MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

ADVANCES AT **MASS GENERAL CANCER CENTER** FALL 2014

A New Paradigm for Mammary Glands

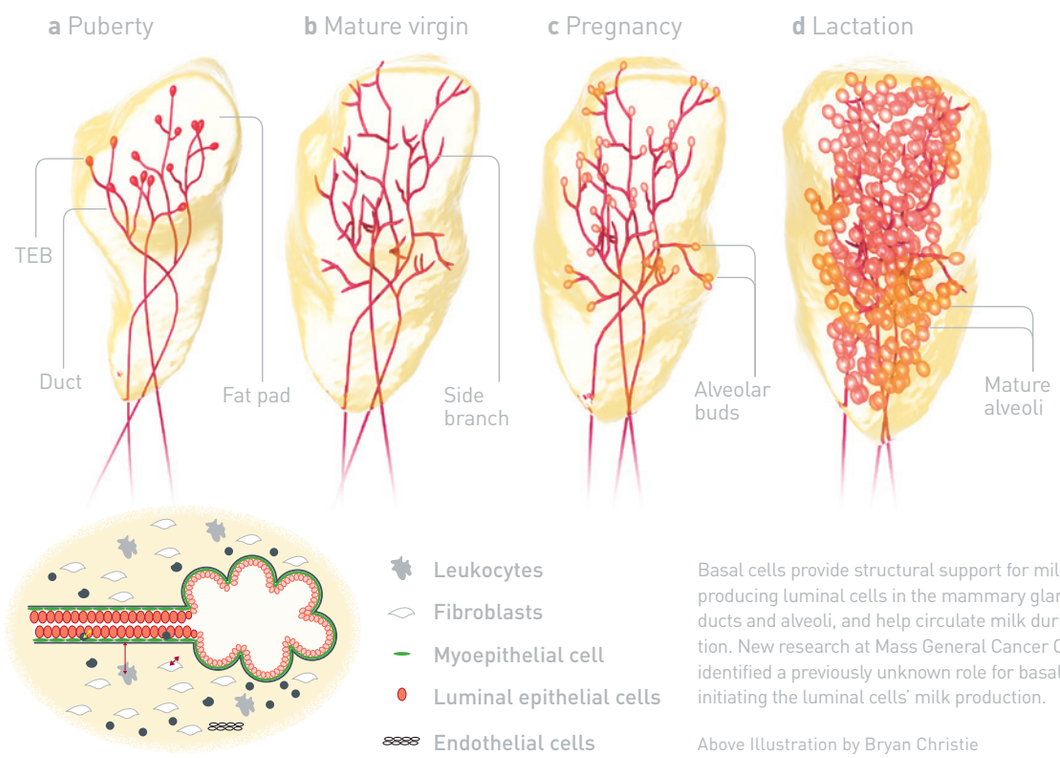
What role do basal cells play in the genesis of breast cancer?

Efforts to understand the changes that the breast undergoes during pregnancy and lactation, and during the early development of cancer, have mostly focused on luminal cells, one of two types of epithelial cells in the mammary gland. Luminal cells carry out the important functions in lactation, lining the milk ducts and alveoli where they secrete milk. One type of luminal cell, known as a luminal progenitor, may also be the precursor to some of the most aggressive forms of breast cancer. The other epithelial cells, basal cells, are thought to function during lactation as mere contractile elements that circulate milk to the nipple, and have seemed to have a negligible role in cancer development.

Now, however, Leif Ellisen, MD, PhD, program director of Breast Medical Oncology at Massachusetts General Hospital Cancer Center, has discovered that it's actually basal cells that initiate the changes that occur in luminal cells during pregnancy and lactation. This happens via a previously unknown basal-to-luminal cell signaling involving the gene p63, a master regulator of basal *(continued on page 2)*

Basal Cells and Luminal Cells

The maturation of luminal cells is spurred by a signal from basal cells, according to new research.



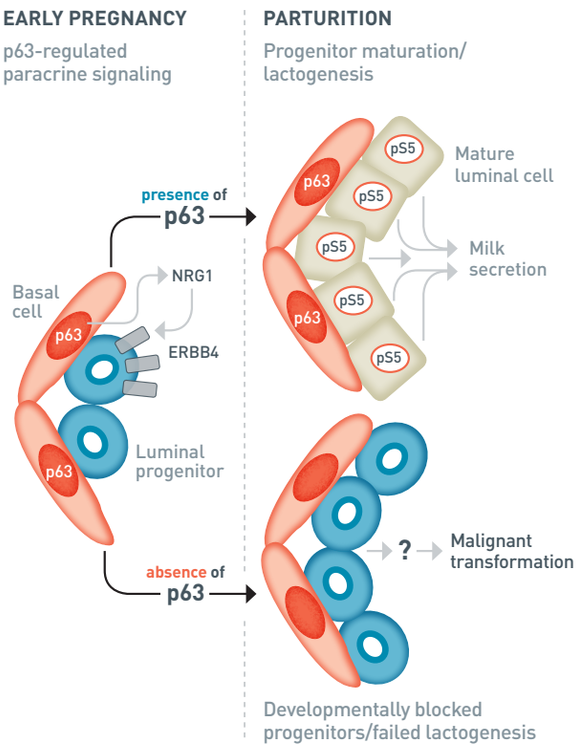
Basal cells provide structural support for milk-producing luminal cells in the mammary gland's milk ducts and alveoli, and help circulate milk during lactation. New research at Mass General Cancer Center has identified a previously unknown role for basal cells in initiating the luminal cells' milk production.

Above Illustration by Bryan Christie

INSIDE →

The Role of p63

Basal cells express p63, which signals the luminal cells to initiate lactation. Failing to do this may contribute to the development of triple negative breast cancer.



