Abstract:

The toxicological effects of many stressors are mediated through unknown, or incompletely characterized, mechanisms of action. We describe the application of reverse engineering complex interaction networks from high dimensional omics data (gene, protein, metabolic, signaling) to characterize adverse outcome pathways (AOPs) for chemicals that disrupt the hypothalamus-pituitary-gonadal endocrine axis in fathead minnows. Gene expression changes in fathead minnow ovaries in response to 7 different chemicals, over different times, doses, and *in vivo* versus *in vitro* conditions were captured in a large data set of 868 arrays. We examined potential AOPs of the antiandrogen flutamide using two mutual information based methods to infer gene regulatory networks and potential adverse outcome pathways. Representative networks from these studies were used to predict network paths from stressor to adverse outcome as candidate AOPs. The relationship of individual chemicals to an adverse outcome can be determined by following perturbations through the network in response to chemical treatment, thus leading to the nodes associated with the adverse outcome. Identification of candidate pathways allows for formation of testable hypotheses about key biologic processes, biomarkers or alternative endpoints which can be used to monitor an adverse outcome pathway. Finally, we identify the unique challenges facing the application of this approach in ecotoxicology, and attempt to provide a road map for the utilization of these tools.

Key Words: mechanism of action, toxicology, microarray, network inference

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