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Delivering a one-two punch: New drug combination shows promise in treating breast cancer

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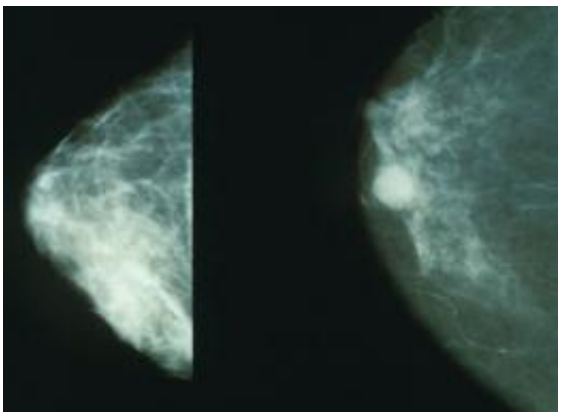

Mammograms showing a normal breast (left) and a cancerous breast (right). Credit: Wikipedia.

The uncontrolled growth of cancer cells arises from their ability to hijack the cell's normal growth program and checkpoints. Usually after therapy, a second cancer-signaling pathway will open after the primary one shuts down—creating an ingenious escape route for the cancer cell to survive. The answer, say Case Western Reserve researchers, is to anticipate and block that back-up track by prescribing two drugs from the start. The results of the project, led by Ruth Keri, PhD, Professor and Vice Chair Department of Pharmacology, and Associate Director for Basic Research in the Case Comprehensive Cancer Center, appeared this fall in the journal *Cancer Research*.

Of course, the effort was hardly so simple as doubling up. The scientists had to pick specific medications that precisely countered the cancer cells' moves. Essentially, Keri and her colleagues used one medicine, rapamycin, to stop the cancer cell growth, and a second one, dasatinib, to trick the cancer cells into thinking that the original growth was still proceeding apace.

The scientists selected the drug rapamycin, an inhibitor of the protein mTOR (mammalian target of rapamycin), and dasatinib, a drug that blocks Src-family kinases (SFKs). Interestingly, neither drug, when used alone, has demonstrated significant clinical efficacy in treating breast cancer. Ongoing clinical trials combining dasatinib or rapamycin with other therapies have been promising; however, this study is the first to show that the combination of these two drugs may be beneficial in treating breast cancer.

Here is how cancer cell growth works and how rapamycin and dasatinib interrupts the process. mTOR sends signals calling for the hyperactive growth of cells characteristic of cancer. If mTOR signals are blocked, another protein, AKT (protein kinase B), takes over and signals cancer growth and survival to continue. SFKs also work in concert with mTOR and AKT in sending signals to promote tumor growth as well.

Researchers in the Keri lab found that the drug dasatinib blocks SFKs from sending signals, and without the SKF signaling, AKT does not get the message that mTOR signaling has been shut down by rapamycin. Therefore, AKT does not know to step in and take over mTOR's job in sending the necessary signals for tumor growth to continue.

"We found if you put the two drugs together, you have much better ability to kill tumors than applying either drug alone," Keri said. "That's the major discovery. Prescribing both is much better than just selecting one or the other."

Investigators used two different mouse models of breast cancer to demonstrate the efficacy of this drug combination. Magnetic resonance imaging (MRI), the same type of imaging that follows patients' tumors, was performed periodically to visualize tumor growth. When the mice eventually developed tumors, one group received the dual treatment with rapamycin and dasatinib, another group with rapamycin alone, still another group with dasatinib alone and a final group with placebo.

In the combination rapamycin and dasatinib treated group, tumors either shrunk, or vanished altogether. None of the mice in this group experienced tumor growth while receiving dual treatment. In contrast, mice in the treatment groups receiving either drug alone experienced continued tumor growth. In the placebo group, tumors grew rapidly throughout the course of the study.

Worse, when treatment was stopped in the groups receiving the single drugs, the tumors grew back to their original size and even larger within a few days. When the combined drug treatment stopped, tumor regrowth was greatly delayed by weeks.

"Dual treatment clearly delays the regrowth of tumors," Keri said.

Keri and her team next hope to launch a clinical trial to determine whether this combination therapy is as effective in humans as it is in mice. The first step will be to assess whether humans can handle the combination of medications without being overwhelmed by their toxicity. For their part, the mice showed no issues with toxicity.

"We hope to see the same effect in humans that we saw in the mouse model, and ultimately, to stop, or significantly delay, tumor growth," Keri said.