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Nuclear Receptors CAR and PXR as Drug-Activating Transcription Factors that Regulate Xeno-Endo Cross Talk in Liver Metabolisms

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Drugs such as phenobarbital (PB) not only induce drug-metabolizing enzymes but also trigger diverse effects on liver function, such as energy metabolism, hormonal homeostasis and bile acid synthesis. Drugs confer their diverse effects by activating the nuclear receptors CAR and/or PXR, drug-activating transcription factors. In addition to drugs, endogenous stimuli such as growth and inflammation also modulate activities of these receptors. Thus, CAR and PXR are placed at the crossroad where both xenobiotics and endogenous stimuli co-regulate liver function. As the function of these receptors has widened, the molecular mechanism of their regulation has evolved from simple protein-DNA binding to regulation by complex protein-protein interactions. Deciphering the molecular mechanism of this receptors-mediated co-regulation is an urgent subject of current investigations.

Drug activation of these receptors begins with their translocation from the cytoplasm into the nucleus, which can be triggered by either direct binding of drugs to these receptors or indirectly without drug binding. Prior to nuclear translocation, CAR undergoes dephosphorylation. In addition, the co-chaperon CCRP undergoes CAR-dependent ubiqutination and proteosomal degradation to release CAR from its complex in the cytoplasm. Endogenous signals such as Gα-protein, growth factor-MEK-ERK pathways, AMP-activated protein kinase and protein kinase C can also play critical roles in regulating activaties of the receptors including their nuclear translocation. For instance, an active ERK represses PB-induced nuclear translocation of CAR in primary hepatocytes.

In the nucleus, drug-activated CAR and PXR directly interact with insulin response transcription factors FOXO1 and FOXA2 and glucagon responsive CREB and PGC1, repressing their ability of regulating target genes such as *G6Pase*, *PEPCK1*, *CPT1 and HMGCS*, the key enzymes involved in gluconeogenesis, fatty acid oxidation and ketogenesis. These receptors also mediate induction of the *SCD1* gene, thus increasing hepatic lipogensis. All these receptor-mediated effects occur in a way consistent with hepatic energy metabolism being decreased following drug treatments. In regenerating mouse liver, on the other hand, PB-activated CAR up-regulates deiodinase 1 increasing thyroid hormone activity. CAR and PXR are also found to directly regulate expression of the genes encoding proliferation/apoptosis signal molecules (*e.g.* GADD45b, ECT2, MDM2 and TRAIL), by which these receptors may mess normal signal activities, thus causing drug toxicity and carcinogenicity. Accordingly, the function of CAR and PXR has now gone beyond just the regulation of drug metabolism and transport, and a simple ligand binding mechanism alone is no longer sufficient to understand the diverse functions of these receptors. For all, exciting research remains for the future in this area. Supported by the Intramural Research Program at NIEHS, NIH.