Susan G. Komen for the Cure
Research Grants – Fiscal Year 2011

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Targeting breast cancer stem cells by blocking both intrinsic (Akt) and extrinsic (IL-6) signaling pathways in metastatic mouse xenograft models

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Awarded: $450,000.00
Grant Mechanism: Career Catalyst Research
Research Focus: Biology

Public Abstract:
Recent evidences have suggested that many cancers, including those of the breast, are maintained by a population of cancer cells that display stem cell properties. These subsets of cells called cancer stem cells (CSCs) have been identified in number of human tumors. In addition, studies indicated that the CSCs may also contribute to tumor metastasis, treatment resistance and relapse in mouse models and clinical settings. Furthermore, the CSCs are regulated by intrinsic (originating from within the tumor cells) and extrinsic (originating from neighboring cells) signals such as cytokines and growth factors. Increased levels of these cytokines mainly interleukin 6 (IL-6) secreted by the neighboring cells in tumor microenvironment is associated with aggressive metastatic breast cancer. Recent studies demonstrated that blocking such cytokines including IL-8 and IL-6 reduces tumor burden. Moreover, one of the most important intrinsic pathway, (PI3-K/Akt signaling) is strongly associated with therapeutic resistance. We previously demonstrated that this signaling pathway indeed regulates breast CSCs. Interestingly cytokines such as IL-8 and IL-6 activates this pathway providing and additional signal for breast CSCs. This feedback loop between the tumor cells and their microenvironment provides a unique opportunity for breast CSCs to proliferate and metastasize to other organs. Most recent studies also suggested that the therapeutic resistance is mediated by CSCs. We previously showed that inhibition of PI3-K/Akt signaling can target breast CSCs reducing tumorigenesis in mouse models. In order to study the mechanism of resistance, we have generated a mouse xenograft model of aggressive metastatic breast cancer. In this model, aggressive metastatic breast tumor cells secreted high level of cytokines (IL-6) resembling to aggressive human breast tumors. We also determined that these cytokines contribute to aggressive CSC phenotype. Currently available standard chemotherapeutic agents do not target breast CSCs in our mouse tumor xenograft models as in the metastatic human breast tumors. However, our studies strongly suggested that targeting intrinsic (PI3-K/Akt) or extrinsic (IL-6) signals significantly reduced the breast CSCs which are the resistant cell population. In this proposal, we aim to investigate the role of signals from tumor microenvironment in regulating breast CSCs and determine whether the inhibition of both intrinsic and extrinsic signals will effectively target aggressive breast CSCs in our mouse xenograft models. Provided that our results indicate better outcome in mouse xenograft models, we strongly believe that our studies can rapidly translate into clinic. IL-6 inhibitor has been already approved by FDA and European Union for rheumatoid arthritis and has been under preclinical studies for number of human malignancies as a single agent. Our approach will be unique in that we will simultaneously target two most important signals which we believe contribute to aggressive/metastatic phenotype.