

Presenter: Emily Whitt

Authors: EMILY C. WHITT, Paula M. Vertino

Title: SUV420H2 REGULATION OF COLLECTIVE INVASION IN TRIPLE-NEGATIVE BREAST CANCER

Abstract

Breast cancer is the second most common cancer in women and metastasis is the leading cause of breast cancer-related mortality. There are several breast cancer subtypes, the most aggressive of which is triple-negative breast cancer (TNBC) which lacks expression of the targetable markers estrogen receptor, progesterone receptor, and HER2. TNBC is difficult to treat due to a lack of targeted therapies and poor response to traditional chemotherapy. For reasons that are not completely understood, TNBC is especially likely to metastasize, and to metastasize to serious locations such as the brain. In the early stages of metastasis, cells from the primary tumor invade the surrounding tissue before breaking away and seeding metastases. In some cases, tumor cells invade as clusters of cells that migrate as a group and maintain their cell-cell contacts through a process known as collective invasion. These clusters of collectively invading cells have been shown to seed circulating tumor cell clusters that are more efficient at forming metastases than single tumor cells. SUV420H2 is a histone methyltransferase that trimethylates histone H4 lysine 20 (H4K20me3), an epigenetic mark associated with transcriptional repression. TNBC has lower H4K20me3 levels than other breast cancer subtypes. Our lab and others have found that downregulation or inhibition of SUV420H2 promotes increased plasticity in the epithelial to mesenchymal transition, a transcriptional program associated with cancer metastasis. To test the role of SUV420H2 in TNBC, I utilized A196, a small molecule inhibitor of SUV420H2. Treatment of TNBC cells with A196 led to broad depletion of H4K20me3 and an increase in CDH1, a cell-cell adhesion molecule not typically expressed in TNBC cells, suggesting that A196 treatment promotes the formation of cell-cell contacts in these cells. Additionally, I found that in TNBC cells grown as spheroids in an extracellular matrix, A196 treatment promoted increased invasion and a shift in invasive phenotype from one where cells invade as single cells to a one where cells invade as collective chains emanating from the central spheroid. These data suggest that reduced levels of SUV420H2 and H4K20me3 in TNBC promote a phenotypic shift from single cell to collective invasion and may be one factor contributing to the increased metastatic potential of this subtype. Future studies will focus on further elucidating the precise transcriptional and epigenetic mechanisms that underly this phenotypic shift with the ultimate hope of gaining a better

understanding of triple-negative breast cancer progression and developing therapies aimed at preventing metastasis before it begins.