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The crossroads of autoimmunity and immunodeficiency: Lessons from polygenic traits and monogenic defects

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Activity Objectives:

1. To recognize the various clinical manifestations of conditions with both immunodeficiency and autoimmunity.
2. To understand the underlying biological defects that contribute to the development of immunodeficiency and autoimmunity.
3. To recall common monogenetic defects underlying primary immunodeficiency, immune dysregulation, and systemic autoimmune disease.

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Autoimmune and immunodeficiency diseases are outcomes of a dysfunctional immune system and represent 2 sides of the same coin. Multiple single-gene defects have been identified, resulting in rare diseases with features of both autoimmunity and immunodeficiency. On the other hand, more common autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, show a polygenic inheritance pattern. Not surprisingly, the genes implicated in single-gene disorders have also been shown to be linked to polygenic disorders. In this review article, we discuss the contribution of various immune system genes to common polygenic autoimmune disorders, as well as the pathophysiologic pathways and clinical features of monogenic defects that result in autoimmune disease. We also explore the hypotheses underlying the development of autoimmune disease and the overlap between immunodeficiency and autoimmunity. (J Allergy Clin Immunol 2016;137:3-17.)

Key words: *Autoimmunity, primary immunodeficiency diseases, B cells, T cells*

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In medical school, we all learned that there is more than one pathway to the development of liver cirrhosis: viral infections, alcohol abuse, and inborn genetic conditions, among others. The outcome of liver cirrhosis is just a common end point of various etiopathologies. Likewise, there are many etiopathologies that

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Abbreviations used

AID:	Activation-induced cytidine deaminase
AIHA:	Autoimmune hemolytic anemia
AIRE:	Autoimmune regulator
ALPS:	Autoimmune lymphoproliferative disease
ANA:	Anti-nuclear autoantibody
APC:	Antigen-presenting cell
APECED:	Autoimmunity–polyendocrinopathy–candidiasis–ectodermal dysplasia
BAFF:	B-cell activating factor
BCR:	B-cell receptor
COP:	Coatomer protein
CRP:	C-reactive protein
CTLA4:	Cytotoxic T-lymphocyte antigen 4
CVID:	Common variable immunodeficiency
DOCK8:	Dedicator of cytokinesis 8
ER:	Endoplasmic reticulum
FoxP3:	Forkhead box P3
GOF:	Gain-of-function
HSCT:	Hematopoietic stem cell transplantation
IC:	Immune complex
ICOS:	Inducible T-cell costimulator
IRF:	Interferon regulatory factor
ITGAM:	Integrin alpha M
ITP:	Idiopathic thrombopenic purpura
LRBA:	LPS-responsive vesicle trafficking, beach and anchor containing protein
NK:	Natural killer
PFS:	Periodic fever syndrome
PID:	Primary immunodeficiency disease
PI3K:	Phosphoinositide 3-kinase
PKCδ:	Protein kinase Cδ
PLCγ2:	Phospholipase Cγ2
PTPN22:	Protein tyrosine phosphatase, nonreceptor type 22
RA:	Rheumatoid arthritis
RAG:	Recombination-activating gene
RF:	Rheumatoid factor
SAMHD1:	SAM and HD domain 1 hydrolase
SCID:	Severe combined immunodeficiency
SLE:	Systemic lupus erythematosus
STAT:	Signal transducer and activator of transcription
TACI:	Transmembrane activator and CAML interactor
TCR:	T-cell receptor
TLR:	Toll-like receptor
TNFSF4:	TNF ligand superfamily 4 (OX40L)
TPP2:	Tripeptidyl peptidase II
Treg:	Regulatory T
TREX1:	Three prime repair exonuclease 1

can result in the development of fibrotic lung disease, vasculitis, or hypogammaglobulinemia.

Autoimmunity is one of the etiopathologies that can cause harm to the integrity of the body's organs by aggressively attacking self-tissue, be it organs or components of the blood. Here we define autoimmunity as the breakdown of immune tolerance to self-antigens. Currently, there are several hypotheses as to why autoimmune conditions develop in human subjects. For the purpose of clarity, we have picked some polygenic traits and monogenic defects exemplifying the affected pathways; however, this list is by no means complete.

POLYGENIC LESSONS FROM SYSTEMIC AUTOIMMUNE DISEASES

Genetic analysis of primary immunodeficiency diseases (PIDs) and systemic rheumatic diseases are paradigmatic fields of modern immunogenetic research. Although nearly 300 monogenic traits have now been observed to be associated with various forms of PIDs and autoinflammatory periodic fever syndromes (PFSs),[1] polygenic inheritance patterns are likely to account for more common systemic autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Not unexpectedly, some of the genetic variants and mutations associated with PIDs have also been identified in systemic autoimmune diseases and *vice versa*.[1-10]

In the largest genome-wide association study meta-analysis of European and Asian subjects (29,880 patients with RA [88.7% anti-citrullinated protein antibody positive] and 73,758 control subjects), 377 candidate genes were identified in 100 non-MHC RA risk loci.[11] Using an *in silico* bioinformatics pipeline, the authors systematically prioritized the most likely biological candidate genes for RA risk and came up with 98 genes with a risk score of greater than 2. Interestingly, there was a considerable overlap with PID genes (n = 15). Among other notable genes were hematological cancer somatic mutation genes (n = 17), genes associated with knockout mouse phenotypes (n = 86), and genes prioritized by molecular pathways analysis (n = 35) and protein-protein interactions (n = 63). Among PID genes, the highest proportion with RA overlap occurred in the categories of immune dysregulation (caspase 8 *[CASP8]*, caspase 10 *[CASP10]*, autoimmune regulator *[AIRE]*, and IL-2 receptor α *[IL2RA]*), followed by combined immunodeficiency (protein tyrosine phosphatase receptor *[PTPR]*, recombination-activating gene 1 *[RAG1]*, *RAG2*, and *CD40*), well-defined syndromes (ataxia telangiectasia mutated *[ATM]* and *TYK2*), primary antibody deficiencies (*CD40* and uracil-DNA glycosylase *[UNG]*), and phagocyte defects (IFN-γ receptor 2 *[IFNGR2]* and interferon regulatory factor 8 *[IRF8]*), whereas no RA risk gene was observed in the innate immunity category of the International Union of Immunological Societies classification of PIDs.[1]

To date, no single-gene defect has been identified to account for cases of adult RA. However, single-gene defects have been identified in patients with autoinflammatory diseases that affect the joints, such as the various PFSs, which include familial Mediterranean fever, TNF-α receptor–associated periodic syndrome, hyper-IgD syndrome, pediatric cryopyrin-associated fever syndromes, and deficiency of the IL-1 receptor antagonist.[1,12]

Strong genetic and environmental components have been identified in the pathogenesis of SLE: among monozygotic and dizygotic twins, the reported concordance rates range between 25% and 40% and 2% and 5%, respectively.[13] The strongest risk association for SLE has been shown to map to several loci within the MHC region,[14,15] and deficiencies of the early complement components C1q, C2, and C4 have long been known to be strongly associated with SLE.[16-24] Moreover, genome-wide association studies have identified more than 50 robust loci associated with SLE susceptibility, and follow-up studies helped to identify causative genetic variants and their biological relevance to a polygenic development of SLE.[25] Non-MHC risk alleles for

SLE comprise 3 groups of genes,[13,26,27] which are discussed further below.

