Research Week 2023

Identification of cellular interactions in the tumor immune microenvironment underlying CD8 T cell exhaustion

Christopher D. Klocke[1], Amy E. Moran[2,3], Andrew C. Adey[3,4], Shannon K. McWeeney[1,3,5], Guanming Wu[1, 3]

[1]Division of Bioinformatics and Computational Biomedicine, Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, Portland, OR, USA
[2]Cell, Developmental and Cancer Biology, Oregon Health & Science University, Portland, OR, USA
[3]Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA
[4]Department of Molecular and Medical Genetics, Oregon Health & Science University, Portland, OR, USA
[5]Oregon Clinical and Translational Research Institute, Oregon Health & Science University, Portland, OR, USA

Keywords

bioinformatics, cancer immunology, immunotherapy, scRNA-seq, gene-regulatory network, CD8 T cell exhaustion

Abstract

Immune checkpoint inhibitors have shown success in treating a subset of patients with certain late-stage cancers. However, these treatments fail in many other patients, due to mechanisms that have yet to be fully characterized. The process of T cell exhaustion, by which T cells become dysfunctional in response to extended exposure to antigen, has been implicated in immunotherapy resistance. Single-cell RNA sequencing (scRNA-seq) produces an abundance of data to analyze this process, facilitating insights into cellular processes related to treatment efficacy. However, due to the complexity of the process, contributions of other cell types to a process within a single cell type cannot be simply inferred. We constructed an analysis framework to first rank human skin tumor samples by degree of exhaustion in tumor-infiltrating CD8 T cells and then identify immune cell type-specific gene regulatory network patterns significantly associated with T cell exhaustion. Using this framework, to better understand the molecular mechanisms of T cell exhaustion in different contexts, we further analyzed scRNA-seq data from human melanoma samples and peripheral blood mononuclear cells from HIV-infected patients to compare the gene-regulatory network patterns related to T cell exhaustion between the tumor microenvironment and the chronic viral infection context. We identified transcription factors and their targets in macrophages that are significantly associated with CD8 T cell exhaustion, some of which are shared between the tumor and viral contexts. These results demonstrate that our analysis framework can identify potential mechanisms driving key cellular processes implicated in the failure of cancer immune checkpoint inhibitors. The framework can be applied to all cell types in the tumor immune microenvironment, expanding our understanding of key biological processes that underpin the effective treatment of cancer.