Medulloblastoma: signalling a change in treatment

Richard J Gilbertson

Medulloblastoma is the most common malignant brain tumour that occurs during childhood. Multimodality treatment regimens have substantially improved survival in this disease; however, the tumour is incurable in about a third of patients with medulloblastoma, and current treatment has a detrimental effect on long-term survivors. Drugs that target cell-signalling pathways provide an alternative to conventional cytotoxic approaches to treatment of cancer. Several pathways have been implicated in medulloblastoma formation, and knowledge of these is now being used to develop new ways of treating children with medulloblastoma.

Lancet Oncol 2004; **5:** 209–18

Brain tumours are the second most common paediatric cancer, affecting 3·3 per 100 000 children.[1] Survival for children with cancer varies according to histology and clinical characteristics. However, brain tumours are generally associated with a worse prognosis than many other common paediatric cancers, and as a group they account for more than a quarter of childhood deaths from cancer.[1] Furthermore, survivors of childhood brain tumours commonly have grave treatment-induced side-effects.[2–5] Such clinical challenges are exemplified by medulloblastoma, the most common malignant brain tumour occurring in childhood.

Histopathological variants

Medulloblastoma is one of five embryonic tumours that can occur in the CNS. It is defined as a malignant tumour of the cerebellum that preferentially occurs in children, and has a tendency to metastasise.[6] Five histological variants of medulloblastoma are recognised.[6,7] In the classic variant, the cells, which have small round nuclei, are generally arranged in sheets, occasionally displaying features of neuroblastic differentiation (figure 1). Desmoplastic medulloblastomas contain nodules of tumour cells that commonly show neurocytic differentiation and are surrounded by collagen-rich tissue (figure 1). Another variant of medulloblastoma has been described that contains large tumour cells with pleiomorphic nuclei, prominent nucleoli, and abundant cytoplasm (figure 1). These tumours, which are also characterised by anaplasia, are called large-cell anaplastic medulloblastomas and are associated with an especially poor prognosis.[8] The melanotic and medullomyoblastoma variants are much less common forms of medulloblastoma.

Clinical management

Current risk stratification

Clinical trials at several institutions have identified three consistent prognostic markers for children with medulloblastoma: patient's age at diagnosis, the extent of postoperative residual disease, and tumour metastasis.[9,10]

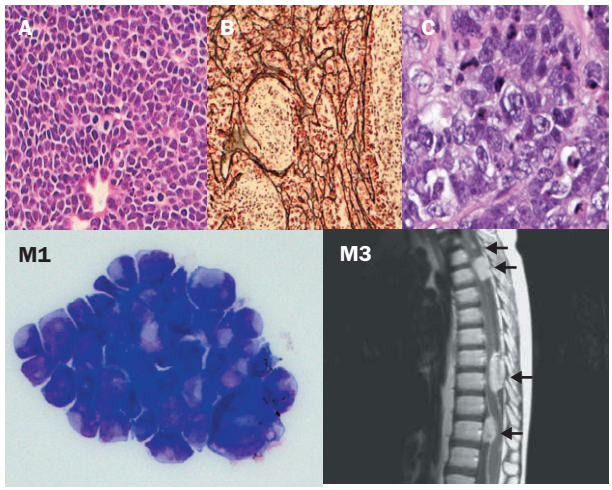

Figure 1. (Upper) Photomicrographs of the three most common histopathological variants of medulloblastoma: classic (a), nodular desmoplastic (b), and large-cell or anaplastic (c). (Lower) Metastatic (M) stage 1 (cytospin of cerebrospinal fluid) and M3 of medulloblastoma.

Patient's age

Medulloblastoma in children aged younger than 3 years is twice as likely to progress within 5 years of diagnosis than medulloblastoma occurring in older children.[10,11] One explanation for age-dependent disease behaviour is the restriction that age imposes on treatment. Although radiation is a highly effective therapy for medulloblastoma, it causes severe damage to the developing brain.[2–5] Thus, initial treatment for young patients with medulloblastoma is generally restricted to surgery and chemotherapy alone; however, this approach is associated with a median time to progression of less than 9 months.[11] Young patients with medulloblastoma might also fare worse than older patients because of inherent differences in disease biology. Studies of very young children with brain tumours have identified the atypical teratoid rhabdoid tumour,[12] a highly aggressive embryonic brain tumour that is genetically and

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Chang's staging classification

T stage

T1 Tumour less than 3 cm in diameter and limited to the classic midline position in the vermis, the roof of the fourth ventricle, and less commonly to the cerebellar hemispheres

T2 Tumour greater than 3 cm and invading one adjacent structure or partly filling the fourth ventricle

T3a Tumour further invading two adjacent structures or completely filling the fourth ventricle, with extension into the aqueduct of Sylvius, foramen of Magendie, or foramen of Luschka, thus producing prominent internal hydrocephalus

T3b Tumour arising from floor of fourth ventricle and filling the fourth ventricle

T4 Tumour spread through aqueduct of Sylvius to involve third ventricle, midbrain, or down into upper cervical cord

M stage

M0 No gross subarachnoid or haematogenous metastasis

M1 Tumour cells found in cerebrospinal fluid on microscopic analysis

M2 Gross nodular seeding in cerebellum, cerebral subarachnoid space, or in third or fourth ventricles

M3 Gross nodular seeding in spinal subarachnoid space

M4 Extraneuraxial metastasis

morphologically distinct from medulloblastoma and is prevalent in children aged younger than 3 years. Atypical teratoid rhabdoid tumour is now classified separately from medulloblastoma. However, patients with this disease were previously included in medulloblastoma clinical trials and probably contributed to the high mortality seen in very young patients.

