Susan G. Komen
Research Grants – Fiscal Year 2014

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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
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Public Abstract:
The 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 in 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 points of cross talk between the E-cadherin and YAP/TAZ which we have uncovered using our comparative proteomics/functional genomics screening strategy. Upon characterization of the most important nodes in these networks, we will investigate whether disruption of E-cadherin/YAP pathway integration or disruption of strong cell-cell adhesion promotes proliferation and invasive activity in vitro and in vivo. Because E-cadherin is downregulated in virtually all lobular carcinomas, we will also analyze the activation of YAP or TAZ in tissue microarrays of lobular carcinomas as well as investigate whether YAP/TAZ regulate aspects of tumorigenesis in established lobular carcinoma cell lines. 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.