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Genetic alterations in glioma and medulloblastoma

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Abstract

Multiple genetic changes take place during tumor development and progression. These genetic changes result in inactivation of tumor suppressor genes and activation of proto-oncogenes. Frequent genetic changes observed in gliomas are losses of chromosomal regions on 9p, 10q, 13q, 17p and on 22. Loss of 10q is seen in more than 80% of the glioblastoma multiforme (GBM) tumors suggesting the presence of a gene critical for GBM formation on this chromosome. Amplification of epidermal growth factor receptor gene and expression of platelet derived growth factor and fibroblast growth factor genes are also common among gliomas. The most common genetic abnormality found in medulloblastomas is loss of 17p. The C-myc gene is amplified in a few primary tumors, but the incidence of amplification is higher in medulloblastoma derived cell lines. These findings suggest that the same two genetic processes, gene amplification and regional chromosomal loss, which characterize other primitive childhood neuroectodermal tumors such as retinoblastoma and neuroblastoma are also important in medulloblastomas.

Introduction

Current evidence suggests that initiation and progression of various neoplasms may be a multistep process involving the accumulation of multiple genetic alterations. These abnormalities include mutations which result in activation of oncogenes as well as inactivation of tumor suppressor genes and gene amplification [1–3]. Evidence for this hypothesis has come from studies carried out on several cancers, particularly colorectal cancer [3–12]. In colon cancer, tumors at different stages of progression are well defined and easily accessible for further study. The genetic alterations detected in different stages of colon cancer include mutation and deletion of APC and MCC gene on 5q, hypomethylation of DNA, mutation of k-ras oncogene, mutation and deletion of DCC gene on 18q and p53 gene on 17p [3–8]. Evidence is accumulating that a similar mechanism of tumorigenesis i.e. acquisition of multiple genetic alterations, may be responsible for the development of other tumors including brain tumors. There are indications that mutations of a few genes (e.g. p53) may be common in a variety of tumors but alterations in some other genes specific to each type of tumor may be necessary for the development of malignant state [9–12]. In this review we describe the molecular alterations found in gliomas (astrocytomas) and medulloblastomas which are the most common types of malignant human brain tumors.

Malignant human gliomas

Gliomas are among the most common primary brain tumors of adults. Low grade gliomas include astrocytomas, oligodendrogliomas and ependymomas. The more aggressive varieties are the intermediate grade anaplastic astrocytoma and the high grade glioblastoma multiforme (GBM). Cytogenetic studies of GBM have demonstrated gains of

chromosome 7 (approximately 80% of cases), losses of chromosome 10 (60% of cases), structural abnormalities of 9p (35% of cases) and the presence of double minute chromosomes (33% of cases) [13–16]. Subsequent allelotyping studies have confirmed some of these cytogenetic findings and have revealed additional regions of chromosomal losses. In one study 37 tumors (15 GBM and 22 grade II and III) were probed with at least one RFLP probe for each chromosome. In addition to loss of alleles on chromosome 10, nonrandom loss of alleles on chromosome 13 in 14% of the tumors, on chromosome 17 in 22%, and on chromosome 22 in 19% of the tumors were detected [17]. In another study 26 GBM and 15 AA tumors were analyzed with a probe each from non-acrocentric chromosomal arms. More than 38% of informative tumors lost alleles on 10p, 10q and 17p; 16–21% lost alleles on 5q, 7p, 11p, 14q and 15q; less than 14% lost alleles on other chromosomes [18].

