

Advances in basic and clinical immunology in 2009

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In 2009, reports on basic and clinical immunology had an increased focus on human disease mechanisms and management. The molecular pathogenesis of familial angioedema associated with estrogen was further explored to find possible factors affecting severity, including polymorphisms in enzymes and receptors related to bradykinin pathways. A placebo-controlled clinical trial of C1 esterase inhibitor concentrate in patients with hereditary angioedema demonstrated the safety of its use and its efficacy to reduce the duration of angioedema attacks. The interaction of innate immunity and adaptive responses was further examined in several reports, establishing the significant role of Toll-like receptor stimulation for the development of optimal specific antibody responses. The 2009 update of the classification of primary immunodeficiencies introduced more than 15 new genetic defects related to the immune response, including of dedicator of cytokinesis 8 (*DOCK8*) mutations, which are responsible for the autosomal recessive form of the hyper-IgE syndrome. Other reports expanded the clinical spectrum of disease and improved the characterization of conditions such as warts, hypogammaglobulinemia, and myelokathexis syndrome or the occurrence of mucormycosis and *Serratia* species infections in patients with chronic granulomatous disease. The frequent presentation of gastrointestinal disorders in patients with humoral immunodeficiencies was recognized, and recommendations for management were reviewed. Clinical research focused on severe combined immunodeficiency included the development and implementation of a state-wide newborn screening program for this condition, a desired goal considering the significant reduction of mortality rate when the diagnosis is made early before opportunistic infections occur. (*J Allergy Clin Immunol* 2010;125:563-8.)

Key words: Basic immunology, B cells, T regulatory cells, T_H17 , clinical immunology, primary immunodeficiency, hyper-IgE syndrome, hereditary angioedema, hematopoietic stem cell transplantation, space immunology, HIV infection

Following the trend of the last 3 decades, progress in basic and clinical immunology in 2009 was documented by the significant number of published reports. Research findings from animal and

Abbreviations used

ADA:	Adenosine deaminase
C1INH:	C1 esterase inhibitor
CVID:	Common variable immunodeficiency
DOCK8:	Dedicator of cytokinesis 8
HIES:	Hyper-IgE syndrome
HSCT:	Hematopoietic stem cell transplantation
PID:	Primary immunodeficiency
RAG:	Recombination activating gene
ROR:	Retinoic acid orphan receptor
SCID:	Severe combined immunodeficiency
STAT:	Signal transducer and activator of transcription
TLR:	Toll-like receptor
TREC:	T-cell receptor excision circle
Treg:	Regulatory T

in vitro experimental models have been translated to similar investigations in patients presenting with immunologic conditions, thus providing insights into the biology of human immunity and leading to the description of additional human gene defects causing immune dysfunction (Table I). This article reviews the reports on basic and clinical immunology published in the *Journal of Allergy and Clinical Immunology* in 2009.

ANGIOEDEMA AND CAPILLARY LEAK SYNDROME: IMMUNOBIOLOGY AND TREATMENT

Advances in the immunobiology of angioedema included molecular investigations of patients presenting with this clinical manifestation and with normal complement C1 esterase inhibitor (C1INH) level and function. Hentges et al¹ reported 4 female patients with recurrent angioedema attacks and normal levels and function of C1INH. All of these patients were taking oral estrogen contraceptives; however, only 1 patient presented with a gain-of-function mutation of Factor XII. The authors were able to demonstrate that the 4 patients had evidence of activation of the contact system with demonstration of complete cleavage of the high-molecular-weight kininogen (Fig 1). They concluded that mutations in multiple genes might explain this phenotype, which was supported by data provided by Joseph et al,² who demonstrated the production of bradykinin by prekallikrein in the absence of Factor XII. Duan et al³ reported 3 affected members of a family with estrogen-dependent angioedema that added further support to the multifactorial pathogenesis of estrogen-dependent angioedema. These patients were heterozygous for the missense mutation Thr328Lys in *F12*, which increases Factor XII activity, and in addition, they presented with polymorphisms in the genes encoding the aminopeptidase P (APP) enzyme and the angiotensin I convertase that are associated with decreased degradation of bradykinin. The combination of mutations in these 3 genes might explain the variability in the risk of angioedema attacks.

