Genetics of Brain Neoplasms

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Transformation of a normal cell into a malignant cell involves a series of events that damage the genome. Gliomas are the most common adult neoplasm of the central nervous system. To develop new therapeutic strategies requires an understanding of the specific lesions that occur and contribute to this malignant process. Initially, data reported from the analyses of human gliomas were quite variable. This has recently changed as more data have become available and the selection of tissue analyzed is coupled with clinical criteria. Specific genetic lesions are now defining different glioma pathways, and some aberrations may be indicative of therapeutic response. This review focuses on the specific genetic aberrations associated with astrocytic and oligodenroglial tumors.

Introduction

Malignant gliomas include a series of tumors originating from the three different glial elements: astrocytes, oligodendroglia, and ependymal cells. The astrocytic tumors include astrocytomas, anaplastic astrocytomas, and glioblastoma multiforme (GBM); the oligodendroglial tumors develop as oligodendrogliomas and anaplastic oligodendrogliomas or mixed gliomas that include a mixture of oligoastrocytoma cells. These two groups of gliomas are being diagnosed more frequently and earlier, due to advances in imaging. They account for about half of the primary intracranial tumors in the adult population. Whenever possible, they are treated aggressively with surgery, radiation, and chemotherapy. However, malignant gliomas recur, and for the most malignant brain tumor, the GBM, median survival is approximately 58 weeks [1••]. Unfortunately, this prognostic figure has not notably improved in the past 25 years, even though the overall 5-year survival rate for all forms of cancer has increased from 39% to 61% in that same period of time.

Genetic Aberrations Associated with Central Nervous System Tumors

Glioma pathways

One of the important concepts to emerge from these molecular genetic investigations was the characterization of at least two different pathways that can produce a glioblastoma [2]. These two pathways were each defined by specific genetic lesions, especially when patient material was carefully selected on the basis of clinical and histopathologic data [3,4]. This is a significant observation because these tumors cannot be distinguished histopathologically.

Type 1 or secondary glioblastoma

The Type I or secondary pathway is a progressive step-wise evolution from a low-grade astrocytoma, to anaplastic astrocytoma, to GBM. Patients diagnosed with this progressive glioma are generally younger (mean age, 39 years) and have a history of a less malignant tumor at the time of diagnosis [3,5]. The astrocytomas (grade II tumors) tend to grow slowly, but are not benign because of their invasive quality and location.

Cytogenetic analysis of astrocytomas reveals the gain of chromosome 7 along with the loss of a single sex chromosome as the most common numerical aberrations. Structural abnormalities are rare, but when they occur they generally involve chromosomes 1p and 9p [1••]. Despite the lack of karyotypic complexity of the astrocytoma, genetic analysis of these low-grade tumors has defined several specific aberrations (Fig. 1).

The most common finding involves a mutation or allelic loss of chromosome 17p, the target gene is the *TP53* (17p13.1) gene, in which more than 200 mutations have been described in human tumors [6]. The genetic lesion is a missense mutation that inactivates the *TP53* gene. There are several so-called "hot spots" in codons 175, 248, and 273 [7], a highly conserved region spanning exons 5, 7, and 8. Before tumors were selected on the basis of their clinical history, *TP53* aberrations appeared to vary widely. The range was as low as 25% in some studies, to a figure as high as 60% in other investigations. With the separation of patient material, a different concept began to emerge. *TP53* mutations became the common mutation in patients between 18 years of age and the mid-40s (44%), compared with older patients who had a mean age of 60 years (9%). The most current assessment of *TP53* mutations in the progressive glioma is now placed at greater than 65% [8,9]. A similar observation has been made with immunohistochemical analysis of the p53 protein. These investigations have shown that approximately three quarters of these gliomas have an abnormal accumulation of p53 protein. This increase in accumulation of p53 protein is expected because it can occur as a result from a mutation in *TP53*, as well as aberrations on other genes controlling the expression of the *TP53* gene [9].

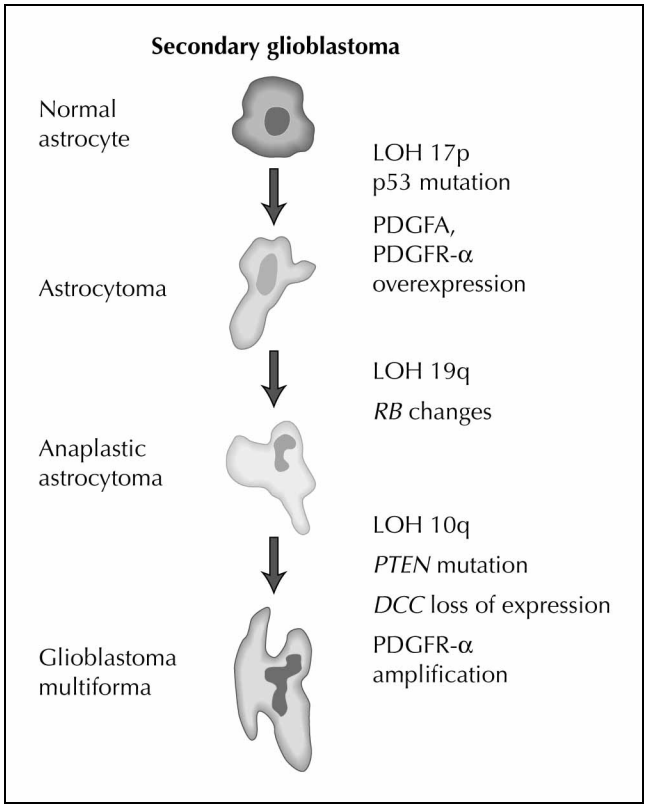

Figure 1. Changes associated with the progressive evolution of Type 1, secondary glioblastoma. (DCC—detected in colon cancer gene; LOH—loss of heterozygosity; PDGF—platelet-derived growth factor; PTEN—phosphate-tensin gene; RB—retinoblastoma gene.)

