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KEY REVIEW ARTICLE

Cytokines in Common Variable Immunodeficiency as Signs of Immune Dysregulation and Potential Therapeutic Targets – A Review of the Current Knowledge

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Abstract Common variable immunodeficiency (CVID) is characterized by low levels of circulating immunoglobulins and compromised specific antibody response leading to frequent infections. Cytokines play an important role in the orchestration of the antibody response. Several previous studies have attempted to identify distinct cytokines responsible for the inflammatory changes and different manifestations of CVID, but there are conflicting results regarding the cytokine profiles in CVID patients. In light of this, an extensive review regarding the level of various cytokines and their potential therapeutic role in CVID patients was performed. This review delineates the contribution of interleukin (IL)-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-21, interferons, tumor necrosis factor (TNF)-α, IL-17, APRIL (a proliferation inducing ligand) and BAFF (B cell activating factor) in CVID disease and outline their potential therapeutic implications in these patients.

Keywords Common variable immunodeficiency · cytokines · treatment · pathogenesis

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Introduction

Common Variable Immunodeficiency (CVID) is the most common primary immunodeficiency disorder, which encompasses a clinically and immunologically heterogeneous group of antibody deficiency disorders with many, mostly unknown causes [1–3].

The diagnosis of CVID could be established according to the criteria of low serum IgG concentration with marked decrease in serum IgA or IgM; poor response to vaccination; onset of immune deficiency after four years of age; and exclusion of other causes of hypogammaglobulinemia [4]. However, there are several concerns in this regard. For instance, there are several patients with hypogammaglobulinemia that other monogenic defects are excluded, but they cannot fully fill the above-mentioned criteria and are classified as CVID.

Due to deficit in specific antibody response, CVID patients are susceptible to recurrent sinopulmonary and gastrointestinal infections as well as an enhanced risk of malignancy, autoimmune and inflammatory disorders.

The immunological work up regarding etiology of CVID has revealed B cell intrinsic defects as well as T cell dysfunction contributing to the immunodeficiency. Since hypogammaglobulinemia is the cardinal manifestation of the disease, a large body of evidence has indicated the primary impairment of B-cell lineage as an important cause of the disease [5].

The observation that B cells from some CVID patients can produce immunoglobulin (Ig), if appropriately stimulated by CpG oligonucleotides [6] or addition of IL-10 in vitro [7] or IL-21 [8] suggests pivotal role of B-cell-extrinsic factors in the pathogenesis of the immunodeficiency in these patients.

In this regard, a vast array of T-cell abnormalities has been described in CVID patients, including T cell activation defects [9–11], lymphopenia and anergy [12], impaired proliferation in response to mitogens [13, 14], apoptosis enhancement [9], impairment in cytokine production [15–18], failure in Ag-primed T cells generation after prophylactic vaccination [19] and neoantigens [20] and reduced expression of CD40L on activated T cells [21] and low levels of IL-2 mRNA in a subset of CVID patients [22] which may contribute to the B-cell differentiation failure.

Impairment in innate immune compartment such as dendritic cells (DC) has also been previously described in patients with CVID [23]. In this regard, Banchereau et al. has shown that several functions of B and T lymphocytes are controlled by DCs [24]. DCs, as the sentinel cells of the immune system, initiate the immune response by processing antigen material and direct it by T and B cells through the expression of co-stimulatory molecules and secretion of diverse chemokines and cytokines [24–26].

Thus the normal immune response is regulated by a local and temporal orchestration of cell-cell contact and cytokines produced by different cells, often referred to as the costimulatory environment of the activation of effector cells. Cytokines have been recognized as such crucial elements of the developing immune response that there are often characterized and divided by the cytokine profile of the dominant T cell population. Depending on the cytokine profile of the main T-helper (Th) $CD4^+$ cells, the responses are divided in Th1, Th2, Th9, Th17 responses and T follicular helper cells (T_{FH}) are critical for the humoral antibody response [27]. While each of these responses has its typical trigger, profile and function, they very rarely occur in an isolated fashion. Th1 cells secrete mainly IL-2, Interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α) with a key role in cell mediated immunity where as Th2 cells secrete IL-4, IL-5, IL-10, and IL-13, which are important in eosinophilic and IgE mediated responses [27, 28].

Both types of cytokine profiles are often involved and shape the general humoral immune response.

Th17 cells mainly produce IL-17A, IL-17 F, IL-21 and IL-22, and contribute to the local inflammatory response by recruiting neutrophils [29].

Th9 cells are characterized by the secretion of IL-9 which seems to be involved in pathogen directed immunity and especially inflammatory responses in the context of allergy [30]. T_{FH} cells are the main T cell population in the germinal center supporting B cell memory and plasma blast formation by the production of IL-21 and other costimulatory molecules [31].

In addition to division of cytokines based in the type of T-helper cell response, cytokines can be classified by their ability to promote or inhibit inflammatory responses.

Pro-inflammatory cytokines are: IL-1β, IL-2, IL-6, IL-8, IL-12, IL-17, IFN-γ, and TNF-α where as the anti-inflammatory cytokines are: IL-4, IL-5, IL-10, IL-13, and transforming growth factor beta (TGF-β). Given the crucial role of cytokines in effective antibody response [8, 32–35], immune regulation and tolerance, disturbed cytokine production may contribute importantly to the immunodeficiency and dysregulation in CVID patients. Therefore several studies have addressed the production of cytokines in CVID [7, 36–39].

The purpose of this article is to review the current literature on cytokines and assess their potential role in CVID.

Cytokines in CVID

The role of the different cytokines in CVID is summarized in Tables I, II, III, IV and V. However, due to the retrospective collection of incomplete data regarding the composition of the examined cell types, the clinical presentation at the time of examination and other potential confounding factors in different studies, there are clear limitations in the comparison of cytokine profiles in patients. Common cytokine profiles might reflect similarities in the underlying immunodeficiency but also common manifestations of secondary events in specific subgroups of CVID [40]. The technique and condition of the investigation as well as the selected cytokines vary significantly between the studies. While some studies measured the serum level of cytokines, others reported in vitro cytokine production with different or without stimulation. Results are reported on RNA transcript and protein level. Few studies also investigated cytokine receptor expression or functional response to specific cytokines adding to the heterogeneity of the literature.

IL-1

The IL-1 family, compromises a group of 11 beta trefoil cytokines where two members IL-1α and IL-1β, play critical roles in immune regulation and the inflammatory response. The pro-inflammatory cytokines, IL-1α and IL-1β, are produced by macrophages and DCs [41].

IL-1 has a natural antagonist IL-1Ra (IL-1 receptor antagonist), which regulates IL-1α and IL-1β proinflammatory activity [42]. In addition to IL-1α and IL-1β, other IL-1 family members including IL-18, IL-33, IL-36α, IL-36β and IL-36γ have proinflammatory properties [43].

