

Autoimmune Disease in Primary Immunodeficiency

At the Crossroads of Anti-Infective Immunity and Self-Tolerance



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KEYWORDS

- Primary immunodeficiency • Autoimmunity • Tolerance • Regulatory T cell
- Apoptosis • Common variable immunodeficiency

KEY POINTS

- Identification of gene defects in primary immunodeficiencies complicated by autoimmune diseases has expanded the understanding of central and peripheral self-tolerance.
- This knowledge is in turn expanding the understanding of more complex, polygenic diseases of immunodeficiency and immune dysregulation, such as common variable immunodeficiency (CVID).
- Certain gene mutations, resulting in autoimmune phenotypes with incomplete penetrance, may act as disease modifiers in complex diseases, such as CVID, increasing predisposition toward autoimmunity.

INTRODUCTION

Autoimmunity and primary immunodeficiency (PID) are frequently associated. This seemingly paradoxical relationship highlights the inherent mechanistic links between proper development of the various elements of the immune system, and the selection and regulatory mechanisms that maintain self-tolerance. Here, various immunologic syndromes are discussed in which this paradoxical relationship occurs, and the lesions in self-tolerance and immunoregulation are systematically explored that contribute to autoimmunity in these diseases. The authors have tried to be comprehensive, but, because this topic is broad, certain immunologic syndromes, such as the autoinflammatory syndromes (periodic fever syndromes), were thought to fall outside the scope

Disclaimers: None.

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Immunol Allergy Clin N Am 35 (2015) 731–752

<http://dx.doi.org/10.1016/j.iac.2015.07.007>

immunology.theclinics.com

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of this review and have been reviewed elsewhere.¹ For defective tolerance mechanisms in various primary immunodeficiencies, the reader is directed to [Table 1](#) for clinical correlations, and to [Fig. 1](#) for a mechanistic diagram.

DEFECTIVE TOLERANCE IN PRIMARY IMMUNODEFICIENCIES

Defects in Thymic Central Tolerance

Central tolerance refers to the deletion of autoreactive T cells during development in the thymus. Single positive thymocytes binding with overly high avidity to self-peptide-major histocompatibility complex undergo apoptosis in the thymic medulla, preventing escape of self-reactive T cells to the periphery (reviewed in²). This process relies in part on ectopic expression and presentation of proteins usually restricted to peripheral tissues, by medullary thymic epithelial cells (mTEC). Promiscuous expression of tissue-restricted antigens (TRAs) by mTEC is regulated by a transcription factor called the autoimmune regulator, or AIRE.³ The mechanism through which AIRE activates expression of TRAs is not fully elucidated, but requires oligomerization, nuclear localization, DNA binding, and interactions with other nuclear factors,⁴ and mutations affecting these functions cause autoimmune polyendocrinopathy, candidiasis, and ectodermal dysplasia (APECED), also known as autoimmune polyendocrinopathy syndrome type 1 (APS-1),^{5,6} a disease characterized by multiorgan autoimmunity with loss of tolerance to AIRE-regulated gene products. The most common organs involved are parathyroid and adrenal glands, β cells in the islets of Langerhans, and the liver. Autoantibody formation against cytokines such as interleukin (IL)-17 and IL-22 may contribute to the immunodeficiency, increasing susceptibility to mucocutaneous candidal infection.^{3,7} In addition, lack of expression of TRAs may lead to a failure in development of regulatory T cells (Treg),⁸ causing impaired peripheral tolerance.

In animal models, AIRE expression in the thymus was shown to require cross-talk between developing thymocytes and stromal cells.⁹ AIRE gene expression was shown to be decreased in the thymi of RAG-deficient patients with T-B-SCID and Omenn syndrome, in conjunction with lymphoid depletion and loss of corticomedullary differentiation.¹⁰ A lack of expression of TRAs was observed, which may permit the few T-cell clones that develop to escape negative selection. The inflammatory manifestations of Omenn syndrome include T-cell-mediated inflammation in skin and intestine. Intestinal goblet cell and hair follicle antigens were shown in a murine model to be among the TRAs regulated by AIRE.³

Abnormal thymic development in DiGeorge syndrome (DGS) may result in impaired expression of AIRE, which may contribute to the autoimmunity seen in DGS.¹¹ Ten to 15% of patients with DGS have autoimmune disease,^{12,13} most commonly idiopathic thrombocytopenic purpura, hemolytic anemia, thyroid disease, and juvenile idiopathic arthritis. The pathophysiology is thought to be a multifactorial failure of T-cell development with autoreactive T-cell escape and restricted Treg diversity.¹⁴

Central deletion can also be evaded due to abnormalities in TCR signaling, leading to defective activation-induced cell death (AICD). Null mutations in ZAP 70, a critical kinase downstream of the TCR, lead to combined immunodeficiency, by impairing positive selection in the thymus. In murine models, hypomorphic mutations in ZAP70 cause a syndrome of autoimmunity because of ineffective negative selection and reduced FoxP3+ Treg formation.¹⁵ A human counterpart to this ZAP70-mediated autoimmune syndrome has not yet been identified. The store operated calcium entry (SOCE)-nuclear factor of activated T cells (NFAT) pathway is another signaling mechanism through which AICD is induced via the TCR. ORAI1, a calcium

Table 1**Correlation of genetic defects, mechanisms of impaired tolerance, and clinical autoimmune and inflammatory conditions in primary immunodeficiencies**

