T Cell Abnormalities in Common Variable Immunodeficiency

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Short title: T cell abnormalities in CVID

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Abstract
Common variable immunodeficiency (CVID) is the most common clinical primary immunodeficiency, which characterized by defect in B cells differentiation to plasma and memory B cells. Moreover, numerous T cell abnormalities have been described in these patients such as, decreased T cell count and proliferative response, increased of T cell activation and apoptosis, and abnormalities in cytokine production. The aim of this review is to describe phenotypic and functional defects of T cells in CVID patients, and to review the literature with respect to the effects of immunoglobulin substitution on the T cell component of CVID patients.

Key words: Common variable immunodeficiency, T cell, T helper cell, Regulatory T cells

Resumen
La inmunodeficiencia común variable (CVID) es la inmunodeficiencia primaria más frecuente. Se caracteriza por un defecto en la diferenciación de linfocitos B hacia células plasmáticas y linfocitos B memoria. Se han descrito numerosas alteraciones en los linfocitos T de estos pacientes, tales como disminución en el número de linfocitos T y en sus respuestas proliferativas, aumento en la activación de células T y en la apoptosis, así como alteraciones en la producción de citokinas. El objetivo de esta revisión es describir las alteraciones funcionales y fenotípicas de los linfocitos T en los pacientes con CVID y revisar la bibliografía en relación a los efectos que la administración de inmunoglobulinas produce en los linfocitos T de los pacientes con CVID.

Palabras clave:
Inmunodeficiencia común variable; células T; células T helper; células T reguladoras.
1. Introduction

Common variable immunodeficiency (CVID) is the most common clinical primary immunodeficiency (PID), which defined by defects in B-cell differentiation into plasma and memory B cells [1, 2]. The affected patients are characterized by increased susceptibility to recurrent infection, because of low levels of immunoglobulin in serum as well as reduced specific antibody response to protein and polysaccharide antigens [3-6]. Patients may also have a wide variety of clinical complications, including autoimmunity and inflammatory condition, lymphoid malignancy, granuloma and enteropathy, which have been recently considered in classification of CVID into clinical phenotypes with variable prognosis [7-11]. The most important cellular alteration in CVID patients is severe B cell defect, which leads to hypogammaglobulinemia. However, alteration in frequency and function of T cells has also been demonstrated in a number of patients with CVID [12-14]. The influence of these defects on the interaction between T and B cells could explain not only the defective antibody production, but also the development of other complications, including recurrent bacterial and viral infections, gastrointestinal disease, lymphoma, autoimmune, inflammatory features and early-onset bronchiectasis in CVID patients [15-17]. In this review, our aim is to describe phenotypic and functional defects of T cells in CVID patients, and to review the literatures with respect to the effects of immunoglobulin intravenous (IGIV) infusion on the T cell components in CVID.

2. T-cell abnormalities in CVID

There are various T cell subsets that all perform different functions, but among them the most important are CD4+ and CD8+ T cells (Table 1). Recent researches demonstrated that a subgroup of patients with clinically diagnosed CVID is T-cell deficient. However, based on revised European Society for Immunodeficiencies (ESID) diagnostic criteria for CVID (2014), there should be no evidence of profound T-cell deficiency. The profound T-cell deficiency in CVID patients are defined as two out of the following: 1- CD4+ cell numbers/µL: 2–6 y <300, 6–12 y <250, >12 y <200; 2- percent of naive CD4+ T cells: 2–6 y <25%, 6–16 y <20%, >16 y <10%; and 3- T-cell proliferation absent [18]. Those CVID patients who undergo profound T-cell deficiency will need to be considered as combined immunodeficiency (CID) [19, 20].
Traditionally the reported T-cell abnormalities in CVID are including a reduced T cell count and decreased lymphocyte proliferation in response to mitogens and antigens, defective T-cell signaling, decline of regulatory T cells (Tregs), uncontrolled T cell polarization, elevated levels of T-cell activation markers and abnormality in cytokine production secondary to the gene polymorphisms [12-14, 21-26].

CVID patients with T-cell abnormalities manifested a severe phenotype which presented more often with gastrointestinal tract disease, splenomegaly, granuloma and lymphoma [27, 28]. Moreover, parental consanguinity in CVID patients (cCVID) is associated with the severe T-cell abnormalities, lower age at onset and diagnosis, severity of disease and higher mortality rate. It is demonstrated that in cCVID patients naive CD4+ T cells are decreased, while activated CD4+, CD95+, CD8+ and HLA-DR+ T cells are increased, compared to patients without parental consanguinity. In these patients splenomegaly, granulomatous disease, polyclonal lymphocytic infiltration, bronchiectasis, enteropathy and opportunistic infections were more frequent [27, 29-31].