Our own previous study did not demonstrate any association between IL-1 (IL-1α, IL-1β, IL-1R and IL-1RA) cytokine gene polymorphism and CVID [44]. Normal IL-1α serum levels were found in some CVID patients compared to

Table I The role of pro-inflammatory cytokines in common variable immunodeficiency

Cytokine	Study	Year	Country	Method and stimulation	Serum level/Tx	Case/control	Etiology/Changes	Ref
IL-1β	Trujillo et al.	2011	Colombia	Protein level (CBA) after stimulation of with PBMCs with LPS* and LTA*	Normal range	6/5	Level of IL-1β in PBMC of both CVID patients and healthy controls increase after stimulation	[46]
IL-1β, IL-4, IL-6, IL-10, IL-12, IL-17, IFN-γ, TNF-α	Haveman et al.	2010	Netherlands	Protein level (multiplex immune assays) after 3 days stimulation of PBMCs with ConA* or viral antigens (EBNA, BZLF1 (EBV) HHV6B-CMV, HSV-1 type antigene, HAdV),	No significant differences	8/4 children 5/4 adults	IL-1β, IL-6 and TNF-α were produced by stimulation with HSV	[47]
IL_1	Rezaei et al.	2009	Iran	PCR	IL-1 gene polymorphisms	30/140	SNPs can affect the production of IL-1, however there is no significant association of this cytokine in CVID.	[44]
IL_1	Aukrust et al.	1994	Norway	Serum	Normal IL-1 serum levels	25/21	No significant difference between patients and control	[16]
IL_1	Zielen et al.	1994	Germany	Activated by LPS*	Reduced amplification of T cell response after addition of exogenous IL-1 in CVID patients	11/10	IL-1 deficiency leads to CD2 TCR* pathway impairment	[45]
TNF-α	Agarwal et al.	2011	USA	Protein level (ELISA) after stimulation of T cells with CD3/CD28 or PHA*, PMA*	Normal range; trend to lower production of TNF-α after CD3/CD28 in CVID/IBD patients,	12/16	Mechanism of inflammation in IBD-CVID patients may be mediated through abnormal cytokine level	[55]
TNF-α	Trujillo et al.	2011	Colombia	Protein level (CBA) after stimulation of with PBMCs with LPS* and LTA*	Increased production after LPS stimulation	6/5	Support the hyper inflammatory state of CVID patients	[46]
TNF-α	Hong et al.	2010	USA	Monocyte derived production after pneumovax-23	Decreased production	14/13	Impairment of TNF-α play an important role in increased susceptibility of CVID patients to S. pneumoniae infection.	[80]
TNF-α IL-6 IL-12	Yu et al.	2009	USA	Protein level (ELISA) after stimulation of PBMCs with TLR* agonists for 24 h	Normal range	46 patients	PBMCs of CVID patients have impaired production of IFN-α on TLR7, TLR8, and TLR9 signaling but normal production of both TNF-α and IL-6	[123]
TNF-α	Koval'chuk et al.	2007	Russia	Stimulated by TLR2/6, TLR4, TLR5, TLR9 ligand	Reduced production of TNF-α	9/11	Less production of TNF-α stimulated by TLR4 and TLR5 ligands in vitro	[158]
TNF-α	Pons et al.	2006	Spain	Protein level (CBA) after stimulation of T cells with CD3 or CD3/CD28 for 16 h	Trend towards increased TNF-α production	14/14	Imbalance between co stimulatory molecules and cytokine production does not explain the B and T cells cooperation deficiency	[55]
TNF-α	Isgrò et al.	2005	Italy	Protein level (ELISA) after in-vitro culture of bone marrow cells after 1–4 days	Increased spontaneous secretion	11/10	Impaired growth and differentiation capacity of progenitor cells in CVID patients	[51]
TNF-α	Ueland et al.	2001	Norway	Serum levels	increased	25/25	persistent immune activation in vivo, with increased levels of proinflammatory cytokines, may be related to disturbed bone homeostasis in CVID patients	[79]
TNF-α	Aukrust et al.	1996	Norway	Serum level Protein level (ELISA) after stimulation of PBMC with LPS	Increased TNF-α level, increased spontaneous	24/20	TNF-α seems to impair T cell proliferation and IL-2 production	[135]

Table I (continued)

Cytokine	Study	Year	Country	Method and stimulation	Serum level/Tx	Case/control	Etiology/Changes	Ref
					secretion but decreased LPS induced secretion in a subgroup			
TNF-α	Pandolfi et al.	1993	Italy	Protein level (ELISA) after stimulation of PBMC with PHA*	Normal range	26 patients	IL-6 levels do not correlate with absolute number of lymphocyte and its increased production is not due to non-specific activation	[159]
TNF-α	Chua et al.	2007	UK	TX* with anti-TNFα (Infliximab)	Tx,3 m induction,5 -53 m maintenance	3 patients	The positive efficacy of anti-TNFα in CVID patients	[136]
TNF-α	Hatab et al.	2005	USA	TX with anti-TNFα (Infliximab)	Tx, a patient with infliximab, every 3 weeks, 4 infusions	1 patient	Success of infliximab in granulomatous inflammation in CVID	[137]
TNF-α	Thatayatikom	2005	USA	TX with anti-TNFα (Infliximab)	Tx, a patient with infliximab, weekly for 6w then monthly for 9 m	1 patient	Successful effect of infliximab in granulomatous CVID	[138]
IL-6	Trujillo et al.	2011	Colombia	Protein level (CBA) after stimulation of PBMCs with LPS*, LTA*, CpG	Normal range	6/5	Number of innate immune cells such as DC and NK is altered.	[46]
IL-6	Hong et al.	2010	USA	Monocyte derived production after pneumovax-23	Decreased IL-6 production	14/13	Impairment of Il-6 plays an important role in increased susceptibility of CVID patients to S. pneumoniae infection.	[80]
IL-6	Cunningham-Rundles et al.	2006	USA	Protein level (ELISA) after stimulation of B cells with CpG	Reduced IL-6 induction	14/5	On exposure to CpG-DNA, IL-6 cytokine is not produced, and CpG ligands could not provide the survival advantage afforded to normal B cells	[6]
IL-6	Pons et al.	2006	Spain	Protein level (CBA) after stimulation of T cells with CD3 or CD3/CD28 for 16 h	Trend towards increased IL-6 production	14/14	Imbalance between co stimulatory molecules and cytokine production does not explain the B and T cells cooperation deficiency	[55]
IL-6	Ueland et al.	2001	Norway	Serum levels	Increased	25/25	persistent immune activation in vivo, with increased levels of proinflammatory cytokines, may be related to disturbed bone homeostasis in CVID patients	[79]
IL-6	Aukrust et al.	1994	Norway	Serum level	Detectable in 48 % of CVID patients but not in controls	25/21	Elevated cytokine levels may be only a marker of chronic immune activation	[16]
IL-6	Pandolfi et al.	1993	Italy	RNA and Protein level (ELISA) after stimulation of PBMC with PHA*	Increased IL-6 production and expression	28 patients	Despite augmentation of IL-6 level after stimulation with PHA, CVID cells do not respond to IL-6 level by increase production of Igs.	[159]
IL-6	Heyden et al.	1993	Germany	Stimulated by LPS	Increased IL-6 level	11/9	Production of Ig does not correlate with IL-6 level	[82]
IL-6	Junker et al.	1993	Germany	Serum level Protein level (ELISA) after stimulation with LPS	Normal range or even increased IL-6 level	10/13	Impairment in B cells is not due inability of the B cells to detect IL6 in the serum.	[160]

