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Hormone Receptor/Human Epidermal Growth Factor Receptor 2-positive breast cancer: Where we are now and where we are going

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ABSTRACT

Near 75% of all breast cancers (BC) express estrogen receptors (ER) and/or progesterone receptors (PgR), while up to 20% of BC show an overexpression/amplification of Human Epidermal Growth Factor Receptor 2 (HER2). Around 50% of all HER2-overexpressing BC show the coexistence of both HER2 overexpression/amplification and ER and/or PgR overexpression. Numerous *in vitro* and *in vivo* studies suggest the existence of a cross-talk between their downstream pathways, which seem to affect the natural history, response to therapy and outcome of patients affected by this subset of BC. Meta-analyses or subgroup analysis of numerous neo-/adjuvant trials demonstrated significant clinical implications deriving from ER/HER2 co-existence, consisting in a different pattern of relapse and dissimilar outcome in response to anti-HER2 therapy. However, only two randomized trials in early disease and three in advanced disease specifically addressed the issue whether a combined approach with both hormonal and anti-HER2 therapy would have a better therapeutic impact in this subset of BC compared to the lone anti-HER2 or hormonal therapies (HT). None of these trials demonstrated improvements in overall survival, even though several efficacy end-points such as progression free survival, in advanced setting, or pCR rates in neoadjuvant setting, often favored the combined hormonal and anti-HER2 therapeutic approach. In the next few years, a certain number of ongoing randomized trials, both in neoadjuvant and advanced setting, will evaluate the efficacy of new anti-HER2 drugs, T-DM1 and pertuzumab, in combination with HT, helping to improve the therapeutic strategy for this specific subtype of breast tumors.

Introduction

Approximately 75% of all breast cancers (BC) express estrogen receptors (ER) and/or progesterone receptors (PgR) [1], while up to 20% of BC show an overexpression/amplification of Human Epidermal Growth Factor Receptor 2 (HER2). In nearly 50% of HER2 positive (+) BC, there is the coexistence of both expression of ER/PgR and iperexpression/amplification of HER2 [2,3]. *In vitro* and *in vivo* models suggested the existence of a cross-talk between the two downstream pathways (Fig. 1) which affects the natural history, response to therapy and outcome of patients affected by this subset of BC. In this paper we will discuss the current preclinical and clinical evidence concerning the bidirectional cross-talk between ER and HER2 pathways and the potential clinical implications of this intriguing coexistence.

An overview of HER2 and ER pathways

HER2 is a member of the HER family, which consists in 4 transmembrane tyrosine kinase receptors: EGFR/HER1, c-erbB2/HER2, HER3 and HER4. HER2 functions as universal co-receptor for the other HER family members and, when overexpressed or amplified, constitutively stimulates tumor growth, invasiveness and survival via activation of several signaling cascades, mostly MAPK and PI3K/Akt pathways [4–6]. More specifically, HER2-EGFR dimers induce proliferation and improve invasive functions, HER2 homodimers alter cell polarity and HER2-HER3 dimers increase tumor cell metabolic functions, favor cell survival, induce proliferation and increase invasiveness [1–3]. Finally, HER2 overexpression also results in an increased production of the rare ΔHER2 isoform with

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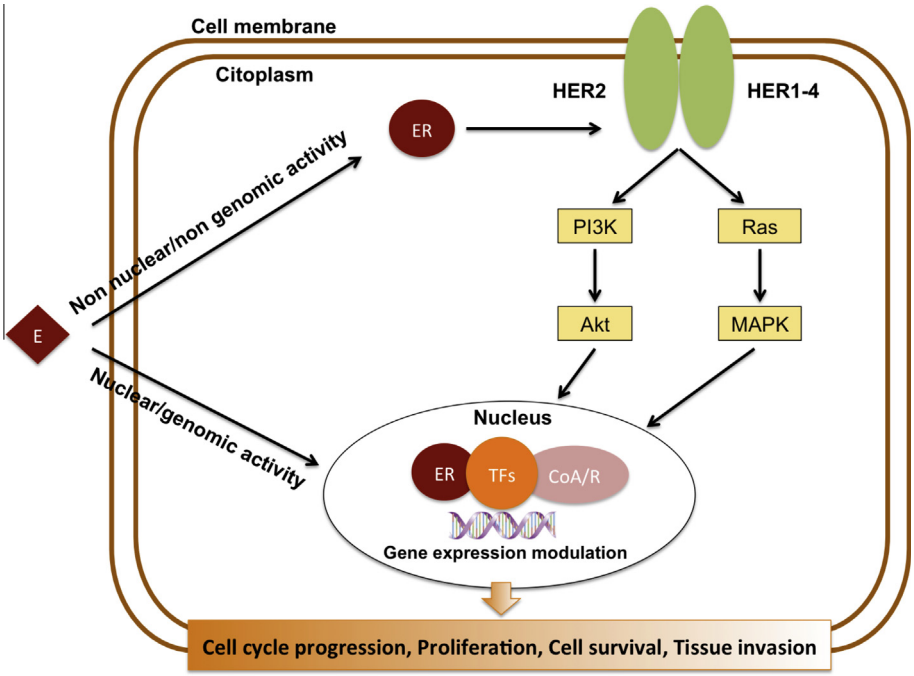

