Primary immunodeficiencies: A rapidly evolving story

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The characterization of primary immunodeficiencies (PIDs) in human subjects is crucial for a better understanding of the biology of the immune response. New achievements in this field have been possible in light of collaborative studies; attention paid to new phenotypes, infectious and otherwise; improved immunologic techniques; and use of exome sequencing technology. The International Union of Immunological Societies Expert Committee on PIDs recently reported on the updated classification of PIDs. However, new PIDs are being discovered at an ever-increasing rate. A series of 19 novel primary defects of immunity that have been discovered after release of the International Union of Immunological Societies report are discussed here. These new findings highlight the molecular pathways that are associated with clinical phenotypes and suggest potential therapies for affected patients. (J Allergy Clin Immunol 2013;131:314-23.)

Key words: *Primary immunodeficiencies, combined immunodeficiencies, well-defined syndromes with immunodeficiency, predominantly antibody defects, defects of immune dysregulation, congenital defects of phagocytes, defects in innate immunity, autoinflammatory disorders, mutation detection*

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Abbreviations used

ADAM17:	A disintegrin and metalloproteinase 17
BCR:	B-cell receptor
EV:	Epidermodysplasia verruciformis
HHV6:	Human herpesvirus 6
HPS:	Hermansky-Pudlak syndrome
HPV:	Human papilloma virus
HSE:	Herpes simplex virus encephalitis
HSV1:	Herpes simplex virus 1
ICA:	Isolated congenital asplenia
ICL:	Idiopathic $CD4^+$ lymphopenia
IL-36Ra:	IL-36 receptor antagonist
ISG15:	Interferon-stimulated gene 15
IUIS:	International Union of Immunological Societies
LCK:	Lymphocyte-specific protein tyrosine kinase
LRBA:	LPS-responsive beige-like anchor
MCM4:	Minichromosome maintenance complex component 4
MSMD:	Mendelian susceptibility to mycobacterial disease
MST:	Mammalian Ste20-like kinase
NEMO:	NF-κB essential modulator
NF-κB:	Nuclear factor κB
NK:	Natural killer
PI3K:	Phosphoinositide 3-kinase
PID:	Primary immunodeficiency
PLCγ2:	Phospholipase Cγ2
RHOH:	Ras homolog gene family member H
TBK1:	TANK-binding kinase 1
TCR:	T-cell receptor
TLR3:	Toll-like receptor 3
TRIF:	Toll/IL-1 receptor domain–containing adaptor inducing IFN-β
UNC119:	Uncoordinated 119
WASP:	Wiskott-Aldrich syndrome protein
WIP:	WASP-interacting protein

Known primary immunodeficiencies (PIDs) include individually rare but collectively diverse genetic defects that influence the development, function, or both of immunity. Taken in a broad sense, these disorders encompass both the hematopoietic and nonhematopoietic arms of host defense. They result in a wide range of clinical symptoms, including but not limited to susceptibility to infections, autoimmunity, inflammation, allergy, and malignancy.[1] Significant progress in the field has recently accelerated thanks to collaborative work around the world; improved techniques to analyze leukocyte subsets; attention paid to new phenotypes, such as infections selectively caused by certain pathogens in otherwise healthy children[2]; and use of high-throughput next-generation sequencing technology (eg, whole-exome sequencing).[3] The International Union of Immunological Societies (IUIS) Expert Committee on PIDs published the biennial update of the classification of PIDs in a recent article dated November 2011.[4] However, the continuously growing number and variety of PIDs make this type of classification difficult and perhaps calls for a revised approach.[5,6] In this review we focus on the 19 new PIDs that appeared in the literature after the release of the last IUIS report. Some of these reports include

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Disclosure of potential conflict of interest: J.-L. Casanova has received grants from the National Institutes of Health (NIH); has been a consultant for Pfizer, GlaxoSmith-Kline, NovImmune, Biogenldec, Merck, and Sanofi-Aventis; and has grants/grants pending from Pfizer and Merck. L. D. Notarangelo is a board member for the Immune Disease Institute, is employed by Children's Hospital Boston, has grants/grants pending with the NIH, the March of Dimes, and the Jeffrey Modell Foundation; and has received payment for lectures, including service on speakers' bureaus for the WAS foundation. M. E. Conley is employed by the University of Tennessee, has received grants/grants pending from the NIH and the March of Dimes, has received payment for lectures from the Immune Deficiency Foundation, and is receiving royalties from the Southern Bio for monoclonal antibodies. N. Parvaneh declares no relevant conflicts of interest.

Received for publication October 2, 2012; revised November 6, 2012; accepted for publication November 29, 2012.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2012.11.051

only a single case, making it difficult to confidently predict the clinical phenotype; however, each new disorder provides valuable insights into the pathways that normally ensure host defense from environmental challenges while not harming the host. We classify these new PIDs according to the latest IUIS classification (Table I).

COMBINED IMMUNODEFICIENCIES

T-cell receptor α gene mutation: T-cell receptor $\alpha\beta^+$ T-cell depletion

