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Cellular origin of a rare form of breast cancer identified

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Identifying the cellular origins of breast cancer might lead to earlier diagnosis and more efficient management of the disease. New research led by Charlotte Kuperwasser of Tufts University School of Medicine (TUSM) has determined that common forms of breast cancer originate from breast cells known as luminal epithelial cells while rarer forms of breast cancer, such as metaplastic carcinomas, originate from basal epithelial cell types. The study was published online ahead of print this week in *PNAS Early Edition* as part of its breast cancer special feature.

Clinicians and researchers classify breast cancers into subtypes based on both clinical features and molecular features, including expression of certain genes and proteins. These classifications help determine diagnosis, treatment decisions, and patient prognosis. The most common form of breast cancer, called invasive ductal carcinoma, is classified broadly into two types based on molecular features of the tumor cells: luminal-like cancers, which are sensitive to hormones, and the more aggressive basal-like cancers, which are not sensitive to hormones and tend to have a poorer prognosis.

However, there are also rare forms of breast cancer, some of which are called metaplastic carcinomas, where the cancer cells no longer resemble cells of the breast. Scientists do not yet fully understand how and why these different types of breast cancers form but one theory is that they originate from adult breast tissue stem cells.

"For the past several decades, most research efforts have been focused

on discovering cancer-causing genes in hope that this information might help us discover better treatments for breast cancer. While these efforts have led to successes in treating some common forms of breast cancer, they have not provided us with information regarding where breast cancer originates and in particular, the origins of rare forms of metaplastic breast cancers for which the best course of treatment has not yet been determined," said Kuperwasser, PhD, associate professor in the department of anatomy and cellular biology, Tufts University School of Medicine, and a member of the genetics and cell, molecular & developmental program faculties at the Sackler School of Graduate Biomedical Sciences at Tufts and the Molecular Oncology Research Institute (MORI) at Tufts Medical Center.

In light of this, the research team chose to study the two major types of cells in the human breast, those that line the ducts and produce milk (luminal cells) and those that surround the ductal cells and contract to move the milk from the ducts (basal/myoepithelial cells) to determine whether they might form different types of breast cancers.

"We found that when basal/myoepithelial breast cells become cancerous they no longer resemble breast tissue; instead they look more like cells of the skin and form rare metaplastic breast cancers. In contrast, when luminal breast cells become cancerous, they retain the structure and molecular features of more common types of breast cancers," said first author Patricia Keller, PhD, post-doctoral associate in the anatomy and cellular biology department at TUSM and a member of the Kuperwasser lab and MORI.

The researchers introduced cancer-causing genes into healthy breast cells obtained from breast reduction surgeries. Using specialized markers, they were able to isolate different types of normal breast cells and evaluate how they behaved as they became cancerous in a mouse model.

"By understanding more about the cellular beginnings of cancer, we can direct our research toward investigating preventive methods and possibly even developing new therapies," said Kuperwasser.

This study adds to Kuperwasser's growing body of work in breast cancer research. Earlier work identified a mechanism behind the preferential formation of aggressive breast cancers in people carrying a mutated BRCA1 gene. A team co-led by Kuperwasser and Philip Hinds, of Tufts Medical Center, also proposed and supported a model for breast cell differentiation that identified two distinct populations of progenitor cells for breast cancer. Her work has been published in *Cell Stem Cell*, *Breast Cancer Research*, *Cancer Cell*, and *Nature Protocols*.

More information: Keller PJ, Arendt LM, Skibinski A, Logvinenko T, Klebba I, Dong S, Smith AE, Prat A, Perou CM, Gilmore H, Schnitt S, Naber SP, Garlick JA, Kuperwasser C. PNAS Early Edition, "Defining the cellular precursors to human breast cancer." Published ahead of print, September 21, 2011, doi:10.1073/pnas.1017626108

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