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T Cells That Promote B-Cell Maturation in Systemic Autoimmunity

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Summary

Follicular helper T (Tfh) cells play an essential role in helping B cells generate antibodies upon pathogen encounters. Such T-cell help classically occurs in germinal centers (GCs) located in B-cell follicles of secondary lymphoid organs, a site of immunoglobulin affinity maturation and isotype switching. B-cell maturation also occurs extrafollicularly, in the red pulp of the spleen and medullary cords in lymph nodes, with plasma cell formation and antibody production. Development of extrafollicular foci (EF) in T-cell-dependent (TD) immune responses is reliant upon $CD4^+$ T cells with characteristics of Tfh cells. Pathogenic autoantibodies, arising from self-reactive B cells having undergone somatic hypermutation with affinity selection and class switching within GCs and EF, are major contributors to the end-organ injury in systemic autoimmunity. B cells maturing to produce autoantibodies in systemic autoimmune diseases, like those in normal immune responses, largely require T-helper cells. This review highlights Tfh cell development as an introduction to a more in-depth discussion of human Tfh cells and blood borne cells with similar features and the role of these cells in promotion of systemic autoimmunity.

Keywords

extrafollicular foci; follicular helper T cells; germinal centers; human; lupus

Introduction

This review briefly discusses T-follicular helper (Tfh) cell development and function in normal immune responses in mice, as we have recently reviewed (1), the details of which we call upon herein. We then review studies of human Tfh cells and blood-borne cells with similar features, before focusing upon studies of these cells in systemic autoimmune syndromes, the prototype of which is systemic lupus erythematosus (SLE). A detailed discussion of the molecular development of Tfh cells and that of newly characterized follicular regulatory T cells and follicular-resident natural killer T (NKT) cells that provide B-cell help for anti-lipid antibody responses, are not undertaken herein, as these topics are reviewed elsewhere in this volume.

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Overview of Tfh cells

Tfh cell differentiation and migration to B-cell follicles

T-cell-dependent B-cell help is essential for immune responses to protein antigens (reviewed in 2), with the subsequent formation of extrafollicular foci (EF) of antibody secreting cells (3, 4) and germinal center (GC) development within B-cell follicles (3, 5, 6). T-B cell contact that initiates these outcomes, EF or GC formation, originates at the border of the T-cell zone and B-cell follicle border (the T/B border) in the spleen (3, 5, 7) and in the interfollicular region in lymph nodes (LNs) (8), after T and B lymphocytes have been primed following antigen encounter.

Antigen priming of naive T cells by dendritic cells (DCs) in T-cell zones initiates the development of Tfh cells (9, 10) (Fig. 1). Costimulatory signaling is also required, as delivered by B7 interactions with CD28, and importantly, that initiated by the inducible costimulator (ICOS), upregulated on T cells with their activation, and provided by its sole ligand (ICOS-L) (11) expressed on DCs (9). Priming of nascent Tfh cells by DCs in T-cell zones leads to downregulation of the chemokine receptor CCR7 (12–14), relieving the response to the chemokines CCL19 and CCL21 required for initial entry of naive T cells into SLOs from the circulation via their engagement to these chemokines expressed on high endothelial venules (in LNs) and on T-cell zone reticular cells (in the spleen and LNs) (15–18). Downregulation of P-selectin glycoprotein ligand-1 (PSGL-1) on naive T cells, like CCR7 needed for T zone via engagement of CCL19 and CCL21 (19), occurs in concert with downregulation of CCR7 (20), with downregulation of CCR7 and presumably that of PSGL-1 abrogating binding to CCL19 and CCL21 allowing T-zone egress (15–18). These changes coincide with upregulation of CXCR5 on nascent Tfh cells (21, 22), which enables entry of primed T cells entry into follicles following a gradient of its ligand CXCL13 [B-lymphocyte chemoattractant (BLC)] expressed by follicular DCs within the B-cell follicle (12, 13). Thus, Tfh cells can be identified by a characteristic cell surface phenotype, with downmodulation of CCR7 and PSGL-1 and upregulation of CXCR5, that is a consequence of the need to emigrate from their initial site of development in the T-cell zone to their site of function in the B-cell follicle.

ICOS upregulation on nascent Tfh cells is developmentally necessary for receipt of costimulation by DCs, as noted above. It is also needed for their maintenance and expansion when they initially contact antigen-primed and ICOSL-expressing B cells before follicular entry (9, 10, 18, 23–25), demonstrating that Tfh cell development is a continual process requiring multiple signals from different cell types for full differentiation, although notably provision of antigen by B cells, in contrast to that presented by DCs, is not necessarily a limiting factor for Tfh maturation (26). Without ICOS signaling, GCs and EF do not form (27, 28), with Tfh cell development substantially diminished (23, 24, 29, 30). ICOS signaling in $CD4^+$ T cells delivers a strong phosphatidylinositol 3-kinase (PI3K) signal that is critical for the induction of the key Tfh cytokines, IL-21 and IL-4 (31), the roles of wthich we will discuss below, with ICOS-driven IL-21 production mediated by the transcription factor c-Maf (32). Expression of SAP [signaling lymphocytic activation molecule (SLAM)-associated protein], an adapter molecule for the signaling of SLAM family receptors expressed by Tfh cells, is also required for their stable interaction with primed B cells, with its deficiency leading defective GC formation and immunoglobulin (Ig) responses (33–35).

