T-Cell Abnormalities in Common Variable Immunodeficiency

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Abstract

Common variable immunodeficiency (CVID) is the most common clinical primary immunodeficiency. It is characterized by a defect in B-cell differentiation to plasma and memory B cells. Moreover, numerous T-cell abnormalities have been reported and include decreased T-cell count and proliferative response, increased T-cell activation and apoptosis, and abnormalities in cytokine production. The aims of this review are to describe phenotypic and functional defects in T cells in CVID patients and to review the literature with respect to the effects of immunoglobulin replacement on the T-cell component in CVID patients.

Key words: Common variable immunodeficiency. T cell. Helper T cells. 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.

Introduction

Common variable immunodeficiency (CVID) is the most common clinical primary immunodeficiency (PID). It is characterized by defects in differentiation of B cells to plasma cells and memory B cells [1,2]. Affected patients are very susceptible to recurrent infection because of low levels of Ig in serum and to reduced specific antibody responses to protein and polysaccharide antigens [3-6]. Patients may also experience a wide variety of clinical complications, including autoimmunity, inflammation, lymphoid malignancy, granuloma, and enteropathy, all of which are included in recent classifications of CVID into clinical phenotypes with different prognoses [7-11].

The most important cellular alteration in CVID patients is severe B-cell deficiency, which leads to hypogammaglobulinemia. However, an alteration in the frequency and function of T cells has also been demonstrated in patients with CVID [12-14]. The influence of these defects on the interaction between T and B cells could explain not only defective antibody production, but also the development of other complications, including recurrent bacterial and viral infections, gastrointestinal disease, lymphoma, autoimmunity, inflammation, and early-onset bronchiectasis in CVID patients [15-17]. In this review, we describe phenotypic and functional T-cell defects in patients with CVID and review the literature on the effects of intravenous immunoglobulin (IVIG) infusion on T-cell components in CVID.

T-Cell Abnormalities in CVID

T-cell subsets perform various functions. The most important subsets are $CD4^+$ and $CD8^+$ (Table 1). Recent research demonstrated that a subgroup of patients with clinically diagnosed CVID are T cell–deficient. However, based on the revised diagnostic criteria for CVID of the European Society for Immunodeficiencies, there is no evidence of profound T-cell deficiency. In CVID patients, profound T-cell deficiency is defined as any 2 of the following: (*1*) $CD4^+$ cells/μL at 2-6 years <300, 6-12 years <250, >12 years <200; (*2*) percentage of naive $CD4^+$ T cells at 2-6 years <25%, 6-16 years <20%, >16 years <10%; and (*3*) absence of T-cell proliferation [18]. CVID patients who experience profound T-cell deficiency are considered to have combined immunodeficiency (CID) [19,20].

Traditionally, the T-cell abnormalities that characterize CVID included a reduced T-cell count, decreased lymphocyte proliferation in response to mitogens and antigens, defective T-cell signaling, decline of regulatory T cell (Tregs) counts, uncontrolled T-cell polarization, elevated levels of T-cell activation markers, and abnormality in cytokine production secondary to gene polymorphisms [12-14, 21-26].

CVID patients with T-cell abnormalities manifest a severe phenotype that commonly presents with gastrointestinal tract disease, splenomegaly, granuloma, and lymphoma [27,28]. Moreover, having consanguineous parents (cCVID) is associated with severe T-cell abnormalities, lower age at onset and diagnosis, severity of disease, and a higher mortality rate.

