AN EXPERIMENTAL APPROACH TO DISTINGUISHING THE PREDOMINANT MECHANISMS OF IMMUNE EVASION IN HIGH-GRADE SEROUS OVARIAN CANCER

Nicole S Little[1,2], Spencer D Martin[1,3], John R Webb[1], Darin A Wick[1], Dave R Kroeger[1], Brad H Nelson[1,2]

Trev and Joyce Deeley Research Centre, British Columbia Cancer Agency[1]; Department of Biochemistry and Microbiology, University of Victoria, Victoria BC[2]; Michael Smith Genome Sciences Centre, BC Cancer Agency, Vancouver BC[3]

Background: There is a strong association between CD4+ and CD8+ tumor-infiltrating lymphocytes (TIL) and survival in high-grade serous carcinoma (HGSC). Further, TIL can recognize tumor-specific antigens, which raises the possibility they exert selective pressure on the evolving tumor. In response, tumors can evade immune pressure by two broad mechanisms: antigen loss or functional impairment/deletion of T cells. Recently, our lab reported anecdotal evidence of deletion of a tumor-reactive T-cell clone in HGSC, leading us to hypothesize this may be a common mechanism of immune evasion. We intend to test this hypothesis in a cohort of 20 HGSC cases by assessing the magnitude and clonal diversity of tumor-reactive TIL harvested at serial time points from HGSC patients undergoing standard treatment. Here we describe our first efforts to develop this experimental approach.
Methods: CD4+ and CD8+ TIL were expanded with high-dose IL-2 from an HGSC ascites sample and assessed by IFN-γ ELISPOT and flow cytometry for tumor recognition.
Preliminary results: Expanded $CD4^+$ and $CD8^+$ TIL showed robust expression of IFN-γ and up-regulation of CD137 upon stimulation with autologous tumor from a synchronous time point, indicating strong tumor recognition.
Next steps: Currently, we are expanding TIL from serial time points from this and other patients and assessing recognition of synchronous and asynchronous tumor samples. In addition, we are developing methods to track individual TIL clonotypes by high throughput TCR sequencing of FACS-purified CD137+ tumor-reactive subpopulations.
Significance: This study is designed to elucidate the predominant mechanisms of immune evasion in HGSC. Our results will help us design an optimal protocol for adoptive T cell therapy of recurrent disease.