Review

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Autoimmunity in Primary Antibody Deficiencies

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Keywords
Primary antibody deficiencies · Autoimmunity · Antibody · Autoimmune hemolytic anemia · Immune thrombocytopenic purpura

Abstract
Primary antibody deficiencies (PADs) are the most common inherited primary immunodeficiencies in humans, characterized by hypogammaglobulinemia, an inability to produce specific antibodies, and recurrent infections mainly caused by encapsulated bacteria. However, it has been shown that inflammatory disorders, granulomatous lesions, lymphoproliferative diseases, cancer, and autoimmunity are associated with the various types of PAD. Both systemic and organ-specific autoimmune diseases could be attributed to B-cell defects in PAD patients. Immune thrombocytopenic purpura and autoimmune hemolytic anemia are the most common autoimmune disorders in this group of patients. The aim of this review is to describe the proposed mechanisms for autoimmunity and to review the literature with respect to the reported autoimmune disorders in each type of PAD.

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Introduction

Primary antibody deficiencies (PADs) are the most common group of primary immunodeficiency disorders (PIDs), resulting from different defects in the development and function of B-cell lineage [1]. The spectrum of PAD is broad, ranging from patients with a severe reduction of all serum immunoglobulin (Ig) classes and total B-cell absence, to patients with selective antibody defi-

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ciency with normal serum Ig [2]. Hypogammaglobulinemia or antibody deficiency is the major hallmark of PAD patients. Affected individuals share a clinical phenotype with common features, such as chronic and recurrent infections, chronic inflammation, and autoimmunity [2], leading to recurrent hospitalization and a decreased quality of life [3–5].

The coexistence of autoimmunity and immunodeficiency appears paradoxical in PAD patients, since one represents a hyperimmune state and the other a hypoimmune state. However, this paradox may not actually be all that implausible due to the complex nature of immune cells, signaling pathways, and their interactions [6]. The most common autoimmune disorders in PADs are immune thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA) [7]. Moreover, other diseases including autoimmune thyroid disease [8], type 1 diabetes (T1D) [9], rheumatoid arthritis (RA) [10], systemic lupus erythematosus (SLE) [11], dermatomyositis [12], inflammatory bowel diseases (IBD) [13], alopecia areata [11], vitiligo [8], and glomerulonephritis [14] are also common in PADs due to the lack of self-tolerance [15].

This review will explore why PAD patients are predisposed to autoimmune diseases and provide an overview of the autoimmune complications in each type of PAD disease.

Primary Antibody Deficiencies

It has been described that PADs are the largest group of PIDs (50–60%) in humans, which includes more than 30 diseases [16, 17]. These disorders can be divided into 6 main categories (Table 1). Mutations in Bruton tyrosine kinase (BTK) are the most common (85%) gene defect that cause early B-cell defects, while mutations in CD40L (70%) and TACI (transmembrane activator and CAML interactor; 10%) are the most common cause of class-switching defects and terminal B-cell defects, respectively [1]. According to the results of different PID registries in the world, selective IgA deficiencies (sIgAD) are the most common PADs, followed by common variable immunodeficiency (CVID) [18–23]. CVID is thought to be a genetically heterogeneous disorder; however, the exact cause of the disorder is unknown in the large majority of cases. Recent attempts to identify the genes responsible for CVID have resulted in the discovery of new monogenic defects during the past few years, including mutations in the *ICOS* (inducible costimulator) [24], *CD19*

Table 1. Antibody deficiency disorders

Disease	Molecular defect(s)
I. Severe reduction in all serum Ig isotypes with profoundly decreased or absent B cells	
BTK deficiency	BTK
μ heavy chain deficiency	μ heavy chain
λ5 deficiency	λ5
Igα deficiency	Igα
Igβ deficiency	Igβ
BLNK deficiency	BLNK
PI3 kinase deficiency	PIK3R1
Thymoma with immunodeficiency	Unknown
II. Severe reduction in at least 2 serum Ig isotypes with a normal or low number of B cells	
CVID	Unknown
ICOS deficiency	ICOS
CD19 deficiency	CD19
CD81 deficiency	CD81
CD20 deficiency	CD20
CD21 deficiency	CD21
TACI deficiency	TACI
LRBA deficiency	LRBA
BAFFR deficiency	BAFF-R
TWEAK	TWEAK
NFκB2 deficiency	NFKB2
WHIM syndrome	Gain-of-function mutations of CXCR4
III. Severe reduction in serum IgG and IgA with normal/elevated IgM and normal numbers of B cells	
CD40L deficiency	CD40L (TNFSF5)
CD40 deficiency	CD40 (TNFRSF5)
AID deficiency	AICDA
UNG deficiency	UNG
IV. Isotype or light chain deficiencies with generally normal numbers of B cells	
Ig heavy chain mutations and deletions	Mutation or chromosomal deletion at 14q32
κ chain deficiency	Mutations in κ gene
IgA with IgG subclass deficiency	Unknown
Selective IgA deficiency	Unknown
PRKC-δ deficiency	PRKCD
Activated PI3K-δ	PIK3CD
IgG subclass deficiency	Unknown
V. Specific antibody deficiency	Unknown
VI. Transient hypogammaglobulinemia of infancy with normal numbers of B cells	Unknown

BTK, Bruton tyrosine kinase; CVID, common variable immunodeficiency; WHIM, warts, hypogammaglobulinemia, infections, myelokathexis syndrome; Ig, immunoglobulin.

