

Advances in basic and clinical immunology in 2012Javier Chinen, MD, PhD,^a Luigi D. Notarangelo, MD,^b and William T. Shearer, MD, PhD^a *Houston, Tex, and Boston, Mass*

Basic and clinical immunology articles published in the *Journal* in 2012 were mostly related to the expanding area of primary immunodeficiencies (PIDs). Novel forms of PID were identified by using whole-exome sequencing or after careful examination of flow cytometric data, as in the reports of lymphocyte-specific protein tyrosine kinase, CD27, and CD21 deficiencies. Absent IgG and IgA memory B cells were described in patients with hyper-IgE syndrome, which is consistent with defective antibody response and suggests a potential benefit of immunoglobulin replacement. Impaired production of antibodies to polysaccharide antigens by the human B-cell subset analog to murine B-1 cells was reported in a child with selective polysaccharide antibody deficiency. Increased production of inflammatory cytokines by monocyte-derived cells on Toll-like receptor activation was reported in patients with X-linked agammaglobulinemia, underscoring the important role of Bruton tyrosine kinase in modulation of inflammation. The mechanisms explaining susceptibility to yeast infections and development of chronic mucocutaneous candidiasis were extensively studied. Universal newborn screening for T-cell deficiencies is being implemented in several states, resulting in the diagnosis of a higher number of immunodeficient newborns than previously estimated. The use of laboratory testing to distinguish PIDs from HIV infection was clarified. In the management of PIDs, refinement of indication and strategies to hematopoietic stem cell transplantation resulted in improved outcomes. The use of anti-IL-6 mAbs showed promise as an alternative treatment in patients with Schnitzler syndrome. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

Key words: Immunology, primary immunodeficiencies, chronic mucocutaneous candidiasis, IL-17, intravenous immunoglobulin, combined variable immunodeficiency, cell immunity, severe combined immunodeficiency, newborn screening

Abbreviations used

ADA:	Adenosine deaminase
AIRE:	Autoimmune regulator
BCR:	B-cell receptor
CARD:	Caspase recruitment domain-containing protein
CD:	Crohn disease
CD40L:	CD40 ligand
CGD:	Chronic granulomatous disease
CMC:	Chronic mucocutaneous candidiasis
CMV:	Cytomegalovirus
CTL:	Cytotoxic T cell
CVID:	Common variable immunodeficiency
HIES:	Hyper-IgE syndrome
HSCT:	Hematopoietic stem cell transplantation
IVIG:	Intravenous immunoglobulin
KREC:	κ -Deleting recombination excision circle
LCK:	Lymphocyte-specific protein tyrosine kinase
LRBA:	LPS-responsive beige-like anchor
PID:	Primary immunodeficiency
SCID:	Severe combined immunodeficiency
STAT:	Signal transducer and activator of transcription
SYK:	Spleen tyrosine kinase
TLR:	Toll-like receptor
TREC:	T-cell receptor excision circle
Treg:	Regulatory T
VODI:	Veno-occlusive disease and immunodeficiency

This report focuses on the increasing research activity in all aspects of human immunodeficiency published in the *Journal* in 2012, from the discovery of new causative genes of inherited immune defects to efforts to improve current therapeutic options.

HUMAN IMMUNOLOGY

The pathogenesis of allergic and autoimmune disorders is closely related to abnormalities in the mechanisms of central and peripheral immune tolerance. Tulic et al¹ investigated the presence and function of regulatory T (Treg) cells in thymi of children who had cardiac surgical procedures and did not have DiGeorge syndrome or other immune abnormalities. They showed that the median percentage of Treg cells among thymocytes increased with age from 3% in infants younger than 6 months of age to 8% in children older than 5 years. By contrast, a slower kinetics of thymic Treg cell development and function was observed in children with allergic disease. The authors noted that thymic stromal lymphopoietin-expressing cells (which favor development of Treg cells) were more abundant in thymi obtained from nonatopic children at birth and decreased with age, whereas numbers remained unchanged from birth in atopic children. This study provided evidence of the

From ^athe Immunology, Allergy and Rheumatology Section, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, and ^bthe Departments of Pediatrics and Pathology, Harvard Medical School, Boston.

Supported by National Institutes of Health (NIH) grants RR0188, AI082978, AI036211, AI06944, and HD052102 and the David Fund of Texas Children's Hospital.

Disclosure of potential conflict of interest: L. D. Notarangelo is a Board member for the Immune Disease Institute; is employed by Children's Hospital Boston; has received one or more grants from or has one or more grants pending with the NIH, the Jeffrey Modell Foundation, and the Wiskott-Aldrich Foundation; and has received royalties from UpToDate. W. T. Shearer has been supported by one or more grants from the NIH (AI082978). J. Chinen declares that he has no relevant conflicts of interest.

Received for publication December 30, 2012; accepted for publication January 7, 2013. Corresponding author: William T. Shearer, MD, PhD, Allergy and Immunology, Texas Children's Hospital, 1102 Bates St, FC 330.01, Houston, TX 77030. E-mail: wtsheare@texaschildrenshospital.org.

0091-6749/\$36.00

© 2013 American Academy of Allergy, Asthma & Immunology
<http://dx.doi.org/10.1016/j.jaci.2013.01.012>

steady development of Treg cells in the thymus and their influence in the pathogenesis of allergy.

Iwata et al² reported the essential role of spleen tyrosine kinase (SYK), a transduction signal protein, in the activation of human memory B cells. A SYK inhibitor reduced proliferation and expression of cytokines and the activation molecules CD80 and CD86 in these cells when stimulated by anti-B-cell receptor (BCR), CD40 ligand (CD40L), and CpG. The authors suggested that SYK might be another therapeutic target for a number of conditions in which it is desirable to inhibit B-cell activation, such as autoimmune diseases.