Upon activation in the T-cell zone, nascent Tfh cells also upregulate programmed death-1 (PD-1) (8, 18), an inhibitory member of the CD28/cytotoxic T-lymphocyte antigen 4 (CTLA4) family of transmembrane receptors, which is necessary for their subsequent interaction with B cells in the GC (36, 37), as discussed in more detail below. Overall, expression of this group of surface markers allows Tfh cells to be identified as

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$CCR7^{lo}PSGL\text{-}1^{lo}CXCR5^{hi}ICOS^{hi}PD\text{-}1^{hi}$. This phenotype not only provides a history of migration of Tfh cells in SLOs and their developmental and functional requirements, but also as importantly, enables their flow cytometric and microscopic identification in normal mice and humans, and in individuals with systemic autoimmunity, in which Tfh cells have a similar phenotype.

In parallel, B cells following antigen priming, while in transient from the circulation through the T-cell zone or after follicular entry, downregulate the expression of CXCR5 that was initially employed for their migration into B-cell follicles following a gradient of its chemokine ligand CXCL13 expressed therein (12, 13). In contrast to Tfh cells, B cells upon their antigen activation upregulate CCR7 (14), leading to migration toward the T-cell zone for initial T-B cell contact. B cells within the follicle also utilize the orphan G-protein coupled receptor, Epstein Barr virus-induced molecule (EBI2) for their proper positioning. EBI2 expressed on recently activated B cells allows for migration to the outer follicular regions to the T/B cell border via an oxysterol gradient (38, 39), with downregulation subsequently associated with GC localization (40, 41). After subsequent interactions with T cells at the T-B cell border and interfollicular regions, primed B cells maintain their expression of CXCR5 facilitating migration deeper into the follicle and eventual GC localization along with their CXCR5-expressing Tfh cell counterparts, both following a CXCL13 gradient.

In summary, by reprogramming receptor expression profiles to appropriately respond to lymphoid chemokines and other chemotactic molecules, nascent Tfh cells and the B cells they ultimately help are able to traffic within SLOs, enabling their migration towards interfollicular regions and T zone/B cell follicular borders. There, both receive signals for continued maturation, with maintenance of CXCR5 expression with homing to B-cell follicles, following a CXCL13 gradient, and eventual GC formation.

Transcriptional regulation of Tfh cells

Bcl6 (B-cell lymphoma 6), a highly conserved zinc finger protein, is a transcriptional repressor that was originally identified in GC B cells, with its expression in these cells necessary for GC formation (42). Its identification by microarrays in human Tfh cells with selective expression compared to other CD^{+} T-effector cell populations (43) indicated that it might function in subset specification like that of the transcription factors T-bet, GATA-3, and RORγt (and RORα) in Th1, Th2, and Th17 differentiation, respectively (44–47). Indeed, subsequent studies demonstrated that Bcl6 is required for Tfh cell autonomous differentiation and function, including an absolute requirement for TD GC development, with its expression sufficient to recapitulate the Tfh cell phenotype (25, 48, 49).

Bcl6 is initially upregulated in nascent Tfh cells following antigen priming and ICOS stimulation delivered by DCs in the T-cell zone (8, 9, 50, 51) and is detected in T cells as early as the first cell division, indicating that Tfh cell generation starts concomitantly with T-cell activation (10). Upon upregulation, it represses expression of genes that dictate the phenotype of other $CD4^{+}$ T-cell effector subsets (25, 48, 49), while enabling expression of proteins needed for T-cell migration and ultimate function within the B-cell follicle, including CXCR5, PD-1, and CXCR4, at least in part via repression of expression of inhibitory microRNAs (miRNAs) (49). Bcl6 also downregulates expression of molecules required for T-zone retention promoting egress of Tfh cells toward the B-cell follicle (20).

Function of Tfh cells in normal immune responses

Tfh cells are necessary for B cell help in T-dependent immune responses, following activation and upon emigration from the T-cell zone to the B-cell follicle (52) and then to

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the GC (53–55). Their secretion of IL-21 therein (43) with IL-21R engagement on GC B cells, collaboratively with B-cell antigen receptor and CD40 engagement, promotes GC development and maturation (56–65). In addition to IL-21, Tfh cells secrete cytokines associated with other $CD4^+$ T-effector cell subsets, including IL-4 and IFNγ (66–69), enabling differential Ig class switching. This plasticity in differentiation, dictated at a transcriptional level (32), leads to the production of Ig isotypes appropriate to the invading pathogen, with IFNγ secretion by Tfh cells critical for B-cell class switching toward inflammatory isotypes, for example, IL-4 synthesis enabling IgE production for helminth clearance. Tfh cells may also produce IL-17 that may contribute spontaneous GC formation in autoimmunity (67).

