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Breast cancer researchers report new insights into ductal carcinoma in situ

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New UC Davis research supports the recent hypothesis that both ductal carcinoma in situ and invasive breast cancer develop from the same breast cancer progenitor cells. The research was reported at the annual meeting of the International Association for Breast Cancer Research in Montreal last month.

"The implication of these studies and others is that the genetic code for breast cancer is probably written at the pre-cancerous stage, so the rest is predestined," said Robert D. Cardiff, professor of pathology and director of the Mutant Mouse Pathology Lab at the UC Davis Center for Comparative Medicine. "This has profound implications for the prevention and treatment of breast cancer."

The conventional belief has been that DCIS, the most common form of localized breast cancer, spreads beyond the milk duct only if the DCIS cells are subjected to additional genetic damage. The newer hypothesis argues that breast cancer progenitor cells are present from the beginning in precancerous lesions, and are genetically programmed to progress not only to DCIS but also right on through to invasive breast cancer.

The UC Davis findings are based on studies in a line of transgenic mice engineered to develop mammary intraepithelial neoplasia, or MIN, the mouse equivalent of human DCIS.

The mouse model, developed by researchers at UC Davis and UC San Diego, is available only at UC Davis.

Cardiff, outgoing president of the International Association for Breast Cancer Research, summarized evidence for the new hypothesis in a presentation titled "Mammary Precancers: Old Concept and New Biology."

"The new hypothesis suggests that we are treating the wrong breast cancer cells," Cardiff said. "We need to determine how to correctly identify breast cancer progenitor cells in high-risk women and destroy these cells before they can become malignant."

At the Montreal meeting, four groups of UC Davis researchers reported on their work in MIN, DCIS and invasive mammary cancer in mice.

Kermit L Carraway III, an associate professor of biochemistry and molecular medicine at UC Davis Cancer Center, reported his research into the role of a substance known as Nrdp1 in the path toward malignancy. Carraway's team discovered that when mouse and human breast cancer cells have excess Nrdp1, the levels of a growth factor known as ErbB3 drop, inhibiting the cancer cells' growth and motility. The same happens in mouse breast cancer cells with excess ErbB2. The growth factor ErbB2 is the mouse counterpart of the human growth factor HER2, which is implicated in a quarter of human breast cancers. The findings suggest Nrdp1 may have a role in the treatment of HER2-positive human breast cancers.

A second team reported that the seemingly inexorable progression of MIN cells towards mammary cancer could be halted in some cases. The team, led by Lawrence Young, a senior research associate in the Center for Comparative Medicine, and Jeff Gregg, an associate professor of pathology, found that the antibiotic rapamycin quickly induced apoptosis, or rapid cell death, in some but not all MIN cell lines. The researchers' next step will be to use micro-array genetic analysis to determine which genes were expressed in the surviving malignant cells.

Such genes could be promising targets for drug development.

A third team presented work suggesting that diuretics may have therapeutic potential in DCIS. Steven Anderson, an associate researcher in physiology and membrane biology, and Peter Cala, professor and chair of physiology and membrane biology, have conducted specializing imaging studies to demonstrate that MIN cells rely on a molecule known as the sodium/hydrogen exchanger to maintain a favorable pH balance within the milk ducts. Diuretics inhibit sodium/hydrogen exchange, resulting in an acidic micro-environment that is lethal to cancer cells.

"This study has potential to provide innovative new treatments for high-risk women with DCIS," Cala said. A fourth team reported on a novel method of determining which genes confer malignancy in breast cancer. Patrizia Damonte, a researcher in the UC Davis Center for Comparative Medicine, and Alexander Borowsky, an assistant professor of pathology, have separated MIN lesions into individual cells, cultured each cell into a multicellular clump and observed each clump to see which developed into cancer. They're now analyzing the genetic makeup of the malignant clumps.

Source: University of California, Davis

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