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Alterations in novel candidate tumor suppressor genes, *ING1* and *ING2* in human lung cancer

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Abstract. The *ING1* gene is involved in the regulation of the cell cycle, senescence, and apoptosis and is a novel candidate tumor suppressor gene. *ING2*, another gene in the *ING* family, was identified and cloned. The functions of *ING1* and *ING2* largely depend on the activity of p53. To determine whether an alteration in these genes plays a role in carcinogenesis and tumor progression in lung cancer, we screened 30 human lung cancer cell lines and 31 primary lung cancer tumors for mutations in these genes using polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) and direct sequencing. Our findings failed to uncover any mutations in these genes. We also examined the expression of *ING1* and *ING2* in lung cancer cell lines that either had or lacked a *p53* mutation, and in a control bronchial epithelium cell line, using quantitative real-time reverse transcription-polymerase chain reaction (RT-PCR). *ING1* expression was up-regulated in all 7 lung cancer cell lines that had a *p53* mutation, while the expression of *ING2* was down-regulated in 6 of 7 lung cancer cell lines that had a p53 mutation. These results suggest that the *ING1* and *ING2* genes have different roles in lung carcinogenesis and progression, and the *ING2* gene may be an independent tumor suppressor candidate on *p53*.

Introduction

Human cancers develop as a result of the stepwise accumulation of multiple acquired genetic defects that include mutations in tumor suppressor genes. A mutation in the *p53* tumor suppressor gene is the most frequently identifiable defect in human cancers (1). Other candidate tumor suppressor genes have been cloned and are referred to as *ING* (2). *ING1*, which is located on chromosome 13q 33~34 (3) and was found to encode a nuclear protein, consists of exons 1a, 1b, and 2 (4). Four alternatively spliced transcripts of *ING1* encode *ING1a*, *ING1b*, *ING1c* and *ING1d* (4-6). *ING2* was cloned and mapped to human chromosome 4q35 by fluorescence *in situ* hybridization and radiation-hybrid analyses (GenBank accession no. AF053537) (7,8). Overexpression of *ING1* and *ING2* led to growth arrest in the G1 phase of the cell cycle and induced apoptosis in several cell types (2,8,9) that largely depend on the activation of p53 (8,10). ING family proteins contain a region that is homologous to plant homeodomain (PHD) finger domains and have been implicated in chromatin-mediated transcriptional regulation (2,11).

ING1 gene mutations are rare in many human cancers, and no report exists on *ING2* gene mutation analysis in human cancers. Reduced expression of the *ING1* gene has been reported in breast (12) and gastric cancers (13), and in lymphoid malignancies (14).

To determine whether alterations in the *ING1b* and/or *ING2* genes are involved in lung carcinogenesis, lung cancer cell lines and primary tumors were examined for such mutations using polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) and DNA sequence analysis. In addition, the expression of *ING1b* and *ING2* was analyzed in lung cancer cell lines using real-time quantitative reverse transcription (RT)-PCR.

Materials and methods

Tissue samples. Primary lung cancers (n=31) and matched control samples were obtained during autopsy of patients previously been admitted to the Fourth Department of Internal Medicine at the Nippon Medical School Main Hospital in Tokyo, Japan, and immediately frozen at -80˚C. The samples included 14 adenocarcinomas, 8 squamous cell carcinomas (SCCs), 6 small cell lung cancers (SCLCs), 2 large cell carcinomas, and 1 adenosquamous cell carcinoma.

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Table I. Sequence of the polymerase chain reaction (PCR) primer used for amplification of the indicated exons in *ING1b* and *ING2*.

Exon		Sense primer sequence	Antisense primer sequence
ING1b			
Exon 1		TGCAGTGCTATTTTTTGAGGGG	CGCCCCCGCCCATCCATCA
Exon 2	a	ACGCCTGTCCTTCTTGCCCC	CTTGCCGCTGTTGCCCGCTG
	b	TTCGAGGCGCAGCAGGAGCT	CTTGGCCTTCTTCTCCTTGGG
	c	CAGCAACCACGACCACGACG	TGAGCCCCACGCACGAGAAG
	d	CCTCCCCATCGACCCCAACG	ACATTTTACACTCCTTGCACCTCA
ING2			
Exon 1		TGCATGTGCGGCTGCTGGATG	TGTCACGGGAGAAAGGGAAG
Exon 2	a	CCTTGGAAATGTTGTGTCTGC	TTCTGGTTGGCTGGAATCC
	b	TGCTGAAAGTGAACGAGCCTC	TCCTATCATCTCCCCATAAGACAC
	c	AAAGAAACGCTCCAAGGC	CCCTTTAAAATGTGGATGGCC

Table II. Sequence of primer and probe used in the real-time reverse transcription-polymerase chain reaction (RT-PCR) indicated gene.

