

Technical Summary

Immunotherapies and targeted therapies are emerging as promising methods of treating cancer, with high response rates and low associated side effects when compared with more traditional methods of cancer treatment. Across these therapies, it has been found that high response rates are correlated with the presence of specific biomarkers that may be cellular, protein-based, or genomic in nature. Specifically, the discovery of cell-based biomarkers via the study of patient biopsies and other related samples remains a key problem due to the limited numbers of cells involved, and current methodologies that do not lend themselves well to the discovery of novel cell subpopulations. In this thesis, we investigate the use of various immunophenotypic and transcriptomic single-cell assays to characterize tumor-infiltrating immune cells from mice exhibiting differential responses to anti-PD-1 immunotherapy. Data analysis pipelines that allow for the mining of this data for novel cell subpopulations are also discussed. Based on our immunophenotypic analysis (multispectral image-based cytometry), we have discovered subpopulations of CD8+ T cells harboring repertoires of immunomodulatory receptors (GITR, CD44, LAG-3) that are enriched upon anti-PD-1 treatment. We have also detected subpopulations of cells resembling B cells and dendritic cells in mice known to show positive responses to anti-PD-1 immunotherapy. This immunophenotypic data was corroborated by single-cell RNA-Seq data obtained via Seq-Well. By clustering the single-cell libraries obtained according to gene signature scores, we identified distinct high-level families of immune cells in specific tumor categories. Downstream differential gene expression analyses on the T cells across tumor categories revealed actionable targets that correlated with response to anti-PD-1 immunotherapy.

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