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The role of stem cells and progenitors in the genesis of medulloblastoma

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Abstract

Cancer results from dysregulation of growth and survival pathways in normal stem cells and progenitors. Identifying the cells from which a tumor arises can facilitate the development of animal models and point to novel targets for therapy. Medulloblastoma is an aggressive tumor of the cerebellum that occurs predominantly in children. Recent genomic studies suggest that medulloblastoma consists of 4 major subgroups, each with distinct mutations and signaling pathway deregulations, and each potentially arising from distinct populations of stem cells and progenitors. Here we review the major types of progenitor cells in the cerebellum and discuss their role in the genesis of medulloblastoma.

Keywords

Medulloblastoma; Cell of origin; Mouse models

Introduction

Medulloblastoma (MB) is the most common malignant brain tumor in children. Current treatments for MB include surgical resection followed by irradiation of the entire neuraxis and high-dose chemotherapy. Many patients die despite these treatments, and those who survive often suffer from cognitive deficits and endocrine disorders as a consequence of therapy (Mulhern et al., 2005). New therapies are urgently needed to improve patients' survival and quality of life.

The World Health Organization (WHO) currently classifies MB based on histology and recognizes several subtypes of the disease: classic, large cell/anaplastic (LCA), nodular/desmoplastic and MB with extensive nodularity (Louis et al., 2007). Patients with nodular/

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desmoplastic histology tend to have favorable outcomes, while those with large cell and anaplastic histology have the worst prognosis (Eberhart et al., 2002; McManamy et al., 2007). Recent advances in microarray and genomic sequencing technologies have enabled a deeper understanding of MB. Based on such analysis, MBs have now been divided into 4 major molecular subgroups: WNT, Sonic Hedgehog (SHH), Group 3 and Group 4 (Jones et al., 2012; Northcott et al., 2012; Pugh et al., 2012; Robinson et al., 2012; Taylor et al., 2012).

WNT-associated tumors, which occur in children and teenagers as well as in adults, normally have disrupted WNT signaling genes, including activating mutations in Ctnnb1 (β-catenin) which activates canonical WNT signaling, and inactivating mutations in the adenomatous polyposis coli (APC) gene, a negative regulator of the WNT pathway (Hamilton et al., 1995; Zurawel et al., 1998). WNT MBs typically have classic histology, with LCA observed only rarely. WNT signaling signatures usually predict favorable outcomes compared to other subgroups of MB, and with current modes of therapy, more than 90% of patients with WNT-associated MB survive for >5 years (Clifford et al., 2006; Ellison et al., 2005).

SHH-associated MB is characterized by activation of the Hedgehog signaling pathway, typically resulting from inactivating mutations in the negative regulators PATCHED1 (PTCH1) or Suppressor of Fused (SUFU), activating mutations in the signal transducing molecule SMOOTHENED (SMO), or amplification of the GLI2 transcription factor (Pfister et al., 2010; Taylor et al., 2012). Many SHH-associated MBs have desmoplastic/nodular histology, although classic and LCA histologies are also observed (Taylor et al., 2012). SHH MB occurs in infants, where the prognosis is favorable, as well as in adults, where the prognosis is more variable (Kool et al., 2012).

The majority of MBs do not exhibit activation of the WNT or SHH pathways, and these tumors can be divided into at least two subtypes – Group 3 and Group 4 – based on gene expression, DNA copy number changes and mutations. Group 3 MB patients commonly exhibit amplification or overexpression of the MYC oncogene and have gene signatures resembling those of photoreceptors and gamma-aminobutyric acid expressing (GABAergic) neurons (Taylor et al., 2012). In contrast, Group 4 tumors often exhibit amplification of CDK6 and MYCN or duplication of the Parkinson's Disease-associated gene synuclein alpha interacting protein (SNCAIP), and have expression profiles reminiscent of glutamate-expressing (glutamatergic) neurons (Northcott et al., 2012; Taylor et al., 2012). These disease subtypes also differ with respect to epidemiology and prognosis: Group 3 MB is predominantly found in children, is frequently associated with metastasis and has the poorest prognosis among all subtypes of MB. Group 4 MB, the most prevalent of all the subgroups, is found in both children and adults and has more variable prognosis.

In addition to the molecular distinctions among MB subtypes, a number of signaling pathways are found to be activated across multiple subtypes of the disease. For example, the phosphatidylinositol 3-kinase (PI3K) pathway is activated in WNT (Robinson et al., 2012), SHH (Northcott et al., 2012), and Group 3 MB (Pei et al., 2012b), and genes responsible for

histone methylation and chromatin remodeling (MLL2, MLL3, KDM6A, EZH2, ZMYM3) are deregulated in both Group 3 and Group 4 MBs (Pugh et al., 2012; Robinson et al., 2012).

