



Natural killer cell evasion by quiescent breast cancer cells drives metastatic dormancy

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Despite the benefits of adjuvant therapy, patients with ER+ breast cancer face a constant risk of recurrence for the remainder of their life. A reservoir of disseminated tumor cells (DTCs) must exist that escape therapy, grow slowly or not at all, and can be reactivated. A major challenge to the understanding of these interactions is the lack of models of estrogen receptor positive dormancy in fully immunocompetent mice. We aim to address this by developing an immunocompetent model of breast cancer dormancy. We investigated five syngeneic murine breast cancer cell lines for long-term and short-term dormancy in vivo. We found three cell lines in which mice survive for >100d after intracardiac inoculation (compared to <20d for non-dormant cell lines). We further investigated the role of the immune system in these models by inoculating cells into mice with varying defects in adaptive or innate immunity. We found each cell line shows differential sensitivity to various immune compartment loss. The D2.0R cell line showed no requirement for dormancy on the adaptive immune system, however survival was significantly reduced in NSG mice compared to NODscid mice. To identify the cell type responsible, we depleted various immune cell populations and found natural killer (NK) cells were responsible for this survival difference. We next investigated the differential response of quiescent vs proliferative D2.0R cells to NK cells and found quiescent cells were resistant to NK cell killing compared to proliferative cells. We investigated the mechanism of this phenotypic difference via bulk RNAseq, single cell RNAseq, and Visium spatial gene expression analysis. We found the transcription factor Bach1 drives NK cell resistance through upregulation of MHC-I and downregulation of NKG2D ligand RAE1. Taken together these models provide a platform for the better understanding of the immune system role in maintaining breast cancer dormancy and identify a mechanism for quiescent tumor cell evasion of NK cell surveillance.

ABOUT the SPEAKER

Dr. Grace G. Bushnell investigates breast cancer dormancy and metastasis, focusing on the mechanisms that drive tumor progression and immune system interactions. She earned her PhD in Biomedical Engineering at the University of Michigan, where her doctoral research focused on engineering biomaterial implants to recruit, detect, and study metastatic tumor cells. She then completed a K99/R00 postdoctoral fellowship in the laboratory of Dr. Max Wicha at the University of Michigan Medical School, where she developed immunocompetent models of breast cancer dormancy and defined the mechanisms of metastatic latency. Dr. Bushnell also holds a BS in Biomedical Engineering from Northwestern University, where she conducted research with Dr. Phillip Messersmith. At the University of Minnesota, she leads the Bushnell Oncomaterials Research Group (BORG), integrating cancer biology, biomaterials, and immunology to uncover new insights into metastatic dormancy.

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1003 Engineering Centers (Tong Auditorium)