Toll-like receptors 7, 8, and 9/type I interferon pathways

This group consists of polymorphic genes, such as Toll-like receptor 7 *(TLR7)*, *TLR8*, and *TLR9*[28-30]; *IRF3*, *IRF5*, and *IRF7*[25,28,31,32]; *Tyk2*[33]; signal transducer and activator of transcription 4 *(STAT4)*[34,35]; osteopontin *(SPP1)*[36]; and IL-1 receptor–associated kinase *(IRAK1)*.[37] These are usually gain-of-function (GOF) variants involved in the IFN-α activation pathway. Interestingly, *IRF5* and *STAT4* additively increase the risk of SLE.[35]

Typically, patients with SLE form anti-nuclear autoantibodies (ANAs), which are produced in response to self-nucleic acids and their associated nuclear proteins. Type I interferon strongly favors loss of self-tolerance and ANA production.[38-40] Sources of nuclear autoantigens include apoptotic and necrotic cells, as well as neutrophils undergoing a specific form of cell death called NETosis. In plasmacytoid dendritic cells, nuclear autoantigens (apoptotic or necrotic debris) can induce a strong type I interferon response either through an endosomal pathway involving ANAs and/or C1q-containing immune complexes (ICs) or a cytosolic pathway supported by genetic loss-of-function variants (three prime repair exonuclease 1 *[TREX1]*, *RNaseH2*, SAM and HD domain 1 hydrolase *[SAMHD1]*, interferon induced with helicase C domain 1 *[IFIH1]*, and hydroxymethylglutaryl-CoA synthase *[MVAS]*), resulting in impaired RNA and single-stranded DNA degradation.[13,41-44] As a consequence of sustained cytosolic sensing of nucleic acids, type I interferon transcripts are upregulated through IRF3, IRF5, or IRF7.[27,42] In addition, enhanced activation of the cytosolic double-stranded DNA sensor cyclic GMP-AMP synthase and the subsequent binding of stimulator of interferon genes[45,46] can provide a pathway leading toward increased type I interferon production (notably IFN-β) and a heightened risk of autoimmunity.[46,47]

Recently, a marked upregulation of type I interferons has also been observed in patients with common variable immunodeficiency (CVID) with inflammatory complications.[48] The authors suggest that whole blood transcriptome analysis of IFN-α response genes might help to identify patients with CVID at risk of inflammatory complications and higher mortality.

Immune system transduction pathways/immune dysregulation

These genes are involved in T-cell signaling and lymphocyte activation pathways, such as protein tyrosine phosphatase, non-receptor type 22 *(PTPN22)*[49]; TNF ligand superfamily 4 (OX40L) *(TNFSF4)*[50,51]; pyruvate decarboxylase 1 *(PDCD1)*[52,53]; or B-cell signaling pathways, such as B-cell scaffold protein with ankyrin repeats 1 *(BANK1)*, B-lymphocyte tyrosine kinase *(BLK)*,[54] and *LYN*.[55] B-cell lymphoma 6 *(BCL6)* is the lineage-specific transcription factor of follicular helper T cells, which show strong inducible T-cell costimulator (ICOS) and CXCR5 expression and provide help to B cells in germinal centers.[56-58] Bcl6 expression is regulated by IL-6 and IL-21 and plays a critical role in murine SLE models. ICOS deficiency ameliorates SLE in murine models[59] and leads to CVID in human subjects.[60] OX40 ligand protein (TNFSF4) promotes the follicular helper T-cell response involved in SLE pathogenesis.[61,62] Some genes have been associated with several autoimmune diseases (eg, *STAT4* with RA and *PTPN22* with RA and insulin-dependent diabetes mellitus), yet others appear to specifically increase the risk for SLE.[26,27] *TNFAIP* (A20)[63] and *TNIP1*[64] are negative regulators of nuclear factor κB signaling, and loss-of-function variants have been associated with SLE.

Immune complex processing mechanisms

In addition to the mutated complement pathway genes *C1qrs*, *C2*, and *C4*, polymorphic variants of *FcyIIB* and *FcyIIIB*,[65,66] the rs1205 variant of C-reactive protein (CRP),[67] and the R77H variant of integrin alpha M (*ITGAM*; CD11b, part of the complement receptor 3) confer an increased risk for SLE.[68] These all play a role in the clearance of necrotic and apoptotic material, and failure to do so increases the risk of autoimmunity. This is further discussed in "Pathophysiologic pathway 7" below.

EFFECT OF MONOGENIC DEFECTS ON AUTOIMMUNITY

In addition to the large number of polygenic SLE genetic risk alleles, there are new insights into SLE pathogenesis through emerging monogenic SLE disease models in both human subjects and mice.[27,43,69] Early disease onset, familial SLE, and syndromal lupus are rare conditions that are likely to involve monogenic defects. Typically in such cases the correlation of a monogenic mutation/deletion with an SLE phenotype is high (>30% to 50%). These rare forms of autoimmunity caused by single-gene defects involve pathways that, if impaired, inevitably lead to severe immune dysregulation and ultimately to autoimmunity. For the purpose of this review, we have identified 9 of these pathways, although these might overlap in some of the monogenic examples.

Pathophysiologic pathway 1: Lymphopenia leads to autoimmunity

RAG1 and RAG2 are recombinases that facilitate the process necessary for V(D)J recombination, allowing rearrangement and recombination of the genes for the immunoglobulin and T-cell receptor (TCR) molecules. RAG1 and RAG2 are critical in early lymphocyte development while the lymphocyte is assembling its antigen receptor. Together with other enzymes, they form the V(D)J recombinase, which initiates the recombination process by cleaving DNA at recombination signal sequence sites, creating a hairpin at the end of the coding region. The recombinase enzyme complex holds the ends together until other enzymes repair the DNA break.

Clinically, RAG deficiency presents with a $T^{-}B^{-}$ natural killer $(NK)^{+}$ severe combined immunodeficiency (SCID) with severe and opportunistic infections. However, in patients with hypomorphic mutations, residual enzyme activity allows for recombination of antigen receptor genes, leading to the differentiation of an oligoclonal repertoire of T and B cells. It is believed that due to their low frequency and an impaired natural selection process, cells with autoreactive TCRs and B-cell receptors (BCRs) survive and clonally expand.[70,71]

Associated with these mutations, a whole spectrum of diseases has been described, including Omenn syndrome, chronic CMV

TABLE I. Revised diagnostic criteria for ALPS*[89]

Required
1. Chronic (>6 mo), nonmalignant, noninfectious lymphadenopathy; splenomegaly; or both
2. Increased $CD3^+TCR\alpha\beta^+CD4^-CD8^-$ DNT cell counts (≥1.5% of total lymphocytes or 2.5% of $CD3^+$ lymphocytes) in the setting of normal or increased lymphocyte counts
Accessory
Primary
1. Defective lymphocyte apoptosis (in 2 separate assays)
2. Somatic or germline pathogenic mutation in *FAS*, *FASLG*, or caspase 10 *(CASP10)*
Secondary
1. Increased plasma sFASL levels (>200 pg/mL) OR increased plasma IL-10 levels (>20 pg/mL) OR increased serum or plasma vitamin B12 levels (>1500 ng/L) OR increased plasma IL-18 levels (>500 pg/mL)
2. Typical immunohistologic findings, as reviewed by an experienced hematopathologist
3. Autoimmune cytopenias (hemolytic anemia, thrombocytopenia, or neutropenia) AND increased IgG levels (polyclonal hypergammaglobulinemia)
4. Family history of a nonmalignant/noninfectious lymphoproliferation with or without autoimmunity

