Neurofibromatosis type 1 (NF1) gene: Implication in neuroectodermal differentiation and genesis of brain tumors

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Abstract

The gene responsible for neurofibromatosis type 1 (NF1), a common autosomal dominantly inherited disease, has been isolated. A region of NF1 gene product has been demonstrated to share structural and functional similarities with the mammalian GTPase activating protein (GAP) and the yeast IRA proteins. Thus, the NF1 protein is thought to play a role in signal transduction by stimulating the conversion of the Ras protein from a GTP-bound active form to a GDP-bound inactive form. The increased risk of malignant tumors in neuroectodermal tissues of NF1 patients may be caused by disruption of growth and differentiation regulatory functions of the NF1 gene. A second type of the NF1-GAP related domain (NF1-GRD) transcript, which has an extra 21-amino-acid insert in the center of the previously reported first type transcript, has been described. This insert significantly changes the hydrophilicity and secondary structure of the central region of NF1-GRD, therefore, suggesting it also changes its function. Alternative splicing is the most likely mechanism by which these two types of transcripts arise. The NF1-GRD alternative splicing has been shown to be intimately involved in differentiation of neuroectodermal tissues. Aberrant regulation of the alternative splicing may contribute to tumor formation in neuroectodermal tissue.

Introduction

Recently, molecular genetic analyses have revealed that the genesis and progression of tumors are the results of accumulated changes in two major classes of growth-regulatory genes – the oncogenes and the anti-oncogenes [1]. Several sequential genetic alterations (i.e. the hyperactivation of growth-promoting genes and the inactivation of growth-constraining genes) appear to be required to direct cells toward the malignant phenotype. Although this notion was originally proposed in colorectal cell carcinogenesis, it follows that similar molecular pathways exist in the progression of nervous system tumors. In support of this, several significant genetic aberrations have been detected in glial cell tumors in brain [2] involving losses of chromosomes 17p, 9p, and 10, alterations of p53 gene, and amplification of EGF-receptor gene. However, the precise nature of the genetic cascade related to the genesis of the brain tumors remains elusive.

Genetic events underlying the development of diverse cell types of brain tumors are not limited only to alterations of oncogenes and anti-oncogenes. Abnormal regulation of cell differentiation-related genes is potentially an important factor for induction or maintenance of a malignant phenotype in specific brain tumors. Pediatric brain tumors, including medulloblastoma, neuroblastoma,
ependymoblastoma, and pineoblastoma, are phenotypically similar to primitive neuroectodermal cells seen in fetal tissue, suggesting that aberrant regulation of cellular differentiation is intimately involved in the development of some neuroectodermal tumors.

Genetic events which regulation differentiation of neuroectodermal cells are less well understood. The normal form of Ras protein is considered to play an intermediary role in signal cascades related to neuronal differentiation \[3, 4\]. However, the nature of the physiologic signals which regulate the activities of the Ras protein during differentiation remain to be elucidated. Recently, one gene which may play an important role in the pathway of Ras-related neuronal differentiation was identified; the neurofibromatosis type 1 (NF1) gene.

Neurofibromatosis type 1 (NF1), also called von Recklinghausen disease, is one of the most common autosomal dominantly inherited disorders, and results in several complex neuroectodermal abnormalities \[5, 6\]. Because this disease affects a large segment of the population across all ethnic groups, intensive efforts were focused on identifying the NF1 locus in human genome. As a result, the NF1 gene responsible for the genesis of NF1 was recently isolated \[7, 8\].

DNA sequence analysis of the NF1 cDNA disclosed a clue to the biological character of this gene product. A 360-residue region of the NF1 gene product has significant homology with the catalytic domains of both mammalian GTPase-activating proteins (GAP) and yeast IRA proteins \[9\]. The mammalian GAP and yeast IRA proteins are known to interact with the Ras gene product and consequently inactivate its function \[10–13\]. This evidence implies that the NF1 gene plays a role in signal transduction by interacting with either the Ras gene product or a Ras-like protein, thereby closely linking the NF1 gene to cell growth and differentiation.

In this article we review the current understanding of the molecular basis of the NF1 gene, and discuss its implication in neuroectodermal differentiation based on our recent data. Furthermore, we propose the involvement of the NF1 gene in the genesis of brain tumors.

### General overview

Neurofibromatoses are genetic disorders which primarily affect both proliferation and differentiation of cells of neuroectodermal origin. Riccardi has proposed a classification which includes seven distinct categories of neurofibromatosis \[6\]. However, this classification has not been widely accepted because type III (mixed form), type IV (variant form), and type VII (late onset forms) are not defined sufficiently to presently allow their general clinical use. Currently, only two distinct categories are commonly recognized. Neurofibromatosis type 1 (NF1), which was formerly known as von Recklinghausen disease or peripheral type neurofibromatosis, is one of the most common autosomal dominantly inherited disorders. Its incidence of about 1 in 3500 individuals shows no predilection for race or sex \[5, 6\]. The mutation rate is estimated to be approximately 1 in 10,000 gametes per generation \[14\]; almost 50% of the cases of NF1 are non-familial and thus considered sporadic \[6\]. This is one of the highest spontaneous mutation rates described in humans \[6\]. NF1 patients display a broad range of clinical features. Characteristic manifestations are neurofibromas, dark skin pigmentation called café au lait spots, mental retardation, Lisch nodules of the iris, and an increased risk of malignant tumors of the nervous system. The degree of expression is variable, but some manifestations of the disorder are progressive and cause significant morbidity and mortality. Familiarity with NF1 extends to society through the classic story of 'The Elephant Man'. In this well known play and film the title character, Joseph Merrick, suffered from a disfiguring condition reported to be von Recklinghausen disease. (Today his disease is actually thought to be another more disfiguring condition called Proteus syndrome.)

Neurofibromatosis type 2 (NF2), which was previously known as bilateral acoustic neurofibromatosis or central type neurofibromatosis, is also an autosomal dominantly inherited disorder occurring in about 1 in 50,000 individuals \[15\]. Bilateral acoustic nerve tumors are the most characteristic feature of this disease. Spinal and other intracranial tumors are also commonly seen in NF2 pa-