AUTHOR COMMENTARIES - From Special Topics

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Gail Prins

From the Special Topic of Epigenetics

One of the key papers in the Research Front Map on Epigenetic Gene Regulation, part of our Special Topics analysis of epigenetics research over the past decade, is the June 2006 Cancer Research *paper, "Developmental exposure to estradiol and bisphenol A increases susceptibility to prostate carcinogenesis and epigenetically regulates phosphodiesterase type 4 variant 4" (Ho SM, Tang WY, de Frausto JB, Prins GS, 66[11]: 5624-32). This paper has accumulated 79 citations in the field of Clinical Medicine in* Essential Science IndicatorsSM *from Thomson Reuters.*

In the interview below, ScienceWatch.com *talks with one of the authors, Dr. Gail Prins, about the paper and the impact it has had on the field. Dr. Prins is Professor of Physiology in the Department of Urology and the Department of Physiology and Biophysics at the University of Illinois at Chicago.*

SW: Would you please describe the significance of your paper and why it is highly cited?

The significance of this work is twofold. First, it is the first study to show that exposure to an environmental disrupting chemical (EDC), in this case Bisphenol A (BPA), an environmental estrogen, during early development could increase the sensitivity of the prostate gland to develop precancerous prostate lesions in response to elevated hormones with aging. Previous studies had not found prostate pathology after early-life exposure to BPA and thus it was assumed that this widely used chemical, which leaches from polycarbonate plastics and expoxy resins, did not pose any harm to this cancer-prone tissue. Our work found that while it did not drive cancer by itself, it markedly increased the sensitivity of the prostate to develop neoplastic lesions following a second estrogenic exposure as adults.

The second significant aspect of this study was that it went on to identify the molecular process whereby a brief early-life exposure can cause life-long effects. We found that the epigenetic memory of the prostate cells had been altered through permanent changes in the DNA methylation patterns of several genes. Thus we conclude that early-life chemical exposures reprogram the epigenome of the developing prostate gland and, in so doing, predispose to prostate disease with aging.

SW: How did you become involved in this research, and were there any particular successes or obstacles that stand out?

We (Drs. Prins and Ho) have been involved in prostate research our entire careers

with a focus on the role of estrogens and prostate cancer. After learning how the brain can be feminized or masculinized by early hormone exposures during development, I asked whether this might also occur in hormone-sensitive end organs such as the prostate gland. With the evolution of the field of epigenetics, it made perfect sense that alterations in the epigenome could be a molecular underpinning of estrogen "imprinting" of the prostate gland.

The major obstacle over the years has been convincing people that events during development could have an impact on prostate health over a lifetime. In particular, people have been skeptical that estrogen, a "female" steroid, could have an effect on the male prostate gland. The successes have been slowly accumulating evidence to document a developmental basis for prostate disease and to finally convince skeptics that this phenomenon is real. The present study went a long way towards accomplishing that task.

"We now have evidence that something as common as an environmentally relevant dose of BPA, a ubiquitous environmental contaminant found in most humans, can alter epigenetic memories that determine our fate."

SW: Where do you see your research and the broader field leading in the future?

First, it will be important in future studies to connect the dots between the epigenetically altered genes that we have identified and the disease at hand. The altered genes, phosphodiesterase 4 and several others, have not been previously connected to prostate cancer, and we next need to determine if they play a previously unidentified role in the disease.

I see future work leading to identifying higher-order chromatin and microRNA events as intimately involved in the developmental estrogenization process. I also would like to document whether the findings in our animal models are applicable to the human. If so, this could translate into better policy-making decisions about EDCs in the environment.

SW: What are the implications of your work for this field?

The implications of this work revolve around epigenetic memory. We now have evidence that something as common as an environmentally relevant dose of BPA, a ubiquitous environmental contaminant found in most humans, can alter epigenetic memories that determine our fate. Even if they appear to have no "harm" in the present, it appears that repressed epigenetic memories may loom in our genes, only to be triggered by future events that may drive disease. This work emphasizes the complexity of gene-environmental interactions and the role they play in complex diseases.

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Gail Prins's current most-cited paper in *Essential Science Indicators*, with 79 cites:

Ho SM, *et al.*, "Developmental exposure to estradiol and bisphenol A increases susceptibility to protate carcinogenesis and epigenetically regulates phosphodiesterase type 4 variant 4," *Cancer Res.* 66(11): 5624-32, 1 June 2006. Source: *Essential Science Indicators* from Thomson Reuters.

KEYWORDS: DEVELOPMENTAL EXPOSURE, ESTRADIOL, BISPHENOL A, BPA, PROSTATE CARCINOGENESIS, PHOSPHODIESTERASE TYPE 4 VARIANT 4, ENVIRONMENTAL DISRUPTING CHEMICAL, EPIGENETICS, EPIGENOME, PROSTATE GLAND, EPIGENETIC MEMORY.

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