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REVIEW

The darker side of follicular helper T cells: from autoimmunity to immunodeficiency

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Follicular helper T (T_{FH}) cells represent a distinct subset of $CD4^+$ helper T (T_H) cells specialized in providing help to B cells. They are characterized by their unique transcriptional profile (Bcl6), surface marker expression (CXCR5, PD-1, ICOS and CD40L) and cytokine production pattern (IL-21 and IL-6). T_{FH} cells provide help to B cells both to form germinal centers (GCs) and to differentiate into memory B cells and plasma cells for generation of humoral responses. However, there is emerging evidence that implicates T_{FH} cells in the development of various human pathologies, such as autoimmune diseases, immunodeficiency and lymphoma. This review focuses on the current progress in this area including mouse and human studies. A clearer understanding of the mechanisms of T_{FH} cell-mediated immunity and pathology may be exploited for rational development of therapeutic strategies.
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INTRODUCTION

Antibody responses are a key component of the adaptive immune system. These responses are mostly dependent on help from antigen-specific $CD4^+$ helper T (T_H) cells. In recent years, follicular helper T (T_{FH}) cells, a specialized subset of T_H cells, have attracted much attention due to their ability to provide critical help to germinal center (GC) B cells. Although T_{FH} and other T_H cell subsets share many phenotypic and functional features, the recent identification of the master transcriptional regulator, B-cell lymphoma-6 (Bcl6), of T_{FH}-cell differentiation has established T_{FH} cells as a distinct subset of T_H cells.[1–3] T_{FH} cells provide help to B cells both to generate and maintain the GCs as well as to differentiate into memory B cells and plasma cells. The plasma cells secrete antigen-specific antibodies for generation of humoral responses against a variety of pathogens, including viruses and bacteria.[4,5] However, if T_{FH}-cell function is not properly regulated, various pathologies ensue.[6–11] Here we present a review of the current literature pertaining to the role of T_{FH} cells in the development of pathologies, such as autoimmunity, immunodeficiency and lymphoma, and the implications of these studies for development of therapies.

CHARACTERISTICS OF T_{FH} CELLS

Phenotypically, T_{FH} cells can be characterized by the high expression of certain surface markers, such as chemokine receptor-5 (CXCR5), programmed death-1 (PD-1), inducible costimulator (ICOS) and CD40 ligand (CD40L).[12] These markers contribute to the migration of T_{FH} cells and the interaction of T_{FH} cells with B cells to promote B-cell responses against pathogens. The binding of CXCR5 on T_{FH} cells with its cognate ligand, CXCL-13, in GC facilitates the migration of T_{FH} cells to B-cell follicles for their interaction with B cells.[13,14] Upon T_{FH}-cell activation, PD-1 induces an inhibitory signal to T_{FH} cells, whereas ICOS functions as a costimulatory molecule, thus determining the outcome of the T_{FH} cell-mediated B-cell response.[15,16] Furthermore, CD40L, a member of the tumor necrosis factor family, is expressed on activated T_{FH} cells, and its interaction with CD40 on B cells is crucial for immunoglobulin isotype switching.[17] In addition, signaling lymphocytic activation molecule-associated protein (SAP) has been shown to play a critical role for T_{FH}-cell function in GC formation and immune homoeostasis.[18]

Cytokines particularly IL-21 and IL-6 have been shown to play a key role in both T_{FH}-cell differentiation and antigen-specific humoral responses. On the one hand, IL-21 has been considered as the master cytokine for the regulation of T_{FH}-cell development that depends on the costimulation *via* CD40–CD40L and ICOS–ICOSL interactions. IL-21 induces production of IL-21 by T_{FH} cells in an autocrine fashion, leading to the differentiation of T_{FH} cells.[19] Furthermore, IL-6 induces both IL-21 production as well as T_{FH}-cell generation.[20] A recent study by Eto *et al.*[21] shows that T_{FH}-cell differentiation requires both IL-6 and IL-21, and that these cytokines alone are not sufficient to drive T_{FH}-cell differentiation, indicating the synergistic relationship between IL-21 and IL-6 that regulates the T_{FH}-cell differentiation. On the other hand, IL-21 is critical for T_{FH} cells to promote B-cell somatic hypermutation and immunoglobulin class switching.[22] T_{FH} cells can also produce other cytokines, similar to other T_H cells such as T_{H1} and T_{H2} cells, which may be relevant to the development of various classes of antibodies.

