PERGAMON

European Journal of Cancer 38 (2002) 675–685

European Journal of Cancer

www.ejconline.com

Paediatric embryonic brain tumours: biological and clinical relevance of molecular genetic abnormalities

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Received 4 April 2001; accepted 25 April 2001

Abstract

Embryonal tumours constitute the largest group of malignant paediatric brain tumours. Their origin and histological classification remain somewhat controversial. However, in recent years real progress has been made in our understanding of the molecular genetic abnormalities that govern the initiation and/or progression of these tumours. A number of these abnormalities appear to involve alterations in signalling systems that control normal cerebellar development. Increasing our understanding of both the biology and clinical relevance of these molecular defects is a major challenge to the field of paediatric neuro-oncology. However, it likely represents the only means by which we will advance the management of these tumours, significantly reducing disease-related morbidity and mortality. This review focuses on the principal molecular genetic abnormalities so far identified in embryonal brain tumours and discusses their biological and clinical relevance. © 2002 Published by Elsevier Science Ltd.

Keywords: Embryonal brain tumours; Paediatric; Molecular genetics

1. Classification and histogenesis of embryonal tumours

Embryonal malignancies constitute one of the ten major subgroups of neuroepithelial tumours within the current World Health Organization (WHO) classification of tumours of the nervous system (see Fig. 1 and [Ref. [1]). Five principal histological diagnoses are recognised. These are medulloblastoma, which is the most frequent of the embryonal tumours, ependymoblastoma, supratentorial primitive neuroectodermal tumour (PNET), medulloepithelioma and atypical teratoid/rhabdoid tumour (ATRT). Medulloepithelioma and ATRT are generally viewed as a separate subgroup with distinct genotypic and histological features. Although there are significant genetic and morphological differences between these five tumour types, they share a relatively undifferentiated round-cell histological background, with varying degrees of divergent differentiation [1]. These common features have led to the use of the term primitive neuroectodermal tumour (PNET), which is frequently used to describe the embryonal tumours.

The histogenesis of embryonal tumours is still a contentious issue. Specifically, debate has surrounded the relationship between the medulloblastoma, which arises in the posterior fossa, and embryonal tumours in other regions of the central nervous system (CNS) [2–6]. One hypothesis has suggested the existence of a unique site-specific cell of origin for each histological subtype, proposing little biological relationship among these tumours other than their derivation from primitive CNS neuroepithelium [2]. In this regard, the external germinal cell layer (EGL), a primitive neuroepithelial layer of the intrauterine and early post-natal cerebellum, has been proposed as the stem cell of origin for medulloblastoma [3]. A more recently proposed variant of this hypothesis suggests that the medulloblastoma may in fact arise in more than one cell type, thereby explaining some of the heterogeneity observed among these tumours [4,5]. Alternatively, it has been suggested that all CNS embryonic tumours, including medulloblastoma, are related and develop from a common precursor cell, e.g. the subependymal matrix cell, that populates the entire embryonal CNS [6]. Current evidence favours a site-specific origin for the embryonic tumours. As discussed below, this evidence has been provided not only by analyses of gross chromosomal

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0959-8049/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0959-8049(01)00315-X

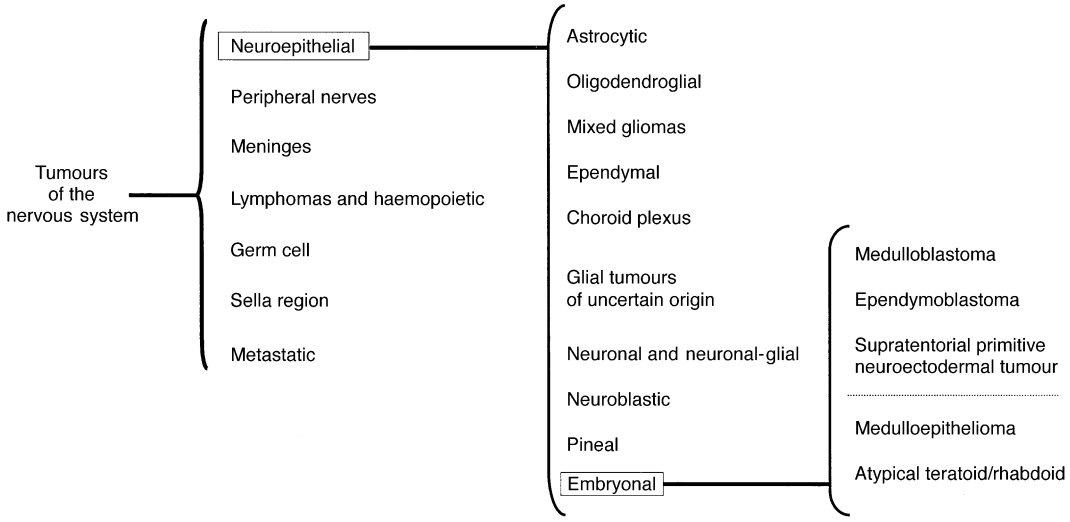

Fig. 1. Flow diagram indicating the position of embryonal tumours within the World Health Organization (WHO) classification of tumours of the nervous system [1].

abnormalities in different embryonal tumour subtypes, but also by more specific studies examining the role of individual genes in CNS development and tumorigenesis.

