Breast cancer can be viewed as a disease of defective development, wherein the processes that guide growth and morphogenesis of the mammary gland are inappropriately activated during tumor proliferation and invasion. Research over the last couple of decades, reviewed by Polyak and Kalluri (2011), has defined some of the key microenvironmental signals that underlie both tissue development and disease progression. Meticulous investigation of animal models has revealed how processes controlling mammary gland development during puberty, pregnancy, lactation, and involution become activated in cancer. For example, some of the same stromally produced matrix metalloproteinases (MMPs) that facilitate outgrowth and branching morphogenesis as the glandular epithelium grows into the fat pad during puberty are also involved in the penetration of the basement membrane by the developing cancer (Wiseman and Werb 2002). In parallel, development of physiologically relevant 3D culture systems has enabled identification of specific biochemical and biophysical signals, required for maintenance of normal tissue structure, that become dysregulated as tumors grow. For example, recent studies have found that increasing the stiffness and collagen composition of the extracellular matrix can cause normal mammary epithelial structures to acquire invasive characteristics (Egeblad et al. 2010).

Although models for studying the impact of the microenvironment on mammary tissue behavior have become increasingly sophisticated, a significant impediment in elucidating the most important changes in breast cancer development is a limited understanding of the specific microenvironmental cues involved at the earliest stages of disease development. The most commonly hypothesized model of breast cancer development posits an evolution through incremental steps of accumulating cellular abnormalities from normal epithelium through proliferative disease without atypia (PDWA), atypical hyperplasia, ductal carcinoma in situ (DCIS), and then invasive breast cancer (Santen and Mansel 2005). This model is supported by epidemiologic studies that show a stepwise increase in relative risk (RR) of subsequent development of invasive breast cancer from PDWA (RR = 2) to atypical hyperplasia (RR = 4) to DCIS (RR = 10) (Arpino et al. 2005). What are the critical factors that influence whether a premalignant lesion will develop into invasive cancer? Although seminal work by Polyak and coworkers (Hu et al. 2005), as well as other researchers, has identified some of the specific characteristics associated with subsequent disease progression for patients with DCIS, such lesions have already accumulated a broad array of genetic and structural abnormalities. Investigations of yet earlier stages of disease may help us...
to identify which alterations are the key drivers of progression to malignancy. This information could lead to entirely novel approaches targeting these processes, toward the ultimate goal of prevention of breast cancer formation.

REFERENCES
* Reference is also in this collection.


On the Role of the Microenvironment in Mammary Gland Development and Cancer

Derek Radisky

*Cold Spring Harb Perspect Biol* 2012; doi: 10.1101/cshperspect.a013458 originally published online May 15, 2012

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