

represent opposite ends of a spectrum of a diathesis in the regulation of helper T-cell phenotype differentiation. Such a simple interpretation, however, is not supported by epidemiologic studies showing that the presence of atopy provides little protection against development of the T_H1-predominant illness rheumatoid arthritis. In fact, some studies have suggested that patients with a T_H1 illness are more likely to have a T_H2 illness, suggesting that they have a common underlying cause.¹⁷ The identification of novel cytokines and regulatory cell subsets, including those producing IL-23 and IL-17, offers hope for deeper understanding of the mechanisms underlying autoimmune and atopic diseases and the development of new and effective therapies.^{8,9}

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2. Update on primary immunodeficiency diseases

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The pace of discovery in primary immunodeficiency continues to accelerate. In particular, lymphocyte defects have been the source of the most impressive expansion in recent years. Novel forms of agammaglobulinemia, class-switch defects, and T-B⁺ severe combined immunodeficiency have been described. Little by little, the genetic heterogeneity of the common variable immunodeficiency and IgA deficiency phenotypes continues to be unraveled as new molecular defects have been reported in these patients as well. The phenotypic spectrum of DiGeorge syndrome has been further developed, along with promising advances in therapy. Defects of nuclear factor κ B regulation and Toll-like receptor signaling have been described, along with defects of chemokine receptors and cytoplasmic proteases. Clinically defined immunodeficiencies, such as hyper-IgE syndrome and idiopathic CD4 lymphocytopenia, are also discussed. Finally, significant adverse effects in some patients have tempered initial enthusiasm for gene therapy. (*J Allergy Clin Immunol* 2006;117:S435-41.)

Key words: Genetic diseases, human, immunodeficiency, immunology, infection

This updated chapter on primary immunodeficiency serves as a companion to the chapter published in the most recent edition of the full *Primer on Allergic and Immunologic Diseases*.¹ This update contains important new material, as well as useful information that was not included in the original chapter because of space constraints. Potential new literature sources for this update were collected through a PubMed search using the MeSH major topic “immunologic deficiency syndromes” with the Boolean operator “NOT” linked to HIV and AIDS. Changes have been made to all of the tables, and they are included here in their entirety. Table I describes the major classes of infectious susceptibilities associated with each of the principal categories of immunodeficiency (lymphocyte defects resulting in antibody deficiencies, cellular immune deficiencies, and combined deficiencies, as well as phagocyte and complement defects). Table II contains a listing and classification of selected molecular defects associated with primary immunodeficiency. Table III indicates the alterations in the major subpopulations of peripheral blood lymphocytes in several forms of severe combined immunodeficiency (SCID). A more

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TABLE I. Infectious organisms frequently associated with or characteristic of major categories of immune deficiency

Organism	Antibody deficiency	Cellular deficiency	Combined deficiency	Phagocyte defect	Complement deficiency
Viruses	Enteroviruses	Herpesviruses	All	No	No
Bacteria	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , <i>Campylobacter fetus</i> , <i>Neisseria meningitidis</i> , <i>Mycoplasma hominis</i> , <i>Ureaplasma urealyticum</i>	<i>Salmonella typhi</i>	As for antibody deficiency and cellular deficiency, also: <i>Listeria monocytogenes</i> , enteric flora	<i>S aureus</i> , enteric flora, <i>P aeruginosa</i> , <i>S typhi</i> , <i>Nocardia asteroides</i>	As for antibody deficiency, also <i>N meningitidis</i> (terminal pathway defect)
Mycobacteria	No	All, including BCG	All, including BCG	All, including BCG	No
Fungi	No	<i>Candida albicans</i> , <i>Coccidioides immitis</i> , <i>Histoplasma capsulatum</i> , <i>Aspergillus fumigatus</i>	<i>C albicans</i> , <i>Cryptococcus neoformans</i> , <i>Pneumocystis jiroveci</i>	<i>Aspergillus fumigatus</i> , <i>C albicans</i> , <i>P jiroveci</i>	No
Protozoa	<i>Giardia lamblia</i>		<i>Toxoplasma gondii</i>		No

