

Insights into the Role of Follicular Helper T Cells in Autoimmunity

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Follicular helper T (T_{FH}) cells are recently highlighted as their crucial role for humoral immunity to infection as well as their abnormal control to induce autoimmune disease. During an infection, naïve T cells are differentiating into T_{FH} cells which mediate memory B cells and long-lived plasma cells in germinal center (GC). T_{FH} cells are characterized by their expression of master regulator, Bcl-6, and chemokine receptor, CXCR5, which are essential for the migration of T cells into the B cell follicle. Within the follicle, crosstalk occurs between B cells and T_{FH} cells, leading to class switch recombination and affinity maturation. Various signaling molecules, including cytokines, surface molecules, and transcription factors are involved in T_{FH} cell differentiation. IL-6 and IL-21 cytokine-mediated STAT signaling pathways, including STAT1 and STAT3, are crucial for inducing Bcl-6 expression and T_{FH} cell differentiation. T_{FH} cells express important surface molecules such as ICOS, PD-1, IL-21, BTLA, SAP and CD40L for mediating the interaction between T and B cells. Recently, two types of microRNA (miRNA) were found to be involved in the regulation of T_{FH} cells. The miR-17-92 cluster induces Bcl-6 and T_{FH} cell differentiation, whereas miR-10a negatively regulates Bcl-6 expression in T cells. In addition, follicular regulatory T (T_{FR}) cells are studied as thymus-derived CXCR5⁺PD-1⁺Foxp3⁺T_{reg} cells that play a significant role in limiting the GC response. Regulation of T_{FH} cell differentiation and the GC reaction via miRNA and T_{FR} cells could be important regulatory mechanisms for maintaining immune

tolerance and preventing autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Here, we review recent studies on the various factors that affect T_{FH} cell differentiation, and the role of T_{FH} cells in autoimmune diseases.

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INTRODUCTION

CD4 helper T cells play a significant role in regulating adaptive immune responses against foreign antigens. Once activated by the antigen, they differentiate into various types of T cells, including Th1, Th2, Th17, Th9, and T_{reg} cells, depend on environmental cytokines to control antigen-specific immune responses. IL-6 and IL-21 contribute to follicular helper T (T_{FH}) cell differentiation when naïve T cells are stimulated with T cell Receptor (TcR) and co-stimulatory molecules such as ICOS and CD28 (1). T_{FH} cells are a distinct subset of T cells by expressing Bcl-6 and are localized to B cell follicle in lymphoid organs with critical roles in the mediation of humoral adaptive immunity (2,3).

Various cytokines, surface molecules, and transcription factors are reported to be involved in T_{FH} cell differentiation (Fig. 1). IL-6 and IL-21 are critical cytokines for T_{FH} cell differ-

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Abbreviations: T_{FH}, Follicular helper T cell; T_{FR}, Follicular regulatory T cell; Bcl-6, B cell lymphoma-6; GC, Germinal Center; PD-1, Programmed cell death protein 1; SAP, SLAM - associated protein; BTLA4, B- and T-lymphocyte attenuator 4; ROR, RAR-related orphan receptor; PSGL-1, P-selectin glycoprotein ligand-1; CCR7, C-C chemokine receptor type 7; SLE, Systemic Lupus Erythematosus; RA, Rheumatoid Arthritis

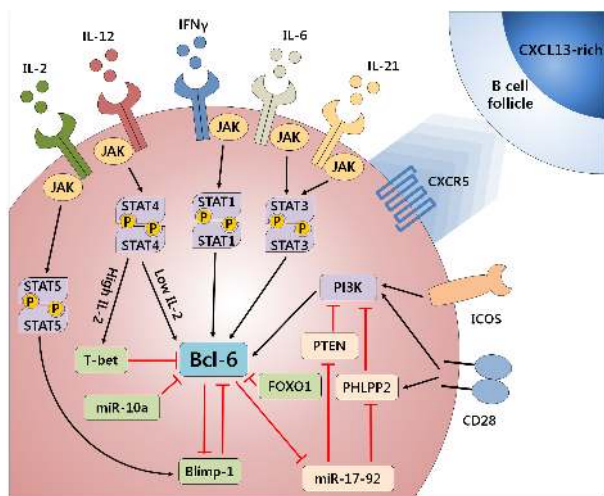


Figure 1. Molecular mechanisms of Bcl-6 expression in T cells. Bcl-6, the master regulator of T_{FH} cell differentiation is controlled by a complex signaling pathway. Co-stimulatory molecules such as CD28 and ICOS activate PI3K to induce Bcl-6 expression. PTEN, PHLPP2 inhibit Bcl-6 expression through interfering PI3K signaling and Foxo1 directly inhibits Bcl-6 expression. Various cytokines, such as IL-6, IL-21, IL-12, and IFN- γ induce Bcl-6 expression through JAK-STAT signaling pathway while high level of IL-2 in combination with IL-12 induces T-bet to inhibit Bcl-6. Blimp-1 and Bcl-6 is reciprocally regulating each other to make a decision of effector T cell fate between T_{FH} and non-T_{FH} effector cells. Some miRNA such as miR-17-92 induces Bcl-6 expression by interfering phosphatases, which inhibit PI3K signaling pathway while miR-10a directly inhibits Bcl-6 expression.

entiation (4). Surface molecules, including ICOS, CD40L, PD-1, BTLA, and SAP are also important for T_{FH} cell differentiation and their functions (5). Inhibiting the interaction between CD40 and CD40L, or deficiency of ICOS or its ligand causes defects in formation of the germinal center (GC) (6) and T_{FH} cell differentiation (7,8). In addition, SAP contributes to T_{FH} cell differentiation by maintaining stable T and B cell interaction (6,9). Cytokine- and co-stimulatory molecule-mediated signaling pathways are essential for expression of the transcription factor B cell lymphoma-6 (Bcl-6), which is the master regulator of T_{FH} cell differentiation and is inhibited by the antagonizing transcription factor Blimp-1. Expression of Bcl-6 and Blimp-1 is reciprocally regulated during T cell differentiation (1).