DNT, Double-negative T.
*A definitive diagnosis is based on the presence of both required criteria plus 1 primary accessory criterion. A probable diagnosis is based on the presence of both required criteria plus 1 secondary accessory criterion.

and EBV infection, idiopathic CD4 lymphopenia, granulomas, selective IgA deficiency, a CVID phenotype, and specific antibody deficiency.[72-79] Omenn syndrome is caused by a limited number of surviving, highly autoreactive T cells that infiltrate host tissues, resulting in symptoms similar to those of graft-versus host disease. Mutations in the Artemis gene (*DCLRE1C* mutations impairing double-strand break repair) have also been shown to result in Omenn syndrome. Artemis deficiency can be hypomorphic and associated with autoimmune cytopenia.[80] Early onset of autoimmunity (with partially preserved B lymphocytes and normal/increased immunoglobulin levels) as the primary presenting feature has also been described with hypomorphic RAG mutations.[81,82]

In patients with RAG deficiency and Omenn syndrome, levels of AIRE (discussed further in "Pathophysiologic pathway 3" below) have also been shown to be reduced, contributing to the escape and peripheral expansion of autoreactive T cells.[83,84] Furthermore, in RAG-deficient patients severe peripheral B lymphopenia is accompanied by an upregulation of the B-cell survival factor B-cell activating factor (BAFF).[85] This finding, along with the presence of autoantibodies, is indicative of disrupted B lymphopoiesis and an impaired negative selection process in the bone marrow.[86] Under physiologic conditions, early B cells receiving sufficient costimulatory signals through specific cognate BCR-antigen interactions differentiate, undergo positive and negative selection, and are recruited into the periphery with the help of BAFF. In a state of lymphopenia with impaired negative selection and plentifully available BAFF, autoreactive B cells benefit from the lack of competition, with the result that autoreactive B-cell clones expand and fill the gap. Under physiologic homeostatic conditions, lymphopenia induces increased growth and survival factors, leading preferentially to expansion of normal B cells and only a few autoreactive clones.

Early hematopoietic stem cell transplantation (HSCT), which replaces the defective adaptive immune system, is the definitive treatment of RAG deficiency (and other SCIDs). There are no clear guidelines for treatment of patients with milder cases with hypomorphic mutations, some of whom have not undergone transplantation and in whom other treatments, such as immunoglobulin replacement alone, have been used.

Pathophysiologic pathway 2: Apoptosis defects lead to autoimmunity

In response to an infectious trigger, cells of the adaptive immune system, which recognize the specific antigen in question, expand and fight the pathogen. However, the controlled retraction of the proliferating cells by apoptosis is as important as their expansion.

Autoimmune lymphoproliferative disease (ALPS) is clinically characterized by lymphadenopathy, hepatosplenomegaly, multilineage autoimmune cytopenias (often Evans syndrome), autoimmune organ disease, and risk of lymphoma.[87] Typical laboratory findings in patients with FAS-deficient ALPS include expansion of $CD3^+\alpha\beta TCR^+$ T cells without CD4 and CD8 expression (double-negative T cells), increased IL-10 and vitamin B12 serum levels, and defective FAS ligand–induced apoptosis *in vitro*.[88] A definitive diagnosis of ALPS is based on required and accessory criteria, including specific clinical and laboratory findings (Table I).[89]

A heterozygous germline mutation of *FAS* is the most commonly identified genotype (70% to 80%). Somatic *FAS* mutations in double-negative T cells and mutations in *FASL* or *CASP10* are rare alternative genotypes causing ALPS, and up to 20% of the clinical ALPS cases thus far remain genetically undefined.[87] Because patients with ALPS often have various autoantibodies, including ANAs and rheumatoid factor (RF), the differential diagnosis of SLE is relevant, all the more because studies in patients with SLE have shown that polymorphisms in *FAS* and *FASL* genes can alter their basal expression and thereby might play an important role in the pathogenesis of SLE.[90]

The treatment of ALPS includes corticosteroids and the steroid-sparing agents mycophenolate mofetil and sirolimus. Splenectomy is not recommended because the risk of subsequent lethal pneumococcal septicemia is particularly high in patients with ALPS. Rituximab treatment of patients with ALPS has resulted in an increased proportion of long-term hypogammaglobulinemias.[87,91]

Pathophysiologic pathway 3: Breakdown of central tolerance in the thymus leads to autoimmunity

DiGeorge syndrome. Most patients with the diagnosis of DiGeorge syndrome have heterozygous deletions on

chromosome 22q11.2, involving genes necessary for the development of the third and fourth branchial pouches, which are (among other factors) responsible for thymus formation. Other features of DiGeorge syndrome include hypocalcemia caused by hypoparathyroidism and cardiac and facial malformation. There is significant heterogeneity in the clinical features of patients with DiGeorge syndrome, with a wide range of severity.

In patients with DiGeorge syndrome, the T-cell deficiency can range from having normal T-cell numbers and function to complete absence of T cells with an SCID-like phenotype. About 0.5% of patients had a severe immunodeficiency (complete DiGeorge syndrome) in one series,[92] but about 30% had mild-to-moderate lymphopenia (partial DiGeorge syndrome) in another series.[93] Accordingly, the severity of infections varies from increased susceptibility to minor infections up to more severe infections relating to T-cell immunodeficiency.

Because of the lack of thymic regulation of autoreactive T cells, as expected, autoimmunity and immune dysregulation have been described in patients with partial DiGeorge syndrome. Several different studies have identified a prevalence of autoimmune disease of 8.5% to 10% in patients with partial DiGeorge syndrome, which was higher than in the healthy population.[94-96] Again, there was heterogeneity in autoimmune diseases, with autoimmune hypothyroidism, RA, monoarticular arthritis with a positive antinuclear antibody result, juvenile idiopathic arthritis, vitiligo, psoriasis, autoimmune neutropenia, idiopathic thrombopenic purpura (ITP), and autoimmune hemolytic anemia (AIHA) all being described.[94-96] The most commonly described autoimmune diseases were arthritis, hypothyroidism, and autoimmune cytopenias.

