Journal of Proteomics xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Journal of Proteomics

journal homepage: www.elsevier.com/locate/jprot

Reprint of: Environmental toxicology and omics: A question of sex

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ARTICLE INFO

Keywords:
Gender difference
Environmental toxicology
Mammalian
Gene expression
Risk assessment
Adverse outcome pathway
Computational biology

ABSTRACT

Molecular initiating events and downstream transcriptional/proteomic responses provide valuable information for adverse outcome pathways, which can be used predict the effects of chemicals on physiological systems. There has been a paucity of research that addresses sex-specific expression profiling in toxicology and due to cost, time, and logistic considerations, sex as a variable has not been widely considered. In response to this deficiency, federal agencies in the United States, Canada, and Europe have highlighted the importance of including sex as a variable in scientific investigations. Using case studies from both aquatic and mammalian toxicology, we report that there can be less than ~20–25% consensus in how the transcriptome and proteome of each sex responds to chemicals. Chemicals that have been shown to elicit sex-specific responses in the transcriptome or proteome include pharmaceuticals, anti-fouling agents, anticorrosive agents, and fungicides, among others. Sex-specific responses in the transcriptome and proteome are not isolated to whole animals, as investigations demonstrate that primary cell cultures isolated from each sex responds differently to toxicants. This signifies that sex is important, even in cell lines. Sex has significant implications for predictive toxicology, and both male and female data are required to improve robustness of adverse outcome pathways.

Biological significance: Clinical toxicology recognizes that sex is an important variable, as pharmacokinetics (ADME; absorption, distribution, metabolism, and excretion) can differ between females and males. However, few studies in toxicology have explored the implication of sex in relation to the transcriptome and proteome of whole organisms. High-throughput molecular approaches are becoming more frequently applied in toxicity screens (e.g. pre-clinical experiments, fish embryos, cell lines, synthetic tissues) and such data are expected to build upon reporter-based cell assays (e.g. receptor activation, enzyme inhibition) used in toxicant screening programs (i.e. Tox21, ToxCast, REACH). Thus, computational models can more accurately predict the diversity of adverse effects that can occur from chemical exposure within the biological system. Our studies and those synthesized from the literature suggest that the transcriptome and proteome of females and males respond quite differentially to chemicals. This has significant implications for predicting adverse effects in one sex when using molecular data generated in the other sex. While molecular initiating events are not expected to differ dramatically between females and males (i.e. an estrogen binds estrogen receptors in both sexes), it is important to acknowledge that the downstream transcriptomic and proteomic responses can differ based upon the presence/absence of co-regulators and inherent sex-specific variability in regulation of transcriptional and translational machinery. Transcriptomic and proteomic studies also reveal that cell processes affected by chemicals can differ due to sex, and this can undoubtedly lead to sex-specific physiological responses.

1. Is there evidence for sexual dimorphic responses in toxicology?

Sexual dimorphism describes differences in characteristics between sexes within the same biological species that go beyond their sexual organs and reproductive physiology. Sexual dimorphism occurs in many animal and plant species, and includes secondary sex characteristics such as size, color, and behavior. These features can be used to categorize male and female, and define in part, the state of being one

DOI of original article: http://dx.doi.org/10.1016/j.jprot.2017.09.010
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https://doi.org/10.1016/j.jprot.2018.03.018

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sex or the other. While there are multiple environmental and genetic factors that control sex and influence gender, the levels of circulating sex steroid hormones and their ratios contribute significantly to the manifestation of male and female characteristics in animals. This in turn has implications for sex-specific gene expression from autosomes, as specific transcriptome responses can be “estrogen” or “androgen” responsive. Moreover, the role of sex steroids in the onset and expression of pathological phenotypes has long been known as an important factor to consider in human disease research, including mental illness, neurodegeneration, cardiovascular disease, nephrology and hepatology disease [1–3]. Thus, an individual's sex is an important factor that influences physiology, behavior, and perhaps ultimately, one's health.

The genomic response to hormonal signals between males and females can be mediated by genetic diversity within promotors [4] or through epigenetic mechanisms that tightly control sex-specific responses. For example, studies show that differences in epigenetics between males and females contribute to metabolic phenotypes in a sex-specific manner [5]. Moreover, studies that investigate sex-specific expression in nuclear receptors have converged on two key hepatic pathways: cholesterol metabolism and detoxification (i.e., sex-dependent expression of cytochrome P450s). Differences in how these hepatic pathways respond in males and females to insult are hypothesized to underlie the reason why women may be more resilient to some liver diseases when compared to men. These differences are also highly relevant to the study of toxicants, as exposure to chemicals can elicit different responses in detoxification and biotransformation. For example, females have been reported to methylate arsenic more readily than males, and this can result in a measureable reduction of the risks for toxicity and carcinogenesis [6]. In another example, males and females appear to differentially methylate in response to cadmium exposure; in-utero cadmium exposure results in hypermethylation in males and hypomethylation in females, and there is overrepresentation of genes associated with organ development, morphology and mineralization of bone in females, the functional consequences of which may explain the incidence of reduced birth weight and head circumference in girls but not boys [7]. Moreover, the preferential expression and methylation of genes related to the pathogenesis of cardiovascular disease in females may explain the sex-specific effects of tobacco smoking on cardiovascular health [8]. These are but a few examples of how the sexes differ in sensitivity to chemical exposures.

