Cells lining milk ducts hold key to spread of common form of breast cancer

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When a form of cancer that begins in the milk ducts of the breast invades neighboring tissue to spread to other parts of the body, the cause lies not in the tumor cells themselves but in a group of abnormal surrounding cells that cause the walls of the duct to deteriorate like a rusty pipe, according to a new study led by Dana-Farber Cancer Institute researchers.

The discovery, reported in the May 6 issue of *Cancer Cell*, may lead to screening tests to determine whether the disease -- known as ductal carcinoma in situ, or DCIS -- is likely to spread beyond the ducts, based on genetic abnormalities in cells in the ducts' lining. And it sets the stage for treatments that, by targeting these abnormalities, shore up the duct walls and keep the cancer contained.

"Women whose DCIS has invaded the ducts are known to have a greater chance of metastasis, or spreading disease. But it hasn't been clear what causes the transition from a localized cancer to invasive disease," according to the study's senior author, Kornelia Polyak, MD, PhD, of Dana-Farber. "This study demonstrates that in DCIS of the breast, and potentially in other cancers that originate in duct tissues, the answer may lie in the tumor's microenvironment -- the cells and tissue that surround the cancer."

DCIS is expected to be diagnosed in nearly 53,000 women in the United States this year. When detected and surgically removed before it has a chance to spread, the disease is nearly always curable. It isn't known how many of these cancers would become invasive breast cancer if they weren't treated, but studies suggest that most of them eventually would.

Researchers initially thought that DCIS might become invasive as a result of genetic changes in the cancer cells. When they surveyed gene activity in immobile DCIS cells and in those that had spread, however, they found no significant differences. That led them to consider the cell's microenvironment.

Polyak and her colleagues focused on myoepithelial cells, which form part of the lining of the milk ducts and are involved in breast development, as well as impeding the growth and invasiveness of some cancer cells. To study what role, if any, these cells play in DCIS, the researchers worked with a specially engineered line of cells known as MCFDCIS.

When injected in laboratory animals, the MCFDCIS cells formed DCIS-like tissue that developed into invasive tumors, providing a good model of what happens in human disease. When researchers injected both MCFDCIS and myoepithelial cells into the mice, DCIS tumors arose, but they were confined to the ducts. When they injected MCFDCIS cells and fibroblasts -- cells found in milk ducts and other connective tissue -- the resulting DCIS tumors broke into the walls of the ducts.

"These findings made it clear that fibroblasts promote tumor growth and invasion, and normal myoepithelial cells suppress it," Polyak remarks. But when certain genes in the myoepithelial layer become under- or overactive, the layer breaks down and disappears, enabling tumor cells to escape.

To identify which genes are affected and what causes their activity level to change, Polyak's team surveyed the activity of thousands of genes in myoepithelial and DCIS cells using advanced SAGE (Serial analysis of gene expression) technology. When DCIS tumors trespass into the lining of the ducts, the activity level of several myoepthelial cell genes is abnormal -- specifically the TGF Beta, Hedgehog, and p63 genes as well as genes that help myoepithelial cells stick to "basement" cells on the ducts' outer layer. The effect is a cacaphony of erratic signals and haywire

activity that prevents myoepithelial cells from fully maturing and forming an effective barrier to DCIS.

"We found a constant, complex interplay of signals among these genes, both within myoepithelial cells themselves, and between myoepithelial cells and their neighbors," Polyak says. "The presence of DCIS causes the pattern of signals to change significantly, upsetting the normal development of myoepithelial cells. The myoepithelial cells fail to fully differentiate" -- act as true 'gatekeepers' for DCIS -- "leading to the disappearance of the myoepithelial layer and the beginning of tumor invasion."

The discovery suggests that by scanning myoepithelial tissue for abnormalities in these key genes, doctors may be able to identify which women with DCIS have the greatest risk of cancer spread, says Polyak, who is also an associate professor of medicine at Harvard Medical School. It also provides numerous targets for future drugs aimed at restoring the normal balance of signals among these genes.

"Our results highlight the importance of the microenvironment in breast tumor progression," Polyak remarks. "And they suggest that therapies that target the interactions of tumor cells with their surroundings may offer a better way of inhibiting tumor progression than those that focus on the tumor epithelial cells alone."

Source: Dana-Farber Cancer Institute