

Advances in basic and clinical immunology in 2013

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A significant number of contributions to our understanding of primary immunodeficiencies (PIDs) in pathogenesis, diagnosis, and treatment were published in the *Journal* in 2013. For example, deficiency of mast cell degranulation caused by signal transducer and activator of transcription 3 deficiency was demonstrated to contribute to the difference in the frequency of severe allergic reactions in patients with autosomal dominant hyper-IgE syndrome compared with that seen in atopic subjects with similar high IgE serum levels. High levels of nonglycosylated IgA were found in patients with Wiskott-Aldrich syndrome, and these abnormal antibodies might contribute to the nephropathy seen in these patients. New described genes causing immunodeficiency included caspase recruitment domain 11 (*CARD11*), mucosa-associated lymphoid tissue 1 (*MALT1*) for combined immunodeficiencies, and tetratricopeptide repeat domain 7A (*TTC7A*) for mutations associated with multiple atresia with combined immunodeficiency. Other observations expand the spectrum of clinical presentation of specific gene defects (eg, adult-onset idiopathic T-cell lymphopenia and early-onset autoimmunity might be due to hypomorphic mutations of the recombination-activating genes). Newborn screening in California established the incidence of severe combined immunodeficiency at 1 in 66,250 live births. The use of hematopoietic stem cell transplantation for PIDs was reviewed, with recommendations to give priority to research oriented to establish the best regimens to improve the safety and efficacy of bone marrow transplantation. These represent only a fraction of significant research done in patients with PIDs that has accelerated the quality of care of these patients. Genetic analysis of patients has demonstrated multiple phenotypic expressions of immune deficiency in patients with nearly identical genotypes,

suggesting that additional genetic factors, possibly gene dosage, or environmental factors are responsible for this diversity. (*J Allergy Clin Immunol* 2014;133:967-76.)

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Reports in clinical immunology published in the *Journal* in 2013 continue to define all aspects of human immunodeficiencies, widening the spectrum of clinical presentation and increasing the number of genes responsible to maintain immune function.

The increasing complexity of primary immunodeficiencies (PIDs) was discussed by Maggina and Gennery,¹ who argued that the current international classification² based on the traditional compartmentalization of the immune system (T cells, B cells, innate immunity, and complement) might no longer be optimal for clinical use. They described several examples of gene defects causing well-known PIDs that also present with widely diverse clinical phenotypes. For example, different types of mutations (gain-of-function, null, and residual function mutations) in the Wiskott-Aldrich syndrome (WAS) protein can manifest as 3 different entities: X-linked thrombocytopenia, X-linked neutropenia, or WAS. The authors propose to develop 2 reference catalogs: one according to primary immunologic function and a second to describe specific gene mutations with genotype/phenotype correlation, if available. In addition, they propose to have a treatment catalog to ensure that patients obtain the most updated and appropriate management. Notarangelo³ reviewed specific disorders of T cells characterized by incomplete loss of function that provide further insight into immune mechanisms. These included recently described gene defects: lymphocyte specific tyrosine kinase (*LCK*) deficiency, Ras homology family member H (*RHOH*) deficiency, macrophage stimulating 1 (*MST1*) deficiency, dedicator of cytokinesis 8 (*DOCK8*) deficiency, IL-2-inducible tyrosine kinase deficiency (*ITK*), and coronin 1A (*CORO1A*) deficiency.

With a different prospective based on regional and geographic differences of disease patterns in patients with immunodeficiency disorders, Al Herz and Al Moussa⁴ highlighted the distinct proportion of defects in recombination-activating gene (RAG) 1 and 2 proteins and MHC class II antigen expression as causes of combined immunodeficiencies (CIDs) in the Middle East (where such defects account for >60% of reported cases) compared with reports from US, Australian, and Asian cohorts, where IL-2 receptor γ deficiency is the predominant cause. They discussed the difficulties for diagnosis and treatment of immunodeficiencies in areas with limited access to current technologies and briefly explained reasons for different distribution of genetic lesions, such as the increased frequency of autosomal

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Abbreviations used

AD:	Autosomal dominant
ADA:	Adenosine deaminase
AR:	Autosomal recessive
AT:	Ataxia telangiectasia
BLNK:	B-cell linker
CARD11:	Caspase recruitment domain 11
CGD:	Chronic granulomatous disease
CID:	Combined immunodeficiency
CMC:	Chronic mucocutaneous candidiasis
CORO1A:	Coronin 1A
CVID:	Common variable immunodeficiency
DOCK8:	Dedicator of cytokinesis 8
G-CSF:	Granulocyte colony-stimulating factor
HIES:	Hyper-IgE syndrome
HSCT:	Hematopoietic stem cell transplantation
IBD:	Inflammatory bowel disease
IL-10R:	IL-10 receptor
JAK3:	Janus-associated kinase 3
KREC:	Kappa-deleting recombination excision circle
MALT1:	Mucosa-associated lymphoid tissue 1
NK:	Natural killer
PEG:	Polyethyleneglycol
PID:	Primary immunodeficiency
RAG:	Recombination-activating gene
SCID:	Severe combined immunodeficiency
STAT:	Signal transducer and activator of transcription
TACI:	Transactivator and calmodulin inactivator
TCR:	T-cell receptor
TREC:	T-cell receptor excision circle
TTC7A:	Tetratricopeptide repeat domain 7A
WAS:	Wiskott-Aldrich syndrome
WASP:	Wiskott-Aldrich syndrome protein
ZAP70:	ζ Chain-associated protein of 70 kDa

recessive (AR) inheritance observed in communities where the practice of consanguineous marriage is common.