The identification of Bcl6 as a master regulator of T_{FH}-cell differentiation has laid the basis for T_{FH} cells as a distinct subset of T_H cells.

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In contrast to the other T_H cell subsets, such as T_H1, T_H2 and T_H17 cells, which are controlled by T-bet, GATA3 and RORγt, respectively, T_{FH} cells are dependent on Bcl6.[1–3] Bcl6-deficient mice failed to develop T_{FH} cells, suggesting that Bcl6 is critical for programming of T_{FH}-cell differentiation.[1–3] In contrast, Blimp-1, another transcription factor, acts as an antagonist of Bcl6 by specifically inhibiting T_{FH}-cell differentiation.[23] Therefore, Bcl6 and Blimp-1 are critical for T_{FH}-cell differentiation, with promoting and regulatory role, respectively.

Although T_{FH} cells act as a distinct subset of T_H cells, they also show considerable plasticity. T_{FH} cell-like features can also be exhibited by other subsets of T cells, including regulatory T (T_{reg}) and invariant natural killer T (iNKT) cells.[24–27] In particular, recent studies have described a population of follicular T regulatory (T_{FR}) cells that share the phenotypic characteristics with T_{FH} and T_{reg} cells. Like classic T_{FH} cells, the so-called T_{FR} cells express high levels of CXCR5 and PD-1, and require Bcl6, SAP and CD28 for their development, but they express Foxp3 and can inhibit the GC reactions, similar to T_{reg} cells. T_{FR} cells are considered to be produced *de novo* from the progenitors of $CXCR5^-$Foxp3 natural T_{reg} cells.[25–27] Interestingly, the expression of T_{FH} cell-like phenotype is not just confined to conventional T cells. Chang *et al.*[24] recently identified a subset of iNKT, $iNKT_{FH}$, cells that share phenotypic, functional and ontological characteristics of T_{FH} cells. These $iNKT_{FH}$ cells showed enhanced expression of CXCR5 and PD-1, and provided help to lipid antigen-reactive B cells *via* production of IL-21. Not surprisingly, the development of $iNKT_{FH}$ cells was found to be dependent on the transcriptional factor Bcl6 and CD28 signaling.[24]

T_{FH} CELLS IN AUTOIMMUNITY

The hallmark of T_{FH}-cell function is to help B cells to generate humoral immune responses, which is a complex physiological process that requires the formation of GC in secondary lymphoid tissues, such as spleen and lymph nodes. Specifically, T_{FH} cells emit instructive signals to B cells to form and maintain GC. The GC provides a podium where T_{FH} cells instruct B cells not only to differentiate into memory B cells, but also to class switch for antibodies through somatic hypermutation and isotype switching, resulting in the formation of antigen-specific high-affinity antibodies to combat infectious agents.[28] However, unwanted antibody responses can come with the risk of autoimmune diseases (Figure 1). Many lupus-prone murine models show the spontaneous generation of GCs that is positively correlated with the production of autoantibodies.[29,30] In human systemic lupus erythematosus (SLE) patients, autoreactive B cells actively participate in GC reactions, which eventually lead to the formation of pathogenic autoantibodies.[31] A growing body of evidence further suggests that the aberrant function of T_{FH} cells plays a critical role in generation of autoantibodies *via* autoreactive GC B cells, which inflict autoimmune pathologies in humans and mice (Table 1).

T_{FH} cells in murine models of autoimmune diseases

The contribution of T_{FH} cells in autoimmune diseases has been mainly studied in murine models of SLE. Most data supporting the role of T_{FH} cells in murine lupus come from studies using sanroque mouse model. Sanroque mice are having a single recessive mutation in the roquin gene that encodes a highly conserved protein, a member of the RING-type ubiquitin ligase protein family. These mice exhibit SLE-like pathologies, such as high-affinity anti-dsDNA antibodies, focal proliferative glomerulonephritis, necrotizing hepatitis, anemia and autoimmune thrombocytopenia. The sanroque mutation not only causes the formation of excessive T_{FH} cells and GCs, but also disrupts a repressor of ICOS and results in aberrant production of IL-21.[6] Using sanroque mice, Linterman *et al.*[32] recently investigated the role of T_{FH} cells in the development of murine lupus. They found that deletion of an allele of Bcl6 reduced the number of GC cells and ameliorated the SLE-like pathological reactions, suggesting that autoimmunity in sanroque mice is largely dependent on GC. Furthermore, they found that deficiency of SAP in sanroque mice resulted in a significant reduction in T_{FH} cells and IL-21, and abrogated GC

