al., 2011). It remains unclear how HDACs selectively deacetylate GLI1/2 in regulatory regions but not histones.

EZH2 function in MYC-driven Group 3 medulloblastoma

The recent generation of mouse Group 3 medulloblastoma models has enabled functional studies of epigenetic regulators in this type of aggressive tumor (Kawauchi et al., 2012; Pei et al., 2012). The overexpression of PRC2 complexes, mutations in *UTX* and the globally high H3K27me3 in Groups 3 and 4 medulloblastomas, together with the oncogenic function of PRC2 in other cancers, suggest that PRC2 subunit EZH2 may promote the development of Group 3 and Group 4 medulloblastoma. It was reported that EZH2 deficiency and EZH2 inhibitor treatment decrease medulloblastoma growth and inhibit tumor sphere formation *in vitro* (Alimova et al., 2012). Liu et al. explored the interaction between EZH2 and MELK and found that both are essential for maintenance of the medulloblastoma cancer stem cell (MBSC) state and that disruption of expression of either factor results in the inhibition of MBSC activity (Liu et al., 2017). EZH2 was also shown to repress the expression of DAB2IP, which may function as a tumor suppressor gene in many cancers including medulloblastoma (Smits et al., 2012).

Most of these studies used cultured medulloblastoma cell lines, and a recent genetic study using the newly generated mouse MYC-driven Group 3 medulloblastoma model demonstrated a surprising tumor suppressor function of EZH2 (Vo et al., 2017). In this medulloblastoma model with MYC overexpression and *TP53* deletion, deleting *EZH2* before or after tumor formation accelerated medulloblastoma development. The authors also showed that the Group 3/4-specific oncogene *GFI1* was repressed by EZH2 (Figure 1B). Further, in the mouse model, overexpression of GFI1 together with MYC bypassed the need for *TP53* deletion to induce medulloblastoma formation.

These studies demonstrate the complex function of epigenetic regulators in tumor development. These factors may regulate both oncogenes and tumor suppressors and the overall effects on tumorigenesis depend on the balance between these seemingly counteracting activities. Therefore mouse models and human xenografts are essential to evaluate the function of epigenetic factors, and these pleiotropic factors may not be appropriate as general treatment targets for all medulloblastoma subgroups.

Epigenetic regulators of multiple medulloblastoma subgroups

In addition to the functions in specific medulloblastoma subgroups, several epigenetic regulators appear to regulate multiple subtypes. PRC1 subunit BMI1 has been shown to be required for stem cell maintenance for a number of cancers (Lessard and Sauvageau, 2003; Valk-Lingbeek et al., 2004). BMI1 binds to the promoter of the *p16^{ink4a}/p19^{Arf}* locus and represses the expression of these tumor suppressors (Lessard and Sauvageau, 2003). BMI1 is expressed in CGNPs and overexpressed in medulloblastoma across subgroups. A high level of *BMI1* expression is associated with poor prognosis (Leung et al., 2004; Manoranjan et al., 2013; Zakrzewska et al., 2011). In SHH medulloblastoma, BMI1 regulates tumor growth through a mechanism that does not involve regulation of GLI-mediated transcription (Figure 1C). Deleting *BMI1* causes reduced cerebellum size and impaired cerebellum development (Leung et al., 2004). RNAi-mediated inhibition of *BMI1* in human medulloblastoma DAOY cells results in the inhibition of growth. Deletion of *BMI1* in a SMO-induced medulloblastoma mouse model blocked tumor expansion (Michael et al., 2008). Transcriptome analyses of *BMI1*-null cerebellum showed that BMI1 regulates genes involved in the TGF β signaling pathway, ECM remodeling and cell adhesion, and particularly, cell cycle control. BMI1 not only represses the well-characterized cell cycle inhibitors p16^{Ink4a} and p19^{Arf} but also p21^{Waf1/Cip1} (Subkhankulova et al., 2010). In addition, a PRC1 complex containing BMI1 binds p53 directly, promoting its ubiquitination and possibly degradation. BMI1-mediated p53 inactivation may abrogate the oncoprotein stress response at medulloblastoma initiation (Calao et al., 2013). BMI1 expression is increased by SHH, possibly by direct GLI1 activation (Wang et al., 2012). In addition, BMI1 is repressed by microRNA Mir128a (Venkataraman et al., 2010). Overexpression of BMI1 alone in CGNPs did not induce medulloblastoma, but reduced CGNP proliferation instead. However, in combination with *TP53* deletion, overexpression of BMI1 causes low incidence of the formation of medulloblastoma (Behesti et al., 2013).

Although most of the functional studies of BMI1 have focused on SHH medulloblastoma, a recent genomic study showed that *BMI1* expression is higher in Group 3 and Group 4 than

in SHH group tumors and is the highest in Group 4 medulloblastoma. Using a xenograft model of Group 4 medulloblastoma and *in vitro* assays, the Marino group showed that BMI1 represses BMP signaling and the expression of cell adhesion genes (Merve et al., 2014). *BMI1* deletion in the xenograft medulloblastoma model affected both tumor volume and parenchymal invasion (Merve et al., 2014) (Figure 1C). The study of BMI1 may help us further understand the Group 4 medulloblastoma, which could also lead to the generation of mouse models for this least understood medulloblastoma subgroup.

REST/NRSF is a master regulator that represses expression of neuronal genes in non-neural cells and neural progenitors (Chong et al., 1995; Schoenherr and Anderson, 1995). REST represses gene expression by incorporating multiple epigenetic co-repressors such as H3K9 methyltransferase G9A, HDACs, and H3K4 demethylase KDM1A/LSD1 (Ballas and Mandel, 2005; Ooi and Wood, 2007). REST has been shown to function as a tumor suppressor in non-neural cancers and as an oncogene in neural tumors (Negrini et al., 2013). REST is highly expressed in medulloblastoma. Expression of REST-VP16, an activator of REST target genes, induced neuronal gene expression and inhibited proliferation and growth of medulloblastoma cell lines and xenograft models (Lawinger et al., 2000). Forced overexpression of REST together with MYC in cultured cerebellum neural stem cells blocks neuron differentiation. When injected into cerebellum, neural stem cells overexpressing REST and MYC grow into medulloblastoma (Su et al., 2006). It will be interesting to see whether these tumors recapitulate certain Group 3 medulloblastoma phenotypes.

A more recent study showed that higher expression of *REST* in human medulloblastoma is associated with poor prognosis (Taylor et al., 2012b). HDAC inhibitors as well as a KDM1A inhibitor both inhibit growth of medulloblastoma cell lines (Pajtler et al., 2013; Taylor et al., 2012b). Inhibition of KDM1A-mediated demethylation of H3K4 might therefore be a promising targeted therapy approach. In addition to neuronal genes, the Gopalakrishnan group showed that REST represses the expression of a tumor suppressor *USP37*, which encodes a deubiquitinase that stabilizes p27/CDKN1B in cerebellum and medulloblastoma (Das et al., 2013; Dobson et al., 2017). This repression is mediated through the interaction of REST with G9A and H3K9 methylation (Dobson et al., 2017). Therefore REST may be an oncogene across the subgroups, and its associated epigenetic regulators could be targeted for medulloblastoma treatment (Figure 1D).

Three groups have used the powerful unbiased Sleeping Beauty transposon screen to identify candidate functional regulators that contribute to medulloblastoma development (Genovesi et al., 2013; Lastowska et al., 2013; Wu et al., 2012b). Using the *PTCHI*^{+/-} mouse model of SHH medulloblastoma, the three groups all identified additional factors whose alteration by transposons accelerated tumor growth. Most of the factors identified from these studies are involved in transcription regulation including several epigenetic regulators such as CREBBP, KDM1A, and BRD4 that were previously identified from human genome-wide sequencing analyses or other studies. Interestingly, although the original tumors generated in *PTCHI*^{+/-} mice are SHH medulloblastoma, tumors induced by *PTCHI*^{+/-} and transposon insertions resemble all four subgroups (Genovesi et al., 2013), suggesting that changes in specific sets of key regulators, especially transcription factors and epigenetic regulators, may reprogram CGNPs to the cells of origin of other subgroups.

Indeed, MYC overexpression in *TP53*^{-/-} CGNPs reprogram CGNPs into stem like cells and induce development into Group 3 medulloblastoma (Kawauchi et al., 2017). Therefore although the four medulloblastoma subgroups display distinct transcription signatures and possibly have different cells of origins, specific common pathways may underlie the different medulloblastoma subgroups.

Epigenetic inhibitors for potential medulloblastoma treatment

The development of specific inhibitors of epigenetic regulators enables epigenetic therapy for targeted treatment of cancers and other diseases (Yoo and Jones, 2006) (Table 1). For medulloblastoma treatment, brain penetrance is a challenge for drug development. For example, none of the EZH2 inhibitors so far developed cross the blood brain barrier (Zhang et al., 2015). The brain penetrant DNA methylation inhibitors, HDAC inhibitors, and bromodomain inhibitors that have been tested in medulloblastoma models are discussed below. Combined treatments with inhibitors to other pathways are often used to increase the efficacy.

HDAC inhibitors

HDAC inhibitors have received considerable attention, and three HDAC inhibitors, vorinostat, romidepsin, and belinostat, have been approved by FDA to treat rare T cell lymphomas. Several clinical trials (e.g., NCT01294670 and NCT02780804) and many pre-clinical studies are ongoing to examine the effects of these inhibitors on medulloblastoma. Initial HDAC inhibitor studies showed that HDAC inhibition alone or in combination with other pathway inhibitors could effectively inhibit medulloblastoma cell proliferation in culture, induce cell death, and prolong xenografted mouse survival (Li et al., 2005; Shu et al., 2006; Wegener et al., 2008). HDAC inhibitors and a tyrosine kinase inhibitor sorafenib synergize to kill central nervous system tumor cells (Tang et al., 2012). Vorinostat and MLN8237 aurora kinase inhibitor have additive inhibition effects on medulloblastoma cell lines (Muscal et al., 2013). Sodium butyrate inhibits survival of human medulloblastoma cells, and might potentiate the effects of etoposide in cancer cell killing (Nor et al., 2013). In addition, panobinostat, a histone deacetylase inhibitor, suppresses leptomeningeal seeding in a medulloblastoma animal model (Phi et al., 2017).

HDAC inhibitors have been shown to affect SHH signaling and SHH medulloblastoma. As described earlier, HDACs may function as activators of transcription factors GLI1/2, and HDAC inhibitors appear to block GLI activities and SHH medulloblastoma growth (Canettieri et al., 2010) (Figure 1A). A comparison between normal cerebellum and SMO-induced medulloblastoma models showed increased expression of HDACs in medulloblastoma. Inhibition of HDACs ameliorates SMO-induced hyperplasia of CGNP cells during postnatal cerebellum development (Lee et al., 2013). Curcumin has been shown to induce apoptosis in medulloblastoma cells, and this is accompanied by reduced HDAC4 expression and increased tubulin acetylation. Curcumin treatment also displayed anti-tumor activity in a SMO-induced medulloblastoma model (Lee et al., 2011).

