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Advances in basic and clinical immunology in 2008

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Abstract

We reviewed selected reports in the field of basic and clinical immunology published in 2008. Research progress in the immunologic mechanisms of allergic disease included the modulation of TH2 responses by specific transcription factors and receptors associated with the innate immunity, underscoring the importance of the interactions between adaptive and innate immune mechanisms. Investigations of the pathophysiology of hereditary angioedema included a variety of host factors with roles in bradykinin metabolism and vasomotor activity, explaining the variable severity of the clinical presentation. The research focus in HIV infection has shifted from control of disease progression to the barriers for viral eradication, and the search for vaccine designs that provide immunity in the short window between infection and establishment of viral reservoirs. HIV-infected individuals who receive antiviral treatment develop a high incidence of asthma, resembling the inflammatory processes associated with immunoreconstitution. The correlation of molecular diagnosis and clinical presentation was analyzed in 4 relatively rare primary immunodeficiencies: hyper-IgE syndrome; immune dysfunction, polyendocrinopathy, enteropathy, X-linked disease; cartilage-hair hypoplasia; and nuclear factor- κ B essential modulator deficiency. Studies of patients with partial DiGeorge syndrome and chronic granulomatous disease unveiled subclinical deficiencies that might have an impact in their care. Long-term outcomes from patients with severe combined immunodeficiency who received bone marrow transplants were considered successful compared with the alternative of no intervention. However, the occurrence of adverse events reinforces the need for coordinate efforts to develop optimal protocols for hematopoietic stem cell transplantation for severe immune defects. (*J Allergy Clin Immunol* 2009;123:328-32.)

Keywords

Basic immunology; antigen presentation; regulatory T cells; clinical immunology; primary immunodeficiency; hereditary angioedema; hematopoietic stem cell transplantation; partial DiGeorge syndrome; HIV infection

We reviewed and selected the articles published in the Journal from January 2008 to December 2008 related to the areas of basic and clinical immunology (Table I).

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BASIC IMMUNOLOGY

The transcription signaling pathways involved in the immune responses observed in allergic diseases were reviewed by Cousins et al¹ and Chatila et al.² They focused on the differentiation mechanisms of T cells into lineages that are characterized by their cytokine production, known as T_H1, T_H2, T_H17, and regulatory T cells. The main transcription factors that control this differentiation program are, respectively, T-box expressed in T cells (T-bet), GATA-binding protein 3 (GATA3), Forkhead box P3 (FOXP3), and retinoid-related orphan receptor γ (RORC). Transcription factors with significant roles in T_H2 responses that mediate allergic disease include signal transducer and activator of transcription 6 (STAT6), musculoaponeurotic fibrosarcoma oncogene (MAF), nuclear factor- κ B, and nuclear factor of activated T cells (NFAT). Investigators are targeting these proteins and others for immunomodulatory strategies, primarily for the control of inflammation, such as the use of nuclear factor-erythroid 2-related factor (NERF2) agonists. NERF2 is a protein that mediates oxidative stress, and its absence causes multiorgan inflammation.² Other novel research efforts toward the control of allergic disease are targeting the immunoglobulin receptors in antigen-presenting cells (APCs). Hulse et al³ presented the immunological properties of H22–Fel d 1, a fusion protein linking the major cat allergen Fel d 1 with the variable region of an antibody that binds the high-affinity IgG receptor Fc γ RI. This protein was engineered to increase the expression of Fel d 1 epitopes in APCs and therefore stimulate the production of specific regulatory T cells. They showed that APCs exposed to this protein were able to induce a T_H2-type response characterized by IL-5 production, associated with an increase of IL-10–expressing T cells regulatory cells. These cells were not detectable with exposure to Fel d 1 alone. The authors proposed that this immune response may be protective for the development of allergic disease. Del Prete et al⁴ used a virulence factor from *Helicobacter pylori* named *H pylori* neutrophils-activating protein (HPNAP) to demonstrate that the T_H2 phenotype can be converted to a T_H1 phenotype *in vivo*, using a parasite-infected mouse model. HPNAP is a Toll-like receptor (TLR)–2 agonist that induces expression of the inflammatory cytokines IL-12 and IL-23. The mice treated with HPNAP had decreased eosinophilia and IgE compared with non-treated animals.

