

Advances in basic and clinical immunology in 2014

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Genetic identification of immunodeficiency syndromes has become more efficient with the availability of whole-exome sequencing, expediting the identification of relevant genes and complementing traditional linkage analysis and homozygosity mapping. New genes defects causing immunodeficiency include phosphoglucomutase 3 (*PGM3*), cytidine 5' triphosphate synthase 1 (*CTPS1*), nuclear factor κ B-inducing kinase (*NIK*), cytotoxic T lymphocyte-associated antigen 4 (*CTLA4*), B-cell chronic lymphocytic leukemia/lymphoma 10 (*BCL10*), phosphoinositide-3 kinase regulatory subunit 1 (*PIK3R1*), *IL21*, and Jagunal homolog 1 (*JAGN1*). New case reports expanded the clinical spectrum of gene defects. For example, a specific recombination-activating gene 1 variant protein with partial recombinant activity might produce Omenn syndrome or a common variable immunodeficiency phenotype. Central and peripheral B-cell tolerance was investigated in patients with several primary immunodeficiencies, including common variable immunodeficiency and Wiskott-Aldrich syndrome, to explain the occurrence of autoimmunity and inflammatory disorders. The role of IL-12 and IL-15 in the enhancement of natural killer cell activity was reported. Newborn screening for T-cell deficiency is being implemented in more states and is achieving its goal of defining the true incidence of severe combined immunodeficiency and providing early treatment that offers the highest survival for these patients. Definitive treatment of severe immunodeficiency with both hematopoietic stem cell transplantation and gene therapy was reported to be successful, with increasing definition of conditions needed for optimal outcomes. Progress in HIV infection is directed toward the development of an effective vaccine and the eradication of hidden latent virus reservoirs. (*J Allergy Clin Immunol* 2015;135:1132-41.)

Key words: Immunology, primary immunodeficiency, dedicator of cytokinesis 8, *HIV1*, recombination-activating gene 1, intravenous immunoglobulin, common variable immunodeficiency, severe combined immunodeficiency, newborn screening

Abbreviations used

ADA:	Adenosine deaminase
ApoE:	Apolipoprotein E
BCL10:	B-cell chronic lymphocytic leukemia/lymphoma 10
CARD:	Caspase recruitment domain
CGD:	Chronic granulomatous disease
CVID:	Common variable immunodeficiency
DOCK8:	Dedicator of cytokinesis 8
ERT:	Enzyme replacement therapy
GvHD:	Graft-versus-host disease
HSCT:	Hematopoietic stem cell transplantation
MALT1:	Mucosa-associated lymphoid tissue lymphoma translocation protein 1
MSD:	Matched sibling donor
NF- κ B:	Nuclear factor κ B
NK:	Natural killer
NLRC4:	NLR family, caspase recruitment domain containing 4
PAP:	Pulmonary alveolar proteinosis
PC:	Plasma cell
PIDTC:	Primary Immune Deficiency Treatment Consortium
RAG:	Recombination-activating gene
SCID:	Severe combined immunodeficiency
SIFD:	Sideroblastic anemia, periodic fever, B-cell deficiency, and developmental delay
STAT:	Signal transducer and activator of transcription
TCR:	T-cell receptor
TLR:	Toll-like receptor
Treg:	Regulatory T
URD:	Matched unrelated donor
WES:	Whole-exome sequencing

In 2014, several reports studied immunodeficiency syndromes that have in common an impaired signal transduction needed for nuclear factor κ B (NF- κ B) activation. These molecular defects result in defective B- and T-cell function with variable clinical manifestations. Turvey et al¹ discussed the pathways in NF- κ B activation by the caspase recruitment domain family (*CARD11*)–B-cell chronic lymphocytic leukemia/lymphoma 10 (*BCL10*)–mucosa-associated lymphoid tissue lymphoma translocation protein 1 (*MALT1*) signalosome complex. They also reviewed the features of *CARD11-BCL10-MALT1* complex defect syndromes and postulated how the study of these gene defects has resulted in identification of novel potential pharmacologic targets for inflammatory diseases and lymphoreticular malignancies.

An example of the diverse clinical presentation associated with genetic defects of NF- κ B signaling is the report by McKinnon et al² of a patient with eczema, skin infections, chronic cheilitis, inflammatory bowel disease, and osteoporosis in whom whole-exome sequencing (WES) revealed a missense mutation in *MALT1*. Findings included absent mitogen and antigen-induced T-cell responses, B-cell lymphopenia, increased IgE levels, and normal IgG levels and antibody responses.

