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biomarkers in breast cancer (prognostic, predictive and pharmacodynamic)

54P Differential expression of the protein phosphatase 2 (PP2A) complex and breast cancer signature genes following suppression of mTOR signalling

C. Saliba[1], S. Baldacchino[2], R. Gauci[2], M.P. Grixti[2], V. Petroni[2], A. Zerafa Simler[2], N. Mallia[2], A. Fenech[3], C. Scerri[1], G. Grech[2]
[1]*Department of Physiology & Biochemistry, University of Malta, Msida, Malta*
[2]*Department of Pathology, University of Malta, Msida, Malta*
[3]*Department of Clinical Pharmacology & Therapeutics, University of Malta, Msida, Malta*

Objective: Deregulation of PP2A and its regulatory subunits is a common event in breast cancer. The cBioPortal for Cancer Genomics shows that PP2A is deregulated in 59.6% of basal breast tumours, providing a possible target for therapy. This study aims to investigate the expression of the PP2A complex components in various breast cancer cell lines and the effect of mTOR signalling suppression on breast cancer signature genes including the PP2A inhibitory subunits CIP2A, SET, SETBP1 and ANP32A.

Methods: RNASeqV2 and clinical data were obtained from the Cancer Genome Atlas to investigate the PP2A enzyme complex across different breast cancer subtypes. Ten human breast cancer cell lines, representing the various subtypes of breast cancer, were used. qRT-PCR was used to measure expression levels of the PP2A subunits. An Affymetrix/Panomics panel was used to assay molecular classifiers and transcripts of interest, in the presence or absence of the mTOR inhibitor, rapamycin and the PP2A activator, FTY720. Immunofluorescence was used to measure pS6K activity and follow the cellular distribution upon addition of FTY720.

Results: *In silico* analysis of datasets show that CIP2A is significantly upregulated in the HER2+ patients and the TNBC subgroup. To support this, qRT-PCR data in our study shows a higher expression of CIP2A in TNBC cell lines. In addition, the TNBC cell lines are more sensitive to low doses of FTY720. Immunofluorescence shows that addition of 5 μM FTY720 resulted in a shift of pS6K from the nuclei of MDA-MB-231 cells to a cytoplasmic localisation. Of interest, drug-induced mTOR suppression, down-regulated the expression of CIP2A and SET by more than 1.5 fold in various breast cancer cell lines.

Conclusion: The TNBC tumours show the greatest overexpression of CIP2A indicating an association between CIP2A and the malignant phenotype of this subset. Decreased expression of the PP2A inhibitory subunits, CIP2A and SET following suppression of mTOR activity imply a restoration of PP2A activity in TNBC cell lines. Hence, subsets of patients with suppressed PP2A activity would be eligible for treatment using therapies which target the PI3K/Akt/mTOR pathway.

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