Loss of chromosome 10 loci

Frequent loss of chromosome 10 observed in both cytogenetic and allelotyping study of gliomas has been interpreted as evidence for the presence of a tumor suppressor gene on this chromosome. As a preliminary step in identifying the tumor suppressor gene, several laboratories have attempted to define a region of chromosome 10 consistently deleted in the tumors [17–22]. In a study reported by James *et al.*, 53 tumors (31 GBM, 10 grade III and 12 grade II) were examined for loss of heterozygosity [17]. Three probes mapped to 10q were used. Loss of heterozygosity (LOH) for all informative loci was seen in glioblastomas but not in lower grade tumors. It was concluded that the loss of chromosome 10 sequences are associated with the more aggressive malignant type of tumor. Fujimoto *et al.* [19] in a study of 13 glioblastoma patients found LOH for one or more chromosome 10 loci in 10 patients and reported a common region of deletion from middle of 10p (pTBQ7) to 10q23.3 (pTHH54). They also studied four anaplastic astrocytomas and found no loss of heterozygosity for chromosome 10 loci. Fults *et al.* [18] carried out allelotype and detailed LOH studies on 32 GBM and 13 anaplastic astrocytomas. Thirteen probes mapped to chromosome 10 were used in their study. Fourteen GBM tumors and 2 anaplastic astrocytomas had lost a copy of chromosome 10 which led them to suggest that loss of an entire copy of chromosome 10 is a common event in GBM. Three other GBM tumors maintained heterozygosity for a single locus, but a common region of deletion was not apparent in these tumors. Jenkins *et al.* using 11 probes studied 46 tumors for loss of chromosome 10 sequences [21]. The tumors studied included 35 astrocytomas (32 grade IV, 2 grade III and 1 grade II), 5 mixed oligoastrocytomas (4 grade III and 1 grade II) and 6 oligodendrogliomas (1 grade IV, 4 grade II and 1 grade I). Twenty two astrocytomas lost a copy of chromosome 10 as indicated by LOH at all loci tested. Four astrocytomas (grade IV), 1 grade II oligodendroglioma and 1 grade III mixed oligo-astrocytoma showed partial deletion of chromosome 10. By analyzing the allelic loss pattern of tumors showing partial deletion they suggested two regions of chromosome 10 likely to contain tumor suppressor gene; one on 10q arm distal to D10S22 (mapped to 10q21.1) the other on 10p extending up to TST1 on 10q (mapped to 10q11.2).

In our analysis [22] of 41 tumors (33 glioblastomas, gliosarcoma 4 anaplastic astrocytomas, 1 astrocytoma, 1 anaplastic oligodendroglioma and 1 oligodendroglioma) using 23 probes, loss of a copy of chromosome 10 was found in 23 tumors (22 GBM and 1 AA). Eleven tumors (8 GBM, 1 anaplastic astrocytoma, 1 astrocytoma and 1 oligodendroglioma) showed partial deletion of chromosome 10. The smallest common region of deletion in these 11 tumors was between markers pHUK-8 and pMCT122.2. The marker pHUK-8 has been mapped to 10q24-qter and pMCT122.2 to 10q26. The common deletion interval in distal 10q spanning from 10q24 to 10q26 is likely to contain the tumor suppressor gene important in glioma tumor formation. The presence tumor of suppressor gene on chromosome 10 is also supported by chromosome transfer study. Partial reversion of tumor phenotype in a glioblastoma cell line upon transfer of chromosome 10 has been reported [23, 24].

The ret protooncogene involved in the papillary thyroid carcinoma is mapped to 10q11.2. The multiple endocrine neoplasia type 2A locus is mapped to the pericentromeric region of chromosome 10. A putative oncogene TCL3 is assigned to 10q24 [25]. The common deletion region detected in gliomas (10q24–q26) is clearly distinct from the ret and MEN 2A loci. However, the same region of chromosome 10 (10q24–q26) is also one of the common deletion region in prostate cancer [11]. A gene involved in melanocytic neoplasia has also been mapped to 10q24–q26 [26]. This suggests that the tumor suppressor gene on 10q may have a role in development of other types of human tumors.

Deletion of retinoblastoma gene

Retinoblastoma gene (RB) is the best studied tumor suppressor gene and is the prototype of Knudson's two-hit theory. Retinoblastoma cells do not express the RB encoded protein because of loss of both functional alleles. Insertion of the normal RB gene has been shown to suppress the transformed phenotype in retinoblastoma and osteosarcoma cell lines [27]. RB mutations are not restricted to retinoblastomas but are also found in adenocarcinoma of the breast, osteosarcomas and small cell lung cancer [27, 28]. The RB locus is mapped to chromosome 13q14. Structural abnormality of chromosome 13 seen cytogenetically in gliomas indicated that RB gene may be altered in gliomas as well. By RFLP analysis using chromosome 13 probes, non random loss of chromosome 13 loci was found in 5 of 37 gliomas in one report [17], and in 2 glioblastomas in another report [29]. In a recent study involving 36 patients analyzed with a VNTR marker located within the RB locus, 3 tumors (out of 16 informative tumors) lost an allele for the marker. All the three tumors which lost an allele were GBMs. Another GBM patient lost an allele as well as a part of the coding region of the remaining allele. The cultured tumor cells of this patient showed a truncated transcript [30]. This study adds gliomas to a list of tumors in which mutations and deletions affecting RB gene are found.

