Primary Immunodeficiency Diseases Due to Defects in Lymphocytes

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The recognition of impaired immunity in children five decades ago1,2 spurred an exponential increase in knowledge of the functions of the immune system. More than 95 inherited immunodeficiency disorders have now been identified.3–4 Genetically determined immunodeficiency can cause not only undue susceptibility to infection but also autoimmune and an increased risk of cancer. The defects may affect one or more components of the immune system, including T cells, B cells, natural killer cells, phagocytic cells, and complement proteins. This review will focus on molecular causes of primary immunodeficiency that affect lymphocytes.

PHENOTYPES

Mutations that impair the function of B or T cells result in deficiencies of antibody production, cellular immunity, or both. It is important to recognize that different molecular defects can cause the same phenotype. Although the true incidence of these deficiencies is unknown, they are estimated to occur in 1 of every 10,000 live births.4

Defects in B-cell function increase the risk of recurrent pyogenic infections. The clinical picture of X-linked agammaglobulinemia or common variable immunodeficiency exemplifies the phenotype of antibody deficiency. Children with deficient immunoglobulin production are protected against infection during the first months of life by maternally transmitted IgG antibodies. Thereafter, they acquire infections with encapsulated organisms, such as Streptococcus pneumoniae, Haemophilus influenzae, and Staphylococcus aureus, and with gram-negative organisms such as pseudomonas species. Chronic fungal infections are uncommon, and Pneumocystis carinii pneumonia is rare. Viruses are usually handled normally, except for the enteroviruses, which can cause persistent meningoencephalitis, sometimes associated with a dermatomyositis-like condition.5 Paralysis can result from chronic infection after vaccination with live attenuated polioviruses. Infections with echoviruses, coxsackieviruses, adenoviruses,6 and Ureaplasma urealyticum7 have been identified in the joint fluid of these patients, even those who are receiving immune globulin-replacement therapy.

The concentrations of all isotypes of immunoglobulins are very low in children with these immunodeficiency syndromes. In X-linked agammaglobulinemia, circulating B cells are usually absent or present in very low numbers, whereas in common variable immunodeficiency B cells are usually present. The tonsils are very small and lymph nodes are rarely palpable in patients with X-linked agammaglobulinemia, and these clinical findings should facilitate early recognition of the disorder. By contrast, these tissues are normal sized or enlarged in patients with common variable immunodeficiency. Neither disorder affects the thymus architecture or the thymus-dependent areas of spleen and lymph nodes. Monthly intravenous infusions of immune globulin are lifesaving in both disorders.

By contrast with the infectious complications in antibody-deficiency diseases, defects in T-cell function lead to susceptibility to opportunistic infections. Severe combined immunodeficiency, a syndrome with a diversity of genetic causes (Fig. 1 and 2, showing my own data) and profound deficiencies of T cells and B cells, exemplifies the phenotype of deficient T-cell function. Affected infants present in the first few months of life with diarrhea and failure to thrive. Persistent infections with Candida albicans, P. carinii, varicella, adenovirus, respiratory syncytial virus, parainfluenza virus type 3, cytomegalovirus, Epstein–Barr virus (EBV), and bacille Calmette–Guérin are fatal. These infants cannot reject allografts, leaving them at risk for fatal graft-versus-host disease when they receive blood transfusions or bone marrow transplants that contain T cells.8

Infants with severe combined immunodeficiency have lymphopenia; recognition of this abnormality alone can lead to an early diagnosis within hours after birth (Fig. 1).9 The lymphocytes of these babies fail to proliferate in vitro when challenged with mitogens, antigens, or allogeneic cells. Levels of serum immunoglobulins are low or undetectable. Thymus-dependent areas of the spleen are devoid of lymphocytes, and lymph nodes and tonsils are absent. The

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The thymus is very small (usually weighing less than 1 g) and lacks thymocytes; boundaries between the cortex and medulla and Hassall’s corpuscles are obscured. However, the success of hematopoietic stem-cell transplantation, which restores the population of circulating T cells in these infants, shows that the thymus can support normal development of T cells.

