Susan G. Komen
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Uncovering mechanisms contributing to metastasis and to drug resistance in breast cancer

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Public Abstract:
Metastasis is the major cause of breast cancer-related death. If a woman presents with a tumor that is not invasive and has not spread to the lymph nodes (LN), she has close to a 100% chance of long-term 5 year survival. However, if the tumor has spread to the LNs or is present in distant organs her chances of being alive at 5-years go down to ~ 80% and 25%, respectively. Thus, we need to know more about the process of tumor dissemination and metastasis. Our hypothesis is that by further molecular analyses of breast cancer metastasis we will be able to identify new approaches to prevent this process.
Metastasis is a complex process whereby tumor cells acquire invasive properties and colonize distant sites. Our experimental plan has 2 aims. In the first aim we will use models of breast cancer metastasis in the bone in order to test the effect of blocking the well-known Jak/Stat pathway. Using bone metastasis models, our work in the past 3 years has shown that this pathway is consistently active in the bone environment. Jak is a tyrosine kinase and importantly, Jak kinase inhibitors, e.g., Ruxolitinib, are currently being tested in clinical trials. Thus, we hope that by analyzing different bone metastasis models for breast cancer, we will see if blocking this kinase has an impact on tumor growth in the bone.
Our second aim is to further analyze the role of an enzyme, Memo, which we have shown to be important for metastasis using breast tumor models growing in rodents. Memo is a novel protein that we discovered about 10 yrs ago. In the original work (Marone et al 2004 Nature Cell Biol 6:515-522), we showed that Memo was required for ErbB2-induced breast cancer cell migration. Thus, we hypothesized at that time that Memo might have a role in the metastatic process in aggressive breast tumors, like those overexpressing ErbB2. More recently, we showed that Memo is required for metastatic spread using breast cancer models growth as xenografts in rodents. Importantly, we have found that elevated Memo levels are present in approximately 40% of primary human breast tumors. Moreover, high Memo correlates with clinical factors of poor prognosis, e.g., estrogen receptor negativity and grade 3 tumors, and high Memo is more common in aggressive tumors like the ErbB2+/HER2+ group. Finally, we now know that Memo is a novel enzyme that uses copper to produce reactive-oxygen species (ROS). Since ROS influences the activity of other proteins that are required for migration, we propose that targeting Memo's enzymatic activity might be a novel anti-cancer approach.
The research we are proposing to accomplish in the next year will be important for 2 reasons: first we hope to gain information on the impact of Jak inhibitors on tumor growth in the bone. These inhibitors are now in early stages of clinical development and are being tested in breast cancer patients whose tumors show phosphorylation of Stat3, a transcription factor that is a direct Jak substrate.