# Advances in basic and clinical immunology in 2016

**Javier Chinen, MD, PhD,[a]* Yousef R. Badran, MD,[b]* Raif S. Geha, MD,[b] Janet S. Chou, MD,[b] and Ari J. Fried, MD[b]**

*Houston, Tex, and Boston, Mass*

**Advances in basic immunology in 2016 included studies that further characterized the role of different proteins in the differentiation of effector T and B cells, including cytokines and proteins involved in the actin cytoskeleton. Regulation of granule formation and secretion in cytotoxic cells was also further described by examining patients with familial hemophagocytic lymphohistiocytosis. The role of prenylation in patients with mevalonate kinase deficiency leading to inflammation has been established. We reviewed advances in clinical immunology, as well as new approaches of whole-genome sequencing and genes newly reported to be associated with immunodeficiency, such as linker of activation of T cells *(LAT)*; B-cell CLL/lymphoma 11B *(BCL11B)*; RGD, leucine-rich repeat, tropomodulin domain, and proline-rich domain–containing protein *(RLTPR)*; moesin; and Janus kinase 1 *(JAK1)*. Trials of hematopoietic stem cell transplantation and gene therapy for primary immunodeficiency have had relative success; the use of autologous virus-specific cytotoxic T cells has proved effective as well. New medications are being explored, such as pioglitazone, which is under study for its role in enhancing the oxidative burst in patients with chronic granulomatous disease. Development of vaccines for HIV infection continues to provide insight into the immune response against a virus with an extraordinary mutation rate. (J Allergy Clin Immunol 2017;140:959-73.)**

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

New research developments in basic and clinical immunology continue to expand the number of immune mechanisms and explain the clinical manifestations resulting from impairment of the immune response. We present selected articles describing progress in basic and clinical immunology that were published in the scientific literature in 2016, with emphasis on themes related to immunodeficiency.

## ADVANCES IN BASIC IMMUNOLOGY

### T cells

T cells play a central role in cell-mediated immunity. Development of T cells in the thymus, their differentiation into different subpopulations, interaction with other cells involved in an immune response, and signaling downstream of surface receptors are all key aspects of understanding T-cell function in health and disease. Wiekmeijer et al[1] studied thymic T-cell development using a xenograft mouse model in which NOD-*Scid*-*Il2rg*$^{-/-}$ mice underwent transplantation with CD34$^+$ stem cells isolated from patients with severe combined immunodeficiency (SCID) caused by different gene defects. The authors showed that common γ chain cytokine signaling is required almost immediately after T-cell progenitors seed the thymus because deleterious mutations in *IL2RG*, encoding IL-2 receptor γ, and *IL7RA*, encoding IL-7 receptor α, block T-cell development at the CD4$^-$CD8$^-$CD7$^-$CD5$^-$ and CD4$^-$CD8$^-$CD7$^+$CD5$^-$ double-negative (DN) stages, respectively (Table I).[1,2] Artemis-deficient cells stop developing at the CD4$^-$CD8$^-$CD7$^+$CD5$^+$ DN stage, demonstrating the importance of T-cell receptor (TCR) rearrangements at this stage.

An alternative approach for studying T-cell development using samples from patients with SCID was reported by Brauer et al.[2] They generated induced pluripotent stem cells (iPSCs) using dermal fibroblasts from patients with recombination-activating gene 1 *(RAG1)* mutations differentiated *in vitro* into CD34$^+$ cells and then into T cells. The differentiated cells had a block at the CD4$^-$CD8$^-$CD7$^+$CD5$^+$CD38$^-$CD31$^{-/lo}$CD45RA$^+$ stage, even those obtained from patients with Omenn syndrome (OS), who had residual RAG1 recombination activity. This was attributed to accumulation of single-strand DNA breaks in cells from patients with OS, resulting in impaired cell survival and differentiation. CD4$^+$ single-positive and CD4$^+$ CD8$^+$ double-positive T-cell precursors generated *in vitro* from iPSCs from patients with OS and those with SCID had comparable severe restriction in repertoire diversity.

