Advances in basic and clinical immunology in 2014

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Genetic identification of immunodeficiency syndromes has become more efficient with the availability of whole-exome sequencing, expediting the identification of relevant genes and complementing traditional linkage analysis and homozygosity mapping. New genes defects causing immunodeficiency include phophoglucomutase 3 *(PGM3)*, cytidine 5′ triphosphate synthase 1 *(CTPS1)*, nuclear factor κB–inducing kinase *(NIK)*, cytotoxic T lymphocyte–associated antigen 4 *(CTLA4)*, B-cell chronic lymphocytic leukemia/lymphoma 10 *(BCL10)*, phosphoinositide-3 kinase regulatory subunit 1 *(PIK3R1)*, *IL21*, and Jagunal homolog 1 *(JAGN1)*. New case reports expanded the clinical spectrum of gene defects. For example, a specific recombination-activating gene 1 variant protein with partial recombinant activity might produce Omenn syndrome or a common variable immunodeficiency phenotype. Central and peripheral B-cell tolerance was investigated in patients with several primary immunodeficiencies, including common variable immunodeficiency and Wiskott-Aldrich syndrome, to explain the occurrence of autoimmunity and inflammatory disorders. The role of IL-12 and IL-15 in the enhancement of natural killer cell activity was reported. Newborn screening for T-cell deficiency is being implemented in more states and is achieving its goal of defining the true incidence of severe combined immunodeficiency and providing early treatment that offers the highest survival for these patients. Definitive treatment of severe immunodeficiency with both hematopoietic stem cell transplantation and gene therapy was reported to be successful, with increasing definition of conditions needed for optimal outcomes. Progress in HIV infection is directed toward the development of an effective vaccine and the eradication of hidden latent virus reservoirs. (J Allergy Clin Immunol 2015;135:1132-41.)

Key words: *Immunology, primary immunodeficiency, dedicator of cytokinesis 8, HIV1, recombination-activating gene 1, intravenous immunoglobulin, common variable immunodeficiency, severe combined immunodeficiency, newborn screening*

Abbreviations used

ADA:	Adenosine deaminase
ApoE:	Apolipoprotein E
BCL10:	B-cell chronic lymphocytic leukemia/lymphoma 10
CARD:	Caspase recruitment domain
CGD:	Chronic granulomatous disease
CVID:	Common variable immunodeficiency
DOCK8:	Dedicator of cytokinesis 8
ERT:	Enzyme replacement therapy
GvHD:	Graft-versus-host disease
HSCT:	Hematopoietic stem cell transplantation
MALT1:	Mucosa-associated lymphoid tissue lymphoma translocation protein 1
MSD:	Matched sibling donor
NF-κB:	Nuclear factor κB
NK:	Natural killer
NLRC4:	NLR family, caspase recruitment domain containing 4
PAP:	Pulmonary alveolar proteinosis
PC:	Plasma cell
PIDTC:	Primary Immune Deficiency Treatment Consortium
RAG:	Recombination-activating gene
SCID:	Severe combined immunodeficiency
SIFD:	Sideroblastic anemia, periodic fever, B-cell deficiency, and developmental delay
STAT:	Signal transducer and activator of transcription
TCR:	T-cell receptor
TLR:	Toll-like receptor
Treg:	Regulatory T
URD:	Matched unrelated donor
WES:	Whole-exome sequencing

In 2014, several reports studied immunodeficiency syndromes that have in common an impaired signal transduction needed for nuclear factor κB (NF-κB) activation. These molecular defects result in defective B- and T-cell function with variable clinical manifestations. Turvey et al[1] discussed the pathways in NF-κB activation by the caspase recruitment domain family *(CARD11)*–B-cell chronic lymphocytic leukemia/lymphoma 10 *(BCL10)*–mucosa-associated lymphoid tissue lymphoma translocation protein 1 *(MALT1)* signalosome complex. They also reviewed the features of *CARD11-BCL10-MALT1* complex defect syndromes and postulated how the study of these gene defects has resulted in identification of novel potential pharmacologic targets for inflammatory diseases and lymphoreticular malignancies.

An example of the diverse clinical presentation associated with genetic defects of NF-κB signaling is the report by McKinnon et al[2] of a patient with eczema, skin infections, chronic cheilitis, inflammatory bowel disease, and osteoporosis in whom whole-exome sequencing (WES) revealed a missense mutation in *MALT1*. Findings included absent mitogen and antigen-induced T-cell responses, B-cell lymphopenia, increased IgE levels, and normal IgG levels and antibody responses.

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TABLE I. Selected advances in B-cell function and immunologic tolerance

- Sphingosine-1-phosphate receptors in human B cells regulate lymphocyte traffic and migration and are modulated by WASP, LRBA, and DOCK8 proteins.[6]
- Kinetics of CD40L/IL-21 activation of B cells was modeled by using chip cytometry and RNA microarray, integrating membrane receptors, signal transduction, class-switch recombination, DNA repair, and cell cycle–related genes.[7]
- Somatic hypermutation in the S region occurs before class-switch recombination and depends on CD40L, uracil-DNA glycosylase, and activation-induced deaminase.[8]
- CD40L and BCR signaling pathways are complementary to eliminate autoreactive clones and provide a balanced B-cell repertoire.[9]
- *BLNK* plays an essential role in pre-B cell differentiation and normal use of IgVk genes.[10]
- CDR3 and junctional diversity were less in patients with Omenn syndrome because of *RAG* mutations than in patients with atypical DiGeorge syndrome or ZAP70.[11]
- Patients with WAS show an expansion of naive-like $CD19^{hi}21^{lo}$ B cells thought to be autoreactive cells and a decreased proportion of memory $CD27^{+}$ B cells that are more pronounced in those with autoimmunity.[12]
- B cells from patients with X-linked lymphoproliferative disease are enriched in autoreactive clones.[13]
- Defective B-cell tolerance and Treg cells were also described in DOCK8-deficient patients with increased autoantibody levels.[14]
- B cells in patients with CVID showed high constitutive extracellular signal-regulated kinase phosphorylation with defective BCR responses, which is in agreement with the anergic nature of B cells.[15]
- A BAFFR variant with less affinity is present in 10% of patients with CVID, suggesting it might be a risk factor for the condition.[16]