Table II The role of Th1 cytokines in common variable immunodeficiency

Cytokine	Study	Year	Country	Method and stimulation	Serum level/Tx	Case/control	Etiology/Changes	Ref
IL-2	Agarwal et al.	2011	USA	Protein level (ELISA) after stimulation of T cells with CD3/CD28 or PHA, PMA	Normal range; trend to lower production of IL-2 after CD3/CD28 in CVID/IBD patients,	12/16	Mechanism of inflammation in IBD-CVID patients may be mediated through abnormal cytokine production	[54]
IL-2	Rezaei et al.	2010	Iran	Protein level (ELISA) after 3d PHA stimulation	Decreased in 7 of 27 patients	27/17	T cell proliferation and secretory defects in some CVID patients	[161]
IL-2	Rezaei et al.	2008	Iran	Serum (ELISA)	Normal range	24/20	Normal function of T helper cells	[28]
IL-2	Giovannetti et al.	2007	Italy	Protein level (flow cytometric detection of cytokine producing cells) after stimulation with PMA* Ionomycin	Normal range in CD4 and CD8 T cells	60/30	Key role of T cell in CVID has been highlighted	[53]
IL-2	Pons et al.	2006	Spain	Protein level (CBA) after stimulation of T cells with CD3 or CD3/CD28 for 16 h	Trend towards increased IL-2 production	14/14	Imbalance between co stimulatory molecules and cytokine production does not explain the B and T cells cooperation deficiency	[55]
IL-2	Isgro et al.	2005	Italy	Protein level (ELISA) after in-vitro culture of bone marrow cells after 1–4 days	Decreased spontaneous secretion	11/10	impaired growth and differentiation capacity of progenitor cells in CVID	[51]
IL-2	Ferrer et al.	1995	Spain	Stimulated by PWM*	Low IL-2 secretion after PWM activated	11/10	Deficiency is due to intrinsic defect in IL-2 pathway, over stimulation of CD4 switch to Th2 cytokines	[37]
IL-2	Inoue et al.	1994	Japan	PBL were stimulated by Con A or PHA	Normal range	6 patients	TH1 function is NL, B-cell dysfunction is responsible for the features	[52]
IL-2	Fisher et al.	1994	Austria	Protein level (ELISA) after stimulation of autologous monocytes and enriched T cells after various stimuli	Decrease IL-2 production stimulated by super Ag	24/10	deficiency in the early phase of T-cell activation after triggering of TCR	[157]
IL-2	Fischer et al.	1993	Austria	Cells stimulated with mAb specific for anti-CD3 and PMA+calcium ionophore ionomycin	Impaired IL-2 expression after antigenic stimulation	3/30	Abnormality confined to T-cell activation by the T-cell receptor	[38]
IL-2	Einstein et al.	1993	USA	mRNA production, stimulated by PHA*, SEB* or anti CD2Ab	Reduced IL-2 secretion	4/10	IL-2 reduction due to abnormal CD4+T cells	[39]
IL-2	Sneller et al.	1990	USA	expression of lymphokine genes in activated T cells by PHA	Decreased IL-2 expression	4patients	selective abnormality of T cell activation	[15]
IL-2	Pastorelli et al.	1989	France	Stimulated by PHA and ConA*	Decreased IL-2 level	15 patients	Normal proliferation of Lymphocytes, IL2 and IL-4 have synergist effect	[36]
IL-2 therapy	Cunningham-Rundles et al.	2001	USA	The proliferative capacities of PBMC were determined by PHA, Con A and PWM	12-18 m Tx/PEG- IL-2*	15/39	Enhance T cell function, decrease infection rate	[58]
IL-2 therapy	Rump et al.	1997	Germany	Nhu *IL-2 was stimulated by PMA *and calcium ionophore	12 m Tx/u IL-2	10/10	Reduction of severe infection	[59]
IL-2 therapy		1995	USA		12w Tx/PEG- IL-2	5/20		[1]

Table II (continued)

Cytokine	Study	Year	Country	Method and stimulation	Serum level/Tx	Case/control	Etiology/Changes	Ref
	Cunningham-Rundle et al.			The proliferative capacities of PBMC were determined by PHA, Con A, PWM, anti-CD3 monoclonal antibody, MAb 446			Enhance T cell proliferation, B cells response to signals, Normal IL-2 production	
IL-2 therapy	Cunningham-Rundles et al.	1994	USA	Stimulated by PHA*	16 m Tx/PEG- IL-2	A 50-year-old woman	Increase B-cell differentiation, Increase IgA & IgM, decrease infection rate	[56]
IL-2 therapy	Cunningham-Rundle et al.	1992	USA	The proliferative capacities of PBMC were determined by PHA, Con A and PWM	12 m Tx/PEG- IL-2	5 patients	Increase in Ig secretion in vitro, but not in vivo, increase T helper activity	[57]
IFN- γ	Agarwal et al.	2011	USA	Protein level (ELISA) after stimulation of T cells with CD3/CD28 or PHA*, PMA*	Normal range; trend to lower production of IFN-γ stimulated by CD3/CD28	12/16	Mechanism of inflammation in IBD*-CVID patients may be mediated through abnormal cytokine level	[54]
IFN-γ	Rezaei et al.	2010	Iran	Protein level (ELISA) after stimulation with PHA for 3days	decreased in 2 of 27 patients	27/17	T cell proliferation and secretory defects in some CVID patients	[161]
IFN-γ	Giovannetti et al.	2007	Italy	Protein level (Flowcytometric detection of cytokine producing cells) after stimulation with PMA* Ionomycin	In CD4 T cells: increased in one subgroup CD8 T cells: increase in subgroups	60/30	Key role of T cell in CVID has been highlighted	[53]
IFN- γ	Pons et al.	2006	Spain	Protein level (CBA) after stimulation of T cells with CD3 or CD3/CD28 for 16 h	Trend towards increased IFN-γ production	14/14	Imbalance between co stimulatory molecules and cytokine production does not explain the B and T cells cooperation deficiency	[55]
IFN-γ	Holm et al.	2003	Norway	Protein level (ELISA) after stimulation of T cells with CD3 for 48 h	Decreased but not reaching significance	6/6	CAMP agonist 8-CPT-cAMP strongly reduced the secreted levels of IFN-γ in anti-CD3/anti-CD28-stimulated T cells from both patients and controls.	[7]
IFN-γ	Inoue et al.	1994	Japan	———————————	Normal range	6 patients	Immune defect cause by B cell rather than T.	[52]
IFN-γ	Fischer et al.	1994	Austria	Protein level (ELISA) after stimulation of autologous monocytes and enriched T cells by various stimuli	Decreased IFN- γ production on TCR stimulation with recall antigens and superantigens.	24 patients	Defect in the early phase of T-cell activation, Decrease level of IFN- γ have implication for B-cell differentiation	[157]
IFN-γ	Fischer et al.	1993	Austria	mRNA level, induction with anti-CD3	Impaired IFN- γ expression	3Patients	Abnormality confined to T-cell activation by the T-cell receptor.	[38]
IFN-γ, IL-2	Hauber et al.	1993	Austria	mRNA level	Aberrant in IFN- γ and IL-2	3patients	Reduction in IL-2 gene expression and IFN- γ transcription	[125]
IFN-γ	Sneller et al.	1990	USA	Lymphokine gene expression, stimulated by PHA*	Decrease IFN- γ expression	4patients	partially due to the abnormality of IL-2 production, Normal IFN- γ production by adding IL-2	[15]

