

Unique Bisphenol A Transcriptome Reveals Novel Effects on Estrogen Receptor Beta Expression that Correspond to AR Responsiveness in Prostate Cancer Cells

Authors: Janet Hess-Wilson¹, Siobhan Webb¹, Ricky Leung², Maureen Sator^{2,3}, Hannah Daly¹, Shuk-mei Ho^{2,3}, Karen Knudsen^{1,3}

¹University of Cincinnati/Cell and Cancer Biology, United States

²University of Cincinnati/Environmental Health, United States

³University of Cincinnati/Center for Environmental Genetics, United States

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There is increasing concern that exposure to low levels of bisphenol A (BPA) may have adverse effects on human health. Recent evidence has demonstrated that BPA exposure adversely affects prostate cancer progression and treatment. Prostate cancer cells are dependent on androgen receptor (AR) activity for growth and progression; as such, therapy is dependent on ablation of AR activity. While initially effective, recurrent tumors ultimately arise wherein AR has been re-activated. A major mechanism of AR restoration is via mutation of the receptor that renders the molecule susceptible to activation by alternate ligands, including BPA. In tumors carrying such mutations, BPA can restore AR activity and promotes therapeutic relapse in mouse model systems. Therefore, it is imperative to determine the molecular mechanism of BPA action in prostate cancer cells. Herein, the transcriptional signature of BPA in prostate cancer cells was delineated and compared to that of the canonical AR ligand, dihydrotestosterone (DHT). Data obtained revealed that BPA and DHT elicit overlapping but distinct transcriptional signatures in prostate cancer cells expressing the BPA-responsive mutant AR-T877A. Strikingly, one of the most dramatic gene alterations induced by BPA was downregulation of estrogen receptor beta (ER β) mRNA (-4.98 fold over vehicle control, compared to -2.6 fold for DHT; also validated by quantitative real time polymerase chain reaction (PCR) and immunoblot). Given the current dogma that ER β functions in prostatic epithelia to antagonize AR function and AR-dependent proliferation, these findings could provide one mechanism by which BPA induces cellular proliferation. Remarkably, the impact of BPA was found to be specific to this sub-class of tumor cell, wherein ER β levels were unaltered by BPA exposure in cells expressing either wild-type AR or the AR-H874Y mutant. Collectively, these data indicate that BPA is a major effector of ER β expression in prostate cancer cells expressing the common, tumor derived AR-T877A mutant, and provide insight as to the molecular underpinnings of BPA action in this tumor type. Based on these studies, future investigation directed at dissecting the importance of ER β in the proliferative response to BPA will establish the contribution of this event to adverse effects associated with human exposure.

Point of Contact:

Janet Hess-Wilson

Postdoctoral Fellow

U.S. EPA/ORD/NCEA

26 W. Martin Luther King Drive

Cincinnati, OH 45268

513-569-7458

hess-wilson.janet@epa.gov