In addition to CXCR5 needed for follicular entry and cytokines needed for B-cell maturation, Tfh cells express CD40L and the inhibitory receptor PD-1. The latter, via signaling through its ligands PD-L1 (B7-H1) and PD-L2 (B7-DC) on GC B cells, promotes the quality of the Tfh cell response (36) and along with synthesis of IL-21 (and IL-4) is necessary for GC maintenance and ultimately for production of long-lived plasma cells (36). Yet, abrogation of PD-1 signaling early in the GC response may enhance Tfh numbers and initial Ig production (37), pointing out the complexity of signaling via this pathway and the need to consider both beneficial and adverse events when considering PD-1 blockade clinically.

Expression of CD40L on Tfh cells is also required for GC development and function, with the absence of GC formation when its gene is deleted, spontaneously in human hyper-IgM syndrome (reviewed in 70) or experimentally in mice (71). CD40L on Tfh cells first promotes B-cell maturation upon T-cell-dependent immunization at initial sites of T-B cell contact at the splenic T-B border or the interfollicular regions of LNs, before GC of Tfh and maturing B cells (72). This is analogous to the role to that ICOS signals delivered by B cells play in Tfh survival and maintenance, as outlined above (and in the case of ICOS, when nascent Tfh cells are activated by DCs in the T-cell zone). It is therefore apparent that the signals that are typically associated with the mature GC response may initially be important at sites of early T-DC and subsequent T-B cell collaboration, before GC formation, with these interactions ongoing as the latter develops and matures.

Human T cells that help B cells

$CD4^+$ T cells that stain for the NK cell marker CD57 were first identified in GCs of human tonsils, lymph nodes, and spleens nearly 3 decades ago (73–77). As expected for GC T cells that have migrated from the T-cell zone, $CD57^{hi}$ cells are $CXCR5^{hi}$ and $CCR7^{lo}$, and can help B cells produce Ig *in vitro* (78). Yet, CD57 staining *per se* does not specify GC origin, as CD40L-expressing cells found among the enriched $CD4^+$ T cells in the light zone of tonsillar GCs are $CD57^{lo}$ (79, 80), with those $CD57^{lo}CXCR5^{hi}$ cells that are $ICOS^{hi}$ as capable of B-cell help *in vitro*, if not more so, than their $CD57^{hi}$ counterparts (78, 80). Thus, while not selective for human Tfh cells, CD57 nonetheless is historically and conceptually useful as a marker of this population, with the transcriptional profile of $CD4^+CD57^h$ $CXCR5^{hi}$ Tfh cells isolated from tonsil among the first indications that they were distinct from their Th1/Th2 counterparts, and the demonstration that these cells were capable of B-cell help via production of IL-4 and IL-21 (43).

Tonsillar $CD4^+CXCR5^{hi}ICOS^{hi}$ cells also express molecules, including the B-cell-attracting chemokine CXCL13 (as do mouse Tfh cells), a ligand for CXCR5, that helps distinguish them from other $CD4^+$ T-cell effector populations (78). $CD4^+$ T cells lacking expression of the α subunit of the IL-7 receptor (IL-7Rα, CD127), important for development and homeostatic proliferation of lymphocytes and for defining terminally differentiated effector

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cells (81), are also exclusively located in GCs and capable of CD40L-dependent B-cell help (82). In aggregate, these data indicate that human Tfh cells can best be identified by expression of CXCR5, ICOS, CD40L, CXCL13, and PD-1, with downregulation of CCR7 and PSGL-1 (as we have shown; S. Kim, J-Y. Choi, J. Craft, unpublished data), in a manner analogous to murine Tfh cells, along with downregulation of CD127.

Since the spleen and lymph nodes are difficult to sample in normal and autoimmune humans, it is important to determine if Tfh cells are found in the circulation, and if so, to what extent do their phenotypes mimic those found in SLOs. Accordingly, analysis of the peripheral blood has focused upon identification of $CD4^+$ T cells that have the capability of recirculating to SLOs with entry into B-cell follicles to provide maturation signals therein. Such recirculating central memory cells have been identified in the blood, with expression of CCR7 and L-selectin necessary for reentry into LNs and tonsils (with CCR7 necessary for splenic entry), and of CXCR5, with the latter marker indicative of the capacity to enter B-cell follicles and of providing B-cell help (53–55, 83). Despite the presence of memory markers, the $CXCR5^{hi}$ population may have a limited life span, compared to their blood borne $CXCR5^{lo}$ memory counterparts (53). The latter can also provide B-cell help, suggesting at the possibility that at least the portion of these cells with such helper capacity derive from the $CXCR5^{hi}$ cells (55). Yet, the $CXCR5^{hi}$ cells, upon exposure to the CCR7 ligands CCL19 and CCL21 *in vitro*, downregulate CCR7, analogous to Tfh cells that necessarily need to emigrate to the B-cell follicle from the T-cell zone, suggesting that they have the capacity to become Tfh cells upon re-entry into secondary lymphoid organs (53). Moreover, a recent study has shown that the $CXCR5^{hi}$ population is comprised of cells with Th1, Th2, and Th17 phenotypes, as determined by expression of the appropriate cytokines and the chemokine receptors CXCR3, CCR4, and CCR6, respectively, that define these subsets (84), with the cytokine expression analogous to that seen in Tfh cells in mice, as discussed above. Like Tfh cells, the circulating Th2 and Th17 populations can also help B cells produce Ig *in vitro* in an IL-21 dependent manner, although the Th1 population does not. All in all, these data suggest that the circulating $CXCR5^{hi}$ memory T-cell pool may indeed represent a Tfh pool, a notion supported by the finding that immunization of normal mice leads to development of splenic $CXCR5^{hi}$ CD4 central memory cells that, upon recall, can activate naive B cells (85), suggesting the capacity to recirculate to lymphoid organs in a manner like that assumed for the blood $CXCR5^{hi}$ memory population in humans.