BAFFR, B cell–activating factor receptor; *BCR*, B-cell receptor; *BLNK*, B-cell linker; *CD40L*, CD40 ligand; *LRBA*, LPS-responsive, beige-like anchor protein; *WAS*, Wiskott-Aldrich syndrome; *WASP*, Wiskott-Aldrich protein; *ZAP70*, ζ Chain–associated protein of 70 kDa.

Hannah and Etzioni[3] reviewed the molecular pathogenesis and clinical and immunologic features of the rare MHC class I and II deficiencies. MHC class II deficiencies commonly present as a combined immunodeficiency, whereas patients with MHC class I deficiency present with chronic lung disease, inflammatory skin disease, and vasculitis.

Lessons in the study of natural killer (NK) cells included the demonstration by Simhadri et al[4] of the need for IL-12 in the generation of NK cells with enhanced function. Another regulator of NK cell activity reported was microRNA-150. Kim et al[5] showed that microRNA-150 binds to the 3′ regions of both the mouse and human perforin-1 *(PRF1)* gene, inhibiting its transcription. IL-15 activation decreased production of microRNA-150, followed by increased perforin expression and NK cell lytic activity.

Mechanisms of B-cell function and central and peripheral tolerance were the object of studies that took advantage of the availability of patients with monogenic diseases, providing explanations for the immune dysregulation that occurs in patients with primary immunodeficiencies (Table I).[6-16]

Dhanju et al[17] established a mouse model of adenosine deaminase (ADA) deficiency to study pulmonary alveolar proteinosis (PAP). PAP was detected early in these mice, and autoantibodies were ruled out as a cause. There was increased apoptosis of alveolar macrophages and impaired surfactant clearance. ADA enzyme supplementation prevented the development of PAP.

Buckner et al[18] investigated plasma cells (PCs) in blood and the colon in patients with conditions that commonly present with noninfectious organ inflammation, such as Crohn disease. Although IgA-secreting PCs were predominant in the gut of healthy subjects, numbers of IgG-secreting PCs were increased in those with intestinal inflammation. The chemokine CXCR4 was strongly expressed in these cells. The authors suggest that $CXCR4^{+}$ IgG-secreting PCs might be markers of intestinal inflammation.

Dijkstra et al[19] studied lymphocytes from cord blood and from infants up to 1 year of age. They showed that regulatory T (Treg) cells can be induced at any age and that T_H17 cells can be induced starting at age 3 months. These findings suggest that development of tolerance and autoimmunity starts at an early age.

The effect of thymectomy in infants undergoing heart defect repair was explored by Schadenberg et al.[20] In agreement with previous reports, they found decreased absolute CD4 T-cell subset counts compared with those in age-matched healthy control subjects. Activated Treg cell counts ($CD45RO^{+}FoxP3^{high}$) were increased, whereas naive Treg cell counts ($CD45RO^{-}FoxP3^{low}$) were decreased. Increased Ki-67 expression in Treg cells indicated increased proliferation, compensating for loss of thymic output. Similar changes in Treg cell counts have been associated with autoimmunity, and therefore the authors recommended long-term evaluation of thymectomized patients and preservation of thymic tissue when feasible.

Apolipoprotein E (ApoE) is expressed in monocytes and macrophages and involved in serum lipoprotein metabolism. There are 3 human isoforms: ApoE2, ApoE3, and ApoE4. ApoE4 has been associated with cardiovascular disease, Alzheimer disease, and inflammatory disorders. Gale et al[21] performed *in vitro* experiments demonstrating that leukocytes from subjects carrying the ApoE3/ApoE4 phenotype expressed higher cytokines levels after stimulation with Toll-like receptor (TLR) 2, TLR4, and TLR5 agonists compared with cells from subjects carrying the ApoE3/ApoE3 phenotype. In a related observation monocyte-derived dendritic cells from Bruton tyrosine kinase–deficient patients showed differential responses to TLR agonists. Lougaris et al[22] showed impaired expression of activation markers and decreased secretion of IL-6, IL-12, and TNF-α in dendritic cells on stimulation with the TLR9 agonist CpG but not LPS.

NEW PRIMARY IMMUNODEFICIENCY GENES

For further information on new primary immunodeficiency genes, see Table II.[23-42]

Zhang et al,[23] Stray-Pedersen et al,[24] and Sassi et al[25] reported biallelic mutations in phophoglucomutase 3 *(PGM3)* in patients with increased IgE levels, severe atopy, autoimmunity, developmental delay, and frequent skin and respiratory tract infections. Aberrant glycosylation in leukocytes was shown, with leukopenia and predominantly T_H2 and T_H17 cytokine secretion.

IL21 deleterious mutations were found in 3 siblings with early-onset inflammatory bowel disease and severe respiratory