Fig. 1. Simplified ER and HER2 signalings' cross-talk. Estrogens (E) act via a non nuclear/non genomic activity and a nuclear/genomic activity. Non nuclear estrogen receptor (ER) interacts directly or indirectly (e.g. via G proteins) with human epidermal growth factor receptor (HER)2/HER1-4 dimers activating their downstream kinase pathways (e.g. Ras-MAPK and PI3K-Akt pathways), which in turn phosphorylate ER and other transcription factors (TFs) and coactivators/corepressors (CoA/R), modulating gene expression. HER2 signaling pathways also reduce ER expression at both mRNA and protein levels. ER also promotes HER2, other tyrosine chinese receptors (TKR) and TKR ligands' gene expression. This bidirectional cross-talk leads to cancer cell cycle progression, proliferation, survival and invasiveness.

more potent signaling characteristics [6]. Apart from being a driver gene for breast tumors, HER2 is also a relevant negative prognostic factor [7] associated with decreased disease/event free survival (DFS/EFS) and overall survival (OS) [8], however it is also the molecular target of HER2-targeted agents such as trastuzumab, pertuzumab, lapatinib and T-DM1. ER modulates the expression of numerous genes. The binding of estrogen determines a receptor dimerization, which regulates gene expression. ER can also function as a co-regulator for other transcriptional factors. Several tyrosine kinase receptors such as EGFR, IGF1 and HER2 may activate ER in a ligand independent manner, via phosphorylation, determining an important cross-talk between ER and tyrosin receptor kinase pathways [1]. Some studies also suggest a non-transcriptional mechanism of action for ER, which can alter the expression of several growth factors-dependent genes [1]. The majority of BCs are driven in growth and survival by constitutively activated ER, expressed in nearly 75% of all breast tumors [1]. HER2+ BC is a heterogeneous disease. In nearly 50% of them there is also the ER and/or PgR expression (HR+) [2,3]. A study from the Cancer Genome Atlas Network [9], based on genomic DNA copy number arrays, DNA methylation, exome sequencing, mRNA arrays, microRNA sequencing and reverse phase protein arrays, confirmed, on a molecular basis, the existence of at least two subtypes of HER2+ BC, as follows:

- HER2E-mRNA-subtype/HER2-clinically positive tumors, which showed a significantly higher expression of a number of tyrosin kinase receptors (RTKs), including HER2 itself and genes within the HER2-amplicon.
- Luminal-mRNA-subtype/HER2-clinically positive tumors, which showed higher expression of the typical Luminal genes, including GATA3, BCL2 and estrogen receptor gene ESR1.

The coexistence of both HR and HER2 overactivated pathways influences the natural history of disease and patients' outcome. In fact, data from prospective cohorts have demonstrated different outcome between the HR+/HER2+ and HR negative (−)/HER2+ population with a distinct pattern of recurrence. The latter experienced more relapses in the first five years, with brain rather than bones as first site of recurrence [10,11]. A retrospective analysis from the HERA trial of adjuvant trastuzumab also demonstrated for the HR− cohort a very high risk of early recurrence, in contrast with HR+ disease, characterized by a relatively consistent risk of relapse over time [12].

Therapeutic implications of HER2 and ER pathways cross-talk: preclinical evidences

The presence of both HR and HER2 amplified pathways seem to impact on therapy efficacy. It is well known that patients with higher levels of HER-2 had statistically significant lower levels of HR than patients with lower levels of HER-2 [3]. Since levels of expression of HR are directly correlated with response to hormone therapy (HT) [3,13,14], the reduced effectiveness of hormonal treatments usually experienced in this subset of patients compared to HR+ HER2 negative breast cancers is not surprising at all. Moreover, several studies have provided numerous evidences that HER2 pathways may directly or indirectly contribute to the development of resistance to HT. The currently identified mechanisms of resistance are summarized below [15]:

- A HER-mediated activation of the PI3K/Akt/mTOR and p42/44 MAPK pathways induces a down-regulation of both ER and PgR expression.
- The PAX2 transcriptional factor loss or deregulation seems to be associated with the acquisition of a HER2-driven phenotype by preventing the HER2 transcriptional repression by estrogen-ER and tamoxifen-ER complexes.
- In BC cell lines some studies have shown a possible role for the membrane ER in promoting an antiapoptotic effect through EGFR, HER2, IGFR1 and their transduction pathways.