PIDs: ADVANCES IN MECHANISMS OF DISEASE

Orange⁵ provided a comprehensive review of the current understanding of natural killer (NK) cell disorders, whether isolated or as part of another immunodeficiency syndrome, with diagnostic criteria and the genetic mutations that have been associated with inherited NK cell dysfunction. Compared with disorders of adaptive immunity, these are fewer in number thus far. Two genes associated with low NK cell counts are GATA-binding protein 2 (*GATA2*) and minichromosome maintenance 4 (*MCM4*). Another gene associated with defective function of NK cells is attributed to a mutant *FCGR3A* gene that encodes the Fc receptor for NK cells (CD16). This defective gene has been identified in 3 unrelated families. Campbell and Hasegawa⁶ reviewed current concepts of NK cell biology, including the classification of NK cells as members of the group 1 innate lymphoid cells, which secrete IFN- γ but not T_H2 cytokines. The list of activating and inhibiting receptors for NK cell function continues to expand. This article also reviewed the crosstalk between innate and adaptive immunity through specific antibodies and cytokines, resulting in the control of viral infections and malignancies.

The process of development and differentiation of human B cells was summarized by Pieper et al,⁷ who highlighted the

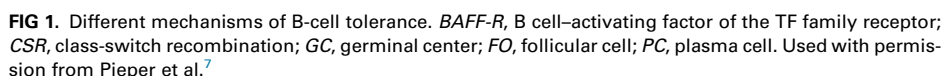
contribution of case reports of genetic immunodeficiencies that help define the function of the putative genes involved. These authors also pointed out differences of function of homologous proteins in mice and human subjects. For example, deletion of B-cell linker (BLNK) protein in mice results in a B-cell development arrest at the pre-B-cell stage; however, with *BLNK* deletion in human subjects, the arrest is in the pro-B-cell stage. Other considerations were B-cell egress from bone marrow to B-cell follicles, formation of germinal centers, and homing into the marginal zones in the spleen. Also discussed in the review were B-cell peripheral differentiation, somatic hypermutation, and development into memory B cells and B-cell plasma cells, as well as the different mechanisms of B-cell tolerance (Fig 1).⁷ Understanding these mechanisms is important for the development of further strategies to treat autoimmunity, malignancy, and immunodeficiency.

Mehling et al⁸ studied the effects of fingolimod, a sphingosine-1-phosphate antagonist used in the management of multiple sclerosis. Fingolimod blocks lymphocyte egression from lymph nodes. By measuring T-cell subsets in peripheral blood, they found that naive CD4⁺ and CD8⁺ T cells were trapped in the lymph nodes within the first 3 hours, whereas central memory T cells were maintained at the same concentration in the circulation. Results from transwell experiments with gradients of the chemokines CXCL12, CCL19, and CCL21 were also consistent with the increased migration of naive T cells compared with memory T cells.

In the last few years, newly described subsets of CD4⁺ helper T cells have added complexity to the T_H1/T_H2 paradigm in modulation of the immune response. These new subsets include T_H17, T_H9, T_H22, follicular helper T, and regulatory T cells. Hirahara et al⁹ discussed the characteristics of these cells and also described the flexibility of their classical phenotypes and overlapping functions. For example, IL-10 is expressed and secreted by more than 1 subset of helper T cells. These changes in phenotype stability are regulated by the expression of specific transcription factors, as well as changes in the cell microenvironment.

Advances in defining the pathophysiology of well-defined syndromes focused on WAS and hyper-IgE syndrome (HIES). Aberrant glycosylation of immunoglobulin has been previously reported in patients with WAS, but Shimizu et al¹⁰ studied serum levels of IgA in patients with WAS older than 10 years and found increased concentrations of these abnormal IgA levels compared with levels seen in control subjects. Circulating IgG-IgA complex levels were also increased. The authors postulate that these findings contribute to the autoimmune glomerulopathy seen in 40% to 70% of patients with WAS. Of note, glomerulopathy cleared in 1 patient with WAS who was studied before and after hematopoietic stem cell transplantation (HSCT). Using a murine model for WAS, Lang et al¹¹ demonstrated decreased viral autoimmunity as measured by interferon production in response to lymphochoriomeningitis virus infection. Compared with control mice, there were fewer CD8⁺ T cells specific to viral proteins in the blood and spleen, with equal numbers of total CD8⁺ T cells.