2. Non-random chromosomal abnormalities in embryonic brain tumours

Various techniques including classical karyotype analysis, fluorescence in situ hybridisation (FISH) and comparative genomic hybridisation (CGH) have been used to identify non-random chromosomal abnormalities (NCAs) in embryonic brain tumours. Most of these studies have focused on the more frequent medulloblastoma, but data for the less common supratentorial PNETs has provided evidence of a separate genetic origin for these tumours.

2.1. Medulloblastoma

Deletions involving the short arm of chromosome 17 represent the most frequent genetic abnormality in medulloblastoma and occur in 40–50% of primary tumours [7–15]. This increased susceptibility to NCA appears to result from the presence of at least four breakpoint cluster regions distributed within the centromeric, Charcot–Marie–Tooth and Smith–Magenis syndrome loci in 17p [11]. Such deletions of 17p may occur in the absence of other gross abnormalities of 17, or more frequently, as a component of an isochromosome of 17q (i(17q)) (see Fig. 2 and Refs. [11,13]). Although a number of studies in the literature have reported a significantly worse prognosis for patients whose tumours harbour deletions of 17p [7,8,12] this has not been a universal finding [9,10]. However, these

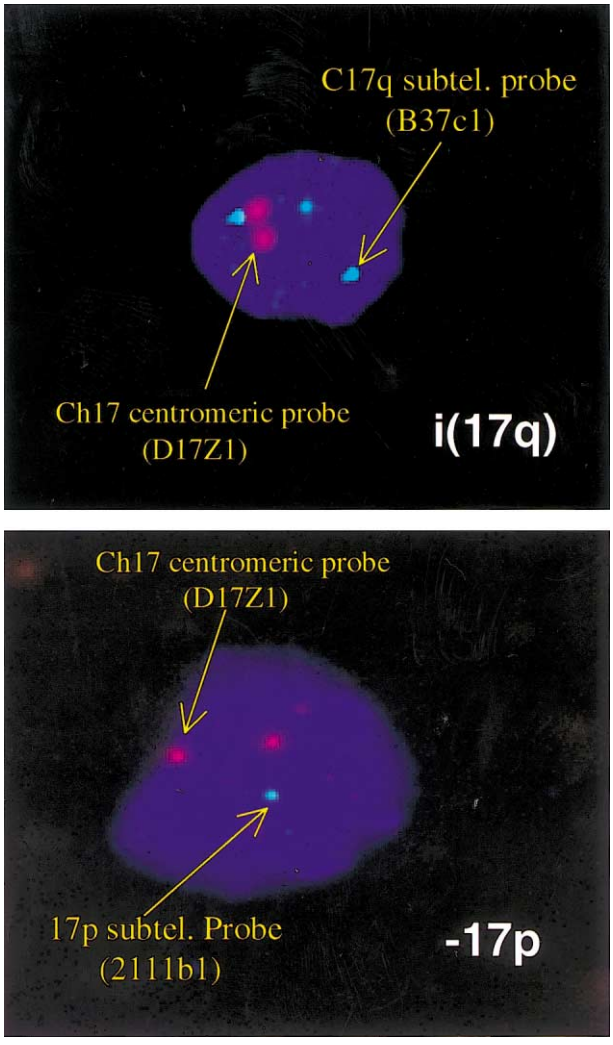

Fig. 2. Fluorescence *in situ* hybridisation (FISH) analysis of medulloblastoma primary tumour samples. (a) 'i(17q)' compatible pattern, showing three 17q subtelomeric (green) and two 17 centromeric (red) probe signals. (b) 17p deletion compatible pattern, showing a single 17p subtelomeric (green) and two 17 centromeric (red) probe signals.

studies have involved only small numbers of cases or employed a variety of techniques with different sensitivities to analyse 17p loss, thereby rendering them difficult to interpret. Larger, prospective studies of homogeneously treated patients will be required to precisely define the clinical significance of 17p loss in medulloblastoma.

The molecular consequence of 17p loss in medulloblastoma has also to be established. High resolution mapping studies have identified a common region of loss of heterozygosity (LOH) at 17p13.3 [14,15]. This region excludes *TP53* which appears to be rarely mutated in medulloblastoma [16–19], but includes the site of a number of other candidate tumour-suppressor genes including the hypermethylated in cancer-1 (*HIC-1*) gene [15]. It remains to be determined whether this gene functions as a tumour suppressor in medulloblastoma.

