Susan G. Komen

Research Grants – Fiscal Year 2015

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Analysis of the integration of cell-cell adhesion & Yap networks regulating tumor growth & invasion

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Lead Organization: Harvard Medical School

Grant Mechanism: Komen Scholars **Grant ID:** SAC130057

Public Abstract:

Interactions between breast epithelial cells play critical roles in regulating cellular processes that are critically important during tumor initiation and progression, e.g. contact inhibition, invasion, dissemination, metastasis. These interactions are misregulated in a high percentage of breast cancers, most prominently in lobular carcinomas where loss of the major receptor for cell-cell interactions, E-cadherin, is associated with almost all cases of this subtype and is a parameter in its clinical diagnosis. However, at the molecular level, E cadherin-mediated cell-cell adhesion is much less understood than other adhesion processes such as cell matrix adhesion. Emerging new evidence indicates that E-cadherin feeds into the control of the recently identified pathway referred to as the Hippo-LATS pathway. Disruption of this pathway in model systems leads to oncogenic transformation in culture and tumorigenesis in mice. This pathway regulates organ size during development via regulation of two proteins called YAP and TAZ. Both cadherin and YAP/TAZ pathways have independently been implicated in contact inhibition of cell proliferation, yet the details of how these pathways integrate remain unclear.

Our proposed research will characterize key aspects of E-cadherin mediated cell-cell adhesion and YAP/TAZ pathways and their crosstalk. Using combined proteomics and siRNA approaches we have identified multiple novel proteins that regulate cell-cell adhesion, four of which are strongly dysregulated in triple negative breast cancers. We are currently characterizing the novel adhesion regulators to define mechanisms whereby they regulate cell-cell adhesion and to establish how their alterations in tumor cells affect cancer invasion. We have also defined a signature associated with YAP in lobular carcinomas and are evaluating YAP regulation of this signature and the importance of this signature in tumor cell growth and survival. In addition, if we validate YAP/TAZ as targets in lobular carcinoma, we will collaborate with others to promote development of therapeutic strategies to inhibit YAP/TAZ in treatment of lobular carcinoma.