Invasive lobular carcinoma (ILC) accounts for 10-15% of primary breast cancer and is typically ER+ and HER2 non-amplified.

There is preclinical evidence that somatic ERBB2 mutation may provide an alternative and tractable mechanism for upregulation of HER2 activity in tumors that do not express HER2 by current clinical criteria.

Using large public datasets, we previously demonstrated that targetable ERBB2 mutations are enriched in ILC versus invasive ductal carcinoma (IDC) and are an independent prognostic factor in ILC (HR=3.7, 95% CI 1.2-11.0; p=0.021) [1].

We next hypothesized that a gene expression signature incorporating HER2 activity due to ERBB2 mutation (ERBB2mut) and/or amplification would validate the prognostic signal we found in ILC.

METHODS

To derive a novel gene expression signature of HER2 activity that accounted for the effect of potentially targetable ERBB2 mutations in ERBB2 non-amplified tumors, we applied a weighted average difference (WAD) method to our gene expression data in cases from the METABRIC 2012 (N=180) and TCGA 2015 (N=817) cohorts (see Figure A for summary diagram).

Gene expression in ERBB2mut cases (N=38, selected by ERBB2 non-amplified status and patient age >50) was compared with the same orders of magnitude of ERBB2 wild-type cases (N=79, selected by ERBB2 non-amplified status, grade >1, stage >1, patient age >50). We then repeated the same model for known activating ERBB2 mutated (oncERBB2mut) cases (N=23) using the same comparator and selection criteria.

To incorporate the effect of HER2 activity via ERBB2 amplification, the overlap of differentially expressed genes (DEGs) shared by both comparisons (ERBB2mut and oncERBB2mut vs. ERBB2 wild-type) with DEGs from a further comparison of ERBB2 amplified (N=247) vs. non-amplified (N=1733) cases in METABRIC was calculated.

Then, to incorporate clinical HER2 status as the downstream phenotype, the overlap of this list with DEGs from a comparison of HER2+ vs. HER2- cases in TCGA was calculated.

In contrast to ERBB2mut cases, matching was not performed for ERBB2 amplified or HER2+ cases because numbers were higher and within an order of magnitude across groups, such that similar variation in gene expression could reasonably be assumed.

Multiple gene expression signatures of HER2 activity have been derived using cell line models and patient cohorts. We compared our novel gene signature with the HER2 activity signature established by Desmedt et al. [2] with respect to its ability to detect potentially targetable ERBB2mut cases in our ILC/IDC dataset.

This was achieved by multivariate regression modeling of response to neratinib for each gene signature using breast cancer cell line pharmacologic data from the Broad Institute, accessed online via the CellMinerCDB portal.

RESULTS

We show that our novel HER2 pathway signature score uniquely enriches for ERBB2 mutated tumors (see Figure B). Using a Cox regression model and stratifying gene expression scores into upper versus lower quartiles, we were able to validate the prognostic signal of ERBB2 mutations in ILC tumors (HR for 10-year OS in ILC=2.3, 95% CI 1.04-5.05; p=0.040) (Figure C). In contrast, no relationship was found between ERBB2 mutation status or novel HER2 pathway enrichment score and patient outcome in cases of IDC.

DISCUSSION & CONCLUSION

We generated a novel gene signature that reflects HER2 pathway activity more broadly than existing signatures. In the current study we applied the novel signature to validate the prognostic effect of ERBB2 mutations in ILC. We conclude that ERBB2 mutations that are enriched in ILC provide a robust biomarker of HER2 pathway activation and could be detected via gene expression signature. Clinical trials of HER2-targeted therapy in ERBB2 non-amplified primary ILC are warranted. Future translational study of our novel gene signature of HER2 activation may reveal further roles as a biomarker for HER2-targeted therapeutics beyond the clinical context of ERBB2 amplification.

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