A subset of B cells representing the human counterpart of the murine B-cell subset B-1 has recently been characterized as CD20⁺CD43⁺CD27⁺CD70⁺ cells.³ Verbinenn et al⁴ measured the antibody responses to the polysaccharide pneumococcal vaccine in this human B-cell subset before and after vaccination and analyzed B-cell expression of specific IgG and IgM against capsular serotypes by means of ELISpot. Specific antibodies to all pneumococcal serotypes were not studied because of limitations in terms of cell numbers (this subset is 2% to 4% of total B cells), but the data showed that the ability to produce anti-pneumococcal antibodies was exclusively in the CD5⁺ fraction of the proposed B-1 population and not in other B-cell subsets. Of interest, these cells were absent in one boy with normal IgG and IgG subclass levels but absent responses to polysaccharide vaccines, suggesting an explanation for this uncommon antibody deficiency.

Posch et al⁵ characterized the effect of HIV opsonization on the ability of dendritic cells to activate HIV-specific cytotoxic T cells (CTLs). Their experiments suggest that dendritic cells exposed to viral particles opsonized with serum containing a high complement/specific immunoglobulin ratio are most efficient to activate CTL activity. In the absence of complement, IgG-opsonized viral particles taken up by dendritic cells appear to induce CTLs into a resting state.

In a clinical study of pulmonary complications of HIV infection, Gingo et al⁶ reported an increased prevalence of asthma. Significant associated factors were family history of asthma, obesity, allergic disease, prior infections, lack of HIV control, and increased levels of inflammatory cytokines, all of which suggested possible pathogenesis, as discussed by Shearer and Corry.⁷

PRIMARY IMMUNODEFICIENCIES: MECHANISMS OF DISEASE

Recent reports of several gene defects associated with diseases presenting with chronic mucocutaneous candidiasis (CMC) have attracted major interest. Engelhardt and Grimbacher⁸ reviewed genes the mutations of which have been associated with an increased risk of CMC and the mechanisms involved in antifungal immune response. The genes discussed included polymorphisms in C-type lectin associated 7, member A (*CLECA7* or *DECTIN1*), at the level of fungal antigen detection and mutations in caspase recruitment domain-containing protein 9 (*CARD9*), an adaptor molecule downstream of DECTIN1 that is essential for the activation of nuclear factor κ B in response to yeast infections. Fig 1 depicts the molecular events resulting from the recognition of *Candida* species on the surface of antigen-presenting cells, leading to secretion of cytokines to induce the T_H17 response. Deleterious mutations in

IL17F and *IL17R* impair the T_H17 response, which plays a fundamental role for fungal clearance. Similarly, signal transducer and activator of transcription 3 (*STAT3*) mutations and gain-of-function mutations in *STAT1* result in decreased T_H17 inflammatory response. Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy, which is caused by autoimmune regulator (AIRE) deficiency, is characterized by CMC, low cortisol levels, diabetes mellitus, and other endocrinopathies. These patients often have antibodies against IL-17A and IL-17F,⁹ resulting in impairment of the T_H17 response and explaining the occurrence of CMC in patients with autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy. The genetic and immunologic mechanisms centered on IL-17 deficiency in the development of CMC were reviewed in depth by McDonald.¹⁰

Pedroza et al¹¹ asked whether the CARD domain in the AIRE molecule could play a role similar to CARD9 in the increased susceptibility to CMC in addition to the described autoantibodies against IL-17. The authors demonstrated that in the absence of AIRE, β -glucan stimulation through DECTIN1 results in decreased TNF- β production by PBMCs, indicating a role of AIRE in signal transduction pathways.

Marodi et al¹² summarized the molecular mechanisms of mucosal and skin immunity working against both *Candida* and *Staphylococcus* species. They noted that patients with chronic and recurrent infections with these organisms often carry gene mutations resulting in impairment of signal pathways in which STAT1 and STAT3 have a central role. These mutations result in inadequate cytokine responses of significance on body surfaces, mainly the T_H17 response.

Akdis et al¹³ further examined this response and proposed the importance of TGF- β for its regulation. When TGF- β is present, a controlled T_H17 response with IL-10 production is induced; however, if IL-6, IL-23, and IL-1 β are predominant, a more inflammatory T_H17 response is induced with increased IFN- γ and IL-22 secretion. IL-22 stimulates the production of antimicrobial peptides by keratinocytes and participates in skin repair but also in the pathogenesis of psoriasis.

Evidence of the role of CD40L in the antifungal activity of dendritic cells was provided by Cabral-Marques et al.¹⁴ They studied the responses to fungal antigens of monocytic cells from patients with CD40L deficiency. Compared with healthy control subjects, there was reduced expression of activation markers, which was restored with the addition of exogenous CD40L. This reduced activation was associated with impaired monocytic maturation and increased IL-10 and decreased IL-12 secretion. Marron et al¹⁵ reported enhanced production of inflammatory cytokines on Toll-like receptor (TLR) stimulation of monocytes derived from patients with X-linked agammaglobulinemia compared with healthy subjects. TNF- α and IL-6 levels were increased after stimulation with LPS and CL097, ligands for TLR4, TLR7, and TLR8. These reports underscore that signal transduction pathways deemed essential for B-cell function also play a regulatory role in the activation and cytokine secretion of monocytic cells.

Touzot et al¹⁶ hypothesized that some patients with classical clinical features of dyskeratosis congenita or the severe Hoyeraal-Hreidarsson syndrome might not present with short telomeres but with telomere dysfunction or telomere fragility. Studies on fibroblast cultures from 5 patients with Hoyeraal-Hreidarsson syndrome showed evidence of accelerated