Historically, women of child-bearing age were excluded from clinical trials in order to reduce any risk of adverse effect on a potential fetus. However, females are under-represented in animal research, in part to reduce variable hormone levels as a confounding variable. Moreover, even in studies inclusive of females, sex-specific analysis is usually not included in the evaluation of the results [9]. Additional reports for this deficiency exist, despite federal mandates for the inclusion of women in scientific study (discussed further in Section 2); a meta-analysis of NIH-funded randomized controlled trials demonstrates that 75% of studies did not report outcomes by sex [10]. Unfortunately, the impact of this type of bias has resulted in multiple cases of drug toxicity or adverse effect in which sex differences were either inappropriately predicted or unknown. For example, twenty years after Zolpidem was approved for use as a hypnotic sleep aid, recommended doses were finally adjusted based on sex, following reports of higher numbers of adverse effects in women that could not be explained by weight differences alone.

As toxicologists, the potential for sex to be an important variable to consider in toxicity assays should therefore be no surprise. In a landmark study, Mennecozzi et al. [11] demonstrated that male and female human primary hepatocytes differ significantly in their response to known liver toxicants, even after only 5 h of exposure. Molecular pathways such as mitochondrial injury, nuclear condensation and plasma membrane permeability were more sensitive in female-derived cells compared with male-derived cells. Furthermore, responses within females could often be further separated according to hormone levels (pre- versus post-menopausal). These data support clinical and epidemiological data demonstrating a higher susceptibility of females to drug-induced liver injury. The implications of this idea are profound; the variable of sex extends well beyond whole animal toxicity testing and into primary cell-based assays.

Recent studies have begun to compare the baseline mammalian transcriptome and proteome of males and females in multiple taxa in order to more comprehensively understand the endogenous sexual dimorphism that exists in development, toxicant susceptibility, and disease susceptibility and progression. For example, the fetal lung transcriptome differs significantly between male and female humans, with a set of 2714 unique genes (13.8%) differentially regulated according to sex [12]. Despite the accumulating knowledge that sex is important to consider for toxicology, there is still some debate regarding the need for separation of biological sex when considering study design and results interpretation [13]. In this review, we discuss transcriptomic and proteomic responses which may reflect sexual dimorphism, as well as the implications of such difference from a toxicological perspective. Here we focus on transcriptomics and proteomics, however studies using metabolomics have also reported sex-specific responses to environmental chemicals [14,15]. We first present regulatory perspectives on the inclusion of sex. This is followed by a synthesis of studies and examples in ecotoxicology and mammalian toxicology that address sex as a variable for transcriptome and proteome responses to environmental contaminants, with the goal being to better appreciate the impact of excluding one sex or the other in chemical evaluations. We point out here the nomenclature for genes and proteins in subsequent sections follow that as recommended for fish (Sections 3–6) and mammals. Gene symbols and names are small-case and italicized in fish while proteins are not italicized and contain an upper-case first letter. In rodents, gene symbols are italicized, with only the first letter in upper-case while protein symbols are not italicized, and all letters are in upper-case.

2. Regulatory perspective on sex-specific responses in environmental/human toxicology

Governmental agencies in the European Union and North America are adopting policies to include sex-specific data in research. In the United States, the Research for All Act of 2015 amends the Public Health Service Act to require the National Institutes of Health (NIH) to ensure that basic research projects involving cells, tissues or animals make efforts to include both sexes [16]. The NIH has recently adopted a policy (NOT-OD-15-102) mandating that NIH-funded research consider sex as a biological variable in vertebrate animal and human studies. The document encourages the integration of sex and gender into biomedical research through the careful design of studies, appropriate analysis and reporting of sex-specific differences. The American Food and Drug Association's (FDA) Office of Women's Health continuously advocates for the equal inclusion of women in clinical studies to allow detection of clinically relevant sex differences in drug efficacy and safety. Moreover, data from clinical trials must be presented separately for men and women. These measures will help discern the role of sex as a biological variable in toxicology and pharmacology, and is expected to address reasons as to why there are higher rates of adverse drug reactions in women. Health Canada also recognizes both sex and gender as having the potential to dramatically influence health outcomes. For that reason, the Government of Canada has mandated Sex and Gender-Based Analysis (SGBA) as an analytical approach to integrate sex and gender perspective into the development of health research, policies and programs, as well as health planning and decision-making processes [17]. Moreover, The European Commission published a recent report in 2013 which outlined the necessity for incorporating sex as an important variable in both animal and cellular research [18].

Considering the role that risk assessment has in protecting wildlife and human health, sex should be a considered variable when extrapolating the results of animal studies, but to the best of our knowledge,

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