LEFT: Basal cells (red cells) express p63, which directs the expression of the growth factor hormone NRG1 (neuregulin). NRG1 binds specifically to ERBB4 on luminal progenitor cells (blue cells).

UPPER RIGHT: Normally, NRG1-mediated ERBB4 activation phosphorylates STAT5A (pS5) and induces luminal progenitor cell proliferation and differentiation (tan cells), resulting in milk production.

LOWER RIGHT: Loss of p63 results in luminal progenitors that are blocked during development and fail to differentiate. Cooperating genetic events may ultimately result in malignant transformation of such progenitors, which are known to be the precursors of a particularly aggressive form of breast cancer, triple negative breast cancer.

(continued from page 1) cell growth and responses. Dr. Ellisen's findings, published in the January 27, 2014, issue of *Developmental Cell*[1], suggest that aberrations in this paracrine signaling (signals from nearby cell types) may also help explain variations in breast cancer risks, particularly among women with germline (inherited) BRCA1 mutations.

THE PARADOX OF TRIPLE NEGATIVE BREAST CANCER RISK

Triple negative breast cancer (TNBC), a very aggressive subtype, occurs in some women with BRCA1 mutations. Once TNBC tumors are established, they do not respond to hormone deprivation therapies. However, blocking hormones early, before the cancer develops, reduces the risk of this hormone-independent breast cancer. "This paradoxical clinical observation tells us that we don't understand enough about the early steps of breast cancer development," says Dr. Ellisen.

Breast cancer arises in the context of the whole mammary gland, in which basal and luminal cells are in close physical contact, yet little is known about their cellular interactions in either normal breast development or in cancer. However, researchers did know that rare germline mutations in the p63 gene affect mammary gland development. Dr. Ellisen's group decided to delete p63 in just the breast's basal cells in adult mice.

BASAL-TO-LUMINAL CELL SIGNALING

Surprisingly, without that gene, the luminal progenitor cells failed to differentiate as normal during pregnancy into mature milk-producing luminal cells. Consequently, the mothers did not lactate.

"Although we manipulated only the basal cells, the effects were all in the luminal cells," Dr. Ellisen says. "This told us that the basal cells normally signal the luminal cells to initiate lactation, and the loss of p63 silenced the signal."

This result provided the first evidence of basal-to-luminal cell signaling. The researchers next identified the signal produced by p63 as the growth factor hormone NRG1, also called neuregulin. Again, this was the first evidence that basal epithelial cells produce NRG1, and that it is regulated by p63.

NRG1 was known to bind to epithelial growth factor receptors, ERBB4, in the luminal progenitor cell, and that ERBB4 activation phosphorylates another signaling molecule, STAT5, triggering its activation. STAT5, in turn, causes the luminal progenitor cells to differentiate into mature luminal cells capable of producing milk. Dr. Ellisen's study now connects all of the dots in this process, showing that p63 in the basal cell initiates this cascade of activity.

Deleting p63 in the basal cells blocked the ERBB4/STAT5 activity and maturation of the luminal progenitor cells, causing lactation failure. Dr. Ellisen thinks that failure of luminal progenitors to differentiate could also potentially set the stage for cancer.

CANCER RISK IMPLICATIONS

Women with BRCA1 mutations have abnormal luminal progenitor cells, and one theory holds that such aberrant cells may be precursors to the most aggressive cancers—TNBC and the more common luminal B subtype—in these women. "Because BRCA1 carriers also have altered proportions of basal and luminal cells," Dr. Ellisen

[1] Forster, Nicole, Srinivas Vinod Saladi, Maaike van Bragt, Mary E. Sfondouris, Frank E. Jones, Zhe Li, and Leif W. Ellisen. "Basal Cell Signaling by p63 Controls Luminal Progenitor Function and Lactation via NRG1." *Developmental Cell* 28, no. 2 (January 27, 2014): http://www.ncbi.nlm.nih.gov/pubmed/24412575.

[2] Polyak, Kornelia, and Andriy Marusyk. "Cancer: Clonal Cooperation." *Nature* 508, no. 7494 (April 3, 2014): 52–53.

[3] Polyak, Kornelia, and Raghu Kalluri. "The Role of the Microenvironment in Mammary Gland Development and Cancer." *Cold Spring Harbor Perspectives in Biology* 2, no. 11 (November 2010).

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explains, “the resulting altered cell-to-cell signaling interactions might underlie the genesis of many if not most breast cancers.”

Researchers have long observed that pregnancy and lactation reduce breast cancer risk. Dr. Ellisen speculates that this risk reduction may result from the depletion of the luminal progenitor cells at the end of pregnancy, when all of the cells have differentiated and are no longer potential cancer precursors. Because basal cell signaling initiates the differentiation of these luminal cells, Dr. Ellisen’s finding supports an emerging view of the basal cell as a tumor suppressor cell.

Dr. Ellisen is now collecting tissue from women with germline BRCA1 mutations who undergo mastectomies to prevent future breast cancers. He will analyze the samples to learn whether dysregulated basal-to-luminal cell signaling is associated with higher breast cancer risks. Is there a marker that can predict cancer before it develops that could facilitate earlier intervention? Once researchers understand how the dysregulated cell signaling leads to cancer, could they eventually develop preventive strategies?

More broadly, the discovery suggests that to understand cancer biology, researchers must study the entire microenvironment as the tumor develops rather than examining only a single tumor cell type once the cancer has formed[2,3]. Says Dr. Ellisen, “We need to look at cancer in the context of how heterogeneous cells interact early in the genesis of the tumor so we can understand how cells cooperate during the initial stages of cancer formation.” ■

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