An expression analyses of HDACs in human medulloblastoma samples revealed that genes encoding class IIa HDACs HDAC5 and HDAC9 showed the highest expression in

prognostically poor subgroups. High *HDAC5* and *HDAC9* expression was significantly associated with poor overall survival. siRNA-mediated silencing of *HDAC5* or *HDAC9* in medulloblastoma cells results in decreased cell growth and cell viability. However, selective class IIa HDAC inhibitors did not inhibit medulloblastoma growth, suggesting that the enzymatic activity-independent functions of HDAC5 and HDAC9 may be important for medulloblastoma development (Milde et al., 2010). The Milde group also developed a Group 3 medulloblastoma cell line and xenograft model that display high HDAC expression levels and growth sensitivity to HDAC inhibitors (Milde et al., 2012). Along the same line, inhibition of class I HDACs resulted in significant reductions in metabolic activity and proliferation of *MYC*-amplified medulloblastoma cells (Ecker et al., 2015). HDAC inhibitors also emerged from a screen for small molecules that would selectively kill *MYC*-driven medulloblastoma cells but not normal cerebellum cells. HDAC inhibitors and PI3K inhibitors cooperate to activate FOXO1 and suppress *MYC*-driven tumors *in vitro* and *in vivo* (Pei et al., 2016) (Figure 1B).

Immunohistochemical staining of human medulloblastoma samples showed strong expression of SIRT1, a NAD-dependent deacetylase. SIRT1 inhibition by siRNA or nicotinamide causes growth arrest of medulloblastoma and apoptosis (Ma et al., 2013). Interestingly, a BCL6/BCOR/SIRT1 complex was identified as a potent repressor of the SHH pathway in normal and oncogenic neural development. SIRT1 is required for BCL6 function in repressing *GLI1/2* expression. Inhibiting the complex activities promoted mouse SHH medulloblastoma growth and human medulloblastoma cell proliferation (Tiberi et al., 2014) (Figure 1A). These different results may reflect the cultured medulloblastoma cell differences or context-dependent function of SIRT1 in different medulloblastoma subgroups.

DNA methylation inhibitors

DNA methylation inhibitors have shown promising anticancer effects. 5-Azacytidine (5-aza-CR) and its variant 5-aza-2'-deoxycytidine (5-aza-CdR) are approved for the treatment of high-risk myelodysplastic syndrome. These inhibitors have been tested for use in combination with other drugs. The combination of 5-aza-CdR and valproic acid to inhibit HDACs reduces medulloblastoma initiation in *PTCH1* mutant mice; however, it has little effect on advanced tumors in these mice (Ecke et al., 2009). Another study showed that although 5-aza-CdR alone has minor effects on medulloblastoma cell growth, its combination with tyrosine kinase inhibitor Gleevec has significantly enhanced cytotoxicity. The HDAC inhibitor 4-phenylbutyrate (4-PB) in combination with 5-aza-CdR and Gleevec treatment reduces global methylation and induction of apoptosis (Marino et al., 2014). Another DNA methylation inhibitor zebularine shows low toxicity and high efficacy and is a promising adjuvant agent for anti-cancer chemotherapy. Zebularine inhibits proliferation and clonogenicity of melanoma cell lines and increases the apoptosis rate. In addition to the repression of expression of *TP53* and other tumor suppressors, zebularine also inhibits expression of SHH pathway components such as SMO and *GLI1*. In addition, the combinations of zebularine with the chemotherapeutic agents vincristine and cisplatin result in synergism and antagonism, respectively (Andrade et al., 2017).

Bromodomain inhibitors

Bromodomain inhibitors, especially those that inhibit the BET family proteins, have been tested extensively *in vitro* and *in vivo* for treating various cancers (Wadhwa and Nicolaides, 2016). The BET family bromodomain proteins (BRD2, BRD3, BRD4) recognize acetyl-lysine and acetylated chromatin, which usually mark active enhancers. BET proteins function as principal mediators of gene activation. The super enhancers that regulate key genes in cancer growth are marked by high levels of H3K27Ac and are especially sensitive to BET inhibition (Loven et al., 2013). These brain penetrant inhibitors are promising drugs for treatment of brain tumors including medulloblastoma. Several BET inhibitors, including the most extensively tested JQ-1, showed significant effects in both SHH and Group 3 medulloblastoma models.

BRD4 has been shown to regulate the GLI and SHH pathway activities. BRD4 inhibition by RNAi or the inhibitor JQ-1 reduces the expression of *GLI1* and *GLI2*, resulting in decreased SHH medulloblastoma proliferation and tumor growth (Tang et al., 2014). Therefore, BET domain inhibitors are promising for treatment of SHH medulloblastomas that show resistance to SMO inhibitors. Another BET protein inhibitor, I-BET151, represses SHH/GLI reporter gene expression by reducing BRD4 binding to the *GLI1* locus and inhibits the SHH pathway in a manner similar to *BRD4* silencing. This inhibition significantly reduced the growth of allograft medulloblastoma derived from *PTCH1*^{+/-} mice (Long et al., 2014) (Figure 1A).

MYC amplification-induced cancers are very sensitive to BET inhibitors. Several studies have evaluated the effect of BET inhibitors in treating MYC-driven medulloblastoma. Henssen et al. found that treating medulloblastoma cell lines with BET inhibitors downregulated *MYC* and MYC target gene expression (Henssen et al., 2013). Interestingly, BET inhibitors also deregulated genes involved in cell cycle and the p53 pathway. In a human Group 3 medulloblastoma xenograft model, JQ-1 treatment significantly prolongs host mouse survival and reduces tumor volumes (Henssen et al., 2013). Bandopadhyay et al. showed that JQ-1 reduces the growth of medulloblastoma cell lines and inhibits the expression of *MYC* and *MYCN* and their downstream target genes and significantly reduces tumor growth and extends the survival of mice harboring medulloblastoma with MYC or MYCN overexpression (Bandopadhyay et al., 2014). Similarly, Venkataraman et al. showed that JQ-1 treatment impairs the MYC-mediated transcription program and reduces MYC-driven medulloblastoma cell growth. In addition, they demonstrated that JQ-1 inhibits stem cell-associated signaling and induces cell senescence in culture and in a mouse xenograft model (Venkataraman et al., 2014). Therefore, BET bromodomain inhibition is a promising therapeutic option for MYC-driven medulloblastoma (Figure 1B).

Conclusions and perspectives

The recent intense effort to determine medulloblastoma molecular genetics pathogenesis has the potential to enable use of precision medicine to treat medulloblastoma patients. Genetic and pharmacological studies of functions of epigenetic regulators in medulloblastoma initiation and progression in mouse models and patient-derived xenografts are keys to understanding the specific functions of these factors in the development of tumors of

different medulloblastoma subgroups. The genome era is opening new frontiers for both pediatric oncologists and chromatin researchers. The demonstration that mutations in a large number of epigenetic regulators are involved in genetic diseases as well as pediatric malignancies provides new treatment opportunities and challenges at the same time. The enzymatic activities of epigenetic regulators are promising drug targets, whereas the pleiotropic functions of these factors in development and in cancers require caution for drug selection. More detailed tumor molecular genetics analyses, as well as functional analyses of epigenetic factors, will further the development of epigenetic therapies for medulloblastoma treatment.

Acknowledgments

The work in the Wu lab is supported by grants from NINDS (R01NS096068, R21NS104596), the American Cancer Society, and the Welch Foundation (to J. Wu).

References

- Alimova I, Venkataraman S, Harris P, Marquez VE, Northcott PA, Dubuc A, Taylor MD, Foreman NK, Vibhakar R. Targeting the enhancer of zeste homologue 2 in medulloblastoma. *Int J Cancer*. 2012; 131:1800–1809. [PubMed: 22287205]
- Andrade AF, Borges KS, Suazo VK, Geron L, Correa CA, Castro-Gamero AM, de Vasconcelos EJ, de Oliveira RS, Neder L, Yunes JA, Dos Santos Aguiar S, Scrideli CA, Tone LG. The DNA methyltransferase inhibitor zebularine exerts antitumor effects and reveals BATF2 as a poor prognostic marker for childhood medulloblastoma. *Invest New Drugs*. 2017; 35:26–36. [PubMed: 27785591]
- Ballas N, Mandel G. The many faces of REST oversee epigenetic programming of neuronal genes. *Curr Opin Neurobiol*. 2005; 15:500–506. [PubMed: 16150588]
- Bandopadhyay P, Berghthold G, Nguyen B, Schubert S, Gholamin S, Tang Y, Bolin S, Schumacher SE, Zeid R, Masoud S, Yu F, Vue N, Gibson WJ, Paoletta BR, Mitra SS, Cheshier SH, Qi J, Liu KW, Wechsler-Reya R, Weiss WA, Swartling FJ, Kieran MW, Bradner JE, Beroukhi R, Cho YJ. BET bromodomain inhibition of MYC-amplified medulloblastoma. *Clin Cancer Res*. 2014; 20:912–925. [PubMed: 24297863]
- Barakat MT, Humke EW, Scott MP. Learning from Jekyll to control Hyde: Hedgehog signaling in development and cancer. *Trends Mol Med*. 2010; 16:337–348. [PubMed: 20696410]
- Batora NV, Sturm D, Jones DT, Kool M, Pfister SM, Northcott PA. Transitioning from genotypes to epigenotypes: why the time has come for medulloblastoma epigenomics. *Neuroscience*. 2014; 264:171–185. [PubMed: 23876321]
- Behesti H, Bhagat H, Dubuc AM, Taylor MD, Marino S. Bmi1 overexpression in the cerebellar granule cell lineage of mice affects cell proliferation and survival without initiating medulloblastoma formation. *Dis Model Mech*. 2013; 6:49–63. [PubMed: 23065639]
- Bourdeaut F, Miquel C, Richer W, Grill J, Zerah M, Grison C, Pierron G, Amiel J, Krucker C, Radvanyi F, Brugieres L, Delattre O. Rubinstein-Taybi syndrome predisposing to non-WNT, non-SHH, group 3 medulloblastoma. *Pediatr Blood Cancer*. 2014; 61:383–386. [PubMed: 24115570]
- Briscoe J, Therond PP. The mechanisms of Hedgehog signalling and its roles in development and disease. *Nat Rev Mol Cell Biol*. 2013; 14:416–429. [PubMed: 23719536]
- Bunt J, Hasselt NA, Zwijnenburg DA, Koster J, Versteeg R, Kool M. OTX2 sustains a bivalent-like state of OTX2-bound promoters in medulloblastoma by maintaining their H3K27me3 levels. *Acta neuropathologica*. 2013; 125:385–394. [PubMed: 23179372]
- Calao M, Sekyere EO, Cui HJ, Cheung BB, Thomas WD, Keating J, Chen JB, Raif A, Jankowski K, Davies NP, Bekkum MV, Chen B, Tan O, Ellis T, Norris MD, Haber M, Kim ES, Shohet JM, Trahair TN, Liu T, Wainwright BJ, Ding HF, Marshall GM. Direct effects of Bmi1 on p53 protein stability inactivates oncoprotein stress responses in embryonal cancer precursor cells at tumor initiation. *Oncogene*. 2013; 32:3616–3626. [PubMed: 22907436]