Gene	Sense primer sequence	Antisense primer sequence	Probe sequence
ING1b	CGAAATACCAAGAGATCCTGAAGG	TGCGCCCCGTCTGTCT	ACGAGTGCTACGAGCGCTTCAGTCG
ING2	GGACTACCTTGAGTGCGTGGA	TCGCAGCACAGACACGTTC	TCGCTGCCCCACGACATGCA
GAPDH	GAAGGTGAAGGTCGGAGTC	GAAGATGGTGATGGGATTC	CAAGCTTCCCGTTCTCAGCC

GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

Lung cancer cell lines. A total of 15 human non-small cell lung cancers (PC1, PC3, PC7, PC9, PC10, PC13, PC14, Lu65, A427, A549, NCI-H23, NCI-H157, NCI-H358, NCI-H441, and NCI-H520) and 15 human small cell lung cancers (Lu24, Lu130, Lu134, Lu135, Lu138, Lu139, Lu140, Lu141, NCI-H69, NCI-H82, NCI-H526, NCI-N230, NCI-N231, NCI-N417, and SBC5) were used for DNA analysis (15). The Lu24, Lu65, and Lu135 cell lines were provided by Dr Y. Shimosato and Dr T. Terasaki (National Cancer Center Research Institute, Tokyo, Japan). The NCI-N231, A549, A427, NCI-H358, NCI-H157, NCI-H23, NCI-H441, NCI-H520, NCI-H82, NCI-N417, NCI-H526, and NCI-H69 cell lines were obtained from the American Type Culture Collection (Rockville, MD) (16), while the PC1, PC3, PC7, PC9, PC10, and PC14 cell lines were obtained from Immuno-Biological Laboratories (Gunma, Japan). The Lu24, Lu130, Lu134, Lu138, Lu139, Lu140, Lu141, and SBC-5 cell lines were provided by Dr J. Yokota (National Cancer Center Research Institute). We also performed transcriptional studies on 8 lung cancer cell lines (NCI-N231, Lu65, A549, NCI-H69, Lu135, PC7, PC9, and PC14) and on a normal human bronchial epithelial cell line (BET2A; American Type Culture Collection, no. ATCC CRL-9443).

DNA and RNA isolation. Genomic DNA was extracted from tumor and normal cells by proteinase K treatment and phenol chloroform extraction using standard protocols. RNAs were prepared using standard protocols described previously (17).

Polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) analysis. PCR-SSCP analysis was performed as previously described (16,18). Each of the two exons of the *ING1b* and *ING2* genes was amplified separately using the PCR primers shown in Table I. PCR was performed using the Gene AMP XL PCR kit (Perkin-Elmer Corp./Roche, Branchburg, NJ), which was followed by 40 cycles of denaturation at 94˚C for 40 sec, annealing at 55˚C for 30 sec, and extension at 68˚C for 90 sec, with a final extension at 68˚C for 8 min. The PCR reaction mixture contained XL buffer with 110 μM $Mg(OAc)_2$, 200 μM deoxynucleotide triphosphate, 0.1 mM of each primer labeled with 5-IAF (Amersham Pharmacia Biotech, Uppsala, Sweden), 0.5 units of rTth DNA polymerase, and 25 ng of genomic DNA. The 5-IAF-labeled PCR products were denatured, cooled on ice, and loaded on neutral 6% polyacrylamide gels with or without 5% (vol/vol) glycerol. Following electrophoresis, the gels were analyzed using the FluorImager 595 (Amersham Pharmacia Biotech).

DNA sequence analysis. DNA sequence analysis was performed as previously described (16,18). Aberrant bands were cut from the gel and further amplified by PCR using sequencing primers with the M13 sequence (TGTAAAACG ACGGCCAGT) added to the appropriate PCR primers. PCR was performed as described above, and the products were purified and sequenced using a fluorescent automated sequencer (Perking-Elmer Corp./Applied Biosystem, Inc., Foster City, CA, USA).