Studies in the molecular pathogenesis of allergic disease included the characterization of the functional deficiency of human β -defensins in atopic dermatitis. Kisich et al⁵ contributed to this concept involving the decreased presence of defensins in patients with atopic dermatitis to explain their frequent colonization with *Staphylococcus aureus* by demonstrating that individuals with atopic dermatitis have keratinocytes with poor ability to mobilize human β -defensin 3 to kill *S aureus*. This effect was mediated by the T_H2 cytokines IL-4 and IL-13. A provocative hypothesis by Akkoc et al⁶ suggests that T_H1 cells from atopic individuals have increased apoptotic activity, compared with T_H2, and with healthy individuals. This research team induced T_H1 and T_H2 differentiation *in vitro* from naive T cells isolated from healthy and from highly atopic individuals. T_H1 cells derived from atopic individuals expressed significant higher amounts of Fas, Fas-ligand, and TNF receptor III than other T cells, consistent with their increased apoptotic activity, and therefore explaining the predominance of T_H2 cells in individuals with allergy. Leb et al⁷ identified and studied a human T-cell receptor specific for an immunodominant epitope of Art v 1, the major allergen of mugwort,

in the context of HLA-DRB1 expression. This work is of importance for the generation of *in vivo* models for specific allergen-induced disease. Jabara et al⁸ observed that cross-linking of the B-cell receptor decreases class-switch recombination induced by LPS and IL-4. The investigators determined that this was the result of a delayed expression of the activation-induced deaminase, caused by a high degree of B-cell receptor cross-linking. The authors propose that this could represent a mechanism of peripheral tolerance, and may contribute to the observed benefit of allergen immunotherapy for allergic disease.

Other reports of interest in basic immunology were the anti-inflammatory effect of epigallocatechin gallate⁹ and the generation of mice with genetic immunodeficiencies using random mutation. Epigallocatechin gallate, the major polyphenol component of green tea, can be immunosuppressive at high doses by impairing maturation of dendritic cells, decreasing their endocytic activity and inducing IL-10 secretion. Jakob et al¹⁰ generated 6 mice strains with immunodeficiencies induced by mutagenesis and identified in 1 of the strains that the gene defect corresponded to a mutation in the kinase domain of the zeta-chain-associated protein kinase (ZAP70) protein. Although the time and resources for this methodology are significant, this effort will result in the identification of more genes that participate in the immune response and will increase the number of animal models available for immunologists.

CLINICAL IMMUNOLOGY

Angioedema

The pathogenesis of angioedema induced by angiotensin-converting enzyme (ACE) inhibitors is explained by action of these medications to increase bradykinin serum concentrations; however, angioedema does not occur in all patients receiving ACE inhibitors. Bas et al¹¹ postulated that acute-phase reactant with vasomotor activity may induce the angioedema symptoms. They showed that ACE-induced angioedema had increased plasma fibrinogen, and that fibrinogen induced the vasodilator potency of bradykinin by 10-fold. Frank¹² reviewed the pathophysiology of hereditary angioedema, caused by deficiency of the C1 esterase inhibitor, and discussed current and proposed therapeutic agents for prophylaxis and termination of acute attacks of angioedema. The prophylactic agents for acute angioedema attacks include androgens, which have proven to be efficacious and are thought to increase the synthesis of the C1 esterase inhibitor. Drouet et al¹³ measured an enzyme that degrades bradykinin, aminopeptidase P, in patients with angioedema receiving androgens. They found that these patients have twice the aminopeptidase P levels found in those who are not receiving androgens and have a lower frequency of severe angioedema attacks.

HIV infection

In the era of highly active antiretroviral therapy (HAART), the question of the possibility of viral eradication is still unanswered. Shen and Siciliano¹⁴ discussed the current evidence suggesting that current HAART therapy is able to suppress HIV replication efficiently; however, residual viremia would persist because of activation of infected T cells that constitute the latent reservoirs. Identification of these reservoirs and strategies to target them

would then lead to viral eradication. Yin et al¹⁵ analyzed parameters of T-cell dynamics in 10 HIV-infected children receiving HAART. These researchers showed a significant restoration of naive CD8⁺ T cells occurring similarly to the expected restoration of CD4⁺ T cells, even though CD8⁺ T-cell absolute counts did not change. This observation was of most significance in those with most severe disease and reflected the improvement of thymus function. In a cohort of 2644 children born to HIV-infected mothers, Foster et al¹⁶ reported a 3-fold higher incidence of asthma at 13 years of age in perinatally HIV-infected children who received HAART compared with those who did not receive this treatment. This observation is linked to the immunoreconstitution occurring in the patients receiving HAART, similar to the association with inflammatory conditions.

