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Induction of Reactive Oxygen Species and Malignant Transformation by Tcdd Through Metabolic Formation of Catechol Estrogens

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2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), a prototype of halogenated aromatic hydrocarbons, is a persistent environmental contaminant and one of the most powerful tumor promoters. The molecular mechanism underlying induction of tumor promotion by TCDD has not been elucidated. In the present work, we found that TCDD induced neoplastic transformation of human mammary epithelial (MCF10A) cells initiated by 7,12-dimethylbenz[a]anthracene. We hypothesize that catechol estrogen metabolites formed from 17β-estradiol by TCDD-induced cytochrome P450s, particularly CYP1A1 and CYP1B1, undergo redox-cycling to generate reactive oxygen species (ROS), which may promote transformation of MCF10A cells. We observed that TCDD induced protein expression and mRNA level of CYP1A1/B1 in MCF10A cells in a time-dependent manner. TCDD caused enhanced accumulation of intracellular ROS in the presence of 17β-estradiols and the antioxidant Trolox attenuated TCDD-induced ROS formation. When 2-Hydroxyestradiol (2-OHE_2) and 4-hydroxyestradiol (4-OHE_2) were added to MCF10A cells, there was increased accumulation of ROS and formation of 8-OH-deoxyguanosine, which were attenuated in the presence of Trolox. We have demonstrated that 2-OHE_2 and 4-OHE_2 are formed from 17β-estradiols by recombinant human CYP1A1 and CYP1B1, respectively. In addition, TCDD induced DNA binding activity of the redox-sensitive transcription factor, nuclear factor-κ B (NF-κ B). The possible inhibitory effect of Trolox on the TCDD-induced transformation of MCF10A cells is under investigation.

Keyword : TCDD, catechol estrogen, Reactive Oxygen Species, Human mammary epithelial cells, Neoplastic transformation