Cells are endowed with mechanisms to protect them from chemical insults. One of such mechanisms is metabolism of chemicals that can be either endogenous, naturally-occurring, or synthetic origin. The metabolisms primarily occur in liver that is followed by kidney and intestine. In general, chemicals are first metabolized by P450 (CYP) enzymes and subsequently are conjugated by transferases, called the Phase I and Phase II enzymes, respectively. To maximize metabolic capability, liver cells induce metabolizing enzymes and also drug transporters. Although induction can be regulated at various steps during synthesis of enzyme proteins, gene transcription plays the primary role in the regulation. There are three major mechanisms that mediate drug-inducible gene transcription: Ah receptor (AhR)-mediated, Nrf2-mediated, and nuclear receptor-mediated mechanisms.

**AhR-mediated mechanism:**
Polycyclic aromatic hydrocarbons (PAHs) activate AhR that is a member of bHLH transcription factors. Binding by PAH translocates AhR in the cytoplasm into the nucleus where it forms a heterodimer with ARNT and binds to XRE elements found in the genes including *CYPIA1* and *CYPIB1*.

**Nrf2-mediated mechanism:**
Endogenous oxidative stress and exogenous antioxidants activate Nrf2 that is a member of bZIP transcription factors. Nrf2 is retained by Keep1 protein in the cytoplasm and translocates to the nucleus where it forms heterodimer with another bZIP protein MAP. Nrf2:MAP binds to ARE element of the transferase genes. Thiol-activity and ERK2 pathway have been suggested for the Nrf2 activation mechanism.

**Nuclear receptor-mediated mechanism:**
The induction of a set of CYP genes by a group of chemicals is mediated by a nuclear receptor (NR). Peroxisome proliferators (PPs) such as fibrate drugs induce CYP4A enzymes. PPs directly bind to PPARα that forms a heterodimer with RXR, and binds to PPRE elements found in the CYP4A genes.
PXR/SXR and CAR mediate induction of CYP2B, CYP2C, CYP3A, and transferases such as UGT1A1. Distinct but overlapped groups of therapeutic drugs activate either PXR or CAR. For example, PCN activates PXR and lead to induction of the 3A and 2B genes, whereas phenobarbital (PB) activates CAR and induces both genes. PXR is always localized in the nucleus and direct binding of PXR to drugs activates PXR to form PXR:RXR heterodimer and to induce gene transcription by binding to NR site. Because a number of specific 3A inducers are PXR activators and that CYP3A enzymes are the major enzymes in human liver microsomes, the roles of PXR played in drug metabolism can not be overemphasized.

The CAR:RXR activation mechanism is complex and interesting as a basic research object. CAR undergoes nuclear translocation and activation in response to PB, which are distinctly regulated. The nuclear translocation is inhibited by a protein phosphatase inhibitor okadaic acid. On the other hand, the Ca²⁺/calumodulin kinase inhibitors KN-62 and KN-93 repress the nuclear activation of CAR, while they do not inhibit the translocation. When the PB-elicited signal pathways converge on CAR, the receptor is activated and leads to the CYP induction. Although direct binding of PB to CAR remains unclear, drugs such as PB may not directly target CAR, yet they modulate CYP genes through this receptor.

**Prospective:**

Nuclear receptors have emerged as a major transcription factor that mediates drug induction of CYP and other drug/steroid metabolizing enzymes. Enormous consequences lie on the receptors in drug development, drug efficacy, drug-drug interactions, and gene therapy.