A second family of genes appears to be important to astrocytoma evolution as well. These genes involve a growth factor and its receptor. The platelet-derived growth factor (PDGF) family consists of an A and B chain (PDGF-A and PDGF-B) and it has two receptors, PDGFR-α and PDGFR-β [10]. The PDGF-A and -B chains dimerize to form AA, BB, or AB homo- or heterodimers. The receptor PDGFR-α binds with AA and AB, whereas PDGFR-β binds with only the BB homodimer. In astrocytomas, the A chain and α-receptor are predominantly over-expressed [11]. This observation is interesting because the most common chromosomal abnormality identified in astrocytomas involves aneuploidy of chromosome 7 [12], the chromosomal location of the PDGF-A chain. This observation may also have some importance in therapy-related issues, because in vitro and in vivo treatment with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) selects for a minor subpopulation of cells containing amplified PDGF-A and -B chains [13]. Changes in the expression of growth factors and their receptors may also initiate local environmental changes that begin to stimulate angiogenesis. Over-expression of PDGFR-α also correlates with the loss of heterozygosity for 17p, although the exact nature of these events is unknown [14••].

In about 30% of the astrocytomas, allelic loss (loss of heterozygosity) has been identified on chromosome 22q, and a likely candidate for this genetic loss was the *NF-2* gene. However, extensive analysis of this gene in all grades of gliomas has failed to detect a consistent abnormality [15]. The allelic loss reported for chromosome 22q occurs more telomeric to the *NF-2* gene, and thus a candidate gene or genes to explain this observation awaits further genetic analysis. Other chromosomes exhibiting allelic loss in astrocytomas include chromosomes 1, 3, and 13. Each allelic loss identified in these studies represents a probable site for tumor suppressor genes, but awaits further confirmation [1••,14••].

Anaplastic astrocytomas

Anaplastic astrocytomas are generally thought to develop from low-grade astrocytomas. They are found in both young and old patients, with the peak incidence occurring in patients in their mid-50s. Like astrocytomas, the gain of chromosome 7 is the most frequent numerical aberration. Additional chromosome gains include 19 and 20, whereas chromosomes 10, 22, and a single sex chromosome are frequently lost. The patterns of gain and loss are more prominent for anaplastic astrocytomas, and structural abnormalities are also more frequent. The majority of breakpoints occur on the p arms of chromosomes 1, 3, and 9 (1p32, 1p36, 3p21, 9p21 and 9p22), with similar clusters in the q arms of chromosomes 6 and 7 (6q21 and 7q22), and occasionally in chromosomes 5p13, 15q11, 17p11, and 19q12.1 [16,17].

Approximately 30% to 40% of anaplastic astrocytomas have a mutation of the *TP53* gene in addition to allelic loss. Over-expression of PDGF and PDGF receptors and allelic loss on 22q are also similar in frequency to astrocytomas, further supporting the concept of the progressive nature of astrocytomas to a more malignant stage, defined as the anaplastic astrocytoma [14••]. Changes that mark this transition from astrocytoma to anaplastic astrocytoma include additional allelic loss on chromosome arms 9p, 11p, 13q, and 19q [16].

Many of the genetic changes in the anaplastic astrocytoma are associated with critical steps in the cell cycle. A key gene in this scenario is the retinoblastoma gene (*RB*), which is located on chromosome 13q14. The Rb1 protein inhibits the transition of the Go/G1 to S phase. When the Rb1 protein is phosphorylated by any of cyclin dependent kinases (CDKs), this protein is inactivated, allowing elongation 2 factor (E2F) to function in promoting the cell to progress from G1 to S in the cell cycle. The *CDK* (*CDK4, CDK6, and CDK2*) genes are both controlled by positive and negative regulators, and the deregulation of either of these genes or genes upstream in the pathway can produce a similar loss of control over the cell cycle.

Other genes involved in growth control, such as transforming growth factor-β (*TGF*-β), or oncogenes such as *ras* or *myc*, can be aberrant. The aberrant expression of these genes will be reflected in the high and low expression of the Cip/Kip proteins. Thus, the cascade of events leading to the inhibition of Rb1 protein is under the control of multiple genes, and the failure of any one of them to function normally will

permit the cell cycle to continue unchecked. In fact, the evidence suggests that it is rare to find more than one DNA lesion in the critical steps of the cell cycle pathway [18].

Not all deregulation is related to allelic loss of genetic material. Several investigations have identified a region on chromosome 12 (12q13-14) that is amplified in 15% of World Health Organization (WHO) grade III (anaplastic astrocytomas) and IV (glioblastomas multiforme) tumors [19]. The over-representation of whole chromosomes or structural rearrangements involving the duplication of parts of chromosomes can contribute to the amplification of proteins affecting the cell cycle. The best example is chromosome region 12q13. The genes *MDM2*, *SAS*, and *CDK4* are mapped to this chromosome region. This segment of chromosome 12q is frequently over-represented in gliomas. Therefore, aneuploidy of either whole or parts of chromosomes are considered to be another mechanism for deregulating the cell cycle when mutations or allelic loss are not present. The *MDM2* gene codes for a cellular protein that complexes with the *p53* tumor suppressor gene product, and this binding inhibits its function. This provides a mechanism for a tumor cell to escape p53-mediated growth regulation despite no mutation or allelic loss of *TP53*. A similar analogy can explain deregulation when genetic material is lost. For example, chromosome 9p21 is a map location for the *CDKN2A* (*P16* gene family), a chromosome region that has been shown to have frequent allelic loss. Loss of this inhibitor protein provides an alternative mechanism leading to the same biologic endpoint (*ie*, amplification of CDK4 and progression through the cell cycle) [19].

Another important site of allelic loss is on chromosome 19q13.2-13.3. The putative tumor suppressor gene has not yet been identified. However, this gene appears to be unique to glial tumors and is primarily limited to the progressive type of glioma. When tissue is selected for Type 1 and Type 2 gliomas, the allelic loss reported was 54% for Type 1 gliomas versus 6% for Type 2 gliomas [20].

