translational research

PROTEOMIC PROFILING OF CHEMOTHERAPY TREATED TRIPLE NEGATIVE BREAST CANCER CELLS

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Aim: Triple negative breast cancer (TNBC), which represents approximately 15% of breast cancers, is defined by lack of expression of ER and PR, and lack of overexpression of HER2. Treatment options for TNBC are limited due to the lack of a clinically validated molecular target. Despite increased sensitivity to standard chemotherapy, TNBC is associated with a higher risk of relapse and poorer overall survival, than other breast cancer subtypes. The aim of this study was to profile chemotherapy-induced changes in TNBC cells, in order to identify new druggable targets that may enhance response to chemotherapy.

Methods: Two TNBC cell lines, MDA-MB-468 (cisplatin sensitive), and HCC-1143 (cisplatin resistant), were treated with cisplatin (2 µM) or docetaxel (2 nM) for 24 hours. Following treatment, proteomic profiling was performed using semi-quantitative label-free LC-MS-based proteomics analysis.

Results: In cisplatin-treated HCC-1143 cells, 7 proteins with significantly (p<0.05) altered abundance (>1.5 fold) were identified, 5 up-regulated and 2 down-regulated. In cisplatin-treated MDA-MB-468 cells, significant changes in 3 proteins were identified, with 2 increased and 1 decreased. Following docetaxel treatment, 43 altered proteins were identified in HCC1143 cells (32 increased, 11 decreased), and 3 proteins in MDA-MB-468 cells (1 increased, 2 decreased). Three proteins have been selected for further evaluation as potential targets to improve response to cisplatin and/or docetaxel. Neuroblast differentiation-associated protein (AHNAK), which has been implicated in activating PKC, is up-regulated in HCC1143 following treatment with both cisplatin (3.0-fold) and docetaxel (1.8-fold). Malate dehydrogenase (MDH2), which has been implicated in docetaxel resistance in prostate cancer, is up-regulated 2.2-fold, in docetaxel-treated HCC1143 cells. DNA-dependent protein kinase (DNA-PK) is up-regulated 1.6-fold in cisplatin-treated MDA-MB-468 cells. Previous studies suggest that DNA-PK plays a role in DNA repair following cisplatin treatment.

Conclusions: In summary, we have identified three potential novel targets for TNBC which are druggable and may improve response to chemotherapy. Therapies targeting these three proteins will be evaluated, in combination with chemotherapy, in TNBC cell lines.

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