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REVIEW PAPER

Medulloblastoma, WNT-activated/SHH-activated: clinical impact of molecular analysis and histogenetic evaluation

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Abstract

Purpose Medulloblastoma (MDB) is a small cell poorly differentiated embryonal tumor of the cerebellum, which more frequently compromises children. Overall prognosis is favorable, but dependent of stage, histopathological pattern and molecular group. Approximately 30% of the affected patients will die from the disease. WHO 2016 Classification of Tumors of the Central Nervous System (CNS) has been classified MDB into four principal groups: WNT-activated MDB, SHH-activated MDB, group 3 MDB, and group 4 MDB. WNT-activated MDB is associated to monosomy 6, CTNNB1, DDX3X and TP53 mutations, beta-catenin nuclear immunoexpression, and a better prognosis than SHH-activated MDB.

Discussion WNT-activated tumors account approximately for 10% of cases of MDBs, and are thought to arise from cells in the dorsal brain stem/lower rhombic lip progenitor cells. SHH-activated MDB more frequently arises in the lateral hemispheres of the cerebellum, and clinical outcome in this group is variable. TP53-mutant SHHactivated MDB usually shows the large cell/anaplastic pattern, and can be related to MYCN amplification, GLI2 amplification and 17p loss. TP53-wildtype SHH-activated MDB is more commonly of desmoplastic/nodular morphology, and can be related to PTCH1 deletion and 10q loss. Gene expression and methylation profiling is the gold standard for defining molecular groups of MDB. In immunohistochemistry assays, anti-GAB1 antibody expression is positive in tumors showing SHH pathway activation or PTCH mutation, while positive immunoexpression for YAP1 antibody can be only found in WNT-activated and SHH-activated MDB.

Keywords Medulloblastoma · WNT-activated · SHH-activated · Embryonal neuroepithelial tumor · Central nervous system tumors · Prognosis

Introduction

Medulloblastoma (MDB) is defined as an embryonal neuroepithelial tumor (WHO grade IV) arising more commonly in the cerebellum or dorsal brain stem of children. MDB is composed of small round undifferentiated cells disposed in densely packed groupings and exhibits mild to moderate nuclear pleomorphism and a high mitotic index (Fig. 1) [1–3]. WHO 2016 Classification of Tumors of the Central Nervous System (CNS) has been classified MDB into four principal groups: WNT-activated MDB, sonic hedgehog (SHH)-activated MDB, group 3 MDB, and group 4 MDB. These groups were established from clustering analyses following transcriptome, methylome profiling, and microRNA [1–4]. There is significant association between these molecular classification and clinical data and histopathological findings [3–7].

WNT-activated MDB accounts approximately for 10% of cases of MDB and are thought to arise from cells in the dorsal brain stem/lower rhombic lip progenitor cells [1, 4, 6, 7]. At microscopy, the great majority of WNT-activated MDB has classic morphology, which denotes a low-risk tumor. Very rare cases of WNT-activated MDB show large cell/anaplastic pattern. Most common genetic alterations of WNT-activated MDB are mutations of *CTNNB1*,

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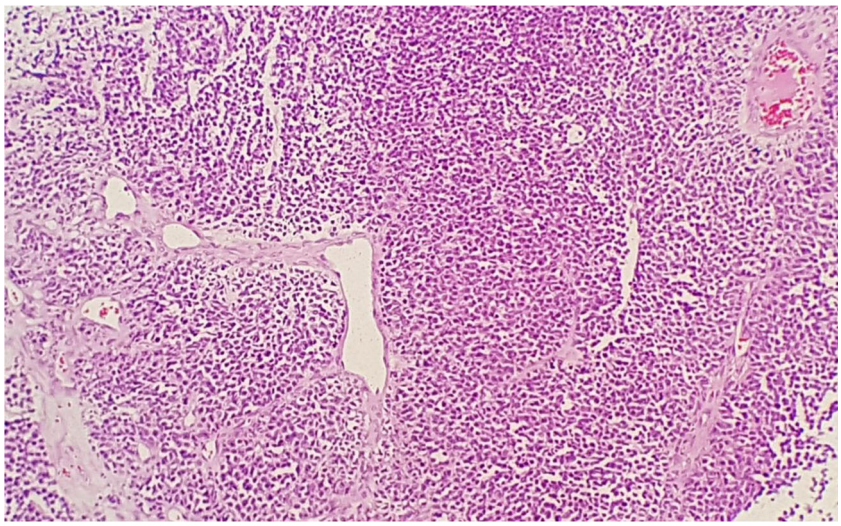