- Canettieri G, Di Marcotullio L, Greco A, Coni S, Antonucci L, Infante P, Pietrosanti L, De Smaele E, Ferretti E, Miele E, Pelloni M, De Simone G, Pedone EM, Gallinari P, Giorgi A, Steinkuhler C, Vitagliano L, Pedone C, Schinin ME, Screpanti I, Gulino A. Histone deacetylase and Cullin3-REN(KCTD11) ubiquitin ligase interplay regulates Hedgehog signalling through Gli acetylation. *Nat Cell Biol.* 2010; 12:132–142. [PubMed: 20081843]
- Cavalli FMG, Remke M, Rampasek L, Peacock J, Shih DJH, Luu B, Garzia L, Torchia J, Nor C, Morrissy AS, Agnihotri S, Thompson YY, Kuzan-Fischer CM, Farooq H, Isaev K, Daniels C, Cho BK, Kim SK, Wang KC, Lee JY, Grajkowska WA, Perek-Polnik M, Vasiljevic A, Faure-Conter C, Jouvett A, Giannini C, Nageswara Rao AA, Li KKW, Ng HK, Eberhart CG, Pollack IF, Hamilton RL, Gillespie GY, Olson JM, Leary S, Weiss WA, Lach B, Chambless LB, Thompson RC, Cooper MK, Vibhakar R, Hauser P, van Veelen MC, Kros JM, French PJ, Ra YS, Kumabe T, Lopez-Aguilar E, Zitterbart K, Sterba J, Finocchiaro G, Massimino M, Van Meir EG, Osuka S, Shofuda T, Klekner A, Zollo M, Leonard JR, Rubin JB, Jabado N, Albrecht S, Mora J, Van Meter TE, Jung S, Moore AS, Hallahan AR, Chan JA, Tirapelli DPC, Carlotti CG, Fouladi M, Pimentel J, Faria CC, Saad AG, Massimi L, Liao LM, Wheeler H, Nakamura H, Elbabaa SK, Perezpena-Diazconti M, Chico Ponce de Leon F, Robinson S, Zapotocky M, Lassaletta A, Huang A, Hawkins CE, Tabori U, Bouffett E, Bartels U, Dirks PB, Rutka JT, Bader GD, Reimand J, Goldenberg A, Ramaswamy V, Taylor MD. Intertumoral Heterogeneity within Medulloblastoma Subgroups. *Cancer Cell.* 2017; 31:737–754. e736. [PubMed: 28609654]
- Chan KM, Fang D, Gan H, Hashizume R, Yu C, Schroeder M, Gupta N, Mueller S, James CD, Jenkins R, Sarkaria J, Zhang Z. The histone H3.3K27M mutation in pediatric glioma reprograms H3K27 methylation and gene expression. *Genes Dev.* 2013; 27:985–990. [PubMed: 23603901]
- Cho YW, Hong T, Hong S, Guo H, Yu H, Kim D, Guszczynski T, Dressler GR, Copeland TD, Kalkum M, Ge K. PTIP associates with MLL3- and MLL4-containing histone H3 lysine 4 methyltransferase complex. *J Biol Chem.* 2007; 282:20395–20406. [PubMed: 17500065]
- Chong JA, Tapia-Ramirez J, Kim S, Toledo-Aral JJ, Zheng Y, Boutros MC, Altshuler YM, Frohman MA, Kraner SD, Mandel G. REST: a mammalian silencer protein that restricts sodium channel gene expression to neurons. *Cell.* 1995; 80:949–957. [PubMed: 7697725]
- Coni S, Antonucci L, D'Amico D, Di Magno L, Infante P, De Smaele E, Giannini G, Di Marcotullio L, Screpanti I, Gulino A, Canettieri G. Gli2 acetylation at lysine 757 regulates hedgehog-dependent transcriptional output by preventing its promoter occupancy. *PLoS One.* 2013; 8:e65718. [PubMed: 23762415]
- Das CM, Taylor P, Gireud M, Singh A, Lee D, Fuller G, Ji L, Fangusaro J, Rajaram V, Goldman S, Eberhart C, Gopalakrishnan V. The deubiquitylase USP37 links REST to the control of p27 stability and cell proliferation. *Oncogene.* 2013; 32:1691–1701. [PubMed: 22665064]
- Diede SJ, Guenthoer J, Geng LN, Mahoney SE, Marotta M, Olson JM, Tanaka H, Tapscott SJ. DNA methylation of developmental genes in pediatric medulloblastomas identified by denaturation analysis of methylation differences. *Proc Natl Acad Sci U S A.* 2010; 107:234–239. [PubMed: 19966297]
- Dietl S, Schwinn S, Dietl S, Riedel S, Deinlein F, Rutkowski S, von Bueren AO, Krauss J, Schweitzer T, Vince GH, Picard D, Eylich M, Rosenwald A, Ramaswamy V, Taylor MD, Remke M, Monoranu CM, Beilhack A, Schlegel PG, Wolf M. MB3W1 is an orthotopic xenograft model for anaplastic medulloblastoma displaying cancer stem cell- and Group 3-properties. *BMC Cancer.* 2016; 16:115. [PubMed: 26883117]
- Dobson THW, Hatcher RJ, Swaminathan J, Das CM, Shaik S, Tao RH, Milite C, Castellano S, Taylor PH, Sbardella G, Gopalakrishnan V. Regulation of USP37 Expression by REST-Associated G9a-Dependent Histone Methylation. *Mol Cancer Res.* 2017
- Dubuc AM, Remke M, Korshunov A, Northcott PA, Zhan SH, Mendez-Lago M, Kool M, Jones DT, Unterberger A, Morrissy AS, Shih D, Peacock J, Ramaswamy V, Rolider A, Wang X, Witt H, Hielscher T, Hawkins C, Vibhakar R, Croul S, Rutka JT, Weiss WA, Jones SJ, Eberhart CG, Marra MA, Pfister SM, Taylor MD. Aberrant patterns of H3K4 and H3K27 histone lysine methylation occur across subgroups in medulloblastoma. *Acta neuropathologica.* 2013; 125:373–384. [PubMed: 23184418]

- Dykhuizen EC, Hargreaves DC, Miller EL, Cui K, Korshunov A, Kool M, Pfister S, Cho YJ, Zhao K, Crabtree GR. BAF complexes facilitate decatenation of DNA by topoisomerase II α . *Nature*. 2013; 497:624–627. [PubMed: 23698369]
- Ecke I, Petry F, Rosenberger A, Tauber S, Monkemeyer S, Hess I, Dullin C, Kimmina S, Pirngruber J, Johnsen SA, Uhmman A, Nitzki F, Wojnowski L, Schulz-Schaeffer W, Witt O, Hahn H. Antitumor effects of a combined 5-aza-2'-deoxycytidine and valproic acid treatment on rhabdomyosarcoma and medulloblastoma in Ptch mutant mice. *Cancer Res*. 2009; 69:887–895. [PubMed: 19155313]
- Ecker J, Oehme I, Mazitschek R, Korshunov A, Kool M, Hielscher T, Kiss J, Selt F, Konrad C, Lodrini M, Deubzer HE, von Deimling A, Kulozik AE, Pfister SM, Witt O, Milde T. Targeting class I histone deacetylase 2 in MYC amplified group 3 medulloblastoma. *Acta Neuropathol Commun*. 2015; 3:22. [PubMed: 25853389]
- Ellison DW, Onilude OE, Lindsey JC, Lusher ME, Weston CL, Taylor RE, Pearson AD, Clifford SC. United Kingdom Children's Cancer Study Group Brain Tumour C. beta-Catenin status predicts a favorable outcome in childhood medulloblastoma: the United Kingdom Children's Cancer Study Group Brain Tumour Committee. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2005; 23:7951–7957. [PubMed: 16258095]
- Feinberg AP, Koldobskiy MA, Gondor A. Epigenetic modulators, modifiers and mediators in cancer aetiology and progression. *Nat Rev Genet*. 2016; 17:284–299. [PubMed: 26972587]
- Fuccillo M, Joyner AL, Fishell G. Morphogen to mitogen: the multiple roles of hedgehog signalling in vertebrate neural development. *Nat Rev Neurosci*. 2006; 7:772–783. [PubMed: 16988653]
- Gajjar A, Bowers DC, Karajannis MA, Leary S, Witt H, Gottardo NG. Pediatric Brain Tumors: Innovative Genomic Information Is Transforming the Diagnostic and Clinical Landscape. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2015; 33:2986–2998. [PubMed: 26304884]
- Gajjar A, Chintagumpala M, Ashley D, Kellie S, Kun LE, Merchant TE, Woo S, Wheeler G, Ahern V, Krasin MJ, Fouladi M, Broniscer A, Krance R, Hale GA, Stewart CF, Dauser R, Sanford RA, Fuller C, Lau C, Boyett JM, Wallace D, Gilbertson RJ. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. *Lancet Oncol*. 2006; 7:813–820. [PubMed: 17012043]
- Gajjar S, Mazloom A, Chintagumpala M, Mahajan A, Paulino AC. Secondary glioblastoma multiform in a patient with CHARGE syndrome and prior radiation therapy for medulloblastoma. *Pediatr Hematol Oncol*. 2014; 31:366–368. [PubMed: 24684140]
- Genovesi LA, Ng CG, Davis MJ, Remke M, Taylor MD, Adams DJ, Rust AG, Ward JM, Ban KH, Jenkins NA, Copeland NG, Wainwright BJ. Sleeping Beauty mutagenesis in a mouse medulloblastoma model defines networks that discriminate between human molecular subgroups. *Proc Natl Acad Sci U S A*. 2013; 110:E4325–4334. [PubMed: 24167280]
- Gibson P, Tong Y, Robinson G, Thompson MC, Curre DS, Eden C, Kranenburg TA, Hogg T, Poppleton H, Martin J, Finkelstein D, Pounds S, Weiss A, Patay Z, Scoggins M, Ogg R, Pei Y, Yang ZJ, Brun S, Lee Y, Zindy F, Lindsey JC, Taketo MM, Boop FA, Sanford RA, Gajjar A, Clifford SC, Roussel MF, McKinnon PJ, Gutmann DH, Ellison DW, Wechsler-Reya R, Gilbertson RJ. Subtypes of medulloblastoma have distinct developmental origins. *Nature*. 2010; 468:1095–1099. [PubMed: 21150899]
- Greer EL, Shi Y. Histone methylation: a dynamic mark in health, disease and inheritance. *Nat Rev Genet*. 2012; 13:343–357. [PubMed: 22473383]
- Hargreaves DC, Crabtree GR. ATP-dependent chromatin remodeling: genetics, genomics and mechanisms. *Cell Res*. 2011; 21:396–420. [PubMed: 21358755]
- Hashizume R, Andor N, Ihara Y, Lerner R, Gan H, Chen X, Fang D, Huang X, Tom MW, Ngo V, Solomon D, Mueller S, Paris PL, Zhang Z, Petritsch C, Gupta N, Waldman TA, James CD. Pharmacologic inhibition of histone demethylation as a therapy for pediatric brainstem glioma. *Nat Med*. 2014; 20:1394–1396. [PubMed: 25401693]
- Henssen A, Thor T, Odersky A, Heukamp L, El-Hindy N, Beckers A, Speleman F, Althoff K, Schafers S, Schramm A, Sure U, Fleischhack G, Eggert A, Schulte JH. BET bromodomain protein inhibition is a therapeutic option for medulloblastoma. *Oncotarget*. 2013; 4:2080–2095. [PubMed: 24231268]

