Cell Reports Medicine

CellPress
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Preview

Distinct T cell sub-clusters may serve as biomarkers for immune related adverse events

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https://doi.org/10.1016/j.xcrm.2022.100902

Identifying biomarkers of irAEs is the prerequisite for maximizing clinical benefits of patients treated by immune checkpoint inhibitors. Bukhari et al.[1] identified significant associations between different peripheral T cell sub-clusters and arthritis, pneumonitis, and thyroiditis.

Immune-related adverse events, induced by immune checkpoint inhibitors (ICIs), lead to substantial morbidity and mortality in patients and may temper the clinical benefits of these drugs.[2] Given that irAEs may involve in any organ or system of human body, strong heterogeneity lies in irAEs, including incidence, time of onset, presentations, and mechanism of action.[3] Therefore, identifying irAE-predictive biomarkers is one of the major challenges surrounding irAEs,[4] and the related achievement will enable mitigating irAEs and improving patient outcomes. Moreover, it could also promote development of prophylactic or therapeutic strategies for irAE management. Recent studies explored the irAE-predictive potential of some factors, such as gender[5] and usage of antibiotics.[6] More importantly, several studies revealed the essential roles of T cell activation in irAEs[7] and demonstrated the potential associations between pathogenic T cells and any irAEs[8] or myocarditis.[9,10] In this study, Bukhari et al.[1] expand the spectrum of T cell sub-clusters associated with arthritis, pneumonitis, and thyroiditis by profiling T cells in blood samples from ICI-treated cancer patients.

Bukhari and colleagues performed single-cell RNA sequencing (scRNA-seq) and cellular indexing of transcriptomes and epitopes sequencing (CITE-seq) to delineate molecular features of peripheral T cells from ICI-treated patient with irAEs affecting different organs. They collected blood samples from 24 patients in a discovery cohort before and during ICI treatment, among whom seven developed pneumonitis, four developed polyarthritis,

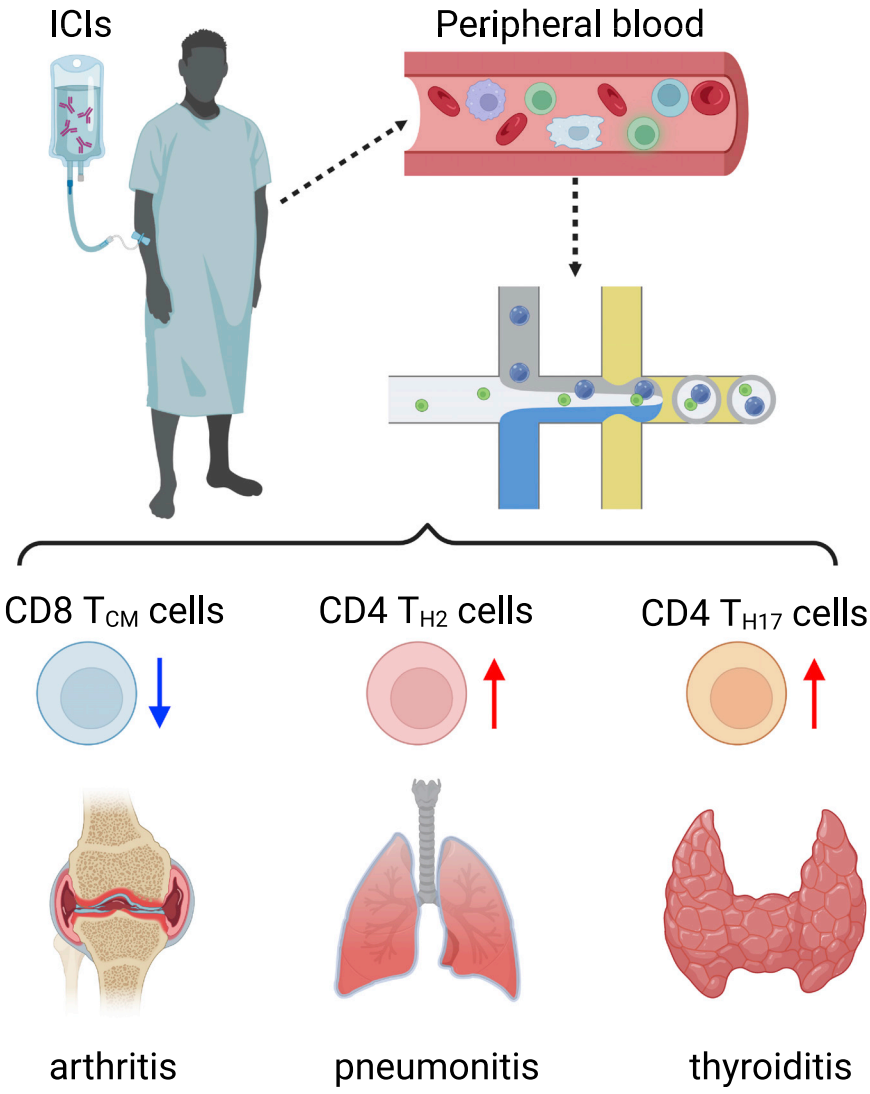

Figure 1. Analysis of T cell sub-clusters for immune-related adverse events impacting different organs
ICIs, immune checkpoint inhibitors. Image created with BioRender.com.

and four developed thyroiditis. Patients with arthritis had significantly more Th1/2 $CXCR3^+GATA3^+$ cells and less Tn $TCF7^+$ $LEF1^+$ cells and Tcm $CXCR3^+$ cells at baseline than patients without irAEs. Flow cytometry analysis on another cohort (n = 16) confirmed the decrease of Tcm cells in ICI patients who developed arthritis. Patients with thyroiditis and pneumonitis had higher proportions of two CD4 T sub-clusters, Th17 $KRT27^+$ cells and Th2 JUN^+ cells, compared with patients without irAEs. In addition, the authors classified pneumonitis into chronic hyperintensity pneumonitis (CHP) and organized pneumonia (OP) based on chest CT scans and identified divergent enrichment of T cell sub-clusters in these two subtypes of pneumonitis. They observed higher proportions of Tcm $CXCR3^+$ cells in patients with OP and more Tn $TCF7^+LEF1^+$ cells in patients with CHP. This result highlights the advantage of linking image data, transcriptomic data, and immune features in future irAE biomarker studies. Beyond discovery of novel links between T cell sub-clusters and irAEs, the authors also explored how these T cell sub-clusters contribute to the development of irAEs. They interrogated a GWAS catalog and identified that signature genes of Th1/2 $CXCR3^+GATA3^+$ cells and upregulated genes of T cells from patients with autoimmune disease overlap. In addition, differentially expressed gene (DEG) analysis on Th1/2 $CXCR3^+GATA3^+$ cells revealed elevated expression of inflammatory genes in arthritis groups, while DEG analysis on Tcm $CXCR3^+$ cells suggested T cell suppression phenotypes in patients with no irAE.

In summary, this study collected two independent ICI patient cohorts to identify potential predictive biomarkers for arthritis, thyroiditis, and pneumonitis (Figure 1). Considering challenges in collecting large cohorts of irAE patients, this study moves a step forward in the development of biomarkers for different kinds of irAEs. Future work is necessary to reveal the functional mechanisms of specific T cell sub-clusters resulting in irAEs in different organs.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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