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Follicular helper T-cells in autoimmune diseases

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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 T 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 T-cell zone and B-cell follicle. This follicular homing process is directed by B-cell lymphoma 6 protein (Bcl-6), by coordinating the downregulation of CCR7, a receptor for certain T-zone chemokines, and the upregulation 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 GC, 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 systemic lupus erythematosus (SLE), shed light on altered T_{FH} profile in autoimmune conditions.

Chronologically first, the significance of interleukin 21 (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^{lpr} mice resulted in diminished lupus-associated features including IgG deposits in glomeruli, circulating dsDNA autoantibodies, total IgG1 and IgG2a production, lymphadenopathy and 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, 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 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$^{san/san}$ (sanroque) mice. They found that deletion of one Bcl-6 allele diminished spontaneous GC formation and lupus phenotype, moreover the deficiency of the Sap molecule caused dramatic reduction in $CD4^+/CXCR5^+/PD\text{-}1^{high}$ 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. Recently, using the IL-27R$\alpha^{-/-}$ pristane-induced lupus model, Batten *et al*. [6] demonstrated that the heterodimeric cytokine IL-27 was critical for the function of T_{FH} cells, as well as for normal and pathogenic GC responses.

Investigations on 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 $CD4^+CXCR5^+ICOS^{high}$

and $CD4^+CXCR5^+PD\text{-}1^{high}$ T_{FH} cells in peripheral blood, they observed an overrepresented population of $CD4^+ICOS^{high}$ and $CD4^+CXCR5^+ICOS^{high}$ T_{FH} cells, which showed association with the high autoantibody titre and the presence of glomerulonephritis [7]. Subsequently, expansion of circulating T_{FH} cells has been reported in patients with various autoimmune diseases, such as Sjögren's syndrome, rheumatoid arthritis, juvenile dermatomyositis and autoimmune thyroid disorders. In primary Sjögren's syndrome, our group demonstrated that the elevated circulating $CD4^+/CXCR5^+/ICOS^+/PD\text{-}1^+$ T_{FH} cell percentages were associated with the presence of systemic extraglandular manifestations and anti-SSA/SSB positivity. Patients with higher T_{FH} cell proportions had also elevated serum levels of IL-12 and IL-21 [8]. Maehara *et al.* [9] 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. Recently, elevated circulating T_{FH} cell proportions were detected in SLE and corticosteroids down-regulated T_{FH} cell numbers [10].

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? Albeit 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 which migrated into the systemic circulation. Recently, a new hypothesis emerged suggesting that T_{FH} cells can generate memory cells. According to Morita *et a.* [11], 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 [10].

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