T Follicular Helper (T_{FH}) Cells in Normal and Dysregulated Immune Responses

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Abstract

T cell help for antibody production is a fundamental aspect of immune responses. Only recently has a better understanding of the cellular and molecular mechanisms for T cell help emerged. A subset of T cells, termed T follicular helper cells (T_{FH} cells), provides a helper function to B cells and represents one of the most numerous and important subsets of effector T cells in lymphoid tissues. T_{FH} cells are distinguishable from Th1 and Th2 cells by several criteria, including chemokine receptor expression (CXCR5), location/migration (B cell follicles), and function (B cell help). Central to the function of $CD4^+$ T cells is IL-21, a "helper" cytokine produced by T_{FH} cells that potently stimulates the differentiation of B cells into Ab-forming cells through IL-21R. Consequently, dysregulation of T_{FH} cell function, and over- or underexpression of T_{FH} cell–associated molecules such as ICOS or IL-21, most likely contributes to the pathogenesis of certain autoimmune diseases or immunodeficiencies.

INTRODUCTION

One of the fundamental discoveries of modern immunology was the finding that antibody (Ab) responses require "help" from cells of thymic origin. In these classic experiments (1, 2), cells from different sources were transferred to irradiated recipients. Because irradiation destroyed the recipient's endogenous immune system, any effect could be attributed to the donor cells. Neither bone marrow cells nor thymocytes alone were sufficient to reconstitute an Ab response to sheep red blood cells. However, irradiated mice that received cells from both bone marrow and thymus responded well. These interacting cells later became known as B and T cells, respectively. Because the bone marrow–derived (B) cells but not the T cells were identified as the actual Ab-forming cells, the response was referred to as T-dependent, and thymus-derived cells were called T "helper" (Th) cells.

The generation of Ab-forming cells occurs during a germinal center (GC) reaction (3, 4). GCs are specialized structures that develop within B cell follicles of secondary lymphoid tissues, such as lymph nodes, spleen, tonsils, and the Peyer's patches of mucosal-associated lymphoid tissues. It is within the GC that critical processes such as somatic hypermutation, class switch recombination, and selection of high-affinity B cells occur (3, 5, 6). The GC reaction is essentially the engine that drives T cell–dependent Ab responses, and the GC is an important site where T cells provide direct help to antigen-specific naive B cells. Importantly, $CD4^+$ T cells are essential for the formation of a GC reaction (7), and they provide developmental cues for the differentiation of antigen-selected high-affinity GC B cells into memory B cells or plasma cells, which together sustain long-term humoral immunity (6–8).

Despite the fundamental role of $CD4^+$ T cells in B cell responses and humoral immunity, there was, until recently, little appreciation of the cellular and molecular mechanisms for T cell help. Th2 cells, which produce cytokines such as IL-4 and direct B cells to undergo Ig isotype switching to IgG and IgE, were long considered to be the cells that provided help to B cells. It is now apparent that a subset of nonpolarized $CD4^+$ T cells termed follicular B helper T cells (T_{FH}) (also referred to simply as T follicular helper cells) are the true helper cells for Ab responses, although other T cells such as Th2 cells, γδ T cells, and NKT cells may also contribute. The important developments that have driven this field of study have been the discovery of numerous molecules that participate in providing T cell help to B cells. The interaction between CD40 on B cells and CD40L (CD154), transiently expressed on activated $CD4^+$ T cells, stimulates B cell proliferation and, in the presence of appropriate cytokines, isotype switching as well (9). Inducible costimulator (ICOS) is another essential costimulatory molecule expressed on activated $CD4^+$ T cells that, when engaged by its ligand (ICOS-L) on antigen-presenting cells (APCs) including B cells, induces the production of helper cytokines such as IL-2, IL-4, and especially IL-10 (10). However, it was the identification of the chemokine receptor CXCR5 that has provided a particular impetus for the understanding of T cell help for B cells, as CXCR5 serves as a marker for T_{FH} cells and promotes the colocalization of T and B cells in lymphoid follicles.

Here, we discuss some of the controversial questions concerning T_{FH} cell differentiation, the relation of T_{FH} cells to other T cell subsets such as Th2 and/or Th17, and the influence of several molecules that are highly expressed by T_{FH} cells and most likely participate in T cell–dependent B cell differentiation. One molecule we discuss in detail is IL-21, which has all the hallmarks of a "helper" cytokine (a separate article in this volume covers the biology of IL-21; see Reference 11). IL-21, despite its roles in other systems, is a T_{FH} cell–secreted cytokine and is one of the most important stimulators of B cell proliferation, isotype switching, and differentiation (12). Indeed, the fields of IL-21 and $CD4^+$ T cell help are rapidly converging.

Finally, we argue that many immunological disorders, including autoimmune diseases, immunodeficiencies, and malignancies, relate to dysfunction of T_{FH} cells or their associated effector molecules. Thus, targeting of T_{FH} cell molecules should offer new opportunities for the therapeutic manipulation of immune responses.

CXCR5 AND THE IDENTIFICATION OF T_{FH} CELLS

The identification of the true $CD4^+$ helper T cell for B cells followed the discovery of CXCR5. CXCR5 is a chemokine receptor expressed by all mature B cells as well as a subset of antigen-experienced $CD4^+$ T cells in lymphoid tissues. CXCR5 is largely absent from $CD8^+$ T cells and naive $CD4^+$ T cells. CXCR5 is responsible for the positioning of B and T cells in the follicular areas of lymphoid tissues (13) through recognition of its ligand, the chemokine CXCL13, which is produced by follicular stromal cells, including follicular dendritic cells (FDCs) (14, 15). Remarkably, ~50% of $CD4^+$ T cells in activated lymphoid tissues, such as human tonsils, are $CXCR5^+$, and a subset of these localizes to the GC (16–18). Indeed, following antigen stimulation, the quantity of $CXCR5^+CD4^+$ T cells in lymphoid tissues far exceeds that of any other type of effector T cell. $CXCR5^+CD4^+$ T cells isolated from human tonsils are efficient at providing help to B cells, thereby facilitating their differentiation into plasma cells (17–21). Because of their ability to provide B cell help, their clear phenotypic distinction from Th1 and Th2 cells, and their predominant localization to B cell follicles, $CD4^+CXCR5^+$ T cells were termed T follicular helper (T_{FH}) cells (17–19).

ORIGIN OF T_{FH} CELLS AND THEIR RELATION TO Th1, Th2, Th17, AND Treg CELLS

Perhaps the most pertinent yet unresolved issue pertaining to T_{FH} cells is their relationship to other T cell subsets, such as Th1, Th2, Th17, and T regulatory (Treg) cells (see **Figure 1**). Various transcription factors determine effector T cell differentiation, and the five main effector T cell subsets express distinct transcription factors (**Figure 1**). The five effector T cell subsets depicted in **Figure 1** secrete different cytokines, express different chemokine receptors, and localize to diverse sites. These functions relate to the cells' specialized roles in immune defense. For instance, Th2 cells produce cytokines associated with defense against large extracellular parasites (**Figure 1**). T cell help for B cells was long attributed to Th2 cells because Th2 clones support Ab production in vitro better than Th1 clones (22) and because IL-4, a Th2 cytokine, stimulates B cell proliferation and class switching and induces upregulation of costimulatory molecules such as CD40 and MHC class II. However, B cell help still occurs in the absence of IL-4, inasmuch as IL-4-deficient mice can generate T-dependent Ab responses (23, 24). A revised model for T cell help shows that T_{FH} cells are the predominant helper cells for B cells, and that Th1 or Th2 cytokines serve to skew responses in particular directions. For instance, IL-4 promotes Ig isotype switching to IgE, which is important for antiparasite responses, whereas IFN-γ favors isotypes important for antiviral immunity.

