Cellular Immunology 315 (2017) 11–17

Contents lists available at ScienceDirect

Cellular Immunology

journal homepage: www.elsevier.com/locate/ycimm

Review article

Abnormality of regulatory T cells in common variable immunodeficiency

Gholamreza Azizi [a,b,c], Nasim Hafezi [d], Hamed Mohammadi [e], Reza Yazdani [f,a], Tina Alinia [a], Marzieh Tavakol [g], Asghar Aghamohammadi [a,c,*], Abbas Mirshafiey [h,*]

[a] Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
[b] Department of Laboratory Medicine, Imam Hassan Mojtaba Hospital, Alborz University of Medical Sciences, Karaj, Iran
[c] Primary Immunodeficiency Diseases Network (PIDNet), Universal Scientific Education and Research Network (USERN), Tehran, Iran
[d] Department of Immunology, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[e] Department of Immunology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[f] Department of Immunology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[g] Department of Allergy and Clinical Immunology, Shahid Bahonar Hospital, Alborz University of Medical Sciences, Karaj, Iran
[h] Department of Immunology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article history:
Received 23 September 2016
Revised 24 December 2016
Accepted 26 December 2016
Available online 29 December 2016

Keywords:
Common variable immunodeficiency
T cell
Regulatory T cells

ABSTRACT

Common variable immunodeficiency (CVID) is a heterogeneous group of primary antibody deficiencies (PAD) which is defined by recurrent infections, hypogammaglobulinemia and defects in B-cell differentiation into plasma cells and memory B cells. T cell abnormalities have also been described in CVID patients. Several studies reported that Treg frequencies and their functional characteristics are disturbed and might account for the aberrant immune responses observed in CVID patients. The aim of this review is to describe phenotypic and functional characteristics of Treg cells, and to review the literature with respect to the reported Treg defects and its association with the clinical manifestation in CVID.

Contents

1. Introduction

Common variable immunodeficiency (CVID) is a heterogeneous group of primary antibody deficiencies (PAD) which is defined by recurrent bacterial infections, marked reduction of serum IgG, IgA, and/or IgM levels, defects in specific antibody production against protein and polysaccharide antigens and defects in B-cell differentiation into plasma cells and memory B cells [1,2]. This poor humoral immunity, results in severe infections, most notably of the upper and lower respiratory tracts and the gastrointestinal tract. About 70% to 80% of CVID patients are involved with recurrent sinopulmonary infections; however, malignancy, autoimmunity and inflammatory conditions are also prevalent [3]. The cellular alterations in CVID comprise a spectrum of B and T cell abnormalities; however, the hallmark of CVID is

* Corresponding authors at: Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran (A. Aghamohammadi).
E-mail addresses: aghamohamadi@sina.tums.ac.ir (A. Aghamohammadi), mirshafiey@tums.ac.ir (A. Mirshafiey).

http://dx.doi.org/10.1016/j.cellimm.2016.12.007
0008-8749/

Table 1
Different types of regulatory cells in immune system.

Types of cells	Subset	Characteristic markers	Mechanism of suppression	Associated pathologies
Treg	Natural Tregs	CD4+ FoxP3+CD25+ CD127(lo/-)	Cell contact dependent and independent (TGF-β, IL-10, IL-35)	Associated with autoimmunity
	Inducible Treg	CD4+Foxp3+	Cell contact dependent and independent	Associated with autoimmunity
	Th3	CD25low FoxP3+ CD4+	Cell contact independent TGF-β-dependent	Deficient in oral tolerance
	Tr1	CD25 low FoxP3- CD4+	Cell contact independent IL-10-dependent	Deficient in tolerance
	CD8+CD28- Treg	CD8+ CD28- FOXP3-	Cell contact dependent (TGF-β, IL-10)	Associated with autoimmunity
	CD8+ Treg	CD25+CD28+ Foxp3+	Cell contact dependent	Associated with autoimmunity
Breg	Immature B cells	CD19+ CD24hiCD38hi	IL-10, PD-L1	Numerical and functional defects in autoimmune diseases
	B10 cells	CD19+ CD24hiCD27+	IL-10	Reduced functional capacity in autoimmune diseases
	Granzyme-B + Breg	CD19+ CD38+CD1d+IgM+ CD147+	GrB, IL-10, IDO	Deficient in peripheral tolerance
	Br1 cells	CD25hiCD71hiCD73lo	IL-10, IgG4	Deficient in peripheral tolerance
	Plasmablasts	CD27intCD38hi	IL-10	?
	Inducible Bregs	?	TGF-β, IDO	?
	?	CD39+ CD73+	Adenosine	?
iNKT cells	Vα24-Jα18	CD4+CD8+ and DN	Th2 cell-polarization	Associated with autoimmunity

hypogammaglobulinemia followed by severe B cell defects. A group of CVID patients named "CVID-like" patients are associated with defects in T cells [1,4–7]. These defects are complex but can be summarized as defective T-cell signaling and cytokine production, accelerated T cell apoptosis, defect of regulatory T cells (Tregs), and defective interactions between T and B lymphocytes, resulting in early-onset bronchiectasis, autoimmune disease and recurrent viral infections [8–10].