Table 2. The mechanisms of induction and breakdown of self-tolerance

Tolerance	Process	Tolerance mechanisms	Mods of tolerance breakdown
T cell	Central tolerance	Clonal deletion	Negative selection failure (defects in genes such as *AIRE*), aberrant expression of MHC-II, release of sequestered self-antigens, coupling of self- and non-self-antigens
		nTreg development	Failure in nTreg development (defects in genes like *FoxP3* and IL-2 receptor)
	Peripheral tolerance	Anergy	Defect in CTLA-4, increased expression of costimulatory molecules, suppression of IDO, aberrant expression of MHC-II, overproduction of self-antigens, release of inflammatory mediators, molecular mimicry
		Tolergenic APCs	Increased expression of costimulatory molecules
		Deletion	Defects in apoptosis signaling, viral apoptosis inhibitors, defects in death receptors
B cell	Central tolerance	Deletion	Failure in apoptosis process, molecular mimicry
		Receptor editing	Molecular mimicry, defects in rearrangement mechanisms
		Ignorance	Consistent inflammation, exogenous modification of antigens
	Peripheral tolerance	Anergy	Inflammatory environment, aberrant activation of T cells
		Deletion	Failure of deletion due to defects in genes such as *Fas/FasL*
		Regulation by inhibitory receptor	Aberrant activation of costimulatory receptors, defects in inhibitory phosphatase such as SHP1
		B regulatory	Defects in cytokine production such as IL-10 and TGF-β

AIRE, autoimmune regulator; MHC, major histocompatibility complex; nTreg, natural regulatory T cell; *FoxP3*, forkhead box P3; IL, interleukin; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IDO, indoleamine 2,3-dioxygenase; APCs, antigen-presenting cells; *FasL*, Fas ligand; TGF-β, transforming growth factor beta.

[25], *CD81* [26], *CD21* [27], *CD20* [28], *LRBA* [29], *PLCG2* [30], and *TWEAK* genes [31]. These new monogenic defects, which share clinical phenotypes with CVID, are actually different entities and may occasionally be misdiagnosed as CVID [1]. The study of different types of PAD has also provided new insights into the genesis of antibody-mediated autoimmunity and checkpoints of B-cell reactivity, as well as into defense against infections [2, 32, 33].

Mechanisms of Tolerance and Autoimmunity in PADs

The immune system becomes tolerant to self-antigens through 2 main mechanisms, which are considered as central and peripheral tolerance. The main mechanisms of central tolerance which cooperate in the induction of tolerance in B and T cells in bone marrow and thymus, respectively, include the deletion of high-affinity autoreactive lymphocytes, while peripheral tolerance or the peripheral regulatory process includes anergy, deletion by apoptosis, antigen ignorance, inhibitory receptors, and inhibition by regulatory T cells (Tregs) [27, 28]. However, defects in self-tolerance development are the main mechanisms of autoimmunity; other mechanisms that may lead to autoimmunity are the occurrence of breaks in tolerance [34]. The main reason for this breakdown is not yet well known but several mechanisms have been suggested which lead to self-tolerance failure and autoimmunity occurrence (Table 2).

Several studies have reported that PAD patients are predisposed to autoimmune complications [35–37]. There is evidence to show that defects in the development, function, and number of Tregs are among the main factors that account for autoimmune complications in patients with PADs [38, 39]. On the other hand, the high similarity of Treg defect features with organ-specific autoimmune diseases confirms an obligatory role of these cells in maintaining tolerance to epithelial and endocrine tissues [40, 41]. Other proposed mechanisms of autoimmunity in immunodeficiency, including defects in T cells and thymic or extrathymic tolerance induction, defects in the development of B cells and class-switch recombination (CSR), defective elimination of self-reactive T cells and B cells (receptor editing and BAFF), defects in Breg cells, expansion of CD21low B cells, impaired activation-induced cell death, increased load and/or decreased clear-