Despite this accumulation of data, the relationship of the circulating $CXCR5^{hi}$ memory cells found in normal humans to Tfh cells localized to B-cell follicles is not entirely clear. This dilemma stems in part from the natural history of the GC response and presumably that of Tfh cells. GCs generate memory B and long-lived plasma cells, with disappearance of these structures when these tasks are completed following in the days to weeks following pathogen challenge and clearance. While $CD4^+$ T cells are found co-localized with memory B cells months after immunization of mice (86), including in follicular structures that stain for the plant lectin peanut agglutinin (PNA) that binds to GC B cells, the relationship of these cells to Tfh cells is uncertain, as is the persistence of the latter. However, as discussed above, memory $CD4^+$ T cells have been identified in the peripheral blood of humans (84) [although comparatively short-lived in contrast to the $CXCR5^{lo}$ memory pool (53)] as well as in SLOs of mice that promote B-cell responses (85). These findings assume the possibility that such cells, at least in part, represent Tfh precursors and can be recalled as such upon antigen rechallenge (85, 87), whereas Tfh cells *per se* do not preferentially develop into long-lived memory cells (88). The relationship of such circulating $CXCR5^{hi}$ memory T cells that help B cells to Tfh cells and their capacity to generate memory is highly relevant to human autoimmunity, given the chronicity of the latter with the findings that such $CXCR5^{hi}$ cells are expanded in the peripheral blood of patients with systemic autoimmune syndromes (89).

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While expression of CXCR5, and with it the capacity to enter B-cell follicles correlates with B-cell helper function, it is also important to note that a population of tonsillar $CXCR5^{lo}$ $ICOS^{lo}$ cells, residing outside B-cell follicles, can also provide CD40L and IL-21 (and IL-10)-dependent help to naïve and memory B cells *in vitro* (83, 90). This population of Bcl6-expressing $CD4^{+}$ T cells that can be distinguished from classical $CD4^{+}Bcl6^{hi}IL\text{-}7^{lo}CXCR5^{hi}ICOS^{hi}$ Tfh cells has been more recently identified in human tonsils (90). These $CD4^{+}IL\text{-}7^{hi}CXCR5^{lo}ICOS^{lo}$ cells bear a memory phenotype yet reside outside B-cell follicles in follicular mantle zones and secrete larger amounts of IL-21 and IL-10 compared to $CXCR5^{hi}ICOS^{hi}$ GC Tfh cells upon activation *in vitro*. The $CXCR5^{lo}ICOS^{lo}$ T cells are more efficient at inducing proliferation and differentiation of naive B cells into Ig-producing cells than GC-resident Tfh cells, and indeed, these cells induce Fas-mediated death of GC B cells in culture. These findings suggest that this population represents a helper population of naïve and memory B cells. Such cells are reminiscent of those identified earlier that are $CD57^{lo}$ and that express preformed CD40L with the capacity to provide B-cell help *in vitro* (79, 80), yet reside outside GCs in the margins of the T-cell zones infiltrated with dendritic cells, suggesting ability to provide cognate help to B cells that have taken up and are now presenting processed antigen, perhaps with promotion of the extrafollicular response (90). The relationship of these cells to the circulating cells and to GC T cells is not yet clear.

Certain characteristics of human Tfh cells, such as divergent Bcl6 populations and circulating Tfh cell memory has not yet been established in mice; however, the role of ICOS is essential in both mouse and human Tfh cell development. In ICOS-deficient patients there is a paucity of memory B cells and switched antibody responses. These patients also have fewer GCs as well as an ablation of $CD57^{hi}CXCR5^{hi}$Tfh cells (29). Peripheral blood from ICOS-deficient patients have fewer circulating $CD4^{+}CXCR5^{hi}$ cells, perhaps of GC Tfh cell origin (54), with impaired migration to the CXCR5 ligand CXCL13 compared to healthy donors. Hence, in both humans and mice, Tfh cells generation requires the upregulation of Bcl6, CXCR5, ICOS, and PD-1 to direct a proper GC response.

Extrafollicular T cells that help B cells

Short-lived plasma cells emerge in extrafollicular regions of SLOs following immunization with TD (or with thymus-independent) antigens (3, 4). $CD4^{+}$ T cells proliferate in the T-cell zone within 2 days following immunization with TD immunogens (91), along with B cells that will ultimately become plasmablasts in the EF (4). The $CD4^{+}$ T cells responsible for the genesis of EF responses in normal and autoimmune mice have more recently been defined (28, 92). In a manner analogous to Tfh cells, they require ICOS and Bcl6 for their development and upregulate molecules required for B-cell maturation, including PD-1, CD40L, and IL-21, with B maturation and plasmablast generation dependent upon CD40L and ICOS (28, 72, 92, 93). While the separable roles of DCs and B cells in the ICOS- and Bcl6-dependent development of the T cells that drive the extrafollicular T-helper response are not clear, presumably they are similar to those necessary for Tfh cell development. It is also not clear if they function to promote B-cell maturation following migration to extrafollicular sites, as opposed to delivering their necessary B-cell helper signals at initial sites of T-B cell collaboration in the T-cell zone.