Abbreviations used

AID:	Activation-induced cytidine deaminase
CVID:	Common variable immunodeficiency
DGS:	DiGeorge syndrome
ICOS:	Inducible T-cell costimulator
IRAK-4:	IL-1 receptor-associated kinase 4
LRRC8:	Leucine-rich repeat-containing 8
NEMO:	Nuclear factor κ B essential modulator
NF- κ B:	Nuclear factor κ B
NK:	Natural killer
RAG:	Recombinase-activating gene
SCID:	Severe combined immunodeficiency
TAC1:	Transmembrane activator and calcium modulator and cyclophilin ligand interactor
TAP:	Transporter of antigenic peptides
UNG:	Uracil nucleoside glycosylase

detailed treatment of diagnosis and management of primary immunodeficiency can be found in a recently published practice parameter.²

ANTIBODY DEFICIENCIES

A form of agammaglobulinemia with absent B cells in a girl with abnormal facies has been ascribed to alteration of the leucine-rich repeat-containing 8 gene (*LRRC8*).³ *LRRC8* belongs to a family of leucine-rich proteins of unknown function.⁴ In the single patient described, a balanced chromosomal translocation permitted expression of

a truncated molecule that exhibited dominant negative activity. B-cell development was arrested in the bone marrow, as in other forms of agammaglobulinemia.⁵ However, the role of *LRRC8* in B-cell development requires clarification.

Uracil nucleoside glycosylase (UNG) deficiency leads to a form of hyper-IgM syndrome (low IgG and IgA levels with normal or increased IgM levels) highly similar to that associated with lack of activation-induced cytidine deaminase (AID).⁶ Both AID and UNG are nucleotide-modifying enzymes expressed only in B cells and operate on sequential steps in the processes of class-switching and somatic hypermutation of immunoglobulin genes.^{7,8} AID and UNG defects have no effect on T-cell function, and patients with these diseases do not have the associated cellular immunodeficiency that is seen with defects of *CD40L* (CD40 ligand or CD154, X-linked hyper-IgM syndrome) and *CD40* (another autosomal recessive form of hyper-IgM syndrome).⁹

Some patients initially given diagnoses of common variable immunodeficiency (CVID) have been found to have mutations in the inducible T-cell costimulator gene (*ICOS*).¹⁰ This molecule is expressed on the surface of activated T cells and interacts with ICOS ligand expressed on B cells. This interaction clearly is important for the development of antibody responses, as evidenced by the panhypogammaglobulinemia and poor antibody formation in those who lack it. One interesting unexplained feature of this disease is that the onset of clinical symptoms does not occur until late childhood or adulthood. Only 9 in 226 patients with CVID screened thus far have been found to have *ICOS* mutations.¹⁰ All have origins in the Black Forest region of Germany