Several other chromosome regions have been reported to undergo allelic loss. The chromosome region spanning 1p36-p32 and chromosome regions 3p21 and 11p15→pter are the most frequent sites of deletion [1••,17]. However, the sampling of anaplastic astrocytomas has been small in these investigations, and additional analyses will be required before the importance of these findings can be determined.

Glioblastoma multiforme

Glioblastoma multiforme represents about 50% of all intracranial neoplasms and is considered the most malignant of the astrocytic tumors. This tumor is highly infiltrative, producing undifferentiated elements as a dominant feature, in addition to mitotic activity and necrosis. Vascular proliferation may also be evident, along with a high bromodeoxyuridine/Ki-67 labeling index [14]. Although the genetic instability of this tumor results in numerous and varied genetic changes, this subset of glioblastomas carries specific nonrandom chromosome changes [16,17].

The most frequent cytogenetic change involves the gain of chromosomes 7 and 20. The loss of chromosomes include 10, 22, and a single sex chromosome, and less frequently chromosomes 9, 13, and 14. In general, numerical changes appear to include more loss of chromosomes rather than gain [17]. Structural rearrangements are also common and highly variable and frequently require fluorescent technologies or spectral karyotyping for positive identification [17].

The frequency of *TP53* mutations and allelic loss is approximately the same in GBM as in anaplastic astrocytomas and astrocytomas. However, there is a substantial increase in the loss of heterozygosity reported for 10p, 10q23.3, and 10q25.3-26 [4,21,22]. The tumor suppressor gene phosphate-tensin (*PTEN*), also called the mutated in multiple advanced cancers 1 gene (*MMAC1*) [23] or telomerase-associated protein 1 (*TEP1*), was identified on chromosome 10q23.3. The *PTEN* gene encodes a dual-specificity phosphatase that has been demonstrated to function in the regulation of cell growth, apoptosis, cell migration, and interactions with the extracellular matrix. Initially, it was thought that the loss of heterozygosity (LOH) of *PTEN* was a late event that initiated the progression of an anaplastic astrocytoma to become a GBM [10]. When GBMs were selected on the basis of their being Type I or Type 2, it was determined that only a small number of the progressive Type I gliomas had a mutation in this gene, whereas the majority of LOH was identified with the Type 2 GBM [22,24]. When allelic loss was detected in Type 1 gliomas, it was primarily confined to 10q.

A second gene, the deleted in malignant brain tumors 1 gene (*DMBT1*), may be the important change on chromosome 10q in the Type 1 gliomas. Aberrations in this gene are thought to contribute to genetic instability. *DMBT1* is located at 10q25.3-26 and is considered the candidate tumor suppressor gene found deleted in some 38% of Type 1 GBMs [25,26].

Platelet-derived growth factor and its receptors have few mutations; however, most GBMs over-express at least one PDGF chain and its respective receptor, with the most common form of over-expression being PDGF-A chain and PDGF-α receptor [27,28]. The PDGF-α receptor is capable of binding all three isoforms, and this suggests an autocrine mechanism for this growth factor similar to the autocrine behavior of epidermal growth factor-receptor (EGFR). Immunohistochemistry and in situ hybridization supported the data that the PDGF-A chain and the PDGF-α receptor were preferentially expressed in tumor cells, in contrast to the PDGF-B chain and the PDGF-β receptor, which were highly expressed in proliferating endothelial cells within the tumor [29–31]. Normal brain tissue also expresses the PDGF-β receptor and the PDGF-A chain; however, the PDGF-β receptor will bind only the PDGF-B chain, so this receptor is not active in normal brain tissue [29]. This suggests that the preferential expression of the PDGF-β receptor in the endothelial component of gliomas is related to the angiogenesis observed in these high-grade tumors.

Other genes found to be aberrant in GBM that might contribute to their malignant and invasive phenotype have been described. For example, the deleted in colon cancer gene (*DCC*) is mapped to chromosome 18q21. This is a transmembrane cell adhesion molecule of the neural cell adhesion nerve cell adhesion molecule (NCAM) family. As the name implies, it was discovered in colon cancer patients. High-grade gliomas have abnormalities of chromosome 18, and several molecular studies have indicated that it is deleted in GBM [32–34] and in some grade II tumors [34]. This has led some investigators to speculate that cell guidance molecules can be involved in tumorigenesis.

The initial molecular studies did not consider the possibility of multiple progressive pathways, and the reported frequency for allelic loss on chromosome 19 was lower for GBM than for anaplastic astrocytomas. When the tissues were selected for possible different evolutionary pathways, the frequency of allelic loss in Type I GBMs was similar to anaplastic astrocytomas.

Type 2 or primary glioblastomas

In contrast to Type I gliomas, the second pathway for GBM appears to arise de novo or very rapidly from a pre-existing tumor cell(s), although they cannot be distinguished from Type 1 glioblastomas histopathologically. Type II GBMs or primary glioblastomas appear to have no evolutionary component. This tumor is usually associated with older patients (mean age, 55 years) who have not had a previous history of a lower grade of tumor [14••,35].

In contrast to Type 1 GBMs, the most common genetic aberration in the primary Type 2 GBM is the amplification of the *EGFR* mapped to chromosome 7p13-p11 (Fig. 2). This gene is amplified or over-expressed in the majority of these tumors [14••]. More than half of these GBMs with amplification of the *EGFR* also have a rearrangement of the gene [36], generally in the form of an internal deletion. This mutated form of the *EGFR* has a high level of tyrosine kinase activity in the absence of the EGF ligand, which essentially keeps this receptor in a "turned on" autocrine mode. Thus, the amplification of *EGFR* can potentially override the normal negative regulation of the *PTEN* gene product [37].

