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Computational assessment of T cell plasticity in immune related adverse events

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Keywords

immune related adverse events (irAEs), immune checkpoint blockade (ICB), T cells, T cell plasticity, single cell RNA sequencing

Abstract

Immune checkpoint blockade (ICB) therapy targets checkpoint proteins to restore normal function to the immune system so that it can attack cancer cells. It is used successfully to treat a variety of cancers; however, many patients suffer from the development of immune-related adverse events (irAEs), which may affect any organ system and can be severe enough to cause the cessation of therapy. There is therefore great interest in understanding the mechanism of irAE development. Pro-inflammatory IL-17-producing CD4+ T helper (Th17) cells have been implicated in the etiology of many autoimmune diseases, such as psoriasis and rheumatoid arthritis. Conversely, regulatory T cells (Tregs) are potent suppressor cells that regulate the autoimmune response through the action of checkpoint proteins such as CTLA-4. Tregs are known to inhibit Th17 pro-inflammatory activity, and the balance between Tregs and Th17 cells has been implicated as an important player in the context of cancer. Previous work has shown that the conversion of Tregs to Th17-like cells in breast cancer results in an inflammatory tumor microenvironment. In this work we hypothesized that Tregs take on a Th17-like phenotype upon ICB treatment that contributes to irAE development. We tested our hypothesis by analyzing previously-published scRNA-seq datasets from patients with or without irAE development upon ICB therapy. We examined the relative proportions of Treg and Th17 cells to determine whether there is an increased proportion of Th17 cells in patients who develop irAEs after ICB treatment. We also employed pseudotime analysis to assess the dynamic trajectory of T cells to test whether there is evidence for a Treg to Th17 conversion after ICB therapy in irAE samples. Our work contributes to the understanding of the role of Treg plasticity and Treg-Th17 balance in the context of ICB treatment and irAE development that will guide future research in the field.