Enhanced Drug Efflux Drives Multidrug Resistance in Radio-Resistant Mouse Breast Cancer Cells

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Abstract:

Multidrug resistance (MDR) cause death in over 90% of cancer patients. Several MDR mechanisms have been proposed, including drug inactivation, impaired apoptosis, and the most common is overexpression of ATP-binding cassette (ABC) transporters, which pump drugs out of cancer cells, thereby reducing drug efficacy. TUBO-P3, radioresistant cell line, was developed through in vivo passages of TUBO-P0, radiosusceptable mouse breast cancer cell line with radiation therapy. Chemo-susceptibility tests using CCK-8 assay revealed that TUBO-P3 cells exhibited 2- to 50-fold increases in IC50 values compared to TUBO-P0 cells for cisplatin, doxorubicin, vinorelbine, cyclophosphamide, paclitaxel, and 5-fluorouracil (5-FU). These data represent the presence of MDR in TUBO-P3 cells; however, the underlying mechanisms remain unclear. This study investigates the mechanisms of MDR in TUBO-P3 cells, with a focus on drug efflux activity. Flow cytometry analysis demonstrated that after treatment with doxorubicin (2.5μM for 1, 4, and 8 hours), drug concentrations in TUBO-P3 were significantly lower than in TUBO-P0 at 8 hours, suggesting that while drug influx was similar at the first 4 hours, enhanced efflux mechanisms in TUBO-P3 contribute to reduced drug retention once saturation is reached. Furthermore, drug efflux tests at 30 minutes and 2 hours showed higher activity in TUBO-P3 and RT-PCR confirmed upregulation of the ABCG2 transporter gene expressions in this cells. These results suggest that the MDR phenotype in radio-resistant mouse breast cancer cells is primarily mediated by alterations in intracellular drug concentrations through enhanced drug efflux activity.

Keywords:

ABC transporter, Drug efflux, Flow cytometry, Mouse breast cancer, MDR mechanism.