Functions of TFH Cells in Common Variable Immunodeficiency

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Common variable immunodeficiency is the most common clinical primary immunodeficiency in adults. Its hallmarks are hypogammaglobulinemia and compromised B-cell differentiation into memory or antibody-secreting cells leading to recurrent infections. This disease is heterogeneous, with some patients harboring multiple complications such as lymphoproliferative disorders, autoimmune manifestations, or granulomatous inflammation. The mechanisms leading to these complications remain elusive despite numerous associations found in the literature. For instance, although described as a B cell intrinsic disease, numerous abnormalities have been reported in other immune cell compartments. Here, we tuned our attention to follicular helper T cells, a CD4+ T cell population specialized in B cell help, considering the recent publications showing an involvement of these cells in CVID pathogenesis.

Keywords: follicular helper T cells, CVID, complications, B cells, IFNγ

INTRODUCTION

Common variable immunodeficiency (CVID) is an umbrella name for the most common symptomatic, but also the most heterogeneous, primary antibody deficiency in adults. Typical clinical features of this heterogeneous group of disorders include recurrent infections, decreased serum immunoglobulin (Ig) and impaired specific antibody (Ab) responses to vaccines reflecting impaired B cell responses (1). Diagnosis criteria recently defined by the European Society for ImmunoDeficiencies include at least one of the following: increased susceptibility to infections, autoimmune manifestations, granulomatous disease, unexplained polyclonal lymphoproliferation, or affected family member with antibody deficiency. Moreover, the following parameters should be present to confirm the diagnosis: diagnosis after the age of 4 years, no evidence of profound T-cell deficiency, deficit in serum Ig (multiple classes) not explained by other known causes, and impaired vaccination responses or low switched memory B cells (smB cells) (2, 3). CVID has a complex genetic basis, with monogenetic causative forms and genetic predispositions (4), as reviewed in Cunningham-Rundles (5). Some CVID forms are inherited, but family members of CVID patients are usually normal and not all individuals who inherit a gene mutation associated with CVID will develop the disease (6). Nevertheless, a genetic cause has been identified in about 25% of CVID patients using next-generation sequencing. As examples, mutations in several genes encoding for B cell receptor complex associated proteins, B cell activating factor receptor (BAFF-R), inducible co-stimulator (ICOS), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), phosphatidylinositol 3-kinase (PI3K), and in lipopolysaccharide-responsive beige-like anchor (LRBA) protein or more recently the NFKB family have been described (5–7). Mutations in the TNFRSF13B gene encoding
the transmembrane activator and CAML interactor (TACI) are found in 8–10% of patients (8) but relatives to CVID patients with mutations in TACI display normal levels of Ig. The identification of mutations in genes encoding factors important in B cell generation or differentiation is not surprising, as CVID patients present abnormalities in the B cell compartment. In fact, impaired B cell differentiation is a hallmark of the disease and, despite normal levels of total B cells in most cases, post-germinall center (GC) B cells are defective and patients harbor lower levels or absence of smB cells (9, 10). Consequently, multiple CVID classifications based on B-cell phenotype have been proposed. On top of these classifications, two groups of patients are often described in the literature, namely one comprising patients that show only recurrent infections, and the other with patients harboring at least one of the following complications: (i) benign, granulomatous, or malignant lymphoproliferation, (ii) chronic enteropathy, and (iii) autoimmune manifestations. Moreover, a report in 2014 of the largest cohort of CVID patients studied so far highlighted that an early-onset of CVID (before the age of 10) is associated with infections (especially pneumonia) rather than other complications, suggesting two distinct disease entities (11). The pathogenesis leading to immune disorders of CVID is still poorly understood, but functional impairments in multiple immune cell types may be responsible for some of the pathophysiology of CVID.