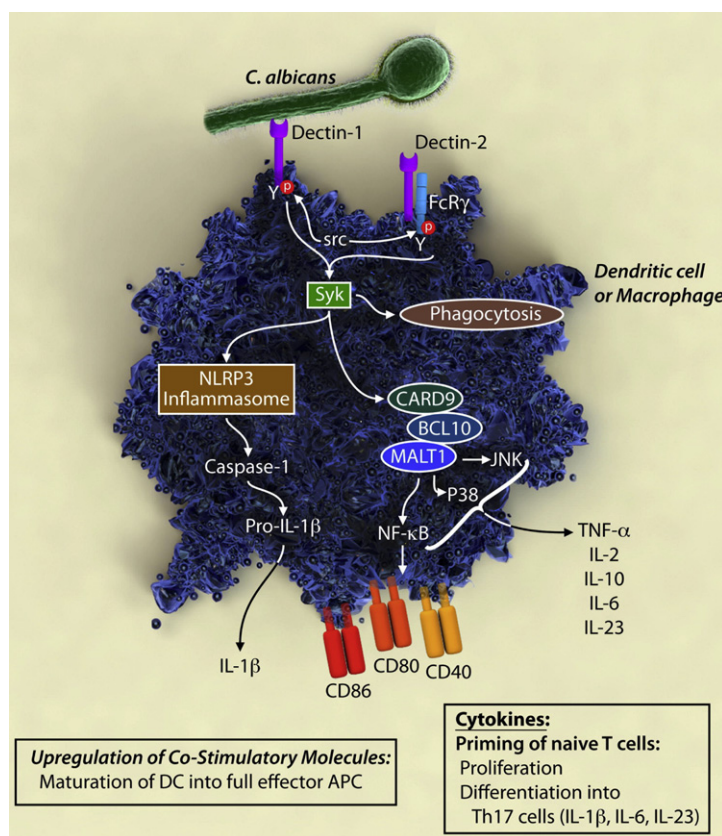


FIG 1. Signaling pathways downstream of dectin-1 and dectin-2 on binding of *Candida albicans*. Binding of *C albicans* to dectin-1 and dectin-2 leads to Src-mediated tyrosine phosphorylation of the hemiTAM of dectin-1 or the immunoreceptor tyrosine-based activation motif of the dectin-2-associated Fc receptor (FcR) γ chain. Subsequent recruitment of Syk drives phagocytosis, formation of a CARD9/BCL10/MALT1 signaling complex, and activation of the NLRP3 inflammasome. The CARD9-containing complex leads to activation of nuclear factor κ B and the mitogen-activated protein kinases p38 and c-Jun N-terminal kinase (JNK), resulting in upregulation of costimulatory molecules and production of T_H17 -priming cytokines. Activation of caspase-1 in the context of the NLRP3 inflammasome results in cleavage of pro-IL-1 β and secretion of active IL-1 β , which also contribute to differentiation of naive T cells into T_H17 cells. Reprinted with permission from Engelhardt et al.⁸

telomere DNA damage, although the telomere length was similar to that seen in cells from a healthy control subject. The authors concluded that Hoyeraal-Hreidarsson syndrome might also result from impairment of factors that protect telomere ends.

Further evidence of the toxicity of nucleotide metabolites on B cells was provided by Somech et al.¹⁷ Two sisters with a novel nonsense mutation in the purine nucleoside phosphorylase gene (*PNP*) presented with characteristic T-cell deficiency and also with B-cell abnormalities that included low B-cell counts, skewed B-cell receptor repertoire, and impaired antibody responses, indicating direct toxicity to B cells.

Janssen et al¹⁸ examined granuloma biopsy specimens from patients with Blau syndrome and Crohn disease (CD) in whom mutations in nucleotide oligomerization 2 (*NOD2*) had been identified. Although the granulomas from patients with Blau syndrome exhibited large lymphocytic coronas and a cytokine expression profile indicative of both a T_H17 response and a T_H1 response, granulomas from patients with CD lacked lymphocytic coronas and were mostly characterized by a prominent expression of IFN- γ only. The authors suggest that this difference might explain the systemic inflammatory

manifestations in patients with Blau syndrome, which is in contrast to manifestations limited to the gastrointestinal tract in patients with CD.

Additional insight into mechanisms of disease came from *in vitro* experiments with B cells. Bloch et al¹⁹ studied EBV-transformed B-cell lines from patients with nuclear body protein SP110 deficiency, which is known to present with veno-occlusive disease and immunodeficiency (VODI) syndrome. They found the expression and secretion of IL-10 by these B cells to be remarkably low. The authors noted that IL-10 deficiency leads to CD and that there is an association between CD and the genomic regions containing the *SP110* and *IL10* genes. Therefore they proposed that *SP110* variants might regulate inflammatory activity in patients with VODI by affecting levels of expression of IL-10.

In another study, van de Ven et al²⁰ performed calcium-signaling studies in B cells obtained peripherally from patients with common variable immunodeficiency (CVID) and reported a decrease in calcium influx after BCR stimulation compared with that seen in healthy control subjects associated with impaired dissociation of CD20 from the BCR during the early phase of B-cell activation.

The immunologic defect in patients with hyper-IgE syndrome (HIES) associated with mutations in *STAT3* has been characterized as a deficient T_H17 response. It has been known from the earliest reports of this syndrome that the antibody response is impaired,²¹ which is consistent with the increased susceptibility to respiratory tract infections. Meyer-Bahlburg et al²² reported the absence of IgG and IgA memory B cells in 25 patients with *STAT3*-deficient HIES, thus supporting the benefit of immunoglobulin replacement in the treatment of these patients.

Marashi et al²³ studied different immune parameters in a cohort of 71 adults with CVID with regard to cytomegalovirus (CMV) infection. They reported an association of CMV infection and an increase in $CD8^+$ T-cell counts with inversion of the $CD4/CD8$ ratio. The authors postulated that the inflammatory complications commonly observed in a subset of patients with CVID might be attributed to CMV infection.

PRIMARY IMMUNODEFICIENCIES: NEWBORN SCREENING

Buckley²⁴ reviewed the efforts to date for the early diagnosis of severe combined immunodeficiency (SCID). If untreated, SCID is fatal within the first years of life, with death resulting from severe and often opportunistic infections. Universal newborn screening for SCID has been a long-term goal of clinical immunologists since it was realized that most children with SCID are born with a normal appearance, and diagnosis had often been made after severe infections had already produced organ damage, limiting the success of definitive treatments, such as bone marrow transplantation. Initial efforts for newborn screening proposed the measurement of absolute lymphocyte counts; however, this approach has significant limitations, including false-negative results caused by maternal lymphocytes in the infants' peripheral blood and an unclear cost/benefit ratio. Enumeration of T-cell receptor excision circles (TRECs) on dried blood spots (Guthrie cards collected at birth and currently used to screen for other inherited diseases) was then proposed as a first-tier assay for newborn screening of SCID. Starting with Wisconsin, several states have now incorporated SCID in their universal newborn screening program.