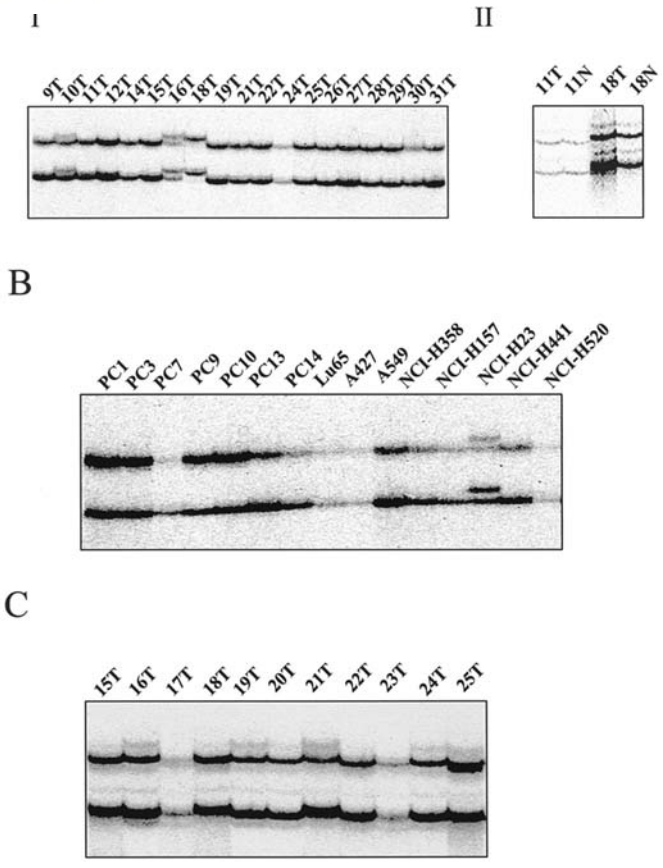

Figure 1. (A) PCR-SSCP analysis of exon 2 of the *ING1b* gene showed mobility shifts in lung cancer tissues [tumors (T) 10, 12, 16, and 18]. Tumor (T) and normal tissue (N) from case 18 showed similar patterns on PCR-SSCP. (B) PCR-SSCP analysis of exon 2 of the *ING1b* gene showed an aberrant band in lung cancer cell line NCI-H23. (C) PCR-SSCP analysis of exon 1 of the *ING2* gene showed mobility shifts in the lung cancer tissues of cases 15, 18, and 21.

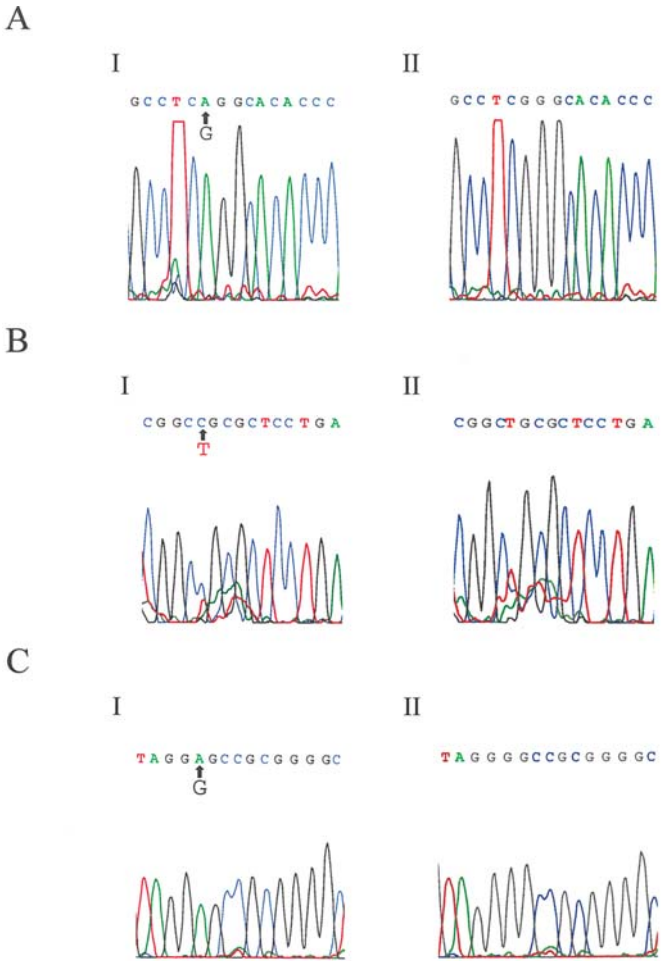

Figure 2. (A), Sequence analysis revealed a nucleotide substitution (G→A, serine to serine) at codon 173 of exon 2 of the *ING1b* gene in case 16. I, DNA sequence of case 16; II, control. (B) DNA sequence of exon 1 of the *ING2* gene revealed a nucleotide substitution (T→C, alanine to alanine) at codon 13. I, case 15; II, control. (C) DNA sequence of exon 1 of the *ING2* gene revealed a nucleotide substitution (G→A) 6 bp downstream of exon 1. I, case 15; II, control.

