



**Susan G. Komen
Research Grants – Fiscal Year 2014**

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Interplay between SRC-3, TRAF4 and ERK3 in breast cancers

Investigator(s): Bert O'Malley, M.D.

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Public Abstract:

SRC-3 is a protein that can function as an oncogene when it is overexpressed in breast cancer cells. It not only functions to promote breast cancer development but also participates in tamoxifen and chemotherapy drug resistance. We recently demonstrated that when we block the expression of SRC-3 in breast cancer cells, they are more sensitive to doxorubicin-induced death. In an effort to identify proteins that are downstream of SRC-3 that are responsible for SRC-3's oncogenic function, we identified TRAF4 (TNF receptor associated factor-4), as a protein that can promote cell resistance to cytotoxic stress. We observed that SRC-3 expression is inversely correlated with the expression of p53-regulated pro-apoptotic genes in breast cancers and further found that SRC-3 and TRAF4 overexpression diminished cytotoxic stress-induced upregulation of the tumor suppressor p53 protein. We also demonstrated that TRAF4 is overexpressed in the tumors of breast cancer patients who have received adjuvant chemotherapy and/or radiotherapy and hormone therapy after surgical removal of the tumor. Also linked with SRC-3 driven breast cancer cell growth is another protein called ERK3 that can drive cancer cell migration and invasion by stimulating the expression of MMP proteins that are responsible for breast cancer cell invasion. Little is known, however, about the upstream stimuli and activators of ERK3. To better understand the ERK3 signaling pathway, we collaborated with Dr. Jun Qin, director of the Proteomics core laboratory in our institution, to identify the interacting partners of ERK3 by immunoprecipitation of ERK3 protein complexes, followed by the mass-spectrometry analysis. A total of 566 candidates were identified. In addition, a recent study of signal transduction protein interaction networks by yeast-two-hybrid screening identified 160 interacting proteins for ERK3. Importantly, among these candidates identified by these two analyses, there are 126 in common. Consistent with our recent finding about ERK3's role in promoting cancer cell migration and invasion, top ERK3-associated network functions identified by the analysis include cellular assembly and movement, cell-to-cell signaling and interaction, and tumor morphology. The involvement of ERK3 signaling in cancer progression and metastasis is further indicated by the identification of top ERK3-associated biological pathways including RhoGDI signaling, TGFP/BMP signaling, serine synthesis, and VEGF signaling which are all responsible for breast cancer progression. Here, we plan to investigate the roles of TRAF4 and ERK3 in driving breast cancer cell growth in greater detail. Specifically, we plan to investigate how SRC-3 coordinately regulates TRAF4 and ERK3 to block apoptosis and drive cell motility and invasion, leading to aggressive, therapy-resistant breast cancer growth.