Idiopathic systemic capillary leak syndrome is included in the differential diagnoses of angioedema and is characterized by intermittent attacks of hypotension, hemoconcentration,

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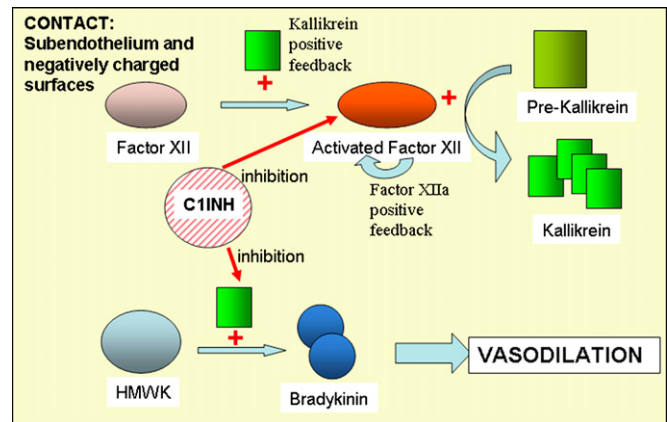
TABLE I. New diseases reported in the 2009 update of the PID classification

I. Combined T- and B-cell immunodeficiencies
A. T ⁺ B ⁺ SCID: coronin-1A deficiency
B. T ⁺ B ⁺ SCID: DNA PK deficiency
C. Reticular dysgenesis caused by mutation in <i>AK2</i>
II. Predominantly antibody deficiencies
A. With normal or low B-cell numbers: BAFF receptor deficiency, TACI deficiency
III. Other well-defined immunodeficiency syndromes
A. DNA repair defects: immunodeficiency with centromeric instability and facial abnormalities, PMS2 deficiency (defective mismatch repair)
B. Immuno-osseous dysplasias: Comel-Netherton syndrome
C. HIESs: autosomal recessive caused by mutations in <i>DOCK8</i>
D. Chronic mucocutaneous candidiasis caused by mutations in <i>CARD9</i>
IV. Diseases of immune regulation
A. Lymphoproliferative syndromes: ITK deficiency
V. Congenital defects of phagocytes
A. Neutropenia with cardiac and urogenital malformations: mutations in <i>G6PC3</i>
B. Glycogen storage disease type 1b, mutations in <i>G6PT1</i>
C. Pulmonary alveolar proteinosis caused by defects in GCSF signaling
VI. Defects in innate immunity
A. MyD88 deficiency
B. Susceptibility to trypanosomiasis caused by mutations in <i>APOL1</i>
VII. Autoinflammatory disorders
A. Deficiency of the IL-1 receptor antagonist
VIII. Complement deficiencies
A. Immunodeficiency associated to ficolin 3 deficiency

AK2, Adenylate kinase; *APOL1*, gene encoding apolipoprotein I; *BAFF*, B cell activating factor; *CARD9*, caspase recruitment domain-containing protein 9; *DNA PK*, protein kinase, DNA activated; *GCSF*, granulocyte colony stimulating factor; *G6PC3*, glucose 6 phosphatase, catalytic 3; *G6PT1*, glucose 6 phosphate transporter 1; *ITK*, IL-2 inducible T cell kinase; *PMS2*, postmeiotic segregation increased 2; *TACI*, transmembrane activator CMLA interactor.

hypoalbuminemia, renal failure, increased weight, and edema. Dowden et al⁴ studied 3 patients with this condition, 2 adults and a 6 year-old boy in whom an angioedema diagnosis was ruled out, and reported that they all had increased serum levels of TNF- α . Based on this finding and subsequent therapeutic response to TNF- α inhibitors, they proposed the use of a 2-tier management approach for idiopathic systemic capillary leak syndrome: initially to use theophylline and terbutaline and then, if no response was evident, to use TNF- α inhibitors, such as infliximab. Bossi et al⁵ developed elegant *in vitro* and *in vivo* experimental models to measure vascular permeability to proteins after exposure to plasma obtained from patients undergoing an angioedema attack. They showed that, in addition to the bradykinin receptor 2, bradykinin receptor 1 also has a significant role in the increased vascular leakage. Furthermore, they showed that inhibition of the interaction of kininogens and the receptor for the globular head of the C1q protein resulted in complete inhibition of vascular leakage induced by the plasma samples. These findings suggest that both the bradykinin receptor 1 and the receptor for C1q are potential therapeutic targets for the control and relief of angioedema attacks.