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TABLE I. Selected advances in B-cell function and immunologic tolerance

- Sphingosine-1-phosphate receptors in human B cells regulate lymphocyte traffic and migration and are modulated by WASP, LRBA, and DOCK8 proteins.⁶
- Kinetics of CD40L/IL-21 activation of B cells was modeled by using chip cytometry and RNA microarray, integrating membrane receptors, signal transduction, class-switch recombination, DNA repair, and cell cycle-related genes.⁷
- Somatic hypermutation in the S region occurs before class-switch recombination and depends on CD40L, uracil-DNA glycosylase, and activation-induced deaminase.⁸
- CD40L and BCR signaling pathways are complementary to eliminate autoreactive clones and provide a balanced B-cell repertoire.⁹
- *BLNK* plays an essential role in pre-B cell differentiation and normal use of IgVκ genes.¹⁰
- CDR3 and junctional diversity were less in patients with Omenn syndrome because of *RAG* mutations than in patients with atypical DiGeorge syndrome or ZAP70.¹¹
- Patients with WAS show an expansion of naive-like CD19^{hi}21^{lo} B cells thought to be autoreactive cells and a decreased proportion of memory CD27⁺ B cells that are more pronounced in those with autoimmunity.¹²
- B cells from patients with X-linked lymphoproliferative disease are enriched in autoreactive clones.¹³
- Defective B-cell tolerance and Treg cells were also described in DOCK8-deficient patients with increased autoantibody levels.¹⁴
- B cells in patients with CVID showed high constitutive extracellular signal-regulated kinase phosphorylation with defective BCR responses, which is in agreement with the anergic nature of B cells.¹⁵
- A BAFFR variant with less affinity is present in 10% of patients with CVID, suggesting it might be a risk factor for the condition.¹⁶

BAFFR, B cell-activating factor receptor; BCR, B-cell receptor; *BLNK*, B-cell linker; *CD40L*, CD40 ligand; *LRBA*, LPS-responsive, beige-like anchor protein; WAS, Wiskott-Aldrich syndrome; WASP, Wiskott-Aldrich protein; *ZAP70*, ζ Chain-associated protein of 70 kDa.

Hannah and Etzioni³ reviewed the molecular pathogenesis and clinical and immunologic features of the rare MHC class I and II deficiencies. MHC class II deficiencies commonly present as a combined immunodeficiency, whereas patients with MHC class I deficiency present with chronic lung disease, inflammatory skin disease, and vasculitis.

Lessons in the study of natural killer (NK) cells included the demonstration by Simhadri et al⁴ of the need for IL-12 in the generation of NK cells with enhanced function. Another regulator of NK cell activity reported was microRNA-150. Kim et al⁵ showed that microRNA-150 binds to the 3' regions of both the mouse and human perforin-1 (*PRF1*) gene, inhibiting its transcription. IL-15 activation decreased production of microRNA-150, followed by increased perforin expression and NK cell lytic activity.

Mechanisms of B-cell function and central and peripheral tolerance were the object of studies that took advantage of the availability of patients with monogenic diseases, providing explanations for the immune dysregulation that occurs in patients with primary immunodeficiencies (Table I).⁶⁻¹⁶

Dhanju et al¹⁷ established a mouse model of adenosine deaminase (ADA) deficiency to study pulmonary alveolar proteinosis (PAP). PAP was detected early in these mice, and autoantibodies were ruled out as a cause. There was increased apoptosis of alveolar macrophages and impaired surfactant clearance. ADA enzyme supplementation prevented the development of PAP.

Buckner et al¹⁸ investigated plasma cells (PCs) in blood and the colon in patients with conditions that commonly present with noninfectious organ inflammation, such as Crohn disease. Although IgA-secreting PCs were predominant in the gut of healthy subjects, numbers of IgG-secreting PCs were increased in those with intestinal inflammation. The chemokine CXCR4 was strongly expressed in these cells. The authors suggest that CXCR4⁺ IgG-secreting PCs might be markers of intestinal inflammation.

Dijkstra et al¹⁹ studied lymphocytes from cord blood and from infants up to 1 year of age. They showed that regulatory T (Treg) cells can be induced at any age and that T_H17 cells can be induced starting at age 3 months. These findings suggest that development of tolerance and autoimmunity starts at an early age.

The effect of thymectomy in infants undergoing heart defect repair was explored by Schadenberg et al.²⁰ In agreement with previous reports, they found decreased absolute CD4 T-cell subset counts compared with those in age-matched healthy control subjects. Activated Treg cell counts (CD45RO⁺FoxP3^{high}) were increased, whereas naive Treg cell counts (CD45RO⁺FoxP3^{low}) were decreased. Increased Ki-67 expression in Treg cells indicated increased proliferation, compensating for loss of thymic output. Similar changes in Treg cell counts have been associated with autoimmunity, and therefore the authors recommended long-term evaluation of thymectomized patients and preservation of thymic tissue when feasible.

