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ESTROGEN RECEPTOR ALPHA INDUCTION BY MITOXANTRONE INCREASES ABCG2 EXPRESSION IN RAT PLACENTAL CELLS

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ABSTRACT

ABCG2/Breast Cancer Resistance Protein highly expresses in the apical membrane of the placental syncytiotrophoblasts constituting the placental barrier, and is thus considered to play a significant role in suppressing fetal transfer of diverse drugs including mitoxantrone. We have clarified that the expression of rat Abcg2 was up-regulated by mitoxantrone treatment in TR-TBT 18d-1 cells, a model cell line of rat syncytiotrophoblasts. Mechanisms underlying induction of Abcg2 expression by its substrates is of particular interest, because it can influence the acquisition of drug resistance as well as the tissue distribution of drugs. The purpose of this study is to identify regulatory factors involved in the increased expression of Abcg2 by mitoxantrone. Quantitative real-time PCR and western blot were performed to measure gene expression levels in TR-TBT 18d-1 cells. In TR-TBT 18d-1 cells treated with 10 μM mitoxantrone for 24 hours, the mRNA and protein expressions of Abcg2 were respectively 4.1-fold and 6.1-fold greater than that in non-treated cells. Of regulatory factors that are known to be involved in ABCG2 expression, estrogen receptor (ER) α and progesterone receptor B expressions in TR-TBT 18d-1 cells were markedly increased by mitoxantrone treatment, while ERβ, arylhydrocarbon receptor, and hypoxia inducible factor 1α mRNA expressions were not. The effect of mitoxantrone on Abcg2 expression in TR-TBT 18d-1 cells was significantly attenuated by fulvestrant, ER antagonist, but not by mifepristone, PR antagonist. In conclusion, ERα induction by mitoxantrone is suggested to increase rat Abcg2 expression in TR-TBT 18d-1 cell.