Susan G. Komen

Research Grants – Fiscal Year 2015

This research grant was approved for FY2015 Research Programs funding. This grant will be funded upon the execution of grant agreements between Komen and the grantee institutions.

Ubiquitin-dependent regulation of EMT in breast cancer metastasis

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Grant Mechanism: PDF Basic and Translational **Grant ID:** PDF15332075

Public Abstract:

Breast cancer is the most common female cancer and the second leading cause of cancer-related death in the United States. When breast cancer is detected early, patients have a five-year survival rate of 98.3%. However, after metastasis, where breast cancer spreads to distal organs, the five-year survival rate plummets to 24%, with most patients eventually die from the disease. Understanding what molecules regulate this process could provide a new therapeutic approach toward blocking metastasis and improving patient survival. There are specific molecular mechanisms, which trigger tumor cells to spread out from the primary tumor, and these gene alterations are orchestrated by a process called epithelial-mesenchymal transition (EMT). EMT is a highly-conserved embryonic development program that allow tumor cells to acquire migratory/invasive properties and escape from the primary tumor. Furthermore, EMT has been to cancer stem cell properties in breast cancer. Therefore, we want to better understand how the main EMT inducers are regulated and how best to generate targeted therapies to block this key step in metastasis.

The transcriptional factor SLUG has been well established as a strong driver of EMT, cancer stem cell function and metastasis in breast cancer. However, the molecular mechanism underlying the increased expression of SLUG protein in invasive breast tumors remains poorly understood. Most transcription factors are degraded rapidly in cells because of the E3 ubiquitin ligase-mediated proteasome degradation pathway, the main mechanism of protein degradation in cells. On the other hand, there are enzymes that ubiquitin marks from proteins, which prevents their degradation by the proteasome. These enzymes are called deubiquitinases (DUBs). We performed genome-wide E3 ligase and

deubiquitinase screens and identified candidate E3 ligase and deubiquitinase regulating SLUG through the ubiquitin/proteasome pathway. We hypothesize that these E3 ubiquitin ligase and deubiquitinase regulates EMT and breast cancer metastasis by modulating the SLUG protein expression level by degradation or stabilization of the protein, respectively.

In our proposed study, we will use a series of biochemical analyses, in vitro and in vivo metastasis assays, and clinical correlation studies to investigate the role of this E3 ubiquitin ligase and deubiquitinase in SLUG protein degradation, EMT, and metastasis. Discovery of a novel E3 ubiquitin ligase targeting the SLUG protein, and especially a deubiquitinase stabilizing SLUG, has significant translational value in providing a new therapeutic approach to block cancer metastasis. Small inhibitors to specifically block the interaction between DUB with SLUG would decrease its stability and promote degradation. This could block EMT, breast cancer stem cell activity and metastasis, and thereby, potentially improve cancer patient survival.