

Species-specific, Compound-conserved Gene Expression of Estrogen Receptor Ligands during Uterotrophy

Authors: Joshua Kwekel, Cora Fong, Lyle Burgoon, Tim Zacharewski
Department of Biochemistry & Molecular Biology and Center for Integrative Toxicology;
Michigan State University, East Lansing, MI. United States

Keywords: species-comparison, estrogen, uterotrophy, microarray, toxicogenomics

It is understood that the discoveries and advances gained in toxicological models will be applied in human risk assessment and medicine; however, this requires accurate and meaningful exchange of biological information between species. The advent of comparative genomic analysis combined with toxicogenomic assessments of chemically induced expression signatures affords us the opportunity to more closely examine cross-species effects. These considerations were applied to the immature, ovariectomized rat and mouse models to better understand estrogen receptor (ER)-mediated signaling during uterotrophy. Animals were dosed once or once daily for 3 days with 100 µg/kg b.w. of ethynylestradiol (EE) or tamoxifen (TAM) and uteri were harvested 2, 4, 8, 12, 18, 24, or 72 hours after treatment. The physiological endpoint was complemented by comprehensive temporal gene expression profiling using complementary-DNA (cDNA) microarrays. Expression profiles for EE, a potent oral estrogen, and TAM, a selective estrogen receptor modulator (SERM) were examined in each species. Comparative analysis has revealed conserved and divergent profiles between mouse and rat. The two-by-two species and compound comparisons of rat and mouse; EE and TAM allow the screening of ER ligand-conserved, but species-specific, sets of genes. This dual-compound approach allows us to minimize gene expression “noise” by filtering for genes which exhibit ER ligand-conserved expression profiles in both species. These comparative genomics approaches to understanding estrogen signaling mechanisms will benefit cross-species extrapolations which are necessary for the application of risk assessments to humans as well as other environmentally sensitive species.

Funded by U.S. Environmental Protection Agency RD 83184701, R21 GM075838 and National Institute of Environmental Health Sciences Training Grant ES07255-16.

Point of Contact:

Joshua Kwekel
Ph.D. Student
Michigan State University
501 Biochemistry
East Lansing, MI 48824
517-432-3100 ext.194
kwekeljo@msu.edu