Figure 1 depicts a relatively simple model for the differentiation of the various T effector subsets; however, the point at which functional T_{FH} cells emerge is uncertain. The development of a follicular homing capability by activated T cells is the first event in the process. Naive T cells are $CXCR5^-$ and use the chemokine receptor CCR7 to enter secondary lymphoid organs and migrate to T cell zones (25). CXCR5 is transiently upregulated on $CD4^+$ T cells following their activation, thereby endowing them with a follicular homing capability. This upregulation occurs prior to proliferation and differentiation and is dependent on costimulatory signals delivered through CD28, OX40, and ICOS

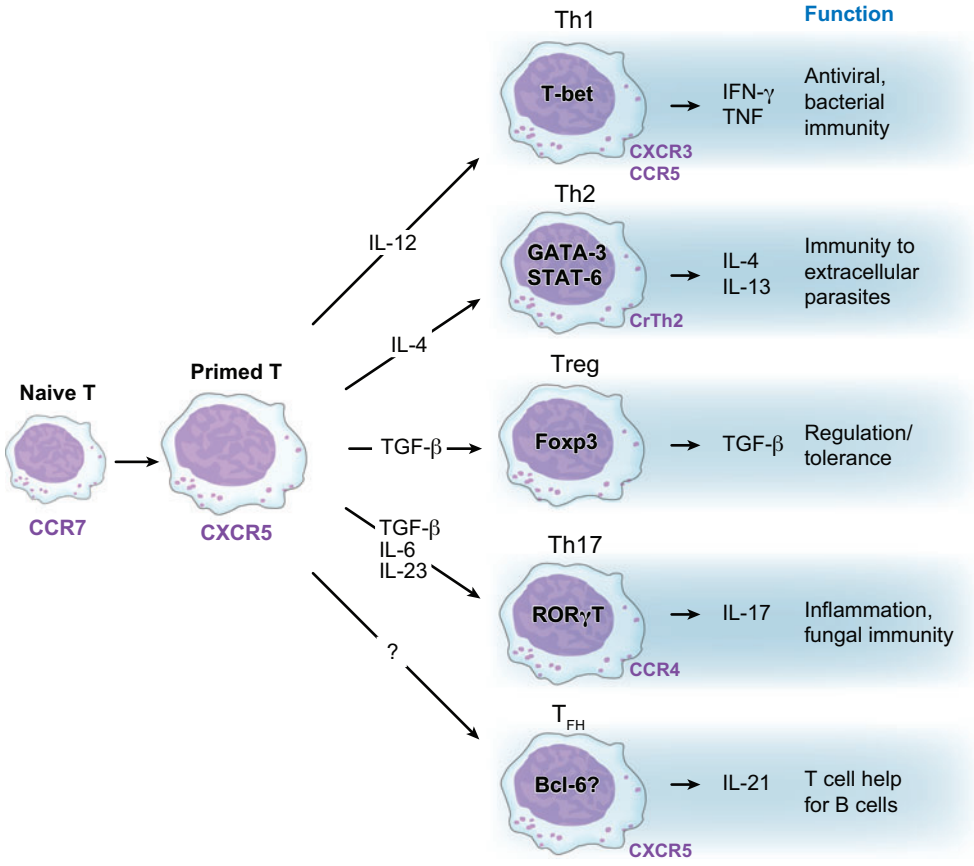

Figure 1

Effector T cell differentiation and the expression of transcription factors, effector cytokines, and chemokine receptors. Transcription factors for each subset have been placed in the nucleus (note that the role of Bcl-6 in T_{FH} cell development still requires confirmation). The list of chemokine receptors, or cytokines, for each of the subsets is not exhaustive. Adapted with additions from Reference 32.

(26–30) (see also **Figure 3** below). However, CXCR5 expression on activated T cells is only transient, and fully polarized Th1 and Th2 cells do not express this chemokine receptor (31).

Several different fates are possible for activated T cells. Many lose expression of CXCR5 and either follow the Th1/Th2 (or Th17/Treg) differentiation pathways or leave the secondary lymphoid tissues to become circulating memory T cells. A fraction of cells, however, retains CXCR5 expression. These antigen-primed cells develop into effector T cells that can home to B cell follicles and, ultimately, provide help to B cells. The capacity to provide help must relate to acquisition of the relevant molecules—such as ICOS, CD40L, and IL-21—that have functional roles in humoral immunity (discussed below). However, these molecules can also be expressed by other T cell subsets, and so the differentiation steps leading to the generation of T_{FH} effector cells are still largely unclear. A possible scenario for the generation of T_{FH} cells has all T helper subsets (i.e., Th1, Th2, Th17, and T_{FH} cells) arising independently from naive T cells, as suggested in **Figure 1**. In this

scenario, activated CXCR5$^+$ T cells serve as an intermediate cell type that gives rise to all the effector subsets depending on additional stimuli. Nevertheless, it must be stressed that a precise understanding of how Th cell fate is determined is still unclear. Activation of transcription factors, which determine cellular fate, must occur at certain points, and we propose that Bcl-6 is the transcription factor most likely to be required for the development of T_{FH} cells.

It is likely that after the initial activation by antigen-loaded APCs in the T cell zone, T cells destined to become T_{FH} cells must receive additional signal(s) provided by cells located in or close to the B cell follicles. Two distinct cell types are excellent candidates for this role: B cells and CD4$^+$CD3$^-$ accessory cells. B cells may influence the differentiation of T cells into T_{FH} cells. Abundant evidence also confirms that B cells direct T cell development, polarization, and memory (33–37). B cells may also influence further differentiation of T_{FH} cells into Th1 or Th2 effector cells, as B cells are capable of producing IL-12 and IL-4 (38, 39), which may induce T cell polarization. CD4$^+$CD3$^-$ accessory cells could also provide the secondary signals for the differentiation of activated CXCR5$^+$ T cells into T_{FH} effector cells (40). These cells are of a nondendritic lineage and interact with antigen-specific CD4$^+$ T cells that have been previously primed by dendritic cells (DCs). This interaction may depend on signals through OX40 and CD30. Furthermore, they are localized at the sites of T-B collaboration: B cell follicles and the T-B interface (40).

A particularly controversial topic is the relationship of T_{FH} cells to Th17 cells. Th17 cells rely on the transcription factor RORγt and cytokines such as TGF-β together with either IL-6 or IL-21 for their differentiation and function, which are clearly distinct from those used by Th1 or Th2 cells (**Figure 1**). Even though Th17 cells were not defined when T_{FH} cells were discovered, T_{FH} cells do show some striking similarities to Th17 cells, particularly autocrine stimulation by IL-21 and provision of B cell help (41) (discussed below). Nevertheless, T_{FH} cells are clearly distinguishable from Th17 cells in that they do not express Th17 cytokines such as IL-17 and IL-22, and Th17 cells do not express CXCR5 (120). However, many of the molecules that characterize T_{FH} cells are also involved in functions associated with other effector subsets, including Th17 cells. Our analysis of T_{FH} cell gene transcription using Affymetrix microarrays has failed to identify many of the gene transcripts associated with Th17 cells, such as RORγt, IL-17, IL-22, IL-23R, or CCR6 (C.R. Mackay, unpublished data).

