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ADVANCES IN BASIC AND CLINICAL IMMUNOLOGY 2010

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Abstract

Reports in basic and clinical immunology in 2010 reflected the use of state of the art genetic and immunological tools to characterize the pathogenesis of immunological diseases, and the development of novel therapies directed to these conditions. B cell biology has been explained in greater detail, significantly with lessons from the genetic defects found in the humoral immunodeficiencies. Monoclonal therapeutic antibodies are given for an increasing number of indications, such as anti-CD20 antibodies or Rituximab, which was initially developed for non-Hodgkin lymphomas and is currently used in diverse autoimmune and inflammatory disorders. The report of an infant with severe combined immunodeficiency in Massachusetts detected by newborn screening and successfully treated with hematopoietic stem cell transplantation validated recent efforts towards newborn screening for severe combined immunodeficiencies (SCID). Improvement of survival outcomes of primary immunodeficiencies patients treated with hematopoietic stem cell transplantation was demonstrated in a large European cohort with significant appreciation of the type of donor graft, particularly the use of HLA-matched unrelated donors for non-SCID patients. Progress in cellular mechanism of drug hypersensitivity included the characterization of nitroso-modified drug metabolites as potent T cell activators and the identification of the relocation of plasmacytoid dendritic cells from blood to skin as a potential risk factor for reactivation of viral disease.

Keywords

Immunology; primary immunodeficiencies; B cell; Innate immunity; hereditary angioedema; drug allergy; cell immunity; SCID; newborn screening

This manuscript reviews the progress in the fields of Basic and Clinical Immunology that were reported in the *Journal* in 2010 (Table I). We are now witnessing an increased proportion of clinical observations and therapeutic options that incorporate the powerful advances in immunology and genetics that have occurred in the last two decades. These advances have resulted in an improvement of the survival and quality of life of patients with immune-mediated diseases.

Advances in B Cell Biology

Vale and Schroeder¹ provided a comprehensive review of the current knowledge of human B cell development and maturation and pointed-out the steps which, when abnormal, are

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known to have clinical consequences as a result of immune dysfunction. Although much has been discovered, there are still gaps of knowledge in human B cell biology, e.g., the control of early B cell development, the physiology of mucosal B cell responses, and what mechanisms are defective in patients who develop common variable immunodeficiency (CVID) and other antibody deficiencies. Defective expression of a few genes are associated with a small proportion of CVID patients, however the mechanisms of pathogenesis attributed to these genes are still not entirely clear. For example, it is not known what factors determine that patients with heterozygous mutations in the transmembrane activator and calcium modulator and cyclophilin ligand interactor (*TACI* or *TNFRSF13B*) gene develop CVID. By testing mice bearing the mouse equivalent of the particularly common *TACI* mutation C104R, Lee and collaborators² demonstrated that TACI function is impaired, at least in part, by haploinsufficiency. Gatto and Brink³ reviewed the role of the germinal center (GC) in B cell activation, terminal maturation and antibody production, including the GC structure association with the control of B cell differentiation and the affinity process and peripheral B cell selection. Disturbance of GC formation is observed in several primary immunodeficiencies, and the dysregulation of GC processes are involved in the development of autoimmunity and B cell lymphomas. Mucosal immunity mechanisms were reviewed by Puga et al,⁴ who analyzed the evidence for molecular signals that induce IgA switching in the mucosa. This class switching of immunoglobulins is thought to be largely initiated by intestinal bacteria through interactions with epithelia, stroma and dendritic cells. Toll-like receptors (TLR), B-cell activating factor (BAFF) and a-proliferation induced ligand (APRIL) are the most studied molecular signals that mediate IgA switch and production.

