Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by B cell hyperactivity leading to the production of autoantibodies, some of which having a deleterious effect. Reducing autoantibody production thus represents a way of controlling lupus pathogenesis, and a better understanding of the molecular and cellular factors involved in the differentiation of B cells into plasma cells could allow identifying new therapeutic targets. Follicular helper T cells (T<sub>FH</sub>) represent a distinct subset of CD4<sup>+</sup> T cells specialized in providing help to B cells. They are required for the formation of germinal centers and the generation of long-lived serological memory and, as such, are suspected to play a central role in SLE. Recent advances in the field of T<sub>FH</sub> biology have allowed the identification of important molecular factors involved in T<sub>FH</sub> differentiation, regulation, and function. Interestingly, some of these T<sub>FH</sub>-related molecules have been described to be dysregulated in lupus patients. In the present review, we give an overview of the aberrant expression and/or function of such key players in lupus, and we highlight their potential as therapeutic targets.

1. Introduction

Systemic lupus erythematosus (SLE) is a severe systemic autoimmune disease and, as such, is characterized by a loss of self-tolerance. The etiology of SLE is not well defined, but genetic, hormonal, and environmental factors, as well as immune disorders, are likely implicated. During SLE, inflammation leads to damage of various tissues, including the joints, skin, kidneys, heart, lungs, blood vessels, and brain. Dysregulation of various components of the immune system can be observed at different stages of disease development, but hyperactivity of B cells, leading to excessive production of multiple autoantibodies (autoAb), is one of the major immunological stigmas of SLE. Indeed, SLE is characterized by the production of antinuclear autoAb (e.g., autoAb specific for chromatin) and by the formation of immune complexes, which contribute to tissue damage. Deposits of immune complexes in organs such as kidneys lead to subsequent inflammation through the activation of the complement system and the recruitment of inflammatory cells. The presence of autoAb is an absolute prerequisite for the development of lupus nephritis [1] and, interestingly, we demonstrated that pathogenic autoAb can be locally produced by plasma cells, which have homed to inflamed kidneys of lupus mice [2]. B cells and derivatives (plasma cells) are thus considered at the center of SLE pathogenesis and this is supported by the observation of a high frequency of plasma cell precursors in the blood of children with SLE [3]. Furthermore, an increase of circulating plasma cells in lupus patients is correlated with disease activity [4].

The generation of Ab can occur via the extrafollicular or the germinal center (GC) responses. The extrafollicular response leads to short-lived plasma cells, which do not go through the affinity maturation process. In contrast, the GC is the theater of intense cell collaboration between GC B cells and follicular helper T cells (T<sub>FH</sub>) leading to the differentiation of long-lived plasma cells harboring high antigen-specificity. Interestingly, lupus autoAb are high affinity, somatically mutated, and class-switched immunoglobulin (Ig)G [5] indicating T and B cell collaboration [6] and intense GC activity. Therefore, it is likely that a dysfunction in B cell differentiation mechanisms occurs in lupus, leading to
excessive numbers of autoreactive plasma cells. It is particularly attracting and plausible to envisage that a dysregulation of T<sub>FH</sub> could be the underlying key factor.

In this review, we succinctly expose recent understanding in T<sub>FH</sub> biology (described in detail elsewhere; see [7] for review), in order to introduce important molecular factors involved in T<sub>FH</sub> differentiation, regulation, and function. We then give an overview of the aberrant expression and/or function of such key players in lupus patients, and we highlight their potential as therapeutic targets.

2. T<sub>FH</sub> Cells: From Their Generation to Their Regulation

The generation of high affinity Ab requires T/B interactions that mainly occur in GC. T<sub>FH</sub> cells represent a distinct subset of CD4<sup>+</sup> T cells involved in GC formation and specialized in providing help to B cells to differentiate into plasma cells or memory B cells [8]. T<sub>FH</sub> express high levels of CXC chemokine receptor type 5 (CXCR5), PD-1 (Programmed Death-1), ICOS (Inducible T cell CO-Stimulator), and the regulator transcription factor Bcl6 (B cell lymphoma 6), which provide excellent markers for their identification. Moreover, secretion of high levels of IL-21 is a critical characteristic of T<sub>FH</sub> cells.

T<sub>FH</sub> are generated after immunization or infection following the interaction of naive CD4<sup>+</sup> T cells with dendritic cells (DC) within the T cell zone of secondary lymphoid organs (SLO). Signals provided by DC induce the expression of a myriad of proteins (transcription factors, surface molecules, and cytokines) that are essential for T<sub>FH</sub> generation, migration, and function. In fact, T<sub>FH</sub> differentiation is a multistage process (Figure 1), which can be sequentially defined as follows: (i) naive CD4<sup>+</sup> T cells are activated by DC (thanks to the MHC-peptide complex/TCR interaction) in the T cell zone and become immature T<sub>FH</sub> (also called pre-T<sub>FH</sub>) [9]; (ii) newly generated pre-T<sub>FH</sub> then migrate to the interfollicular zone, where cognate interactions with B cells allow the final maturation step; (iii) these mature T<sub>FH</sub> reach the GC in which T<sub>FH</sub>-GC B cell interactions will favor isotype class switch, somatic hypermutations, and affinity maturation.

2.1. Pre-T<sub>FH</sub> Generation: DC as the Stage Director. The initial priming of CD4<sup>+</sup> T cells requires cognate interactions and costimulatory signals delivered by DC through CD40, CD80/86, ICOSL, and OX40L (Table 1). CD28 (that binds CD80/86) was shown to be essential to T<sub>FH</sub> development as mice deficient for CD28 display CD4<sup>+</sup> T cells that fail to upregulate CXCR5 and OX40, leading to disrupted GC formation [10]. In addition, upregulation of OX40L on DC following CD40-induced maturation allows CXCR5 expression by OX40<sup>+</sup> T cells [11]. Moreover, ICOS signaling leads to an increased expression of the transcription factors Bcl6 and Ascl2 (achaete-scute homologue-2). The latter promote both the reciprocal CXCR5 upregulation and CCR7 downregulation on activated CD4<sup>+</sup> T cells, which then become pre-T<sub>FH</sub> [12, 13]. In turn, Bcl6 induces the expression of ICOS, PDI, CD40L, and SAP (SLAM- (Signaling Lymphocytic Activation Molecule-) Associated Protein; critical for T-B interaction).

Cytokines secreted by DC also play a pivotal role in pre-T<sub>FH</sub> development (Table 1). IL-6, a DC-derived proinflammatory cytokine, has been demonstrated to be the main soluble factor driving T<sub>FH</sub> differentiation in mice [14]. In humans, IL-12 has been shown to be the key cytokine that promotes T<sub>FH</sub>-like cell differentiation [15, 16]. If, in the initial work, neither IL-6 nor IL-21 were described as being able to promote T<sub>FH</sub> differentiation [15], a recent study suggests that human plasmablasts produce IL-6, which is responsible for the subsequent differentiation of naive CD4<sup>+</sup> T cells into B cell helpers CXCR5<sup>+</sup>ICOS<sup>+</sup>Bcl6<sup>+</sup>IL-21<sup>+</sup> T cells [17]. IL-21 is required for T<sub>FH</sub> function but it is also an important factor for T<sub>FH</sub> generation [18] and, interestingly, both IL-6 and IL-12 are potent inducers of IL-21 expression in mice [19] and humans, respectively [15]. As IL-21 is an autocrine cytokine for pre-T<sub>FH</sub> generation, further studies are required to better clarify individual cytokine contributions. Cytokine signaling involves the subsequent activation of Janus kinase-STAT (Signal Transducer and Activator of Transcription) signaling pathway. STAT3 is a major signaling molecule for IL-6 and IL-21 [20, 21], whereas IL-12 signaling occurs through STAT4 activation. However, IL-12-induced expression of IL-21 by human CD4<sup>+</sup> T cells is compromised in patients with functional STAT3 deficiency, suggesting that IL-12 ability to promote IL-21-producing CD4<sup>+</sup> T cells is predominantly STAT3 dependent [22]. Moreover, STAT3-deficient patients have reduced numbers of circulating T<sub>FH</sub>-like cells [23]. Altogether, these data suggest that the STAT3 signaling pathway plays an important role in T<sub>FH</sub> differentiation and subsequent B cell help.

