

Novel Regulatory Mechanisms of Cell Survival During Bone Metastasis of Breast Cancer

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Our proposal will address the following overarching challenges: eliminate the mortality associated with metastatic breast cancer and identify why some breast cancers become life threatening metastases. Breast cancer is a complex disease that involves multiple genetic events, which are involved in promoting unrestrained cellular growth. These cancers spread to distal organs, such as bone, lungs, brain and lymph nodes and the magnitude of metastatic spread disease is staggering. Over 70% of breast cancer patients have metastases that usually represent the end stage of cancer and cause more than 40,000 deaths annually in the United States alone. Spreading of cancer cells can be viewed as a stepwise sequence of events in which cancer cells break away from a primary tumor, enter the bloodstream or lymphatic system and form a new tumor in a different organ (e.g., bone), the new tumor is a metastatic tumor.

Current understanding of the regulatory mechanisms of bone metastasis is still not clear. The unique characteristics of the bone provide homing signals (e.g., growth factors) to the cancer cells that is advantageous for tumor cell growth. In the past few years, bioinformatics combined with gene profiling of primary and metastatic tumors from patients and cancer cell lines has provided important data for identification of different classes of genes activated during spreading of cancer cells. The majority of these genes are secreted factors or cell surface receptors. However, there is lack of knowledge of regulators that control the levels of surface receptor of growth factors in metastatic cancer cells. Most metastatic cancers show an abnormal increase of the insulin-like growth factor-1 receptor (IGF-1R) survival pathway, but how IGF-1R remains active and supports metastatic tumor in bone is not understood. In this proposal we will investigate how IGF-1R remains high in metastatic breast cancer and how to identify patients which will benefit from anti-IGF-1R therapy.

We identified a novel regulatory pathway required for regulation of IGF-1R levels in bone metastatic breast cancer cells. We found that reduction of master gene regulator Runx2 protein in these cells decreases initial tumor growth in an experimental model of metastatic disease. Surprisingly, the residual tumors re-grew at later stages and showed higher IGF-1R protein levels. We found that these high levels of IGF-1R are due to reduction in Runx2 and β -Arrestin (β -Arr: an adaptor protein responsible for IGF-1R degradation). This suggested regulatory mechanism of adaptation of metastatic cells in the bone microenvironment led to our central hypothesis – the Runx2/ β -Arr axis plays a central role in survival of bone metastatic cancer cells by regulating IGF-1R signaling.

Using a series of complementary approaches, including imaging of metastatic cancer cells tagged with luminescent proteins for tracking these cells, we will define the stages of IGF-1R increase in metastatic breast cancer and will test combinatorial inhibition of Runx2 and IGF-1R pathway. To achieve these aims, we have established a novel organ culture system utilizing mouse bones cultured with luminescence reporter labeled metastatic breast cancer cells. The proposed studies are significant because they will identify novel targets and strategies to sensitize stage IV metastatic tumors to FDA approved inhibitors. Most significantly, as heterogeneity among cancers pose a major challenge for effective treatments; our studies will identify a group of breast cancers where these strategies might directly benefit the patients with stage IV metastatic disease. The proposed approach for regulation of IGF-1R via Runx2/ β -Arr will generate data that can directly be used to develop new therapeutic strategies for targeting of metastatic breast cancers and will reduce patient mortality due to metastasis.