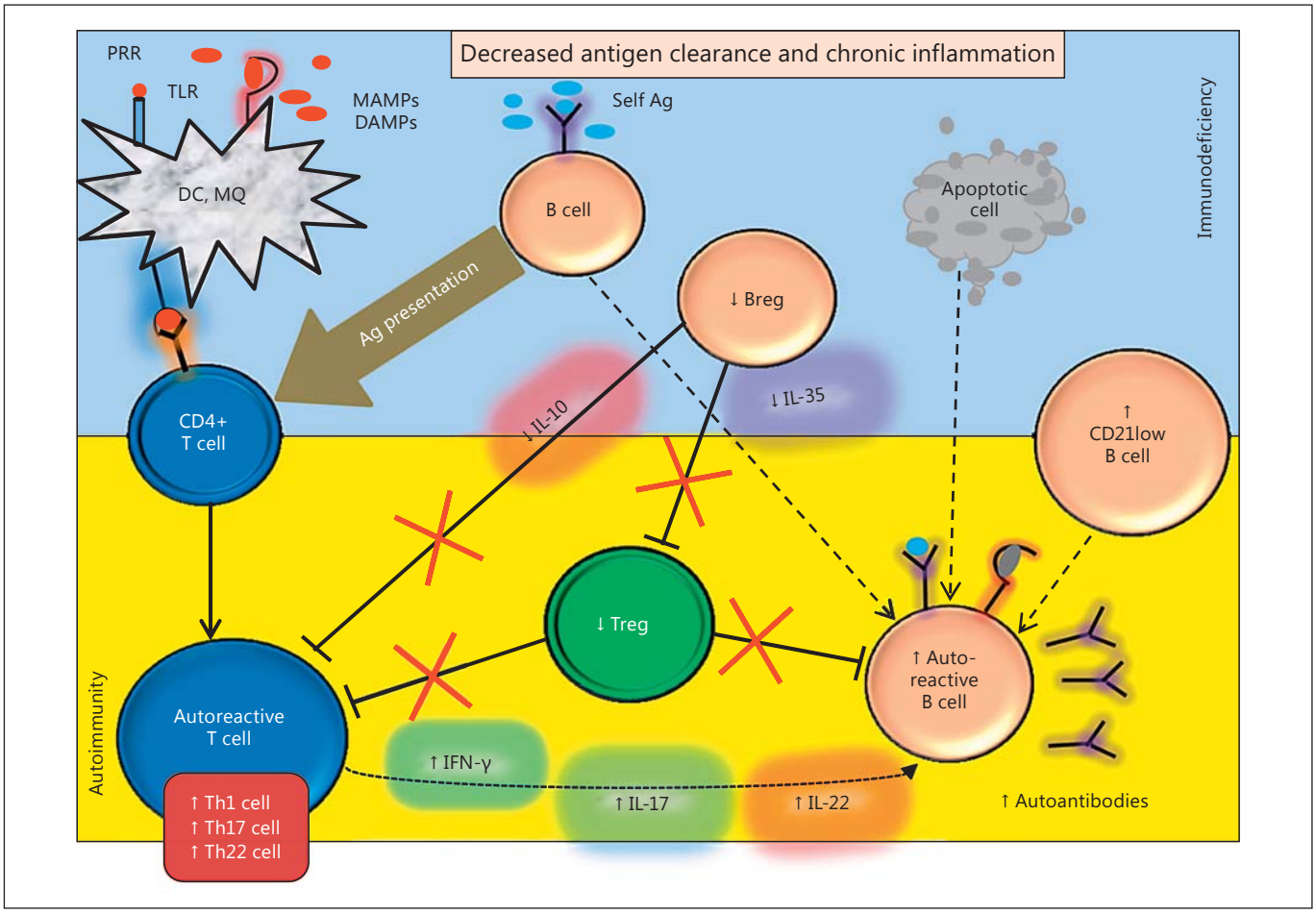

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Fig. 1. Mechanism of autoimmunity in immunodeficiency. Low frequency of regulatory cells, defects in elimination of self-reactive T cells and B cells along with persistent infection and decreased clearance of apoptotic cells and immune complexes leads to chronic inflammation and predisposes PAD patients to autoimmunity. PRR, pattern recognition receptor; TLR, toll-like receptor; MAMPs, microbe-associated molecular patterns; DAMPs, damage-associated molecular patterns; Ag, antigen; DC, dendritic cell; MQ, macrophage.

ance of apoptotic cells and immune complexes, persistent infections and inflammation (Fig. 1), as well as defects in genes which affect multiple cellular subsets, are the most common defects which predispose immunodeficient patients to autoimmunity (Table 3, 4) [35, 37, 42–45]. Recent studies suggest that defects in inhibitory signaling molecules (such as CD32b, CD22, and SIAE), common genetic polymorphisms, rare loss-of-function genetic variants (such as *PTPN22, FcγRIIB, CTLA4, PD1,* and *SIAE*), the possible errors in clonal somatic mutations, epigenetic modifications (DNA methylation, small non-coding RNA transcripts, and histone modifications), and the role of the intestinal microbiome in affecting the polarization of T-helper cells, may also contribute to the pathogenesis of autoimmunity [46, 47]. However, some data have been presented in favor of the idea that a massive antigen load as a result of recurrent or persistent infections may affect either tolerance or ignorance, for example by molecular mimicry or the presence of superantigens [35]. Moreover, it has been revealed that in some antibody-deficient patients the basis of autoimmunity lies in the inability of the host immune system in the complete eradication of microbial antigens through the usual immune pathways. The result is a compensatory, exaggerated, and chronic inflammatory response by less effective alternative immune pathways, which causes damage not only to infected cells, but also surrounding healthy tissues. Thus, in some cases autoimmunity is not always a subsequence of self-tolerance breakdown; rather, it could be a result of tissue damage incurred as the host at-

Table 3. Pathogenesis of autoimmunity in PADs

Mechanism	Studies	Year
Defective B-cell tolerance to self-antigen	Meffre [32]	2011
Proliferation of CD21low B cells	Warnatz et al. [85]	2002
Altered BAFF/APRIL survival signaling	Knight et al. [70]	2006
Impaired somatic hypermutation	Bonhomme et al. [127]	2000
Reduced switch memory B cell	Warnatz et al. [128]	2002
Presence of IgM autoantibodies	Melegari et al. [129]	2007
Loss of tolerance against IgA	Ferreira et al. [105]	2010
Loss of FcγRIIB inhibitory signaling	Horton et al. [130]	2011
Defective development of Tregs	Arumugakani et al. [41]	2010
Molecular mimicry	Arason et al. [35]	2010
Immune complex deposition	Patiroglu et al. [11]	2012
Genetic defects	Azizi et al. [131]	2016

tempts to get rid of foreign antigens [48–50]. Therefore, it is important to control even minor infections in PAD patients to prevent subsequent serious complications, such as inflammatory and autoimmune disorders.