IMMUNOLOGICAL FEATURES OF CVID PATIENTS WITH NON-INFECTIONOUS COMPLICATIONS

More than half of the patients harbor non-infectious complications causing increased morbidity and mortality (12). Cancers occur in 20% of CVID patients, the majority of cancers being lymphoma (13, 14). More than 25% of CVID patients have autoimmune complications (15). Immune thrombocytopenia (ITP) and autoimmune hemolytic anemia are the most frequent disorders, but many others such as vitiligo, pernicious anemia, systemic lupus erythematosus, rheumatoid arthritis, antiphospholipid syndrome, juvenile idiopathic arthritis, Sjögren’s disease, psoriasis, thyroiditis, uveitis, and vasculitis can also be found in CVID patients (15). As impairment of B cell maturation is a hallmark of the disease, these cells have drawn a lot of attention. Wehr et al. have shown a significant decrease in isotype-switch memory B cells in patients with non-infectious complications such as autoimmune, granulomatous disease, lymphoid hyperplasia, or splenomegaly (12). Intriguingly, despite defects in B cell differentiation and serum Ig, CVID patients develop autoantibodies and autoimmune manifestations. Such a paradigm might be due to a default in specific checkpoints for autoreactive B cells, although this hypothesis has yet to be proven. Interestingly, autoimmunity in CVID has been associated with the presence of CD21low B cells, an “innate-like” population expressing low levels of CD38 but exhibiting autoreactivity (16, 17). Moreover, an increase of CD21low B cells has been observed in CVID patients presenting immune thrombocytopenia (ITP) (18). It has been shown that CD21low cells may develop from memory B cells under chronic inflammatory conditions and are present at high levels in autoimmune patients (19). These observations suggest a role for these CD21low smB cells in the development of autoimmune complications observed in CVID patients, but this possibility remains to be explored.

Beyond the impairment of B cell functions, numerous immune alterations have been described in CVID patients with non-infectious manifestations. For instance, dysfunctions in monocytes/macrophages, dendritic cells (20), NK cells and innate lymphoid cells (ILCs) have been reported. Monocytes have impaired antigen-presenting capacities but increased capacity to produce reactive oxygen species or IL-12 (21). By contrast, IL-12 production by dendritic cells from CVID patients is lower than that of healthy donors, reflecting a defective maturation of these cells (22, 23). Two studies have reported a decrease in ILCs, either in CD127+CD90+ ILCs (24) or in ILC2s (25). By contrast, a study from Cols et al. (26) shows an expanded population of ILCs harboring an IFNγ signature in patients with non-infectious complications, suggesting that ILCs may be a critical source of IFNγ in these patients. Overall, defining the roles of ILCs in CVID pathogenesis still needs further investigation.

Numerous studies have reported abnormalities in the T-cell compartment [as reviewed in (27)], which is not surprising given the central role of T cells, especially CD4+ T cells, in B cell activation and differentiation into memory and Ig-producing cells. Patients with complications usually have low numbers of naive CD4+ T cells but increased activated CD4+ T cell counts (28–30), defective T cell functions (lower proliferative capacities, abnormalities in cytokine production) and reduced levels of regulatory T cells (31). Given their function as B helper cells, TFH represent a CD4+ T cell subset of great interest in CVID pathogenesis and will now be discussed.

OVERVIEW OF TFH CELL FUNCTIONS

TFH are a CD4+ T cell subset specialized in providing B cell help. They are essential for B cell differentiation into Ig-producing plasma cells and for generation of memory B cells. TFH are characterized by a unique set of molecules associated with their functions. The hallmark of TFH is CXCR5 expression, which allows their migration into GC follicles of secondary lymphoid organs through the attractive effect of the CXCL13 chemokine (32–34). Moreover, they express the transcription factor B cell lymphoma 6 (BCL-6), the co-receptors CD40L, programmed cell death 1 (PD-1) and ICOS, and they produce IL-21 (34), all of which being involved in their functions.

Mouse models have led to a better understanding of TFH biology over the past decade and these discoveries have already been reviewed (34–37). Here, we will focus on human TFH and their subsets. In fact, recent studies have considerably increased our knowledge of the human counterpart. The discovery of human circulating TFH within the memory CD4+ T cell compartment has enabled a better understanding of these cells, since access to blood samples is much easier than access
to secondary lymphoid organs such as spleen from cadaveric organ donors or tonsils from children (38). They are considered as memory cells and reflect the \textit{bona fide} TFH present in GC counterparts, even if they lack BCL-6 and ICOS expression. Interestingly, a recent and elegant study from Vella et al. comparing TFH from LN, thoracic duct lymph and blood shows that these cells share TCR clonotype, phenotype and transcriptional signatures, thus reinforcing the idea that the examination of circulating cells reflects what happens in GC (39).

