



**The mitochondrial protein SLC25A43 and its possible role in  
HER2-positive breast cancer**

av

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## Abstract

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In breast cancer, overexpression of the human epidermal growth factor receptor (HER) 2 along with altered activity of several downstream signaling pathways, are associated with poor prognosis and shortened survival for the patient.

In *paper I*, we identified a common deletion covering the gene encoding the mitochondrial solute carrier SLC25A43, a relatively unknown protein, in HER2-positive breast tumours. Using immunohistochemistry we analysed the protein expression of SLC25A43 in HER2-positive breast cancers (*papers I and IV*). Tumours with negative or low SLC25A43 protein expression were shown to have lower S phase fraction (SPF) compared to tumours with medium or high expression. In *paper II*, siRNA mediated silencing was used to evaluate the effect of SLC25A43 in different breast epithelial cell lines. Silencing SLC25A43 altered the G<sub>1</sub>-to-S cell cycle phase transition and cell proliferation rate as well as the expression of the proliferation marker Ki-67 and the cell cycle regulatory protein p21. We also investigated if silencing SLC25A43 affects the cytotoxicity of different cytostatic drugs (*paper III*). This result show that SLC25A43 influenced the cytotoxic effect of paclitaxel and the paclitaxel-induced G<sub>2</sub>/M-block, in addition, the inhibitory effect of trastuzumab on cell proliferation was also found to be altered through an altered trastuzumab-induced G<sub>0</sub>/G<sub>1</sub>-block.

Altered mitochondrial function has become an emerging hallmark of cancer thereby connecting sustained uncontrolled cell proliferation with mitochondrial involvement in the pathogenesis of cancer. Our data suggests that the mitochondrial transporter SLC25A43 is involved in regulation of cell proliferation and drug efficacy. Taken together, these data further strengthen the connection between mitochondrial function and the cell cycle, both in non-malignant and in cancer cells.

**Keywords:** SLC25A43, breast cancer, HER2, mitochondria, proliferation, S phase fraction, Ki-67, p27, drug efficacy, patient outcome, transfection, flow cytometry, immunohistochemistry.

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