Table III The role of Th2 cytokines in common variable immunodeficiency

Cytokine	Study	Year	Country	Method and stimulation	Serum level/Tx	Case/control	Etiology/Changes	Ref
IL-4	Borte et al.	2010	Germany	Molecular dynamics simulation.	No differences in pediatric cases in IL4R function detected	32 pediatric patients	The function of the IL-21R : IL-4R system seems not to be related to the etiology of CVID	[67]
IL-4, IL-10	Rezaei et al.	2010	Iran	genotyping	IL4 promoter polymorphism	30 patients	High production of IL-4 could be due to haplotypes frequencies of this cytokine gene polymorphism.	[101]
IL-4	Rezaei et al.	2010	Iran	Protein level (ELISA) after 3d PHA stimulation	Altered in 7 of 27	27/17	T cell proliferation and secretory defects in some CVID patients	[161]
IL-4	Rezaei et al.	2008	Iran	Serum (ELISA)	Higher IL-4 level	24/20	Bias toward Th2 cytokines	[28]
IL-4	Giovannetti et al.	2007	Italy	Protein level (Flowcytometric detection of cytokine producing cells) after stimulation with PMA* Ionomycin	CD4 T cells: Normal,CD8 T cells: significantly increased proportion in all patient groups	60/30	Key role of T cell in CVID has been highlighted	[53]
IL-4	Pons et al.	2006	Spain	Protein level (CBA) after stimulation of T cells with CD3 or CD3/CD28 for 16 h	increased IL-4 production	14/14	Imbalance between co stimulatory molecules and cytokine production does not explain the B and T cells cooperation deficiency	[55]
IL-4	Kokron et al.	2004	Brazil	Serum	decreased IL 4 synthesis	71 patients	Increase in susceptibility to apoptosis following activation, may be responsible for Th2 cytokines synthesis reduction	[64]
IL-4	Holm et al.	2003	Norway	Protein level (ELISA) after stimulation of T cells with CD3 for 48 h	Decreased but not significant	6/6	cAMP agonist 8-CPT-cAMP strongly reduced the secreted levels of IFN-γ and IL-4 in anti-CD3/anti-CD28-stimulated T cells in CVID patients	[7]
IL-4	Thon et al.	1997	Austria	Stimulation for 60 h with MoAb anti-TCR, anti-CD4, anti-CD2, anti-CD28, anti-CD8 or PMA*	Impaired IL4 secretion in CVID	8/8	Activating signals derived from the TCR and co-stimulatory molecules is defective in CVID patients	[63]
IL-4	Ferrer et al.	1995	Spain	Stimulated with PWM*	High IL-4 secretion after PWM activated	11/10	over stimulation of CD4 switch to Th2 cytokines	[37]
IL-4	Aukrust et al.	1994	Norway	Serum level	Detectable in 36 % of CVID patients but not in controls	25/21	elevated cytokine levels may be only a marker of chronic immune activation	[16]
IL-4	Pastorelli et al.	1989	France	Stimulation with PHA and ConA*	Decreased IL-4 level	15 patients	Reduce in IL-4 was not observed after stimulation. Proliferation of lymphocytes was Normal, IL2 and IL-4 has synergist effect, one is deficient, the other is suboptimal.	[162]
IL-5	Rezaei et al.	2010	Iran	Protein level (ELISA) after 3d PHA stimulation	Decreased in 4 of 27 patients	27/17	T cell proliferation and secretory defects in some CVID patients	[161]
IL-5	Kokron et al.	2004	Brazil	Serum	Decreased IL 5 synthesis	71 patients	Increase in susceptibility to apoptosis following activation, may be responsible for Th2 cytokines synthesis reduction	[64]
IL-5	Einstein et al.	1993	USA		Reduced IL-2 secretion	4/10		[39]

Table III (continued)

Cytokine	Study	Year	Country	Method and stimulation	Serum level/Tx	Case/control	Etiology/Changes	Ref
				mRNA production, stimulated by PHA*, SEB* or anti CD2Ab			Primary abnormality of lymphokine production exists in the CD4+ T cells of a subset of CVID patients.	
IL-5	Rezaei et al.	2010	Iran	Protein level (ELISA) after 3d PHA stimulation	Decreased in 4 of 27 patients	27/17	T cell proliferation and secretory defects in some CVID patients	[161]
IL-5	Kokron et al.	2004	Brazil	Serum	Decreased IL 5 synthesis	71 patients	Increase in susceptibility to apoptosis following activation, may be responsible for Th2 cytokines synthesis reduction	[64]

controls [16]. One other study has investigated IL-1 in CVID and has revealed a decreased proliferative response to low dose anti CD2 in combination with IL-1 in the presence of monocytes [45]. For clarifying the underlying mechanism, levels of IL-1RA from monocytes after lipopolysaccharide (LPS) stimulation were measured which revealed no significant difference between patients with CVID and controls [45].

Trujillo et al. who measured protein level of diverse cytokines has also shown normal range of IL-1β production after stimulation of peripheral blood mononuclear cells (PBMC) with LPS and lipoteichoic acid [46].

In addition, Haveman et al. also revealed no significant difference in IL-1β production after 3 days stimulation of PBMC with concanavalin A (ConA) or diverse viral antigens including EBNA1, BZLF1 (EBV), HHV-6B, CMV, HSV1 and HAdV [47]. Thus, in summary no major alteration was detected in the production of IL-1 in CVID.

IL-2

IL-2, the first in a series of lymphocytotrophic cytokines to be recognized, plays a central role in the regulation of growth, differentiation and function of lymphocytes [48].

The critical role for IL-2 and its receptor, IL-2R in T cell survival, particularly in T regulatory biology has been pointed out by previous studies [49, 50].

Up to now, numerous studies have investigated the IL-2 serum level or its mRNA production by T cells of CVID patients; however, contrary results have been obtained.