Extent of disease

Subtotal tumour resection ($\geq$1·5 cm^2 on postoperative MRI) and the presence of metastatic disease are also established indicators of poor clinical outcome among children with medulloblastoma.

Medulloblastoma has an inherent tendency to metastasise (figure 1); around a third of patients have evidence of dissemination in the CNS at diagnosis.[9,10] Furthermore, a small but important group of patients develop extraneural metastasis to the bone, bone marrow, lymph nodes, liver, or lung.[13] Metastatic medulloblastoma is staged according to Chang's criteria (see panel), and metastases remain one of the most important prognostic markers for this disease.

Current risk-adapted therapy

Recognition that the clinical outcome of patients with medulloblastoma varies according to age, postoperative tumour residuum, and metastatic (M) stage has led to the development of risk-adapted treatment for this disease. In the USA, children with medulloblastoma are classified in two risk groups. Patients with average-risk medulloblastoma are those diagnosed after the age of 3 years with non-

Results of clinical trials in medulloblastoma

Trial	Accrual period	Eligible patients	Treatment (Gy, posterior fossa/ craniospinal axis)	Progression-free survival at 5 years (%)	p	Ref
Average risk						
HIT '91	1991–97	118	Ifosfamide, etoposide, methotrexate, cisplatin, cytarabine preradiation (55·2/35·2) *vs* vincristine, lomustine, cisplatin postradiation (55·2/35·2)	65 *vs* 78	<0·03	9
SIOP III	1992–2000	179	Radiation (55/35) *vs* vincristine, etoposide, carboplatin, cyclophosphamide preradiation (55/35)	60 *vs* 74	0·036	14
CCG9892	1990–94	65	Vincristine, lomustine, cisplatin postradiation (55·2/23·4)	79	··	15
SJMB'96	1996–99*	34	High-dose cyclophosphamide, cisplatin, vincristine postradiation (55/23·4)	94†	··	16
POG8631/ CCG923	1986–90‡	81	Radiation (54/36) *vs* radiation (54/23·4)	67 *vs* 52	0·14§	17
High risk						
CCG921	1986–92	203	Eight drugs in 1 day preradiation and postradiation (54/36) *vs* vincristine, lomustine, prednisolone postradiation (54/36)	43 *vs* 63	0·006	10
SJMB'96	1996–99*	19	Topotecan window preradiation (55/36–39·6) then high-dose cyclophosphamide, cisplatin, vincristine	84†	··	16
Limited institution CHOP/CNMC/CMCD	1983–93	15	Vincristine, lomustine, cisplatin postradiation (55·2/36)	67	··	20

*Accrual period for initial feasibility phase of the study. SJMB'96 remained open until August, 2003. †2 years after radiation. ‡Protocol closed prematurely because initial interim analysis showed increased risk of relapse among patents receiving reduced-dose radiotherapy. §Final analysis at 8 years showed non-significant trend in favour of patients receiving 36 Gy neuraxis radiation.