During this first step of the T<sub>FH</sub> differentiation process, both cell surface interactions and cytokine signaling play a crucial role in Bcl6 induction. Bcl6 requirement for T<sub>FH</sub> development was reported in 2009 by 3 independent groups [24–26]. Indeed, Bcl6 is a master regulator for T<sub>FH</sub> lineage commitment as its expression can inhibit Th1, Th2, and Th17 differentiation [26]. Bcl6 expression is influenced by IL-6 and IL-21 via STAT1 and STAT3 signaling and by ICOS-PI3K (Phosphoinositide 3-Kinase) signaling. Moreover, Bcl6 expression is controlled by a complex regulatory network of activating factors (see [7] for detailed review) such as basic leucine zipper transcriptional factor ATF like (BATF; [27]), transcription factor 1 (TCF-1; [28]), lymphoid enhancer-binding factor (LEF-1; [28]), and B cell Oct-binding protein 1 (Bob1; [29]), while forkhead box protein 0i (FOXO1; [30]) negatively regulates Bcl6 expression.

2.2. Pre-T<sub>FH</sub> Migration to the T-B Border and T<sub>FH</sub> Maturation: B Cells Enter the Scene. Thanks to CXCR5 expression enhancement and CCR7 downregulation (Table 2), pre-T<sub>FH</sub> cells migrate to the B cell follicle in response to a CXCL13 gradient and their interaction with antigen-specific B cells at the T-B border contributes to final T<sub>FH</sub> differentiation. Indeed, the lower frequency of T<sub>FH</sub> cells in B cell-deficient mice suggests that B cells are also important for the generation of T<sub>FH</sub> cells [24]. At this stage, B cells act
Figure 1: T\textsubscript{FH} differentiation in secondary lymphoid organs is a multistep process required to establish a high affinity antibody response. (1) Naive CD\textsuperscript{4}\textsuperscript{+} T cells localized in the T cell zone are first primed by DC thanks to MHC-II-peptide-TCR interactions. (2) Once activated, CD\textsuperscript{4} T cells upregulate costimulatory molecules such as CD40L, OX40, and ICOS, favoring their crosstalk with DC. Combined with this interaction DC-derived cytokines (IL-6 in mice and IL-12 in humans) drive differentiation of activated T cell into pre-T\textsubscript{FH} cells. (3) Thanks to CXCR5 upregulation and CCR7 downregulation, pre-T\textsubscript{FH} cells are attracted to the T-B border by a CXCL13 gradient. (4) A SAP/SLAM-stabilized interaction between ICOSL-expressing B cells and pre-T\textsubscript{FH} cells occurs at the T-B border, finalizing T\textsubscript{FH} cell differentiation. (5) Finally, mature T\textsubscript{FH} cells migrate toward the GC, where they provide help to B cells. This crosstalk induces both B cell differentiation in plasma cells and memory B cells, thanks to IL-21/IL-21R and CD40/CD40L signals, and B cell survival via BAFF/BR3 and PD1/PD-L1 interactions (6). as the major antigen-presenting cells (APC) for primed-T\textsubscript{FH} that will then fully differentiate into GC T\textsubscript{FH} cells. Mature T\textsubscript{FH} and B cells that have formed stable T-B conjugates move together into the follicle to form GC [31]. Stable T-B conjugate formation requires interaction between ICOS on T\textsubscript{FH} and ICOSL expressed by B cells, as well as SLAM interactions (Table 2). SLAM are transmembrane receptors expressed on both T\textsubscript{FH} and B cells. SAP, which is the adaptor signaling protein downstream of SLAM, was demonstrated to be important for stabilizing cognate T-B interactions. Indeed, SAP-deficient CD\textsuperscript{4} T cells have an impaired capacity to stably interact with cognate B cells, resulting in a failure to induce B cell clonal expansion [32]. Moreover, patients with X-linked Lymphoproliferative disease (XLP), an immunodeficiency resulting from mutations in the SH2D1A gene which encodes SAP, harbor humoral defects characterized by hypogammaglobulinemia and reduced numbers of T\textsubscript{FH} [33]. B cells thus play a key role in the T\textsubscript{FH} maturation step by both acting as APC and stabilizing T\textsubscript{FH}-GC B cell interactions through ICOSL and SLAM.

2.3. T\textsubscript{FH} Function: The Final Act of the Story. The major function of T\textsubscript{FH} is to enhance high affinity memory Ab responses following migration to GC. In the follicles, T\textsubscript{FH}-GC B cell crosstalk involves CD40L, IL-21, PD-1, and BAFF (B cell Activating Factor) (Table 3). The signal delivered through interaction between PD-1 on T\textsubscript{FH} and PD-L1 expressed by GC B cells is crucial for GC B cell survival [34]. IL-21 production by T\textsubscript{FH} directly regulates B cell proliferation and class-switch, and the IL-21 pathway has been identified as a critical
component of the memory B cell response as secondary antigen-specific IgG responses are impaired in IL-21R-knockout mice [35]. BAFF is a cytokine that belongs to the Tumor Necrosis Factor (TNF) ligand family and its receptors are BCMA (B cell maturation antigen), TACI (Transmembrane Activator and Calcium modulator and Cyclophilin ligand Interactor), and BAFF Receptor 3 (BR3). BAFF is produced by stromal cells in the SLO and involved during GC development by influencing ICOSL expression on B cells and thus regulating the ability of GC B cells to promote T<sub>FH</sub> expansion [36]. Moreover, BAFF production by T<sub>FH</sub> is critical for the survival of high affinity B cell clones [37].

In summary, molecules that have been described to play a key role in T<sub>FH</sub> biology do not display equivalent functions. Some are necessary for T<sub>FH</sub> migration from the T cell zone to the GC, others are absolutely required for their development or function, and finally some of them are essential for T<sub>FH</sub> maintenance and survival (Tables 1–3).

### Table 1: Function of T<sub>FH</sub>-related molecules during T<sub>FH</sub> differentiation.

| T cell molecule | Ligand | Function in mice | Function in humans |
|-----------------|--------|------------------|--------------------|
| CD28            | CD80/86| T cell accumulation in B cell follicles relies on CD40-dependent maturation of DC [11] | ND |
| CD40L           | CD40   | T cells do not migrate to B cell follicles in immunized OX40<sup>−/−</sup> mice [11] | ND |
| OX40            | OX40L  | T cells fail to upregulate OX40 [10] | OX40 signal promotes CD4<sup>+</sup> T cells to express T<sub>FH</sub> molecules and to become functional B cell helpers [84] |
| ICOS            | ICOSL  | ICOS provides a critical early signal to induce Bcl6 [12] | LOF mutations in ICOS reduce cT<sub>FH</sub> frequencies [133] |
| IL6R            | IL-6   | IL-6 promotes the differentiation of naive T cells in helper B cells [14] | Plasmablasts-derived IL-6 induces T<sub>FH</sub> differentiation [17] |
| IL-12R          | IL-12  | T cells activated by IL-21 acquire T<sub>FH</sub> gene expression and function [18] | IL-12 induces CD4<sup>+</sup> T cells to become IL-21-producing T<sub>FH</sub>-like cells [15] |
| IL-21R          | IL-21  | T cells activated by IL-21 acquire T<sub>FH</sub> gene expression and function [18] | LOF mutations in IL-21R skewed T<sub>FH</sub> differentiation toward an IFNγ<sup>+</sup>PD1<sup>+</sup> phenotype [133] |

GC: germinal center; DC: dendritic cells; ND: not determined; LOF: loss of function; cT<sub>FH</sub>: circulating T<sub>FH</sub>; PC: plasma cells.