Autoimmunity in PADs

X-Linked Agammaglobulinemia

X-linked agammaglobulinemia (XLA) is a congenital PAD caused by mutations in a tyrosine kinase named Bruton tyrosine kinase *(Btk)*. Although, Btk is essential for B-cell receptor-mediated proliferation and survival, it has been demonstrated that a small number of B cells, or "leaky B cells," are present in the peripheral blood pool of most patients with XLA [51]. Patients with XLA are not expected to produce autoantibodies, however the "leaky" production of autoantibodies and defects in B-cell central tolerance has been reported [52, 53]. These observations are supported by Meffre and colleagues [52], who demonstrated that Btk is essential for human B-cell tolerance. Therefore, BTK is a good target for controlling autoreactive B cells in patients with systemic autoimmune disease. Moreover, small-molecule inhibitors of BTK have shown impressive activity in experimental models for SLE and RA [54].

Although patients with XLA are generally considered to have a low risk of autoimmune or inflammatory diseases compared with other PID patients, evidence from survey studies suggests that some XLA patients show symptoms with similar diagnostic features to RA, IBD, or other conditions, including alopecia, enteropathy, AIHA, ITP, neutropenia, and Kawasaki disease [55–57]. It has been reported that 21% of XLA patients show symptoms of chronic diarrhea; however only 4% of them are diagnosed with Crohn's disease [56]. In cases with joint inflammation, 10–30% of XLA patients seem to have a form of joint inflammation, 7% are diagnosed with arthritis, and 2% of these patients are reported with a diagnosis of RA, while 5% have "other" arthritis. Moreover, an idiopathic progressive encephalopathy has been demonstrated in some PID patients. In a recent report, Sag et al. [58] described the clinical features of this progressive neurodegenerative dementing disorder in a young XLA patient. In this patient dysregulated immune responses caused the autoimmunity, but the exact mechanism has not been fully clarified. However, Tuzankina et al. [59] previously suggested that cytotoxic T lymphocytes mediate neuronal damage and progressive neurodegenerative disorder in XLA patients.

CVID Disorder

CVID is the most common clinically significant PAD, defined by recurrent bacterial infections (and rarely by virus infections) and hypogammaglobulinemia [60–64]. The cellular alterations in CVID comprise a spectrum of B- and T-cell abnormalities, including defects in B-cell differentiation into plasma cell and memory B cells, defects in Treg and Breg cells, accelerated T-cell apoptosis, and abnormality in cytokine production secondary to gene polymorphisms [6, 65–68]. The influence of these defects on the interaction between T and B cells not only could explain the immunodeficiency, but also the development of autoimmunity in CVID patients [6]. The frequency of autoimmune disorders in CVID patients may include approximately 30% (21–42%) of cases [10, 37].

The most prevalent autoimmune disorder in patients with CVID is autoimmune cytopenia, by far the most common occurring variably in 4–20% (ITP develop in 6–14% and AIHA in 5–7%), but pernicious anemia (1–9%), RA (1–10%), IBD (6–10%), SLE, autoimmune thyroid disease, hepatitis, vitiligo, psoriasis, Sjögren syndrome, and now primary biliary cirrhosis as well as inflammatory relapsing polychondritis have also less frequently been reported [6, 69–72]. It should be noted that autoimmune disorders may be the first or at the time the only clinical manifestation of CVID diagnosis [73, 74]. Two separate studies showed that 54% [75] and 62% [76] of subjected CVID patients had the first episode of ITP or AIHA prior to the diagnosis. In another study conducted by Heeney et al. [77] it was reported that 4 children with autoimmune cytopenia had low Ig levels that led to the diagnosis of CVID.

Recent studies show a significant decrease in the repertoire of naïve CD4 and CD8 T cells, with a reduction in both total CD4 and recent thymic emigrant numbers of T cells in CVID patients, which is most prevalent in those patients involved with autoimmune cytopenia [78, 79]. Moreover, in CVID-associated autoimmune cytopenia, an activated phenotype of T cells can be detected which are characterized with an increase in HLA-DR and CD95 expression [80]. Boileau et al. [80] claimed that this T- and B-cell phenotypic profile cannot be seen in CVID patients with other autoimmune manifestations, and only the serum IgG level in CVID patients with autoimmunity (cytopenia and others) is greater than in CVID patients without autoimmunity.