Characterization of Lymphocyte Subsets

Two manuscripts assessed the value of studying established control ranges for lymphocyte measurements to determine levels of immunocompetence in children of different communities around the world. Mandala et al.⁵ noted in Malawi children that there were some expected similarities with reported lymphocyte counts ranges in children in Western countries, such as the peak lymphocyte counts that occurs by 2 years of age with subsequent decreasing trend; however, Malawi children had higher absolute B and T cell counts than Western countries children. Of particular interest was the steady level of the CD4 T cell percentage during the first five years of life. In developed countries, the CD4 T cell percentage median drops from 46% to 38%, but in Malawi it remains relatively constant between 35% and 39%. This difference is of significance for the management of HIV infections and the assessment of immunodeficiency. Similarly, Ananworanich and collaborators⁶ examined lymphocyte subsets in 222 HIV-positive Thai children with no AIDS related illnesses and 15–24% CD4 T cells, using healthy Thai children as the reference. As expected, the authors found lower CD4 T cell percentages in HIV-positive children than in normal children, with corresponding increased percentages of CD8 T cells. However, the subset of long-term non progressors (LTNP) children had more expression of lymphocyte activation markers than the overall HIV-infected population. These two publications make a strong recommendation for the inclusion of country-specific healthy children as controls for the assessment of immune alterations induced by HIV infections.

Progress in the characterization of lymphocyte subsets included the development of techniques to measure single epitope-specific CD4 T cells. Kwok et al.⁷ studied subjects with cat allergy and defined peptides specific for six common HLA class II DRB molecules, and using tetramer technology they were able to estimate the frequency of Fel d 1 specific CD4 T cells between 1 in 7,000 to 1 in 300,000. In addition, they were able to confirm the T_H2 memory phenotype of these allergen-specific cells.

Pneumococcal Disease and Immunization

In an interesting epidemiological study addressing factors that predispose to invasive pneumococcal disease, Jung et al.⁸ proposed that the presence of atopic dermatitis might confer increased risk of pneumonia. They identified 174 cases of invasive pneumococcal disease from a total of 3,941 medical records and analyzed for selected risk factors using age-matched controls. Allergic rhinitis was found in 3.7% in both infected and control groups; however, asthma and atopic dermatitis were found in at least twice as many in those with pneumococcal infection than in controls. The authors suggested that immune mechanisms might in part explain this increased susceptibility, and recommended the administration of pneumococcal vaccine in subjects with atopic dermatitis. Regarding this vaccine, a significant observation reported by Balloch and collaborators⁹ may result in cost savings in underdeveloped communities. They immunized infants at 12 month of age with the anti-pneumococcal polysaccharide vaccine, Pneumovax™, and showed that 98% of the infants achieved either post-immunization titers with a four-fold increase, or above 1.3 ug/mL (protective specific antibody level). Pneumovax™ is currently licensed to be given after two years of age for concerns of efficacy in younger children; however it is less expensive than the newer conjugated anti-pneumococcal vaccines.

Use of Immunoglobulins

Marodi and Casanova¹⁰ wrote an essay highlighting the consequences of the ever-increasing clinical use of therapeutic antibodies that are directed to molecules involved in the immune responses. Well-studied primary immunodeficiencies are known to show the expected effect of some of these therapeutic antibodies. The authors propose to examine the clinical course of children with these congenital diseases to predict possible complications of the therapies. Perhaps, the most representative example is Rituximab (monoclonal anti-CD20 antibody) which depletes B cells and may cause iatrogenic hypogammaglobulinemia similarly to primary humoral immune defects. Other molecules discussed by the authors are: anti-IL-12 p40 antibody (Ustekinumab), which may increase susceptibility to salmonellosis and mycobacterial infections; anti-integrin VL4 antibody (Natalizumab); and anti-interferon gamma (IFN- γ) antibody (Fontolizumab). Lee and Ballow¹¹ provided an in-depth review of the therapeutic monoclonal antibodies directed to B cells, with application in the control of autoimmune diseases, specifically rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (Figure 1). Other targets for biological agents currently available and in development include CD20, BAFF, APRIL and the IL-6 receptor. Monoclonal antibody structures vary, and the most preferred design is a humanized antibody. Soluble receptor fusion proteins have also been engineered. The most widely used of these biological agents is Rituximab, which was approved for the treatment of B-cell non-Hodgkin lymphoma in 2006. It has shown promise in a number of conditions with autoimmune basis, such as RA, SLE, immune thrombocytopenia, multiple sclerosis and vasculitis. Farcet et al.¹² measured anti-hepatitis A virus (HAV) antibody titers and neutralization capacity in over a thousand plasma pools from the US and Europe that were used to prepare intravenous immunoglobulins (IVIG), and also in the IVIG final products. They found significant reduction of antibody titers in the American products as compared to those of Europe, mainly from donors from the Czech Republic, Austria and Germany. The authors hypothesized that the observed reduced titers in American IVIG products is explained by decreasing incidence of HAV infection, which is in part due to the introduction of mandatory anti-HAV vaccine in children. Nevertheless, these reduced antibody levels remain at a titer of 14.6 IU/mL, about 1,000 times of what is considered protective to prevent HAV infection.

