Molecular Genetics of Brain Tumors

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As many as 40,000 patients are newly diagnosed each year as having brain tumors. About half of these are metastatic foci of tumors originating outside the central nervous system, while the other half are primary tumors of central nervous system tissues. These are a diverse group of neoplasms. Currently, primary brain tumors are classified in a manner that reflects their histological appearance and location. The identification of cancer as a disorder of genes, however, has opened the possibility of classifying tumors according to the genetic alterations that underlie their pathogenesis and that regulate their malignant behavior. Two major classes of genes critical for the development of all types of cancer, including brain tumors, are now recognized: tumor suppressor genes, which encode genes that function to inhibit cell proliferation and tumor development, and oncogenes, which encode proteins that stimulate proliferation and mediate biological activities important for invasion, neoangiogenesis, immune escape, and other characteristics of malignancy. While in most cases the specific pathways regulating tumor characteristics such as tumor neoangiogenesis and tissue invasion remain to be defined, recognition of the genetic changes characteristic of individual tumor types should provide opportunities to develop more effective, less toxic therapies.

Astrocytomas are the most common primary brain tumors in both children and adults. They are classified by grade based on such features as the presence of mitoses, necrosis, hypercellularity, nuclear and cytoplasmic atypia, and endothelial proliferation within the tumor. The identification of the genetic alterations commonly found in astrocytomas has led to the recognition that there may be a sequential series of genetic changes that are oftentimes, although clearly not always, associated with the enhanced degree of malignancy corresponding to increased clinical grade (Figure). In order of increasing malignancy, other astrocytic tumors are classified as astrocytoma, anaplastic astrocytoma, or glioblastoma multiforme (GBM). Pilocytic astrocytomas are of a particularly low histological grade and are frequently cured by surgery.

A tumor suppressor gene frequently implicated in the pathogenesis of astrocytoma is p53, located on chromosome 17p. The p53 protein has been found to influence multiple cellular functions including progression through the cell cycle, DNA repair after damage, genomic stability, and the tendency for a cell to undergo apoptosis following treatment. p53 Acts as a transcription factor to induce or repress the transcription of multiple genes through sequence-specific interaction with DNA. p53 mutations have been reported in approximately 40% of astrocytic tumors of all grades. These are found most commonly in gliomas occurring in young adults. In contrast, p53 mutations have not been observed in supratentorial astrocytic tumors of children, although they occur in brainstem gliomas of childhood. The prognostic implication of p53 mutations has not yet been defined clearly. It remains a strong candidate for being clinically significant, since p53 mediates the response of tumors to irradiation, which is an important modality of treatment for these tumors.
Pilocytic astrocytomas are generally benign and occur most frequently in the cerebellum or optic nerve of children. They usually do not progress to more malignant, high-grade tumors. Patients with neurofibromatosis type 1, which results from inactivation of the \textit{NF1} gene, have an increased frequency of pilocytic astrocytomas. Also, 20% of spontaneous pilocytic astrocytomas have a deletion of chromosome 17q (the location of the \textit{NF1} gene), although structural analysis of the \textit{NF1} gene in these tumors has not yet been reported. Deletion or mutation of the \textit{p53} locus is rare in pilocytic astrocytomas, although deletion of loci on chromosome 17p (the location of the \textit{p53} locus) has been reported in a small number of pilocytic astrocytomas. A second tumor suppressor locus on this chromosomal arm may be important in the pathogenesis of these tumors. Gains of chromosomes 7 and 8 have also been noted in some pilocytic astrocytomas.

In contrast to tumor suppressor gene mutations that result in the loss of function of proteins key for the inhibition of cell proliferation, the activation of oncogenes results in enhanced function leading to increased cell proliferation. Amplification is a frequent mechanism by which oncogenes are activated. Gene amplification is a manifestation of genetic instability, an important characteristic of many if not all cancers. Recently, the development of a new technology, comparative genomic hybridization, which characterizes the copy number of long stretches of DNA along tumor cell chromosomes, has led to the recognition that there is much more gene amplification in astrocytic brain tumors than previously appreciated.\textsuperscript{3} The \textit{EGFR} (epidermal growth factor receptor) gene is the gene most frequently found to be amplified in malignant astrocytomas.\textsuperscript{6} \textit{EGFR} encodes a protein that functions as a receptor for the epidermal growth factor, an important growth stimulant for astrocytes. Amplification of a mutated \textit{EGFR} allele is infrequently found in low-grade astrocytomas but is detectable in about one third of glioblastomas, especially those occurring in elderly patients. Numerous other genes have been found to be amplified occasionally in individual astrocytic tumors, but few have been found to be frequently affected. These include \textit{CDK4} and \textit{MDM2} that are amplified in approximately 10% to 15% of astrocytic tumors. Point mutations that result in the expression of an activated gene product have only rarely been reported. Recently recognized chromosomal regions frequently amplified in high-grade astrocytomas and in which no known oncogenes are located include 1q, 9q, and 12q.