- Hock H. A complex Polycomb issue: the two faces of EZH2 in cancer. *Genes Dev.* 2012; 26:751–755. [PubMed: 22508723]
- Holgado BL, Guerreiro Stucklin A, Garzia L, Daniels C, Taylor MD. Tailoring Medulloblastoma Treatment Through Genomics: Making a Change, One Subgroup at a Time. *Annu Rev Genomics Hum Genet.* 2017
- Hovestadt V, Jones DT, Picelli S, Wang W, Kool M, Northcott PA, Sultan M, Stachurski K, Ryzhova M, Warnatz HJ, Ralser M, Brun S, Bunt J, Jager N, Kleinheinz K, Erkek S, Weber UD, Bartholomae CC, von Kalle C, Lawrenz C, Eils J, Koster J, Versteeg R, Milde T, Witt O, Schmidt S, Wolf S, Pietsch T, Rutkowski S, Scheurlen W, Taylor MD, Brors B, Felsberg J, Reifenberger G, Borkhardt A, Lehrach H, Wechsler-Reya RJ, Eils R, Yaspo ML, Landgraf P, Korshunov A, Zapatka M, Radlwimmer B, Pfister SM, Lichter P. Decoding the regulatory landscape of medulloblastoma using DNA methylation sequencing. *Nature.* 2014; 510:537–541. [PubMed: 24847876]
- Ingham PW, McMahon AP. Hedgehog signaling in animal development: paradigms and principles. *Genes Dev.* 2001; 15:3059–3087. [PubMed: 11731473]
- Jiang J, Hui CC. Hedgehog signaling in development and cancer. *Dev Cell.* 2008; 15:801–812. [PubMed: 19081070]
- Jin Q, Yu LR, Wang L, Zhang Z, Kasper LH, Lee JE, Wang C, Brindle PK, Dent SY, Ge K. Distinct roles of GCN5/PCAF-mediated H3K9ac and CBP/p300-mediated H3K18/27ac in nuclear receptor transactivation. *Embo J.* 2011; 30:249–262. [PubMed: 21131905]
- Jones DT, Jager N, Kool M, Zichner T, Hutter B, Sultan M, Cho YJ, Pugh TJ, Hovestadt V, Stutz AM, Rausch T, Warnatz HJ, Ryzhova M, Bender S, Sturm D, Pleier S, Cin H, Pfaff E, Sieber L, Wittmann A, Remke M, Witt H, Hutter S, Tzaridis T, Weischenfeldt J, Raeder B, Avci M, Amstislavskiy V, Zapatka M, Weber UD, Wang Q, Lasitschka B, Bartholomae CC, Schmidt M, von Kalle C, Ast V, Lawrenz C, Eils J, Kabbe R, Benes V, van Sluis P, Koster J, Volckmann R, Shih D, Betts MJ, Russell RB, Coco S, Tonini GP, Schuller U, Hans V, Graf N, Kim YJ, Monoranu C, Roggendorf W, Unterberg A, Herold-Mende C, Milde T, Kulozik AE, von Deimling A, Witt O, Maass E, Rossler J, Ebinger M, Schuhmann MU, Fruhwald MC, Hasselblatt M, Jabado N, Rutkowski S, von Bueren AO, Williamson D, Clifford SC, McCabe MG, Collins VP, Wolf S, Wiemann S, Lehrach H, Brors B, Scheurlen W, Felsberg J, Reifenberger G, Northcott PA, Taylor MD, Meyerson M, Pomeroy SL, Yaspo ML, Korbel JO, Korshunov A, Eils R, Pfister SM, Lichter P. Dissecting the genomic complexity underlying medulloblastoma. *Nature.* 2012; 488:100–105. [PubMed: 22832583]
- Jones DT, Northcott PA, Kool M, Pfister SM. The role of chromatin remodeling in medulloblastoma. *Brain Pathol.* 2013; 23:193–199. [PubMed: 23432644]
- Jones PA, Baylin SB. The epigenomics of cancer. *Cell.* 2007; 128:683–692. [PubMed: 17320506]
- Jones PA, Issa JP, Baylin S. Targeting the cancer epigenome for therapy. *Nat Rev Genet.* 2016; 17:630–641. [PubMed: 27629931]
- Kadoch C, Hargreaves DC, Hodges C, Elias L, Ho L, Ranish J, Crabtree GR. Proteomic and bioinformatic analysis of mammalian SWI/SNF complexes identifies extensive roles in human malignancy. *Nat Genet.* 2013; 45:592–601. [PubMed: 23644491]
- Kadoch C, Williams RT, Calarco JP, Miller EL, Weber CM, Braun SM, Pulice JL, Chory EJ, Crabtree GR. Dynamics of BAF-Polycomb complex opposition on heterochromatin in normal and oncogenic states. *Nat Genet.* 2017; 49:213–222. [PubMed: 27941796]
- Kawauchi D, Ogg RJ, Liu L, Shih DJH, Finkelstein D, Murphy BL, Reh JE, Korshunov A, Calabrese C, Zindy F, Phoenix T, Kawaguchi Y, Gronych J, Gilbertson RJ, Lichter P, Gajjar A, Kool M, Northcott PA, Pfister SM, Roussel MF. Novel MYC-driven medulloblastoma models from multiple embryonic cerebellar cells. *Oncogene.* 2017
- Kawauchi D, Robinson G, Uziel T, Gibson P, Reh J, Gao C, Finkelstein D, Qu C, Pounds S, Ellison DW, Gilbertson RJ, Roussel MF. A mouse model of the most aggressive subgroup of human medulloblastoma. *Cancer Cell.* 2012; 21:168–180. [PubMed: 22340591]
- Kim KH, Kim W, Howard TP, Vazquez F, Tsherniak A, Wu JN, Wang W, Haswell JR, Walensky LD, Hahn WC, Orkin SH, Roberts CW. SWI/SNF-mutant cancers depend on catalytic and non-catalytic activity of EZH2. *Nat Med.* 2015; 21:1491–1496. [PubMed: 26552009]

- Kool M, Jones DT, Jager N, Northcott PA, Pugh TJ, Hovestadt V, Piro RM, Esparza LA, Markant SL, Remke M, Milde T, Bourdeaut F, Ryzhova M, Sturm D, Pfaff E, Stark S, Hutter S, Seker-Cin H, Johann P, Bender S, Schmidt C, Rausch T, Shih D, Reimand J, Sieber L, Wittmann A, Linke L, Witt H, Weber UD, Zapatka M, Konig R, Beroukhi R, Bergthold G, van Sluis P, Volckmann R, Koster J, Versteeg R, Schmidt S, Wolf S, Lawerenz C, Bartholomae CC, von Kalle C, Unterberg A, Herold-Mende C, Hofer S, Kulozik AE, von Deimling A, Scheurlen W, Felsberg J, Reifenberger G, Hasselblatt M, Crawford JR, Grant GA, Jabado N, Perry A, Cowdrey C, Croul S, Zadeh G, Korbel JO, Doz F, Delattre O, Bader GD, McCabe MG, Collins VP, Kieran MW, Cho YJ, Pomeroy SL, Witt O, Brors B, Taylor MD, Schuller U, Korshunov A, Eils R, Wechsler-Reya RJ, Lichter P, Pfister SM. Genome sequencing of SHH medulloblastoma predicts genotype-related response to smoothened inhibition. *Cancer Cell*. 2014; 25:393–405. [PubMed: 24651015]
- Kool M, Korshunov A, Remke M, Jones DT, Schlanstein M, Northcott PA, Cho YJ, Koster J, Schouten-van Meeteren A, van Vuurden D, Clifford SC, Pietsch T, von Bueren AO, Rutkowski S, McCabe M, Collins VP, Backlund ML, Haberler C, Bourdeaut F, Delattre O, Doz F, Ellison DW, Gilbertson RJ, Pomeroy SL, Taylor MD, Lichter P, Pfister SM. Molecular subgroups of medulloblastoma: an international meta-analysis of transcriptome, genetic aberrations, and clinical data of WNT, SHH, Group 3, and Group 4 medulloblastomas. *Acta neuropathologica*. 2012; 123:473–484. [PubMed: 22358457]
- Kruidenier L, Chung CW, Cheng Z, Liddle J, Che K, Joberty G, Bantscheff M, Bountra C, Bridges A, Diallo H, Eberhard D, Hutchinson S, Jones E, Katso R, Leveridge M, Mander PK, Mosley J, Ramirez-Molina C, Rowland P, Schofield CJ, Sheppard RJ, Smith JE, Swales C, Tanner R, Thomas P, Tumber A, Drewes G, Oppermann U, Patel DJ, Lee K, Wilson DM. A selective jumonji H3K27 demethylase inhibitor modulates the proinflammatory macrophage response. *Nature*. 2012; 488:404–408. [PubMed: 22842901]
- Lastowska M, Al-Afghani H, Al-Balool HH, Sheth H, Mercer E, Coxhead JM, Redfern CP, Peters H, Burt AD, Santibanez-Koref M, Bacon CM, Chesler L, Rust AG, Adams DJ, Williamson D, Clifford SC, Jackson MS. Identification of a neuronal transcription factor network involved in medulloblastoma development. *Acta Neuropathol Commun*. 2013; 1:35. [PubMed: 24252690]
- Lawinger P, Venugopal R, Guo ZS, Immaneni A, Sengupta D, Lu W, Rastelli L, Marin Dias Carneiro A, Levin V, Fuller GN, Echelard Y, Majumder S. The neuronal repressor REST/NRSF is an essential regulator in medulloblastoma cells. *Nat Med*. 2000; 6:826–831. [PubMed: 10888935]
- Lee MG, Villa R, Trojer P, Norman J, Yan KP, Reinberg D, Di Croce L, Shiekhata R. Demethylation of H3K27 regulates polycomb recruitment and H2A ubiquitination. *Science*. 2007; 318:447–450. [PubMed: 17761849]
- Lee SJ, Krauthausen C, Maduskuie V, Fawcett PT, Olson JM, Rajasekaran SA. Curcumin-induced HDAC inhibition and attenuation of medulloblastoma growth in vitro and in vivo. *BMC Cancer*. 2011; 11:144. [PubMed: 21501498]
- Lee SJ, Lindsey S, Graves B, Yoo S, Olson JM, Langhans SA. Sonic hedgehog-induced histone deacetylase activation is required for cerebellar granule precursor hyperplasia in medulloblastoma. *PLoS One*. 2013; 8:e71455. [PubMed: 23951168]
- Lessard J, Sauvageau G. Bmi-1 determines the proliferative capacity of normal and leukaemic stem cells. *Nature*. 2003; 423:255–260. [PubMed: 12714970]
- Leung C, Lingbeek M, Shakhova O, Liu J, Tanger E, Saremaslani P, Van Lohuizen M, Marino S. Bmi1 is essential for cerebellar development and is overexpressed in human medulloblastomas. *Nature*. 2004; 428:337–341. [PubMed: 15029199]
- Lewis PW, Muller MM, Koletsky MS, Cordero F, Lin S, Banaszynski LA, Garcia BA, Muir TW, Becher OJ, Allis CD. Inhibition of PRC2 activity by a gain-of-function H3 mutation found in pediatric glioblastoma. *Science*. 2013; 340:857–861. [PubMed: 23539183]
- Li XN, Shu Q, Su JM, Perlaky L, Blaney SM, Lau CC. Valproic acid induces growth arrest, apoptosis, and senescence in medulloblastomas by increasing histone hyperacetylation and regulating expression of p21Cip1, CDK4, and CMYC. *Molecular cancer therapeutics*. 2005; 4:1912–1922. [PubMed: 16373706]
- Lin CY, Erkek S, Tong Y, Yin L, Federation AJ, Zapatka M, Haldipur P, Kawauchi D, Risch T, Warnatz HJ, Worst BC, Ju B, Orr BA, Zeid R, Polaski DR, Segura-Wang M, Waszak SM, Jones DT, Kool M, Hovestadt V, Buchhalter I, Sieber L, Johann P, Chavez L, Groschel S, Ryzhova M,