Primary Immunodeficiency	Genetic Defect	Mechanisms	Autoimmune Features	Ref.
APECED	AIRE	• Impaired TRA presentation by mTECs • Impaired negative selection in thymic medulla • Impaired Treg development	• Hypoparathyroidism, hypothyroidism, adrenal insufficiency, type 1 diabetes, gonadal dysfunction, AIH, pernicious anemia, vitiligo, alopecia, primary biliary cirrhosis • Chronic mucocutaneous candidiasis	5–7,9,138
Omenn syndrome	Hypomorphic RAG1, RAG2, others	• Paucity of thymocytes • Defective thymic stromal, epithelial development • Decreased AIRE gene expression	• Destructive T-cell mediated inflammation in skin (erythroderma) and intestines • Lymphadenopathy, hepatosplenomegaly	10
ORAI1 deficiency	ORAI1	• Defective TCR mediated calcium flux and NFAT signaling • Defective AICD • Reduction of Tregs	• ITP, AIHA, lymphoproliferation	16,17
STIM1 deficiency	STIM1	• Defective TCR-mediated calcium flux and NFAT signaling • Reduction of Tregs	• ITP, AIHA, lymphoproliferation	18,19
DGS	Chromosome 22q11 deletion, TBX1	• Impaired thymic development and AIRE gene expression • Reduction in Treg numbers and function	• Hypoparathyroidism, ITP, AIHA, thyroid disease, and JRA	12–14,139,140
IPEX	FOXP3	• Impaired Treg development	• Severe early-onset enteropathy, type 1 diabetes, autoimmune cytopenias, hypothyroidism, eczema	44,45
IPEX-like	STAT5b CD25 ITCH	• Impaired IL-2 receptor signaling • Impaired function, regulatory cytokine production by Treg • Dysregulated FoxP3 transcription	• Lymphoproliferation, IPEX-like autoimmunity	48–51

(continued on next page)

Table 1
(continued)

Primary Immunodeficiency	Genetic Defect	Mechanisms	Autoimmune Features	Ref.
CTLA-4 deficiency	CTLA-4	Defective Treg development and function	Enteropathy, GLILD, autoimmune cytopenias, hepatitis, thyroiditis, arthritis, psoriasis	53,54
LRBA deficiency	LRBA	Impaired Treg survival	Lymphoid interstitial pneumonia/GLILD, enteropathy, autoimmune cytopenias, thyroiditis, myasthenia gravis, atrophic gastritis	57–60
ALPS	FAS FAS ligand Caspase 8 Caspase 10 FADD PKC- δ NRAS, KRAS	Impaired FAS-mediated apoptosis	- Autoimmune cytopenias - Organ-specific autoimmunity - Lymphadenopathy, hepatosplenomegaly	23–27,36
		Impaired mitochondrial apoptosis		29–31
Complement deficiencies	C1q, C1r, C1s, C4, C2	- Defective clearance of apoptotic bodies - Impaired clearance of immune complexes	SLE, ANCA vasculitis	34,35
Hyper-IgM syndromes	CD40L/CD40	- Defective peripheral tolerance - Reduced Treg, elevated BAFF levels	AIHA, chronic neutropenia, ITP, polyarthritis, IBD, biliary tract/liver disease, thyroiditis	82,141
	AID	- Defective central tolerance - Defective peripheral tolerance - Reduced Treg, elevated BAFF	AIHA, ITP, polyarthritis, IBD, type I DM, AIH, chronic uveitis, lymphadenopathy	78–80
	UNG NEMO I κ B α	- Unclear - Unclear	- Lymphadenopathy - Enteropathy, autoimmune cytopenias	142 143,144
XLA	BTK	- Impaired BCR signaling - Impaired central tolerance	(Rare): JRA, RA, IBD, cytopenias, hypothyroidism, vasculitis, dermatomyositis	70,145

CVID	Unknown in majority; TACI, ICOS, BAFF-R, CD19, CD20, CD21, CD81, MSH5	• Mechanisms unclear • Defective central tolerance in some (TACI mutations) • Reduced Treg • Elevated BAFF levels • Increased type 1 IFN signaling • Increased IL-12 in gut • IFN-γ in liver • TNF-α polymorphisms • Defective BCR-mediated calcium signaling	• Autoimmune cytopenias • Enteropathy • GLILD • Hepatitis • Rheumatologic diseases	61–63,76,87,89, 106,108,116, 124,127
CGD	gp91phox p22phox p47phox p67phox p40phox	• Ineffective clearance of antigens leading to chronic stimulation, enhanced type 1 IFN signature • Defective induction of Tregs	• Colitis, discoid lupus, carriers with rheumatologic disease	38,39,41
Familial HLH	PRF1 UNC13D STX11 STXBP2 RAB27A LYST AP3B	• Impaired cytotoxic function in • Persistence of DCs presenting viral antigen • Production of IFN-γ, IL-6, and TNF-α • Infiltration of tissues, bone marrow by hyperactivated, destructive histiocytes	• Severe inflammatory syndrome • Persistent fever • Hepatosplenomegaly • Liver dysfunction • Cytopenias • CNS inflammation	94–97
XLP	SH2D1A XIAP	• Partially defective NK cell and CTL cytotoxic activity	• Lymphoproliferation • HLH	98
WAS	WASp	• Intrinsic signaling abnormality in B cells • Reduction in Treg numbers and function	• Thrombocytopenia, AIHA, neutropenia, IBD, arthritis, vasculitis, renal disease	65,146
Hyper-IgE syndrome	STAT3 DOCK8	• Altered Treg and cytokine signaling • Decreased number and function of Tregs • Autoreactive B cells	• Cytopenias, organ-specific autoimmunity (lung, gastrointestinal, hepatic, and/or endocrine), enteropathy, type 1 diabetes mellitus, lymphadenopathy • SLE	66,67

Abbreviations: AIHA, autoimmune hemolytic anemia; CNS, central nervous system; DM, diabetes mellitus; ITP, immune thrombocytopenia; JRA, juvenile rheumatoid arthritis; WAS, Wiskott-Aldrich syndrome; XLP, x-linked lymphoproliferative disease.