Table 1. Types of T Lymphocytes

Cell Type	Subset	Characteristic Markers	Normal Function	Associated Diseases
T CD4	T_H1	T-bet, IFN-γ	Cell-mediated immunity, antiviral and antimicrobial immunity	Autoimmunity, susceptibility to intercellular pathogens
	T_H2	STAT6, GATA3, IL-4, IL-5, IL-13	Immunity to extracellular parasites	Allergy and asthma
	T_H9	PU.1, IL-9	Protection against parasite infections	Allergy and asthma
	T_H17	RORγt, IL-17, CD161 (human)	Antimicrobial immunity, protection at mucocutaneous sites	Autoimmunity, susceptibility to fungal infections
	T_H22	AHR, IL-22	Barrier immunity, enhancement of innate immunity, tissue regeneration	Skin inflammation, allergy, autoimmunity, and rheumatic disease
	TFH	BCL-6, IL-21	Help for B-cell activation and differentiation, generation of long-lived antibody responses	Humoral immunodeficiency, autoimmunity, T-cell lymphoma
	Treg	CD25, FoxP3, IL-10, TGF-β	Induction of tolerance and immunosuppression	Autoimmunity, inflammatory conditions, allergy, and cancer
T CD8	CTL	CD3, CD8, perforin and granzyme	Killing of infected and transformed cells	Chronic hepatitis and hepatocellular carcinoma
Innate-like T cell	γδ T	γδ TCR, $CD3^+$, $CD7^+$, $CD2^+$, $CD4^-$, $CD8^-$	Pro- and anti-inflammatory functions in both innate and adaptive immunity	Autoimmune and inflammatory diseases
	NKT	CD161, CD56	Pro- and anti-inflammatory functions, modulation of immune responses	Autoimmunity, allergy, and cancer

Abbreviations: CTL, cytotoxic T cell; IFN, interferon; IL, interleukin; NKT, natural killer T; STAT, signal transducer and activator of transcription; TCR, T-cell receptor; TFH, follicular helper T cells; TGF-β, transforming growth factor beta; T_H, helper T; Treg, regulatory T cells.

Naive CD4+ T-cell counts are decreased in cCVID patients, while activated CD4+, CD95+, CD8+ and HLA-DR+ T-cell counts are increased, compared with non-cCVID patients, in whom splenomegaly, granulomatous disease, polyclonal lymphocytic infiltration, bronchiectasis, enteropathy, and opportunistic infections were more frequent [27, 29-31].

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

CD4+ T-Cell Defects in CVID

Phenotypic and functional defects of CD4+ T cells in CVID patients have been reported during the last decade [35-37]. These abnormalities include increased activated CD4+ T-cell counts and decreased total, naive, and memory CD4+ T-cell counts (Table 2), along with functional impairment, such as reduced proliferative capacity and failure in cytokine production [37,38]. This reduction in CD4+ T-cell counts is associated with a decrease in thymic output, increase in T-cell turnover, and spontaneous apoptosis [12].

Naive CD4+ T Cells

CVID patients have reduced naive CD4+ T-cell and recent thymic emigrant (RTE) cell counts. In a study by Oraei et al [35], CVID patients had fewer naive and RTE CD4+ T cells than healthy controls. Interestingly, this reduction was more apparent in male than in female patients [35]. The reduction in total CD4+ and RTE T-cell counts was most pronounced in CVID patients with autoimmune cytopenia or polyclonal lymphoid proliferation [13,39]. Several studies showed that the severity and prognosis of CVID is reflected in a parallel loss of naive CD4+ T cells and that there is 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 lymphoid proliferation, cytopenias, organ-specific autoimmunity, lymphoid malignancy, and enteropathy), the autoimmune cytopenia and organ-specific autoimmunity groups had the most significantly reduced naive CD4+ T-cell counts, followed by the polyclonal lymphoid proliferation group [13]. Therefore, a new classification system based on naive CD4+ T-cell counts was proposed, and CVID patients were divided into 3 separate groups. Group A has significantly decreased numbers of naive CD4+ T cells along with massive T-cell activation. Other characteristics include increased apoptosis, disruption of normal T-cell receptor (TCR) repertoires, splenomegaly, and more severe clinical immunodeficiency. Group B had the same features as group A, although these are less pronounced. Group C has normal naive CD4+ T-cell counts, but patients also have an alteration in the CD8+ T-cell compartment. In addition, splenomegaly is less common in group C than in the other groups and is correlated with a milder clinical prognosis [12,41,42].