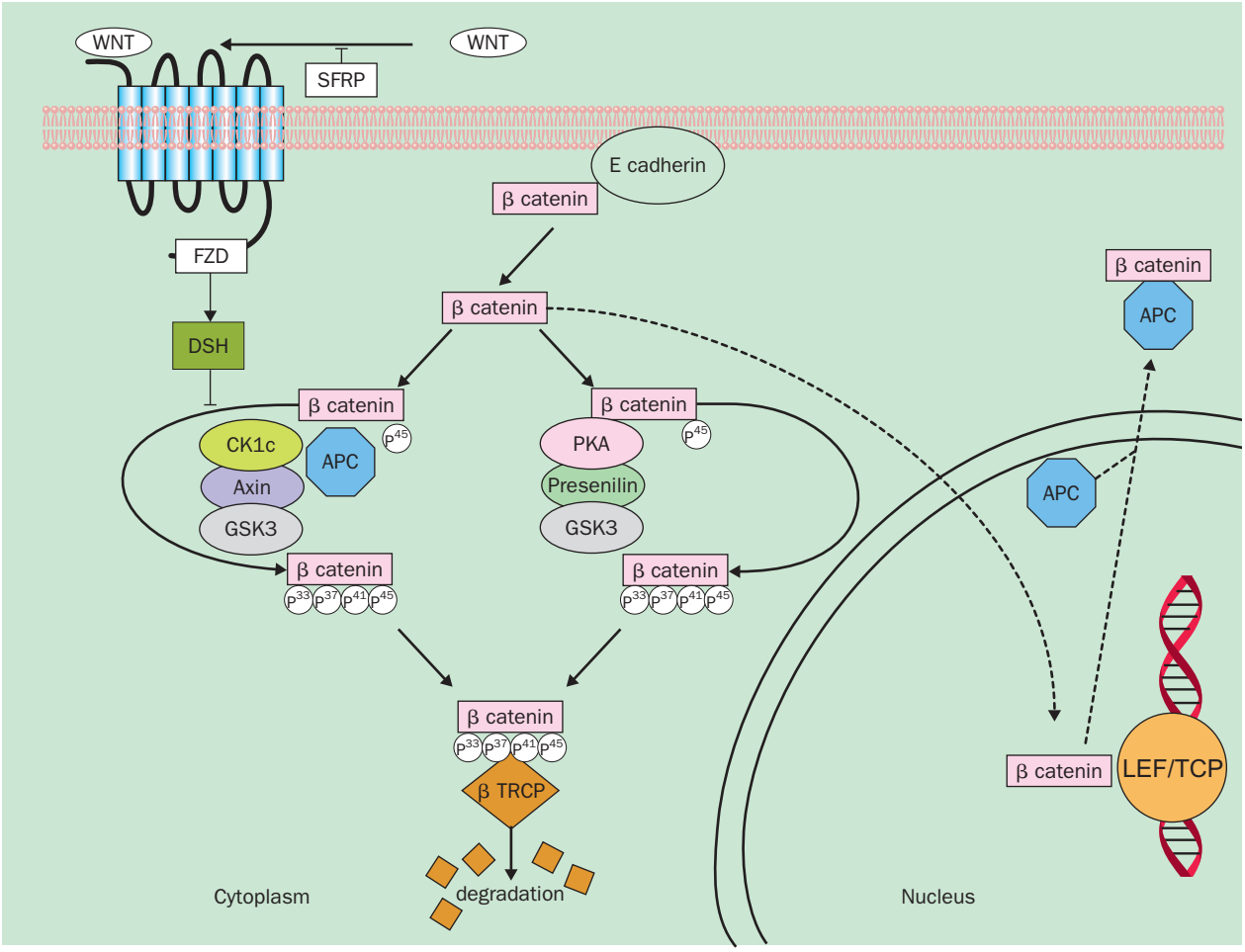

Figure 2. The wingless (WNT) signal pathway. SFRP, secreted frizzled-related proteins; FZD, frizzled protein; DSH, dishevelled protein, CK1α, casein kinase 1α; APC, adenomatous polyposis coli protein; GSK3, glycogen synthase kinase 3; PKA, protein kinase A; β-TRCP, β-transducin repeat-containing protein; LEF, lymphoid enhancer factor; TCF, T-cell factor.

metastatic and totally, or near totally, resected disease (<1·5 cm^2 on postoperative MRI). Patients who do not meet these criteria are classified as high risk. In Europe, the patient's age and M stage (≤M1 *vs* ≥M2) alone are used to assign disease risk.

Average-risk medulloblastoma

At present, average-risk medulloblastoma is treated with maximum surgical resection, followed by chemotherapy and whole neuraxis radiotherapy (see table).[9,14–16] Radiotherapy is a very effective treatment for medulloblastoma, but it also damages the surrounding disease-free brain. Therefore, in the USA, the standard neuraxis radiation dose used to treat children with average-risk medulloblastoma has been reduced from 36·0 Gy to 23·4 Gy (see table). The concurrent introduction of adjuvant chemotherapy has enabled this reduction in radiation dose to be made without a negative effect on the number of children cured (see table).[15–17] However, a radiation dose of 23·4 Gy is still associated with neurological toxic effects, especially in children younger than 8 years.[5] Consequently, the Children's Oncology Group is planning a phase III study that will test the safety of a further reduction of neuraxis radiation to 18·0 Gy for patients with average-risk medulloblastoma who are aged between 3 and 8 years. Although these additional reductions in radiation dose might decrease morbidity in surviving patients, whether this effect will occur at the expense of disease control remains unclear. Postoperative chemotherapy and radiation are also used to treat average-risk patients in Europe, although the neuraxis dose used has not yet been reduced from 35·0 Gy.

Several chemotherapeutic regimens have been investigated for the treatment of average-risk medulloblastoma (see table). These include preradiation (or so-called sandwich) regimens, which have been investigated mainly in Europe,[14] and postradiation chemotherapy used by US cooperative groups.[15,16] These studies have shown that a combination of postoperative chemotherapy and radiation is more effective for treatment of average-risk medulloblastoma than surgery and radiation. However, which of the adjuvant chemotherapy regimens, if any, has the greatest survival advantage remains unclear. Indeed, studies that have used these different multimodality treatment protocols report a very similar event-free survival of around 75% at 5 years (see table).

High-risk medulloblastoma

Historically, progression-free survival in children with high-risk medulloblastoma has been less than 50%.[18] Some combined chemotherapy and radiation treatments have yielded more promising results (table).[10,16,19] For example, a continuing study[16] coordinated by St Jude Children's Research Hospital (called SJMB'96) has used radiation followed by high-dose chemotherapy and autologous stem-cell rescue to treat patients with high-risk medulloblastoma. This treatment is tolerated well, and short-term survival has been encouraging (table). However, the study is not yet mature, and further follow-up is required before the efficacy of this approach can be fully assessed

Patients whose disease recurs after combined-modality therapy have a very poor chance of being cured. Although several studies have shown the efficacy of high-dose chemotherapy for these patients, only children with isolated local relapse, chemosensitive disease, and minimal residual disease at the time of high-dose chemotherapy benefit.[18]

How can treatment be improved?

Physicians and scientists seeking to improve further the outcome for children with medulloblastoma are faced with two clear challenges. First, both average-risk and high-risk medulloblastoma are still associated with substantial mortality. Therefore, to improve the chances of survival for all children with medulloblastoma remains an important goal. Second, survivors of medulloblastoma have severe long-term side-effects that greatly affect their quality of life. The reduction of treatment-related toxic effects is therefore an additional important objective. These goals are unlikely to be achieved through further empirical changes in treatment. Rather, there is a general consensus that a greater understanding of medulloblastoma biology will ultimately lead to the identification of new treatments and improvements in the way existing therapies are used. The aberrant activation of several cell-signalling pathways has been implicated in medulloblastoma formation, and investigation of these pathways should lead to the development of new treatments and risk-stratification tools for medulloblastoma in the near future.