Common Variable Immunodeficiency

Lucas and collaborators¹³ reported a retrospective review of ninety patients with a diagnosis of CVID who were followed in one center to test the hypothesis that a reduction of breakthrough of infections can be achieved by increasing trough IgG levels. Their policy was to increase the IVIG dose by 0.15 g/kg/month when patients present with a serious infection, or 3 or more moderate infections over a year. This recommendation could be an alternative to patients who have persistent infections; although other factors contributing to infections such as airway inflammation may need to be assessed before these increased doses are made permanent for a specific patient. Approximately 86% of infections affected the respiratory tract and were attributed to bacterial cause. Kainulainen and collaborators¹⁴ reported a contrasting observation regarding the microbial cause of infections. Their patients with hypogammaglobulinemia (ten with CVID diagnoses and two with X-linked agammaglobulinemia (XLA)) who had been receiving immunoglobulin supplementation had respiratory infections of viral etiology in about half of the episodes reported, with a median of five or more respiratory infection over a 12 month period. Rhinovirus shedding was persistent after acute infection symptoms resolved. The authors alerted clinicians that the association of respiratory viral infections with predominantly cellular immunity defects may not be exclusive, and these infections may significantly impact patients with antibody defects.

Severe Combined Immunodeficiency

Progress in developing universal newborn screening for severe combined immunodeficiency (SCID) was reported with the first case of SCID detected in Massachusetts out of 100,597 infants tested.¹⁵ Validation of this screening test for SCID has previously been reported in Wisconsin.¹⁶ This finding is consistent with the previously minimum estimate of the incidence of SCID, namely 1 in 100,000 live births. The reported case was found to have Janus kinase 3 (JAK3) protein deficiency, and the infant was immediately isolated, thus reducing the risks of opportunistic infections and increasing his chances of optimal treatment outcome. In this report, seventy-eight other infants (0.08%) had the newborn screening test suggesting SCID and required confirmatory testing. After lymphocyte phenotyping was performed in blood samples of these children, the results indicated that only 29 infants (0.03%) needed a clinical evaluation, among whom the SCID patient was diagnosed. This low rate of false positives contributes to support the favorable cost-benefit ratio of the proposed screening protocol. Roifman et al.¹⁷ studied three patients with ZAP-70 immunodeficiency and found peripheral blood T cells with more matured stages of T cell development compared to X-linked SCID. The authors described a well represented diversity of T cell receptor V β repertoire, in both CD4 T cell and CD8 T cell populations. The investigators attributed the “leakiness” of the ZAP-70 defect to the ability of Syk, another tyrosine kinase, to function as a replacement for ZAP70.

The mechanisms of tolerance breakage that contribute with the phenotype of Omenn syndrome was further studied by Cassani and collaborators¹⁸ in eight patients with recombination activation gene (RAG)1/2 deficiency. Cells expressing FOXP3 were present at normal ranges, although with markers of activated memory T cells and failed to suppress CD4 T cells in two the patients who were studied. This cell phenotype did not correspond to regulatory T cells, suggesting that Omenn syndrome dysregulation can be explained by a decrease of these cells.

Buckley¹⁹ reviewed the B cell function of patients with severe combined immunodeficiency after hematopoietic stem cell transplantation (HSCT) or gene therapy. The author concluded that the use of myeloablative conditioning in HSCT for SCID did not ensure B cell function,

and compromised the overall survival rate. Cant et al.²⁰ reviewed the European experience of HSCT for primary immunodeficiencies treated between 1968 and 2005. The investigators reported a significant improvement of survival outcomes, reaching 90% for patients with SCID, when HLA-matched sibling donors were used. Survival was also associated to the B(+) phenotype and absence of respiratory disease or viral infections. For patients with non-SCID primary immunodeficiencies, the survival rate using HLA-matched unrelated donor approached the survival rate using HLA-matched siblings as donors, at 76%. The large size of this cohort gives reassurance of the improvement of survival outcomes achieved over the last two decades.