Table 2. T-Cell Defects and Related Manifestations in CVID

T Cell	Frequency	Related Manifestation in CVID	Reference
CD4+ T cells	↓Total ↓Naive ↑Activated ↓Memory	- Recurrent infection - Autoimmunity (especially autoimmune cytopenia) - Splenomegaly - Lymphoid proliferation - Poor response to protein antigens and vaccines	Bateman et al [13] Resnick et al [98] Carbone et al [43]
	↓T_H17 ↑T_H1	- Germinal center disruption - Negative correlation with naive CD4+ T cells	Barbosa et al [48] Resnick et al [98] Moratto et al [99]
	↓Treg	-Decrease in suppressive capacity of autoreactive effector cells	Arandi et al [36]
CD8+ T cells	↓Total ↓Naive ↑Activated ↓Memory	- Susceptibility to viral infection - Polyclonal expansions of large granular lymphocytes - Increase in granzyme B	Carter et al [68] Holm et al [67] Baumert et al [100] Viallard et al [69] Kuntz et al [101]
Innate-like	↓iNKT	- Autoimmunity - Increase in IFN-γ	Paquin-Proulx et al [89] Carvalho et al [102]
	↑γδ-T	- Granulomatous lesions - Inflammation	Viallard et al [69]

Abbreviations: CVID, common variable immunodeficiency; IFN, interferon; NKT, natural killer T; T_H, helper T; Treg, regulatory T cells.

Activated CD4+ T Cells

Elevations in the $CD4^+$ T-cell count and activation markers have also been demonstrated in CVID patients [43]. These abnormalities include an increase in HLA-DR, CD29, CD45RO, and CD95 (APO-1/Fas) and a decrease in CD27, CD45RA, and CD62L, especially in patients with increased $CD21^{low}$ B-cell counts and decreased memory and regulatory B-cell counts [25,44]. CVID patients present with both low regulatory B cell counts and increased IFN-γ^+TNF-α^+CD4^+ T-cell counts [44,45]. The defect in regulatory B-cell responses to T-cell stimulation and differentiation explains the excessive $CD4^+$ T-cell activation that is a frequent finding in CVID patients.

In a study by Carbone et al [43], activated $CD4^+$ T cells were more common in patients with suspected IgG hypercatabolism and in patients with clinical complications including lymphoid proliferation, splenomegaly, and autoimmune disease [43]. Another study showed that CVID patients with autoimmune cytopenia have increased numbers of activated $CD4^+$ T cells, decreased numbers of naive T cells, and an increased proportion of $CD21^{low}$ B cells [15]. However, Boileau et al [15] proposed that this concurrent T- and B-cell phenotypic picture is not seen in CVID patients with other autoimmune manifestations and/or patients with splenomegaly [15,46]. Overall, according to recent findings on the correlation between $CD21^{low}$ B cells in CVID and autoimmunity (such as autoimmune cytopenia and rheumatoid arthritis) [15,46], a restricted B-cell subset and help from activated $CD4^+$ T cells are needed to break down B-cell tolerance to self-antigens. On the other hand, it has been demonstrated that BLK dysfunction in B cells from CVID patients perturbs proliferation and the 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.

Memory CD4+ T Cells

CVID patients also have memory $CD4^+$ T-cell deficiencies; however, few studies are available. Giovannetti et al [12] showed that absolute counts of central memory $CD4^+$ T cells decrease in CVID patients, whereas no significant differences were detected for effector memory cells [12]. Bateman et al [13] revealed that within $CD4^+$ memory subpopulations, both central and effector memory cells differed signficantly between CVID clinical groups. The authors reported that $CD4^+$ central memory T-cell counts were lower in patients with autoimmune cytopenia than in both healthy controls and controls with disease [13]. Given that memory T cells have different capacities to proliferate in response to antigens and/or cytokines to perform effector functions, recurrent infections and poor response to vaccine in CVID patients may be the result of long-term defective immunity not caused by memory T cells.

