The SNP Communications in Drug Metabolism and Pharmacokinetics, the official journal of the Japanese Society for the Study of Xenobiotics (JSSX), provide us with increasing information on mutations of genes encoding proteins related to xenobiotic metabolism and disposition. Generally, such mutations can cause the decrease in or the loss of the activities of drug-metabolizing enzymes and transporters, hence the increase in the plasma concentrations of drugs. It is believed that the increased drug concentration or the increased bodily drug exposure often leads to the drug-induced toxicity. In this regard, the SNPs of the genes for xenobiotic metabolism and disposition are deeply involved in the toxicity. Although I agree with the concept that the toxicodynamics is a function of the toxicokinetics, I believe that we should have a slightly different view regarding the drug toxicity, particularly which observed clinically in the patients. The toxicity found in the patients is very often idiosyncratic with an extremely low incidence, one patient out of more than ten thousands to hundred thousands patients as contrasted with a high frequency of gene mutations in drug metabolizing enzymes and transporters, most typically more than 1%. High frequency of mutations in genes for drug-metabolizing enzymes and transporters hardly gives a rational explanation to a low incidence of the idiosyncratic drug toxicity. A good example would be the liver injury caused by troglitazone. Gene analyses of the twenty five patients suffered from the troglitazone-induced liver injury demonstrated that 40% of the case patients are associated with null type of both glutathione S-transferase M1 and glutathione S-transferase T1, clearly indicating the increased exposure in these patients to chemically reactive metabolites produced from troglitazone (p<0.05). Unexpectedly, however, 15% of the eighty five control patients who did not develop the liver toxicity at all after taking troglitazone were also associated with the null type of both isoforms of glutathione S-transferase, strongly suggesting that other genetic factors than the genotype of glutathione S-transferase are quite likely involved simultaneously in the troglitazone liver injury. To date, we have no further findings on these factors that could interpret this phenomenon, while SNPs in the genes encoding the major histocompatibility complex (MHC) class I proteins, which have been reported recently for Stevens-Johnson syndrome caused by carbamazepine and for the skin toxicity caused by allopurinol, would have a possibility to provide us with a clue to the solution. Although the underlying mechanism is still not fully understood, we could assume that the immune system or the cytotoxic T lymphocytes, which play a major part in self and non-self recognition, killed the cells which have been modified by chemically reactive metabolites. It is known that proteins in the supernatant fraction of the cells undergo a proteasomal processing, and the peptide fragments thus produced are transported to the cell surface after binding to MHC class I proteins, which thereby present these peptides to the immune system. Since the peptides are produced from the self proteins, the immune system is naturally tolerant, and no toxic actions would take place. On the other hand, the peptide fragments originated from the chemically modified proteins by the reactive metabolites would be different from those from normal proteins in the point that they have either the haptenized amino acid or the amino acid sequence dissimilar to the normal one, and therefore, would be recognized as foreign body-derived peptides by the immune system. Therefore, it is quite likely that the chemically reactive metabolites give the foreignness to the peptide fragments and induce the toxic actions by the immune system. The SNPs in MHC class I serving as a biomarker for idiosyncratic drug toxicity such as Stevens-Johnson syndrome strongly suggests that the chemically modified peptides are not always presented by MHC class I to the immune system, allowing us to assume that only the isofrom of MHC class I with SNPs, which presumably occur at a very low frequency, can bind the drug-modified peptides to present them to the immune system. Otherwise, the drugs producing the chemically reactive metabolites would cause the toxicity in every patient who took such drugs without exception. In this regard, therefore, I encourage everyone investigating the SNPs in drug-metabolizing enzymes and transporters in relation to drug-induced toxicity to check the SNPs in MHC class I proteins at the same time. I would predict that any drug toxicity caused by the chemically reactive metabolites will be somehow associated with SNPs in MHC class I proteins together with SNPs in drug-metabolizing enzymes and transporters.
References


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