Short Abstract:

We developed a Boolean Network model to simulate nuclear receptor mediated interactions with growth factor crosstalk pathways. The model explains some of the experimental evidence on the impact of nuclear receptor activation on hepatocyte proliferation, and can be useful for evaluating the mitogenic effects of chemicals using *in vitro* data.

Long Abstract:

A Boolean Network Model of Nuclear Receptor Mediated Cell Cycle Progression

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Nuclear receptors (NRs) are ligand-activated transcription factors that regulate a broad range of cellular processes. Hormones, lipids and xenobiotics have been shown to activate NRs with a range of consequences on development, metabolism, oxidative stress, apoptosis, and proliferation. However, the molecular mechanisms by which NRs regulate pathways are poorly understood. A number of environmental chemicals have the potential to activate different members of the NR superfamily. Chronic stimulation of some NRs is a mechanism of nongenotoxic rodent liver cancer with unclear relevance to humans. Sustained increased cell proliferation is one of the 'hallmarks' of NR mediated hepatocarcinogenesis. Here we investigated the hypothesis that differential activation of NRs perturbs the growth factor (GF) crosstalk network with varying consequences on hepatocellular proliferation. First, we used a Boolean Network (BN) formalism to calibrate the dynamics of GF crosstalk leading to the expression of the immediate early genes, c-Jun and c-Fos, during cell cycle progression.

Second, we extended the model to include interactions with the NRs, PPARα, PPARγ and PXR. Third, we evaluated this model using *in vitro* data on human hepatocytes treated with 20 chemicals. The results of our simulations, using deterministic and nondeterministic updating schemes, highlight differential responses for chemicals based on their NR activity, and will be used to guide future experiments and model enhancements.

This work was reviewed by EPA and approved for publication but does not necessarily reflect official agency policy.

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