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Mammary Gland Cells Formed During Maternity Have Stem Cell Properties

A class of cells that arises in mammary glands during maternity has stem cell-like properties, according to findings by researchers at the National Cancer Institute (NCI), part of the National Institutes of Health. These parity-induced mammary epithelial cells (PI-MEC) have the ability to self-renew over many generations and to differentiate into numerous cellular subtypes. These results, appearing in *Oncogene** online on December 6, 2004, also demonstrate that PI-MEC growth can be curtailed by expression of the growth factor TGF-beta1, potentially providing a mechanism for prevention of some types of breast cancer.

In mice, rats, and humans, pregnancy has a dual effect on the risk of breast cancer. It is known that a full-term pregnancy early in adulthood reduces the long-term risk of breast cancer; however, during each pregnancy there is a transient, short-term increase in breast cancer risk. The alteration of the mammary tissue during pregnancy likely provides the basis for these risk effects, although the exact mechanisms remain unclear.

Gilbert H. Smith, Ph.D., in NCI's Mammary Biology and Tumorigenesis Laboratory, and Kay-Uwe Wagner, Ph.D., at the University of Nebraska Medical School, had previously co-discovered a new subtype of mammary epithelial cells present only in mice that had given birth. Starting around the third trimester of pregnancy, these cells expanded and contributed to the formation of mammary ducts and lobules. "After lactation, a vast majority of these cells die," said Smith, "but we saw remnants hanging along the ends of the ducts. During subsequent pregnancies, these ancestors get reactivated and form new milk-secreting lobules." Smith and Wagner also observed that these PI-MEC were targets for transformation into cancer cells when mice were exposed to mouse mammary tumor virus during multiple pregnancies.

Smith's new findings help explain why these cells might facilitate tumor formation. Since PI-MEC act as ancestors for mammary growth, Smith and his lab examined how much growth and differentiation potential these cells had. They performed serial transplantations of bits of mammary tissue and observed that PI-MEC (specially marked so they can stain blue) were able to stay in the tissue over a length of four transplants, which corresponds to about 40 doublings. The researchers also transplanted PI-MEC into mice and then initiated pregnancy to examine mammary outgrowth. They discovered that the marked PI-MEC could differentiate into all the epithelial subtypes present in mammary tissue.

"PI-MEC have two critical features of stem cells," said Smith, "self-renewal of their population, and the ability to produce progeny of multiple cellular subtypes." Smith, however, did point out that PI-MEC did not exhibit the full developmental capacity of true stem cells, as additional experiments showed that PI-MEC only expanded and differentiated when they were in contact with other epithelial cell types. "Still, these cells are more likely to expand than other cells during pregnancy, and that increased expansion increases the risk of cancer development," said Smith.

However, when Smith and his lab targeted the expression of TGF-beta1 to PI-MEC, they observed that these cells could no longer rapidly proliferate and maintain themselves in serial transplants of mammary tissue. In pregnant females, TGF-beta1 expression slowed down PI-MEC differentiation and increased the rate of cell death, leading to incomplete development of the secretory lobules. These mice could not lactate, but they were also protected from breast cancer development when infected by mouse mammary tumor virus.

"Importantly, though," said Smith, "we only observed this effect when we induced TGF-beta1 expression

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within the cells. Adding external growth factor did not produce the same result. This is an important point to consider for any treatment or prevention measures."

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* Boulanger CA, Wagner K, Smith GH. Parity-induced mojse mammary epithelial cells are pluripotent, self-renewing and sensitive to TGF-beta 1 expression. *Oncogene*. Published online December 6, 2004.

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