- Korshunov A, Chen W, Chizhikov VV, Millen KJ, Amstislavskiy V, Lehrach H, Yaspo ML, Eils R, Lichter P, Korbel JO, Pfister SM, Bradner JE, Northcott PA. Active medulloblastoma enhancers reveal subgroup-specific cellular origins. *Nature*. 2016; 530:57–62. [PubMed: 26814967]
- Lindsey JC, Kawauchi D, Schwalbe EC, Solecki DJ, Selby MP, McKinnon PJ, Olson JM, Hayden JT, Grundy RG, Ellison DW, Williamson D, Bailey S, Roussel MF, Clifford SC. Cross-species epigenetics identifies a critical role for VAV1 in SHH subgroup medulloblastoma maintenance. *Oncogene*. 2015; 34:4746–4757. [PubMed: 25531316]
- Lindsey JC, Schwalbe EC, Potluri S, Bailey S, Williamson D, Clifford SC. TERT promoter mutation and aberrant hypermethylation are associated with elevated expression in medulloblastoma and characterise the majority of non-infant SHH subgroup tumours. *Acta neuropathologica*. 2014; 127:307–309. [PubMed: 24337442]
- Liu H, Sun Q, Sun Y, Zhang J, Yuan H, Pang S, Qi X, Wang H, Zhang M, Zhang H, Yu C, Gu C. MELK and EZH2 Cooperate to Regulate Medulloblastoma Cancer Stem-like Cell Proliferation and Differentiation. *Mol Cancer Res*. 2017
- Long J, Li B, Rodriguez-Blanco J, Pastori C, Volmar CH, Wahlestedt C, Capobianco A, Bai F, Pei XH, Ayad NG, Robbins DJ. The BET bromodomain inhibitor I-BET151 acts downstream of smoothened protein to abrogate the growth of hedgehog protein-driven cancers. *J Biol Chem*. 2014; 289:35494–35502. [PubMed: 25355313]
- Loven J, Hoke HA, Lin CY, Lau A, Orlando DA, Vakoc CR, Bradner JE, Lee TI, Young RA. Selective inhibition of tumor oncogenes by disruption of super-enhancers. *Cell*. 2013; 153:320–334. [PubMed: 23582323]
- Ma JX, Li H, Chen XM, Yang XH, Wang Q, Wu ML, Kong QY, Li ZX, Liu J. Expression patterns and potential roles of SIRT1 in human medulloblastoma cells in vivo and in vitro. *Neuropathology*. 2013; 33:7–16. [PubMed: 22537175]
- Malatesta M, Steinhauer C, Mohammad F, Pandey DP, Squatrito M, Helin K. Histone Acetyltransferase PCAF Is Required for Hedgehog-Gli-Dependent Transcription and Cancer Cell Proliferation. *Cancer Res*. 2013; 73:6323–6333. [PubMed: 23943798]
- Manoranjana B, Wang X, Hallett RM, Venugopal C, Mack SC, McFarlane N, Nolte SM, Scheinemann K, Gunnarsson T, Hassell JA, Taylor MD, Lee C, Triscott J, Foster CM, Dunham C, Hawkins C, Dunn SE, Singh SK. FoxG1 interacts with Bmi1 to regulate self-renewal and tumorigenicity of medulloblastoma stem cells. *Stem Cells*. 2013; 31:1266–1277. [PubMed: 23592496]
- Marino AM, Frijhoff J, Calero R, Baryawno N, Ostman A, Johnsen JI. Effects of epigenetic modifiers in combination with small molecule inhibitors of receptor tyrosine kinases on medulloblastoma growth. *Biochem Biophys Res Commun*. 2014; 450:1600–1605. [PubMed: 25026552]
- Martin DM. Epigenetic Developmental Disorders: CHARGE syndrome, a case study. *Curr Genet Med Rep*. 2015; 3:1–7. [PubMed: 25685640]
- Martinez-Garcia E, Licht JD. Deregulation of H3K27 methylation in cancer. *Nat Genet*. 2010; 42:100–101. [PubMed: 20104248]
- Mazza D, Infante P, Colicchia V, Greco A, Alfonsi R, Siler M, Antonucci L, Po A, De Smaele E, Ferretti E, Capalbo C, Bellavia D, Canettieri G, Giannini G, Screpanti I, Gulino A, Di Marcotullio L. PCAF ubiquitin ligase activity inhibits Hedgehog/Gli1 signaling in p53-dependent response to genotoxic stress. *Cell Death Differ*. 2013; 20:1688–1697. [PubMed: 24013724]
- Merve A, Dubuc AM, Zhang X, Remke M, Baxter PA, Li XN, Taylor MD, Marino S. Polycomb group gene BMI1 controls invasion of medulloblastoma cells and inhibits BMP-regulated cell adhesion. *Acta Neuropathol Commun*. 2014; 2:10. [PubMed: 24460684]
- Michael LE, Westerman BA, Ermilov AN, Wang A, Ferris J, Liu J, Blom M, Ellison DW, van Lohuizen M, Dlugosz AA. Bmi1 is required for Hedgehog pathway-driven medulloblastoma expansion. *Neoplasia*. 2008; 10:1343–1349. 1345p–1349. [PubMed: 19048113]
- Milde T, Lodrini M, Savelyeva L, Korshunov A, Kool M, Brueckner LM, Antunes AS, Oehme I, Pekrun A, Pfister SM, Kulozik AE, Witt O, Deubzer HE. HD-MB03 is a novel Group 3 medulloblastoma model demonstrating sensitivity to histone deacetylase inhibitor treatment. *Journal of neuro-oncology*. 2012; 110:335–348. [PubMed: 23054560]

- Milde T, Oehme I, Korshunov A, Kopp-Schneider A, Remke M, Northcott P, Deubzer HE, Lodrini M, Taylor MD, von Deimling A, Pfister S, Witt O. HDAC5 and HDAC9 in medulloblastoma: novel markers for risk stratification and role in tumor cell growth. *Clin Cancer Res*. 2010; 16:3240–3252. [PubMed: 20413433]
- Miyake N, Koshimizu E, Okamoto N, Mizuno S, Ogata T, Nagai T, Kosho T, Ohashi H, Kato M, Sasaki G, Mabe H, Watanabe Y, Yoshino M, Matsuishi T, Takanashi J, Shotelersuk V, Tekin M, Ochi N, Kubota M, Ito N, Ihara K, Hara T, Tonoki H, Ohta T, Saito K, Matsuo M, Urano M, Enokizono T, Sato A, Tanaka H, Ogawa A, Fujita T, Hiraki Y, Kitanaka S, Matsubara Y, Makita T, Taguri M, Nakashima M, Tsurusaki Y, Saitsu H, Yoshiura K, Matsumoto N, Niikawa N. MLL2 and KDM6A mutations in patients with Kabuki syndrome. *Am J Med Genet A*. 2013; 161A:2234–2243. [PubMed: 23913813]
- Moreno N, Schmidt C, Ahlfeld J, Poschl J, Dittmar S, Pfister SM, Kool M, Kerl K, Schuller U. Loss of Smar proteins impairs cerebellar development. *J Neurosci*. 2014; 34:13486–13491. [PubMed: 25274825]
- Muscal JA, Scorsone KA, Zhang L, Ecsedy JA, Berg SL. Additive effects of vorinostat and MLN8237 in pediatric leukemia, medulloblastoma, and neuroblastoma cell lines. *Invest New Drugs*. 2013; 31:39–45. [PubMed: 22669335]
- Negrini S, Prada I, D'Alessandro R, Meldolesi J. REST: an oncogene or a tumor suppressor? *Trends Cell Biol*. 2013; 23:289–295. [PubMed: 23414932]
- Nor C, Sassi FA, de Farias CB, Schwartzmann G, Abujamra AL, Lenz G, Brunetto AL, Roesler R. The histone deacetylase inhibitor sodium butyrate promotes cell death and differentiation and reduces neurosphere formation in human medulloblastoma cells. *Mol Neurobiol*. 2013; 48:533–543. [PubMed: 23516101]
- Northcott PA, Dubuc AM, Pfister S, Taylor MD. Molecular subgroups of medulloblastoma. *Expert Rev Neurother*. 2012a; 12:871–884. [PubMed: 22853794]
- Northcott PA, Jones DT, Kool M, Robinson GW, Gilbertson RJ, Cho YJ, Pomeroy SL, Korshunov A, Lichter P, Taylor MD, Pfister SM. Medulloblastomics: the end of the beginning. *Nat Rev Cancer*. 2012b; 12:818–834. [PubMed: 23175120]
- Northcott PA, Lee C, Zichner T, Stutz AM, Erkek S, Kawauchi D, Shih DJ, Hovestadt V, Zapatka M, Sturm D, Jones DT, Kool M, Remke M, Cavalli FM, Zuyderduyn S, Bader GD, VandenBerg S, Esparza LA, Ryzhova M, Wang W, Wittmann A, Stark S, Sieber L, Seker-Cin H, Linke L, Kratochwil F, Jager N, Buchhalter I, Imbusch CD, Zipprich G, Raeder B, Schmidt S, Diessl N, Wolf S, Wiemann S, Brors B, Lawrenz C, Eils J, Warnatz HJ, Risch T, Yaspo ML, Weber UD, Bartholomae CC, von Kalle C, Turanyi E, Hauser P, Sanden E, Darabi A, Siesjo P, Sterba J, Zitterbart K, Sumerauer D, van Sluis P, Versteeg R, Volckmann R, Koster J, Schuhmann MU, Ebinger M, Grimes HL, Robinson GW, Gajjar A, Mynarek M, von Hoff K, Rutkowski S, Pietsch T, Scheurlen W, Felsberg J, Reifemberger G, Kulozik AE, von Deimling A, Witt O, Eils R, Gilbertson RJ, Korshunov A, Taylor MD, Lichter P, Korbel JO, Wechsler-Reya RJ, Pfister SM. Enhancer hijacking activates GFI1 family oncogenes in medulloblastoma. *Nature*. 2014; 511:428–434. [PubMed: 25043047]
- Northcott PA, Nakahara Y, Wu X, Feuk L, Ellison DW, Croul S, Mack S, Kongkham PN, Peacock J, Dubuc A, Ra YS, Zilberberg K, McLeod J, Scherer SW, Sunil Rao J, Eberhart CG, Grajkowska W, Gillespie Y, Lach B, Grundy R, Pollack IF, Hamilton RL, Van Meter T, Carlotti CG, Boop F, Bigner D, Gilbertson RJ, Rutka JT, Taylor MD. Multiple recurrent genetic events converge on control of histone lysine methylation in medulloblastoma. *Nat Genet*. 2009; 41:465–472. [PubMed: 19270706]
- Northcott PA, Pfister SM, Jones DT. Next-generation (epi)genetic drivers of childhood brain tumours and the outlook for targeted therapies. *Lancet Oncol*. 2015; 16:e293–302. [PubMed: 26065614]
- Northcott PA, Shih DJ, Peacock J, Garzia L, Morrissy AS, Zichner T, Stutz AM, Korshunov A, Reimand J, Schumacher SE, Beroukhi R, Ellison DW, Marshall CR, Lionel AC, Mack S, Dubuc A, Yao Y, Ramaswamy V, Luu B, Rolider A, Cavalli FM, Wang X, Remke M, Wu X, Chiu RY, Chu A, Chuah E, Corbett RD, Hoad GR, Jackman SD, Li Y, Lo A, Mungall KL, Nip KM, Qian JQ, Raymond AG, Thiessen NT, Varhol RJ, Birol I, Moore RA, Mungall AJ, Holt R, Kawauchi D, Roussel MF, Kool M, Jones DT, Witt H, Fernandez LA, Kenney AM, Wechsler-Reya RJ, Dirks P, Aviv T, Grajkowska WA, Perek-Polnik M, Haberler CC, Delattre O, Reynaud SS, Doz FF, Pernet-