Severe combined immunodeficiency is a pediatric emergency. Nearly all cases can be diagnosed at birth by white-cell counts and manual differential white-cell counts and by flow cytometry and studies of T-cell function when absolute lymphocyte counts are below the normal range for newborns (2000 to 11,000 per cubic millimeter). Unless bone marrow transplantation or gene therapy succeeds, death during infancy is inevitable. Transplantation of hematopoietic stem cells during the first three months of life offers patients up to a 95 percent chance of survival. There are more than 375 patients worldwide who have survived severe combined immunodeficiency as a result of successful transplantation of HLA-identical or haploidentical bone marrow.

**GENETIC ASPECTS**

Until recently, little was known about fundamental causes of primary immunodeficiency diseases. As a result of remarkable advances in human molecular genetics during the past seven years, however, the genetic abnormalities in a number of defects have been identified (Table 1). Genes essential for immune function are distributed throughout the genome. However, there is a clear dominance of X-linked immunodeficiency as a result of hemizygosity in males for the considerable number of immune system genes in the X chromosome. Moreover, spontaneous new mutations in these X-linked genes are relatively frequent. In female carriers of X-linked immunodeficiency, there is skewed inactivation of the X chromosome in the cell lineages affected; almost all mature cells of the affected lineages in female carriers contain the normal
X chromosome, whereas in other cells X-inactivation is random. This phenomenon indicates that the cells with the abnormal X chromosome failed to mature. This feature can be used clinically to assess whether a female relative of an affected male patient is a carrier.

In an evaluation of patients with suspected immunodeficiency, questions about consanguinity are key, since children whose parents were from genetically restricted populations are at increased risk for homozygosity for autosomal recessive immunodeficiency disorders. Other chromosomal regions that contain interesting immune-function genes include 6p, where histocompatibility genes are located, and 5q, which includes many cytokine genes.

Previous classifications of these diseases have been based on characteristic clinical features and specific alterations in immune status. Advances in molecular genetics now allow them to be grouped according to the types of genetically altered molecules involved, beginning with those on the cell surface and progressing inward (Table 1 and Fig. 3). It is important for physicians to determine the molecular causes of disease in their patients so that they can provide appropriate genetic counseling, prenatal assessment, and when perfected, gene therapy to correct the defect.

**GENETIC DEFECTS CAUSING IMMUNOGLOBULIN DEFICIENCIES**

**Deficiencies of B-Cell Receptors**

Deficiencies of B-cell receptors are caused by mutations in the genes that encode immunoglobulin heavy or light chains or their associated signaling molecules, leading to agammaglobulinemia or hypogammaglobulinemia. Mutations affecting the \( \mu \) chain; the surrogate light chain (A5/14.1); \( \text{Ig} \alpha \) (CD79a), a B-cell–receptor signaling molecule; and the B-cell linker adapter protein are associated with the absence of circulating B cells (Fig. 4B). Other mutations in immunoglobulin heavy-chain genes (such as \( g_1, 2, 3, \text{or } 4; \alpha_1 \text{ or } 2; \) and \( \epsilon \)) cause deficiencies of individual classes or subclasses of immunoglobulins, but circulating B cells are present and overall antibody function is usually normal. Mutations in the \( k \) light-chain gene result in a population of immunoglobulin molecules with only \( l \) light chains instead of the usual mixture of \( k \) and \( l \) types (Table 1).

**Deficiency of One Member of a Ligand Pair**

In the X-linked hyper-IgM syndrome, the serum levels of IgG, IgA, and IgE are very low, but the serum level of IgM is either normal or markedly elevated. Patients with this syndrome are susceptible to recurrent pyogenic infections and \( P. \text{carinii} \) pneumonia. They also have an increased frequency of autoimmune disorders and cancer. Paradoxically, the X-linked hyper-IgM syndrome is a T-cell defect rather than a B-cell defect. Until the T-cell defect was discovered, coexistent neutropenia had been considered the explanation for the susceptibility to \( P. \text{carinii} \) infection.

The abnormal gene in the X-linked hyper-IgM syndrome was traced to Xq26.3–27.1 and identified in 1993. The gene product is a T-cell surface molecule known as CD154 (or the CD40 ligand); it is present primarily on activated CD4+ cells, and it in-
interacts with its receptor, CD40, on B cells (Fig. 3 and Table 1).