Bcl-6-deficient T cells failed to differentiate into T_{FH} cells and the GC responses are hardly developed, demonstrating the absolute requirement for Bcl-6 (2,3). T_{FH} cell differentiation program involves a dramatic change in surface expression of chemokine receptors. Reciprocal up-regulation of CXCR5 and down-regulation of

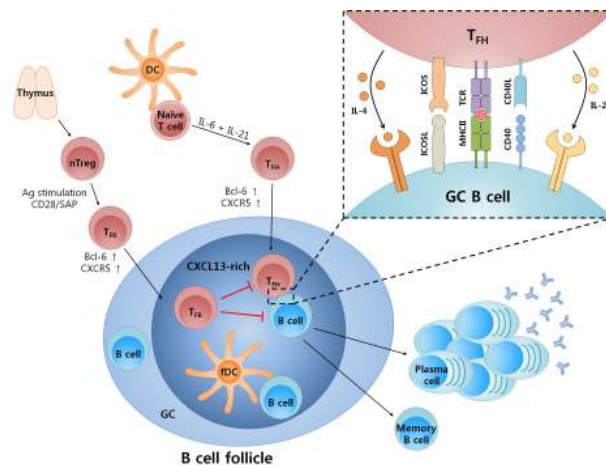


Figure 2. Germinal center reaction controlled by T_{FH} and T_{FR} cells. Naive T cells following stimulation with TcR and co-stimulatory molecules with IL-6 and IL-21 by dendritic cells can differentiate into T_{FH} cells and migrate to the CXCL13-rich B cell follicle region. In the B cell follicle, T_{FH} cells interact with B cells via TcR and co-stimulatory molecules such as ICOS and CD40L. Upon interaction between T_{FH} cells and B cells, IL-4 and IL-21 from T_{FH} cells allow B cells to differentiate into memory B cells or plasma cells, which are involved in long-lasting antibody production. T_{FR} cells derived from nT_{reg} precursor cells from the thymus by expressing Bcl-6 and CXCR5 migrate to B cell follicle and inhibit both T_{FH} cell and B cell function.

CCR7 enables T_{FH} cells to migrate into B cell follicles by responding to CXCL13, the ligand of CXCR5 (10-12). Inside of B cell follicles, T_{FH} cells provide B cell help signals by expressing co-stimulatory molecules and secreting cytokines such as IL-4 and IL-21, which are essential for germinal center B cells to undergo class switch recombination, somatic hyper-mutation, affinity maturation, and differentiation of plasma cells and memory B cells in the GC (13-15).

Recently, it was reported that some microRNAs (miRNAs) have a regulatory role in T_{FH} cell differentiation and the GC reaction. The miR-17-92 cluster acts as a positive regulator of T_{FH} cell differentiation via suppression of phosphatases that inhibits ICOS-mediated PI3K signaling pathways (16). In addition, the miR-17-92 cluster represses the expression of ROR α , which induces inappropriate gene expression during T_{FH} cell differentiation (17). By contrast, miR-10a directly inhibits Bcl-6 expression (18), which strongly indicating that miRNAs are involved in dynamic regulation of T_{FH} differentiation.

If the GC reaction mediated by T_{FH} cells is dysregulated or if autoreactive T and B cells are activated, high levels of autoantibody can be accumulated through abnormal GC formation, which contributes to the development of autoimmune

diseases (19). Thus, T_{FH} cells should be tightly regulated to prevent autoimmunity by limiting germinal center reactions to self antigen (20). Recently, follicular regulatory T (T_{FR}) cells expressing CXCR5 were demonstrated to limit the GC reaction and reduce antibody production by migrating into B cell follicles (21). The regulation of germinal center reaction by T_{FH} and T_{FR} cells for normal immunity is summarized as figure (Fig. 2).

In this review, we discuss the function of cytokines, transcription factors, and signaling pathways related to the differentiation or characteristics of T_{FH} cells. Additionally, we discuss the role of the GC reaction related to T_{FH} and T_{FR} cells in the maintenance of immune homeostasis and provide both a better understanding of the importance of T_{FH} cells in autoimmunity and their clinical relevance in human autoimmune diseases.

SIGNALING PATHWAYS REQUIRED FOR T_{FH} CELL DIFFERENTIATION

ICOS, PI3K, and Foxo1

It has been reported that a strong interaction between the TcR and major histocompatibility complex (MHC) class II molecules triggers T_{FH} cell differentiation, which indicates that a strong TcR signal is essential for T_{FH} cell differentiation (22). In addition, among surface co-stimulatory molecules being expressed by T_{FH} cells, ICOS is induced when CD4 T cells become activated by recognizing antigen through TcRs, which then interact with ICOS-L that is expressed on B cells (7,11,23,24). Its binding to the ligand ICOS-L triggers activation signals in a similar way to other members of CD28 family co-stimulatory receptors (25,26). ICOS plays a significant role in increasing T cell proliferation and the production of cytokines, including IL-21 and IL-4 (11,27,28).

ICOS-mediated PI3K activation is crucial for T_{FH} cell differentiation, as a point mutation on the cytoplasmic tail of ICOS, where PI3K binds to and activates, led to a severely impaired T_{FH} cell differentiation of CD4 T cells (28). In contrast, overexpression of ICOS is sufficient to maintain T_{FH} cells in CD28-deficient mice (7). Among PI3K subunit p110 γ appears to convey ICOS-mediated T_{FH} cell differentiation signaling pathway, as p110 γ deficiency resulted in a defective T_{FH} cell differentiation, further strongly indicating that ICOS and PI3K are important for either differentiation or survival of T_{FH} cells. These results imply that ICOS-mediated PI3K signaling is crucial for the differentiation of T_{FH} cells (25). Moreover,

Heping et al. reported that ICOS signaling is critical for motility of T_{FH} cells into the B cell follicle in a Bcl-6 independent manner (29).

PI3K signaling pathways following TcR and co-stimulation regulate the phosphorylation of Foxo1 to relocate it from the nucleus to the cytoplasm (30,31). A recent study revealed that Foxo1 negatively regulates T cell activation and contributes to T cell tolerance (32). Foxo1-deficient CD4 T cells contribute to the development of autoimmune phenotypes including increased autoantibody production with reduced Foxp3⁺ regulatory T cell development and function, and augmented generation of T_{FH} cells and GC formation. In addition, the presence of Foxo-binding elements has been identified in the promoter region of Bcl-6 (33), which suggests that Foxo1 might act as a transcriptional repressor of Bcl-6 and, if so, Foxo1 might negatively regulate T_{FH} differentiation. Thus, ICOS and PI3K signaling is crucial for T_{FH} differentiation and Foxo1 could be a regulator of GC reaction.

