Katzir Center
Weizmann Institute of Science
Israel

Genes and the microenvironment: the two faces of breast cancer

Mina J. Bissell
Distinguished Scientist, Life Sciences Division
Lawrence Berkeley National Laboratory, Berkeley, CA

That development, differentiation and cancer are fundamentally connected has been appreciated for decades. How and why, however, still need much exploration. In the last three and a half decades we have developed a number of concepts and assays to study how a normal mammary gland controls the processes of branching, lactation, remodeling during involution and maintaining homeostasis. Given that each of us has somewhere between 10-70 trillion cells in our bodies- all with the same genetic information- our working hypothesis, for which we have much evidence, is that the architecture of the organs and tissues are the final arbitrators of tissue specificity and cancer. We have developed the first organotypic assay where nonmalignant and malignant cells can be distinguished from each other rapidly and robustly. We modeled the formation of the unit structure of the mammary gland, i.e. a polar 'acinus', using both mice and human luminal epithelial cells, and have followed the consequences of loss of its structural integrity. Once the structure of an organ is altered, cells and tissues are on their way to malignancy. We show that when we make the 'form' of the malignant cells in 3D gels to mimic a normal acinus, the function is restored in malignant cells.

We have discovered that myoepithelial cells are crucial regulators of homeostasis and functional differentiation in the mammary gland because of their ability to make laminin111 (Ln-1), an extracellular matrix molecule (ECM) essential for formation and maintenance of glandular tissues, homeostasis and functional differentiation. Both Ln1 and myoepithelial cells are essentially lost in invasive breast cancers. We have evidence that the mechanisms that destroy tissue structure and polarity such as inflammation and MMPs, are involved in tumor progression; conversely, restoration of the unit structure can 'reverse' the malignant phenotype. Thus in addition to oncogenic mutation, the microenvironment of the tissues plays important roles in tissue-specificity and cancer.

We also have modeled invasion and branching of the normal gland in virgin mice to understand how breast cancer disrupts and 'hijacks' these processes; more recently we have engineered human breast cancer 'dormancy' models finding a crucial role for blood vessels in both dormancy and metastasis. Such models have helped us define the plasticity of both normal and malignant cells and the possibility of combining microenvironmental therapies to treat breast and other forms of cancer.

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