MOLECULES ASSOCIATED WITH T_{FH} CELL FUNCTION

The features of CXCR5$^+$ T_{FH} cells that distinguish them from Th1, Th2, Th17, or other T cells (42) are summarized in **Figure 2**. Like other effector T cells, T_{FH} cells in lymphoid tissues express markers indicative of activation, such as CD69, CD95, and ICOS, and also express low levels of CCR7 and CD62L (similar to Th1 and Th2 cells). They also have effector function, namely provision of help for Ab production (16–18, 20, 21). Furthermore, although CXCR5$^+$ T cells have a very limited repertoire of cytokine secretion, they do express IL-21, which, despite its association with NKT cells (43) and Th17 cells (44, 45), is highly associated with T_{FH} cells (**Figure 2**) (discussed below). The primary function of T_{FH} cells—provision of help for the differentiation of B cells into effector cells during a GC reaction—is substantiated by reports that T_{FH} cells, compared with non-T_{FH} cells, express increased levels of CD40L, ICOS, and IL-10 (17, 18, 20, 46). These molecules positively regulate B cell differentiation, and humoral immune responses are compromised in mice or humans with mutations in the *CD40L* and *ICOS* genes (47–50).

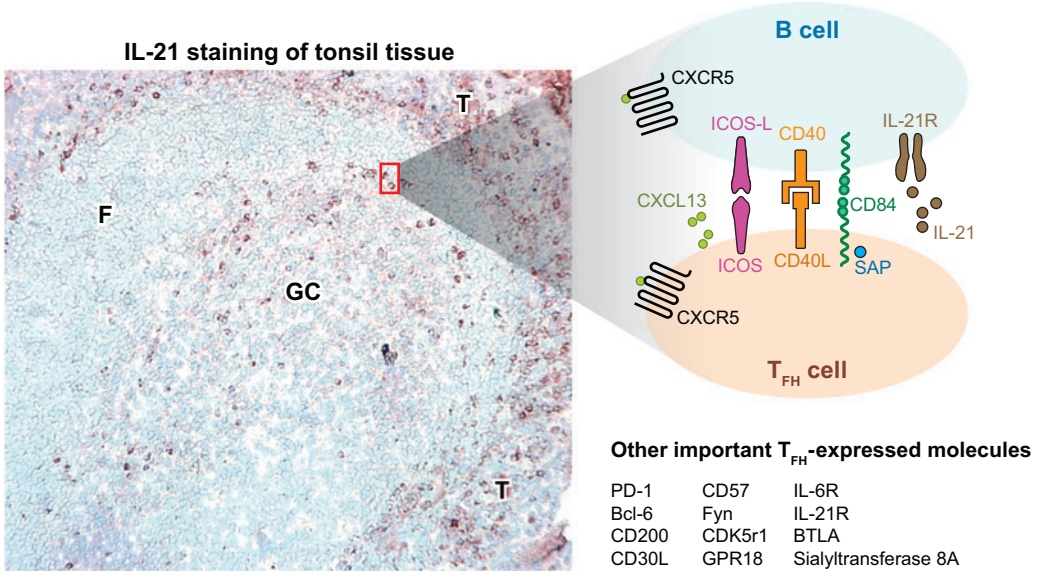

Figure 2

Important molecules for T_{FH} cell function. (*Left*) Human tonsil stained for IL-21 expression using an anti-IL-21 mAb. Regions of the tonsil are indicated, including T cell areas (T), the B cell follicle (B), and the germinal center (GC). Note the positioning of IL-21-expressing cells at the rim of the GC. IL-21 expression is not restricted to the GC, and numerous cells in the T cell zone express IL-21. Whether these represent T_{FH}-like cells or Th17 cells remains to be determined. (*Right*) Some of the best-characterized interacting molecules for T_{FH} and B cells. Listed below are numerous other molecules overexpressed in T_{FH} cells that presumably play an important role in their function.

Interestingly, circulating T_{FH} cells are deficient in humans with mutations in *CD40L* or *ICOS* genes (29).

Recent microarray analyses showed that T_{FH} cells express an extensive array of genes that distinguishes them from Th1- and Th2-type $CD4^+$ T cells (51–54). For instance, compared with conventional $CD4^+$ T cells, human T_{FH} cells express higher levels of IL-21, the intracellular adaptor protein SAP (SLAM-associating protein), SAP-associating transmembrane receptors CD84 and CD229 (Ly9), the protein tyrosine kinase FynT, as well as the GC-restricted transcription factor Bcl-6 (51, 52, 54) (see also **Figure 2**). Using the Roquin mouse, which has expanded T_{FH} cells as a result of a defect in degradation of ICOS transcripts (discussed below), Vinuesa et al. (53) showed that mouse T_{FH} cells have a molecular profile remarkably similar to that of human T_{FH} cells, as they also preferentially express transcripts for *IL-21*, *CD84*, *CXCL13*, *Bcl-6*, *PD-1*, and many others. The relevance of some of the more important T_{FH} cell-expressed molecules is discussed below.

Bcl-6

Transcription factors determine T cell fate, and the important elements that drive Th1, Th2, Th17, and Treg cell differentiation have now been identified (see **Figure 1**). For instance, T-bet determines Th1 cell lineage commitment and cytokine production, and GATA-3 and c-Maf drive Th2 cytokine production (55). Th17 differentiation is initiated by TGF-β and either IL-6 or IL-21, which activate signal transduction and activator of transcription (STAT) 3 and induce expression of the transcription factor RORγt, ultimately resulting in lineage specification (56, 57). Currently there is no definitive

evidence for a particular transcription factor directing the commitment of naive $CD4^+$ T cells to the T_{FH} cell lineage, although circumstantial evidence favors Bcl-6. The expression of Bcl-6 is tightly regulated and is largely confined to GC B cells (58–60). Also, Bcl-6 is preferentially expressed by T_{FH} cells but not by Th1 or Th2 cells (51). In B cells, Bcl-6 is a master regulator of GC lineage commitment and is a suppressor of plasma cell differentiation (61). Bcl-6-deficient mice display defective T-dependent Ab responses and have limited Ab affinity maturation owing to the absence of GCs (62, 63). Bcl-6 expression also represses GATA-3 and downregulates secretion of IL-4 by T cells, thus providing further support of a dynamic role for Bcl-6 in T cell differentiation and fate (64). However, expression of Bcl-6 by T cells in follicles is by no means uniform: Only 10%–15% of $CD4^+$ T cells in GCs appear to express Bcl-6 protein (65). It is conceivable that Bcl-6 determines T_{FH} commitment at stages before or after Th1, Th2, or Th17 differentiation.