Defective IL-2 production by CD4+ T cells [39] associated with impaired growth and differentiation capacity of progenitor cells [51] have been reported before. However, normal IL-2 production has been found in other studies [28, 52].

Pasterolli et al. who examined production of lymphokines by peripheral blood lymphocytes (PBL) of CVID patients revealed reduced production of IL-2 and IL-4 compared to PBL of healthy donors after stimulation with PHA and ConA. In contrast, Giovannetti et al. found no significant differences in IL-2 production after ionomycin and PMA (phorbol myristate acetate) stimulation of CD4+ and CD8+ T cells between CVID and controls [53].

Analyzing cytokines in CVID patients with inflammatory bowel disease, Agarwal et al. observed a trend toward reduction in IL-2 production after stimulation of T cells with anti CD3/CD28, but not following stimulation by PHA (phytohaemagglutinin)/PMA which highlighted that defective TCR signaling might be involved [54]. In contrast, Pons et al. described a trend toward increased IL-2 production after stimulation of T cells with CD3 or CD3/CD28 in CVID patients [55].

Given the immunostimulatory function of IL-2 and the data of reduced IL-2 production mentioned above, two groups

Table IV The role of T-regulatory and Th17 cytokines in common variable immunodeficiency

Cytokine	Study	Year	Country	Method and stimulation	Serum level/Tx	Case/control	Etiology/Changes	Ref
IL-10	Agarwal et al.	2011	USA	Protein level (ELISA) after stimulation of T cells with CD3/CD28 or PHA,* PMA*	Normal range; trend to lower production of IL-10 after CD3/CD28	12/16	Mechanism of inflammation in IBD-CVID patients may be mediated through abnormal cytokine production	(54)
IL-10	Kasztalska et al.	2011	Poland	Plasma level	Higher plasma level of IL-10	17/7	IVIG therapy has positive effect in IL-10, IL-2 serum level and percentage of CD4 T Cells	(100)
IL-10	Trujillo et al.	2011	Colombia	Protein level (CBA) after stimulation of with PBMCs with LPS*,LTA*, CpG	Normal range	6/5	Number of innate immune cells such as DC and NK is altered	(46)
IL-10	Hong et al.	2010	USA	Monocyte derived production after pneumovax-23	Normal range	14/13	Impairment of Il-10 plays an important role in increased susceptibility of CVID patients to S. pneumoniae infection.	(80)
IL-10	Rezaei et al.	2010	Iran	Genotyping	High production of IL-10 due to lowfrequency of IL-10 ACC low producing haplotype	30/140	Elevated Il-10 serum level is due to genetic polymorphism	(101)
IL-10	Rezaei et al.	2008	Iran	Serum level	Increase IL-10 serum level	24/20	Increased of Th2 cytokine level as IL-4 and IL-10	(28)
IL-10	Giovannetti et al.	2007	Italy	Protein level (Flowcytometric detection of producing cells) after stimulation with PMA* Ionomycin	Decreased proportion of IL-10 producing CD4 and CD8 T cells in all patient groups	60/30	Key role of T cell in CVID has been highlighted	(53)
IL-10	Pons et al.	2006	Spain	Protein level (CBA) after stimulation of T cells with CD3 or CD3/CD28 for 16 h	Normal range, slight trend towards decreased IL-10 production	14/14	Imbalance between co stimulatory molecules and cytokine production does not explain the B and T cells cooperation deficiency	(55)
IL-10	Cunningham-Rundles et al.	2006	USA	Protein level (ELISA) after stimulation of B cells with CpG	Reduced IL-10 induction	14/5	On exposure to CpG-DNA, IL-10cytokine is not produced, and CpG ligands could not provide the survival advantage afforded to normal B cells	(6)
IL-10	Holm et al.	2003	Norway	Protein level (ELISA) after stimulation of T cells with CD3 for 48 h	Impaired secretion of IL-10 by CVID T cells	21/18	Involvement of the CAMP/PKAI system in IL-10 deficiency	(7)
IL-10	Zhou et al.	1998	USA	Protein level (ELISA) after stimulation of T cells for 24 h with CD3, CD3/CD2,8 PHA*; adherent cells with LPS*, TNF-α	Decreased IL-10 secretion of T cells, increased IL-10 secretion of enriched adherent cells	25/12	Deficient secretion of IL-10 from CVID T cells	(99)
IL-10	Oliva et al.	1997	Italy	Protein level (ELISA) after stimulation of PBMCs with both anti-CD3 or anti-CD3 plus PMA	Same level of IL-10 in CVID and control	16 patients	IL-10 do not play a major role, Cd40L appears to be Normal, but functionally defective.	(21)
IL-10	Zielen et al.	1994	Germany	TX with IL-10	Tx of CVID patients with IL-10 and CD-40	7 patients	Normal B cell function in Ig synthesis after activated through CD40 plus IL-10	(45)
IL-17	Barbosa et al.	2011	Portugal	Th 17 cell frequency	PBMC were assessed for cytokine production after 4-h culture with PMA plus ionomycin	31patients/30 healthy individuals	no significant differences in the proportion of IFN-γ+cells within the IL-17-producing CD4 subset as compared to healthy subjects	(139)

Table V The role of other cytokines in common variable immunodeficiency

Cytokine	Study	Year	Country	Method and stimulation	Serum level/Tx	Case/Control	Etiology/Changes	Ref
IL-7	Isgrò et al.	2005	Italy	Protein level (ELISA) of stromal cell cultures	Decreased secretion	7/3	Impaired growth and differentiation capacity of progenitor cells in CVID patients	(51)
IL-7	Holm et al.	2005	Norway	ELISA	Elevated IL-7 level	72/23	Inverse correlation between IL-7 and in-vitro T-cell proliferation	(92)
IL-12p70	Trujillo et al.	2011	Colombia	Protein level (CBA) after stimulation of with PBMCs with LPS*, LTA*, CpG	Normal range	6/5	Level of IL-12p70 in PBMC of both CVID patients and healthy controls increase after stimulation	(46)
IL-12	Cunningham et al.	2005	USA	DC* Stimulated with LPS, TNF-α or CD40-L fusion protein	Decreased IL-12 level	31/25	Reduced IL-12level due to DC malfunction	(109)
IL-12	Cambronero et al.	2000	UK	Stimulated with LPS	Increased IL-12 level	12/12	Abnormality in the IL-12/IFN- γ circuit play a key role in CVID	(105)
IL-21	Clemente et al.	2013	Spain	Anti-CD40,CpG-ODN and IgM stimulus	B cell function with or without IL-21	22/22	IL-21 rescued unstimulated CD27 (−) B cells and improved the rescue of anti-CD40-stimulated CD27 (+) B cells.	(163)
IL-21	Borte et al.	2010	Germany	Molecular dynamics simulation	Function of IL-21 is not related to CVID etiology in pediatric patients	32 patients	IL-21 may be suitable for regenerative therapy in CVID	(67)
IL-21	Borte et al.	2009	Germany	mRNA level after stimulation of T cells with anti-CD3 for 14 h	No deficiency in IL-21 expression, slightly decreased expression with and without stimulation	30/22	Therapeutic role of IL-21 in Ig production and Ig switching	(8)

