

Epigenetic Reprogramming Induced by Environmental Estrogens

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Environmental Estrogen-Bisphenol A (BPA)

Bisphenol A (Figure 1) is an industrial chemical used primarily to make polycarbonate plastic and epoxy resins that have a variety of applications including use in some food and drink packaging, e.g., water and infant bottles, compact discs, and sports and medical devices. Epoxy resins are used as internal liners of water supply pipes, coatings on the inside of many food and beverage cans, composites of some dental sealants, thermal papers used for sale receipts. Human being intakes BPA mainly via consumption of food and beverage into which BPA leached under high temperature or long-time storage. BPA concentrations in human detected in 92.6% urine samples were in the range of 0.4 ng/L (1.75 nM) to as high as 149 µg/L (or 0.65 µM) based on National Health and Nutrition Examination Survey (NHANES) 2003-2004 [1,2]. A person's exposure level to BPA varies, which is largely determined by a person's life style and to which microwaved long-storage canned food might contribute the most. Infants fed with liquid formula are among the most exposed. A study funded by the Environment Working Group detected an average of 2.8 ng/mL (~13 nM) BPA in the blood of 9 out of the 10 umbilical cords tested. Children are more susceptible to BPA exposure than adults according to a study that found higher urinary concentrations in young children than in adults under typical exposure conditions because their body metabolism systems/organs are not well-developed before adulthood [3,4]. Though there is not a concrete concentration of BPA intake in ordinary human body, the range in blood or urine could be from the low nM to as high as 1 µM based on above-mentioned reports.

Though products using bisphenol A-based plastics have been in commercial use since 1957, BPA was not found to be an environmental estrogen substance until 1993, nor a human health threatening environmental hazard until recent. Based upon numerous previous studies, xenoestrogens, also called "environmental estrogens or hormones" or "Endocrine Disrupting Compounds (EDC)", are considered as serious environmental hazards that have hormone disruptive effects on human and wildlife health [5,6]. Studies have found that fetuses and young children exposed to BPA are at risk for secondary sexual developmental changes, brain and behavior changes and immune disorders [7]. More and more recent studies linked BPA to carcinogens. Perinatal and pubertal exposure to E2 and BPA alters the prostate epigenome and increase susceptibility to carcinogenesis in adult male. Susceptibility to cancer may be a result of developmental exposure rather than exposure existing at or near the time of tumor appearing. As a result, consumers are recommended by relevant authorities to pay caution to use BPA-containing products and BPA was banned to be used in manufacturing baby bottle in most Western country and California since 2013. Consequently, the BPA alternative, BPS (Figure 1), has been used since then. However, BPA substitute could not be better: Experiments in Watson's laboratory at UTMB showed bisphenol S also disrupted hormone activity [8]. Therefore, the studies on the risk of BPA or its alternative BPS used in "BPA-free" products to human health have not ended.

Epigenetic Reprogramming by BPA

Though the in-depth mechanism how xenoestrogens cause diseases is not completely known, genome instability and epigenetic reprogramming may be taken into account, as evidenced by recent studies in which diethylstilbestrol (DES) and estrogen E2 (17

β-estradiol) (Figure 1) have been shown to induce a cascade of intracellular phosphorylation signaling through a membrane form of ERs resulting in phosphorylation of EZH2 and subsequent inactivity of the enzyme and a significant reduction of global histone H3 lysine 27 tri-methylation [9,10]. However, another study showed that EZH2 expression and histone H3 K27 tri-methylation are increased in human breast cancer MCF7 cells treated with DES or BPA and in mammary glands of six-week-old mice exposed to DES or BPA *in utero* [11]. These seemingly contradictory results might be reflected by the inconsistent treatment conditions between two studies, such as treatment doses and time that might switch the balance between genomic and non-genomic regulation of gene expression. Neither study had a second analytical method like mass spectrometry to confirm the accuracy of measurements. Recent research has showed that xenoestrogen exposure affects the earliest stages of egg production in the ovaries of the developing mouse fetuses, thus suggesting that the next one or two generations may suffer genetic defects in such biological processes as mitosis and DNA replication. Such transgenerational effects of xenoestrogens have gained support from studies of DES. In humans, prenatal DES treatment was known to be associated with an increased risk of abnormality in reproduction and tumor induction in the reproductive tract, not only in individuals exposed to DES *in utero*, but also in the subsequent at least two generations of offspring [12]. In mice, perinatal exposure to DES resulted in genital tract abnormalities and cancers in the first (F1) that could be transmitted to the third generation [13]. In other studies, maternal exposure of bisphenol-A (BPA) has been shown to promote the development of experimental asthma in mouse pups [14,15]. Interestingly, the increase of asthma prevalence among children started in the 1970s, 20 years (approximately one generation) after large-scale BPA production started in several industrialized regions of the world [16] implied an inherited exposure from the parents. Taken together, it is implied that an epigenetic reprogramming and inheritance mechanism is associated with xenoestrogen exposure [17]. It seems that histone H3 K27 global methylation change is a direct consequence from xenoestrogen exposure. Whether transgenerational epigenetic reprogramming and inheritance of xenoestrogen exposure result from histone H3 K27 tri-methylation remains to be addressed.

