**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.

- **a** Puberty
- **b** Mature virgin
- **c** Pregnancy
- **d** Lactation

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
**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.

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**EARLY PREGNANCY**

* p63-regulated paracrine signaling

**PARTURITION**

* Progenitor maturation/lactogenesis

**Mature luminal cell**

**Milk secretion**

**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.

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(continued from page 1) cell growth and responses. Dr. Ellisen’s findings, published in the January 27, 2014, issue of Developmental Cell, 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.

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**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
Ceritinib: A potent second-generation ALK inhibitor for non-small-cell lung cancer

Will ceritinib prove to be a breakthrough therapy?

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer death in the United States, yet until recently it had no effective treatments. Now, however, by gaining a better understanding of the molecular biology of NSCLC, researchers have identified genetic subtypes that can be targeted with selected inhibitors. The Massachusetts General Hospital Cancer Center has led many of the studies and trials of first- and second-generation targeted therapies for specific NSCLC subtypes. The latest results concern NSCLCs driven by chromosomal rearrangements in the anaplastic lymphoma kinase (ALK) gene that have become resistant to the first-generation ALK inhibitor, crizotinib.

In a phase I trial, ceritinib caused marked tumor shrinkage in patients with advanced cancer who had developed resistance to crizotinib as well as in those who had received other treatments, according to Alice Shaw, MD, PhD, a thoracic oncologist at the Mass General Cancer Center and lead investigator of that trial. Trial results appeared in the March 27 New England Journal of Medicine, while the March 27 Cancer Discovery published a molecular analysis of the treatment. (continued on page 4)

Lung Tumor Shrinkage

PET scan showing response to ceritinib in ALK-rearranged non–small-cell lung cancer (NSCLC). Positron-emission tomographic scans taken at baseline (left) and after 3.5 weeks of ceritinib treatment (right) in a patient with crizotinib-resistant disease. Subsequent computed tomographic scans after six weeks of ceritinib treatment showed a 52 percent reduction in tumor burden.

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