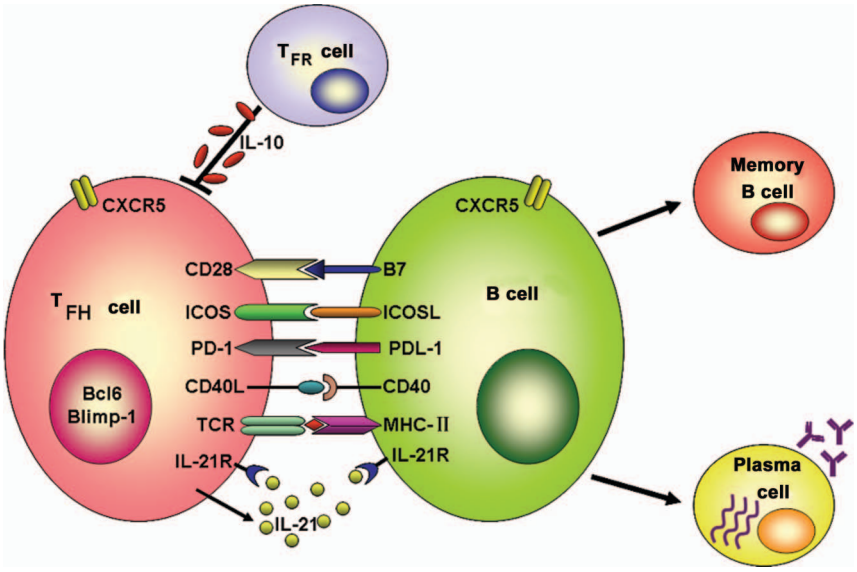

Figure 1 Interaction between T_{FH} and B cells to induce humoral responses. Activated T_{FH} cells upregulate CXCR5 and migrate toward B-cell follicles to form GC. In GC, T_{FH} cells interact with antigen-specific B cells through various molecules such as ICOS–ICOSL, PD-1–PDL-1, CD40–CD40L and IL-21R–IL-21, resulting in the production of memory B and plasma cells. The plasma cells secrete long-lived antibodies to combat infectious agents. However, aberrant T_{FH} cell function leads to the production of autoantibodies that may result in autoimmune pathologies. T_{FR} cells can inhibit the self-reactive B-cell responses such as autoantibody production *via* secretion of IL-10. CD40L, CD40 ligand; CXCR5, chemokine receptor-5; GC, germinal center; ICOS, inducible costimulator; PD-1, programmed death-1; T_{FH}, follicular helper T; T_{FR}, follicular T regulatory.