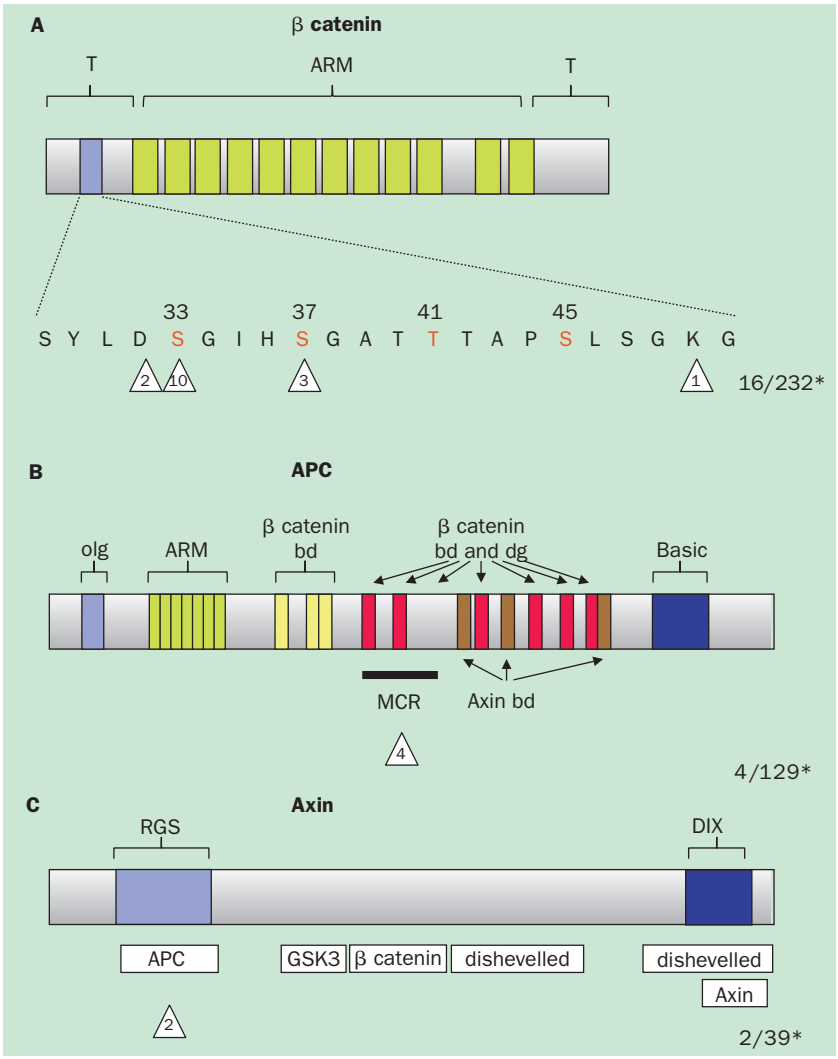

*Figure 3. Wingless (WNT) pathway mutations in sporadic medulloblastoma. (A) β-catenin protein sequence. Phosphorylation pathway of glycogen synthase kinase 3 (GSK3, light purple box) expanded to show aminoacid sequence. S33, S37, S45, and T41 shown in red. White triangles indicate residues targeted by mutations in medulloblastoma. Number in triangles is total number of tumours reported to contain each mutation. T, transcriptional-activating domain; ARM, armadillo-repeat domain. (B) Adenomatous polyposis coli (APC) protein sequence. Four medulloblastomas have been reported with mutations (white triangle) within the mutation cluster region (MCR). Olg, oligomerisation domain; bd, binding domain; dg, degradation domain. (C) Axin protein sequence. White boxes are binding sites for WNT signal pathway members. Two medulloblastomas with mutations in the APC binding region have been identified. RGS, regulator-of-G-protein-signalling; DIX, domain shared with dishevelled protein.*Mutations identified/tumours investigated.*

Aberrant signal transduction in medulloblastoma

Wingless (WNT) signalling

The wingless (WNT) pathway coordinates a diverse array of developmental processes, including the proliferation and fate of neural progenitor cells.[20,21] The deregulation of WNT signalling has emerged as an important step in human oncogenesis.[22] Mutations in proteins on the WNT pathway occur in about 15% of sporadic medulloblastomas,[23–28] and when transmitted in the germline, cause heritable forms of the disease. In general, these mutations cause aberrant WNT signalling by blocking the degradation of β catenin—the downstream effector of the WNT pathway.

The activity of the WNT pathway is directly related to the amount of free

cytosolic β catenin (figure 2). In healthy cells, the absence of WNT keeps concentrations of β catenin low and the pathway is silent. This suppression is achieved by the sequestration of β catenin in cadherin-containing cell junctions and by constitutive degradation of β catenin. Two independent pathways mediate degradation of β catenin (figure 2). In the first pathway, β catenin is drawn into a multiprotein complex that includes the scaffold protein axin, casein kinase 1α, and glycogen synthase kinase 3. Casein kinase 1α phosphorylates β catenin on S45, which primes β catenin for further phosphorylation by glycogen synthase kinase 3 on residues 41, 37, and 33. These phosphorylated residues provide binding sites for the β-transducin repeat-containing protein, which promotes the polyubiquitination and complete proteolysis of β catenin. A second, similar protein complex that degrades β catenin has also been described that includes presenilin 1.[29]