In addition to *EGFR* aberrations, the allelic loss on chromosome 10 was almost entirely restricted to the primary, Type 2 glioma [24]. It has been suggested that the loss of chromosome 10 is a major factor in the evolution of the highly malignant GBM. In some tumors, two different grades of tumor can coexist side by side. Chromosome 10 loss is not a feature associated with the diffuse astroctyoma. It is postulated that it is the loss of chromosome 10 that permits the abrupt change from a low-grade to high-grade malignant mass. Thus, the major difference between the primary, Type 2 GBM and the secondary, Type I GBM is that the former tends to lose the entire chromosome 10 as opposed to the latter, which demonstrates only a loss of 10q [38].

The *MDM2* gene product also appears to be restricted to the primary de novo pathway [39]. As discussed previously, amplification of *MDM2* protein by virtue of binding to p53 will essentially inactivate this protein. Thus, this is an alternative mechanism that allows a tumor cell to be removed from the control of normal p53 expression. Furthermore, most of the tumors that over-express *MDM2* lack a mutation or allelic loss in *TP53* gene [39].

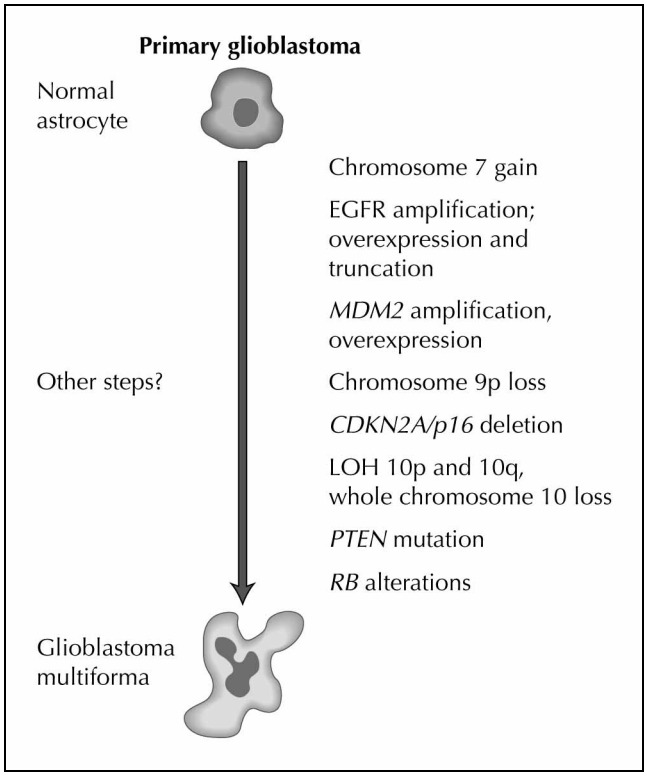

Figure 2. Changes associated with the evolution of Type 2, primary glioblastoma. (CDK— cyclin dependent kinase; EGFR—endothelial growth factor receptor; LOH—loss of heterozygosity; PTEN— phosphate-tensin gene; RB— retinoblastoma gene.)

Genes important in the cell cycle also appear to be associated with the primary Type 2 GBM. The loss of genes such as *CDKN2* locus that codes for p16INK4A and p14ARF, the amplification or over-expression of the CDKs, or the amplification, allelic loss, or mutation of Rb1 are all capable of deregulating the cell cycle that contributes to the uncontrolled proliferation associated with GBM.

Platelet-derived growth factor A is also over-expressed in GBM, as are many other growth factors [40]. PDGF-A over-expression may be less frequent in GBMs, but its autocrine regulation suggests that like EGFR, it could provide a selective growth advantage to tumor cells that are identified in the highly proliferative masses.

Oligodendrogliomas

Oligodendrogliomas are tumors that occur primarily in adults, with a peak incidence in the fifth and sixth decades of life. Oligodendrogliomas account for 10% of the gliomas diagnosed and are generally considered a slow-growing tumor. The location of oligodendrogliomas is

roughly related to the amount of white matter in the different lobes of the brain. Although these tumors arise in white matter, they tend to infiltrate the cerebral cortex more than do astrocytomas of a similar grade. Histologically, oligodendroglial tumors comprise a continuous spectrum, ranging from very well-differentiated neoplasms to malignant invasive tumors. Similar features (*ie*, high cell density, mitotic activity, and necrosis) are used to grade these tumors. With increasing anaplasia these tumors begin to become more astrocytic in appearance, and they can develop areas of necrosis [41••]. However, unlike astrocytomas, the histopathology does not always correlate with survival. This situation has created the need for diagnostic and prognostic markers important to the evolution of this tumor.

Normal G-banded karyotypes are the most frequent descriptions used to describe untreated oligodendrogliomas. When loss or gain of chromosomes is observed, the most common loss is that of a single sex chromosome (25% of the cases), and the most common gain is chromosome 7 (5% of the cases). Structural abnormalities are rare, although several have been localized to chromosome 1p and chromosome 22q [17].

Molecular analyses of the tumor have been more informative (Fig. 3). Allelic loss on chromosomes 1p and 19q appear to be preferential for oligodendrogliomas [42–46]. The most frequent allelic loss occurs on chromosome 19q. It has been observed in 50% to 80% of the tumors analyzed [45,47,48], despite their being little evidence of numerical or structural abnormalities of chromosome 19 [17]. A putative tumor suppressor gene has been mapped to 19q13.2-13.3 [46]. Although this loss is most notable in oligodendrogliomas, the actual target gene for the allelic loss remains undefined.

Chromosome 1 contains the second most frequent allelic loss. Reports describing allelic loss on chromosome 1p range from 40% to 97%. These disparate results frequently relate to different methods of analysis or probes used [44,48,49]. Generally, tumors carrying 1p deletions also carry 19q allelic loss [44,48]. The location of this potential tumor suppressor gene(s) is not well characterized for chromosome 1p. Several potential sites have been localized. They include 1p35-p36, with a second site closer to the centromere, 1p36.3 and 1p34-p35 [41••]. Located on chromosome 1p32 is a negative regulator of the cell cycle *CDKN2C* (*P18INK4C*), although several investigations determined that it was rare for oligodendrogliomas to contain an aberration in this gene, as the aberrations were identified in a single recurrent tumor, and this was an anaplastic oligodendroglioma [50,51]. A homologue of *p53*, called *p73*, is located within the 1p36 region. In one study of 20 oligodendrogliomas, no mutation within this gene was observed, suggesting that this is not the gene critical to this deletion [52].