### Table 2: Function of T<sub>FH</sub>-related molecules during T<sub>FH</sub> migration and interaction at the T/B border.

| T cell molecule | Ligand | Function in mice | Function in humans |
|-----------------|--------|------------------|--------------------|
| CXCR5           | CXCL13 | CXCR5 induction is necessary for T cell homing to the follicles [135] | T cells localized into B cell follicles express CXCR5 and provide B cell help [136, 137] |
| CCR7            | CCL19/CCL20 | Maintenance of CCR7 expression impedes the entry of T cells on the follicles [135] | CXCR5<sup>+/−</sup> CD4<sup>+</sup> T cells loose CCR7 expression in SLO [136, 137] |
| ICOS            | ICOSL  | CD4<sup>+</sup> T cells fail to develop in T<sub>FH</sub> and to promote optimal GC responses when follicular B cells do not express ICOSL [75] | ND |
| SAP             | SLAM   | CD4<sup>+</sup> T cells from SAP<sup>−/−</sup> mice are unable to stably interact with cognate B cells [32] | XLP patients display reduced T<sub>FH</sub> numbers and no mem B cells [33] |

GC: germinal center; SLO: second lymphoid organs; XLP: X-linked lymphoproliferative disease; ND: not determined; mem B cells: memory B cells.
2.4. **T<sub>FH</sub> Regulation.** Considering the important role of T<sub>FH</sub> cells in humoral immunity, a balance between stimulatory and inhibitory mechanisms regulating their function is required for immune homeostasis. However, while signals important for T<sub>FH</sub> development are clearly defined nowadays, little is known about mechanisms involved in their regulation. The coinhibitory PD-1/PD-L1 pathway can limit T<sub>FH</sub> expansion and consequently the humoral Ig response [38]. Similarly, it was demonstrated that the inhibitory receptor B and T Lymphocyte Attenuator (BTLA) suppresses GC B cell development and subsequent IgG responses by inhibiting IL-21 production by T<sub>FH</sub> cells [39] (Table 3). Recently, the existence of regulatory T cells (Treg) able to inhibit GC responses was described. This subset of regulatory T cells of thymic origin was first identified in mice [40] and named T<sub>FR</sub> (follicular regulatory T cells). They express typical markers of both T<sub>FH</sub> cells (Bcl6, CXCR5, PD-1, and ICOS) and classical Treg (Foxp3); they localize in the GC and possess suppressive activity. A CD4<sup>+</sup> T cell population coexpressing Foxp3, Bcl6, and CXCR5 was also visualized in human tonsils [41].

Moreover, microRNA have recently emerged as potent regulators of T<sub>FH</sub> differentiation. Indeed, the miR-17–92 cluster was shown to promote T<sub>FH</sub> differentiation by repressing PTEN (Phosphatase and TEnsin homolg), PHLPP2 (Pleckstrin Homology domain and Leucine-rich repeat Protein Phosphatase) (phosphatases that inhibit Bcl6 expression through interfering with PI3K signaling), and RORα (Retinoic acid-related Orphan Receptor α) expression [42, 43]. On the other hand, miR-10a negatively regulates T<sub>FH</sub> differentiation by directly inhibiting Bcl6 expression [44]. Similarly, miR-146a, a microRNA that is highly expressed in T<sub>FH</sub> cells, was recently described as a negative regulator of T<sub>FH</sub> cell numbers [45]. miR-146a deficiency leads to accumulation of both T<sub>FH</sub> and GC B cells, likely due to enhanced ICOSL and ICOS expression on GC B cells and T<sub>FH</sub> cells, respectively [45].

Finally, IL-2 signaling is also an important negative regulator of T<sub>FH</sub> differentiation by inducing STAT5-dependent expression of Blimp1, a Bcl6 repressor [46–48]. Moreover, high IL-2 production by Th1 cells induces T-bet, which in turn inhibits Bcl6 expression and T<sub>FH</sub> differentiation [49].

3. **Evidences Supporting the Involvement of T<sub>FH</sub> in Systemic Lupus Erythematosus (SLE)**

The main function of T<sub>FH</sub> cells consists in regulating the clonal selection of GC B cells and providing B cells with signals for Ig production, isotype switching, and somatic hypermutations. As abnormal activation of B cells and autoAb production are central to autoimmune diseases, such as lupus, altered T<sub>FH</sub> differentiation, function, and regulation were suspected to play a role in lupus pathogenesis. First hypotheses regarding the role of T<sub>FH</sub> cells in SLE development are based on studies using mice deficient for Roquin1 (a negative regulator of ICOS mRNA stability) in which an
excessive number of $T_{FH}$ cells and GC reactions and high levels of IL-21 are associated with a lupus-like phenotype [50, 51]. Other evidences come from studies on IL-21, the main cytokine produced by $T_{FH}$, in lupus mice. High IL-21 mRNA as well as elevated IL-21 serum levels were described in BXSBYaa mice, which develop an SLE-like disease [52]. The use of a fusion protein consisting in the IL-21R linked to the Fc domain of a mouse IgG2a (IL-21R.Fc, which therefore binds to IL-21 and prevents activation of its receptor) revealed a complex biphasic role of IL-21 in this mouse model as it increases or diminishes the disease severity depending of the stage of the disease at the time of IL-21 neutralization (at early or late stages). This could be related to the action of IL-21 on B cells but also on T cell responses [53]. In lupus MRL/lpr mice, activated CD4+ T cells secrete 10 times more IL-21 than control mice [54] and IL-21R deficiency leads to reduced numbers of $T_{FH}$ cells [55]. In addition, abundant $T_{FH}$-like cells are located outside the GC where they support extracellular B cell differentiation and plasmablast maturation in BXSBYaa and MRL-Fasbr lupus mice [56, 57]. In the latter and contrary to what was expected, the extracellular pathway was shown to be the most important way to generate hypermutated autoAbs [58]. However, there is no evidence to date supporting the involvement of such extracellular response in human SLE.

$T_{FH}$ cells are located in SLO; therefore the major problem encountered in studies of human $T_{FH}$ is that lymphoid tissues of lupus patients cannot be easily accessed, making it difficult to identify $T_{FH}$ cells and to determine whether the generation or function of these cells is dysregulated. First studies were based on the enumeration of CD4+CXCR5+ in peripheral blood as GC $T_{FH}$ counterparts. Using this strategy, it was shown in human SLE that circulating $T_{FH}$ cells (c$T_{FH}$) defined as CD4+CXCR5+PD-1+/high and/or ICOS+ T lymphocytes are expanded in lupus patients and their presence correlates with a more severe disease phenotype [59–64]. Recent studies have more rigorously characterized peripheral CXCR5+CD4+ T cells. Morita et al. have described a circulating population in healthy donors that shares common phenotypic and functional characteristics with $T_{FH}$ cells from GC [65]. The authors named it T$_{FH}$-like cells. Moreover, they distinguished three subclasses, that is, $T_{FH17}$, $T_{FH12}$, and $T_{FH1}$, defined according to the expression of the CCR6 and CXCR3 chemokine receptors: $T_{FH17}$ cells are CXCR3+CXCRR6- cells whereas $T_{FH2}$ cells are CXCR3+CXCR6- cells and $T_{FH1}$ cells are CXCR3+CXCR6+ cells. $T_{FH17}$ and $T_{FH2}$ cells were identified as able to provide help to B cells via IL-21 production, resulting in IgM and IgG secretion, whereas $T_{FH1}$ have limited helper functions. However, ICOS expressing $T_{FH1}$ are able to help memory B cells (but not naive B cells) to produce Ab following influenza vaccination [66]. Moreover, Morita and colleagues showed that patients with juvenile dermatomyositis displayed a profound skewing of c$T_{FH}$ cells towards $T_{FH2}$ and $T_{FH17}$ cells that correlated with disease activity, suggesting that an altered balance of $T_{FH}$ subtypes contributes to human autoimmunity [65]. Recently, the differential expression of ICOS, PD-1, and CCR7 interestingly allowed distinguishing three memory c$T_{FH}$ subsets defined as activated cells (ICOS+PD1+CXCR7+) or quiescent cells (ICOS+PD1+CXCR7+ and ICOS+PD1−CXCR7−) [67, 68]. In SLE patients, the frequency of CXCR7+PD1+CXCR5+ CD4+ T cells is significantly higher than in healthy individuals [67]. The CXCR7+PD1hi subset is indicative of active $T_{FH}$ differentiation and its overrepresentation is associated with elevated autoAb titers and high disease activity [67]. By analyzing CXCR3 and CCR6 expression, we also interestingly described an altered phenotype of c$T_{FH}$ cells characterized by the enhanced frequency of B cell helper $T_{FH17}$-like CXCR3+CCR6+ cells and a decreased frequency of CXCR3+CCR6−$T_{FH1}$-like cells (not able to provide B cell help) in lupus patients with an active disease [69].