CD154 is a type II integral membrane glycoprotein that is structurally related to tumor necrosis factor. Cross-linking of CD40 on either normal B cells or B cells from patients with the X-linked hyper-IgM syndrome with a monoclonal antibody to CD40 or soluble CD154 in the presence of cytokines (interleukin-2, 4, and 10) causes the B cells to proliferate and secrete immunoglobulins of various types. Mutations in the CD154 gene prevent T cells from signaling B cells through the CD40 pathway. In the absence of T-cell help, the B cells cannot produce IgG, IgA, or IgE; they can, however, produce IgM. Lymph nodes show only abortive germinal centers, because of the failure of T cells to signal B cells to undergo isotype switching and to expand in number.

The lack of cross-linking of CD40 by CD154 also results in failure of the B cells to up-regulate CD80 and CD86, important costimulatory molecules that interact with immunoregulatory molecules on T cells called CD28 and CTLA-4. The breakdown of these

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*SCID denotes severe combined immunodeficiency; Jak3 Janus kinase 3; RAG1 and RAG2 recombinase-activating gene 1 and 2, respectively; MHC major histocompatibility complex; TAP1 and TAP2 transporter associated with antigen processing 1 and 2, respectively; ZAP-70 zeta-associated protein 70; and EBV Epstein–Barr virus.

†Such deficiencies also cause Omenn’s syndrome.
Figure 3. Locations of Mutant Proteins in CD4+ T Cells (Panel A) and B Cells (Panel B) Identified in Primary Immunodeficiency Diseases.

Each mutant protein is identified by a red X. ZAP-70 denotes zeta-associated protein 70; SLAM signaling lymphocyte activation molecule; ATM ataxia telangiectasia mutation; NFAT nuclear factor of activated T cells; Jak3 Janus kinase 3; WASP Wiskott–Aldrich syndrome protein; TAP1 and TAP2 transporter associated with antigen processing 1 and 2, respectively; Btk Bruton tyrosine kinase; BLNK B-cell linker adapter protein; b2-M beta2-microglobulin; and RFX, RFXAP, and CIITA transcription factors.
pathways in the thymus in the hyper-IgM syndrome results in defective purging of autoreactive thymocytes and, hence, the susceptibility to autoimmune diseases. Similarly, the lack of extrathymic interaction of these regulatory molecules results in defective recognition of tumor cells.

Many distinct point mutations or deletions in the CD154 gene have been identified. Analysis of a highly polymorphic microsatellite dinucleotide (CA) repeat region in the 3' untranslated end of the gene is useful for identifying carriers and making a prenatal diagnosis.

An indication that the hyper-IgM syndrome has more than one genetic cause is the autosomal recessive form of the disorder that can affect females. In such patients, there is an intrinsic B-cell defect that prevents the B cells from switching from the production of IgM to IgG, IgA, or IgE, even when they are cultured with monoclonal antibodies to CD40 and cytokines. CD40 is present on such B cells, implying the existence of defects associated with CD40-mediated signaling. One such defect has recently been discovered: mutations in the gene at 12p13 encoding an activation-induced cytidine deaminase, a messenger-RNA–editing enzyme.

**Deficiencies of Signaling Molecules**

In 1993, two groups independently discovered the mutated gene in X-linked agammaglobulinemia, which is now called the Bruton tyrosine kinase (BTK) gene (Fig. 3 and Table 1). Bruton tyrosine kinase is a member of the Tec family of cytoplasmic protein tyrosine kinases. This kinase is necessary for the growth of B-cell precursors and their development into mature B cells, which is why there are no circulating B cells in patients with X-linked agammaglobulinemia. The mutant BTK gene has not been detected in T cells but has been found in myeloid cells, a finding that could be relevant to the intermittent neutropenia in boys with X-linked agammaglobulinemia. More
than 300 different mutations in the \( BTK \) gene have been identified, but there has not been any clear correlation between the type of mutation and the phenotype.\(^9\) In families in which the mutation has been identified, the disease has been diagnosed prenatally in male fetuses on the basis of the detection of the mutant gene in chorionic-villus or amniocentesis samples.

