Modeling Nuclear Receptor-Mediated Activity and Hepatotoxicity with Boolean Networks.
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Predicting the human health risk of chronic exposure to environmental contaminants remains an open problem. Chronic exposure to a wide array of chemicals – e.g., conazoles, perfluourinated chemicals and phthalates – has been associated with a range of hepatic lesions in rodents that can progress to cancer, but extrapolating these effects to humans remains challenging. The US EPA Virtual Liver (v-Liver^{TM}) project applies *in silico* methods to gain insight into *in vitro* assay results and the pathways perturbed by chemicals, their relationship to adverse effects, and the degree of conservation between rodents and humans. As a proof of concept, we focus on 20 environmental chemicals in the ToxCast^{TM} project that activate nuclear receptors (NR) and are implicated in rodent liver cancer.

We developed a model of NR-mediated molecular interactions using curated information from the v-Liver Knowledgebase (KB). The model captures the putative signaling, gene expression and enzymatic interactions mediated by CAR, PXR, PPAR-α, LXR and FXR in human hepatocytes. A Boolean Network formalism was used to simulate pathway perturbations and crosstalk due to the activation of NRs by environmental chemicals. We investigated the dynamics of the system using human *in vitro* data on NR activation from ToxCast. The 20 chemicals perturbed the system by differentially activating NRs, resulting in variable changes to downstream gene expression and protein activation. The NR-mediated network is being further developed to investigate signaling cascades that are potentially responsible for the altered hepatocellular phenotypes observed in acute tissue lesions.

[*This work may not necessarily reflect official Agency policy.*]

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