T cells comprise 2 distinct lineages that express either αβ or γδ T-cell receptor (TCR) complexes that perform different tasks in immune responses. During T-cell maturation, the precise order and efficacy of TCR gene rearrangements determine the fate of the cells.[7] Productive β-chain gene rearrangement produces a pre-TCR on the cell surface in association with pre-Tα invariant peptide (β-selection). Pre-TCR signals promote α-chain recombination and transition to a double-positive stage ($CD4^+CD8^+$).[8] This is the prerequisite for central tolerance achieved through positive and negative selection of thymocytes. Additional insight into the development of $TCR\alpha\beta^+$ T cells was provided by the characterization of 2 patients from 2 unrelated Pakistani families who had the same homozygous mutation in the TCRα constant (*TRAC*) gene and shared increased susceptibility to infections, autoimmunity, and profound T-cell proliferative impairments but apparently had normal antibody responses.[9] One of the cases showed predisposition to herpes virus infections (including protracted varicella zoster and chronic EBV/HHV6 viremia) and chronic lung disease. In addition to immunodeficiency, both children had evidence of immune dysregulation with a combination of eosinophilia, vitiligo, alopecia areata, autoimmune hemolytic anemia, eczema, and the presence of autoantibodies. T cells from affected subjects were devoid of surface expression of the TCRαβ complex; all existing $CD3^+$ T cells expressed TCRγδ. Both patients were successfully treated with matched sibling bone marrow transplants. This study is of interest because it is the first pure $TCR\alpha\beta^+$ T-cell immunodeficiency, allowing a fine definition of the role of this major cell lineage. Previously described disorders affected all T-cell lineages alone or in combination with B-cell or natural killer (NK) cell deficits. This experiment confirms that γδ T cells alone cannot ensure adequate host defense. It would be interesting to identify patients with a selective γδ T-cell deficiency because the exact role of these T cells remains unknown.

Ras homolog gene family member H deficiency: Loss of naive T cells and persistent human papilloma virus infections

Human papilloma viruses (HPVs) are double-stranded DNA viruses with a tropism for keratinocytes, causing chronic epithelial lesions that can progress to cancer.[10] Susceptibility to HPV infection can be genetically determined, as seen in epidermodysplasia verruciformis (EV). EV is characterized by early development of widespread, refractory flat warts and pityriasis-like lesions and occasional development of skin carcinomas caused by certain types of HPV, called EV-HPV (or β-HPV types), in otherwise healthy subjects.[11] Mutations in *EVER1* or *EVER2* have been identified in most but not all patients with EV.[12] To date, the exact mechanisms leading to persistent EV-HPV infections in EVER-deficient patients are unknown; there is a clear keratinocyte phenotype[13] but only mild T-cell anomalies in EVER-deficient patients.[14] A recent study explored the genetic basis of an EV-like phenotype in 2 French siblings with persistent cutaneous EV-HPV infections and other clinical manifestations, including bronchopulmonary disease and Burkitt lymphoma in one of them, indicating that the phenotypic spectrum of the disease is not restricted to susceptibility to HPV.[15] Therefore this condition is related to but distinct from EV. The patients were homozygous for a nonsense allele of the Ras homolog gene family member H *(RHOH)*, which encodes an atypical Rho GTPase (RHOH) expressed predominantly in hematopoietic cells. RHOH is crucial for pre-TCR and TCR signaling and has a role during β-selection and positive selection in the thymus.[16,17] The patients displayed a lack of circulating naive T cells, a lower than normal proportion of skin-homing $\beta7^+$ T cells, and impaired TCR signaling. The combination of these T-cell defects might explain the pathogenesis of susceptibility to cutaneous EV-HPVs. EV-like features were also recently reported in a child with mammalian Ste20-like kinase (MST) 1 deficiency (described below).[18]

MST1 deficiency: Loss of naive T cells

New insight into the role of MST1 as a critical regulator of T-cell homing and function was provided by the characterization of 8 patients from 4 unrelated families who had homozygous nonsense mutations in *STK4*, the gene encoding MST1.[18-20] MST1 was originally identified as an ubiquitously expressed kinase with structural homology to yeast Ste20.[21] MST1 is the mammalian homolog of the Drosophila Hippo protein, controlling cell growth, apoptosis, and tumorigenesis.[22] It has both proapoptotic and antiapoptotic functions.[19] Clinically, the patients had recurrent bacterial, viral, and candidal infections; lymphopenia; intermittent neutropenia; EBV-driven lymphoproliferation; lymphoma; autoimmune cytopenias; and subtle cardiac anomalies. Of note is the development of HPV (both EV-HPV and non-EV-HPV) infections in 3 of the patients.[18,19] MST1-deficient patients demonstrated hypergammaglobulinemia and variable humoral responses. However, B-cell numbers (especially memory B-cell numbers) were significantly reduced in one report.[19] Peripheral T cells displayed markedly impaired survival/proliferation to mitogens and antigens, a response that worsened with time.[20] Moreover, the T-cell compartment showed a restricted TCR repertoire and a severe reduction in circulating naive ($CD45RA^+$) cell numbers. Together with RHOH deficiency, MST1 deficiency seems to affect naive T-cell development and homing, predisposing to various infections in affected subjects.

Lymphocyte-specific protein tyrosine kinase deficiency: T-cell deficiency with $CD4^+$ lymphopenia

Defects in pre-TCR– and TCR-mediated signaling lead to aberrant T-cell development and function (Fig 1). One of the earliest biochemical events occurring after engagement of the (pre)-TCR is the activation of lymphocyte-specific protein tyrosine kinase (LCK), a member of the SRC family of protein tyrosine kinases.[23,24] This kinase then phosphorylates immunoreceptor tyrosine-based activation motifs of intracellular domains of CD3 subunits. Phosphorylated immunoreceptor tyrosine-based activation motifs recruit ζ-chain associated protein kinase of 70 kDa, which, after being phosphorylated by LCK, is