**OLIGODENDROGLIOMA**

Oligodendrogliomas are uncommon gliomas (<10% of all intracranial tumors) that appear to arise from oligodendrogial cells. Cytogenetic studies have indicated that the genetic alterations associated with these tumors are distinctive from those that are found in astrocytic tumors. Oligodendrogliomas characteristically exhibit a loss of chromosomal regions on 1p and 19q.\textsuperscript{13} Other chromosomal regions sometimes lost from oligodendrogliomas include 1p36, 9p, and 22, and there is frequently evidence of increased numbers of chromosome 7 in these tumors. Other molecular genetic events common in astrocytic tumors seem...
to be rare in oligodendrogliomas; p53 mutations and EGFR amplification are almost never present. LOH for chromosome 9p loci, observed in some oligodendrogliomas, suggests the possible loss of the p16 locus.

**MENINGIOMAS**

Meningiomas are tumors that arise from the dura, the membrane that encloses the brain, and are almost invariably benign. Elderly patients are more frequently affected and women more often than men. Patients with neurofibromatosis type 2 may be affected by multiple meningiomas and bilateral vestibular schwannomas. The gene that encodes the propensity of patients to develop neurofibromatosis type 2, NF2, is located on chromosome 22q12. The protein product of the NF2 gene, known as merlin, is a cytoskeletal protein. Most reported NF2 mutations to date predict a truncated protein product. Deletion of loci on chromosome 22q occurs in approximately 30% of sporadic meningiomas, suggesting a role for NF2 in their development. Interestingly, mutations in NF2 are not found in dural hemangiopericytomas, a tumor sometimes considered a variant of classic meningioma. Amplification or high level expression of oncogenes and deletion or mutation of p53 appear to be infrequent events in meningioma. One exception may be expression of the ROS1 receptor tyrosine kinase oncogene, which has been reported in as many as 35% of meningiomas. Malignant meningiomas may be associated with deletion of loci on chromosome 1p and less commonly on 6p, 9q, 10q, 14q, and 17p. p53 mutations have also been reported in malignant meningioma.

**PRIMITIVE NEUROECTODERMAL TUMORS**

Primitive neuroectodermal tumors typically appear histologically as sheets of small round malignant cells with scant cytoplasm, and include a number of different pathologic entities that usually present during childhood. The most common chromosomal alteration in primitive neuroectodermal tumors is isochromosome (17q). Medulloblastomas are primitive neuroectodermal tumors that arise in the cerebellum, and these tumors occur in 2 inherited cancer syndromes, Turcot syndrome and basal cell nevus syndrome. Turcot syndrome is characterized by germline mutations of the APC gene in patients with adenomatous polyposis coli. Somatic mutations of APC have not been detected in sporadically occurring medulloblastomas; however, infrequent mutations of the β-catenin gene, which encodes a protein that interacts with the APC gene product in medulloblastomas, suggest strongly that this pathway is important in the pathogenesis of this tumor. Patients with basal cell nevus syndrome carry germline mutations of the PTCH gene at 9q22.3-9q31 and can develop medulloblastoma. Mutation of PTCH is also occasionally found in sporadic medulloblastoma, especially desmoplastic medulloblastoma. Cytogenetic studies of medulloblastomas have identified chromosome 17p as a frequent site of deletions, but this seems to involve a site telomeric to p53 at 17p13. p53 is rarely mutated in these tumors. Other molecular genetic changes sometimes found in medulloblastomas are deletions of chromosomes 2p, 6q, 8p, 10q, 11p, 11q, and 16q and rare amplifications of CMYC. Less information is available about primitive neuroectodermal tumors of the cerebral hemispheres and ependymomas, a related tumor that can be easily distinguished by its rather characteristic appearance. The most commonly described genetic alterations in ependymomas are deletions of 17p and monosomy 22.

**CONCLUSIONS**

Brain tumors arise as the result of progressive genetic alterations, and while our knowledge of the specific alterations critical for the development of any specific tumor type remains incomplete, a compelling picture of commonly occurring molecular genetic changes in gliomas is now available. Glioblastoma multiforme is the best described of these tumors, and testable models to describe the development of these tumors have been proposed. Histologically distinguishable entities that were first described many decades ago can now be recognized as corresponding to genetically distinct entities. Further molecular genetic characterization of brain tumors is likely to reveal new nosological entities and based on these, more specific therapies.

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