

Title: Targeting Lipocalin2 to Prevent Brain Metastasis in Inflammatory Breast Cancer

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ABSTRACT

Inflammatory breast cancer (IBC) is an aggressive variant of locally advanced breast cancer that comprises 2-5% of all breast cancer cases in the United States but accounts for 10% of breast cancer mortality. IBC disproportionately affects minority population particularly African American women and that black women with IBC had a shorter median survival time than their white counterparts. Although studies of several molecular factors in IBC tumors and IBC cell lines suggest robust expression of RhoC, E-cad, p53 and transcription factors associated with a stem cell phenotype, no IBC specific molecular target or biomarker has been identified to date highlighting the need to better understand the pathobiology of this disease. Brain metastasis is exceedingly common in patients with IBC and advanced stage breast cancers and has dismal patient outcomes. The majority of patients with clinically significant brain metastases die within months. Thus, the treatment of brain metastasis remains a major challenge with an imminent need to define the mechanisms underlying metastatic dissemination to the brain for an improved patient care. Our preliminary data showed significantly higher levels of lipocalin 2 (LCN2) in IBC versus non-IBC cell lines and in metastatic brain sublines compared to lung metastatic sublines. However, the significance and how LCN2 is involved in IBC metastasis remains elusive. We hypothesize that LCN2 promotes brain metastasis in IBC and could serve as a promising therapeutic target to prevent brain metastasis. Herein, we propose to delineate the functional role of LCN2 in promoting brain metastasis using our novel preclinical mouse models and test the efficacy of siRNA-targeted LCN2 alone or in combination with standard treatments to prevent brain metastasis. The outcome of these findings will expedite further dissection of the mechanisms underlying LCN2 function in IBC metastasis, and its utility as a potential therapeutic target to prevent brain metastasis.