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Team discovers new mechanism of acquired resistance to breast cancer drugs

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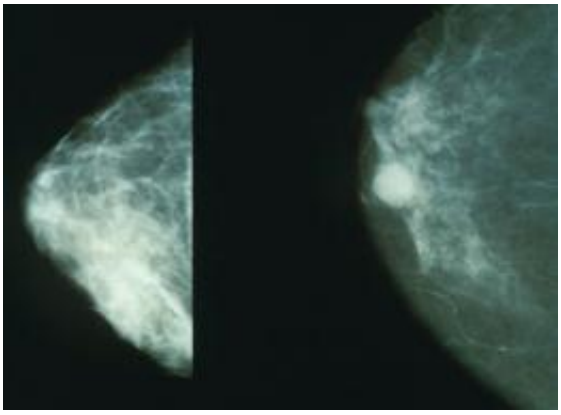

Mammograms showing a normal breast (left) and a cancerous breast (right). Credit: Wikipedia.

In the search for new approaches to treat ERBB2 (also known as HER2) positive breast cancers that have become drug-resistant, Dartmouth's Norris Cotton Cancer Center investigator Manabu Kurokawa, PhD, led a team in discovery of a novel cancer resistance mechanism with findings published in *Cell Cycle*.

"Approximately 25% of breast cancers overexpress and depend on the protein ERBB2 for survival," said Kurokawa. "Current therapies take advantage of this by using targeted drugs such as Trastuzumab or Lapatinib to specifically inhibit ERBB2, but eventually they become ineffective as the cancer develops resistance to those drugs."

The team's investigation showed that ERBB4 (also known as HER4) is a driver protein in ERBB2-postive breast cancers that have developed resistance to first- or second-line treatments. After seeing that pan-ERBB inhibitors remain effective against ERBB2-positive breast cancer cells with acquired resistance to anti-ERBB2 drugs, they used siRNA knockdowns of individual ERBB members to identify ERBB4 as crucial for the survival of resistant, but not naïve, ERBB2-positive breast cancer cells. Then, they confirmed the importance of ERBB4 via immunohistochemistry analysis of Lapatinib-resistant tumors in mice.

The role of ERBB4 in breast cancer has been controversial. Some studies say that ERBB4 does not play a role in breast cancer, and others have even suggested that it has anti-proliferative effects. "We have shown that when ERBB2-postive breast cancers develop resistance to anti-ERBB2 drugs, they shift their dependence from ERBB2 to ERBB4, which acts as a new driver of cancer survival and proliferation," explained Kurokawa.

The discovery of ERBB4 as a driver protein in ERBB2-positive cells with resistance to anti-ERBB2 drugs suggests that anti-ERBB4 drugs would be highly beneficial to patients who no longer respond to first or second-line treatments. "Identifying a cancer driver is crucial for cancer treatment because it allows the use of targeted therapies, which have less side-effects than conventional chemotherapy drugs, against a particular protein," said Kurokawa.

The next step for Kurokawa's Dartmouth team is to elucidate the mechanisms by which ERBB2-positive breast cancers shift their dependence from ERBB2 to ERBB4. The PI3K/AKT pathway is a suspect, and its well-known links to cellular proliferation and survival may be connected to mediating the change at the cellular level.

More information: *Cell Cycle*, www.tandfonline.com/doi/abs/10 … 15384101.2014.994966

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