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## "Investigating the Function of Insulin-Like Growth Factor 1 Receptor in Metastatic Progression of Wnt1-Driven Mammary Tumors"

by
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Molecular Biology, Genetics, and Cancer Program

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Tuesday, March 28th, 2023
9:00 AM
Cancer Center, G1196

Join Zoom Presentation:
https://rutgers.zoom.us/j/95613573698?pwd=K3pXSWpDSU0zNm5ibWhrbUV3WnB2Zz09

Meeting ID: 956 1357 3698
Password: 101386

## ABSTRACT

Breast cancer is the most common form of cancer in women. Most, if not all, breast cancer related deaths are caused by the spread of malignant cells from the breast to other organs, in a process referred to as metastasis. Triple negative breast cancer (TNBC) is an aggressive subset of breast cancer that accounts for 15% of all cases and is characterized by the loss of estrogen and progesterone receptor and a lack of HER2 amplification. While only representing a relatively small percentage of all breast cancer diagnoses, TNBC is responsible for about 30% of all breast cancer deaths due to its heightened capacity for metastasis. Consequently, it is essential to identify the molecular mechanisms that contribute to a metastatic phenotype.

Traditionally, the insulin-like growth factors, IGF1 and IGF2, and the insulin-like growth factor type 1 receptor (IGF1R) have been shown to enhance the proliferative and invasive properties of breast cancer *in vitro* and in both xenograft and transgenic mouse models *in vivo*. Surprisingly, recent work from our lab has shown that disrupting IGF1R signaling in the breast epithelium of a mouse model of basal-like breast cancer (MMTV-*Wnt1*) through simultaneous expression of a dominant-negative human IGF1R transgene (MMTV-*Wnt1*/*dnIGF1R*) increases both the number of basal-like epithelial cells, and, more importantly, metastatic potential of the mammary tumors. However, the exact mechanism through which reduction in IGF1R expression or signaling contributes to a more aggressive, metastatic breast cancer phenotype remains poorly understood.

It has recently been discovered that the MMTV-*Wnt1* mouse mammary tumor model produces two unique tumor phenotypes distinguished by latency. When we compared early tumors from both the MMTV-*Wnt1* and the MMTV-*Wnt1*/*dnIGF1R* lines, they appeared macroscopically similar in their histology and epithelial populations. However, single-cell RNA sequencing (scRNAseq) on dissociated tumors revealed unexpected epithelial heterogeneity within tumors and shifts in epithelial populations between them. Upon further investigation, we observed intravasated epithelial cells within MMTV-*Wnt1*/*dnIGF1R* tumors as both single cells and clusters expressing markers representative of all the previously known epithelial subpopulations present within the primary tumor. Immunofluorescent analysis identified compromised vascular junctions and an increase in the number of Keratin 14-expressing circulating tumor cells in MMTV-*Wnt1*/*dnIGF1R* animals. Additionally, following tail vein injection the smallest micrometastases formed by MMTV-*Wnt1*/*dnIGF1R*-expressing epithelial cells were almost exclusively Keratin $14^+$, consistent with their increased presence in the bloodstream. A major Keratin $14^+$ epithelial cluster identified in the scRNAseq analysis was also found to be positive for Keratin 6a, both of which are markers of a more aggressive tumor phenotype and correlate inversely with *IGF1R* expression in the Cancer Genome Atlas human breast cancer database. Taken together, these data suggest that basal-like breast tumors with low IGF1R expression contain compromised vasculature and harbor an increased Keratin 14/6a population, resulting in permissive conditions for metastasis.