Deletions and mutations in 17p

The loss of chromosome 10 loci mostly occurred in high grade tumors and rarely in low grade tumors. By contrast, the loss of loci on 17p was found in both low grade and high grade tumors with equal frequency [29, 31, 32]. James *et al.*, found LOH for chromosome 17 loci in 8 of 24 astrocytomas [27]. El-Azouzi *et al.* observed loss of 17p loci in 5 of 10 astrocytomas [31]. Fults *et al.* reported loss of 17p loci in six of 15 anaplastic astrocytomas and in 8 of 20 glioblastomas [32]. These findings suggested the presence of a suppressor gene on 17p associated with early steps of tumorigenesis common to both astrocytomas and glioblastomas. Allelic deletion of 17p loci occurs in a number of tumors including colon, lung and breast cancer [3, 4, 9, 33]. In colorectal cancer, the common region of loss on 17p contains the suppressor gene p53 [34]. In a number of tumors with LOH for 17p, point mutations in the coding region of the remaining allele of p53 have been discovered confirming the functional inactivation of both copies of p53 in these tumors [35]. Above study included five GBM tumors and the point mutations were identified in 4 tumors. The mutations were clustered in the same hot spots as were seen in colon, breast and lung carcinomas. The tumor without a point mutation, expressed p53 mRNA but p53 protein could not be detected in western blots.

Another study indicated that patients whose glioblastomas contained p53 mutations were significantly younger (mean age 31.4 yrs) than those whose tumors contained wild type sequence (58.7 yrs). In the same study loss of alleles on chromosome 10 was seen in only 1 of 4 tumors with p53 mutation compared to 5 of 6 tumors with the wild type sequence. It was suggested that p53 mutation and loss of a tumor suppressor gene on chromosome 10 may be alternative mechanisms of glioblastoma formation and that glioblastomas with p53 mutations may represent a subgroup of tumors characterized by early age onset and a better survival [36].

Available evidence suggests that p53 is the target of allelic deletion on 17p in gliomas. However, involvement of other genes on 17p can not be ruled

out. Recently, by inducing the expression of wild type p53, an inhibition of cell proliferation was achieved in tumor cells derived from human GBM [37]. This observation further supports the suppressor function of wild type p53 in gliomas.

Deletions in 9p

Structural abnormalities and loss of 9p is commonly seen in gliomas. Consistent with the cytogenetic findings, when genomic DNA from 19 cell lines established from malignant glioma were probed with the interferon α and β genes, Miyakoshi *et al.* [38] found complete loss of both IFNA and IFNB gene in 5 cell lines and loss of IFNA sequences in 3 other cell lines. Both IFNA and IFNB genes have been mapped to 9p22. Similar homozygous deletion of interferon α and β genes had been earlier reported in neoplastic hematopoietic and leukemia cells [39]. James *et al.* have extended these studies by analyzing LOH in 30 primary tumor tissue using interferon gene probes and 5 other probes mapped to 9q [40]. They found LOH for IFNB1 in six of 15 informative patients. Among the six only one tumor lost 9q locus. By comparing the signal intensity they found loss of IFNB1 sequences in four more tumors. Deletion of IFNA gene sequences were observed in all the tumors lacking IFNB, and in two additional tumors positive for IFNB. All of the tumors which lost interferon genes were intermediate or high grade tumors (anaplastic astrocytoma and glioblastoma). There are other reports of rearrangements, homozygous and hemizygous deletion of interferon gene sequences in glioma derived cell lines and in primary tumor tissue [41, 42]. There may be yet another tumor suppressor gene on chromosome 9 that is involved in progression of tumors. It is speculated that the interferon genes themselves may have a suppressor function or are closely linked to a tumor suppressor gene.