Tfh cells in autoimmunity

Systemic lupus erythematosus (SLE) is the prototypical systemic autoimmune disease characterized by the generation of pathogenic autoantibodies. In both humans and mice with spontaneous lupus, such autoantibodies have undergone affinity maturation, indicative of a breakdown in germinal center B-cell tolerance (94), although aberrant extrafollicular B-cell

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maturation also leads to the genesis of switched and mutated antibodies like those arising from GC responses (95). While the latter may be initiated in disease models absent T-cell help (96), such help contributes to the ongoing EF response in murine lupus, as it does for the aberrant GC response (as we will see below). Indeed, increased numbers of Tfh cells can be observed in SLOs in murine lupus, with expansion of EF sites (28, 97), with circulating cells resembling Tfh cells found in SLE in humans (89). Thus, expansion of dysfunctional Tfh cells or of T cells that promote the extrafollicular response is a main contributor to the development of systemic autoimmunity, since abrogation of Tfh cell development or function in murine and human lupus, also as discussed in the following paragraphs, is therapeutically beneficial.

Murine lupus models

Mouse models have highlighted the contribution of Tfh cells in the generation of autoantibodies in systemic autoimmune syndromes. *Sanroque* mice homozygous for deficiency of *roquin*, a RING-type ubiquitin ligase, are a prototypical example (98). These animals have increased ICOS expression in $CD4^+$ T cells as a consequence of defective post-transcriptional degradation of ICOS mRNA (99). As a result, they have excessive generation of Tfh cells, with development of spontaneous GCs as occurs in other lupus models (100), and development of systemic autoimmunity with autoantibody production and immune-complex glomerulonephritis as occur in human lupus. The Tfh cell expansion with consequent abnormal GC B-cell selection leads to the lupus syndrome in these animals (101), although subsequent investigation suggests that this mutation promotes autoimmunity by an as-yet-unidentified mechanism (102), and IL-21, the canonical Tfh cytokine, does not appear to contribute to the disease phenotype (101). Nonetheless, *Sanroque* mice provided evidence that ICOS overexpression can lead to aberrant Tfh cell formation and function with the result a clinical lupus syndrome.

As ICOS is highly expressed on Tfh cells and has only a single ligand (11), it is an appealing therapeutic target in lupus. The importance of ICOS in regulating Tfh cells is underscored by the finding in ICOS-deficient patients of a paucity of memory B cells and switched antibody responses. These patients also have fewer GCs as well as an ablation of $CD57^{hi}$ $CXCR5^{hi}$ Tfh cells (29). Peripheral blood from ICOS-deficient patients have fewer circulating $CD4^+CXCR5^{hi}$ cells, perhaps of GC Tfh cell origin (54), with impaired migration to the CXCR5 ligand CXCL13 compared to healthy donors. Likewise, the role if ICOS in promotion of autoimmunity is supported by the observation that administration of an ICOSL blocking antibody to lupus-prone New Zealand black/New Zealand white (NZB × NZW)F_1 mice interrupted Tfh cell development and GC formation with a decrease in autoantibody formation and immune-complex glomerulonephritis (103, 104). These effects occurred without an acute impact on GC B-cell maturation, suggesting the ameliorative benefit on autoantibody production and related end-organ injury was a consequence of the decreasing Tfh cell formation (104). Genetic deletion of ICOS in another polygenic model, Fas-deficient MRL mice, also blocks formation of T cells that promote the aberrant B-cell development typical of murine and human lupus, with resultant decrease in autoantibody formation and the consequent renal injury (28). These data, from two different autoimmune mouse models, emphasize the importance that ICOS signaling has in the development of Tfh cells (see *Tfh cell differentiation and migration to B-cell follicles*, above) and their subsequent promotion of autoreactive B-cell maturation, and provide evidence that inhibition of Tfh cell formation by impeding ICOS signaling may be beneficial in the treatment of SLE in humans. Of course, for such intervention to be useful, it would necessarily need to be employed therapeutically after onset of clinical disease, rather than prophylactically as is often the case for treatment of murine disease models. Thus, it is

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noteworthy that blockade of ICOS signaling has a therapeutic benefit in lupus-prone mice (103), a finding contributing to the use of anti-ICOS-L in early stage clinical trials in SLE.

