Editorial

Predicting Individual Differences in Drug-metabolizing Enzymes

Patients have individual and different responses to drug toxicity and efficacy. To avoid toxicity and side effects while obtaining the desired efficacy, medical therapies must be suited for individual patients. To date, genetic polymorphisms in drug-metabolizing enzymes are thought to be the main cause of these individual differences. Therefore, analyses of the human genome and identification of genetic polymorphisms in drug-metabolizing enzymes have been major issues of global projects. While some individual differences in drug-metabolizing enzymes have been identified and linked to genetic polymorphisms, it is also evident that all individual differences in drug-metabolizing enzymes cannot fully be explained by these genetic polymorphisms.

In general, activities of drug-metabolizing enzymes are affected greatly by environmental factors. For example, enzymatic activity can be inhibited or induced by chronic exposures to xenobiotic compounds or may largely vary by patients’ demographic backgrounds, such as the type of disease and aging. In addition, it is also thought that drug metabolic activity is altered by drug-drug interactions, nutrition, and patient’s physiologic conditions varying on temporary bases. Among these factors, the inhibition of enzymatic activity by drugs can relatively easily and quantitatively be predicted using recombinant enzyme systems. However, it is not an easy task to predict the effects of above physiological changes, since they involve many complicated elements, such as transcription factors, signal transduction pathways, etc.

The phenomenon of drug-metabolizing enzyme was discovered by A. Conney, H. Remmer and R. Kato (1959). Notably, the role of the aryl hydrocarbon receptor (AhR) in CYP1A1 induction has been extensively studied and the detailed molecular mechanisms of this process are being elucidated. Unlike the nuclear receptor, AhR is a receptor that belongs to the bHLH/PAS (basic helix-loop-helix/Per-Arnt-Sim) family. The nuclear receptors are involved in basic transcriptional activation of many genes. Of these nuclear receptors, pregnane X receptor (PXR), constitutive androstane receptor (CAR), and hepatocyte nuclear factor-4 (HNF-4) are involved in the induction of a drug-metabolizing enzyme. PXR and CAR form a heterodimer with retinoid X receptor α (RXRα) and activate gene transcription. These receptors have been reported to be involved in the homeostasis of bile acids, lipids, hormones, glucose, inflammation, vitamins, etc., and crosstalk with other nuclear receptors or transcription factors that control signaling pathways. These crosstalks are expected to cause individual differences in xenobiotic/drug disposition and toxicity. In this themed issue, three invited mini-reviews describe the interplays of PXR, CAR, and HNF-4.

Meanwhile, it has long been known that inflammatory responses and infections reduce hepatic P450 expression. Recently, the mechanism of CYP3A4 suppression was linked to NF-kB activation. NF-kB activation disrupts the association of the PXR/RXRα complex with the CYP3A4 gene. This suppressive mechanism by NF-kB activation may occur with other nuclear receptors that form a heterodimer with RXRα. More recently, microRNAs were also reported to be involved in P450 expression.

These results, in addition to the analyses of genetic polymorphisms, indicate that studying the transcriptional activation of genes is very important to understand individual differences in drug-metabolizing enzymes. However, it is difficult to directly predict individual in vivo differences from these data. Therefore, a new method that predicts individual differences in drug-metabolizing enzymes in vivo is necessary to effectively treat patients.

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