IL-21, IL-6, and STATs

IL-6 and IL-21 are well-known pro-inflammatory cytokines with important roles in Bcl-6 expression and T_{FH} cell differentiation (4). IL-21 induces B cell proliferation and class switch recombination and IL-21R is required for antibody response and GC formation (34). The IL-6-mediated STAT3 activation is also important for IL-21 expression in human and mouse naïve CD4 T cells upon TcR stimulation (35,36). STAT3 is phosphorylated by JAK upon IL-6 stimulation, and activated STAT3 was shown to bind to Bcl-6 in T cells (33). IL-6 is an important factor for Bcl-6 induction in CD4 T cells during dendritic cell priming stage of CD4 T cell activation (37). However, other signaling pathways could compensate for IL-6 dependent T_{FH} differentiation pathway, as T_{FH} cells are normally found at the peak of the immune response to infection and immunization (38,39). IL-6 signaling is required for IL-21 expression via c-Maf (40-42). Once being produced, IL-21 further increases its own production through a positive feedback mechanism (43).

Augmented IL-21 was reported to induce the expression of the master regulator for T_{FH} cell differentiation, Bcl-6 (44), while controversies exist whether IL-21 is a critical factor for Bcl-6 induction in CD4 T cells (37-39). At a downstream level, Choi et al. showed that IL-6-mediated STAT1 signaling can also prime T_{FH} cells by compensating for STAT3 and inducing Bcl-6 expression. Another recent study demonstrated that IL-12-mediated STAT4 signaling can induce expression of

both Bcl-6 and T-bet, and T-bet inhibits the function of Bcl-6 (45). The balance between T-bet and Bcl-6 expression might be regulated by IL-2 concentration (33). Furthermore, IFN- γ was accounted to lead to abnormal T_{FH} cell differentiation in the sanroque mouse model (46). Given that IFN- γ induced Bcl-6 via pSTAT1 which binds to an IRE in an exon of Bcl-6 (47), IFN- γ could function as a positive regulator by directly inducing Bcl-6 expression in CD4 T cells. This supported by recent study by Lee et al., which demonstrated that T cell specific deletion of IFN- γ R resulted in decreased T_{FH} cell differentiation in sanroque mice (46). Further studies are needed to clarify how this complex cytokine network regulates Bcl-6 expression and T_{FH} cell differentiation.

Bcl-6 and Blimp-1

The zinc-finger-containing transcriptional repressor Bcl-6 was originally described as a key molecule in GC formation and B cell response (48,49). Bcl-6-deficient mice cannot develop somatic hyper-mutation in B cell, result impaired GC formation (50,51). In addition, B cells from these mice do not undergo affinity maturation, somatic hyper-mutation, and class switch recombination of immunoglobulin (49). Recently, Bcl-6 was identified as a crucial factor for T_{FH} cell differentiation (3). Bcl-6-deficient mice show impaired T_{FH} cell differentiation (2) and non-T_{FH} CD4 T cells do not express increased levels of Bcl-6 (2,52). Bcl-6 directly inhibits a number of transcription factors, including T-bet and ROR γ t, which are key modulators of differentiation of Th1 and Th17 cells, respectively (3). Bcl-6 also inhibits expression of CCR7 and PSGL-1, which negatively regulate the migration of T cells into B cell follicles (39,53). Moreover, Bcl-6 regulates the expression of various T_{FH} cell-related molecules, including ICOS, PD-1, PTLA, CD200, and SAP (23). Turner et al. identified the mouse form of Blimp-1, which is induced by cytokine-mediated B cell differentiation (54). Recent studies reported that the transcription factor Blimp-1 has an antagonistic role of Bcl-6 (1,52,55) and inhibits T_{FH} cell differentiation (1). Blimp-1 is highly expressed in non-T_{FH} effector T cells such as Th1, Th2, and Th17 cells (1,52), whereas Bcl-6 is highly expressed only in T_{FH} cells. Moreover, constitutive expression of Blimp-1 inhibited T_{FH} cell formation (1) and Blimp-1 is important for terminal differentiation of both CD4⁺ and CD8⁺ T cells, which is characterized by high levels of effector molecule secretion and low proliferative potential (52). IL-2 mediated STAT5 signaling in activated CD4⁺ T cells induces expression of Blimp-1, which suppresses Bcl-6 and

T_{FH} cell differentiation (56). High level of IL-2, especially in effector Th1 cells, induces T-bet, which also inhibits Bcl-6 expression and T_{FH} cell differentiation (33). Th1 cells might have the flexibility to regulate the expression of T-bet and Bcl-6 depending on environmental conditions (33). IL-6- and IL-21-mediated STAT3 signaling can also induce Blimp-1 or Bcl-6 (57) through the participation of additional transcription factors (5). To summarize, effector T cell fate seems to rely on the expression of Bcl-6 or Blimp-1 and they are reciprocally inhibit each other via complex signaling pathway, eventually act as a decision maker between T_{FH} cell and other effector T cell differentiation.

REGULATION OF T_{FH} CELL DIFFERENTIATION VIA T_{FR} CELL AND miRNA

Follicular regulatory T cells

Foxp3-expressing regulatory T (T_{reg}) cells contribute to the maintenance of immune tolerance by suppressing the dysregulated immune response to self-antigens (58). Scurfy mice without Foxp3⁺ T cells demonstrate severe systemic autoimmune phenotype. In addition, CD4 T cells isolated from scurfy mouse are hyper-responsive to TcR stimulation (59,60).

It has been recently reported that the mice with CXCR5-deficient T_{reg} cells have more GC with augmented immunoglobulin production owing to the limited capability of these cells to migrate into B cell follicular region. This suggests that CXCR5 expression of T_{reg} cells is crucial for regulation of the GC reaction (61). In addition, T_{reg} cells expressing Bcl-6 and CXCR5, which originate from CXCR5- natural T_{reg} cell precursors, are found in GC (21). In the absence of CXCR5⁺Bcl-6⁺ T_{reg} cells, the GC reaction was not controlled efficiently leading to enhanced immunoglobulin production and increased B cell population in GCs. This result implies that T_{reg} cells expressing CXCR5 have important roles in regulation of the GC reaction. T_{reg} cells in GC are called follicular regulatory T (T_{FR}) cells, which share characteristics of both T_{FH} and T_{reg} cells since Bcl-6, CD28 and SAP also affect development of T_{FR} cells. 5~25% of T_{FH} cells expressing CXCR5 and PD-1 are also Foxp3⁺ T_{FR} cells and are located in the B cell follicle region (62). Recent study demonstrated that lack of the PD-1-PD-L1 pathway induced increase of T_{FR} cells and its suppressive ability, suggesting the regulatory role of PD-1 in the differentiation of T_{FR} cells (63). Co-transfer experiments with thymus-derived Foxp3⁺ CD4 T cells and Foxp3⁻ CD4 T cells into recipient demonstrated that Foxp3⁺