Additional genetic lesions have been reported on chromosomes 9p and 10q. These genetic changes have been

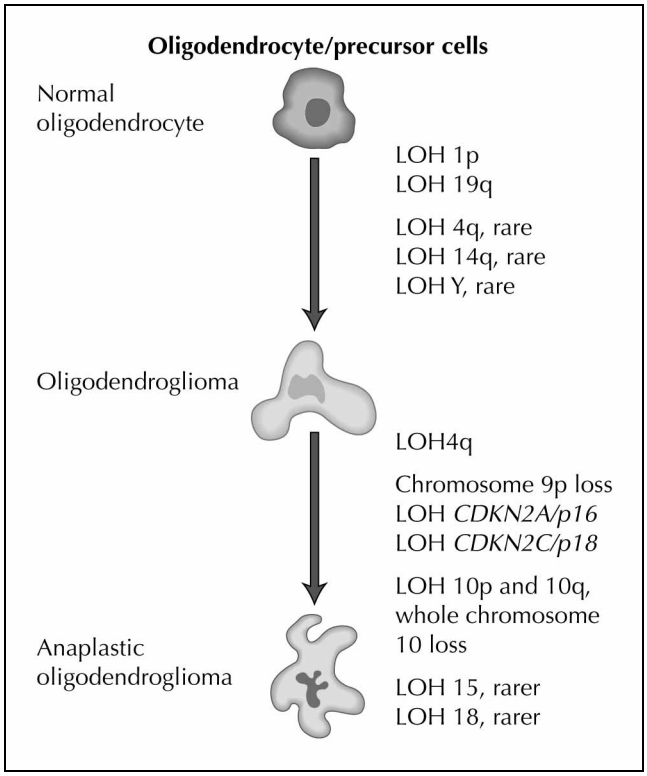

Figure 3. Changes that have been identified with the progressive evolution of the oligodendroglioma into an anaplastic oligiodendroglioma. (CDK—cyclin dependent kinase; LOH—loss of heterozygosity.)

associated with the transition of the well-differentiated oligodendroglioma to anaplastic oligodendroglioma [53••]. A potential target gene on 9p21 is the cell cycle inhibitor, *CDKN2A* (*P16INK4A*). In studies that assessed the involvement of this gene, no allelic loss or mutations were observed for the *CDKN2A* gene in well-differentiated oligodendrogliomas. This is in contrast to the findings for anaplastic oligodendrogliomas, in which 42% of the cases had an allelic loss or mutation [53••]. For chromosome 10 involvement, both the well-differentiated oligodendrogliomas and the anaplastic oligodendrogliomas (Grade III) showed a loss of heterozygosity on 10p, 10q23, and 10q25. However, none of these tumors had a mutation of *PTEN*, suggesting this is not the targeted gene [54]. Other chromosomes reported to have occasional LOH include chromosomes 4q, 14, 15, 11p, 18, and 22q [41••,44,53••], but additional cases are needed for study to determine the relative importance of these findings.

Occasionally, oligodendrogliomas have mutations in the *TP53* gene, but with far less frequency than that observed in astrocytic tumors [16,41••,53••]. This is in contrast to the immunohistochemistry studies for p53 protein. A much higher percentage of oligodendrogliomas express the p53 protein, yet only a few of the tumors have either allelic loss or a mutation of the *TP53* gene [53••,55]. This observation is similar to that for the astrocytic tumors and is explained in part by the aberrant expression of other genes that can directly affect the expression of *TP53*.

Although these tumors are considered to be slow growing, many will develop anaplasia in the form of increased cellularity, nuclear atypia, cellular pleomorphism, and high mitotic activity. This can be accompanied by angiogenesis and the formation of vessel proliferation and necrosis [41••]. Growth factors and their receptors most likely play an important role in oligodendrogliomas, as evidenced by the increasing number of reports describing the aberrant expression of growth factors or their receptors in this neoplasm. PDGF-A and -B, as well as their receptors PDGF-α and -β, are expressed in all the reported cases of oligodendrogliomas [56,57]. Despite the aberrant expression of this growth factor and its receptor, gene amplification was only detected in the anaplastic oligodendroma and anaplastic oligoastrocytoma [56]. The aberrant expression of *EGFR* has also been identified in both oligodendrogliomas and anaplastic oligodendrogliomas, but does not appear to be the result of gene amplification [58,59]. Several reports have been able to detect the aberrant expression of vascular endothelial growth factor and its receptor [60], although other studies were unable to detect this protein [61,62]. The discrepancy in results has been attributed to the antibodies used in these studies.

Mixed Tumors

Mixed tumors are composed of oligodendroglial and astrocytic cells. The proportion of cells in this mixture can vary considerably and is, therefore, a frequent point of disagreement among neuropathologists. The combination of glial cells most frequently observed in a mixed tumor are fibrillary astrocytes and oligodendrocytes. Mixtures of astrocytes and ependymal cells can occur, but this is thought to be a very rare tumor and difficult to separate from ependymal tumors that have begun to acquire astrocytic phenotypes. The cytogenetic literature is reviewed elsewhere [17]. A summary of those findings demonstrates that oligoastrocytomas have a similar pattern of gain and loss to oligodendrogliomas without an astrocytic component.

