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. - DTU Orbit (28/03/2019)

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 mediator of resistance to low docetaxel concentrations (first-phase response), whereas additional resistance mechanisms appeared to be 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).

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, Functional Human Variation, University of Copenhagen, BGI-Shenzhen, University of Southern Denmark
Number of pages: 14
Pages: 4327-4338
Publication date: 2015
Peer-reviewed: Yes
Early online date: 2015

Publication information
Journal: Tumor Biology
Volume: 36
Issue number: 6
ISSN (Print): 1010-4283
Ratings:
BFI (2019): BFI-level 1
Web of Science (2019): Indexed yes
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): CiteScore 3.27 SJR 1.149 SNIP 0.825
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.15 SJR 1.089 SNIP 0.863
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): CiteScore 2.79 SJR 1.047 SNIP 0.815
Web of Science (2015): Impact factor 3.65
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 3.12 SJR 1.105 SNIP 1.015
Web of Science (2014): Impact factor 3.611
BFI (2013): BFI-level 1
Scopus rating (2013): CiteScore 2.61 SJR 1.124 SNIP 1.077
Web of Science (2013): Impact factor 2.84
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): CiteScore 2.24 SJR 0.989 SNIP 0.836
Web of Science (2012): Impact factor 2.518
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): CiteScore 2.02 SJR 0.934 SNIP 0.86
Web of Science (2011): Impact factor 2.143
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.917 SNIP 0.84
Web of Science (2010): Impact factor 2.026
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.95 SNIP 0.683
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.151 SNIP 0.668
Scopus rating (2007): SJR 1.061 SNIP 0.666
Scopus rating (2006): SJR 1.066 SNIP 0.654
Scopus rating (2005): SJR 0.705 SNIP 0.612
Scopus rating (2004): SJR 0.91 SNIP 0.744
Scopus rating (2003): SJR 0.781 SNIP 0.809
Scopus rating (2002): SJR 0.506 SNIP 0.552
Scopus rating (2001): SJR 0.516 SNIP 0.563
Scopus rating (2000): SJR 0.502 SNIP 0.626
Scopus rating (1999): SJR 0.525 SNIP 0.618
Original language: English
Keywords: Breast cancer, Docetaxel, Resistance, Microarray analysis, Gene set enrichment analysis, Pgp
DOIs:
10.1007/s13277-015-3072-4
Source: PublicationPreSubmission
Source-ID: 105042326
Research output: Research - peer-review › Journal article – Annual report year: 2015