Review

CellPress

T follicular regulatory cells in the regulation of B cell responses

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High affinity antibodies result from interactions between B cells and T follicular helper (Tfh) cells in germinal centers (GCs). Recent studies have identified an effector subset of T regulatory cells termed T follicular regulatory (Tfr) cells that specifically controls GC responses by suppressing Tfh and B cells. The discovery of Tfr cells has shed new light on pathways regulating humoral immunity that enable potent and specific responses to pathogens while restricting autoimmunity. Here, we review the current understanding of the cellular and molecular mechanisms underlying the differentiation and function of Tfr cells. In this context we discuss recent insights into the role of Tfh cells in disease, how this knowledge may be translated therapeutically, and important areas of further research.

New insights into regulation of B cell responses

Production of high-affinity class-switched antibodies and memory B cells is essential for clearance of pathogens and immunity elicited by vaccination. These antibodies, as well as memory B cells, are produced during a multistep process called the GC reaction. During the GC reaction, B cells interact with Tfh cells, which specialize in providing B cell help. These interactions result in somatic hypermutation, affinity maturation, and class switch recombination. The antibodies produced can clear invading pathogens through neutralization, opsonization, and/or antibody dependent cell cytotoxicity (ADCC) [1,2].

Elegant studies of B cell and Tfh cell dynamics in the GC have elucidated many key steps in the GC response [3–5]. The GC reaction requires regulation so as to ensure appropriate levels of antibody production, while limiting inflammation and autoimmunity. Central tolerance is one mechanism that prevents autoimmunity because self-reactive T and B cells are largely deleted. Some self-reactive cells, however, escape into the periphery [6]. In the periphery, the requirement for innate receptor-mediated 'stranger/danger' signals for antibody production is another mechanism that prevents autoimmunity [7,8]. These mechanisms only partially control B cell responses. It has been hypothesized that more direct regulation is necessary to control the GC. Therefore, a central question has been how are GC B and Tfh cells regulated after the start of the GC reaction?

Recent work has identified a subset of CD4+ T regulatory (Treg) cells that potently and specifically inhibit B cells responses [9–11]. Here we review the current understanding of the phenotype and functions of these cells, termed Tfr cells. We discuss how Tfr cells exert their suppressive functions, the roles of Tfr cells in health and disease, and important areas for future inquiry.

Discovery of Tfr cells

Studies of FoxP3+ Treg cells suggested that Treg cells may control B cell responses. The absence of Treg cells results in increased antibody production. Scurfy and FoxP3 knockout mice (which lack Treg cells due to absence of functional FoxP3 expression) have sharp increases in serum IgG1 and IgE levels [12,13] basally, and in the context of allergic responses [14]. Similarly, patients with immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome (in which Treg cells are lacking) have a broad spectrum of autoantibodies in their sera [15,16]. Treg-specific deletion (using a FoxP3-driven Cre strain) of molecules important in Treg effector function, such as IRF4 or CTLA-4, also results in heightened levels of serum IgG and IgE antibodies [17,18].

Complementary studies linked Treg populations with B cell responses. Human CD57−CD69−CD25+CD4+ cells (which are enriched for Treg populations) can inhibit IgA production and AID expression when cultured with B cells [19]. Murine CD25+CD4+ cells can kill B cells through cytolysis [20]. FoxP3+ cells can express CXCR5 and be found in GCs of human tonsils or immunized mice [19,21,22]. However, it was not clear whether the CXCR5-expressing Treg cells represented a specialized cell subset or represented Tregs that entered GCs stochastically. Also unclear was whether CXCR5+ Treg cells could specifically suppress B cell responses *in vivo*. These ambiguities reflected the lack of functional and definitive experiments and the need for strategies to rigorously purify these cells.

In 2011, three separate papers described a specialized population of Treg cells that express CXCR5, Bcl6, PD-1 and ICOS, and therefore phenotypically resembled Tfh cells (Table 1) [9–11]. By demonstrating that Bcl6, SAP, or B cell deficient mice lack CXCR5+FoxP3+cells (but not Treg cells), and that CXCR5+FoxP3+ cells have a distinct transcriptional signature compared with other Treg cells,

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Keywords: humoral immunity; vaccination; regulatory T cells; Tfr; Tfh; germinal center.

1471-4906/
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Table 1. Molecular phenotype of Tfr cells compared with naïve CD4+ T cells, Tfh cells, and Treg cells.

	Tfr	Treg	Tfh	T naïve	Refs
CD4	++	++	++	++	[9–11,24]
CXCR5	++	–	+++	–	[9–11,24,25]
FoxP3	++	++	–	–	[9–11,24]
ICOS	+++	+	++	+	[9,24,25]
PD-1	++	–, +	++	–	[9–11,24,72]
Bcl6	+	–	++	–	[9,10]
Blimp1	+	+	–	–	[9,24,48]
CTLA-4	+++	++	+	–	[9,40,41]
CD25	++	+++	–	–	[9,24]
GITR	+++	++	–	–	[9–11,24]
Ki67	++	–, +	+++	–, +	[11,24]
CD44	++	–	++	–	[10,24]
IL-21	–	–	+	–	[9]