Although different subtypes of MB tumors have distinct histological and molecular characteristics, the current treatment strategy for most MB patients is the same. Given the physical and molecular distinctions among tumor types, it is reasonable to assume that subgroup-specific therapies could be designed to target the dysregulated pathways and intracellular programs intrinsic to each MB subtype, thereby improving the efficacy of treatment and, ultimately, patient survival.

The heterogeneity of MB might be due to distinct cells of origin, different mutations acquired by the same cells, or a combination of these factors. While expression analysis, copy number analysis and sequencing have provided extensive information about the mutations in each of the MB subgroups, the functional role of these mutations remains poorly understood. Likewise, animal models have begun to shed light on the cells from which these tumors arise, but many questions and controversies remain. In order to discuss the current state of knowledge about the cell of origin for MB, it may be helpful to briefly review the program of cerebellar development.

Stem cells and progenitors in the developing cerebellum

MB is a primitive neuroectodermal tumor of the cerebellum. Thus, in considering cells of origin for the disease, it is important to focus on stem cells and progenitors in and around the cerebellum. There are two major germinal zones in the cerebellum: the ventricular zone (VZ) adjacent to the fourth ventricle, which gives rise to the majority of neurons and glia; and the external granule layer (EGL), around the outside of the cerebellum, which generates restricted populations of glutamatergic neurons.

Ventricular zone

During embryogenesis, multipotent stem cells in the VZ undergo active proliferation and then differentiate to produce neuronal and glial progenitors. These cells migrate radially into the cerebellum and give rise to Purkinje, basket, stellate and Golgi neurons, as well as astrocytes and oligodendrocytes. GABAergic neurons all appear to come from a common progenitor (Leto et al., 2006), which expresses the basic helix-loop-helix (bHLH) transcription factor Ptf1a. In the mutant mouse *Cerebelless*, which lacks Ptf1a expression in the cerebellum, glutamatergic neurons develop normally while there is a complete deficiency in GABAergic neurons (Hoshino et al., 2005).

After birth, stem cells from the VZ migrate into the cerebellar white matter. Many of these cells become restricted to neuronal, oligodendroglial and astrocytic fates and ultimately give rise to mature neurons and glia (Milosevic and Goldman, 2002; Zhang and Goldman, 1996), but some retain multipotency. These cells, identified by expression of Prominin1 and lack of neuronal and glial lineage markers, can generate self-renewing neurospheres in vitro and can differentiate into neurons and glia in culture and after transplantation into the mouse cerebellum (Lee et al., 2005). A subset of cells in the white matter also expresses the human GFAP promoter, and these cells have been shown to give rise to cerebellar interneurons and

glia in lineage tracing experiments (Silbereis et al., 2009). The relationship between hGFAP + cells and Prominin1+ Lineage− cells remains unclear. Cerebellar stem cells have intrinsic regional character that distinguishes them from forebrain neural stem cells, and may persist into adulthood (Klein et al., 2005).

External granule layer

During mid-gestation, a subset of VZ progenitor cells migrates laterally to the upper rhombic lip (URL), and under the influence of bone morphogenetic protein (BMP) signaling (Alder et al., 1999), initiates expression of the bHLH transcription factor Atoh1 (Math1) and becomes restricted to the neuronal lineage. The majority of URL progenitors then migrates around the outside of the cerebellum to form the EGL. Progenitor cells in the EGL (granule neuron precursors, or GNPs) proliferate extensively in response to SHH secreted by neighboring Purkinje cells (Dahmane and Ruiz i Altaba, 1999; Wallace, 1999; Wechsler-Reya and Scott, 1999). Ultimately (in response to signals that are poorly understood), GNPs exit the cell cycle, migrate inward to the internal granule layer (IGL), and differentiate into mature granule neurons, the most abundant type of neuron in the brain.