Resop et al[3] demonstrated that expression of sphingosine-1-phosphate (S1P) receptor 1 on mature thymocytes is essential for their egress from the thymus. Using *in vitro* transwell migration assays, the authors showed that mature CD3$^{hi}$CD27$^+$CD45RA$^+$CD62L$^+$CD69$^-$ thymocytes had the greatest migration toward S1P and that thymocytes downregulate S1P receptor 1 on interaction with S1P. The investigators also suggested a role for S1P receptor 2 in thymocyte retention in the thymus. Modulation of the interaction between S1P and its receptor was proposed as a potential strategy for increasing T-cell counts in primary immunodeficiencies (PIDs) characterized by

From [a]the Immunology, Allergy and Rheumatology Section, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, and [b]the Division of Immunology, Boston Children's Hospital, and Department of Pediatrics, Harvard Medical School, Boston.

*These authors contributed equally to this work.

Disclosure of potential conflict of interest: J. S. Chou is employed by Boston Children's Hospital and has received a grant from the National Institute of Allergy and Infectious Disease. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication May 18, 2017; revised July 12, 2017; accepted for publication July 22, 2017.

Available online August 19, 2017.

Corresponding author: Javier Chinen, MD, PhD, Pediatrics–Immunology, Allergy and Rheumatology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX 77384. E-mail: jxchinen@texaschildrens.org.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749/$36.00



http://dx.doi.org/10.1016/j.jaci.2017.07.023

*Abbreviations used*
AIP1: Actin-interacting protein 1
APDS: Activated PI3Kδ syndrome
BCL11B: B-cell CLL/lymphoma 11B
BCR: B-cell receptor
CARD9: Caspase recruitment domain-containing protein 9
CC: Coiled-coil leucine zipper
CD40L: CD40 ligand
CE: C-terminal extension
CGD: Chronic granulomatous disease
CNV: Copy number variant
COPA: Coatomer protein complex subunit α
CTLA-4: Cytotoxic T-lymphocyte antigen 4
CVID: Common variable immunodeficiency
DN: Double negative
DOCK8: Dedicator of cytokinesis 8
FHL: Familial hemophagocytic lymphohistiocytosis
GEF: Guanine exchange factor
HIES: Hyper-IgE syndrome
HLH: Hemophagocytic lymphohistiocytosis
HPS2: Hermansky-Pudlak syndrome type 2
HSCT: Hematopoietic stem cell transplantation
ILC: Innate lymphoid cell
iPSC: Induced pluripotent stem cell
JAK1: Janus kinase 1
KIR: Killer cell immunoglobulin-like receptor
LAT: Linker for activation of T cells
LFA-1: Leukocyte function–associated antigen 1
LRBA: LPS-responsive beige-like anchor protein
LYST: Lysosomal trafficking regulator
mTOR: Mammalian target of rapamycin
MVK: Mevalonate kinase
nAIGA: Neutralizing anti–IFN-γ autoantibody
NF-κB: Nuclear factor κB
NGS: Next-generation sequencing
NK: Natural killer
OS: Overall survival
OTULIN: OTU deubiquitinase with linear linkage specificity
PID: Primary immunodeficiency
PI3K: Phosphoinositide 3-kinase
POLE2: DNA polymerase ε subunit 2
PRF1: Perforin 1
PTEN: Phosphatase and tensin homolog
RAG1: Recombination-activating gene 1
RLPR: RGD, leucine-rich repeat, tropomodulin domain, and proline-rich domain–containing protein
ROS: Reactive oxygen species
RV: Rubella virus
SCID: Severe combined immunodeficiency
S1P: Sphingosine-1-phosphate
STAT: Signal transducer and activator of transcription
STING: Stimulator of interferon genes
TAP1: Transporter, ATP-binding cassette, major histocompatibility complex 1
TCR: T-cell receptor
$T_{FH}$: Follicular helper T
TFRC: Transferrin receptor
THI: Transient hypogammaglobulinemia of infancy
TLR: Toll-like receptor
TMEM: Transmembrane protein
UNG: Uracil N-glycosylase
VST: Virus-specific T cell
WAS: Wiskott-Aldrich syndrome
X-HIGM: X-linked hyper-IgM syndrome