Apolipoprotein E (ApoE) is expressed in monocytes and macrophages and involved in serum lipoprotein metabolism. There are 3 human isoforms: ApoE2, ApoE3, and ApoE4. ApoE4 has been associated with cardiovascular disease, Alzheimer disease, and inflammatory disorders. Gale et al²¹ performed *in vitro* experiments demonstrating that leukocytes from subjects carrying the ApoE3/ApoE4 phenotype expressed higher cytokines levels after stimulation with Toll-like receptor (TLR) 2, TLR4, and TLR5 agonists compared with cells from subjects carrying the ApoE3/ApoE3 phenotype. In a related observation monocyte-derived dendritic cells from Bruton tyrosine kinase-deficient patients showed differential responses to TLR agonists. Lougaris et al²² showed impaired expression of activation markers and decreased secretion of IL-6, IL-12, and TNF-α in dendritic cells on stimulation with the TLR9 agonist CpG but not LPS.

NEW PRIMARY IMMUNODEFICIENCY GENES

For further information on new primary immunodeficiency genes, see Table II.²³⁻⁴²

Zhang et al,²³ Stray-Pedersen et al,²⁴ and Sassi et al²⁵ reported biallelic mutations in phosphoglucomutase 3 (*PGM3*) in patients with increased IgE levels, severe atopy, autoimmunity, developmental delay, and frequent skin and respiratory tract infections. Aberrant glycosylation in leukocytes was shown, with leukopenia and predominantly T_H2 and T_H17 cytokine secretion.

IL21 deleterious mutations were found in 3 siblings with early-onset inflammatory bowel disease and severe respiratory

TABLE II. Novel gene defects as a cause of primary immunodeficiencies

Gene	Inheritance	Immunodeficiency syndrome	References
<i>PGM3</i>	Autosomal recessive	Atopy, autoimmunity, frequent infection, developmental delay	Zhang et al, ²³ Stray-Pedersen et al, ²⁴ Sassi et al ²⁵
<i>IL21</i>	Autosomal recessive	Inflammatory bowel disease, hypogammaglobulinemia	Salzer et al ²⁶
<i>CTLA4</i>	Autosomal dominant	CVID, ALPS	Schubert et al, ²⁷ Kuehn et al ²⁸
<i>PIK3R1</i>	Autosomal recessive	Hypogammaglobulinemia, frequent infections	Deau et al, ²⁹ Lucas et al ³⁰
<i>MAP3K14</i>	Autosomal recessive	Combined immunodeficiency	Willmann et al ³¹
<i>BCL10</i>	Autosomal recessive	Combined immunodeficiency	Torres et al ³²
<i>CTPS1</i>	Autosomal recessive	Combined immunodeficiency	Martin et al ³³
<i>JAGN1</i>	Autosomal recessive	Congenital neutropenia	Boztug et al ³⁴
<i>TMEM173</i>	Autosomal dominant	Skin and pulmonary vasculopathy, early-onset inflammation	Liu et al ³⁵
<i>NLRC4</i>	Autosomal dominant	Fever, rash, arthralgia induced by cold	Kitamura et al ³⁶
		Periodic fever, macrophage activation syndrome	Romberg et al, ³⁷ Canna et al ³⁸
<i>CECR1</i>	Autosomal recessive	Polyarteritis nodosa and hypogammaglobulinemia	Zhou et al, ³⁹ Navon-Elkan et al ⁴⁰
		Livedo reticularis and neurovascular disease (Sneddon syndrome)	Bras et al ⁴¹
<i>TNRT1</i>	Autosomal recessive	SIFD	Chakraborty et al ⁴²

ALPS, Autoimmune lymphoproliferative syndrome; *CECR1*, cat eye syndrome chromosome region, candidate 1; *CTLA4*, cytotoxic T lymphocyte-associated antigen 4; *CTPS1*, cytidine 5' triphosphate synthase 1; *JAGN1*, Jagunal homolog 1; *MAP3K14*, mitogen-activated protein kinase kinase kinase 14; *NLRC4*, NLR family CARD domain-containing 4; *PGM3*, phosphoglucomutase 3; *PIK3R1*, phosphoinositide-3 kinase regulatory subunit 1; *TMEM173*, transmembrane protein 173; *TNRT1*, transfer RNA nucleotidyltransferase, CCA adding, candidate 1.

tract infections associated with B-cell lymphopenia, low IgG levels, and poor antibody responses.²⁶ Immunologic studies showed that loss of IL-21 signal interfered with B-cell development. Schubert et al²⁷ and Kuehn et al²⁸ identified heterozygous mutations in the cytotoxic T lymphocyte-associated antigen 4 (*CTLA4*) gene, causing a common variable immunodeficiency (CVID)-like syndrome with incomplete penetrance. Some patients had a clinical presentation that resembled that of autoimmune lymphoproliferative syndrome.

Gain-of-function mutations in the phosphoinositide 3-kinase signaling pathway result in a CVID-like syndrome. Deau and collaborators²⁹ and Lucas et al³⁰ independently reported that loss of the p110 binding domain of the inhibitory protein phosphoinositide-3 kinase regulatory subunit 1 also results in increased phosphorylation of the downstream AKT kinase, resulting in decreased B- and T-cell activation and proliferation.

