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).

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 (27), 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 $p27^{Kip1}$. The induction of $p27^{Kip1}$ by anti-HER2 antibodies contributes to their effects on growth inhibition (8). However, in SKBR3/IGF-IR cells, the baseline levels of $p27^{Kip1}$ were very low compared with those in SKBR3/neo control cells, and trastuzumab could not induce $p27^{Kip1}$ expression. This ef-945e8664.3834 -1.15 T2(eftro9)-43mighftro9mediato9interfereno9bet HER29. i29.signalin29.patslin29.tha29.p27

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