Loss of chromosome 22

Cytogenetically, loss of chromosome 22 has been demonstrated in a subgroup of gliomas [13–15]. This has been confirmed by RFLP studies [17, 18, 29]. In two reports the loss was restricted to glioblastomas [18, 29]. Loss of alleles on 22 is common in meningiomas and neurofibromatosis type 2 [43, 44]. Recently the meningioma locus has been localized to 22q12.3-qter [45] and neurofibromatosis to near centromere on 22q [46], suggesting the involvement of separate genes in these tumors. Detailed RFLP studies are necessary to determine the locus lost in gliomas.

Gene amplification

Gene amplification is often recognized cytogenetically as DMs. In majority of gliomas containing DMs the EGFR gene is amplified [47–51]. In a typical study, densitometric analysis of Southern blots indicated approximately 8–25 fold amplification of the genomic sequences in 14 of 31 tumors examined [48]. Majority of tumors with EGFR gene amplification were high grade tumors (GBM). Increase in mRNA level (10–20 fold) was seen only in tumors with amplified EGFR gene. The normal EGFR gene product is a 170 kDa membrane glycoprotein resembling erbB oncoprotein. Its cytoplasmic domain contains tyrosine kinase activity, extracellular domain binds epidermal growth factor and transforming factor α. In another study amplification of EGFR gene was found in only one of 30 lower grade tumors analyzed and none showed rearrangement of the gene [52]. The levels of pre-pro TGF-α mRNA and pre-pro EGF mRNA was also unchanged. In the same study 16 of 32 GBM tumors showed amplification of EGFR gene among which 10 had rearrangement of the gene. The level of mRNA for pre-pro TGF-α was normal, however two tumors showed increased levels of pre-pro EGF mRNA. These findings suggest the possibility of an autocrine loop in growth stimulation by simultaneous expression of the receptor and its ligand. The fact that all but one of the tumors with amplified EGFR gene were GBM indicated that EGFR amplification is a late event occurring in the progression of tumors. Particularly interesting was one tumor which showed two histopathologically distinct regions (astrocytoma grade

II and GBM grade IV), both of which showed loss of chromosome 17 loci, but only the grade IV region of the tumor showed EGFR gene amplification.

Frequently, the amplified EGFR gene is rearranged as indicated by the loss or altered size of bands in Southern blot. In most cases the rearrangements produce smaller transcripts, resulting in the expression of truncated EGFR proteins (ranging in size from 100 to 145 kDa) with deletions in the extracellular ligand binding domain. Tumors expressing truncated EGFR bind EGF with a lesser capacity or did not bind EGF as in one case [49]. Sequence analysis has shown that the abnormal transcripts fall into two groups with each group having identical deletions. In one group, 802 nucleotides near the end of the gene were deleted. In the second group 250 nucleotides located more distally, but still in the region coding for the extracellular domain of the protein were deleted. In each case the junction nucleotides reconstituted a glycine codon and produced a novel amino acid sequence at the junction site [53, 54]. The receptor protein's high level of expression and frequent aberrations in gliomas, make it an attracive target for immunodiagnostic and immunotherapeutic procedures. It has been shown that antiserum raised against the 14 amino acid peptide at the junction site of one aberrant EGFR protein, detected the mutant protein but failed to react with tumors or normal tissue expressing the wild type EGFR protein [53]. This demonstrates that antibodies against the novel epitopes in the mutant EGFR protein are highly selective for the tumor associated mutant protein and may be used in imaging, diagnosis and therapy of a subset of gliomas.

In contrast to biopsies and xenografts which commonly contain EGFR gene amplification, there are only rare examples of permanent cultured cell lines derived from gliomas which contain amplification of EGFR gene [55, 56]. Careful analysis of xenografts and permanent cultured cell lines established from two different glioblastomas, revealed that the amplified and rearranged gene was lost as the tumors established in culture [57]. However, the gene amplification and rearrangement seen in tumor biopsies were strictly maintained in the corresponding xenografts. These studies suggest that amplified, rearranged EGFR genes provide a growth advantage for glioma cells *in vivo* but not *in vitro*. In contrast to biopsies and xenografts, the majority of glioma cell lines produce structurally normal EGFR proteins. The receptor number varies from barely detectable levels to 10^6 receptors/cell which is in the same range as A431 cells (cell line derived from squamous cell carcinoma), although the EGFR gene copy number and quantity of mRNA are correlated with the copy number of chromosome 7 which the line contains.