A multicenter, randomized, placebo-controlled trial involving 125 patients with hereditary angioedema demonstrated the safety and efficacy of a human C1INH concentrate product for facial and abdominal attacks in patients with hereditary angioedema.⁶ Overall, there was a significant reduction of time to relief from 1.5 to 0.5 hours using this preparation at a dose of 20 U/kg within the first 6 hours of onset. The effect was more significant for severe attacks

**FIG 1.** Mechanisms of bradykinin-induced vasodilation in angioedema. Increased activation of Factor XII or decreased activity of C1INH leads to increased levels of kallikrein, which induced the formation of bradykinin from high-molecular-weight kininogen (HMWK).

and for facial swelling than for abdominal symptoms. A dose of 10 U/kg did not have an effect that was significantly different from that of placebo. Safety was assessed by monitoring adverse events possibly related to the administration of C1INH and extensive testing of blood-borne viruses. No significant safety differences between the placebo and treatment groups were found.

INNATE IMMUNITY AND INFLAMMATORY DISORDERS

Autoinflammatory syndromes result from mutations in genes involved in the control of inflammatory responses. Goldbatch-Mantsky and Kastner⁷ reviewed the genetic causes of these rare conditions, which have helped to improve our understanding of the mechanisms of inflammation and the role of the initial immune response to trigger the adaptive immunity. Most of these genes encode proteins that participate in an intracellular molecular complex called the “inflammasome” and lead to the secretion of the proinflammatory cytokine IL-1. These conditions include familial Mediterranean fever, TNF- α receptor-associated periodic syndrome, cryopyrin-associated periodic syndrome, and hyper-IgD syndrome. The progress in the understanding of these diseases has led to clinical trials with IL-1 inhibitors, such as anakinra, with promising results. The therapy of these inflammatory disorders was reviewed by Hoffman,⁸ who pointed out that these disorders have been traditionally managed with colchicine, but both TNF- α inhibitors and IL-1 receptor antagonists were increasingly used because their mechanisms of action were based on the pathogenesis of the disease, resulting in less adverse effects.

Investigations in animal models help to further refine the action of molecules involved in inflammation. As an example, it was shown that the mutation of a tyrosine in position 145, but not in position 112 and 128, of the lymphocyte cytosolic protein 2 abrogates the development of inflammation in a serum-induced arthritis murine model.⁹ The lymphocyte cytosolic protein 2 regulates cell signaling in myeloid cells mediated by Fc γ R and specific integrins. Similar findings are directed to identify novel targets for the treatments of inflammatory conditions.

INVESTIGATIONS ON CYTOKINES

Gold et al¹⁰ studied the cytokine responses to stimulation with mitogens, antigens, and Toll-like receptor (TLR) agonists in

mononuclear cells of 558 cord blood samples. They analyzed the association of differences in these responses with variables such as the presence of maternal allergic disease, infection, or season of birth. Those associations that were statistically significant included the presence of maternal asthma and respiratory syncytial virus infection associated with decreased response of proinflammatory cytokines. IFN- α responses were higher if babies were born in January to March compared with the other 3-month seasons. The authors concluded that innate cytokine responses were associated with maternal allergic disease and season of birth, as well as somatic growth and ethnicity. Cytokine responses were also studied in a space-flight model using the head-tilted bed-rest position to simulate antigravity effects.¹¹ TNF- α levels were increased and associated with impaired kinetics of antibody responses to immunization with the neoantigen Phi174. Interestingly, routine exercise used as a countermeasure ablated the increase of TNF- α levels, possibly related to a concomitant increase in the levels of the IL-1 receptor antagonist and of the chemokine RANTES.

Fibronectin was identified as a T_H1-specific molecule by comparing mRNA expression of T_H1- and T_H2-differentiated cells using microarray techniques. Sandig et al¹² showed that T_H1 cells, but not T_H2 cells, secrete fibronectin, and after binding to receptors in macrophages, secretion of the proinflammatory cytokine IL-6 was induced. These findings further define the molecular events regulating cytokines and other chemical messengers that regulate the immune response.