The reasons for the autoimmunity are not completely clear but might be related to a lack of thymic tissue resulting in incomplete negative selection or compromised AIRE expression.[97] A breakdown in peripheral tolerance has also been suggested as a possible explanation. $CD3^+CD4^+CD25^+$ regulatory T (Treg) cell numbers have been shown to be reduced in patients with partial DiGeorge syndrome, although there is no difference in the numbers between patients with and without autoimmune disease.[96,98]

Treatment of complete DiGeorge syndrome is difficult. HSCT has been used but does not work very well because in the absence of a thymus, T-cell differentiation is incomplete.[99] Thymic transplantations have been performed in a few centers.[100]

AIRE/autoimmunity–polyendocrinopathy–candidiasis–ectodermal dysplasia. Mutations in AIRE lead to autoimmunity–polyendocrinopathy–candidiasis–ectodermal dysplasia (APECED) syndrome, also known as autoimmune polyendocrine syndrome type 1, caused by breakdown of central T-cell tolerance in the thymus.[101,102]

The *AIRE* gene encodes a transcription factor involved in the maintenance of central tolerance. It is most strongly expressed in medullary thymic epithelial cells, with lower expression in thymic dendritic cells. AIRE appears to act as a transcriptional regulator by acting as a coactivator in a large transcriptional complex.[103] It enables expression of multiple tissue-specific antigens on the medullary thymic epithelial cells, allowing for clonal deletion of the autoreactive T lymphocytes that bind strongly to these self-antigens (a process known as negative selection). Its exact role in the maintenance of central T-cell tolerance is not fully worked out, but several mechanisms have been suggested. These include processing of self-antigens by the medullary thymic epithelial cells[104] but also thymocyte maturation, attraction of thymocytes to the correct location for negative selection, control of cross-presentation of antigens, and differentiation of thymic medullary epithelium.[105-108]

More than 70 mutations in *AIRE* have been identified in patients with APECED syndrome, and typically, the disease follows an autosomal recessive mode of inheritance, although autosomal dominant inheritance has also been described.[109-111] Patients with APECED syndrome present with variable patterns of autoimmune disease. Almost all organs and tissues can be affected by autoimmune disease, resulting in a broad range of clinical features. The diagnosis of APECED syndrome is dependent on the presence of 2 of 3 major symptoms: Addison disease, hypoparathyroidism, and/or chronic mucocutaneous candidiasis.[112] Only 1 of the major components is required if a sibling has APECED syndrome. Genetic analysis of *AIRE* can be helpful in atypical presentations. Additionally, the presence of anti-interferon antibodies is a useful biomarker and is included in the diagnostic criteria.

Other features that might develop include ectodermal dystrophy and other endocrine diseases, including hypergonadotrophic hypogonadism, autoimmune diabetes, and thyroid and pituitary disease. Gastrointestinal manifestations (chronic atrophic gastritis, pernicious anemia, and autoimmune hepatitis), skin disease (alopecia and vitiligo), keratoconjunctivitis, and asplenia have been described. Rarer symptoms include neurologic manifestations (chronic inflammatory demyelinating polyneuropathy and posterior reversible encephalopathy syndrome), tubulointerstitial nephritis, and autoimmune bronchiolitis.[113-115] Patients with dominant negative mutations in the PHD1 domain of AIRE have been found to present with later onset and milder organ-specific autoimmune disease compared to those with full-blown APECED syndrome.[111]

Despite this being a monogenic disorder, analysis of the clinical features and many gene mutations indicates a relatively poor genotype-phenotype correlation, suggesting that other factors are likely to play a role in the development of autoimmunity in patients with this condition.

Specific autoantibodies have been correlated to the various manifestations found in patients with APECED syndrome.[116] Of particular note, autoantibodies against the T_H17-related cytokines IL-22, IL-17A, and IL-17F have been found with chronic mucocutaneous candidiasis in patients with APECED syndrome, which might explain this particular susceptibility.[117,118]

Pathophysiologic pathway 4: Lack of peripheral tolerance (impaired Treg cell function) leads to autoimmunity

Forkhead box P3. Forkhead box P3 (FoxP3) is the lineage-defining transcription factor for naturally occurring $CD4^+CD25^+$ Treg cells. The gene *FOXP3* is encoded on the X-chromosome. Male subjects afflicted with a mutation in *FOXP3* have immunodysregulation, polyendocrinopathy and enteropathy, X-linked (IPEX) syndrome. Affected patients often experience a triad of autoimmune enteropathy, autoimmune endocrinopathy (particularly diabetes), and eczematous dermatitis early on in life.[119-121] Other autoimmune diseases, including cytopenias and liver and renal disease, can occur; severe atopic disease, such as eczema and food allergy, is often present with a marked

TABLE II. Features of monogenic SLE[27,69,145]

Mutated gene/protein	Locus	Inheritance	Clinical phenotype	References
TREX1/TREX1 (DNAse III)	3p21	AD	Chilblain lupus, intracerebral calcification, AGS	142, 156
DNAse1/DNase1	16p13	AD	SLE, Sjögren, high levels of anti-nucleosomal antibody	149, 150
DNAse1L3/DNase 1L3	3p14	AR	Familial early-onset SLE, ANA, anti-dsDNA antibody, ANCA	151
RNAseH2 (AGS2, AGS3, AGS4)/RNase H2 (degrades DNA:RNA hybrids)	A: chromosome 19, B: chromosome 13, C: chromosome 11	AR	AGS, SLE, pivotal for genome stability and DNA repair	145
AGS5/SAMHD1	20q11	AD	Chilblain lupus, mental retardation, intracerebral calcification, AGS	152, 153
ACP5/TRAP (= tartrate-resistant acid phosphatase; dephosphorylates OPN)	19p13	AR	Growth retardation, spondyloenchondrodysplasia (SPENCD), SLE, Sjögren, myositis, vitiligo, ANA, anti-dsDNA	154, 155

AD, Autosomal dominant; *AGS*, Aicardi-Goutieres syndrome; *ANCA*, anti-neutrophil cytoplasmic antibody; *AR*, autosomal recessive; *dsDNA*, double-stranded DNA; *OPN*, osteopontin.

peripheral eosinophilia and increased IgE levels. A variety of autoantibodies have also been identified in patients.[122]

Mutations in *FOXP3* result in immunopathogenesis of the disease. $CD4^+CD25^+$ Treg cells are critical for peripheral tolerance and prevention of autoimmunity,[123] and their absence leads to unchecked effector T-cell activation because of loss of dominant suppression. This observation in patients with IPEX syndrome taught us the necessity of Treg cells for the control of (immune-mediated) colitis and endocrinopathies, including insulin-dependent diabetes mellitus. Histology of the affected organs shows inflammatory infiltrates (although without any pathognomonic pattern),[124] emphasizing the role of Treg cells in the downregulation of inflammatory cells.

Because of the rarity of the condition, it is difficult to define the best treatment for IPEX syndrome, although HSCT and immunosuppressive therapies have both been used with variable success.

CD25 deficiency. The IL-2 receptor chain CD25 is the α chain of this trimeric cytokine receptor and a stimulation marker of T cells. CD25 is also constitutively expressed on naturally occurring Treg cells. Patients with autosomal recessive mutations in CD25 display a phenotype similar to IPEX syndrome with enteropathy, eczematous dermatitis, and autoimmunity, as well as a marked susceptibility to viral, bacterial, and fungal infections.[125-127]

Two of the case reports of CD25 deficiency included normal percentages of $Foxp3^+$ Treg cells. This suggests that CD25 signaling is not essential for Treg cell development. However, CD25 that is constitutively expressed on Treg cells allows them to competitively bind IL-2 and deprive effector cells of the cytokine, promoting their apoptosis.[128,129] IL-2 also appears to be essential for Treg cell regulatory function[130,131] and is required for the generation of inducible Treg cells.[132] It is likely that the absence of CD25 results in abrogation of these functions and might be responsible in part for the autoimmunity seen in patients with CD25 deficiency.

The absence of CD25 also highlights the role of IL-2 in generating effector T-cell populations for antimicrobial immunity. IL-2 plays a role in the development and expansion of T_H1 and T_H2 cells, generation of cytotoxic T cells, and activation of NK cells and in B-cell responses. Its diverse effects in the immune system explain the susceptibility to fungal, bacterial, and viral infections in patients with CD25 deficiency.

