Review

Emerging cellular networks for regulation of T follicular helper cells

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The cellular networks that regulate humoral immune responses have been a focus of research over the past three decades. Studies have shown that inhibition of immune responses can be attributed to both suppressor T cells and B cells. More recently, T follicular helper (Tfh) cells have been identified as a target of immune regulation. Tfh cells are a subset of highly activated T helper cells specialized for providing cognate help to B cells during germinal center reactions. In this review, we describe emerging evidence for cellular networks that alter Tfh cell phenotype and function and regulate antibody production during the germinal center reaction. We discuss how these new findings influence our understanding of Tfh cells.

T follicular helper cells and the humoral immune response

During the humoral immune response, antigen is transported into the T cell zone and B cell follicles, which initiates the activation and interaction of T and B cells resulting in the germinal center (GC) reaction. GC are discrete structures within the B cell follicles of secondary lymphoid organs in which the processes of somatic hypermutation (SHM), class switch recombination and affinity maturation of activated B cells occur accompanied by production of memory B cells and antibody secreting plasma cells (PC) [1–3]. *In vivo*, PC can arise from two developmental routes. Short-lived PC are generated in the extra-follicular pathway. Antibody from these PC are critical for the immune response to acute and cytolytic infections and constitute the majority of antibody detected soon after primary infection or immunization. By contrast, PC generated in the GC reaction are selected after the time-consuming processes of SHM and affinity maturation; these PC secrete high-affinity class switched antibody and persist in survival niches such as the bone marrow [4,5]. PC and memory B cells generated from the GC are poised to respond rapidly to re-encounter with antigen.

For GC to develop, B cells must receive cognate help from $CD4^+$ T helper cells [6,7]. The absence of T cell help during B cell priming leads to apoptosis, thereby preventing differentiation of B cells into memory B cells or plasma cells [8]. T follicular helper (Tfh) cells are the specialized subset of T helper cells that provide help within GC. The migration of Tfh cells into the B cell follicle and GC is dependent upon the coordinated downregulation of CC chemokine receptor 7 (CCR7), reducing attraction to CC chemokine ligand (CCL)19 and CCL21 in the T cell zone, and upregulation of C-X-C chemokine receptor type 5 (CXCR5), increasing attraction to CXCL13-rich follicular dendritic cell (FDC) networks in the GC [9–13]. Tfh cells are a highly activated subset of T helper cells, but whether Tfh cells comprise a distinct lineage remains controversial.

T cell help in the GC is a crucial component of the generation of an affinity-matured antibody response. However, the important functional role of Tfh cells in driving the affinity maturation of PC has been an underappreciated feature in recent studies describing Tfh-phenotype cells. This is partly because of the focus on the early primary response to infection or immunization when the contribution of affinity-matured antibody remains unclear; and the fact that many recently activated $CD4^+$ T cells in the T cell zone and at the T cell–B cell border share phenotypic features with Tfh cells, including expression of CXCR5, GL7, inducible T-cell co-stimulator (ICOS), programmed death 1 (PD-1), GL7 and the transcriptional repressor B cell lymphoma 6 protein (Bcl6). Therefore, many aspects of Tfh cell biology remain unresolved. An improved appreciation of the similarities and distinctions between T helper cells that provide help to B cells at extrafollicular sites, the T cell–B cell border of lymphoid tissues, and Tfh cells that reside in the GC will be an important step forward.

The cellular and humoral arms of the immune system share many features both in terms of their activation kinetics and migration through lymphoid tissues as well as the growth factors that generate and sustain immune responses following infection or immunization. This offers the potential for a variety of regulatory mechanisms to control the expansion of lymphocyte clones with specificity for self-antigens as well as imposing limits upon the magnitude and duration of immune responses to foreign antigen. These control mechanism are those mediated by T cells and B cells, which operate through antigen-specific means as well as non-specific mechanisms, such as through the release of inhibitory cytokines. Recent studies have identified Tfh cells as a target of immune regulation. In this review, we discuss recent findings of Tfh cell inhibition by $CD8^+$ suppressor T cells, $FoxP3^+$ $CD4^+$ T regulatory cells

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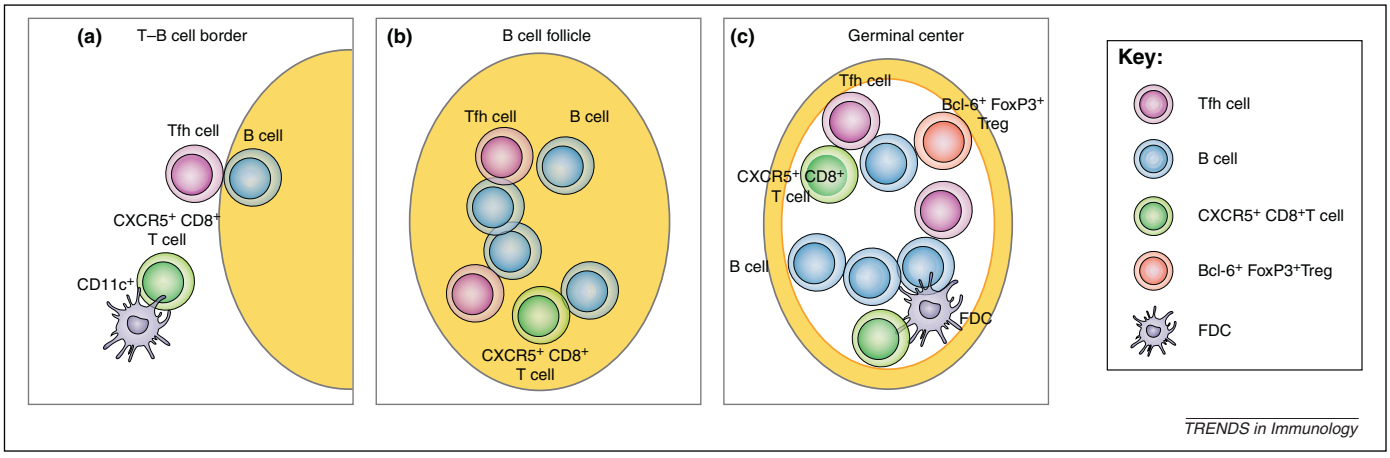