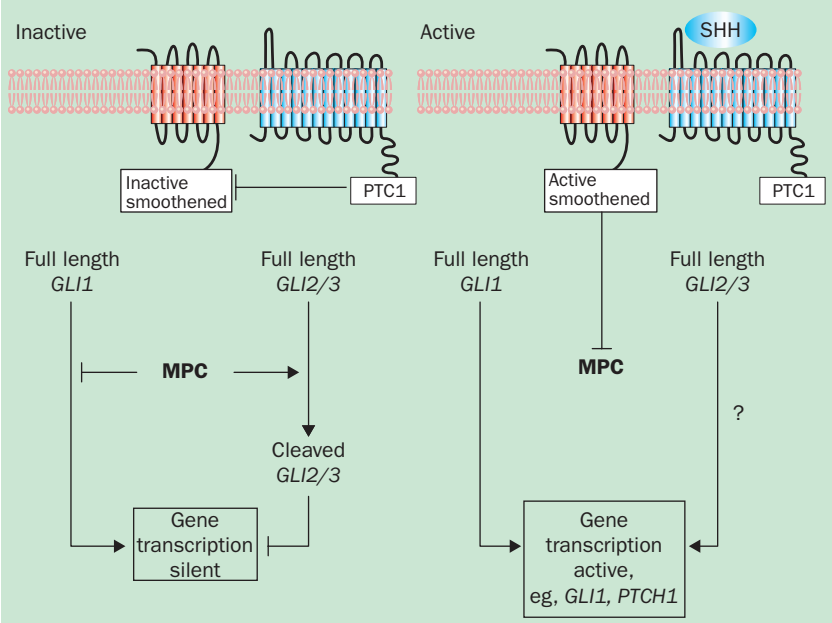

Figure 4. The sonic hedgehog (SHH) signal pathway. (a) The pathway is inactive when SHH is absent and is activated when SHH binds to PTC1 (b). MPC, fused or suppressor-of-fused-containing multiprotein complex.

The WNT pathway is activated through the binding of WNT to the frizzled receptor protein on the cell surface (figure 2). Frizzled then phosphorylates the dishevelled protein, which in turn inactivates the axin, glycogen synthase kinase 3, and adenomatous polyposis coli (APC) complex, blocking β-catenin degradation.[20] Consequently, the amount of β catenin increases and shuttles to the nucleus to activate the transcription of genes such as cyclin D1 and *MYC*.[21]

Most of the WNT-pathway mutations reported in sporadic medulloblastomas target residues S33 and S37 of β catenin (figure 3). These mutations prevent phosphorylation-dependent degradation of β catenin by glycogen synthase kinase 3. β catenin increases unchecked and activates oncogenic gene transcription. Other, less common mutations have been described in *APC* and the axin gene in medulloblastoma. Mutations in *APC* are also the cause of Turcot's syndrome, a tumour-predisposition syndrome characterised by the development of bowel tumours and medulloblastoma.[30]

Sonic hedgehog (SHH) signalling

The *SHH* pathway (figure 4) has also been implicated in the development of sporadic and heritable forms of medulloblastoma.[20,31–34] SHH, desert hedgehog, and indian hedgehog are vertebrate orthologues of the *Drosophila melanogaster* gene, hedgehog. These secreted glycoproteins have key roles in tissue patterning.

PTC1 is a 12-pass transmembrane receptor that suppresses the activity of the protein smoothened—a seven-pass transmembrane protein closely related to the frizzled family of WNT receptors. Evidence suggests that PTC1 might suppress smoothened indirectly, possibly by acting as a transmembrane transporter for a small molecule intermediary.[35] In the absence of smoothened activity, GLI (glioma-associated oncogene homologue) transcription factors (the effectors of the SHH pathway) are tethered to microtubules in the cytoplasm by a multiprotein complex that includes fused and suppressor-of-fused. GLI1 is sequestered in this complex, preventing it from activating gene transcription; GLI2 and GLI3 are cleaved to produce truncated transcriptional repressors. The binding of SHH to PTC1 relieves the suppression of smoothened. Active smoothened then disrupts the multiprotein complexes containing fused and suppressor-of-fused. Subsequently, GLI1 is released and activates gene transcription, whereas cleavage of GLI2 and GLI3 is blocked.[32–34] Although full-length GLI2 and GLI3 can enter the nucleus, how this ability affects gene transcription remains unclear.

SHH signalling was first implicated in human oncogenesis after the finding that germline mutations in the PTC1 gene *PTCH1* cause the basal-cell naevus syndrome (also called Gorlin's syndrome).[36] This is a familial cancer syndrome characterised by a predisposition to basal-cell carcinomas, medulloblastomas, and rhabdomyosarcomas.[31,33,34] Germline mutations in the suppressor-of-fused gene have also been identified in patients with medulloblastoma,[37] suggesting that heritable forms of the disease can result from various changes in the SHH pathway. Mutations in several components of the SHH pathway also occur in sporadic medulloblastoma. These include inactivating mutations in both *PTCH1* and the suppressor-of-fused gene (in about 10% of tumours), and less common activating mutations in the smoothened gene (about 5% of tumours).[37–42] Medulloblastomas that carry mutations in the SHH pathway preferentially, but not exclusively, show nodular desmoplastic morphology.[7]

Precisely how changes in PTC1 and other pathway components predispose to medulloblastoma is the subject of

