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Benzyl butyl phthalate upregulate breast cancer resistance protein-mediated resistance to paclitaxel in breast cancer cell

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The aim of the study is to investigate the benzyl butyl phthalate (BBP) induce breast cancer resistance protein (BCRP) in breast cancer cell lines and to determine the correlation with response to chemotherapy. P-glycoprotein (P-gp), multidrug resistance protein 1 (MRP1) and BCRP activity in MCF-7 and MDAMB-231 were assessed by multidrug resistance direct dye efflux assay and the resistance induced by phthalate was measured by proliferation assays. Real-time quantitative PCR and western blot were performed for the expression of estrogen receptor alpha (ERα), aryl hydrocarbon receptor (AhR) and BCRP. Finally, a model of nude mice xenograft MCF-7 was used to assess the paclitaxel resistance induced by phthalate in vivo. Immunohistochemistry assay (IHC) of tumor tissue of mice to measure the level of ERα, AhR and BCRP. Efflux assay results suggested BBP increased BCRP function but not P-gp or MRP1, in ERα positive MCF-7 cells and cancer stem cell R2d and R2dE. The phenomenon was not found in ERα negative MDAMB-231 cells. qPCR and western blot results both showed the BCRP expression was upregulated by BBP in MCF-7, R2d and R2dE. The phenomenon was inhibited by only ER inhibitor, but not by AhR inhibitor. And BBP didn't influence the BCRP expression in MDAMB-231. These results suggested that BBP upregulated BCRP via ERα. IHC result showed the BCRP expression in tumor tissue treated with BBP higher than control group. These results suggested BBP induced BCRP expression via ERα. The increasing of BCRP also raised the resistance to paclitaxel chemotherapy.