Techniques of Need to Analyze Epigenetic Reprogramming Events

Antibody-based measurement of global H3 K27 tri-methylation is currently used for xenoestrogen studies. Histone H3 K27 and its nearby K36 can be mono-, di-, and tri-methylated; K27 can also be acetylated;

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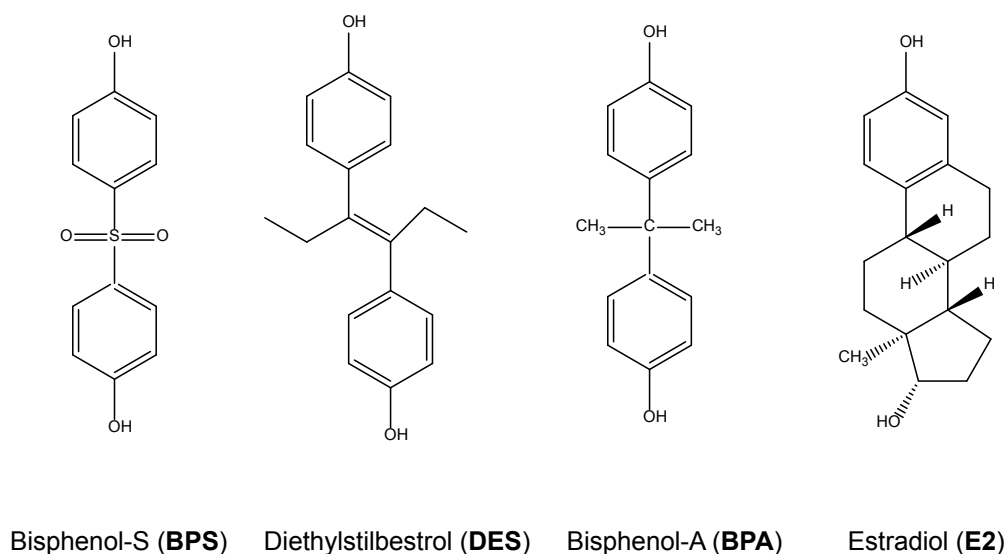


Figure 1: Structures of BPS, DES, BPA and E2.

and H3 has three isoforms H3.1, H3.2, and H3.3. Theoretically, there are more than 30 H3 K27 modification forms including at least 8 K27 tri-methylated forms. The commercially available H3 K27 tri-methylation antibody, such as Abcam H3 Kme3 antibody (#ab6002), was raised from immunogens derived from synthetic N-terminal peptide of human histone H3, tri-methylated at K27. Therefore, the antibody was designed to target at one form of K27 tri-methylation. It is not known this antibody is also responsive to or influenced by other forms of K27 tri-methylated H3 whose neighbor residues, for example K36, are modified. Furthermore, beside H3 K27 tri-methylation, a broad modification patterns including acetylation or methylation at other sites should also be analyzed for better understanding epigenetic modification pattern changes. It is also very important not only to measure the expression level of methyltransferase EZH2, the key enzyme responsible for H3 K27 methylation, but also to measure the expression levels of EZH2 interaction proteins that form either complexes with EZH2, such as EED in polycomb PRC2 or interaction networks with PRC2, PRC1, and their bridging partners including transcription factor YY1 and its associated factor YAF2 [18]. In addition, the expression levels of H3 K27 demethylases such as JMJD3 and other epigenetic modifiers associated with histone modifications are also needed to be evaluated. In this view, a targeted proteomics may be the best approach of choice to assess epigenetic reprogramming induced by xenoestrogens.

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