Specialized Tfh cell subsets driving type-1 and type-2 humoral responses in lymphoid tissue

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Abstract

Effective antibody responses are essential to generate protective humoral immunity. Different inflammatory signals polarize T cells towards an appropriate effector phenotype during an infection or immunization. Th1 and Th2 cells have been associated with the polarization of humoral responses for several decades. However, it is now established that T follicular helper cells (Tfh) have a unique ability to access the B cell follicle and support the Germinal Centre (GCs) responses by providing help to B cells. We investigated the specialization of Tfh cells induced under type-1 and type-2 conditions. We first studied homogenous Tfh cell populations generated by adoptively transferred TCR-transgenic T cells in mice immunized with type-1 and type-2 adjuvants. Using a machine learning approach, we established a gene expression signature that discriminates Tfh cells polarized towards type-1 and type-2 response, defined as Tfh1 and Tfh2 cells. The Tfh1 and Tfh2 distinct signature was validated against datasets of Tfh cells induced following LCMV or helminth infection. Using single-cell transcriptomics, we also dissected the heterogeneity of Tfh cells from the two immunizing conditions. Our results show that Tfh cells acquire a specialized function under distinct types of immune responses, but with the coexistence of a small population of Tfh cells of the alternative type. Furthermore, the specific molecular hallmarks of Tfh1 and Tfh2 cells identified herein offer putative new targets for tuning humoral responses.