Real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR). RT quantitative-PCR was performed using the ABI Prism 7700 sequence detector (Perkin-Elmer Corp./Applied Biosystem, Inc.). The PCR primers and the Taq Man fluorescence probes (Table II) were designed using the Primer Express software program (Perkin-Elmer Corp./Applied Biosystem, Inc.). The total RNA sample (1 μg) was reverse transcribed using a random hexamer and a pre-amplification system (Life Technologies). A portion of each cDNA was used for quantitative PCR in a volume of 50 μl, and the reaction mixture contained the designed primers, Taqman probes, and Master Mix that included the PCR buffer, $MgCl_2$, dATP, dCTP, dGTP, dUTP, AmpErase UNG, and AmpliTaq Gold DNA polymerase (Perkin-Elmer Corp./Applied Biosystem, Inc.). PCR was carried out at 50˚C for 2 min, then 95˚C for 10 min, followed by 40 cycles at 95˚C for 15 sec and 60˚C for 1 min. The degree of gene expression was reported as the ratio of a given gene's mRNA in a particular sample to the level of *GAPDH* mRNA in that sample.

Results

Mutation analysis of the ING1b and ING2 genes in human lung cancers and lung cancer cell lines. PCR-SSCP analysis of exon 2 of the *ING1b* gene revealed aberrant bands in 6 of 31 lung cancer tissues (cases 5, 6, 10, 12, 16 and 18) with or without normal bands (Fig. 1A), and 1 of the 30 lung cancer cell lines i.e. NCI-H23, which is a non-small cell lung cancer (Fig. 1B). DNA sequence analysis of these bands revealed a G to A substitution at codon 173 (Fig. 2A), which does not result in an amino acid substitution. Matched normal tissues had these same aberrant bands, which suggested that they were due to polymorphisms. In exon 1 of the *ING2* gene, we detected aberrant bands in 6 of 31 lung cancer tissues (cases 5, 8, 12, 15, 18 and 21) with or without normal bands (Fig. 1C). Sequencing of these bands showed a T to C substitution at codon 13 (Fig. 2B) that did not alter the encoded amino acid, and a G to A substitution in the non-coding region of intron 1 of the *ING2* gene 6 bp downstream of exon 1 (Fig. 2C), which also appeared to be due to polymorphisms.

Expression of mRNA for ING1b and ING2 in human lung cancers and lung cancer cell lines. The expression of *ING1b* mRNA was up-regulated in 7 of 8 lung cancer cell lines compared to the human bronchial epithelium cell line,

Table III. *ING1b* mRNA levels in lung cancer cell lines.

cDNA	*ING1b/GAPDH*	Fold difference[a]
NCI-N231	6.743	6.643
Lu65	5.298	5.220
A549	1.490	1.468
NCI-H69	10.952	10.790
Lu135	5.710	5.626
PC7	14.297	14.086
PC9	2.241	2.208
PC14	2.281	2.247

[a]Fold difference, intensity of *ING1b* expression of sample/intensity of its expression in BET2A.

Table IV. *ING2* mRNA levels in lung cancer cell lines.

cDNA	*ING2/GAPDH*	Fold difference[a]
NCI-N231	0.382	0.288
Lu65	0.737	0.555
A549	0.340	0.256
NCI-H69	0.375	0.282
Lu135	0.381	0.287
PC7	0.280	0.211
PC9	0.086	0.065
PC14	0.491	0.370

[a]Fold difference, intensity of *ING2* expression of sample/intensity of its expression in BET2A.

Table V. *p53* status in lung cancer cell line.