Fattet SS, Cho BK, Kim SK, Wang KC, Scheurlen W, Eberhart CG, Fevre-Montange M, Jouvett A, Pollack IF, Fan X, Muraszko KM, Gillespie GY, Di Rocco C, Massimi L, Michiels EM, Kloosterhof NK, French PJ, Kros JM, Olson JM, Ellenbogen RG, Zitterbart K, Kren L, Thompson RC, Cooper MK, Lach B, McLendon RE, Bigner DD, Fontebasso A, Albrecht S, Jabado N, Lindsey JC, Bailey S, Gupta N, Weiss WA, Bogner L, Klekner A, Van Meter TE, Kumabe T, Tominaga T, Elbabaa SK, Leonard JR, Rubin JB, Liau LM, Van Meir EG, Fouladi M, Nakamura H, Cinalli G, Garami M, Hauser P, Saad AG, Iolascon A, Jung S, Carlotti CG, Vibhakkar R, Ra YS, Robinson S, Zollo M, Faria CC, Chan JA, Levy ML, Sorensen PH, Meyerson M, Pomeroy SL, Cho YJ, Bader GD, Tabori U, Hawkins CE, Bouffet E, Scherer SW, Rutka JT, Malkin D, Clifford SC, Jones SJ, Korbel JO, Pfister SM, Marra MA, Taylor MD. Subgroup-specific structural variation across 1,000 medulloblastoma genomes. *Nature*. 2012c; 488:49–56. [PubMed: 22832581]

Ntziachristos P, Tsirogas A, Welstead GG, Trimarchi T, Bakogianni S, Xu L, Loizou E, Holmfeldt L, Strikoudis A, King B, Mullanders J, Becksfort J, Nedjic J, Paietta E, Tallman MS, Rowe JM, Tonon G, Satoh T, Kruidenier L, Prinjha R, Akira S, Van Vlierberghe P, Ferrando AA, Jaenisch R, Mullighan CG, Aifantis I. Contrasting roles of histone 3 lysine 27 demethylases in acute lymphoblastic leukaemia. *Nature*. 2014

Ong CT, Corces VG. Enhancer function: new insights into the regulation of tissue-specific gene expression. *Nat Rev Genet*. 2011; 12:283–293. [PubMed: 21358745]

Ooi L, Wood IC. Chromatin crosstalk in development and disease: lessons from REST. *Nat Rev Genet*. 2007; 8:544–554. [PubMed: 17572692]

Pajtlter KW, Weingarten C, Thor T, Kunkle A, Heukamp LC, Buttner R, Suzuki T, Miyata N, Grotzer M, Rieb A, Sprussel A, Eggert A, Schramm A, Schulte JH. The KDM1A histone demethylase is a promising new target for the epigenetic therapy of medulloblastoma. *Acta Neuropathol Commun*. 2013; 1:19. [PubMed: 24252778]

Parsons DW, Li M, Zhang X, Jones S, Leary RJ, Lin JC, Boca SM, Carter H, Samayoa J, Bettgowda C, Gallia GL, Jallo GI, Binder ZA, Nikolsky Y, Hartigan J, Smith DR, Gerhard DS, Fuets DW, VandenBerg S, Berger MS, Marie SK, Shinjo SM, Clara C, Phillips PC, Minturn JE, Biegel JA, Judkins AR, Resnick AC, Storm PB, Curran T, He Y, Rasheed BA, Friedman HS, Keir ST, McLendon R, Northcott PA, Taylor MD, Burger PC, Riggins GJ, Karchin R, Parmigiani G, Bigner DD, Yan H, Papadopoulos N, Vogelstein B, Kinzler KW, Velculescu VE. The genetic landscape of the childhood cancer medulloblastoma. *Science*. 2011; 331:435–439. [PubMed: 21163964]

Pei Y, Liu KW, Wang J, Garancher A, Tao R, Esparza LA, Maier DL, Udaka YT, Murad N, Morrissey S, Seker-Cin H, Brabetz S, Qi L, Kogiso M, Schubert S, Olson JM, Cho YJ, Li XN, Crawford JR, Levy ML, Kool M, Pfister SM, Taylor MD, Wechsler-Reya RJ. HDAC and PI3K Antagonists Cooperate to Inhibit Growth of MYC-Driven Medulloblastoma. *Cancer Cell*. 2016; 29:311–323. [PubMed: 26977882]

Pei Y, Moore CE, Wang J, Tewari AK, Eroshkin A, Cho YJ, Witt H, Korshunov A, Read TA, Sun JL, Schmitt EM, Miller CR, Buckley AF, McLendon RE, Westbrook TF, Northcott PA, Taylor MD, Pfister SM, Febbo PG, Wechsler-Reya RJ. An animal model of MYC-driven medulloblastoma. *Cancer Cell*. 2012; 21:155–167. [PubMed: 22340590]

Petrij F, Giles RH, Dauwerse HG, Saris JJ, Hennekam RC, Masuno M, Tommerup N, van Ommen GJ, Goodman RH, Peters DJ, et al. Rubinstein-Taybi syndrome caused by mutations in the transcriptional co-activator CBP. *Nature*. 1995; 376:348–351. [PubMed: 7630403]

Pfister S, Rea S, Taipale M, Mendrzyk F, Straub B, Itrich C, Thuerigen O, Sinn HP, Akhtar A, Lichter P. The histone acetyltransferase hMOF is frequently downregulated in primary breast carcinoma and medulloblastoma and constitutes a biomarker for clinical outcome in medulloblastoma. *Int J Cancer*. 2008; 122:1207–1213. [PubMed: 18058815]

Pfister S, Schlaeger C, Mendrzyk F, Wittmann A, Benner A, Kulozik A, Scheurlen W, Radlwimmer B, Lichter P. Array-based profiling of reference-independent methylation status (aPRIMES) identifies frequent promoter methylation and consecutive downregulation of ZIC2 in pediatric medulloblastoma. *Nucleic Acids Res*. 2007; 35:e51. [PubMed: 17344319]

Phi JH, Choi SA, Kwak PA, Lee JY, Wang KC, Hwang DW, Kim SK. Panobinostat, a histone deacetylase inhibitor, suppresses leptomeningeal seeding in a medulloblastoma animal model. *Oncotarget*. 2017

- Poschl J, Stark S, Neumann P, Grobner S, Kawauchi D, Jones DT, Northcott PA, Lichter P, Pfister SM, Kool M, Schuller U. Genomic and transcriptomic analyses match medulloblastoma mouse models to their human counterparts. *Acta neuropathologica*. 2014; 128:123–136. [PubMed: 24871706]
- Pugh TJ, Weeraratne SD, Archer TC, Pomeranz Krummel DA, Auclair D, Bochicchio J, Carneiro MO, Carter SL, Cibulskis K, Erlich RL, Greulich H, Lawrence MS, Lennon NJ, McKenna A, Meldrim J, Ramos AH, Ross MG, Russ C, Shefler E, Sivachenko A, Sogoloff B, Stojanov P, Tamayo P, Mesirov JP, Amani V, Teider N, Sengupta S, Francois JP, Northcott PA, Taylor MD, Yu F, Crabtree GR, Kautzman AG, Gabriel SB, Getz G, Jager N, Jones DT, Lichter P, Pfister SM, Roberts TM, Meyerson M, Pomeroy SL, Cho YJ. Medulloblastoma exome sequencing uncovers subtype-specific somatic mutations. *Nature*. 2012; 488:106–110. [PubMed: 22820256]
- Rao RC, Dou Y. Hijacked in cancer: the KMT2 (MLL) family of methyltransferases. *Nat Rev Cancer*. 2015; 15:334–346. [PubMed: 25998713]
- Remke M, Ramaswamy V, Peacock J, Shih DJ, Koelsche C, Northcott PA, Hill N, Cavalli FM, Kool M, Wang X, Mack SC, Barszczyk M, Morrissy AS, Wu X, Agnihotri S, Luu B, Jones DT, Garzia L, Dubuc AM, Zhukova N, Vanner R, Kros JM, French PJ, Van Meir EG, Vibhakkar R, Zitterbart K, Chan JA, Bogner L, Klekner A, Lach B, Jung S, Saad AG, Liao LM, Albrecht S, Zollo M, Cooper MK, Thompson RC, Delattre OO, Bourdeaut F, Doz FF, Garami M, Hauser P, Carlotti CG, Van Meter TE, Massimi L, Fults D, Pomeroy SL, Kumabe T, Ra YS, Leonard JR, Elbabaa SK, Mora J, Rubin JB, Cho YJ, McLendon RE, Bigner DD, Eberhart CG, Fouladi M, Wechsler-Reya RJ, Faria CC, Croul SE, Huang A, Bouffet E, Hawkins CE, Dirks PB, Weiss WA, Schuller U, Pollack IF, Rutkowski S, Meyronet D, Jouvett A, Fevre-Montange M, Jabado N, Perek-Polnik M, Grajkowska WA, Kim SK, Rutka JT, Malkin D, Tabori U, Pfister SM, Korshunov A, von Deimling A, Taylor MD. TERT promoter mutations are highly recurrent in SHH subgroup medulloblastoma. *Acta neuropathologica*. 2013; 126:917–929. [PubMed: 24174164]
- Robinson G, Parker M, Kranenburg TA, Lu C, Chen X, Ding L, Phoenix TN, Hedlund E, Wei L, Zhu X, Chalhoub N, Baker SJ, Huether R, Kriwacki R, Curley N, Thiruvengadam R, Wang J, Wu G, Rusch M, Hong X, Becksfort J, Gupta P, Ma J, Easton J, Vadodaria B, Onar-Thomas A, Lin T, Li S, Pounds S, Paugh S, Zhao D, Kawauchi D, Roussel MF, Finkelstein D, Ellison DW, Lau CC, Bouffet E, Hassall T, Gururangan S, Cohn R, Fulton RS, Fulton LL, Dooling DJ, Ochoa K, Gajjar A, Mardis ER, Wilson RK, Downing JR, Zhang J, Gilbertson RJ. Novel mutations target distinct subgroups of medulloblastoma. *Nature*. 2012; 488:43–48. [PubMed: 22722829]
- Romero OA, Torres-Diz M, Pros E, Savola S, Gomez A, Moran S, Saez C, Iwakawa R, Villanueva A, Montuenga LM, Kohno T, Yokota J, Sanchez-Cespedes M. MAX inactivation in small cell lung cancer disrupts MYC-SWI/SNF programs and is synthetic lethal with BRG1. *Cancer discovery*. 2014; 4:292–303. [PubMed: 24362264]
- Rutkowski S, von Hoff K, Emser A, Zwiener I, Pietsch T, Figarella-Branger D, Giangaspero F, Ellison DW, Garre ML, Biassoni V, Grundy RG, Finlay JL, Dhall G, Raquin MA, Grill J. Survival and prognostic factors of early childhood medulloblastoma: an international meta-analysis. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2010; 28:4961–4968. [PubMed: 20940197]
- Santen GW, Aten E, Sun Y, Almomani R, Gilissen C, Nielsen M, Kant SG, Snoeck IN, Peeters EA, Hilhorst-Hofstee Y, Wessels MW, den Hollander NS, Ruivenkamp CA, van Ommen GJ, Breuning MH, den Dunnen JT, van Haeringen A, Kriek M. Mutations in SWI/SNF chromatin remodeling complex gene ARID1B cause Coffin-Siris syndrome. *Nat Genet*. 2012; 44:379–380. [PubMed: 22426309]
- Schoenherr CJ, Anderson DJ. The neuron-restrictive silencer factor (NRSF): a coordinate repressor of multiple neuron-specific genes. *Science*. 1995; 267:1360–1363. [PubMed: 7871435]
- Schwalbe EC, Williamson D, Lindsey JC, Hamilton D, Ryan SL, Megahed H, Garami M, Hauser P, Dembowska-Baginska B, Perek D, Northcott PA, Taylor MD, Taylor RE, Ellison DW, Bailey S, Clifford SC. DNA methylation profiling of medulloblastoma allows robust subclassification and improved outcome prediction using formalin-fixed biopsies. *Acta neuropathologica*. 2013; 125:359–371. [PubMed: 23291781]
- Schwartzentruber J, Korshunov A, Liu XY, Jones DT, Pfaff E, Jacob K, Sturm D, Fontebasso AM, Quang DA, Tonjes M, Hovestadt V, Albrecht S, Kool M, Nantel A, Konermann C, Lindroth A, Jager N, Rausch T, Ryzhova M, Korbel JO, Hielscher T, Hauser P, Garami M, Klekner A, Bogner

