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“Targeting cellular mechanotransduction in breast cancer metastasis”

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SCIENTIFIC ABSTRACT

Breast tumors are often detected through physical palpation due to their apparent “hardness” compared to normal mammary tissues. The presence of a fibrotic focus in breast tumors, which is associated with a 20-50 fold increase in tissue rigidity, is a prognostic marker of distant metastasis and poor survival. Direct measurement of tissue rigidities in human breast cancer samples also revealed that increased matrix stiffness is correlated with poor survival in breast tumors with the same clinical diagnoses. Increasing matrix stiffness without altering the biochemical composition of the extracellular matrix (ECM) can induce cell invasion in 3D human mammary epithelial acini. These findings demonstrate that mechanical forces generated by rigid matrices play a functional role in tumor metastasis. Our ongoing studies have identified a novel mechanotransduction pathway by which breast tumor cells sense increasing mechanical forces generated by the rigid tumor stromal matrix and translate this into activation of a biochemical mechanotransduction signaling pathway to induce tumor cell invasion, thus promoting breast tumor metastasis. The proposed research aims to study two protein kinases Lyn and EPHA2 that we recently implicated in breast cancer mechanotransduction and to perform pre-clinical studies in mice to evaluate whether inhibiting these kinases could block tumor invasion and metastasis. This proposal takes advantage of the expertise in breast cancer metastasis and mechanotransduction (the Yang lab) and in EPH signaling (the Pasquale lab) to delineate and target novel pathways linking tissue stiffness and breast cancer metastasis.

LAY ABSTRACT

Breast tumors are frequently detected through physical palpation due to their apparent “hardness” compared to the soft normal mammary tissue. The “hardness” of breast tumors correlates with distant metastasis and poor outcome in breast cancer patients. Recent studies show that breast tumors show a 10-50-fold increase of mechanical force exerted on tumor cells compared to normal breast tissues and that mechanical force generated by increasing hardness of breast tumors promotes breast cancer metastasis. However, it is unknown how mechanical force impacts breast cancer metastasis and whether therapeutic targeting of this regulatory mechanism could halt breast cancer progression and metastasis.

Our ongoing studies have identified two druggable candidate proteins that are likely to play essential roles in promoting breast tumor invasion and metastasis in response to high matrix rigidities in the tumor microenvironment. In this proposal, we aim to further characterize these two proteins in this novel metastasis regulatory pathway and determine whether therapeutic targeting these two proteins could inhibit breast cancer invasion of surrounding normal tissue and the formation of metastases. In the short term, the proposed research provides new prognostic markers to identify high-risk breast cancer patients for personalized treatment options. In the long term, the proposed research could lead to novel therapeutic regimens targeting cellular mechanotransduction for high-risk breast cancer patients with dense and stiff breast tumors.