Table 1 T_{FH} cells in autoimmunity

Autoimmune condition	*Clinical manifestations*	*Phenotype of T_{FH} cells*	*Mechanism of T_{FH} cell dysfunction*	*Reference*
SLE	Autoantibodies against dsDNA, hypergammaglobulinemia, thrombocytopenia, glomerulonephritis lymphadenopathy	$CD4^+CXCR5^+PD\text{-}1^{hi}ICOS^{hi}$	GC expansion T_{FHC} cell overrepresentation	51
SS	Anti-SSA and SSB hypergammaglobulinemia, lymphadenopathy	$CD4^+CXCR5^+PD\text{-}1^{hi}ICOS^{hi}$	T_{FHC} cell overrepresentation	51
Primary SS	Anti-SSA, SSB hypergamma-bulinemia salivary gland damage	$CD4^+CXCR5^+CCR6^+PD\text{-}1^{hi}ICOS^{hi}$	T_{FHC} cell overrepresentation	55
AITD	Autoantibodies, such as anti-TSH receptor, anti-thyroglobulin and anti-thyroperoxidase antibodies, thyroid dysfunction	$CD4^+CXCR5^+PD\text{-}1^{hi}ICOS^{hi}$	T_{FHC} cell overrepresentation	54
RA	Circulating autoantibodies inflammation of joints	$CD4^+CXCR5^+ICOS^{hi}$	T_{FHC} cell overrepresentation	53
JDM	Skin and muscle inflammation	$CD4^+CXCR5^+$	Overrepresentation of T_H2 and T_H17 cell-like T_{FHC} cells	52
Sanroque mouse	Hypergammaglobulinemia, lymphadenopathy, glomerulonephritis	$CD4^+CXCR5^+PD\text{-}1^{hi}ICOS^{hi}$	T_{FH} cell overrepresentation, spontaneous GC formation, increased ICOS expression	32
BXSB-Yaa mouse	Hypergammaglobulinemia, lympgadenopathy, glomerulonephritis UV-induced dermatitis	$CD4^+CXCR5^+PD\text{-}1^{hi}ICOS^{hi}$	GC expansion, aberrant IL-21 secretion	41
Pristane-induced lupus in BALB/c mouse	Hypergammaglobulinemia, lympgadenopathy, glomerulonephritis	$CD4^+CXCR5^+PD\text{-}1^{hi}ICOS^{hi}$	GC expansion, overexpression of ICOS and IL-21	46
NZB/W F1 mouse	Hypergammaglobulinemia, lympgadenopathy, glomerulonephritis	$CD4^+CXCR5^+ICOS^{hi}$	T_{FH} cell overrepresentation, altered production of IL-21 and IL-17	45

Abbreviations: AITD, autoimmune thyroid diseases; CXCR5, chemokine receptor-5; GC, germinal center; ICOS, inducible costimulator; JDM, juvenile dermatomyositis; PD-1, programmed death-1; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjogren's syndrome; T_{FH}, follicular helper T; T_{FHC}, circulating T_{FH}; TSH, thyroid-stimulating hormone, UV, ultraviolet.

formation, autoantibody production and renal pathology. More convincingly, adoptive transfer of sanroque T_{FH} cells into wild-type recipient mice led to the spontaneous GC formation that resulted in pathology, confirming the direct involvement of T_{FH} cells in the pathogenesis of the lupus-like diseases.[32] Overall, these data suggest that dysregulation of the GC response through excessive formation of T_{FH} cells is responsible for autoimmunity in sanroque mice. However, some studies showed that roquin represses autoimmunity by limiting ICOS mRNA expression through a microRNA-independent post-translational repression.[33,34] In addition, a recent study showed that the loss of roquin induced early death and immune dysregulation but not autoimmunity in sanroque mice.[35] Therefore, future studies are required to completely elucidate the mechanisms behind pathogenesis of lupus in sanroque mice.

T_H-cell differentiation is polarized toward T_{FH} cells to generate B-cell responses against infections.[36,37] These responses, if exaggerated by aberrant T_{FH}-cell function, may also promote autoimmune diseases. A recent interesting study examined the role of T_{FH} cells in the development of autoimmunity during chronic *Salmonella* infection in mice. The study showed that mice deficient in MyD88 when challenged with recombinant-attenuated *Salmonella enterica* serovar *Typhimurium* vaccine strain resulted in chronic infection, which was subsequently followed by the development of autoimmune pathologies, such as autoimmune hypergammaglobulinemia and deposition of immune complexes in the kidneys. In these mice, a population of T_{FH} cell-like cells expressing the higher levels of PD-1, CXCR5, ICOS and IL-21 was found to be significantly expanding compared with healthy controls. In addition, blocking the function of these cells by anti-ICOS or anti-PD-1 antibodies ameliorated hyper-IgG in recombinant-attenuated *Salmonella enterica* serovar *Typhimurium* vaccine-infected MyD88-deficient mice. These observations suggest that the overrepresentation of T_{FH}-like cells in chronic bacterial infection elicits autoimmune pathologies in a PD-1- and ICOS-dependent fashion.[38]