Data from Refs. 5–7,9,10,12–14,16–19,23–27,29–31,34–36,38,39,41,44,45,48–51,53,54,57–63,65–67,70,76,78–80,82,87,89,94–98,106,108,116,124,127,138–146

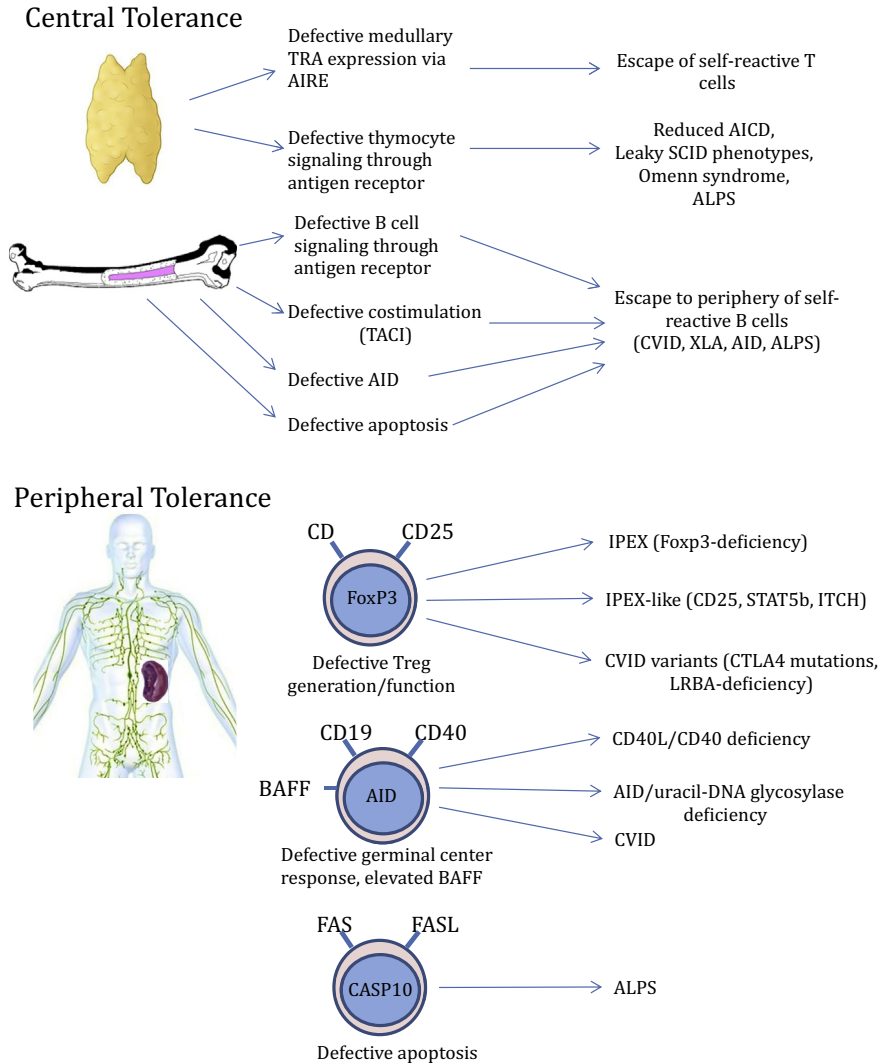


Fig. 1. Mechanisms of autoimmunity in PID disorders and some of the major mechanisms through which loss of self-tolerance and autoimmunity occur in PID syndromes, as discussed in the text.

release activated channel (CRAC channel), is a major route of calcium entry after TCR engagement, and its absence prevents apoptosis through reduced nuclear localization of NFAT.¹⁶ ORAI1-deficiency in humans leads to severe combined immunodeficiency (SCID) with associated autoimmunity.¹⁷ Deficiency in STIM1, an endoplasmic reticulum membrane protein responsible for activating CRAC channels during SOCE signaling, also presents with the combination of immunodeficiency and autoimmunity, arguing for defects in negative selection, although this relates at least in part to defects in Treg development and impaired peripheral tolerance.^{18,19} Defective signaling leading to escape from AICD-mediated clonal deletion could conceivably explain the inflammatory diseases seen in other forms of hypomorphic or “leaky” SCID in

humans. Additional defects in apoptosis and clonal deletion are discussed in the next section.

Apoptosis in Tolerance

Programmed cell death or apoptosis plays a key role in the elimination of self-reactive T and B cells at central and peripheral tolerance checkpoints.²⁰ Its importance in negative selection of lymphocytes was demonstrated with the discovery of a mutation in FAS, a member of the tumor necrosis factor (TNF) receptor family, in the autoimmune-prone MRL/lpr mouse.²¹ FAS signals through a death-inducing signaling complex or DISC, which includes FAS-associated protein death domain (FADD) and caspase 8, to activate downstream caspases and ultimately apoptosis (reviewed in²²).