Based on the expression of the chemokine receptors CXCR3 and CCR6, Morita et al. have identified three subsets of TFH harboring different functions and affiliated with the classical helper subsets Th1, Th2, and Th17 (38) (Table 1). TFH1 are CXCR3$^+$CCR6$^-$, express T-bet and produce IFNγ; TFH2 are CXCR3$^-$CCR6$^+$, express GATA3 and produce IL-21 and IL-4; and TFH17 are CXCR3$^+$CCR6$^+$, express RORγT and produce IL-21 and IL-17A. More importantly, these subsets are divided into two groups based on their B helper cell functions, in particular their capacity to induce naïve B cells to produce Ig: TFH2 and TFH17 are considered efficient helper cells, while TFH1 are non-efficient helpers (38, 42, 43). Based on CCR7, PD-1 and ICOS expression, these subsets can be further divided into different functional subpopulations, leading to the proposition by Ueno's group to include all these markers for human blood subsets and disease, as reviewed in Ueno et al. (35), Crotty (36), and Ma and Deenick (64). They are involved in protection against numerous pathogens through the induction of Ab responses and vaccine-induced immunity, as well as in autoimmune diseases or HIV infection. The role of TFH in human primary immunodeficiency has already been well documented and reviewed (64, 65). For instance, distinct monogenic mutations in STAT3, CD40LG, BTK, IL10R, or NEMO that lead to different types of primary immune deficiency are associated with decreased circulating TFH number (66).

**Table 1** | Main characteristics of circulating TFH subsets.

| TFH1 | TFH2 | TFH17 | TFR |
|------|------|-------|-----|
| B helper function | ±    | +    | +   | CD25$^+$ |
| Surface marker     | CXCR3 | −    | CCR6 | CD127$^+$ |
| Transcription factor | T-bet | Gata3 | RORγT | FoxP3$^+$ |
| Cytokine profile   | IL21$^+$ | IFNγ | IL21; IL4; IL13 | IL21; IL17; IL-22; IL-10 |

The main characteristics of the circulating CD4$^+$CD45RA$^-$CXCR5$^-$ follicular helper T cell subsets are described.

*Both FoxP3$^+$ and FoxP3$^-$ TFH have been reported (40, 41).

are key regulators of this process. Dermal CD14$^+$ DCs have been found as the best skin DC subset to drive TFH differentiation (60). Others have identified CD1a$^+$ dermal DCs and Langerhans cells as able to polarize CD4 T cell into IL-21 producer cells (61, 62). Recently, Durand et al. have uncovered tonsil CD2C as the best TFH polarization inducer among the DC subsets they tested, and have shown that the interaction with tonsil macrophages located in B cell follicles is necessary for optimal TFH function (63).

TFH are involved in numerous biological processes of health and disease, as reviewed in Ueno et al. (35), Crotty (36), and Ma and Deenick (64). They are involved in protection against numerous pathogens through the induction of Ab responses and vaccine-induced immunity, as well as in autoimmune diseases or HIV infection. The role of TFH in human primary immunodeficiency has already been well documented and reviewed (64, 65). For instance, distinct monogenic mutations in STAT3, CD40LG, BTK, IL10R, or NEMO that lead to different types of primary immune deficiency are associated with decreased circulating TFH number (66).

**TFH AND CVID**

As mentioned earlier, CVID is defined by B cell defects leading to low levels of serum Ig and impaired Ab responses. Nevertheless, defects in other immune cells are also present. Given their role as B helper cells, it is of interest to analyze TFH subsets in CVID patients. One series of evidence for TFH involvement in CVID pathogenesis is given by genetic analysis. The most striking is the rare deficiency in inducible T-cell COStimulator (ICOS), a co-receptor expressed by T cells. In these patients, B cells are genetically normal but do not receive optimal help from T cells, which leads to impaired T-cell dependent B-cell activation, absence of memory B cells, and failure in class-switching leading to hypogammaglobulinemia (67–69). Warnatz et al. studied nine patients with ICOS deletion and showed that combining all clinical features of the patients outlines the full range of associated complications to CVID (69). Interestingly, Bossaller et al. showed that ICOS deficiency is associated with a defect of TFH in germinal centers (68), showing that ICOS is essential for TFH generation in humans as well as in mice (70). Similarly, patients with a mutated NFKB2 gene showed decreased levels of circulating TFH (71, 72). By contrast, Romberg et al. showed that a single TACI mutation leads to increased
levels of circulating THF in CVID patients which correlate with levels of anti-nuclear antibodies suggesting that THF may favor autoreactive B cell activation (73). Interestingly, Ellyard et al. also observed increased THF, particularly circulating THF1, in TACI mutant patients and of PD-1hi CCR7lo THF cells in CTLA4 mutant patients (74).