Aberrant production of T_{FH} cell-associated cytokines, particularly IL-21 has been shown to be critical for the development of autoimmunity in lupus-prone mice. IL-21 is mainly produced by T_{FH} cells and appears to be crucial for T_{FH}-cell differentiation and GC reactions.[18,39,40] Several studies using lupus-prone mouse models have provided strong evidence for the involvement of IL-21 in autoimmunity. Ozaki *et al.*[41] showed that BXSB-Yaa mice, which reveal features of lupus, had overexpansion of T_{FH} cells and excessive production of IL-21. Additionally, blocking IL-21 in the lupus-prone MRL^{lpr} mice led to reduced lupus pathologies, such as pathogenic autoantibodies, lymphadenopathy and deposition of immune complexes in the kidney.[42] Consistently, when MLR^{lpr} mice were made deficient in IL-21R, they showed reduced splenomegaly, lymphadenopathy and autoantibody production, and lacked spontaneous GC formation and plasma-cell accumulation.[43] Moreover, the role of IL-21 is also shown in another model of murine lupus, NZB/W F1 mice, which exhibit clinical features that resemble those of human SLE, including autoantibody production and immune complex-mediated nephritis.[44,45] Upon intranasal administration of anti-CD3 antibodies, NZB/W F1 mice exhibited suppressed lupus development characterized by reduced levels of autoantibodies and diminished glomerulonephritis.[45] It was found that the treatment with anti-CD3 antibody affected the function of $CD4^+CXCR5^+ICOS^+$ T_{FH} cells, characterized by decreased IL-21 and IL-17 production in these mice which was associated with the autoimmune pathologies.[45] Moreover, a recent *in vivo* study found IL-27 to be crucial for promoting autoimmune pathologies through inducing the production of IL-21 by T_{FH} cells in a murine model of pristane-induced lupus.[46] Using IL-27α-receptor-deficient ($IL\text{-}27R\alpha^{-/-}$) mice, Batten *et al.*[46] showed that IL-27 is important for

IL-21 production and T_{FH}-cell survival. They found that mice deficient in IL-27Rα, when treated with pristane, exhibited diminished autoantibody production and mild renal lesions compared with pristane-treated wild-type mice.

The identification of T_{FR} cells has further deepened our understanding of how overexpansion of GC is prevented from autoantibody production.[25–27,47] Lim *et al.*[47] first reported that T_{FR} cells migrate to follicles in human tonsils and elicit suppressive effect on the T_{FH} cell-mediated B-cell responses, such as antibody production, B-cell survival and expression of activation-induced cytosine deaminase. *In vivo* studies in mice have further provided direct evidence to show a critical role for T_{FR} cells in inhibiting the GC responses.[25–27]

T_{FH} cells in human autoimmune diseases

Although less clearer than that in murine models, the implications of T_{FH} cells in the development of human autoimmune diseases have started to be appreciated.[6,32] Earlier studies have provided indirect evidence to indicate the role of T_{FH} cells in promoting human autoimmunity, e.g., production of pathogenic autoantibodies in SLE patients caused by dysregulated GC reactions,[31,48] presence of the aggregates of T and B cells containing plasmablasts in the kidneys of patients with lupus nephritis[49] and reduced GC reactions upon blocking CD40L–CD40 interactions in patients with active SLE.[50] Recent studies have further provided clearer evidence on the role of T_{FH} cells in promotion of both systemic and organ-specific autoimmune diseases in humans.[51–55] Simpson *et al.*[51] performed an elegant study investigating the role of T_{FH} cells in patients with SLE and Sjogren's syndrome. They found an overrepresented population of $CD4^+CXCR5^+$ T_{FH} cell-like cells in the blood, referred to as circulating T_{FH} (T_{FHC}) cells, of a subset of the SLE patients (14 out of 46), which expressed ICOS and PD-1 compared with healthy controls. Furthermore, the expansion of T_{FHC} cells was found to be positively correlated with severity of the SLE as evidenced by high autoantibody titer, glomerulonephritis and thrombocytopenia that resulted in end-organ damages. The alteration of T_{FHC} cells has been reported in patients with various autoimmune diseases, such as rheumatoid arthritis, primary Sjogren's syndrome, juvenile dermatomyositis and autoimmune thyroid diseases, where T_{FHC} cells are present at a higher frequency and show positive correlation with serum autoantibody titer in the patients.[52–55] Overall, these observations suggest an important role for T_{FHC} cells in human autoimmunity. However, it should be noted that although T_{FHC} cells resemble T_{FH} cells in terms of ICOS and PD-1 expression, T_{FHC} cells in SLE patients do not express Bcl6 and IL-21 that are hallmarks of classic T_{FH} cells.[51] This discrepancy poses a pertinent question as to whether T_{FHC} and T_{FH} cells are indeed related. It may be that T_{FHC} cells are a subset of T_{FH} cells residing in the lymphoid organs that may downregulate Bcl6 while migrating to the systemic circulation as T_{FHC} cells. This is in accordance with the fact that T_{FH} cells may downregulate Bcl6 over weeks after antigenic challenge.[56] Recently, Morita *et al.*[52] shed light on the relationship between T_{FHC} ($CD4^+CXCR5^+$) and T_{FH} cells and convincingly demonstrated that T_{FHC} cells share functional, and to some extent phenotypic, properties of T_{FH} cells present in the lymphoid organs of humans and mice, and constitute a subset of circulating pool of memory T_{FH} cells. They found T_{FHC} cells to be potent at providing help for B-cell responses, such as production of plasmablasts and promotion of class switching through IL-21. Furthermore, T_{FHC} cells showed expression of ICOS and PD-1 but not Bcl6, similar to T_{FHC} cells in lupus patients.[52] Evidence from other recent studies also points toward a relationship between T_{FHC} and T_{FH} cells. The patients deficient in ICOS and CD40L lack T_{FHC} cells, whereas T_{FHC} cells expressing ICOS are overrepresented in SLE and rheumatoid arthritis patients.[10,51,53]

