Molecular Mechanisms of Paclitaxel Resistance and Resveratrol Sensitivity in MDA-MB-231 Breast Cancer Cells

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Treatment of drug-resistant cancer cells remains a difficult problem in cancer therapy because most resistant cells can pump out drugs or upregulate other survival pathways to bypass a targeted therapy. To study cancers that are resistant to the common cancer drug, paclitaxel, a novel paclitaxel-resistant cell line was generated from the breast cancer cell line MDA-MB-231. A "spiking" method of paclitaxel treatment was used to select for a population of cells that are resistant to the drug. This method mimics the development of resistance in recurrent tumors in patients. However, it is difficult to study such a heterogeneous population. To better study these cells, the paclitaxel-resistant cell line was cloned using a limiting dilution method to provide more homogeneous populations of resistant cells. The 29 clones obtained exhibited a paclitaxel IC50 range of 8 µM to 78 µM which was equivalent to a 200- to 2000-fold increase in resistance compared to the parent line. It has been suggested that the polyphenol natural compound, resveratrol, which has been shown to inhibit cell growth of multiple cancer types, may be useful as a combination anti-cancer treatment or novel therapeutic for drug-resistant cancer cells. The parent line, the heterogeneous resistant line, the least paclitaxel-resistant clone and the most paclitaxel-resistant clone were similarly sensitive to resveratrol treatment. We observed that treatment with 10-100 µM concentrations of resveratrol in all cell lines showed a reduction in cell proliferation and increased apoptosis within 72 hours ($p<0.05$), with the paclitaxel-resistant cells to a greater extent. In addition, resveratrol decreased the ability of the parent, heterogeneous resistant and the highest resistant clone cells to form colonies (an indication of reduced cell survival capacity). This resistant cell line and its clones provide a powerful tool to study paclitaxel-resistance in and therapeutics for breast cancer.

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