TABLE I. Novel PID genes and their phenotypes

Gene	Protein	Inheritance	Phenotype
Combined immunodeficiencies			
TRAC	TCRα	AR	TCRαβ$^+$ T-cell deficiency, viral infections, autoimmunity
RHOH	RHOH	AR	Loss of naive T cells, HPV infection
STK4	MST1	AR	Loss of naive T cells, EBV infection, HPV infection, autoimmunity
LCK	LCK	AR	T-cell deficiency, CD4$^+$ lymphopenia
UNC119	UNC119	AD, dominant negative	ICL
Well-defined syndromes with immunodeficiency			
WIPF1	WIP	AR	Wiskott-Aldrich syndrome-like
PLCG2	Phospholipase Cγ2	AD, dominant negative	Cold urticaria, humeral deficiency, autoimmunity, atopy (S707Y)
		AD, hypermorphic	Autoinflammatory syndrome (deletions)
Predominantly antibody defects			
PIK3R1	p85α subunit of PI3K	AR	Agammaglobulinemia, absent B cells
CD21	CD21	AR	Hypogammaglobulinemia
LRBA	LRBA	AR	Hypogammaglobulinemia, autoimmunity, colitis
Defects of immune dysregulation			
PLDN	Pallidin	AR	HPS type 9, albinism, immunodeficiency
CD27	CD27	AR	EBV-associated lymphoproliferation, hypogammaglobulinemia
Congenital defects of phagocyte number, function, or both			
ISG15	ISG15	AR	MSMD
Defects in innate immunity			
NKX2-5	NKX2-5	AD, dominant negative	ICA
TRIF	TRIF	AR	Herpes simplex encephalitis
TBK1	TBK1	AD, dominant negative (G159A), haploinsufficiency (D50A)	Herpes simplex encephalitis
MCM4	MCM4	AR	NK cell deficiency, infection with herpesviruses, growth retardation, and adrenal insufficiency
Autoinflammatory disorders			
ADAM17	ADAM17	AR	Inflammatory skin and bowel disease, high IL-1 and IL-6 production
IL36RN	IL-36Ra	AR	Generalized pustular psoriasis

responsible for activation of critical downstream events. Major consequences include activation of the membrane-associated enzyme phospholipase Cγ1, activation of the mitogen-activated protein kinase, nuclear translocation of nuclear factor κB (NF-κB), and Ca^{2+}/Mg^{2+} mobilization. Through these pathways, LCK controls T-cell development and activation.[25] In mice lacking LCK, T-cell development in the thymus is profoundly blocked at an early double-negative stage.[26] Although 3 cases of combined immunodeficiencies with altered LCK protein expression had been reported in human subjects, the molecular defects at the genomic level were not documented.[27-29] Recently, autosomal recessive LCK deficiency was described as the cause of profound T-cell immunodeficiency and immune dysregulation.[30] A French infant presented with early-onset protracted diarrhea, recurrent respiratory tract infections, failure to thrive, autoimmune thrombocytopenia, and skin/mucosal inflammatory disorders. Laboratory studies in the affected patient showed CD4$^+$ T-cell lymphopenia and low Treg cell numbers. The residual T lymphocytes had an oligoclonal T-cell repertoire and exhibited a severe TCR signaling defect, with only weak tyrosine phosphorylation signals and no Ca^{2+} mobilization after TCR stimulation. Moreover, the patient's T cells were resistant to activation-induced cell death. She was found to have a homozygous missense mutation of the *LCK* gene (c.1022T>C; L341P) resulting from maternal uniparental disomy. Anti-TNF therapy was partially effective in treating the serositis and skin inflammation. She underwent matched unrelated hematopoietic stem cell transplantation at 30 months, but unfortunately, she died of post-transplantation veno-occlusive disease. This study highlights the importance of LCK for the development of a normal T-cell repertoire and also maintenance of central and peripheral T-cell tolerance.

Uncoordinated 119 deficiency: Idiopathic CD4$^+$ lymphopenia

Idiopathic CD4$^+$ lymphopenia (ICL) is a very heterogeneous clinical entity that is defined, by default, by persistent CD4$^+$ T-cell lymphopenia (<300 cells/μL or <20% of total T cells) in the absence of HIV infection or any other known cause of immunodeficiency.[31] The few studies examining the pathogenesis of ICL suggest that in some patients accelerated apoptosis and diminished proliferative capacity are partly due to disturbed TCR signaling.[32,33] Uncoordinated 119 (UNC119), an activator of LCK, delivers LCK to the plasma membrane through an endosomal route and initiates the enzymatic activity of LCK on TCR stimulation.[34,35] Through LCK, UNC119 regulates some T-cell functions, including immunologic synapse formation, proliferation, and differentiation into effector cells.[34-37] Recently, a heterozygous dominant-negative missense mutation (V22G) of UNC119 was reported in a patient with ICL.[38] The patient was a 32-year-old woman with a history of recurrent respiratory tract infections, persistent fungal infections of the skin and nails, recurrent shingles, and oral herpes simplex lesions. The patient's cells showed reduced response to TCR stimulation, with impairment in LCK localization/activation resulting in decreased cell proliferation. Transduction of the mutant UNC119 but not wild-type UNC119 into normal T cells reproduced the signaling and