ICOS

ICOS is a CD28-like costimulatory molecule with an important role in T-dependent Ab responses. Expression of ICOS is regulated during T cell activation and differentiation, such that ICOS upregulation occurs following the receipt of signals during T cell activation (**Figure 3**). T cells stimulated through the T cell receptor (TCR), CD28, and ICOS proliferate and produce cytokines, such as IL-4 and IL-10, that facilitate T:B interactions and antibody production (10, 37, 66). ICOS is expressed at very high levels on T_{FH} cells within the light zone of GCs (10, 17, 67), and a direct correlation exists between the expression of ICOS by $CD4^+$ T cells and the amount of IL-10 produced (37, 68). This correlation suggests an important role for this pair of effector molecules in regulating B cell responses. Indeed, ICOS deficiency is associated with impaired IL-10 production in human and murine $CD4^+$ T cells (48, 69, 70).

ICOS is also expressed by other T cells, notably Th2 cells, whereas its ligand, ICOS-L, is expressed on APCs, including B cells (71, 72). In contrast to CD28, ICOS is not constitutively expressed, but is instead induced after T cell activation (10) (**Figure 3**). ICOS signaling enhances T cell proliferation, the secretion of cytokines, especially IL-10, as well as the upregulation of cell-cell interaction molecules. The genes upregulated following engagement of ICOS are similar to those upregulated by CD28 in both human- and murine-stimulated $CD4^+$ T cells, although the magnitude of gene upregulation induced by ICOS is less than that induced by CD28 (73, 74). Probably the most important difference between signals delivered through CD28 and ICOS is that their ligands are expressed at high levels on different cell types (DCs and B cells, respectively). This difference relates to the specific roles of these two molecules, first for the regulation of T cell priming, and subsequently for T-B interactions (see **Figure 3**).

Homozygous loss of ICOS is associated with late-onset common variable immunodeficiency (CVID) in humans (49). Patients with CVID due to ICOS deficiency lack GC in their lymph nodes, consequently show a dramatic reduction in the number of IgM-expressing memory B cells, and are essentially devoid of isotype-switched memory cells. Interestingly, these patients also have a deficiency in the number of $CXCR5^+CD4^+$ T cells in their peripheral blood. This finding may explain the reduced production of IL-10 and IL-17 by their $CD4^+$ T cells (29, 49). Consistent with these results, mice deficient in ICOS or ICOS-L also have impaired GC formation and isotype switching, diminished T_{FH} cell numbers in their spleens, and reduced production of B cell helper cytokines, such as IL-4 and IL-10 (29, 30, 48, 78–81). These findings suggest that ICOS signaling is important for the maintenance and/or generation of T_{FH} cells (29, 30) and reinforce the association between ICOS expression and IL-10 production. In support of this

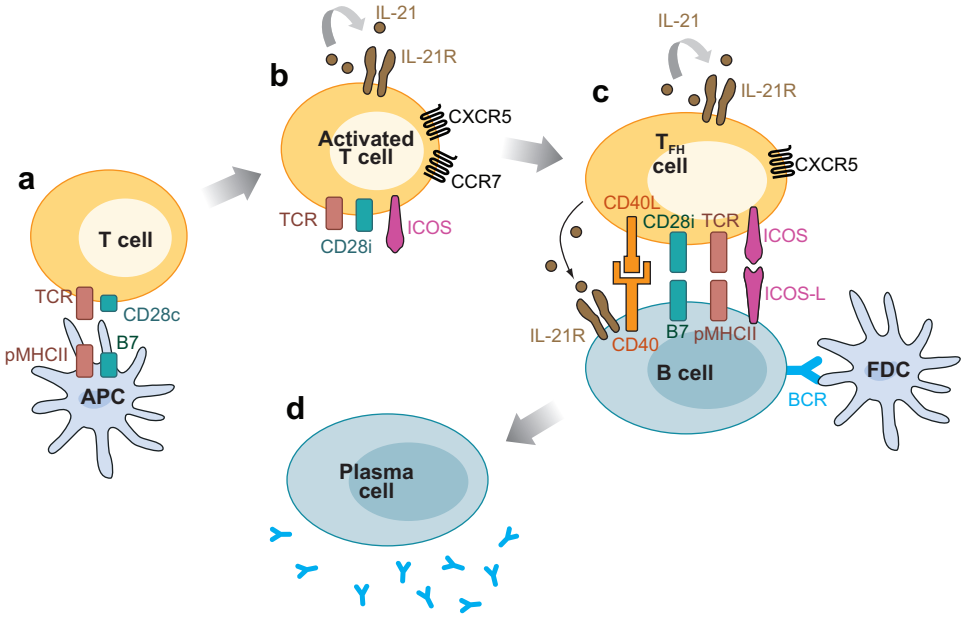

Figure 3

Multiple signals and steps for the generation of T_{FH} cells and T-dependent antibody responses. CD28 and ICOS, together with IL-21, costimulate T cells activated through the T cell receptor (TCR). The ordered expression of the various costimulatory molecules, cytokines, and receptors facilitates the various steps in the process of T_{FH} cell differentiation and function. (*a*) In the T cell zone of lymphoid tissues, mature DCs expressing B7.1 and B7.2 present peptide-MHC class II (pMHCII) ligand to the TCR of naive $CD4^+$ T cells, which constitutively express CD28 (CD28c). CD28 provides the early costimulatory signal that, with TCR stimulation, induces expression of other costimulatory receptors belonging to the Ig and TNFR/TNF superfamilies (75). Ligation of CD28 amplifies the TCR signal rather than delivering a qualitatively different signal (75, 76). (*b*) Activated $CD4^+$ T cells produce IL-21 and induce expression of CD28 (CD28i) and ICOS. (*c*) Sustained signaling of activated $CD4^+$ T cells through the TCR, CD28, and IL-21R in the T zone and at the T-B cell interface leads to modulation of the expression of molecules important for migration, such as CXCR5, CCR7, and costimulatory receptors including ICOS, CD40L, and OX40 (28, 75, 77). (*d*) Migration of functional T_{FH} cells to follicles and delivery of T cell help support the selection of activated Ig-secreting B cells in germinal centers.

association, one study showed that the B helper activity of tonsillar T_{FH} cells corresponded with a high level of expression of ICOS, such that only the $CXCR5^{hi}ICOS^{hi}$ $CD4^+$ T cells were potent inducers of IgG production by cocultured B cells (82). Thus, the reduced GC response associated with ICOS deficiency might simply result from reduced numbers of T_{FH} cells.

The high expression of both ICOS and IL-21 are defining features of T_{FH} cells, and ICOS expression defines the subsets of Th cells that are prolific producers of IL-21. However, where these two axes meet at the level of T_{FH} cell generation remains unclear. On the one hand, IL-21 may drive ICOS expression. We think this is unlikely because IL-21-deficient mice have a defect in T_{FH} cell generation but express an abundance of ICOS on all $CXCR5^-$ $CD4^+$ T cells (A. Vogelzang & C. King, submitted manuscript). On the other hand, the assumption that ICOS expression is necessary for IL-21 production is also unlikely because blockade of ICOS:ICOS-L interactions significantly reduces but does not eliminate IL-21 production, and T cells from ICOS-deficient mice can produce limited amounts of IL-21 (H. McGuire

& C. King, submitted manuscript). Our view is that both IL-21 and ICOS are necessary for T_{FH} cell generation and that T helper cells utilize ICOS:ICOS-L interactions that quantitatively contribute to IL-21 production.

