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Epigenetic regulation in medulloblastoma

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A B S T R A C T

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.

1. 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; M.D. Taylor et al., 2012). 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, the exact 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.

1.1. WNT subgroup

The WNT subgroup accounts for about 10% of medulloblastoma patients (M.D. Taylor et al., 2012). 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).

1.2. 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

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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
Brg1/SMARCA4		ATPase subunit of SWI/SNF chromatin remodeler	Mutation/WNT and Group 3	Support SHH MB	No
BMI1	Writer	Subunit of PRC1 H2AK119 E3 ubiquitin ligase	Overexpression/across subgroups	Support SHH and group 4 MB	Yes
EZH2		Subunit of PRC2 H3K27 methytransferase	High expression/Groups 3 and 4	Inhibit Group3 MB***	Yes
MLL2/KMT2D		H3K4 methytransferase	Mutation/across subgroups	Not clear	No
MLL3/KMT2C		H3K4 methytransferase	Mutation/across subgroups	Not clear	No
G9A/EHMT2		H3K9 methytransferase	Not known	Support MB as REST corepressor	Yes
CREBBP		H3K27 acetyltransferase	Mutation/SHH	Not clear	Yes
PCAF/KAT2B		Histone acetyltransferase	Not known	Support SHH MB***	Yes
UTX/KDM6A	Eraser	H3K27me3 demethylase	Mutation or deletion/Group 4	Not clear	Yes
JMJD3/KDM6B		H3K27me3 demethylase	Not known	Support SHH MB	Yes
LSD1/KDM1A		H3K9me1/2 demethylase	Not known	Support MB as REST corepressor	Yes
HDAC1/2		Histone deacetylase	Not known	Support SHH MB	Yes
SIRT1		NAD-dependent histone deacetylase	High expression/multiple subgroups	Prevent SHH MB***	Yes
BRD2/3/4	Reader	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.

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).

1.3. 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 3α. 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 3β medulloblastoma (Cavalli et al., 2017; Northcott et al., 2014). *MYC* amplification is highly associated with Group 3γ medulloblastoma. Group 3γ medulloblastoma patients have high rates of metastasis and poor treatment outcomes with < 50% 5-year survival rates, whereas other Group 3 patients have intermediate survival rates (Cavalli et al., 2017; M.D. Taylor et al., 2012).

1.4. Group 4

Group 4 tumors account for > 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 (M.D. Taylor et al., 2012). Group 4α tumors are enriched for *MYCN* amplifications, and Group 4β are strongly enriched for *SNCAIP* duplications. Groups 4α and 4γ 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.

2. 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). > 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