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Single-cell analysis techniques reveal a striking heterogeneity of human CD4$^+$ T cell subsets

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Distinct CD4$^+$ T cell subsets are necessary for efficient immune responses against various pathogens. Among these, Th17 cells play a critical role in mucosal immunity. On the other hand, Th17 cells are pathogenic in several autoimmune disease models. In addition to IL-17A, Th17 cells also produce the IL-10-related cytokine IL-22. However, recent reports have suggested that human IL-22-producing CD4$^+$ T cells may represent a distinct T helper cell subset indicating an unexpected level of heterogeneity of CD4$^+$ T cell "lineages".

The goal of this study was determine the heterogeneity of inflammatory human CD4$^+$ T cell subsets using single-cell techniques.

Individual IL-17 or IFN-g-producing cells were isolated using cytokine secretion assays (CSA) and single-cell sorting. Single-cell gene expression profiling was performed by qRT-PCR using BioMark technology.

We first determined which human CD4$^+$ T cell populations secrete IL-17, IL-22, and IFN-g. Analysis of cytokine production at the single cell level revealed that only a small proportion of IL-22-producing cells also produced IL-17, whereas the major IL-22-secreting cell populations were a subset of Th1 cells and "Th22" cells that produce neither IL-17 nor IFN-γ. Finally, we identified a small population of CD4$^+$ T cell producing the 3 cytokines.

To define the molecular basis for the observed heterogeneity of inflammatory T cell subsets, we isolated individual IL-17A and IFN-g-producing CD4$^+$ T cells using CSA and analyzed the expression of 48 "marker" genes for Th1, Th2, and Th17 subsets. Hierarchical clustering revealed that the gene expression profiles of Th1 and Th17 cells are distinct at the single-cell level. However, we observed large differences in the expression levels and a remarkable heterogeneity of the expression of marker genes for individual Th1 and Th17 cells.

Our data reveal a striking heterogeneity of gene expression within inflammatory T cell populations, which may provide an explanation for the diverse functions of CD4$^+$ T cell subsets in orchestrating immune responses.

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