Regions of gene amplification have also been identified in approximately 10% of medulloblastomas [20–23]. Rather than identifying a common region of gain, these studies have detected a diverse array of amplified loci including the *ErbB1* (7p12), *MYC* (8q24) and *MYCN* (2p24.1) oncogenes and a variety of other amplified loci, including 11q22.3 and 5p15.3, which are also amplified in glioblastoma [22–25]. Although the clinical significance of the majority of these abnormalities remains unclear, evidence suggests that *MYC* amplification is associated with aggressive disease. In two of the largest series in the literature, no long-term survivors were observed among a total of 17 cases with evidence of *MYC* amplification [26,27]. Furthermore, Scheurlen and colleagues [12] reported a *MYC* amplification rate of 17%, 3 times that observed by other authors [26–28], among a population of clinically high-risk patients.

Other frequent NCAs detected in medulloblastoma include gains of 7, gains and losses of chromosome 1q and loss of chromosome 22. Chromosome 1 is frequently involved in NCAs in medulloblastoma. While no consistent breakpoint has been identified in its alteration, gross rearrangement often results in partial or complete gain of 1q [22,24,25,29]. Significant loss of genetic material from this region has also been reported [20]. Indeed, chromosome 1q31-32 is a known hot spot for deletions in breast cancer and may harbour a tumour suppressor gene. However, a recent microsatellite analysis failed to demonstrate the loss of 1q31 in primary medulloblastoma or metastases [12]. Gain of chromosome 7 also occurs with significant frequency in medulloblastoma and may be associated with the presence of i(17q) [24,29]. Finally, a variety of other NCAs including loss of 1p, 3q, 6q, 9q, 11p, 11q, 16q have also been identified. With the exception of loss of 9q (locus of *patched (PTCH)* see below), the significance of these alterations remains largely unclear.

2.2. Other embryonal tumours

While fewer cytogenetic studies of other embryonal tumour types have been published, emerging data suggests that they may have a molecular genetic basis that is significantly different from medulloblastoma. Of particular note are the rarity of chromosome 17 rearrangements [11,20,25,29–33], but the significantly higher incidence of 14q and 19q loss [33] in supratentorial PNET, and loss of 22q in ATRT. The molecular significance of this latter abnormality is discussed in detail below. A variety of other chromosomal abnormalities have also been identified in non-medulloblastoma embryonal tumours, although the numbers involved in these studies are too small to establish their significance [20,33].

3. Specific gene dysregulation and embryonal tumorigenesis in the central nervous system

3.1. Medulloblastoma

Normal neuronal development is dependent on the activation of membrane bound receptors by polypeptide growth factors and the subsequent transduction of these messages by intracellular pathways. There is increasing evidence in the literature that dysregulation of genes encoding elements within these pathways significantly contributes to the development of CNS malignancies including embryonal tumours.

3.1.1. Abnormalities in signal transduction pathways in medulloblastoma

3.1.1.1. The hedgehog signalling pathway. *Sonic* (*Shh*), *Desert* (*Dhh*) and *Indian hedgehog* (*Ihh*) are vertebrate orthologues of the Drosophila gene, *hedgehog,* which plays a key role in regulating cellular proliferation and identity (for expert reviews, see Refs. [34–36]). Each of the family members appears to act through a common signal transduction pathway (Fig. 3), while their unique expression patterns enables them to exert organ-specific developmental functions [35]. *Shh* appears to be the principal family member involved in cerebellar development [37].

The involvement of *PTCH* pathway dysregulation in medulloblastoma tumorigenesis was first suggested following the discovery that *PTCH* is mutated in Gorlin's syndrome, a tumour predisposition syndrome characterised by an increased risk of medulloblastoma and basal-cell carcinoma [40–43]. Subsequent studies detected mutations in the *PTCH* gene in approximately 8% of sporadic medulloblastoma [44–49] and a potential, but not exclusive relationship with the desmoplastic phenotype [46,49]. Furthermore, genetic evidence that *PTCH* may function as a tumour suppressor gene in

medulloblastoma has been provided by studies of transgenic mice bearing a hemizygous disruption of the *PTCH* locus. A significant proportion of these animals developed medulloblastoma [39]. Interestingly, a number of cases of human medulloblastoma have been reported in which LOH at the *PTCH* locus (9q22.3-q31) is associated with preservation of the remaining wild-type allele [47]. Wetmore and colleagues [50] recently provided a possible explanation for this observation, demonstrating haploinsufficiency at the *PTCH* locus to be sufficient to predispose to tumour development in $PTCH^{+/-}$ mice. *PTCH* appears to be the principal target for transforming deletions and mutations in this pathway since analyses of other *hedgehog* pathway members have identified only a single case with a mutation of *Shh* and no abnormality of *Smo* [51].

