Unraveling Resistance to Trastuzumab (Herceptin): Insulin-Like Growth Factor-I Receptor, a New Suspect

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Trastuzumab (Herceptin) is a humanized antibody directed against the extracellular domain of the tyrosine kinase receptor HER2 that has shown clinical activity against HER2-overexpressing breast tumors (1-4). HER2, the targeted receptor, is a member of the epidermal growth factor (EGF) receptor family of receptors, also known as the type I receptor tyrosine kinase family [for review, see (5)]. HER2 is overexpressed in 25%-30% of breast cancers, and its overexpression is associated with a high risk of relapse and death (6). In this group of tumors with unfavorable prognosis, trastuzumab has been a valuable addition to standard therapy, with the pivotal studies demonstrating a clear survival benefit (2,3). However, even in the selected group of patients with very high levels of HER2 overexpression who derive the greatest benefit from trastuzumab therapy, the response rate from this highly specific, targeted agent is limited in magnitude and duration (7).

This observation leads to the fundamental questions about the mechanism of action of trastuzumab in HER2-positive breast cancer cells and how these cells escape from its antitumor effects. The answer to these questions is particularly challenging because the mechanisms of action of trastuzumab have not been characterized fully and appear to be complex [for review, see (8,9)]. To date, the known mechanisms of trastuzumab’s action include decreased expression of HER2 from the tumor cell surface (10), initiation of G1 arrest and induction of the cyclin-dependent kinase inhibitor p27Kip1 (8), prevention of HER2 cleavage (11), inhibition of angiogenesis (12), and induction of immune mechanisms (13). Alterations in the HER2 receptor or in downstream signaling pathways that mediate any of these effects may be responsible for some cases of primary or acquired resistance to trastuzumab. Possible mechanisms could be expression of truncated HER2 receptors that cannot bind antibodies, mutations of downstream molecules (i.e., ras activation or PTEN deletion), a low level of p27Kip1, and a decreased immune function in patients with advanced breast cancer.

Resistance to trastuzumab, however, may not only depend ultimately on its efficacy (or lack of efficacy) in inhibiting HER2 but also on whether HER2 activation is responsible, single-handedly, for the sustained growth, proliferation, and survival of a well-established tumor. In this regard, it is highly unlikely that a single, active tyrosine kinase receptor or intracellular tyrosine kinase may be solely responsible for a malignant phenotype (14), although a notable exception to this rule may be the critical role that the BCR-ABL tyrosine kinase plays in chronic myeloid leukemia and the high response rate of this disease to STI-571, a specific inhibitor of the BCR-ABL kinase (15). The emerging single-agent efficacy data with trastuzumab and other anti-growth factor receptor agents in epithelial tumors are demonstrating modest response rates, further supporting the theory that targeting just one receptor may not be enough to optimize responses (16). Furthermore, HER2 is a receptor without a cognate ligand, and transactivation of HER2 by other members of the EGF receptor family is important for the growth of HER2-overexpressing breast cancer cells. As a result, combined therapies with trastuzumab and a specific inhibitor of the EGF receptor tyrosine kinase result in enhanced growth inhibition and apoptosis (17-20).

The report by Lu et al. (21) in this issue of the Journal represents a further step ahead to unravel resistance to trastuzumab because it provides evidence for a critical role of insulin-like growth factor-I receptor (IGF-IR) signaling in the response to trastuzumab. The IGF-IR is a transmembrane tyrosine kinase receptor that is activated by binding of the IGF ligands. The hypothesis that IGF-IR signaling could influence the response to trastuzumab was raised from an extensive body of data indicating that this receptor plays an important role in breast cancer [reviewed in (22)], as follows: IGFs exert proliferative and anti-apoptotic effects in many breast cancer cell lines (23,24), targeted disruption of the IGF-IR with anti-receptor antibodies or antisense RNAs to this receptor limits breast cancer proliferation, the IGF-IR and its ligands are expressed in many human breast tumors, and high levels of circulating IGF-I predict an increased risk of breast cancer in premenopausal women (25).