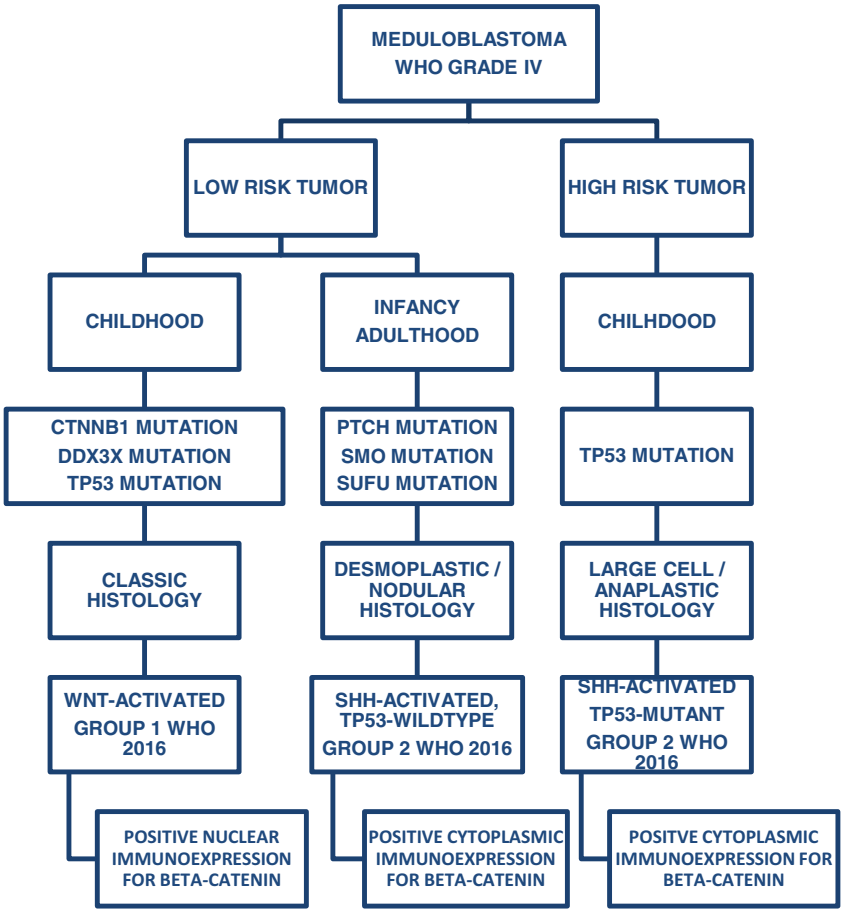
Fig. 1 Medulloblastoma: a small cell neuroectodermal tumor of the cerebellum, hematoxylin-eosin, 40×

DDX3X, and *TP53* genes [1, 2, 5, 7, 8]. SHH-activated MDB corresponds to a heterogeneous group that can be subdivided in *TP53*-mutant and *TP53*-wildtype, and account around 30% of cases of MDB. All nodular/desmoplastic MDB and MDB showing extensive nodularity are SHH-activated MDB. SHH-activated MDB looks to be derived from *ATOH1*-positive cerebellar granule neuron precursor. A proportion of SHH-activated MDB seems to arise from cerebellar granule neuron cell precursor of the external granule cell layer/cochlear nucleus [4, 6, 7, 9–13]. Non-WNT and non-SHH groups 3 and 4 MDB are considered provisional variants by WHO 2016, since these cases are not well divided in molecular analyses/clinical laboratory assays as WNT-activated/SHH-activated MDB [1, 3, 4, 6, 7, 14–16]. Proposed cell of origin of group 3 MDB is a CD133+ neural stem cell and is usually MDB with classic pattern (standard-risk tumor) or large cell/anaplastic morphology high-risk tumor). Group 3 MDB account for 20% of cases and are related to *MYC* amplification and isodicentric 17q [1, 3, 4, 6, 7, 14–16]. Group 4 MDB accounts for 40% of cases, is also related to *MYC* amplification and isodicentric 17q, and can compromise all age groups. Frequent genetic alterations of group 4 MDB are *KDM6A* and *GFI1*/*GFI1B* structural variants and 11p deletion [4, 7, 10, 16–19]. Although not included in the WHO 2016 Classification of Tumors of the Central Nervous System, immunohistochemical assays for *MYC*, Beta-catenin, and *TP53* antibodies also can be employed to determine a more integrated molecular/histopathological diagnosis, and anti-GAB1 antibody expression is positive in tumors showing SHH pathway activation or *PTCH* mutation [1, 4, 6, 7, 9, 19–21]. Table 1 demonstrates general findings of WNT-activated/SHH-ativated MDB.

