Cancer Cell
Previews

Tissue States Provide Novel Insights into Attributes that Drive Metastasis

Thea D. Tlsty[1,2,*]
[1]Helen Diller Comprehensive Cancer Center
[2]Department of Pathology
University of California, San Francisco, 513 Parnassus Avenue, San Francisco, CA 94143-0511, USA
*Correspondence: thea.tlsty@ucsf.edu
DOI 10.1016/j.ccr.2011.08.018

Recently, in *Nature Medicine*, Schedin and colleagues define attributes within the involuting postpartum breast microenvironment that promote breast cancer metastasis. Cell invasiveness is controlled by a positive feedback loop involving COX-2 and fibrillar collagen. NSAIDs suppress tumor progression during postpartum involution, potentially providing effective agents for intervention in pregnant women.

The acquisition of malignant phenotypes is a long-term, interactive, nonlinear process that results in the generation of a collection of diseases termed cancer. This multistep, probabilistic process is not easy to study, and consequently, much remains to be accomplished in managing this disease in any of its states. In select instances, unique physiological conditions in specific tissues have provided key insights into isolated steps of the initiation and progression of malignancies and opportunities to interrupt the process. Groundbreaking studies that identified the human papilloma virus in cervical cancer, its biological relationship to malignant transformation, and the development of a vaccine to control this disease provide a prime example (zur Hausen, 2009). The fundamental lessons provided by these physiologically unique studies extend far beyond the specific tissue(s) in which they are conducted. A recently published study by Dr. Schedin and colleagues exemplifies this informative type of approach and provides insights that will be valuable to a broad audience of biologists and clinicians (Lyons et al., 2011). The Schedin group focused on a physiologically distinct state of breast tissue that is associated with increased risk for poor prognosis breast cancer. This state, called postpartum involution, coincides with cessation of milk production. Soon after birth in the absence of nursing, or within days of termination of nursing, the mammary gland initiates a program that activates epithelial cell death and stromal remodeling to restore the breast tissue to a nonsecretory state typical of nonpregnant tissue.

Epidemiological studies of breast cancer have taught us that the reproductive history of an individual woman is of paramount importance in determining risk and outcome. However, deciphering these influences is often difficult, and the ensuing linear assumptions can be paradoxical. For example, while it is appreciated that a full-term pregnancy in young women is protective against breast cancer in the long term, a substantial transient increase in breast cancer risk has been observed in the short-term—i.e., after each pregnancy, in particular in the increasing group of older first-time mothers (Lyons et al., 2009). In addition to this higher tumor incidence, women diagnosed with breast cancer within five years of childbirth have a poorer prognosis and a higher incidence of cancer-related deaths compared to nulliparous women or those diagnosed during pregnancy. This epidemiological study suggests that events that follow pregnancy, but not pregnancy itself, are responsible for the poor prognosis that accompanies postpartum breast cancer. This information, coupled with insights from previous studies (Schedin and Keely, 2011), led the authors to hypothesize that exposure to stromal conditions that occur during postpartum involution promotes several steps in cancer development.

To test this hypothesis, the authors utilized state-of-the-art biology and clinical samples to provide insights into the mechanistic basis of cancer progression associated with postpartum involution (Lyons et al., 2011). Three major difficulties in studying the malignant process include the multistep nature of this process, the long latency between initial events and visible tumor formation, and the relative infrequency of tumor formation. Lyons et al. cleverly bypassed these difficulties by using a premalignant cell population and choosing a transient time window during which the incidence of breast cancer was increased.

In a set of elegantly designed and beautifully executed experiments, the authors introduced a single bolus of premalignant human breast cells, MCF10DCIS, into the mammary glands of murine hosts that were either nulliparous or experiencing postpartum involution. Focusing on tumor progression, the authors measured the well-established functional endpoints: proliferation, motility, invasion, and tumor formation. By three days after the initial injection, differences in functionally relevant phenotypes were already observed. While the nulliparous tissue supported localized growth of MCF10DCIS cells, in contrast, the postpartum involuting tissue additionally exhibited small foci of cells within the mammary gland distal to the primary site, cells within the mammary vasculature, and cells within the lung. By three weeks, the total tumor burden in involuting tissue was ten-fold that in nulliparous samples. Tumor cell dispersion was independent of tumor size.