Helper T-Cell Defects

Few authors have investigated helper T subsets and their pathogenic relationship with CVID. Barbosa et al [48] were the first authors to report a decline in the frequency of circulating T_H17 cells in CVID patients. No association was demonstrated between the frequency of T_H17 cells and transitional B cells. In contrast, the authors showed a negative correlation between T_H17 cells and expansion of activated nondifferentiated $CD21^{low}$ B cells. Therefore, the decline in the frequency of circulating T_H17 cells is matched by B-cell disturbances, a representative feature of germinal center disruption [48]. Moreover, the frequency of T_H17 cells correlated negatively with activated $CD4^+$ T cells in patients with CVID, while there was no correlation with naive and memory T-cell balances. The frequency of T_H1 cells correlated negatively with that of naive $CD4^+$ T cells and positively with levels of activated $CD4^+$ T cells in CVID patients [48]. Ganjalikhani-Hakemi et al [49] evaluated T_H17 cell–specific gene expression in CVID patients. Their results showed that the frequency of T_H17 cells in CVID patients was markedly lower than in healthy individuals. Moreover, mRNA levels of IL-17 and RORC2 were much lower in these patients than in healthy controls, although a slight reduction in IL-23R expression has been observed in CVID patients [49]. As IL-17 and possibly T_H17 cells can contribute to germinal center function [50], these findings are consistent with the results of Barbosa et al, who propose that levels of IL-17 and T_H17 cells correlate negatively with the pathological expansion of a B-cell population associated with impaired germinal center function in CVID [48]. In addition, IL-17 is also produced by follicular helper $CD4^+$ T cells. According to Romberg et al [51], levels of circulating follicular helper $CD4^+$ T cells were significantly lower in CVID patients than in healthy individuals [51]. Therefore, the reduction in IL-17 in CVID patients, as is the case with T_H17 defects, may be attributable to their diminished follicular helper T-cell population.

Several studies have demonstrated that T_H17 cell counts and proportions increased in a variety of autoimmune diseases such as autoimmune hemolytic anemia and immune thrombocytopenia [52], rheumatoid arthritis [53], psoriasis [54], and lupus [55]. However, Barbosa et al [15] found no increase in the frequency of T_H17 cells in CVID patients with autoimmune manifestations, even when CVID patients were subdivided based on the type of autoimmune disorder, including organ-specific autoimmunity and autoimmune cytopenias. In contrast, the $CD21^{low}$ B-cell subset was significantly increased in CVID patients with autoimmunity [15,48]. In conclusion, no obvious association between autoimmune manifestations and frequency of T_H17 cells and their proinflammatory cytokines was observed in CVID patients. However, a recent study reported findings for the T_H1/T_H2 balance in CVID patients. T_H1 cells seem to be more involved in pathogenesis than T_H2 cells. CVID patients with hepatomegaly had higher IL-2 and IFN-γ levels in stimulated $CD4^+$ T cells, and patients with granuloma were found to have higher CCR5 expression in $CD4^+$ T cells, suggesting that T_H1 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 T_H subsets has been reported in CVID patients [59]. Some of these cytokines play a pivotal role in antibody synthesis. Rezaei et al [58] investigated T_H1 and T_H2 cytokine levels in the serum of CVID patients and found that the levels of IL-4 and IL-10 as T_H2 cytokines were significantly higher in CVID patients. However, there were no significant differences in T_H1 cytokines (IL-2 and IFN-γ) compared with healthy

controls [58]. Paradoxically, Del Vecchio et al [60] found no differences in IL-4 production by peripheral $CD4^+$ T cells, although production of IL-5 (a cytokine involved in the late regulation of B-cell differentiation into plasma cells) was reduced. Despite the small sample and low number of CVID patients (4 patients), the authors concluded that the reduction in IL-5 could contribute to defective antibody production in CVID patients [60]. The data presented regarding the altered cytokine signature in CVID patients are contradictory. We proposed that the altered cytokine profile could be attributed to the different types of specimen (serum, peripheral blood mononuclear cells, or purified $CD4^+$ T cells), cytokine secretion or gene expression, differences in sample size between studies, and patients' clinical status and associated complications, as well as to activation of myeloid and lymphoid lineages, which could be driven by the high prevalence of bacterial infections in the gastrointestinal or respiratory tract in some CVID patients.

