Defining the Biological Domain of Applicability of Adverse Outcome Pathways Across Diverse Species: The Estrogen Receptor/Aromatase Case Study

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Aromatase inhibitors (e.g. fadrozole, prochloraz) and estrogen receptor antagonists (e.g. tamoxifen) reduce the circulating concentration of 17β-estradiol, leading to reproductive dysfunction in affected organisms. While these toxic effects are well-characterized in fish and thought to be conserved across mammals, it is of interest to assess conservation of these effects in other taxonomic groups to inform our understanding of cross-species variation in toxicity pathways. Here we explore how the AOP construct can be interpreted across diverse species using a comparative pathway approach.

A set of computational scripts has been developed to retrieve Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway information for a specified input gene list, such as the gene target corresponding to the Molecular Initiating Event (MIE) or Key Events (KE) described in an Adverse Outcome Pathway (AOP). The expanded KEGG gene-pathway annotations for available species are then used as input for comparative analysis, with the goal of identifying shared and unique genes, computing enrichment of pathways, and visualizing KEGG Pathway maps between species.

For this initial case study we have curated genes and pathways related to Estrogen Receptor (ER) antagonism and related Aromatase inhibition. Pathway similarity between species (zebrafish, human, chicken, rat, and fruit fly) was analyzed using Bioconductor tools in R and the publically-available pathway analysis tool EC2KEGG. Our findings illustrate that pathways relevant to the ER/Aromatase AOPs show broad similarity between zebrafish, human, chicken, and rat. We find that fruit fly (*D. melanogaster*) lacks gene orthologs for the estrogen receptor, a key molecule that catalyzes estradiol synthesis. This finding suggests that the ER antagonism and Aromatase inhibition AOPs are not applicable to fruit fly, and may have implications to relevance in other invertebrate species.