CVID: Common Variable Immunodeficiency; PBMC: Peripheral Blood Mononuclear Cell; SNP: Single Nucleotide Peptide; TCR: T Cell Receptor; IBD: Inflammatory bowel Disease; DC: Dendritic Cell; TLR: Toll like Receptor; nhu: Natural human; PEG: polyethylene glycol; LPS: lipopolysaccharide; LTA: lipoteichoic acid; ConA: Concanavalin A; PHA: Phytohaemagglutinin; PMA: phorbol myristate acetate; PWM: pokeweed mitogen,SEB: staphylococcal enterotoxin B, Tx: Therapy; w: Week; m: Month

have investigated the effects of in vivo IL-2 treatment [1, 3, 56]. Cunningham-Rundles et al., who treated 5 CVID patients with polyethylene glycol-conjugated human recombinant interleukin-2 (PEG- IL-2) intravenously, have shown improved T cell helper activity [57]. Thereafter, the same group has demonstrated enhancement in T cell proliferation, increased IL-2 production and renewed production of serum antibody after 12 subsequent weeks of treatment with subcutaneous PEG-IL-2 [1]. One patient of this study was selected randomly for continuous PEG-IL-2 treatment for 16 months to assess the long-term effect of this therapy [56]. This 50-year-old CVID woman had higher numbers of circulating mononuclear cells, IL-2 and IL-6 cellular secretion and immunoglobulin concentration [56] after 16 months of treatment. In addition, the therapy was accompanied by several clinical benefits such as ending chronic diarrhea and decreasing respiratory tract infections [56].

Several years later, Cunningham-Rundles et al. examined the role of long-term PEG-IL-2 in 15 additional randomly chosen CVID patients [58]. Also, this study revealed enhanced T cell function, increase of the antibody response and reduced duration of infections after 6–12 months and 12–18 months which indicated IL-2 as an adjuvant therapy in CVID patients [58].

Similarly, Rump et al. found in a crossover study with natural human IL-2 (nhuIL-2) in combination with intravenous gamma globulin (IVIG) in 10 CVID patients a significant reduction of severe infection in patients treated with nhu IL-2, especially in the first 6 months; however nhu IL-2 therapy was ineffective in eliciting spontaneous IgG synthesis [59].

In the two mentioned papers on in vivo IL-2 therapy, no severe side effects except local skin reactions of the therapy were reported [58, 59]. Only one patient with prior splenectomy had elevated liver function tests, in whom liver biopsy revealed possible (preexisting) nodular regenerative hyperplasia [59].

Taken together, dysregulation of IL-2 possibly plays an important role in the immunopathogenesis of some patients and therefore IL-2 therapy might be beneficial in the therapy of selected CVID patients, but further trials are necessary to account for the correct selection of patient and the benefit-risk ratio of this systemic therapy.

IL-4

Interleukin-4 is produced by T cells and some innate cells. It mainly serves as an inducer in the differentiation of naïve T cells to Th2 lymphocytes, it co-stimulates proliferation of activated B- and T-cells, and induces B-cell class switching to production of IgE and IgG [60] and is associated with the manifestation of allergy [61].

Several studies have shown high serum levels of IL-4 in CVID patients [16, 28, 37, 55] inducing a predominance of Th2 activity in some CVID patients [28, 62], however, other studies showed contrary results [63, 64]. Despite previous studies have revealed association of allergic asthma [65] and allergic rhinitis [66] with CVID, no clear link of IgE up-regulation or Th2 increase in CVID has been shown so far.

This overproduction may be explained by specific IL-4 gene polymorphisms enriched in CVID patients [71]. On the other hand, an impaired IL-4 secretion by CD4+ lymphocytes following TCR/anti-CD28 stimulation [63] or decreased synthesis of IL-4 due to increased susceptibility of lymphocytes to apoptosis [64] have been reported. One study analyzed the IL-4 receptor function in pediatric cases without detecting an abnormal function in the analyzed cases [67].

Taken together, contrary results probably reflect the heterogeneity of the CVID cohort regarding predominant Th1/Th2 differentiation and further studies are important to correlate these phenotypes to clinical and other immunological phenotypes.

IL-5

IL-5, a Th2 cytokine, stimulates B cell growth and increases immunoglobulin secretion [68].

Reduced IL-5 production by peripheral T cells of CVID patients may therefore contribute to defective antibody production in CVID patients [15, 69]. Eisenstein et al. revealed impaired IL-5 mRNA production in CVID patients [39].

Kokron et al. have proposed increased susceptibility to apoptosis in lymphocyte following activation also as a cause for decreased synthesis of IL-5 [64].

However, one report found a similar frequency of IL-5 producing mononuclear cells inhypogammaglobulinemia as compared to controls by insitu hybridization after pokeweed mitogen (PWM) stimulation [70]. In summary, most, but not all studies found reduced IL-5 production by T cells of CVID patients.

IL-6

IL-6 is a cytokine produced by different cell types including antigen presenting cells, B cells and Th2 cells. Albeit its well known proinflammatory role [71], IL-6 is a pleiotropic cytokine with multiple functions on multiple cell types including anti-inflammatory effects [72].

One of the mechanisms IL-6 exhibits its immunoregulatory functions is by directing the differentiation of regulatory versus Th17 cells [73]. In addition, in the context of humoral immunodeficiency the role of IL-6 as a plasma cell growth factor has to be mentioned [74]. Up regulation in IL-6 production has previously been implicated in autoimmune disorders like rheumatoid arthritis [75], systemic lupus erythematosus (SLE) [76] and others [77, 78] possibly inducing hypergammaglobulinemia in these disorders.

In CVID patients, results reaching from increased production [55, 79], normal range [46] to decreased production of IL-6 after mitogen stimulation [80] have been reported suggesting a heterogeneity in the cohort.

Pandolfi et al. has shown an increased production of IL-6 in vitro which did not correlate with specific lymphocyte subpopulations [81]. Previous data have indicated that the increase in IL-6 production does not lead to improved immunoglobulin production in CVID after in vitro stimulation [82].

Another study which evaluated genotype frequencies of a number polymorphic genes coding IL-6 in CVID patients and healthy individuals revealed an increased level of IL-6 which could be due to single nucleotide polymorphism in these patients, however the functional importance of these polymorphisms is still doubtful [44]. In contrast to mentioned studies, Hong et al. revealed Pneumovax-23-induced monocytes produce less IL-6 in CVID patients as compared with controls.

Taken together, majority of studies represent a higher production of IL- 6 in CVID patients.

IL-7

Interleukin 7 (IL-7), a T cell growth factor and a regulator of Th1 and Th2 cytokine production, stimulates differentiation of stem cells into lymphoid progenitor cells and promotes survival and expansion of lymphoid precursors [83–85]. It has also been shown that IL-7 stimulates proliferation of in the lymphoid lineage cells including T cells and NK cells [86]. While IL-7 is crucial in murine early B cell development, normal B cell differentiation in IL7Ra deficiency in humans negates an important influence of IL-7 on early human B cell differentiation [87, 88].