T_{FH} CELLS AND IMMUNODEFICIENCY

Immunodeficiency is a pathological condition where the immune response is compromised or absent. Defects in humoural immune response lead to the humoral immunodeficiencies, such as common variable immunodeficiency (CVID), X-linked hyper IgM syndrome (HIGM) and X-linked lymphoproliferative disease (XLP). The clinicopathological presentation of these diseases includes severely impaired humoral immune responses characterized by the absence of GC and altered production of antigen-specific memory B cells and antibodies.[57] The underlying etiology and molecular mechanisms of these diseases remain unclear. Recent studies have, however, implicated various genes such as ICOS, CD40L and SAP to be involved in pathogenesis of the diseases. Deficiency of ICOS or CD19 can cause CVID, whereas SAP deficiency results in XLP. HIGM develops as a result of the absence of CD40L. Mice that are deficient in ICOS, CD40L or SAP reflect clinical features similar to those of patients of the immunodeficiencies.[58]

Since ICOS, CD40L and SAP are highly expressed by T_H cells, especially T_{FH} cells, and that mutations in them can lead to altered development and/or function of T_H/T_{FH} cells, it is highly likely that T_{FH} cells play a critical role in humoral immunodeficiencies. Bossaller *et al.* recently studied the frequencies of $CXCR5^+$ T_{FH} cells in CVID patients and ICOS-deficient mice and found that $CXCR5^+$ T_{FH} cells were severely reduced in the peripheral blood of CVID patients compared with healthy individuals. Consistently, ICOS-deficient mice were significantly depleted of $CXCR5^+$ T_{FH} cells in the blood and lymphoid tissues, and that the lack of GC was associated with reduced numbers of $CXCR5^+$ T_{FH} cells in B-cell follicles.[10] Furthermore, deletions of CD19 can also cause CVID, which is characterized by defective B-cell responses and lack of T_{FH} cells.[59] Similar to these findings, individuals suffering from XLP and SAP-deficient mice also exhibit severely impaired B-cell responses with altered development and/or function of T_{FH} cells.[60] Ma *et al.* showed that XLP patients had reduced numbers of $CD4^+$ T cells compared with healthy individuals. The $CD4^+$ T cells produced lower quantities of IL-10 and failed to provide help for B-cell responses.[61] Similarly, mice deficient in SAP show severe functional defects in $CD4^+$ T cells as evidenced by their inability to confer long-lived humoral responses.[62] Studies further demonstrate that $CD4^+$ T-cell function in HIGM patients, which lack CD40L, is strictly compromised.[63]