Wiskott-Aldrich syndrome protein (WASP) participates in regulation of T-cell activation and actin reorganization. Watanabe et al¹² demonstrated that T-cell receptor (TCR)/CD3 ligation decreases intracellular WASP levels, an event that is blocked when a protease inhibitor is present. It was further shown that



Patients with autosomal dominant (AD) HIES syndrome present with high serum IgE levels, although with relatively mild allergy manifestations compared with those seen in patients with primarily allergic disorders and similar high serum IgE levels. Siegel et al¹⁴ compared patients with AD-HIES with patients with severe atopic dermatitis and a group of healthy control subjects. Both patient groups presented with eczema and had similar geometric means of total serum IgE and food-specific IgE (milk and egg) levels; however, the percentage of patients reporting food-induced anaphylaxis was lower in the AD-HIES group than in patients with eczema (8.5% vs 33.3%). The authors hypothesized that this observation could be explained by decreased mast cell degranulation induced by IgE. Patients with AD-HIES had wheals induced by histamine with sizes

Poliani et al¹⁷ studied thymi from 2 infants with defects of ζ chain-associated protein of 70 kDa (ZAP70). Compared with control subjects, these patients had smaller thymic medullary areas and reduced expression of autoimmune regulator and

markers of mature medullary thymic epithelial cells. These observations might help explain the clinical manifestations of immune dysregulation that have been observed in some patients with ZAP70 deficiency. Perez de Diego et al¹⁸ took advantage of proteomic technology to identify therapeutic targets for inherited susceptibility to herpes simplex. They analyzed fibroblasts from a patient with a defect in unc-93 homolog B1 (*Caenorhabditis elegans* [*UNC93B*]) and compared these with fibroblasts of a healthy control subject. The authors identified specific protein networks and identified the upregulation of superoxide dismutase 2 as a candidate for potential intervention.

Driessen et al¹⁹ explored mechanisms of antibody deficiency in a cohort of 15 patients with ataxia telangiectasia (AT), from which only 3 patients presented with hypogammaglobulinemia in infancy and 4 patients presented with late-onset AT. T- and B-cell phenotyping demonstrated changes that were most significant in patients with low IgG levels: low B-cell numbers, low percentages of naive and transitional B cells, and increased CD21^{low}CD38^{low} anergic B cell numbers. Naive CD4⁺ and CD8⁺ T-cell numbers were also reduced. The somatic hypermutation rate was not affected, suggesting affinity maturation was conserved. However, class-switching recombination events were reduced when measured based on the quantification of *IGH* transcripts. The authors conclude that patients with AT might have decreased immunity because of reduced B- and T-cell production secondary to deficient VDJ recombination and reduced recombination of distal *IGH* constant genes (*IGHG2*, *IGHG4*, and *IGHA2*). Because those with late-onset AT did not present these findings, the degree of immune deficiency is likely dependent on residual ATM kinase activity.

The role of transactivator and calmodulin inactivator (TACI) in the pathogenesis of common variable immunodeficiency (CVID) has become unclear, with reports of relatives of patients with CVID carrying the same mutations yet not presenting with hypogammaglobulinemia. Martinez-Gallo et al²⁰ showed that peripheral blood B cells isolated from members of 7 families presenting with TACI mutations and normal IgG levels were defective *in vitro*. TACI expression was decreased and could not be upregulated by Toll-like receptor 9 stimulation. In addition, a proliferation inducing ligand binding was impaired. The authors suggest that deleterious heterozygous mutations in TACI participate in the development of CVID; however, environmental events or other gene defects might be necessary for pathogenesis.

In a cohort of 193 patients with primary antibody disorders, Chew et al²¹ investigated whether the 1858T allele of the protein tyrosine phosphatase nonreceptor type 22 (*PTPN22*) was associated with the occurrence of autoimmunity because this association occurs in immunocompetent populations. The presence of this allele has been associated with increased risk of type I diabetes, Graves disease, rheumatoid arthritis, and lupus. Sixteen (43%) of 37 patients with antibody disorders and autoimmunity had at least 1 T allele compared with 27 (1%) of 156 without autoimmune disease.

Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis syndrome is an inflammatory disease of unknown pathogenesis with a diagnosis based on clinical presentation. Kolly et al²² studied 15 patients with periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis syndrome, reporting

that IL-1 β production by stimulated monocytes is increased at baseline and during a febrile attack.

PIDs: REPORTS OF NOVEL GENE DEFECTS

The accelerated rate of discovering primary immune defects was illustrated by a review of 19 new gene defects responsible for immunodeficiency disorders, which was published within 1 year of the last international classification report. Parvaneh et al²³ summarized the clinical phenotypes of these gene defects: 4 resulted in CIDs, 4 were defects of innate immunity (2 presenting with herpes encephalitis), 3 were predominantly antibody defects, and there were 2 each in the categories of well-defined syndromes with immunodeficiency and deficiencies of immune dysregulation and autoinflammatory disorders. There was one description of a new defect in the group of congenital defects of phagocytes.