Moir and Fauci¹⁷ reviewed the consequences of HIV infection in the B-cell compartment. They pointed out the hypergamma-globulinemia with paradoxical loss of specific antibody responses, which correspond to increased B-cell activation and terminal differentiation, was one of the initial observations of immune dysfunction in this infection. In advanced HIV disease, loss of CD4⁺ T cells is associated with expansion of immature/transitional B cells, with decreased specific antibody responses to new and recall antigens. Most of these changes appear to reverse with antiretroviral therapy, with the exception of the memory B-cell numbers. Haynes and Shattock¹⁸ discussed a related issue, the poor protective capacity of anti-HIV neutralizing antibodies. They noted that the barriers to induce an adequate antibody response to HIV include the inefficient polyclonal B-cell activation and the characteristics of the HIV envelope, with epitopes that are not optimal to induce specific antibodies because of their posttranslational modifications or location within the molecule. They also reviewed the events occurring from mucosal exposure to HIV and systemic infection and the current efforts for the development of an anti-HIV vaccine. Ideally, this vaccine should elicit neutralizing antibodies and specific cytolytic T cells to avoid the establishment of a CD4⁺ T-cell viral reservoir. Also desirable would be the stimulation of the innate immunity, as shown by Singh et al,¹⁹ who reported an association of low expression of mannose binding lectins with more rapid HIV disease progression, especially neurologic complications. The role of mannose binding lectins is being described to confer protection against severe forms of other infections, including community-acquired pneumonia.²⁰ New approaches for vaccine development are needed to prevent HIV infection.

Primary immunodeficiencies: Genetic and immunopathogenesis studies

Notarangelo and Sorensen²¹ discussed the importance of understanding the advantages and limitations of identifying gene defects in the diagnosis of primary immunodeficiencies. Gene mutation analysis is used in combination with biomarkers for diagnosis and is clinically useful for genetic counseling and prognosis. Its application for therapeutic purposes currently helps only a fraction of affected patients. It is expected that the progressive understanding of human immunology based on these discoveries will eventually lead to novel therapies for these conditions. The report of hyper-IgE syndrome (HIES) by Renner et al²² illustrates this discussion. They described 38 patients with HIES and identified deleterious mutation in the signal transducer and activator of transcription 3 gene (*STAT3*) in all but 1 patient. All patients had decreased frequency of T_H17 cells. Although identifying the gene defects in these patients does not currently lead to curative treatment, it presumably

contributes to the diagnosis and prevention of known complications by increasing awareness. In addition, this report confirms that absence of T_H17 cells can be used as a marker of this disease, and provides new insights into the immunopathogenesis of HIES. Two reports of Omenn syndrome caused by adenosine deaminase (ADA) deficiency²³ and DNA IV ligase deficiency,²⁴ respectively, also highlight the importance of molecular diagnoses. Omenn syndrome is a form of severe combined immunodeficiency, most commonly known to result from recombination-activation gene 1 (*RAG1*) or *RAG2* gene hypomorphic mutations, and their management should consider hematopoietic stem cell transplantation (HSCT) for definite treatment.²⁵ For ADA deficiency, treatment with polyethylene glycol-adenosine deaminase (PEG-ADA), a preparation of bovine ADA enzyme, can restore lymphocyte number and immune function in patients with this condition. In cases of unusual presentations, molecular diagnosis may help to clarify rare cases such as the description of 2 primary immunodeficiencies presenting in 1 patient, ataxia-telangiectasia and IL-12 β -1 deficiency.²⁶ IL-12 β -1 deficiency and other conditions conferring increased susceptibility to mycobacterial diseases were discussed by Al-Muhsen and Casanova,²⁷ who noted that although recessive inheritance is most common, autosomal-dominant and mitochondrial inheritance patterns have been described to result in immune defects.