The mechanism by which PTCH signal dysregulation contributes to tumorigenesis remains unclear. However, this appears to involve upregulation of cyclin gene expression [52] and require expression of insulin like growth factor-2 [53]. The recent finding that the Shh signal antagonist cyclopamine can reverse the effect of oncogenic *Smo* and *PTCH* mutations in murine cells *in vitro,* suggests that this pathway may prove a valuable novel therapeutic target in those patients whose tumours are affected by such alterations [54].

3.1.1.2. The Neurotrophin signalling pathway. The neurotrophin family promote the growth, differentiation and survival of neurons (reviewed in Refs. [55–57]). They include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5). Although all four are known to bind the low affinity p75 receptor ($p75^{NTR}$), the characteristics of this signalling system are less clear than those of the high affinity Trk receptors.

Three members of the Trk receptor family have been identified and designated TrkA, TrkB and TrkC [56]. Each is a single chain, transmembrane receptor tyrosine kinase, that preferentially binds to at least one of the four neurotrophins. TrkA binds NGF, TrkB binds NT-4/5 and BDNF and TrkC binds NT-3 [56]. The Trk proteins function as classical growth factor receptors, undergoing ligand-induced dimerisation, kinase activation, autophosphorylation and activation of second messenger signalling pathways including phospholipase C-γ and the shc-Grb-SOS-Ras pathway [59,60].

There is considerable evidence in the literature that the neurotrophin signalling pathway plays a major role

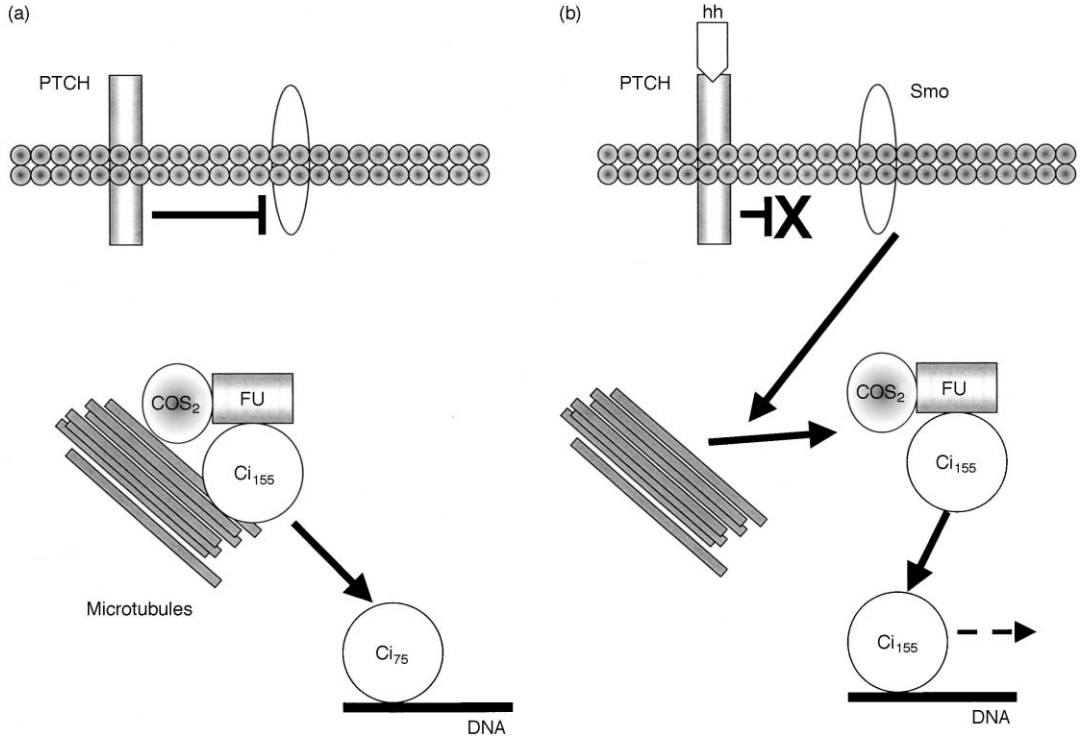

Fig. 3. (a) In the unbound form, PTCH suppresses the activity of a second membrane associated protein, smoothened (Smo). In the absence of Smo activity, the intracellular components of the *hedgehog* pathway including fused (FU), costal-2 (COS2) and Ci/Gli (Ci155), are held in a microtubule-associated complex. In this state, the full length active form of Ci/Gli is cleaved, generating a truncated transcription repressor (Ci75). (b) Binding of hedgehog (hh) to PTCH releases suppression of Smo, permitting dissociation of the microtubule-associated complex and release of full length transcription activating Ci/Gli (Ci155) which in turn mediates the transcription of a number of genes, including *PTCH* itself and members of *decapentaplegic* and *Wnt* families [34–36]. Loss of PTCH expression may similarly relieve Smo suppression. Signalling via this pathway is critical for normal cerebellar development, specifically cells of the external germinal cell layer [37–39].

