

Prenatal exposure to BPA induces changes in genomic DNA methylation in rat mammary gland

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Prenatal exposure to environmental estrogens (xenoestrogens) may be responsible for the increased incidence of breast cancer observed over the last 50 years. The xenoestrogen bisphenol A (BPA) has been shown to leach from plastic containers and dental materials among other consumer products. Previous studies in our laboratory revealed that fetal BPA exposure is sufficient to induce the development of preneoplastic and neoplastic lesions in the adult rat mammary gland. The mechanism underlying the origin and progression of neoplastic lesions after developmental exposure to xenoestrogens remains largely unknown. In this regard, the link between epigenetic changes and carcinogenesis is being investigated intensively. Perinatal exposure to various xenoestrogens has been suggested to induce trans-generational effects via germ line DNA methylation, a topic that is currently being studied.

We postulate that prenatal exposure to BPA induces epigenetic changes through DNA methylation in the rat mammary glands which may be associated with tumor formation in adulthood.

To explore this hypothesis, Wistar-Furth rats were exposed to 250µg BPA/kg BW/day or vehicle from gestational day 9 to postnatal day (PND) 1. The animals were sacrificed at PND4, PND21 and at first estrous after PND50, and the genomic DNA was isolated from the mammary glands. We examined the changes in the methylation profile between BPA- and vehicle-treated animals using the Nimblegen ChIP array. We observed that 1) as expected, a large part of the genome was unaffected, 2) BPA-treated animals displayed changes in methylation status in several chromosomal regions compared to control, 3) the total number of hypo- and hyper-methylation events was similar in all BPA-treated animals regardless of age, and 4) the majority of the methylation changes occurred on PND21 (pre-pubertal) and PND50-60 (puberty). Certain chromosomal regions including Chr1q4, Chr6q2.4, Chr7q3.4 and Chr8q3.2 were found to be especially rich in hypo- or hyper-methylated areas. Anti-apoptotic Bcl-2 and tumor-associated Wnt7b were among the genes with consistent changes in promoter methylation status on PND21 and PND50-60. These preliminary results may help understand the underlying developmental mechanisms that contribute to breast cancer initiation and progression in adulthood.