Puck²⁵ explained the immunologic basis of using TRECs to estimate *de novo* generation of T cells, which are deficient in patients with SCID and other inherited T-cell cytopenias, and the successful demonstration of the feasibility of using the Guthrie cards. The data collected from several states suggest that the SCID incidence might be higher than the previously estimated value of 1:100,000 live births.

Verbsky et al²⁶ reported the initial 3-year experience of universal newborn screening in Wisconsin. After screening 207,696 newborns, 72 had low TREC numbers, of whom 38 had normal T-cell counts, resulting in a false-positive rate of 0.018% and a specificity of 99.98%. Thirty-three infants had a primary or secondary T-cell lymphopenia, and 5 infants were given a diagnosis of a form of SCID. These infants benefited from isolation measures and definitive treatment before contracting opportunistic infections. One of the differential diagnoses in newborn screening for SCID is neonatal HIV infection. Hanson and Shearer²⁷ prepared an easy-to-grasp side-by-side comparison of differences in results of diagnostic tests of SCID versus HIV infection. Speckmann et al²⁸

examined Guthrie cards obtained from a patient who was given a diagnosis of delayed-onset adenosine deaminase (ADA) deficiency at 7 years of age and had normal TREC levels but decreased κ -deleting recombination excision circles (KRECs), and increased adenosine metabolites were found. KRECs have been proposed for screening of B-cell deficiencies in an analogous manner to TRECs.²⁹ This case report supports the inclusion of these analytes to improve the early diagnosis of immunodeficiencies.

PRIMARY IMMUNODEFICIENCIES: DIAGNOSIS AND DESCRIPTION OF GENES CAUSING PRIMARY IMMUNODEFICIENCIES

Leiding and Holland³⁰ reviewed the clinical and immunologic characteristics of patients with primary immunodeficiencies (PIDs) with increased susceptibility to warts caused by human papillomavirus and provided an algorithm to help guide the diagnostic workup. They classified diseases in which warts were a major clinical finding: EVER 1 and 2 deficiency, WHIM syndrome, DOCK8 deficiency, idiopathic T-cell lymphopenia, GATA2 deficiency, Netherton syndrome, and STK4 deficiency. A second group of PIDs presenting with warts as a common occurrence were also described: NEMO deficiency, ataxia telangiectasia, SCID, CVID, LAD-I, Wiskott-Aldrich syndrome, and CD40L deficiency.

Ohnishi et al³¹ reported the diagnosis of a dominant negative mutant of inhibitor of κ light chain gene enhancer in B cells, α (*IKBA*), using a flow cytometric protocol that detects TNF- α expression in $CD14^+$ PBMCs after stimulation with LPS. This assay was originally developed to screen for IL-1 receptor–associated kinase 4 deficiency. After demonstration of reduced intracellular TNF- α production by the patient's $CD14^+$ cells, the authors investigated the genes associated with ectodermal dysplasia and found the Q9X mutation in *IKBA*. The authors emphasize the simplicity of the test to screen for deficiencies involving TLR pathways.

Licciardi et al³² revised the limitations on the use of the pneumococcal polysaccharide vaccine in children at 12 months of age and reported significant (although not optimal) antibody responses after 1 immunization dose. Less than 24% of infants immunized had an adequate functional response to at least 11 of 22 serotypes studied, as measured by using the avidity index.

Two previously unrecognized conditions associated with ADA deficiency were reported: dermatofibrosarcoma and pulmonary alveolar proteinosis. Kesserwan et al³³ described the occurrence of dermatofibrosarcoma protuberans in 8 of 12 patients with ADA deficiency and suggested routine screening for this malignant subcutaneous tumor in patients with this condition. Pulmonary alveolar proteinosis was reported in 5 patients in a series of 10 patients with ADA,³⁴ which resolved after treatment with enzyme replacement or bone marrow transplantation. Autoantibodies to GM-CSF were investigated and not deemed to play a role in these cases.

Cliffe et al³⁵ examined 9 European patients with VODI. This rare PID presents with veno-occlusive disease, hypogammaglobulinemia, and T-cell dysfunction and is due to deleterious mutations in *SP110*. The authors demonstrated decreased B-cell activation and differentiation in response to T cell–dependent stimuli.

Chou et al³⁶ reported the cases of 2 siblings in whom homozygosity for a missense recombination-activating gene 2 (*RAG2*)

mutation led to distinct clinical and immunologic phenotypes: hyper-IgM syndrome and Omenn syndrome. These cases expand our knowledge of the heterogeneity of the clinical phenotype associated with *RAG* mutations.

The power of exome sequencing on the discovery of genetic causes of primary immunodeficiency was demonstrated by Alangari et al.³⁷ They studied a consanguineous family with several members affected with an autosomal recessive syndrome that included hypogammaglobulinemia, autoimmune cytopenias, and inflammatory bowel disease, resembling a severe CVID phenotype. They first identified homozygosity blocks shared by the affected members and subsequently performed exome sequencing targeting those blocks. From 1245 variant nucleotides in genes within the homozygosity blocks, only 1 was identified as novel and corresponded to a mutation in the LPS-responsive beige-like anchor (*LRBA*) gene. The identified mutation resulted in absent LRBA protein expression. It is not clear how LRBA contributes to immunodeficiency. *LRBA* deleterious mutations were recently described in 5 members affected from 4 different families presenting with CVID symptoms by using linkage analysis, followed by sequencing of candidate genes.³⁸ Burns et al.³⁹ used exome sequencing to identify the gene defect in a 4-year-old patient with autoimmune cytopenias and arthritis who had antibody deficiency after using rituximab. The authors found a homozygous deletion of 252 kb removing the first 30 exons of the *LRBA* gene.