CD57

Immunohistochemical studies performed over the past two decades identified a small population of $CD4^+$ T cells that were distinguishable by their coexpression of the NK cell marker CD57. These cells comprise ~10% of all tonsil $CD4^+$ T cells and localize to GCs (20, 21, 83, 84). Interestingly, all tonsillar $CD4^+CD57^+$ T cells also express CXCR5 and thus represent ~20% of the $CXCR5^+$ subset (20, 21). Furthermore, $CD4^+$ $CXCR5^+CD57^+$ T cells in human tonsils express the activation molecules CD69, ICOS, HLA-DR, PD-1, OX40, and CD45RO and downregulate CCR7 and CD62L (20, 85; S. G. Tangye, unpublished observations), suggestive of an activated phenotype and/or effector function. Accordingly, CD57 has been described as a defining marker for T helper cells for B cells (20, 83). Despite these observations, the function of the CD57 molecule remains uncertain, and inconsistent findings have prompted researchers to question whether CD57 is actually a valid marker for T_{FH} cells. For instance, $CD57^+CD4^+$ T cells are incapable of producing B cell helper cytokines such as IL-4 and IL-10, and they are inefficient at inducing differentiation of cocultured autologous B cells into Ig-secreting cells in vitro (85–91). These findings are consistent with the proposal that $CD57^+$ GC T cells are anergic (88) and exhibit regulatory activity by suppressing the function of $CD4^+CD57^-$ T cells (92).

In contrast, other recent studies have reported that $CXCR5^+CD57^+$ $CD4^+$ T cells isolated from human tonsils exhibit increased cytokine production and induce greater B cell differentiation than do $CXCR5^+CD57^-$ $CD4^+$ T cells (20, 46, 83, 93, 94). The use of $CD57^+$ $CD4^+$ T cells from blood in some studies and from tonsils in others may have produced some of these differences. The fact that $CXCR5^+$ and $CXCR5^-$ $CD4^+$ T cells in blood and lymphoid tissues differ substantially with respect to their function and phenotype may have also contributed to the varying results. Our own studies have revealed that both tonsillar $CXCR5^+CD57^-$ and $CXCR5^+CD57^+$ $CD4^+$ T cells can induce differentiation of autologous B cells in vitro, whereas $CXCR5^-CD57^-$ $CD4^+$ T cells cannot. However, more Ig secretion was detected in cultures containing $CXCR5^+CD57^-$ T cells than in those with $CXCR5^+CD57^+$ T cells (21). The most likely cause of these differences is the fact that $CXCR5^+CD57^+$ $CD4^+$ T cells undergo apoptosis more rapidly than $CXCR5^+CD57^-$ $CD4^+$ T cells (46, 54, 95). Furthermore, expression of CD95 and PD-1 is higher on $CXCR5^+CD57^+$ T cells than on $CXCR5^+CD57^-$ $CD4^+$ T cells (S.G. Tangye, unpublished data), suggesting that in addition to the heightened intrinsic susceptibility of $CXCR5^+CD57^+$ T cells to death, these cells may undergo greater apoptosis following engagement of death receptors by ligands expressed on B and T cells. High expression of ICOS, rather than CD57, probably better defines T_{FH} cells capable of inducing Ig secretion from B cells (46, 51). Because ICOS is expressed at the highest level on $CXCR5^+CD57^+$ T cells (S.G. Tangye, unpublished data), $CXCR5^+CD57^+$ and $CXCR5^+ICOS^{hi}$ $CD4^+$ T cells probably share many phenotypic and functional characteristics.

IL-21: A T_{FH} CELL–EXPRESSED HELPER CYTOKINE

IL-21 was recently identified as a cytokine that costimulates lymphocyte proliferation and drives the differentiation of NK cells in vitro (96). IL-21 is a member of the common γ chain (γc)-signaling family of cytokines (96; see also Reference 11, in this volume). The

receptor for IL-21 (IL-21R) can be expressed by many cell types (97), but it is found predominantly on B cells as well as on some NK cells and T cells (51, 96, 98, 99). The IL-21R consists of a unique cytokine-binding protein (IL-21Rα) and the γc (98, 100), which is also a component of receptor complexes for IL-2, IL-4, IL-7, IL-9, and IL-15 (101).

In vivo and in vitro studies have demonstrated a central role for IL-21 in lymphocyte activation, survival, and differentiation. Initial studies of the in vitro effects of IL-21 focused on its ability to enhance effector functions, such as IFN-γ production and cytotoxic function of $CD8^+$ T cells and NK cells (102). More recently, IL-21 was shown to play a role in NKT cell and $CD4^+$ T cell effector function (43). Notably, IL-21 greatly enhanced proliferation of human $CD4^+CD25^-$ T cells, rendering them resistant to Treg-mediated suppression (103). The ability of IL-21 to enhance the proliferation of T cells is in marked contrast to other γc-signaling cytokines such as IL-2 and IL-15 because IL-21 does not induce proliferation in the absence of stimulation through the TCR (96). Thus, IL-21 is a genuine T cell costimulator, and its potential for amplifying signals through the TCR is supported by evidence demonstrating that IL-21:IL-21R interactions generate signals through the Jak-STAT, MAPK, and PI3K pathways (104).

The study of the role of IL-21 in Th cell differentiation is a rapidly evolving field, and the findings from a number of studies resonate with the important role of IL-21 in humoral responses. Recent studies have revealed that IL-21 is important for the generation and migration of Th2 cells (105–107), and T_{FH} cells, in turn, express significantly greater amounts of IL-21 than do Th1 or Th2 subsets (51). Our own work with IL-21- and IL-21R-deficient mice indicates that IL-21 is an autocrine growth factor for T_{FH} cells (**Figure 3**) (A. Vogelzang & C. King, submitted manuscript). IL-21 is a crucial component of T_{FH} cell generation through its ability to modulate expression of the chemokine receptors CXCR5 and CCR7 on activated T cells (A. Vogelzang & C. King, submitted manuscript). A defect in T_{FH} cell generation in IL-21-deficient mice suggests a role for IL-21 that precedes the upregulation of CXCR5 and movement of T_{FH} cells into the B cell follicle. Collectively, these studies indicate that IL-21 has a fundamental role in T helper cell differentiation.

One major target of IL-21 is B cells. Studies of ex vivo isolated human and murine B cells have demonstrated that IL-21 greatly enhances proliferation induced by ligation of CD40 (96, 108–110). In contrast, IL-21 inhibits proliferation of murine B cells induced by TLR ligands, namely LPS and CpG, by inducing apoptosis (108, 111, 112). Interestingly, some of the pro- and antiproliferative effects of IL-21 on murine B cells appear to be strain specific (108). IL-21 also modulates isotype switching and Ig production by human and murine B cells, as it can act as a switch factor for secretion of IgG1 and IgG3 by human B cells stimulated with anti-CD40 mAb (113), and induces differentiation of murine and human naive, GC and memory B cells into Ig-secreting cells (21, 110, 114).