TABLE II. Some immunodeficiencies associated with known molecular defects

Disorders	Molecules
Antibody deficiencies	
The agammaglobulinemias	
X-linked	Bruton's tyrosine kinase (BTK)
Autosomal recessive	IgM heavy chain, Ig- α , surrogate light chain, B cell-linker protein (BLNK), LRRC8
Hyper-IgM syndrome, autosomal recessive	AID, UNG
ICF syndrome	DNA methyltransferase 3B
CVID	TACI, ICOS
Cellular deficiencies	
IFN- γ /IL-12 axis	IFN- γ receptor α and β chains, IL-12 p40 subunit, IL-12 receptor α chain, signal transducer and activator of transcription 1 (STAT-1)
Autoimmune polyglandular syndrome type 1	Autoimmune regulator (AIRE)
Defective NK function (CD16 deficiency)	Fc γ RIII
Combined deficiencies	
SCID	
Defective cytokine signaling	
X-linked	Cytokine receptor common γ chain
Autosomal recessive	IL-2 receptor α chain, IL-7 receptor α chain, Janus kinase 3 (JAK3)
Defective T-cell receptor signaling	CD45, CD3 γ , CD3 δ , CD3 ϵ
Defective receptor gene recombination	RAG1, RAG2, DNA cross-link repair 1C (DCLRE1C, ARTEMIS)
Defective nucleotide salvage pathway	Adenosine deaminase, purine nucleoside phosphorylase
Defective MHC class I expression	Transporter of antigenic peptides 1 and 2 (TAP1, TAP2), TAP-binding protein
Defective MHC class II transcription	Four components of the MHC class II gene transcription complex: CIITA,
complementation groups A-D	RFXANK, RFX5, and RFXAP
Other	Winged-helix nude transcription factor
Wiskott-Aldrich syndrome	Wiskott-Aldrich syndrome protein (WASP)
Ataxia-telangiectasia group	Ataxia-telangiectasia mutated (ATM), nibrin
DGS	Chromosome 22q11 deletion, T box-1 transcription factor (TBX1)
Hyper-IgM syndrome	
X-linked	CD40 ligand
Autosomal recessive	CD40
X-linked lymphoproliferative syndrome	SLAM-associated protein (SAP)
Defects of NF- κ B regulation	NF- κ B essential modulator (NEMO), I κ B kinase α chain
Defects of Toll-like receptor signaling	IL-1 receptor associated kinase 4 (IRAK-4)
WHIM syndrome	CXC chemokine receptor 4 (CXCR4)
Caspase 8 deficiency	Caspase 8
Phagocyte defects	
Chronic granulomatous disease	
X-linked	Cytochrome b558 α chain (gp91phox)
Autosomal recessive	Cytochrome b558 β chain (p22phox), neutrophil cytosolic factors 1 (p47phox) and 2 (p67phox), ras-related C3 botulinum toxin substrate 2 (RAC2)
Chediak-Higashi syndrome	Lysosomal trafficking regulator (LYST)
Leukocyte adhesion deficiency 1, 2	β 2 integrin (CD18), fucose transporter (solute carrier family 35, member C1)
Neutrophil-specific granule deficiency	CCAAT/enhancer binding protein (C/EBP)- ϵ
Cyclic neutropenia, Kostmann's syndrome	Elastase 2
X-linked neutropenia	Wiskott-Aldrich syndrome protein
Complement defects	
	All soluble complement components except factor B

ICF, Immunodeficiency, centromeric instability, and facial anomalies; WHIM, warts, hypogammaglobulinemia, infection, myelokathexis.

and have the same genetic deletion, which is indicative of a founder mutation.

More recently, mutations of *TNFRSF13B* encoding the transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) have been described in patients with CVID (17 of a total 181 screened) and IgA deficiency (1/16).^{11,12} TACI is expressed on B cells and interacts with the ligands BAFF (B-cell activating factor, TNFSF13B) and APRIL (a proliferation-inducing

ligand, TNFSF13) expressed on macrophages and dendritic cells. These interactions have important roles in B-cell activation and immunoglobulin class switching. Most patients are heterozygous for a *TACI* mutation, although some homozygotes have been found.¹² Disease severity varies widely. With the exception of the single patient with IgA deficiency, all patients exhibit hypogammaglobulinemia. Additional manifestations include autoimmune disease, lymphoproliferation and

TABLE III. Lymphocyte phenotypes characteristically associated with particular forms of SCID

Form of SCID	T cells			B cells	NK cells
	CD3	CD4	CD8		
Common γ chain, JAK3, IL-2R α chain, CD45	↓	↓	↓	NL	↓
IL-7R α chain, CD3 δ	↓	↓	↓	NL	NL
RAG1, RAG2	↓	↓	↓	↓	NL
Adenosine deaminase	↓	↓	↓	↓	↓
MHC class II	NL	↓	NL	NL	NL
ZAP70, MHC class I	NL	NL	↓	NL	NL

↓, Decreased; NL, normal; ZAP70, ζ -associated protein, 70 kd.

hepatosplenomegaly, and malignancy. As expected, patients exhibit impaired antibody responses to immunization-infection. They also have reductions in peripheral blood switched memory B cells, which is also seen in a majority of patients with CVID (most of who probably do not have a *TACI* mutation).¹³

There are additional reports of patients with phenotypes consistent with CVID ultimately found to have mutations in genes associated with distinct immunodeficiencies. These include *BTK* (mutated in X-linked agammaglobulinemia)^{14,15} and *SH2D1A* (SLAM-associated protein, mutated in X-linked lymphoproliferative disorder).¹⁶

In a recent review of 127 cases of IgA deficiency, 50% had recurrent infections (predominantly involving the respiratory tract), 28% had autoimmune disease, and 13% exhibited asthma and allergies.¹⁷ In this group of patients, poor responses to pneumococcal polysaccharide vaccines correlated with low serum IgG2 levels (found in 8%), although, interestingly, not with respiratory infections. Low levels of IgG3 and IgG4 were found in 29% and 2% of patients, respectively; these did not correlate with other clinical or laboratory features.