The first description of a patient with immunodeficiency caused by lack of lymphocyte-specific protein tyrosine kinase (*LCK*) expression was made by means of a careful analysis of the flow cytometric data. Hauck et al.⁴⁰ studied a child with recurrent infections, panniculitis, and autoimmunity and noticed that both CD4 and CD8 T cells were expressed at very low density on the surfaces of circulating T cells. Because a similar finding is a characteristic of *Lck*^{-/-} mice, *LCK* gene sequence analysis was obtained, revealing a homozygous mutation resulting in the amino acid change L341P, which was found to destabilize the protein and render it nonfunctional. Of interest, the father did not carry the mutation, and the patient inherited 2 maternal copies of the entire chromosome 1 that carried the mutant allele. At 30 months of age, hematopoietic stem cell transplantation (HSCT) was attempted; unfortunately, the patient died at day 7 after transplantation of veno-occlusive disease.

Two newly described genetic immunodeficiencies were reported as a result of studying the expression of well-known cell-surface markers by using flow cytometry. CD27 deficiency was reported by van Montfrans et al.⁴¹ in 2 brothers with humoral and cellular dysfunction presenting with severe EBV infection and lack of CD27 expression in T and B lymphocytes. CD21 deficiency was reported in 1 patient with recurrent infections⁴² associated with moderate hypogammaglobulinemia, reduction of memory B cells and impaired responses to polysaccharides but intact antibody responses to protein antigens.

Roifman et al.⁴³ reviewed immune parameters in a series of 103 patients with primary T-cell deficiencies or T-cell dysregulatory disorders. They found that patients with initial CD3 T-cell counts of less than 500 cells/ μ L invariably present with a SCID phenotype. Patients with molecular defects that do not directly affect T-cell development, such as CD40L, forkhead box protein 3, and IL-10 deficiencies, had T-cell counts in the normal range, a significant lymphoproliferative response to mitogens, and significant TREC values. This category includes hypomorphic mutations in genes that otherwise would cause SCID, such as the

R222C mutation in IL-2 receptor γ (*IL2RG*) and other mutations causing delayed-onset ADA deficiency.

The increasing use of genetic testing for PIDs brings additional diagnostic considerations for the clinical immunologist. Spielberger et al.⁴⁴ reminded us of mosaicism when findings do not fit common inheritance patterns. They reported a family of 3 siblings with a diagnosis of HIES and a known deleterious mutation in *STAT3*. However, the parents were healthy, and analysis of a sample of their blood DNA did not demonstrate the mutation. This mutation was eventually found in DNA obtained from a semen sample from the father, indicating that the disease was due to germinal mosaicism.

Analyzing 3 CVID patient cohorts (ie, a Northern European cohort, the French DEFI study group, and the Mount Sinai cohort) including a total of 848 patients, Chapel et al.⁴⁵ updated a previously proposed clinical classification of patients with CVID, which identified 5 phenotypes of patients with CVID in more than 80% of patients: (1) no complications, (2) autoimmunity, (3) polyclonal lymphocytic infiltration, (4) enteropathy, and (5) lymphoid malignancy.⁴⁶ The analysis of the larger patient cohort resulted in a revised classification of 4 phenotypes: (1) no complications other than infections, (2) autoimmune cytopenias, (3) polyclonal lymphoproliferation, and (4) unexplained persistent enteropathy. Several conclusions of prognostic value could be made. There was a 14% increase in the risk of cytopenias for every 1 g/L increase in serum IgG level and a 69% increase in the risk of lymphoproliferation for every 1 g/L increase in serum IgA level. The survival expectancy was least in the enteropathic CVID group, followed by the lymphoproliferation phenotype and the autoimmune group. The authors concluded that these data might help define the prognosis of patients with CVID within 5 years from the diagnosis.

PRIMARY IMMUNODEFICIENCIES: MANAGEMENT

A major goal of the clinical immunologist is a reduction in the risk of morbidity and mortality associated with treatment. In patients with severe PIDs, curative treatment with HSCT has different outcomes attributed to a number of variables, including age, specific genetic defect, and pretransplantation morbid conditions.⁴⁷ Martinez et al.⁴⁸ reported 100% survival with minimal graft-versus-host disease in a series of 11 patients with chronic granulomatous disease (CGD) treated with HSCT using matched related or matched unrelated donors, underscoring that these patients benefit of early transplantation, with negligible differences regarding the type of donor.

Rachid and Bonilla⁴⁹ reviewed the evidence reporting adverse reactions, including anaphylaxis, associated with the use of immunoglobulins in patients with IgA deficiency. Reactions have occurred with intravenous immunoglobulin (IVIG) products with the highest IgA content at 50 μ g/mL, and almost all 27 patients reported in the literature as having moderate symptoms or anaphylaxis to immunoglobulin products had undetectable IgA levels. Anti-IgA IgG antibodies have been reported in up to 30% of the patients with a humoral immunodeficiency; however, they did not present with adverse reactions when receiving IgG. The authors concluded that the pathogenesis of these adverse reactions is not clear, although they recommend switching to an IVIG product with low IgA content or trying subcutaneous administration if adverse reactions to IVIG occur.

IVIG at high doses has a potent anti-inflammatory effect and is used in a variety of autoimmune disorders. Massoud et al⁵⁰ studied the use of IVIG in a mouse model and demonstrated an increase in Treg cell counts when IVIG is used at anti-inflammatory doses for ovalbumin-induced airway reactivity. Five days after IVIG treatment at 2 g/kg, there were 4- to 6-fold increases in forkhead box protein 3-expressing CD4 T-cell counts with antigen-specific regulatory function in the spleen, lung, and lymph nodes compared with control animals who received human albumin.

Micol et al⁵¹ studied a cohort of 111 French patients with humoral immunodeficiencies and noted that those with hyper-IgM syndrome (n = 25) had less frequency of respiratory tract infections, specifically those caused by nontypeable *Haemophilus influenzae*, compared with those patients with panhypogammaglobulinemia (n = 86), suggesting that patients with preserved IgM production had effective antibodies against encapsulated organisms. The authors conclude that antibiotic therapy might be necessary to complement IVIG replacement in panhypogammaglobulinemic patients.