The human homologue in which ineffective apoptosis leads to autoimmunity is autoimmune lymphoproliferative syndrome (ALPS). Patients present with lymphoproliferation, autoimmune cytopenias, and organ-specific autoimmunity (reviewed in²³). The most common mutations in human ALPS affect FAS, involving either germline or somatic mutations. Mutations in Fas ligand,²⁴ caspase 10,²⁵ caspase 8,²⁶ FADD,²⁷ and protein kinase c δ (PKC- δ)²⁸ cause ALPS due to impaired FAS-mediated apoptosis. Furthermore, newer genetic causes of a phenotypically similar disease called RAS-associated autoimmune leukoproliferative disorder impair non-FAS-mediated mitochondrial apoptosis and include germline and somatic mutations in small GTPases NRAS and KRAS.^{29–31}

Defects in clearance of apoptotic bodies and immune complexes can lead to a breakdown in tolerance.³² The classical complement pathway is required for safe elimination of immune complexes and apoptotic bodies.^{33–35} Systemic lupus erythematosus (SLE) is found in association with classical complement deficiencies. SLE is found in 90% of patients with C1q deficiency, 75% of patients with complete C4 deficiency, 50% to 65% of patients with C1r/s deficiencies, and 10% to 30% of patients with C2 deficiency.^{36,37} Homozygous C2 deficiency is the most common complement component deficiency.³⁶

Defects in phagocyte function such as in chronic granulomatous disease (CGD) are also associated with autoimmune and inflammatory disease (reviewed in³⁸). Functional oxidative burst in phagocytes is important in clearance of apoptotic cells and antigen, and defects in CGD are postulated to lead to prolonged inflammatory cell recruitment and cytokine production.³⁸ Notably, a prominent type I interferon (IFN) responsive gene expression signature was noted in murine models and humans with CGD mutations, in association with autoimmunity.³⁹ A similar gene expression profile has been shown in SLE, rheumatoid arthritis (RA), and Sjogren syndrome.⁴⁰ Furthermore, nicotinamide adenine dinucleotide phosphate (NAPDH) oxidase activity in macrophages is important for the induction of Tregs.⁴¹

Regulatory T Cells and Peripheral Tolerance

The critical role of a subset of CD4+ CD25+ T cells in maintaining peripheral tolerance was first demonstrated by Sakaguchi and colleagues⁴² in murine models. Forkhead box protein P3 (Foxp3) is the central transcriptional regulator of the development and function of Treg.⁴³ Mutations in FOXP3 cause reductions in number and diversity of Tregs, and a severe break in peripheral tolerance leading to immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX), which is a profound autoimmune and inflammatory syndrome characterized clinically by intractable diarrhea, multiorgan autoimmunity, and eczema before 1 year of age.^{44–46} Tregs depend on IL-2 signaling for development and function, and defects in IL-2 signaling lead to IPEX-like syndrome, with similar autoimmune and inflammatory manifestations.⁴⁷ These

manifestations include mutations in the α chain of the IL-2 receptor (CD25),⁴⁸ and mutations in STAT5b, an intracellular mediator of IL-2 signaling.⁴⁹ Mutations in ITCH, which regulates FoxP3 transcription, also cause IPEX-like disease.^{50,51} As discussed earlier, STIM1 deficiency in humans leads to reduced Tregs in the periphery, arguing for important roles for SOCE and NFAT signaling in their development.¹⁸

Other mutations found to cause defective Treg development and function, associated with autoimmune and lymphoproliferative disease in humans, include those in cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and lipopolysaccharide responsive beige-like anchor protein (LRBA). CTLA-4 is an inhibitory receptor constitutively expressed on Tregs, and upregulated on activated effector T cells (reviewed in⁵²). CTLA-4 knockout mice display a severe autoimmune syndrome similar to IPEX.^{53,54} Heterozygous CTLA-4 mutations were recently shown to cause a syndrome of immunodeficiency, autoimmunity, and lymphoproliferation in humans, with reduced Treg function.^{55,56} This is particularly interesting from 2 perspectives. First, CTLA-4 heterozygous mice do not display an abnormal phenotype,⁵³ and second, the penetrance of the disease phenotype in humans is incomplete.^{55,56} Treg function, however, is impaired in both healthy and affected family members with CTLA-4 mutations,⁵⁵ suggesting that although CTLA-4 haploinsufficiency affects Treg function in humans, other genetic or environmental factors may be required for manifestation of immunodeficiency, autoimmunity, and lymphoproliferation in this setting.

LRBA has been implicated in endosomal trafficking and cell survival, and its deficiency has been shown to have a selective effect on Treg survival, postulated to relate to impaired autophagy and abnormal mTOR signaling.^{57,58} Homozygous LRBA deficiency in humans has recently been shown to impair Treg function and lead to a similar syndrome of immunodeficiency, autoimmunity, and lymphoproliferation.^{57–60} Reductions in Treg numbers and function have been shown in other primary immunodeficiencies in which autoimmunity occurs, such as common variable immunodeficiency (CVID),^{61–64} Wiskott-Aldrich syndrome,⁶⁵ hyper-immunoglobulin E (IgE) syndromes,^{66,67} CGD,⁴¹ and DGS.⁶⁸

Central and Peripheral B-Cell Tolerance

The initial stages of B-cell development occur in the bone marrow, during which lymphoid progenitor cells progress through pro-B, pre-B, and immature B-cell stages and rearrange the B-cell receptor (BCR). The second stage occurs in lymphoid tissues, when B cells enter follicles, undergo class-switch recombination (CSR) and somatic hypermutation (SHM), and differentiate into memory B cells and antibody secreting plasma cells. The initial checkpoint to prevent emergence of self-reactive B cells from the bone marrow requires signaling through the newly rearranged BCR (reviewed in⁶⁹). High signal strength results in receptor internalization and downregulation of the B-cell activating factor (BAFF) receptor, which reduces survival signaling to the developing B cell. In addition, high signal strength induces RAG gene activity, and subsequent receptor editing, allowing the cell another opportunity to rearrange a non-self-reactive receptor. If a less self-reactive receptor is not expressed within 1 to 2 days, the cell dies because of activation of the mitochondrial apoptosis pathway, which is unopposed due to downregulation of BAFF-R.

