Researchers discover new hormone receptors to target when treating breast cancer

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According to the United States Centers for Disease Control and Prevention, breast cancer is the most common cancer in women. For patients whose breast cancers are hormone-dependent, current treatment focuses on using drugs that block estrogen (a type of hormone) from attaching to estrogen receptors on tumor cells to prevent the cells from growing and spreading.

In a new study, first study author, Sandro Santagata, MD, PhD, Brigham and Women's Hospital (BWH) Department of Pathology, and senior study author Tan A. Ince MD, PhD, University of Miami Miller School of Medicine (formerly of BWH Department of Pathology), along with a team of researchers from both institutions found that there are other receptors that can be targeted—androgen and vitamin D receptors.

The findings offer the possibility of expanding the ways patients with breast cancer are treated with hormone therapy.

"These findings may change how we treat breast cancer," said Santagata. "Since at least 50 percent of patients with breast cancer express all three receptors—estrogen, androgen and vitamin D in their tumor cells, this may allow clinicians to consider triple hormone treatments, which is a new concept, as opposed to treating patients by targeting only estrogen receptors."

The study published online in the *Journal of Clinical Investigation*.

When clinicians categorize human breast cancer tumors, they do so by grouping them into one of three categories based on the type of receptor present or absent on the tumor: estrogen receptor (ER positive/negative), progesterone receptor (PR positive/negative), and human epidermal growth factor receptor 2 (HER2 positive/negative).

In the study, the researchers explored the landscape of cells that make up the surfaces of breast tissue to provide a better definition of the subtypes of cells present on these surfaces. They studied more than 15,000 normal breast cells and discovered eleven previously undefined cell subtypes. Interestingly, these eleven normal breast cell types were categorized into four new hormonal differentiation groups (HR 0, 1, 2, 3), which were characterized by vitamin D, androgen and estrogen hormone receptor expression.

The researchers took this information and compared it against 3,157 human breast tumors of patients and found that the patients' tumor make-up were similar to one of the eleven normal cell types they discovered. Moreover, the patients had different survival rates and responses to hormone treatments depending on whether the cell types were in the HR 0, 1, 2, or 3 sub-group.

According to the researchers, the HR categories may be helpful in refining classifications presently used to classify breast cancers. Moreover, the findings open the door to the option of triple hormone treatments, which may be more effective than single hormone treatments and may help patients who are resistant to anti-estrogen treatments.

"There are many other interesting treatment opportunities that our findings may lead to," said Santagata. "For instance, early data suggest that targeting androgen and vitamin D receptors in addition to standard chemotherapy may increase effectiveness, and may allow for lower doses of chemotherapy with the same effect."

Also, according to Santagata, there are tumors

called triple-negative breast carcinomas, which cannot be treated with conventional endocrine-targeted therapies. The study results suggest that two-thirds of these patients may be candidates for androgen and vitamin D-targeted hormone therapy. Perhaps equally important, researchers found that some breast tumor subtypes, such as basal-like carcinoma, have been classified erroneously due to inaccurate taxonomy of normal cell types.

"It is very exciting to show that there is a similar molecular diversity in normal breast cells and in breast cancer itself, and then to use this information to suggest interesting new therapeutic possibilities," said Santagata. "We have much more to learn about why normal breast cells are so diverse and how that information can help us better improve the diagnosis, prognosis and treatment of breast cancer patients."

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