Cell line	Type of mutation	Codon	Exon	Change
NCI-N231	Missense	298	8	GAG→TAG
Lu65	Missense	11	2	GAG→CAG
A549	Wild-type			
NCI-H69	Missense	171	5	GAG→TAG
Lu135	Missense	244	7	GGC→TGC
PC7	Missense	214	6	CAT→CGT
PC9	Missense	248	7	CGG→CAG
PC14	Missense	248	7	CGG→TGG

BET2A (Table III). All 7 cell lines with up-regulated *ING1b* mRNA had a *p53* mutation, and the remaining cell line expressed wild-type *p53*. The expression of *ING2* mRNA was down-regulated in 7 of 8 lung cancer cells (Table IV). Six of the 7 cell lines that had a *p53* mutation also showed reduced *ING2* mRNA expression. The mean relative intensity of *ING1b* and *ING2* expression (intensity of *ING* expression of sample/intensity of its expression in BET2A) was 6.036 (1.468-14.086) and 0.289 (0.065-0.555), respectively ($p<0.01$ using a paired t-test).

Discussion

Mutation of the *ING1* gene has previously been reported in neuroblastoma (2) and gastrointestinal cancer cell lines (13), breast tumors (12), esophageal squamous cell tumors (19), and head and neck squamous cell carcinomas (4). Although *ING1* gene mutations are rare in many human cancers, *ING1* expression is down-regulated in several types of human cancers including breast (12), gastric (13), esophageal (19), and lymphoid cancers (14). The *ING1* gene may serve as a type II tumor suppressor since it inactivates cellular function at transcriptional and post-transcriptional levels (20).

We studied the degree of mutation and expression of the *ING1b* and *ING2* genes in human lung cancer cell lines and tumors. No point mutations in the *ING1b* and *ING2* genes were found in human lung cancers. However, we did observe a single polymorphism at codon 173 (G-to-A) in exon 2 of the *ING1b* gene. This polymorphism has previously been reported in Indian patients with oral squamous cell carcinoma (21) and Japanese breast cancer patients, but not in Canadian cancer patients (12). We also detected a single polymorphism in exon 1 and intron 1 of the *ING2* gene. There were differences in the frequency of polymorphisms between cancer tissues and cell lines in this study. The cancerous tissues were obtained from Japanese patients, while the cell lines were nearly all established in the U.S. Thus, this polymorphism may be more frequent in Japanese patients.

ING proteins have a PHD finger motif that plays a role in chromatin remodeling (11,22), and nuclear localization sequences (NLS) and nucleolar targeting sequences (NTS) (23) that can target ING proteins to nucleoli when ING proteins are overexpressed. One such protein, *ING1b*, has been shown to bind to proliferating cell nuclear antigen (PCNA) through the PCNA-interacting protein (PIP) domain after DNA damage, and to regulate the induction of apoptosis (24) and enhance the repair of UV-damaged DNA (25). This protein contains histone acetyltransferase (HAT) (26-29) and histone deacetyltransferase (HDAC) (30,31). On the other hand, *ING1a* was shown to inhibit histone acetylation by binding to HDAC1 complexes (29). These findings suggest that *ING1b* may regulate the switch from DNA replication to DNA repair.

Previous studies reported that *ING2* mRNA expression was up-regulated in human colon cancers (7). By Western blot analysis, the expression of ING2 protein was found to be diminished in colorectal and hepatocellular carcinomas, and prostate and pancreatic cancers (8). *ING2* was shown to negatively regulate cell proliferation through the induction of *p53* acetylation at lysine 382 (8), and activation of *p53* by acetylation reportedly resulted in the induction of growth inhibitor genes and proteins that activated the mitochondrial apoptotic pathway through the release of cytochrome C (32). In this study, *ING2* mRNA expression was found to be primarily down-regulated in lung cancer cell lines. Previous studies have reported that the overexpression of *ING1b* and *ING2* negatively regulated cell growth through the induction of apoptosis and G1-phase cell cycle arrest in a *p53*-dependent manner (2,8,9). It is interesting that lung cancer cells with inactivated p53 had reduced expression of the *ING2* gene in our study (Table V). It has been reported that

ssion of *ING1* and *ING2* was independent of *p53* (33).

Our results suggest that mutations in the *ING1b* gene are rare, and its mRNA expression is primarily up-regulated in lung cancers. Inactivation of the *p53* gene in lung cancers may play a role in the overexpression of the *ING1b* gene. Our results suggest that the inactivation of *ING2* may play an important role in the development and/or progression of lung cancer, even in cancers that exhibit a *p53* mutation. Since the *ING2* gene was not mutated in these cancer cells, the *ING2* gene may have been negatively transcriptionally regulated, possibly as a result of hypermethylation of the gene promoter or transcriptional factor.

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