these studies conclusively showed that CXCR5+FoxP3+ cells are a distinct effector subset of Treg cells, termed Tfr cells [9–11]. Demonstrating specialized *in vivo* function was essential for proving that Tfr cells were a distinct lineage/subset. Three initial *in vivo* experiments showed that Tfr cells specifically inhibit B cell responses. Chung *et al.* performed an adoptive transfer experiment in which CD4+ T cells were transferred with WT or $Bcl6^{-/-}$ CD25hi (i.e., Treg enriched) CD4+ T cells into $Tcr\beta^{-/-}$ mice that were immunized with NP-KLH [10]. Recipients of $Bcl6^{-/-}$ CD25hi cells (which cannot form Tfr cells) exhibited higher antigen-specific antibody production. Linterman *et al.* generated chimeric mice (in which $Rag2^{-/-}$ mice were reconstituted with FoxP3-diphtheria toxin receptor (DTR) and either WT or SAP deficient cells) that were immunized with sheep red blood cells (SRBCs) and given tamoxifen to delete FoxP3 Tregs [9]. The SAP deficient chimeras (which cannot generate Tfr cells) had elevated GC B cells. Wollenberg *et al.* used an adoptive transfer approach in which $OTII^+$ CD4 T cells were transferred along with WT or $Cxcr5^{-/-}$ $FoxP3^+$ Tregs to $Tcr\alpha^{-/-}$ recipients which were immunized with ovalbumin (OVA). The $Cxcr5^{-/-}$ Treg group had substantially increased antigen-specific antibody levels [11]. Together, these initial Tfr studies not only elucidated the precise phenotype of Tfr cells, but also demonstrated their specialized function in suppressing B cell responses *in vivo*.

Currently, Tfr cells are defined as an effector subset of Tregs that express CXCR5, which directs them by gradients of CXCL13 to migrate to GCs and suppress B cell responses. Tfr cells phenotypically resemble Tfh cells: both Tfr and Tfh cells express CXCR5, PD-1, ICOS, and Bcl6 (Table 1 and Box 1). Although phenotypically similar, Tfr cells originate from natural Treg precursors, whereas Tfh cells originate from FoxP3– naïve CD4 T cells [9,10,23]. Tfr cells can be distinguished from Tfh cells by expression of FoxP3, CD25, and/or GITR [9–11,24].

Signals for Tfr cell differentiation

Types of APC needed for Tfr cell generation

The cues responsible for Tfr cell differentiation are currently being elucidated. Tfr cells differentiate in response to a wide variety of stimuli including SRBCs, foreign antigens such as OVA or keyhole limpet hemocyanin (KLH) in adjuvant, self-antigens such as myelin oligodendrocyte glycoprotein (MOG), and viruses including LCMV and influenza (Box 2) [9,10,24,25]. Tfr cells in skin draining lymph nodes (dLN) require DCs for optimal differentiation after subcutaneous immunization with NP-OVA. When mice that express DTR on DCs were immunized and given diphtheria toxin to deplete DCs [25], there was a marked reduction in the percentage of Tfr cells. The DC subsets most directly responsible for stimulating Tfr cell differentiation remain unclear. A recent study suggested that Tfh cell development requires contributions by both non-migratory and migratory DCs for complete differentiation [26]. Therefore, it is plausible that Tfr cells may require multiple lineages of DCs for optimal differentiation. Tfr cells have been found in LNs, spleen, blood, lymph, and Peyer's patches (PPs). Since Tfr cells are present in a number of tissues and differentiate in response to a number of different stimuli, it is likely that many types of DCs/APCs may promote Tfr cell generation, and the most important DC subset may be depend on the tissue and stimulus.

Similar to Tfh cells, Tfr cells in the LNs and spleen require B cells for optimal differentiation and/or expansion [9,25,27]. However, one study reported that human patients treated with rituximab (anti-CD20) and tacrolimus after renal transplant have reduced naïve and GC B cell numbers, but roughly similar Tfr cell numbers compared with non-rituximab treated patients [28]. These findings may be unique to transplantation settings or due to immunosuppression. In murine systems, Tfh cells require prolonged interaction with GC B cells to fully develop an effector phenotype [29]. Further work is needed to understand if similar interactions with GC B cells influence Tfr cell generation and maintenance.

Circulating Tfr cells are memory-like cells that persist for long periods of time, similarly to circulating Tfh cells in both mice and humans [25,30–32]. Interestingly, neither circulating Tfr nor Tfh cells require B cells for differentiation [25,31]. Circulating Tfr (and Tfh) cells do need DCs for differentiation, similar to their LN counterparts [25]. Efferent lymph and circulating Tfr cells express lower levels of ICOS compared with LN Tfr cells. Since circulating Tfr cells are thought to bypass the B cell zone and exit the lymph node, it is likely that B cells are responsible for stimulating maximum expression of ICOS on Tfr cells. These studies suggest that the APC requirements for differentiation of lymph node and circulating Tfr cells are distinct. The LN Tfr cell 'effector' phenotype is probably initiated during contact with DCs in the T cell zone, strengthened in the interfollicular region during contact with B cells, and optimized in the GC after prolonged contact with cognate GC B cells (Figure 1). Circulating Tfr cells likely divert away from the B cell zone and migrate to the efferent lymph before the full effector program occurs. The transcriptional programs of circulating memory-like Tfr cells and dLN 'effector' Tfr cells probably differ to some extent, considering changes in expression of molecules such as ICOS on circulating and dLN Tfr cells.

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