Homozygosity mapping and WES were used to identify deleterious mutations in the mitogen-activated protein kinase kinase kinase 14 (*MAP3K14*) gene, which encodes the NF- κ B-inducing kinase (NIK), in 2 patients from a consanguineous family who presented with frequent viral and bacterial infections.³¹ Immunologic findings were consistent with impaired NF- κ B signaling, including defective B-cell development and normal T-cell proliferation to mitogens but not to antigens.

Torres et al³² reported the case of a 3-year-old boy with chronic and recurrent gastroenteritis and respiratory tract infections. T and B cells were predominantly naive, with conserved lymphocyte proliferation to mitogens but decreased T-cell receptor (TCR) stimulation. NF- κ B-mediated functions were impaired.

WES analysis uncovered a homozygous mutation in *BCL10*, resulting in absent protein expression. Mutations in cytidine 5' phosphate synthase 1 (*CTPS1*) were found in 5 families with immunodeficiency characterized by severe chronic viral and bacterial infections associated with lack of T-cell proliferative responses, although with conserved TCR signal activation pathways.³³ These findings underscore the importance of *de novo* cytidine 5' phosphate (CTP) synthesis in DNA replication in lymphocytes.

Boztug et al³⁴ reported 14 patients with congenital neutropenia as a result of homozygous mutations in Jagunal homolog 1

(*JAGN1*). *JAGN1* was shown to be essential for neutrophil differentiation, granulocyte colony-stimulating factor signaling and apoptosis regulation.

Defective genes were reported in patients with autoinflammatory syndromes. Liu et al³⁵ found heterozygous activating mutations in *TMEM173*, which encodes the stimulator of interferon genes (STING), in 5 unrelated children presenting with early-onset systemic autoinflammation and skin and lung vasculopathy. The mutant STING protein caused increased production of IFN- β and constitutive signal transducer and activator of transcription (STAT) 1 phosphorylation.

Kitamura et al³⁶ described a heterozygous missense mutation in the NLR family, caspase recruitment domain containing 4 (*NLRC4*) gene in family members with familial cold autoinflammatory syndrome; Romberg et al³⁷ and Canna et al³⁸ reported other patients with missense mutations in *NLRC4* associated with periodic fevers, macrophage activation syndrome, and early-onset enterocolitis. The mutations affected *NLRC4* oligomerization and resulted in hyperactivation of the caspase 1, apoptosis-related cysteine peptidase (*CASP1*) gene with increased secretion of IL-1 β .

Mutations in 2 genes were associated with syndromes involving immunodeficiency in addition to autoinflammation. Early-onset polyarteritis nodosa and hypogammaglobulinemia were found by 3 independent groups³⁹⁻⁴¹ to result from deleterious mutations in the cat eye syndrome chromosome region candidate 1 (*CECR1*). This gene encodes ADA2, levels of which were reduced in the studied patients. ADA2 was found to be essential for the development of endothelial cells and monocyte/macrophage and B-cell differentiation.

Chakraborty et al⁴² used single nucleotide polymorphism mapping and WES to identify defects in transfer RNA nucleotidyltransferase, CCA adding, 1 (*TNRT1*) as cause of a syndrome consisting of sideroblastic anemia, periodic fever, B-cell deficiency, and developmental delay (SIFD). In addition to severe anemia, patients with SIFD present with profound B-cell lymphopenia, variable progressive hypogammaglobulinemia, and defective antibody responses. The authors suggest that the essential role of *TNRT1* in protein expression explains the phenotype involving different cell types.

TABLE III. New immunodeficiency phenotypes for known gene defects

Gene mutated	Associated immunodeficiency	New description	References
<i>TTC7A</i>	Multiple intestinal atresias with immunodeficiency	Early-onset enteropathy, autoimmunity	Lemoine et al ⁴³
<i>STAT1</i>	Susceptibility to mycobacterial, bacterial infections	Combined immunodeficiency, autoimmunity, endocrinopathy	Sharfe et al ⁴⁴
<i>NFKB2</i>	CVID	B-cell lymphopenia, agammaglobulinemia	Lee et al ⁴⁵
<i>IKBKB</i>	Combined immunodeficiency	EDA-ID	Burns et al ⁴⁶
<i>XIAP</i>	X-linked lymphoproliferative disease	Crohn disease	Aguilar et al ⁴⁷
<i>DOCK8</i>	CID	Severe atopic disease and VZV neurologic vasculopathy	Sabry et al ⁴⁹
<i>GATA2</i>	Monocytopenia, myelodysplasia	CVID	Chou et al ⁵⁰
<i>CD3D</i>	SCID	CID with CD4 $\gamma\delta$ T cells	Garcillán et al ⁵¹
<i>ITK</i>	EBV-induced lymphoproliferative disease	CID	Serwas et al ⁵²
<i>PIK3CD</i>	Respiratory tract infections, antibody deficiencies	EBV, CMV-induced lymphadenopathy, respiratory tract infection	Lucas et al ⁵³
<i>RAG1</i>	SCID, Omenn syndrome	Autoimmunity, CVID	Chen et al, ⁵⁵ Abolhassani et al ⁵⁶

