Follicular helper T cells in autoimmune diseases

A good therapeutic target?

In autoimmune diseases, the breakdown of immune tolerance leads to the development of autoreactive immune responses targeting self-structures, and subsequent tissue and organ damage. Although the complex immunobiological mechanisms of autoimmune processes are still not fully clear, altered B cell function and autoantibody production seem to play a special role in the development of numerous autoimmune diseases. Understanding the process of B cell activation and autoantibody production is particularly important not only for early diagnosis, but also for development of novel effective treatments.

Follicular helper (T_{FH}) cells are special CD4 + T cells mediating antigen-specific naive or memory B cell activation within the B cell follicles of secondary lymphoid organs. T_{FH} cells are generated from peripheral naive CD4 + T cells in the T cell zone of these lymphoid organs. The differentiation of T_{FH} cells begins with their migration to the border of the T cell zone and B cell follicles. This follicular homing process is directed by B cell lymphoma 6 protein (Bcl-6), by coordinating the down-regulation of CCR7, a receptor for certain T zone chemokines, and the up-regulation of CXCR5, the receptor for CXCL13. CXCL13 is a chemokine ligand secreted by follicular stromal cells in B cell follicles, which attracts primed T cells to the follicle edge, where they interact with antigen-primed B cells and differentiate into T_{FH} cells. Interplay of T_{FH} and activated B cells is essential for the generation of extrafollicular short-lived plasma cells producing low-affinity antibodies, and for germinal centre (GC) responses as well. Within GCs, T_{FH} cells promote the development of high-affinity memory B cells and long-lived plasma cells by providing survival signals to centrocytes, which have undergone somatic hypermutation. Regarding the critical role of T_{FH} cells in B cell activation and antibody production, their failure to maintain self-tolerance and potential contribution to autoimmunity has drawn much attention.

Lessons learned from animal models, mainly murine models of SLE, shed light on altered T_{FH} profiles in autoimmune conditions. First, the significance of IL-21, now considered the hallmark cytokine of T_{FH} cells, was recognized in autoimmunity. Ozaki et al. [1] demonstrated enhanced IL-21 production in BXSB-Yaa mice, a model exhibiting lupus-like disease. IL-21 blockade or IL-21 receptor deficiency in lupus-prone MRL-Fas 

spontaneous GC formation [2, 3]. Further studies examining T_{FH} cells directly showed an aberrantly expanded T_{FH} population. Interestingly, when Wu et al. [4] investigated the effect of nasal anti-CD3 on T_{FH} cells in NZB/WF1 mice, CD4+/ICOS+/CXCR5+ T_{FH} cells obtained from anti-CD3-treated mice showed decreased IL-21 and IL-17 expression and induced less IgG, IgG1 or IgG2a anti-dsDNA antibody production in an in vitro co-culture with naive CD19 + B cells. Recent observations in autoimmune animal models have further enriched our knowledge about the development and function of T_{FH} cells. In an elegant study, Linterman et al. [5] investigated the deletion of Sap (Sh2d1a) and the loss of one Bcl-6 allele in Roquin 

Moreover, the deficiency of the Sap molecule caused a dramatic reduction in CD4 + CXCR5+/PD-1+ T_{FH} cells, IL-21 production, renal pathology, formation of GC and autoantibodies. Moreover, adoptive transfer of sanroque T_{FH} cells into wild-type recipients resulted in spontaneous GC formation, underscoring the direct role of T_{FH} cells in the development of lupus-associated autoimmunity.

Investigations of human autoimmune diseases also suggest that aberrant T_{FH} cell development and function can drive autoimmunity. Simpson et al. were the first to demonstrate altered T_{FH} proportions in SLE patients. By determining CD4 +CXCR5+ICOS 

Subsequently expansion of circulating T_{FH} cells has been reported in patients with various autoimmune diseases, such as SS, RA, JDM and autoimmune thyroid disorders. In primary SS, our group demonstrated that the elevated circulating CD4 + CXCR5+/ICOS+/PD-1+ T_{FH} cell percentages are associated with the presence of systemic extraglandular manifestations and anti-SSA/SSB positivity. Patients with higher T_{FH} cell proportions also had elevated serum levels of IL-12 and IL-21 [7]. Maehara et al. [8] investigated the selective localization of Th1, Th2, Th17, regulatory T and T_{FH} cells in labial salivary gland biopsies. They found that the expression of T_{FH} and Th2-related molecules in infiltrating lymphocytes with ectopic GCs was higher than in those without ectopic GCs. An elevated percentage of circulating T_{FH} cells was found in SLE. High T_{FH} cell
proportions correlated with disease activity and ANA positivity. Corticosteroid pulse therapy down-regulated the number of aberrant circulating T_{FH} cells, indicating that T_{FH} cells may be good therapeutic targets in SLE [9]. Overall, these observations suggest that perturbations to T_{FH} cells potentially contribute to numerous human autoimmune diseases. However, it should be noted that although circulating CD4^{+}/CXCR5^{+} T_{FH} cells are similar to follicular T_{FH} cells in terms of ICOS and PD-1 expression, circulating T_{FH} cells in SLE patients do not express Bcl-6 and IL-21. This divergence raises an important question: are circulating T_{FH} cells really related to classic T_{FH} cells? Although the fate of T_{FH} cells generated during GC reaction is still unclear, circulating T_{FH} cells may be a special subset of T_{FH} cells that migrated into the systemic circulation. Recently a new hypothesis has emerged suggesting that T_{FH} cells can generate memory cells. According to Morita et al. [10], circulating CD4^{+}/CXCR5^{+} T_{FH} cells share functional properties of T_{FH} cells present in lymphoid organs and constitute a subset of memory T_{FH} cells persisting for a long time in peripheral blood. Upon subsequent antigenic challenge, these memory cells may form T_{FH} cells more quickly and promote GC responses. Although in recent years significant progress has been made, further studies are needed to better understand the origins and function of T_{FH} cells. T_{FH} cells may be good therapeutic targets in these autoimmune diseases [9].

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