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Cancer-causing protein strongly tied to hormone resistance in breast cancer

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In dozens of experiments in mice and in human cancer cells, a team of Johns Hopkins scientists has closely tied production of a cancer-causing protein called TWIST to the development of estrogen resistance in women with breast cancer. Because estrogen fuels much breast cancer growth, such resistance — in which cancers go from estrogen positive to estrogen negative status — can sabotage anticancer drugs that work to block estrogen and prevent disease recurrence after surgery. Estrogen resistance develops in over half of women taking estrogen-blocking medications, such as tamoxifen, and exists from the start in many other women.

The Johns Hopkins-led team of cancer experts also reports that stalling TWIST production significantly reverses estrogen resistance.

“Now that we know TWIST has a major role in controlling estrogen resistance in breast cancer, we can investigate the value of anti-TWIST therapies and how they make possible postsurgical hormone therapy for all women who have had invasive breast cancer,” says senior study investigator and breast cancer biologist Venu Raman, Ph.D. “We suspect that TWIST production may be an underlying cause of estrogen resistance,” adds Raman, an associate professor in the Department of Radiology at the Johns Hopkins University School of Medicine and its Kimmel Cancer Center.

Estrogen resistance, Raman says, not only renders tamoxifen or aromatase inhibitors, such as anastrozole and letrozole, ineffective in

women whose original estrogen receptor status was positive, but also rules out these standard treatment options for the one-quarter of women who at the time of their diagnosis already are estrogen receptor negative.

The latest findings of Raman and his team, to be published in the journal *Oncogene* online Nov. 7, are the first to demonstrate a detrimental link between TWIST activity and estrogen resistance. Previous work by Raman and others had shown that TWIST was more active in women with aggressive breast cancer and less active in women whose breast tumors were benign. But researchers had not yet established the direct connection to lowered levels of estrogen receptors.

In five separate cancerous cell lines grown in the laboratory, some from women with aggressive forms of breast cancer and the rest without, TWIST activity was shown in all cells to be strongly active where estrogen receptor activity was low. Further tests in human tissue samples showed the same result. In additional experiments in mice injected with breast cancer cells, researchers found that TWIST activation led to continuous and aggressive tumor growth despite tamoxifen therapy, while in mice tumors with low levels of TWIST, tumor growth waned within two months of treatment.

The new experiments are also believed to be the first to show that estrogen resistance is not a permanent condition, the researchers report. Halting TWIST production in two cell lines resulted in some return of anti-estrogen drug sensitivity. Almost 40 percent of cells tested reverted from being estrogen receptor negative to estrogen receptor positive, and some 30 percent of these cell receptors became tamoxifen sensitive, allowing the drug to target the cancerous cells.

As part of the same set of experiments, Raman and his colleagues revealed how TWIST lowers estrogen receptor activity so that it can no longer bind with the estrogen hormone or drugs designed to counteract

its cancerous effects. Researchers found that increased levels of TWIST attracted and pulled in another protein, DNMT3B, which causes methylation, or addition of methyl chemical groups to a key part of the estrogen receptor, shutting down its action. TWIST also interacts with another protein, HDAC1, which causes the de-acetylation, or removal of acetyl chemical groups from a key part of the estrogen receptor, and leads to the structural compression and blocking of the estrogen receptor.

“Our study results are particularly exciting because we went beyond establishing an association to identifying several new routes for potentially controlling and possibly reversing estrogen resistance in breast cancer,” says lead study investigator and breast cancer biologist Farhad Vesuna, Ph.D., an instructor at Johns Hopkins.

Vesuna says the team’s next steps are to look at various, specific means of interrupting TWIST protein production, on its own or by some combination with stalling or reversing methylation and de-acetylation of estrogen receptors, done by blocking DNMT3B or HDAC1.

Vesuna points out that TWIST is usually found at very low levels in adults, but is nevertheless an essential component to human embryonic development. However, raised TWIST levels have been shown in most other cancers, including tumors of the prostate, head and neck, bladder and lung. So the team’s scientific investigations of TWIST could extend to the role it plays in all cancers, not just breast cancer.

This year alone, more than 230,000 women in the United States are estimated to be diagnosed with invasive breast cancer, with an estimated 39,000 deaths. More than 2.6 million American women are breast cancer survivors.

More information: www.nature.com/onc/index.html

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