- L, Ebinger M, Schuhmann MU, Scheurlen W, Pekrun A, Fruhwald MC, Roggendorf W, Kramm C, Durken M, Atkinson J, Lepage P, Montpetit A, Zakrzewska M, Zakrzewski K, Liberski PP, Dong Z, Siegel P, Kulozik AE, Zapatka M, Guha A, Malkin D, Felsberg J, Reifenberger G, von Deimling A, Ichimura K, Collins VP, Witt H, Milde T, Witt O, Zhang C, Castelo-Branco P, Lichter P, Faury D, Tabori U, Plass C, Majewski J, Pfister SM, Jabado N. Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. *Nature*. 2012; 482:226–231. [PubMed: 22286061]
- Shi J, Whyte WA, Zepeda-Mendoza CJ, Milazzo JP, Shen C, Roe JS, Minder JL, Mercan F, Wang E, Eckersley-Maslin MA, Campbell AE, Kawaoka S, Shareef S, Zhu Z, Kendall J, Muhar M, Haslinger C, Yu M, Roeder RG, Wigler MH, Blobel GA, Zuber J, Spector DL, Young RA, Vakoc CR. Role of SWI/SNF in acute leukemia maintenance and enhancer-mediated Myc regulation. *Genes Dev*. 2013; 27:2648–2662. [PubMed: 24285714]
- Shi X, Wang Q, Gu J, Xuan Z, Wu JI. SMARCA4/Brg1 coordinates genetic and epigenetic networks underlying Shh-type medulloblastoma development. *Oncogene*. 2016; 35:5746–5758. [PubMed: 27065321]
- Shi X, Zhang Z, Zhan X, Cao M, Satoh T, Akira S, Shpargel K, Magnuson T, Li Q, Wang R, Wang C, Ge K, Wu J. An epigenetic switch induced by Shh signalling regulates gene activation during development and medulloblastoma growth. *Nat Commun*. 2014; 5:5425. [PubMed: 25370275]
- Shih DJ, Northcott PA, Remke M, Korshunov A, Ramaswamy V, Kool M, Luu B, Yao Y, Wang X, Dubuc AM, Garzia L, Peacock J, Mack SC, Wu X, Rolider A, Morrissy AS, Cavalli FM, Jones DT, Zitterbart K, Faria CC, Schuller U, Kren L, Kumabe T, Tominaga T, Shin Ra Y, Garami M, Hauser P, Chan JA, Robinson S, Bogner L, Klekner A, Saad AG, Liao LM, Albrecht S, Fontebasso A, Cinalli G, De Antonellis P, Zollo M, Cooper MK, Thompson RC, Bailey S, Lindsey JC, Di Rocco C, Massimi L, Michiels EM, Scherer SW, Phillips JJ, Gupta N, Fan X, Muraszko KM, Vibhakkar R, Eberhart CG, Fouladi M, Lach B, Jung S, Wechsler-Reya RJ, Fevre-Montange M, Jouvet A, Jabado N, Pollack IF, Weiss WA, Lee JY, Cho BK, Kim SK, Wang KC, Leonard JR, Rubin JB, de Torres C, Lavarino C, Mora J, Cho YJ, Tabori U, Olson JM, Gajjar A, Packer RJ, Rutkowski S, Pomeroy SL, French PJ, Kloosterhof NK, Kros JM, Van Meir EG, Clifford SC, Bourdeaut F, Delattre O, Doz FF, Hawkins CE, Malkin D, Grajkowska WA, Perek-Polnik M, Bouffet E, Rutka JT, Pfister SM, Taylor MD. Cytogenetic prognostication within medulloblastoma subgroups. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2014; 32:886–896. [PubMed: 24493713]
- Shu Q, Antalffy B, Su JM, Adesina A, Ou CN, Pietsch T, Blaney SM, Lau CC, Li XN. Valproic Acid prolongs survival time of severe combined immunodeficient mice bearing intracerebellar orthotopic medulloblastoma xenografts. *Clin Cancer Res*. 2006; 12:4687–4694. [PubMed: 16899619]
- Simon JA, Lange CA. Roles of the EZH2 histone methyltransferase in cancer epigenetics. *Mutat Res*. 2008; 647:21–29. [PubMed: 18723033]
- Skousen GJ, Wardinsky T, Chenaille P. Medulloblastoma in patient with Rubinstein-Taybi syndrome. *Am J Med Genet*. 1996; 66:367. [PubMed: 8985503]
- Smits M, van Rijn S, Hulleman E, Biesmans D, van Vuurden DG, Kool M, Haberler C, Aronica E, Vandertop WP, Noske DP, Wurdinger T. EZH2-regulated DAB2IP is a medulloblastoma tumor suppressor and a positive marker for survival. *Clin Cancer Res*. 2012; 18:4048–4058. [PubMed: 22696229]
- Stanton BZ, Hodges C, Calarco JP, Braun SM, Ku WL, Kadoch C, Zhao K, Crabtree GR. Smarca4 ATPase mutations disrupt direct eviction of PRC1 from chromatin. *Nat Genet*. 2017; 49:282–288. [PubMed: 27941795]
- Su X, Gopalakrishnan V, Stearns D, Aldape K, Lang FF, Fuller G, Snyder E, Eberhart CG, Majumder S. Abnormal expression of REST/NRSF and Myc in neural stem/progenitor cells causes cerebellar tumors by blocking neuronal differentiation. *Mol Cell Biol*. 2006; 26:1666–1678. [PubMed: 16478988]
- Subkhankulova T, Zhang X, Leung C, Marino S. Bmi1 directly represses p21Waf1/Cip1 in Shh-induced proliferation of cerebellar granule cell progenitors. *Mol Cell Neurosci*. 2010; 45:151–162. [PubMed: 20600931]

- Sze CC, Shilatfard A. MLL3/MLL4/COMPASS Family on Epigenetic Regulation of Enhancer Function and Cancer. *Cold Spring Harbor perspectives in medicine*. 2016;6.
- Tang Y, Gholamin S, Schubert S, Willardson MI, Lee A, Bandopadhyay P, Berghold G, Masoud S, Nguyen B, Vue N, Balansay B, Yu F, Oh S, Woo P, Chen S, Ponnuswami A, Monje M, Atwood SX, Whitson RJ, Mitra S, Cheshier SH, Qi J, Beroukhi R, Tang JY, Wechsler-Reya R, Oro AE, Link BA, Bradner JE, Cho YJ. Epigenetic targeting of Hedgehog pathway transcriptional output through BET bromodomain inhibition. *Nat Med*. 2014; 20:732–740. [PubMed: 24973920]
- Tang Y, Yacoub A, Hamed HA, Poklepovic A, Tye G, Grant S, Dent P. Sorafenib and HDAC inhibitors synergize to kill CNS tumor cells. *Cancer Biol Ther*. 2012; 13:567–574. [PubMed: 22406992]
- Taylor MD, Northcott PA, Korshunov A, Remke M, Cho YJ, Clifford SC, Eberhart CG, Parsons DW, Rutkowski S, Gajjar A, Ellison DW, Lichter P, Gilbertson RJ, Pomeroy SL, Kool M, Pfister SM. Molecular subgroups of medulloblastoma: the current consensus. *Acta neuropathologica*. 2012a; 123:465–472. [PubMed: 22134537]
- Taylor P, Fangusaro J, Rajaram V, Goldman S, Helenowski IB, MacDonald T, Hasselblatt M, Riedemann L, Laureano A, Cooper L, Gopalakrishnan V. REST is a novel prognostic factor and therapeutic target for medulloblastoma. *Molecular cancer therapeutics*. 2012b; 11:1713–1723. [PubMed: 22848092]
- Tiberi L, Bonnefont J, van den Ameel J, Le Bon SD, Herpoel A, Bilheu A, Baron BW, Vanderhaeghen P. A BCL6/BCOR/SIRT1 complex triggers neurogenesis and suppresses medulloblastoma by repressing Sonic Hedgehog signaling. *Cancer Cell*. 2014; 26:797–812. [PubMed: 25490446]
- Tsurusaki Y, Okamoto N, Ohashi H, Kosho T, Imai Y, Hibi-Ko Y, Kaname T, Naritomi K, Kawame H, Wakui K, Fukushima Y, Homma T, Kato M, Hiraki Y, Yamagata T, Yano S, Mizuno S, Sakazume S, Ishii T, Nagai T, Shiina M, Ogata K, Ohta T, Niikawa N, Miyatake S, Okada I, Mizuguchi T, Doi H, Saito H, Miyake N, Matsumoto N. Mutations affecting components of the SWI/SNF complex cause Coffin-Siris syndrome. *Nat Genet*. 2012; 44:376–378. [PubMed: 22426308]
- Valk-Lingbeek ME, Bruggeman SW, van Lohuizen M. Stem cells and cancer; the polycomb connection. *Cell*. 2004; 118:409–418. [PubMed: 15315754]
- Venkataraman S, Alimova I, Balakrishnan I, Harris P, Birks DK, Griesinger A, Amani V, Cristiano B, Remke M, Taylor MD, Handler M, Foreman NK, Vibhakkar R. Inhibition of BRD4 attenuates tumor cell self-renewal and suppresses stem cell signaling in MYC driven medulloblastoma. *Oncotarget*. 2014; 5:2355–2371. [PubMed: 24796395]
- Venkataraman S, Alimova I, Fan R, Harris P, Foreman N, Vibhakkar R. MicroRNA 128a increases intracellular ROS level by targeting Bmi-1 and inhibits medulloblastoma cancer cell growth by promoting senescence. *PLoS One*. 2010; 5:e10748. [PubMed: 20574517]
- Vo BT, Li C, Morgan MA, Theurillat I, Finkelstein D, Wright S, Hyle J, Smith SM, Fan Y, Wang YD, Wu G, Orr BA, Northcott PA, Shilatfard A, Sherr CJ, Roussel MF. Inactivation of Ezh2 Upregulates Gfi1 and Drives Aggressive Myc-Driven Group 3 Medulloblastoma. *Cell reports*. 2017; 18:2907–2917. [PubMed: 28329683]
- Wadhwa E, Nicolaides T. Bromodomain Inhibitor Review: Bromodomain and Extra-terminal Family Protein Inhibitors as a Potential New Therapy in Central Nervous System Tumors. *Cureus*. 2016; 8:e620. [PubMed: 27382528]
- Wang X, Venugopal C, Manoranjan B, McFarlane N, O'Farrell E, Nolte S, Gunnarsson T, Hollenberg R, Kwiczen J, Northcott P, Taylor MD, Hawkins C, Singh SK. Sonic hedgehog regulates Bmi1 in human medulloblastoma brain tumor-initiating cells. *Oncogene*. 2012; 31:187–199. [PubMed: 21685941]
- Wegener D, Deubzer HE, Oehme I, Milde T, Hildmann C, Schwienhorst A, Witt O. HKI 46F08, a novel potent histone deacetylase inhibitor, exhibits antitumoral activity against embryonic childhood cancer cells. *Anticancer Drugs*. 2008; 19:849–857. [PubMed: 18765999]
- Wilson BG, Roberts CW. SWI/SNF nucleosome remodellers and cancer. *Nat Rev Cancer*. 2011; 11:481–492. [PubMed: 21654818]
- Wilson BG, Wang X, Shen X, McKenna ES, Lemieux ME, Cho YJ, Koellhoffer EC, Pomeroy SL, Orkin SH, Roberts CW. Epigenetic antagonism between polycomb and SWI/SNF complexes during oncogenic transformation. *Cancer Cell*. 2010; 18:316–328. [PubMed: 20951942]

