Probing the ToxCast™ Chemical Library for Predictive Signatures of Developmental Toxicity

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EPA's ToxCast™ project is profiling the *in vitro* bioactivity of chemical compounds to assess pathway-level and cell-based signatures that correlate with observed *in vivo* toxicity. We hypothesize that cell signaling pathways are primary targets for diverse environmental chemicals that disrupt embryogenesis via combinatorial effects on cellular functions. To test this hypothesis, we built statistical associations based on *in vitro* high-throughput screening (HTS) data from ToxCast™ and *in vivo* developmental toxicity data from ToxRefDB. Feature (assay from HTS)-class (specific in vivo endpoint from ToxRefDB) associations from 2x2 contingency tables were used to filter HTS assays based on statistical correlation with distinct *in vivo* endpoints. Linear discriminant analysis with five-fold cross validation was used to build the models using 80% of the data for training and 20% for test. Species specific models of developmental toxicity revealed strong (Balanced Accuracy (BA) >0.7) and unique correlations between assay targets such as TGFβ and retinoic acid receptor signaling in rat, and inflammatory signals in the rabbit. Further analysis revealed 423 feature-class associations, with distinctly different patterns for rat (301 associations) and rabbit (122 associations) across a variety of assay technology platforms. Additionally, species specific endpoints could be associated with one another through similar Gene Ontology (GO) biological processes. This work demonstrates the utility of ToxCast HTS assays for developing pathway level signatures correlating to developmental defects. *This abstract does not necessarily reflect US EPA policy.*