Expression of other growth factors

In addition to EGF, several other growth factors and/or their receptors are expressed in gliomas. The possibility of an autocrine loop involving platelet derived growth factor (PDGF) and its receptor was first observed in malignant glioma derived cell lines [58]. Subsequent study using primary tumor tissue has yielded similar results. In northern analysis of 27 GBM and 7 AA, Maxwell *et al.* [59] found expression of c-sis/PDGF2 protooncogene in all tumors. C-sis gene was not expressed in normal brain tissue. PDGF-1 gene was expressed in 27 of 29 tumors. Messenger RNA for the PDGF-R was present in all tumors as well as in normal brain. Some tumors displayed aberrant PDGF-R transcripts. In situ hybridization of primary tissue demonstrated the expression of c-sis in tumor cells and in capillary endothelial cells. By contrast, nonmalignant brain tissue displayed expression of PDGF-R but not c-cis protooncogene. Coexpression of a growth factor and its receptor seen in tumor cells suggest the possibility of an autocrine mechanism contributing to the unregulated growth of the malignant astrocytes leading to increasing degrees of malignancy.

Expression of fibroblast growth factors (FGF) and interleukins were observed in gliomas as well as other types of brain tumors [60, 61]. The transcript for basic fibroblast growth factor (FGF) was detected in 17 of 18 gliomas and in 20 of 22 meningiomas [60]. In gliomas, the expression levels of basic FGF were greater in high grade than in low

grade gliomas. Acidic FGF mRNA was more frequently expressed in gliomas than in meningiomas (in 13 of 18 gliomas compared to in 3 of 22 meningiomas). In another study expression of basic FGF was found in a medulloblastoma tumor biopsy [61]. It is suggested that both basic and acidic FGF contribute to tumor angiogenesis and thus play a role in tumor progression. Transcripts coding for interleukin-1β and interleukin-6 have been detected by northern analysis in a medulloblastoma and a glioma, and in two glioma derived cell lines [61].

Expression of oncogenes

Birchmeier *et al.* found increased (10-60 fold) level of ros oncogene transcript in glioma derived cell lines but not in cell lines derived from other tissues [62]. Elevated expression was seen in 5 of 12 glioma cell lines. The ros gene was not amplified in any overexpressing cell line. However, a point mutation was present in one of the cell line. The ros oncogene encodes a transmembrane protein, homologous to EGFR, with tyrosine kinase activity. Transcription mapping studies in RNA derived from 25 primary tumor tissue (both GBM and lower grade) failed to detect overexpression of ros oncogene in the primary tumors [63]. Approximately 5% of gliomas contain amplification of the n-myc or gli genes [64, 65]. Other oncogenes expressed in glioma cell lines include c-myc [66], and N-ras [67]. In a glioblastoma derived cell line rearrangement of human Abl oncogene is reported [68].

A model for tumorigenesis in gliomas

Based on the molecular alterations observed in tumors of different histologic and malignancy grades, it is possible to postulate a model of tumorigenesis in gliomas (Fig. 1). Since deletion in 17p (possibly p53 gene) is seen in all grades of tumors it is likely that it represents an early event in tumorigenesis. The next step may involve allelic loss on 9p because deletions in 9p are seen in intermediate and high grade tumors. Deletions in retinoblastoma gene is observed mainly in high grade tumors and probably represent later steps involved in tumor progression. In about half the tumors the above described deletions were not detected. Such tumors may represent subtypes of tumors or may have small deletions or point mutations that are beyond the limits of detection by RFLP analysis. Amplification of EGFR gene occurred mainly in high grade tumors. However, at least half the GBM tumors do not have amplified EGFR suggesting that gene amplification may not be directly involved in tumor development. Coexpression of growth factor receptors (EGFR and PDGF) and their ligands (prepro EGF, and c-sis/PDGF2), may play a role in uncontrolled growth of glial cells leading to more malignant phenotypes. The deletions involving chromosome 22 is not examined in detail but may have a role in a subset of tumors.

Allelic loss on 10q is virtually restricted to glioblastomas and is seen in more than 80% of GBM tumors. Loss of function of a gene on 10q may be pivotal for the development of GBM. In colorectal model, progressive accumulation of genetic changes was more important in tumor progression than the order of their occurrence. Similarly, in gliomas the accumulation rather than order of genetic alterations described here may be important in tumor progression.

