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2,3,7,8-TETRACHRODIBENZO-p-DIOXIN-INDUCED AIG POSITIVE COLONY FORMATION IN A BELL-SHAPED DOSE RESPONSE MANNER IS INVOLVED IN MAPK ACTIVATION ON HUMAN BREASL EPITHELIAL CELL

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Even if 2,3,7,8-tetrachlorodibenzo-p -dioxin (TCDD) was known as a potent tumor promoter in several experimental animal species, the tumorigenic effect in human has not been clearly understood. Using M13SV1, Simian virus 40-immortalized cells line from normal human breast epithelial cells with stem cells and luminal characteristics (Cancer Res, 1999, 59:6118-6123), we examined whether TCDD is capable of inducing tumorigenicity in these non-tumorigenic immortalized cells. Cells were treated with 0.1% DMSO or 0.01, 0.1, 1, 10, or 100 nM TCDD for 2 weeks. Anchorage independent growth (AIG) of cells was determined using growth in soft agar.

After 28 days in soft agar, TCDD induced the increase of large colonies in dose-dependent manner.

One nanomolar TCDD was most effective. However, the AIG+ large colonies diminished in higher concentrations. To identify the responsive gene of TCDD, we performed the reverse transcription and polymerase chain reaction. Cytochrome P450 1A1 (CYP1A1) mRNA was increased in dose-dependent manner and maximum increase of CYP1A1 mRNA was observed at 100nM TCDD.

Inductions of plasminogen actiator inhibitor-2 (PAI-2) and interleukin-1 β (IL-1P) mRNA were also increased in response to TCDD-treatment. In Western blot, extracellular signal-regulated kinase 2(Erk2) was increased in the same manner of the result of AIG assay, while the expression of Erk1 and p53 remained in steady level. In this study, we showed TCDD promoted the proliferation and anchorage-independency of the immortalized human breast epithelial cell. These results suggested that TCDD alone might promote neoplastic transformation involving the elevation of Erk2 expression in human breast. It is concluded that TCDD may be a tumor-promoter during human breast carcinogenesis.