The role of WNT and SHH pathways in the neoplastic transformation of cerebellum/dorsal stem cells and development of MDB

MDB is the most common CNS embryonal tumor of childhood and accounts for 25% of all intracranial neoplasms. Of all patients with MDB, around 78% are aged inferior to 19 years [4, 6, 7, 22]. Most cases of MDB arise into the cerebellar vermis or fourth ventricle as a gray circumscribed mass that determine increased intracranial pressure. On CT/MR, MDB is usually found as a solid, intensely contrast-enhancement tumoral mass [4, 10, 19, 23, 24]. MDB has potential to metastasize through the cerebrospinal fluid or spread outside the CNS. Morphological variants of MDB include classic pattern (Fig. 2), desmoplastic/nodular MDB, large cell/anaplastic MDB, and MDB with extensive nodularity [1, 4, 6, 7, 10, 19, 25]. Rare cases of MDB show areas with melanotic or myogenic differentiation [1, 4, 6, 7, 10, 19, 25]. Differential diagnosis includes high-grade small cell gliomas, embryonal tumor with multilayered rosettes, and atypical teratoid/rhabdoid tumors. Most MDB show positive immunoexpression for neuronal differentiation such as synaptophysin, NeuN, NCAM1, MAP2, neuron-specific enolase, and class III beta-tubulin [4, 6, 7, 10, 22, 26]. Positive expression for GFAP in immunohistochemistry evaluation is found in approximately 10% of cases of MDB, and positivity for NFP is rare. Rare cases of MDB show positive immunoexpression for desmin, myogenin, HMB-45, and melan-A [4, 6, 7, 10, 22, 26]. Almost all MDB show some cytoplasmic immunoreactivity for beta-catenin. WNT-activated MDB exhibits nuclear immunoreacivity for beta-catenin in most cells. Nuclear *SMARCB1* and *SMARCA4* expression is found in all MDB variants, and the loss of

Table 1 WNT-activated and SHHactivated medulloblastomas: general findings



expression of one of these antibodies is a characteristic of atypical teratoid/rhabdoid tumor [4, 6, 7, 22, 26, 27]. Almost all MDB cases are sporadic, but the tumor is eventually associated to rare hereditary syndromes, compromising less than 5% of patients. Familial cancer syndromes featuring MDB include Nevoid basal-cell carcinoma syndrome (Gorlin syndrome), Turcot syndrome, subtype 1 Fanconi anemia, Rubenstein-Taybi syndrome, Coffin-Siris syndrome, and Li-Fraumeni syndrome [1, 4, 7, 8, 11, 15, 21, 27].

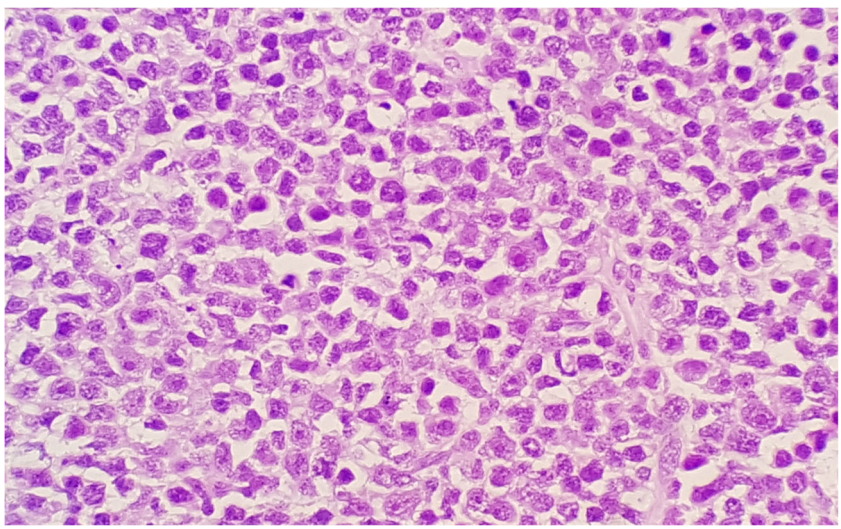


Fig. 2 Classic Medulloblastoma: A high grade densely cellular tumor exhibiting a solid pattern and prominent nuclear and cellular atypias, hematoxylin-eosin, 400×