BCR signaling through Bruton tyrosine kinase (BTK) has been shown to play a role in central B-cell tolerance. Although few B cells develop in x-linked agammaglobulinemia (XLA) patients, those new emigrant/transitional B cells that emerge are enriched in self-reactive clones.⁷⁰ Antibody-mediated autoimmunity is rare in these patients however, because defective BCR signaling impairs antibody secretion in the periphery, and peripheral tolerance mechanisms are intact. Another signaling protein

downstream of the BCR, PTPN22, has recently been recognized as important in tolerance, and polymorphisms in this gene are strongly associated with autoimmunity in patients with CVID and other primary antibody deficiencies.⁷¹

Toll-like receptor signaling was shown to be important in central B-cell tolerance, as patients with null mutations in IRAK-4 or MyD88 were shown to have a high frequency of self-reactive new emigrant/transitional B cells in circulation. However, autoantibody was not detected, and no clinical autoimmunity was reported, arguing that peripheral tolerance mechanisms are sufficient to prevent clinical manifestation of autoimmunity in these patients.⁷²

Transmembrane activator, calcium modulator, and cyclophilin ligand interactor (TACI) mutations, occurring in 8% to 10% of patients with CVID,^{73,74} are shown to increase susceptibility to autoimmunity and inflammation in those patients (reviewed in⁷⁵). Individuals with mutations in TACI were shown to have a high frequency of self-reactive new emigrant/transitional B-cell clones escaping the bone marrow, which occurred in both CVID patients and healthy family members with heterozygous TACI mutations.⁷⁶ Interestingly, both TACI-mutant and non-TACI mutant CVID patients had self-reactive clones in the mature naïve B-cell compartment in the periphery, while healthy controls (whether TACI mutant or non-TACI mutant) did not. Thus, defective central tolerance due to TACI mutations was insufficient to cause autoimmunity, but in CVID patients, peripheral tolerance mechanisms were also defective, independent of TACI mutations. TACI mutations may therefore be disease modifiers in CVID, increasing the likelihood of autoimmunity by increasing the frequency of self-reactive clones escaping the bone marrow, but requiring additional lesions in peripheral tolerance for full manifestation of autoimmunity.

Activation-induced cytidine deaminase (AID) plays an important role in CSR and SHM. AID activity ultimately results in single-stranded DNA breaks, which are processed and repaired, allowing completion of CSR and SHM.⁷⁷ AID deficiency causes autosomal-recessive hyper-IgM syndrome, manifest by recurrent infections, lymphoid hyperplasia, and diverse autoimmune manifestations.^{78,79} Although previously thought to be expressed only in germinal center B cells in the periphery, AID was recently shown to be expressed in immature B cells and play roles in both central and peripheral tolerance.⁸⁰ Impaired peripheral tolerance in AID patients correlated with increased circulating BAFF levels as well as reduced Treg frequency, the mechanisms for which were unclear.

Mutations in CD40-ligand (CD40L) affect peripheral tolerance. CD40/CD40L signaling plays roles in peripheral B-cell maturation, CSR, and SHM, as well as in optimal function of antigen-presenting/phagocytic cells and CTL. CD40L-deficient patients develop recurrent bacterial and opportunistic infections and frequent hematologic and organ-specific autoimmunity (reviewed in⁸¹). New emigrant/transitional B cells from CD40L-deficient patients were not enriched in self-reactive clones, suggesting that central B-cell tolerance was intact.⁸² However, a higher proportion of autoreactive clones was found in the mature naïve B-cell compartment, arguing for defective peripheral tolerance. As in patients with AID deficiency, this correlated with elevated BAFF levels and reduced Treg, the latter presumed to be related to the previously demonstrated role of CD40-CD40L interactions in Treg development.⁸³

Overexpression of BAFF in mice leads to B-cell hyperplasia, hypergammaglobulinemia, splenomegaly, and autoimmunity,⁸⁴ and is shown to rescue self-reactive B cells from deletion in the periphery, as well as facilitating entry into B-cell follicles.^{85,86} Elevated serum BAFF levels have been found in patients with AID deficiency and CD40L deficiency (discussed earlier) as well as in patients with CVID and systemic autoimmune disease.^{87,88} The mechanisms leading to its overexpression in these diseases are unclear.

Impaired calcium mobilization after BCR signaling has been shown in CVID patients prone to autoimmunity, granulomata, and splenomegaly.⁸⁹ Impaired BCR-induced calcium mobilization in these patients is associated with the expansion of CD21low B cells, a polyclonal population containing mostly autoreactive clones, expressing a gene profile suggestive of anergy, and a pattern of inflammatory chemokine receptors directing these cells to inflamed tissues.^{90,91} The specific role these CD21low B cells play in autoimmune and inflammatory disease is unknown, but notably, similar CD21low B cell populations are seen in systemic lupus and RA patients.^{90–92}