Molecular studies have also not been able to identify a consistent genetic lesion that would indicate oligoastrocytomas are genetically distinct from either oligodendrogliomas or astrocytomas [44]. Approximately 30% of the oligoastrocytomas carry genetic lesions that are frequently found in astrocytic gliomas, especially *TP53* mutations and LOH on 17p [63,64]. However, if a 17p loss or *TP53* mutation was identified in the sample, no allelic loss on 1p and 19q could be detected. The reverse was also true. Oligoastrocytomas with a 1p and 19q deletion had no 17p deletions or *TP53* mutations. An extensive study comparing allelic loss between astrocytic tumors and oligodendrogliomas for chromosomes 1p, 17p, and 19q suggested two genetic subsets in mixed tumors [58]. One subset is genetically related to astrocytomas, and the other is genetically related to oligodendrogliomas.

When these tumors acquire anaplastic features they are also thought to acquire changes in 9p, 10, and 11p, with occasional amplification of the *PDGF* genes and *EGFR* gene or changes similar to the progressive changes of the anaplastic oligodendroglioma and astrocytoma [44,53••,57].

Defining the genetic aberrations associated with the progression of a low-grade oligodendroglioma to the more malignant anaplastic astrocytoma or anaplastic oligoastrocytoma is extremely important because it provides markers that are helpful in diagnosis. The most important information to evolve from the allelic loss of chromosome 1p is that this loss of 1p is an important predictor of tumor response to chemotherapeutic drugs for the anaplastic oligodendroglioma [14••,65]. Patients with high-grade anaplastic oligodendrogliomas that demonstrated a chromosome 1p loss responded to procarbazine (PCV) chemotherapy and had a median survival of more than 10 years compared with patients that had no allelic loss. Patients with no allelic loss generally failed to respond to PCV treatment, and the median survival for this group of patients was 2 years [14••]. A second study tested seven additional patients with a diagnosis of GBM or anaplastic oligoastrocytoma that had allelic loss of 1p to determine if this marker would also predict response [65]. Although the results were not as dramatic as the initial study, the results did suggest a similar trend. Larger studies will have to be undertaken to resolve the issue of treatment response in high-grade gliomas that do not have oligodendroglial components. It is important to ascertain that it is the allelic loss on 1p that is responsible for the therapeutic response and long-term survival, not other genetic alterations that have not been evaluated.

Conclusions

The initiation and progression of human malignant gliomas continues to be an area of intense investigation. Initially, the cytogenetics, allelic loss, and gene amplification reported for a specific tumor type and grade were quite variable. As more data were acquired, patterns of specific abnormalities identified with tumor type and tumor grade became evident. Thus, specific genetic markers are now beginning to define pathways of evolution and potentially, at least in the case of anaplastic astrocytomas, therapeutic response.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.•• Shapiro WR, Shapiro JR, Walker RW: **Central nervous system.** In *Clinical Oncology.* Edited by Abeloff MD, Armitage JO, Lichter AS, Niederhuber JE. New York: Churchill Livingstone; 2000:1103–1192.

This article characterizes in detail the genetic changes identified in gliomas. No distinction is made between primary and secondary gliomas.

2. James CD, Carlbom E, Dumanski J P, *et al.*: **Clonal genomic alterations in glioma malignancy stages.** *Cancer Res* 1988, **48:**5546–5551.

3. Kleihues P, Lübbe J, Watanabe K, *et al.*: **Genetic alterations associated with glioma progression.** *Verh Dtsch Ges Path* 1995, **78:**43–47.

4. von Deimling A, von Ammon K, Schoenfeld D, *et al.*: **Subsets of glioblastomas multiforme defined by molecular genetic analysis.** *Brain Pathol* 1993, **3:**19–26.
5. Kleihues P, Ohgaki H: **Primary and secondary glioblastoma: from concept to clinical diagnosis.** *Neuro Oncol* 2000, **1:**44–51.
6. Hollstein M, Sidransky D, Vogelstein B, *et al.*: **p53 mutations in human cancers.** *Science* 1991, **253:**49–53.
7. de Fromentel CC, Soussi T: **TP53 tumor suppressor gene: a model for investigating human mutagenesis.** *Genes Chromosomes Cancer* 1992, **4:**1–15.
8. Lang FF, Miller DC, Koslow M, *et al.*: **Pathways leading to glioblastoma multiforme: a molecular analysis of genetic alterations in 65 astrocytic tumors.** *J Neurosurg* 1994, **81:**427–436.
9. Watanabe K, Sato K, Biernat W, *et al.*: **Incidence and timing of p53 mutations during astrocytoma progression in patients with multiple biopsies.** *Clin Cancer Res* 1997, **3:**523–530.
10. Kirsch M, Wilson JC, Black P: **Platelet-derived growth factor in human brain tumors.** *J Neurooncol* 1997, **35:**289–302.
11. Nistér M, Claesson-Welsh L, Eriksson A, *et al.*: **Differential expression of platelet-derived growth factor receptors in human malignant glioma cell lines.** *J Biol Chem* 1991, **266:**16755–16763.
12. Bigner SH, Mark J, Mahaley MS, *et al.*: **Patterns of the early, gross chromosomal changes in malignant human gliomas.** *Hereditas* 1984, **101:**103–113.
13. Scheck AC, Mehta BM, Beikman MK, *et al.*: **BCNU-resistant human glioma cells with over-representation of chromosomes 7 and 22 demonstrate increased copy number and expression of platelet-derived growth factor genes.** *Genes Chromosomes Cancer* 1993, **8:**137–148.
14.•• Cavenee WK, Furnari FB, Nagane M, *et al.*: **Astrocytic tumours.** In *Pathology & Genetics. Tumours of the Nervous System.* Edited by Kleihues P, Cavenee WK. Lyon, France: IARC Press; 2000:9–54.

Excellent review of pathology and molecular genetic changes associated with all central nervous system tumors.