PRIMARY IMMUNODEFICIENCIES

Classification and policy guidelines

The field of primary immunodeficiencies (PIDs) was significantly represented in the progress achieved in basic and clinical immunology in 2009. The International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies reported on the biennial update of the classification of PIDs in an article by Notarangelo et al.¹³ In this updated classification the relative frequency of each condition among PIDs based on published reports was included. Several new gene defects have been included in each of the 8 PID categories, and some of them are described below. Particularly expanded are those affecting the innate immunity and atypical genetic immunodeficiencies, such as the one conferring susceptibility to trypanosomiasis, which is attributed to mutations in the gene encoding apolipoprotein I (*APOLI*). In a Primary Immunodeficiency Treatment Consortium report by Griffiths et al,¹⁴ experts from North American academic centers that focus on the management of PIDs authored guidelines for the recognition of PIDs, indications for hematopoietic stem cell transplantation (HSCT), and the care before and after HSCT, with emphasis on antimicrobial prophylaxis. Limitations of the available literature about the management of these rare diseases were recognized, as well as the need for National Institutes of Health-sponsored multicenter efforts to provide evidence and consensus for future clinical trials.

New findings on rare immunodeficiency disorders

McCarl et al¹⁵ studied the immunodeficiency caused by defects in the Ca²⁺ release-activated Ca²⁺ channels, which are encoded by the *ORAI* genes. The dysfunction of intracellular calcium release results in immunodeficiency, autoimmunity associated with myopathy, and ectodermal dysplasia. This clinical presentation might

also be caused by pathogenic mutations in the ER protein stromal interaction molecule 1, which is involved in the activation of *ORAI1*. The authors characterized 6 patients from 3 families with *ORAI1* mutations who presented with characteristic clinical features and decreased lymphoproliferative responses to mitogens and antigens. Their *in vitro* experiments demonstrated that all mutations resulted in impaired calcium mobilization.

In a similar effort to improve characterization of a rare immunodeficiency syndrome, Tassone et al¹⁶ studied 10 patients with deleterious mutations in the gene encoding the chemokine receptor CXCR4, which is defective in the warts, hypogammaglobulinemia, infections, and myelokathexis syndrome. These 10 patients were identified after analyzing the *CXCR4* gene sequence of 53 patients who presented with chronic neutropenia. The authors found that 3 of the 10 patients had hypogammaglobulinemia, and 4 patients had serum IgG levels close to the lower limit of normal range. All patients had recurrent infections, mainly respiratory, with only 1 presenting with genital warts. The authors concluded that *CXCR4* gene analysis should be considered in patients with chronic neutropenia, even in the absence of hypogammaglobulinemia and warts. Renner et al¹⁷ reported several defective immunologic parameters, especially defective isotype switching and B-cell memory, in 9 patients with the Comel-Netherton syndrome, a complex genetic disease caused by mutations of the serine peptidase inhibitor Kazal type 5 (*SPINK5*) gene. The clinical phenotype of this syndrome is characterized by ichthyosis, bamboo hair, recurrent infections, and allergic disease. Interestingly, 5 patients with suboptimal antibody responses reported clinical benefit after initiation of intravenous immunoglobulin at replacement doses, with decreased skin inflammation and healthier scalps.

Two reports advanced our knowledge of infections by pathogens that present selectively in patients with chronic granulomatous disease: molds and *Serratia* species. Vinh et al¹⁸ found 4 patients with invasive mucormycosis from a cohort of 278 patients evaluated at the National Institutes of Health. All patients had an intensive steroid-based regimen for 3 or more weeks immediately before the presentation of their infections. Although the total number of patients who received a similar steroid treatment was not reported, this finding suggests that nicotinamide adenine dinucleotide phosphate oxidase-independent mechanisms are important for the development of mucormycosis. This research group also reported their experience with *Serratia* species infections in 15 patients with chronic granulomatous disease who were 8 to 39 years of age.¹⁹ The most significant findings were as follows: (1) *Serratia* species-induced osteomyelitis was uncommon beyond infancy, (2) skin infections require prolonged antibiotic treatment, and (3) isolated *Serratia* species-induced pneumonias were unlikely to become systemic and spread to other organs.