Although IL-10 had been considered the most potent inducer of plasma cell differentiation on human B cells, IL-21 exceeds its effects on CD40-stimulated human B cells by up to 100-fold (21). Human B cells stimulated with CD40 mAb and IL-21 are induced to express the enzyme activation-induced cytidine deaminase (AID) and the transcription factor B-lymphocyte maturation protein-1 (Blimp-1) (110), which play critical roles in Ig isotype switching and commitment to the plasma cell lineage, respectively. Importantly, the ability of human tonsillar T_{FH} cells to provide B cell help for their differentiation into plasma cells is IL-21 dependent, as this effect was greatly reduced by neutralizing endogenous IL-21 present in these cultures (21). The action of IL-21 on the differentiation of human naive B cells into Ig-secreting cells could be reduced by

IL-4 (21, 110)—through the ability of IL-4 to antagonize the IL-21-induced expression of Blimp-1 (21)—whereas the combination of IL-4 and IL-21 resulted in increased production of IgE in cultures of enriched human B cells (113, 115). In contrast to its effects on human B cells, IL-21 inhibited IgE production by murine B cells stimulated with LPS and IL-4 (116). Together, these findings demonstrate a dynamic interplay among several different γc-binding cytokines.

Several of the findings from in vitro cultures have been confirmed in vivo. For instance, mice transgenic for expression of human IL-21 have increased numbers of splenic B cells, including Ig isotype–switched cells and plasma cells (114). However, a deficiency of either IL-21 or its receptor results in an impaired ability to produce antigen-specific IgG following immunization with a T cell–dependent antigen. Furthermore, the levels of total as well as antigen-specific IgE are elevated in the serum of these mice (117, 118). This finding confirms the negative regulatory effects of IL-21 on IgE production by murine B cells (116, 117). Notably, T-dependent immune responses are completely abrogated in mice deficient in IL-4 and IL-21R (117), suggesting that signaling through both IL-4R and IL-21R is necessary for optimal humoral immune responses.

Recently, IL-21 was described as an essential autocrine factor for the generation and differentiation of Th17 cells (44, 45, 119), challenging a previous study that demonstrated unimpeded Th17-driven experimental autoimmune myocarditis in the absence of IL-21R signaling (105). These dramatic new findings bring into question the precise role of IL-21 and the relationship between T_{FH} cells and Th17 cells. If Th17 cells produce copious amounts of IL-21, as indicated, it would imply that these T cells may also deliver a helper signal to B cells. However, one factor that may limit the interaction of Th17 cells with B cells is their expression of chemokine receptors: Th17 cells express CCR4 and CCR6 but lack CXCR5 (41, 120), which would recruit Th17 cells to sites of inflammation but would exclude them from entry into B cell follicles.

MIGRATION AND LOCALIZATION OF T_{FH} EFFECTOR AND MEMORY CELLS

Chemoattraction to the CXCR5 ligand CXCL13 allows T_{FH} cells to localize to B cell follicles, where they can directly provide help to B cells. CXCR5 is also expressed by most B cells and is required for the development of B cell follicles in secondary lymphoid tissues. Mice lacking either CXCR5 or CXCL13 show major aberrations in follicular architecture and reduced numbers of lymph nodes and Peyer's patches (13, 121). Expression of CXCR5 is transiently upregulated when T cells interact with peptide-MHC class II and with costimulatory molecules on APCs (122, 123), and levels of CXCR5 expression following priming may reflect qualitative or quantitative aspects of this stimulation. For instance, antigen-specific TCR-transgenic $CD4^+$ T cells exhibit a higher and more homogenous expression of CXCR5 following immunization than do their polyclonal counterparts (123). One factor that distinguishes T_{FH} from recently activated $CD4^+$ T cells is their continued expression of CXCR5. Further interaction with peptide-MHC class II ligand and costimulatory molecules on B cells at the B cell/T cell interface and within the GC is likely to preserve CXCR5 expression on T_{FH} cells.

Interaction between effector T cells and B cells occurs first in T cell areas and later in B cell follicles within secondary lymphoid organs (3, 4, 124). After the first engagement, B cells either migrate to extrafollicular foci, where they differentiate into plasma cells that rapidly secrete low-affinity antibodies, or they migrate (along with T cells) into follicles and form GCs, where somatic mutation and affinity maturation occur. As emphasized previously, the GC reaction is strongly dependent on help from antigen-specific T cells,

which must migrate into the follicle to support this response (123–126).

The chemoattractant receptor characteristically expressed by T_{FH} cells is CXCR5, which facilitates T_{FH} cell migration to follicles. However, the conditions under which T_{FH} cells localize to follicles may vary. Naive T cells that recirculate through lymphoid tissues gain entry primarily through their expression of L-selectin and the chemokine receptor CCR7. T cells colocalize with DCs in the T cell zone, allowing unprimed T cells to first receive signals from professional APCs rather than from B cells. A remarkable sequence of cellular movements follows successful T cell priming (15): Activated T cells (which have upregulated CXCR5) migrate to the B cell follicles and position themselves at the edge of the follicle, where they meet antigen-primed B cells that have specifically migrated outward. Physical interactions then facilitate CD40-CD40L-dependent B cell activation. Thereafter, antigen-primed T cells are distributed throughout the entire follicle, including the GC, to provide helper signals to B cells. Whether T_{FH} cells can enter follicles directly from the blood is an interesting but unresolved question.

Although T_{FH} cells have all the hallmarks of an activated, effector subset of T cells, unresolved issues remain: The exact proportion of $CXCR5^+CD4^+$ T cells in lymphoid tissues that can provide help to B cells and the precise location of these T cells are unknown. Certainly, $CXCR5^+CD4^+$ T cells in GC can be considered true T_{FH} cells; however, T cells closely related in phenotype and function most likely exist outside of follicles (for instance, note the large numbers of IL-21^+ cells in the T cell zone shown in **Figure 2**). Moreover, at least six different follicular T cell subsets have been identified on the basis of surface markers and/or anatomical location (reviewed in Reference 42). In human tonsils, follicular T cells are located in the mantle zone, the outer zone, and the light zone of the GC. Although they are all defined by CXCR5 expression, they differentially express other markers such as CD57 and ICOS (discussed below). A subset of $CXCR5^+CD4^+$ T cells also exists in blood (~10%) (16), but these cells are in a resting state and are incapable of providing help to B cells. They coexpress CD62L and CCR7 and probably represent a subset of T_{FH} cell–derived memory T cells.

