ErbB-Dependent Signaling as a Determinant of Trastuzumab Resistance

Commentary on Ritter et al., p. 4909

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The pathogenesis of breast cancer is profoundly influenced by the signaling cascades downstream of the human epidermal growth factor receptor (HER; also known as the ErbB receptor) family of receptor tyrosine kinases and by the HER ligands (1, 2). Abnormalities in the expression and activity of HERs and resulting signaling pathways in human breast tumors contribute to the invasion and progression of breast tumors and maintenance of the malignant phenotype. For example, overexpression of the HER2 receptor gene product is frequently associated with an aggressive clinical course, decreased disease-free survival duration, poor prognosis, and increased metastasis in human breast cancer (3). A large body of work over the past decade has established that the biological outcome of overexpression of HER family members, particularly HER2 and epidermal growth factor receptor (EGFR), is affected not only by the signals originating from the given receptor but also by the trans-heterodimerization of HER family members on stimulation of cancer cells with the HER ligands (1–4). Thus, formation of various combinational HER heterodimers in growth factor–stimulated breast cancer cells is accompanied by differential stimulation of signaling pathways, some of which are overlapping whereas others select to a specific heterodimer or heterodimers. In spite of these developments, the role of HER-triggered signaling pathways as potential determinants of the sensitivity of breast cancer to HER2-directed therapies remains poorly understood and is just beginning to unfold.

The last decade has been one of the most exciting periods in breast cancer therapy, leading to significant treatment advances in patients with HER2-overexpressing breast cancer with targeting of the ectodomain of HER2 with the anti-HER2 monoclonal antibody trastuzumab (Herceptin; ref. 5). Trastuzumab induces clinical responses in three HER2-positive breast cancers and prolongs the survival of patients with breast cancer when combined with chemotherapy. However, regardless of the presence of HER2 overexpression, a significant proportion of patients with breast cancer do not have a response to trastuzumab-based therapy, and most who do have a response eventually experience resistance to it (6–8). The mechanism of trastuzumab resistance is not fully understood at the moment but is believed to result from the inability of trastuzumab to interfere with the formation of HER2 heterodimers by EGFR or HER3 in HER ligand–stimulated cells (9–11), hyperactivation of phosphatidylinositol 3-kinase caused by either defective phosphatase and tensin homologue (12) or increased levels of insulin-like growth factor 1 receptor (13, 14), and generation of kinase-active COOH-terminal fragments of HER2 (15). Although this research has been very fruitful, a more complete understanding of critical intrinsic signaling cascades in the context of trans-regulation of HERs by their ligands in physiologically relevant models clearly should be combined with examination of human breast tumor specimens for further gains. A deeper understanding of signaling pathways that may still be active in the presence of trastuzumab and further understanding of HER heterodimerization will not only provide a mechanistic explanation for the widely acknowledged clinical phenomenon of trastuzumab resistance of HER2-positive breast tumors but also offer unique opportunities to enhance the sensitivity of antibody-based therapy.

In this issue of Clinical Cancer Research, Ritter et al. (16) report an association between active involvement of EGFR-initiated signals and trastuzumab resistance in the absence of detectable defects in the cell-surface expression of HER2 and its binding affinity to radiolabeled trastuzumab in the model cells. Investigators have used a variety of biochemical, cellular, and animal-based assays to draw the conclusion that acquired trastuzumab resistance in the model system is accompanied by a significant increase in the levels of tyrosine-phosphorylated EGFR and EGFR/HER2 dimers at the cell surface because of increased expression of EGFR ligands. The translational novelty of these findings is supported by evidence showing that such trastuzumab-resistant breast cancer cells remain sensitive to designer small-molecule inhibitors of HER tyrosine kinase such as gefitinib, erlotinib, and lapatinib, which are rapidly progressing through preclinical development (17–19).

Because trastuzumab-resistant breast cancer cells continue to proliferate even in the presence of trastuzumab, Ritter and colleagues have put forward EGFR ligands and their resulting EGFR stimulation as potential significant mechanisms for sustaining the proliferation of trastuzumab-resistant breast cancer cells, which otherwise remain sensitive to EGFR tyrosine kinase inhibitors. These findings are significant because they offer proof of the notion that the growth of trastuzumab-resistant breast cancer cells may be inhibited by targeting of the EGFR pathway by small molecules that target EGFR tyrosine kinase activity. However, at least at the moment, whether similar phenotypic effects can be achieved by treatment with the therapeutic EGFR-blocking antibody C225, the founding member of the concept of receptor tyrosine kinase ectodomain–directed antibody therapy in human cancer (20),...
remains unknown. Possibly, the growth of trastuzumab-resistant cells can only be blocked by the small molecules and not by C225 or similar blocking antibodies, which primarily work at the cell surface. This may result from inherent differences in the modes of action of approaches targeting the ligand-binding sites on the ectodomain of EGFR versus those targeting the tyrosine kinase activity in the COOH-terminal domain of EGFR. These are important issues that are likely to shape the choice of combinational therapies targeting HER2 and EGFR in human breast cancer and, perhaps, other HER2-overexpressing cancers.

