Stony Brook University
The Graduate School

Doctoral Defense Announcement

Abstract

Immune Regulation of Cancer Dormancy, Recurrence, and Metastasis: Insights from Breast and Pancreatic Cancer Models

By

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Breast cancer can recur after a prolonged latency period whereas pancreatic ductal adenocarcinoma (PDAC) can recur within months. This can be explained that persisted tumor cells survive immune responses by entering a dormant state.

To investigate immune regulation of breast cancer dormancy, D2.0R murine mammary carcinoma cell orthotopic transplantation mouse model was used. $CD4^+$ and $CD8^+$ T cell-mediated adaptive immune response effectively eliminated tumor formation, however, a subset of D2.0R cells persisted. Remarkably, these residual cells fueled recurrent tumors in 3-16 months in about 50% of the mice. Transcriptomic and proteomic analyses of cell lines derived from these recurrent tumors ("late-escaper") revealed a reduced endoplasmic reticulum stress phenotype that facilitates cell proliferation. Furthermore, "late-escaper" cancer cells acquired diverse genetic and phenotypic alterations, e.g., *Myc* amplification, MHC-I downregulation, epithelial-to-mesenchymal transition—that promoted immune evasion and enabled tumor formation.

In parallel, we established a PDAC mouse model by immunizing mice with PDAC cells and intrasplenic injection of PDAC cells to allow dissemination in liver. While most deiminated cancer cells (DCCs) were eliminated by immune response, some solitary DCCs persisted in a dormant state for > 20 months, with < 6% DCCs expressing proliferation markers. T cell depletion only causes few metastases in these DCC-hosting mice. Glucocorticoids (GCs) treatment, simulating elevated levels observed in PDAC patients, increased the proportion of proliferative DCCs to > 35%, and reduced T cells while increasing neutrophils via GC-GR axis. GC-treated mice exhibited more metastasis-associated neutrophil extracellular traps (NETs) and awakening-triggering cleaved laminin. Intriguingly, combining GC treatment with T cell depletion led to multiple metastases in mice harboring either GR or GR-deficient PDAC cells in the liver.

Together, I found that dormant breast and pancreatic cancer cells require proliferative cues and immune evasion to establish recurred tumor. Targeting signals that trigger proliferation and/or immune suppression could prevent recurrence.

Date: May 20, 2025 **Program**: Genetics
Time: 10:00 am **Dissertation Advisor**: Mikala Egeblad
Place: Life Sciences Building, Room 038