Molecular Pathology of the Central Nervous System

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TUMORS OF THE CENTRAL NERVOUS SYSTEM (CNS)

Overview

- While morphologic and immunohistochemical evaluations remain the gold standard in the diagnosis of CNS neoplasms, molecular techniques and cytogenetic analysis are serving an expanding role in supplementing the classification of the more difficult and challenging cases.
- The recent findings that certain genetic alterations may influence the survival or therapeutic responsiveness of some CNS neoplasms, add a whole new dimension to the significance of ancillary molecular testing in these tumors.
- More importantly, the discovery of new candidate genes in CNS tumors may allow for molecular-targeted therapy (so-called gene therapy), which in theory is more specific to tumor cells and less toxic to normal cells.
- Among the most commonly utilized techniques in the genetic characterization of CNS neoplasms, are fluorescence in situ hybridization (FISH), loss of heterozygosity (LOH), and comparative genomic hybridization (CGH).
- Gene expression profiling of CNS tumors by cDNA macroarrays provides genetic fingerprinting, which promises to serve both a diagnostic and therapeutic role.

GLIAL TUMORS

Astrocytomas

- General molecular concepts in diffuse (fibrillary) astrocytomas:
  - Definition:
    - A group of diffusely infiltrative gliomas characterized by astrocytic features and variable expression of glial fibrillary acidic protein (GFAP). They are the most common (~40%) among primary CNS neoplasms and encompass a heterogeneous group of neoplasms (Table 1).
    - Diffuse astrocytomas, particularly glioblastoma, have been the most studied human gliomas in the past two decades.
  - Genetic susceptibility:
    - Several inherited tumor syndromes impose an increased susceptibility to developing astrocytomas; these include:
      - Li-Fraumeni syndrome and TP53 germline mutations syndrome: chromosome 17q11/17p13
      - Turcot syndrome: chromosome 5q21 (APC), 3q21 (MLH1), or 7p22 (PMS2)
      - Tuberous sclerosis (TS [TSC1: 9q34; TSC2: 16p13])
      - Neurofibromatosis type 1 (NF1): chromosome 17q11
      - Neurofibromatosis type 2 (NF2): chromosome 22q12
      - Retinoblastoma (RB): chromosome 13q14
      - Multiple enchondromatosis (Maffucci/Ollier disease)
  - Genetic alterations implicated in the pathogenesis of diffuse astrocytomas:
    - Tumor suppressor genes:
      - TP53 gene:
        - Maps to chromosome 17p13.1
        - TP53 is a transcriptional transactivator, which has various regulatory functions involving cell cycle, cell differentiation, apoptosis, angiogenesis, and DNA repair.
        - TP53 inactivation appears to be an early event in astrocytoma tumorigenesis and later progression toward secondary glioblastoma. Thus, the frequency of TP53 mutations does not significantly increase during malignant progression.
        - TP53 mutations are a genetic hallmark of secondary glioblastoma (>65%) and observed in >60% of grade II astrocytomas.
        - TP53 mutations are observed in ~25% of primary (de novo) glioblastomas.
        - The underlying mechanisms for TP53 mutations in primary vs secondary glioblastomas appear different.

<table>
<thead>
<tr>
<th>Table 1. Diffuse Astrocytomas and Their Corresponding WHO Grade</th>
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<tbody>
<tr>
<td>Fibrillary astrocytoma (low grade: grade II or anaplastic: grade III)</td>
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<tr>
<td>Gemistocytic astrocytoma (grade II or III)</td>
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<tr>
<td>Protoplasmic astrocytoma (grade II)</td>
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<tr>
<td>Glioblastoma (grade IV)</td>
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<td>Gliosarcoma (grade IV)</td>
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<td>Gliomatosis cerebri (grade III)</td>
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