Approximately 75% of cases of immunodeficiency, centromeric instability, and facial anomalies syndrome result from mutation of *DNMT3B* (DNA methyltransferase 3B).^{18,19} Most have a variable hypogammaglobulinemia, and a few have minor *in vitro* abnormalities of T-cell function. About two thirds have recurrent respiratory tract bacterial infections. A similar proportion has abnormal facies, consisting of flat nasal bridge and hypertelorism with epicanthal folds. The disorder can be diagnosed on the basis of the pathognomonic karyotypic finding of abnormal structures of chromosomes 1, 9, and 16.

CELLULAR DEFICIENCIES

Idiopathic CD4 lymphocytopenia is a rare immunodeficiency of unknown cause that clinically closely resembles HIV infection, but the absence of this and related viruses by means of all serologic and molecular methods of detection is a crucial element of the case definition.²⁰ Patients have persistently low CD4 T-cell counts (<300 cells/mm³) and experience opportunistic infections, autoimmune disease, and hematologic malignancies.

As yet poorly characterized isolated defects of natural killer (NK) cell number, function, or both (without other identifiable abnormalities of humoral or cellular immune responses) have been described in some patients with apparent predisposition to infections with herpesviruses, papillomaviruses, or both.²¹ In general, immunologic evaluation might only reveal reduction in the number or activity of NK cells (CD3⁻ and CD16⁺ or CD56⁺), with the preservation of T cells and B cells. In these patients, care should be taken to exclude other immunodeficiencies known to be associated with defects of NK cell number or function, such as SCID,²² Chediak-Higashi syndrome,²¹ X-linked lymphoproliferative disorder,²¹ CD40 ligand deficiency,²¹ Wiskott-Aldrich syndrome,²¹ X-linked agammaglobulinemia,²¹ and nuclear factor (NF) κ B essential modulator (NEMO) deficiency.²³

COMBINED DEFICIENCIES

A novel form of T⁻B⁺NK⁺ SCID has been described in association with defects of the CD3 δ chain (*CD3D* mutation).²⁴ The CD3 complex transduces signals initiated by interaction of the T-cell receptor with an MHC-peptide complex. Defects of other components of the CD3 complex (γ and ϵ chains) and associated kinases (ζ -associated protein, 70 kd) have been associated with SCID or deficient cellular immunity.^{1,2} Interestingly, SCID caused by a CD3 δ defect might be distinct from others in that a thymus shadow is clearly visible on chest radiographs. The thymus becomes populated with developing thymocytes, but they fail to mature completely, and no functioning T cells enter the peripheral circulation.

A novel form of MHC class I deficiency caused by mutations affecting the molecular chaperone transporter of antigenic peptides (TAP)-binding protein (tapasin) has been described.²⁵ The phenotype is very similar to MHC-I deficiency caused by *TAP1/TAP2* mutation, although a low level of MHC-I expression might occur.

DiGeorge syndrome (DGS) and velocardiofacial syndrome are in the phenotypic spectrum of chromosome 22q11 deletion.^{1,2} Of the many genes contained in the deleted region, attention focused on a transcription factor, T-box 1, because hemizygous deletion in a murine model reproduced several elements of the human phenotype.²⁶

Recently, 13 patients with DGS–velocardiofacial syndrome without 22q11 deletion were studied for mutations in T-box 1, which were detected in 5 individuals.²⁷