**GENETIC DEFECTS CAUSING CELLULAR OR COMBINED IMMUNODEFICIENCIES**

**Defects of Genes of the CD3 Complex**

Cellular and combined immunodeficiencies caused by mutations in the genes encoding the \( \gamma \) or \( \epsilon \) chains lead to impaired expression of the T-cell receptor (CD3) is a complex of five polypeptide chains that are associated with and essential to the T-cell receptor) (Fig. 3A). Patients with such mutations have variable levels of autoimmunity and susceptibility to infection. They have few circulating CD3+ T cells or none at all, poor responses to T-cell mitogens, and various immunoglobulin deficiencies.

**Deficiencies of Cytokine Receptor Chains**

**X-Linked Severe Combined Immunodeficiency**

Deficiency of the common \( \gamma \) chain (\( \gamma c \)) of the interleukin-2 receptor is one of several defects leading to severe combined immunodeficiency (referred to as SCID-X1) (Table 1 and Fig. 2)\(^9,10\) and is the most common form, accounting for approximately 46 percent of cases in the United States.\(^10\) The abnormal gene was mapped to the Xq13 region and later identified as the gene encoding the \( \gamma c \) chain that is common to the cell-surface receptors for five interleukin molecules (interleukin-2, 4, 7, 9, and 15) (Table 1 and Fig. 4).\(^42,44\) Among the first 136 patients with X-linked severe combined immunodeficiency who were studied, 95 distinct mutations were identified. They resulted in abnormal \( \gamma c \) chains in two thirds of the patients and in the absence of \( \gamma c \) protein in the remainder.\(^45\)

The finding that the mutated gene does not permit normal signaling by several cytokine receptors explains how T cells, B cells, and natural killer cells can all be affected by a single mutation.\(^46,47\) The single exception to the rule that severe combined immunodeficiency is invariably fatal in the absence of marrow transplantation occurred in one infant, who had a spontaneous clinical improvement and was found to have reversion of a documented mutation in the gene encoding \( \gamma c \), presumably in T-cell precursors.\(^48\) Recently, retroviral gene transfer was used to transduce complementary DNA from a normal \( \gamma c \) chain into autologous marrow cells of two infants with X-linked severe combined immunodeficiency, with subsequent full correction of the defects in their T cells and natural killer cells.\(^49\)

**Lymphoproliferative T-Cell Deficiency**

In one infant, a mutation in the gene encoding the \( \alpha \) chain of the interleukin-2 receptor paradoxically produced too many, rather than too few, T cells, with extensive infiltration of the lungs, liver, gut, spleen, lymph nodes, and bone (Table 1).\(^50\) Serum levels of IgG and IgM were elevated, but the serum level of IgA was low. The infant had lymphopenia, and in vitro his T cells responded poorly to antibodies against CD3, phytohemagglutinin, and interleukin-2. This defect is probably one of many in which lymphoproliferation and autoimmunity are caused by an imbalance of positive and negative signals as a result of mutations in genes that encode regulatory components of the immune system.

**T-Cell–Negative, B-Cell–Positive, Natural-Killer-Cell–Positive Autosomal Recessive Severe Combined Immunodeficiency**

Three of my patients who had previously been shown not to have a deficiency of either \( \gamma c \) chains or Janus kinase 3 (Jak3) had T-cell–negative, B-cell–positive, natural-killer-cell–positive severe combined immunodeficiency. Mutations in the gene for the \( \alpha \) chain of the receptor for interleukin-7 on chromosome 5p13 were found in all three patients (Table 1).\(^51\) These findings imply that the T-cell defect but not the defect in natural killer cells in patients with X-linked severe combined immunodeficiency and Jak3-deficient severe combined immunodeficiency (see below) results from selective inactivation of interleukin-7 signaling.