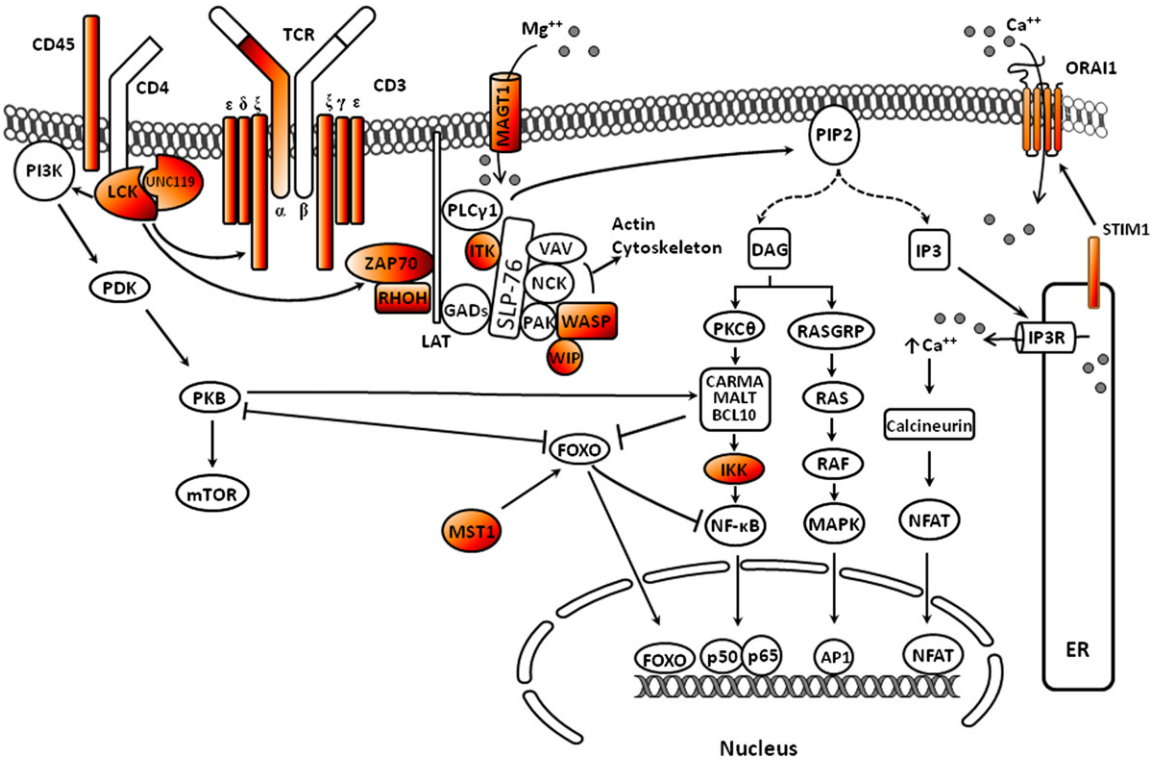

FIG 1. TCR signaling. Multiple signal transduction pathways are stimulated through the TCR. These pathways collectively activate transcription factors that organize T-cell survival, proliferation, differentiation, homeostasis, and migration. Mutant molecules in patients with TCR-related defects are indicated in *red*. *AP1*, Activator protein 1; *BCL10*, B-cell lymphoma/leukemia 10; *CARMA*, CARD-containing MAGUK protein; *DAG*, diacylglycerol; *ER*, endoplasmic reticulum; *FOXO*, forkhead box O; *GAD*, GRB2-related adaptor protein; *IKK*, IκB kinase; *IP3*, inositol trisphosphate; *IP3R*, inositol trisphosphate receptor; *LAT*, linker of activated T cells; *MALT*, mucosa-associated lymphoid tissue lymphoma translocation protein; *MAPK*, mitogen-activated protein kinase; *mTOR*, mammalian target of rapamycin; *NCK*, noncatalytic region of tyrosine kinase adaptor protein; *NFAT*, nuclear factor of activated T cells; *PDK*, phosphoinositide-dependent kinase; *PIP2*, phosphatidyl inositol bisphosphate; *PKB*, protein kinase B; *PKCθ*, protein kinase C θ; *RASGRP*, RAS guanyl nucleotide–releasing protein; *SLP-76*, SH2 domain–containing leukocyte protein of 76 kDa; *STIM1*, stromal interaction molecule 1; *ZAP70*, ζ-chain associated protein kinase of 70 kDa.

proliferation defects, confirming the inhibitory function of G22V mutation. These findings shed light on the molecular mechanisms for a subset of patients with ICL.

WELL-DEFINED SYNDROMES WITH IMMUNODEFICIENCY

Wiskott-Aldrich syndrome protein–interacting protein deficiency: Wiskott-Aldrich syndrome-like phenotype

In hematopoietic cells Wiskott-Aldrich syndrome protein (WASP) is stabilized through forming a complex with WASP-interacting protein (WIP).[39] A female Moroccan infant presented in early infancy with recurrent infections, eczema, thrombocytopenia, T-cell lymphopenia, and decreased NK cell function reminiscent of WAS.[40] Despite normal WAS sequence and mRNA expression levels, WASP was not detected in the patient's cells, suggesting WASP protein degradation caused by the absence of WIP. Further studies showed that WIP could not be detected in the patient's T-cell blasts, and a homozygous nonsense mutation (S434X) was detected in *WIPF1*, which encodes WIP. Despite clinical similarities with patients with WAS, the WIP-deficient patient displayed some immune abnormalities that have not been documented in patients with WAS. They include impaired T-cell response to IL-2, complete failure to proliferate in response to TCR ligation with anti-CD3, and complete abrogation of T-cell chemotaxis.[41-43] Moreover, the mean platelet volume was normal in the patient, as seen in WIP-deficient mice.[44] Unrelated cord blood transplantation was performed at 4.5 months, and the child is now doing well at age 21 months. This study is interesting because it reports the first autosomal recessive form of WAS, one of the most emblematic X-linked recessive PIDs and arguably one of the first PIDs described, first by Wiskott in 1937[45] and then again by Aldrich in 1954.[46]

Phospholipase Cγ2 gain-of-function mutations: Cold urticaria, immunodeficiency, and autoimmunity/autoinflammatory

