Genetic Profiling Signature of Multi-Drug Resistance in Breast Cancer

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Success in Breast cancer chemotherapy is challenged by development of tumors having a multi-drug resistance (MDR) phenotype. It is one of the major causes of failure to cancer chemotherapy. MDR is a multi-factorial problem, where several mechanisms are acting in concert with each other. The current study aims to evaluate differential expression profiles of some genes mediating MDR in resistant breast cancer cells. Genetic profiling signature of resistant MCF-7/Dox cells treated with doxorubicin (Dox) and chemo-sensitized with 2-methoxyestradiol (2ME, a natural estrogen metabolite) was identified using RT Profiler PCR Array. Out of 84 genes examined, 47 genes were found to have changes in gene expression in different treatment groups. Based on significance of results, four genes were chosen as representatives of the genetic events mediating development of MDR phenomenon. MDR1, Bcl2, P53 and Cyclin D1 genes were selected for complete evaluation because of their role in drug efflux systems, apoptotic signaling and cell cycle regulation. 2ME significantly increased sensitivity of the resistant MCF-7/Dox cells to cytotoxic effect of Dox by 2.9-folds. 2ME chemosensitizes resistant breast cancer cells by significantly down regulating expression of Bcl2 and Cyclin D1 genes by 2 and 3-folds respectively, confirmed by western blotting. Combination of 2ME to Dox increased caspase activity by 27 folds and arrested cell cycle in G1 and S phases compared to Dox alone. In conclusion, our results suggest that down regulation of expression of Bcl2 and Cyclin D1 genes, augmented caspase 3 acivity and cell cycle block may account for chemosensitizing resistant breast cancer cells by 2ME.