Medulloblastoma

Medulloblastomas are small cell neoplasms which occur in the cerebellum of children. They are also called primitive neuroectodermal tumors. The most consistent cytogenetic abnormality seen in medulloblastomas is i(17q). Other less frequent changes are gains of portions of chromosome 1, deletions of 6q, 11 and 16q [69, 70].

Loss of chromosomal regions

The i(17q) seen in medulloblastomas result in the loss of one copy of 17p. This has been confirmed by RFLP analysis [71–73]. In a study of 23 tumors, LOH for 17p loci was found in six tumors, for 6q in

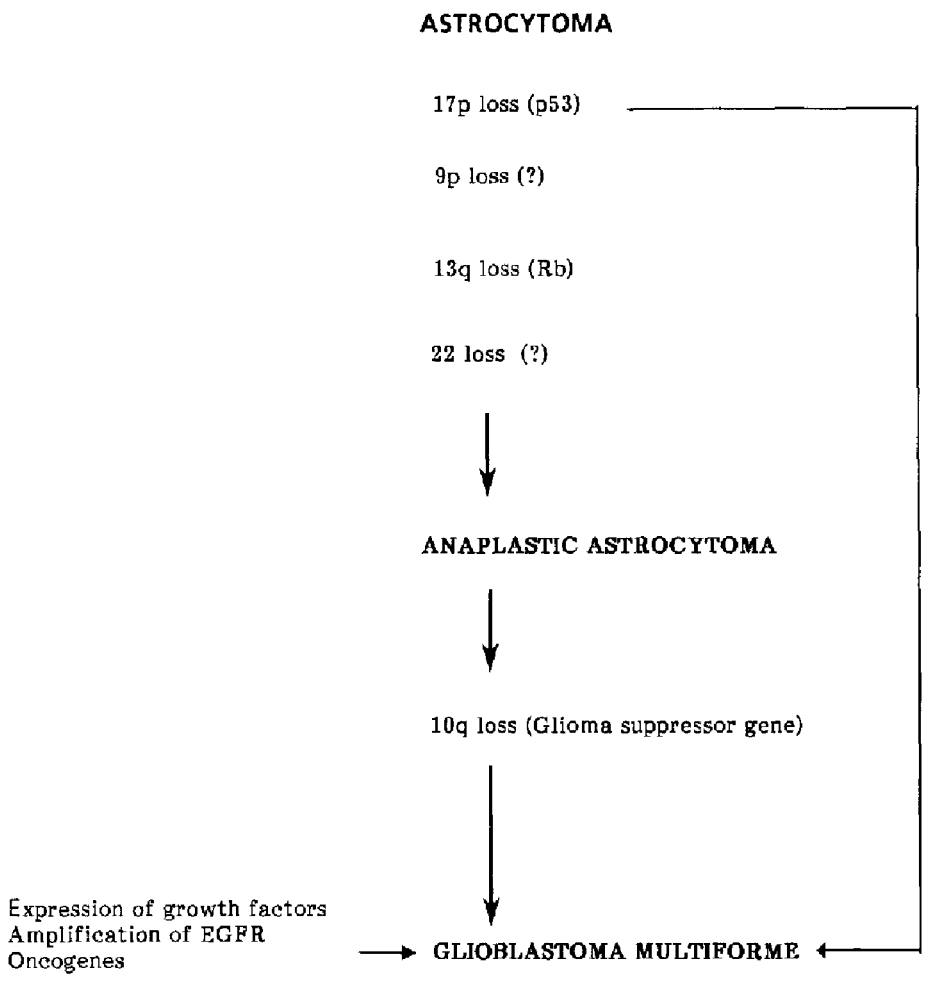

Fig. 1. The genetic changes detected in low and intermediate grade tumors include loss of chromosomal segments on 17p, 9p, 13q and 22. Suppressor genes important in early stages of tumorigenesis may be located in these chromosomal regions. In majority of cases, the tumor progression appears to proceed through the loss of a putative glioma suppressor gene located on 10q. However, in a subgroup of tumors GBM formation may proceed without gene loss on 10q. Other genetic changes which could influence tumor progression in subgroups of tumors include amplification of EGFR and expression of growth factors and oncogenes.