Recently, T-cell receptor excision circles (TRECs) and kappa-deleting recombination excision circles (KRECs) as circular DNA segments that persist in the T cells and B cells, are considered markers of new lymphocyte output [32]. Kamae et al. (2013) indicated that low TREC and/or KREC levels are useful biomarkers that associated with the overall survival rate in CVID patients [33]. Moreover, TRECs and KRECs are positively correlated to absolute counts of naive T and naive B, as well as to memory B cells, respectively. Accordingly, low TRECs and KRECs values reflect low naive T and B cells in some CVID patients with the potential to develop the CID phenotype [34]. In conclusion, TREC and KREC are valuable biomarkers for assessment of clinical severity, pathogenesis and prognosis of CVID patients in addition to distinguish between CVID and CID.

3. CD4+ T cells defects in CVID

Phenotypic and functional defects of CD4+ T cells in CVID patients have been known for a decade [35-37]. These abnormality are including increased number of activated CD4+ T cells and reduced number of total, naive and memory CD4+ T cells (Table 2), along with functional impairment such as reduced proliferation capacity and failure in cytokine production [37, 38]. This reduction in CD4+ T cells is associates with decrease in thymic output, increase in T-cell turnover and spontaneous apoptosis [12].
3.1. Naive CD4⁺ T cell: As mentioned, CVID patients have reduced number of naive CD4⁺ T cells and RTE cells. In a study by Oraei et al. (2012), CVID patients have lower number of naive and RTE CD4⁺ T cells in comparison with healthy controls. Interestingly, they showed that this reduction in male were more apparent than female patients [35]. Meanwhile, reduction in both total CD4⁺ and RTE counts of T cells, most pronounced in those CVID patients whom are involved with autoimmune cytopenia or polyclonal lymphoproliferation [13, 39]. Several studies shown that the severity and prognosis of CVID is reflected in a parallel loss of naive CD4⁺ T cells and there are a strong correlation between naive CD4⁺ T cell counts and clinical features [12, 13, 39, 40]. In this regard, when CVID patients were classified on the basis of clinical phenotypes (infection only, polyclonal lymphoproliferation, cytopenias, organ-specific autoimmunity, lymphoid malignancy and enteropathy), the autoimmune cytopenia and organ-specific autoimmunity groups had the most significantly reduced number of naive CD4⁺ T cells, followed by the polyclonal lymphoproliferation group [13]. Therefore, a new classification system according to the number of naive CD4⁺ T cells has been proposed and CVID patients were divided into three separate groups. Group A has significant decreased numbers of CD4⁺ naive T cells along with massive T-cell activation. Other characteristics including elevated apoptosis, disruption of normal TCR repertoires, splenomegaly and clinically more severe immunodeficiency are also attributed to this group. In group B, these mentioned features for group A were also present but they were less pronounced. Group C had normal numbers of naive CD4⁺ T cells, but an alteration in the CD8⁺ T cell compartment was presented. In addition, in group C, splenomegaly was less common than in the other groups and was correlated with a milder clinical future [12, 41, 42].

3.2. Activated CD4⁺ T cell: Elevation in CD4⁺ T cell count and its activation markers are also demonstrated in CVID patients [43]. These abnormalities are including an increase in HLA-DR, CD29, CD45RO, CD95 (APO-1/Fas) and a decrease in CD27, CD45RA and CD62L, especially in patients with increased number of CD21low B cells and decreased number of memory and regulatory B cells [25, 44]. CVID patients present with both low numbers of regulatory B cells and increased numbers of IFN-γ⁺TNF-α⁺CD4⁺ T cells [44, 45]. The defect in regulatory B cell responses, to T cell stimulation and differentiation explains the excessive CD4⁺ T cells activation that is a frequent finding in CVID patients.
In a study by Carbone et al. (2006), higher frequency of activated CD4\(^+\) T cells in patients with suspected IgG hyper catabolism was reported, as well as in those patients with clinical complications including lymphoid proliferation, splenomegaly and autoimmune disease [43]. Another study showed that CVID patients with autoimmune cytopenia have increased number of activated CD4\(^+\) T cells, decrease numbers of naive T cell along with an increased proportion of CD21 low B cells [15]. However, Boileau et al. (2011) proposed that this concurrent T and B cells phenotypic picture cannot be seen in CVID patients with other autoimmune manifestations and/or patients with splenomegaly [15, 46]. Overall, according to recent findings on correlation of CD21 low B cells in CVID and autoimmunity such as autoimmune cytopenia and rheumatoid arthritis (RA) [15, 46], it is suggested that in order to break down the B cell tolerance against auto-antigens, restricted subset of B cell and help from activated CD4\(^+\) T cells are needed. On the other hand it is demonstrated that dysfunctional BLK in B-cells of CVID patients perturbs proliferation and ability of B cells to elicit antigen-specific CD4\(^+\) T-cell responses [47]. These findings prove that T and B cell abnormalities in CVID are partially related to each other.