Tocilizumab (anti-IL-6 mAb) proved successful in the treatment of all 3 patients with Schnitzler syndrome treated with this biological agent who were resistant to conventional treatment, including IL-1 inhibitors.⁵² Schnitzler syndrome is characterized by increased IgM levels, rash, fever, lymphadenopathy, and other signs of systemic inflammation. Further follow-up is planned to demonstrate the advantages and disadvantages with regard to current therapy, most importantly the development of lymphoproliferative disorders.

Initial studies of natural killer cell function of patients with familial hemophagocytic lymphohistiocytosis type 5 because of defects in the syntaxin-binding protein 2 gene (*STXBP2*) have suggested that cytolytic activity could be partially restored by stimulation with IL-2.⁵³ However, Saltzman et al⁵⁴ reported a patient with familial hemophagocytic lymphohistiocytosis type 5 with decreased natural killer cell function whose symptoms did not improve with the use of IL-2 and warned that more studies are needed to define which patient subset might benefit from this treatment.

CONCLUSIONS

In 2012, the *Journal* recorded the significant progress in the field of PIDs, encompassing a wide variety of molecular defects and clinical topics. Newborn screening for T-cell deficiencies is now been implemented in many states, with the goal of obtaining early treatment of SCID before complications occur. The diagnosis of PID is being enhanced with new molecular genetics technology that has allowed the identification of new genetic deficiencies, such as the LRBA defect. Increased use of flow cytometric analysis has led to the identification of other gene defects affecting immunity: LCK, CD21, and CD27 deficiencies. Dermatofibrosarcoma and pulmonary alveolar proteinosis have been added to the clinical findings of ADA deficiency, and a proposed clinical classification of CVID could be helpful to guide physicians to advise patients on their prognosis. Advances in early treatment for PIDs include data on excellent survival in patients with CGD after HSCT and the successful use of anti-IL-6 for patients with Schnitzler syndrome. From the explanation of molecular pathogenesis to the therapeutic progress, these spectacular advances in all aspects of PIDs continue to provide excitement to the area of human immunology.

Key advances

Human immunology

- Differentiation of Treg cells is decreased in thymus of atopic children.
- SYK is essential for optimal B-cell activation.
- Human B-cell analogs of murine B-1 cells produce antibodies against polysaccharides.
- IgG-opsonized HIV requires complement for optimal activation of T-cell cytolytic responses.
- Asthma prevalence is increased among patients with HIV.

Primary immunodeficiencies: Mechanisms

- Gene defects associated with susceptibility to chronic mucocutaneous candidiasis have been identified.
- TGB- β might regulate the intensity of the T_H17 response.
- TLR-mediated activation of monocytes and dendritic cells is impaired in patients with CD40L deficiency and those with X-linked agammaglobulinemia.
- Dyskeratosis congenita might be caused by telomere dysfunction in addition to traditional defects leading to short telomeres.
- B cells from SP110-deficient patients produce very low levels of IL-10.
- HIES might present with absent IgA and IgG memory B cells.

Primary immunodeficiencies: Diagnosis

- Universal newborn screening for T-cell deficiencies is being implemented in several states.
- Use of KREC's might expand the number of immunodeficiencies detected by means of newborn screening.
- Examination of flow cytometric analysis led to the description of human deficiencies in CD21, CD27, and LCK.
- Exome sequencing was used to diagnose LRBA deficiency.
- Dermatofibrosarcoma and pulmonary alveolar proteinosis were added as characteristics of ADA deficiency.
- A clinical classification of CVID into 4 groups: no complications, autoimmune cytopenias, polyclonal lymphoproliferation, and persistent enteropathy are helpful in determining prognosis.

Primary immunodeficiencies: Management

- Excellent survival was reported in a series of patients with CGD treated with HSCT.
- Compared with patients with hyper-IgM syndrome, patients with pangammaglobulinemia have an increased risk of infection by nontypeable *H influenzae*.
- Anti-IL-6 mAb has been successfully used to treat Schnitzler syndrome.

REFERENCES

1. Tulic MK, Andrews D, Crook ML, Charles A, Tourigny MR, Moqbel R, et al. Changes in thymic regulatory T-cell maturation from birth to puberty: differences in atopic children. *J Allergy Clin Immunol* 2012;129:199-206.
2. Iwata S, Yamaoka K, Niino H, Nakano K, Wang SP, Akashi K, et al. Amplification of Toll-like receptor-mediated signaling through spleen tyrosine