Cytokines produced by Tfh cells also appear to contribute to the lupus phenotype in mice. This is not unexpected, given their role in GC B cell maturation in immunity, such as that of IL-21 with its requirement for GC stability with normal memory B and plasma cell formation (62, 63). IL-21, at least in conjunction with IL-6, also promotes Tfh cell development via STAT3 signaling in these cells (24, 64), although IL-21 signaling alone may not substantively contribute to Tfh development (62–64, 105). In BXSB.*Yaa* lupus-prone mice, with the *Yaa* designation indicative of the Y chromosome-linked autoimmune accelerator mutation borne by these mice, now known to be secondary to a duplication of Toll-like receptor 7 (106, 107), elevated IL-21 levels produced by splenic $CD4^{+}CXCR5^{hi}ICOS^{hi}$ cells are essential for autoantibody production and immune-complex glomerulonephritis (59, 97). Numbers of these Tfh-like cells in these mice increase with age, with subsequent expansion beyond their normal GC location to EF sites (hence, the designation 'Tfh-like'), an expansion presumably secondary to the parallel expansion of B and myeloid cells and consequent role of as antigen-presenting cells, conferred by enhanced Toll-like receptor signaling, as well as perhaps a contribution from the excessive IL-21 and myeloid IL-6 production signaling through Tfh cell expressed STAT3. BXSB.*Yaa* mice, in which IL-21R has been genetically disrupted, had amelioration of the atypical GC formation, associated with a decrease in hypergammaglobulinemia, autoantibody production, renal disease, and premature morbidity (97). These animals also had a decrease in numbers of cells with a Tfh-phenotype ($CXCR5^{hi}$ $ICOS^{hi}$). While the lupus phenotype in the above-cited *sanroque* mice with Tfh expansion does not appear to be a consequence of excessive IL-21 signaling, IL-21 blockade nonetheless has therapeutic appeal in human lupus, given the phenotype of the IL-21R-deficient BXSB.*Yaa* mice, with similar results in IL-21R-deficient, Fas-deficient MRL mice, and given such therapy leads to a reduction in autoantibody production and consequent tissue injury in both these strains (108–110).

IFNγ, made by Tfh cells during inflammatory conditions (68), also promotes the murine lupus phenotype (111), at least in part via its promotion of B-cell class switching from IgM to inflammatory Ig isotypes. The latter deposit in peripheral tissues, including the lupus kidney, with initiation of tissue injury (111). The role that this cytokine plays in promotion of SLE in humans is less clear, although as in mice, it may contribute to renal injury (112). In a like manner, IL-4 is produced by Tfh cells (68, 69, 113), with resultant B-cell class switching to IgE and murine IgG1 isotypes, with the former apparently a contributor to end-organ injury in murine and human lupus (114).

CD40L signaling, as for IL-21, is required for Tfh cell-dependent GC B-cell maturation. As such, abrogation of CD40L-CD40 interactions is an attractive strategy for intervention in systemic autoimmunity, with this notion supported by the findings that lupus-prone mice lacking CD40L, or animals treated with anti-CD40L antibodies, have marked improvement in disease phenotypes (115–117). These results lend credence to the causative role of Tfh cells in systemic autoimmune syndromes, and have been extended to humans with SLE in which anti-CD40L was therapeutically beneficial, with an improvement in disease activity indices in concert with a decrease in pathogenic autoantibodies and immune-complex-mediated glomerulonephritis (118). These effects were a consequence in the interruption of the aberrant Tfh-B-cell interactions in lupus, as evidenced by blockade of pathological GC B-cell maturation. Even though anti-CD40L antibody administration was complicated by thrombosis, seemingly secondary to its binding to platelet FcRs and with engagement of the surface-associated CD154 and platelet aggregation (119), these data indicate that targeting CD40L-CD40 interactions in lupus remains a possible therapeutic approach.

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The extrafollicular B-cell response in lupus

Autoantibody production in lupus-prone strains also arises in EF sites of spleen and lymph nodes, sites for maturation and somatic Ig mutation of autoreactive B cells in MRL mice (95, 120), and for T-cell migration and autoreactive B-cell maturation in other lupus and inflammatory disease models (28, 97, 121). For example, short-lived antibody-forming cells (AFCs) with a plasmablast phenotype (proliferating cells that express intracellular and membrane Ig and that are MHC class II^+ and $CD80/86^{hi}$; hence, competent for ongoing T-cell interactions) dominate the autoantibody response in spleens of Fas-deficient MRL mice, rather than long-lived AFCs that have a plasma cell phenotype (non-proliferating, class II^{neg} and $CD80/86^{neg}$, with intracellular Ig only)(95, 122). The short-lived AFCs mutated their *Ig* genes in extrafollicular sites at the border of T-cell zones and the red pulp in association with $CD4^+$ T cells, indicating T-cell dependence, with continued development in the marginal sinus bridging channels with rapid proliferation and turnover (95). By contrast, few mutating cells were seen in the GC, suggesting that the AFC with Ig mutations arose via a GC-independent pathway. These findings were in concert with earlier work that the GC response is lost in older Fas-deficient MRL/Fas^{lpr} mice, in the setting of continually increasing Ig production, providing support for the importance of extrafollicular sites in generation of autoantibodies, including anti-dsDNA (123). Production of class-switched and mutated autoantibodies in extrafollicular sites is not the exclusive province of Fas-deficiency or a single background strain. Short-lived plasmablasts contribute to class-switched IgG autoantibody (anti-dsDNA) responses in (NZB × NZW)F_1 mice, although mutations in the short-lived AFC were not assessed in this work [these mice also have long-lived splenic plasma cells that produce autoantibodies (121)]. As noted above, the extrafollicular response in SLOs, with T cells emerging beyond GCs, is an important histological component of disease in BXSB.*Yaa* mice (97), an abnormality that is diminished with disease down modulation.