in cerebellar development. Both the neurotrophins themselves and the Trk receptors demonstrate closely regulated, spatiotemporal expression patterns in the developing cerebellum. BDNF, NT-4/5 and TrkB signalling appear to control the final stages of differentiation in postmigratory granule cells [61]. In contrast, NT-3 is expressed in premigratory granule cells of the EGL, and may support the proliferation of granule cell precursors and the survival of more mature granule cells, both of which express TrkC [62–64]. The development of neurotrophin-deficient mice has provided further evidence that this signalling system is critical for cerebellar development. Both the NT-3 conditional mutant and $BDNF^{-/-}$ animals demonstrate major abnormalities in cerebellar morphology, particularly foliation [65,66].

Analyses of neurotrophin signalling in medulloblastoma cells *in vitro* [67–69] and *in vivo* [68], and studies of Trk receptor expression by primary tumour samples [68–71], suggest that this signalling system is correlated with a less aggressive phenotype. Segal and colleagues [70] first reported a potential association between tumour cell expression of the full length TrkC transcript and favourable disease outcome. When this study was subsequently expanded to include 42 cases of medulloblastoma [68], the prognostic significance of TrkC expression was preserved, with the median survival for the high expressers being 92 months compared with only 39 months for the low expressers (progression-free survival $P=0.02$, overall survival $P<0.0001$). Late relapses were, however, observed in the high expressing group. More recently, a much larger study of TrkC expression in 81 medulloblastomas and 6 supratentorial PNETs has been published [71]. In this study, TrkC expression was analysed using *in situ* hybridisation and the TrkC signal normalised to the sense probe signal. This study also identified significantly better progression-free and overall survival in patients whose tumours expressed high levels of TrkC, independent of the other clinicopathological variables in the multivariant analysis. In contrast to TrkC, Trk A does not appear to be expressed by medulloblastoma primary tumours or cell lines [68,70].

A limited number of *in vitro* and *in vivo* studies have been performed in attempt to elucidate the mechanism by which neurotrophin signalling may confer an improved survival in medulloblastoma. Such studies have employed medulloblastoma cell lines engineered to express Trk receptors, since Northern blot analyses have revealed only very low or absent expression levels in cell lines [67–69]. In general, these studies have demonstrated the capacity of TrkC- and TrkA-mediated neurotrophin signalling to significantly increase medulloblastoma apoptotic cell death. However, given the lack of TrkA expression by medulloblastoma primary tumours, the clinical and biological relevance of neurotrophin-induced apoptosis through this receptor is unclear.

3.1.1.3. ErbB receptor signalling pathway. Analogous to the hedgehog and neurotrophin signalling systems, evidence suggests that the class I receptor tyrosine kinases (RTK I), also termed ErbB or HER receptors, constitute a signal transduction pathway that is important in both cerebellar development and medulloblastoma tumorigenesis.

The four members of the RTK I family, ErbB1 (also known as epidermal growth factor (EGF) receptor), ErbB2 (HER2/neu), ErbB3 and ErbB4, interact to form homo- and hetero-dimers following ligand binding (reviewed in Refs. [72,73]). While this process affords cells with a diverse signalling capability, it is governed by a strict hierarchy, mediated by differential receptor ligand binding affinities [73]. Within this network, the ErbB2 receptor appears to play a central role. ErbB2 lacks a direct ligand, but is the preferred heterodimer partner of ErbB1, ErbB3 and ErbB4, following their binding to cognate ligand [73]. Furthermore, ErbB2-containing heterodimers have significantly increased signalling potency, which may result from a reduced rate of receptor ligand dissociation, and greater efficiency in mitogen activated protein kinase (MAPK) second messenger activation [74,75]. Consequently, signalling from ErbB2 results in increased cell proliferation, colony formation in soft agar [76] and cell migration and invasion [77,78]. These properties of the ErbB2 receptor may explain its potent oncogenicity, and prominence in a number of human cancers [73].

ErbB-NRG signalling is a key component in the processes controlling normal CNS development and maintenance [72,79], with the cerebellum emerging as one site in which this system appears to have particular relevance. Transgenic mice bearing homozygous deletions of either the *ErbB2* [80], *ErbB3* [81], *ErbB4* [82] or *Neuregulin* (*NRG*)*-1* (encoding an ErbB3- and ErbB4-specific ligand) [83] develop with a variety of central and peripheral neurological abnormalities, including defects in the formation of cranial ganglia and the cerebellum.