Although most patients with partial DGS have varying degrees of T lymphopenia, significant defects of cell-mediated immunity occur almost exclusively in those with complete lack of thymus (complete DGS).²⁸ T-cell numbers in partial DGS are often lower in infancy and increase in the first year or two. Subsequently, although they often remain less than the normal range, they appear not to decrease.²⁹ Furthermore, 2 retrospective studies of children with partial DGS who received live viral vaccines (measles, mumps, and rubella; varicella; or both) did not reveal any increased incidence of adverse events associated with these immunizations.^{30,31} Only one study offered criteria for safe administration of live vaccines (CD4 cell count of >500 cells/mm³ and adequate response to polyclonal mitogens, not further specified).³¹ However, in both studies, some patients with lower CD4 T-cell counts received these vaccines without serious adverse events.

Some patients with complete DGS might have oligoclonal populations of T cells that do not function normally. These T cells might generate an autoimmune inflammatory response very similar to Omenn's syndrome (SCID with erythrodermia, hepatosplenomegaly and lymphadenopathy with histiocytic tissue infiltration, eosinophilia and IgE production with oligoclonal expansion of T cells expressing activation markers), which is characteristically associated with recombinase-activating gene (*RAG1/RAG2*) mutations.^{32,33} Complete DGS is a SCID phenotype and is fatal without immunoreconstitution. Although broader experience and longer follow-up are still required for complete knowledge regarding outcomes, thymus transplantation is emerging as a reproducible means for restoring T-cell function in patients with complete DGS, with or without the Omenn's syndrome phenotype.^{28,32}

As mentioned above, the Omenn's syndrome phenotype was described initially in patients with *RAG1/RAG2* mutations.³³ In addition to its possible association with complete DGS, the Omenn's syndrome phenotype has also been associated with defects of *ARTEMIS* (gene designation *DCLRE1C*).³⁴

Defects of NEMO (*IKBK* mutation, X-linked) were initially described in male patients with hypohidrotic ectodermal dysplasia and combined immunodeficiency.^{35,36} One patient with this phenotype has been found to have an activating mutation in the *IKBA* gene (encoding the I κ B α chain), leading to reduced NF- κ B activity.³⁷ Recently, 2 patients have been reported to have immunodeficiency caused by NEMO mutation but without ectodermal dysplasia.^{38,39}

IL-1 receptor–associated kinase 4 is a kinase critical for signaling by the majority of Toll-like receptors. Defects of the *IRAK4* gene have been found in a few patients with extreme susceptibility to serious infections mainly caused by encapsulated gram-positive bacteria.⁴⁰ The results of standard screening tests of immune function are generally normal in these patients.

The warts, hypogammaglobulinemia, infections, myelokathexis syndrome is the first described clinical immunodeficiency caused by mutation of a gene encoding a chemokine receptor (*CXCR4*).^{41,42} These patients have diffuse warts, hypogammaglobulinemia, and neutropenia caused by retention of neutrophils in the bone marrow (myelokathexis).

Caspases are a family (>10 members) of cytoplasmic cysteine proteases that have roles in cellular apoptosis (programmed cell death) in a variety of tissues or cell types.⁴³ Caspase 8 deficiency (*CASP8* mutation) leads to growth retardation, lymphadenopathy and hepatosplenomegaly, bacterial respiratory tract infections, and herpesvirus infections.⁴⁴ Laboratory immunologic abnormalities can include poor pneumococcal polysaccharide vaccine responses and selective CD4 lymphocytopenia.

PHAGOCYTE DEFECTS

It is now clear that both cyclic neutropenia and a subset of Kostmann's syndrome, or congenital agranulocytosis, can result from deficiency of elastase 2.⁴⁵ Mutations in the granulocyte colony-stimulating factor receptor (*CSF3R* gene) that had previously been identified in patients with Kostmann's syndrome were found to have been acquired, possibly because of an underlying genetic instability in this disorder. Note that X-linked neutropenia has been associated with particular mutations of the *WASP* gene responsible for Wiskott-Aldrich syndrome.⁴⁶ This should be sought in male patients with chronic neutropenia who do not have elastase 2 deficiency.