CD3D, CD3 antigen δ subunit; *CID*, combined immunodeficiency; *EDA-ID*, ectodermal dysplasia associated to immunodeficiency; *GATA2*, GATA-binding protein 2; *IKBKB*, inhibitor of kappa light chain gene enhancer in B cells kinase β ; *ITK*, inducible tyrosine kinase; *NFKB2*, NF- κ B subunit 2; *PIK3CD* phosphatidylinositol-3 kinase, catalytic δ ; *TTC7A*, tetratricopeptide repeat domain containing 7A; *VZV*, varicella zoster virus; *XIAP*, X-linked inhibitor of apoptosis.

PRIMARY IMMUNODEFICIENCIES: NEW PHENOTYPES FOR KNOWN GENE DEFECTS

Taking advantage of the current genomic sequencing techniques, several articles described gene defects associated with clinical syndromes that were different from original descriptions (Table III).⁴³⁻⁵⁹ These reports underscore the importance of molecular diagnosis, as well as the spectrum of clinical and immunologic manifestations that might result from defects in a single gene. An example of such phenotypic heterogeneity is represented by recombination-activating gene 1 (*RAG1*) and *RAG2* defects, which are commonly associated with severe combined immunodeficiency (SCID) and Omenn syndrome. A variety of other clinical and immunologic phenotypes have been recently described, ranging from granulomatous lesions to autoimmunity, CVID-like features, or hyper-IgM syndrome. In some cases a variable degree of impairment of T- and B-cell development and function has been reported, even in patients sharing the same mutations.⁵⁴⁻⁵⁹

Lee et al⁵⁸ analyzed 79 *RAG1* variants and found correlation between *RAG1 in vitro* recombination activity and severity of clinical presentation. This correlation was not absolute, suggesting the influence of environmental factors as disease modifiers. This hypothesis was supported by IJspeert et al,⁵⁹ who presented 22 patients with *RAG* mutations resulting in similar residual recombination activity but a variable clinical phenotype.

In patients with leukocyte adhesion type III, van de Vijver et al⁴⁸ reported normal and impaired neutrophil adhesion after formyl-methionyl-leucyl-phenylalanine stimulation measured in the same patient over time and in 6 patients with absent kindlin-3 expression. Neutrophil adhesion of these patients occurs consistently after strong stimuli, such as phorbol myristate, in contrast to the variable response to TLR agonists.

PRIMARY IMMUNODEFICIENCIES: DIAGNOSIS AND CLINICAL FEATURES

Platt et al⁶⁰ classified modern strategies for the molecular diagnosis of primary immunodeficiencies into 3 categories: educated guesses, similarity to clinical phenotypes and animal

models, and unbiased genetic approaches. The authors examined hurdles for the genetic approaches, such as detection of deleterious mutations in noncoding regions, the heterozygous nature of autosomal dominant diseases, and identification of chromosomal abnormalities (deletions and duplications) causing disease. Finally, they discussed considering incomplete penetrance when family members with identical gene variants are clinically discordant.

A novel diagnostic approach based on next-generation gene sequencing was presented by Nijman et al.⁶¹ They simultaneously analyzed 306 genes and successfully confirmed genetic lesions in patients with immunodeficiencies, including exonic deletions. An important drawback was the limitation to examine genes with high guanosine-cytosine content, such as *IKBKG*.

Meazza et al⁶² measured NK cell cytotoxicity enhanced with anti-2B4 antibody using CD107a as a marker of NK cell degranulation. 2B4 is an NK cell coreceptor that recruits activating signals by binding signaling lymphocyte activation molecule-associated protein (SAP), which is mutated in X-linked lymphoproliferative disease type 1 (XLP1). The authors recommend this test to screen patients who are candidates for gene sequencing for the diagnosis of XLP1. Another method complementary to genetic testing was developed by Pai et al⁶³ for the diagnosis of dedicator of cytokinesis 8 (*DOCK8*) deficiency by using flow cytometry detection of *DOCK8* protein expression.

