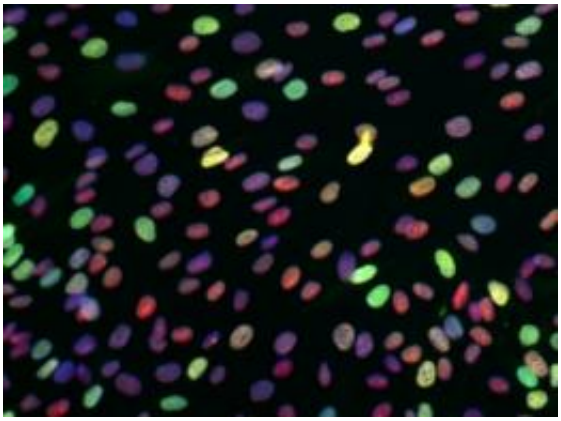
MedicalXpress

One-two punch knocks out aggressive breast cancer cells

May 11 2012



Differential cell responses to chemotherapy treatment. The photo shows a range of responses of similar cells to the chemotherapeutic drug doxorubicin. The most intensely responding drugs are shown in yellow, many of which will die. Green cells are alive but not dividing. Red cells are continuing to grow and divide. Yaffe and colleagues have figured out how to increase the proprotion of triple negative breast cancer cells that can be killed by a specific time-ordered regiment of growth factor inhibitors and chemotherapy, with direct application to clinical treatment. Image courtesy of Neil Ganem, Michael Yaffe and David Pellman

Doctors have long known that treating patients with multiple cancer drugs often produces better results than treatment with just a single drug. Now, a study from MIT shows that the order and timing of drug administration can have a dramatic effect.

In the new paper, published in *Cell* on May 11, the researchers showed that staggering the doses of two specific drugs dramatically boosts their ability to kill a particularly malignant type of breast cancer cells.

The researchers, led by Michael Yaffe, the David H. Koch Professor of Biology and Biological Engineering at MIT, are now working with researchers at Dana-Farber Cancer Institute to plan clinical trials of the staggered drug therapy. Both drugs — erlotinib and doxorubicin — are already approved for cancer treatment.

Yaffe and postdoc Michael Lee, lead author of the *Cell* paper, focused their study on a type of breast cancer cells known as triple negative, meaning that they don't have overactive estrogen, progesterone or HER2 receptors. Triple-negative tumors, which account for about 16 percent of breast cancer cases, are much more aggressive than other types and tend to strike younger women.

"For triple-negative breast cancer cells, there is no good treatment. The standard of care is combination chemotherapy, and although it has a good initial response rate, a significant number of patients develop recurrent cancer," says Yaffe, who is a member of the David H. Koch Institute for Integrative Cancer Research at MIT.

Uncontrolled growth

For the past eight years, Yaffe has been studying the complex cell-signaling pathways that control cells' behavior: how much they grow, when they divide, when they die. In cancer cells, these pathways often go haywire, causing the cells to grow even in the absence of any stimulus and to ignore signals that they should undergo cell suicide.

Yaffe became intrigued by the idea that drug-induced changes in these signaling pathways, if staggered in time, could switch a cancerous cell

into a less malignant state. “Our previous systems-biology work had primed us to the idea that you could potentially drive a cell from a state in which only a fraction of the tumor cells were responsive to chemotherapy into a state where many more of them were responsive by therapeutically rewiring their signaling networks in a very time-dependent way,” he says.

Specifically, he and Lee thought it might be possible to sensitize cancer cells to DNA-damaging drugs — the backbone of most chemotherapy — by first giving them another drug that shuts down one of the haywire pathways that promote uncontrollable growth. They tested different combinations of 10 DNA-damaging drugs and a dozen drugs that inhibit different cancerous pathways, using different timing schedules.

“We thought we would retest a series of drugs that everyone else had already tested, but we would put in wrinkles — like time delays — that, for biological reasons, we thought were important,” Lee says. “I think had it not worked, we would have gotten a lot of pushback, but we were pretty convinced that there was a lot of information being left on the table by everyone else.”

Of all combinations they tried, they saw the best results with pretreatment using erlotinib followed by doxorubicin, a common chemotherapy agent. Erlotinib, approved by the FDA to treat pancreatic cancer and some types of lung cancer, inhibits a protein found on cell surfaces called the epidermal growth factor (EGF) receptor. When constantly active, as it is in many cancer cells, the EGF receptor stimulates a signaling pathway that promotes uncontrolled growth and division.

The researchers found that giving erlotinib between four and 48 hours before doxorubicin dramatically increased cancer-cell death. Staggered doses killed up to 50 percent of triple-negative cells, while simultaneous

administration killed about 20 percent. About 2,000 genes were affected by pretreatment with erlotinib, the researchers found, resulting in the shutdown of pathways involved in uncontrolled growth.

“Instead of looking like this classic triple-negative type of tumor, which is very aggressive and fast-growing and metastatic, they lose their tumorigenic quality and become a different type of tumor that is actually quite unaggressive, and very easy to kill,” Lee says.

However, if the drugs were given in the reverse order, doxorubicin became less effective than if given alone.

Targeted treatment

This treatment worked not only in cancer cells grown in a lab dish, but also in mice with tumors. When treated with a one-two punch of erlotinib and doxorubicin, the tumors shrank and did not grow back for the duration of the experiment (two weeks). With chemotherapy alone, or when the two drugs were given at the same time, the tumors initially shrank but then grew back.

A combination of high-throughput measurements and computer modeling was used to reveal the mechanism for increased tumor killing, and to identify a biomarker for drug response. The researchers found that the treatment was most effective in a subset of triple-negative breast cancer cells with the highest levels of EGF receptor activity. This should allow doctors to screen patients’ tumors to determine which would be most likely to respond to this novel treatment.

The research is “groundbreaking in its demonstration that the principles of order and time are essential to the development of effective therapies against complex diseases,” Rune Linding, research group leader at the Technical University of Denmark, and Janine Erler, associate professor

at the University of Copenhagen, wrote in a commentary accompanying the paper in *Cell*. “As disease researchers, we must consider network states, and this and other studies serve as a model for a new generation of cancer biologists.”

The concept of staggering drug treatments to maximize impact could be very broadly applicable, Yaffe says. The researchers found similar boosts in tumor killing by pretreating HER2-positive breast cancer cells with a HER2 inhibitor, followed by a DNA-damaging drug. They also saw good results with erlotinib and doxorubicin in some types of lung cancer.

“The drugs are going to be different for each cancer case, but the concept that time-staggered inhibition will be a strong determinant of efficacy has been universally true. It’s just a matter of finding the right combinations,” Lee says.

The findings also highlight the importance of systems biology in studying cancer, Yaffe says. “Our findings illustrate how systems engineering approaches to cell signaling can have large potential impact on disease treatment,” he says.

The research was funded by the National Institutes of Health Integrative Cancer Biology Program and the Department of Defense.

Provided by Massachusetts Institute of Technology