Recently developed genetic technologies, such as whole-genome and whole-exome sequencing, continue to uncover genes causing inherited defects. Greil et al²⁴ described an infant of consanguineous parents who has *Pneumocystis jiroveci* pneumonia at 6 months of age. Immunologic investigations showed normal T- and B-cell counts, but T-cell proliferation to mitogens was strongly impaired. Phenotyping revealed that T cells were predominantly naive T cells. Whole-genome sequencing suggested only 1 potential defect, which was identified as a premature stop codon in the gene caspase recruitment domain 11 (*CARD11*). Reconstitution studies with a *CARD11*-deficient Jurkat T-cell line demonstrated that the mutated *CARD11* protein did not facilitate IL-2 production and cell proliferation after CD3/CD28 stimulation.

Stepensky et al²⁵ reported a 9-month-old patient with an upper respiratory tract infection who was found to have panhypogammaglobulinemia. Lymphocyte phenotype and T-cell receptor excision circle (TREC) test results were reported to be within the normal range. Mitogen-stimulated proliferation of lymphocytes was normal. However, B-cell phenotyping suggested a block in the transitional stage of B-cell development. Because of parent consanguinity, whole-genome sequencing demonstrated a homozygous deletion of exon 21 in the gene *CARD11*. T-cell proliferation induced by CD3/CD28 was nonreactive. HSCT from the patient's brother resulted in complete immune reconstitution.

Jabara et al²⁶ studied 2 siblings from consanguineous parents who presented with recurrent pneumonia, meningitis, and failure to thrive. T- and B-cell percentages were within the normal range; however, T-cell proliferation to mitogens and antigens was decreased. Whole-genome sequencing revealed a homozygous missense mutation in mucosa-associated lymphoid tissue 1 (*MALT1*) that was predicted to result in protein degradation. Reconstitution experiments were performed with cells from *Malt1* knockout mice: IL-2 secretion after phorbol 12-myristate 13-acetate/ionomycin stimulation in murine T cells was detected when these cells were transduced with wild-type human *MALT1* stimulation but not when they were transduced with the mutated *MALT1*. The authors suggest testing for mutations in this gene in patients with CIDs and normal T- and B-cell counts.

Congenital multiple intestinal atresias is a rare inherited condition that can associate with CID. Chen et al²⁷ performed whole-exome sequencing in 15 subjects from 5 families with CID with multiple intestinal atresias. Deleterious mutations in

the tetratricopeptide repeat domain 7A (*TTC7A*) gene were found in all 5 families. *TTC7A* has been previously shown to play a role in cellular functions, including cell-cycle control, protein scaffolding, and intracellular signaling.

Magerous-Chatinet et al²⁸ reported an infant of consanguineous parents with repeated infections, hepatosplenomegaly, and lymphadenopathy who had lymphocytosis consisting mostly of double-negative (ie, CD4[−]CD8[−]) lymphocytes and suggesting autoimmune lymphoproliferative disease. When the FAS ligand in serum was not detected, sequence analysis of TNF ligand superfamily, member 6 (*TNFSF6* or *FASLG*), showed a premature stop codon in exon 1, resulting in absent protein expression.

The simultaneous occurrence of 2 or more gene defects in a patient might modify traditional phenotypes. This case is illustrated by the report of 4 brothers of consanguineous parents who presented with severe eczema, diarrhea, prolonged failure to thrive, and frequent respiratory tract infections.²⁹ The forkhead box protein 3 (*FOXP3*) gene sequence was normal, and regulatory T cells had normal suppressive activity. Genome-wide genotyping identified homozygous pathogenic mutations in *DOCK8* and *CLEC7A*, which were previously associated with AR-HIES and CMC, respectively. The authors postulate that the combination of gene defects was responsible for the unusual clinical presentation in this family.

Hsu et al³⁰ reported 2 unrelated patients with moderate clinical symptoms corresponding to AD-HIES. Molecular analysis revealed *STAT3* mutations with 33% mosaicism in several tissues, including blood cells, hair follicles, and stomach biopsy specimens. The authors postulate that mosaicism might explain the incomplete clinical presentation and represents a diagnostic challenge because detection requires careful examinations of sequencing output and might be missed by the automated software programs used in gene sequencing.

Giancane et al³¹ studied a 5-month-old girl with severe pneumonia and sepsis who was found to have low serum IgG levels with increased IgM levels. Opportunistic infections, female sex, and hypohydrosis suggested investigation of IκBα protein as a cause of the AD form of ectodermal dysplasia with immunodeficiency. The authors report a newly characterized missense *IKBA* mutation predicted to prevent IκBα from activating nuclear factor κB.

PIDs: NEW PHENOTYPES FOR KNOWN GENE DEFECTS

The spectrum of immunologic disorders caused by *RAG1* mutations continues to expand. Abraham et al³² reported a patient with T-cell lymphopenia presenting at 38 years of age with a clinical syndrome including mildly increased IgE levels and chronic dermatitis. *RAG1* sequencing detected a heterozygous mutation previously reported to cause severe combined immunodeficiency (SCID) or Omenn syndrome when present in a homozygous mutation. The authors suggested that *RAG1* hypomorphic mutations might explain this patient's T-cell lymphopenia.

Henderson et al³³ reported early-onset autoimmunity as a clinical phenotype within the spectrum of RAG deficiency in 2 sisters with T-cell lymphopenia, preserved B-cell counts, and normal immunoglobulin levels. These sisters had low antibody responses to childhood vaccines, and one of the sisters had autoimmune cytopenias, polymyositis, and Raynaud symptoms.