Magnani et al⁶⁴ reported the frequency of inflammatory episodes in a French cohort of 98 patients with chronic granulomatous disease (CGD). Sixty-eight patients had at least 1 inflammatory event, which occurred twice more often in patients with X-linked CGD than in patients with autosomal recessive forms. A survey of 2212 patients with CVID collected by the European Society for Immunodeficiencies Registry Working Party⁶⁵ indicated that the disease had an early onset in 34% of the patients, which is higher than previously reported. Enteropathy, autoimmunity, and granulomas were commonly associated in individual patients. Gao et al⁶⁶ noted a significant decrease in invariant natural killer T-cell counts in patients with CVID who also had decreased switched memory B cells. In 6 patients with CVID-associated lung disease, Maglione et al⁶⁷ described lymphoid hyperplasia resembling germinal centers in

lung granulomas. The authors discussed treatments using immunomodulatory therapy targeting lymphoproliferation in lung sites. Kracker et al⁶⁸ identified 8 patients with *PIK3CD* gain-of-function mutations in a cohort of 139 patients with an unknown antibody deficiency.

Rose et al⁶⁹ reported systemic infection by *Mycobacterium intracellulare* in a patient with IFN- γ receptor 1 (*IFNGR1*) deficiency. They reviewed the association of mycobacterial infections in infancy and mutations in genes involved in the IFN- γ response, advising genetic screening in patients with pulmonary mycobacterial infections after HIV and cystic fibrosis have been excluded.

Jing et al⁷⁰ investigated the discrepancy of DOCK8 protein expression in T cells in patients whose *DOCK8* mutations were predicted to abrogate protein expression. They identified 17 of 34 patients with somatic repair in T cells, including gene mutation site reversion, second site mutation, gene conversion, and intragenic cross-over. Although patients with DOCK8 deficiency and somatic mosaicism remained susceptible to infections, eosinophilia and the severity of allergic diseases were less frequent than that in patients without somatic reversion. Frequent somatic reversion can be explained by the location of *DOCK8* in a recombination hotspot region; moreover, selective advantage for DOCK8-expressing cells might facilitate emergence of somatic reversion within the T-cell lineage. DOCK8 deficiency without severe infections was reported by Ruiz-Garcia et al⁷¹ in patients who presented with deletion of exons 2 to 8 in one allele and a splicing mutation in exon 17 in the other allele.

OPPORTUNISTIC FUNGAL INFECTIONS AND PRIMARY IMMUNODEFICIENCIES

Frans et al⁷² reported chronic mucocutaneous candidiasis, enamel defects and delayed dental shedding, recurrent infections, esophageal dysmotility, and diaphragmatic hernia in a patient with a gain-of-function mutation in *STAT1*. Lee et al⁷³ reported 3 patients with *STAT1* gain-of-function mutations who had systemic mycosis caused by *Penicillium marneffei*, and Kumar et al⁷⁴ reported a patient with a *STAT1* gain-of-function mutation who had systemic mucormycosis without trauma or another predisposition condition. Thus susceptibility to systemic mycosis should be included in the presentation of STAT1 gain-of-function disease. Wang et al⁷⁵ described 4 CARD9-deficient patients who had persistent fungal infections on their cheeks caused by *Phialophora verrucosa*, but not candidiasis, as originally described in patients with CARD9 deficiency.

NEWBORN SCREENING OF T-CELL DEFICIENCIES

The first nationwide report of newborn screening of T-cell deficiencies involved 11 state programs and a total of 3,080,083 newborns.⁷⁶ Fifty-two cases of typical SCID, leaky SCID, and Omenn syndrome were detected, defining the incidence of these conditions to occur 1 in 58,000 infants. Forty-five (92%) of 49 patients who received hematopoietic stem cell transplantation (HSCT), gene therapy, or ADA enzyme replacement are alive, strongly supporting early diagnosis to optimize the chance of survival.

La Marca et al⁷⁷ proposed the use of tandem mass spectrometry for the diagnosis of purine nucleoside phosphorylase deficiency

using neonatal dried blood spots. Purine nucleoside phosphorylase deficiency might not be detected by using the T-cell receptor excision circle assay, which is used for screening of T-cell deficiency. Considering the high frequency of familial hemophagocytic lymphohistiocytosis caused by Unc-13 homolog D (*C elegans* [*UNC13D*]) defects in Scandinavian countries, Borte et al⁷⁸ developed an assay that incorporates the detection of the prevalent *UNC13D* gene inversion together with the detection of T-cell receptor excision circles and kappa-deleting recombination excision circles in dried blood spot samples.

Mandala et al⁷⁹ stressed the importance of establishing local reference values of lymphocyte subsets. They reported significant differences of normal ranges of T- and B-cell counts in healthy subjects from 3 different countries: Thailand, Malawi, and the United States. Those differences were particularly noted in the first year of life, possibly secondary to genetic and environmental factors.

PRIMARY IMMUNODEFICIENCIES: MANAGEMENT

The Primary Immune Deficiency Treatment Consortium (PIDTC) is the result of an extraordinary effort to join the experiences of more than 33 North American centers to study the outcomes of treatments for primary immunodeficiencies. The PIDTC reported their research protocols, achievements, and future goals.⁸⁰ Research goals include the identification of optimal treatments for SCID and the definition of which children with CGDs should receive HSCT.

