Advances and highlights in primary immunodeficiencies in 2017

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This manuscript reviews selected topics in primary immunodeficiency diseases (PIDDs) published in 2017. These include (1) the role of follicular T cells in the differentiation of B cells and development of optimal antibody responses; (2) impaired nuclear factor κB subunit 1 signaling in the pathogenesis of common variable immunodeficiency, revealing an association between impaired B-cell maturation and development of inflammatory conditions; (3) autoimmune and inflammatory manifestations in patients with PIDDs in T- and B-cell deficiencies, as well as in neutrophil disorders; (4) newly described gene defects causing PIDDs, including exostosin-like 3 *(EXTL3)*, TNF-α–induced protein 3 *(TNFAIP3 [A20])*, actin-related protein 2/3 complex-subunit 1B *(ARPC1B)*, v-Rel avian reticuloendotheliosis viral oncogene homolog A *(RELA)*, hypoxia upregulated 1 *(HYOU1)*, BTB domain and CNC homolog 2 *(BACH2)*, *CD70*, and *CD55*; (5) use of rapamycin and the phosphoinositide 3-kinase inhibitor leniolisib to reduce autoimmunity and regulate B-cell function in the activated phosphoinositide 3-kinase δ syndrome; (6) improved outcomes in hematopoietic stem cell transplantation for severe combined immunodeficiency (SCID) in the last decade, with an overall 2-year survival of 90% in part caused by early diagnosis through implementation of universal newborn screening; (7) demonstration of the efficacy of lentiviral vector–mediated gene therapy for patients with adenosine deaminase–deficient SCID; (8) the promise of gene editing for PIDDs using CRISPR/Cas9 and zinc finger nuclease technology for SCID and chronic granulomatous disease; and (9) the efficacy of thymus transplantation in Europe, although associated with an unexpected high incidence of autoimmunity. The remarkable progress in the understanding and management of PIDDs reflects the current interest in this area and continues to improve the care of immunodeficient patients. (J Allergy Clin Immunol 2018;142:1041-51.)

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M.J.C. receives partial funding from NIH grant U54-AI082973.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication July 19, 2018; revised August 18, 2018; accepted for publication August 22, 2018.

Available online August 29, 2018.

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0091-6749/$36.00

https://doi.org/10.1016/j.jaci.2018.08.016

Key words: *Immunology, primary immunodeficiency, nuclear factor κB, autoimmunity, intravenous immunoglobulin, common variable immunodeficiency, severe combined immunodeficiency, newborn screening, gene therapy*

This Advances article focuses on progress in the field of primary immunodeficiency diseases (PIDDs) published in 2017. In addition to reporting new gene defects associated with PIDDs characterized by an increased susceptibility to infections, other recently described PIDDs have been found to present with significant autoimmune and inflammatory manifestations, which are often of more concern than the increased risk of infection.

FOLLICULAR HELPER H CELLS

Follicular helper T (T_{FH}) cells have a prominent role in B-cell terminal differentiation to memory B cells and plasma cells, which takes place in germinal centers, and the subsequent development of antigen-specific antibody responses (Fig 1). IL-12 and IL-21 stimulation induces differentiation of T_{FH} cells, which are identified by expression of CXCR5, CXCL13, inducible T-cell costimulator (ICOS), programmed cell death 1, B-cell lymphoma 6, B- and T-lymphocyte attenuator, and SLAM-associated protein. Increased numbers of peripheral T_{FH}-like cells have been described in patients with autoimmune disorders, including psoriasis, lupus erythematosus, and rheumatoid arthritis. Conversely, impaired differentiation of T_{FH} cells has been reported in patients with PIDDs, such as ICOS deficiency and immunodeficiencies caused by signal transducer and activator of transcription 1 *(STAT1)* gain-of-function (GOF) and *STAT3* loss-of-function mutations. Current research efforts are aimed at further characterizing the induction and regulation of these cells.

Hosokawa et al[1] reported IL-21 protein expression by IκBNS (encoded by NFKB inhibitor delta, *NFKBID*) binding to the *IL21* gene promoter site in CD4 T cells. Previous data suggested that overexpression of achaete-scute homologue 2 *(ASCL2)* induces T-cell differentiation into T_{FH} cells.[2] Interestingly, it has been shown that IκBNS-null T cells overexpressing *ASCL2* do not develop into T_{FH} cells, whereas overexpression of both IκBNS and *ASCL2* rescues the phenotype. These data indicate that IκBNS might act downstream of the ASCL2 transcription signal pathway.

T_{FH} cell differentiation induced by coculture with thymic stromal lymphopoietin–activated dendritic cells was reported by Pattarini et al.[3] They further characterized OX40 ligand as the most essential cell-to-cell ligand for this process and found that the resulting antibody class secretion was predominantly IgE, suggesting that this interaction results in T_H2 bias.