Further testing demonstrated biallelic *RAG1* mutations, leading to reduced recombinase activity. This report adds to the list of conditions that present with autoimmunity in early infancy.

Cattaneo et al³⁴ reported 3 patients with a state of increased frequency of infections with normal T- and B-cell numbers, although with different subset abnormalities, such as reduced memory B-cell numbers in 2 patients. Their T-cell repertoires were restricted, and TREC levels were undetectable. Compound heterozygous gene mutations were found in Janus-associated kinase 3 (*JAK3*). Of note, there was significant engraftment of maternal T cells in 1 of the patients older than 33 months. Farnault et al³⁵ reported a 27-month-old boy with recurrent infections and with a hypomorphic mutation in *JAK3*, presenting with expansion of a CD56[−]CD16⁺KIR⁺NKG2C⁺ subset of NK cells. Blood NK cells were 58% of lymphocytes, and the *IL7R* gene sequence was normal. These 2 cases represent unusual manifestations of *JAK3* deficiency, which has traditionally been described as a T[−]B⁺NK[−] SCID.

CORO1A deficiency has been associated with an SCID phenotype. Moshous et al³⁶ reported 3 siblings with EBV-associated B-cell lymphomas presenting in infancy. Whole-exome sequencing revealed a missense mutation in *CORO1A*, with considerably reduced protein expression. Immunologic studies showed T-cell lymphopenia with absent naive T cells, TCR Vβ repertoire, and oligoclonality with expansion of memory T cells. The authors conclude that *CORO1A* defects should be suspected in infants with EBV-associated B-cell lymphomas.

The list of gene defects that might present with characteristics of Omenn syndrome is growing. Henderson et al³⁷ reported an infant who had severe desquamative eczema and was shown to have neurosensory deafness, absolute neutropenia, and lymphopenia with the presence of T cells, which were found to be oligoclonal. He was the brother of a girl given a previous diagnosis of reticular dysgenesis and had a homozygous mutation in the adenylate kinase 2 (*AK2*) gene. Testing for *AK2* mutations revealed the same homozygous genetic lesion.

AD *STAT1* gain-of-function mutations are associated with CMC. Wang et al³⁸ reported a 6-year-old girl who had chronic granulomas caused by *Fusarium solani*. Exome sequencing resulted with a previously described pathogenic *STAT1* mutation. Sampaio et al³⁹ reported *STAT1* gain-of-function mutations in 3 patients with histoplasmosis and 2 patients with refractory coccidioidomycosis. These articles extend the range of infectious agents affecting patients with *STAT1* mutations in addition to *Candida* species. Because these *STAT1* mutations are also associated with autoimmunity, Uzel et al⁴⁰ examined a series of 73 patients with immunodeficiency, polyendocrinopathy, enteropathy, X-linked-like syndrome who did not have *FOXP3* mutations. They found 5 patients presenting with *STAT1* gain-of-function mutations, with 4 of these patients also having chronic candidiasis. Romberg et al⁴¹ described 4 members of a family with the gain-of-function *STAT1* mutation pE235A who had, in addition to CMC, B-cell lymphopenia and antibody deficiency. It is still unclear what factors determine which immunologic functions are affected when *STAT1* gain-of-function mutations are present.

Allenspach et al⁴² reported a patient who presented with frequent infections and hypogammaglobulinemia in childhood and received a diagnosis of CVID. At 20 years of age, he had pure red cell aplasia and profuse diarrhea. A colon biopsy showed

massive apoptosis of crypt cells, suggesting dyskeratosis congenita. Pathogenic mutations were found in the dyskeratosis congenita (*DKC1*) gene and decreased expression of dyskerin protein. This report reminds us that patients with defects in *DKC1* might initially present with hypogammaglobulinemia.

PIDs: DIAGNOSTIC ISSUES

Two articles report patients with unusual clinical findings. Bacon et al⁴³ reported a patient with DNA ligase 4 deficiency who had a B-cell lymphoma that was not associated with EBV. Al-Zahrani et al⁴⁴ described costochondral dysplasia in a premature infant with a diagnosis of reticular dysgenesis. Costochondral dysplasia has not previously been associated with an immune disorder other than adenosine deaminase (ADA) deficiency.

Defects of the IL-12/IFN- γ axis might require an additional event to show susceptibility to mycobacterial infection, as shown by Tassone et al.⁴⁵ They reported a patient with autoimmune hepatitis who received immunosuppression for more than 10 years and was found to have intra-abdominal mycobacterial granulomas. Decreased expression of *IL12RB* and IL-12-induced IFN- γ led to gene sequencing studies and confirmation of *IL12RB1* deficiency.

