Stony Brook University
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Doctoral Defense Announcement

Abstract

Systemic Host Response to Urinary Tract Infection Alters Mammary Tissue Homeostasis and Development and Accelerates Tumorigenesis in Models of BRCA1 deficiency and Basal Breast Cancer in a TIMP1-dependent manner

By

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Lineage plasticity is a critical mechanism in development and cancer initiation. The particular genetic, epigenetic and environmental factors that drive epithelial plasticity during breast cancer (BC) initiation remain incompletely understood. Our previous work identified an unexpected connection between urinary tract infection (UTI) and alterations in the distal mammary tissue to the extracellular matrix (ECM), dependent on TIMP1, which altered the epigenetic state of MECs. We found that the UTI-host response not only altered Brca1 KO mammary ECM, but also accelerated tumor emergence. Using single cell RNA-sequencing (scRNA-seq) of Brca1 KO pre-tumor mammary tissue, we discovered a unique population of basal-luminal (BL) cells that emerged two weeks after UTI. These BL cells exhibit lineage plasticity. To test the hypothesis that UTI-induced BL cells are TICs, we sorted these cells using surface expression of Itgβ6. After transplantation, Itgβ6+ BL cells from Brca1 KO tumors formed tumors faster than controls. Therefore, we sought to identify the activating factor within the ECM driving growth of these TICs. Because Itgβ6 is a sensor of ligands within the ECM, including tenascin and fibronectin, we identified an increase in tenascin, but not fibronectin, within Brca1-UTI relative to Brca1-PBS tissue by immunofluorescence. Furthermore, using TIMP1 neutralization during UTI and recombinant TIMP1 treatment without UTI, we demonstrated that TIMP1 is necessary and sufficient for ECM remodeling of tenascin and collagen, which are necessary to drive BL emergence. In fact, by preventing these UTI-induced ECM changes that drive Itgb6 responses in BL cells by neutralizing TIMP1 in UTI mice, we normalized tumor kinetics. This work provides the first example of how a local infection, commonly experienced by women globally, can impact the expressivity of a high-risk BC mutation and presents an avenue for improved prevention and surveillance efforts in the BRCA1 population.

Date: March 19, 2025 **Program**: Genetics
Time: 3:00 PM **Dissertation Advisor**: Camila dos Santos, PhD
Place: Hawkins Auditorium, Cold Spring Harbor Laboratory
To attend virtually, contact the Program Director at martha.furie@stonybrook.edu.