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Single-cell gene profiling analysis of human regulatory T cell subsets

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Negative regulation of the immune system is of critical importance to prevent pathology. This level of regulation is compromised in autoimmunity and graft-versus-host disease, a life-threatening complication of hematopoietic stem cell transplantation. $CD4^+CD25^+FOXP3^+$ regulatory T cells (Treg) are potent suppressors of these adverse immune reactions. Treg also play critical roles in the maintenance self-tolerance and the control of immune homeostasis. Recent reports have suggested that human Treg cells may not be a homogenous cell population.

The aim of this study was to identify and characterize human Treg sub-populations.

Treg subpopulations were isolated by cell sorting and characterized by immuno-phenotyping, functional assays and gene expression profiling. Single-cell gene expression profiling was performed by qRT-PCR using BioMark technology.

We have identified three different subsets of Treg in human peripheral blood: $CD25^{hi}FOXP3^{hi}CD127^-CD45RA^-HLADR^+$ ("activated" Treg), $CD25^{hi}FOXP3^{int}CD45RA^-HLADR^-$ ("memory" Treg) and $CD25^{hi}FOXP3^{int}CD127^-CD45RA^+HLADR^-$ ("naïve" Treg). We noted substantial differences in the expression of several Treg markers, such as FOXP3 and CTLA4, in the three subsets. Gene expression profiling combined with global pathway analysis revealed clearly distinct immune signatures. In particular, we found that memory Treg, but not naïve or activated Treg, expressed transcripts encoding cytokines such as IL-17A, IL-22, IFN-γ, IL-10, and IL-4. Despite their heterogeneity, all three human Treg subsets suppressed the proliferation of effector cells *in vitro* and are already present at birth, although in different proportions.

Single-cell gene expression profiling revealed substantial heterogeneity within the three Treg subsets, in particular within the memory Treg population. Of note, cytokine-expressing memory Treg did not downregulate FOXP3 and other Treg marker molecules. Current work addresses a potential "plasticity" and the ontogeny of this cell population.

In conclusion, our data revealed a striking heterogeneity of the human Treg compartment, indicating that Treg may use multiple mechanisms to exert their immunoregulatory functions.

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