4. Molecules and/or Cytokines Involved in $T_{FH}$ Generation/Regulation Are Associated with Lupus Pathogenesis

Aberrant expression and/or function of $T_{FH}$-related molecules are associated with lupus-like disease in mice [54, 70]. Similarly, in lupus patients, numbers of molecules involved in $T_{FH}$ generation and/or regulation have been described to be dysregulated.

4.1. Surface Molecules. CD40/CD40L pathway plays an essential role in the initial phase of $T_{FH}$ development (T-DC interaction in the T cell zone; Figure 1, [11]) and function ($T_{FH}$-GC B cell crosstalk in the GC; [71]). Interestingly, CD40L was found to be constitutively expressed at abnormally high levels on T cells (but also on B cells and monocytes) from lupus patients [72, 73]. Furthermore, CD4+ T cells from female lupus patients, which overexpressed CD40L mRNA, were able to promote autologous B cell stimulation and autoAb production [74].

ICOS-mediated PI3K signaling is absolutely required for $T_{FH}$ differentiation, for $T_{FH}$ migration into the follicle [75], and also for $T_{FH}$ maintenance [76]. PTEN acts as a negative regulator of the PI3K signaling pathway, leading to the inhibition of Bc6 expression and $T_{FH}$ differentiation. Interestingly, PTEN expression is significantly decreased in SLE B cells [77]; however, to the best of our knowledge, its expression in lupus CD4+ T cells (especially $T_{FH1}$) has not been investigated yet. ICOS expression has been found to be enhanced in CD4+ T cells from lupus patients compared to healthy donors [78, 79] and ICOS levels were higher in patients with nephris than in those without nephritis [80]. Moreover, infiltrated ICOS+ T cells were shown to be in close contact with B cells in lupus kidneys [79].

Interactions between OX40L (on DC) and OX40 (on activated CD4+ T cells) is also important for $T_{FH}$ development. OX40 expression by lupus peripheral blood cells was found to be predominantly restricted to memory CD45RO+ CD4+ T cells and its levels correlated with disease activity [81]. Moreover, OX40 has also been found to be highly expressed in kidneys of patients with lupus nephritis [82]. Importantly, the upstream region of the OX40 gene contains a single risk haplotype for SLE, which is correlated with increased expression of OX40 mRNA and protein [83]. Finally, it was...
recently shown that OX40 signal promotes, \textit{ex vivo}, the generation of T\textsubscript{FH}-like cells that are functional B cell helpers [84].

4.2. Cytokines. Cytokine signals are absolutely required for T\textsubscript{FH} differentiation. Elevated levels of IL-6 have been found in the serum and in the urine of active SLE patients [85–87]. The increased frequency of IL-6-producing peripheral blood mononuclear cells (PBMC) correlates with disease severity/activity and treatment response [88]. Raised expression of gp130 (one of the two subunits of the IL-6 receptor) has been found on CD4\textsuperscript{+} T cells and B cells from patients with active SLE, while an important reduction in the gp130 expression by B lymphocytes was observed upon immunosuppressive treatment leading to milder disease activity [89]. Factors responsible for the constitutive expression of IL-6 in SLE have not been elucidated yet.

Serum IL-21 levels were found to be elevated in patients with SLE [69, 90], especially in patients with lupus nephritis, and to correlate with disease severity [90]. The real-time PCR analysis of skin biopsies taken from 3 lupus patients also revealed that IL-21 transcripts were significantly increased compared to control individuals [91]. Furthermore, the percentages of CD4\textsuperscript{+} T cells producing IL-21 are significantly enhanced in lupus patients [92]. Finally, polymorphisms within the IL-21R and the IL-21 genes have been reported and may confer risk for SLE: a polymorphism in IL-21R (namely, rs3093301) was found to associate with lupus in 2 independent cohorts [93], a genetic association of two SNPs located in intronic regions of the IL-21 gene (rs2221903 and rs907715) was described [94], and the variant allele rs2055979A of the IL-21 gene was recently found to be associated with increased IL-21 levels [95].

Regarding BAFF, lupus sera have been shown to contain elevated levels of this cytokine and those levels correlate with both anti-dsDNA titers [96–98] and disease activity [99]. Finally, it has been reported that IL-2 production (which inhibits T\textsubscript{FH} differentiation) upon TCR stimulation is impaired in SLE T lymphocytes [100, 101]. This lower IL-2 production could be explained by imbalanced expression between the transcription factors cAMP response element (CRE) binding protein (CREB) and the CRE-modulator (CREM), which, respectively, enhance and suppress the IL-2 gene transcription [102].

4.3. Transcription Factors, miRNA, and Regulatory T Cells. STAT3, which is activated by cytokines such as IL-6 and IL-21, binds to the Bcl6 promoter leading to high levels of Bcl6 expression and is thus important for T\textsubscript{FH} differentiation. T cells from patients with SLE display increased levels of total and phosphorylated STAT3 [103, 104].

Reduced expression of miR-146a (a negative regulator of T\textsubscript{FH} development) has been reported in PBMC from SLE patients [105] and seems to correlate with disease activity [105]. Moreover, a genome-wide association study has highlighted a variant, that is, rs2431697, in an intergenic region between PTTG1 (Pituitary Tumor-Transforming 1) and miR-146a, associated with lupus susceptibility [106]. Interestingly, the risk allele of this SNP correlates with a diminution of miR-146a levels [107].

To date, the analysis of frequency and/or functionality of T\textsubscript{FH} cells in an autoimmune context has not been reported. However, although there may be some discrepancies due to variations in phenotype analysis, peripheral regulatory T cells (CD4\textsuperscript{+}CD25\textsuperscript{+} T cells) seem to play a role in human lupus pathogenesis. Several studies reported that a decreased number of Treg might contribute to the pathogenesis [108–111], but there were conflicting data regarding Treg function in lupus patients. The \textit{in vitro} suppressive activity of these cells was found to be defective in some reports [111, 112] but other studies showed that the suppressive activity of highly purified Treg from lupus patients is not altered. It has been proposed that defective suppression in lupus could be attributed either to a higher sensitivity of Treg to Fas-mediated apoptosis in an SLE context [108] or to a lower susceptibility of effector T cells to Treg suppression [113]. Finally, it has been shown that IFN-\textgreekalpha production by lupus APCs might be responsible for altered Treg functionality [114].

5. Targeting T\textsubscript{FH}: From Lupus Mice to Lupus Patients

Data obtained from various lupus mouse models have already highlighted how blockade of signaling pathways involved in T\textsubscript{FH} generation could lead to disease improvement. The administration of a blocking ICOS-L specific monoclonal Ab (mAb) to lupus NZB/W mice interrupted T\textsubscript{FH} cell development leading to a decrease of autoAb levels and glomerulonephritis [115, 116]. Similar results were obtained in MRL/lpr lupus mice displaying a genetic deletion of ICOS [57].