In addition to GNPs, a small population of URL progenitors expresses the T-box transcription factor Tbr2/Eomes. Instead of migrating around the outside of the cerebellum, these cells migrate radially through the white matter and give rise to unipolar brush cells (UBCs) in the internal granule layer (IGL). Notably, the production of UBCs is Atoh1 dependent (Englund et al., 2006). An additional group of URL progenitor cells migrates toward the deep cerebellar nuclei (DCN), the main output centers of the cerebellum, to form DCN neurons (Fink et al., 2006; Machold and Fishell, 2005; Wang et al., 2005). Finally, a unique class of progenitor cells resides in the lower rhombic lip (LRL) of the cerebellum and in the dorsal brainstem; these cells migrate away from the dorsal brainstem to the pontine grey nucleus (PGN), which is involved in motor activity (Gibson et al., 2010).

The diverse array of stem cells and lineage-restricted progenitors described above all represent candidates for MB cells of origin. Investigating whether each of these cell types can actually give rise to tumors requires targeted expression of putative MB oncogenes in these cells, either by identifying cell type-specific promoters and using them to generate oncogene-expressing transgenic mice, or by isolating cells, transducing them with viruses encoding oncogenes, and transplanting them into naïve hosts. These approaches are challenging, and the results are not always definitive. But the value of such experiments is significant: identifying cells of origin not only provides insight into the biology of the disease, but also yields important models that can be used for preclinical studies. In the next section, we review what is currently known about the cells of origin for the subtypes of MB.

Cells of origin for medulloblastoma

SHH-associated MB

The association between the SHH pathway and MB was first recognized when Gorlin syndrome, a hereditary disease characterized by skin tumors, craniofacial abnormalities and an increased incidence of MB, was found to result from mutations in PTCH1 (Gorlin and Goltz, 1960). Subsequently, mice with germline mutations in Ptch1 were reported to develop

MB (Goodrich et al., 1997), suggesting a causal role for SHH signaling in tumorigenesis. The observation that SHH functions as a potent mitogen for GNPs (Wechsler-Reya and Scott, 1999) raised the possibility that these tumors resulted from dysregulated proliferation in the granule lineage. But the cell of origin for these tumors remained controversial until it became possible to selectively activate the SHH pathway in GNPs. The demonstration that GNP-specific deletion of Ptch1 or activation of Smo results in MB formation strongly supported the notion that SHH-associated tumors arise from GNPs (Schuller et al., 2008; Yang et al., 2008). Although activation of the SHH pathway in VZ stem cells also results in tumors, stem cells must turn on expression of Atoh1 and commit to the granule lineage before becoming transformed. Recently, it was shown that SHH-associated MB can also arise from granule neuron precursors of the cochlear nucleus of the brainstem (Grammel et al., 2012). Interestingly, like cerebellar GNPs, cochlear GNPs are derived from the rhombic lip and express Atoh1. These studies suggest that Atoh1 + neuronal progenitors are the cells of origin for SHH-associated MB.

WNT-associated MB

Magnetic resonance imaging of patients with WNT-associated MB demonstrated that this subtype of MB, unlike SHH-associated MB, often encompasses the dorsal brainstem (Gibson et al., 2010). Moreover, WNT-associated tumors have a transcriptional profile resembling that of dorsal brainstem progenitors. These observations suggested that WNT-associated tumors might arise from the dorsal brainstem rather than the cerebellum. To test this, Gibson and colleagues generated mice expressing a stabilized form of Ctnnb1 (and lacking p53) in Blbp-positive radial glial cells in the hindbrain. These animals exhibit defects in differentiation and migration of dorsal brainstem progenitors, and a subset goes on to develop tumors that resemble human WNT-associated MB (Gibson et al., 2010). These tumors develop only in a subset of mice, but concomitant activation of the PI3K pathway in Blbp + cells significantly increases tumor incidence and decreases tumor latency (Robinson et al., 2012); the identification of PI3K activating mutations in human WNT-associated MB suggests that this model is relevant to the human disease. Notably, activation of Ctnnb1 in GNPs does not cause increased proliferation or lead to tumor formation (Gibson et al., 2010; Pei et al., 2012a), suggesting that WNT-associated tumors do not arise from the granule lineage. Together these studies support the notion that WNT-associated MBs arise from dorsal brainstem progenitors.