ErbB4 appears to be particularly important in early development of the nervous system. With regard to the cerebellum, this receptor is expressed at high levels in rodent [84], avian [85] and human [86] granule cells of the EGL during early development, declining rapidly after birth [84,86]. Conflicting results are available for normal ErbB2 expression. Although there is some evidence that this receptor is expressed in the rodent cerebellum throughout development [87], it does not appear to be expressed by human cerebellum [86,88]. The ErbB receptor ligands and NRGs in particular, are expressed throughout development of the cerebellum [83,86,89]. For example, NRG-1b expression has been detected in the most superficial layer of the human EGL, coincident

with adjacent underlying cell ErbB4 expression, indicating the potential role for an ErbB4-NRG-1b juxta/autocrine loop in the proliferation of primitive neuroepithelial cells of the EGL [86].

In addition to expression studies, functional analyses of ErbB-NRG interactions within cerebellar cells also suggest a role for this signalling network in granule cell biology. ErbB1- and ErbB4-specific ligands induce a marked proliferative response in EGL cells *in vitro* [90], while ErbB4-NRG signalling appears to be important in the migration and differentiation of EGL cells [91].

With regard to medulloblastoma, Gilbertson and colleagues first reported an association between elevated ErbB2 receptor expression and reduced patient survival in a study of 55 patients with this disease [92]. When the study population was extended to 70 cases, the prognostic significance of high ErbB2 expression was maintained, with 25 year survival rates for cases with $<50\%$ and $\geqslant 50\%$ ErbB2 tumour cell expression being 46% and 17%, respectively (Log Rank, $P=0.004$). Elevated expression rates for the three other ErbB family members, especially ErbB4, were also noted in this study [93]. Indeed, heterodimerisation between the ErbB2 and ErbB4 receptors was readily detected in fresh tumour material and, in contrast to any individual receptor including ErbB2, the presence of co-expressed ErbB2 and ErbB4 was significantly associated with reduced overall survival, independent of other clinicopathological variables. A second group has also reported a significant relationship between ErbB2 expression and poor prognosis medulloblastoma, although they did not analyse the expression of the other ErbB family members [94]. These data suggest that co-expression of ErbB2 and ErbB4 receptors by medulloblastoma cells may allow the formation of ErbB2-ErbB4 heterodimers that are important in supporting an aggressive phenotype. More recently Gilbertson and colleagues demonstrated that expression of ErbB2 and ErbB4, but not ErbB1 or ErbB3, mRNAs is dysregulated in medulloblastoma primary tumours relative to normal cerebellum [86] and that ErbB4 expression by medulloblastoma includes a variety of novel, tumour-specific splice variants [95].

Studies are underway to further assess the biological and prognostic significance of ErbB2 and ErbB4 signalling in medulloblastoma. If the ErbB receptors were proved to be significant in the pathology of medulloblastoma, they may provide valuable targets for novel therapies. The recent success of the anti-ErbB2-monoclonal antibody Herceptin™ (Genentech inc.) in the treatment of patients with advanced ErbB2-overexpressing breast cancer provides a precedent for such a strategy [96].

3.1.1.4. Adenomatous polyposis coli *(*APC*) gene and the Wnt signalling pathway*. The Wnt proteins are a large family of signalling molecules that interact with Frizzled receptors to activate downstream pathways important in regulating cell proliferation and fate [97,98]. Many of the Wnt proteins activate gene transcription through a pathway controlled by β-catenin (Fig. 4). Expression studies have demonstrated high levels of *APC* gene transcripts in developing brain tissue [99]. Of particular note, is the increased expression of APC in the deeper, more mature pre-migratory region of the EGL relative to the proliferative superficial zone. Wnt-3a and Wnt-7a expression also appear to be important in granule cell development and cell–cell interactions.

Dysregulation of the Wnt signalling pathway has been implicated in the development of a number of human cancers including carcinomas, melanoma and medulloblastoma [97]. Oncogenic activation appears to result from mutations, in either the *APC* or *β-catenin* genes, that disrupt normal β-catenin regulation, increasing its stability and thereby potentiating the Wnt signalling pathway [97]. Mutations in *APC* usually generate a truncated protein that lack the β-catenin regulatory site, while alterations in the *β-catenin* coding region most often affect one of the putative phosphorylation sites thought to be responsible for ubiquitination and degradation targeting [97].