The correlation genotype-phenotype was examined in patient series of relatively rare primary immunodeficiencies. Gambineri et al²⁸ reported 14 patients with diagnosis of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX). A total of 12 patients with IPEX presented neonatally with hyperglycemia or severe diarrhea, which led to malabsorption and failure to thrive. The analysis of their cohort did not suggest correlation of genotype and phenotype. Kavadas et al²⁹ reported 12 patients with cartilage hair hypoplasia, a type of chondrodysplasia with immunodeficiency caused by pathogenic mutations in the gene encoding the ribonuclease mitochondrial RNA processing enzyme. Of interest, all patients had immune dysfunction, but 3 of 12 did not have growth abnormalities. In addition, patients with identical mutations had different presentations, including CD8⁺ T-cell lymphopenia that had not been described previously. Clinical and immunological characteristics of 72 individuals with hypomorphic mutations of the nuclear factor- κ B essential modulator (*NEMO*) gene were examined by Hanson et al.³⁰ They reported that specific mutations are associated with different clinical characteristics. Most but not all *NEMO* gene mutations were associated with ectodermal dysplasia, and although all patients had immunodeficiency, the occurrence of pyogenic, mycobacterial, or viral infections, as well as inflammatory diseases, was found at different frequencies. Other characteristics, such as deficiency of Toll-like receptor signaling, were also variable.³¹ These studies contributed to characterize further functional domains of NEMO and to predict susceptibility to particular infections in this condition.

The expression of TLRs and adhesion molecules in neutrophils from patients with chronic granulomatous disease (CGD) was studied by Hartl et al.³² They showed that CGD neutrophils are deficient in the expression of TLR-5 and TLR-9 and have a decreased expression of the adhesion molecule CD18. These findings could be reproduced *in vitro* by inhibiting NADPH oxidase in normal neutrophils, suggesting molecular mechanisms related to the association of this enzyme activity and cell activation. These newly described defects

may have a role in the pathogenesis of granulomatous processes and in the increased incidence of auto-inflammatory disorders³³ described in patients with CGD.

The immune characteristics of patients with partial DiGeorge syndrome (pDGS) were explored by Davis et al³⁴ and McLean-Tooke et al.³⁵ Patients with pDGS exhibit several abnormalities of their cellular immunity. Approximately one third of the patients with adequate immunization to tetanus would not develop specific antitetanus responses as measured by *in vitro* assays.³⁴ Patients with pDGS have approximately half the proportion of peripheral FOXP3⁺CD4⁺ T cells and a decreased percentage of memory CD27⁺ B cells.³⁵ These immunologic characteristics are of importance in the discussion of safety of live viral vaccines and in the observed increased frequency of autoimmune conditions in this population.

Treatment of primary immunodeficiencies

Ballow³⁶ reviewed recommendations for immunoglobulin supplementation using an intravenous and subcutaneous route of administration. Both routes have advantages and disadvantages related to adverse reactions and convenience to patients that need to be considered. Bonagura et al³⁷ suggested the individualization of the immunoglobulin dosing, arguing that the standard recommendation of trough IgG levels (400-600 mg/dL) may not be protective in all patients. They reported 2 patients who required maintaining trough IgG levels at above the recommended range. It is important to consider that the levels of specific antibodies to different pathogens may be variable in the various lots of intravenous immunoglobulins, as noted by Lejtenyi and Mazer.³⁸

Patel et al³⁹ and Slatter et al⁴⁰ reported the long-term outcomes of HSCT for severe combined immunodeficiency (SCID). Patel et al³⁹ used anti-CD6 mAb for T-cell depletion of HLA-haploidentical grafts in 20 patients with SCID, without myeloablative conditioning. After 10 to 25 years of follow-up, there was a 50% overall survival rate, or 83% of those who were successfully engrafted. Most of the mortality was caused by severe infections acquired pretransplantation, underscoring the importance of early diagnosis. Almost all survivors were doing remarkably well, completing school or college classes. Slatter et al⁴⁰ reported survivors from 2 groups of patients with SCID who received HSCT with pretransplant myeloablative conditioning using haploidentical donors. Nineteen patients survived from 27 patients who received a graft depleted of T cells using anti-CD52 mAb, and a second group of 19 patients survived from 22 who received CD34⁺ cell-enriched grafts. Optimization of HSCT protocols for primary immunodeficiencies requires a higher number of patients than those reported in these studies. A multicenter consortium is being discussed to achieve the required number of patients needed to provide definitive answers.⁴¹ This consortium will answer questions remaining in HSCT for primary immunodeficiencies (Fig 1) and will test hypothesis and observations coming from single-center studies, such as the advantages of myeloablative regimens for HSCT, the use of methylprednisolone for treatment of acute graft-versus-host disease,⁴² and the persistent susceptibility to develop colitis in patients with NEMO deficiency who have successfully immunoreconstituted.⁴³

