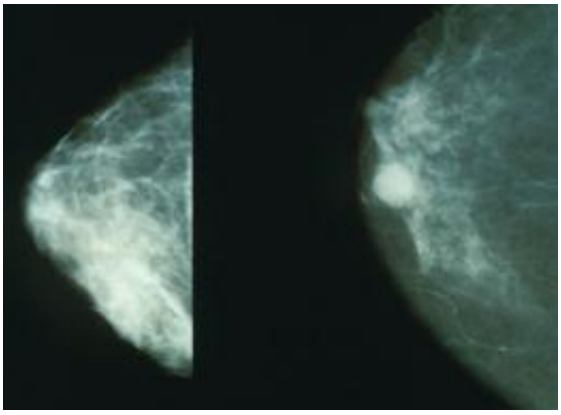
MedicalXpress

Toughest breast cancer may have met its match

December 8 2014



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

Triple-negative breast cancer is as bad as it sounds. The cells that form these tumors lack three proteins that would make the cancer respond to powerful, customized treatments. Instead, doctors are left with treating these patients with traditional chemotherapy drugs that only show long-term effectiveness in 20 percent of women with triple-negative breast cancer. Now, researchers at The Johns Hopkins University have discovered a way that breast cancer cells are able to resist the effects of chemotherapy—and they have found a way to reverse that process.

A report of their findings was published online in the journal *Proceedings of the National Academy of Sciences* on Dec. 1.

Triple-negative breast cancers account for about 20 percent of all breast cancers in the United States, and 30 percent of all breast cancers in African-American women. In addition to being resistant to chemotherapy, they are known to include a high number of breast cancer stem cells, which are responsible for relapses and for producing the metastatic tumors that lead to the death of patients with cancer. Previous research revealed that triple-negative breast cancer cells show a marked increase in the activity of many genes known to be controlled by the protein hypoxia-inducible factor (HIF). Given these past results, a research team directed by Gregg Semenza, M.D., Ph.D., decided to test whether HIF inhibitors could improve the effectiveness of chemotherapy.

"Our study showed that chemotherapy turns on HIF and that HIF enhances the survival of breast cancer stem cells, which are the cancer cells that must be killed to prevent relapse and metastasis," says Semenza, the C. Michael Armstrong Professor of Medicine at Johns Hopkins and a Johns Hopkins Kimmel Cancer Center expert. "The good news is that we have drugs that block HIF from acting."

Semenza's study began by treating lab-grown triple-negative breast cancer cells with the chemotherapy drug paclitaxel and looking for changes in HIF levels. After four days of treatment, HIF protein and activity levels had increased, as had the percentage of breast cancer stem cells among the surviving cells. When Semenza's team, led by postdoctoral fellow Debangshu Samanta, Ph.D., genetically altered the cancer cells to have less HIF, the cancer stem cells were no longer protected from death by chemotherapy, demonstrating that HIF was required for the cancer stem cells to resist the toxic effects of paclitaxel, Semenza says.

At the molecular level, the team found that one of the ways HIF enhances the survival of the stem cells is by increasing the levels of a

protein, multidrug resistance protein 1 (MDR1), which acts like a pump to expel chemotherapy from cancer cells. However, when triple-negative breast cancer cells were given paclitaxel plus the HIF inhibitor digoxin, MDR1 levels went down rather than up.

In mice that were implanted with triple-negative breast cancer cells, treatment with digoxin and paclitaxel decreased tumor size by 30 percent more than treatment with paclitaxel alone. The combination therapy also decreased the number of breast cancer stem cells and the levels of MDR1. Treatment with digoxin plus a different chemotherapy drug, gemcitabine, brought tumor volumes to zero within three weeks and prevented the immediate relapse at the end of treatment that was seen in mice treated with gemcitabine alone.

Analysis of patient databases showed that among women with triple-negative breast cancer who are treated with chemotherapy, those with higher-than-average levels of HIF activity in their tumor were much more likely to die of breast cancer than those with lower-than-average HIF levels. Samanta notes that the HIF inhibitor digoxin is already approved by the Food and Drug Administration for treating heart failure. Several other drugs that inhibit HIF have also been identified and are currently being tested in patients with cancer. If the team's work is verified in clinical trials, the researchers think that potentially unresponsive patients could be identified before treatment and given a more effective combination therapy.

More information: View the article at *PNAS*: dx.doi.org/10.1073/pnas.1421438111

Provided by Johns Hopkins University School of Medicine