New universal breast cancer marker predicts recurrence and clinical outcome

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Reporting online in the *American Journal of Pathology*, researchers from the Kimmel Cancer Center at Jefferson have implicated the loss of a stromal protein called caveolin-1 as a major new prognostic factor in patients with breast cancer, predicting early disease recurrence, metastasis and breast cancer patient survival.

The absence of caveolin-1 in the stroma also appeared to be a marker for drug resistance in patients receiving tamoxifen, according to Michael Lisanti, M.D., Ph.D., professor in the departments of Cancer Biology, Medical Oncology and Biochemistry and Molecular Biology at Jefferson Medical College of Thomas Jefferson University.

According to Dr. Lisanti, who is also director of the Jefferson Stem Cell Biology and Regenerative Medicine Center at the Kimmel Cancer Center, caveolin-1 is expressed by cells in the stroma called fibroblasts, which are present in the connective tissue surrounding cancer cells. When cancer cells arise, the fibroblasts stop making caveolin-1.

"The idea that a prognostic biomarker is present in the stroma rather than the epithelial cancer cell is paradigm-shifting," Dr. Lisanti said. "Importantly, these findings could be developed into a diagnostic test that would not require DNA-based technologies. This inexpensive and cost-effective test would allow doctors to identify high-risk breast cancer patients at diagnosis and treat them more aggressively."

Dr. Lisanti, along with first author Agnieszka Witkiewicz, M.D.,

assistant professor of Pathology, Anatomy and Cell Biology at Jefferson, and other colleagues analyzed breast tissue samples from 154 women diagnosed with breast cancer. All samples were obtained from the University of Michigan. They used three tissue cores from each patient tumor sample, and analyzed each core for stromal caveolin-1 using immunohistochemistry staining.

The absence of stromal caveolin-1 was strongly associated with other predictors of more aggressive disease, such as higher tumor stage and lymph node metastasis. Among each subgroup of patients - grouped by prognostic factors such as hormone status, disease stage or lymph node status - a loss of stromal caveolin-1 remained the single strongest predictor of breast cancer patient outcome.

Also of note, among patients with ER-positive breast cancer who were taking tamoxifen, a loss of stromal caveolin-1 still predicted recurrence and poor clinical outcome. As many as 40 percent of patients who take tamoxifen in this setting relapse despite its significant effect on survival when used in the early stages of the disease.

"Resistance to tamoxifen is thought to be an epithelial 'cancer cell' phenomenon, but we show here that it is clearly a 'stromal' phenomenon," Dr. Lisanti said.

Progression-free survival (PFS) was also affected by the loss of stromal caveolin-1. Overall, the PFS in patients with an absence of stromal caveolin-1 was reduced by approximately 3.6-fold. In lymph-node positive patients, the difference in PFS was especially pronounced: The approximate five-year survival rate for patients positive for stromal caveolin-1 was 80 percent, vs. 7 percent for patients negative for stromal caveolin-1. That is an approximate 11.5-fold reduction in five-year PFS.

"This marker serves not only as a prognostic marker, but also as a means

of therapeutic stratification," Dr. Lisanti said. "We can identify this marker at breast cancer diagnosis, which is important because high-risk patients would benefit from more aggressive treatment and/or anti-angiogenic therapy."

In an additional study, published online in Cancer Biology & Therapy, the researchers also found that the loss of stromal caveolin-1 in ER-positive non-invasive breast cancers called ductal carcinoma in situ (DCIS) serves as a biomarker for progression to invasive breast cancer.

"This marker was highly predictive of development of invasive breast cancer in patients with DCIS," said Gordon Schwartz, M.D., a professor of Surgery at Jefferson, who was involved with the DCIS study. "We have been searching for a marker to separate patients with DCIS who require further treatment from those who might be treated with lumpectomy alone. If this marker can be validated further, then high-risk patients may be identified and treated to prevent the development of an invasive breast cancer. Those at low-risk would be spared from radiation therapy and/or mastectomy."

The prognostic value of a loss of caveolin-1 has now been validated in three independent patient populations. In an editorial appearing online in Cell Cycle, the researchers propose a "stromal" classification system that divides patients into high-risk and low-risk groups based on caveolin-1 status. Patients without caveolin-1 should be offered more aggressive therapy in addition to standard treatments.

"These are significant findings that do have to be validated in prospective breast cancer clinical trials," said Richard Pestell, M.D., Ph.D., director of the Kimmel Cancer Center at Jefferson, who was also involved with the studies. "However, we should start taking the breast tumor stroma into our clinical considerations sooner, rather than later."

Source: Thomas Jefferson University (news : web)