Cytotoxic T-lymphocyte antigen 4. Cytotoxic T-lymphocyte antigen 4 (CTLA4) is a member of the CD28 costimulatory family. *CD28*, *ICOS*, and *CTLA4* reside very close together on a tight stretch on chromosome 2q, suggesting that these genes developed from gene duplication events. In contrast to CD28 and ICOS, however, CTLA4 downregulates T-cell activation. Compared with CD28, CTLA4 has a higher affinity and avidity for the B7 molecules (CD80 and CD86) and hence effectively competes with CD28 for their binding. Once CTLA4 has bound to the B7 molecules, it captures these molecules from the antigen-presenting cell (APC) surfaces in a process called trans-endocytosis. Therefore, CTLA4-mediated transendocytosis renders APCs devoid of immune-activating B7 molecules, effectively downregulating the immune response. CTLA4 is constitutively expressed on Treg cells, demonstrating that CTLA4 is one of the important molecules by which Treg cells exert their immune suppression. In 2014, 3 reports[133-135] have described that if the human immune system is haploinsufficient in CTLA4 or *CTLA4* has mutations in the ligand-binding domain or in the CTLA4 dimerization domain, CTLA4-mediated immune downregulation is insufficient and an immune activation syndrome will develop. CTLA4 deficiency is characterized by the presence of multiple autoimmune lymphocytic organ disorders, such as ITP, AIHA, inflammatory bowel disease, granulomatous lymphocytic interstitial lung disease, lymphocytic encephalitis, and lymphoproliferation. Not surprisingly, this immune dysregulation leads to an increase of effector T-cell counts and a decrease in B-cell counts and hypogammaglobulinemia. Whether this is through infiltration of activated T cells into the B cell's bone marrow niche or whether overstimulation of B cells (through CD28 binding to the B7 molecules) directly kills B cells is still a matter of current research.

LPS-responsive vesicle trafficking, beach and anchor containing protein. The LPS-responsive vesicle trafficking, beach and anchor containing protein (LRBA) is a large (319-kDa) multidomain protein with poorly understood functions belonging to the BEACH-WD40 protein family.[136] LRBA has been shown to be expressed in activated murine B cells and macrophages. The subcellular location of LRBA at the plasma membrane, in vesicles, in the trans-Golgi, in the endoplasmic reticulum (ER), and in lysosomes suggests that LRBA functions as an anchor or adapter protein to direct proteins to membranes and organelles.[136,137]

By analyzing the genetic origins of early-onset antibody deficiencies in infants, a subgroup of 5 patients carrying homozygous mutations in *LRBA* was identified.[138] These mutations caused an immune dysregulation syndrome characterized by

inflammatory bowel disease, hypogammaglobulinemia, autoaggressive infiltrative lung disorder, and recurrent infections. Infections affected the upper respiratory tract and led to recurrent pneumonia and bronchiectasis in all patients. All patients had immune dysregulation, manifesting as autoimmune enteropathy, autoimmune cytopenias, granulomatous lymphocytic interstitial lung disease, diabetes, or autoimmune hepatitis.[139] Studying lymphocyte subsets in LRBA-deficient subjects revealed that not only were the switched memory B-cell compartment reduced and plasmablasts absent, but also numbers of Treg cells were greatly reduced.[140] In addition to the low prevalence of Treg cells, their CTLA4 surface expression (characteristic for Treg cells, see above) was reduced. This finding and the observation that treatment of these patients with the fusion protein CTLA4-Fc (abatacept) ameliorated their lung disease prompted Lo et al[141] to study the interaction of LRBA with CTLA4, which constantly shuttles from the membrane to the cytosol and back to the surface. The authors were able to show that the tail of CTLA4 binds to the BEACH domain of LRBA, linking CTLA4 function to intact LRBA expression and possibly explaining the similarity of the phenotypes.[141] Hence, as in those with CTLA4 deficiency, patients with deleterious biallelic mutations in LRBA lack proper CTLA4 function, have impaired Treg cell function, and have autoimmune conditions.

Pathophysiologic pathway 5: An increased type I interferon signature leads to autoimmunity

Recent genomic studies in patients with early-onset and familial SLE identified several new genes involved in IFN-α production. It started with the identification of mutations in genes encoding the intracellular nuclease TREX1 (the most abundant 3′ to 5′ DNA exonuclease), followed by RNase H2 (digests DNA:RNA hybrids) and SAMHD1 (a putative nuclease), all causing the Aicardi-Goutieres syndrome in children.[41,43,142-145] Aicardi-Goutieres syndrome mimics an intrauterine viral infection with high intracranial INF-α levels, calcification of the basal ganglia, mental retardation, seizures, and gradual development of an SLE-like phenotype. *TREX1* mutations are found in 0.5% to 2.7% of large SLE cohorts. Because these mutations are absent in control subjects, they represent the most frequent form of monogenic SLE. *TREX1* mutations cause impaired degradation of intracellular cytosolic DNA. The risk allele is associated with neurologic complications (seizures), particularly in patients of European descent,[43,142,144,146,147] and a *TREX1* single nucleotide polymorphism shows a strong association with anti-nuclear ribonucleoprotein autoantibodies.[144] *Trex1* knockout mice produce high levels of IFN-α and a lethal inflammatory myositis with anti-nuclear antibodies. *Trex1* knockout mice lacking the type I interferon receptor are protected against this pathology.[148] Table II summarizes the main Mendelian forms of SLE involving impaired intracellular DNA/RNA degradation.[27,69,142,145,149-156]

Mutations in *STAT1*. STAT1 is a member of the STAT family of transcription factors and forms part of the Janus kinase/STAT signaling pathway downstream of cytokine receptors. STAT1 is critical for signal transduction from both type I (IFN-α and IFN-β) and type II (IFN-γ) interferons. IFN-γ stimulation results in phosphorylation and homodimerization of STAT1, which then translocates to the nucleus and upregulates IFN-γ–regulated genes. Stimulation by IFN-α or IFN-β results in formation of STAT1 homodimers, as well as a heterotrimer comprising STAT1, STAT2 and p48 (ISGF3G).

STAT1 deficiency has been described either as an autosomal dominant disease affecting IFN-γ production alone, resulting in susceptibility to mycobacterial infection,[157,158] or an autosomal recessive disorder resulting in deficiency of both the type I and II interferons with susceptibility to both mycobacterial and viral disease.[159,160]

STAT1 GOF mutations result in a different phenotype. This is a highly variable autosomal dominant disorder resulting in immunodeficiency and immune dysregulation. Patients typically present with chronic mucocutaneous candidiasis in childhood but also have variable susceptibility to bacterial, viral, fungal, and mycoplasma infections. Autoimmune diseases, including hypothyroidism, autoimmune diabetes, autoimmune hepatitis, enteropathy, ITP, and AIHA, can also be present. Some patients also have nonimmunologic features, including osteopenia, delayed puberty, and intracranial aneurysms.[161-164]

Increased STAT1 phosphorylation was detected in patients, along with a reduction in IL-17 and IL-22 levels, which was thought to account for the susceptibility to chronic mucocutaneous candidiasis.[162] One study showed initial hyperresponsiveness to IFN-γ stimulation, which became impaired on restimulation, suggesting that IFN-γ tachyphylaxis might be the main problem.[165] Treg cell numbers and function were found to be normal when checked.[164]

The pathogenesis of the autoimmune features in patients with this condition is not yet fully elucidated but might be due to increased IFN-α signaling (caused by STAT1 hyperactivity).[164]

Mutations in *STAT3*. STAT3 is another member of the STAT family of transcription factors and is upregulated in response to stimulation with various cytokines, including IL-5, IL-6, epidermal growth factor, leukemia inhibitory factor, ciliary neurotrophic factor, leptin, and IL-11. It is involved in the expression of multiple genes and has a role in various cell processes, including cell growth, apoptosis, and cell movement. Importantly, it plays a role in the differentiation of T_H17 helper cells, which are important in the development of autoimmune disease.