Contraction of the Immune Response

Hemophagocytic lymphohistiocytosis (HLH) is an inflammatory syndrome caused by impaired regulation of the adaptive immune response. Familial HLH is caused by mutations in genes, including UNC13D, STX11, STXBP2, RAB27A, LYST, and AP3B, involved in cytotoxic granule formation, trafficking or release, or encoding granule contents themselves (PRF1) (reviewed in⁹³). Mice with mutations in these genes, which develop HLH in the setting of viral infection, have been helpful in understanding the mechanisms of HLH. Cytotoxic CD8+ T cells were found to regulate the number of dendritic cells (DCs) presenting viral antigen, such that in the setting of mutations affecting cytotoxicity, a larger number of DCs persisted and presented viral antigen.⁹⁴ Comparison of mice deficient in PRF1, LYST, RAB27A, STX11, and AP3B showed that the severity and timing of disease correlated with the degree of impairment in cytotoxicity and persistence of viral antigen, and a similar severity gradient was demonstrated in human disease caused by these various mutations.⁹⁵ The end result of this persistent antigen presentation is exuberant production of cytokines, including IFN- γ , IL-6, and TNF- α ,⁹⁶ and a destructive infiltrative process with hyperactivated macrophages and histiocytes.⁹⁷ As discussed earlier, impaired antigen clearance causes abnormal cytokine expression and inflammatory disease in other settings, such as CGD. Other genetic defects causing HLH include SH2D1A, BIRC4, ITK, CD27, and MAGT1, which encode signaling proteins involved in activation of cytotoxic function as well as survival, differentiation, and migration of T and natural killer (NK) cells. Abnormalities in these genes result in susceptibility to HLH and lymphoproliferative disease (reviewed in⁹⁸).

AUTOIMMUNE AND INFLAMMATORY COMPLICATIONS OF COMMON VARIABLE IMMUNODEFICIENCY

CVID is the most common clinically relevant PID, with prevalence estimated at 1:25,000. Although many single gene mutations are shown to present with a CVID phenotype (see [Table 1](#)), in most cases, no genetic lesion is known, and familial inheritance of CVID is rare.⁹⁹ CVID is frequently complicated by a wide range of autoimmune and inflammatory conditions, including enteropathy, granulomatous lymphocytic interstitial lung disease (GLILD), and liver disease, as well as lymphomas, which significantly shorten survival.^{100–102} Abbott and colleagues,¹⁴⁷ have discussed the clinical aspects and management of these conditions in CVID patients. The mechanisms through which the autoimmune and inflammatory complications of CVID develop are not clear, but there has been a great deal of work on this in recent years, which is summarized in later discussion. Proposed mechanisms include many of those described earlier in monogenic primary immunodeficiencies. Furthermore, the diversity of mechanistic findings for each of these autoimmune and inflammatory complications highlights the likely polygenic and multifactorial nature of this disease.

Autoimmune Cytopenias and Rheumatologic Complications

Twenty percent of patients with CVID have associated autoimmunity.⁹⁹ Autoimmune cytopenias are the most common, and rheumatologic diseases, including a polyarticular arthritis resembling RA, occur in 10% to 30%.¹⁰³ This polyarthritis is distinct from RA in that it is typically seronegative, is nonerosive, and runs a benign course, resolving spontaneously.¹⁰⁴ Classic RA occurs less frequently, documented in 2% to 3% of CVID patients.^{100,105}

A wide spectrum of additional systemic and organ-specific autoimmune diseases has been documented in CVID, including SLE, pernicious anemia, antiphospholipid syndrome, diabetes mellitus, juvenile RA, uveitis, multiple sclerosis, autoimmune thyroid disease, lichen planus, vasculitis, vitiligo, and psoriasis.^{100,101}

Mechanistically, as discussed earlier, mutations in TACI may be found in 8% to 10% of CVID patients and seem to increase the predisposition to autoimmunity.⁷⁵ TACI mutations are shown to compromise central tolerance⁷⁶ and may thereby increase the risk of autoimmunity in these patients by increasing the frequency of self-reactive B cells escaping the bone marrow.

Peripheral tolerance was shown to be compromised in CVID patients regardless of TACI mutations,⁷⁶ and several potential lesions may contribute to this. The frequency and function of Treg cells are depressed in CVID patients with autoimmune cytopenias, thyroiditis, polyendocrinopathy, arthritis, and inflammatory manifestations including granulomatous disease and enteropathy.^{61–63} Prosurvival signaling and entry of self-reactive cells into otherwise restricted B-cell follicles are allowed via elevated circulating BAFF levels in CVID patients.^{87,106} Calcium signaling through the BCR is dysfunctional in a subgroup of CVID patients prone to autoimmunity and infiltrative disease⁸⁹; correlating with poor class-switching and memory formation, and expansion of anergic, CD21lo B cells, with altered trafficking properties.^{90–92} Interestingly, similar CD21lo populations have been shown in SLE and RA, and in fact, infiltrate synovial tissues.^{90,91,107} The specific role of these cells is unclear. Last, an IFN-responsive gene expression signature is noted in CVID patients with autoimmunity, similar to SLE and RA patients.^{40,108}

In summary, a plethora of potential mechanisms may explain the autoimmune and rheumatologic complications of CVID, including breakdown in central tolerance, and several defects affecting peripheral tolerance, expansion of abnormal B-cell populations with altered trafficking and effector functions, and altered cytokine expression and signaling.