CD4 T cells become T_{FR} cells in mice immunized with antigen suggesting T_{FR} cells are derived from T_{reg} cell precursors. A recent study demonstrated Ag-specific antibody production was increased in the mice with Bcl-6-deficient T_{reg} cells (21). Furthermore, increased levels of high affinity antibody, plasma cells, and memory B cells are found in the mice demonstrating that T_{FR} cells expressing Bcl-6 control the GC reaction including plasma cell production and affinity maturation. By contrast, Blimp-1 down-regulates the number of T_{FR} cells, suggesting that Bcl-6 and Blimp-1 also reciprocally regulate differentiation of T_{FH} and T_{FR} cells to control the GC reaction (1). T_{FR} cells therefore seem to play a crucial role in the maintenance of immune tolerance, preventing autoimmune response by inhibiting the GC reaction and antibody production.

micro RNAs

miRNAs are functional single stranded RNAs (ssRNAs), which are encoded endogenously, and are involved in immune cell development and differentiation (64,65). Recent study reported that the miR-17-92 cluster was regulated by Bcl-6 in CD4 T cells (3). T cells overexpressing Bcl-6 demonstrated diminished expression of the miR-17-92 cluster, as do T_{FH} cells, which, suppresses the expression of CXCR5. However, several studies have shown that the miRNA-17-92 cluster induces T_{FH} cell differentiation (16,17). T cell specific miR-17-92 transgenic mice demonstrate spontaneous Bcl-6 expression, T_{FH} cell differentiation, and GC formation (16). In contrast, miR-17-92-deficient mice show impaired T_{FH} cell differentiation during acute and chronic virus infection. The miR-17-92 cluster induces T_{FH} cell differentiation through suppression of PTEN and PHLPP2 expression, which regulate the ICOS-PI3K pathway. The miR-17-92 cluster also directly inhibits expression of ROR α , which is involved in gene expression of non-T_{FH} effector T cell differentiation (17). In addition, miR-10a, which is specifically expressed in T_{reg} cells by TGF- β and retinoic acid, directly suppresses Bcl-6 expression (18). Some induced-T_{reg} (iT_{reg}) cells migrate to GC in Peyer's patch and have T_{FH}-like phenotypes, miR-10a expression is down-regulated in these iT_{reg} cells and overexpression of miR-10a significantly inhibits the conversion of iT_{reg} into T_{FH}-like cells. More studies on the role of T_{FR} cells and miRNA in T_{FH} differentiation are needed to improve our understanding on dynamic regulation of germinal center reaction.

T_{FH} CELLS IN AUTOIMMUNE DISEASES

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease with a complex phenotype that includes systemic inflammation, fever, fatigue, and chills (66). Diagnosis of SLE is very difficult because its phenotype overlaps with other diseases. Recent studies have suggested that the pathogenesis of SLE is profoundly related to T_{FH} cells (44,67,68). Spontaneous GC formation and autoantibody production have been reported in many mouse models of SLE (44,67), suggesting that T_{FH} cells might be associated with pathogenesis of SLE. Indeed, recent studies demonstrated that T_{FH} cell differentiation is spontaneously induced in these mouse models (44,67,68). Also, dysregulated T_{FH} cell activity contributes to the pathogenesis of SLE through aberrant GC formation and massive production of autoantibodies, such as anti-dsDNA and ANA. T_{FH} cells induce these phenomena via cytokines and co-stimulatory molecules which stimulate B cells (69,70). Autoimmune phenotypes were alleviated when T_{FH} cell differentiation was inhibited in sanroque mice, which have increased GC formation and T_{FH} cell differentiation (70). Linterman et al. crossed sanroque mice with IL-21- or SAP-deficient mice, or mice heterozygous for Bcl-6 to examine the role of Bcl-6 in development of the lupus-like phenotype (71). They found that the deficiencies of Bcl-6 or SAP ameliorate the lupus-like phenotype in sanroque mice IL-21 independently. However, lupus-like autoimmune phenotypes were reduced in another study when IL-21 signaling is not present in BXS_B-Yaa mice, another mouse model of human SLE (72), recapitulating the complexity of pathogenesis of SLE in human. Remarkably, IL-21 expression was up-regulated in SLE patients than in healthy controls (73), and elevated production of T_{FH} relating factors such as CXCL13, BAFF were reported in human SLE patients (74). These results suggest that abnormal T_{FH} cell differentiation strongly related to SLE pathogenesis.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disorder, which is recently studied that it is associated with dysregulated T_{FH} cell differentiation. Deborah et al. found that blockade of IL-21 signaling by IL-21R-Fc fusion protein treatment reduces disease severity in mouse and rat RA models (75). Furthermore, IL-21 blockade in animal models results in decreased IL-6 expression. A recent study by Victoratos et al. found that

T_{FH} cells have a critical role in the maintenance of follicular dendritic cell (FDC)-mediated GC formation and autoantibody production in KRN/B mice that spontaneously develop RA (76,77). In addition, Jang et al. reported that IL-21 receptor-deficient KBx/N mice have less severe RA with reduced T_{FH} cell population in draining lymph node (43). An IL-21R-Fc fusion protein that inhibits IL-21 signaling can delay disease onset and progression. Platt et al. also found increased T_{FH} cells and antibody production in an OVA-induced RA mouse model (78). In this study, they showed that abatacept, a fusion protein composed of the Fc region of IgG and the extracellular domain of CTLA-4 has a role in regulation of T_{FH} cell differentiation in OVA-induced RA mouse models. In human RA patients, up-regulated IL-21 level was reported with increased T_{FH}-like cells that enhanced IL-21R expression (79). This increased T_{FH}-like cells population correlated with enhanced 28-joint count disease activity score and anti-CCP antibody, which indicate disease severity.

Synthetically, T_{FH} cells seem to be involved in the pathogenesis of human autoimmune diseases such as SLE, RA, etc., therefore, regulation of T_{FH} cell differentiation could be an important strategy for the suppression of autoimmune diseases.