A novel form of hyper-IgE syndrome with autosomal recessive inheritance has been described; the gene defect is unknown.^{47,48} In common with the autosomal dominant form, these patients have increased serum IgE levels, a chronic eczematous dermatitis with frequent staphylococcal superinfection, and lung infections with *Aspergillus* species. Patients with the autosomal recessive form have more severe viral illnesses (eg, molluscum contagiosum), do not have skeletal or dental abnormalities, and do not tend to form pneumatoceles with lung infections. Several have a novel feature: vasculitis with central nervous system involvement. Additional variants of hyper-IgE syndrome might exist.⁴⁸

THERAPY OF IMMUNODEFICIENCY

Two forms of SCID have been treated successfully with gene therapy: X-linked SCID (*IL2RG* mutation) and adenosine deaminase deficiency.^{49,50} Approximately 20 patients in France, the United Kingdom, and the United States have been treated this way. Unfortunately, leukemia has developed in 3 patients thus far, apparently because of integration of the vector in a sensitive site for regulation of cell division (the *LMO2* gene).⁵¹ For this reason, gene therapy trials are currently under review.

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3. Cytokines and chemokines

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Cytokines and chemokines are secreted proteins with growth, differentiation, and activation functions that regulate the nature of immune responses. Cytokines are involved in nearly every facet of immunity and inflammation, from induction of the innate immune response to the generation of cytotoxic T cells and the development of antibodies by the humoral immune system. The combination of cytokines that are produced in response to an immune insult determines which arm of the immune system will be activated. For this update, recent advances in our understanding of cytokines will be discussed, which includes the IL-10, IL-17, and IL-27 families. (J Allergy Clin Immunol 2006;117:S441-5.)

Key words: *Interleukin, cytokine, chemokine, T cell*

EVOLUTION OF CYTOKINE BIOLOGY AND NOMENCLATURE

Identification and classification of cytokines has undergone 3 phases of development. Initially, cytokines were identified purely by their biologic activities and termed *factors*, reflecting that activity (eg, T-cell growth factor). The development of cloning strategies and the ability to generate purified recombinant proteins (eg, IL-2) led to the recognition of how confused the factor phase was, with the recognition of the tremendously pleiotropic and redundant activities of cytokines. Subsequently, cytokines were identified on the basis of their unique expression patterns, such as in activated T helper lymphocytes. This *recombinant cloning* phase led to much of our current understanding of cytokines. However, cytokine biology has now evolved into a third phase driven primarily by genomics and, in particular, the human genome project. With the identification of the complete repertoire of human genes, a major effort is now being applied to assigning a

Abbreviations used

APC: Antigen-presenting cell
NK: Natural killer
Treg cell: Regulatory T cell

function for the huge library of previously unrecognized proteins. One of the more effective approaches to achieve this objective is through sequence comparison with previously known genes and predicting that homologous proteins should have related functions. In the current genomic phase of cytokine development, numerous candidate cytokines have been identified on the basis of their homologies to previously described cytokines. In the exact reverse of the factor phase of cytokine development, the predicted protein is expressed, and its biologic activities are assessed in a series of biologic assays. These assays include, most importantly, assessment of the phenotype of mice genetically engineered to either knock out the gene or overexpress it either locally or systemically. At present, at least 70 candidate cytokines have been proposed. After identification and consensus is achieved regarding each candidate's biologic activity, a cytokine nomenclature is assigned. For this review, recent advances in our understanding of cytokines since the *2003 Primer on Allergic and Immunologic Diseases*¹ will be discussed and in particular the IL-17/IL-25 and IL-10 families of cytokines.

NEW MEMBERS OF THE CYTOKINE FAMILY IL-28 and IL-29

A new family of cytokines was identified after a genome search for cytokines with core sequences composed of α -helical bundles. This family is clustered on chromosome 19q13.13 and contains IL-28A, IL-28B, and IL-29.² IL-28A and IL-28B share 96% amino acid identity, whereas IL-28A and IL-29 share 81% amino acid identity. At the amino acid level, IL-28 and IL-29 appear closely related to the α/β IFNs, but the genomic organization is more similar to members of the IL-10 family. This family of cytokines signals through a heterodimeric receptor consisting of an interferon receptor subunit, IL-28R α ,

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