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Genetic approach provides new insight into trastuzumab resistance in breast cancer

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A new study provides important insight into the mechanisms involved in resistance to treatment of breast cancer patients with trastuzumab (Herceptin). The research, published by Cell Press in the October issue of the journal *Cancer Cell*, identifies markers that may help to identify patients who are unlikely to respond to trastuzumab treatment and provides a potential strategy for treating these patients.

Trastuzumab is an antibody used as a therapy for patients whose breast cancers produce excess amounts of the protein HER2. However, almost half of these breast cancer patients are nonresponsive to trastuzumab therapy or become resistant during treatment. To better understand the antitumor activity of trastuzumab, Dr. Rene Bernards from The Netherlands Cancer Institute and his colleagues used a large-scale genome-wide RNA interference screen to search for genes involved in trastuzumab resistance in breast cancer.

The researchers identified only the tumor suppressor PTEN as a modulator of trastuzumab sensitivity in a breast cancer cell line. Earlier findings had associated PTEN with resistance to trastuzumab-based therapy, and loss of PTEN is known to result in hyperactivation of the PI3K pathway. Abnormal activation of this cell survival signaling pathway has been identified in many primary breast cancers. Hyperactivation of the PI3K pathway also can be caused by activating mutations of the PIK3CA gene.

“This finding, along with the high frequency of PIK3CA activating

mutations in breast cancer, led us to investigate whether PI3K pathway activity, as assessed by cancer-associated activating mutations (of PIK3CA) or altered levels of PTEN, was able to predict trastuzumab resistance in the clinic," explains Dr. Bernards. This combined analysis identified twice as many patients at increased risk for disease progression as would analyzing PTEN alone and proved to be statistically significant as a biomarker for prognosis after trastuzumab therapy, indicating that assessment of PTEN expression together with PIK3CA mutation is required for optimal prediction of disease progression after trastuzumab therapy for breast cancer.

"Importantly, this study also illustrates the power of in vitro RNAi screens combined with confirmation on patient samples to identify biomarkers useful for predicting treatment response in the clinic," says Dr. Bernards. "It is too early to use these biomarkers; further validation studies are required before they can be used in the clinic. Nevertheless, it is likely that these findings will lead to a better understanding of resistance mechanisms and how to circumvent them as well as more reliable identification of the most effective treatment for individual patients."

Source: Cell Press