Frequent Somatic Mutation of the MTS1/CDK4I (Multiple Tumor Suppressor/Cyclin-dependent Kinase 4 Inhibitor) Gene in Esophageal Squamous Cell Carcinoma

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Abstract

We previously reported frequent loss of heterozygosity on chromosome 9p in esophageal carcinomas and suggested that a tumor suppressor gene located on this chromosomal arm might be involved in development of these cancers. Since recently published studies have shown that a gene mapped on chromosome 9p21, MTS1/CDK4I (multiple tumor suppressor 1/cyclin-dependent kinase 4 inhibitor), is frequently mutated in various types of tumors, we chose to examine esophageal squamous cell carcinomas for mutations in this candidate gene. DNA sequence analyses revealed somatic mutations of MTS1/CDK4I in 14 of 27 tumors examined; 8 were frame-shift mutations and 6 were missense mutations. These results suggested that the MTS1/CDK4I gene is a tumor suppressor the inactivation of which plays an important role during carcinogenesis of the squamous cell type of esophageal carcinoma.

Introduction

Recent advances in molecular biology have revealed that the genesis and/or progression of tumors is due to accumulation of multiple genetic alterations, including inactivation of tumor suppressor genes and/or activation of protooncogenes (1-3). However, the molecular features of ESC have remained unclear; the somatic mutations found thus far in this type of tumor have been limited to inactivation of the p53 gene (4) and amplification of the cyclin D gene (5).

We previously reported an allelotype study of ESC which indicated that putative tumor suppressor genes on chromosomal arms 3p, 5q, 9p, 9q, 10p, 13q, 17p, 17q, 18q, and 21q might be associated with carcinogenesis in the esophagus (6). We were especially interested in 3p, 9p, and 9q with reference to ESC, because cyogenetic and molecular abnormalities in these chromosomal regions are frequently noted in squamous cell tumors of the esophagus, lung, head, and neck (7-9).

A putative tumor suppressor gene, MTS1/CDK4I, was isolated recently and mapped on one of these candidate loci, at 9p21 (10, 11). Mutations of MTS1/CDK4I have been reported in melanoma cell lines and in lymphoblastoid cell lines derived from dysplastic nevus syndrome (10, 11). Therefore, we considered it a candidate gene for ESC and looked for somatic mutations in 27 ESCs. Here we present evidence that inactivation of MTS1/CDK4I does play a significant role during esophageal carcinogenesis.

Results and Discussion

We have examined exon 2 of the MTS1/CDK4I gene, which covers the majority of the coding region, in esophageal tumors by the DNA-sequencing method. Fig. 1 shows two examples of results that revealed MTS1/CDK4I mutations; in case 111, a missense mutation at codon 66 resulting in a change from aspartic acid to asparagine is clearly observed; in case 117, extra bands indicate deletion of one base at codon 97. The experiments were repeated to confirm these genetic alterations. Comparisons of these DNA sequences with DNA from corresponding normal tissues confirmed that the changes were somatic events. A total of 14 somatic mutations of the MTS1/CDK4I gene were detected among 27 tumors examined as shown in Table 1. Among them, 8 were frame-shift mutations due to deletion of 1, 2, or 50 base pairs, and 6 were missense mutations. The results clearly indicated that inactivation of the MTS1/CDK4I gene plays an important role in development or progression of ESC.

We venture to predict that allelic deletions on 9p21 and on 17p at the p53 locus occur during transformation of precancerous dysplastic cells to cancer cells in the esophagus, as p53 mutations do in colorectal carcinoma (3). Because the protein encoded by MTS1/CDK4I, p16, has been proposed as a general inhibitor of cdk4 (10, 11) and p53 is thought to regulate S-phase entry through interaction with p21CIP1/WAF1 (13-17), loss of function with respect to G1 arrest seems to be necessary for progression of a precancerous lesion to malignancy. Inasmuch as other reported molecular aberrations in ESC include amplification of the cyclin D1 locus (PRAD1) (5, 18) and alteration of Rbl mRNA (19), accumulation of mutations among cell cycle regulators may be responsible for carcinogenesis and/or progression of ESC.

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1 To whom requests for reprints should be addressed.
2 The abbreviations used are: ESC, esophageal squamous cell carcinoma; MTS1, multiple tumor suppressor 1; CDK4I, cyclin-dependent kinase 4 inhibitor.

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