CONCLUSIONS

Significant progress in immunology continued in the last year. After 2 decades of impressive advances in basic research for the characterization of the immune responses, we are now witnessing an increasing application of these concepts to improve our understanding of human disease. Published reports documenting the advances in the molecular, immunologic, and clinical characterization of primary immunodeficiency diseases and of HIV infection have been significant and may lead to the development of effective strategies for the control and management of these conditions. Coordinated multicenter efforts to optimize protocols for definite treatment of SCID and other severe cellular immunodeficiencies are in progress.

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Abbreviations used

ACE	Angiotensin-converting enzyme
ADA	Adenosine deaminase
APC	Antigen-presenting cell
CGD	Chronic granulomatous disease
HAART	Highly active antiretroviral therapy
HIES	Hyper-IgE syndrome
HPNAP	<i>Helicobacter pilori</i> neutrophils-activating protein
HSCT	Hematopoietic stem cell transplantation
IPEX	Immunodeficiency, polyendocrinopathy, enteropathy, X-linked
NEMO	Nuclear factor- κ B essential modulator
pDGS	Partial DiGeorge syndrome
SCID	Severe combined immunodeficiency
TLR	Toll-like receptor

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FIG 1.

Factors affecting the immunoreconstitution of primary immunodeficiencies by HSCT.

GvHD, Graft-versus-host disease.

TABLE I.

Key developments in basic and clinical immunology in 2008

Basic immunology

1. Increased epitope presentation by APC using a fusion protein (the allergen Fel d 1 and Fc γ RI) induces the differentiation of regulatory T cells.
2. HPNAP, a *H. pylori* virulence factor, can stimulate the conversion of a T_H2 response to a T_H1 response in mice.
3. Susceptibility to *S. aureus* skin infections in patients with AD is explained in part by poor ability to mobilize β -defensins.
4. T_H1 cells from atopic individuals have increased apoptotic activity, contributing to the predominance of T_H2 responses.
5. B-cell receptor cross-linking delays the expression of activation-induced deaminase and immunoglobulin class-switch recombination.

Clinical immunology

1. Patients with ACE-induced angioedema have increased plasma fibrinogen concentrations.
2. Serum levels of aminopeptidase P, an enzyme that degrades bradykinin, is high in patients with angioedema treated with androgens.
3. Naive CD8⁺ T-cell counts recover similarly to CD4⁺ T-cell counts in children with HIV receiving HAART.
4. Patients with HIV receiving HAART present with a significant high incidence of asthma.
5. Patients with HIES had decreased frequency of peripheral blood T_H17 cells.
6. ADA deficiency and DNA IV ligase deficiency can result in Omenn syndrome.
7. There were not strict genotype-phenotype correlations in a study of 14 patients with IPEX and a study of 12 patients with cartilage hair hypoplasia.
8. A study of 72 patients with hypomorphic mutations of the *NEMO* gene showed that not all patients present with ectodermal dysplasia, although increased susceptibility to different pathogens is always present, but it may vary with specific gene mutations.
9. Neutrophils from patients with CGD may have decreased expression of TLRs and adhesion molecules.
10. A subset of patients with pDGS with an adequate immunization schedule did not develop specific cellular responses to *Candida* or tetanus toxoid.
11. Patients with pDGS have decreased peripheral regulatory T cells and memory B cells.
12. Long-term outcomes studies of bone marrow transplantation for SCID demonstrate sustained immunoreconstitution and adequate quality of life, although multicenter studies are needed to optimize treatment protocols.