In Fas-deficient MRL mice, the Th cells associated with development of EF promote activation-induced cytidine deaminase (AID)-dependent class switching and hypermutation of autoantibodies, in conjunction with upregulation of Bcl6. While B-cell maturation can be initiated experimentally in the absence of T-cell help (96), it is necessarily dependent upon IL-21 and CD40L (28, 124), findings similar to extrafollicular helper T cells identified in the above noted BXSB.*Yaa* mice (97). Likewise, (NZB × NZW)F_1 animals also contain extrafollicular T cells (28). These features, expression of IL-21 and CD40L, and requirements for ICOS and B cells for development, are the same as for Tfh cells; however, unlike the latter, extrafollicular $CD4^+$ T cells, at least in MRL mice, lack expression of CXCR5 (28). This absence, combined with expression of CXCR4, presumably enables their movement to extrafollicular locations via attraction to its ligand CXCL12 [stromal cell–derived factor-1 (SDF-1)] expressed in the splenic red pulp and lymph node medullary cords (125).

While B-cell maturation with autoantibody production occurring via an EF pathway is critical to the murine lupus phenotype, it is unclear if this pathway is operative in humans with SLE. Yet, studies of short-lived plasmablasts as producers of potentially pathogenic autoantibodies in murine lupus assume greater significance given data that peripheral blood B cells with a plasmablast phenotype are found in the peripheral blood of patients with SLE (126–129). The numbers of these cells and that of circulating plasma cells also correlate with disease activity (130). These disturbances in B-cell homeostasis in human lupus are corrected by anti-CD20 monoclonal antibody therapy (129), pointing out the potential power in understanding the regulation and control of these cells in human lupus, although long-lived plasma cells also contribute to the serum autoantibody pool in a CD20-independent manner (129). Regardless, it seems critical to fully understand the maturation steps of short-

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lived autoantibody-producing cells in lupus and the T cell-dependence of these events. As the characteristics of these helps of EF overlap with those of Tfh cells, therapies blocking the function of the latter will likely hamper extrafollicular responses as well.

Tfh cells in human lupus

While Tfh cells are critical for the murine lupus phenotype, their role in SLE in humans is less clearly defined, although strongly inferred from observations of aberrant tolerance and regulation of GC B-cell maturation (118, 131) from study of peripheral blood T cells. Abnormal GC reactions in patients with lupus can be detected by analysis of circulating B cells, with class-switched CD38^{hi} Ig-secreting population found in active disease, with aberrant selection of autoreactive clones (131). Also as highlighted above, CD154-CD40 treatment of patients with active lupus led to a decline in this plasma cell subset, strongly suggestive of a role for Tfh and/or extrafollicular T-helper cells in its development (118).

ICOS^{hi} cells are found in the blood of lupus patients (132), although their relationship to Tfh cells is uncertain. Yet, up to a third of patients with lupus and the related condition primary Sjögren's syndrome have circulating CD4^{+}CXCR5^{hi}PD-1^{hi}ICOS^{hi} Tfh cells in their blood, with numbers that correlated with both increasing anti-double-stranded DNA titers and severity of end-organ involvement (89). This blood-borne population, called circulating Tfh cells, phenotypically resembled Tfh cells found in secondary lymphoid organs of humans and mice, yet it lacked expression of Bcl6 and IL-21 classically found in Tfh cells and its role in B-cell help was not discussed. The lack of Bcl6 expression in a circulating population is perhaps not so surprising, however, since it is downregulated in Tfh cells as the GC matures following immunization of mice (50). Moreover, the circulating CXCR5^{hi} cells in humans that are good B-cell helpers are Bcl6^{lo}, with its upregulation upon stimulation (83), suggesting that this circulating population with its presumed follicular access mediated by CXCR5 and B-cell helper capacity may be circulating Tfh cells (83, 84). Upregulation of ICOS and PD-1 in the CXCR5^{hi} population from SLE patients, molecules that are critical for B-cell helper function in secondary lymphoid tissues, indicate potential therapeutic targets to abrogate T-B cell collaboration for autoantibody production in systemic autoimmunity, a notion underscored by the close similarities of Tfh cells in humans and mice.

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Conclusions

There is increasing evidence from mouse models that Tfh cells play a key role in promotion of the systemic autoimmune responses, with their expansion linked to aberrant extrafollicular and GC responses with production of class-switch and high-affinity autoantibodies that promote tissue injury. It follows that abrogation of their function would be therapeutically beneficial in disease, a notion supported by investigations in both mice and humans with lupus. Further study of these cells in autoimmune animals, combined with knowledge of the molecules necessary for their function and the events that maintain ongoing T-B-cell collaboration in autoimmune diseases, is critically important to better understanding disease biology and to maintain the pipeline of disease targets and ultimately that of therapeutic agents.