Several studies report that Treg frequency and their functional characteristics are disturbed and might account for aberrant immune responses observed in CVID patients [39, 81–83]. These abnormalities in Tregs may result in elevated levels of activated T cells, autoimmunity, and chronic inflammation [39, 81]. Yu et al. [82] showed that sorted Tregs from CVID patients with autoimmune disease are compromised in their suppressive activities and have a reduced ability to suppress the proliferation of autologous and allogenic CD4+ effector cells compared with CVID patients without autoimmunity. Furthermore, the downregulation of FOXP3, granzyme A, pSTAT5, and reduction in inhibitory markers such as CTLA-4 and GITR were significantly correlated with the degree of Treg cell dysfunction in CVID [82]. Defects in Tregs are also correlated with the expansion of CD21low B cells in CVID patients with autoimmunity [41, 47, 84]. Warnatz et al. [85] described the size of the peripheral CD21low B-cell pool as a marker for CVID patients with autoimmune cytopenia and splenomegaly. This was confirmed by Boileau et al. [80], who proposed that the increased proportion of CD21low B cells is significantly associated with CVID-associated autoimmune cytopenia, but it seems to be independent from the presence of other autoimmune diseases. Although it remains unclear how CD21low B cells are related to the autoimmune phenomenon, it has been demonstrated that most CD21low B cells derived from CVID patients produce autoreactive antibodies in the germline, which bind to nuclear and cytoplasmic structures [86]. Overall, according to recent findings on CD21low B cells in CVID and autoimmunity, a restricted subset of B cells and help from T cells are needed in order to breakdown the B-cell tolerance against membrane autoantigens.

Hyper-IgM Syndrome

Hyper-IgM syndrome relates to a group of PIDs characterized by the defective CD40 signaling of B cells which subsequently affects the class switch recombination and somatic hypermutation. The most common hyper-IgM syndrome is X-linked and due to mutations of CD40L expressed by activated CD4+ T cells. Four other genes (*CD40, AICDA, UNG, NEMO*) expressed by B cells have been associated with the hyper-IgM phenotype [87]. In addition to the susceptibility to recurrent and opportunistic infections, these patients are also prone to autoimmune complications, especially hematologic abnormalities, autoimmune thyroid disease, nephritis, IBD, and RA. Moreover, organ-specific autoantibodies are commonly found in hyper-IgM patients [88–90]. Autoimmune complications mostly occur in patients with activation-induced cytidine deaminase (AID; 25%), NF-κB essential modulator (NEMO; 23%), and CD40 ligand (CD40L; 20%) defects [72]. In another study of 56 patients with X-linked hyper-IgM syndrome conducted by Levy et al. [91], seronegative arthritis and IBD affected 11 and 6% of the cases, respectively, while 3 patients reported ITP and there was a single case of AIHA [91]. Furthermore, it has been reported that in patients with hyper-IgM syndrome a main cause of death is liver failure due to autoimmune sclerosing cholangitis [91, 92]. Cryptosporidium infection is also frequent in these patients. The inability of T cells to induce apoptosis in infected cells is the major cause of pathogen persistence and chronic inflammation, and consequently autoimmune sclerosing cholangitis [93]. Other uncommon features of autoimmune disorders such as autoimmune retinopathy have been reported in association with CD40L deficiency [94].

The mechanisms by which hyper-IgM syndrome associates with the autoimmune condition are not fully understood, but a defect in Treg cells development, the increased presence of IgM, and defects in peripheral B-cell tolerance checkpoints have been proposed to participate in this paradoxical condition [88]. Lacroix-Desmazes et al. [95] reported that patients with CD40L deficiency present a decline in self-reactive antibodies. They proposed that functional interactions between CD40 and CD40L are essential for the natural selection process of a self-reactive B-cell pool. In contrast, Herve et al. [96] reported that mature naïve B cells harvested from patients with CD40L deficiency present a high ratio of self-reactive antibodies, including antinuclear antibodies, which may indicate a main role for CD40L/CD40 interaction in mediating tolerance in peripheral B cells. In addition, they suggested that a decreased frequency of MHC class II-restricted CD4+ Treg lymphocytes in CD40L-deficient patients may also contribute in tolerance breakdown as these Treg cells might participate in mediating peripheral B-cell tolerance by CD40L-CD40 and MHC class II-TCR interactions. In another study, Tang et al. [97] reported that the prevalence of peripheral blood Treg cells is significantly declined in comparison with healthy controls, but there are no statistically significant differences in the frequency of Th17 and Th1 in this comparison. Furthermore, they suggested that dysregulated Treg, Th17/Treg and Th1/Treg profiles may be correlated with immune responses and autoimmunity.