One of the distinctive features of the model reported by Ritter et al. is the manner in which they established the trastuzumab-resistant breast cancer cells. In contrast with previous models of trastuzumab-resistant cells, these authors used a highly physiologic milieu to establish cell lines from BT-474 xenografts that initially responded to trastuzumab-based therapy but eventually recurred even with continuous treatment with trastuzumab. This model recapitulates the scenario commonly seen in the clinical development of trastuzumab resistance in patients with breast cancer. Unexpectedly, such trastuzumab-resistant HR5 and HR6 cell lines continue to have HER2 overexpression with active binding sites to trastuzumab. These results also substantiate the previously proposed notion that a lack of efficient HER2 down-regulation by trastuzumab may be associated, at least in part, with a lack of beneficial therapeutic effects of this antibody in certain situations. The availability of HR5 and HR6 cell lines with acquired trastuzumab resistance offers new opportunities to learn about the fundamental molecular insights that may be responsible for the development of the phenotypes summarized by Arteaga and colleagues.

Another unique feature of the findings reported by Ritter et al. (16) is the implied importance of EGFR ligands in trastuzumab-resistant cells as compared with the levels of HER2 in trastuzumab-sensitive parental BT-474 cells. These findings highlight the significance of elevated levels of EGFR ligands in promoting the noted increase in the levels of EGFR/HER2 heterodimers in breast cancer cells with acquired trastuzumab resistance. Ritter and colleagues present data supporting increased levels of expression of mRNAs of various HER ligands and supporting the bioactivity of some but not all such EGFR ligands, which presumably are responsible for the reported high levels of EGFR/HER2 heterodimers in trastuzumab-resistant breast cancer cells. Because increased expression of HER ligands in such cells in xenografts must be positively regulated on prolonged treatment with trastuzumab, establishing the potential cause-and-effect relationship between increased expression of HER ligands and trastuzumab resistance is important. At the moment, why treatment of xenografts with trastuzumab leads to elevated levels of expression of mRNAs of HER ligands, whether effect of trastuzumab-based treatment is caused by transcriptional or mRNA stability, and how exactly these effects are regulated by the signals triggered by the cell-surface HER family members under constant pressure by trastuzumab are not known. In addition, Ritter et al. provide preliminary evidence of up-regulation of heregulin, which binds to HER3 and HER4 and contributes to the formation of HER3/HER2 and HER4/HER2 heterodimers. Therefore, the development of trastuzumab resistance likely is driven by heregulin in addition to EGFR ligands. However, this was not the primary goal of the study reported by Ritter et al. (16) and thus should be formally analyzed in future studies.

A piece of the puzzle about the phenomenon of acquired trastuzumab resistance that remains missing is why resistance to trastuzumab developed in some but not all BT-474 xenografts in the study reported by Ritter et al. (16), a situation similar to that in patients with breast cancer. Clearly, this is intimately linked with the recurrence of such tumors even with the use of effective doses of therapeutic antibodies. There are very likely inherent molecular or cellular determinants of eventual trastuzumab-resistant clones. Could cellular heterogeneity play a role in such biological events? Because the trastuzumab-resistant xenografts used in this study to establish the HR5 and HR6 cell lines were obtained from a presumptively homogenous BT-474 cell line, cellular heterogeneity may or may not be the cause of recurrence of some trastuzumab-resistant BT-474 xenografts. Alternatively, the status of certain components of HER-responsive cellular pathways in an ill-defined subset of BT-474 cells may have subtle differences that become dominant on binding of trastuzumab to HER2 in such cells. In addition, one cannot rule out the influence of host components in shaping the resistant phenotype of some xenografts from where these cell lines were developed. In brief, we must be very cautious about these possibilities, which are not intended to undermine other putative molecular determinants with causative effects on acquired trastuzumab resistance in breast cancer cells.

Regardless of an apparent lack of answers to the questions above, the model system presented by Ritter et al. is a step forward in modeling the clinical scenario of acquired trastuzumab resistance in patients with breast cancer. The findings described by these investigators reaffirm the widely suspected role of EGFR, HER trans-regulation, and resulting signaling pathways in the development and/or maintenance of acquired trastuzumab-resistance phenotypes in human breast tumors. In summary, the results reported by Ritter et al. fulfilled the intended objective of the study to define a set of cellular markers to predict the potential lack of responsiveness of breast tumors to trastuzumab. Clearly, the conclusions drawn in their study should be tested in a large cohort of human breast tumor specimens with differential responsiveness to trastuzumab. As with any new study, this one reported by Ritter et al. has raised a new set of intriguing questions for further research and should help to move forward the field of trastuzumab resistance in human breast tumors.

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