15. Hoang-Xuan K, Merel P, Vega F, *et al.*: **Analysis of the NF2 tumor-suppressor gene and of chromosome 22 deletions in gliomas.** *Int J Cancer* 1995, **60:**478–481.
16. Bigner SH, Mark J, Bigner DD: **Cytogenetics of human brain tumors.** *Cancer Genet Cytogenet* 1990, **47:**141–154.
17. Shapiro JR, Scheck AC: **Brain tumors.** In *Cytogenetic Markers of Human Cancer.* Edited by Wolman SR, Sell S. New Jersey: The Humana Press; 1997:319–368.
18. He J, Olson JJ, James CD: **Lack of p16INK4 or retinoblastoma protein pRb, or amplification-associated overexpression of cdk4 is observed in distinct subsets of malignant glial tumors and cell lines.** *Cancer Res* 1995, **55:**4833–4836.
19. Dirks PB, Rutka JT: **Current concepts in neuro-oncology: the cell cycle—a review.** *Neurosurg* 1997, **40:**1000–1015.
20. Nakamura M, Yang F, Fujisawa H, *et al.*: **Loss of heterozygosity on chromosome 19 in secondary glioblastomas.** *J Neuropathol Exp Neurol* 2000, **596:**539–543.
21. Fults D, Pedone C: **Deletion mapping of the long arm of chromosome 10 in glioblastoma multiforme.** *Genes Chromosomes Cancer* 1993, **7:**173–177.
22. Lang FF, Miller DC, Koslow M, *et al.*: **Pathways leading to glioblastoma multiforme: a molecular analysis of genetic alterations in 65 astrocytic tumors.** *J Neurosurg* 1994, **81:**427–436.
23. Steck PA, Pershouse MA, Jasser SA, *et al.*: **Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers.** *Nature Genet* 1997, **15:**356–362.
24. Tohma Y, Gratas C, Biernat W, *et al.*: **PTEN mutations are frequent in primary glioblastomas de novo. but not in secondary glioblastomas.** *J Neuropath Exp Neurol* 1998, **57:**684–689.
25. Mollenhauer J, Wiemann S, Scheurlen W, *et al.*: **DMBT1, a new member of the SRCR superfamily, on chromosome 10q25.3-26.1 is deleted in malignant brain tumours.** *Nature Genet* 1997, **171:**32–39.
26. Somerville RP, Shoshan Y, Eng C, *et al.*: **Molecular analysis of two putative tumour suppressor genes, PTEN and DMBT, which have been implicated in glioblastoma multiforme disease progression.** *Oncogene* 1998, **17:**1755–1757.
27. Guha A, Dasher K, McL.Black P, *et al.*: **Expression of PDGF and PDGF receptors in human astrocytoma operation specimens supports the existence of an autocrine loop.** *Int J Cancer* 1995, **60:**168–173.
28. Harsh GR, Keating MT, Escobedo JA, *et al.*: **Platelet derived growth factor (PDGF) autocrine components in human tumor cell lines.** *J Neurooncol* 1990, **1:**1–12.
29. Hermanson M, Nistér M, Betsholtz C, *et al.*: **Endothelial cell hyperplasia in human glioblastoma: coexpression of mRNA for platelet-derived growth factor PDGF. B chain and PDGF receptor suggests autocrine growth stimulation.** *Proc Natl Acad Sci U S A* 1988, **85:**7748–7752.
30. Hermanson M, Funa K, Hartman M, *et al.*: **Platelet-derived growth factor and its receptors in human glioma tissue: expression of messenger RNA and protein suggests the presence of autocrine and paracrine loops.** *Cancer Res* 1992, **52:**3213–3219.
31. Plare KH, Breier G, Farrell CL, *et al.*: **Platelet-derived growth factor receptor-beta is induced during tumor development and upregulated during tumor progression in endothelial cells in human gliomas.** *Lab Invest* 1992, **67:**529–534.
32. Ekstrand BC, Bigner SH, Fearon ER: **DCC gene mutations and loss of expression in glioblastomas.** *Proc Am Assoc Cancer Res* 1995, **36:**574–574.
33. Reyes-Mugica M, Rieger-Christ K, Ohgaki H, *et al.*: **Loss of DCC expression and glioma progression.** *Cancer Res* 1997, **573:**382–386.
34. Scheck AC, Coons SW: **Expression of the tumor suppressor gene DCC in human gliomas.** *Cancer Res* 1993, **53:**5605–5609.
35. Watanabe K, Tachibana O, Sato K, *et al.*: **Overexpression of the EGF receptor and p53 mutations are mutually exclusive in the evolution of primary and secondary glioblastomas.** *Brain Pathol* 1996, **6:**217–224.
36. Ekstrand AJ, Sugawa N, James CD, *et al.*: **Amplified and rearranged EGFR genes in human glioblastomas reveal deletions of sequences encoding portions of the N-and/or C- terminal tails.** *Proc Natl Acad Sci U S A* 1992, **89:**4309–4313.
37. Tang P, Steck PA, Yung WK: **The autocrine loop of TGF-a/EGFR and brain tumors.** *J Neurooncol* 1997, **353:**303–314.
38. Fujisawa H, Kurrer M, Reis RM, *et al.*: **Acquisition of the glioblastoma phenotype during astrocytoma progression is associated with loss of heterozygosity on 10q25-qter.** *Am J Pathol* 1999, **1552:**387–394.
39. Reifenberger G, Liu L, Ichimura K, *et al.*: **Amplification and overexpression of the MDM2 gene in a subset of human malignant gliomas without p53 mutations.** *Cancer Res* 1993, **53:**2736–2739.
40. Black P, Westphal M: **Growth factors in brain tumors.** *J Neurooncol* 1997, **353:**193–372.
41.•• Reifenberger G, Kros JM, Burger PC, *et al.*: **Oligodendroglial tumors.** In *Pathology and Genetics: Tumours of the Nervous System.* Edited by Kleihues P, Cavenee WK: Lyon, France: IARC Press, 2000:55–70.

Excellent review of the histopathology, characteristics, and molecular genetic abnormalities associated with oligodendroglial tumors.

