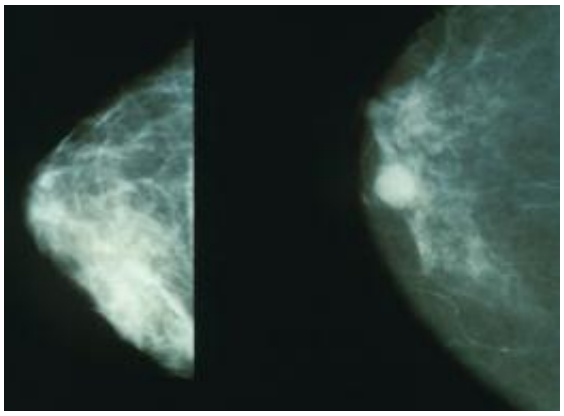
Scientists link gene to tamoxifen-resistant breast cancers

25 November 2014



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

After mining the genetic records of thousands of breast cancer patients, researchers from the Johns Hopkins Kimmel Cancer Center have identified a gene whose presence may explain why some breast cancers are resistant to tamoxifen, a widely used hormone treatment generally used after surgery, radiation and other chemotherapy.

The gene, called MACROD2, might also be useful in screening for some aggressive forms of breast cancers, and, someday, offering a new target for therapy, says Ben Ho Park, M.D., Ph.D., an associate professor of oncology in the Kimmel Cancer Center's Breast Cancer Program and a member of the research team.

The drug tamoxifen is used to treat estrogen receptor-positive breast cancers. Cells in this type of breast cancer produce protein receptors in their nuclei which bind to and grow in response to the hormone estrogen. Tamoxifen generally blocks the binding process of the estrogen-receptor, but some estrogen receptor-positive cancers are resistant or become resistant to tamoxifen therapy, finding ways to elude its effects. MACROD2 appears to code for a biological path to tamoxifen resistance by diverting the drug from its customary blocking process to a different way of latching onto breast cancer cell receptors, causing cancer cell growth rather than suppression, according to a report by Park and his colleagues published online Nov. 24 in the *Proceedings of the National Academy of Sciences*.

Specifically, the team's experiments found that when the gene is overexpressed in breast cancer cells—producing more of its protein product than normal—the cells become resistant to tamoxifen.

One piece of evidence for the gene's impact was demonstrated when the Johns Hopkins scientists blocked MACROD2's impact in breast cancer cell cultures by using an RNA molecule that binds to the gene to "silence," or turn off, the gene's expression. But the technique only partially restored the cells' sensitivity to tamoxifen.

To conduct the study, the scientists examined two well-known databases of breast cancer patients' genetic information, The Cancer Genome Atlas and the Molecular Taxonomy of Breast Cancer International Consortium study. Patients who had MACROD2 overexpressed in primary breast cancers at the original breast cancer site had significantly worse survival rates than those who did not, according to an analysis of the patient databases.

With this in mind, the Johns Hopkins scientists suggest that clinicians may be able to look at MACROD2 activity to help them identify aggressive breast cancers at early stages of growth.

The team's analysis also found that MACROD2 overexpression was present in the majority of metastases in patients with tamoxifen-resistant tumors and in tumor cells that had spread from their original site in the breast. The latter finding, says Park, suggests that tamoxifen resistance caused by the gene might be a process that develops over

time as women take the drug.

Finding a small group of a patient's cancer cells that overexpress MACROD2, he explained, means those cells are likely to be the "survivors" of early treatment with tamoxifen that go on to multiply and cause metastatic tumors. "The resultant cells—or the vast majority of them—are now all overexpressing MACROD2, and are the cells that are aggressive and will cause trouble," he adds.

Park and his team cautioned that there may be other genetic factors that control tamoxifen resistance, and that nothing in their study should suggest that tamoxifen use should be avoided.

More information: MACROD2 overexpression mediates estrogen independent growth and tamoxifen resistance in breast cancers , www.pnas.org/cgi/doi/10.1073/pnas.1408650111

Provided by Johns Hopkins University School of Medicine