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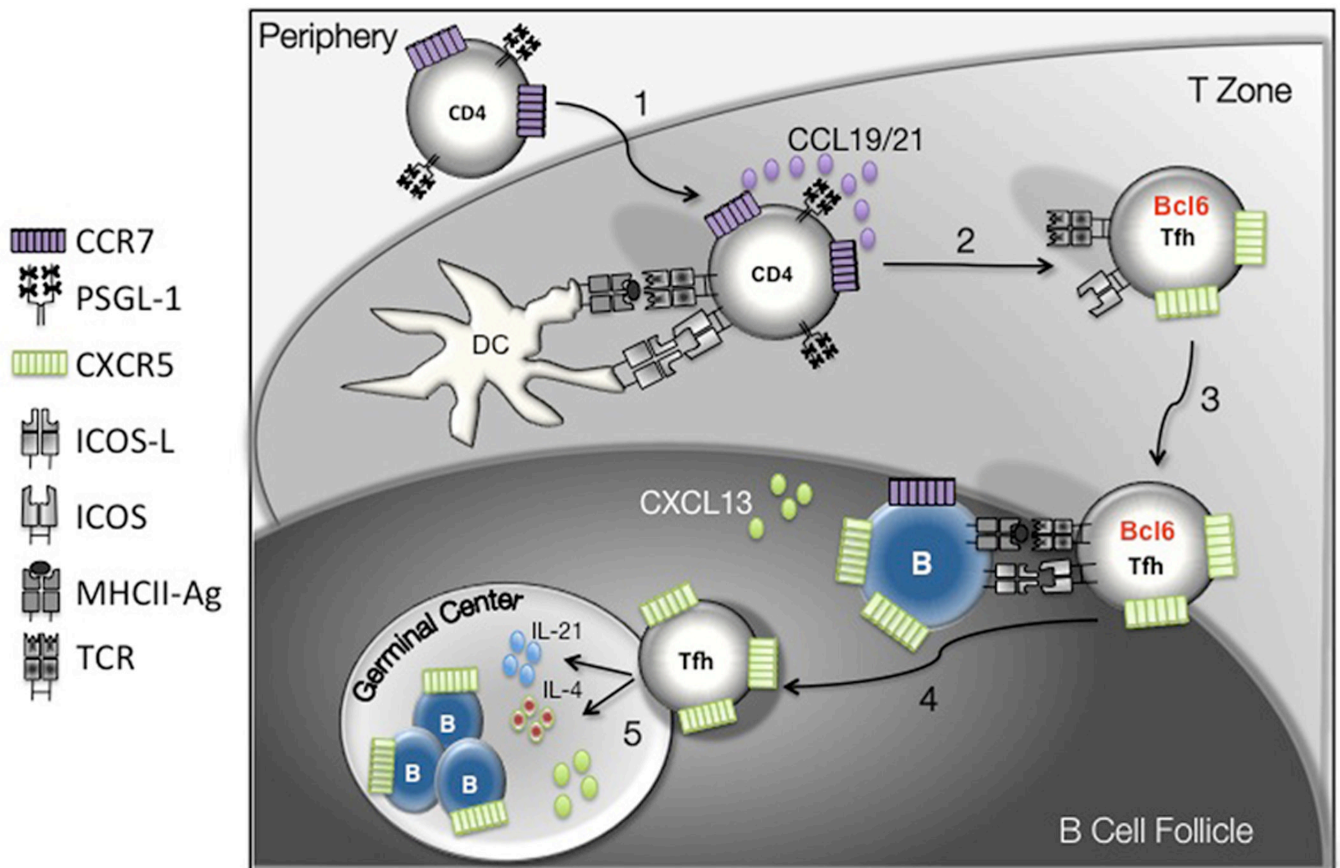

Fig. 1. Model of Tfh migration, development, and Tfh-B cell collaboration in extrafollicular and GC responses

1. Naive T and B cells migrate to the T-cell zones and B-cell follicles in secondary lymphoid organs (here, the spleen) following a chemokine gradient of the T-cell zone chemokines CCL19 and CCL21 that engage CCR7 and PSGL-1 on T cells, and the follicular chemokine CXCL13 that engages CXCR5 on B cells. 2. Upon antigen activation and costimulation (particularly via ICOS) by dendritic cells (DCs), nascent Tfh cells upregulate Bcl6 and CXCR5 and downregulate CCR7 and PSGL-1, relieving engagement to CC19 and 21, and enabling migration to the splenic T-B cell border (or the interfollicular region in lymph nodes) where they contact antigen-activated B cells. In a parallel manner, antigen-activated B cells upregulate CCR7 with migration from the follicle to sites of T cell engagement. 3. At these locations, signaling from cognate B cells via MHC-peptide and ICOSL to TCR and ICOS promotes Tfh cell survival with maintenance of Bcl6 and CXCR5 expression, the latter necessary for subsequent migration of both subsets deeper into the follicles for GC formation; in some circumstances, antigen delivery by B cells may not be necessary for Tfh cell maintenance. 4. The outcome of T-B collaboration is development of extrafollicular foci where short-lived plasmablasts early after immune challenge produce antibodies (not shown), or development of GCs. 5. In the latter, Tfh cells promote B-cell maturation with class switching and affinity selection via cytokines, in particular IL-21 and IL-4, and cell bound molecules, including CD40L and PD-1. Both Tfh and GC B-cell development and function are necessarily dependent upon the transcriptional regulator Bcl6. The GC response leads to B-cell memory and long-lived plasma cell formation (not shown).