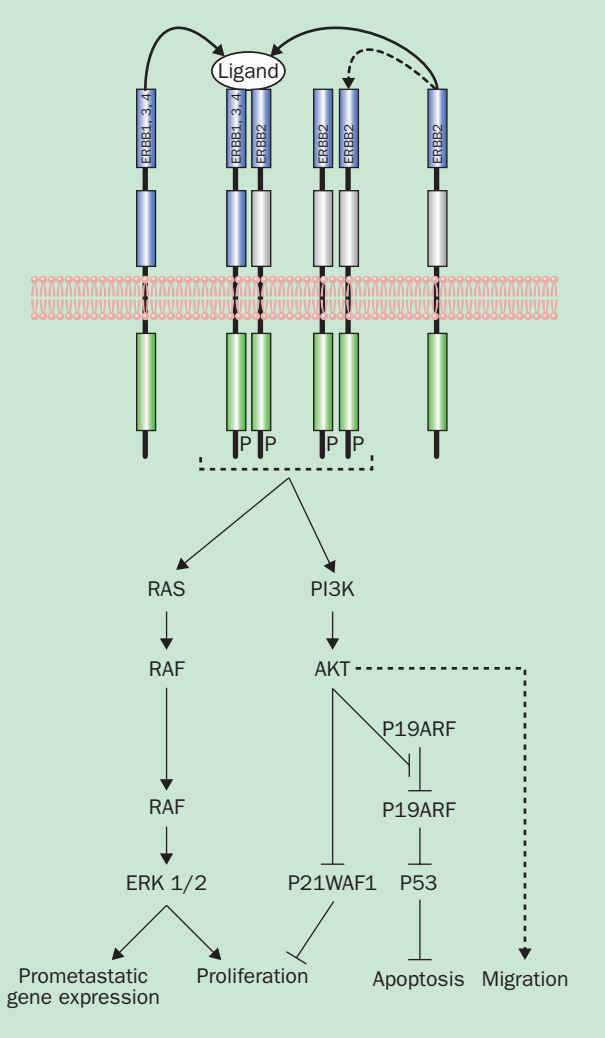

Figure 5. ERBB2 is activated through ligand-mediated heterodimerisation with other ERBB family members, or when overexpressed, through aberrant homodimerisation. Resultant receptor autophosphorylation (P) activates the RAS/MAPK and AKT pathways to mediate oncogenic effects. PI3K, phosphatidylinositol 3 kinase.

current research. In disease-free cerebellum, SHH is secreted by Purkinje cells and maintains developing granule-neuron precursor cells in an undifferentiated, proliferating state.[32,43,44] Most medulloblastomas are thought to arise from transformed granule-neuron precursor cells (although some may arise from neuronal precursor cells in the subventricular zone). Therefore, because PTC1 is a negative regulator of the pathway, deletion of *PTCH1* in granule-neuron precursor cells might result in malignant transformation. However, studies of medulloblastoma in mice are showing a much more complex picture. First, only 14% of mice with a heterozygous loss of *Ptch* develop medulloblastoma, indicating that so-called second hits in the genome are required for tumours to develop. Efforts to identify these second-hit mutations have shown that these tumours occur more frequently and more rapidly in mice that are heterozygous for *Ptch* and carry deletions in *P53*.[45] However, *P53* mutations are not detected in medulloblastomas that arise in *Ptch* heterozygous, P53 wild-type mice.[45] Thus, *P53* loss probably accelerates *Ptch* tumorigenesis by destabilising the genome rather than by disrupting the P53 tumour-suppressor pathway, and second-hit mutations in *Ptch* tumours remain to be identified. Second, whether the remaining *Ptch* allele is silenced in heterozygous *Ptch* mouse medulloblastoma also remains unclear;[46–48] tumours could form in the context of *Ptch* haploinsufficiency. Third, evidence suggests that overexpression of Shh in granule-neuron precursor cells can induce medulloblastoma even in the absence of Gli1.[49] Further study of both animal models and human tumours will undoubtedly clarify the role of *SHH* signalling in medulloblastoma development.

ERBB signalling

The four members of the receptor tyrosine kinase I family—ERBB1, ERBB2, ERBB3, and ERBB4—interact through a complex network of homodimers and heterodimers.[50] ERBB dimers trigger the cell-signal pathways of mitogen-activated protein kinase (MAPK), AKT, and STAT, thereby regulating important cellular processes such as cell proliferation, apoptosis, migration, and differentiation.[50]

The aberrant upregulation of ERBB2 signalling results in cell transformation. In rodents, a single point mutation (V664→E) in the transmembrane domain of *Neu* (the rodent orthologue of *ERBB2*) strikingly increases receptor homodimerisation and induces tumour formation in the CNS and mammary glands.[51–53] Although an equivalent mutation in human *ERBB2* transforms cells,[54] this mutation has not been identified in sporadic human tumours. However, the overexpression of wildtype *ERBB2* is oncogenic.[50,54] Wildtype *ERBB2* is amplified and over-expressed in about 25% of human breast cancers, and overexpression of wildtype *Neu* leads to mammary tumours in transgenic mice.[55]

There is evidence that aberrant expression of ERBB2 in granule-neuron precursor cells of the cerebellum might have a role in medulloblastoma formation. In studies of more than 150 paediatric medulloblastomas, ERBB2 protein expression was shown in 80% of the tumour samples.[56–58] This finding contrasts starkly with healthy cells in the cerebellum, which do not express ERBB2 at any stage during development.[59] Furthermore, overexpression of ERBB2 in medulloblastomas has been consistently associated with a poor clinical outcome.[56–58]

High expression of ERBB2 is likely to contribute to tumour development through the promotion of aberrant heterodimer and homodimer signalling (figure 5). The MAPK and AKT1 pathways are crucial downstream regulators of ERBB-mediated transforming signals. For example, after activation by ERBB2 and PI3K, AKT phosphorylates P21WAF1, a cell-cycle inhibitor.[60] This step results in relocalisation of P21WAF1 to the cytoplasm and increased cell proliferation. ERBB2 signalling has also been suggested to inhibit P53-dependent apoptosis through the interruption of the HDM2-P14ARF interaction,[61] and to activate components of the metastatic[50] and angiogenic cascades (figure 5).[62] Some of these mechanisms might

operate in medulloblastoma, since ERBB2 has been shown to form homodimers, activate ERK1/2 and AKT signals,[63] and upregulate prometastatic genes[64] when overexpressed in medulloblastoma cells.