Immune Regulation Disorders with Immunodeficiency

McMurchy et al.²¹ investigated the molecular mechanisms of FOXP3 deficiency to induce the development of immunodeficiency polyendocrinopathy X-linked (IPEX) disease. Three different aminoacid mutations of FOXP3 were found in the studied patients. Two of the mutations that affected the forkhead domain resulted in a low upregulation of CD25 and different degrees of suppressive activity, compared with wild type FOXP3. The investigators were not able to demonstrate any functional defect with the third mutated protein, which was outside the forkhead domain. The authors concluded that factors other than generation of regulatory T cells were likely involved in the pathophysiology of IPEX. While we are still trying to understand the molecular mechanisms of FOXP3 function, treatment with HSCT for IPEX has fortunately been met with success, as reported by Burroughs et al.²² This group presented the experience of two cases with significant pre-transplant morbidity who received HSCT with a modified myeloablative conditioning regimen, including fludarabine and total body irradiation, followed by GvHD prophylaxis using mycophenylate and cyclosporine. This treatment resulted in persistent donor engraftment, immunoreconstitution, and resolution of previous morbidity, except for diabetes.

Another primary immunodeficiency of immune regulation: autoimmunity, polyendocrinopathy, candidiasis and ectodermal dystrophy (APECED), was studied by Ng and collaborators.²³ They reviewed 18 patients with a diagnosis of chronic mucocutaneous candidiasis with and without concomitant APECED, and assessed T_H17 responses to *Candida* antigen. Patients without APECED had decreased *in vitro* T_H17 responses, while those with APECED required the addition of their own plasma in these experiments to demonstrate this same decreased T_H17 responses. These results suggested a variability of immune mechanisms that impair T_H17 responses and lead to the increased susceptibility to *Candida* infections.

Woellner and collaborators²⁴ presented clinical and immunological features of a cohort of 100 patients with diagnosis of autosomal dominant hyper IgE syndrome (AD-HIES), another condition characterized by severe reduction of T_H17 cells and susceptibility to *Candida* infections. Sixty-four patients were found to have a *STAT3* mutation. Using logistic regression analysis, they reported that 5 clinical features (pneumonias, pathological bone fracture, characteristic facies, newborn rash and high palate) predicted the presence of *STAT3* mutations with 85% accuracy. The authors recommended using these criteria before ordering genetic analysis for *STAT3*. Of interest, eleven of 13 patients without *STAT3* mutation had low frequency of T_H17 cells.

Other advances included the experience of using HSCT in a patient with autosomal recessive hyper IgE (AR-HIES),²⁵ using a matched sibling as a donor, and with myeloablative conditioning. Full chimerism was detected in T cells and neutrophils with emerging naïve CD4 T cells by day 37, even though patient was receiving cyclosporine for

GvHD prophylaxis. Unfortunately, on day 58 post transplant, the patient died after developing a fulminant sepsis due to *Klebsiella* infection.

Wiskott-Aldrich Syndrome

Trafari and collaborators²⁶ studied a 28 year-old patient with Wiskott -Aldrich syndrome (WAS) in whom a second mutation in the *WASP* gene permitted the expression of the *WASP* protein in about 50% of his T cells. The first *WASP* mutation resulted in a premature stop codon, and the second mutation restored the reading frame with a single aminoacid change. The expressed protein localized to the immunological synapse, as expected. Likely due to selective advantage, these corrected cells increased in proportion from 10% to 70% over 8 years of life, developed a diversity of the TCR repertoire, and showed normal proliferative responses to TCR stimulation. These mutation-revertant T cells were also found to be predominant in his spleen and lymph nodes taken at 10 years of age, indicating that organs become populated with corrected cells before appearing in the peripheral blood. However, it was disappointing that this expansion of corrected T cells was not associated with clinical improvement and the patient continued to present with frequent infections.