3.3. Memory CD4\(^+\) T cells: CVID patients also have defects in memory CD4\(^+\) T cells; however, literatures review showed a few key studies in this field. In a study, Giovannetti et al. (2007) showed that absolute counts of central memory CD4\(^+\) T cells have decrease in CVID patients, whereas no significant differences were detected for the effector memory cells [12]. In another study Bateman et al. (2012) revealed that within CD4\(^+\) memory subpopulations both central and effector memory cells had a significant difference between CVID clinical groups. They report CD4\(^+\) central memory T cells were reduced in the patients of autoimmune cytopenias group compared to both healthy and disease controls [13]. Regarding, memory T cells has different capacities to proliferate in response to antigen and/or cytokines to perform effectors functions, therefore recurrent infections and poor response to vaccine in CVID patients maybe a result of long-term defective immunity which is not caused by memory T cells.
4. **T helper cells defects**

There is little literature available that investigates T helper subsets and their pathogenic relationship with CVID. Barbosa et al. (2011) for the first time reported a decline in the frequency of circulating Th17 cells in CVID patients. In this study no association was demonstrated between the frequency of Th17 cells and transitional B cells. In contrast, they showed a negative correlation between Th17 cells and expansion of activated non-differentiated CD21 low B cells. Therefore, decline in the frequency of circulating Th17 cells are matched by the B-cell disturbances, a representative feature of germinal centers disruption [48]. Moreover, the frequency of Th17 cells was found to negatively correlate with activated CD4+ T cell in patients with CVID, while there was no correlation with naive and memory T cell balances. The frequency of Th1 cells was found to negatively correlate with naive CD4+ T cells and positively with the levels of activated CD4+ T cell in CVID patients [48]. In another study Ganjalikhani-Hakemi et al. (2014) evaluated the Th17 cell specific genes expression in CVID patients. Their result showed that frequencies of Th17 cells in the CVID patients were markedly decreased compared with the healthy individuals. Moreover, the mRNA levels of IL-17 and RORC2 in these patients was strongly lower than healthy controls, but slight reduction in the IL-23R expression has seen in the CVID patients [49]. As IL-17 and possibly Th17 cells can contribute to germinal centers function [50], these findings are consistent with the results of Barbosa et al. which propose the levels of IL-17 and Th17 cells were presenting a negative correlation with the pathological expansion of a B cell population associated with impaired germinal centers function in CVID [48]. In addition, IL-17 is also produced by follicular helper CD4+ T cells. According to the study by Romberg et al. (2014), the circulating follicular helper CD4+ T cells were significantly diminished in the CVID patients compared with the healthy subjects [51]. Therefore, the reduction of IL-17 in the CVID patients, in addition to Th17 defects, may be attributable to their diminished follicular helper T cells population.