The fate of T_{FH} cells following the GC response has significant implications for immunological memory, vaccine development, and autoimmunity. Until recently, T_{FH} cells were considered fully differentiated cells, prone to apoptosis due to high expression of CD95 (54). However, a recent study demonstrated that a local memory $CXCR5^+$ $CD69^+$ T_{FH} cell compartment is retained in B cell follicles after resolution of the GC response (127). A population of high-affinity $CXCR5^+$ T cells remained for an extended period of time in the proximity of CXCL13-expressing FDCs and were reactivated upon secondary immunization (127). Thus, immunological memory associated with T_{FH} cells probably differs markedly from memory associated with other types of T cells. Furthermore, because the site for T_{FH} cell function is lymphoid tissue, it would not be surprising if immunological memory in this T cell population were more sessile than that in, for instance, a $CD8^+$ T cell or Th1 population. Although the possibility that CXCR5 expression on T_{FH} memory cells becomes fixed during differentiation remains, it is more likely that the microenvironment supplies some factor(s) that maintains their $CXCR5^{hi}$ phenotype. T_{FH} memory cells were found in the vicinity of peptide-MHC class II depots in draining lymph nodes after immunization (127), suggesting that local triggering of TCR maintains expression of CXCR5 and CD69 on T_{FH} cells. The maintenance of CXCR5 expression on T_{FH} cells would be consistent with a continued interaction between a small number of remaining antigen-specific T cells and B cells, or other APCs, near the FDC network after resolution of the GC. However, the level of ongoing stimulation was not

adequate to maintain expression of T_{FH} effector cell molecules such as ICOS and IL-21, which require antigen challenge for their reexpression. Thus, T_{FH} effector cells differ markedly in their localization and recirculation patterns compared with other effector T cell subsets (128). Whereas most effector T cells, such as IFN-γ-producing Th1 cells or cytotoxic $CD8^+$ T cells, localize to peripheral tissues or inflammatory lesions, T_{FH} effector or memory cells localize to lymphoid tissues, particularly B cell follicles.

$CXCR5^+$ γδ T CELLS

Although T cell help for B cells has historically been viewed in the context of conventional $CD4^+$ αβ TCR^+ cells, the fact that αβ T cell–deficient mice can mount Ab responses to T-dependent Ag suggests that other lymphocytes may provide help for B cells (129). Subsequent studies demonstrated that γδ T cells underlie the ability of αβ T cell–deficient mice to produce GCs and relatively normal levels of serum Ig (129). Researchers (130) also recently found that ~15% and 50% of γδ T cells present in peripheral blood and tonsils, respectively, express CXCR5. These frequencies are similar to those of $CXCR5^+$ $CD4^+$ T cells in these sites. Furthermore, $CXCR5^+$ γδ T cells in tonsils display a phenotype, helper cytokine profile, and effector function that resemble those of tonsillar $CXCR5^+CD4^+$ T cells: $CXCR5^+$ γδ T cells express CD45RO, CD27, HLA-DR, CD40L, and ICOS, but not CCR7 and CD62L (130); they produce vast amounts of IL-4 and IL-10, but low levels of IFN-γ and TNF-α; and they have the ability to induce differentiation of cocultured B cells (130). The in vitro findings are consistent with the detection of γδ T cells within the FDC network of established GC in human lymphoid tissues (131). Determining whether IL-21 plays any role in the helper function of $CXCR5^+$ γδ T cells may provide some interesting insights.

Of note, γδ T cells express IL-21R and CXCL13 (a signature molecule of T_{FH} cells) when stimulated with IL-21 (132). Autocrine production of IL-21 by T_{FH} cells may also regulate their production of CXCL13, and together these molecules guide both γδ and αβ $CXCR5^+$ T cells to follicular areas of lymphoid tissues, where they would be positioned to provide B cell help. Because αβ and γδ T cells recognize different repertoires of Ag, the compartmentalization of a subset of each of these populations capable of inducing Ig secretion would provide a mechanism whereby humoral immune responses could be elicited against a diverse array of Ag irrespective of the type of responding T cell.

T_{FH} CELL DYSREGULATION AND DEVELOPMENT OF AUTOIMMUNITY

New B cell receptor specificities, including those with autoreactivity, arise continuously during the GC reaction. Ab-forming cells that emerge from the GC reaction need to be tightly controlled, owing to their longevity and production of high-affinity antibodies. Consequently, most B cell responses depend on T cell help. The absence of T cell help during B cell priming leads to apoptosis, rather than differentiation of B cells into GC cells or plasma cells. Thus, self-reactive follicular B cells are usually precluded from differentiation within GCs and are normally absent from the memory and plasma cell compartments (133). B cells must compete for T cell help, and the presence of self-reactive T cells leads to the emergence of high-affinity self-reactive B cells. Accordingly, any dysregulation of T cell function or tolerance induction can have a significant effect on the selection of Ab specificities.

There is substantial evidence for a T cell basis for autoantibody responses in certain autoimmune diseases. GC formation has been described in many autoimmune strains of mice, and these arise during onset of autoantibody production (134). In patients with autoimmune diseases, for example systemic lupus erythematosus (SLE),

self-reactive B cells survive within GCs and differentiate to plasma cells and memory cells (133). The involvement of T_{FH} cells in autoantibody production is evident in various strains of mice that either over- or underexpress important T_{FH} cell–associated molecules such as CD40L, ICOS, SAP, and IL-21. Blocking CD40-CD40L interactions prevents GC formation, autoantibody production, and the aberrant accumulation of GC-like B cells and plasmablasts in the peripheral blood of patients with SLE (135) as well as in murine models of lupus (134). Moreover, two different murine models of human lupus are characterized by a T_{FH} cell–like transcriptome in their spleens (53, 136). IL-21 is also overexpressed in BXSB mice, which develop murine lupus (114). Interestingly, human SLE patients and lupus-prone mice have an increased frequency of $ICOS^+CD4^+$ T cells in their peripheral blood (137) and spleens (138), respectively, suggesting an expansion of T_{FH} cells in these pathogenic conditions. Likewise, $Roquin^{-/-}$ mice exhibit a clear increase in numbers of T_{FH} cells as a result of excessive signaling through ICOS. It is unclear whether dysregulated signaling though ICOS results in the characteristic increase in *il-21* message noted for lupus-prone mice. However, because blocking ICOS/ICOS-L interactions (138) or neutralizing IL-21 (139, 140) ameliorates disease in animal models of human lupus and rheumatoid arthritis, increased expression of ICOS may augment production of IL-21, which subsequently promotes B cell activation and secretion of pathogenic autoantibodies. In summary, immunological tolerance among T cells appears to be particularly relevant for the control of autoimmune antibody specificities, and it is likely that T_{FH} cells provide inappropriate helper signals to self-reactive B cells in cases of antibody-mediated autoimmune diseases.

Beyond their restricted role in T cell help for B cells, T_{FH} cells may also promote chronic inflammation. Prototypic T_{FH} cells express CXCR5 and localize to B cell follicles in lymphoid tissues. These two factors distinguish them from Th17 cells, which localize to nonlymphoid tissues. However, in dysregulated immune responses, T_{FH} cells have been identified in nonlymphoid tissues, particularly in autoimmune diseases; this may result from CXCL13 production at these sites. T_{FH} and Th17 cells both express high levels of ICOS, and the costimulation provided by IL-21 promotes their generation (see **Figure 3**). In this context, dysregulated T_{FH} cells producing large amounts of IL-21 at nonlymphoid sites could elicit widespread effects that contribute to chronic T cell–mediated autoimmune inflammation, including the bystander generation of Th17 cells.