Regulatory T-Cell Defects

Treg cells are key regulators of the immune response and play a crucial role in limiting unwanted and persistent immune activation. Several studies have demonstrated that Treg counts are reduced in CVID patients [61-63]. Moreover, residual Treg cells appear to have reduced suppressive capacity [36] with downregulation of FoxP3 protein and diminished expression of inhibitory markers such as CTLA-4 and GITR [64]. In contrast, Kutukculer et al [14] recently suggested that Treg cells do not play an important role in the pathogenesis of CVID. The authors reported percentages and absolute counts of Treg cells, with no significant difference between CVID patients and healthy controls or between patients with severe disease and patients with moderate disease [14].

There is a significant correlation between low numbers of Treg cells and autoimmune manifestations [61,63,65,66], granulomatous lesions [65], and splenomegaly [61]. Genre et al [66] reported that CVID patients who were likely to develop autoimmunity had a significantly reduced frequency of Treg cells accompanied by decreased intensity of Foxp3 expression. Moreover, levels of expression of Foxp3 in CVID patients without autoimmunity did not differ from those in healthy individuals [66]. Arumugakani et al [61] showed that a low frequency of Treg cells was correlated with expansion of $CD21^{low}$ B cells in CVID patients with autoimmunity, while a significantly reduced frequency and number of Treg cells was observed in patients with splenomegaly. In a similar study, Arandi et al [64] showed that CVID patients with autoimmune diseases had a noticeably lower percentage of Treg cells than CVID patients without autoimmune diseases. It is clear that most of the studies cited rely on phenotypic analysis of Treg cells in peripheral blood and focus less on the study of Treg function. Yu et al [63] showed that the suppressive activity of sorted Treg cells from CVID patients with autoimmune disease is compromised and that the cells are less able to suppress proliferation of autologous and allogenic effector $CD4^+$ T cells than CVID patients without autoimmune disease. Furthermore, the downregulation of FoxP3, granzyme A, and pStat5 was significantly correlated with the degree of Treg dysfunction in CVID [63]. In a study performed at our research center, Arandi et al [36] used the Treg suppression assay to prove that the suppressive function of Treg cells was impaired. Moreover, IL-10 was produced at markedly lower amounts by Treg cells in CVID patients. No differences were seen in the TGF-β concentration between patients and the control group [36]. Genre et al [66] and Holm et al [67] reported a decreased level of IL-10 in CVID. Regarding abnormality of Treg cells in CVID patients, it could be concluded that cellular dysregulation, including an elevated activated $CD4^+$ T-cell count, may be a consequence of lower numbers and reduced suppressive capacity of Treg cells, especially in patients with autoimmune manifestations.

CD8 T-Cell Defects in CVID

Like $CD4^+$ T cells, $CD8^+$ T cells are deficient in CVID patients: levels of both naive and effector memory $CD8^+$ T cells are reduced [13], although levels of activated $CD8^+$ T cells are increased [43,68]. Bateman et al [13] reported that the reduction in naive $CD8^+$ T-cell counts was more significant in CVID patients with autoimmune cytopenia [13].

Marked expansion of activated $CD8^+$ T cells has also been reported in CVID patients [68,69]. It has been demonstrated that $CD8^+HLA\text{-}DR^+$, $CD8^+CD38^+$, and $CD8^+CD38^+HLA\text{-}DR^+$ T-cell counts are higher in CVID patients [43] and that this increase is restricted to patients with clinical complications [70], including autoimmune disease, splenomegaly, lymphoid proliferation, and granulomatous disease. Moreover, CVID patients with activated $CD8^+$ T cells showed reduced diversity in their TCR repertoire that was more severe in CVID patients with the above-mentioned complications [69]. In addition to HLA-DR, $CD8^+$ T cells from CVID patients with autoimmunity have higher expression levels of granzyme B [68]. Moreover, $CD8^+HLA\text{-}DR^+$ T-cell counts are increased in CVID patients with impaired memory B-cell differentiation. Viallard et al [24] showed a correlation between $CD8^+HLA\text{-}DR^+$ T cells and low numbers of $CD19^+CD27^+$ memory B cells.

