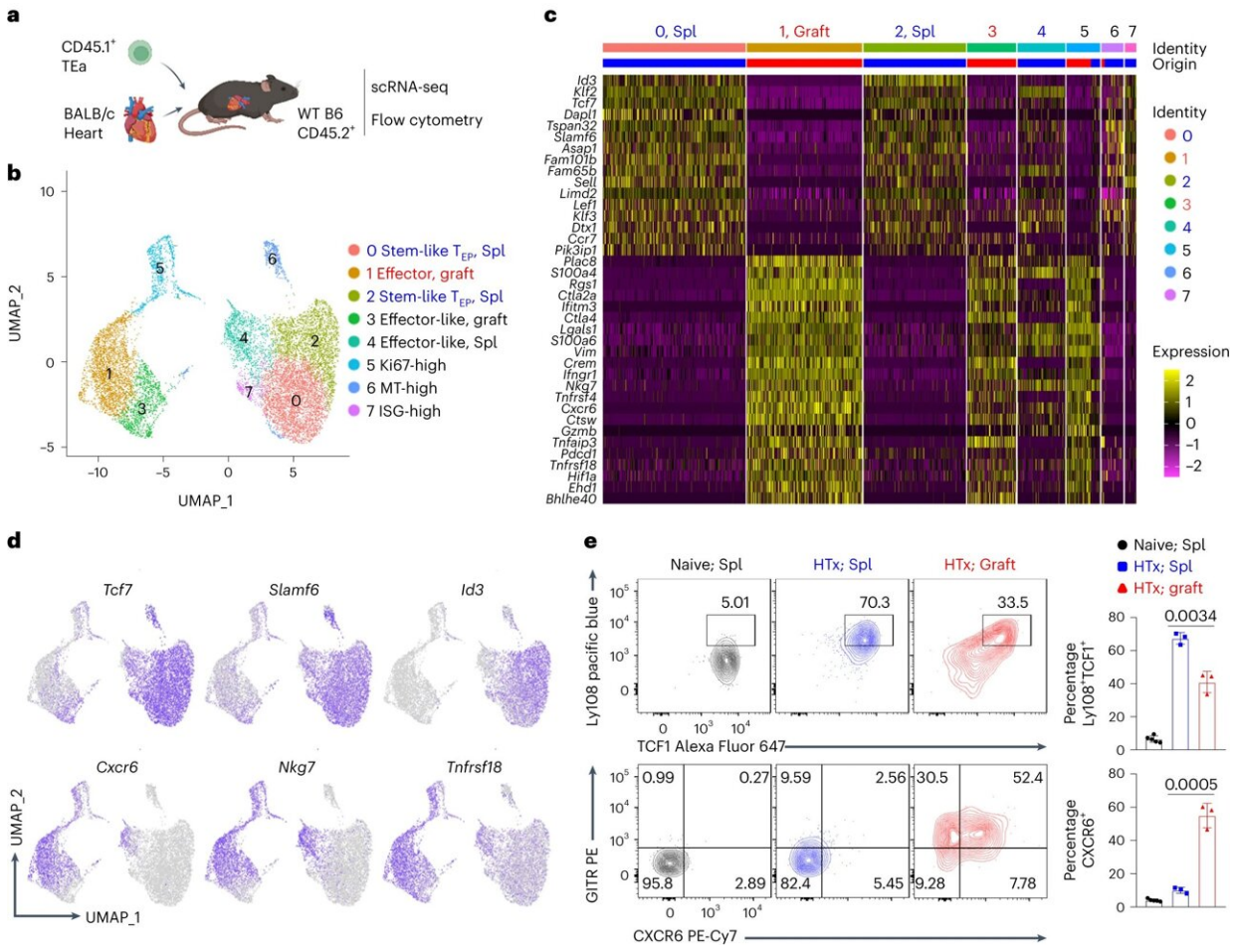
Researchers may have found key to deprogram cells that lead to transplant rejection

March 14 2024



Single-cell transcriptomics identifies alloimmune $CD4^+$ T_{EP} cells and effectors. **a–e**, $CD45.2^+$ WT B6 mice were adoptively transferred with $CD45.1^+$ TEa transgenic $CD4^+$ T cells and transplanted with BALB/c hearts, followed by scRNA-seq and flow cytometric analyses of TEa cells at 7 d post-transplantation.

