Astrocytoma Cell Line

TO THE EDITOR: It has long been established clinically that patients with neurofibromatosis Type 1 (NF1) have an increased susceptibility to develop many central and peripheral tumors. The nature of the genetic alterations underlying NF1 have recently begun to be characterized. It has been demonstrated that the *NF1* gene plays a critical role as a tumor suppressor and that patients with NF1 harbor mutations in the *NF1* gene, which codes for neurofibromin, a functional negative regulator of signal transduction through Ras. Neurofibromatosis Type 1 is an autosomal-dominant cancer predisposition syndrome in which 15 to 20% of affected individuals develop astrocytomas that are most commonly pilocytic.

The power of cell culture as a foundation of current molecular and cell biology is often not apparent to clinicians in the direct daily management of their patients. In the article by Kurimoto, et al. (Kurimoto M, Hirashima Y, Ogiichi T, et al: Establishment and characterization of a novel malignant astrocytoma cell line derived from a tumor removed in a patient with neurofibromatosis Type 1. *J Neurosurg 94:*301–308, February, 2001), the authors have established in tissue culture an immortalized cell line (TM-31) from a high-grade glioma in a patient with NF1. Although malignant glioma lines are established routinely in most laboratories in which intracranial tumors are studied, to date there has been no available established glioma line from a patient with NF1. This cell line offers a unique opportunity to study the genetic alterations, growth, and invasive characteristics in vitro.

Pilocytic astrocytomas of the optic nerve are closely associated with NF1, and allelic losses of the *NF1* gene region on chromosone 17q occur in sporadic pilocytic astrocytomas.[6] Loss of neurofibromin expression has been demonstrated to be an important primary genetic event in the pathogenesis of NF1-associated astrocytomas.[2,4] Because most of the pilocytic astrocytomas in these patients are clinically benign in nature, it is likely that such a loss is an early and primary event. Loss of neurofibromin expression is observed in the tumor and is associated with elevated levels of Ras-guanosine triphosphate (GTP),[4] results that support the role of neurofibromin as a critical GTPase activating protein (Ras-GAP) in the molecular pathogenesis of NF1 astrocytomas. The role of neurofibromin in the genesis of sporadic astrocytomas is less clear, with elevations of neurofibromin expression noted by some authors; this indicates a role of neurofibromin in attempting to reduce uncontrolled growth signals in these cells, which is perhaps less a primary pathological event in tumorigenesis but rather a secondary compensatory elevation in these tumor cells.[3,5] Last, a striking association has been observed between the presence of optic glioma and other central nervous system (CNS) tumors in NF1, which is an association not seen between optic glioma and non-CNS tumors in these patients, indicating that fundamental pathophysiological differences exist between patients with and without optic glioma.[1]

It is expected that the well-characterized line described herein will provide molecular insights into genetic alterations associated with gliomas in these patients, and perhaps through differential display methods we may ultimately learn how this tumor differs from gliomas that occur in patients without neurofibromatosis. Molecular profiling will ultimately shed light on potential mechanisms of tumorigenesis and hopefully offer windows into any therapeutic avenues in the treatment and/or prevention of these tumors in the susceptible host. The availability of the line to the American Type Culture Collection, Riken Gene Bank, and the Japanese Cancer Resource Bank should facilitate further characterization of the tumor by other investigators to achieve these goals.

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RESPONSE: We appreciate Dr. Couldwell's comments on our article. The TM-31 cell line is a novel astrocytoma cell line, which has been derived from a patient with NF1. This cell line is unique in several ways. First, the cell line shows decreased neurofibromin expression. Second, the TM-31 cell line has a resistance to drug-induced morphological differentiation. Third, this line is susceptible to a farnesyltransferase inhibitor (B1620). These observations might be important clues for understanding tumorigenesis in a patient with NF1, as well as the molecular biology and pathogenesis of astrocytomas. Although characterization of TM-31 cells has not been completed, the availability of this cell line is important for further studies. We will submit the TM-31 cell line to standard tissue culture repositories such as the American Type Culture Collection, the Riken Gene Bank, and the Japanese Cancer Resource Bank.

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