Environmental Estrogen Exposure During Fetal Life: A Time Bomb for Prostate Cancer

Jean-Marc A. Lobaccaro and Amalia Trousson

Clermont Université, Université Blaise Pascal, Génétique Reproduction et Développement (GReD), and Centre de Recherche en Nutrition Humaine d’Auvergne, F-63000 Clermont-Ferrand, France; and Centre National de la Recherche Scientifique, Unité Mixte de Recherche (UMR) 6293, and Inserm, UMR 1103, GReD, F-63177 Aubière, France

In this issue, Prins et al (1) elegantly describe how exposure to bisphenol A (BPA) during development could modify prostate cell fate in adulthood. This group, involved in research to understand prostate cancer (PCa) development for many years, first determined the effect of BPA on human prostate epithelial stem-like cells obtained from young men. This allowed them to determine that these cells are highly and equally sensitive to estrogens and BPA and are able to amplify. Estradiol and BPA maintain the stem-like state within the normal prostate epithelial population as demonstrated by a higher accumulation of genes such as \( \text{TBX3} \) and \( \text{NANOG} \). Conversely, epithelial differentiation genes such as \( \text{NKX3.1} \) and \( \text{CK18} \) are at a low level. In addition to this work on cell culture, Prins et al (1) demonstrated estradiol and BPA effects during prostate development using an ingenious mouse model by xenografting chimeric human-rat prostate tissues in Nude mice (2) and found that low-dose BPA exposure increases estrogen-driven carcinogenesis of human prostate epithelium. As a result of this experimental tour de force, this team has described the missing link between estrogen-like endocrine disrupters and PCa. The Holy Grail has been found: environmental estrogen exposure will modify the fate of prostate stem cells, making them more sensitive to estrogen during adulthood and more prone to develop PCa.

Development is a tightly controlled process that involves thousands of genes and hundreds of signaling molecules (hormones and growth factors) and cell interactions (junctions and synapses) that will allow correct cell migration. Like a Lego model, all of the interlocking “bricks” must be assembled correctly to produce a normal individual. Such precise mechanisms are involved that it is easy to understand that any defect in a signaling molecule or, on the contrary, an abnormal activation of a usually silent pathway can produce cell defects. Estrogen-like endocrine disruptors have been considered for many years as putatively responsible for various health defects by interfering with the synthesis, metabolism, binding, or cellular responses of natural estrogens (3). These molecules can be found in various plastic products, flame retardants, pesticides, and many other products that are needed for daily use. Among them, BPA is considered as the paradigm of these environmental estrogen-like molecules. Even though BPA was banned from being used in baby bottles by the European Union in 2011 (4) and by the United States in 2012, over 3 million tons per year of this estrogenic monomer have been used to manufacture polycarbonate plastic products, in resins lining metal cans, in dental sealants, and in blends with other types of plastic products, thus suggesting that adults can be overexposed to it. The ester bond linking BPA molecules in polycarbonate and resins undergoes hydrolysis, resulting in the release of free BPA into food, beverages, and the environment, and numerous monitoring studies now show almost ubiquitous human exposure to biologically active levels of this chemical. BPA exerts estrogenic effects through the classical nuclear estrogen receptors, and BPA acts as a selective estrogen receptor modulator (5). However, BPA also initiates rapid responses via estrogen receptors presumably associated with the plasma membrane. Similar to estradiol, BPA causes changes in some cell functions at the tiniest con-
centrations (from picomolar to nanomolar), and the mean and median range of unconjugated BPA measured by multiple techniques in human pregnant maternal, fetal, and adult blood and other tissues exceeds these levels. In contrast to these published findings, BPA manufacturers have persisted in describing BPA as a weak estrogen and insist there is little concern with human exposure levels. Interestingly, data from the 2007–2009 Canadian Health Measure Survey (6) showed that BPA is present in the urine of 91% of the population, with a concentration of 1.16 μg/L. Children aged 6 to 11 years had presented higher BPA concentrations than did other age groups. Given the short half-life of orally ingested BPA and the high frequency of detection, Bushnik et al (6) concluded that continual widespread exposure to BPA was present in the Canadian population. Furthermore, data from the National Health and Nutrition Examination Survey 2003–2004 (7) indicated that higher urinary BPA concentrations were associated with cardiovascular diagnoses in age-, sex-, and fully adjusted models. Finally, a higher BPA exposure, reflected in higher urinary concentrations of BPA, may be associated with avoidable morbidity in the community-dwelling adult population.

The incidence of PCa is constantly increasing due in part to new diagnostic methods and also to the increase in life expectancy (8). Indeed, this cancer has a slow evolution, and about 85% of diagnosed PCa occurs in patients older than 65 years of age. The development and the cause of the disease is still poorly understood, and various factors such as genetic/ethnic origin, diet, lifestyle, and environmental factors have been suggested to play a role (9). As already stated, great differences in the incidence of PCa are observed depending on ethnic origin or the country of residence. A Caucasian American has 30% less risk of developing PCa compared with an African American (10), but at the same time, Asians develop half as much PCa as Americans. These differences are in part due to the ethnic factors and thus to the genetic background and the lifestyle of the individuals. However, it could also show disparities in the accessibility of the diagnostic tests and treatments. Genetic background cannot explain all of the differences because first-generation Asian migrants living in the United States have a higher risk of PCa than those living in Asia (11). Alterations of the nuclear receptor pathway have also been extensively studied, including alterations in the classical androgen (12) and estrogen (Nakamura Y, McNamara K, Sasano H., unpublished data) receptors as well as orphan nuclear receptors such as those for oxysterols (13). Interestingly, these receptors are the target of estrogen-like endocrine disruptors!

This outstanding work could thus become the keystone of a new paradigm as the authors demonstrate the action of BPA not only in vitro using prostaspheres but also in vivo with a chimeric prostate (rat urogenital mesenchyme.
plus human normal prostate stem-progenitor cells) xenografted under the rat kidney capsule. Altogether, it appears that in utero exposure to BPA increases the risk of developing PCa at an older age upon exposure to estrogen/androgen, an endocrine situation that occurs in humans with aging (Figure 1), representing a scary situation for future generations considering the levels of estrogen-like endocrine disruptors in blood neonate.

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Address all correspondence and requests for reprints to: Jean-Marc A. Lobaccaro, GReD Lab, UMR CNRS 6293, Clermont Université Inserm U1103, 24 Avenue des Landais, BP80026, F-63177 Aubière, France. Email: j-marc.lobaccaro@univ-bpclermont.fr.

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