A prominent feature of involuting mammary gland tissue is a transient increase in fibrillar collagen and collagen protein, whose presence correlates with increased breast cancer risk and tumor cell proliferation, motility, and invasion. Strikingly, epithelial cells exposed to fibrillar collagen exhibited an increase in COX-2 enzymatic activity and subsequent production of

proinflammatory prostaglandins. Since COX-2 is known to promote epithelial cell proliferation, motility, and invasion, it suggested itself as an attractive candidate for controlling the protumorigenic phenotypes associated with postpartum involutionary tissue. Indeed, consistent with this hypothesis, exposure to nonsteroid anti-inflammatory drugs (NSAIDs), a class of drugs that inhibit COX-2, reversed the increased tumor cell proliferation, motility, and invasion.

To determine if the increases in proliferation, motility, and invasion would be maintained ex vivo and were dependent on collagen, tumor cells from the nulliparous or involuting tissue were placed on matrigel or collagen substrates and analyzed for relevant phenotypes. Tumor cells isolated from the involuting tissue showed an increase in proliferation and motility compared to cells isolated from the nulliparous tissue. Increased invasiveness was also detected but only in the presence of collagen. Both cell isolates were noninvasive when placed in matrigel without collagen, even when COX-2 activity was upregulated. These data indicate that postpartum involutionary tissue conditionally promotes malignant phenotypes in a collagen-dependent manner.

Having determined that COX-2 expression and collagen deposition collaborate to generate a conditional positive feedback loop that controls tumor cell phenotypes, the authors sought relevant evidence in postpartum human breast cancer. They found that collagen deposition and orientation in breast tissue of young nulliparous women differed from that in postpartum women. Involuting breast tissue had increased collagen deposition and more radially aligned fibers. Importantly, coincident expression of collagen I and COX-2 proteins identified a group of women at increased risk for early relapse of breast cancer and decreased metastasis-free and overall survival. Expression of either variable alone did not correlate with poor prognosis, consistent with the interpretation that both fibrillar collagen and COX-2 are required to drive cellular invasion.

Taken together, the data in this report indicate that premalignant cells, exposed to increasing amounts of fibrillar collagen, acquire malignant phenotypes that are cell autonomous and whose activation is conditionally dependent on the proper context, i.e., exposure to fibrillar collagen. The reversal of these phenotypes upon exposure of postpartum involutionary tissue, but not nulliparous tissue, to COX-2 inhibitors indicates that multiple inputs into tumor progression are present but that a substantial fraction of risk can be modulated by targeted suppression of COX-2 activity alone. These results identify windows of opportunity for effective administration of specific agents, such as NSAIDS, in reducing the appearance of breast cancers in postpartum women.

The significance and implications of these studies extend beyond the unique and specific physiological condition that is observed in postpartum breast tissue. The stromal characteristics that are so important in enhancing tumor progression in this example are also seen in other instances of tissue states associated with a high risk for cancer and accompanied by poor prognosis, such as in wounded or damaged tissues within other sites of the body and by stromal changes that are associated with the peritumoral microenvironment (Tlsty and Coussens, 2006). Future studies need to address the modulation of these attributes for clinical purpose.

REFERENCES

Lyons, T.R., Schedin, P.J., and Borges, V.F. (2009). J. Mammary Gland Biol. Neoplasia *14*, 87–98.

Lyons, T.R., O'Brien, J., Borges, V.F., Conklin, M.W., Keely, P.J., Eliceiri, K.W., Marusyk, A., Tan, A.C., and Schedine, P. (2011). Nature Med., in press. Published online August 7, 2011. 10.1038/nm.2416.

Schedin, P., and Keely, P.J. (2011). Cold Spring Harb. Perspect. Biol. *3*, a003228.

Tlsty, T.D., and Coussens, L.M. (2006). Annu. Rev. Pathol. *1*, 119–150.

zur Hausen, H. (2009). Virology *384*, 260–265.