Several studies demonstrated that Th17 cells and their proportion increased in a variety of autoimmune diseases such as autoimmune hemolytic anemia and immune thrombocytopenia [52], RA [53], psoriasis [54], and lupus [55]. However, Barbosa et al. found no increase in the frequency of Th17 cells in CVID patients with autoimmune manifestations, even when CVID patients were subdivided based on the
type of autoimmune disorders including organ specific autoimmunity and autoimmune cytopenias. In contrast, the CD21 low B cell subset was significantly increased in those CVID patients who have autoimmunity [15, 48]. In conclusion, no obvious association between autoimmune manifestations and frequency of Th17 cells and its pro-inflammatory cytokines was observed in CVID patients. However, in recent study, there were some findings about Th1/Th2 balance in CVID patients. Th1 cells seem to be more involved in the disease pathogenesis than Th2 cells. Those CVID patients with hepatomegaly had higher IL-2 and IFN-γ on stimulated CD4^+ T cells, and patients with granuloma were found to have higher CCR5 expression on CD4^+ T cells suggesting that Th1 cells may play a role in granuloma formation in CVID patients [14]. Overall, increased production of some chemokines [56] and cytokines, including IFN-γ [57], TNF-α [12], IL-12 [57], IL-9 [49], IL-4 and IL-10 [58] by Th subsets have been reported in in CVID patients [59]; some of these cytokines play a pivotal role in antibody synthesis. Rezaei et al. (2008) investigated Th1 and Th2 cytokine levels in serum of CVID patients. The results showed that the levels of IL-4 and IL-10 as Th2 cytokines were significantly higher in the CVID patients. However, there were no significant differences in Th1 cytokines (IL-2 and IFN-γ) compared to healthy controls [58]. Paradoxically, in a report by Del Vecchio et al. (2008), there is not seen any difference in IL-4 production by peripheral CD4^+ T cells but reduced IL-5 productions (a cytokine involved in the late regulation of B cell differentiation into plasma cells) was observed by these cells. Although the sample size of this study was low and only four CVID patients were evaluated, they concluded that the reduction of IL-5 may contribute to the defective antibody production in CVID patients [60]. The presented data regarding the altered cytokine signature in CVID patients are contradictory. We proposed that these altered cytokine profile may be attributed to the different type of specimen (serum, PBMCs or purified CD4^+ T cells), evaluation of cytokine secretion or its gene expression, different sample size in studies, patients clinical status and associated complications, as well as myeloid and lymphoid lineages activation which possibly driven by the high prevalence of bacterial infections in the gastrointestinal or respiratory tracts in some of CVID patients.
5. Regulatory T cell defects

Treg cells are key regulators of immune responses and play a crucial role in limiting unwanted and persistent immune activation. Several studies demonstrated that Tregs are reduced in CVID patients [61-63]. Moreover, residual Tregs appear to have reduced suppressive capacity [36] with down-regulation of FoxP3 protein and diminished expression of inhibitory markers such as CTLA-4 and GITR [64]. In contrast, recently Kutukculer et al. (2015) proposed Tregs do not play an important role in the pathogenesis of CVID. They reported not only percentages, but also absolute counts of Treg cells did not show any significant difference between CVID patients and healthy controls and also between severe and moderate disease patients [14].

Totally, there is a significant correlations between low numbers of Treg cells and autoimmune manifestations [61, 63, 65, 66] as well as granulomatous lesion [65] and splenomegaly [61]. Firstly, Genre et al. (2009) reported that CVID patients with autoimmune future had a significantly reduced frequency of Treg cells accompanied by a decreased intensity of Foxp3 expression. Moreover, the expression levels of Foxp3 in CVID patients without autoimmunity did not differ from those in healthy subjects [66]. Arumugakani et al. (2010) revealed low frequency of Treg cells is correlated with expansion of CD21low B cells in CVID patients with autoimmunity, while patients with splenomegaly have significant reduction in frequency and number of Treg cells [61]. In similar study Arandi et al. (2013) showed that CVID patients with autoimmunity have noticeably reduced proportion of Treg cells compared to those CVID patients without autoimmune complications [64]. As can be seen, the majority of the studies cited relies on phenotypic analysis of Treg cells in peripheral blood and have less focus on the study of Treg cell functions. Yu et al. [63] showed that sorted Tregs from CVID patients with autoimmune disease are compromised in their suppressive activity and has reduced ability to suppress proliferation of autologous and allogenic effector CD4+ T cells, compared with CVID patients without autoimmunity. Furthermore, the down regulation of FoxP3, granzyme A and pStat5 was significantly correlated with the degree of Treg cell dysfunction in CVID [63]. In another study in our research center, Arandi et al. (2013), using Tregs suppression assay proved that suppressive functions of Tregs were impaired. Moreover, IL-10 was produced at markedly lower amounts by Tregs in CVID.
patients. No difference was seen in TGF-β concentration between patients and the control group [36]. Moreover, in two other studies by Holm et al. (2003) and Zhou et al. (1998) the authors reported a decreased level of IL-10 in CVID [66, 67]. Regarding abnormality of Treg cells in CVID patients, it could be concluded that cellular dysregulations including elevation in activated CD4+ T cell count especially in those with autoimmune manifestation may be a consequence of lower number and reduced suppressive capacity of Tregs.

