M & I
Microbiology
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University of North Carolina at Chapel Hill

DISSERTATION SEMINAR

Sarah Vick

"Immunosuppressive mechanisms of cancer and where to find them."

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1131 Bioinformatics

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ABSTRACT

Sarah Vick: Immunosuppressive mechanisms of cancer and where to find them.
(Under the direction of Jon Serody)

Breast cancer is the leading site of new cancer cases in women and the second leading cause of cancer related deaths. Improvements in detection and treatment in the past three decades has led to a significant decline in breast cancer deaths, yet just this year more than 42,000 people are expected to die from breast cancer. Immunotherapy, boosting the anti-tumor immune response, is a valuable advancement for the field of cancer therapy. Immune checkpoint therapy focuses on blocking inhibitory receptors expressed on activated immune cells. Two prominent checkpoint inhibitory receptors are cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death protein 1 (PD-1). Unfortunately, most triple negative breast cancer patients do not benefit from immune checkpoint inhibition despite immune infiltration into the tumors. In the work presented here, we aim to find ways to improve immunotherapy through projects studying the effectiveness of immune checkpoint blockade in cancer.

First, we evaluated several models of breast cancer and found the heavily immune infiltrated claudin-low subtype was not able to respond to immunotherapy due to the suppressive tumor microenvironment. This subtype of breast cancer responded to checkpoint inhibition only in the context of specific and complete regulatory T cell (T_{reg}) depletion. Second, we studied the role of PD-1 blockade on T_{regs} in a model of claudin-low breast cancer. We found that PD-1 blockade increased proliferation and survival of T_{regs} in the tumor microenvironment, leading to increased immunosuppression. Third, we observed the role of PD-1 expression on NK cells in cancer and chronic viral infection. We saw that NK cells may not be a beneficial target for immunotherapy due to the inconsistency of PD-1 expression.

Together, this work provides insight into potential mechanisms involved in the poor response to immune checkpoint therapy in some cancers. Although tumors may be heavily immune infiltrated, this does not predict response to immunotherapy, and a more thorough analysis of the tumor microenvironment should be done such as determining which subsets of immune cells in the tumor expressing PD-1 can potentially be affected by checkpoint blockade.