Two case reports were illustrative of the complex nature of PIDs and provided valuable teaching points. The importance of the history and physical examination in the evaluation of PIDs was underscored by the report by Shah et al,²⁰ who described a 5-year-old patient with recurrent infections, short stature, and skeletal dysmorphism and was later given a diagnosis of Schwachman-Bodian-Diamond syndrome. Further investigations revealed a hypocellular bone marrow and low absolute counts of B cells and natural killer cells, as well as evidence of pancreatitis, supporting the clinical diagnosis. Fiorini et al²¹ showed 2 different genetic mechanisms leading to an autosomal recessive condition. They reported a case of leukocyte adhesion deficiency type

I caused by a nonsense mutation in *ITGB2*, the gene encoding the integrin $\beta 2$, which was inherited with the maternal allele, and a *de novo* deleted ring 21 chromosome comprising 69 genes, including *ITGB2*. This case emphasizes the importance of cytogenetic analysis in patients with complex clinical phenotypes.

Hyper-IgE syndrome

One of the newly described gene defects is one affecting the dedicator of cytokinesis 8 (DOCK8) signal transducer, which is associated with autosomal recessive hyper-IgE syndrome (HIES).²² Both microdeletions involving this gene and deleterious mutations in *DOCK8* were found in 21 patients with autosomal recessive HIES, a syndrome characterized by very high eosinophilia, increased serum IgE levels, and recurrent pneumonia, skin abscesses, and viral infections (especially molluscum contagiosum and herpes viruses) but, in contrast to the autosomal dominant form, does not present with skeletal or dental disease. Kim et al²³ reported a missense mutation in the linker domain of the signal transducer and activator of transcription (STAT) 3 in a patient with autosomal dominant HIES, expanding the range of genetic defects causing this syndrome, because previous reports had found mutations in either the DNA-binding domain transactivation domain or the SH2 domain. Of note, this 5-year-old boy did not have any skeletal or dental anomalies. He did have impairment in *in vitro* T_H17 differentiation. Alkhatib et al²⁴ showed that impaired T_H17 differentiation was a characteristic of all patients with HIES, regardless of the causative gene defect. These investigators studied a cohort of 25 Turkish children with HIES diagnoses, and although only 6 subjects had mutations in the *STAT3* gene, all studied patients had decreased T_H17 responses with conserved T_H1 responses. The pathways involving the described gene products STAT3, tyrosine kinase 2, and DOCK8, leading to T_H17 differentiation, and their role in HIES have not been well defined. Burgler et al²⁵ studied the *in vitro* differentiation of human T_H17 cells and demonstrated high expression of the retinoic acid orphan receptor (ROR) C2, a human homologue of the murine ROR γ . This group stimulated naive T cells with TGF- β , and induction of IL-17A and IL-17F secretion was achieved by exposing the cells to IL-6, IL-23, and IL-1 β . However, TGF- β also induced differentiation of regulatory T (Treg) cells when also exposed to anti-IL-12 and anti-IFN- γ antibodies. Furthermore, Treg cells also expressed RORC2. The authors emphasized that human T_H17 cells need to be identified based on IL-17 secretion and not RORC2 expression. Further definition of the clinical features of HIES included the work of Melia et al²⁶ to investigate the frequency of nontuberculous mycobacterial infections in patients with autosomal dominant HIES. All of those patients with lung structural damage in the form of bronchiectasis or lung cysts were investigated for mycobacterial infections. Five of 32 patients were found to have positive cultures and clinical criteria to define active infection. All 5 responded to antimycobacterial therapy.

Antibody immunodeficiencies

Agarwal and Meyer²⁷ reviewed gastrointestinal conditions that commonly present in patients with deficiencies in antibody responses. They classified these conditions into 4 groups: infections, malignancies, autoimmune conditions, and inflammatory disorders. They postulated that their clinical characteristics

are more likely the result of cellular immunity dysfunction accompanying the antibody defect and that treatment might need to be patient tailored because it is often necessary to use immunomodulators in these immunocompromised patients. The authors focused on the description of pathologies occurring in 3 conditions: X-linked agammaglobulinemia, selective IgA deficiency, and common variable immunodeficiency (CVID). They noted that the gastrointestinal conditions in these diseases resemble common illnesses, such as ulcerative colitis and celiac sprue; however, they do not have a typical clinical picture, suggesting different pathogenetic mechanisms from those that explain the same diseases in immunocompetent subjects.