This is a unique phenotype, sharing features of antibody deficiency, autoinflammatory diseases, and immune dysregulatory disorders, making its classification difficult. Two recent studies validated the pleiotropy of genetic alterations in the same gene.[47,48] In the first study genomic deletions in *PLCG2* were

detected in 3 distinct families with a dominantly inherited syndrome of cold urticaria and variable immune dysregulation.[47] *PLCG2* encodes phospholipase Cγ2 (PLCγ2), a signaling molecule expressed in B cells, NK cells, mast cells, and platelets. PLCγ transmits information from activated receptors to downstream signal cascades by triggering receptor-mediated Ca^{2+} entry.[49,50] Cold urticaria occurred in all 27 affected subjects. Interestingly, skin test results were positive for evaporative cooling but negative on ice-cube and cold-water immersion. Other variable manifestations included atopy, sinopulmonary infections, autoimmune diseases, and granulomatous rashes in order of frequency. Laboratory findings were also variable and included low serum IgM and IgA levels in some patients, diminished numbers of circulating $CD19^+$ B cells and switched memory B cells, and low NK cell numbers, whereas IgE levels were increased in most of the subjects. The C-terminal SH2 deletions in PLCγ2, which were seen in all 3 families, resulted in the failure of autoinhibition and caused constitutive phospholipase activity when transfected into COS7 cells.[47] Paradoxically, B cells and NK cells clearly had decreased PLCγ2-dependent signaling and function; the exact mechanisms are not yet clear. Affected mast cells showed increased mast cell degranulation at cold temperatures without receptor stimulation, indicating that the altered function of mutant PLCγ2 was the cause of cold urticaria. Another study by the same research group defined a hypermorphic dominant mutation within *PLCG2* (p.Ser707Tyr) as the cause of a novel autoinflammatory syndrome in 2 affected members of a family.[48] A father and his daughter both had epidermolysis bullosa–like eruptions in infancy, interstitial pneumonitis, arthralgia, eye inflammation, enterocolitis, cellulitis, and recurrent sinopulmonary infections. Immunologic workup showed low circulating IgM/IgA levels and absence of class-switched memory B cells. The inflammatory manifestations were refractory to treatment with nonsteroidal anti-inflammatory drugs and TNF inhibitors but responsive to high-dose corticosteroids and, to a lesser extent, to IL-1 blockade. B cells showed increased PLCγ2-dependent signaling after receptor cross-linking, as indicated by increased levels of inositol trisphosphate production, intracellular Ca^{2+} release, and extracellular signal-regulated kinase phosphorylation.

In conclusion, a central role for PLCγ in controlling Ca^{2+} signaling and thus a plethora of cellular responses could explain the various clinical features, with the involvement of the humoral immune system and various forms of inflammation as the common theme. Allelic heterogeneity at the *PLCG2* locus apparently further contributes to the diversity of cellular and clinical phenotypes.

PREDOMINANTLY ANTIBODY DEFECTS

Defect in the p85α subunit of phosphoinositide 3-kinase: Agammaglobulinemia and absent B cells

Early B-cell development is under lineage-specific genetic control. Genetic defects of Bruton tyrosine kinase and components of the pre–B-cell receptor (BCR), such as the μ heavy chain, λ5, Igα, Igβ, and the downstream scaffold protein B-cell linker, have been described in more than 90% of patients with isolated defects in B-cell development and agammaglobulinemia.[51] A report has recently described a homozygous premature stop codon in *PIK3R1*, which encodes 3 regulatory subunits of phosphoinositide 3-kinase (PI3K) by use of alternative splicing.[52] The patient, a young woman with agammaglobulinemia and absent B cells, had early onset of infections and multiple complications, including colitis, as a teenager.[52] PI3Ks are a broadly expressed group of enzymes that respond to extracellular signals to activate a variety of cellular functions.[53] Although the mutation did not affect the expression of p50α and p55α, the other regulatory subunits encoded by *PIK3R1*, it did result in a marked decrease in levels of p110δ, the catalytic subunit of PI3K. The developmental arrest in the patient was at the pro–B-cell stage, earlier than that seen in patients with defects in the BCR signaling pathway.[51] The extracellular signal that requires activation of the PI3K pathway at this early stage of development is unknown; however, it was noted that the chemokine CXCR4 transduces through PI3K[54] and that defects in CXCR4 in mice cause a similar block in B-cell development.[55] The patient had neutropenia at the time of diagnosis that was not seen during follow-up evaluations. Patients with early defects of B-cell development might present with neutropenia before they are started on gammaglobulin replacement.[56-58] Mice with p85α deficiency show a wide range of defects, including a B-cell defect similar to that seen in mice with mutations in *Btk*, hypersensitivity to insulin, defective platelet function, and abnormal mast cell development.[59,60] In contrast, in human subjects the absence of p85α results in a severe isolated defect in development of early stages of B lineage cells without associated findings.

CD21 deficiency: Hypogammaglobulinemia

CD21, the complement receptor type 2, is expressed on mature B cells and follicular dendritic cells.[61] In addition to binding the complement component C3d, CD21 also binds interferon α and CD23[62] and serves as the main cellular entry receptor for EBV.[63,64] CD21 forms a part of the CD19 complex, decreasing the threshold for antigen stimulation of B cells through the BCR.[65] A 28-year-old man presented with recurrent infections, splenomegaly, hypogammaglobulinemia, and reduced class-switched memory (IgD^-CD27^+) B-cell numbers but a normal antibody response to vaccine antigens.[66] Compound heterozygous mutations in the *CD21* gene prohibited CD21 receptor expression. Functional studies showed a complete loss of costimulatory activity of C3d in enhancing B-cell receptor stimulation. Vaccination response to pneumococcal polysaccharide vaccination was moderately impaired, but the responses to protein antigens were preserved. The patient's B cells were unable to bind to the EBVgp350 antigen; however, the patient underwent EBV seroconversion *in vivo*, and his B cells were easily immortalized by EBV *in vitro*. This indicates that CD21 is not required for EBV infection *in vitro* and *in vivo*. The patient's clinical condition improved on prophylactic antibiotics and intermittent gammaglobulin substitution. CD21 deficiency shares many features with CD19 and CD81 deficiency, although with less clinical severity.[67,68] Preservation of specific antibody responses and normal responses to direct BCR stimulation in patients with CD21 deficiency probably contribute to this clinical variability.[66] This case suggests that patients with CD21 deficiency present with recurrent infections and low serum IgG levels but uneventful EBV infection.

