T CELLS

Flexibility in humans

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Different types of $CD4^+$ T helper (T_H) cell — such as T_H1, T_H2 and T_H17 cells — protect the host against diverse classes of microorganisms through the production of distinct cytokines. These T_H cell subsets were originally considered to be alternative fates of differentiating naive $CD4^+$ T cells, but T_H cell plasticity has been shown recently in *in vitro* and animal experiments. Now, Federica Sallusto and colleagues show that there is a vast flexibility in human $CD4^+$ T cell responses, as multiple kinds of T_H cells can act against a single pathogen and pathogen challenge can induce a single naive T cell to adopt multiple T_H cell fates.

To investigate the heterogeneity of human $CD4^+$ T cells, the authors isolated four memory T_H cell subsets — T_H1, T_H2, T_H17 and non-conventional T_H1 cells (which express the lineage-specifying transcription factors T-bet and retinoic acid receptor-related orphan receptor-γt) — from the blood of healthy donors on the basis of their chemokine receptor profiles. The T_H cells were labelled with a fluorescent dye and stimulated with *Candida albicans* in the presence of autologous monocytes *in vitro*; dilution of the fluorescent dye indicated proliferation of specific T_H cell subsets. Similarly to previous results, the authors found high numbers of proliferating T_H17 cells and non-conventional T_H1 cells, and low numbers of proliferating T_H1 cells and T_H2 cells in the cultures. Thus, human memory $CD4^+$ T cells primed by *C. albicans* are functionally heterogeneous.

Next, the authors carried out deep sequencing to analyse the unique T cell receptor (TCR) clonotypes of antigen-specific memory T cells within each T_H cell subset. The number of clonotypes was similar for each T_H cell subset, although the frequency of antigen-specific cells in the T_H cell subsets differed. Furthermore, several of the TCR clonotypes were shared between all of the T_H cell subsets, and the overlap was highest between T_H17 cells and non-conventional T_H1 cells. Whereas several of the shared clonotypes had a high frequency in both T_H17 cell and non-conventional T_H1 cell subsets, several clonotypes were found only in one T_H cell subset. Thus, *C. albicans*-specific memory T cells are highly polyclonal and include both clones that are polarized to a single fate and clones that have diversified into multiple fates.

So, is clonotype sharing a general property of memory T cell subsets or specific for the response to *C. albicans*? To address this, the authors analysed memory T cells specific for *Mycobacterium tuberculosis* or for the tetanus toxoid vaccine. The diversity of TCR clonotypes among T_H cell subsets in *M. tuberculosis*-specific memory T cells was similar to that of *C. albicans*-specific T_H cells, despite differences in proliferation. However, only very few clonotypes were shared between *M. tuberculosis*-specific T_H17 cells and non-conventional T_H1 cells. Interestingly, memory T cells primed by the tetanus toxoid vaccine showed similar levels of proliferation in all T_H cell subsets and a high level of clonotype sharing between all T_H cell subsets. Hence, the pattern and extent of clonotype sharing between different T_H cell subsets depend on the antigen.

Finally, the authors primed highly purified naive $CD4^+$ T cells *in vitro* with *C. albicans* to investigate whether one round of stimulation could imprint heterogeneous fates on a single naive T cell. Indeed, proliferating $CD4^+$ T cell subsets produced various combinations of cytokines and not only the cytokines that are characteristic of each specific subset; that is, some interferon-γ- and some interleukin-17 (IL-17)-sorted T cells acquired the ability to produce IL-4.

In summary, these results show that human memory $CD4^+$ T cells primed by pathogens or vaccines are highly heterogeneous and indicate that polarized T cell responses result from selective expansion rather than the priming of naive T cell clones.

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ORIGINAL RESEARCH PAPER Becattini, S. *et al.* Functional heterogeneity of human memory $CD4^+$ T cell clones primed by pathogens or vaccines. *Science* http://dx.doi.org/10.1126/science.1260668 (2014)