Yu et al²⁸ reported impaired activation of CVID B cells mediated by TLR7 and TLR9. The authors showed impaired cell proliferation, immunoglobulin production, and expression of activation-induced deaminase, when patients' B cells were stimulated with TLR7, TLR7/8, and TLR9 agonists, strongly suggesting a role of innate immunity in the pathogenesis of this immunodeficiency. The effect of the TLR agonist resiquimod was shown to induce IgG production in normal naive B cells, especially when costimulated with IL-2 and IL-10.²⁹ This effect was also seen with B cells from a patient with X-linked hyper-IgM syndrome, indicating that class-switch and IgG production can occur in the absence of B-cell receptor cross-linking and CD40-CD40 ligand interaction. Additional evidence of the role of TLR stimulation in the immunoglobulin production by B cells was provided by Ozcan et al.³⁰ They used a murine model to demonstrate the synergism of LPS, a TLR4 agonist, and a proliferation-induced ligand (APRIL) to induced B cell proliferation. APRIL binds to the receptor named transmembrane activator and CAML interactor (TACI), which has been found defective in a subset of CVID patients.

Other advances related to humoral immunodeficiencies included a small trial to compare the use of immunoglobulin supplementation through intravenous and subcutaneous routes.³¹ Twelve patients were enrolled in a randomized, 2-arm crossover trial, with 6 months in each route and the same total monthly dose. There were no differences in systemic adverse effects or incidence of infection between the 2 arms of the study. The authors concluded that the results of this pilot trial supported the need of a larger protocol with greater statistical power to compare the efficacy of these 2 routes of administration for IgG replacement.

Of interest, von Gunten et al³² studied the anticarbohydrate antibodies present in 3 commercial intravenous immunoglobulin preparations using a glycan microarray with high-throughput testing. They found that antibodies to half of more than 370 different glycans tested were present in the different preparations. Depletion of IgG2 did not eliminate the carbohydrate-specific antibodies, suggesting that IgG1 also targets carbohydrate moieties and that T-cell immunity is likely to be involved in the generation of anticarbohydrate antibodies. Specificity to endogenous carbohydrates was absent, and the most frequent antibody specificities corresponded to glycans found in bacteria. The authors pointed out that these findings are of potential significance for the development of vaccines, with the consideration of new targets.

Hare et al³³ found that many patients had increased concentrations of antibodies against the different serotype antigens included in the nonconjugated 23-valent pneumococcal serotype vaccine and estimated preimmunization values at which the chance of achieving a 4-fold increase in titers after immunization

was nearly zero. These data are of clinical value in the often difficult interpretation of antibody responses.

Severe combined immunodeficiency

Advances in the diagnosis and management of severe combined immunodeficiency (SCID) reported in 2009 included the first development of a state-wide newborn screening program for the early diagnosis of this condition. Baker et al³⁴ reported their efforts to implement this program in Wisconsin. They tested 5,766 dried blood spot samples obtained from newborn screening cards by measuring T-cell receptor excision circles (TRECs) using real-time quantitative PCR. The absence of TRECs strongly indicates an SCID diagnosis. With an estimated frequency of 1 in 50,000 live births, a larger number of samples needed to be tested to identify these patients. The demonstration of its feasibility constituted significant progress, considering the improved outcomes of treatment with HSCT when diagnosis is made early. This publication was followed by the same group reporting the outcomes of this program over 12 months.³⁵ After 71,000 samples were tested, 8 infants with T-cell lymphopenia were subsequently given diagnoses of DiGeorge syndrome (n = 2), idiopathic CD4 T-cell lymphopenia (n = 2), extravascular extravasation of lymphocytes (n = 3), and Rac2 deficiency (n = 1). Early diagnosis of SCID is of utmost importance to reduce the frequency of severe infections and also to avoid adverse consequences of administering live vaccines in an immunocompromised patient, as demonstrated by reports of intractable diarrhea when rotavirus immunization has inadvertently been given to 2-month-old infants as scheduled but before SCID diagnosis was made.³⁶

