Researchers find new approach to treat drug-resistant HER2-positive breast cancer

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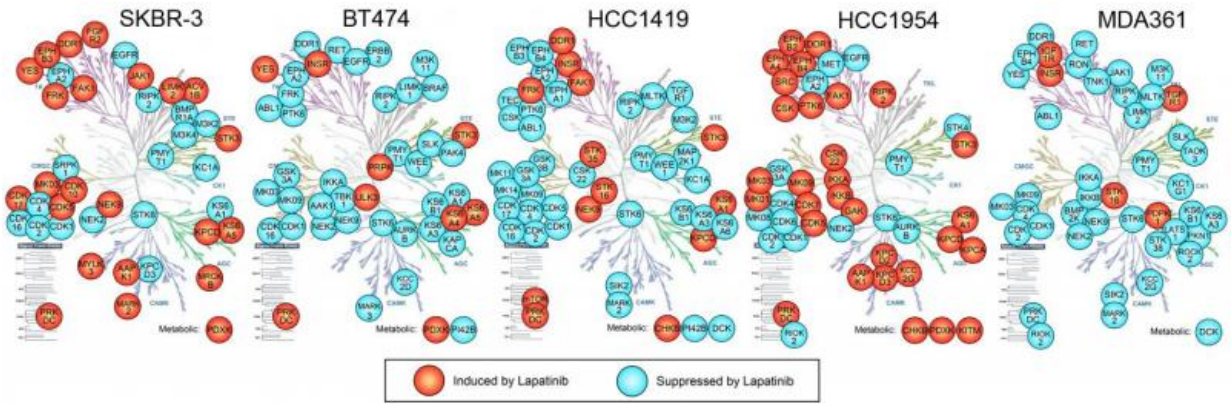

When the drug lapatinib inhibits the expression of the HER2 kinase in five different HER2-positive breast cancer cell lines, other kinases are also tamped down (blue) but several more kinases are activated (red), leading to drug resistance and tumor growth. Credit: Tim Stuhlmiller, PhD, UNC School of Medicine

Resistance to therapy is a major problem in the cancer field. Even when a treatment initially works, the tumors often find ways around the therapy. Using human cell lines of the HER2-positive breast cancer subtype, researchers from the UNC School of Medicine and UNC Lineberger Comprehensive Cancer Center have detailed the surprising ways in which resistance manifests and how to defeat it before it happens.

The discovery, published today in the journal *Cell Reports*, provides the experimental evidence for the potential development of a novel combination therapy for HER2-positive breast cancer. The combination includes the FDA approved drug lapatinib and a new experimental drug called a BET bromodomain inhibitor, which works by disrupting the expression of specific genes.

This study, a collaboration of 20 University of North Carolina researchers, is the first time a BET bromodomain inhibitor has been shown to prevent the onset of resistance to drugs such as lapatinib in breast cancer cells.

"This research was done in cell lines of human HER2-positive breast cancer, not in patients; but the results are very striking," said Gary Johnson, PhD, Kenan Distinguished Professor and chair of the department of pharmacology, member of the UNC Lineberger Comprehensive Cancer Center, and senior author of the paper. "The combination treatments are currently being tested in different mouse models of breast cancer. Our goal is to create a new kind of therapy that could help oncologists make the response to treatment more durable and lasting for breast cancer patients."

The HER2-positive subtype accounts for 15 to 20 percent of all breast cancer diagnoses. Only about one-third of these patients respond well to standard therapy. But even patients that initially respond eventually develop resistance. This is a universal problem of drugs that target specific proteins called kinases that drive tumor growth. Kinases are essential for cellular activities, such as movement, division, and signaling to other proteins to promote cell survival and growth. In this subtype of breast cancer, HER2 is the primary kinase involved in the growth of these tumors. When it's blocked with a drug like lapatinib, cancer cells have ways to get around the roadblock by using other kinases.

Tim Stuhlmiller, PhD, a postdoctoral fellow in Johnson's lab and first author of the paper, conducted experiments using a technique to determine kinase activity on a global scale throughout a group of given cells - a technology that Johnson's lab had previously developed.

Stuhlmiller was able to see what happened to HER2-positive human cancer cells when treated with the HER2 inhibitor lapatinib. As expected, each cell line developed resistance to the drug. But, surprisingly, each cell line resisted in different ways. Not just one or two kinases activated to beat the lapatinib. Many kinases responded. And they were not the same kinases from cell line to cell line. But they did the same thing: they ensured that the cancer cells survived and grew.

"It was amazing," Stuhlmiller said. "We found this massive up-regulation of many different kinases that could either reactivate the main HER2 signaling pathway or bypass it entirely. In fact, we discovered that nearly 20 percent of the cell's entire gene expression profile was dysregulated when we treated the cells with lapatinib."

Dysregulated genes lead to abnormal amounts of proteins. These proteins - the kinases - drive resistance to anti-cancer drugs. This research strongly suggests that there are many different ways HER2-positive cancer cells can compensate for the initial blockage of the HER2 protein. Thus, targeting all of these specific kinases would be extremely difficult.

"Because of toxicity concerns, you couldn't inhibit all these kinases that potentially help cancer cells compensate in the face of a HER2 inhibitor," Stuhlmiller said. "The more drugs you try to use, the more toxic that would be for patients and the lower the dose people would be able to tolerate.

"So that's one take home message," he said. "But the main message is we

used a different kind of drug to block that entire massive kinase response before it ever happened."

For that, Johnson's team used a BET bromodomain inhibitor. It's part of a new class of drugs that targets proteins involved in gene transcription - when particular parts of DNA are copied into RNA; this is the first step in the creation of enzymes, such as kinases.

Johnson's team tested several BET bromodomain inhibitors, including one currently in clinical trials to treat blood cancers and a specific type of leukemia. During experiments, Johnson's team found that BET bromodomain inhibitors targeted the gene transcription of most of the kinases responsible for resistance. By combining lapatinib with a BET bromodomain inhibitor, Stuhlmiller found that the HER2 kinase was blocked, as planned. Also, the massive kinase activation that typically followed HER2 inhibition never happened. The second drug suppressed the kinase response.

"We blocked it before it could happen," Stuhlmiller said. "In all five cell lines we tested, there were no cancer cells left because the combination therapy blocked their growth. Essentially, we made the activity of lapatinib durable." As a result, the cancer cells were annihilated.

Johnson's lab and their UNC collaborators are currently working to replicate their findings in animal models of HER2-positive breast cancer. They think these types of combination therapies are going to be necessary to prevent resistance in the clinic. They're also studying the effects of BET bromodomain inhibitors on other breast cancer subtypes, such as triple-negative breast cancer, another subtype that is difficult to treat.

Provided by University of North Carolina Health Care

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