Acquisition of docetaxel resistance in breast cancer cells reveals upregulation of ABCB1 expression as a key mediator of resistance accompanied by discrete upregulation of other specific genes and pathways.

The microtubule-targeting taxanes are important in breast cancer therapy, but no predictive biomarkers have yet been identified with sufficient scientific evidence to allow clinical routine use. The purposes of the present study were to develop a cell-culture-based discovery platform for docetaxel resistance and thereby identify key molecular mechanisms and predictive molecular characteristics to docetaxel resistance. Two docetaxel-resistant cell lines, MCF7RES and MDARES, were generated from their respective parental cell lines MCF-7 and MDA-MB-231 by stepwise selection in docetaxel dose increments over 15 months. The cell lines were characterized regarding sensitivity to docetaxel and other chemotherapeutics and subjected to transcriptome-wide mRNA microarray profiling. MCF7RES and MDARES exhibited a biphasic growth inhibition pattern at increasing docetaxel concentrations. Gene expression analysis singled out ABCB1, which encodes permeability glycoprotein (Pgp), as the top upregulated gene in both MCF7RES and MDARES. Functional validation revealed Pgp as a key resistance mediator at low docetaxel concentrations (first-phase response), whereas additional resistance mechanisms appeared to be prominent at higher docetaxel concentrations (second-phase response). Additional resistance mechanisms were indicated by gene expression profiling, including genes in the interferon-inducible protein family in MCF7RES and cancer testis antigen family in MDARES. Also, upregulated expression of various ABC transporters, ECM-associated proteins, and lysosomal proteins was identified in both resistant cell lines. Finally, MCF7RES and MDARES presented with crossresistance to epirubicin, but only MDARES showed cross-resistance to oxaliplatin. In conclusion, Pgp was identified as a key resistance mediator at low docetaxel concentrations (first-phase response), whereas additional resistance mechanisms were prominent at higher docetaxel concentrations (second-phase response). Supporting Pgp upregulation as one major mechanism of taxane resistance and cell-line-specific alterations as another, both MCF7RES and MDARES were crossresistant to epirubicin (Pgp substrate), but only MDARES was cross-resistant to oxaliplatin (non-Pgp substrate).

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