MAR14-2014-021099

Abstract for an Invited Paper
for the MAR14 Meeting of
the American Physical Society

Interplay of Genes and Mechanics in the Disorganization of Multicellular Structures

JAN LIPHARDT, Bay Area Physical Sciences Oncology Center and Department of Physics, University of California, Berkeley

As of last count, there are at least 10 risk factors for breast cancer. Some of these risk factors are genetic, such as mutations in the BRCA1 and 2 genes. Other risk factors are based on bulk tissue characteristics such as the degree to which the tissue attenuates x-rays ("mammographic density") or its mechanical stiffness. Finally, risk and outcomes are also correlated with specific micro-anatomical features, such as collagen lines or tracts that extend radially outwards from the tumor-stromal interface. Despite significant progress in discovering risk factors, it is not understood if and how these risk factors interact. We have developed a simple model system for studying how genes, mechanics, and geometry interact to drive defined multicellular structures to an invasive phenotype. We have found that pairs or groups of Ras-transformed mammary acini with thinned basement membranes and weakened cell-cell junctions can generate collagen lines that then coordinate and accelerate transition to an invasive phenotype. When two or more acini mechanically interact by collagen lines, the pairs or groups of acini begin to disorganize rapidly and in a spatially coordinated manner, whereas acini that do not interact mechanically with other acini disorganize slowly and to a lesser extent. When acini were mechanically isolated from other acini and also from the bulk gel by directed laser cutting of the collagen matrix, transition to an invasive phenotype was blocked in 20 of 20 experiments. Thus, pairs or groups of mammary acini can interact mechanically over long distances through the collagen matrix and these directed mechanical interactions are necessary for rapid transition to an invasive phenotype. This new model system may help to understand the interplay of genes, mechanics, and geometry in transition to an invasive phenotype.

In collaboration with Quanming Shi, Rajarshi P. Ghosh, Hanna Engelke, Bay Area Physical Sciences Oncology Center and University of California, Berkeley; Chris H. Rycroft, Bay Area Physical Sciences Oncology Center, University of California, Berkeley, and Lawrence Berkeley National Laboratory; Luke Cassereau, Bay Area Physical Sciences Oncology Center and University of California, San Francisco; James A. Sethian, Bay Area Physical Sciences Oncology Center, University of California, Berkeley, and Lawrence Berkeley National Laboratory; and Valerie M. Weaver, Bay Area Physical Sciences Oncology Center and University of California, San Francisco.

Reference:

Rapid disorganization of mechanically interacting systems of mammary acini Q. Shi, RP. Ghosh, H. Engelke, CH. Rycroft, L. Cassereau, JA. Sethian, VM. Weaver, and J. Liphardt, PNAS 111(2), 658-663 (2014)