The Wnt signalling pathway was first implicated in medulloblastoma tumorigenesis following the identification of *APC* as the 'target' gene mutated in a subgroup of patients with Turcot syndrome. This heterogeneous familial cancer syndrome is characterised by the co-occurrence of colonic carcinoma and a malignant brain tumour [100]; individuals affected by the *APC* mutation frequently develop medulloblastoma [101]. While initial attempts to identify *APC* mutations [102] or LOH at the *APC* locus on chromosome 5q [103,104] in sporadic tumours were unsuccessful, more recent analyses have identified Wnt pathway alterations. Studies of *β-catenin* mutation in medulloblastoma have focused on exon 3, the coding region containing the four potential GSK-3β phosphorylation sites. Seven of 113 cases (6%) of sporadic medulloblastomas have been identified with mutations [105,106]. Codons 33 and 37, which encode serine residues, appear to be targeted, suggesting potential hotspots for medulloblastoma mutation. *APC* mutations have been detected in 2/46 cases [106]. Interestingly, all were missense mutations in contrast to the truncating alterations normally seen in medulloblastoma patients with Turcot syndrome. *APC* and *β-catenin* mutations appear to be mutually exclusive in sporadic medulloblastoma, generating an overall incidence of Wnt pathway alterations in this disease of around 13% [106]. It is still not known whether Wnt pathway alterations confer a particular clinical behaviour in medulloblastoma or whether this pathway may afford alternative therapeutic targets for novel therapies.

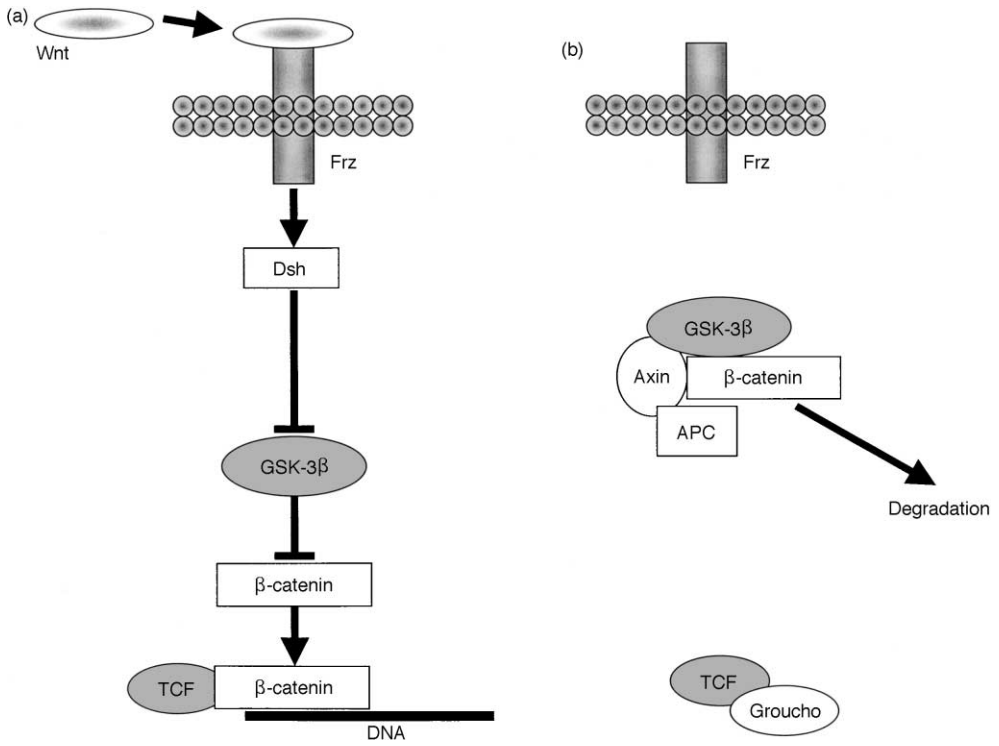

Fig. 4. (a) Wnt binding to Frizzled (Frz) receptors activates Dishevelled (Dsh) which in turn inhibits glycogen synthase kinase-3β (GSK-3β) and results in the stabilisation of β-catenin. β-catenin forms nuclear complexes with TCF transcription factors, thus regulating the expression of numerous genes [98]. (b) When Wnt is not active, β-catenin is held in a complex with GSK-3β, Axin and the product of the adenomatous polyposis coli tumour suppressor gene (APC). This enables the phosphorylation of β-catenin by GSK-3β, targeting it for ubiquitination and degradation. In the absence of active β-catenin, the TCF transcription factors associate with Groucho, a transcription inhibitor. Hence through this signalling system, the presence or absence of Wnt can control the positive or negative influence, respectively, of TCF on gene expression [97,98].

3.2. Other embryonic tumours

3.2.1. Atypical teratoid/rhabdoid (ATRT) tumours and the INI1/hSNF5 gene

Rhabdoid tumours are rare, aggressive malignancies that usually develop in the kidney in children under five years of age [107]. The CNS is the second most frequent primary site. Rhabdoid tumours developing within the brain have been termed 'atypical teratoid/rhabdoid tumours' (ATRT) and are composed of rhabdoid cells, with or without fields resembling a classical PNET, epithelial tissue and neoplastic mesenchyme [107].

