AL08 Studies on Drug Metabolism and Safety Based on the Understanding of Gene Regulation Mechanisms

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Drug metabolism is a key factor that determines the pharmacokinetics and safety of chemical compounds such as pharmaceutical drugs. Its inter-individual variations are closely associated with those of the efficacy and adverse effects of drugs. The expression levels of drug-metabolizing enzymes are influenced by the exposure to chemical compounds including drugs and foods, and nutritional and disease status. We have been investigating the molecular mechanisms for the transcriptional regulations of the genes encoding drug-metabolizing enzymes, especially major cytochrome P450 (CYP) forms.

The increase in the expression of drug-metabolizing enzymes upon the exposure to drugs, a phenomenon called “enzyme induction”, often enhances the metabolisms of co-administered drugs and may cause drug-drug interactions. It has been well known that the enzyme induction is basically mediated by three drug-inducible transcription factors calls AHR, PXR and CAR. In principle, AHR, PXR, and CAR are involved in the induction of CYP1A, CYP3A and CYP2B subfamily members, respectively. We have analyzed the detailed mechanism of the inducible expression of human *CYP1A1*/*1A2* and *CYP3A4* and found that *CYP1A1* and *CYP1A2* expressions are up-regulated by not only AHR but also CAR and LXRα, a nuclear receptor involved in sterol homeostasis, and that LXRα is involved in the *CYP3A4* expression and inhibits PXR- and CAR-mediated inducible expression of *CYP3A4*. These results suggest that the mechanism of enzyme induction is more complex than expected.

The expression levels of drug-metabolizing enzymes are affected also by nutritional and physiological conditions and various diseases, but the mechanisms have remained unclear. We have investigated the association between nutritional cholesterol intake and hepatic CYP3A expression and found a novel mechanism for the basal CYP3A expression in mouse livers. When cholesterol intake is decreased, a sterol-responsive transcription factor called SREBP-2 is activated in the liver and reduces the basal *Cyp3a11* expression through inhibiting its HNF4α/PGC-1α-mediated transcription. These results suggest a novel crosstalk between the regulation mechanisms of drug and sterol metabolisms.

While it is well known that CAR activation induces hepatocyte proliferation and hepatocarcinogenesis at least in rodents, it has remained unclear whether PXR has similar functions. We have investigated the association of PXR with hepatocyte proliferation. As results, we have found in mice that PXR activation alone does not induce hepatocyte proliferation but enhances the hepatocyte proliferation induced by not only CAR and PPARα activators but growth factors and liver injury as well through the suppression of transcription factor FOXO3-mediated expression of cell cycle suppressor genes. These results suggest that PXR have both beneficial and unfavorable effects on the chemical hepatotoxicity: PXR activation may promote the recovery from liver injury and partial hepatectomy and increase the susceptibility to hepatocarcinogens. In addition, our findings indicate a importance of combination effects for the chemical safety assessment.

In this presentation, I will introduce parts of these findings.