An increase in a subgroup of $CD8^+$ T cells with cytotoxic effector memory expression markers has been reported in CVID patients. These $CCR7^-$ T cells are similar to chronically activated T cells with an impaired proliferation response [71]. Within the $CD8^+$ T-cell subpopulation, $CD8^+$ effector memory cells are significantly less frequent in organ-specific autoimmune disease, whereas terminally differentiated $CD8^+$ cells are significantly more frequent in CVID patients with polyclonal lymphoid proliferation and autoimmune cytopenias [13].

In conclusion, $CD8^+$ T-cell abnormalities in CVID patients, in particular increased levels of activated $CD8^+$ T cells, might be associated with clinical manifestations or even viral infections, which are common in this group.

T-Cell Signaling Defects in CVID

Several studies recently demonstrated signaling defects in immune cells in 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].

Table 3. Defective Signaling Molecules in T Cells of CVID Patients

Defective Molecules	Normal Function	Cause of Defect	References
TCR signal transduction	T-cell activation, development, proliferation, and differentiation	Mutations	Fischer et al [74,79]
Lck	Regulation of T-cell maturation, activation, and differentiation	A defective splicing product of the Ick gene and decrease in expression of lck	Sawabe et al [83]
IP3	Release of calcium from the endoplasmic reticulum	Defective TCR-mediated Ins(1,4,5) P3 formation	Fischer et al [74,79]
Vav expression and F-actin reorganization	T-cell activation and reorganization of the T-cell actin cytoskeleton	Impaired Vav expression and defective F-actin reorganization/mutations	Capitani et al [103]
CTLA-4	Negative regulator expressed on activated T cells and Treg cells	Mutations and low expression	Arandi et al [36]
Calcium mobilization	Cell proliferation and activation	Defective calcium flux	Fischer et al [74,79]
LRBA	Vesicle trafficking regulator required for CVID genes such as CD19, CD20, and BAFFR	Mutations	Charbonnier et al [87]
CARD11	B-cell receptor– and T-cell receptor–mediated activation of the IKK complex	Mutations	Stepensky et al [104]
PI3Kδ	Development, activation, and migration of B cells, T cells, and NK cells	Gain-of-function mutation in the *PIK3CD* gene	Elgizouli et al [105]

Abbreviations: CARD11, caspase recruitment domain family, member 11; CTLA-4, cytotoxic T-lymphocyte-antigen 4; CVID, common variable immunodeficiency; IKK, IκB kinase; IP3, inositol 1,4,5-triphosphate; LRBA, lipopolysaccharide-responsive beige-like anchor; PI3Kδ, phosphatidylinositol-3-kinase delta; TCR, T-cell receptor.

T-Cell Signaling-Associated Surface Molecules and the Resulting Defects

Defects in TCR signal transduction and activation in CVID patients have been demonstrated in several studies. A deficiency was detected in release of IL-2 and IFN-γ upon activation of TCR by various stimuli in $CD4^+$ T cells [76]. Other studies reported defective activation of TCR and costimulatory (CD40L) molecules in $CD4^+$ and $CD8^+$ T cells [72,77]. CD40L have an important role in delivering functional signals in both $CD4^+$ and $CD8^+$ T cells [78], since a defect in the amplification of TCR-derived activation by costimulatory signals could be responsible for impaired T-cell activation and defective amplification of TCR-dependent signal transduction in CVID patients [79,80]. Aspalter et al [81] also found significant selective impairment in costimulatory TNF-receptor II (TNF-R II) signaling events that resulted in reduced TRAF1 expression and TCR/TNF-RII–driven T-cell proliferation [81]. The above-mentioned studies proposed defects of TCR signaling and costimulation, thereby elucidating the molecular basis of T-cell defects in CVID patients [82]. It is conceivable that the reduced costimulatory and signaling capacity of TCR could contribute to the impaired interaction between T cells and B cells, which results in the hypogammaglobulinemia in CVID patients.