In addition to the identification of genetic lesions, confirmation of the mode of inheritance is important for predicting the risk of recurrence. Geeden et al⁴⁶ reported an infant with recurrent infections who was found to have ADA deficiency. Molecular diagnosis revealed a homozygous deletion mutation in the *ADA* gene that produced a premature stop codon. The father but not the mother was a carrier of this mutation. A single nucleotide polymorphism array revealed uniparental disomy of chromosome 20, which carries a very low risk of recurrence should the parents consider conceiving again. Alsina et al⁴⁷ reported a patient with X-linked SCID, with the mutation pR226C in the *IL2RG* gene, which was previously known to cause SCID. His mother was a heterozygous carrier who had the mutation at different percentages according to the tissue examined. Her mosaicism was lowest at 8% in lymphocytes and highest at 20% for neutrophils and other tissues examined, reflecting the selective advantage of lymphocytes expressing the wild-type IL-2R γ protein for their development. Her risk of having another boy with SCID might be decreased by this mosaicism.

By reporting the analysis of Bruton tyrosine kinase (*BTK*) gene missense mutations in 12 patients with antibody deficiencies, Abbott et al⁴⁸ reminded us that not every amino acid change results in loss of function. Identification of gene mutations should be followed by assessment of stability, expression, and function of the mutant protein.

CVID is characterized by late-onset B-cell deficiency with absent or reduced production of antibodies and hypogammaglobulinemia. In addition, various T-cell defects can occur, and the diagnosis of CID is often considered in these cases. Those with T-cell defects are more susceptible to opportunistic infections and might present with autoimmunity and malignancies. To improve the accuracy of patient diagnosis and prognosis, Kamae et al⁴⁹ studied TRECs and kappa-deleting recombination excision circles (KRECs) in a cohort of 40 hypogammaglobulinemic patients who did not have a molecular diagnosis and classified them into 4 groups according to the presence of normal numbers of TRECs and immunoglobulin KRECs: group A (TREC⁺KREC⁺), 19 patients; group B (TREC⁺KREC⁻), 7

patients; group C (TREC⁻KREC⁺), 8 patients; and group D (TREC⁻KREC⁻), 6 patients. Group D most resembles the description of CID and presented with a high incidence of opportunistic infections, autoimmunity, and malignancy. Group C did not fulfill the criteria for CID with B cells; however, both groups C and D are likely to benefit from patient management similar to those with SCID/CID. Autoimmunity was significant in group B. The authors proposed to use this classification to consider therapeutic options for individual patients with CVID.

NEWBORN SCREENING OF T-CELL DEFICIENCIES

Kwan et al⁵⁰ reported 2-year period data from the SCID newborn screening program in California. From approximately 1 million newborns tested, 50 cases with low TREC counts were later confirmed to have T-cell lymphopenia. Fourteen of these 50 cases had diagnoses of SCID and received HSCT. One was given a diagnosis of complete DiGeorge syndrome and received a thymus transplant. Survival of these patients with these severe conditions was remarkable at 93%. The diagnoses of the other 35 patients with T-cell lymphopenia were secondary T-cell lymphopenia (n = 9), nonimmunologic genetic syndromes (n = 12), extreme prematurity (n = 8), and CIDs (n = 6). In addition to improvement of survival outcomes, universal newborn screening has helped to establish the true incidence of these relatively rare diseases in California, which for SCID appears to be 1 in 66,250 live births. Of significance, 3 research groups reported patients with SCID who had normal TREC counts at birth. La Marca et al⁵¹ reported 3 patients with delayed-onset ADA-SCID with diagnosis at 3, 4, and 7 years of age and studied their newborn dried blood spots. TREC analyses were within normal limits, but adenosine levels were increased. This report proposes that newborn screening should include tandem mass spectrometry, considering its low cost. Lev et al⁵² reported 8 patients with MHC class II deficiency and reported TCR V β spectratyping and TREC quantification as a measure of thymic activity. Analysis of the TCR V β repertoire appeared normal when performed on total lymphocytes; however, clonal expansion was evident when only CD4⁺ T cells were examined. In contrast, the CD8⁺ T-cell V β repertoire distribution was normal. When TREC counts were measured, they were detected in the normal range. Similarly, Kao et al⁵³ reported 2 patients with MHC class II deficiency who had normal TREC counts at birth. The authors emphasize that normal TREC counts would not rule out MHC class II deficiency.

PIDs: MANAGEMENT

Cole et al⁵⁴ reported a cohort of 62 patients with chronic granulomatous disease (CGD) identified in the United Kingdom and Ireland, 52 (92%) of whom were male and had X-linked inheritance. The median age at diagnosis was 5.21 years in male patients and 4.06 years in female patients. Thirty (48%) patients received HSCT, 28 of whom were male. The authors compared survival and complication rates with HSCT. Survival was similar in both groups at 90%; patients without HSCT had a rate of severe infections at 0.71 episodes/CGD life year compared with 0.15 episodes/CGD life year after receiving HSCT. Although the contrast of infectious episodes did not control for disease severity or patient age, the results support considering HSCT early in the management of patients with

CGD. Koker et al⁵⁵ presented a series of 89 Turkish patients with a diagnosis of CGD. Fifty-five (61.8%) patients were suspected of having AR inheritance. The authors investigated nicotinamide adenine dinucleotide phosphate oxidase activity, as measured using the dihydrorhodamine assay, and studied correlation with disease severity. The authors emphasized that severity of clinical presentation is associated with residual nicotinamide adenine dinucleotide phosphate but not with the specific gene that is mutated and should be considered for assessment of prognosis and use of HSCT. Notarangelo⁵⁶ commented on the long road to optional management of patients with CGD and predicted better outcomes with improvement in methods of HCST and gene therapy.