Patel et al³⁷ reported the outcomes of 23 patients with SCID who underwent HSCT at a single institution between 1998 and 2007. Five of the patients underwent HSCT with matched related donors, and all have survived. The other 18 underwent HSCT with a haploidentical related donor or a matched unrelated donor, with all but 1 patient receiving a conditioning regimen. The 1-year survival rate was 72%. No significant differences were obtained when this outcome was compared with a previous reported experience in the same center consisting of 25 patients with SCID who underwent transplantation without conditioning regimens. The assessment of the risks and benefits of pretransplantation conditioning regimens requires further follow-up of these patients and similar cohorts from other centers.

Other significant progress related to SCID included the description of 2 interesting cases presenting with Omenn syndrome. Sheehan et al³⁸ reported the association of Omenn syndrome and aniridia, in which further genetic investigation revealed microdeletion of chromosome 11p13, including the genes recombination activating gene 1 (*RAG1*), *RAG2*, and paired box gene 6 (*PAX6*) in one allele and missense mutations in the second allele. The authors call to our attention that in autosomal recessive disease, apparent homozygous mutation in autosomal chromosomes might be further investigated to rule out heterozygous deletions. Somech et al³⁹ studied one patient with *RAG2* deficiency who presented with erythroderma, lymphadenopathy, splenomegaly, and *Pneumocystis* species-induced pneumonia. T-cell oligoclonality was demonstrated, as well as absence of TRECs. The authors found that this patient had reduced expression in peripheral blood of the autoimmune regulator protein but not forkhead box protein 3 and hypothesized that central tolerance, and not Treg cells, plays a role in the autoimmunity

associated with Omenn syndrome. This group also described one patient with partial adenosine deaminase (ADA) deficiency and mild immunodeficiency who started treatment with polyethylene glycol-ADA at 20 months because of interstitial pneumonitis.⁴⁰ This patient had also had autoimmune hepatitis that did not improve with this treatment but ultimately responded to prednisone. They concluded that polyethylene glycol-ADA improves lung disease but not liver disease in patients with partial adenosine deaminase deficiency.

The development of a functional diagnostic assay based of IL-2-induced STAT5 phosphorylation was reported to identify patients with SCID with defects in the Janus kinase 3 and γ c pathways.⁴¹ These patients characteristically present with absence of T cells and natural killer cells and with dysfunctional B cells. However, this phenotype might be modified by the presence of maternally engrafted cells, oligoclonal T-cell expansion, or extrinsic factors that induce lymphopenia. In these cases, and in those in which genetic analysis is equivocal, functional studies, such as the one described in this report, might prove clinically useful.

CONCLUSIONS

Scientific reports published in 2009 reflect that the progress in basic and clinical immunology increasingly focused on the elucidation of mechanisms that regulate the human immune response and results in immunologic diseases (Table II). New genetic lesions were described, such as mutations in *DOCK8*, which is responsible for the autosomal form of HIES, or familial angioedema not mediated by a defective C1INH. The role of effector cells and molecules of the innate immunity to trigger inflammation and efficient antibody responses has been further defined. From the molecular characterization of individual patients or small case series, research efforts are being translated into matters of public health to reduce the burden of the most severe forms of the primary immunodeficiency diseases through early detection with universal neonatal screening.

Key advances in basic and clinical immunology, 2009

- Increased vascular protein leakage is mediated by activation of bradykinin receptors 1 and 2.
- Innate cytokine responses in cord blood cells are associated with maternal allergic disease and season of birth.
- Increased TNF- α levels and impaired antibody responses to neoantigens were observed in a space-flight model.
- Fibronectin was identified as a T_H1-specific molecule.
- *CXCR4* gene defects were identified in patients with chronic neutropenia who did not present with warts or hypogammaglobulinemia.
- *DOCK8* gene defects lead to the autosomal recessive form of HIES.
- B cells from patients with CVID present with impaired activation mediated by TLR7 and TLR9 agonists.
- APRIL* and LPS can induce B-cell proliferation, differentiation, and immunoglobulin secretion.
- The feasibility of newborn screening for SCID was demonstrated.

*APRIL, A proliferation-inducing ligand.

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