Blockade of the CD40L-CD40 signaling pathway also led to the reduction of lupus symptoms in different mouse models [117, 118]. Treatment of MRL/lpr lupus mice with a neutralizing anti-IL-6R mAb has favorable effects on renal function and leads to a reduction of anti-dsDNA Ab levels [119]. In NZB/W mice, chronic administration of anti-IL-6 or anti-IL-6R mAb improves survival and reduces the progression of proteinuria and anti-dsDNA levels [120, 121]. In lupus-prone NZB/W and MRL/lpr mice, raised levels of BAFF are detected at the onset of the disease [122] and treatment with either TACI-Ig or BR3-Ig is effective at preventing clinical disease and ameliorating renal injury [123]. Regarding IL-21, its neutralization using IL-21R.Fc showed an improvement of biological and clinical signs of the disease in MRL/lpr lupus mice and BXSB-Yaa mice [53, 54]. Moreover, the administration of Ab specific for the IL-21R to MRL/lpr mice significantly reduced anti-dsDNA Ab titers and IgG deposits in the kidneys when compared to control mice [124]. In NZB/W mice, such IL-21R blocking even allowed reversing nephritis and halting disease progression in mice with preexisting lupus [125]. By using a miRNA-delivery approach via bacteriophage MS2 virus-like particles, Pan and colleagues recently showed that restoring the loss of miR-146a was effective in abolishing autoAb production and delaying SLE progression in lupus-prone mice [126]. Interestingly...
Figure 2: Therapeutic \( T_{FH} \)-related targets in SLE: present and future. \( T_{FH} \) function and differentiation can be affected by several biological drugs already used in SLE therapies or currently in clinical trials. Belimumab, Atacicept, and NNC0114-0006 are mAbs targeting the soluble molecules BAFF, APRIL, and IL-21, respectively. Moreover, the blocking of T cell costimulatory molecules with AMG-557 (ICOSL), Abatacept (CD28), and IDEC-131 (CD40L) could modulate \( T_{FH} \) differentiation by decreasing the strength of T-B interactions. Finally, promising therapies could consist in inhibiting \( T_{FH} \) differentiation by blocking their signaling pathways either directly with the Jak-STAT inhibitor Tofacitinib or indirectly by the blockade of cytokine receptors such as IL-6R (Tocilizumab) or IL-21R (ATR-07).

6. Concluding Remarks

Although prognosis in SLE has improved markedly in the last 40 years, a better knowledge of the disease remains of prime importance to develop more potent and specific treatments. New targeted therapies designed to block pathways involved in disease pathogenesis are on the horizon. One promising option could be to specifically target factors involved in the generation of plasma cells responsible for the production of pathogenic autoAb in lupus. \( T_{FH} \) play a critical role in B cell activation and differentiation, and recent data have evidenced their involvement in lupus pathogenesis. Signals required for \( T_{FH} \) development may thus represent interesting targets in order to reduce \( T_{FH} \) numbers (and/or to correct the altered proportion of \( T_{FH} \) subsets) or to qualitatively...
and/or quantitatively modulate their function. Another exciting therapeutic option consists in enhancing the negative molecular and cellular regulators of $T_{FH}$, such as miRNA or $T_{FR}$.

Competing Interests
The authors declare that they have no competing interests.

Acknowledgments
This study was supported by the French Centre National de la Recherche Scientifique (CNRS) and by a grant from the Fondation Arthritis-Courtin.

References
[1] M. R. Arbuckle, M. T. McClain, M. V. Rubertone et al., “Development of autoantibodies before the clinical onset of systemic lupus erythematosus,” *The New England Journal of Medicine*, vol. 349, no. 16, pp. 1526–1533, 2003.

[2] S. Lacotte, H. Dumortier, M. Décossas, J.-P. Briand, and S. Muller, “Identification of new pathogenic players in lupus: autoantibody-secreting cells are present in nephritic kidneys of (NZBxNZW)F1 mice,” *The Journal of Immunology*, vol. 184, no. 4, pp. 3937–3945, 2010.

[3] E. Arce, D. G. Jackson, M. A. Gill, L. B. Bennett, J. Banchereau, and V. Pascual, “Increased frequency of pre-germinal center B cells and plasma cell precursors in the blood of children with systemic lupus erythematosus,” *The Journal of Immunology*, vol. 167, no. 4, pp. 2361–2369, 2001.

[4] A. M. Jacobi, M. Odenahol, K. Reiter et al., “Correlation between circulating CD27high plasma cells and disease activity in patients with systemic lupus erythematosus,” *Arthritis & Rheumatism*, vol. 48, no. 5, pp. 1332–1342, 2003.

[5] C. T. Ravirajan, M. A. Rahman, L. Papadaki et al., “Genetic, structural and functional properties of an IgG DNA-binding monoclonal antibody from a lupus patient with nephritis,” *European Journal of Immunology*, vol. 28, no. 1, pp. 339–350, 1998.

[6] A. C. Grammer, R. Slota, R. Fischer et al., “Abnormal germinal center reactions in systemic lupus erythematosus demonstrated by blockade of CD154–CD40 interactions,” *The Journal of Clinical Investigation*, vol. 112, no. 10, pp. 1506–1520, 2003.

[7] C. G. Vinuesa, M. A. Linterman, D. Yu, and I. C. M. MacLennan, “Follicular helper T cells,” *Annual Review of Immunology*, vol. 34, pp. 335–368, 2016.

[8] S. Croft, “Follicular helper CD4 T cells (TFH),” *Annual Review of Immunology*, vol. 29, pp. 621–663, 2011.

[9] N. Fazilleau, L. J. McHeyzer-Williams, H. Rosen, and M. G. McHeyzer-Williams, “The function of follicular helper T cells is regulated by the strength of T cell antigen receptor binding,” *Nature Immunology*, vol. 10, no. 4, pp. 375–384, 2009.

[10] L. S. K. Walker, A. Gulbranson-Judge, S. Flynn et al., “Compromised OX40 function in CD28-deficient mice is linked with failure to develop CXCL12 chemokine receptor 5-positive CD4 cells and germinal centers,” *The Journal of Experimental Medicine*, vol. 190, no. 8, pp. 1115–1122, 1999.

[11] S. Fillatreau and D. Gray, “T cell accumulation in B cell follicles is regulated by dendritic cells and is independent of B cell activation,” *Journal of Experimental Medicine*, vol. 197, no. 2, pp. 195–206, 2003.

[12] Y. S. Choi, R. Kageyama, D. Eto et al., “ICOS receptor instructs T follicular helper cell versus effector cell differentiation via induction of the transcriptional repressor Bcl6,” *Immunity*, vol. 34, no. 6, pp. 932–946, 2011.

[13] X. Liu, X. Chen, B. Zhong et al., “Transcription factor achaete-scute homologue 2 initiates follicular T-helper-cell development,” *Nature*, vol. 507, no. 7493, pp. 513–518, 2014.

[14] F. Eddahri, S. Denanglair, F. Bureau et al., “Interleukin-6/STAT3 signaling regulates the ability of naive T cells to acquire B-cell help capacities,” *Blood*, vol. 113, no. 11, pp. 2426–2433, 2009.

[15] N. Schmitt, R. Morita, L. Bourdery et al., “Human dendritic cells induce the differentiation of interleukin-21-producing T follicular helper-like cells through interleukin-12,” *Immunity*, vol. 31, no. 1, pp. 158–169, 2009.

[16] C. S. Ma, S. Suryani, D. T. Avery et al., “Early commitment of naive human CD4+ T cells to the T follicular helper (Tfh) cell lineage is induced by IL-12,” *Immunology and Cell Biology*, vol. 87, no. 8, pp. 590–600, 2009.

[17] K.-M. Chavele, E. Merry, and M. R. Ehrenstein, “Circulating plasmablasts induce the differentiation of human T follicular helper cells via IL-6 production,” *Journal of Immunology*, vol. 194, no. 6, pp. 2482–2485, 2015.

[18] R. I. Nurieva, Y. Chung, D. Hwang et al., “Generation of T follicular helper cells is mediated by interleukin-21 but independent of T helper 1, 2, or 17 cell lineages,” *Immunity*, vol. 29, no. 1, pp. 138–149, 2008.

