Reciprocal Activation of Breast Cancer Micrometastases and the Lung Epithelium During Metastatic Outgrowth

Jessica L. Christenson1, Nicole S. Spoelstra2, G. Devon Trahan3, Kathleen I. O’Neill4, Michelle M. Williams1, Kenneth Jones5, Jennifer K. Richer1

1University of Colorado, School of Medicine, Department of Pathology or 2Department of Pediatric Hematology, Oncology and Bone Marrow Transplantation; 3University of Oklahoma, Department of Cell Biology

Introduction

• The lung is one of the most common sites of breast cancer (BC) metastasis.
• Triple-negative breast cancers (TNBC) preferentially metastasize to the lung.
• The overall prognosis for BC patients diagnosed with metastatic disease is 2-3 years. Patients diagnosed specifically with lung metastases has a poorer prognosis of approximately 1 year.
• No metastasis-specific therapeutic strategies are available to effectively treat patients with metastatic disease.
• Tumors are known to alter the surrounding microenvironment.
• Preparation of the metastatic niche/microenvironment, prior to metastasis, is known to promote metastatic colonization.
• How established lung micrometastases remodel the lung microenvironment and how this contributes to metastatic outgrowth is not well understood.
• We have identified an association between aberrant lung wound healing and metastatic outgrowth that has identified tangible targets for intervention.

Hypothesis

We hypothesize that BC lung micrometastases activate surrounding lung epithelial cells which, in turn, support the survival/outgrowth of metastases within the lung.

Overall Goal

The overall goal of these studies is to identify factors secreted by lung resident cells that could be used as lung metastasis-specific therapeutic targets.

Methods

Mouse Models of BC Metastasis

• MMTV-PyMT (mouse mammary tumor virus long terminal repeat) transgenic mice. Develop spontaneous mammary tumors that metastasize to the lung.
• Late-stage metastasis model: Male 1 mouse mammary carcinoma cells injected intravenously (IV). MRI of lungs prior to sequencing as confirmed metastatic burden. Lung micrometastases have been defined.
• Single cell gen expression data with cells grouped by gene expression.
• Cell nuclei were defined by the most highly expressed genes per cluster.
• Overall gene expression pathway analysis of the top significantly expressed genes per sample using DIAMOND tool.

Ecor4 is associated with aggressive micrometastases

Changes in the AT2 secreteme promote TNBC growth

Conclusions and Future Directions

• Abrupt wound repair develops during metastatic outgrowth.
• Lung AT2 cells adjacent to growing metastases become activated, which is characterized by significant pro-tumor alterations to their secretome.
• BC metastasis-secreted Ecor4 may influence AT2 signaling in the metastatic lung.
• AT2 secreted factors may reciprocally promote metastatic tumor cell growth.

Summary: Our studies demonstrate that targeting the lung microenvironment, in addition to directly targeting malignant cells, may be an effective way to treat and manage BC lung metastases.

Future studies include continuation of how activated resident lung cell populations promote metastatic progression and could lead to the development or repurposing of therapeutic strategies to prevent destructive metastatic outgrowth.

Funding

• R01 CA187733-01A1 (JRK), NIH T32CA190216-01A1 (JLG), ACS IRG 18-164-56 (JLC)
• University of Colorado Cancer Center Support Grant (P30CA84639). and shared resources