6. CD8 T cell defects in CVID

Like CD4+ T cells, CD8+ T cells also have defect in CVID patients. It is revealed that naive and effector memory CD8+ T cells are reduced in CVID patients [13], while activated CD8+ T cell are increased [43, 68]. Bateman et al. (2012) reported that the reduction in naive CD8+ T cells count was most significant in those CVID patients with autoimmune cytopenia [13].

A high expansion of activated CD8+ T-cells has also been reported in CVID patients [68, 69]. It is demonstrated that CD8+HLA-DR+, CD8+CD38+ and CD8+CD38−HLA-DR+ T-cells are expanded in CVID patients [43], and this is restricted to patients with clinical complications [70], including autoimmunity, splenomegaly, lymphoid proliferation and granulomatous disease. Moreover, CVID patients with activated CD8+ T-cells showed a reduction of their TCR repertoire diversity which was more severe in those CVID patients with above mentioned complications [69]. In addition to the HLA-DR, CD8+ T cells of CVID patients with autoimmunity have higher expression levels of granzyme B [68]. Moreover, CD8+HLA-DR+ T cells are increased in CVID patients with impaired memory B-cell differentiation. Viallard et al. (2006) showed a correlation between CD8+HLA-DR+ T cells with low numbers of CD19+CD27+ memory B cells [24].

An increase in a subgroup of CD8+T cells with cytotoxic effector memory expression markers are reported in CVID patients. These CCR7− T cells are similar to chronically activated T cells with impaired proliferation response [71]. Within the CD8+ T cell subpopulation, CD8+ effector memory has significantly lower frequency in organ-specific autoimmune disease, whereas CD8+ terminally differentiated are significantly
higher in the polyclonal lymphoproliferation and autoimmune cytopenias groups of clinically subdivided CVID patients [13].

In conclusion, CD8$^+$ T cell abnormalities specially increased levels of activated CD8$^+$ T-cells in CVID patients, might be associated with clinical manifestations or even viral infections, which commonly observed in these patients.

7. T cell signaling defects in CVID

Recently, several studies demonstrated signaling defects in immune cells of CVID patients (Table 3). These include defects in TCR dependent signal transduction [72], BCR signaling [73], TLR signaling [74], and FcγRIIa signaling-associated molecules [75].

7.1. T cell signaling-associated surface molecules and consequence defects

Defect in TCR signal transduction and activation in CVID patients has been demonstrated in several studies. It has been revealed a deficiency in IL-2 and IFN-γ release upon TCR activation by various stimuli which have founded in CD4$^+$ T cells [76]. Other studies reported defective TCR and co-stimulatory (CD40L) molecules activation in CD4$^+$ and CD8$^+$ T cells [72, 77]. CD40L have important role in delivering functional signals in both CD4$^+$ and CD8$^+$ T cells [78], as defect in the amplification of TCR-derived activation by co-stimulatory signals could be responsible for impaired T-cell activation as well as defective amplification of the TCR-dependent signal transduction in CVID patients [79, 80]. Aspalter et al. (2007) found also a significant selective impairment in TNF-Receptor II (TNF-R II) co-stimulatory signaling events, which resulted in reduced TRAF1 expression and TCR/TNF-RII-driven T-cell proliferation [81]. The above mentioned studies proposed defects of TCR signaling and co-stimulation, thereby helping to understand the molecular basis of T-cell defects in CVID patients [82]. It would be conceivable that the reduced co-stimulatory and signaling capacity of TCR may contribute to the impaired interaction of T and B cell, resulting to the hypogammaglobulinaemia in CVID patients.

7.2. T cell signaling-associated cytoplasmic molecules and consequence defects

In addition to defect in TCR and co-stimulatory molecule, several defects in cell signaling-associated cytoplasmic molecules such as lymphocyte-specific protein tyrosine
kinase (LCK) [83], inositol-1,4,5-trisphosphate (IP3) [80], Vav [84], phospholipase C
gamma-1 (PLCγ-1) [85], Calcium mobilization [76], protein kinase C-δ (PKCδ) [86] and
LPS-responsive beige-like anchor (LRBA) [87] are also described in the pathogenesis of
immunodeficiency. Although these new monogenic defects share clinical phenotypes
with CVID, they could be considered as distinct entities that may occasionally be
misdiagnosed as CVID [88].

