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Association of *CYP1A1* Germ Line Polymorphisms with Mutations of the *p53* Gene in Lung Cancer[1]

Kaname Kawajiri,[2] Hidetaka Eguchi, Kei Nakachi, Takao Sekiya, and Mitsunobu Yamamoto

Departments of Biochemistry [K. K., H. E.] and Epidemiology [K. N.], Saitama Cancer Center Research Institute, and Department of Thoracic Surgery, Saitama Cancer Center Hospital [M. Y.], 818 Komuro, Ina-machi, Kitaadachi-gun, Saitama 362, and Oncogene Division, National Cancer Center Research Institute, 1–1, Tsukiji 5-chome, Chuo-ku, Tokyo 104 [T. S.], Japan

ABSTRACT

We reported an association of smoking-induced lung cancer susceptibility with the human cytochrome P450 1A1 (*CYP1A1*) polymorphisms in our previous studies. To investigate a relationship between genetically determined individual predispositions and mutations of target genes in the early stage of lung carcinogenesis, we examined *p53* mutations in relation to germ line polymorphisms of the *CYP1A1* and *GSTM1* genes, using surgical specimens of 148 non-small cell lung cancer patients who were smokers. The frequency of *p53* mutations among heavy smokers was higher than in patients who had never smoked [$P < 0.01$; odds ratio (OR), 3.74; 95% confidence interval (CI), 1.46–9.56]. By single-strand conformational polymorphism, aberrant migration bands of *p53* gene fragments were detected in 56 cases (38%). Smokers with susceptible rare homozygous alleles of either the *MspI* or *Ile-Val* polymorphism of the *CYP1A1* gene have a 4.5-fold ($P < 0.005$; OR, 4.48; 95% CI, 1.64–12.26) or 5.5-fold ($P < 0.01$; OR, 5.52; 95% CI, 1.55–19.64) higher risk of having a mutation of the *p53* gene than those with nonsusceptible predominant homozygous alleles of the gene. Non-small cell lung cancer patients with a susceptible *CYP1A1* genotype were at remarkably high risk of having a mutation of the *p53* gene when the genotype was combined with a deficient genotype, *GSTM1(−)*. However, there was no difference between the types of *p53* mutation and genotypes of the drug-metabolizing enzymes. These results showed that *CYP1A1* germ line polymorphisms, which were associated with the genetic predisposition for lung cancer, were related to cigarette smoking-associated *p53* mutations.

INTRODUCTION

Human lung carcinogenesis usually requires exposure to the procarcinogens that are contained mainly in cigarette smoke, and many aromatic hydrocarbons, such as benzo(*a*)pyrene, first require metabolic activation by CYP1A1[3] to their ultimate DNA-binding, mutagenic, or carcinogenic forms (1, 2). Activated metabolites of benzo(*a*)pyrene are subjected in part to metabolic detoxication by GSTM1 (3). Thus, the expression and catalytic activity of CYP1A1 and GSTM1 enzymes in the lung and their metabolic balance may be an important determinant host factor underlying lung cancer (4–6).

It is an established fact that genetic variations of these drug-metabolizing enzymes exist within a human population, leading to interindividual differences in metabolic capacity (4–6). In our previous reports, we showed that high susceptibility to lung cancer is associated with two mutually linked polymorphisms (*MspI* and *Ile-Val* polymorphisms) of the *CYP1A1* gene (7–9). This genetically derived difference in lung cancer susceptibility has depended on the cigarette dose, showing a high relative risk at a low dose level of cigarette smoking for individuals with susceptible genotypes (10). Furthermore, individuals with a susceptible *CYP1A1* genotype were shown to be at remarkably high risk when the genotype was combined with a deficient *GSTM1* genotype, *GSTM1(−)* (11, 12). The functional significance of the polymorphic human *CYP1A1* gene may be associated with the inducible expression or different catalytic activity of the CYP1A1 enzyme (9, 13, 14). The *GSTM1(−)* genotype was associated completely with deficient GSTM1 enzyme activity (15).

Multiple genetic lesions either activating dominant oncogenes or inactivating tumor suppressor genes have been characterized in human lung cancer(16–18). In NSCLC, dominant oncogene activation includes a *Ki-Ras* mutation, predominantly in adenocarcinoma, and deregulation of growth factor receptor genes. On the other hand, suppressor genes on chromosomes 3p, 13q (*RB* gene) and 17p (*p53* gene) are affected frequently by deletions or mutations, resulting in inactivation of the gene products. Among such genetic alterations, mutations of the *p53* gene seem to be the most common genetic changes in lung cancer, existing in about 60% with squamous carcinoma and 30% with adenocarcinoma (19–22). A crucial role of the *p53* gene, which regulates cell cycle-related genes as a transcription factor (23), is also underscored by the finding that wild-type p53 suppresses the growth of human lung cancer cell lines bearing other-multiple-genetic lesions (24).

However, there is no clear understanding of the mechanisms of genetic predisposition to lung cancer. Lung carcinogenesis seems to start from a clonal expansion of the cells that gained a selective growth advantage by early genetic changes in the cells. Because the committed stem cells in the lung are exposed widely to environmental carcinogens, such as benzo(*a*)pyrene in cigarette smoke, early genetic lesions may be present in normal-appearing bronchial mucosa; the progression toward full tumorigenicity then would be acquired through accumulation of further genetic alterations. Thus, genetic predisposing factors to smoking-induced lung cancer, such as *CYP1A1* and *GSTM1* polymorphisms, may affect the mutational frequencies of target genes in early genetic alterations. To date, somatic alteration of the *p53* gene seems to be a candidate in the precancerous genetic event found in both metaplastic and dysplastic lesions of the lung (25, 26). Furthermore, it has been suggested that the incidence of *p53* mutations is associated with lifetime cigarette consumption (22, 27). Mutations of the *p53* gene in lung tumor DNA are scattered over many codons, and G to T transversions are observed most frequently (19, 20, 27), indicating that benzo(*a*)pyrene in cigarette smoke may be involved as a mutagen of the *p53* gene (28–30). Thus, it will be essential in understanding lung carcinogenesis to investigate whether the mutation frequency of the *p53* gene in the lung tumor is influenced by lung cancer predisposition factors, such as *CYP1A1* and *GSTM1* polymorphisms. In this article, we show first that the mutation frequency of the *p53* gene is associated with cigarette smoking. We then found that *CYP1A1* germ line polymorphisms are related to cigarette smoking-associated *p53* mutations.

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[2] To whom requests for reprints should be addressed, at Department of Biochemistry, Saitama Cancer Center Research Institute, 818 Komuro, Ina-machi, Saitama 362, Japan. Fax: 81-48-722-1739; E-mail: Kawajiri@Saitama-cc.go.jp.

[3] The abbreviations used are: CYP1A1, human cytochrome P450 1A1; SSCP, single-strand conformational polymorphism; GSTM1, glutathione *S*-transferase Mu-1; NSCLC, non-small cell lung cancer; OR, odds ratio; CI, confidence interval.