- kinase in human B-cell activation. *J Allergy Clin Immunol* 2012;129:1594-601.
3. Griffin DO, Holodick NE, Rothstein TL. Human B1 cells in umbilical cord and adult peripheral blood express the novel phenotype CD20+ CD27+ CD43+ CD70-. *J Exp Med* 2011;208:67-80.
 4. Verbinen B, Covens K, Moens L, Meyts I, Bossuyt X. Human CD20+CD43+CD27+CD5- B cells generate antibodies to capsular polysaccharides of *Streptococcus pneumoniae*. *J Allergy Clin Immunol* 2012;130:272-5.
 5. Posch W, Cardinaud S, Hamimi C, Fletcher A, Mühlbacher A, Loacker K, et al. Antibodies attenuate the capacity of dendritic cells to stimulate HIV-specific cytotoxic T lymphocytes. *J Allergy Clin Immunol* 2012;130:1368-74.
 6. Gingo MR, Wenzel SE, Steele C, Kessinger CJ, Lucht L, Lawther T, et al. Asthma diagnosis and airway bronchodilator response in HIV-infected individuals. *J Allergy Clin Immunol* 2012;124:708-14.
 7. Shearer WT, Corry DB. High prevalence of asthma in HIV-infected adults: new insights. *J Allergy Clin Immunol* 2012;129:715-6.
 8. Engelhardt KR, Grimbacher B. Mendelian traits causing susceptibility to mucocutaneous fungal infections in human subjects. *J Allergy Clin Immunol* 2012;129:294-305.
 9. Puel A, Döffinger R, Natividad A, Chrabieh M, Barcenas-Morales G, Picard C, et al. Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. *J Exp Med* 2010;207:291-7.
 10. McDonald DR. TH17 deficiency in human disease. *J Allergy Clin Immunol* 2012;129:1429-35.
 11. Pedrosa LA, Kumar V, Sanborn KB, Mace EM, Niinikoski H, Nadeau K, et al. Autoimmune regulator (AIRE) contributes to Dectin-1-induced TNF- α production and complexes with caspase recruitment domain-containing protein 9 (CARD9), spleen tyrosine kinase (Syk), and Dectin-1. *J Allergy Clin Immunol* 2012;129:464-72.
 12. Maródi L, Cypowij S, Tóth B, Chernyshova L, Puel A, Casanova JL. Molecular mechanisms of mucocutaneous immunity against *Candida* and *Staphylococcus* species. *J Allergy Clin Immunol* 2012;130:1019-27.
 13. Akdis M, Palomares O, van de Veen W, van Splunter M, Akdis CA. TH17 and TH22 cells: a confusion of antimicrobial response with tissue inflammation versus protection. *J Allergy Clin Immunol* 2012;129:1438-49.
 14. Cabral-Marques O, Arslanian C, Ramos RN, Morato M, Schimke L, Soeiro Pereira PV, et al. Dendritic cells from X-linked hyper-IgM patients present impaired responses to *Candida albicans* and *Paracoccidioides brasiliensis*. *J Allergy Clin Immunol* 2012;129:778-86.
 15. Marron TU, Martinez-Gallo M, Yu JE, Cunningham-Rundles C. Toll-like receptor 4-, 7-, and 8-activated myeloid cells from patients with X-linked agammaglobulinemia produce enhanced inflammatory cytokines. *J Allergy Clin Immunol* 2012;129:184-90.
 16. Tuzot F, Gaillard L, Vasquez N, Le Guen T, Bertrand Y, Bourhis J, et al. Heterogeneous telomere defects in patients with severe forms of dyskeratosis congenita. *J Allergy Clin Immunol* 2012;129:473-82.
 17. Somech R, Lev A, Simon AJ, Hanna S, Etzioni A. T- and B-cell defects in a novel purine nucleoside phosphorylase mutation. *J Allergy Clin Immunol* 2012;130:539-42.
 18. Janssen CE, Rose CD, De Hertogh G, Martin TM, Bader Meunier B, Cimaz R, et al. Morphologic and immunohistochemical characterization of granulomas in the nucleotide oligomerization domain 2-related disorders Blau syndrome and Crohn disease. *J Allergy Clin Immunol* 2012;129:1076-84.
 19. Bloch DB, Nobre R, Steinbicker AU, Al-Herz W, Notarangelo LD, Recher M. Decreased IL-10 production by EBV-transformed B cells from patients with VODI: implications for the pathogenesis of Crohn disease. *J Allergy Clin Immunol* 2012;129:1678-80.
 20. van de Ven AA, Compeer EB, Bloem AC, van de Corput L, van Gijn M, van Montfrans JM, et al. Defective calcium signaling and disrupted CD20-B-cell receptor dissociation in patients with common variable immunodeficiency disorders. *J Allergy Clin Immunol* 2012;129:755-61.
 21. Sheerin KA, Buckley RH. Antibody responses to protein, polysaccharide, and phi X174 antigens in the hyperimmunoglobulinemia E (hyper-IgE) syndrome. *J Allergy Clin Immunol* 1991;87:803-11.
 22. Meyer-Bahlburg A, Renner ED, Rylaarsdam S, Reichenbach J, Schimke LF, Marks A, et al. Heterozygous signal transducer and activator of transcription 3 mutations in hyper-IgE syndrome result in altered B-cell maturation. *J Allergy Clin Immunol* 2012;129:559-62.
 23. Marashi SM, Raeiszadeh M, Enright V, Tahami F, Workman S, Chee R, et al. Influence of cytomegalovirus infection on immune cell phenotypes in patients with common variable immunodeficiency. *J Allergy Clin Immunol* 2012;129:1349-56.
 24. Buckley RH. The long quest for neonatal screening for severe combined immunodeficiency. *J Allergy Clin Immunol* 2012;129:597-604.
 25. Puck JM. Laboratory technology for population-based screening for severe combined immunodeficiency in neonates: the winner is T-cell receptor excision circles. *J Allergy Clin Immunol* 2012;129:607-16.
 26. Verbsky J, Thakar M, Routes J. The Wisconsin approach to newborn screening for severe combined immunodeficiency. *J Allergy Clin Immunol* 2012;129:622-7.
 27. Hanson IC, Shearer WT. Ruling out HIV infection when testing for severe combined immunodeficiency and other T-cell deficiencies. *J Allergy Clin Immunol* 2012;129:875-6.e5.
 28. Speckmann C, Neumann C, Borte S, la Marca G, Sass JO, Wiech E, et al. Delayed-onset adenosine deaminase deficiency: strategies for an early diagnosis. *J Allergy Clin Immunol* 2012;130:991-4.
 29. Borte S, von Döbeln U, Fasth A, Wang N, Janzi M, Winiarski J, et al. Neonatal screening for severe primary immunodeficiency diseases using high-throughput triplex real-time PCR. *Blood* 2012;119:2552-5.
 30. Leiding JW, Holland SM. Warts and all: human papillomavirus in primary immunodeficiencies. *J Allergy Clin Immunol* 2012;130:1030-48.
 31. Ohnishi H, Miyata R, Suzuki T, Nose T, Kubota K, Kato Z, et al. A rapid screening method to detect autosomal-dominant ectodermal dysplasia with immune deficiency syndrome. *J Allergy Clin Immunol* 2012;129:578-80.
 32. Licciardi PV, Balloch A, Russell FM, Burton RL, Lin J, Nahm MH, et al. Pneumococcal polysaccharide vaccine at 12 months of age produces functional immune responses. *J Allergy Clin Immunol* 2012;129:794-800.
 33. Kesserwan C, Sokolic R, Cowen EW, Garabedian E, Heselmeyer-Haddad K, Lee CC, et al. Multicentric dermatofibrosarcoma protuberans in patients with adenosine deaminase-deficient severe combined immune deficiency. *J Allergy Clin Immunol* 2012;129:762-9.
 34. Grunebaum E, Cutz E, Roifman CM. Pulmonary alveolar proteinosis in patients with adenosine deaminase deficiency. *J Allergy Clin Immunol* 2012;129:1588-93.
 35. Cliffe ST, Bloch DB, Suryani S, Kamsteeg EJ, Avery DT, Palendira U, et al. Clinical, molecular, and cellular immunologic findings in patients with SP110-associated veno-occlusive disease with immunodeficiency syndrome. *J Allergy Clin Immunol* 2012;130:735-42.
 36. Chou J, Hanna-Wakim R, Tirosh I, Kane J, Fraulino D, Lee YN, et al. A novel homozygous mutation in recombination activating gene 2 in 2 relatives with different clinical phenotypes: Omenn syndrome and hyper-IgM syndrome. *J Allergy Clin Immunol* 2012;130:1414-6.
 37. Alangari A, Alsultan A, Adly N, Massaad MJ, Kiani IS, Aljebreen A, et al. LPS-responsive beige-like anchor (LRBA) gene mutation in a family with inflammatory bowel disease and combined immunodeficiency. *J Allergy Clin Immunol* 2012;130:481-8.
 38. Lopez-Herrera G, Tampella G, Pan-Hammarström Q, Herholz P, Trujillo-Vargas CM, Phadwal K, et al. Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity. *Am J Hum Genet* 2012;90:986-1001.
 39. Burns SO, Zenner HL, Plagnol V, Curtis J, Mok K, Eisenhut M, et al. LRBA gene deletion in a patient presenting with autoimmunity without hypogammaglobulinemia. *J Allergy Clin Immunol* 2012;130:1428-32.
 40. Hauck F, Randriamampita C, Martin E, Gerart S, Lambert N, Lim A, et al. Primary T-cell immunodeficiency with immunoregulation caused by autosomal recessive LCK deficiency. *J Allergy Clin Immunol* 2012;130:1144-52.
 41. van Montfrans JM, Hoepelman AI, Otto S, van Gijn M, van de Corput L, de Weger RA, et al. CD27 deficiency is associated with combined immunodeficiency and persistent symptomatic EBV viremia. *J Allergy Clin Immunol* 2012;129:787-93.
 42. Thiel J, Kimmig L, Salzer U, Grudzien M, Lebrecht D, Hagen T, et al. Genetic CD21 deficiency is associated with hypogammaglobulinemia. *J Allergy Clin Immunol* 2012;129:801-10.
 43. Roifman CM, Somech R, Kavadas F, Pires L, Nahum A, Dalal I, et al. Defining combined immunodeficiency. *J Allergy Clin Immunol* 2012;130:177-83.
 44. Spielberger BD, Woellner C, Dueckers G, Sawalle-Belohradsky J, Hagl B, Anslinger K, et al. Challenges of genetic counseling in patients with autosomal dominant diseases, such as the hyper-IgE syndrome (STAT3-HIES). *J Allergy Clin Immunol* 2012;130:1426-8.
 45. Chapel H, Lucas M, Patel S, Lee M, Cunningham-Rundles C, Resnick E, et al. Confirmation and improvement of criteria for clinical phenotyping in common variable immunodeficiency disorders in replicate cohorts. *J Allergy Clin Immunol* 2012;130:1197-8.
 46. Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. *Blood* 2008;112:277-86.
 47. Griffith LM, Cowan MJ, Notarangelo LD, Puck JM, Buckley RH, Candotti F, et al. Improving cellular therapy for primary immune deficiency diseases: recognition, diagnosis, and management. *J Allergy Clin Immunol* 2009;124:1152-60.