CONCLUSION

Recently, characterization of T_{FH} cells and germinal center reaction has been highlighted in immunology field that T_{FH} cells have crucial roles in B cell response in adaptive immunity. IL-6 and IL-21 signaling induce expression of CXCR5, which enables the migration of T cells into B cell follicles with expressing Bcl-6, a master transcription factor for T_{FH} cell differentiation. These characteristics of T_{FH} cells distinguish them from other helper T cells. T_{FH} cells can induce affinity maturation, somatic hyper-mutation which mediate memory B cells and long-lived plasma cells with increased germinal centers. However, abnormally activated T_{FH} cell function give rise to an immune reaction against auto-antigens, and subsequently could trigger autoimmune diseases such as SLE, RA, etc. There are several ways including miRNAs, T_{FR} cells, and IL-21 blockade to potentially correct abnormal germinal center reaction by negatively regulating aberrant T_{FH} cell differentiation. Through better understanding of current knowledge of T_{FH} cell mediated dynamic germinal center reaction, we hope to discover novel therapeutic approaches by targeting T_{FH} cells in human autoimmune diseases.

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CONFLICT OF INTEREST

The authors have no financial conflicts of interest to declare.

REFERENCES

1. Johnston, R. J., A. C. Poholek, D. DiToro, I. Yusuf, D. Eto, B. Barnett, A. L. Dent, J. Craft, and S. Crotty. 2009. Bcl6 and Blimp-1 are reciprocal and antagonistic regulators of T follicular helper cell differentiation. *Science* 325: 1006-1010.
2. Nurieva, R. I., Y. Chung, G. J. Martinez, X. O. Yang, S. Tanaka, T. D. Matskevitch, Y. H. Wang, and C. Dong. 2009. Bcl6 mediates the development of T follicular helper cells. *Science* 325: 1001-1005.
3. Yu, D., S. Rao, L. M. Tsai, S. K. Lee, Y. He, E. L. Sutcliffe, M. Srivastava, M. Linterman, L. Zheng, N. Simpson, J. I. Ellyard, I. A. Parish, C. S. Ma, Q. J. Li, C. R. Parish, C. R. Mackay, and C. G. Vinuesa. 2009. The transcriptional repressor Bcl-6 directs T follicular helper cell lineage commitment. *Immunity* 31: 457-468.
4. Nurieva, R. I., Y. Chung, D. Hwang, X. O. Yang, H. S. Kang, L. Ma, Y. H. Wang, S. S. Watowich, A. M. Jetten, Q. Tian, and C. Dong. 2008. Generation of T follicular helper cells is mediated by interleukin-21 but independent of T helper 1, 2, or 17 cell lineages. *Immunity* 29: 138-149.
5. Crotty, S. 2011. Follicular helper CD4 T cells (TFH). *Annu. Rev. Immunol.* 29: 621-663.
6. Qi, H., J. L. Cannons, F. Klauschen, P. L. Schwartzberg, and R. N. Germain. 2008. SAP-controlled T-B cell interactions underlie germinal centre formation. *Nature* 455: 764-769.
7. Dong, C., U. A. Temann, and R. A. Flavell. 2001. Cutting edge: critical role of inducible costimulator in germinal center reactions. *J. Immunol.* 166: 3659-3662.
8. Iwai, H., M. Abe, S. Hirose, F. Tsushima, K. Tezuka, H. Akiba, H. Yagita, K. Okumura, H. Kohsaka, N. Miyasaka, and M. Azuma. 2003. Involvement of inducible costimulator-B7 homologous protein costimulatory pathway in murine lupus nephritis. *J. Immunol.* 171: 2848-2854.
9. Lu, K. T., Y. Kanno, J. L. Cannons, R. Handon, P. Bible, A. G. Elkhouloun, S. M. Anderson, L. Wei, H. Sun, J. J. O'Shea, and P. L. Schwartzberg. 2011. Functional and epigenetic studies reveal multistep differentiation and plasticity of *in vitro*-generated and *in vivo*-derived follicular T helper cells. *Immunity* 35: 622-632.
10. Breitfeld, D., L. Ohl, E. Kremmer, J. Ellwart, F. Sallusto, M. Lipp, and R. Förster. 2000. Follicular B helper T cells express CXC chemokine receptor 5, localize to B cell follicles, and support immunoglobulin production. *J. Exp. Med.* 192: 1545-1552.