Selective IgA Deficiency

sIgAD is the most common PID and is defined by a decreased serum level of IgA in the presence of normal levels of other Ig isotypes. Most sIgAD cases show no clinical features and are identified accidently. However, some cases may be characterized with recurrent infections, allergic conditions, and autoimmune complications [8, 98–100]. Since 30% of sIgAD patients have considerable titers of IgG antibodies against IgA, a breakdown of tolerance against IgA itself or against other factors that contribute to the class switching process, such as TACI, APRIL, and BAFF, probably accounts for the pathophysiological mechanism [101–104]. Evidence in support of this hypothesis includes that the pathogenesis of sIgAD is an autoimmune process [105]. Todoric et al. [72] proposed that sIgAD manifestations can be seen in association with both organ-specific and systemic autoimmunity in 7–36% of patients. These percentages incorporate celiac patients (10–20%), SLE patients (1–5%), and RA patients (2–4%). This association has also been seen sporadically in patients with autoimmune thyroiditis, AIHA, ITP, T1DM, MG, vitiligo, psoriasis, and pemphigus [11, 72, 106]. The most prevalent hematological autoimmune complication of sIgAD is ITP, with an occurrence of 1 in 200 patients [106]. However, different studies report different prevalences of autoimmunity in sIgAD. While Shkalim et al. [107] reported that 20.6% of IgAD children in Israel showed manifestations of autoimmunity, Edwards et al. [108] reported 28%, Aytekin et al. [109] reported 17%, and more recently Abolhassani et al. [8] reported 29.8%. In this study the most common autoimmune manifestations were thyroiditis, vitiligo, and AIHA, followed by celiac disease, juvenile rheumatoid arthritis, dermatomyositis, autoimmune alopecia, and T1D. Moreover, significant associations were detected between autoimmunity and an increased duration of follow-up, serum level of IgM, Treg count, and class-switched memory B-cell count. Interestingly, 4 cases of autoimmune SIgAD (23.5%) progressed to CVID during the follow-up period.

Although the basic mechanism of autoimmune complications in sIgAD still remains unclear, it has been demonstrated that the genetic background is significant in the development of sIgAD and many autoimmune disorders. A significant correlation with the MHC polymorphic region has also been reported. Furthermore, non-MHC genes, including interferon-induced helicase 1 (*IFIH1*) and c-type lectin domain family 16 member A (*CLEC16A*), have been reported to have association with sIgAD development and some of the above-mentioned autoimmune diseases [101]. Apart from the genetic susceptibility, the failure of antigen clearance from mucosal surfaces with resultant immune complex deposition is also hypothesized to induce autoimmune disease in IgAD. This can lead to tissue damage following lymphocyte activation and persistent inflammation with subsequent confrontation of autoantigens, which can result in peripheral tolerance breakdown [11]. It should be noted that these activated lymphocytes might start to expand when they recognize autoantigens presented by dendritic cells (DCs) [110]. Another theory explains autoimmune disorders to be a result of the defective clearance of exogenous intraluminal antigens, which show molecular mimicry to self-tissue antigens or to exposure by superantigens, resulting in a breakdown of peripheral tolerance and cause autoimmunity [35, 111]. This latest hypothesis does not focus on defective clearance but, similarly to CVID, points to the defects in inhibitory signaling constitutively expressed by the FcαR1 protein in patients suffering from sIgAD [106]. In relation to the pathogen-