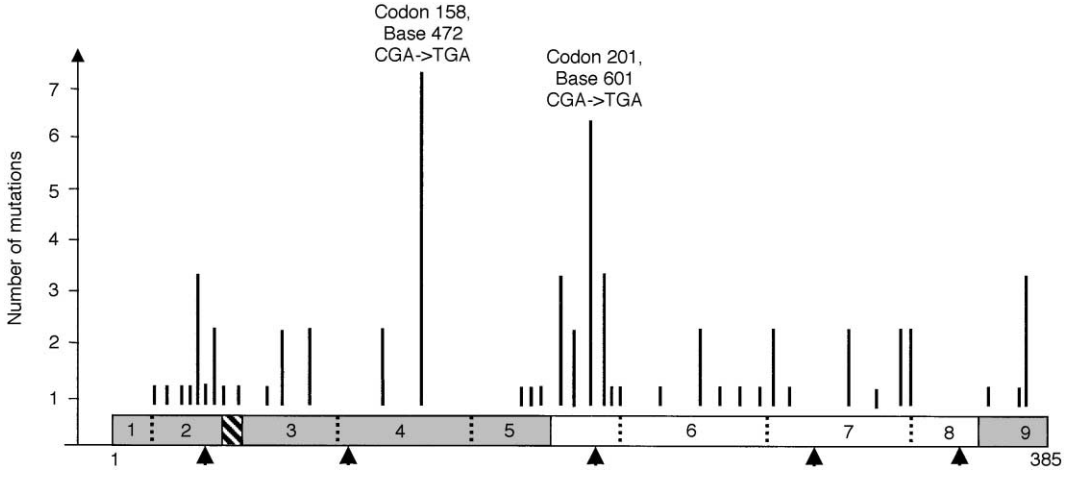

Fig. 5. Atypical teratoid/rhabdoid tumours. Distribution of point mutations of the *hSNF5/INI1* gene along the coding sequence. The protein is shown with the respective coding exon numbers in italics. The clear box represents the SNF5 domain and the hatched area indicates a peptide sequence that can be present or absent in the protein, depending on the use of a cryptic splice site in exon 2. Bars above the protein represent the site and frequency of truncating mutations. Positions of missense and editing mutations are depicted as arrows below.

Early cytogenetic studies demonstrated monosomy 22 or deletion of 22q11.2, but few other abnormalities, in most rhabdoid tumours [108 and references therein]. Subsequent, positional cloning within this region led to the identification of the *hSNF5/INI1* gene as the target of characteristic biallelic inactivating alterations [109]. A number of families have since been described in which *de novo* or inherited germline mutation of the *hSNF5/INI1* gene have resulted in the development of renal and/or CNS rhabdoid tumours in infants, supporting a common genetic origin for these tumours, irrespective of the location of the tumour [110–112].

A number of genetic alterations appear to account for *hSNF5/INI1* inactivation in rhabdoid tumours (Fig. 5). Whether any particular alteration predominates either in rhabdoid tumours as a whole or in ATRTs of the CNS still has to be determined. Biegel and colleagues reported deletion of exon 1 to be a frequent feature of rhabdoid tumours [112], but Sevenet and colleagues [108] identified no exon 1 deletions in a study which included 72 renal and extra-renal rhabdoid tumours. Their data suggests that point mutations rather than deletion are the commonest genetic change in CNS ATRT (Fig. 5).

The molecular consequence of *hSNF5/INI1* loss of function is unclear. *hSNF5/INI1* encodes a subunit of the larger SWI/SNF complex which modifies nucleosomal organisation in an adenosine triphosphate (ATP)-dependent manner [113]. Two additional subunits termed BRG-1 and brm interact with p105Rb, increasing the efficiency of p105Rb-induced repression of E2F activity. Further study is required to elucidate the precise mechanism by which disrupted *hSNF5/INI1* contributes to the deregulation of SWI/SNF function and, thereby, malignant transformation.

4. Conclusion

In recent years, a great deal of progress has been made in our understanding of the molecular processes governing the development and/or progression of embryonal CNS tumours. A number of these defects include the dysregulation of signalling pathways important in normal CNS development. Understanding the significance of these defects will hopefully lead to the development of successful novel treatment approaches for children with primary brain tumours. These goals will only be met by close collaboration between the clinic and the laboratory. Consistent cure of these terrible childhood diseases with minimal long-term side-effects is the final objective.

Acknowledgements

I am grateful to Drs Bouffet, Wetmore and Ellison for their helpful comments on the manuscript, to Dr David Ellison for providing the FISH images employed in Fig. 2 and to Dr Olivier DeLattre for providing Fig. 5.

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