Innate Immunity Defects: Lessons from Case Studies

Look et al.²⁷ provided suggestive evidence of the etiology of Schnitzler syndrome, a condition characterized by elevated serum IgM levels and chronic urticaria, mostly occurring in adults. Because of the inflammatory features of this syndrome, the authors sequenced the *NACHT, LRR and PYD domains-containing protein 3 (NLRP3)* gene in one patient and found an activation mutation that is known to cause the cryopyrin-associated periodic syndromes. Interestingly, the patient and any of her relatives carrying the mutation had not presented with periodic syndromes. An excessive secretion of IL-1 β , but not IL-1 α , was demonstrated when her PBMC's were activated *in vitro*. In addition, administration of anakinra, an inhibitor of IL-1 binding, produced a therapeutic response. It remains to be demonstrated whether *NLRP3* activating mutations cause Schnitzler syndrome, or is an associated clinical feature.

Mooster et al.²⁸ reported a patient who presented with recurrent sinopulmonary infections, no evidence of ectodermal dysplasia and a family history of a cousin with severe mycobacterial infection. NF κ B essential modulator (NEMO) deficiency was suspected in this case, however deleterious mutations were not found in the gene coding sequence. The investigators further pursued a potential defect in the NF κ B pathway and found that cytokine responses to TLR stimulation were defective. *NEMO* mRNA and protein expression were decreased, which led to the examination of non-coding regions of this gene and the detection of a mutation in the 5' untranslated region of the gene. This report reminds us that gene defects may occur in regulatory regions that are not commonly examined, and that the clinical diagnosis may not be ruled-out by initial genetic testing.

McDouglas and collaborators²⁹ studied a patient with interleukin 1 receptor associated kinase 4 (IRAK4) deficiency to illustrate the importance of TLR stimulation in T cell activation. Compared to cells from a healthy donor, the expression of the activation markers CD25 and CD69 of this patient's T cells were both decreased by half when activating with anti-CD3 and anti-CD28 antibodies, which target the T cell receptor, but were normal when stimulation with phorbol-myristate acetate (PMA) and ionomycin was used. IL-6 and IFN- γ secretion were also impaired if stimulated through TCR, but not reduced if stimulated with PMA and ionomycin. These results suggest that TLR stimulation is needed to fully activate T cells after antigen recognition.

Cellular Immune Mechanisms of Drug Allergy

Cell-mediated hypersensitivity to drugs was explored by two groups. Castrejon and collaborators³⁰ studied the interaction of sulfamethoxazole (SMX)-derived metabolites with T cells in patients with drug hypersensitivity to SMX. They focused on the role of nitroso-modified sulfamethoxazole metabolites and found that T cell clones obtained from patients with SMX hypersensitivity had three different patterns of reactivity, which depend on the individual antigen processing: SMX specific (14%), SMX-nitroso modified metabolite specific (44%), or crossreactive (43%). The authors concluded that molecules resulting from drug modification with nitroso groups might constitute potent T cell stimulators that mediate severe drug hypersensitivity reactions. Kabashima et al.³¹ studied the skin of patients with drug hypersensitivity syndrome to anticonvulsants to improve our understanding of the association of this condition with herpes virus (HHV) reactivation, such as HHV-6. An excess of plasmacytoid dendritic cells (pDCs) were found infiltrated in the skin dermis of patients with drug reaction, as compared with healthy controls or other maculopapular eruptions. In contrast, blood circulating pDCs were decreased. Because HHV-6 is detected in the skin of patients with this hypersensitivity syndrome and pDCs have antiviral activity, the investigators suggested that the decreased pDC in circulation may contribute to the immune dysfunction observed in these patients, resulting in systemic viral reactivation.

Hereditary Angioedema

The mechanisms of hereditary angioedema (HAE) were reviewed by Kaplan.³² Mutations of the complement C1 inhibitor (C1INH) result in HAE types I and II, while type III results from activation-inducing changes of Factor XII (FXII) that render C1INH ineffective. Understanding of the mechanisms of disease has led to novel therapies focused on inhibiting the bradykinin cascade, including a kallikrein inhibitor and a bradykinin receptor inhibitor. Lopez-Lera and collaborators³³ reported a severe case of angioedema due to a homozygous missense mutation in *C1INH*, R378C, and analyzed the capacity of the protein to bind complement C1s and kallikrein, as well as their conformational activity. Using specific antibodies that recognized specific structural states, the authors were able to determine that the mutated C1INH was in a cleaved inactivated form, providing with evidence that explains the functional consequences of this mutation.