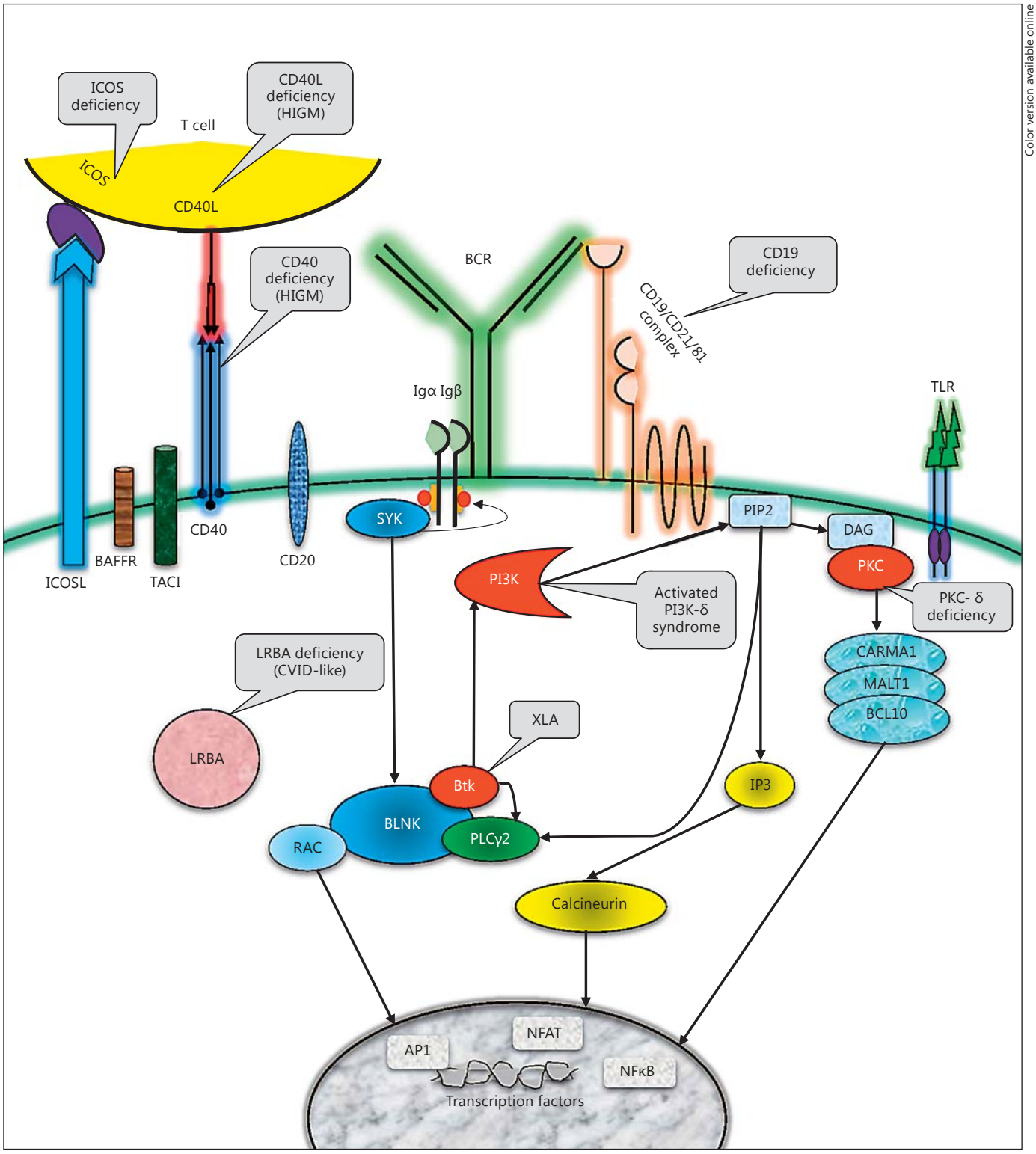

Fig. 2. Molecular defects which lead to PAD associated with autoimmunity. The most common B- and T-cell defects found in PAD patients considered to have autoimmune complications are shown in callouts. HIGM, hyper-IgM syndrome; BAFFR, B-cell-activating factor receptor; BCR, B-cell receptor; TLR, toll-like receptor.

Table 4. The main molecular defects and mechanisms of autoimmunity in PADs

PAD	Main molecular defect(s)	Autoimmune disease	Mechanisms of autoimmunity
XLA	Mutations in Btk	RA, IBD, AA, AN, PND, KD	Defective development of Tregs; presence of IgM autoantibodies; failure of deletion of autoreactive B cells; deranged T-cell activation by the innate system; continuous BCR editing with peripheral survival advantage for autoreactive B cells
Good syndrome	Unknown	ITP, MG, PRCA, PA, T1D	Aberration of cells and cytokines responsible for cellular immunity; abnormal processes of positive and negative selection of thymocytes; loss of self-tolerance, defect of Tregs
CVID	Unknown	ITP, AIHA, RA, SLE, IBD, ATD, PA, SS, PBC, vitiligo	Proliferation of autoreactive (CD21low) B cells; loss of FcγRIIB inhibitory signaling; altered BAFF/APRIL survival signaling; decreased Tregs; impaired TCR signaling
ICOS deficiency	ICOS	RA, SLE, MS, EAE	Defect in IL-10-producing Tregs and peripheral T-cell tolerance
LRBA deficiency	Mutations in LRBA	ITP, AIHA, AN, IBD, EN, RA	Failure of inhibitory signaling; defect in the elimination of autoreactive lymphocytes; Treg deficiency
HIGM	Mutations in CD40L, CD40	ATD, IBD, RA, AIHA, AGN	Defect in Tregs; presence of IgM autoantibodies; failure of deletion of autoreactive B cells; deranged T-cell activation by innate system
PKC-δ deficiency	PKC-δ	AGN, SLE, APS, ALPS	Overactivation of lymphocytes; defective B-cell tolerance to self-antigen; defect in apoptosis; increase of autoreactive (CD21low) B cells
Activated PI3K-δ syndrome	PIK3CD gain-of-function mutations	RA, SLE, AN, MS, EAE	Defect in T- and B-cell tolerance; hyperactivation of T cells
Selective IgA deficiency	Unknown (maybe TACI)	ITP, IBD, AIHA, PV, MG, SLE, RA, T1D, ATD, CD, psoriasis, vitiligo	Loss of tolerance against IgA, molecular mimicry, resultant immune complex deposition and breakdown in peripheral tolerance; lack of inhibitory signaling

XLA, X-linked agammaglobulinemia; CVID, common variable immunodeficiency; HIGM, hyper-IgM syndromes; AA, alopecia areata; AN, autoimmune neutropenia; RA, rheumatoid arthritis; IBD, inflammatory bowel disease; PND, progressive neurodegenerative disease; KD, Kawasaki disease; MG, myasthenia gravis; PRCA, pure red cell aplasia; PA, pernicious anemia; T1D, type 1 diabetes; ITP, idiopathic thrombocytopenic purpura; AIHA, autoimmune hemolytic anemia; SLE, systemic lupus erythematosus; SS, Sjögren syndrome; PBC, primary biliary cirrhosis; MS, multiple sclerosis; EAE, experimental autoimmune encephalomyelitis; EN, erythema nodosum; ATD, autoimmune thyroid disease; APS, antiphospholipid syndrome; ALPS, autoimmune lymphoproliferative syndrome; CD, celiac disease; PV, pemphigus vulgaris; AGN, autoimmune glomerulonephritis.

esis of sIgAD, it has been suggested that failure to develop switched memory B cells may result in frequent recurrent bacterial infections and autoimmune disorders. Aghamohammadi et al. [112] reported that sIgAD patients with reduced switched memory B cells are prone to severe clinical features, including pneumonia, bronchiectasis, and autoimmunity. In addition, dysregulated switched isotype production is responsible for the development of many autoimmune-like diseases. Due to this, it is obviously important to identify and characterize the mediators that control the isotype switching process, and to reveal their roles in other aspects of the B-cell response.