STAT3 deficiency has been shown to result in autosomal dominant hyper-IgE syndrome (also known as Job syndrome).[166,167] In contrast, STAT3 hyperactivity caused by germline GOF mutations has been identified, resulting in autoimmune disease.[168,169] Patients were identified in a cohort with early-onset diabetes and enteropathy[168] but also in a cohort with ALPS-like features, including lymphoproliferation, prominent autoimmune cytopenias, and motor deficiency.[169] Patients had childhood onset of autoimmune disease affecting multiple organs with neonatal autoimmune diabetes, autoimmune cytopenias affecting up to all 3 lineages, autoimmune enteropathy, and celiac disease, as well as hypothyroidism and autoimmune arthritis. Other features included short stature, eczema, dental abnormalities, and delayed puberty. Some patients also had recurrent infections and hypogammaglobulinemia.

The *STAT3* GOF mutations result in increased STAT3 activity, impaired cytokine-induced phosphorylation of STAT5 and STAT1, and reduced Treg cell numbers with reduced CD25 expression. Some of these findings might be mediated through the STAT3 target, suppressor of cytokine signaling 3 (SOCS3), which negatively regulates other STAT molecules and can suppress Treg cell function.

TABLE III. Complement deficiencies and autoimmunity[22,69]

Deficient C′ component	Locus	Inheritance	Clinical phenotype	Infection susceptibility	References
C1q	1p36.3-p34.1	AR	>90% Risk for pediatric SLE, anti-dsDNA antibody, nephritis, NPSLE, skin rash	Encapsulated bacteria	18, 19, 174
C1r/C1s	12p13	AR	66% Risk for pediatric SLE, nephritis	Encapsulated bacteria	21
C4	6p21.3	AR	SLE multiorgan involvement, nephritis	Encapsulated bacteria	20
C2	6p21.3	AR	Mild SLE, photosensitivity, arthritis, mild or absent renal, neurologic, or pleuropericardial involvement	Pyogenic infections; encapsulated bacteria; streptococcal pneumonia, sepsis and meningitis	16, 17
C3	19q13	AR	Malar rash, photosensitivity, arthralgias, Raynaud's phenomenon	Recurrent pyogenic infections	176, 177
C5-C9	C5: 9p34 C6/7: 5p13 C8: 1q32 C9: 5p13	AR	Multiorgan involvement	*Neisseria* species infections	23, 178

AR, Autosomal recessive; *dsDNA*, double-stranded DNA; *NPSLE*, neuropsychiatric SLE.

Although not fully worked out, STAT3 hyperactivity is hypothesized to cause autoimmunity through impaired absolute Treg cell function caused by reduced STAT5 signaling, possibly as a result of increased SOCS3 activity.[169]

Two patients have been treated with HSCT: one survived with complete remission of autoimmune disease, and the other died with severe graft-versus-host disease and disseminated adenoviral infection. One patient had a treatment response to anti–IL-6 therapy with tocilizumab, suggesting that this might be a potential therapeutic option in the future.[169]

Somatic GOF mutations in *STAT3* have been found to be associated with lymphoproliferative tumors, aplastic anemia, and acquired myelodysplasia, but patients with these mutations are not reported to have autoimmunity.[170,171]

Pathophysiologic pathway 6: Defects of early complement components lead to autoimmunity

The rare complete primary deficiencies of the early C′ components C1q, C1r/s, C2, and C4 show a respective risk association for having SLE of 90%, 50%, 30%, and 70%.[23,27,172] In families with 2 or more patients with SLE, absent complement activity (50% hemolytic complement, CH50 = 0) is mainly found among those less than 18 years of age.[173,174] Early complement components, together with serum amyloid A and CRP, are acute-phase proteins with strong opsonizing potential for ICs, apoptotic cells, and carbohydrate-rich bacterial surfaces. Therefore early complement deficiencies go along with decreased clearance of ICs and apoptotic cell material, resulting in a higher probability that nuclear self-antigens induce INF-α in plasmacytoid dendritic cells and break self-tolerance in autoreactive T and B cells. Early complement components are also thought to play a pivotal role in negative selection of immature autoreactive B cells, whereas mature B and T cells receive activating signals, mainly through complement receptor 2 (CD21).[24,175] Table III summarizes some characteristics of complement deficiencies.[16-23,69,174-178]

Pathophysiologic pathway 7: Lack of appropriate removal of cell debris leads to autoimmunity

FcγRII and FcγIII polymorphisms, CRP, and complement receptor for C3bi (ITGAM). Removal of apoptotic and necrotic cell material is of the utmost importance for organ homeostasis, wound healing, and tissue remodeling. The acute-phase proteins CRP, C1q, and serum amyloid A, together with natural IgM and specific IgG antibodies, play a crucial role in opsonizing cell debris, making them palatable for phagocytes and accelerating their degradation. High INF-α levels and a polymorphic CRP variant (rs1200) inhibit the IL-6–induced CRP synthesis in patients with SLE, thereby reducing the opsonizing potential of a major acute-phase protein.[67]

The response of phagocytes to ICs is further modulated by receptors for the Fc region of IgG (FcγR), and alteration in their affinity and function has been associated with risk of autoimmune diseases, notably SLE.[65] The low-affinity FcγR locus is complex and contains regions of copy number variations that might alter receptor expression and reduce leukocyte phagocytic activity toward IgG-containing ICs. Interestingly, low copy numbers of the activating FcγRIIIB are associated with SLE in white and Chinese populations. The inhibitory FcγRIIB plays a critical role in negative regulation of B cells and macrophages. The I232T single nucleotide polymorphism of this receptor has been shown to abrogate the inhibitory potential of FcγRIIB and is strongly associated with SLE independent of the copy number variation in FcγRIIIB.[179] Interestingly, the I232T variant protects against malaria and is most prevalent in Africa and South Asia.[66] Among African Americans, the I232T allele is in part responsible for the higher frequency and severity of SLE.

The complement receptor for C3bi, which is composed of CD18 and CD11b *(ITGAM)*, is an important phagocytosis promoter on monocytes. The R77H variant of *ITGAM* is highly associated with SLE[54,180] and has recently been shown to exhibit a profoundly impaired phagocytosis of C3bi-coated erythrocytes and pathogens.[68]

Coatomer protein A. The correct and efficient sorting of proteins within a given cell is very important for cellular homeostasis and antigen presentation. In case of defects in protein trafficking, ER stress ensues, which can be overcome by an increase in the unfolded protein response or improved autophagy. Coatomer protein (COP) II shuttles proteins from the ER to the Golgi and from there to the plasma membrane, whereas COP-I facilitates retrograde transport. COPA is a subunit of COP-I and has been found to be mutated in patients with autoimmune lung disease and arthritis. The mutations act in a heterozygous autosomal dominant negative fashion and were shown to impair the binding of di-lysine–tagged proteins targeted

to be shuttled to the ER. The accumulation of these proteins led to an increased ER stress response in cells.