Gene expression and methylation profiling is the gold standard for defining molecular groups of MDB. WNT-activated MDB (group 1 of WHO 2016 Classification of Tumors of the Central Nervous System) is typically found in children between 7 and 14 years and has an excellent prognosis with standard therapeutic approaches [1, 2, 4, 6, 7, 16, 19, 22, 28]. Nearly all WNT-activated MDB cases are classic tumors. Frequently mutated genes in WNT-activated MDB are *CTNNB1* (90% of cases), *TP53* (12.5% of cases), *SMARCA*4 (27% of cases), *KMT2D* (12.5% of cases), and *DDX3X* (50% of cases). Around 85% MDB that are characterized by WNT pathway activation show monosomy 6 and/or harbor a *CTNNB*1 mutation in exon 3, and these genetic alterations determine the positive immunoexpression for beta-catenin antibodies in tumor cell nuclei [1, 2, 7, 12, 16, 22, 29, 30]. *TP53* mutations in WNT-activated MDB are not related to a worse prognosis, and the presence of *APC* germline mutations rare in this group of tumors [4, 5, 7–10, 22, 31]. WNT pathway is fundamental for the normal development and organogenesis, including neural cells. This pathway regulates intracellular localization of the beta-catenin protein. Inactive WNT pathway determines the association between beta-catenin with a multimeric protein complex, which include *AXIN1* protein, glycogen synthase kinase-3-beta, and APC gene [4, 8, 9, 11, 16–18, 28, 31, 32]. With this ligation, beta-catenin is phosphorylated and targeted for degradation via ubiquitin-dependent proteasomal pathways. Activation of WNT pathway determines glycogen synthase kinase-3-beta inhibition, destabilization of the *APC*/glycogen synthase kinase-3-beta/*AXIN1* complex, and accumulation of beta-catenin in the nucleus. Translocation of beta-catenin to the nucleus leads to upregulation of *cyclin D1* and *MYC* (promitotic genes) [7–9, 11, 16, 18, 26, 28, 31, 32]. *CTNNB1* mutation compromises specifically the glycogen synthase kinase-3-beta phosphorylation domain of beta-catenin and promotes upregulation and nuclear accumulation of aberrant *TCF*/*LEF* target genes and tumorigenesis. *CTNNB1* stimulates the producing of inhibitors such as Frizzled-related protein (*sFRP*) and WNT inhibitor factor 1 (*WIF-1*). Positive nuclear beta-catenin immunoexpression is strongly associated to *CTNNB1* mutations in more than 80% of cases of MDB. The presence of APC mutations in sporadic cases of MDB does not determine upregulation of the WNT pathway [4, 7–9, 11, 16–18, 26, 28, 31, 32].

Clinical outcomes in SHH-activated MDB (group 2 of WHO 2016 Classification of Tumors of the Central Nervous System) are variable. SHH-activated MDB less frequently determines metastatic lesions than group 3 MDB [1, 5, 7, 22, 23, 28, 33]. Spread within the neuroaxis is a common feature of SHH-activated and *TP53* mutant MDB. The analysis of PTHC mutations in sporadic MDBs identified the SHH signaling pathway in MDB tumorigenesis. Positive immunoexpression for *YAP1* antibody can be only found in WNT-activated and SHH-activated MDB. Positive immunoexpression for GAB1 and YAP1 is widespread and strong in the great majority of cases of non-desmoplastic SHH-activated MDB. In nodular/desmoplastic MDB, strong expression for BAG1 and YAP1 is found within internodular regions [4, 6, 7, 22, 26, 28, 34]. SHH-activated MDB with cytological anaplasia is more prone to exhibit strong p53 expression, which is related to germline *TP53* mutations. Desmoplastic/nodular MDB shows pathological activation of the SHH pathway, which is related to *PTCH1*, *SMO*, *SHH*, *GLI2*, *MYCN*, and *SUFU* gene mutations. Desmoplastic/nodular MDB correspond approximately for 20% of cases of this tumor and are not related to isochromosome 17q [1, 4, 6, 7, 10, 28, 31, 32, 35]. Activation of SHH pathway can be evaluated by *GAB1* and *TNFRSF16* in immunohistochemistry technique, in special in internodular areas [4, 8, 10, 11, 14, 26, 36]. MDB with extensive nodularity is usually SHH-activated tumor with an excellent prognosis, with overall survival rates of 95%. Large cell/anaplastic MDB is most frequent between SHH-activated and group 3 MDB, and are associated to *GLI2* and *MYCN* amplification, *TP53* mutations, a massive genomic rearrangement called chromothripsis, and a poor outcome with standard therapies. Five-year progression-free survival for large cell/anaplastic MDB is 30–40% [4, 5, 7, 9, 19, 31, 32, 37].

