TARGETED THERAPIES

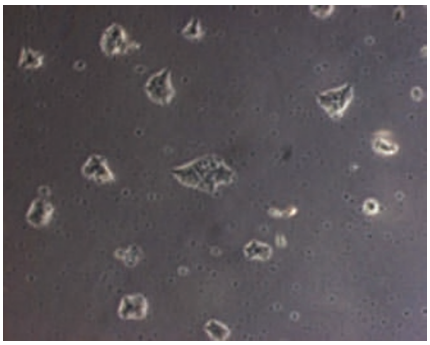
Activated PI3K/AKT confers resistance to trastuzumab but not lapatinib

Despite clinical benefits of HER2-targeted therapies in breast cancer, little progress has been made in understanding the resistance to such therapies. Now a study by O'Brien and coauthors has unraveled the role of PI3K/AKT signaling. "We observed that the majority of our trastuzumab resistant cell lines remain sensitive to lapatinib, providing further evidence that these two agents have independent mechanisms of resistance."

A major limitation of previous studies is that they have used only one or two cell models to identify specific alterations. To address this issue, O'Brien's team adopted rigorous screening of 18 HER2-positive breast cancer cell lines by two-dimensional and three-dimensional drug response assays. "We calculate the growth rate of cells in the presence and absence of drug, which allows for any error in cell seeding," O'Brien explains.

Cell lines with increased PI3K/AKT activity were resistant to trastuzumab but not lapatinib, as demonstrated by the lack of effect on AKT phosphorylation in trastuzumab-treated cells but reduced phosphorylation in response to lapatinib. Levels of HER2 protein did not correlate with response to trastuzumab, but did correlate significantly with lapatinib response. Moreover, HER2 phosphorylation and levels of p95HER2, a truncated HER2 with intact kinase activity, were not associated with trastuzumab response; however, lapatinib response significantly correlated with increased levels of phosphorylated HER2 and p95HER2. Total HER2 levels correlated closely with p95HER2 levels, suggesting that this may not be an independent marker of response to lapatinib.

High levels of PTEN protein were strongly associated with trastuzumab sensitivity, whereas high levels of phosphorylated AKT associated with trastuzumab resistance. Interestingly, across the cell-line panel, lapatinib response was independent of *PI3K* mutation and PTEN status. "The immediate implications from this research are that other research groups can use the library of response data we have created to study and bring forward the field of resistance to HER2-targeted therapy," comments O'Brien.



BT-474 cells and lapatinib sensitivity. Courtesy of N. O'Brien

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