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'Cancer prognosis gene' found to control the fate of breast cells

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Scientists have discovered an unsuspected role for a gene known to be one of the best predictors of human breast cancer outcome.

The gene, called GATA-3, is in a family of genes that guides development of stem cells into mature cells. University of California, San Francisco researchers have now found that GATA-3 is also required for mature mammary cells to remain mature in the adult. In research focusing on mice mammary glands, they found that without GATA-3, mature cells revert to a less specialized, “undifferentiated” state characteristic of aggressive cancer.

The new finding suggests that this gene may play a key role in the development of breast cancer, the scientists report in the December 1 issue of the journal CELL.

Cancer researchers know that breast cancers with high GATA-3 expression have a good prognosis. The cancers tend to be well-differentiated – retaining estrogen receptors and other characteristics of normal mature breast cells. Cancers with low GATA-3 expression tend to be poorly differentiated, with a poor prognosis. The new research may explain why this is so.

“Perhaps the loss of GATA-3 and subsequent failure to maintain this mature state is what leads to loss of differentiation during cancer progression,” said Hosein Kouros-Mehr, PhD, a medical student at UCSF and lead author of the new study. “This gene is part of the

instruction manual that controls how a stem cell can mature into a normal mammary cell and remain that way for its lifetime. The finding suggests that the differentiation, or maturity, of cells is a process that must be actively maintained throughout the lifetime of an organism."

How GATA-3 controls cell fate, and its possible role in breast cancer is now the focus of the team's research.

The UCSF study is part of the work of the Bay Area Breast Cancer and the Environment Research Center, one of four centers funded by the National Cancer Institute and the National Institute of Environmental Health Sciences.

The UCSF scientists found that when the GATA-3 gene activity was knocked out in adult mice, the mammary ductal cells - the principal cell type in breast cancer - regressed to a less differentiated state, which is one of the hallmarks of invasive, metastatic cancer. The cells began to proliferate uncontrollably and then died within the ducts of the mammary gland, they reported.

Previously, little was known about the differentiation of the ductal cells, also known as luminal cells, which form the lining of the breast ducts that carry milk during lactation. The researchers carried out a screen of all genes active in the mammary ducts during puberty and found that GATA-3 was the most abundant transcription factor – a gene that directs the activation of other genes. They further found the GATA-3 protein in all luminal cells of mature mammary ducts, both in mice at puberty and in adult virgin mice.

"We are very excited because we now know that it is not enough for cells to become breast cells but they need an active program to remain in their specialized state and perhaps be kept from wandering off," said Zena Werb, PhD, professor and vice chair of anatomy and senior author of the

paper. “Maybe we should view cancer as telling us what cells become if they lose their ‘homesteading’ genes and then start wandering.”

The scientists hope that further investigation of the precise role of GATA-3 in breast cancer can identify new ways of understanding, diagnosing and treating the disease.

Source: University of California - San Francisco

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