LPS-responsive beige-like anchor deficiency: Hypogammaglobulinemia with autoimmunity and early colitis

Linkage analysis and whole-exome sequencing conducted by 2 groups led to the identification of homozygous, autosomal

recessive, LPS-responsive beige-like anchor *(LRBA)* gene mutations in 10 patients from 5 unrelated families.[69,70] The clinical symptoms and laboratory findings in these patients were highly variable. Most had early onset of recurrent bacterial infections, autoimmune disease, or both. A subset had severe nonbloody diarrhea. One of the patients also had recurrent EBV-related lymphoproliferative disease.[69] Decreased serum IgG and IgA concentrations were seen in 8 of the 10 patients. $CD19^+$ B-cell counts were variable, but switched memory B-cell counts were low in all patients who were tested. In addition, an increased susceptibility to apoptosis was documented in LRBA-deficient EBV immortalized B cells.[70] T cells were phenotypically normal, with variable proliferative responses to mitogens and anti-CD3.[69]

The product of the *LRBA* gene (LRBA) is a cytosolic protein expressed in many tissues believed to be involved in endocytosis of ligand-activated receptors and also control of apoptosis.[71,72] The authors suggest that the autoimmune features seen in LRBA-deficient patients were attributable to increased apoptosis and defective inhibitory receptor signaling.[69,70] LRBA deficiency should be considered in the presence of early-onset hypogammaglobulinemia associated with colitis, autoimmune features, or both. The mechanism of disease remains to be deciphered.

DEFECTS OF IMMUNE DYSREGULATION

Pallidin deficiency: Hermansky-Pudlak syndrome type 9

Hermansky-Pudlak syndrome (HPS) subtypes present with some degree of albinism and variable bleeding diathesis.[73] However, some subtypes have additional features, such as neutropenia and defective lymphocyte-mediated cytotoxicity, as seen in HPS-2.[74] Two recent articles reported the same homozygous nonsense (c.232C>T) *PLDN* mutation in 2 unrelated patients with HPS-like phenotype.[75,76] *PLDN* is mutated in the HPS mouse model *pallid* (or HPS-9) and encodes the protein pallidin that interacts with the early endosomal t-SNARE syntaxin-13.[77,78]

A 17-year-old Italian girl with partial albinism, nystagmus, and normal neurologic development presented with recurrent cutaneous infections.[75] She had leukopenia and thrombocytopenia at presentation. NK cell degranulation and cytolysis were shown to be defective.[75] In addition, a 9-month-old Indian boy presented at birth with generalized hypopigmentation and respiratory distress but no history of infections or cytopenias.[76] Electron microscopy of platelets at 9 months showed absent platelet delta granules, which is consistent with HPS. Neither of the patients had a bleeding history, and results of platelet aggregation studies were normal.[76] The clinical picture of the Italian patient was reminiscent of the accelerated phase of hemophagocytic lymphohistiocytosis, a feature that was not substantiated in a *pallid* mouse model. The milder clinical phenotype of the second case might be attributed to his younger age. Identification of more patients with hemophagocytic lymphohistiocytosis presentation could list PLDN deficiency as a novel cause of albinism and immunodeficiency.

CD27 deficiency: Immune dysregulation and persistent EBV infection

In clinical practice CD27 is recognized as a marker for memory B cells and is used to subclassify patients with a variety of B-cell immunodeficiencies.[79] After binding its natural ligand, CD70, CD27 regulates differentiation and cellular activity in subsets of T, B, and NK cells.[80,81] Two independent reports have recently described a similar presentation of abnormal adaptive human immunity and persistent EBV viremia attributed to CD27 deficiency.[82,83] Ten patients from 4 independent families (from Morocco, Turkey, and Lebanon) were confirmed to have homozygous mutations in the gene encoding CD27. The clinical picture varied from asymptomatic memory B-cell deficiency to persistent symptomatic EBV viremia and malignant lymphoma. After EBV infection, hypogammaglobulinemia developed in 3 of the affected subjects. T cell–dependent B-cell responses were abnormal,[82] whereas antipolysaccharide antibodies were detectable.[83] Moreover, $CD8^+$ T-cell function was disturbed, and invariant NK T-cell numbers were diminished. Three patients died, 2 others underwent successful allogeneic hematopoietic stem cell transplantations, and 2 received anti-CD20 therapy repeatedly. CD27 deficiency predisposes to symptomatic and potentially fatal EBV infection and hypogammaglobulinemia, a phenotype that is similar to that of X-linked lymphoproliferative disease.

CONGENITAL DEFECTS OF PHAGOCYTE NUMBER, FUNCTION, OR BOTH

Interferon-stimulated gene 15 deficiency: Mendelian susceptibility to mycobacterial diseases

Mendelian susceptibility to mycobacterial diseases (MSMD) predisposes subjects to severe disease on infection by weakly virulent mycobacteria, such as nontuberculous environmental mycobacteria and BCG. Germline mutations in 6 autosomal and 2 X-linked genes involved in IFN-γ–mediated immunity have been reported to cause MSMD (Fig 2).[84-86] Recently, another genetic cause of MSMD was described in 2 kindreds.[87] Three children from 2 distinct kindreds from Iran and Turkey presented with BCG-induced clinical disease starting in early infancy and were found to carry homozygous interferon-stimulated gene 15 *(ISG15)* mutations.[87] The clinical and immunologic phenotypes of these patients resembled those of IL-12 receptor β1 deficiency,[88] with impaired IFN-γ immunity and relatively mild MSMD responsive to antimycobacterial therapy. In mice ISG15 is induced by IFN-α/β, which is produced in response to viral infection and has been shown to play a role in antiviral defense.[89,90] However, it seems that the antiviral function of ISG15 is redundant in human subjects because the patients did not experience unusual viral infections. During phagocytosis, granulocytes are a major source of ISG15 secretion.[87] Free ISG15 then potentiates the secretion of IFN-γ, mostly by NK cells.[91] ISG15 is therefore not only an IFN-α/β–inducible, intracellular, ubiquitin-like molecule involved in ISGylation but also an IFN-γ–inducing secreted cytokine. This function complements the role of the IL-12–IFN-γ circuit in the control of mycobacterial infection. The IL-12–IFN-γ circuit involves mostly mononuclear phagocytes and T cells, whereas the ISG15–IFN-γ circuit involves mostly granulocytes and NK cells. In granulocytes ISG15 was found to be expressed in secretory granules. The mechanisms by which ISG15 stimulates NK and T cells are not yet known.