Enteropathy

Noninfectious gastrointestinal disease occurs in 9% to 15% of CVID patients.^{100,109} Histologically, findings in the small intestine include villous blunting, increased intraepithelial lymphocytes (IELs), mild duodenitis, and nodular lymphoid hyperplasia.^{110,111} Findings in stomach include chronic gastritis, ranging from mild to severe mucosal atrophy in the body and antrum, with vitamin B12 deficiency and serologic evidence of pernicious anemia.^{111,112} Graft versus host disease (GVHD)-like pathologic abnormality has been demonstrated in the colon.¹¹¹ Of note, a paucity of plasma cells in the gastrointestinal mucosa has been a unifying finding among these studies.^{111,112}

The pathophysiology of CVID-enteropathy remains unclear. Parallels have been drawn with celiac disease, given the frequent findings of villous blunting and epithelial atrophy in a spruelike pattern. However, several studies have addressed the frequency of celiac-specific HLA haplotypes (HLA DQ2, DQ8) in CVID patients with enteropathy and have found no clear correlation, nor does the presence of these haplotypes in CVID patients portend responsiveness to gluten withdrawal.^{111,113,114}

Regarding the absence of plasma cells in the gastrointestinal mucosa, gene expression analysis in the jejunum of B cell and IgA-deficient mice identified a “dialogue” between adaptive immunity, jejunal mucosal enterocytes, and intestinal microbiota.¹¹⁵ When germ-free mice were populated by normal microbiota, gene expression in jejunal enterocytes was characterized by a Gata4-regulated metabolic pattern dictating fat absorption and leptin expression. In the absence of B cells or IgA, this switched to an IFN-responsive gene expression pattern. Similar IFN-response profiles were found in duodenal biopsies from CVID patients. This study suggests an interesting interplay between plasma cell-mediated mucosal IgA production, the intestinal microbiome, and enterocytes in setting the stage for intestinal inflammation in CVID.

Lamina propria mononuclear cells (LPMCs) isolated from intestinal biopsies from CVID patients with enteropathy produced significantly more IL-12 and IFN- γ , when stimulated in culture with innate stimuli or via the TCR, than LPMCs from CVID patients without enteropathy.¹¹⁶ When compared with LPMCs from patients with Crohn disease, similar levels of IL-12 and IFN- γ were produced, but significantly less IL-23, IL-17, and TNF. Thus, CVID enteropathy involves a T-cell-mediated inflammatory process driven by IL-12 and IFN- γ , which is distinct from Crohn disease.

A role for impaired regulatory T-cell function in this condition is suspected given the recent findings of CTLA-4 mutations affecting Treg function, in patients who meet criteria for and were previously diagnosed with CVID,^{55,56} as discussed earlier. Malabsorptive enteropathy was the most common clinical manifestation of immune dysregulation in those studies. The incomplete penetrance of this phenotype argues that heterozygous CTLA-4 mutations, which affect the function of Treg, may be disease modifiers in CVID, enhancing the susceptibility of CVID patients to autoimmune and inflammatory complications but requiring additional mutations or environmental factors to manifest clinically. Similarly, hypogammaglobulinemia, autoimmunity, and inflammatory enteropathy were shown in patients with homozygous mutations in LRBA, which are known to affect Treg survival and function,^{57–60} and CTLA4 protein expression.¹¹⁷

Last, a genome-wide association study (GWAS) by Orange and colleagues¹¹⁸ showed a strong association between CVID enteropathy and a polymorphism in the CACNA1C gene on chromosome 12; this is the α subunit of a voltage-gated calcium channel, which has been shown to play a role in smooth muscle motility in rat intestine.¹¹⁹ The specific role of this polymorphism in immunoregulation or the pathophysiology of CVID enteropathy has not yet been determined.

In summary, CVID is complicated by noninfectious enteropathy at a rate of 9% to 15%, and this subpopulation is at increased risk for autoimmune disease and death. Characteristic features include villous blunting, increased IELs, and nodular lymphoid hyperplasia in the small bowel, and GVHD-like apoptosis in the colon, with a paucity of plasma cells in the mucosa. The pathophysiology remains unclear, although it may involve changes in innate immune signaling by enterocytes due to reduced mucosal IgA, reduced Treg function, and an IL-12 and IFN- γ -driven T-cell-mediated inflammatory process.

Granulomatous Lymphocytic Infiltrative Lung Disease

Noninfectious lung disease in CVID includes bronchiectasis, isolated granulomata, and a more diffuse infiltrative process that involves loose granulomata and a mixed infiltrate of T cells, B cells, histiocytes, and stromal cells, which has recently been named granulomatous interstitial lung disease, or GLILD.¹⁰²

The histopathology of GLILD has been studied in depth.¹²⁰ It has been described as an expansion of bronchus-associated lymphoid tissue (BALT), tertiary lymphoid neogenesis in the lung, or pulmonary lymphoid hyperplasia (PLH), and involves a variable

lymphocytic infiltrative process with formation of ectopic germinal centers. PLH may present in several histologic patterns, including those of lymphocytic interstitial pneumonia, follicular bronchiolitis, nodular lymphoid hyperplasia, and reactive lymphoid hyperplasia. All of these include mixed infiltrates of T cells, B cells, antigen presenting cells, stromal cells, and loosely organized granulomata, all of which fall under the umbrella term GLILD. Peribronchial lymphocytic infiltrates in this process are organized into CD20+ B-cell-rich follicles surrounded by more diffuse T-cell zones. Follicles are Ki67 and Bcl6+ and contained CD23+ follicular DCs, identifying these as actively proliferating ectopic germinal centers. In general, there is a predominance of CD4+ T cells. Tertiary lymphoid neogenesis occurs in other autoimmune and inflammatory diseases, including Sjogren syndrome and RA. These diseases have been shown to be responsive to B-cell depletion therapies, arguing that these ectopic B-cell-rich germinal centers may drive the expansion or persistence of the infiltrative process.¹²⁰

In murine models, the development of BALT is dependent on follicular dendritic cells, which in turn require lymphotoxin α/β (LT $\alpha\beta$) and CXCL13 (reviewed in¹²¹). In mice, depletion of dendritic cells or inhibition of lymphotoxin can induce regression of BALT. Treg have been shown to inhibit the formation of BALT in mice. Pulmonary disease is a rare manifestation of human IPEX,¹²² but GLILD is seen frequently in patients with mutations in CTLA-4^{55,56} and LRBA,^{57,58} arguing that abnormalities of Treg function may contribute to this process.

