Molecular pathogenesis of childhood brain tumors

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Summary

In the last decade, the molecular biology revolution has advanced considerably. These advances have enhanced our understanding of the genetic underpinnings of human brain tumors in general, and pediatric brain tumors in particular. We now know that many pediatric brain tumors arise from disturbances in developmentally regulated signaling pathways. The medulloblastoma, a tumor in which the developmental Hedgehog and WNT pathways have gone awry, is a prime example of this. New techniques in genetic engineering have allowed for the creation of sophisticated mouse models of brain tumors that recapitulate the human disease. Many laboratories are now using cDNA microarrays to study the expression level of thousands of genes that may be aberrantly expressed in brain tumors when compared to normal control cells. In the next decade, the use of several new molecular techniques to establish brain tumor diagnoses will likely become standard tools in the diagnostics and treatment stratification of children with central nervous system tumors.

Introduction

Our understanding of the pathogenesis of childhood brain tumors has advanced considerably over the past 20 years. While this advancement can be ascribed in part to knowledge that has been acquired for other tumors or cancers in which various oncogenes and tumor suppressor genes are known contributors, it can also be stated with some confidence that certain childhood brain tumors have specific or unique genetic alterations that have been uncovered through detailed analysis of the molecular genetics of these neoplasms. In this report, we will review the salient features of the molecular pathogenesis of the most common childhood brain tumors including primitive neuroectodermal tumors (PNETs)/medulloblastomas, astrocytomas, ependymomas, choroid plexus tumors, and atypical teratoid/rhabdoid tumors.

Primitive neuroectodermal tumors – medulloblastomas

PNETs represent the most frequent malignant brain tumors in childhood. They are composed of primitive neural cells resembling immature progenitor cells. Some PNETs can show signs of differentiation along neuronal, glial, myogenic and rarely melanocytic or retinal lineages [1]. The prototype PNET is the medulloblastoma of the cerebellum. In the last years crucial genetic steps contributing to the molecular pathogenesis of this entity have been identified.

A possible causative agent for the development of medulloblastoma currently under discussion is infection with polyoma viruses especially JC virus. In a recent study, virus genomic sequences have been detected in medulloblastomas as well as large T-protein, an oncogenic virus product [2]. In fact, medulloblastomas can be induced in hamsters...
when JC virus is inoculated into the brains [3,4]. In other studies, however, JC virus was not detectable in a significant fraction of PNETs [5–7]. Therefore, the significance of JC virus infection as a causative agent in human medulloblastomas is still unclear.

Genetic aberrations are believed to contribute to the pathogenesis of medulloblastomas. Initial cytogenetic and molecular genetic studies identified several genetic aberrations including losses of chromosomes 1, 9, 10, 11, 16 and 17 [8–13]. Later, these data were supported by the analysis of tumors by comparative genomic hybridization [14–21]. Approximately 10% of the medulloblastomas carry double minute chromosomes as a cytogenetic sign of amplification of the C-MYC or N-MYC genes [22–24]. The large cell/anaplastic medulloblastoma variants which are associated with bad outcome have a high incidence of MYC gene amplification [25]. Although this aberration is relatively rare, it was found to represent a predictor for bad clinical outcome [26,27]. Loss of chromosome 17p is the most frequent finding in medulloblastomas present in up to 50% of the cases, in many tumors related to the occurrence of an isochromosome 17q [8]. This suggests the presence of one or more medulloblastoma-related tumor suppressor gene(s) on chromosome arm 17p [28–30]. The TP53 tumor suppressor gene frequently mutated in astrocytic gliomas was found to be affected only in a small proportion of medulloblastomas [31–33]. Recently, the HIC-1 tumor suppressor gene encoding a transcription factor and located on 17p13.3 has been found inactivated by hypermethylation in the majority of cases [34]. The functional significance of this finding is still unclear. Interestingly, chromosome 17 alterations are mostly present in medulloblastoma of the classic (non-nodular) type but are absent in most nodular/desmoplastic type medulloblastomas. In the latter type, loss of chromosome 9q and inactivation of the PTCH tumor suppressor gene has been described [35,36]. This finding as well as an elegant study of mRNA expression profiles [37] has led to the hypothesis of two distinct entities of medulloblastomas (Figure 1). The variants of medulloblastomas seem to differ in their clinicopathological and genetic features, their cell of origin, and also in molecular

![Diagram of the histogenesis of medulloblastoma (MB) variants](image)

Figure 1. Hypothetical diagram of the histogenesis of medulloblastoma (MB) variants. The most common classic variant is characterized by frequent alterations of chromosome 17 while the desmoplastic subtype shows frequent activation of the hedgehog pathway. While the latter variant is believed to be derived from external granule cell precursors the cellular origin of classic type, which is mostly located in the midline, is still under discussion but may be the ventricular matrix. There seems to be a continuum from the classic to the anaplastic variant, with the latter frequently displaying MYC gene amplification. Medulloblastoma with extensive nodularity represents a variant of the desmoplastic type medulloblastomas in young children and is associated with good prognosis.