DEFECTS IN INNATE IMMUNITY

NKX2-5 deficiency: Isolated congenital asplenia

Congenital asplenia, which can be diagnosed based on the results of ultrasonography or the presence of Howell-Jolly bodies in blood smears, is often associated with complex visceral defects

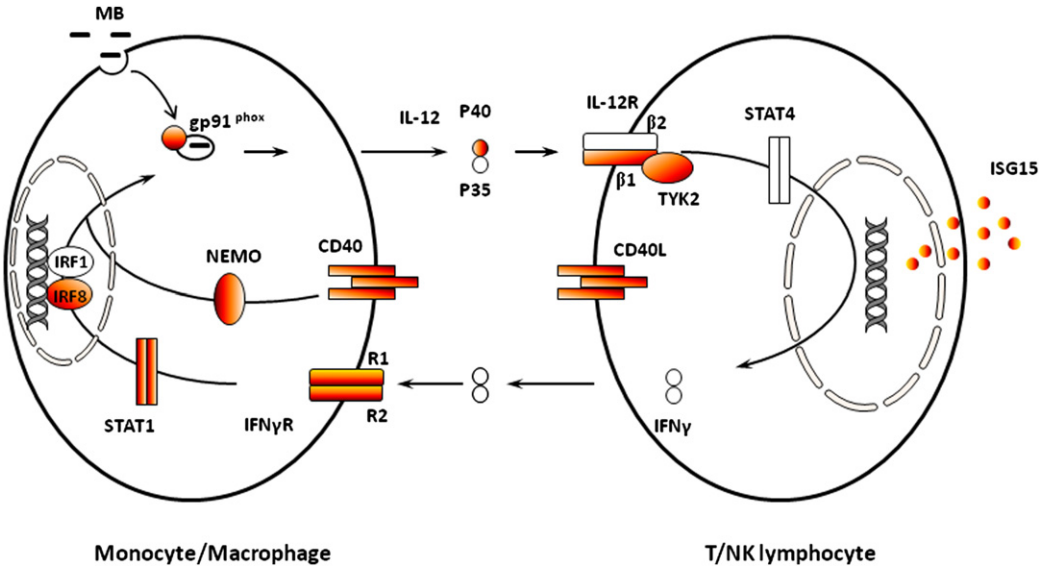

FIG 2. Cross-talk between monocyte/macrophage cells and T/NK lymphocytes. Genes in the IL-12/IFN-γ pathway are particularly important for protection against mycobacterial disease. IRF8 is an IFN-γ–inducible transcription factor required for the induction of various target genes, including IL-12. The NF-κB essential modulator *(NEMO)* mutations in the LZ domain impair CD40-NEMO–dependent pathways. Some gp91phox mutations specifically abolish the respiratory burst in monocyte-derived macrophages. ISG15 is secreted by neutrophils and potentiates IFN-γ production by NK/T cells. Genetic defects that preclude monocyte development (eg, GATA2) can also predispose to mycobacterial infections (not shown). Mutant molecules in patients with unusual susceptibility to infection are indicated in *red*. *IFNγR*, IFN-γ receptor; *IL-12R*, IL-12 receptor; *MB*, mycobacterium; *STAT*, signal transducer and activator of transcription; *TYK2*, tyrosine kinase 2.

as part of heterotaxy syndromes.[92,93] The causative mutations have been identified in various genes controlling left-right laterality.[94,95] In contrast, isolated congenital asplenia (ICA; ie, in the absence of heterotaxy or cardiac anomalies) was first thought to be rare and sporadic.[96] Studies of case reports and rare national surveys suggested probable autosomal dominant, as well as spontaneous, occurrences.[97,98] The most frequent pathogens in patients with ICA are encapsulated bacteria, with *Streptococcus pneumonia* as the leading infectious agent.[98,99] The infections associated with ICA can be fatal in childhood but tend to improve with age.[98] Using mouse models of spleen morphogenesis to help focus the exome sequencing data of a family with ICA led to the discovery of a heterozygous missense mutation in *NKX2*-5.[100] Pbx1, a prime regulator of the organogenesis of the spleen, governs spleen development through transactivation of the *Nkx2-5* gene product (Nkx-2).[101] Moreover, both Pbx1 and Nkx-2 control spleen growth by repression of CDK inhibitor p15Ink4b.[102] Mice deficient for Pbx/Nkx2-5/p15 components exhibit disrupted spleen development.[100] Finding of a *NKX2-5* mutation as a possible cause of human ICA reinforces the central role of PBX target genes in the development of spleen. This study also paves the way for the investigation of ICA in other kindreds.