Figure 1. Cellular interactions that regulate Tfh cells in lymphoid tissues. (a) Naive $CD4^+$ T cells interact with $CD11c^+$ dendritic cells in the T cell zone. Activated $CD4^+$ T cells that have upregulated CXCR5 and downregulated CCR7 migrate towards the B cell follicle. At the border of the T cell zone and B cell follicle, Tfh cells interact with B cells. (b) $CXCR5^+$ $CD8^+$ T cells interact with B cells and Tfh cells in the B cell follicle and within the germinal center. Whether this interaction occurs directly or indirectly remains incompletely understood. (c) $CXCR5^+Bcl\text{-}6^+FoxP3^+$ Treg cells regulate T follicular helper cells and reduce the magnitude of the germinal center reaction. (b and c) Plasma (B) cells can also regulate Tfh cells by imposing a negative feedback loop.

and B cells (Figure 1) in the context of our current knowledge of immune regulation of antibody responses.

A brief history of $CD8^+$ suppressor T cells

T cell-mediated inhibition of antibody responses was initially focused on the role of a subset of $CD8^+$ T cells, named $CD8^+$ suppressor T cells. The molecular mechanisms that explain $CD8^+$ T cell suppression of humoral immune responses have been controversial for longer than 3 decades. In the 1970s, a subset of $CD8^+$ T cells was described that caused a progressive decrease in the proliferation of $CD4^+$ T cells in response to the antigen-presenting cell (APC) used for priming during multiple mixed-lymphocyte reactions (MLR) [14,15]. These and subsequent studies resulted in a substantial body of literature demonstrating that $CD8^+$ T cells could broadly inhibit immune responses. $CD8^+$ suppressor T cells were found to be antigen specific, and were $abTCR^+$ and major histocompatibility complex (MHC) class I or HLA restricted [16,17]. The suppressive effects of $CD8^+$ T cells applied to IgE as well as IgA and IgG production and occurred in both primary and secondary responses to both virus infection and non-replicating antigens [18,19]. Infection with LCMV provided a sound model of $CD8^+$ T cell-mediated suppression, establishing that virus-triggered, T cell-mediated immunopathology caused the antigen-specific suppression of B cells and antibody responses and led to the suggestion that such a mechanism may permit certain viruses to establish persistent infections [19–22].

However, despite the wealth of evidence for $CD8^+$ T cell-mediated suppression of immune responses, interest in the field began to wane when these cells were reported to be phenotypically and functionally distinct from other effector and memory-phenotype $CD8^+$ T cells, and especially in being able to secrete soluble suppressive factors mapped to the I-J region within the MHC. The nail in the coffin came when DNA sequencing of the MHC failed to identify a coding region for I-J [23,24]. The idea that T cells could have suppressive function then collapsed abruptly, but was revived a number of years later following the identification of $CD4^+$ $CD25^{hi}$ FoxP3 regulatory T cells and then $CD8^+$ $FoxP3^-$ T regulatory cells. These two subsets were shown to play a crucial role in the maintenance of self-tolerance.

Mechanisms of CD8 T cell suppression

The mechanisms reported to account for $CD8^+$ T cell-mediated suppression of immune responses include the same effector mechanisms employed by $CD8^+$ T cells to defend against infection. They can be broadly divided into lytic and non-lytic mediated mechanisms. $CD8^+$ T cells activated in response to peptide ligand–MHC class I complexes can lyse target cells; for example, via the perforin-mediated granule exocytosis pathway and by inducing Fas-mediated death via upregulation of FasL (CD95L). In addition, $CD8^+$ T cells may exhibit non-lytic mechanisms of suppression that remain poorly understood, but include competition for growth factors or release of soluble factors such IL-10 and TGF-β [25,26] and production of IFN-γ, which has been shown to skew switching patterns in responding B cells from IgG1 to IgG2a and IgG2b [27].

$CD8^+$ T cells in B cell follicles

In considering the ability of $CD8^+$ T cells to regulate Tfh cells and antibody responses, it is notable that $CD8^+$ T cells enter B cell follicles during the GC reaction (Figure 1). Several studies indicate that $CD8^+$ T cells are activated close to B cells during immune responses and this proximity is likely to be important whether $CD8^+$ T cells act on Tfh cells directly or indirectly, which is still unclear.

$CD8^+$ T cell division has been observed inside murine B cell follicles after T-dependent immunization; also, in HIV infection, mitotic $CD8^+$ cells containing TIA-1, a granule-associated protein, are observed inside follicles [28]. More recently, a subset of human $CD8^+$ T cells was described in human tonsil tissue that expressed the chemokine receptor CXCR5 [29]. $CXCR5^+$ $CCR7^-$ $CD8^+$ T cells were found scattered in the follicular mantle and dark zone of B cell follicles [29]. Antigen-specific $CD8^+$ T cells identified with MHC class I-ovalbumin (OVA) peptide tetramers (Tet) have been defined in histological sections of spleen following