[19] O. Dienz, S. M. Eaton, J. P. Bond et al., “The induction of antibody production by IL-6 is indirectly mediated by IL-21 produced by CD4+ T cells,” *The Journal of Experimental Medicine*, vol. 206, no. 1, pp. 69–78, 2009.

[20] R. Spolski and W. J. Leonard, “Interleukin-21: basic biology and implications for cancer and autoimmunity,” *Annual Review of Immunology*, vol. 26, pp. 57–79, 2008.

[21] P. C. Heinrich, I. Behrmann, S. Haan, H. M. Hermanns, G. Müller-Newen, and F. Schaper, “Principles of interleukin (II)-6-type cytokine signalling and its regulation,” *Biochemical Journal*, vol. 374, no. 1, pp. 1–20, 2003.

[22] C. S. Ma, D. T. Avery, A. Chan et al., “Functional STAT3 deficiency compromises the generation of human T follicular helper cells,” *Blood*, vol. 119, no. 17, pp. 3997–4008, 2012.

[23] F. Mazerolles, C. Picard, S. Kracker, A. Fischer, and A. Durandy, “Blood CD4+CD45RO+CXCR5+ T cells are decreased but partially functional in signal transducer and activator of transcription 3 deficiency,” *The Journal of Allergy and Clinical Immunology*, vol. 130, no. 4, pp. 1146–1156, 2013.

[24] R. J. Johnston, A. C. Poholek, D. DiToro et al., “Bcl6 and Blimp-1 are reciprocal and antagonistic regulators of T follicular helper cell differentiation,” *Science*, vol. 325, no. 5943, pp. 1006–1010, 2009.

[25] R. I. Nurieva, Y. Chung, G. J. Martinez et al., “Bcl6 mediates the development of T follicular helper cells,” *Science*, vol. 325, no. 5943, pp. 1001–1005, 2009.

[26] D. Yu, S. Rao, L. M. Tsai et al., “The transcriptional repressor Bcl-6 directs T follicular helper cell lineage commitment,” *Immunity*, vol. 31, no. 3, pp. 457–468, 2009.

[27] B. C. Betz, K. L. Jordan-Williams, C. Wang et al., “Baf5 coordinates multiple aspects of B and T cell function required for normal antibody responses,” *Journal of Experimental Medicine*, vol. 207, no. 5, pp. 933–942, 2010.
[28] Y. S. Choi, J. A. Gullicksrud, S. Xing et al., “LEF-1 and TCF-1 orchestrate T(HF) differentiation by regulating differentiation circuits upstream of the transcriptional repressor Bcl6,” Nature Immunology, vol. 16, no. 9, pp. 980–990, 2015.

[29] D. Stauss, C. Brunner, F. Berberich-Siebelt, U. E. Ho pken, M. Lipp, and G. Mu ller, “The transcriptional coactivator Bob1 promotes the development of follicular T helper cells via Bcl6,” The EMBO Journal, vol. 35, no. 8, pp. 881–898, 2016.

[30] E. L. Stone, M. Pepper, C. D. Katayama et al., “ICOS coreceptor signaling inactivates the transcription factor FOXP1 to promote Th1 cell differentiation,” Immunity, vol. 42, no. 2, pp. 239–251, 2015.

[31] S. M. Kerfoot, G. Yari, J. R. Patel et al., “Germinal center B cell and T follicular helper cell development initiates in the interfollicular zone,” Immunity, vol. 34, no. 6, pp. 947–960, 2011.

[32] H. Qi, J. L. Cannons, F. Klauschen, P. L. Schwartzberg, and R. N. Germain, “SAP-controlled T-B cell interactions underlie germinatal centre formation,” Nature, vol. 455, no. 7214, pp. 764–769, 2008.

[33] C. S. Ma, N. J. Hare, K. E. Nichols et al., “Impaired humoral immunity in X-linked lymphoproliferative disease is associated with defective IL-10 production by CD4+ T cells,” Journal of Clinical Investigation, vol. 115, no. 4, pp. 1049–1059, 2005.

[34] L. V. Riella, A. M. Paterson, A. H. Sharpe, and A. Chandraker, “Role of the PD-1 pathway in the immune response,” American Journal of Transplantation, vol. 12, no. 10, pp. 2575–2587, 2012.

[35] A. L. Rankin, H. MacLeod, S. Keegan et al., “IL-21 receptor is critical for the development of memory B cell responses,” Journal of Immunology, vol. 186, no. 2, pp. 667–674, 2011.

[36] X. Ou, S. Xu, and K.-P. Lam, “Deficiency in TNFRSF13B (TACI) expands T follicular helper and germinal center B cells via increased ICOS-ligand expression but impairs plasma cell survival,” Proceedings of the National Academy of Sciences of the United States of America, vol. 109, no. 38, pp. 15401–15406, 2012.

[37] R. Gonenka, A. H. Matthews, B. Zhang et al., “Local BllyS production by T follicular cells mediates retention of high affinity B cells during affinity maturation,” The Journal of Experimental Medicine, vol. 211, no. 1, pp. 45–56, 2014.

[38] E. Hams, M. J. McCarron, S. Amu et al., “Blockade of B7-H1 (programmed death ligand 1) enhances humoral immunity by positively regulating the generation of T follicular helper cells,” The Journal of Immunology, vol. 186, no. 10, pp. 5648–5655, 2011.

[39] D. Kashiwakuma, A. Suto, Y. Hiramatsu et al., “B and T lymphocyte attenuator suppresses IL-21 production from follicular Th cells and subsequent humoral immune responses,” The Journal of Immunology, vol. 185, no. 5, pp. 2730–2736, 2010.

[40] M. A. Linterman, W. Pierson, S. K. Lee et al., “Foxp3+ follicular regulatory T cells control the germinal center response,” Nature Medicine, vol. 17, no. 8, pp. 975–982, 2011.

[41] Y. Chung, S. Tanaka, F. Chu et al., “Follicular regulatory T cells expressing Foxp3 and Bcl-6 suppress germinal center reactions,” Nature Medicine, vol. 17, no. 8, pp. 983–988, 2011.

[42] S. G. Kang, W.-H. Liu, P. Lu et al., “MicroRNAs of the miR-17–92 family are critical regulators of TFH differentiation,” Nature Immunology, vol. 14, no. 8, pp. 849–857, 2013.

[43] D. Baumjohann, R. Kageyama, J. M. Clingan et al., “The microRNA cluster miR-17–92 promotes TFH cell differentiation and represses subset-inappropriate gene expression,” Nature Immunology, vol. 14, no. 8, pp. 840–848, 2013.

[44] H. Takahashi, T. Kanno, S. Nakayama et al., “TGF-β and retinoic acid induce the microRNA miR-10a, which targets Bcl-6 and constrains the plasticity of helper T cells,” Nature Immunology, vol. 13, no. 6, pp. 587–595, 2012.

[45] A. Pratama, M. Srivastava, N. J. Williams et al., “MicroRNA-146a regulates ICOS-ICOSL signalling to limit accumulation of T follicular helper cells and germinal centres,” Nature Communications, vol. 6, article 6436, 2015.

[46] A. Ballesters-Tato, B. León, B. A. Graf et al., “Interleukin-2 inhibits germinal center formation by limiting T follicular helper cell differentiation,” Immunity, vol. 36, no. 5, pp. 847–856, 2012.

[47] R. J. Johnston, Y. S. Choi, J. A. Diamond, J. A. Yang, and S. Crotty, “STAT5 is a potent negative regulator of THF cell differentiation,” Journal of Experimental Medicine, vol. 209, no. 2, pp. 243–250, 2012.

[48] R. I. Nurieva, A. Podd, Y. Chen et al., “STAT5 protein negatively regulates T follicular helper (Thf) cell generation and function,” The Journal of Biological Chemistry, vol. 287, no. 14, pp. 11234–11239, 2012.

[49] K. J. Oestreich, S. E. Mohn, and A. S. Weinmann, “Molecular mechanisms that control the expression and activity of Bcl-6 in Tfh1 cells to regulate flexibility with a Tfh1-like gene profile,” Nature Immunology, vol. 13, no. 4, pp. 405–411, 2012.