Several studies reported that Treg frequencies and their functional characteristics are disturbed and might account for the aberrant immune responses observed in CVID patients [11–14]. These abnormalities in Tregs may result in elevated levels of activated T cells, autoimmunity and chronic inflammation [11,12,15].

In this review, our aim is to describe phenotypic and functional characteristics of Treg cells (Table 1), and to review the literature with respect to the reported Treg defects in CVID.

2. T-cell abnormalities in CVID

T-cell defects have been reported in approximately one-third of patients with CVID [16,17]. The reductions in T-cell receptor excision circles, naïve T cells, invariant NKT cells and Treg cells suggest a diminished thymic output, while CD8 T cells are driven towards exhaustion either via an antigen-dependent or -independent manner [18,19]. Based on the revised ESID diagnostic criteria in 2014, CVID patients should not have profound T-cell deficiency. Profound T-cell deficiency is defined by meeting two out of the following three criteria: 1- $CD4^+$ cell numbers/μL: 2–6 y < 300, 6–12 y < 250, >12 y < 200; 2- naïve $CD4^+$ T cell percentage: 2–6 y < 25%, 6–16 y < 20%, >16 y < 10%; and 3- absent T-cell proliferation [20].

CVID patients have various complications that might be related to their T-cell defects. The most important of which are opportunistic infections, malignancies, autoimmune and inflammatory diseases, which are similar to those showed in patients with combined immunodeficiency (CID) [4,5,21]. Malphettes et al. defined a subgroup of CVID patients as late onset CID (LOCID) for the first time in 2009. This subgroup of CVID differs from classic CVID in its clinical and immunologic specifications. The inclusion criteria for LOCID consists of either a $CD4^+$ T-cell count less than 200 cell/μl in peripheral blood or the manifestation of an opportunistic infection [22]. Consanguinity of the parents, gastrointestinal tract disease, splenomegaly, granuloma and lymphoma are more frequent in LOCID patients than in classic CVID patients [22,23]. The evaluation of LOCID patients showed a significant reduction in $CD4^+$ T cell, $CD8^+$ T-cell, natural killer (NK) cell and B-cell counts in all patients [24].

Interestingly, parental consanguinity in CVID patients (cCVID) is also associated with the severe phenotype presenting at lower ages at onset and diagnosis, higher mortality rates and severe T-cell dysfunction. In these patients naïve $CD4^+$ T cells are decreased, while activated $CD4^+$ and $CD8^+$ T cells are increased, in contrast to patients without parental consanguinity. In cCVID patients, splenomegaly, granulomatous disease, polyclonal lymphocytic infiltration, bronchiectasis, enteropathy and opportunistic infections were more frequent [23,25,26].

3. Regulatory T cell defects in CVID

3.1. Low frequency of Tregs

After Fevang et al. [14] who first demonstrated a lower frequency of $CD4^+CD25^+FOXP3^+$ Tregs in patients with CVID, several other studies demonstrated a reduction in Tregs in CVID patients (Table 2) [13,27,28]. However, in a recent study, Kutukculer et al. [29] reported that the percentages and absolute numbers of $CD4^+$ $CD25^+$ $FOXP3^+$ cells did not show any significant difference between CVID cases and healthy controls or between patients with severe and moderate disease. The results of this study were contradictory and showed that Tregs do not play an important role in the pathogenesis of CVID. The authors proposed that low numbers of CVID patients with autoimmune complication may be the reason for this non-significant result [29]. Also, in a study by Kofod and Olsen, where the CVID group was divided into autoimmune and non-autoimmune patients, a slightly higher level of Tregs in the non-autoimmune patients was observed which was not significantly different from the control group. But the noteworthy point about the Kutukcule study is the lower frequency of $CD4^+CD25^+$-$FOXP3^+$ cells in the healthy individual in comparison to its reported frequency in other studies [11,27,30].

There are interesting reports given about the possible contribution of the high affinity IL-2 receptor (CD25) as a regulatory mechanism employed by Treg cells [31,32]. Moreover, IL-2 is important for the generation and maintenance of FOXP3 expression in Treg cells [33]. Accumulating evidence suggests that CVID patients have reduced gene expression and production of IL-2 [34–36], therefore,