Group 3 MB

Group3 MB, characterized by overexpression or amplification of the MYC oncogene, has the least favorable prognosis of all subtypes of the disease. Although the cell of origin for these tumors remains unclear, recently generated animal models of Group 3 MB (Kawauchi et al., 2012; Pei et al., 2012b) suggest at least two possibilities. In one study (Pei et al., 2012b), Prominin1 + Lineage − cerebellar stem cells were infected with retroviruses encoding MYC and a mutant form of p53 (DNp53). When these cells were transplanted into the cerebellum of immunocompromised mice, they formed tumors that resemble human Group 3 MB at a histological and molecular level: in addition to LCA histology, the tumors also displayed gene expression profiles reminiscent of human MYC-driven MB. In a second study (Kawauchi et al., 2012), cerebellar granule neuron precursors overexpressing MYC

and lacking p53 were transplanted into the cerebellum, and were also found to form tumors. Interestingly, granule lineage markers were absent from established tumors, suggesting that GNPs may dedifferentiate during the course of transformation (Kawauchi et al., 2012; Pei et al., 2012b). While these studies point to GNPs and stem cells as cells of origin for Group 3 MB, it remains possible that other classes of progenitors could give rise to these tumors as well. The fact that Group 3 tumors often express markers of GABAergic neurons (Taylor et al., 2012) suggests that the tumorigenic potential of GABAergic progenitors should also be investigated.

Group 4 MB

Group 4 MB is the most prevalent of the subgroups, comprising 35– 40% of MB cases. A recently generated transgenic mouse expressing MYCN under the control of a Glt1 promoter develops tumors that exhibit classic or LCA histology, lack markers of SHH or WNT-associated MB, and appear to resemble Group 4 MB at a molecular level (Swartling et al., 2010, 2012). Since Glt1 is expressed in progenitors and stem cells in the developing cerebellum (Swartling et al., 2010, 2012), the cell of origin for these tumors may be a primitive progenitor or stem cell. Indeed, a recent study by Swartling et al. (2012) demonstrates that expression of a stabilized form of MYCN in stem cells from the postnatal cerebellum results in similar tumors. Interestingly, the same study showed that MYCN expression in stem cells from the embryonic cerebellum results in SHH-associated MB, highlighting the importance of the cell of origin and the stage of differentiation in determining tumor phenotype.

Group 4 MB is a heterogeneous disease, so it is possible that multiple cell types may give rise to tumors of this subtype. For example, since many Group 4 MBs express markers of glutamatergic neurons, it will be important to test the tumorigenic potential of glutamatergic progenitors (UBC precursors or GNPs (Taylor et al., 2012)). The recent identification of recurrent mutations in Group 4 tumors (Jones et al., 2012; Northcott et al., 2012) provides several important candidate driver genes (e.g. Ctdnep1, SNCAIP, and KDM6A) that should be evaluated in this context.

Perspectives

The molecular diversity of MB subtypes underscores the complex nature of MB tumor development. In addition to the role of oncogenes and tumor suppressors in cellular transformation, the properties of different MB subtypes are also dependent on the specific cellular context from which the tumors originate. Identification of the cell of origin for each MB subtype is thus crucial if we are to understand the biology of these tumors, and develop robust animal models that can be used to test therapies. In addition, knowing the signaling pathways that regulate survival of normal progenitors and stem cells may point to novel approaches to targeting the tumors that arise from them. Ultimately, our ability to effectively target MB may depend on uncovering the origins of the disease.

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References

Alder J, Lee KJ, Jessell TM, Hatten ME. Generation of cerebellar granule neurons in vivo by transplantation of BMP-treated neural progenitor cells. Nat Neurosci. 1999; 2:535–540. [PubMed: 10448218]

Clifford SC, Lusher ME, Lindsey JC, Langdon JA, Gilbertson RJ, Straughton D, Ellison DW. Wnt/Wingless pathway activation and chromosome 6 loss characterize a distinct molecular sub-group of medulloblastomas associated with a favorable prognosis. Cell Cycle. 2006; 5:2666–2670. [PubMed: 17172831]

Dahmane N, Ruiz i Altaba A. Sonic hedgehog regulates the growth and patterning of the cerebellum. Development. 1999; 126:3089–3100. [PubMed: 10375501]

Eberhart CG, Kepner JL, Goldthwaite PT, Kun LE, Duffner PK, Friedman HS, Strother DR, Burger PC. Histopathologic grading of medulloblastomas: a Pediatric Oncology Group study. Cancer. 2002; 94:552–560. [PubMed: 11900240]

Ellison DW, Onilude OE, Lindsey JC, Lusher ME, Weston CL, Taylor RE, Pearson AD, Clifford SC. beta-Catenin status predicts a favorable outcome in childhood medulloblastoma: the United Kingdom Children's Cancer Study Group Brain Tumour Committee. J Clin Oncol. 2005; 23:7951–7957. [PubMed: 16258095]

Englund C, Kowalczyk T, Daza RA, Dagan A, Lau C, Rose MF, Hevner RF. Unipolar brush cells of the cerebellum are produced in the rhombic lip and migrate through developing white matter. J Neurosci. 2006; 26:9184–9195. [PubMed: 16957075]