**Deficiencies of Signaling Molecules**

**T-Cell–Positive, B-Cell–Positive, Natural-Killer-Cell–Positive Autosomal Recessive Severe Combined Immunodeficiency**

A two-month-old boy who presented with bacterial, viral, and fungal infections was found to have lymphopenia and hypogammaglobulinemia. B cells and natural killer cells were present, but the number of CD4+ T cells was low.\(^52\) In vitro responses to T-cell mitogens were variable. The patient’s T cells did not express the activation marker CD69 when they were stimulated through the T-cell receptor, but they did express CD69 when stimulated with phorbol 12-myristate 13-acetate diester and a calcium ionophore, suggesting the presence of a proximal signaling defect. Molecular studies revealed an alternatively spliced transcript for p56\(^{1k}\) that lacked the kinase domain (Fig. 3A and Table 1).\(^52\) The tyrosine kinase signaling molecule p56\(^{1k}\) is important in the differentiation, activation, and proliferation of T cells.

**CD8 Lymphopenia**

CD8 lymphopenia is due to mutations in a gene at chromosome 2q12 that encodes zeta-associated protein 70 (ZAP-70), a tyrosine kinase important in T-cell signaling (Fig. 3A and Table 1).\(^53,54\) ZAP-70 has an essential role in the positive and negative se-
lection of maturing T cells in the thymus. Patients with this condition may present with moderate infections or infections as severe as those in patients with severe combined immunodeficiency. Eight patients have been described, the majority of whom were Mennonites. These patients had normal or elevated numbers of circulating CD4+ T cells, but essentially no CD8+ T cells. The defect is presumably due to defects in the signaling pathways that are essential for the development of CD8+ cells within the thymus. The thymus of one patient had normal architecture, with normal numbers of CD4+CD8+ double-positive thymocytes, but no CD8+ (single-positive) thymocytes. In affected patients, circulating CD4+ T cells fail to respond normally to mitogens or to allogeneic cells in vitro or to become cytotoxic cells. By contrast, the activity of natural killer cells, the number of B cells, and serum immunoglobulin levels are normal.

**T-Cell–Negative, B-Cell–Positive, Natural-Killer-Cell–Negative Autosomal Recessive Severe Combined Immunodeficiency**

Infants with Jak3 deficiency resemble patients with other types of severe combined immunodeficiency with respect to their susceptibility to infection and to graft-versus-host disease caused by allogeneic T cells in transfused blood or bone marrow transplants. They resemble infants with X-linked severe combined immunodeficiency, because they have elevated levels of B cells and very low levels of T cells and natural killer cells in the blood (Fig. 1). Jak3 is the only signaling molecule known to be associated with the \( g \) chain and serves as a transducer of \( g \)-chain–dependent intracellular signals (Table 1 and Fig. 4). Thus far, 18 patients who lack Jak3 have been identified. Like patients with X-linked severe combined immunodeficiency, they continue to have very low levels of natural killer cells even after successful marrow transplantation.

**T-Cell–Negative, B-Cell–Negative, Natural-Killer-Cell–Positive Autosomal Recessive Severe Combined Immunodeficiency and Omenn’s Syndrome**

Infants with T-cell–negative, B-cell–negative, and natural-killer-cell–positive severe combined immunodeficiency as a result of mutations in recombinase-activating gene 1 or 2 (\( RAG1 \) or \( RAG2 \)) resemble patients with other types of severe combined immunodeficiency with respect to their susceptibility to infection and the absence of functional T cells and B cells. However, they differ in that the lymphocytes in their circulation are primarily natural killer cells. RAG1 and RAG2 are required for the rearrangement of T-cell–receptor and B-cell–receptor genes (Table 1).

Patients with Omenn’s syndrome also have mutations in the \( RAG1 \) or \( RAG2 \) gene, which result in impaired (but not absent) rearrangement of both the B-cell receptor and T-cell receptor genes. Omenn’s syndrome is characterized by the development of a generalized erythrodema and desquamation, diarrhea, hepatosplenomegaly, hyperesinophilia, and markedly elevated serum IgE levels soon after birth. The eosinophilia and elevated serum IgE levels are caused by circulating activated oligoclonal helper type 2 T cells that do not respond normally to mitogens or antigens in vitro. Circulating B cells are absent, and lymph nodes lack germinal centers. The condition is fatal unless it is corrected by bone marrow transplantation.

**Mutation of Common Leukocyte Surface Protein (CD45)**

The most recently discovered molecular defect causing severe combined immunodeficiency is a mutation in the gene encoding the common leukocyte surface protein CD45. This hematopoietic-cell–specific transmembrane tyrosine phosphatase regulates src tyrosine kinases required for signal transduction of T-cell and B-cell receptors.

