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Development of parallel reaction monitoring (prm)-based quantitative proteomics applied to her2-positive breast cancer

Introduction

Treatments targeting the HER2/ERBB2 tyrosine kinase receptor such as trastuzumab have improved the natural history of HER2-positive breast cancer. However, except HER2 protein expression/gene amplification, there is no predictive biomarker allowing the selection from the various available HER2-targeted therapies. We developed Parallel reaction monitoring (PRM), a powerful mass spectrometry-based targeted proteomics approach to quantify pre-specified proteins, to evaluate key proteins involved in the HER2 pathway and/or anti-HER2 treatment sensitivity.

Methods

Protein lysates were obtained from breast cancer cell lines (BCLs), including BCLs exposed to anti-HER2 agents, patient-derived xenografts (PDXs) and frozen breast cancer samples. A PRM-based assay measuring HER2, phospho-HER2, EGFR, HER3, and PTEN was developed using proteotypic peptides. The assay sensitivity, linearity and reproducibility were evaluated and tested on biological samples. PRM-based measurements were compared to immuno-cyto/histo-chemistry, western blot and transcriptomic data.

Results

In BCLs, PRM measurements correlated with western blot immunocytochemistry and transcriptomic data. At baseline, a higher expression of HER2, EGFR, PTEN and HER3 but lower expression of phospho-HER2 correlated with trastuzumab sensitivity. Under trastuzumab treatment, PRM demonstrated a decrease in HER2 and an increase in phospho-HER2, which correlated with drug sensitivity, whereas the opposite was observed under lapatinib. HER2 quantification was also correlated with immunohistochemistry in PDXs and clinical breast cancer samples but displayed a large range of expression.

DIscussion

PRM-based assay, developed to quantify proteins of the HER2 pathway in breast cancer samples revealed a large magnitude of expression, which may have relevance in terms of treatment sensitivity

References

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