IDENTIFICATION OF SINGLE NUCLEOTIDE POLYMORPHISMS IN THE PROMOTER REGION OF TWO CARBOXYLESTERASE 1 GENES AND ALTERATION OF IMIDAPRIL RESPONSIVENESS BY TRANSCRIPTION BINDING SITE

Mika Yohimura\textsuperscript{1,3}, Tomomi Kimura\textsuperscript{1}, Eichi Geshi\textsuperscript{2}, Takashi Katagiri\textsuperscript{2}, Masakiyo Hosokawa\textsuperscript{1} and Masaaki Muramatsu\textsuperscript{1}
\textsuperscript{1}Department of Molecular Epidemiology, Medical Research Institute, Tokyo Medical Dental University, 2-3-10 Kanda-surugadai, Chiyoda-ku, Tokyo 101-0062, \textsuperscript{2}Third Department of Internal Medicine, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666 and \textsuperscript{3}Laboratory of Drug Metabolism and Biopharmaceutical Sciences, Chiba Institute of Science, 15-3 Shiomi-Chou, Choushi, Chiba 288-0025

Carboxylesterase (CES, EC 3.1.1.1) is a family of enzymes that hydrolyzes a variety of prodrugs to active metabolites, and plays an important role in their pharmacokinetic behavior. There are two CES1 genes, CES1A1 and CES1A2, but have been undistinguishable for their extremely high homology. An angiotensin-converting enzyme inhibitor, Imidapril, is widely used in treating hypertension, although the responses vary among individuals. Previously, we reported that a single nucleotide polymorphism (SNP) at position -816 of the CES1A2 gene was involved in the responsiveness to imidapril medication. In this study, we screened 100 Japanese patients with hypertension and identified novel 11 polymorphisms in CES1A2, and 6 polymorphisms in CES1A1. Haplotype analysis revealed that the -816 SNP is in linkage disequilibrium with some other SNPs including one on a putative Sp1 transcription factor recognition site of the CES1A2 promoter region. The luciferase assay demonstrated that these SNPs consist of Sp1 binding site in CES1A2 gene, and possibly regulate the gene expression level individually. Our results could provide important information for studying personalized efficacy to drug responsiveness.

ANTI-TUMOR PROTEIN P53 ACTIVATES THE TRANSCRIPTION OF THE HUMAN CYP1A1 GENE

Norihito Shibahara\textsuperscript{1}, Shunsuke Iwano\textsuperscript{1,2} and Tetsuya Kamataki\textsuperscript{1,2}
\textsuperscript{1}Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812 and \textsuperscript{2}Faculty of Pharmacy, Takasaki University of Health and Welfare, Takasaki-shi, Gunma 370-0033, Japan

CYP1A1 is responsible for the detoxication and the metabolic activation of environmental carcinogens. The induction of CYP1A1 is known to elevate the risk of cancer. Also, the polymorphism of CYP1A1 alters lung cancer risk. Furthermore, it has been reported that patients with a susceptible CYP1A1 genotype carrying a mutation in p53 tumor suppressor shows a greater risk for lung cancer. However, little information is available on the effects of p53 expression on the expression of CYP1A1. Therefore, the purpose of this study was to examine the possibility of whether p53 affects the transcription of the CYP1A1 gene. Over-expression of wild type p53 resulted in the significant induction of CYP1A1 mRNA in H1299 (p53\textminus/-) cells. Consistent with results, doxorubicin, a p53 inducer, promoted the transcription of CYP1A1 in A549 (p53\textplus/+\textsuperscript{a}) cells in dose-dependent fashion. These results indicate that p53 is involved in the transcriptional regulation of CYP1A1. In addition, transient transfection assays revealed that p53 responsive element(s) (p53RE) were located in the CYP1A1 gene. Introduction of site-directed mutations into the p53RE reduced p53-activated luciferase activity compared to non-mutated control. These results suggest that the p53RE in the CYP1A1 gene play a central role in the p53 mediated up-regulation of CYP1A1. Taken together, we confirmed that wild-type p53 is responsible for the transcriptional mechanism of CYP1A1. Further analysis is now underway to examine the detailed mechanism.