Shearer et al⁸¹ reviewed clinical records of 332 children with SCID and developed diagnostic criteria for SCID and Omenn syndrome. The authors noted the need to complete laboratory evaluations of patients for diagnostic classification, which would guide the choice of treatment.

Haddad et al⁸² gathered data from the PIDTC and 5 European cohorts to formulate the criteria for retransplantation of children with SCID whose initial HSCT failed. They found significant variability on decisions regarding retransplantation in engrafted patients with poor immunity and made on a case-by-case basis.

Dvorak et al⁸³ analyzed the outcomes of HSCT for SCID performed during the 1993-2002 decade using matched sibling donors (MSDs) or matched unrelated donors (URDs) and without conditioning other than serotherapy. A total of 37 URDs and 66 MSDs were compared. URD recipients had lower 5-year-survival than MSD recipients (71% vs 92%, respectively) and higher rates of graft-versus-host disease (GvHD; 50% vs 22%, respectively). More than 90% of patients in each group engrafted T cells. These results hold clinical significance for patients who are too sick to receive chemotherapy.

Pai et al⁸⁴ reviewed outcomes from 240 patients with SCID who received HSCT from 2000-2009. Survival at 5 years, immunoglobulin production, and normal T-cell counts were more likely in MSD recipients than in recipients of other donor types. The survival rate was high regardless of donor type for infants who received transplants before 3.5 months of age (94%) and for infants without prior infection (90%) or with resolved infection (82%). The use of a conditioning regimen was associated with T-cell engraftment and antibody production; however, for patients with active infection at the time of transplantation and who lacked matched donors, survival after haploidentical transplantation was superior if no conditioning regimen was used.

Eighty patients with SCID who received HSCT without conditioning were investigated to determine whether the presence of host NK cells affects donor cell engraftment and survival. NK-negative patients were more likely to engraft and survive after HSCT than NK-positive patients (87% vs 62%).⁸⁵ The authors recommended using a conditioning regimen for patients with NK-positive SCID receiving HSCT. The importance of NK cell engraftment is highlighted by the report of a high frequency of severe and disseminated papilloma virus warts in patients with SCID who present with low NK cell numbers after HSCT.⁸⁶

Schuetz et al⁸⁷ studied whether early and late complications after HSCT would occur more frequently in patients with Artemis deficiency than in those with other forms of SCID. They reviewed 69 patients with Artemis deficiency and 76 patients with RAG1/2 deficiencies who received HSCT. Survival and immune reconstitution were similar in both groups. Secondary malignancies were not observed. Artemis-deficient patients had a significantly high occurrence of infections in long-term follow-up. Dental abnormalities, endocrinopathy, and poor growth were associated with use of alkylating drugs.

Kharya et al⁸⁸ presented a patient with Wiskott-Aldrich syndrome who received haploidentical marrow depleted of CD19 B cells and $\alpha\beta$ TCR T cells using a conditioning regimen and GvHD prophylaxis. There was no GvHD, and 100% chimerism was achieved. The authors proposed that this alternative method might result in better outcomes than the traditional CD34 selection.

Acute complications observed in patients receiving HSCT, such as capillary leak syndrome and sinusoidal obstruction syndrome, start with endothelial damage. Touzot et al⁸⁹ found increased circulating endothelial cell counts in 11 patients with primary immunodeficiencies undergoing HSCT and with vascular events compared with none of 23 patients who did not have these events. High circulating endothelial cell counts predicted the development of vascular complications, except for sinusoidal obstruction.

Outcomes of treatments with enzyme replacement therapy (ERT) and gene therapy in ADA-deficient patients were compared by Brigida et al.⁹⁰ They studied B-cell precursors in bone marrow of 7 untreated ADA-deficient patients, 6 ERT-treated patients, and 8 patients treated with gene therapy. In untreated patients there were B cells at all stages of maturation. There was an increase in the numbers of pre-B1 cells with a corresponding decrease in numbers of pre-B2 and immature B cells. These changes normalized after gene therapy or ERT. An increased proportion of transitional B cells and decreased B-cell proliferation and autoimmunity were seen only in patients undergoing ERT, suggesting that gene therapy was superior to ERT.

Advances in gene therapy for other primary immunodeficiencies proceeded cautiously, as shown by Van Til et al⁹¹ on an animal model of Rag1 deficiency. They obtained low T-cell reconstitution, with autoreactive T cells and skewed T-cell repertoires and rashes resembling Omenn syndrome. The authors discussed the efficacy of *Rag1* gene therapy and the need to balance increasing expression levels with genotoxicity.