42. Bello MJ, Leone PE, Nebreda P, *et al.*: **Allelic status of chromosome 1 in neoplasms of the nervous system.** *Cancer Genet Cytogenet* 1995, **83:**160–164.
43. Ransom DT, Ritland SR, Kimmel DW, *et al.*: **Cytogenetic and loss of heterozygosity studies in ependymomas, pilocytic astrocytomas and oligodendrogliomas.** *Genes Chromosomes Cancer* 1992, **5:**348–356.
44. Reifenberger J, Reifenberger G, Liu L, *et al.*: **Molecular genetic analysis of oligodendroglial tumors shows preferential allelic deletions on 19q and 1p.** *Am J Pathol* 1994, **145:**1175–1190.

45. von Deimling A, Louis DN, von Ammon K, *et al.*: **Evidence for a tumor suppressor gene on chromosome 19q associated with human astrocytomas, oligodendrogliomas, and mixed gliomas.** *Cancer Res* 1992, **52:**4277–4279.
46. Yong WH, Chou D, Ueki K, *et al.*: **Chromosome 19q deletions in human gliomas overlap telomeric to D19S219 and may target a 425 kb region centromeric to D19S112.** *J Neuropath Exp Neurol* 1995, **54:**622–626.
47. Bello MJ, Leone PE, Vaquero J, *et al.*: **Allelic loss at 1p and 19q frequently occurs in association and may represent early oncogenic events in oligodendroglial tumors.** *Int J Cancer* 1995, **643:**207–210.
48. Kraus JA, Koopmann J, Kaskel P, *et al.*: **Shared allelic losses on chromosomes 1p and 19q suggest a common origin of oligodendroglioma and oligoastrocytoma.** *J Neuropath Exp Neurol* 1995, **54:**91–95.
49. Bello MJ, Vaquero J, de Campos JM, *et al.*: **Molecular analysis of chromosome 1 abnormalities in human gliomas reveals frequent loss of 1p in oligodendroglial tumors.** *Int J Cancer* 1994, **57:**172–175.
50. Husemann K, Wolter M, Buschges R, *et al.*: **Identification of two distinct deleted regions on the short arm of chromosome 1 and rare mutation of the CDKN2C gene from 1p32 in oligodendroglial tumors.** *J Neuropathol Exp Neurol* 1999, **5810:**1041–1050.
51. Pohl U, Cairncross JG, Louis DN: **Homozygous deletions of the CDKN2C/p18INK4C gene on the short arm of chromosome 1 in anaplastic oligodendrogliomas.** *Brain Pathol* 1999, **9:**639–643.
52. Mai M, Huang H, Reed C, *et al.*: **Genomic organization and mutation analysis of p73 in oligodendrogliomas with chromosome 1p-arm deletions.** *Genomics* 1998, **51:**359–363.
53.•• Bigner SH, Matthews MR, Rasheed BK, *et al.*: **Molecular genetic aspects of oligodendrogliomas including analysis by comparative genomic hybridization.** *Am J Pathol* 1999, **1552:**375–386.
An excellent review of oligodendrogliomas, analyzed by comparing comparative genomic hybridization, cytogenetics, and molecular technologies.
54. Jeuken JW, Nelen MR, Vermeer H, *et al.*: **PTEN mutation analysis in two genetic subtypes of high-grade oligodendroglial tumors. PTEN is only occasionally mutated in one of the two genetic subtypes.** *Cancer Genet Cytogenet* 2000, **1191:**42–47.
55. Kros JM, Godschalk JJ, Krishnadath KK, *et al.*: **Expression of p53 in oligodendrogliomas.** *J Pathol* 1993, **171:**285–290.
56. Di Rocco F, Carroll RS, Zhang J, *et al.*: **Platelet-derived growth factor and its receptor expression in human oligodendrogliomas.** *Neurosurgery* 1998, **42:**341–346.
57. Smith JS, Wang XY, Qian J, *et al.*: **Amplification of the platelet-derived growth factor receptor-A PDGFRA. gene occurs in oligodendrogliomas with grade IV anaplastic features.** *J Neuropathol Exp Neurol* 2000, **596:**495–503.
58. Reifenberger G, Reifenberger J, Liu L, *et al.*: **Molecular genetics of oligodendroglial tumors.** In *Brain Tumor Research and Therapy.* Edited by Nagai M. Tokyo: Springer-Verlag; 1998:187–209.
59. Reifenberger J, Reifenberger G, Ichimura K, *et al.*: **Epidermal growth factor receptor expression in oligodendroglial tumours.** *Am J Pathol* 1996, **149:**29–35.
60. Chan AS, Leung SY, Wong MP, *et al.*: **Expression of vascular endothelial growth factor and its receptors in the anaplastic progression of astrocytoma, oligodendroglioma, and ependymoma.** *Am J Surg Pathol* 1998, **227:**816–826.
61. Nishikawa R, Cheng SY, Nagashima R, *et al.*: **Expression of vascular endothelial growth factor in human brain tumors.** *Acta Neuropathol Berlin* 1998, **965:**453–462.
62. Pietsch T, Valter MM, Wolf HK, *et al.*: **Expression and distribution of vascular endothelial growth factor protein in human brain tumors.** *Acta Neuropathol Berlin* 1997, **932:**109–117.
63. Maintz D, Fiedler K, Koopmann J, *et al.*: **Molecular genetic evidence for subtypes of oligoastrocytomas.** *Neuropathol Exp Neurol* 1997, **5610:**1098–1104.
64. Reifenberger J, Ring GU, Gies U, *et al.*: **Analysis of p53 mutation and epidermal growth factor receptor amplification in recurrent gliomas with malignant progression.** *Neuropathol Exp Neurol* 1996, **55:**822–831.
65. Ino Y, Zlatescu MC, Sasaki H, *et al.*: **Long survival and therapeutic responses in patients with histologically disparate high-grade gliomas demonstrating chromosome 1p loss.** *J Neurosurg* 2000, **92:**983–990.