In the first report of this condition, about 70% of mutation carriers were affected by autoimmune features; investigators showed that disease had developed particularly in subjects who were unable to increase their autophagic flux. Patients had ANAs, anti-neutrophil cytoplasmic antibodies, and RF. Autoimmune features were limited to autoimmune lung disease (21/21 patients), arthritis (20/21), and autoimmune renal disease (4/21). Interestingly, the autoimmune lung disease was characterized by lymphocytic infiltration and germinal center formation.

ER stress and the unfolded protein response have previously been linked to autoimmunity[181-183]: ER stress increases the polarization of T cells toward the proinflammatory T_H17 cell subset, which is often found to be increased in patients with autoimmune conditions, such as spondyloarthritis, RA, SLE, multiple sclerosis, and sarcoidosis.[184-187] Supporting this line of pathogenesis, APCs from patients with mutations in *COPA* produced significantly more T_H17 cell–polarizing cytokines, such as IL-1β, IL-6, and IL-23, feeding into the above-described pathomechanism for autoimmunity by Treg cell/T_H17 cell imbalance.

Tripeptidyl peptidase II. In 6 patients (2 Palestinian, 2 Pakistani, and 2 Canadian First Nation siblings of consanguineous families) with early-onset Evans syndrome (5/6), respiratory infection with susceptibility to bacterial and viral pathogens (4/6), and developmental delay (4/4), homozygous deleterious mutations in tripeptidyl peptidase II *(TPP2)* were discovered.[188,189] The function of the peptidase TPP2 includes postproteasomal cytosolic protein modification and intracellular amino acid homeostasis. In the absence of TPP2, cellular glycolysis is severely reduced, which impedes certain aspects of T-cell activation and might contribute to the observed accelerated immune senescence.[189] All patients presented within the first 5 years of life with autoimmune cytopenia, which became increasingly treatment resistant in some of these patients. Reported laboratory data included intermittent hypergammaglobulinemia and mildly reduced T- and B-cell counts. The extended phenotyping revealed immune senescence in several patients. Diagnostic criteria cannot be proposed based on the described patients, but the differential diagnosis should be considered, especially in patients with an ALPS-like phenotype. Prognosis is affected by additional organ manifestations, such as stroke and hepatitis, which were reported in 1 patient each. The overall prognosis seems to be mixed with 1 patient who died at 3 years of age because of a treatment-resistant hemolytic crisis and 2 patients who had treatment-related deaths after stem cell and liver transplantation, respectively. Currently, 2 patients are alive a few months after HSCT, and 1 patient is in her teens and receiving immunosuppressive therapy.

Pathophysiologic pathway 8: Hyperactivation of lymphocytes leads to autoimmunity

Phosphoinositide 3-kinase δ and its regulatory subunit. Activating mutations in the phosphoinositide 3-kinase (PI3K) δ subunit, which is selectively expressed in leukocytes, and a splice site mutation in its regulatory subunit R1 lead to a complex immune dysregulation syndrome, including lymphoproliferation, susceptibility to upper respiratory tract infections most likely caused by hypogammaglobulinemia, and autoimmune cytopenias. Because these mutations act in a dominant fashion, only 2 years after its first description,[190-193] dozens of patients have already been identified.

PI3Kδ is activated downstream of CD28 ligation in T cells, leading to increased production of phosphatidylinositol (3,4,5)-trisphosphate, which in turn is the substrate of Akt. Increased Akt signaling increases mammalian target of rapamycin–serine/threonine kinase signaling, which blocks autophagy and stimulates T-cell proliferation and terminal differentiation, such as through phosphorylation of the S6 kinase. The cellular phenotype resembles CTLA4 deficiency. T cells are activated and terminally differentiated (with an increase in the effector memory RA T-cell compartment), leading to immune pathology and lymphoproliferation.

The humoral immune system is also impaired, leading to hypogammaglobulinemia. How the increased PI3Kδ signaling in B cells contributes to the observed B-cell phenotype is still a focus of research.

Current clinical trials are evaluating the safety and efficacy of inhaled and systemic PI3Kδ-specific inhibitors to ameliorate this monogenic condition.

Phospholipase Cγ2–associated antibody deficiency and immune dysregulation

Dominantly inherited cold-induced urticaria, antibody deficiency, susceptibility to infection, and autoimmunity caused by heterozygous in-frame deletions in the autoinhibitory domain of phospholipase Cγ2 (PLCγ2) have been identified in 27 patients from 3 families.[194] PLCγ2 is a signaling molecule in B cells, mast cells, and monocytes that is critical for the downstream activation of the BCR linking early signals to the activation of Ca^{2+} and canonical nuclear factor κB activation. Interestingly, the described mutations led to decreased BCR signaling at physiologic body temperatures but increased signaling at reduced temperatures, triggering histamine release in mast cells and subsequent cold urticaria in affected patients. All patients had urticaria after exposure to cold air, 75% had hypogammaglobulinemia of at least 1 isotype, and about half of the patients presented with recurrent infections. However, only 3 patients fulfilled the criteria for CVID, and in many patients increased IgE levels and symptomatic allergic disease was observed. Fifty-six percent presented with autoimmune phenomena, 7 patients had early-onset granulomatous disease, and 13 of 21 patients had detectable ANAs. Most patients had reduced numbers of total and switched memory B and NK cells. None of the markers are distinctive, and therefore diagnosis needs to be suspected based mainly on the clinical presentation. Functional tests exploring temperature-sensitive BCR signaling can be used in experienced laboratories to support the identified diagnosis. Management of the disorder is supportive. IgG replacement therapy should be implemented in symptomatic patients. No reports on the benefit of HSCT are available, although it could be curative.

One additional family has been described with an autosomal dominant inherited GOF mutation in *PLCG2* interfering with the autoinhibition caused by a Ser707Tyr substitution. The father and 1 daughter presented with recurrent blistering skin lesions, bronchiolitis, arthralgia, ocular inflammation, enterocolitis, and mild immunodeficiency (reduced IgA and IgM levels and lack of switched memory B cells).[195] Neither fulfilled the criteria for CVID, and no autoantibodies were detected. The manifestations were partly responsive to steroid and anti-inflammatory therapies.