Abbreviations used

ADA: Adenosine deaminase
ADAM: A disintegrin and metalloprotease
APDS: Activated phosphoinositide 3-kinase δ syndrome
ARPC: Actin-related protein complex
ASCL2: Achaete-scute homologue 2
BACH2: BTB domain and CNC homolog 2
BTK: Bruton tyrosine kinase
Cas9: CRISPR-associated protein 9
CGD: Chronic granulomatous disease
CHH: Cartilage-hair hypoplasia
CMV: Cytomegalovirus
CRISPR: Clustered regularly interspaced short palindromic repeats
CVID: Combined variable immunodeficiency
EXTL3: Exostosin-like 3
FMF: Familial Mediterranean fever
GOF: Gain of function
HSCT: Hematopoietic stem cell transplantation
HYOU1: Hypoxia upregulated 1
ICOS: Inducible T-cell costimulator
ICOSL: ICOS ligand
IKZF1: IKAROS family zinc finger protein 1
IL2RG: IL-2 receptor γ
LAD: Leukocyte adhesion deficiency
NF-κB: Nuclear factor κB
NK: Natural killer
PIDD: Primary immunodeficiency disease
PI3Kδ: Phosphoinositide 3-kinase δ
PIK3CD: Phosphatidylinositol 3-kinase, catalytic, delta
REDD1: Regulated in development and DNA damage responses 1
SCID: Severe combined immunodeficiency
STAT: Signal transducer and activator of transcription
T_{FH}: Follicular helper T
TNFAIP3: TNF-α–induced protein 3
Treg: Regulatory T
WES: Whole-exome sequencing

Achour et al[4] reported the negative influence of regulatory B cells on T_{FH} cell differentiation induced by IL-12 and IL-21 *in vitro*, with both decreasing expression of surface markers and their capacity to induce B-cell differentiation and antibody production. The presence of regulatory B cells was associated with an expansion of follicular regulatory T (Treg) cells, which were characterized by simultaneous expression of programmed cell death 1, CXCR5, and forkhead box protein 3.

Because of the importance of ICOS–ICOS ligand (ICOSL) binding to mediate B-cell differentiation and antibody production by T_{FH} cells, Lownik et al[5] asked whether proteases involved in shedding of ICOSL from B cells could affect antibody production. They found that a disintegrin and metalloprotease 10 (ADAM10), but not ADAM17, was the most significant enzyme that participated in cleavage of ICOSL and therefore in activation of B-cell differentiation in germinal centers. By using mouse models, both ADAM10 and ADAM17 were shown to cleave ICOSL; however, most of the effect could be attributed to ADAM10 alone.

Given the role of T_{FH} cells in autoimmune conditions and antibody deficiencies (Table I),[6] elucidation of these molecular mechanisms, including the cytokines involved, could lead to the development of strategies helpful in the diagnosis and management of disorders of antibody production.

NUCLEAR FACTOR κB SUBUNIT 1 IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY

Deleterious monoallelic mutations in the gene encoding nuclear factor κB (NF-κB) subunit 1 (NF-κB1; p105/p50) have been demonstrated in patients with common variable immunodeficiency (CVID) and were reported to be the most common genetic defect in a large cohort of 390 patients with CVID, accounting for 16 (4%) cases.[7] Patients with these mutations present with reduced NF-κB1 protein levels and an expanded $CD21^{low}$ B-cell subset compared with healthy control subjects. Clinical presentation was variable, with autosomal dominant inheritance and variable penetrance. A penetrance of 60% was found in a cohort of 18 subjects carrying familial *NFKB1* mutations.

In a study conducted in 3 families in Finland,[8] 12 of 15 subjects carrying *NFKB1* mutations (H67R, R157X, and I553M) had disease, resulting in a penetrance of 80%, clinical variability, and a strong environmental and/or polygenic influence in the clinical presentation of CVID. In addition to defective antibody responses, affected patients in these families presented with inflammatory bowel disease, Behçet disease, and vasculitis (Fig 2 and Table II).[7,8]

Keller et al[9] reported that B cells from some patients with CVID have impaired NF-κB1 signaling and calcium mobilization after B-cell receptor stimulation. This impairment was most significant in those patients with an expanded $CD21^{low}CD38^{low}$ B-cell subset and was associated with reduced IκBα degradation. These patients had increased frequency of autoimmunity. Of note, $CD21^{low}CD38^{low}$ B-cell expansion has been described in patients with HIV infection and autoimmune conditions, such as lupus erythematous. $CD21^{low}CD38^{low}$ B cells from patients with lupus also show reduced IκBα degradation, suggesting that this is characteristic of the cell type.

Lougaris et al[10] reported 2 patients with CVID with monoallelic *NFKB1* mutations (A506Vfs and D191L), leading to a truncated p50 protein and absent p105, expansion of $CD21^{low}CD38^{low}$ B cells, and autoimmune enteropathy. Taken together, these data contribute to the characterization of the subset of patients with CVID who have inflammatory and autoimmune complications, who are likely to present with an expansion of $CD21^{low}CD38^{low}$ B cells and can have monoallelic mutations in *NFKB1*.

IMMUNE CONSEQUENCES OF SPLENECTOMY AND NEONATAL THYMECTOMY

The immune consequences of splenectomy and neonatal thymectomy are summarized in Table III.[11-15]

Patients who have been splenectomized are considered to be at significant risk of severe bacterial infections, even after pneumococcal immunization. Karasatova et al[11] investigated the anti-pneumococcal–specific lymphoproliferation in patients who have been splenectomized after spleen trauma to determine whether T-cell function was impaired. After pneumococcal immunization, there was a decrease in antigen-specific lymphoproliferation, which was most significant for the T_H1 cell subset, suggesting that the spleen is important for optimizing both T- and B-cell responses. Asplenic children with heterotaxy syndrome similarly have a significantly increased risk of invasive bacterial infections compared with patients with heterotaxy