Fink AJ, Englund C, Daza RA, Pham D, Lau C, Nivison M, Kowalczyk T, Hevner RF. Development of the deep cerebellar nuclei: transcription factors and cell migration from the rhombic lip. J Neurosci. 2006; 26:3066–3076. [PubMed: 16540585]

Gibson P, Tong Y, Robinson G, Thompson MC, Currle 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]

Goodrich LV, Milenkovic L, Higgins KM, Scott MP. Altered neural cell fates and medulloblastoma in mouse patched mutants. Science. 1997; 277:1109–1113. [PubMed: 9262482]

Gorlin RJ, Goltz RW. Multiple nevoid basal-cell epithelioma, jaw cysts and bifid rib. A syndrome. N Engl J Med. 1960; 262:908–912. [PubMed: 13851319]

Grammel D, Warmuth-Metz M, von Bueren AO, Kool M, Pietsch T, Kretzschmar HA, Rowitch DH, Rutkowski S, Pfister SM, Schuller U. Sonic hedgehog-associated medulloblastoma arising from the cochlear nuclei of the brainstem. Acta Neuropathol. 2012; 123:601–614. [PubMed: 22349907]

Hamilton SR, Liu B, Parsons RE, Papadopoulos N, Jen J, Powell SM, Krush AJ, Berk T, Cohen Z, Tetu B, Burger PC, Wood PA, Taqi F, Booker SV, Petersen GM, Offerhaus GJA, Tersmette AC, Giardiello FM, Vogelstein B, Kinzler KW. The molecular basis of Turcot's syndrome. N Engl J Med. 1995; 332:839–847. [PubMed: 7661930]

Hoshino M, Nakamura S, Mori K, Kawauchi T, Terao M, Nishimura YV, Fukuda A, Fuse T, Matsuo N, Sone M, Watanabe M, Bito H, Terashima T, Wright CV, Kawaguchi Y, Nakao K, Nabeshima Y. Ptf1a, a bHLH transcriptional gene, defines GABAergic neuronal fates in cerebellum. Neuron. 2005; 47:201–213. [PubMed: 16039563]

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, Lawerenz 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]

Kawauchi D, Robinson G, Uziel T, Gibson P, Rehg 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]

Klein C, Butt SJ, Machold RP, Johnson JE, Fishell G. Cerebellum- and forebrain-derived stem cells possess intrinsic regional character. Development. 2005; 132:4497–4508. [PubMed: 16162650]

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 Neuropathol. 2012; 123:473–484. [PubMed: 22358457]

Lee A, Kessler JD, Read TA, Kaiser C, Corbeil D, Huttner WB, Johnson JE, Wechsler-Reya RJ. Isolation of neural stem cells from the postnatal cerebellum. Nat Neurosci. 2005; 8:723–729. [PubMed: 15908947]

Leto K, Carletti B, Williams IM, Magrassi L, Rossi F. Different types of cerebellar GABAergic interneurons originate from a common pool of multipotent progenitor cells. J Neurosci. 2006; 26:11682–11694. [PubMed: 17093090]

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol. 2007; 114:97–109. [PubMed: 17618441]

Machold R, Fishell G. Math1 is expressed in temporally discrete pools of cerebellar rhombiclip neural progenitors. Neuron. 2005; 48:17–24. [PubMed: 16202705]

McManamy CS, Pears J, Weston CL, Hanzely Z, Ironside JW, Taylor RE, Grundy RG, Clifford SC, Ellison DW. Nodule formation and desmoplasia in medulloblastomas-defining the nodular/desmoplastic variant and its biological behavior. Brain Pathol. 2007; 17:151–164. [PubMed: 17388946]

Milosevic A, Goldman JE. Progenitors in the postnatal cerebellar white matter are antigenically heterogeneous. J Comp Neurol. 2002; 452:192–203. [PubMed: 12271492]

Mulhern RK, Palmer SL, Merchant TE, Wallace D, Kocak M, Brouwers P, Krull K, Chintagumpala M, Stargatt R, Ashley DM, Tyc VL, Kun L, Boyett J, Gajjar A. Neurocognitive consequences of risk-adapted therapy for childhood medulloblastoma. J Clin Oncol. 2005; 23:5511–5519. [PubMed: 16110011]