[50] C. G. Vinuesa, M. C. Cook, C. Angelucci et al., “A RING-type ubiquitin ligase family member required to repress follicular helper T cells and autoimmunity,” Nature, vol. 435, no. 7041, pp. 452–458, 2005.

[51] M. A. Linterman, R. J. Rigby, R. K. Wong et al., “Follicular helper T cells are required for systemic autoimmunity,” Journal of Experimental Medicine, vol. 206, no. 3, pp. 561–576, 2009.

[52] K. Ozaki, R. Spolski, R. Ettinger et al., “Regulation of B cell differentiation and plasma cell generation by IL-21, a novel inducer of Blimp-1 and Bcl-6,” The Journal of Immunology, vol. 173, no. 9, pp. 5361–5371, 2004.

[53] J. A. Bubier, S. M. Bennett, T. J. Sproule et al., “Treatment of BXSB-Yaa mice with IL-21R-Fc fusion protein minimally attenuates systemic lupus erythematosus,” Annals of the New York Academy of Sciences, vol. 1100, pp. 590–601, 2007.

[54] D. Herber, T. P. Brown, S. Liang, D. A. Young, M. Collins, and K. Dunussi-Joannopoulos, “IL-21 has a pathogenic role in a lupus-prone mouse model and its blockade with IL-21R.Fc reduces disease progression,” The Journal of Immunology, vol. 178, no. 6, pp. 3822–3830, 2007.

[55] A. L. Rankin, H. Guay, D. Herber et al., “IL-21 receptor is required for the systemic accumulation of activated B and T lymphocytes in MRL/MpJ-Fas lpr/lpr/J mice,” Journal of Immunology, vol. 188, no. 4, pp. 1656–1667, 2012.

[56] J. A. Bubier, T. J. Sproule, O. Foreman et al., “A critical role for IL-21 receptor signaling in the pathogenesis of systemic lupus erythematosus in BXSB-Yaa mice,” Proceedings of the National Academy of Sciences of the United States of America, vol. 106, no. 5, pp. 1518–1523, 2009.

[57] J. M. Odegard, B. R. Marks, L. D. Diplacido et al., “ICOS-dependent extracellular helper T cells elicit IgG production via IL-21 in systemic autoimmunity,” Journal of Experimental Medicine, vol. 205, no. 12, pp. 2873–2886, 2008.

[58] J. William, C. Euler, S. Christensen, and M. J. Shiroma, “Evolution of autoantibody responses via somatic hypermutation outside of germinal centers,” Science, vol. 297, no. 5589, pp. 2066–2070, 2002.

[59] N. Simpson, P. A. Gatenby, A. Wilson et al., “Expansion of circulating T cells resembling follicular helper T cells is a fixed
phenotype that identifies a subset of severe systemic lupus erythematosus," *Arthritis and Rheumatism*, vol. 62, no. 1, pp. 234–244, 2010.

[60] J.-Y. Choi, J.-H.-E. Ho, S. G. Pasoto et al., "Circulating follicular helper-like T cells in systemic lupus erythematosus: association with disease activity," *Arthritis and Rheumatology*, vol. 67, no. 4, pp. 988–999, 2015.

[61] X. Feng, D. Wang, J. Chen et al., "Inhibition of aberrant circulating Tfh cell proportions by corticosteroids in patients with systemic lupus erythematosus," *PLoS ONE*, vol. 7, no. 12, Article ID e59892, 2012.

[62] X. Zhang, E. Lindwall, C. Gauthier et al., "Circulating PD-1+CXCR3-CXCR5+memory Tfh cells are highly antigenic, and contain specific subsets that differentially support antibody secretion," *Immunity*, vol. 34, no. 1, pp. 108–121, 2011.

[63] S. E. Bentebibel, S. Lopez, G. Obermoser et al., "Induction of ICOS CXCR3 CXCR5 TH cells correlates with antibody responses to influenza vaccination," *Science Translational Medicine*, vol. 5, no. 7, Article ID 176ra32, 2013.

[64] J. He, L. M. Tsai, Y. Leong et al., "Circulating precursor CCR7loPD-1hi CXCR5+ CD4+ T cells indicate Tfh cell activity and promote antibody responses upon antigen reexposure," *Immunity*, vol. 39, no. 4, pp. 770–781, 2013.

[65] M. Locci, C. Havenar-Daughton, E. Landais et al., "Human circulating PD-1+CXCR3-CXCR5+ memory Tfh cells are highly functional and correlate with broadly neutralizing HIV antibody responses," *Immunity*, vol. 39, no. 4, pp. 758–769, 2013.

[66] C. Le Coz, A. Joublin, J.-L. Pasquali, A.-S. Korganow, H. Dumortier, and F. Monneaux, "Circulating Tfh subset distribution in lupus is strongly affected by lupus patients with a active disease," *PLoS ONE*, vol. 8, no. 9, Article ID e75319, 2013.

[67] G. C. Zeller, J. Hirahashi, A. Schwarting, A. H. Sharpe, and V. R. Kelley, "Inducible co-stimulator null MRL-Faslp mice: uncoupling of autoantibodies and T cell responses in lupus," *Journal of the American Society of Nephrology*, vol. 17, no. 1, pp. 122–130, 2006.

[68] Y.-J. Liu, D. E. Joshua, G. T. Williams, C. A. Smith, J. Gordon, and I. C. M. MacLennan, "Mechanism of antigen-driven selection in germinal centres," *Nature*, vol. 342, no. 6252, pp. 929–931, 1989.

[69] A. Desai-Mehta, L. Lu, R. Ramsey-Goldman, and S. K. Datta, "Hyperexpression of CD40 ligand by B and T cells in human lupus and its role in pathogenic autoantibody production," *Journal of Clinical Investigation*, vol. 97, no. 9, pp. 2063–2073, 1996.

[70] C. G. Katsiari, S.-N. C. Liossis, A. M. Dimopoulos, D. V. Charalambopoulos, M. Mavrikakis, and P. P. Sfikakis, "CD40L overexpression on T cells and monocytes from patients with systemic lupus erythematosus is resistant to calcineurin inhibition," *Lupus*, vol. 11, no. 6, pp. 370–378, 2002.

[71] Y. Zhou, J. Yuan, Y. Pan et al., "T cell CD40LG gene expression and the production of IgG by autologous B cells in systemic lupus erythematosus," *Clinical Immunology*, vol. 132, no. 3, pp. 362–370, 2009.

[72] H. Xu, X. Li, D. Liu et al., "Follicular T-helper cell recruitment governed by bystander B cells and ICOSL-driven motility," *Nature*, vol. 496, no. 7446, pp. 523–527, 2013.

[73] D. Liu, H. Xu, C. Shih et al., "T-B-cell entanglement and ICOSL-driven feed-forward regulation of germinal centre reaction," *Nature*, vol. 517, no. 7533, pp. 214–218, 2015.

[74] X.-N. Wu, Y.-X. Ye, J.-W. Niu et al., "Defective PTEN regulation contributes to B cell hyperresponsiveness in systemic lupus erythematosus," *Science Translational Medicine*, vol. 6, no. 246, Article ID 246ra99, 2014.

[75] J.-H. Yang, J. Zhang, Q. Cai et al., "Expression and function of inducible costimulator on peripheral blood T cells in patients with systemic lupus erythematosus," *Rheumatology*, vol. 44, no. 10, pp. 1245–1254, 2005.

[76] A. Hutloff, K. Büchner, K. Reiter et al., "Involvement of inducible costimulator in the exaggerated memory B cell and plasma cell generation in systemic lupus erythematosus," *Arthritis and Rheumatism*, vol. 50, no. 10, pp. 3211–3220, 2004.

[77] W.-X. Li, H.-F. Pan, G.-P. Chen, J.-H. Tao, X.-P. Li, and D.-Q. Ye, "Expression of inducible co-stimulator on peripheral blood T lymphocytes in patients with lupus nephritis," *Rheumatology International*, vol. 32, no. 7, pp. 2051–2055, 2012.