Horn and Cowan⁵⁷ reviewed the published literature concerning outcomes of HSCT for SCID. On the basis of available data for immunoreconstitution and mortality, they report on the most optimal conditioning regimens and graft-versus-host prophylaxis for the different SCID phenotypes. The authors propose that the currently increased number of infants with SCID identified through the newborn screening program should receive the best treatment protocols. The authors also discussed the need to define long-term immune reconstitution and potential late effects of transplantation, such as neurologic deficits, delayed growth, and development. Haddad et al⁵⁸ reviewed B-cell immunity outcomes after HSCT in patients with SCID with regard to the use of conditioning regimens. They concluded that available studies did not allow a definitive answer to this question; however, the data suggested that some genetic defects, such as *IL7R* deficiency, would result in normal B-cell function without B-cell chimerism. Potential long-term adverse effects should be considered in the decision of whether to use conditioning regimens and graft-versus-host disease prophylaxis to improve B-cell chimerism.

Along these lines, the neuropsychological evaluation of 21 patients with hemophagocytic lymphohistiocytosis who received HSCT was reported by Jackson et al.⁵⁹ Cohort characteristics included that most patients were diagnosed with perforin deficiency (n = 11) and that 16 had reduced-intensity conditioning. Full-scale intelligence quotient, social communication, and quality of life were reduced to 80% compared with values seen in healthy siblings. The authors acknowledged that these late neurologic effects might also result from the hemophagocytic lymphohistiocytosis because it is unclear whether these deficiencies were present before transplantation.

Lawrence et al⁶⁰ reported the presence of allergic disorders in 9 (50%) of a cohort of 18 patients with ADA-SCID who received HSCT, gene therapy, and/or polyethyleneglycol (PEG)-ADA. Eight of the 9 patients with allergy symptoms were receiving PEG-ADA compared with 3 of 9 patients not currently receiving PEG-ADA, suggesting that severity of disease, management success, or both are determinant factors for allergy.

Al-Mousa et al⁶¹ reported 1 patient with *DOCK8* deficiency who received an HLA-matched stem cell transplant without a conditioning regimen. Their patient presented with lymphoid and myeloid chimerism at 12 months. He was able to clear *Cryptosporidium* species infection and viral infections, although he had chronic graft-versus-host disease. The authors raised the questions of whether HSCT for *DOCK8* deficiency can be successful with limited conditioning for patients in critical condition.

Patients with deficiencies in the IL-10 receptor or IL-10 are characterized by refractory inflammatory bowel disease (IBD)

TABLE I. Selected key advances in basic and clinic immunology in 2013

PIDs: Mechanisms of disease
• High levels of nonglycosylated IgA contribute to nephropathy in patients with WAS. • TCR ligation causes WASP degradation, controlling T-cell activation. • Defective STAT3 signaling impairs mast cell degranulation and CD8 T-cell activation. • Antibody deficiency in patients with AT is caused by disturbed B- and T-cell homeostasis and reduced immune repertoire diversity. • <i>TACI</i> mutations impair B-cell function in healthy mutation carriers.
PIDs: New genes
• <i>CARD11</i> inactivation is associated with SCID. • <i>MALT1</i> mutation causes CIDs. • <i>TTC7A</i> mutations are associated with multiple atresia with CID. • Combined <i>DOCK8</i> and <i>CLECL7A</i> mutations cause immunodeficiency.
PIDs: New phenotypes
• Adult-onset idiopathic T-cell lymphopenia and early-onset autoimmunity might be due to a heterozygous <i>RAG1</i> mutation. • Hypomorphic <i>JAK3</i> mutations might allow maternal T-cell engraftment and development of hypofunctional NK cells. • <i>CORO1A</i> deficiency might present with immunodeficiency and EBV-associated B-cell lymphoproliferation.
PIDs: Diagnosis
• Newborn screening in California established the incidence of SCID at 1 in 66,250 live births. • Patients with MHC class II deficiency and late-onset ADA-SCID might have normal TREC levels at birth.
PIDs: Treatment
• Patients with ADA-SCID on PEG-ADA present with increased frequency of allergic disease. • IL-10R-deficient patients significantly decrease symptoms after HSCT. • G-CSF therapy for isolated CMC might result in complete remission.

presenting in childhood. In a series of 40 children with IBD, Engelhardt et al⁶² searched for mutations in the *IL10* and IL-10 receptor (*IL10R*) genes. Seven (18%) patients were found with deleterious mutations in the *IL10R* genes, 3 patients with homozygous mutations in *IL10RA*, 1 patient with compound heterozygous mutations in *IL10RB*, and 2 patients with a homozygous mutation in *IL10RB*. Compared with the other 33 patients without mutations in this series, IL-10R-deficient patients were younger, although with a similarly severe course of disease. One of the patients received an HLA-matched HSCT and was doing well after a year. By contrast, the other 6 patients continue with colitis requiring multiple immunosuppression regimens and surgeries. Two patients with IL-10 deficiency and IBD also received HSCT and resolved their colitis. The authors recommend looking for defects of IL-10/IL-10R in pediatric patients with IBD because HSCT might be curative.