Northcott PA, Shih DJ, Peacock J, Garzia L, Morrissy AS, Zichner T, Stutz AM, Korshunov A, Reimand J, Schumacher SE, Beroukhim 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, Jouvet 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, Bognar 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, Vibhakar 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. 2012; 488:49–56. [PubMed: 22832581]

Pei Y, Brun SN, Markant SL, Lento W, Gibson P, Taketo MM, Giovannini M, Gilbertson RJ, Wechsler-Reya RJ. WNT signaling increases proliferation and impairs differentiation of stem cells in the developing cerebellum. Development. 2012a; 139:1724–1733. [PubMed: 22461560]

Pei Y, Moore Colin E, Wang J, Tewari Alok K, Eroshkin A, Cho YJ, Witt H, Korshunov A, Read TA, Sun Julia L, Schmitt Earlene M, Miller CR, Buckley Anne F, McLendon Roger E, Westbrook Thomas F, Northcott Paul A, Taylor Michael D, Pfister Stefan M, Febbo Phillip G, Wechsler-Reya Robert J. An animal model of MYC-driven medulloblastoma. Cancer Cell. 2012b; 21:155–167. [PubMed: 22340590]

Pfister SM, Korshunov A, Kool M, Hasselblatt M, Eberhart C, Taylor MD. Molecular diagnostics of CNS embryonal tumors. Acta Neuropathol. 2010; 120:553–566. [PubMed: 20882288]

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]

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, Thiruvenkatam 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]

Schuller U, Heine VM, Mao J, Kho AT, Dillon AK, Han YG, Huillard E, Sun T, Ligon AH, Qian Y, Ma Q, Alvarez-Buylla A, McMahon AP, Rowitch DH, Ligon KL. Acquisition of granule neuron precursor identity is a critical determinant of progenitor cell competence to form Shh-induced medulloblastoma. Cancer Cell. 2008; 14:123–134. [PubMed: 18691547]

Silbereis J, Cheng E, Ganat YM, Ment LR, Vaccarino FM. Precursors with glial fibrillary acidic protein promoter activity transiently generate GABA interneurons in the postnatal cerebellum. Stem Cells. 2009; 27:1152–1163. [PubMed: 19418461]

Swartling FJ, Grimmer MR, Hackett CS, Northcott PA, Fan QW, Goldenberg DD, Lau J, Masic S, Nguyen K, Yakovenko S, Zhe XN, Gilmer HC, Collins R, Nagaoka M, Phillips JJ, Jenkins RB, Tihan T, Vandenberg SR, James CD, Tanaka K, Taylor MD, Weiss WA, Chesler L. Pleiotropic role for MYCN in medulloblastoma. Genes Dev. 2010; 24:1059–1072. [PubMed: 20478998]

Swartling FJ, Savov V, Persson AI, Chen J, Hackett CS, Northcott PA, Grimmer MR, Lau J, Chesler L, Perry A, Phillips JJ, Taylor MD, Weiss WA. Distinct neural stem cell populations give rise to disparate brain tumors in response to N-MYC. Cancer Cell. 2012; 21:601–613. [PubMed: 22624711]

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 Neuropathol. 2012; 123:465–472. [PubMed: 22134537]

Wallace VA. Purkinje-cell-derived Sonic hedgehog regulates granule neuron precursor cell proliferation in the developing mouse cerebellum. Curr Biol. 1999; 9:445–448. [PubMed: 10226030]

Wang VY, Rose MF, Zoghbi HY. Math1 expression redefines the rhombic lip derivatives and reveals novel lineages within the brainstem and cerebellum. Neuron. 2005; 48:31–43. [PubMed: 16202707]

Wechsler-Reya RJ, Scott MP. Control of neuronal precursor proliferation in the cerebellum by Sonic Hedgehog. Neuron. 1999; 22:103–114. [PubMed: 10027293]

Yang ZJ, Ellis T, Markant SL, Read TA, Kessler JD, Bourboulas M, Schuller U, Machold R, Fishell G, Rowitch DH, Wainwright BJ, Wechsler-Reya RJ. Medulloblastoma can be initiated by deletion of Patched in lineage-restricted progenitors or stem cells. Cancer Cell. 2008; 14:135–145. [PubMed: 18691548]

Zhang L, Goldman JE. Generation of cerebellar interneurons from dividing progenitors in white matter. Neuron. 1996; 16:47–54. [PubMed: 8562089]

Zurawel RH, Chiappa SA, Allen C, Raffel C. Sporadic medulloblastomas contain oncogenic beta-catenin mutations. Cancer Res. 1998; 58:896–899. [PubMed: 9500446]