Stony Brook University
The Graduate School

Doctoral Defense Announcement

Abstract

The Unconventional Secretion of Immune Suppressive KRT19 and its Implications on Cancer-Associated Fibroblast Populations in Pancreatic Cancer

By

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Cancer immunotherapy targeting immune checkpoint inhibitors on T cells has failed in pancreatic ductal adenocarcinoma (PDA) because T cells are excluded from cancer cell nests. T cell exclusion is mediated by the interaction between CXCR4 on T cells, and CXCL12 derived from the cancer associated fibroblasts (CAFs). Cancer cells capture CXCL12 by externalizing KRT19 to form a CXCL12-KRT19 coating. Knockout of *Krt19* from cancer cells results in loss of CXCL12 capture, enhanced T cell influx, and responsiveness to anti-PD-1 therapy. For KRT19 to capture extracellular CXCL12 it must be externalized, but KRT19 lacks the canonical endoplasmic reticulum (ER)-directing signal peptide (SP). By using an ER-restricted TurboID system we show KRT19 enters the ER without a SP and that its secretion is sensitive to canonical secretion inhibitors. Furthermore, KRT19 follows a similar trajectory to other ER-targeted proteins by interacting with both the signal recognition particle and Sec61, by entering the ER and being secreted cotranslationally, and by entering the ER and being secreted via Sec61. We find that KRT19 can also enter the ER in tumors. KRT19 is most stable when in complex with its binding partner, KRT8, and cancer cells externalize KRT8. KRT8 does not enter the ER, but we find KRT8 is secreted via secretory autophagy, while KRT19 is secreted via both the canonical and autophagy pathways.

We wanted to evaluate how the CAF compartment was affected by loss of the CXCL12-KRT19 coating. CAFs normally inhibit immune function, but normal fibroblasts can inhibit and promote immune activation. We used two genetic models to remove the CXCL12-KRT19 coating to study how CAFs respond to conditions of immune activation and found a new subset of CAFs with low *Cxcl12* and high *Cxcl9* expression, a chemokine profile which would enhance T cell influx. This CAF population, termed T-CAF, is induced by T cells, enriches near *Ifng* expressing cells, and increases T cell migration.

This work identifies a novel means of using the ER to direct the secretion of a SP-lacking protein in KRT19 and provides new insights into how PDA uses the CXCL12-KRT19 coating to establish an immunosuppressive microenvironment.

Date: February 23, 2024 **Program**: Graduate Program in Genetics
Time: 2:00 pm **Dissertation Advisor**: Douglas T. Fearon, MD
Place: Hawkins Conference Room, Wendt Laboratory, Cold Spring Harbor Laboratory
To attend virtually, contact the Program Director at martha.furie@stonybrook.edu.