11. Schaerli, P., K. Willmann, A. B. Lang, M. Lipp, P. Loetscher, and B. Moser. 2000. CXC chemokine receptor 5 expression defines follicular homing T cells with B cell helper function. *J. Exp. Med.* 192: 1553-1562.
12. Balkwill, F. 2004. Cancer and the chemokine network. *Nat. Rev. Cancer* 4: 540-550.
13. Jacob, J., G. Kelsoe, K. Rajewsky, and U. Weiss. 1991. Intraclonal generation of antibody mutants in germinal centres. *Nature* 354: 389-392.
14. Berek, C., A. Berger, and M. Apel. 1991. Maturation of the immune response in germinal centers. *Cell* 67: 1121-1129.
15. Liu, Y. J., F. Malisan, O. de Bouteiller, C. Guret, S. Lebecque, J. Banchereau, F. C. Mills, E. E. Max, and H. Martinez-Valdez. 1996. Within germinal centers, isotype switching of immunoglobulin genes occurs after the onset of somatic mutation. *Immunity* 4: 241-250.
16. Kang, S. G., W. H. Liu, P. Lu, H. Y. Jin, H. W. Lim, J. Shepherd, D. Fremgen, E. Verdin, M. B. Oldstone, H. Qi, J. R. Teijaro, and C. Xiao. 2013. MicroRNAs of the miR-17 approximately 92 family are critical regulators of T(FH) differentiation. *Nat. Immunol.* 14: 849-857.
17. Baumjohann, D., R. Kageyama, J. M. Clingan, M. M. Morar, S. Patel, D. de Kouchkovsky, O. Bannard, J. A. Bluestone, M. Matloubian, K. M. Ansel, and L. T. Jeker. 2013. The microRNA cluster miR-17-92 promotes T_{FH} cell differentiation and represses subset-inappropriate gene expression. *Nat. Immunol.* 14: 840-848.
18. Takahashi, H., T. Kanno, S. Nakayamada, K. Hirahara, G. Sciumè, S. A. Muljo, S. Kuchen, R. Casellas, L. Wei, Y. Kanno, and J. J. O'Shea. 2012. TGF-beta and retinoic acid induce the microRNA miR-10a, which targets Bcl-6 and constrains the plasticity of helper T cells. *Nat. Immunol.* 13: 587-595.
19. Vinuesa, C. G. and M. C. Cook. 2001. The molecular basis of lymphoid architecture and B cell responses: implications for immunodeficiency and immunopathology. *Curr. Mol. Med.* 1: 689-725.
20. King, C., S. G. Tangye, and C. R. Mackay. 2008. T follicular helper (TFH) cells in normal and dysregulated immune responses. *Annu. Rev. Immunol.* 26: 741-766.
21. Chung, Y., S. Tanaka, F. Chu, R. I. Nurieva, G. J. Martinez, S. Rawal, Y. H. Wang, H. Lim, J. M. Reynolds, X. H. Zhou, H. M. Fan, Z. M. Liu, S. S. Neelapu, and C. Dong. 2011. Follicular regulatory T cells expressing Foxp3 and Bcl-6 suppress germinal center reactions. *Nat. Med.* 17: 983-988.
22. Fazilleau, N., L. J. McHeyzer-Williams, H. Rosen, M. G. McHeyzer-Williams. 2009. The function of follicular helper T cells is regulated by the strength of T cell antigen receptor binding. *Nat. Immunol.* 10: 375-384.
23. Chtanova, T., S. G. Tangye, R. Newton, N. Frank, M. R. Hodge, M. S. Rolph, and C. R. Mackay. 2004. T follicular helper cells express a distinctive transcriptional profile, reflecting their role as non-Th1/Th2 effector cells that provide help for B cells. *J. Immunol.* 173: 68-78.
24. Choi, Y. S., R. Kageyama, D. Eto, T. C. Escobar, R. J. Johnston, L. Monticelli, C. Lao, and S. Crotty. 2011. ICOS receptor instructs T follicular helper cell versus effector cell differentiation via induction of the transcriptional repressor Bcl6. *Immunity* 34: 932-946.
25. McAdam, A. J., T. T. Chang, A. E. Lumelsky, E. A. Greenfield, V. A. Boussiotis, J. S. Duke-Cohan, T. Chernova, N. Malenkovich, C. Jabs, V. K. Kuchroo, V. Ling, M. Collins, A. H. Sharpe, and G. J. Freeman. 2000. Mouse inducible costimulatory molecule (ICOS) expression is enhanced by CD28 costimulation and regulates differentiation of CD4⁺ T cells. *J. Immunol.* 165: 5035-5040.
26. Hutloff, A., A. M. Dittrich, K. C. Beier, B. Eljaschewitsch, R. Kraft, I. Anagnostopoulos, and R. A. Kroczeck. 1999. ICOS is an inducible T-cell co-stimulator structurally and functionally related to CD28. *Nature* 397: 263-266.
27. Vogelzang, A., H. M. McGuire, D. Yu, J. Sprent, C. R. Mackay, and C. King. 2008. A fundamental role for interleukin-21 in the generation of T follicular helper cells. *Immunity* 29: 127-137.
28. Gigoux, M., J. Shang, Y. Pak, M. Xu, J. Choe, T. W. Mak, and W. K. Suh. 2009. Inducible costimulator promotes helper T-cell differentiation through phosphoinositide 3-kinase. *Proc. Natl. Acad. Sci. USA* 106: 20371-20376.
29. Xu, H., X. Li, D. Liu, J. Li, X. Zhang, X. Chen, S. Hou, L. Peng, C. Xu, W. Liu, L. Zhang, and H. Qi. 2013. Follicular T-helper cell recruitment governed by bystander B cells and ICOS-driven motility. *Nature* 496: 523-527.
30. Brunet, A., A. Bonni, M. J. Zigmond, M. Z. Lin, P. Juo, L. S. Hu, M. J. Anderson, K. C. Arden, J. Blenis, and M. E. Greenberg. 1999. Akt promotes cell survival by phosphorylating and inhibiting a Forkhead transcription factor. *Cell* 96: 857-868.
31. Yuan, T. L. and L. C. Cantley. 2008. PI3K pathway alterations in cancer: variations on a theme. *Oncogene* 27: 5497-5510.
32. Kerdiles, Y. M., E. L. Stone, D. R. Beisner, M. A. McGargill, I. L. Ch'en, C. Stockmann, C. D. Katayama, and S. M. Hedrick. 2010. Foxo transcription factors control regulatory T cell development and function. *Immunity* 33: 890-904.
33. Oestreich, K. J., S. E. Mohn, and A. S. Weinmann. 2012. Molecular mechanisms that control the expression and activity of Bcl-6 in TH1 cells to regulate flexibility with a TFH-like gene profile. *Nat. Immunol.* 13: 405-411.
34. Spolski, R. and W. J. Leonard. 2008. Interleukin-21: basic biology and implications for cancer and autoimmunity. *Annu. Rev. Immunol.* 26: 57-79.
35. Diehl, S. A., H. Schmidlin, M. Nagasawa, B. Blom, and H. Spits. 2012. IL-6 Triggers IL-21 production by human CD4(+) T cells to drive STAT3-dependent plasma cell differentiation in B cells. *Immunol. Cell Biol.* 90: 802-811.
36. Eddahri, F., S. Denanglaire, F. Bureau, R. Spolski, W. J. Leonard, O. Leo, and F. Andris. 2009. Interleukin-6/STAT3 signaling regulates the ability of naive T cells to acquire B-cell help capacities. *Blood* 113: 2426-2433.
37. Choi, Y. S., D. Eto, J. A. Yang, C. Lao, and S. Crotty. 2013. Cutting edge: STAT1 is required for IL-6-mediated Bcl6 induction for early follicular helper cell differentiation. *J. Immunol.* 190: 3049-3053.
38. Eto, D., C. Lao, D. DiToro, B. Barnett, T. C. Escobar, R. Kageyama, I. Yusuf, and S. Crotty. 2011. IL-21 and IL-6 are critical for different aspects of B cell immunity and redundantly induce optimal follicular helper CD4 T cell (T_{fh})