T-Cell Signaling–Associated Cytoplasmic Molecules and Associated Defects

In addition to defects in TCR and costimulatory molecules, several defects in cell signaling–associated cytoplasmic molecules have been reported in the pathogenesis of immunodeficiency. These molecules include 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]. Although these new monogenic defects share clinical phenotypes with CVID, they could be considered distinct entities that may occasionally be misdiagnosed as CVID [88].

Effects of IVIG on T Cells in CVID Patients

The most common treatment for CVID is IgG replacement, which is often administered as IVIG. Recent evidence shows that immune reconstitution with IVIG has diverse effects on the immune system of CVID patients [89-91]. IVIG resulted in elevation of $CD4^+$ T-cell percentages [92], correction of the inverted CD4/CD8 ratio, and improvement in T-cell function [93]. Paquin-Proulx et al [94] showed that immunotherapy with IVIG 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 and of PD-1 and CTLA-4 as exhaustion markers. Expression levels of activation and exhaustion markers remained elevated for up to 1 year in patients receiving IVIG [94]. Paradoxically, one study showed that treatment with IVIG could reduce expression of

PD-1 on $CD4^+$ T cells and improve the response to bacterial infections [37].

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

CVID patients have higher plasma levels of IL-2 and IL-10 and more pronounced expression of FcγRIIb on $CD19^+$ B cells before infusion of IVIG. Infusion of IVIG leads to further increases in the plasma levels of these cytokines 30 minutes after the infusion has finished [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 have been reported following IVIG in CVID patients, although IFN-γ and expression of the activation marker CD69 were not affected by IVIG [95].

As with $CD4^+$ T cells, $CD8^+$ T cells in treatment-naive CVID patients show increased expression of activation markers Ki67 and coexpression of CD38 and HLA-DR [94]. IVIG reduces expression of the activation markers Ki67, CD38, and HLA-DR on $CD8^+$ T cells [94]. However, Artac et al [96] reported that expression of CD69 and HLA-DR by $CD8^+$ T cells is not affected by IVIG. The immunological mechanisms by which IVIG can normalize T-cell counts and function in CVID patients remains unclear, but Dolcino et al [97] reported that lower expression of *LEPR*, a major gene in $CD4^+$ T-cell proliferation, returned to normal values after IVIG treatment [97]. Artac et al also showed that IVIG causes an increase in the expression of CD95 and CD25 in CVID patients and suggested that CD95 may play a critical role in the effects of IVIG for control of autoimmunity and inflammation in CVID patients.

IVIG resulted in elevation of $CD4^+$ T-cell percentages and serum levels of some cytokines after the infusion. However, this effect was not seen in all the T-cell subsets. As some compartments of immune cells, such as Treg and iNKT cells, are not restored after initiation of IVIG, loss of these immune cells may clarify why some CVID patients still experience severe inflammatory complications despite receiving IVIG therapy [89]. In addition, the loss of these cells could predispose CVID patients to increased risks of autoimmune disease, including autoimmune enteropathy and interstitial lung disease.

Conclusion

Although CVID is primarily characterized by hypogammaglobulinemia and failure of specific antibody production as a result of B-cell defects, a wide range of T-cell abnormalities have been reported. Given the essential dependence of normal B-cell function on T-cell function, many defects in CVID are due to T-cell dysfunction. Consequently, T cells may play a key role in the pathogenesis of CVID. It is essential to establish a proper classification for CVID that focuses on more detailed genetic and immunologic features (phenotypic and functional characterization of B cells and evaluation of T-cell function and frequency) and on clinical phenotypes.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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