Human autoimmune diseases mostly affect nonlymphoid tissues, which often contain large numbers of infiltrating, activated lymphocytes (141), as well as lymphoid-like tissues with an ectopic GC (134, 142–145). These ectopic GCs may be a site for generating high-affinity antibodies through somatic hypermutation. Understanding the mechanisms that enable the development of these outposts of lymphoid tissue in peripheral tissues, and the mechanisms that favor their maintenance rather than resolution, remains relevant for also understanding the pathogenesis of certain autoimmune diseases. Chemokines produced in ectopic GCs as well as in other lymphoid tissues are likely to be instrumental for the development and maintenance of these structures. TNF-α and lymphotoxin play a well-established role in lymphoid neogenesis, mediated in part through regulated production of the homeostatic chemokines CXCL13, CCL19, and CCL21 (146). Analysis of CXCL13, CCL19, and CCL21 expression in synovium of patients with rheumatoid arthritis suggests that the formation of a GC is dependent on the concentrations of both CXCL13 and lymphotoxin (147). CXCL13 is usually produced by FDCs in secondary lymphoid tissues. However, in rheumatoid arthritis, CXCL13-producing cells were identified as vascular

endothelium and synoviocytes (147, 148). A possible scenario within inflamed tissue is that TNF-α, secreted by infiltrating inflammatory cells, induces production of CXCL13 by vascular endothelium and synoviocytes, and the CXCL13 then recruits circulating B cells and T_{FH} cells and induces expression of lymphotoxin and development of ectopic GC.

MECHANISM FOR REGULATION OF T_{FH} CELLS

Normally, various mechanisms operate to prevent delivery of inappropriate help to self-reactive B cells. For instance, follicular $CD4^+CD25^+CD69^-$ Tregs that express CXCR5 localize to the follicles and suppress the helper effects of follicular $CXCR5^+CD57^+$ cells for Ab production by GC B cells (149). Another mechanism hinges on the suppressive effects of Roquin, a ubiquitin ligase that prevents differentiation and activation of self-reactive T_{FH} cells (53) Large numbers of T cells in *sanroque* mice (which bear a single base pair substitution in *roquin)* develop a T_{FH} phenotype and accumulate in the follicles. These T cells resemble human T_{FH} cells in that they express high levels of ICOS, CXCR5, CD200 and PD1 and transcripts for IL-21 (53). *sanroque* mice form spontaneous GCs and develop an autoimmune-like syndrome associated with high levels of autoantibodies. Roquin negatively regulates ICOS expression in T cells by promoting the degradation of Icos mRNA. A conserved segment in the Icos 3′ untranslated mRNA is important for regulation by Roquin. This segment comprises a 47–base pair region complementary to T cell–expressed microRNAs. The repressive activity of this segment is disrupted by base pair inversions in *sanroque* mice, which are predicted to abrogate miR-101 binding (150). These findings highlight the central role of ICOS mRNA regulation (and, indirectly, T_{FH} cells) in the pathogenesis of T-dependent Ab-mediated autoimmune diseases.

T_{FH} CELLS AND IMMUNODEFICIENCIES

Ineffective T cell help to B cells appears to underlie certain humoral immunodeficiencies. Examples of such immunodeficiencies include X-linked lymphoproliferative disease (XLP), ICOS deficiency, and CVID, conditions in which affected individuals experience progressive hypogammaglobulinemia as well as an impaired ability to form GCs and generate long-lived memory B cells and serological immunity (49, 69, 70, 151, 152). Such defects are also observed in mice that have been rendered deficient in genes associated with T_{FH} cells, such as CXCR5, CD40/CD40L, ICOS/ICOS-L, and SAP (79, 153–155). Interestingly, $CXCR5^+CD4^+$ T cells are deficient in mice and humans lacking functional CD40-L (29), ICOS (29, 30), or CD28 (28). Furthermore, $CD4^+$ T cells from patients with XLP and from $sap^{-/-}$ mice are unable to upregulate ICOS expression in vivo and in vitro and are defective in production of B helper cytokines, such as IL-4 and IL-10 (70, 152, 156). These findings have shed light on some of the molecular requirements for the generation and effector function of T_{FH} cells. Because T_{FH} cells express an array of molecules involved in the provision of B cell help—ICOS, CD40L, OX40, IL-21, SAP—it is likely that compromised development or function of T_{FH} cells contributes to impaired B cell differentiation and humoral immunity in conditions of immunodeficiency.

T_{FH} CELLS AND LYMPHOMAS

Human T_{FH} cells have a distinct phenotype and genotype (**Figure 2**) (discussed above). Accordingly, several recent studies that have compared the transcriptome or phenotype of malignant T cells have recognized that the malignant cell phenotype in angioimmunoblastic T cell lymphoma (AITL) shares many similarities with that of T_{FH} cells. Specifically, malignant AITL cells are $CD4^+$ T cells that express Bcl-6 (65, 157, 158),

CXCR5, CD40L, OX40, and PD1 (159–161) and produce CXCL13 (162). However, the malignant cells in AITL are unique in their expression of CD10 (163). This marker may therefore serve as a means of discriminating between normal and malignant T_{FH} cells.

Hallmarks of AITL are B cell activation, hyperplastic B cell follicles within lymph nodes, hypergammaglobulinemia, and proliferation of FDCs (163). Furthermore, within reactive lymph nodes of patients with AITL, the malignant T cells are in close association with activated B cell follicles and FDCs (163). For these reasons, researchers (159, 162) recently proposed that the dysregulated production of CXCL13 and constitutive expression of CD40L by malignant T_{FH} cells may result in the increased recruitment of B cells into follicles, their aberrant activation, and subsequent hypergammaglobulinemia. It is certainly possible that CXCL13 produced by malignant $CD4^+$ T_{FH} cells is responsible for recruiting large numbers of B cells into reactive follicles in lymph nodes of patients with AITL. However, given the potent effects of IL-21 on the activation and differentiation of human B cells into Ig-secreting cells (109, 110, 113), the sustained production of IL-21, rather than CXCL13, by T_{FH} cells may more likely underlie the exaggerated B cell activation and hypergammaglobulinemia characteristic of this disease.

SUMMARY POINTS

1. T_{FH} cells are one of the most numerous and important subsets of effector T cells. T_{FH} cells are distinguishable from Th1 and Th2 cells in several respects: chemokine receptor expression (CXCR5), location and migration (follicles), function (B cell help), cytokine production (IL-21), and expression of transcription factors (Bcl-6).
2. IL-21 serves as a "helper" cytokine produced by T_{FH} cells that stimulates B cells through IL-21R. IL-21 may also serve as an autocrine factor for T_{FH} cells.
3. Many of the important molecules for T_{FH} cell function, such as ICOS and IL-21, contribute to the pathogenesis of autoimmune diseases or immunodeficiencies.
4. The identification of T_{FH} cells and the molecules they express provides opportunities for new therapeutic approaches to autoimmune diseases. Indeed, a number of companies are targeting T_{FH}-associated molecules such as IL-21 and ICOS.

FUTURE ISSUES

1. Is Bcl-6 a transcription factor for T_{FH} cells and does it determine their differentiation?
2. T_{FH} cells are only now becoming accepted as a bona fide subset distinct from Th2 or Th1 cells; however, their relation to Th17 requires further clarification.
3. The study of the precise role of IL-21 in T_{FH} cell differentiation and function, and its effects on other cell types, is a rapidly evolving field. IL-21 has been implicated in the function of numerous T cell subsets. Is IL-21 a classical "helper" cytokine that facilitates T cell help to many lymphocyte types, other than B cells?
4. How effective will inhibitors of T_{FH} cell effector molecules be for the treatment of human autoimmune diseases?

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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