Conclusions

Significant progress in the field of clinical immunology has been achieved with the use of current genetic and immunological tools and provided with explanation of the disease manifestations that might eventually result in novel therapies. Outcomes of HSCT for primary immunodeficiencies have improved over the last decades for SCID and non-SCID patients, although the factors that determine B cell reconstitution are still not clear. The role of T_H17 cells in diseases of immunoregulation are being explored, clearly determining susceptibility to Candida infection.

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Abbreviations

APECED autoimmunity, polyendocrinopathy, candidiasis and ectodermal dystrophy

CVID	combined variable immunodeficiency
GC	germinal center
HAV	hepatitis A virus
HHV	human herpes virus
HIES	Hyper IgE syndrome
HSCT	hematopoietic stem cell transplantation
IPEX	immunodeficiency, polyendocrinopathy, X-linked
IVIG	intravenous immunoglobulins
SCID	severe combined immunodeficiency
TACI	transmembrane activator and calcium modulator and cyclophilin ligand interactor
WAS	Wiskott-Aldrich syndrome

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Monoclonal therapeutic antibodies targeting different steps of the humoral immune response. (Reproduced with permission from Lee SL, Ballow M. Monoclonal antibodies and fusion proteins and their complications: Targeting B cells in autoimmune diseases. *J Allergy Clin Immunol* 2010; 125:814–20)

Table I

Selected key advances in basic and clinic immunology in 2010.

Primary Immunodeficiencies	
•	The <i>TACI</i> mutation C104R impairs B cell function by haploinsufficiency
•	Increasing the IVIG dose might be considered in the treatment of common variable immunodeficiency patients who have persistent infections
•	Viral respiratory infections cause significant morbidity in patients with common variable immunodeficiency
•	Newborn screening for severe combined immunodeficiency was shown to effectively detect patients with this condition
•	Patients with ZAP-70 deficiency have a well represented diversity of T cell receptor V β repertoire, in both CD4 and CD8 T cells
•	Omenn syndrome immune dysregulation can be explained by a decrease of regulatory T cells
•	IPEX has been successfully treated with bone marrow transplantation
•	Impaired T _H 17 responses leads to increased risk of chronic <i>Candida</i> infections.
•	A simplified criteria to predict <i>STAT3</i> mutations was developed for the diagnosis of autosomal dominant hyper IgE
•	Full donor chimerism was reported in a patient with autosomal recessive hyper IgE who received a bone marrow transplantation of matched sibling donor
•	Expansion of mutation-revertant T cells were reported in a patient with Wiskott-Aldrich Syndrome
•	A <i>NLRP3</i> activating mutation was found in a patient with Schnitzler syndrome
•	NEMO gene defects may occur in regulatory sequences that are not commonly analyzed
•	TLR stimulation is needed to fully activate T cells after antigen recognition
Cellular Immunity and Allergy	
•	Sulfamethoxazole modification with nitroso groups might result in potent T cell stimulators that mediate drug hypersensitivity reactions
•	Decreased plasmacytoid dendritic cells in circulation might contribute to systemic viral reactivation in patients with drug hypersensitivity syndrome to anticonvulsants
•	The frequency of Fel d 1 specific CD4 T cells was estimated between 1 in 7,000 to 1 in 300,000 cells
Other Advances	
•	Lymphocyte subset values of healthy Malawi and Thai children exhibit significant differences from children in Western populations emphasizing the importance of including country – specific controls
•	HIV infected children without AIDS-related illnesses may present with low CD4 T cell counts
•	Atopic dermatitis is associated with increased risk of invasive pneumococcal disease
•	Anti-pneumococcal polysaccharide vaccine can elicit protective antibody titers in infants at 12 months of age
•	There is significant reduction of anti-hepatitis A virus (HAV) antibody titers and neutralization capacity in the American IVIG products, although titers remain at protective levels