A two-month-old boy who presented with symptoms of severe combined immunodeficiency was found to have a very low number of T cells but a normal number of B cells. The T cells did not respond to mitogens, and serum immunoglobulin levels diminished with time. A point mutation in one CD45 allele that caused an alteration of the intervening sequence 13 donor splice site and a deletion of a large part of the other allele were identified.

**Metabolic Defect**

An absence of the purine-salvage-pathway enzyme adenosine deaminase has been observed in approximately 15 percent of patients with severe combined immunodeficiency (T-cell–negative, B-cell–negative, natural-killer-cell–negative autosomal recessive severe combined immunodeficiency) (Fig. 2). Patients with adenosine deaminase deficiency have the same clinical characteristics as those with other forms of severe combined immunodeficiency but in addition have chondro-osseous dysplasia, which is evidenced by the presence of multiple skeletal abnormalities on radiographic examination, including flaring of the costochondral junctions and a “bone-in-bone” anomaly in the vertebral bodies.

Infants with adenosine deaminase deficiency have a more profound lymphopenia than do infants with other types of severe combined immunodeficiency, with mean absolute lymphocyte counts of less than 500 per cubic millimeter (Fig. 1). The adenosine deaminase deficiency primarily affects T cells, which are absent just as they are in all forms of severe combined immunodeficiency. Because milder forms of this condition have been reported, the disease may not be diagnosed until adulthood.

The adenosine deaminase deficiency caused by mutations in the gene on chromosome 20q13.2–q13.11 (Table 1) results in marked accumulations of adeno-
sine, 2’-deoxyadenosine, and 2’-O-methyladenosine. The accumulation of these toxic deoxyadenosine nucleotides directly or indirectly leads to apoptosis of lymphocytes. Enzyme-replacement therapy with once-weekly subcutaneous injections of polyethylene glycol–modified bovine adenosine deaminase resulted in clinical and immunologic improvement in more than 100 patients. However, the resulting immunocompetence is less complete than that achieved by bone marrow transplantation; therefore, bone marrow transplantation remains the treatment of choice. Gene therapy has thus far been unsuccessful in this condition.

DEFICIENCIES OF MAJOR-HISTOCOMPATIBILITY-COMPLEX CLASS I AND II MOLECULES

Deficiencies of Transcription Factors

More than 70 patients with autosomal recessive deficiencies of major-histocompatibility-complex (MHC) class II molecules have been identified, many of whom are of North African descent. They present in infancy with persistent diarrhea, often associated with cryptosporidiosis, bacterial pneumonia, P. carinii pneumonia, sepsis, and viral or monilial infections. Nevertheless, the immunodeficiency is not as severe as in severe combined immunodeficiency, since neither systemic mycobacterial disease nor graft-versus-host disease develops after vaccination with bacille Calmette–Guérin or transfusions of nonirradiated blood products, respectively.

Patients with deficiencies of MHC class II molecules have a very low number of CD8+ T cells but normal or elevated numbers of CD4+ T cells. Lymphopenia is only moderate. The MHC class II antigens HLA-DR, DQ, and DP are undetectable on B cells and monocytes, and immune responses are impaired because of the absence of these antigen-presenting molecules. As would be expected, B cells from these patients fail to stimulate allogeneic cells in mixed-leukocyte cultures; in vitro, their lymphocytes respond normally to mitogens but not to antigens. The thymus and other lymphoid organs are severely hypoplastic. Since recognition of HLA molecules by thymocytes is central to positive and negative selection, the development of the peripheral T-cell repertoire in the absence of MHC class II molecules leads to the presence of T cells with altered T-cell–receptor amino acid profiles within the potential antigen-combining site. The defects of both B-cell–mediated and T-cell–mediated immunity in this disease emphasize the importance of HLA determinants in immune-cell cooperation.