Identification of other cell-signal abnormalities

The WNT, SHH, and ERBB pathways are unlikely to be the only cell-signalling systems that are deregulated during medulloblastoma formation. For instance, the amplification of MYC occurs quite commonly in large-cell anaplastic medulloblastomas and might be associated with a poor clinical outcome. Conversely, tumour-cell expression of the neurotropin receptor, TRKC, has been associated with a favourable prognosis in children with medulloblastoma.[7] More and more studies are showing serendipitous medulloblastoma development in mice that have disrupted DNA repair, cell-cycle control, and cytokine signal pathways.[65–68] Investigation of these models could identify previously unknown genetic events that are important for medulloblastoma formation. Attempts to identify new oncogenic pathways in medulloblastoma by the use of microarray expression profiling are also under way.[64,69,70] These studies have identified the platelet-derived growth-factor receptor (PDGFR) system and components of the RAS or MAPK pathway as potential mediators of medulloblastoma metastasis.[69,71] Microarray expression profiling of several mouse models of medulloblastoma has identified a group of 21 genes, including proteins on the WNT and SHH pathways, that are upregulated in mouse medulloblastoma. That study also showed that the same genes are upregulated in a large subset of human medulloblastomas.[72] These findings show important similarities between mouse models of medulloblastoma and the human disease and might identify a cohort of genes that are central to medulloblastoma tumorigenesis.

Exploitation of signal pathways for clinical benefit

Elucidation of how oncogenic signal pathways contribute to medulloblastoma formation could substantially improve the clinical management of medulloblastoma. First, changes in cell-signal pathways could be accurate predictors of disease risk. Second, inhibitors of signal pathways that drive medulloblastoma development might prove to be highly effective new treatments for this disease.

Disease-risk stratification

The current disease-risk stratification system for medulloblastoma is imprecise. In particular, the system does not identify the 20–30% of patients with average-risk resistant medulloblastoma or the unknown number of patients with average-risk medulloblastoma who might be overtreated with current protocols.

Accurate disease-risk assignment for children with medulloblastoma could be possible by the use of a combination of clinical, histopathological, and molecular prognostic markers (figure 6). A multicentre study[58] of molecular defects in paediatric medulloblastoma has provided evidence to support this approach. The study showed that a combination of tumour ERBB2 expression (assessed by western-blot analysis) and analysis of the clinical characteristics of the patient provides a more accurate way of assessing disease risk than clinical factors alone. All the children in this study with average-risk, ERBB2-negative disease were alive at 5 years with a median follow-up of 5·6 years, compared with only 54% for children with average-risk ERBB2-positive tumours (p=0·0001).

Although ERBB2 is emerging as a potential prognostic marker for medulloblastoma, this finding needs to be validated in a large prospective clinical trial. Furthermore, identification of other molecular defects that might also be prognostic markers will be important. In the next few years, the Children's Oncology Group, International Society of Paediatric Oncology (SIOP), and St Jude Children's Research Hospital plan to assess the role of several molecular prognostic markers—including ERBB2 expression—in predicting survival in children with medulloblastoma. The hope is that these studies will identify a definitive clinical and molecular disease-risk stratification system for medulloblastoma.

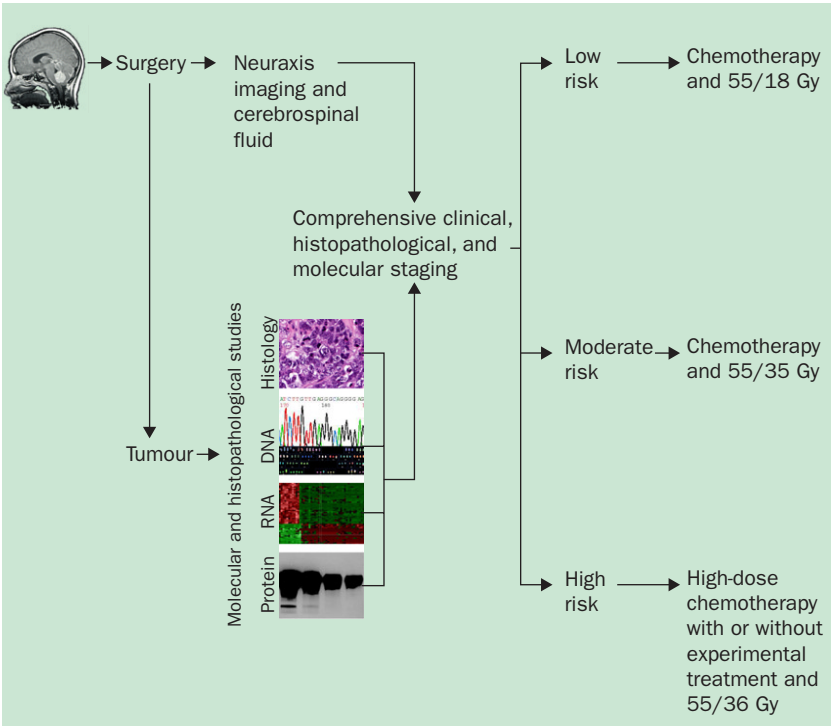

Figure 6. Increased knowledge of medulloblastoma histopathology and biology might lead to a highly accurate system for predicting disease risk. Combined molecular and histopathological analysis of tumours together with clinical staging might identify patients who can be cured with very low-intensity treatment, patients requiring moderate therapy, or patients who require very intensive or experimental treatment.

