FOLLICULAR HELPER T CELLS

More pieces of the puzzle

Follicular helper T (T_{FH}) cells are a subset of $CD4^+$ T cells that are confined to the B-cell areas of lymphoid organs and have a role in the selection of memory B cells or long-lived plasma cells that produce high-affinity antibodies. Now, three papers have broadened our understanding of T_{FH} cells, describing features of their functional development, their role in shaping antibody responses and how their dysfunction contributes to systemic autoimmunity.

In the first study, Fazilleau *et al.* examined the total antigen-specific T_H -cell compartment in the draining lymph nodes following protein vaccination. The antigen-specific T_H cells could be divided into three subsets: a T-zone-restricted B-lymphocyte-induced maturation protein 1 (BLIMP1)-expressing 'lymphoid' T_H -cell subset ($CD62L^{hi}CXCR5^{low}$), an 'emigrant' T_H -cell subset ($CD62L^{low}CXCR5^{low}$) and a 'resident' T_H -cell subset ($CD62L^{low}CXCR5^{hi}$) that uniquely expressed B-cell lymphoma 6 (BCL6) and had other features of T_{FH} cells. The authors then determined the relationship between the development of these T_H -cell subsets and the affinity and diversity of their T-cell receptors (TCRs). They found that naive $CD4^+$ T cells that expressed TCRs with high affinity for antigen preferentially developed into T_{FH} cells. In addition, these T_{FH} cells had the strongest peptide-MHC class II binding and a more restricted TCR repertoire compared with the lymphoid or emigrant T_H cells. So, the strength of TCR binding is causally linked to the development of antigen-specific T_{FH} cells *in vivo*.

In the second study, Reinhardt and colleagues sought to determine the exact role for T_H -cell-derived cytokines in the selection of high-affinity antibodies and the induction of class switching in B cells. In response to infection, all interleukin-4 (IL-4)-producing T cells in the draining lymph nodes were restricted to the B-cell follicles and germinal centres and had a T_{FH} -cell phenotype. These IL-4-producing T_{FH} cells were phenotypically and functionally distinct from IL-4-producing T_H2 cells in the periphery. Further investigation showed that some T_{FH} cells formed conjugates with B cells undergoing immunoglobulin class switching; IL-4-producing T_{FH} -cell-B-cell conjugates contained IgG1 transcripts, whereas interferon- γ -producing T_{FH} -cell-B-cell conjugates contained IgG2a transcripts. In addition, T_{FH} -cell-derived IL-4 was shown to be specifically required for the generation of high-affinity IgG1 antibodies. This study therefore shows that the production of cytokines by T_{FH} cells shapes the isotype and affinity of the antibody response.

In the third study, Linterman *et al.* determined the role of T_{FH} cells in systemic lupus erythematosus (SLE) using *Roquin*^{san/san} mice (roquin is a RING-type ubiquitin ligase that regulates mRNA stability in T cells). These mice develop a spontaneous SLE-like autoimmune disease with features that include autoantibody production, spontaneous germinal centre formation and high numbers of

T_{FH} cells. The expansion of T_{FH} cells and the spontaneous formation of germinal centres were shown to be the result of a T_{FH} -cell-intrinsic defect in these mice. Deletion of SLAM-associated protein (SAP; required for germinal centre formation) in these mice resulted in a selective reduction in the number of T_{FH} cells, but not other T_H cells, and abrogated the spontaneous formation of germinal centres and the production of autoantibodies. By contrast, T_{FH} cells isolated from *Roquin*^{san/san} mice induced spontaneous germinal centre formation in wild-type mice. So, expansion of the T_{FH} -cell population and defective positive selection of germinal centre B cells has a role in the development of autoimmunity, possibly owing to reduced competition between B cells for T-cell help.

Together, these three papers provide us with a considerable advancement in our understanding of the differentiation and function of T_{FH} cells.

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ORIGINAL RESEARCH PAPERS

Fazilleau, N. *et al.* The function of follicular helper T cells is regulated by the strength of T cell antigen receptor binding. *Nature Immunol.* 1 Mar 2009 (doi:10.1038/nri.1704) | Reinhardt, R. L., Liang, H.-E. & Locksley, R. M. Cytokine-secreting follicular T cells shape the antibody repertoire. *Nature Immunol.* 1 Mar 2009 (doi:10.1038/nri.1715) | Linterman, M. A. *et al.* Follicular helper T cells are required for systemic autoimmunity. *J. Exp. Med.* 16 Feb 2009 (doi:10.1084/jem.20081886)