Previous studies have shown that serum level of IL-7 is elevated in lymphopenia such as low CD4+ T-cell in HIV infection and the level declines as T-cell numbers recover [89, 90].

Moreover, IL-7 increases cell numbers and function of leukocytes by reducing activated T lymphocyte apoptosis and promote INF- γ and other cytokines [91].

Concerning CVID and IL-7, a brief report has reported elevated plasma levels of IL-7 in a subgroup of CVID patients [92], while, Isgro et al. revealed reduced IL-7 secretion from bone marrow mononuclear cells of CVID patients in vitro [51].

IL-7 plays an important role in T-cell homeostasis by inducing proliferation and differentiation of immature thymocytes and by enhancing the peripheral expansion T-cell subsets.

Regarding correlation between IL-7 levels and in vitro T-cell proliferation, it has also been demonstrated that T cells from CVID patients secrete less TGFβ1, a negative regulator of IL-7 secretion, suggesting a functional link [93].

In summary, studies regarding Il-7 and CVID are scarce and it remains to be clarified whether it has a role in immune dysregulation in a subgroup of CVID patients.

IL-10

IL-10, an anti-inflammatory cytokine, is secreted by different cells, especially T cells and monocytes. It is capable of inhibiting synthesis of pro-inflammatory cytokines such as IFN-γ, IL-2, IL-3, TNFα. In addition, IL-10 regulates differentiation of B cells, T helper cells and NK cells [33, 94] and plays a role in plasma cell differentiation [95]. IL-10 plays an important role in the control of inflammation by T regulatory (Treg) cells [96]. Association of altered Treg has been evaluated in different autoimmune disorders. In this regard, several papers have revealed a decreased number of Treg in CVID patients especially when presenting with splenomegaly and increased inflammatory markers [97]. The authors reported a significant correlation between IL-10 production in vitro with the number of Tregs [7] suggesting Tregs to be the major T cell source of IL-10.

Increased serum level of IL-10 have been reported in SLE and arthritis rheumatoid patients [33]. Interestingly, IL-10 deficient patients present with normal Ig serum levels and specific antibody responses excluding a non-redundant role of IL-10 in plasma cell differentiation [98].

In CVID patients two studies demonstrated reduced IL-10 production by T cells in vitro [7, 99], one study found no difference [21]. At the same time Zhou et al. found increased IL-10 production by monocytes [99]. Holm et al. associated low IL-10 production by T cells with altered cAMP/PKAI signaling, opening a potential therapeutic target in CVID [7]. The potential therapeutic use of IL-10 in CVID was suggested by in vitro experiments in which the addition of IL-10 to IL-2 and SAC activated PBMC supported IgG secretion in 6/7 tested children [35]. This was not supported by an Italian study on 17 patients where only one patient responded to IL-10 co-stimulation [21]. Finally, a recent study by Kasztalska et al. has detected higher plasma levels of IL-10 in 17 CVID patients [100], potentially due to a lower frequency of a genetic haplotype associated with low IL-10 production in CVID [101].

In summary, the dysregulation of IL-10 production in CVID is complex. While T cells might produce less IL-10, a higher production of IL-10 by monocytes and in serum has been detected in CVID patients. Given the availability of therapeutic IL-10 it is worth revisiting the question of the potential therapeutic use in selected patients.

IL-12

The best known function of IL-12 is the induction of IFN-γ and differentiation of naïve T cells to Th1 [102]. The

administration of IL-12 aggravates autoimmune manifestations in different mouse and rat models [103, 104].

A higher proportion of intracellular IL-12 producing monocytes has been disclosed in CVID patients, which was associated with increased frequency of IFN-γ positive T cells [105]. Compatible with this finding one study described increased levels of plasma IL-12p40, which was not related to IL-12p40 gene or promoter polymorphism [106]. Another study detected an increased expression of IL-12Rbeta1 on CD45RA+CD4+ and CD45RA+CD8+ T cells of CVID patients as a sign of the Th1 predominance in the examined patients [107]. Based on these findings, one study recommended the use of an oral IL-12/IL-23 inhibitor named Apilimod for CVID as it was suggested for other immune disorders such as Crohn's disease and rheumatoid arthritis [108]. Currently, no data are however available.

On the other hand, Cunningham Rundles et al. have demonstrated a lower rate of IL-12 secretion by DCs of CVID patients as compared to DCs of normal controls as a result of a functional DC defect [109]. The low IL-12 production upon CD40 signaling in DCs of CVID patients was confirmed by Bayry et al. [23]. In summary, IL-12 production might be regulated differently in different cellular compartments. The impact of the dysregulation in IL-12 production needs to be addressed separately in the different subgroups of CVID patients.

IL-21

IL-21, a recently identified CD4+ T cell human cytokine is mainly expressed in T_{FH} cells, but also Th2 and Th17 cells [110, 111]. IL-21 is involved in multiple processes of the immune system including NK cell maturation, B cell and T cell proliferation and especially plasma cell differentiation [112, 113]. IL-21, which is related to IL-2 and IL-15, sharing a common receptor gamma chain, is the master regulator of Ig production and Ig isotype switching [114].

One study revealed the capacity of exogenous IL-21 to restore the antibody producing capacity in 32 CVID patients [8]. Since there was no mutation in the coding region of IL-21 or IL-21R and no difference in mRNA induction in stimulated T cells the underlying failure of sufficient IL-21 co-stimulation in vivo remains open [67]. Subsequently, monogenetic IL-21R deficiency has been identified in 4 children of two unrelated families resembling combined immunodeficiency, interestingly, not fulfilling the current diagnostic criteria for CVID in any of the patients [115]. The role and potential therapeutic use of IL-21 in CVID deserves more attention in the future.

IFN

Interferons (IFNs) are cytokines, which were first reported in the context of antiviral defense [116]. Three major types of IFNs, based on the receptor type through which they signal have been classified [117]. Type I IFNs can be produced by all cells especially upon activation of cytosolic receptors that recognize nucleic acid [118] with plasmacytoid dendritic cells being the most potent producers. They play an important role in antiviral defense among others by inducing MHC expression [119] and can enhance isotype switching, increase the amount and long-term production of Ig [120]. Increased type I IFN has been shown in diverse autoimmune disorders such as SLE and rheumatic arthritis [121]. In CVID, a previous report by Strannegård et al. has revealed over-production of type I IFN [122]. Studies by the group of C. Cunningham-Rundles have revealed reduced type I IFN release on TLR7 or TLR9 stimulation by B cells and plasmacytoid dendritic cells of CVID patients [6, 123].