impaired T-cell egress. On thymic egress, T cells undergo a short period of postthymic maturation in the periphery, which has now been shown to be important for tolerance induction to tissue-restricted antigens.[4] The outcome of this T-cell interaction with tissue-restricted antigens is determined by the context of the interaction: in the absence of inflammation, recent thymic emigrants are tolerized; in the presence of inflammation, recent thymic emigrants are directed toward effector cell differentiation in which mature T cells contribute to autoimmune disease.

The ability of naive $CD4^+$ T cells to differentiate into effector populations *in vitro* was studied in patients with different PIDs.[5] IL-12 receptor β1/TYK2 and IFN-γ receptor/signal transducer and activator of transcription (STAT) 1 signaling were demonstrated to be important for induction of $T_H1$ cells, and IL-21/IL-21 receptor/STAT3 signaling was demonstrated to be important for induction of $T_H17$, follicular helper T ($T_{FH}$), and IL-10–secreting cells. Signaling by IL-12 receptor β1/TYK2 and nuclear factor κB (NF-κB) essential modulator were also proved to be necessary for $T_H17$ induction. The authors showed that hyperactivation of STAT1 inhibits STAT3 signaling by showing that gain-of-function STAT1 and dominant-negative STAT3 mutations had a similar effect on $T_{FH}$ and $T_H17$ cells. Noster et al[6] demonstrated that $T_H17$ cells assume an anti-inflammatory function and produce IL-10 in the absence of IL-1β, thereby suppressing $T_H$ cell proliferation and downregulating cytokines secreted by monocytes. However, exposure to IL-1β impairs IL-10 secretion by $T_H17$ cells, which is seen in patients with Schnitzler syndrome, a disease characterized by spontaneous IL-1β secretion. IL-1β inhibition in patients with Schnitzler syndrome rescued IL-10 production by $T_H17$ cells.

Yee et al[7] identified the functions of the coiled-coil leucine zipper (CC) and C-terminal extension (CE) domains in the filamentous actin-binding protein coronin 1A through the study of patients expressing a truncated coronin 1A mutant lacking the CC and CE domains. The CC and CE domains were shown to be important for coronin 1A oligomerization and subcellular localization, regulation of filamentous actin content, *in vivo* T-cell survival, and host defense against viruses but were not essential for calcium flux or cell cytotoxicity.

Two studies have further delineated the role of the guanine exchange factor (GEF) dedicator of cytokinesis 8 (DOCK8) in T-cell function. Janssen et al[8] showed that DOCK8 interacts directly with Wiskott-Aldrich syndrome (WAS)–interacting protein, which bridges DOCK8 to WAS protein and actin in T cells. The GEF activity of DOCK8 is essential for TCR-driven WAS protein activation, actin cytoskeleton reorganization, and subcortical actin cytoskeletal integrity, which in turn are important for filamentous actin assembly, immune synapse formation, actin foci formation, mechanotransduction, T-cell transendothelial migration, and homing of T cells to the lymph nodes. Hyper-IgE syndrome (HIES) caused by autosomal dominant mutations in *STAT3* or autosomal recessive mutations in *DOCK8* have multiple overlapping features, including $T_H17$ dysfunction.

Keles et al[9] demonstrated that patients with mutations in *DOCK8* have a block in $T_H17$ differentiation similar to that previously reported in patients with autosomal dominant *STAT3* mutations. The authors showed that DOCK8 constitutively associates with STAT3 and regulates its phosphorylation through DOCK8 GEF activity. DOCK8 also promotes STAT3