GEORGETOWN UNIVERSITY

Lombardi Comprehensive Cancer Center

Nuclear HER2-ER crosstalk in HR+/HER2+ breast cancer

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Abstract: 1545

BACKGROUND

- ~50% of HER2+ breast cancers are also hormone receptor positive (HR+) and express estrogen and/or progesterone receptors (ER, PR).
- HR+/HER2+ tumors are less responsive to neoadjuvant anti-HER2 therapy and exhibit lower rates of pathologic complete response (pCR).
- While HER2 primarily functions as a transmembrane receptor and mediates cytoplasmic signaling, a portion of HER2 resides in the nucleus.
- Prior studies have shown that chromatin-associated HER2 can serve as a transcriptional co-regulator, and its presence in tamoxifen-treated, ER+ (non-HER2-amplified) breast cancer correlates with shorter disease-free survival.
- **We hypothesized that nuclear HER2 may reprogram ER function in HR+/HER2+ breast cancer, thereby contributing to reduced pCR rates.**

METHODS

- Immunofluorescence
- Chromatin fractionation
- Chromatin immunoprecipitation and PCR (ChIP-qPCR) for ER target genes
- CUT&RUN for ER
- KMPlotter and ROCplot analyses

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RESULTS

Nuclear and chromatin localization of HER2

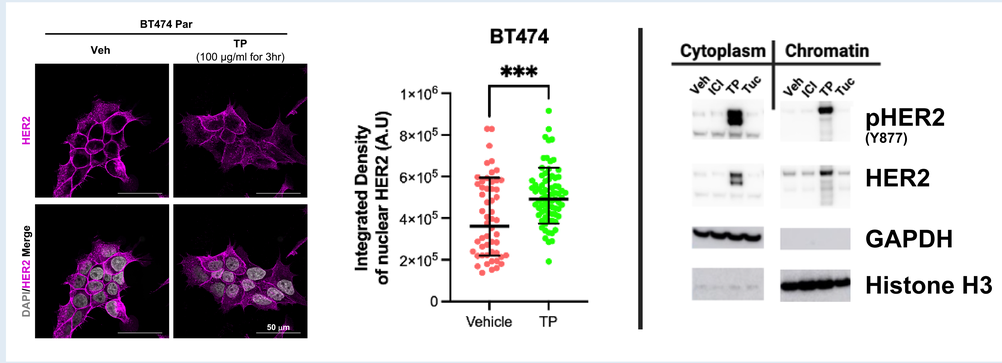


FIGURE 1 - Left - Immunofluorescence of HER2 in HR+/HER2+ BC BT474 cells and quantification of nuclear HER2 staining following TP treatment (***p<0.001, unpaired t test). Right - chromatin fraction of ICI (fulvestrant), TP, and anti-HER2 tucatinib treated BT474 cells.

ER target gene binding with TP

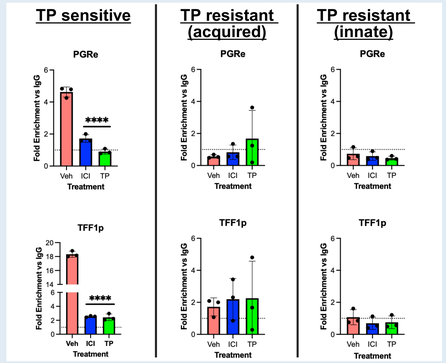
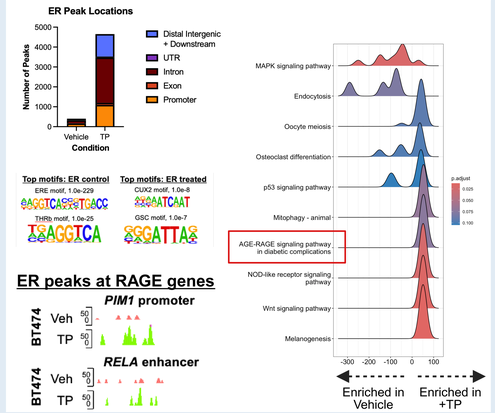


FIGURE 2 - ER ChIP-qPCR in BT474 (left), TP resistant BT474 (middle), and MDA-MB-361 cells (right) at the PGR enhancer and TFF1 promoter (****p<0.0001, one-way ANOVA and Dunnett's multiple comparison test).

ER genomic binding with TP treatment



TP induced ER target genes and BC outcomes

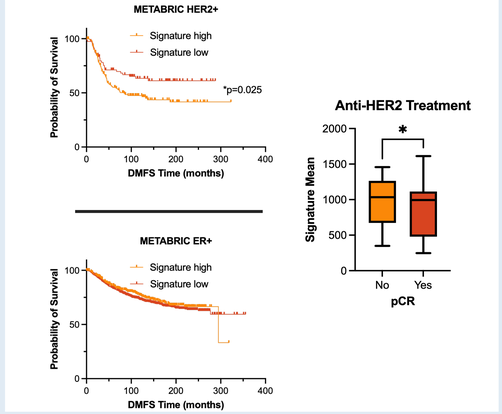


FIGURE 4 - HER2+ BC and ER+ BC patient distant metastasis-free survival (DMFS) and pCR were characterized by high or low (above or below median) expression signature of the ER-bound genes identified by CUT&RUN (*p<0.05, Log-Rank test or Mann Whitney test).

Nuclear HER2 in HER2+, HR+/HER2+ BC

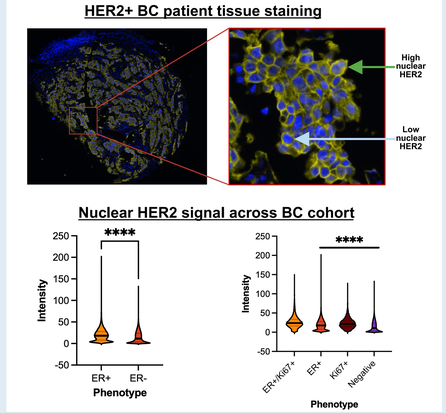


FIGURE 5 - Immunofluorescence of HER2 on a tissue microarray of 31 HR+/HER2+ vs. 19 HER2+ BC samples (****p<0.0001, Welch's t test or Kruskal Wallis ANOVA and Dunn's multiple comparison test).

CONCLUSIONS

- Trastuzumab/pertuzumab (TP) treatment induces nuclear/chromatin localization of HER2 in HR+/HER2+ cells.
- TP treatment, and TP resistance, are associated with a reduction in ER binding to classical target genes.
- However, TP treatment expands ER binding genome-wide to novel sites, including to RAGE signaling genes.
- RNA expression of TP induced ER-bound genes predicts poorer DMFS and lack of pCR in HER2+ BC patient tumors.
- Nuclear HER2 is more prevalent in HR+/HER2+ BC compared to HER2+ BC patient tumors.

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