T_{FH} CELLS AND LYMPHOMA

Emerging evidence supports the relationship between T_{FH} cells and lymphoma, particularly peripheral T-cell lymphoma (PTCL). PTCLs are a rare family of lymphomas with unfavorable prognosis. They may be classified into three types, anaplastic large-cell lymphoma, angioimmunoblastic T-cell lymphoma (AITL) and unspecified PTCL. AITL is the most widely studied type of PTCL, and thus considered as the prototype of T-cell lymphoma. Recent studies have suggested that T_{FH} cells and neoplastic AITL cells share the expression of many phenotypic markers, and that the AITL cells may be derived from T_{FH} cells.[64–68] Examples of these markers expressed by both T_{FH} cells and neoplastic AITL cells include Bcl6, CXCR5, PD-1, CD40L, OX40 and CXCL13. However, neoplastic AITL cells, in contrast to T_{FH} cells, express CD10, which is a cell surface zinc metalloendopeptidase expressed in a variety of normal and neoplastic tissues. Thus, CD10 may be used as a phenotypic marker to distinguish neoplastic AITL

cells from T_{FH} cells. More recently, the expression of T_{FH} cell markers (Bcl6, PD-1 and CXCL13) and CD10 has also been demonstrated in a subset of non-AITL PTCL, analogous to the neoplastic AITL cells.[11] In a recent study, de Leval *et al.*[69] using gene-expression profiling demonstrated that the AITL cells are characterized by the overexpression of several genes of normal T_{FH} cells, including CXCL13, Bcl6 and CD40L. Rodríguez Pinilla *et al.*[70] showed an atypical subset of primary cutaneous small/medium-sized pleomorphic $CD4^+$ T-cell lymphomas, which not only expressed T_{FH} cell markers, such as PD-1, CXCL13 and Bcl6, but also localized in vicinity of B cells, leading to the formation of clusters. Although these data support the derivation of the AITL cells from T_{FH} cells, the underlying molecular mechanism for neoplastic transformation of T_{FH} cells into AITL and primary cutaneous small/medium-sized pleomorphic $CD4^+$ T-cell lymphomas remains obscure.

Since T_{FH} cells are critical constituents of the micromilieu of B-cell lymphoma, and can influence the development of neoplastic B cells, they are likely to have an important role in development of B-cell lymphoma. This concept is supported by a recent study which described a population of T_{FH} cell-like cells in the vicinity of follicular lymphoma that develops from GC B cells. These cells shared surface markers of T_{FH} cells, such as CD4, CXCR5 and ICOS, and could be divided into two functionally distinct subpopulations, $CD4^+CXCR5^{hi}ICOS^{hi}CD25^+$ and $CD4^+CXCR5^{hi}ICOS^{hi}CD25^-$ T cells. In contrary to T_{FH} cells, the gene profiling of these cells showed that they expressed many genes, tumor necrosis factor, LTA, IL-4 and CD40LG, which are involved in the process of lymphoma development.[71]

CONCLUDING REMARKS

In recent years, significant advances have been made in understanding the immunobiology of T_{FH} cells and relevance of these cells with various diseases. T_{FH} cells have surfaced as a distinct subset of T_H cells that provide help to B cells, and play a critical role in generation and maintenance of humoroul immune responses. Emerging evidence also illustrates that the aberrations in T_{FH} function may lead to development of a variety of pathologies, such as autoimmune diseases, immunodeficiencies and lymphomas. A better understanding of the role of T_{FH} cells both in protective immunity and pathology is crucial for designing specific therapies for pathologies like autoimmune diseases and immunodeficiencies. For example, T_{FH} cell-associated molecules, such as PD-1, ICOS and CD40L may be interesting targets for treating autoimmunity and immunodeficiency. Suppressing the expression of these molecules may contain autoimmune responses, whereas promoting their expression may ameliorate immunodeficiency. Specifically, further studies are required to answer important mechanistic questions behind the T_{FH} cell-mediated development of pathologies and to address the potential to target T_{FH} cells:

1. What is the basis for the aberrations in T_{FH}-cell function and the subsequent development of pathologies in autoimmunity and immunodeficiency in the mouse models and patients?
2. What is the role of T_{FR} cells in controlling autoimmune diseases and what approaches can be taken to promote the role of these cells?
3. How to translate the knowledge on T_{FH} cells gained from mouse model studies into human autoimmune diseases and is it possible for circulating T_{FHC} cells to be a biomarker in disease diagnosis and treatment?

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