Four different molecular defects can impair the expression of MHC class II molecules. These defects do not affect the MHC class II genes themselves, but genes that regulate the transcription of MHC class II genes. Three of the mutations affect subunits of RFX, a multiprotein transcription factor complex that binds the X-box motif of the MHC class II promoter and is responsible for regulating the expression of MHC class II molecules (Table 1). These subunits are termed RFX5, RFX-associated protein, and RFXANK. Mutations of RFXANK are the most common cause of MHC class II defects. A fourth type of mutation involves a novel MHC class II transactivator (CIITA), a master switch that controls the cellular specificity and inducibility of the expression of class II MHC genes. All four of these defects impair the coordinate expression of MHC class II molecules on the surface of B cells and macrophages.

Deficiencies of Transporter Proteins

An isolated deficiency of MHC class I molecules is rare, and the resulting immunodeficiency is milder than that in severe combined immunodeficiency. In this disorder, MHC class I molecules, normally found on all cells in the body, are absent. There is a deficiency of CD8+ T cells but not of CD4+ T cells. Mutations have been found in two genes — TAP1 and TAP2 — within the MHC locus on chromosome 6 that encode the peptide-transporter proteins associated with antigen processing, or TAPs (Fig. 3B and Table 1). TAPs transport peptide antigens from the cytoplasm across the Golgi apparatus to join the α chain of MHC class I molecules and β2-microglobulin. The complex can then move to the surface of the cell; if the assembly of the complex cannot be completed because there is no peptide antigen, the MHC class I complex is destroyed in the cytoplasm.

IMMUNODEFICIENCY DISEASES WITH UNIQUE PHENOTYPES

X-Linked Lymphoproliferative Disease

In X-linked lymphoproliferative disease there is a failure to control the proliferation of cytotoxic T cells that is evoked by infection with EBV. Patients with this disorder (which is also called Duncan disease, after the Duncan family in which the condition was first described) appear healthy until they become infected with EBV, usually when they are less than five years of age. The most common form of presentation (occurring in 75 percent of cases) is severe infectious mononucleosis, and the infection is fatal in 80 percent of patients, primarily because of extensive liver necrosis caused by activated cytotoxic T cells. Most boys who survive EBV infection have global cellular immune defects, and lymphomas, aplastic anemia, and hypogammaglobulinemia ultimately develop.

The defective gene in X-linked lymphoproliferative disease is at Xq25 and encodes an adapter protein present in T cells and natural killer cells that interferes with the binding of downstream signaling molecules to a protein on the surfaces of T and B cells that is called “signaling lymphocyte activation molecule,” or SLAM. SLAM is unusual in that it is a mem-

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brane protein that is both a growth-promoting mol-
ecule and a receptor for itself.32-34 The adapter protein,
which is officially called SH2D1A but also referred to
as SAP (for SLAM-associated adapter protein) and
DSHP (for Duncan syndrome human protein), inhib-
its signal transduction by SLAM so that the prolifer-
tion of T cells and natural killer cells does not con-
tinue unchecked (Fig. 3 and Table 1).30 Fewer than 10
patients with X-linked lymphoproliferative disease have
received HLA-identical bone marrow transplants, and
approximately half have had no subsequent signs of the
disease.

Wiskott–Aldrich Syndrome

The Wiskott–Aldrich syndrome is an X-linked syn-
drome characterized by eczema, undue susceptibili-
ty to infection, and thrombocytopenic purpura with
small, defective platelets.1 Patients usually present dur-
ing infancy with bloody diarrhea or excessive bruising.

Atopic dermatitis and recurrent infections with pneumococci and other encapsulated bacteria usually
occur during the first year of life. Later, infections with
opportunist agents such as P. carinii and the her-
pesviruses become more problematic. Autoimmune
cytophenias and vasculitis are common in patients who
live beyond infancy. Infections and bleeding are fre-
cent causes of death, but the most common cause of
death is EBV-induced lymphoma.

Immunoglobulin concentrations vary in these pa-
ients but usually are near normal.35 Nevertheless, the
antibody response to polysaccharide antigens is im-
paired, and blood-group isohemagglutinins are ab-
sent.3 In addition, there is a gradual decrease in anti-
body titers to protein antigens, such as diphtheria and
tetanus toxoids, over time. The patients have moder-
ately reduced percentages of CD3+, CD4+, and
CD8+ T cells, and lymphocyte responses to mitogens
are depressed in vitro.