Finally, it should be noted that, similarly to CVID, autoimmunity could be the first or only clinical manifestation of sIgAD patients [113]. For instance, in patients with SLE and celiac disease, an increased prevalence of IgA deficiency was demonstrated [114, 115]. Based on evidence relating to the concurrence of sIgAD and autoimmune disorders, screening of the IgA level in autoimmune patients is suggested.

LRBA Deficiency

LRBA (lipopolysaccharide-responsive and beige-like anchor) deficiency is a rare genetic disorder caused by biallelic loss-of-function mutations in the gene *LRBA* [116]. Affected individuals show reduced levels of at least 2 Ig isotypes (IgM, IgG, or IgA) and suffer from recurrent infections, hepatosplenomegaly, chronic pulmonary and gastrointestinal disorders, as well as autoimmune conditions including ITP, AIHA, IBD, and autoimmune enter-

opathy [29, 116, 117]. In a cohort study of 22 LRBA-deficient patients, 12 (57%) had AIHA, 11 (52%) had ITP, and 8 (38%) had granulomatous-lymphocytic interstitial lung disease, while 5 presented (24%) with T1D or neutropenia. Chronic autoimmune hepatitis was observed in 3 patients (14%). Finally, 1 patient (5%) had alopecia at the age of 12 years [118]. Burns et al. [117] reported a *LRBA* gene deletion in a patient presenting with autoimmunity without hypogammaglobulinemia. This 4-year-old female patient was described with a systemic lymphadenopathy, splenomegaly, autoimmune enteropathy, neutropenia, and thrombocytopenia. Serological tests also showed the presence of antineutrophil antibodies in this patient. Over time she presented new autoimmune complications such as an episode of erythema nodosum, as well as transient arthritis in both feet and recurrent AIHA [117]. In recent research, Charbonnier et al. [119] reported a patient affected with an IPEX-like syndrome. This child was described as having a severe Treg deficiency and carrying a nonsense mutation in the *LRBA* gene. Investigations on individuals suffering from LRBA deficiency showed that although 81% of LRBA-deficient patients have normal T-cell counts, 73% have reduced Treg numbers and also a marked decline in the expression of common Treg cell-characterizing markers, such as FOXP3, CD25, Helios, and CTLA-4. Defective Treg-mediated suppression has also been reported. Such patients show a tendency toward memory T cells and increased autoantibody production, with a marked expansion of T follicular regulatory cells and high contraction of TFHs [119]. Finally, this data revealed that *LRBA* gene mutation-associated deficiency may initially present through autoimmune complications. Thus, mutations in the *LBRA* gene should be considered for a wide spectrum of patients with PID and autoimmunity [117].

PKC-δ Deficiency

PKC (protein kinase C)-δ deficiency is a newly identified PID caused by a defect in PKC-δ encoded by the *PRKCD* gene. PKC-δ has a negative regulatory role in T-cell activation by preventing the assembly of CARMA1 signalosome (Fig. 2). It has been reported that PKC-δ overexpression is associated with preventing CARMA1-mediated NF-κB activation; therefore, PKC-δ deficient T cells have an increased TCR-triggered NF-κB activation and a raised IL-2 secretion [120]. Moreover, PKC-δ acts as a downregulator of activated B cells and plays a noticeable role in B-cell tolerance. PKC-δ-deficient mice represent elevation of a B-cell lineage-specific expansion, such as naïve and activated follicular mature B cells, and also show defective B-cell tolerance to self-antigens [121, 122]. In humans, PKC-δ deficiency is known as a genetic defect leading to B-cell deficiency, impaired apoptosis, and consequently to SLE [123, 124]. Salzer et al. [125] reported a patient with a PKC-δ mutation who was suffering from recurrent infections and severe SLE as well as autoimmune disorders such as membranous glomerulonephritis and antiphospholipid syndrome. This patient also showed a progressive decline in CD19+ B cells, failure in class switching, and an increased number of CD21low B cells and IL-6 protein level. Further studies suggested that PKC-δ deficiency results in decreased ERK pathway signaling and impaired T-cell activation, which may lead to idiopathic and hydralazine-induced lupus due to the modification of T-cell DNA methylation [126].

Conclusion

Autoimmunity has long been known to be a part of the presenting symptoms and clinical course of many PADs. Although the pathogenesis of autoimmunity in PAD remains obscure for the most part, the use of novel approaches, such as whole-exome sequencing and mouse genetic engineering, as well as the careful dissection of immune mechanisms, has led to a greater understanding of autoimmunity in general. The identification of mechanisms by which immunodeficiency may lead to autoimmunity or, in some instances, PAD induces antibody-mediated autoimmunity, can provide important insights into the underlying pathogenic processes and ultimately a better diagnosis and treatment for the patient. On the other hand, in some PAD patients autoimmunity (especially ITP and AIHA) could be the first or only clinical manifestation of disease. Thus, routine screening of Igs is suggested for children with chronic or recurrent ITP and AIHA.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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