48. Martinez CA, Shah S, Shearer WT, Rosenblatt HM, Paul ME, Chinen J, et al. Excellent survival after sibling or unrelated donor stem cell transplantation for chronic granulomatous disease. *J Allergy Clin Immunol* 2012;129:176-83.
49. Rachid R, Bonilla TA. The role of anti-IgA antibodies in causing adverse reactions in gammaglobulin infusion in immunodeficient patients. A comprehensive review of the literature. *J Allergy Clin Immunol* 2012;129:628-30.
50. Massoud AH, Guay J, Shalaby KH, Bjur E, Ablona A, Chan D, et al. Intravenous immunoglobulin attenuates airway inflammation through induction of forkhead box protein 3-positive regulatory T cells. *J Allergy Clin Immunol* 2012;129:1656-65.
51. Micol R, Kayal S, Mahlaoui N, Beauté J, Brosselin P, Dudoit Y, et al. Protective effect of IgM against colonization of the respiratory tract by nontypeable *Haemophilus influenzae* in patients with hypogammaglobulinemia. *J Allergy Clin Immunol* 2012;129:770-7.
52. Krause K, Feist E, Fiene M, Kallinich T, Maurer M. Complete remission in 3 of 3 anti-IL-6-treated patients with Schnitzler syndrome. *J Allergy Clin Immunol* 2012;129:848-50.
53. Côte M, Ménager MM, Burgess A, Mahlaoui N, Picard C, Schaffner C, et al. Munc18-2 deficiency causes familial hemophagocytic lymphohistiocytosis type 5 and impairs cytotoxic granule exocytosis in patient NK cells. *J Clin Invest* 2009;119:3765-73.
54. Saltzman RW, Monaco-Shawver L, Zhang K, Sullivan KE, Filipovich AH, Orange JS. Novel mutation in STXBP2 prevents IL-2-induced natural killer cell cytotoxicity. *J Allergy Clin Immunol* 2012;129:1666-8.