TNF- α is known to play a key role in granuloma formation¹²³ and may play a role in granulomatous disease and GLILD in CVID patients. An uncommon TNF- α polymorphism was shown to correlate significantly with the occurrence of pulmonary granulomatous disease and splenomegaly in CVID.¹²⁴

A role for chronic viral infection in GLILD pathogenesis was proposed, and one group has shown an association between PCR positivity for human herpesvirus 8 and GLILD, while others have not seen the same association.^{125,126}

Last, a role for stromal cell function in the pathogenesis of GLILD is suggested by the finding of a single nucleotide polymorphism (SNP) in the FGF14 gene found to be highly associated with lymphoid interstitial pneumonitis in CVID patients in the GWAS study mentioned previously.¹¹⁸

In summary, GLILD is an infiltrative disease of the lung, involving tertiary lymphoid neogenesis. The pathogenesis is not well understood, but murine studies have demonstrated roles for LT $\alpha\beta$ and follicular DCs in tertiary lymphoid neogenesis and formation of BALT, and Treg in regulating its formation. Treg dysfunction may predispose to GLILD in CVID, as evidenced by the prevalence of GLILD in the setting of mutations in CTLA-4 or LRBA, which have clear impacts on Treg function. TNF- α polymorphisms may play a role in granulomatous disease in CVID. Chronic viral infection could be a trigger or driver in the formation of GLILD in CVID patients, although this is in debate. The strong association of GLILD with a polymorphism in FGF14 suggests an as-yet unexplored role of stromal cells in this inflammatory disease.

Nodular Regenerative Hyperplasia and Autoimmune Hepatitis

Noninfectious liver disease occurs in 5% to 12% of CVID patients^{127,128} and shortens survival.¹⁰⁰ Most CVID patients biopsied to evaluate hepatic disease had nodular regenerative hyperplasia (NRH), characterized by diffuse transformation of the hepatic parenchyma into small, regenerative nodules, without significant fibrosis.^{129,130} In CVID, intrasinusoidal lymphocytic infiltrates of CD8+ T cells are often present in conjunction with this.^{127,130} Importantly, portal hypertension, a known complication of NRH, was present in 20% to 75%.^{127,128,130}

In a subsequent study, more than half of the patients had associated portal and lobular inflammatory infiltrates, sometimes occurring in conjunction with interface hepatitis and bridging necrosis, which was termed autoimmune hepatitis (AIH)-like disease. Of note, there was a paucity of plasma cells in biopsies. Interestingly, in one patient, followed with serial biopsies over 6 years, the disease was shown to progress from mild NRH to this more severe AIH-like illness. The interface hepatitis in these patients was shown to involve CD8+ T cells and IFN- γ expression. Furthermore, patients with this AIH-like disease, unlike typical NRH, developed hepatic synthetic dysfunction in addition to portal HTN.

NRH occurs in other disease settings as well, including autoimmune and hematologic illnesses and infections, and in the setting of treatment with certain medications (reviewed in¹²⁹). The prevalence of NRH in autopsy studies is approximately 2%.^{131,132} Interestingly, the frequency with which portal hypertension is found in association with NRH in autopsy studies was low, at 4.7%,¹³¹ arguing that both the frequency and the severity of this entity may be increased in CVID patients.

The underlying cause of NRH is thought to involve disturbances in perfusion in the hepatic microvasculature, leading to a local hyperplastic response in hepatocytes,¹²⁹ possibly caused by congenital anomalies in portal vasculature, hematologic or prothrombotic disorders, toxic, or immunologic injury to endothelial cells.^{129,133,134} CD8+ T cells may play a role in pathogenesis in some patients.¹³⁴ Cytokines, including IFN- γ ¹²⁷ and IL-6,¹³⁵ have been postulated to play roles in this disease. Autoantibodies, particularly antiphospholipid antibodies contributing to prothrombotic states, have been shown in association with NRH and may play a role in some patients.¹³⁶ In the GWAS study cited earlier, NRH in CVID patients was significantly associated with 2 SNPs on chromosome 1, the specific identity and function of which are unknown.¹¹⁸ Other polymorphisms or single-gene mutations mentioned in previous sections on enteropathy and GLILD, such as CTLA-4, LRBA, and TNF- α , have not been clearly associated with NRH. That being said, infiltrative liver disease and hepatomegaly were noted in patients with CTLA-4 mutations,⁵⁵ and hepatitis has been seen in a minority of patients with IPEX,¹³⁷ arguing that the more severe AIH-like variant discussed earlier may be related to abnormalities in T-cell regulation or Treg function.

SUMMARY

Identification of genetic lesions in primary immunodeficiencies complicated by autoimmune and inflammatory diseases has illuminated numerous mechanisms bridging immune development with central and peripheral tolerance, and regulation of the immune response. This knowledge is facilitating advancements in the understanding of more complex, multifactorial syndromes of autoimmunity and immunodeficiency, such as CVID, SLE, and RA, and it is hoped will soon lead to advancements in therapy for these diseases.

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