Molecular-targeted treatments

An increasing number of anticancer drugs are designed to target specific proteins in cell-signalling pathways. The therapeutic potential of several of these agents is now being investigated for medulloblastoma.

Cyclopamine is a plant-derived teratogen that inhibits the SHH pathway by binding to, and inactivating, smoothened protein.[73] Cyclopamine specifically targets the SHH pathway in medulloblastoma cells, causing inhibition of GLI-mediated gene expression, cell-cycle arrest, and antitumour activity.[46] Other inhibitors of smoothened are in preclinical development and should reach early clinical trials in medulloblastoma within the next few years.

Small-molecule inhibitors of receptor tyrosine kinases are a second class of potential molecular-targeted therapies for medulloblastoma. A diverse range of agents that inhibit ERBB2 expression and function are under development. These include dual-specific inhibitors of ERBB1 or ERBB2 activity (eg, erlotinib also known as gefitinib). Erlotinib inhibits ERBB2 signalling in human medulloblastoma cells both in vitro and in vivo.[64] Treatment with this drug selectively blocked the expression of several ERBB2-dependent prometastatic genes in these cells and reduced the invasive capacity of medulloblastoma cells. Phase I and II trials of these drugs in children with brain tumours are under way in the Children's Oncology Group and the US Pediatric Brain Tumor Consortium.

Although inhibitors of the SHH and ERBB2 pathways hold great promise as first-generation molecular-targeted therapies for medulloblastoma, the development of these agents and others like them for routine clinical use will not be easy. Rigorous assessment of the activity and efficacy of these drugs in preclinical and clinical trials presents a major challenge.[18] However, the extent to which these drugs can be combined to block oncogenic pathways might ultimately determine the success of this treatment approach. Rational combination of molecular-targeted drugs will require an understanding of the crosstalk that occurs between signal pathways during tumour development.

Bringing it all together: pathway crosstalk and combination therapies

Crosstalk between different classes of cell-surface receptors is now recognised as an important component of both normal and oncogenic signal transduction. Pathway crosstalk is highly likely to be involved in medulloblastoma development. Confirmation of this idea will require simultaneous analyses of many cell-signal pathways in individual human medulloblastoma samples. Studies of other human malignant disorders have identified crosstalk among the WNT, SHH, and ERBB pathways; such crosstalk might also occur in medulloblastoma.

ERBB1 and ERBB2 interact directly with, and phosphorylate, β catenin in breast-cancer cells.[74] This phosphorylation disrupts the formation of a complex between β catenin and E cadherin, and thereby increases the amount of free cytosolic β catenin. Interactions between β catenin and ERBB occur most commonly in invasive breast cancers, which suggests that crosstalk between these pathways is important during tumour metastasis. Crosstalk might also take place between the WNT and SHH pathways: studies of colon-cancer cells show that suppressor-of-fused can suppress WNT signalling through the export of β catenin from the nucleus.[75] Consequently, mutations in the suppressor-of-fused gene that affect around 5% of medulloblastomas might activate both the SHH and the WNT pathways. If pathway crosstalk proves to be an important mechanism in medulloblastoma development, a possible approach would be to design highly effective treatments that use combinations of signal-pathway inhibitors. Elucidation of how signal pathways mediate resistance to cytotoxic chemotherapy and radiotherapy might also allow the combination of molecular and conventional therapies.

Search strategy and selection criteria

Studies for this review were identified by searches of the PubMed and OMIM databases with the search terms "medulloblastoma", "PNET", "cell signal(l)ing", "WNT", "hedgehog", "PTCH", "catenin", "APC" and "ERBB". Only papers published in English were selected from 1980 to the present.

Outstanding questions and future directions

The WNT, SHH, and ERBB pathways are emerging as central signalling systems in the formation of medulloblastoma. The detailed mechanisms of how these pathways mediate an oncogenic effect need to be identified if we are to exploit these pathways fully in the clinic. Achievement of this aim will require answers to several outstanding questions. First, which pathways initiate medulloblastoma formation, and do they differ from the pathways involved in disease progression? Second, which signal pathways are interdependent during medulloblastoma development? Third, how do specific pathway changes affect disease histopathology and behaviour? Fourth, which signal pathways are crucial for tumour growth, and which, if any, display redundancy? Fifth, do any signal pathways mediate resistance to conventional treatments?

Although we are just beginning to understand how aberrant cell signalling contributes to medulloblastoma development, this limited knowledge is already being translated into clinical practice. The continued study of signal transduction in medulloblastoma should lead to substantial improvements in the treatment of this disease in the near future.

Conflict of interest

None declared.

Acknowledgments

RJG is supported by US National Institutes of Health grants CA96832-01, CA21765, a Translational Grant from the V-Foundation for Cancer Research, the Sontag Foundation's distinguished scientist award, and the American Lebanese Syrian Associated Charities (ALSAC). I thank A Gajjar, M Thompson, and T Curran for helpful discussion.

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