Type II IFNs are represented by IFN-γ, a dimerized cytokine. IFN-γ is the key Th1 cytokine and therefore plays an important role in both innate and adaptive immune systems [124]. IFN-γ has been investigated in multiple CVID studies with variable results. Inoue et al. has shown a normal range of IFN-γ and IL-2 serum level in CVID patients [52]. In contrast, Hauber et al. have demonstrated a dramatic reduction of IL-2 and IFN-γ mRNA levels in CVIDs [125]. Fischer et al. corroborated this finding demonstrating a deficiency in IFN-γ mRNA expression after stimulation with antigen in a subgroup of CVID patients [38], while Serrano et al. has revealed increased production of IFN-γ in purified T cells of CVID patients upon CD3 or PMA/PMH stimulation after 24 h [126]. North et al. also showed an increase production of IFN-γ in CD4+ and CD8+ T cells of CVID patients upon PMA/ionomycin stimulation after 12 h [127]. Thus IFN-γ profile seems to vary strongly according to the patients examined. There is a subgroup of CVID patients with increased Th1 profile. Thus, the characterization of the exact profile of these patients needs to be addressed in more detail.

TNF-α

TNF-αá, an inflammatory cytokine secreted by macrophages, monocytes, neutrophils, T-cells and NK-cells, is involved in systemic inflammation and stimulates the acute phase reaction. TNF-á has been shown to play an essential role in regulating the production of other pro-inflammatory cytokines [128].

TNF-á is associated with a variety of human diseases including asthma [129], Alzheimer's disease [130], major depression [131] and inflammatory bowel disease [132]. Moreover, the therapeutic role of anti-TNF-á has been demonstrated in several studies [128, 133, 134]. Aukrast et al. has shown a higher spontaneous TNF-á serum level in CVID patients despite its down regulation after stimulation of PBMC with LPS [135]. Isgro et al. also indicated elevated levels of TNF-á in CVID patients [51]. Years later, Trujillo et al. has

observed a significant increase in TNF- á production by CVID derived PBMC upon stimulation with LPS in comparison with healthy controls which support the inflammatory state in CVID patients [46]. In contrast, T cells of CVID patients seem to produce less TNF-α after stimulation by anti-CD3+CD28 [54].

We have also examined the role of gene polymorphism in TNF-á variability in CVID patients as compared to controls [44]. The study has revealed an over-representation of an uncommon TNF-á allele with A instead of G at position −308 in CVID patients as compared to healthy individuals. This genotype is associated with a higher production of TNF-á.

TNF-á targeted therapies have been suggested for specific indications in CVID. Chua et al. reported the beneficial effect of anti-TNF-á (infliximab) therapy in 3 CVID patients suffering from severe enteropathy [136]. In addition, single cases have been treated successfully for granulomatous disease especially of the skin [137, 138].

Therefore, majority of studies supported the increase level of TNF-α in CVID and suggested anti TNF-α therapy for specific secondary complications. However its final value needs to be determined in regard to benefit and risk of secondary infections.

IL-17

Interleukin-17 (IL-17), a pro-inflammatory cytokine produced by Th17 cells, has been reported to be involved in different autoimmune and inflammatory conditions [139]. The IL-17 family consists of 6 family members; including IL-17A, IL-17B, IL-17C, IL-17days, IL-17E and IL-17 F.

Among IL17 family members, only IL-17A and IL-17 F are produced by Th17. The mentioned two cytokines share patterns of expression and most of their biological function [140].

IL-17 induces the production of many cytokines including IL-6, IL-8, G-CSF, GM-CSF, IL-1â, TGF-â and TNF-á [141] and plays a major role in the defense against mucocutaneous Candida infection.

Th17 cells require IL-23 for maturation and cytokine secretion [142]. Increased expression of IL-17A has been detected in a variety of autoimmune disorders but no increase in the frequency of Th17 cells has been found in CVID patients [139]. Expansion of $CD21^{low}CD38^{low}$ B cells is accompanied by a reduction in Th17 cells suggesting an inverse correlation between both populations in CVID [139]. Importantly, Mannon et al. has revealed less IL-17A being produced by lamina propria mononuclear cells in CVID autoimmune enteropathy than in Crohn's disease [143] suggesting a different pathogenesis. In summary, studies on IL-17A in CVID are rare and currently do not suggest a major disturbance in CVID.

APRIL and BAFF

APRIL (a proliferation inducing ligand) and BAFF (B cell activating factor) are members of the TNF family which are primarily produced by monocytes, neutrophils, macrophages and dendritic cells [144].

APRIL binds to B cell maturation antigen (BCMA) and transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI), while BAFF can bind to BAFF-Receptor, TACI and only poorly to BCMA. These members of the TNF family have a crucial role in the development and maintenance of humoral immunity [145]. They maintain B cell and plasma cell survival, can act as a potent B cell activator [146], increase immunoglobulin production and influence class switching [147, 148].

Overexpression of BAFF and APRIL has been found in number of autoimmune diseases, including rheumatoid arthritis, multiple sclerosis and SLE which indicated the role of TNF family member cytokines in autoimmunity states [149–151].

Mutations in BAFF-receptor and TACI have been identified as predisposing factors in some CVID patients [152], while so far no mutations in BCMA, April and BAFF have been found in sporadic or familial CVID cases [145, 153].

Results of previous studies have shown that serum levels of BAFF, APRIL and also soluble TACI are noticeably elevated in CVID [154, 155]. While there has been no association of serum APRIL or BAFF levels to clinical manifestations, soluble BAFF levels seem to be inversely correlated to peripheral B cell numbers [156]. This finding was corroborated by the high BAFF serum levels in X-linked agammaglobulinemia [155]. It remains to be determined whether elevated BAFF and APRIL serum levels might contribute to the autoimmune phenomena in CVID.

Conclusions

Patients suffering from CVID have diverse underlying molecular mechanisms leading to immunodeficiency and therefore present with different clinical manifestations [157].

The cytokine family has been extensively studied and different perturbations in cytokine pathways have been suggested to contribute to the development or different form and manifestations of CVID.

This overview over the different cytokines implicated in the pathophysiology of CVID revealed a very heterogeneous image of the underlying cytokine imbalance partly reflecting the heterogeneity of the syndrome and partly the limited comparability of the studies. Several studies could demonstrate that either the relative lack of cytokines like IL-2 or potentially IL-21 may contribute to the immunodeficiency in some patients while in others the overexpression for example

of Th1-cytokines or TNF-α contributes to the local or global immune dysregulation.

From these findings already first therapeutic conclusions were drawn serving as proof of principle in single patients while failing in others.

Future studies on cytokine imbalance in CVID need to report the clinical and immunological phenotype of the patients, consider differences between various compartments (i.e., blood vs. tissue sites) in order to achieve a higher comparability between studies.

Only by this way, we will be able to dissect the complexity of the altered immune response in CVID and hopefully one day, we will be able to apply targeted therapies to selected patient groups as has been successfully implemented in different autoimmune diseases. Even more interesting, restoring immune function and regulation by supplementing missing cytokines without confining systemic side effects will be a challenge for the future.

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