Schematic of the experimental design (**a**). Created with BioRender.com. Uniform Manifold Approximation and Projection (UMAP) analysis of 10,964 single TEa cells from both spleens and allografts (**b**). Eight clusters (0–7) were identified and visualized with distinct color scheme. Heat map showing the expression of selected genes across all TEa cells (**c**). The top differentially expressed genes in the major T_{EP} cell clusters (0 and 2) versus the major effector cell cluster 1 are shown. The blue and red color bar indicates cell origin (blue, derived from spleens (Spl); and red, derived from grafts). Normalized expression of indicated genes projected onto the UMAP (**d**). Frequencies of $Ly108^{+}TCF1^{+}$ and $CXCR6^{+}$ cells among the transferred TEa cells in the spleens of B6 mice without transplantation (naive; Spl; $n = 5$ mice) or in the spleens (HTx; Spl) and the allografts (HTx; graft) of transplant recipients ($n = 3$ mice) (**e**). HTx, heart transplantation. Flow plots are gated on live TEa cells. Data are presented as mean ± s.d. (**e**). Results are representative of two independent experiments. *P* values are from a two-tailed unpaired Student's *t*-test. Credit: *Nature Immunology* (2024). DOI: 10.1038/s41590-023-01682-z

Houston Methodist researchers identified a troublesome subset of T-cells in transplant recipients that may be a more effective therapeutic target for preventing transplant rejection in patients.

Each day, 17 people die waiting for organ transplants, but getting a new organ doesn't guarantee survival. Despite immunosuppressive medications, rejection of transplanted organs happens in up to 50% of patients, depending on the type of organ transplanted and the time since the transplantation.

Wenhao Chen, Ph.D., associate professor of transplant immunology with the Houston Methodist Research Institute, and his team used single-cell RNA sequencing to analyze the $CD4^{+}$ T-cell response in transplantation scenarios and identified a subset that he referred to as "troublemakers." They also discovered the mechanism behind what directs that T-cell

response in animal transplant models.

This troublesome subset of $CD4^+$ T-cells they discovered acts like stem cells and continuously generates functionally mature effector T-cells that attack transplanted organs. They also found that the transcription factor IRF4 is required for T-cells in that subset to become those organ-attacking effector T-cells. Thus, Chen says IRF4 is what needs to be targeted to solve the problem of transplant rejection or to develop an autoimmunity cure.

"T-cells play a central role in fighting infections and cancer, but they are also the key players in mediating autoimmune diseases and transplant rejection," Chen said. "Our study demonstrated that IRF4 is a master regulator of T-cell function; a discovery that will allow the development of innovative therapies for patients with chronic infections, cancers, autoimmune diseases, and transplanted organs."

Eliminating undesired $CD4^+$ T-cell responses that could potentially lead to the loss of transplanted organs could eventually apply to all transplant patients, he said of this discovery.

"How to therapeutically inhibit IRF4 is the Nobel-prize winning question," Chen said in reference to a past research study on this challenge. "If we can find a way to inhibit IRF4 as desired in activated T-cells, then I think most autoimmune diseases and transplant rejection will be solved."

Their findings are described in an article titled "$CD4^+$ T cell immunity is dependent on an intrinsic stem-like program" in a recent issue of *Nature Immunology*.

"This revelation about the true troublemaker within the $CD4^+$ T-cell population is just the tip of the iceberg," Chen said. "I sincerely hope our

findings garner widespread attention, motivating both researchers and patients to recognize the significance of targeting these troublemakers."

More information: Dawei Zou et al, CD4+ T cell immunity is dependent on an intrinsic stem-like program, *Nature Immunology* (2024). DOI: 10.1038/s41590-023-01682-z

Provided by Houston Methodist