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New study sheds new light on the progression and invasiveness of ductal breast cancer

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Ductal carcinoma in situ (DCIS) is considered a precursor lesion for invasive breast cancer if untreated, and is found in approximately 45% of patients with invasive ductal carcinoma (IDC). Patients with DCIS only (not accompanied by invasive disease) have a 5-year-survival of nearly 100%, compared to 89% for all stages of invasive breast cancer (24% for patients with distant metastasis). A new study has found that despite an enormous degree of intercellular heterogeneity in both DCIS and IDC, the evolution from noninvasive to invasive disease is determined by recurrent patterns of genomic imbalances in most cases. This study is published online in advance of the November issue of *The American Journal of Pathology*.

"For patients with cancer, the transition from locally controlled disease to a disseminated stage and metastases is probably the most critical threshold, because that transition makes surgical intervention considerably less likely to succeed," says lead investigator Thomas Ried, Section Chief, Genetics Branch, Center for Cancer Research, National Cancer Institute (NCI), National Institutes of Health (NIH), Bethesda, MD. "We looked at gene copy number changes during the transition from DCIS to IDC and, if so, what patterns of genetic imbalances drive this process."

The study was based on archived clinical samples for which the co-occurrence of DCIS and IDC in the same patient had been tracked at the National Naval Medical Center. It was led by researchers from the NCI and also included researchers from the National Center for

Biotechnology Information, the National Naval Medical Center, Bethesda, MD, and Carnegie Mellon University, Pittsburgh, PA.

Investigators compared the genetic makeup of individual cells from 13 patients with DCIS and IDC and analyzed the gain or loss of specific genes that are frequently affected in DCIS and IDC. These genes included cancer promoting oncogenes and cancer suppressing tumor suppressor genes. Fluorescence in situ hybridization (FISH) probe panels, which use fluorescent copies or clones of the relevant DNA sections to identify gene copy numbers, were hybridized to intact cells prepared from histomorphologically identified areas from lesions from several patients. Subsequent hybridizations of multicolor probe panels resulted in multiplexing of probes that further allowed for simultaneous analysis of copy numbers of five oncogenes and three tumor suppressor genes within each cell analyzed.

A high degree of chromosomal instability from one cell to another was observed, reflected by the fact that identical signal clones were only present in less than 20% of the cells. Despite this instability, the distribution of gains and losses in most cases was consistent with known genetic aberration profiles for breast cancer, and investigators found patterns consistent with non-random distribution of genomic imbalances. CDH1, a tumor suppressor that triggers cancer invasion and metastases upon reduced expression, was most commonly lost in DCIS and IDC. MYC, a strong oncogene that drives cell proliferation and regulates cell growth and differentiation, was most frequently gained from DCIS to IDC. MYC appears to play a major role in the transition from "in situ" to invasive breast disease.

"DCIS and IDCs are genetically related lesions as they both have similar imbalance patterns. However, according to their aberration patterns, the DCIS lesions are far further advanced than other precursor lesions with more stable genomes, such as colorectal polyps or cervical dysplasias,"

notes Dr. Ried. "The considerable degree of intercellular heterogeneity in the DCIS convincingly attests to the fact that chromosomal instability precedes the transition to invasive disease."

Dr. Ried observes that the advanced aberration profiles of DCIS associated with IDC make it unlikely that progression to invasive disease can be prevented with measures other than surgery, radiation, and adjuvant hormonal therapy.

"This of course raises the question of what precisely determines this critical transition between pre-invasive and invasive disease. Identifying the differences in the full catalog of genes in DCIS and IDC could have the potential of identifying a gene expression signature that is ultimately responsible for invasion and progression," he concludes.

More information: "Single-cell genetic analysis of ductal carcinoma in situ and invasive breast cancer reveals enormous tumor heterogeneity, yet conserved genomic imbalances and gain of MYC during progression," by Kerstin Heselmeyer-Haddad, Lissa Y. Berroa Garcia, Amanda Bradley, et al. dx.doi.org/10.1016/j.ajpath.2012.07.012 . It appears in *The American Journal of Pathology*, Volume 181, Issue 5 (November 2012)

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