The mutant gene responsible for these defects was
mapped to Xp11.22 and identified in 1994 (Fig. 3A
and Table 1).36 It was found to be preferentially ex-
pressed in lymphocyte and megakaryocyte lineages.36
The gene product, a proline-rich protein of 501 ami-
no acids,37 controls the assembly of actin filaments re-
quired for the formation of microvesicles. A large
number of mutations in the gene have been identified
among patients with the Wiskott–Aldrich syndrome.88
Isolated X-linked thrombocytopenia is also caused by
mutations in this gene.89

Carriers can be identified by the finding of nonran-
dom inactivation of the X chromosome in hematopo-
etic cell lineages or by the presence of the mutant
gene.90 The disease can be diagnosed prenatally by
chorionic-villus sampling or amniocentesis. Two fam-
ilies with apparent autosomal inheritance of a pheno-
type similar to that of the Wiskott–Aldrich syndrome
have been described.91,92 However, in another report,
a girl with the Wiskott–Aldrich syndrome was found
to have an extremely unusual example of severely
skewed inactivation of the X chromosome so that the
active X chromosome had a mutation at the X-linked
locus of the Wiskott–Aldrich syndrome gene.93

In a number of patients with the Wiskott–Aldrich
syndrome, the platelet and the immunologic abnor-
malities have both been completely corrected by trans-
plantation of bone marrow or cord blood from an
HLA-identical sibling or an HLA-matched unrelat-
ed donor after a conditioning regimen that included
irradiation or busulfan and cyclophosphamide.11,94 Sev-
eral patients who required splenectomy for uncontrol-
bleeding had impressive increases in their platelet
counts and have done well clinically when given pro-
phylactic treatment with antibiotics and intravenous
immune globulin.95

Ataxia Telangiectasia

Ataxia telangiectasia is a complex syndrome of com-
bined immunodeficiency associated with neurologic,
endocrinologic, hepatic, and cutaneous abnormali-
ties.5,96 The main features are progressive cerebellar
ataxia, oculocutaneous telangiectasias, recurrent bac-
terial sinopulmonary disease, increased susceptibility
to cancer,97 and humoral and cellular immunodefi-
ciency of variable severity. One of my patients with
ataxia telangiectasia died of varicella, and transfusion-
associated graft-versus-host disease has also been re-
ported in these patients.98

Selective IgA deficiency is present in 50 to 80 per-
cent of patients with ataxia telangiectasia, and serum
levels of IgG2 or total IgG may also be decreased.
In vitro tests of lymphocyte function have generally
shown moderately depressed proliferative responses to
mitogens. The thymus is hypoplastic, has poor organ-
ization, and lacks Hassall’s corpuscles.

Cells from patients and carriers of the abnormal
gene are unusually sensitive to ionizing radiation and
have defective DNA repair and frequent chromoso-
amal abnormalities.96,99 Lymphoreticular cancers and
progressive neurologic disease are the most common
causes of death,96,99 but adenocarcinoma and other
forms of cancer have also been causes of death.

The defective gene in ataxia telangiectasia, ATM,
resides on chromosome 11q22.3 (Table 1).96,100 This
gene encodes a phosphatidylinositol 3-kinase–like pro-
tein that also has similarities to the catalytic subunit
of DNA-dependent protein kinase. It is involved in mi-
togenic signal transduction, meiotic recombination,
the response to DNA damage, and control of the cell
cycle.101,102

DISEASES ASSOCIATED WITH
UNIDENTIFIED MOLECULAR DEFECTS

Despite the enormous progress that has occurred
in identifying molecular causes of immunodeficiency,
many challenges remain. Among the diseases for which
the fundamental causes remain unknown are common
variable immunodeficiency, selective IgA deficiency, and the hyper-IgM syndrome. Patients with common variable immunodeficiency and those with IgA deficiency are frequently found in the same family and often have a common HLA haplotype; many have rare alleles or deletions of genes within the MHC class III region on chromosome 6, suggesting that a susceptible gene is located there. The gene responsible for the hyper-IgM syndrome, which is characterized by abscesses of the skin, lungs, and viscera; osteopetrosis; cosinophilia; and unusual facial features has been mapped to chromosome 4. However, neither the fundamental host defect nor the defective gene has yet been identified.

REFERENCES

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