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Genetic Polymorphism of CYP2A6 as a Key Factor Determining the Risk of Tobacco-related Cancers

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During the course of pharmacokinetic studies of SM-12502 which was under development as an anti-PAF (platelet-activating factor) agent, we found three subjects who showed a slow metabolic phenotype in its pharmacokinetics. After extensive studies, we found that this compound was S-oxidized specifically by CYP2A6. Thus, we analyzed the genes for CYP2A6 of the three subjects, expecting that these subjects had some mutations in the *CYP2A6* gene. The results indicated that the three subjects possessed the whole *CYP2A6* gene deletion: this type of the *CYP2A6* variant was later termed as *CYP2A6*4C* by the P450 nomenclature committee. Accordingly, we developed a gene diagnosis method for this genotype.

In another project in our laboratory, genetically engineered *Salmonella* YG7108 cells expressing human CYP2A6 or CYP2E1 together with the NADPH-CYP reductase were established to compare the mutagen-producing capacity of these enzymes for various *N*-nitrosamines. We found that CYP2E1 was responsible for the metabolic activation of *N*-nitrosamines with relatively short alkyl chains, whereas CYP2A6 was involved in the metabolic activation of *N*-nitrosamines possessing relatively bulky alkyl chains such as a tobacco-specific nitrosamine, NNK (4-(methylnitrosamino)-1-(3-pyridyl) -1-butanone), which has been known to cause lung tumor in rodents.

Combining the above mentioned two concepts, it seemed reasonable to hypothesize that individuals possessing the *CYP2A6*4C* have the reduced risk of cancers due to the lack of the metabolic activation of certain carcinogens in tobacco smoke. A large scale case-control study was performed. The results clearly indicated the existence of a significant association between the CYP2A6 genotype and a lung cancer risk in smokers. In contrast, there was no significant relationship between them in non-smokers.

The concept that subjects possessing the deletional genotype, *CYP2A6*4C*, have low risk

of lung cancer could be applicable to other tobacco-related cancers such as colon cancer in cigarette smokers and oral cancer in tobacco chewers in Sri Lankan.

In addition to *CYP2A6*4C*, we discovered some other variants causing the reduction of the enzyme activity or the enzyme expression. Analyzing the epidemiological data including these variants, we confirmed that the activity of CYP2A6, but not the linkage of the gene deletion with possible mutations of oncogenes or anti-oncogenes, determines the risk of tobacco-related cancers. Therefore, we further postulated that the inhibition of CYP2A6 by an inhibitor of CYP2A6 enzyme resulted in the prevention of the occurrence of lung tumors caused by NNK, a representative nitrosamine contained in cigarette smoke condensate. Thus, we treated A/J strain of mice with NNK together with methoxsalene, a potent inhibitor of CYP2As. The results were dramatic; our hypothesis was correct. The treatment of mice with methoxsalene completely inhibited the appearance of adenomas caused by NNK in the mouse lung (Fig.).