Interestingly, our group (75) and others (76–78) observed an increase of circulating THF (memory CXCR5+ CD4 T cells) in CVID patients harboring non-infectious complications. Moreover, THF expressing PD-1 were present at higher levels in CVID patients with complications (75–78). Patients classified as smB– based on the EUROClass have <2% of switched memory B cells among circulating CD19+ cells (12). Interestingly, smB– patients have higher levels of circulating THF (77) which is even more pronounced in the smB– CD21low subgroup (78) than smB+ patients. The switched memory B cell population (IgG+) contains some autoreactive B cells in normal adults (79), and CD21low memory B cells are increased in several autoimmune contexts (18). One can then hypothesize that smB cells in CVID patients, despite their low levels, contribute to autoimmunity, so THF could participate to autoimmune manifestations through their role as smB cell inducers. Nevertheless, patients with autoimmune complications present similar levels of THF or THF subtypes to patients harboring other types of comorbidities (75), meaning that further experiments are needed to determine the impact of THF on autoreactive Ab generation in CVID patients.

As explained earlier, THF can be divided into two subsets: the non-efficient helper THF1 and the efficient helpers THF2 and THF17. Interestingly, we (75) and others (77, 78, 80) highlight a specific increase of the circulating THF1 only in non-infectious CVID patients. Moreover, CXCR3hi (75) or T-bet+ (78) cells were amplified in secondary lymphoid organs of CVID patients, suggesting that the blood observations reflect the GC counterpart. In contrast, Th17-oriented THF were decreased. An increase in CD25+CD127–CXCR5+PD-1+ cells was observed, but these cells do not present regulatory functions and still need to be further characterized (80). THF1 are not efficient B helper cells, partly due to their poor production of IL-21 (38). The combination of IL-21 and CD40 stimulation is able to restore Ig production and to improve memory B cell survival in in vitro settings using cells from CVID patients (81, 82). Moreover, addition of IL-4 and IL-21 (cytokines produced by THF2) improved IgG production in some patients (83). Thus, the imbalance between THF subsets, stable over time (75), could lead to poor IgG production. As THF1 are good IFNγ producers and are increased in patients, one may hypothesize involvement of this cytokine in CVID pathogenesis. Surprisingly, even though two groups observed enhanced IFNγ production by THF in CVID patients (77, 78), Le Coz et al. did not, rather finding increased IL-21+ cells and accordingly efficient helper B cell function in CVID THF despite observing a THF1/THF2-17 imbalance (80). Moreover, studies on putative IFNγ function in CVID are also puzzling. In fact, Desjardin et al. reported that addition of IFNγ to cultured B cells from CVID patients did not modulate IgG production (83), while Unger et al. showed that exogenous IFNγ reduced IgG and IgA production in T/B co-cultures (78). Moreover, the impact of IFNγ on CD21low cell generation and/or on autoreactive B cell activation has not been directly addressed, therefore still awaiting determination. Altogether, these data highlight that more experiments are necessary to determine THF1 functions and putative IFNγ implication in the diverse clinical manifestations of CVID.

A question one may ask is the origin of the skewed THF populations in CVID patients. A recent study from Le Coz et al. highlighted that part of the naïve CD4 T cells from CVID patients with autoimmune cytopenias (AIC) are skewed toward a follicular commitment based on their expression of specific markers (CXCR5, PD-1, CCR7, CD38, ICOS, T-cell factor 1). In addition, some recently identified thymic emigrant cells (defined as CD45RA+CD31+) express CXCR5 and PD-1 in CVID patients with AIC (80). These data suggest that CD4 T cells present follicular aspects as early as thymic egress stage. Moreover, THF1 can differentiate from naïve CD4+ T cells by interacting with different dendritic cell subsets or under the influence of several cytokines such as IL-12 (55), TGFβ (56) or Activin A (57). Notably, Martinez-Pomar et al. reported high amounts of IL-12 in the sera of CVID patients (84), which was not confirmed by Le Coz et al. (80). By contrast, they found an increase in plasma levels of Activin A, correlating with circulating THF frequencies. They also observed increased ICOSL expression on monocytes and demonstrated that endotoxemia is involved in THF1 differentiation in CVID patients with AIC (80). Altogether, despite recent studies, the mechanisms leading to the imbalance of THF1 vs. THF2/THF17 in CVID patients still need to be fully decoded.

**CONCLUSION**

Evidence from the literature strongly suggests a role for THF in pathogenesis of the more severe forms of CVID, but more experiments are necessary to determine the mechanisms involved. A better understanding of these mechanisms would be of great interest to apprehend the immune context in CVID patients harboring non-infectious complications.

**AUTHOR CONTRIBUTIONS**

CL and DD wrote and edited the manuscript. SL, PB, and J-FV contributed to writing and critically revised the paper. All authors read, corrected, and approved the final manuscript.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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