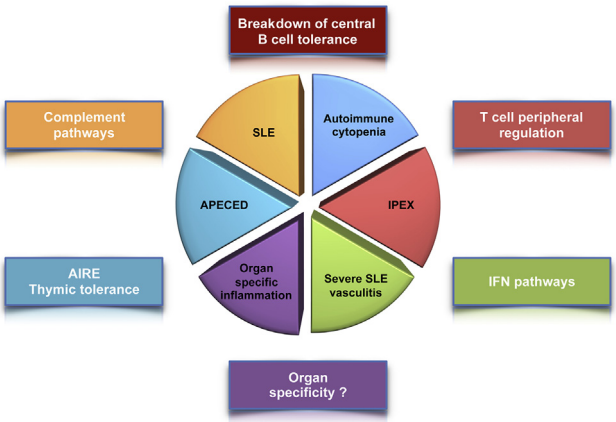

FIG 1. Monogenic defects and autoimmunity. Autoimmune expression of monogenic PIDs allows determination of major pathophysiologic pathways. Breakdown of central B-cell tolerance is required for the emergence of ANA-positive cells in patients with SLE, and deficiency of early complement components can be part of the pathogenesis. Treg cell dysregulation and/or activation of T cells, as seen in patients with CTLA4, LRBA, or FAS deficiency, are associated with autoimmune cytopenia. Type I interferon overproduction, as documented in TREX1- or stimulator of interferon genes *(STING)*–deficient patients, can lead to severe vasculitis. Mutations in *AIRE* or other defects of the thymus with impairment of negative T-cell selection through organ-specific autoantigen presentation leads to autoimmune endocrinopathies. Also, impairment in thymic Treg cell function, as in patients with IPEX syndrome, is associated with organ-specific autoimmunity. It is likely that organ characteristics influence the development of autoimmunity; another example is the exclusive joint and lung disease in patients with mutations in *COPA*.

Protein kinase Cδ deficiency. Currently, 5 patients from 3 families have been described with homozygous deleterious mutations in *PRKCD*, with no expression of protein kinase Cδ (PKCδ) in 2 patients and disturbed phosphorylation in the third family.[196-198] PKCδ is ubiquitously expressed, but targeted gene deletion of this regulatory protein kinase in mice has revealed an intrinsic dysregulation of B-cell tolerance as the predominant phenotype.[199] In the absence of PKCδ, tonic and antigen receptor–induced BCR signaling is increased, and an additional signalosome-independent pathway is activated, resulting in decreased apoptosis of activated B cells, possibly impaired tolerance induction and autoantibody-mediated immune disease. Likewise, all 5 patients with *PRKCD* deficiency presented before age 10 years with autoimmunity; there was renal involvement in 4 patients, with positive autoantibodies resembling early-onset SLE and lymphoproliferation, including hepatosplenomegaly. One patient presented with hypogammaglobulinemia. The immune phenotype was not remarkable except for the increase in $CD21^{low}$ B-cell counts and reduced switched memory B-cell counts.

Thus the rare diagnosis of *PRKCD* deficiency should be considered, especially in families with early-onset SLE and lymphoproliferation. The relevance of the hyperproliferative response to anti-IgM in the diagnosis of these patients is awaited. Management should include evaluating the humoral immune response and considering IgG replacement therapy when indicated. Currently, there is no targeted therapy for these patients, and immunosuppressive therapy follows the guidelines for patients with SLE. HSCT might be an option based on the observed predominant B-cell phenotype of the disease.

Pathophysiologic pathway 9: Impairment of B-lymphocyte function/BCR production leads to autoimmunity

Activation-induced cytidine deaminase. Activation-induced cytidine deaminase (AID), encoded by *AICDA*, is an RNA-editing deaminase. It is involved in the process of immunoglobulin class-switch recombination, somatic hypermutation, and gene conversion.

Autosomal recessive AID deficiency is one of a group of genetic mutations resulting in an immunoglobulin class-switch recombination deficiency. These disorders present with a hyper-IgM syndrome, with reduced IgG and IgA levels but increased or normal IgM levels. Patients with AID deficiency experience recurrent bacterial infections, mostly affecting the respiratory and gastrointestinal tract, although there is no increased susceptibility to opportunistic infections. Seventy-five percent of patients with AID deficiency have significant lymphadenopathy, with biopsy specimens showing follicular hyperplasia and giant germinal centers. More than a quarter of patients also have autoimmune disease, with AIHA, ITP, autoimmune hepatitis, arthritis, Crohn disease, and SLE all being described.[200] The autoimmune disease can be severe and can occur despite immunoglobulin replacement therapy; treatment with steroids, anti-CD20 mAbs, and immunosuppressive agents have been used.

Defects in both the central and peripheral B-cell tolerance checkpoints have been demonstrated.[201] The central checkpoint for B-cell tolerance occurs in the bone marrow between early immature and immature B cells and removes most clones expressing polyreactive antibodies. The peripheral checkpoint occurs between new emigrant and mature naive B cells and further removes B cells that are reactive against autoantigens not expressed in the bone marrow.

Patients with AID deficiency have both higher proportions of new emigrant/transitional B cells with an abnormal immunoglobulin repertoire and a high frequency of polyreactive antibodies and mature naive B cells that express autoreactive antibodies (including ANAs).[201] ANAs of the IgM isotype were also found in the serum of patients with AID deficiency. The role of AID in central B-cell tolerance is not certain, although somatic hypermutation and class-switch recombination are probably not involved because antibodies cloned from transitional B cells of both AID-deficient patients and healthy donors were of the IgM isotype and not somatically mutated. Control of peripheral B-cell checkpoints is even less understood, although T cells might play a role in this, and Treg cell counts have been shown to be decreased in patients with AID deficiency.[201] Serum BAFF levels are increased as well, and overexpression of BAFF in mice has been shown to result in autoimmune disease.[202]

The reasons for the development of autoimmunity in patients with AID deficiency remain not fully elucidated. The available data suggest that this could be due to a B cell–intrinsic defect with the lack of AID, resulting in autoreactive B cells being more resistant to apoptosis and increased BAFF levels promoting the expansion of these autoreactive cells. T-cell regulation might also be deficient, with reduced Treg cell numbers, and there are data showing that T cells transiently express AID.[203] Finally, T-cell/B-cell interaction can also be affected, such as with autoreactive B cells presenting antigen to autoreactive T cells.[200]

Different immune deficiencies can affect B-cell tolerance processes

TNFRSF13B mutations lead to transmembrane activator and CAML interactor (TACI) defects in patients with CVID and to an increased risk for autoimmune cytopenia and autoimmunity. TACI helps with class-switch recombination, plasma cell differentiation, and antibody production. Central B-cell tolerance has been shown to be defective in TACI-deficient patients, with a significant increase in autoreactive and nuclear-reactive new migrant B-cell clones. The increase in Hep-2–reactive B-cell numbers persists in the mature naive B-cell compartment, also demonstrating an impairment in peripheral B-cell tolerance in TACI-deficient patients.[204]

Dedicator of cytokinesis 8 *(DOCK8)* has been identified as a causative gene in patients with hyper-IgE syndrome. Thus it is associated with atopic manifestations, susceptibility to viral cutaneous infections, and impaired antibody responses. In addition, DOCK8-deficient patients can be affected by autoimmune manifestations, including AIHA, vasculitis, enteropathies, and dysthyroidism.[205-207] Central tolerance is preserved in DOCK8-deficient patients, and the frequency of autoreactive clones in new migrant B cells is similar to that in control subjects. However, DOCK8 impairment leads to an increased frequency of ANA-reactive mature naive B cells. This breakdown in peripheral B-cell tolerance is likely to be due to decreased Treg cell numbers and Treg cell suppressive activity.[208]

CONCLUSION

Recent advancements in immunologic and molecular detection methods, in particular next-generation sequencing, have led to identification of several different genetic defects associated with autoimmune phenotypes. Each monogenic defect described above interrupts the equilibrium of the immune system. From these gene defects in human subjects, we have learned and are still learning about the biological effects and roles of these immune receptors or proteins within the human immune system, as presented in Fig 1. Most importantly, this knowledge has already started to influence and change patient management, as described in this review.

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