8. The effects of IGIV on T cell in CVID patients

The common treatment for CVID is IgG replacement, often given as IGIV. Recent
evidence shows that immune reconstitution treatment with IGIV has diverse effects on
the immune system of CVID patients [89-91]. It is revealed that IGIV therapy resulted
in elevation of the percentages of CD4+ T cells [92], correction of CD4/CD8 inverse
ratio and improvement of T cell function [93]. Paquin-Proulx et al. (2013) showed
that immunotherapy with IGIV in CVID patients alleviates the state of persistent
immune activation and suppressed CD4+ T cell counts [94]. CD4+ T cells in CVID
patients have elevated levels of Ki67, CD38, and HLA-DR as the activation markers,
PD-1 and CTLA-4 as exhaustion markers. It is revealed that the expression levels of
activation and exhaustion markers remained elevated for up to one year on IGIV
treatment [94]. Paradoxically, a study showed that IGIV treatment could reduce PD-1
expression on CD4+ T cells and improve their response to bacterial infections [37].

In addition, an increase in Tregs was reported 30 min after IGIV infusion in CVID
patients [92]. This elevation seems to be transient, because no sustained effect of
IGIV therapy on Treg cell counts was observed between samples obtained at baseline
and up to one year after initiation of IGIV infusion [94]. On the other hand, the
frequency of iNKT cells as another subset of T cells with suppressor function does not
restore and HLA-DR remains elevated following IGIV therapy. However, expression
of PD-1 and CD161 is reduced when CVID patients are under IGIV treatment [94].
This data indicate that IGIV can attenuate iNKT cell activation and exhaustion in
CVID patients.

CVID patients have higher plasma levels of IL-2 and IL-10 as well as a higher
expression of FcγRIIb on CD19+ B cells before IGIV infusion. It is demonstrated that
the infusion of IGIV lead to further increases in the plasma levels of these cytokines
30 minutes after the termination of the infusion [92]. In addition, a significant increase in IL-2 expression in CD4+ T cells and an increase in TNF-α expression in CD8+ T cells has been reported following IGIV in CVID patients, while IFN-γ and expression of activation marker CD69 were not affected by IGIV infusion [95].

Similar to what was listed for the CD4+ T cell, CD8+ T cells in treatment-naive CVID have increased expression of activation markers Ki67 and co-expression of CD38 and HLA-DR [94]. It is showed that IGIV therapy reduces the expression of activation markers Ki67, CD38, and HLA-DR on CD8+ T cells [94]. However, Artac et al. (2010) reported CD69 and HLA-DR expressions of CD8+ T cells are not affected by IGIV infusion [96]. The immunological mechanisms by which IGIV can normalize T cell counts and function in CVID patients remains unclear, but Dolcino et al. (2014) reported that lower expression of LEPR, a gene important for CD4+ T cell proliferation, was normalized after IGIV treatment in this patients [97]. Other results showed that IGIV replacement causes an increase in the CD95 and CD25 expressions in CVID patients. Recent report suggests that the CD95 may have a critical role in the effects of IGIV for control of autoimmunity and inflammation in CVID patients [96].

Totally, IGIV infusion resulted in elevation of the percentages of CD4+ T cells and serum level of some cytokine after the infusion. However, this effect has not seen on the all T cell subsets. As, some compartments of immune cells such as Tregs and iNKT cells are not restoring after initiation of IGIV. Therefore, loss of these immune cells may clarifying why some of CVID patients despite the IGIV therapy still suffer from severe inflammatory complications [89]. In addition, it is possible that the loss of these cells is a predisposing factor in CVID patients to increase risks of autoimmunity including autoimmune enteropathy and interstitial lung disease.

9. Conclusion

Although CVID primarily characterized by hypogammaglobulinaemia and failure of specific antibody production as a result of B cell defects, a wide range of T cell abnormalities have been described in patients. According to essential dependence of normal function of B cell to T cell, it should be noted that many defects observed in CVID is due to T cell dysfunction, hence T cells my play a key role in the pathogenesis of CVID. Therefore, a proper classification for CVID by focus in more
detailed genetic and immunologic features (phenotypic and functional characterization of B cells and evaluation of T cell function and frequency) along with clinical phenotypes of patients is required.

Conflict of interest
The authors declare no conflict of interest.

