Advances in clinical immunology in 2015

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Advances in clinical immunology in the past year included the report of practice parameters for the diagnosis and management of primary immunodeficiencies to guide the clinician in the approach to these relatively uncommon disorders. We have learned of new gene defects causing immunodeficiency and of new phenotypes expanding the spectrum of conditions caused by genetic mutations such as a specific regulator of telomere elongation *(RTEL1)* mutation causing isolated natural killer cell deficiency and mutations in ras-associated RAB (*RAB27*) resulting in immunodeficiency without albinism. Advances in diagnosis included the increasing use of whole-exome sequencing to identify gene defects and the measurement of serum free light chains to identify secondary hypogammaglobulinemias. For several primary immunodeficiencies, improved outcomes have been reported after definitive therapy with hematopoietic stem cell transplantation and gene therapy. (J Allergy Clin Immunol 2016;138:1531-40.)

Key words: *Immunology, primary immunodeficiency, whole-exome sequencing, hematopoietic stem cell transplantation, common variable immunodeficiency, severe combined immunodeficiency, hyper-IgE syndrome*

Abbreviations used

AD:	Autosomal dominant
AR:	Autosomal recessive
BCL10:	B-cell lymphoma 10
CARD:	Caspase recruitment domain
CGD:	Chronic granulomatous disease
CID:	Combined immunodeficiency
CTLA-4:	Cytotoxic T-lymphocyte antigen 4
CVID:	Common variable immunodeficiency
DOCK:	Dedicator of cytokinesis
GOF:	Gain of function
GvHD:	Graft-versus-host disease
HIES:	Hyper-IgE syndrome
HSCT:	Hematopoietic stem cell transplantation
ICOS:	Inducible T-cell costimulator
IRF7:	Interferon regulatory factor 7
LRBA:	LPS-responsive beige-like anchor protein
MALT1:	Mucosa-associated lymphoma translocation gene
NF-κB:	Nuclear factor κB
NK:	Natural killer
PID:	Primary immunodeficiency
PI3K:	Phosphoinositide 3-kinase
PKCδ:	Protein kinase Cδ
PSTPIP1:	Proline/serine/threonine phosphatase interacting protein 1
RORC:	Retinoic acid–related orphan receptor C
ROS:	Reactive oxygen species
SCID:	Severe combined immunodeficiency
SNP:	Single nucleotide polymorphism
STAT:	Signal transducer and activator of transcription
TACI:	Transmembrane activator and CAML activator
T_{FH}:	T follicular helper
Treg:	Regulatory T
WAS:	Wiskott-Aldrich syndrome
WES:	Whole-exome sequencing

Progress in clinical immunology in 2015 included advances in the diagnosis and management of primary immunodeficiencies (PID) (Table I). On behalf of the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology; and the Joint Council of Allergy and Immunology, Bonilla led a group of experts who gathered current information and formulated practice parameters for the management of PIDs.[1] There is an increasing awareness of these disorders that were once considered rare, and nearly 300 different conditions have been reported in the last update of the classification of PIDs by the International Union of Immunological Societies.[2] Newborn screening of T-cell deficiencies, including severe combined immunodeficiency (SCID), is being implemented in the United States, and similar efforts are proposed internationally.

Clément et al[3] reported an economic analysis of newborn screening for T-cell defects in France. In addition to medical benefits of early detection to minimize the risk of fatal infections, the authors estimated a reduction of medical costs between €50,000 and €100,000 per patient identified and treated.

To investigate allergic disease in patient with PIDs, Tuano et al[4] queried the US Immunodeficiency Network registry and obtained responses from 2263 patients with PID. The prevalence of food

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TABLE I. Selected key advances in clinical immunology in 2015

- Nearly 300 PIDs have been described to date.
- TACI haploinsufficiency results in lower protein expression in memory B cells and is associated with impaired isotype switching.
- RAC2 deficiency might present as antibody deficiency.
- EBV lymphadenopathy and severe infections can be caused by deleterious mutations in CD27.
- About 18% of patients with "difficult-to-treat" chronic rhinosinusitis might have an antibody deficiency.
- Neutrophil function was shown to be affected in patients with PKCδ deficiency and in those with IFN-γ receptor 1 and IFN-γ receptor 2 deficiencies.
- Sera of patients with WAS and RAG deficiency contain a broad spectrum of autoantibodies.
- CARD9 deficiency might be found in patients with systemic yeast infections.
- Defect in the gene *TYK2* might not result in increased serum IgE levels.
- Correlation of *DCLRE1C* mutations, protein function, and clinical phenotype was observed in patients with Artemis deficiency.
- Detection of both free light chains identifies secondary hypogammaglobulinemias.
- Newly described gene defects associated with PIDs included *DOCK2*, *INO80*, *IRF7*, *RORC*, *IL17RC*, and *RNF31*.
- Patients with RAB27 defects might present with immunodeficiency without albinism.
- Improved outcomes after HSCT have been shown for CD40L deficiency, patients with CVID with serious complications, and patients with LRBA deficiency with autoimmunity.
- Innovative approaches for HSCT included sequential cadaveric lung transplantation, followed by bone marrow transplantation, CD45RA depletion of donor marrow, and use of monocyte-derived cells to prevent GvHD.
- Long-term gene therapy studies show immunologic recovery in patients with WAS and those with X-linked SCID.
- Pioglitazone, a drug used for type 2 diabetes, was shown to improve phagocyte function in patients with CGD.