- differentiation. *PLoS One* 6: e17739.
39. Poholek, A. C., K. Hansen, S. G. Hernandez, D. Eto, A. Chandele, J. S. Weinstein, X. Dong, J. M. Odegard, S. M. Kaech, A. L. Dent, S. Crotty, and J. Craft. 2010. *In vivo* regulation of Bcl6 and T follicular helper cell development. *J. Immunol.* 185: 313-326.
 40. Takeda, K., T. Kaisho, N. Yoshida, J. Takeda, T. Kishimoto, and S. Akira. 1998. Stat3 activation is responsible for IL-6-dependent T cell proliferation through preventing apoptosis: generation and characterization of T cell-specific Stat3-deficient mice. *J. Immunol.* 161: 4652-4660.
 41. Nurieva, R., X. O. Yang, G. Martinez, Y. Zhang, A. D. Panopoulos, L. Ma, K. Schluns, Q. Tian, S. S. Watowich, A. M. Jetten, and C. Dong. 2007. Essential autocrine regulation by IL-21 in the generation of inflammatory T cells. *Nature* 448: 480-483.
 42. Yang, Y., J. Ochando, A. Yopp, J. S. Bromberg, and Y. Ding. 2005. IL-6 plays a unique role in initiating c-Maf expression during early stage of CD4 T cell activation. *J. Immunol.* 174: 2720-2729.
 43. Jang, E., S. H. Cho, H. Park, D. J. Paik, J. M. Kim, and J. Youn. 2009. A positive feedback loop of IL-21 signaling provoked by homeostatic CD4⁺CD25⁻ T cell expansion is essential for the development of arthritis in autoimmune K/BxN mice. *J. Immunol.* 182: 4649-4656.
 44. Ozaki, K., R. Spolski, R. Ettinger, H. P. Kim, G. Wang, C. F. Qi, P. Hwu, D. J. Shaffer, S. Akilesh, D. C. Roopenian, H. C. Morse, 3rd, P. E. Lipsky, and W. J. Leonard. 2004. Regulation of B cell differentiation and plasma cell generation by IL-21, a novel inducer of Blimp-1 and Bcl-6. *J. Immunol.* 173: 5361-5371.
 45. Nakayamada, S., Y. Kanno, H. Takahashi, D. Jankovic, K. T. Lu, T. A. Johnson, H. W. Sun, G. Vahedi, O. Hakim, R. Handon, P. L. Schwartzberg, G. L. Hager, and J. J. O'Shea. 2011. Early Th1 cell differentiation is marked by a Th cell-like transition. *Immunity* 35: 919-931.
 46. Lee, S. K., D. G. Silva, J. L. Martin, A. Pratama, X. Hu, P. P. Chang, G. Walters, and C. G. Vinuesa. 2012. Interferon-gamma excess leads to pathogenic accumulation of follicular helper T cells and germinal centers. *Immunity* 37: 880-892.
 47. Zhou, G. and S. J. Ono. 2005. Induction of BCL-6 gene expression by interferon-gamma and identification of an IRE in exon I. *Exp. Mol. Pathol.* 78: 25-35.
 48. Dent, A. L., A. L. Shaffer, X. Yu, D. Allman, and L. M. Staudt. 1997. Control of inflammation, cytokine expression, and germinal center formation by BCL-6. *Science* 276: 589-592.
 49. Klein, U. and R. Dalla-Favera. 2008. Germinal centres: role in B-cell physiology and malignancy. *Nat. Rev. Immunol.* 8: 22-33.
 50. Ye, B. H., G. Cattoretti, Q. Shen, J. Zhang, N. Hawe, R. de Waard, C. Leung, M. Nouri-Shirazi, A. Orazi, R. S. Chaganti, P. Rothman, A. M. Stall, P. P. Pandolfi, and R. Dalla-Favera. 1997. The BCL-6 proto-oncogene controls germinal-centre formation and Th2-type inflammation. *Nat. Genet.* 16: 161-170.
 51. Toyama, H., S. Okada, M. Hatano, Y. Takahashi, N. Takeda, H. Ichii, T. Takemori, Y. Kuroda, and T. Tokuhiya. 2002. Memory B cells without somatic hypermutation are generated from Bcl6-deficient B cells. *Immunity* 17: 329-339.
 52. Crotty, S., R. J. Johnston, and S. P. Schoenberger. 2010. Effectors and memories: Bcl-6 and Blimp-1 in T and B lymphocyte differentiation. *Nat. Immunol.* 11: 114-120.
 53. Haynes, N. M., C. D. Allen, R. Lesley, K. M. Ansel, N. Killeen, and J. G. Cyster. 2007. Role of CXCR5 and CCR7 in follicular Th cell positioning and appearance of a programmed cell death gene-1-high germinal center-associated subpopulation. *J. Immunol.* 179: 5099-5108.
 54. Turner, C. A. Jr., D. H. Mack, and M. M. Davis. 1994. Blimp-1, a novel zinc finger-containing protein that can drive the maturation of B lymphocytes into immunoglobulin-secreting cells. *Cell* 77: 297-306.
 55. Martins, G. and K. Calame. 2008. Regulation and functions of Blimp-1 in T and B lymphocytes. *Annu. Rev. Immunol.* 26: 133-169.
 56. Johnston, R. J., Y. S. Choi, J. A. Diamond, J. A. Yang, and S. Crotty. 2012. STAT5 is a potent negative regulator of TFH cell differentiation. *J. Exp. Med.* 209: 243-250.
 57. Kwon, H., D. Thierry-Mieg, J. Thierry-Mieg, H. P. Kim, J. Oh, C. Tunyaplin, S. Carotta, C. E. Donovan, M. L. Goldman, P. Taylor, K. Ozato, D. E. Levy, S. L. Nutt, K. Calame, and W. J. Leonard. 2009. Analysis of interleukin-21-induced Prdm1 gene regulation reveals functional cooperation of STAT3 and IRF4 transcription factors. *Immunity* 31: 941-952.
 58. Sakaguchi, S. 2004. Naturally arising CD4⁺ regulatory T cells for immunologic self-tolerance and negative control of immune responses. *Annu. Rev. Immunol.* 22: 531-562.
 59. Kanangat, S., P. Blair, R. Reddy, M. Daheshia, V. Godfrey, B. T. Rouse, and E. Wilkinson. 1996. Disease in the scurfy (sf) mouse is associated with overexpression of cytokine genes. *Eur. J. Immunol.* 26: 161-165.
 60. Clark, L. B., M. W. Appleby, M. E. Brunkow, J. E. Wilkinson, S. F. Ziegler, and F. Ramsdell. 1999. Cellular and molecular characterization of the scurfy mouse mutant. *J. Immunol.* 162: 2546-2554.
 61. Wollenberg, I., A. Agua-Doce, A. Hernández, C. Almeida, V. G. Oliveira, J. Faro, and L. Graca. 2011. Regulation of the germinal center reaction by Foxp3⁺ follicular regulatory T cells. *J. Immunol.* 187: 4553-4560.
 62. Linterman, M. A., W. Pierson, S. K. Lee, A. Kallies, S. Kawamoto, T. F. Rayner, M. Srivastava, D. P. Divekar, L. Beaton, J. J. Hogan, S. Fagarasan, A. Liston, K.G. Smith, and C. G. Vinuesa. 2011. Foxp3⁺ follicular regulatory T cells control the germinal center response. *Nat. Med.* 17: 975-982.
 63. Sage, P. T., L. M. Francisco, C. V. Carman, A. H. Sharpe. 2013. The receptor PD-1 controls follicular regulatory T cells in the lymph nodes and blood. *Nat. Immunol.* 14: 152-161.
 64. Cobb, B. S., T. B. Nesterova, E. Thompson, A. Hertweck, E. O'Connor, J. Godwin, C. B. Wilson, N. Brockdorff, A. G. Fisher, S. T. Smale, and M. Merkenschlager. 2005. T cell lineage choice and differentiation in the absence of the RNase III enzyme Dicer. *J. Exp. Med.* 201: 1367-1373.
 65. Muljo, S. A., K. M. Ansel, C. Kanellopoulou, D. M. Livingston, A. Rao, and K. Rajewsky. 2005. Aberrant T cell differentiation in the absence of Dicer. *J. Exp. Med.* 202:

- 261-269.
66. Doria, A., M. Zen, M. Canova, S. Bettio, N. Bassi, L. Nalotto, M. Rampudda, A. Ghirardello, and L. Iaccarino. 2010. SLE diagnosis and treatment: when early is early. *Autoimmun. Rev.* 10: 55-60.
 67. Luzina, I. G., S. P. Atamas, C. E. Storrer, L. C. daSilva, G. Kelsoe, J. C. Papadimitriou, and B. S. Handwerker. 2001. Spontaneous formation of germinal centers in autoimmune mice. *J. Leukoc. Biol.* 70: 578-584.
 68. Simpson, N., P. A. Gatenby, A. Wilson, S. Malik, D. A. Fulcher, S. G. Tangye, H. Manku, T. J. Vyse, G. Roncador, G. A. Huttley, C. C. Goodnow, C. G. Vinuesa, and M. C. Cook. 2010. Expansion of circulating T cells resembling follicular helper T cells is a fixed phenotype that identifies a subset of severe systemic lupus erythematosus. *Arthritis Rheum.* 62: 234-244.
 69. Daikh, D. I., B. K. Finck, P. S. Linsley, D. Hollenbaugh, and D. Wofsy. 1997. Long-term inhibition of murine lupus by brief simultaneous blockade of the B7/CD28 and CD40/gp39 costimulation pathways. *J. Immunol.* 159: 3104-3108.
 70. Vinuesa, C. G., M. C. Cook, C. Angelucci, V. Athanasopoulos, L. Rui, K. M. Hill, D. Yu, H. Domaschensz, B. Whittle, T. Lambe, I. S. Roberts, R. R. Copley, J. I. Bell, R. J. Cornall, and C. C. Goodnow. 2005. A RING-type ubiquitin ligase family member required to repress follicular helper T cells and autoimmunity. *Nature* 435: 452-458.
 71. Linterman, M. A., R. J. Rigby, R. K. Wong, D. Yu, R. Brink, J. L. Cannons, P. L. Schwartzberg, M. C. Cook, G. D. Walters, and C. G. Vinuesa. 2009. Follicular helper T cells are required for systemic autoimmunity. *J. Exp. Med.* 206: 561-576.
 72. Bubier, J. A., T. J. Sproule, O. Foreman, R. Spolski, D. J. Shaffer, H. C. Morse 3rd, W. J. Leonard, and D. C. Roopenian. 2009. A critical role for IL-21 receptor signaling in the pathogenesis of systemic lupus erythematosus in BXSb-Yaa mice. *Proc. Natl. Acad. Sci. USA* 106: 1518-1523.
 73. Dolff, S., W. H. Abdulahad, J. Westra, B. Doombos-van der Meer, P. C. Limburg, C. G. Kallenberg, and M. Bijl. 2011. Increase in IL-21 producing T-cells in patients with systemic lupus erythematosus. *Arthritis Res. Ther.* 13: R157.
 74. Wong, C. K., P. T. Wong, L. S. Tam, E. K. Li, D. P. Chen, and C. W. Lam. 2010. Elevated production of B cell chemokine CXCL13 is correlated with systemic lupus erythematosus disease activity. *J. Clin. Immunol.* 30: 45-52.
 75. Young, D. A., M. Hegen, H. L. Ma, M. J. Whitters, L. M. Albert, L. Lowe, M. Senices, P. W. Wu, B. Sibley, Y. Leathurby, T. P. Brown, C. Nickerson-Nutter, J. C. Keith Jr, and M. Collins. 2007. Blockade of the interleukin-21/interleukin-21 receptor pathway ameliorates disease in animal models of rheumatoid arthritis. *Arthritis Rheum.* 56: 1152-1163.
 76. Kouskoff, V., A. S. Korganow, V. Duchatelle, C. Degott, C. Benoist, and D. Mathis. 1996. Organ-specific disease provoked by systemic autoimmunity. *Cell* 87: 811-822.
 77. Victoratos, P. and G. Kollias. 2009. Induction of autoantibody-mediated spontaneous arthritis critically depends on follicular dendritic cells. *Immunity* 30: 130-142.
 78. Platt, A. M., V. B. Gibson, A. Patakas, R. A. Benson, S. G. Nadler, J. M. Brewer, I. B. McInnes, and P. Garside. 2010. Abatacept limits breach of self-tolerance in a murine model of arthritis via effects on the generation of T follicular helper cells. *J. Immunol.* 185: 1558-1567.
 79. Liu, R., Q. Wu, D. Su, N. Che, H. Chen, L. Geng, J. Chen, W. Chen, X. Li, and L. Sun. 2012. A regulatory effect of IL-21 on T follicular helper-like cell and B cell in rheumatoid arthritis. *Arthritis Res. Ther.* 14: R255.