Genetic Alterations of Nervous System Tumors

ROBERT L. MARTUZA¹

Introduction

The last decade has witnessed revolutionary advances in our understanding of the basic molecular changes associated with carcinogenesis in general and with nervous system tumorigenesis in particular. This report discusses the genetic alterations in nervous system tumors from two viewpoints. The first represents a summary of the descriptive changes that have been documented in various nervous system tumors. Here, the molecular and chromosomal changes associated with schwannomas, meningiomas, gliomas, and other nervous system tumors are described. These represent the naturally occurring genetic alterations associated with tumorigenesis and tumor progression. The second discusses alterations in tumor cells that may be purposefully induced in order to study their cellular biology or to test novel therapeutic approaches. This section represents a new era in tumor studies which is still in its elemental stages, but its impact could result in the development of new therapies for some tumors which are invariably fatal despite maximal conventional therapy.

Molecular Genetic Studies of Neurofibromatosis-2, Acoustic Neuroma, and Meningioma

Among the first central nervous system tumors to be studied using molecular genetic techniques was the acoustic neuroma. My colleagues and I initially chose this tumor for a variety of reasons: (1) we were interested in localizing and understanding the gene for neurofibromatosis-2 (NF2) [1], (2) we postulated that the gene associated with acoustic neuroma formation in NF2 would probably be the same gene associated with the much more common acoustic neuromas occurring unilaterally and sporadically in the general population, (3) meningiomas occur in NF2 and have been shown to have a loss of one copy of chromosome 22 in many instances [2] and thus became a candidate area for

¹Molecular Neurogenetics Laboratory, Massachusetts General Hospital, Charlestown, MA 02129, USA
Genetic Alterations of Nervous System Tumors

study (4) acoustic neuromas have such a low mitotic rate that they do not lend themselves to other approaches such as karyotypes which require cell division in culture, making direct molecular techniques essential, (5) acoustic neuromas are the most common Schwann cell tumors in humans (we operate on approximately one per week at the Massachusetts General Hospital), and (6) acoustic neuromas are histologically relatively pure masses of Schwann cells, thus contaminating cell populations present in some other tumors, such as neurofibromas or astrocytomas, are less likely to confound the results.

NF2 is a serious, debilitating autosomal dominant genetic disorder associated with bilateral acoustic neuromas (eighth cranial nerve schwannomas) in almost all cases as well as with other nervous system tumors such as meningiomas, spinal root schwannomas, and ependymomas in a variable number of cases [1]. Studies of DNA extracted from acoustic neuromas in the general population as well as from patients with NF2 tumors had demonstrated loss of genetic material on chromosome 22 but no losses on other chromosomes studied [3]. Similar results were obtained with other tumors in patients with NF2 tumors including spinal schwannomas [4]. This suggested that the locus associated with tumorigenesis in NF2 is on chromosome 22. Further linkage analysis study of a large kindred with NF2 demonstrated that the inherited locus of the NF2 gene is on the long arm of chromosome 22 [5,6]. Taken together, these studies have localized the NF2 gene (and the gene for acoustic neuromas in the general population) to the long arm of chromosome 22, with the mechanism appearing to be similar to that described for retinoblastoma. Thus, it is currently thought that the long arm of chromosome 22 contains a gene, NF2, which is involved with the growth suppression of Schwann cells (and others). Loss of function of both copies of this gene leads to tumor formation.

Meningiomas were next studied by this approach and also demonstrated loss of genetic material on the long arm of chromosome 22 [7]. However, other areas of genetic change have also been noted, most commonly on chromosome 14 and on the Y-chromosome in males [8]. This suggests the possibility that there may be an initiator locus for meningiomas on chromosome 22 as well as other progressor loci on other chromosomes. This also fits with the clinical data that indicate that whereas acoustic neuromas virtually never progress to become malignant, meningiomas may progress to become aggressive or even frankly malignant. Thus, further study of these progressor loci may have clinical relevance. Additionally, the chromosome 22 locus for meningiomas may not be identical with that for acoustic neuromas [9]. Once both are cloned, this issue will be finally resolved and the interactions of these two putative loci will be available for study.

Gliomas, Neurofibromas, Neurofibrosarcomas, and Neurofibromatosis-1

Gliomas are of even greater complexity and interest. Karyotype studies have demonstrated that the most common chromosomal abnormalities in human malignant gliomas are losses of chromosomes 10 and 22 and gains of chromo-