IL17RC, IL-17 receptor C; *RAC2*, Ras-related C3 botulinum toxin substrate; *RAG*, recombination-activating gene; *RNF31*, ring finger factor 31.

allergy and atopic dermatitis was 1.8% and 6%, respectively, with significant variability according to type of immunodeficiency, reflecting the role of immune dysregulation in atopic disorders.

IMMUNOBIOLOGY

Mace and Orange[5] described recent advances in immunobiology that have been achieved by using microscopy imaging and classified them in processes involving cytoskeletal function, cell signaling, intracellular trafficking, and host defense. These included studies clarifying the role of the Wiskott-Aldrich syndrome (WAS) protein in formation of the immunologic synapse and the involvement of leukocyte adhesion molecules in cell-cell interaction and describing cytotoxicity granule and lysosome trafficking.

Annunziato et al[6] discussed their proposed classification of immune responses into 3 types, integrating both adaptive and innate immune responses and consistent with the current designation of most known helper T cells (Fig 1). The type 1 immune response would be characterized by the involvement of cells secreting IFN-γ and expressing the T-box transcription factor (T-bet), such as natural killer (NK) cells, type 1 innate lymphoid cells, cytotoxic CD8 T cells, and CD4 T_H1 cells. Type 2 cells include type 2 innate lymphoid cells and CD4 T_H2 cells secreting IL-4, IL-5, and IL-13, expressing GATA-binding protein 3 (GATA-3) and inducing IgE mediated responses. Type 3 immune responses are involved in inflammation and express the transcription signal retinoic acid–related orphan receptor γt, inducing expression of IL-17 and IL-22. Type 3 immune response cells include T_H17 cells and type 3 innate lymphoid cells.

T follicular helper (T_{FH}) cells are essential to B-cell differentiation into antibody-producing specific B cells. de Wit et al[7] showed that *Salmonella typhimurium*–stimulated human B cells, but not dendritic cells, induce T-cell differentiation into T_H1 and T_{FH} cells. Ma et al[8] studied the development of T_{FH} cells in different monogenic PIDs to improve our understanding of their signaling pathways. The researchers described reduced T_{FH} cell counts in patients with genetic mutations in signal transducer and activator of transcription 3 *(STAT3)*, *IL10R*, CD40 ligand *(CD40LG)*, NF-Kappa-B essential modulator *(IKBKG)*, inducible T cell costimulator *(ICOS)*, or Bruton's tyrosine kinase *(BTK)*, which is consistent with the need for these proteins for T_{FH} cell differentiation.

Bochner and Zimmerman[9] reviewed the biology and function of sialic acid–binding immunoglobulin-like lectins and other glycan-binding proteins in the regulation of the immune response. They emphasized that all cells are covered with various glycans and that only recently the field of glycobiology has started to be explored. Two families of glycan-binding proteins, sialic acid–binding immunoglobulin-like lectins and selectins, are involved in identifying pathogens, cell-cell interaction, and survival, playing a role in immunodeficiencies, cancer, and inflammation.

INVESTIGATIONS IN ANTIBODY RESPONSES: GENE DEFECTS AND VACCINE DEVELOPMENT

Common variable immunodeficiency (CVID) is a PID characterized by low serum IgG levels and impaired antibody responses, with a range of manifestations, including immunodeficiency and autoimmunity. Bone marrow aspirates from 10 patients with CVID who had only infections as disease manifestations were compared with bone marrow samples from healthy control subjects. Counts of pre-BII large cells and immature B cells were significantly reduced, suggesting a block at these differentiation stages.[10] Romberg et al[11] investigated the role of *TNFRSF13B* (encoding transmembrane activator and CAML activator [TACI]) hemizygosity in the pathogenesis of CVID. By studying B cells from patients with Smith-Magenis syndrome, who have a hemizygous deletion involving this gene, and patients with CVID with the heterozygous mutations p.C104R and p.A181E in *TNFSFR13B*, the researchers showed that autoantibody levels were low or not detected in patients with Smith-Magenis syndrome, which is consistent with their absence of autoimmunity findings. Furthermore, TACI expression was decreased in memory but not naive B cells and was associated with decreased isotype switching. In contrast, patients with CVID had autoimmunity and increased autoantibodies. These results suggest that high TACI expression might be required for terminal B-cell differentiation and that the p.C104R and p.A181E *TNFSFR13B* variants interfere with immune tolerance.

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