Microenvironment changes cell non-autonomously impose functional phenotypes in epithelial progenitors causing increased susceptibility to breast cancer

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Microenvironment is a crucial determinant of tissue and lineage specificity of cells. My lab mainly studies human mammary epithelia in the context of the aging process to explore this relationship because more than 75% of women diagnosed with breast cancer each year are over 55 years of age. We have found that mammary epithelial cells are unable to maintain strict lineage specificity with age, which results in deleterious tissue-level changes making the tissue more susceptible to malignant transformation. Two processes likely contribute to these changes and increased cancer incidence the accumulation of mutations over time, along with numerous changes to the tissue microenvironment. Microenvironment changes are essential for allowing expression of malignant phenotypes in cells and for imposing metastable non-genetic functional phenotypes in progenitors, which leads to an epithelium that is more susceptible to transformation. Microenvironment is defined as the combination of cell-cell, -ECM and -soluble factor interactions surrounding each cell in a tissue. These components exchange information with cells via a combination of physical, chemical and electrical signals, frequently activating or deactivating the same pathways triggered by oncogenes. To better understand, the genesis of age-related states of breast, we developed cell culture systems that maintain primary human epithelial cells in ways that maintain the molecular and functional fingerprint of chronological age and enable robust and repeated experimentation relevant to *in vivo*. We examine consequences of the age-related changes by examining functional responses in bioengineered cell culture substrata and *in vitro* microtissue assemblies that recapitulate aspects of *in vivo* tissues. We found that the aging process results in a continuum of different microenvironments that impose aging phenotypes that are metastable. We provide evidence that aging in epithelial progenitors and soma is cell non-autonomously communicated by microenvironment cues over at least one cell diameter.

Speaker Biography

Mark A LaBarge is a Cell Biologist with expertise in aging in the context of breast cancer. He has earned a PhD in Molecular Pharmacology from Stanford and then performed his Post-doctoral training with Dr. Mina Bissell in the field of Microenvironment Biology. During that period of training, he has focused on development of novel technologies that would enable cell-based functional interrogation of tissue microenvironments (e.g. the combinatorial microenvironment microarray (MEMA)). As a Junior Faculty at the Lawrence Berkeley National Lab, his lab focused on the role of microenvironment in age-related breast cancers. He is a recipient of the prestigious Era of Hope Award for his research in Breast Cancer and is currently a Professor at the Beckman Research Institute at City of Hope near Los Angeles.

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