References


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Th, T helper; Treg, regulatory T cells; CTL, Cytotoxic T cell; NKT, Natural killer T; IFN, Interferon; IL, Interleukin; STAT, Signal Transducer and Activator of Transcription; TGF-β, Transforming growth factor beta.
Table 2. T cell defects and related manifestation in CVID

<table>
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<td>↓Naive</td>
<td>- Autoimmunity (especially autoimmune cytopenia)</td>
<td>Resnick et al. 2012</td>
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<td>↑Activated</td>
<td></td>
<td>Carbone et al. 2006</td>
</tr>
<tr>
<td></td>
<td>↓Memory</td>
<td>- Splenomegaly</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Lymphoid proliferation</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Poor response to protein antigens and vaccines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑Th17</td>
<td>↑Th1</td>
<td>Germinal centers disruption</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Negatively correlate with naive CD4+ T cells</td>
<td>Resnick et al. 2012</td>
</tr>
<tr>
<td></td>
<td>↓Treg</td>
<td>- Decrease in suppressive capacity of autoreactive effectors cell</td>
<td>Aghamohammadi et al. 2005</td>
</tr>
<tr>
<td>CD8+ T cells</td>
<td>↓Total</td>
<td>- Susceptibility to viral infection</td>
<td>Carter et al. 2013</td>
</tr>
<tr>
<td></td>
<td>↓Naive</td>
<td>- Polyclonal expansions of LGL</td>
<td>Holm et al. 2006</td>
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<tr>
<td></td>
<td>↑Activated</td>
<td>- Increase in granzyme B</td>
<td>Baumert et al. 1992</td>
</tr>
<tr>
<td></td>
<td>↓Memory</td>
<td></td>
<td>Viallard et al. 2013</td>
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<td></td>
<td></td>
<td></td>
<td>Kuntz et al. 2011</td>
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<tr>
<td>Innate like</td>
<td>↓iNKT</td>
<td>- Autoimmunity</td>
<td>Paquin-Proulx et al. 2014</td>
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<tr>
<td></td>
<td></td>
<td>- Increase in IFNγ</td>
<td>Carvalho et al. 2010</td>
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<td></td>
<td>↑γδ-T</td>
<td>- Granulomatous lesions</td>
<td>Viallard et al. 2002</td>
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<tr>
<td></td>
<td></td>
<td>- Inflammation</td>
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</table>

CVID, Common variable immunodeficiency; Th, T helper; Treg, Regulatory T cell; iNKT, Invariant natural killer cell; LGL, large granular lymphocytes
Table 3. Defective signaling molecules in T cells of CVID patients

<table>
<thead>
<tr>
<th>Defective molecules</th>
<th>Normal function</th>
<th>Cause of defect</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>TCR signal transduction</td>
<td>T cell activation, development, proliferation and differentiation</td>
<td>Mutations</td>
<td>Fischer et al.</td>
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<tr>
<td>Lck</td>
<td>Regulation of T cell maturation, activation and differentiation</td>
<td>A defective splicing product of Ick gene and decrease in expression of Ick</td>
<td>Sawabe et al.</td>
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<td>IP3</td>
<td>Calcium releasing from endoplasmic reticulum</td>
<td>Defective TCR-mediated Ins(1,4,5)P3 formation</td>
<td>Fischer et al.</td>
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<td>Vav expression and F-actin reorganization</td>
<td>T cell activation and reorganization of the T cell actin cytoskeleton</td>
<td>Impaired Vav expression and defective F-actin reorganization/ Mutations</td>
<td>Capitani et al</td>
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<tr>
<td>CTLA-4</td>
<td>negative regulator expressed on activated T cells and Treg cells</td>
<td>Mutations and low expression</td>
<td>Arandi et al.</td>
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<td>Calcium mobilization</td>
<td>Cell proliferation and activation</td>
<td>Defective Calcium Flux</td>
<td>Fischer et al.</td>
</tr>
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<td>LRBA</td>
<td>Vesicle trafficking regulator required for CVID genes such as CD19, CD20 and BAFFR</td>
<td>Mutations</td>
<td>Charbonnier et al.</td>
</tr>
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<td>CARD11</td>
<td>B cell receptor- and T cell receptor-mediated activation of the IKK complex</td>
<td>Mutations</td>
<td>Stepensky et al.</td>
</tr>
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<td>PI3Kδ</td>
<td>development, activation and migration of B cells, T cells and NK cells</td>
<td>gain-of-function mutation in the PIK3CD gene</td>
<td>Elgizouli et al.</td>
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