MDB, SHH-activated, and *TP53* mutant are rare tumors with poor prognosis that compromise patients between 4 and 17 years and are defined as embryonal tumors of the cerebellum with evidence of SHH pathway activation and either germline or somatic *TP53* mutation [1, 4, 7, 12, 28, 30, 33]. SHH pathway activation in TP53-mutant tumors is related to MYCN amplification, 17p loss, and *GLI2*, *MYCN*, or *SHH* gene amplification, and mutations in *PTCH*, *SUFU*, and *SMO* are uncommon. *TP53*-mutant SHH-activated MDB usually shows the large cell/anaplastic pattern. *GLI2* amplification denotes a high-risk tumor [1, 4, 7, 12, 28, 33].

MDB, SHH-activated, and *TP53*-wildtype are related to germline or somatic mutations in the negative regulators *PTCH* or *SUFU* and somatic mutations in *SMO*, and generally compromise children aged four or less years [1, 7, 12, 22, 24, 25, 38]. Mutations *DD3X* or *KMT2D* genes, and amplification of *MYCN* or *MYCL* also can be found between these lesions. Some cases are associated to deletions in 9q and 14q chromosomes. *TP53*-wildtype SHH-activated MDB is more commonly of desmoplastic/nodular morphology, and is associated to *PTCH* deletion and 10q loss, which denote a low-risk tumor in infants [1, 4, 7, 12, 22, 24, 25, 37].

The SHH pathway plays a critical role in normal cerebellar development. SHH ligand is secreted by Purkinje neurons, which promote mitogenesis in external granular layer progenitor cells [4, 6, 10, 24, 28]. The response to SHH signal is controlled by *PTCH* and *SMO*, which are transmembrane proteins. *PTCH* suppresses *SMO* activity in the absence of SHH ligand. If there is SHH stimulation, this inhibition is released

and promotes *SMO*-induced transcriptional response, which is regulated by *GLI-1*, *GLI-2*, and *GLI-3*, a family of transcription factors. *SUFU* (suppressor of fused) cooperate with *Slimb* (*BTRCP*, F-box protein) to inhibit *GLI-1* mediated transcription [1, 24, 25, 37, 39–42]. SHH-activated MDB (20% of cases) arise through multiple alternative components, such as *PTCH* mutations (around 10% of cases), *SMO*-activating mutations (around 5% of cases), and *SUFU* mutations (0–10% of cases) [1, 24–26, 37, 39–41]. Genetic alterations of the SHH pathway determines an inadequate constitutive activation of the signaling cascade, downstream mitotic effects regulated by overexpression of *GLI* proteins and *PTCH* gene (a GLI-dependent target gene), and downstream *MYCN*, *cyclin D1*, and *BMI-1* function. Common genetic alterations in MDB also include *MYC* amplifications (5–15%), *MYCN* amplifications (5–15%), *PIK3CA* mutation (5%), *CASP8* (35%), *HIC-1* (35%), and *RASSF1A* (90%) [1, 24, 26, 37, 39, 40, 43].