5 tumors, and for 16q in 3 tumors. None of the tumors lost markers on 22q. The common deletion region on 17p was between 17p11.2 and 17pter [72]. Another study found loss of 17p loci in 45% of the tumors and common deletion location of 17p12–13.1 [73]. The p53 locus lies within this region of chromosome 17. Efforts to identify point mutations on the remaining allele of p53 in medulloblastoma have failed suggesting to the possibility of a gene other than p53 as the target for allele loss [74]. Loss of 10q loci was reported in a small percentage of medulloblastoma tumors [in 1 of 9 in ref. 71 and in 2 of 9 in ref. 73]. However, no loss of alleles was detected with RB gene or markers linked to RB gene [71, 73]. In a limited number of medulloblastoma cases, loss of 17p loci has been correlated with poor response to treatment [73].

C-myc amplification

Approximately 10–20% of human medulloblastomas contain DMs. Friedman *et al.* in 1988, demonstrated amplification of c-myc in a medulloblasto-

ma derived cell line, D-341 Med [75]. The c-myc gene codes for a nuclear phosphoprotein whose precise function is not known. However, it is believed that expression of the myc family of genes has a role in transduction of signals that induce cell differentiation and cell proliferation. In an analysis of 7 medulloblastomas, c-myc amplification was found in xenografts (D-341 Med-X, D-382 Med-X, D-384 Med-X and D-425 Med-X) and in cell lines (D-341 Med-C, D-384 Med-C and D-425 Med-C) established from four tumors with DMs [76]. However, c-myc gene was amplified in only 2 (D-341-Bx and D-384-Bx) of the 4 biopsies from which the xenografts and the cell lines with amplification of this gene were derived. In the two cases (D-382 Med-Bx and D-425 Med-Bx) where amplification was not seen in the biopsies, it is possible that the original biopsies either contained a small population of tumor cells with gene amplification and that these cells had a growth advantage, or that low level c-myc amplification was present in many cells of the biopsy but that incresing levels of gene amplification occurred during passage *in vitro* and *in vivo*. In either case, these findings suggest that amplification of the c-myc gene provides a selcctive advantage for medulloblastoma cells when propagated *in vitro* or in athymic mice. The gene was not amplified in three other xenografts or biopsies of tumors which did not contain DMs, but a rearrangement of the gene occurred in 1 of the 3 tumors. In another study c-myc amplification was observed in 1 of 10 tumors [71]. By northern analysis, elevated levels of c-myc mRNA was observed in 3 of 6 medulloblastoma tumor samples [77].

In neuroblastomas N-myc gene is amplified in about 1/3 of the cases and is established as an indicator of poor prognosis. The significance of c-myc amplification as a prognostic factor in medulloblastomas remains to be established. It is interesting that the only reported case of c-myc amplification in a glioma occurred in a child [66], raising the possibility that amplification of this gene may be associated with childhood malignant brain tumors in general rather than being associated with medulloblastoma alone.

Other oncogenes

Other oncogenes amplified in medulloblastomas include n-myc and erbB1 [78, 79]. In a survey of 20 primary medulloblastomas, for various oncogene amplification (erbB1, gli, neu, myc, l-myc, n-myc, h-ras, k-ras, n-ras, sis and src), only one tumor showed amplification of erbB1. By contrast, 3 out of 4 medulloblastoma derived cell lines showed amplification of an oncogene. C-myc, n-myc and erbB1 was amplified, in each case in a single tumor [79]. These results suggest that the frequency of oncogene amplification is much higher in medulloblastoma derived cell lines than biopsies.

Conclusion

The common genetic abnormalities in glioma are loss of alleles on 9p, 10q, 13q, 17p and on chromosome 22. Loss of loci on 17p occurs in early stages of tumorigenesis and is associated with point mutations in the p53 gene. Other chromosomal regions commonly lost in gliomas probably contain yet unidentified tumor suppressor genes whose loss may trigger tumor progression. The gene which is most often amplified in gliomas is the EGFR gene. Expression of PDGF and FGF are also observed in many cases and may contribute to the malignancy.

Compared to gliomas there are fewer reports of detailed molecular studies in medulloblastomas. Even though a gene on 17p appears to be important in tumorigenesis, a clear picture of genetic alterations occurring in medulloblastomas is yet to emerge.

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