Ovarian cancer growth was induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin through the regulation of CYP1A1 gene in an estrogen receptor-dependent pathway in BG-1 ovarian cancer cells

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Abstract

Environmental factors such as high meat consumption, caffeine, cigarette smoking, and endocrine disrupting chemical (EDCs) may enhance the risk of ovarian cancer. Cytochrome P450 (CYP) 1A1 may play a major role in metabolic activation of procarcinogens to carcinogens. 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is a commonplace pollutant and a promoter of carcinogenesis as the most potent substance. In this study, we examined the effects of TCDD in the presence of 17beta-estradiol (E2) on the expression of CYP1A1, CYP1B1, and aryl hydrocarbon receptor (AhR) by RT-PCR and western blot analysis. In addition, the cell viability by TCDD and E2 was examined in BG-1 human ovarian cancer cells by MTT assay. To evaluate the cell viability, BG-1 cells were cultured with control (0.1% DMSO), E2 (1 x 10^-10 M) or TCDD (10^-10 M). E2 markedly increased BG-1 cell viability about 5 times and TCDD also induced BG-1 cell viability the most at 1 x 10^-10 M compared to control. When co-treated with IC50 TCDD, 20 x 10^-8 M, an ER antagonist, BG-1 cell viability was reverted to the level of control. Although mRNA expression of CYP1A1 or AhR was not altered by E2 or TCDD, the translational level of CYP1A1 appeared to be increased by E2 or TCDD in a time-dependent manner. Furthermore the translational level of AhR and CYP1A1 appeared to be increased by E2 or TCDD in a time-dependent manner. In xenografted mouse models transplanted with BG-1 cells, E2 treatment significantly increased the tumor mass formation about 6 times and TCDD induced tumor formation about 2 times compared to vehicle (0.1% DMSO) during 80 days. In addition, expression levels of proliferation cell nuclear antigen, AhR and CYP1A1 are increased in E2 or TCDD-treated tumor section compared to the control. Taken together, TCDD may induce ovarian cancer growth by CYP1A1 gene expression and may have a disruptive effect in ER expressing cells or tissues.

Key words: 2,3,7,8-tetrachlorodibenzo-p-dioxin; endocrine disruption; estrogen receptor; cytochrome P450; ovarian cancer cells

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Result

1. In a cell viability assay, the treatment of E2 or TCDD induced a significant proliferation in BG-1 ovarian cancer cells. When IC50 TCDD was treated with E2 or TCDD, E2 or TCDD-induced cell proliferation was reversed more than 50% compared to the control (0.1% DMSO). These results suggested that AhR and CYP1A1 are involved in ovarian cancer cell proliferation via ER dependent pathway, as did E2.

2. In the present study, the treatment of E2 or TCDD induced the increased mRNA expression of CYP1A1, which was also reduced partially by co-treatment of IC50 TCDD. 17β-Estradiol stimulation reversed the co-treatment of IC50 TCDD. By the way, there were no alterations in the expression level of AhR mRNA by the treatment of E2 or TCDD.

3. The exposure of E2 or TCDD in BG-1 ovarian cancer cells induced the increased expression of both AhR and CYP1A1 proteins in a time-dependent manner, which was also reduced completely or partially by the co-treatment of IC50 TCDD. These results suggest TCDD induced the increased expression of CYP1A1 in mRNA or protein level via ER dependent pathway in BG-1 ovarian cancer cells.

4. In vitro results were confirmed in vivo. The immunohistochemical expression of phosphorylated ER, estrogen receptor alpha were up-regulated in the ovaries of mice treated with E2 or TCDD. The expression of total ERα was increased by the treatment of E2 or TCDD in vivo. As a result, this study confirms that TCDD activates AhR and CYP1A1 in mRNA or protein level via ER dependent pathway in vivo.

5. In the present study, the exposure of E2 or TCDD induced the increased expression of both AhR and CYP1A1 proteins in a time-dependent manner, which was also reduced completely or partially by the co-treatment of IC50 TCDD. These results suggest TCDD induced the increased expression of CYP1A1 in mRNA or protein level via ER dependent pathway in vivo.

6. In conclusion, the present study shows that AhR and CYP1A1 are involved in ovarian cancer cell proliferation via ER dependent pathway. These results are important for developing more effective cancer treatments targeting this process.

7. In addition, this study also provides that ER signaling pathway is related to TCDD induced cancer cell proliferation pathway and TCDD may have a potential estrogenic activity to promote the proliferation of ER expressing cancer cells by affecting cancer cells in relation to ER and AhR pathways and its importance in estrogen responsive cell proliferation.

8. Based on these results, further studies should be conducted to elucidate the role of ER and AhR pathways in ovarian cancer cell proliferation and to assess its clinical relevance.

References


Figure 1. Altered protein expressions of AhR following the treatment with E2 or TCDD. BG-1 cells were seeded in 6-well plate and treated with 0.1% DMSO (negative control), E2 (1 x 10^-10 M), or TCDD (1 x 10^-10 M) for 8h (A). Quantification of protein by Western Blotting was conducted by scanning the density of bands on a transfer membrane using Gel Doc 2000 (B). *: Mean values were significantly different from E2 (1 x 10^-10 M) (P<0.05). (Barkey’s multiple comparison test).