Lu et al. (21) have demonstrated that an increased level of IGF-IR signaling adversely interferes with trastuzumab’s action on cell growth. They used two human breast cancer cell line models complementary in terms of IGF-IR expression—MCF-7/HER2-18 cells, which overexpress HER2 by transfection and endogenously express activated IGF-IRs, and SKBR3 cells, which endogenously overexpress HER2 but express few IGF-IRs (about 10% the number in MCF-7/HER2-18 cells). In MCF-7/HER2-18 cells, trastuzumab inhibited growth only when IGF-IR signaling was blocked by cotreatment with the anti-IGF-IR antibody α-IR3 or the IGF-binding protein-3 (IGFBP-3). In contrast to the basal resistance of MCF-7/HER2-18 cells to trastuzumab, SKBR3 cells, which have a low level of IGF-IR expression, were sensitive to trastuzumab. Additional compelling evidence to link the IGF-IR to the trastuzumab response was provided by the observation that SKBR3 cells became resistant to trastuzumab when cells were genetically altered to overexpress IGF-IRs (SKBR3/IGF-IR). Addition of IGFBP-3, which decreased IGF-IR signaling, restored the ability of trastuzumab to suppress growth. On the basis of these studies,
Lu et al. (21) appropriately propose that strategies that target IGF-IR signaling may prevent or delay development of resistance to trastuzumab. A link between IGF-IR signaling in the modulation of response to monoclonal antibodies has been shown also for the EGF receptor, which is closely related to HER2. In this regard, a recent study (26) has shown that IGF-I signaling temporarily prevented the apoptosis mediated by the anti-EGF receptor monoclonal antibody C225 in the EGF receptor auxotroph cell line DiFi. It is interesting that such inhibition was sensitive to an inhibitor of the phosphatidylinositol 3-kinase (PI-3K)/Akt pathway (26). Because the PI-3K/Akt pathway is poorly suppressed by trastuzumab in breast cancer cells (17), it is tempting to speculate that this pathway may play an important role in the observations by Lu et al. (21).

What are the molecular signaling events underlying the interference of IGF-IR signaling in trastuzumab response? Lu et al. (21) characterized opposing effects of trastuzumab and IGF-IR on p27kip1. The induction of p27kip1 by anti-HER2 antibodies contributes to their effects on growth inhibition (8). However, in SKBR3/IGF-IR cells, the baseline level of p27kip1 were very low compared with those in SKBR3/neo control cells, and trastuzumab could not induce p27kip1 expression. This effect might be mediated by interference between the IGF-IR and HER2 in signaling pathways that regulate p27kip1. Such downstream pathways include ras/raf/mitogen-activated protein kinase or, as mentioned above, PI3-K/Akt signaling, and it would be of practical interest to characterize this possibility because we have inhibitors of these pathways in clinical development. In addition, because IGF-IR signaling has been linked to antiapoptotic effects and resistance to several anticancer treatments (22,26,27), it would be relevant to study whether IGF-IR targeting when combined with trastuzumab results in an enhanced apoptosis. Searching for interactions between both receptor systems will not be an easy task, because diverse study models have revealed different hierarchical cross-regulations between HER2 and the IGF-IR (28,29).

It is evident that trastuzumab development has been a model of a rationally designed targeted treatment, where laboratory predictions have been followed by remarkably successful clinical studies. There are, however, many unanswered biologic questions regarding the mechanisms of action of trastuzumab and causes of resistance to this antibody that warrant further investigation. In the meantime, the study by Lu et al. (21) sheds light on a potential strategy—the inhibition of IGF-IR signaling—to prevent or reverse resistance to trastuzumab. Based on the results obtained by Lu et al., it would be important to characterize the coexpression of HER2 and members of the IGF-IR signaling pathway in breast tumors. In particular, analysis of baseline breast tumor biopsy specimens from patients treated with trastuzumab would provide critical insights into the possible role of IGF-IR in primary clinical responsiveness to the antibody. If an association between IGF-IR activation and resistance to trastuzumab were established in the clinic, it would be a strong signal to combine anti-IGF-IR and anti-HER2 therapies in patients with breast cancer.

REFERENCES


(22) Zhang X, Yee D. Tyrosine kinase signalling in breast cancer: insulin-like...