Toll/IL-1 receptor domain–containing adaptor inducing IFN-β and TANK-binding kinase 1 deficiencies: Herpes simplex encephalitis

Herpes simplex virus 1 (HSV1) is an ubiquitous pathogen that causes acute, self-limiting infection after primary exposure. However, it can trigger debilitating and fatal herpes simplex virus encephalitis (HSE) on rare occasions.[103] Thanks to recent studies, the Toll-like receptor 3 (TLR3)–interferon pathway emerged as the major player in localized immunity against herpes simplex virus in the central nervous system.[104,105] A recent study of patients with HSE explored the Toll/IL-1 receptor domain–containing adaptor inducing IFN-β (TRIF) protein as another component of the TLR3 antiviral pathway.[106] Two patients with HSE with TRIF deficiency were identified, one with a homozygous nonsense mutation, resulting in complete recessive TRIF deficiency, and another with a heterozygous missense mutation, leading to partial dominant (probably by negative dominance) TRIF deficiency. TRIF is an adaptor protein serving as the sole adaptor to TLR3 and as an alternative adaptor through TRIF-related adaptor molecule to TLR4.[107,108] Once activated by agonist-induced TLR3 dimerization, TRIF activates downstream signaling events, culminating in production of IFN-α/β, IFN-λ, and proinflammatory cytokines.[109,110] TRIF-deficient patients' fibroblasts did not produce interferons after stimulation with TLR3 agonists and showed increased susceptibility to HSV1 infections *in vitro*.[106]

Another study also brings to light new facts about genetic susceptibility to HSE. Two different heterozygous missense mutations in TANK-binding kinase 1 *(TBK1)* were identified as causing HSE in 2 patients from Poland and France.[111] *TBK1* encodes TBK1, a noncanonical IκB kinase of the NF-κB signaling pathway, which controls the activity of transcription factors of the interferon regulatory factor family, mainly interferon regulatory factor 3.[112] Through this process, TBK1 exerts its antiviral role through regulation of the production of multiple interferons. Both mutant *TBK1* alleles were loss-of-function mutations underlying an autosomal dominant trait in heterozygous patients by haploinsufficiency (D50A) or negative dominance (G159A).[111] TLR3-related antiviral activities were blunted in both mutant fibroblasts; however, the defects were rescued by IFN-α2b. The

elucidation of TRIF and TBK1 deficiencies substantiates the obligatory role of the TLR3 pathway in immunity against HSV1 in the central nervous system and its redundancy for protective immunity otherwise.

Minichromosome maintenance complex component 4 deficiency: NK cell deficiency associated with growth retardation and adrenal insufficiency

NK cells are cells of the innate immune system that exert antiviral and antitumor surveillance functions in mice.[113] Some cases of selective quantitative circulating human NK cell deficiencies with specific susceptibility to viral infections have been reported.[114-117] However, the mechanisms that control NK cell development in human subjects remain unclear. Two groups of researchers have shown that human NK cell deficiency is caused by a homozygous mutation in the minichromosome maintenance complex component 4 *(MCM4)* gene in patients from the Irish traveler community.[118,119] In addition, patients with NK cell deficiency displayed growth retardation, increased chromosomal breakage, adrenal insufficiency, and, in 1 case, lymphoma. From an infectious perspective, the patients had unusual susceptibility to herpes viruses.[118] The studied patients shared the same splice defect, probably because of a founder effect. MCM4 is a highly conserved DNA helicase that is required for DNA replication and cell proliferation.[120] Patients' fibroblasts contained high numbers of DNA breaks and showed cell-cycle abnormalities.[118] MCM4 deficiency contributed to a developmental defect in transition of $CD56^{bright}$ to $CD56^{dim}$ NK cells, as evidenced by the lack of $CD56^{dim}$ NK cells in the peripheral blood and the preservation of the small $CD56^{bright}$ NK cell population.[118,121]

AUTOINFLAMMATORY DISORDERS

A disintegrin and metalloproteinase 17 deficiency: Inflammatory skin and bowel disease

Two siblings born to consanguineous parents of Lebanese origin came to medical attention with early-onset pustular dermatitis, short and broken hair, paronychia, frequent cutaneous bacterial infections, and diarrhea.[122] The younger sister died at 12 years of age after parvovirus B19–induced myocarditis, and the affected brother was found to have mild cardiomyopathy. A loss-of-function mutation in a disintegrin and metalloproteinase 17 *(ADAM17)* was identified as the cause of this syndrome. ADAM17 is a major membrane-bound proteinase that cleaves cell-surface proteins, such as cytokines (eg, TNF-α), cytokine receptors (eg, IL-6 receptor and TNF receptor), growth factors (eg, TGF-α), and adhesion proteins (eg, L-selectin).[123] *In vivo*, ADAM17 has a role in controlling inflammation and tissue regeneration. PBMCs obtained from the affected brother showed impaired release of TNF-α but high levels of LPS-induced production of IL-1β and IL-6. Lack of TNF-α was considered partly responsible for their increased susceptibility to infection and development of cardiomyopathy.[122,124]

IL-36 receptor antagonist deficiency: Generalized pustular psoriasis

Generalized pustular psoriasis is a life-threatening, multisystemic inflammatory disease characterized by episodic, widespread, diffuse erythematous pustular rash associated with high fever, malaise, and leukocytosis.[125,126] By using homozygosity mapping and exome sequencing, a total of 19 patients were found to have homozygous or compound heterozygous mutations in the *IL36RN* gene, encoding IL-36 receptor antagonist (IL-36Ra).[127,128] IL-36Ra (also known as IL-1F5) is an antagonist of 3 cytokines of the IL-1 family (IL-36A, IL-36B, and IL-36G) that have NF-κB– and mitogen-activated protein kinase–activating properties.[129,130] Defective expression and function of IL-36Ra thus could direct uncontrolled inflammatory processes on pathogen stimulation through mucosal surfaces. Generalized pustular psoriasis provides one more example that highlights the central role of IL-1 signaling in tissue inflammation,[131] illuminating a rational target for its treatment.[132]

CONCLUSION

The field of PIDs is advancing at full speed in 2 directions. New genetic causes of known PIDs are being discovered (eg, CD21 and TRIF). Moreover, new phenotypes qualify as PIDs with the identification of a first genetic cause (eg, generalized pustular psoriasis). Recent findings contribute fundamental knowledge about immune system biology and its perturbation in disease. They are also of considerable clinical benefit for the patients and their families. A priority is to further translate these new discoveries into improved diagnostic methods and more effective therapeutic strategies, promoting the well-being of patients with PIDs.

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