[78] S. Patschan, S. Dolf, A. Kribben et al., "CD134 expression on CD4+ T cells is associated with nephritis and disease activity in patients with systemic lupus erythematosus," *Clinical and Experimental Immunology*, vol. 145, no. 2, pp. 235–242, 2006.

[79] J. Aten, A. Roos, N. Claessen, E. J. M. Schilder-Tol, I. J. M. ten Berge, and J. J. Weening, "Strong and selective glomerular localization of CD134 ligand and TNF receptor-1 in proliferative lupus nephritis," *Journal of the American Society of Nephrology*, vol. 11, no. 8, pp. 1426–1438, 2000.

[80] D. S. C. Graham, R. R. Graham, H. Manku et al., "Polymorphism at the TNF superfamily gene TNFSF4 confers susceptibility to systemic lupus erythematosus," *Nature Genetics*, vol. 40, no. 1, pp. 83–89, 2008.

[81] C. Jacquemin, N. Schmitt, C. Contin-Bordes et al., "OX40 ligand contributes to human lupus pathogenesis by promoting T follicular helper responses," *Immunity*, vol. 42, no. 6, pp. 1159–1170, 2015.

[82] H.-Y. Chun, J.-W. Chung, H.-A. Kim et al., "Cytokine IL-6 and IL-10 as biomarkers in systemic lupus erythematosus," *Journal of Clinical Immunology*, vol. 27, no. 5, pp. 461–466, 2007.

[83] G. Grondal, I. Gunnarsson, J. Rönnelid, S. Rogberg, L. Klareskog, and I. Lundberg, "Cytokine production, serum levels and disease activity in systemic lupus erythematosus," *Clinical and Experimental Rheumatology*, vol. 18, no. 5, pp. 565–570, 2000.

[84] Y. Horii, M. Iwano, E. Hirata et al., "Role of interleukin-6 in the progression of mesangial proliferative glomerulonephritis," *Kidney International*, vol. 39, pp. S71–S75, 1993.

[85] P. Esposito, M. M. Balletta, A. Procino, L. Postiglione, and B. Memoli, "Interleukin-6 release from peripheral mononuclear cells is associated to disease activity and treatment response in patients with lupus nephritis," *Lupus*, vol. 18, no. 14, pp. 1329–1330, 2009.
C.M. Hedrich, T. Rauen, S. A. Apostolidis et al., "Stat3 promotes IL-10 expression in lupus T cells through trans-activation and chromatin remodeling," Proceedings of the National Academy of Sciences of the United States of America, vol. III, no. 37, pp. 13457–13462, 2014.

Y. Tang, X. Luo, H. Cui et al., "MicroRNA-146a contributes to abnormal activation of the type I interferon pathway in human lupus by targeting the key signaling proteins," Arthritis and Rheumatism, vol. 60, no. 4, pp. 1065–1075, 2009.

B. A. Kiberd, "Interleukin-6 receptor blockage ameliorates murine lupus nephritis," Journal of the American Society of Nephrology, vol. 4, no. 1, pp. 58–61, 1993.
[120] B. K. Finkl, B. Chan, and D. Wofsy, "Interleukin 6 promotes murine lupus in NZB/NZW F1 mice," Journal of Clinical Investigation, vol. 94, no. 2, pp. 585–591, 1994.

[121] M. Mihara, N. Takagi, Y. Takeda, and Y. Oh sugi, "IL-6 receptor blockade inhibits the onset of autoimmune kidney disease in NZB/W F1 mice," Clinical and Experimental Immunology, vol. 112, no. 3, pp. 397–402, 1998.

[122] J. A. Gross, J. Johnston, S. Mudri et al., "TACI and BCMA are receptors for a TNF homologue implicated in B-cell autoimmune disease," Nature, vol. 404, no. 6781, pp. 995–999, 2000.

[123] M. Ramanujam, R. Bethunaickan, W. Huang, H. Tao, M. P. Madaio, and A. Davidson, "Selective blockade of BAFF for the prevention and treatment of systemic lupus erythematosus nephritis in NZM2410 mice," Arthritis and Rheumatism, vol. 62, no. 5, pp. 1457–1468, 2010.

[124] Y. Vugmeyster, H. Guay, P. Szklut et al., "In vitro potency, pharmacokinetic profiles, and pharmacological activity of optimized anti-IL-21R antibodies in a mouse model of lupus," mAbs, vol. 2, no. 3, pp. 335–346, 2010.

[125] M. Zhang, G. Yu, B. Chan et al., "Interleukin-21 receptor blockade inhibits secondary humoral responses and halts the progression of preestablished disease in the (NZB × NZW)F1 systemic lupus erythematosus model," Arthritis & Rheumatology, vol. 67, no. 10, pp. 2723–2731, 2015.

[126] Y. Pan, T. Jia, Y. Zhang et al., "MS2 VLP-based delivery of microRNA-146a inhibits autoantibody production in lupus-prone mice," International Journal of Nanomedicine, vol. 7, pp. 5957–5967, 2012.

[127] L. J. Edwards, M. Mizui, and V. Kyttaris, "Signal transducer and activator of transcription (STAT) 3 inhibition delays the onset of lupus nephritis in MRL/lpr mice," The Journal of Experimental Medicine, vol. 993–1006, 2015.

[128] N. M. Haynes, C. D. C. Allen, R. Lesley, K. Killeen, and J. G. Cyster, "Role of CXCR5 and CCR7 in follicular Th cell positioning and appearance of a programmed cell death gene-1High germinal center-associated subpopulation," Journal of Immunology, vol. 179, no. 8, pp. 5099–5108, 2007.

[129] D. Breitfeld, L. Ohl, E. Kremmer et al., "Follicular B helper T cells express CXC chemokine receptor 5, localize to B cell follicles, and support immunoglobulin production," The Journal of Experimental Medicine, vol. 192, no. 11, pp. 1545–1551, 2000.

[130] P. Schaerli, K. Willmann, A. B. Lang, M. Lipp, P. Loetscher, and B. Moser, "CXC chemokine receptor 5 expression defines follicular homing T cells with B cell helper function," The Journal of Experimental Medicine, vol. 192, no. 11, pp. 1553–1562, 2000.

[131] T. M. Foy, J. D. Laman, J. A. Ledbetter, A. Aruffo, E. Claassen, and R. J. Noelle, "gg39-CD40 interactions are essential for germinal center formation and the development of B cell memory," The Journal of Experimental Medicine, vol. 180, no. 1, pp. 157–163, 1994.

[132] S. Salek-Ardakani, Y. S. Choi, M. R.-E. Benhnia et al., "B cell-specific expression of B7-2 is required for follicular Th cell function in response to vaccinia virus," The Journal of Immunology, vol. 186, no. 9, pp. 5294–5303, 2011.

[133] V. L. Bryant, C. S. Ma, D. T. Avery et al., "Cytokine-mediated regulation of human B cell differentiation into Ig-secreting cells: predominant role of IL-21 produced by CXCR5+ T follicular helper cells," Journal of Immunology, vol. 510, no. 12, pp. 8180–8190, 2007.

[134] R. L. Reinhardt, H.-E. Liang, and R. M. Locksley, "Cytokine-secreting follicular T cells shape the antibody repertoire," Nature Immunology, vol. 10, no. 4, pp. 385–393, 2009.

[135] I. Yusuf, R. Kageyama, L. Monticelli et al., "Germinal center follicular helper cell II-4 production is dependent on signaling lymphocytic activation molecule receptor (CD150)," Journal of Immunology, vol. 185, no. 1, pp. 190–202, 2010.

[136] K. L. Good-Jacobson, C. G. Szumilas, L. Chen, A. H. Sharpe, M. M. Tomayko, and M. J. Shlomchik, "PD-1 regulates germinal center B cell survival and the formation and affinity of long-lived plasma cells," Nature Immunology, vol. 11, no. 6, pp. 535–542, 2010.