TP53 is a fundamental regulator of the cell cycle and apoptosis. *TP53* pathway includes $p14^{ARF}$, a cell cycle inhibitor that is expressed due to cellular stress and/or oncogene activation and is encoded by the *INK4A/ARF* locus. $p14^{ARF}$ stabilizes p53 by sequestering *MDM2*, thus leading cells to apoptosis or cell cycle arrest [9, 12, 27, 36, 39]. Disruption of p53 pathway is related to $p14^{ARF}$ hypermethylation, deletion or mutation, *TP53* mutation, or amplification of *MDM2* gene. *PIK3CA* is a member of the family of phosphatidylinositol 3′-cinase catalytic subunits, and its mutations has been identified in approximately 05% of MDBs. Epigenetic tumor suppressor gene inactivation in MDB is associated to *RASSF1A* (ras association domain protein 1), *CASP8* (caspase 8), and *HIC-1* genes [9, 12, 27, 36, 39, 44]. Table 2 exhibits the most frequent genetic alterations and clinical aspects of WNT-activated/SHH-ativated MDB.

Final considerations and therapies targeting WNT and/or SHH pathways in cases of medullobastoma

Molecular indicators in MDB with favorable outcome include WNT-activated tumors, monosomy 6, *CTNNB1* mutation, and beta-catenin nuclear immunoexpression. Molecular indicators indicative of poor outcome include *MYC*/*MYCN* amplifications, loss of chromosome 17p, and gain of chromosome 17q [4, 6, 7, 30, 45, 46]. Patients who developed MDB can be treated with a combination of surgery and/or radiotherapy/chemotherapy regimens. Surgery is considered a standard part of treatment for histologic confirmation of tumor type and as a means to improve outcome [1, 42, 43, 45–48]. Standard-risk medulloblastoma can be defined as total or near-total surgical resection with less than or equal to 1.5 cm^2 (measured on axial plane) of residual tumor on early postoperative MRI, no CNS metastasis on MRI, no tumor cells on the cytospin of lumbar CSF, and no clinical evidence of extra-CNS metastasis. Low-risk MDB includes the WNT subgroup, which exhibits ß-catenin mutation (mandatory testing), or ß-catenin nuclear immuno-positivity by IHC (mandatory testing) ß-catenin nuclear immuno-positivity by IHC and monosomy 6 (optional testing). MDB can be grouped as a low-risk tumor if the patient has undergone total/near-total tumor resection. These cases can receive conventionally fractionated radiotherapy (once a day) with a dose of 54 Gy to the primary tumor and 18.0 Gy to the craniospinal axis. Chemotherapy is also a standard element in the treatment of MDB. Chemotherapy can be used to delay the need for radiation therapy in 20 to 40% of children younger than 3 to 4 years with non-disseminated MDB. Distinct chemotherapeutic regimens have been used, including the use of cisplatin, lomustine, vincristine, cyclophosphamide, etoposide,

Table 2 Medulloblastomas subtypes: most common molecular, histopathological, and clinical findings

Genetic profile	Most common histological pattern	Prognosis	Age at presentation	Frequent genetic alterations	Proposed cell of origin
MDB, WNT-activated	Classic	Low-risk tumor	Childhood	CTNNB1 mutation DDX3X mutation TP53 mutation	Lower rhombic lip progenitor cell
MDB, SHH-activated and TP53-mutant	Large cell / Anaplastic	High-risk tumor	Childhood	TP53 mutation	Cerebellar granule neuron cell precursors of external granule cell layer and cochlear nucleus
MDB, SHH-activated and TP53-wildtype	Desmoplastic Nodular	Low-risk tumor	Infancy Adulthood	PTCH1 mutation SMO mutation (adults) SUFU mutations (Infants)	

MDB medulloblastoma

or even concomitant high-dose intravenous methotrexate and/or intrathecal methotrexate or mafosfamide, and/or intraventricular methotrexate [1, 42, 43, 45–49].

Prognosis in children is dependent on age, metastatic status at presentation, postoperative Karnofsky Performance Scale (KPS) score, molecular subtype, and completeness of surgical resection. Histopathologic subclassification of MDBs can modify therapeutic planning [4, 6, 7, 9, 19, 22, 30, 50, 51]. A higher prevalence of *PTCH* and *SMO* mutations in adult SHH-activated MDBs can predict responsiveness to inhibitors of the receptor SMO, and SHH-inhibiting drugs like vismodegib that act downstream SMO activity are currently in development. Investigation of target drugs able to suppress the WNT pathway can be also future adjuvant therapeutic modality [7, 13, 19, 41, 43, 45, 47, 52].

Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interests.

Ethical approval This article does not contain any studies with human participants or animals performed by the author.

Informed consent Not applicable.

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