Three articles favor the use of HSCT for treatment of severe immunodeficiencies while patients were active with chronic viral infections. Kim et al⁶³ reported clearance of bacterial and viral infections in patients with ZAP70 deficiency using an HLA-matched donor. Slatter et al⁶⁴ reported that 4 of 5 patients cleared cytomegalovirus, respiratory syncytial virus, and adenoviral infections after receiving HSCT. Toyoda et al⁶⁵ used a cord blood transplant with myeloablative conditioning, rituximab, and antiviral medications in an 18-month-old boy with WAS who had refractory thrombocytopenic purpura and chronic cytomegalovirus infection. The patient was immunoreconstituted without thrombocytopenic purpura recurrence.

THERAPEUTIC USE OF IMMUNOGLOBULINS

Gelfand et al⁶⁶ reviewed indications for the use of IgG replacement therapy in antibody deficiency conditions and discussed scenarios in which the use of this therapy might not be justified, such as for patients with IgG subclass deficiency not associated with increased frequency of infections. They emphasized the need for establishing objective criteria to determine whether a patient benefits from IgG replacement therapy, chief among them a validated functional assay of antibody avidity. Agarwal and Cunningham-Rundles⁶⁷ developed and proposed a scoring system for establishing the need for IgG replacement based on a review of 65 patients who were evaluated for suspected antibody deficiency. Serum immunoglobulin levels and specific antibody responses, as well as clinical history, were considered.

A pharmacoeconomic comparison of the subcutaneous administration of IgG products at home with the intravenous administration of IgG in a hospital was conducted in a Canadian center, resulting in less expenditure when using the subcutaneous route.⁶⁸ It is still unclear whether similar results would occur in different communities.

While screening for mRNA levels of the receptor FcγRIIa in patients with CVID, van der Heidjen et al⁶⁹ found a novel FcγRIIa isoform that expressed an additional exon caused by a point mutation. Neutrophils expressing this isoform showed increased elastase release in response to dimeric IgG, whereas responses to the stimulant N-formyl-methionyl-leucyl-phenylalanine were not different, suggesting specificity for IgG. This isoform was found in 3 of 8 patients with CVID who had anaphylaxis with intravenous immunoglobulin infusions but in none of 45 patients with CVID who received intravenous immunoglobulin without side effects. Two of the 3 patients had been shown to have anti-IgA antibodies. The allele was also found in 2.4% of 208 patients with Kawasaki disease; however, they did not report side effects. The authors suggest that the novel isoform might increase the risk of anaphylaxis in patients with CVID and possibly only in those who present with anti-IgA antibodies.

OTHER THERAPEUTIC INTERVENTIONS OF IMMUNOLOGIC IMPORTANCE

Wildbaum et al⁷⁰ described the use of granulocyte colony-stimulating factor (G-CSF) for the control of CMC in a 59-year-old woman with a diagnosis of CMC for more than 30 years and a heterozygous gain-of-function mutation in *STAT1*. The patient has received G-CSF weekly for 19 years. While taking G-CSF, T_H17 cell counts were comparable with those seen in healthy control subjects; however, within 4 weeks of stopping G-CSF, symptoms recurred, and T_H17 cell numbers decreased considerably.

Autophagy is a cellular mechanism that allows cell survival, avoiding apoptosis, and is thought to play a significant role in T-cell homeostasis. van Loosdregt et al⁷¹ investigated the modulation of autophagy in human T cells by hydroxychloroquine, an anti-inflammatory drug that is thought to affect lysosomes and inhibits autophagy. At concentrations known to be anti-inflammatory in human subjects, exposure to hydroxychloroquine increases the number of autophagosomes in CD4⁺ T cells and induces apoptosis. When CD4⁺CD45RA⁺ naive T cells and CD4⁺CD45RO⁺ memory T cells were analyzed, the effect of this drug was markedly more significant

in CD45RO⁺ T cells. The authors conclude that this mechanism might explain the modulatory effect of hydroxychloroquine in inflammation.

Motivated by reports of antibody deficiency by use of valproic acid, an antiepileptic medication, Kienzler et al⁷² studied B-cell differentiation after exposure to valproic acid. Differentiation into memory B cells and plasmablasts was significantly reduced, most likely as a result of inhibition of proliferation. The authors suggest that valproic acid can be used in the treatment of autoimmunity.

CONCLUSIONS

Research activity in PIDs continues to produce new information on genes affecting the differentiation and function of cells of the immune system (Table I). New pathogenic mutations and molecular mechanisms have been reported. With improved access to gene sequencing, different clinical presentations are attributed to gene defects that, in the past, appeared to have a traditional presentation only. Despite the signal advance afforded by genotype analysis, patients with the same genetic mutations are found to express different phenotypes, thus issuing another challenge to the clinical immunologist to look for other factors, both genetic and nongenetic, to account for this wondrous diversity of gene expression.

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