

Title: Targeting the Warburg Effect Blocks Metastatic Potential in Triple Negative Breast Cancer Cells

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Metastasis remains a challenge to treat and is the primary cause of death in women with breast cancer. Preventing metastatic spread is an important therapeutic goal; however there are no existing drugs that specifically target metastatic processes. The Warburg effect refers to the metabolic phenomenon that cancer cells favor glycolysis as their main source of energy production even in the presence of oxygen and functional mitochondria. Cancer cells exhibit increased glucose uptake and lactate production which are indicators for this preference of glycolytic metabolism. Expression of pyruvate dehydrogenase kinase isoform-4 (PDK4) promotes glycolysis by inactivating pyruvate dehydrogenase and is a target of interest in triple negative breast cancer. MDA-231 cells exemplify the triple negative breast cancer phenotype and are characterized by the lack of three receptors: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Triple negative breast cancer is highly aggressive and is commonly associated with poor clinical outcomes.

We hypothesize that inhibiting PDK4 will target the Warburg effect and reduce the metastatic potential in MDA-231 cells. We show that a small molecule inhibitor, PDK4-In1, decreased lactate production providing evidence of the on target effects of the drug. Additionally, in the presence of oxygen PDK4-In1 decreased cell migration in a scratch assay lacking directional cues, but this effect was absent in hypoxic conditions. Utilizing a transwell assay, we investigated directional movement using a defined chemoattractant gradient across a porous membrane. The cells were initially plated in the upper chamber and allowed to migrate over 24 hours. Migratory cells were stained, imaged, and then quantified using ImageJ software. Upon addition of PDK4-In1 to the transwell, a notable decrease in cell migration was observed with a chemoattractant gradient. These data support our hypothesis, and suggest that PDK4-In1 is a viable therapeutic approach to prevent metastases in triple negative breast cancer.