Chemical Modulations on Dose-Response of Nuclear Receptor-Mediated Cell Functions

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Nuclear receptors (NRs) regulate many biological functions that are essential for growth, development, and maintenance of normal physiology. Many xenobiotics produce their pharmacological and toxicological effects through interaction with NRs, thus dose-response data on xenobiotic interactions with NR is essential for realistic human health risk assessment. A growing body of evidence supports that the shape of the dose-response curve for NR activation is often nonlinear and nonmonotonic, implying that linear extrapolation is inappropriate. Our long-term research objective was to develop a dose-response model of NR signaling in relation to environmentally-relevant exposure to NR-reactive compounds. We hypothesized that xenobiotic activation of NR depends on external doses in a nonlinear fashion and often exhibits a binary-type response. We proposed to test this hypothesis by examining the dose-response relationship based on NR-mediated target gene expression and cell proliferation. Specifically, we intended to study the dose-response characteristics based on the activation of the sex hormone receptor androgen receptor (AR) and the xenobiotic receptor constitutive androstane receptor (CAR). The specific aims of this project were to examine binary vs. graded response patterns in AR- and CAR-induced gene expression and to examine the role of protein phosphorylation mediated by the mitogen-activated protein kinase (MAPK) pathways in NR-mediated signal transduction. Our studies generated critical biological information that will lead to an improved understanding on how cells respond to NR activation by xenobiotics and will facilitate the development of computational models to assess health risk of environmental exposure to xenobiotics.

Start and end date: January 2005 – December 2005

Presentation(s):

Zhang, F. and You, L. (2006). Mechanism of p53 mitogen-activated protein kinase involved in the constitutive androstane receptor signaling pathway. *The Toxicologist* 90(S-1): 271. (Abstract 1329).

Peer-reviewed publication(s): None to date.

Other publication(s): None to date.

Sponsors in addition to the LRI: None.

Abstract revision date: March 2007