New insights into breast cancer spread could yield better tests and treatments

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A study combining tumor cells from patients with breast cancer with a laboratory model of blood vessel lining provides the most compelling evidence so far that a specific trio of cells is required for the spread of breast cancer. The findings could lead to better tests for predicting whether a woman's breast cancer will spread and to new anti-cancer therapies. The study, led by researchers at the NCI-designated Albert Einstein Cancer Center and Montefiore Einstein Center for Cancer Care(MECCC), was published online today in *Science Signaling*.

According to the National Cancer Institute, more than 232,000 American women developed breast cancer last year and nearly 40,000 women died from the disease. It is the most common cancer among women in the United States. Most breast cancer deaths occur because the cancer has spread, or metastasized, which means that cells in the primary tumor have invaded blood vessels and traveled via the bloodstream to form tumors elsewhere in the body.

In earlier studies involving animal models and human cancer cell lines, researchers found that breast cancer spreads when three specific cells are in direct contact: an endothelial cell (a type of cell that lines the blood vessels), a perivascular macrophage (a type of immune cell found near blood vessels), and a tumor cell that produces high levels of Mena, a protein that enhances a cancer cell's ability to spread. Where these three cells come in contact is where tumor cells can enter blood vessels—a site called a tumor microenvironment of metastasis, or TMEM. Tumors with high numbers of TMEM sites (i.e., they have a high TMEM "score")

were more likely to metastasize than were tumors with lower TMEM scores. In addition, the researchers found that cancer tissues high in a form of Mena called MenaINV were especially likely to metastasize. (MenaINV refers to the invasive form of Mena.)

"Those studies revealed new insights into how cancer might spread, but they didn't necessarily show what is happening in patients," said study leader Maja Oktay, M.D., Ph.D., associate professor of pathology at Albert Einstein College of Medicine Yeshiva University and attending cytopathologist at Montefiore. Since then, the scientists have extended their research to include patients with breast cancer. In 2011 they published findings on 40 patients showing a correlation between high MenaINV levels and high TMEM scores. The present study combines results from those 40 patients plus an additional 60 patients. All 100 patients had been diagnosed with invasive ductal carcinoma and were being treated at MECCC. Invasive ductal carcinoma is the most common type of invasive breast cancer, accounting for 80 percent of cases. In this disease, the cancer has grown through the duct walls and into the surrounding breast tissue.

For the subset of more recent patients, the researchers assessed tumor cell behavior—in particular, cancer cells' ability to cross the endothelium (inner layer) of blood vessels. They obtained tumor cells using fine needle aspiration and placed them in a novel engineered tissue assay designed to replicate the endothelium of a blood vessel—the barrier that cells must cross so they can spread from a primary tumor to distant sites. Biopsied tumor tissue from all 60 new patients was fixed in formalin and embedded in paraffin so that TMEM sites in the tissue could be counted.

Breast cancer cells able to cross the endothelial layer in this assay were found to have higher MenaINV levels compared with the total population of patients' aspirated cells. In addition, finding high levels of MenaINV correlated with finding high numbers of TMEM sites in

paraffin biopsy specimens from the same patients. The TMEM "score" for each biopsy specimen was calculated by counting the total number of TMEM sites observed within ten 400x magnification fields. Combining the results from all 100 patients showed that the findings were consistent across the three most common clinical subtypes of invasive ductal carcinoma.

"These results confirm that TMEM sites and MenaINV are essential for the spread of breast cancer in humans," said Dr. Oktay. "They also imply that MenaINV expression and TMEM score measure related aspects of a commonly used mechanism that human breast cancers use to metastasize."

Dr. Oktay noted that "the outcome for patients with metastatic breast cancer hasn't improved in the past 30 years despite the development of targeted therapies. It's critically important to learn more about the metastatic process so we can develop new ways to predict whether cancer will spread and identify new treatments."

The Einstein team is currently working with MetaStat, Inc., a biotechnology company located in Montclair, N.J., to develop a commercial TMEM test for assessing a patient's risk for metastatic breast cancer.

More information: The paper is titled "Invasive Breast Carcinoma Cells from Patients Exhibit MenaINV- and Macrophage-Dependent Transendothelial Migration."

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