Nine patients with X-linked SCID received autologous CD34⁺ cells transduced with a self-inactivating γ c vector without conditioning.⁹² This vector was designed to reduce genotoxicity by eliminating the vector promoter activity after genomic

insertion. Eight of the children are alive after follow-up of 1 to 3 years, with T-cell recovery and resolution of infections. Neoplasias were not observed, and the frequency of insertions near leukemia-associated oncogenes *in vivo* was lower than in previous trials.

Use of immunoglobulins and other therapeutic interventions

The mechanism of action of immunoglobulins as an anti-inflammatory agent in patients with autoimmune diseases was investigated by Seite et al.⁹³ Human B cells exposed *in vitro* to intravenous immunoglobulin exhibited defects in receptor expression, signalosome formation, and cell activation signaling, similar to anergic B cells. Massoud et al⁹⁴ reported on an animal model sensitized to ovalbumin. Administration of the sialic fraction of IgG induced Treg cells and decreased ovalbumin-induced airway hyperresponsiveness.

The Medical Advisory Committee of the Immune Deficiency Foundation published guidelines for immunizations in immunodeficient patients.⁹⁵ Immunologic evaluation was recommended in every patient to assess the safety of receiving live vaccines. Marciano et al⁹⁶ gathered the worldwide experience of BCG vaccination in patients with SCID because this immunization for tuberculosis is recommended to be given at birth, which is before most patients with SCID receive a diagnosis. About half of 349 patients with SCID from 17 countries had BCG disease. Forty-six deaths were reported among 160 patients who became symptomatic and received antimycobacterial therapy. The authors proposed that BCG should be recommended at an older age to protect potential T cell–deficient patients.

Use of IFN- α in DOCK8-deficient patients (Fig 1)

Successful treatment of a herpes simplex–induced tumorous blepharoconjunctivitis in a DOCK8-deficient patient was achieved by using IFN- α (IFN α -2b). Papan et al⁹⁷ reasoned that IFN α -2b would increase antigen presentation and help with viral clearance. Within 24 hours of treatment with pegylated IFN α -2b at 1 μ g/kg/wk, the lesion started regressing and was significantly smaller after 3 days, and there were no significant side effects. In 2 other patients with DOCK8 deficiency and progressive drug-resistant oral herpes labialis, subcutaneous weekly doses of pegylated IFN α -2b at 40 to 80 μ g/m²/wk resulted in regression of the lesions starting after 4 weeks and complete remission after 6 months of treatment.⁹⁸

HIV INFECTION

Campillo-Gimenez et al⁹⁹ addressed the chronic low-level inflammation often found in patients with HIV. Neutrophils, but not monocytes, from HIV-infected patients showed increased expression of activation markers, increased production of reactive oxidative species, and decreased apoptosis. Cagigi et al¹⁰⁰ investigated the impairment of antibody responses to influenza vaccine in 59 aviremic HIV-infected children. They reported a high frequency of mature activated B cells and IgD⁺ B cells, suggesting immune senescence. This B-cell population was associated with poor response to influenza vaccine. IL-21 receptor–positive B-cell counts and B cell–activating factor production were decreased and might constitute markers for vaccine responses.

BEFORE TREATMENT**AFTER TREATMENT**

FIG 1. Treatment of herpesvirus-induced tumors in 3 DOCK8-deficient patients by using IFN α -2b. *Top panels*, Before IFN α -2b treatment; *bottom panels*, after IFN α -2b treatment. Reproduced with permission from Papan et al⁹⁷ and Keles et al.⁹⁸

Haynes et al¹⁰¹ summarized the recent development of an anti-HIV vaccine and the persistent problems in accomplishing this goal. Major advances included the definition of Env targets for protective antibodies, the definition of broad neutralizing antibodies, and the demonstration that CD8 T cells can control HIV infection. Immune correlates of the only vaccine trial that has shown any efficacy demonstrated that antibodies to the second variable region of Env correlated with decreased risk of infection.

Siciliano and Siciliano¹⁰² reviewed current antiretroviral therapy, which is able to suppress HIV viremia to less than detection limits and maintain that level indefinitely, thus allowing the recovery of CD4 T-cell counts and restoration of immunity. However, when treatment is discontinued, HIV viral levels increase to pretreatment levels in only 2 weeks. This is explained by viral latency in long-lived resting memory CD4 T cells. The most popular approach to eliminate reservoirs is to induce HIV gene expression in latently infected cells. This has been pursued with T cell-activating agents, although it is usually associated with release of large amounts of cytokines. Two classes of T cell-activating agents being studied are histone deacetylase inhibitors, such as vorinostat, and protein kinase C agonists, including prostratin and bryostatine.

CONCLUSIONS

Research advances in basic and clinical immunology in 2014 provided new molecular mechanisms in the development and regulation of the immune response. Reports in primary

immunodeficiency syndromes showed increasing variability in clinical manifestations and immunologic abnormalities and advances for an optimal patient management. Progress in HIV infection is directed toward development of an efficacious vaccine and eradication of latent viral infection.

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