Overexpression of BLM promotes DNA damage and increased sensitivity to platinum salts in triple negative breast and serous ovarian cancers

Platinum based therapy is an effective treatment for a subset of triple negative breast cancer and ovarian cancer patients. In order to increase response rate and decrease unnecessary use, robust biomarkers that predict response to therapy are needed. We performed an integrated genomic approach combining differential analysis of gene expression and DNA copy number in sensitive compared to resistant triple negative breast cancers in two independent neoadjuvant cisplatin treated cohorts. Functional relevance of significant hits was investigated in vitro by overexpression, knockdown and targeted inhibitor treatment. We identified two genes, the Bloom helicase (BLM) and Fanconi anemia complementation group I (FANCI), that have both increased DNA copy number and gene expression in the platinum sensitive cases. Increased level of expression of these two genes was also associated with platinum but not with taxane response in ovarian cancer. As a functional validation, we found that overexpression of BLM promotes DNA damage and induces sensitivity to cisplatin, but has no effect on paclitaxel sensitivity. A biomarker based on the expression levels of the BLM and FANCI genes is a potential predictor of platinum sensitivity in triple negative breast cancer and ovarian cancer. Through integrated analysis of gene expression and copy number data from two independent clinical trials in triple negative breast cancer, we identify two genes, BLM and FANCI, involved in double-strand DNA repair where increased expression is related to sensitivity to platinum induced DNA damage. Further functional validation reveals that overexpression of BLM alone promotes DNA damage.

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