

Lactational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) alters proliferation and gene expression of the rat mammary gland during development

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BACKGROUND: 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is a member of the chlorinated dioxins and one of the most potent environmental contaminants.

OBJETIVES: This work studied cell proliferation and gene expression in mammary glands of 21, 35, 50 and 100 days old rats exposed to TCDD during lactation (prepubertal treatment).

METHODOLOGY: To study prepubertal exposure, on the 14th and 17th days post-delivery, lactating dams received 0, 6.67ng or 20.0ng TCDD/g BW, via gavage. When the female offspring reached 21, 35, 50 and 100 days of age, they were sacrificed and their mammary glands extracted for cell proliferation or gene expression analyses. Proliferation was analyzed in ten rats/group using 5-bromo-2'-deoxyuridine (BrdU). Another ten rats/group were processed for gene expression analysis using Agilent microarray platform. Differentially expressed genes ($p < 0.01$) were determined by empirical Bayes moderated one sample t-test, and categorized accordingly to biological functions and canonical pathways. Important genes were validated using real time RT-PCR.

RESULTS: Prepubertal TCDD treatment reduced cell proliferation in the 35 and 50 day-old rats and increased it in the 100 day-old rat mammary glands, mainly in the terminal end buds. TCDD induced changes in the expression of genes with a wide range of biological functions, especially with the higher dose. The most activated canonical pathway was via aryl hydrocarbon receptor signaling. Cyp1a1 and Cyp1b1, important genes in estradiol biosynthesis and metabolism, were highly up regulated at different ages. Following this pathway, we found other enhanced genes (Hsd17b12 and Sod1), while others had no alteration (Comtd1 and Gstp1), indicating that this pathway was inducing the production of genotoxic metabolites. In addition, several of the dysregulated genes were related to protection against establishment of mutations (DNA damage repair, apoptosis, and tumor suppressor genes), among other groups of genes, such as, oncogenes, lipid metabolism and immunity.

CONCLUSIONS: TCDD induced changes in cell proliferation and gene expression of the rat mammary gland. The genomic changes observed indicate that the mammary cell has been submitted to genotoxic stimuli and DNA repair genes, such as tumor suppressor genes, are activated to maintain the genomic stability.

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