- Wu G, Broniscer A, McEachron TA, Lu C, Paugh BS, Becksfort J, Qu C, Ding L, Huether R, Parker M, Zhang J, Gajjar A, Dyer MA, Mullighan CG, Gilbertson RJ, Mardis ER, Wilson RK, Downing JR, Ellison DW, Zhang J, Baker SJ. Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. *Nat Genet.* 2012a; 44:251–253. [PubMed: 22286216]
- Wu JI. Diverse functions of ATP-dependent chromatin remodeling complexes in development and cancer. *Acta Biochim Biophys Sin (Shanghai).* 2012; 44:54–69. [PubMed: 22194014]
- Wu X, Northcott PA, Dubuc A, Dupuy AJ, Shih DJ, Witt H, Croul S, Bouffet E, Fults DW, Eberhart CG, Garzia L, Van Meter T, Zagzag D, Jabado N, Schwartzentruber J, Majewski J, Scheetz TE, Pfister SM, Korshunov A, Li XN, Scherer SW, Cho YJ, Akagi K, MacDonald TJ, Koster J, McCabe MG, Sarver AL, Collins VP, Weiss WA, Largaespada DA, Collier LS, Taylor MD. Clonal selection drives genetic divergence of metastatic medulloblastoma. *Nature.* 2012b; 482:529–533. [PubMed: 22343890]
- Yoo CB, Jones PA. Epigenetic therapy of cancer: past, present and future. *Nat Rev Drug Discov.* 2006; 5:37–50. [PubMed: 16485345]
- Zakrzewska M, Zakrzewski K, Gresner SM, Piaskowski S, Zalewska-Szewczyk B, Liberski PP. Polycomb genes expression as a predictor of poor clinical outcome in children with medulloblastoma. *Child's nervous system: ChNS: official journal of the International Society for Pediatric Neurosurgery.* 2011; 27:79–86.
- Zhan X, Shi X, Zhang Z, Chen Y, Wu JI. Dual role of Brg chromatin remodeling factor in Sonic hedgehog signaling during neural development. *Proc Natl Acad Sci U S A.* 2011; 108:12758–12763. [PubMed: 21768360]
- Zhang P, de Gooijer MC, Buil LC, Beijnen JH, Li G, van Tellingen O. ABCB1 and ABCG2 restrict the brain penetration of a panel of novel EZH2-Inhibitors. *Int J Cancer.* 2015; 137:2007–2018. [PubMed: 25868794]
- Zhao X, Liu Z, Yu L, Zhang Y, Baxter P, Voicu H, Gurusiddappa S, Luan J, Su JM, Leung HC, Li XN. Global gene expression profiling confirms the molecular fidelity of primary tumor-based orthotopic xenograft mouse models of medulloblastoma. *Neuro Oncol.* 2012; 14:574–583. [PubMed: 22459127]
- Zhukova N, Ramaswamy V, Remke M, Pfaff E, Shih DJ, Martin DC, Castelo-Branco P, Baskin B, Ray PN, Bouffet E, von Bueren AO, Jones DT, Northcott PA, Kool M, Sturm D, Pugh TJ, Pomeroy SL, Cho YJ, Pietsch T, Gessi M, Rutkowski S, Bogner L, Klekner A, Cho BK, Kim SK, Wang KC, Eberhart CG, Fevre-Montange M, Fouladi M, French PJ, Kros M, Grajkowska WA, Gupta N, Weiss WA, Hauser P, Jabado N, Jouvett A, Jung S, Kumabe T, Lach B, Leonard JR, Rubin JB, Liao LM, Massimi L, Pollack IF, Shin Ra Y, Van Meir EG, Zitterbart K, Schuller U, Hill RM, Lindsey JC, Schwalbe EC, Bailey S, Ellison DW, Hawkins C, Malkin D, Clifford SC, Korshunov A, Pfister S, Taylor MD, Tabori U. Subgroup-specific prognostic implications of TP53 mutation in medulloblastoma. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology.* 2013; 31:2927–2935. [PubMed: 23835706]

Highlights

- Medulloblastoma are heterogeneous and are classified into four subgroups.
- High percentages of somatic alterations of genes encoding chromatin regulators suggest that epigenetic deregulation is a major driver of medulloblastoma.
- Epigenetic regulators often display subgroup specific and pleiotropic functions in medulloblastoma development.
- Genetic and pharmacological analyses of epigenetic regulators in medulloblastoma mouse models and patient-derived xenografts provide valuable information about their function in tumorigenesis.
- Epigenetic inhibitors may be promising drugs for personalized targeted medulloblastoma treatment.

Figure 1. Molecular functions of epigenetic regulators in medulloblastoma development

A. Epigenetic regulators of SHH signaling and SHH medulloblastoma. Constitutively active SHH signaling induces the binding of GLI1/2 activators (GLI-Act) to target genes. GLI-Act recruit an epigenetic co-activator complex including Brg1 containing BAF complexes, JMJD3, MLL/SET and PCAF, which removes H3K27me3 and adds H3K4me3 and H3K9Ac histone marks. They are required for GLI-Act mediated target gene activation and possibly SHH medulloblastoma (MB). The unmarked grey shape represents other unidentified co-activators. HDACs activate GLI-Act by deacetylating (-Ac) GLI-Act, whereas HDAC inhibitors (HDACi) inhibit SHH signaling and SHH medulloblastoma. BET bromodomain inhibitors (BETi) as well as a BCL6/BCOR/SIRT1 (BCL6) complex repress *GLI-Act* expression and SHH medulloblastoma growth.

B. Epigenetic regulation of Group 3 medulloblastoma mouse models driven by *MYC* overexpression in *TP53*-null neural stem/progenitor cells. EZH2 inhibits medulloblastoma formation and progression by repressing the expression of Group 3/4 specific oncogene *GFII*. HDACi and PI3Ki cooperatively inhibit MYC-driven medulloblastoma by activating tumor suppressor *FOXO1*. BETi inhibits *MYC* expression and MYC-mediated transcription program, which results in tumor growth arrest.

C. BMI1 function in medulloblastoma. BMI1 deletion has been shown to repress SHH medulloblastoma growth and Group 4 medulloblastoma growth and invasion. BMI1 regulates the expression of genes encoding cell cycle inhibitors and BMP signaling-

dependent extracellular matrix proteins (ECM). BMI1 also ubiquitinates (+Ub) and destabilizes p53.

D. REST function in medulloblastoma. REST transcription repressor coordinates a group of epigenetic co-repressors to inhibit neuronal gene expression and neuronal differentiation, which antagonizes medulloblastoma growth. These co-repressors include HDACs, LSD1/KDM1A and G9A. G9A also mediates the repression of a tumor suppressor *USP37* by REST. USP37 stabilizes p27/CDKN1B by deubiquitination (–Ub).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Summary of functions of genes encoding epigenetic regulators in medulloblastoma.

Genes	Epigenetic function of gene products*	Recurrent abnormalities in MB/Subgroup enrichment	Functions in MB**	Availability of inhibitors
<i>Brg1/S MARCA 4</i>	ATPase subunit of SWI/SNF chromatin remodeler	Mutation/WNT and Group 3	Support SHH MB	No
<i>BMII</i>	Subunit of PRC1 H2AK119 E3 ubiquitin ligase	Overexpression/across subgroups	Support SHH and Group 4 MB	Yes
<i>EZH2</i>	Subunit of PRC2 H3K27 methyltransferase	High expression/Groups 3 and 4	Inhibit Group3 MB ***	Yes
<i>MLL2/K MT2D</i>	H3K4 methyltransferase	Mutation/across subgroups	Not clear	No
<i>MLL3/K MT2C</i>	H3K4 methyltransferase	Mutation/across subgroups	Not clear	No
<i>G9A/E HMT2</i>	H3K9 methyltransferase	Not known	Support MB as REST corepressor	Yes
<i>CREBBP</i>	H3K27 acetyltransferase	Mutation/SHH	Not clear	Yes
<i>PCAF/K AT2B</i>	Histone acetyltransferase	Not known	Support SHH MB ***	Yes
<i>UTX/K DM6A</i>	H3K27me3 demethylase	Mutation or deletion/Group 4	Not clear	Yes
<i>JMID3/KDM6B</i>	H3K27me3 demethylase	Not known	Support SHH MB	Yes
<i>LSD1/K DM1A</i>	H3K9me1/2 demethylase	Not known	Support MB as REST corepressor	Yes
<i>HDAC1/2</i>	Histone deacetylase	Not known	Support SHH MB	Yes
<i>SIRT1</i>	NAD-dependent histone deacetylase	High expression/multiple subgroups	Prevent SHH MB ***	Yes
<i>BRD2/3/4</i>	Recognition of acetyl-lysine on histones	Not known	Support SHH and Group 3 MB	Yes

* Writer adds histone marks; Eraser removes histone marks; Reader recognizes histone marks.

** Functions listed are current understanding demonstrated by in vivo studies; functions in other subgroups are unknown.

*** Conflicting results observed in different studies; functions listed in the table are from in vivo studies.