

REVIEW ARTICLE

MEDICAL PROGRESS

THE PRIMARY IMMUNODEFICIENCIES

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THE primary immunodeficiency disorders reflect abnormalities in the development and maturation of cells of the immune system. These defects result in an increased susceptibility to infection; recurrent pyogenic infections occur with defects of humoral immunity, and opportunistic infections with defects of cell-mediated immunity. These two broad categories of illness correspond roughly to defects in the two principal types of immunocompetent cells, B lymphocytes and T lymphocytes. Defective development of B cells results in abnormalities in humoral immunity, whereas defects in the development of T cells cause problems with cellular immunity.

When pathogens are taken up by macrophages or dendritic cells, their antigens are degraded and presented on the cell surface to T cells, which subsequently induce the maturation of B cells through the release of cytokines. T cells also recruit other cells (macrophages, eosinophils, basophils, and mast cells) to induce an inflammatory response. The specific immune responses of T cells and antibodies (along with components of serum complement) result in resistance to infection. These responses are assisted by natural killer cells, which nonspecifically kill tumor cells and virus-infected cells.

We describe recent advances in the understanding of six of the primary immunodeficiencies: X-linked agammaglobulinemia, the hyper-IgM syndrome, common variable immunodeficiency, severe combined immunodeficiency, defects in the expression of the major histocompatibility complex (MHC), and the Wiskott-Aldrich syndrome. The underlying defects in each can be better understood by reference to Figure 1, which shows the development and maturation of T and B lymphocytes from the multipotent hematopoietic stem cell.

X-LINKED AGAMMAGLOBULINEMIA

X-linked agammaglobulinemia was first described 43 years ago and remains the prototypic syndrome of a pure B-cell deficiency. The disorder has a relatively homogeneous clinical presentation — a characteristic that suggested a monogenic defect, inherited as an

X-linked recessive trait. Recently, the genetic defect has been shown to result from mutations in a hitherto unknown cytoplasmic signal-transducing molecule.^{6,7} This discovery has broadened the description of the phenotype and led to the realization that X-linked agammaglobulinemia is more common than was previously thought.

Affected boys are usually well for the first 9 to 12 months of life because they are passively protected by transplacentally acquired IgG from their mothers. Subsequently, they have recurrent pyogenic infections such as otitis media, sinusitis, conjunctivitis, pneumonia, and pyoderma. These infections are mainly due to *Haemophilus influenzae* and *Streptococcus pneumoniae* and less frequently to *Staphylococcus aureus* and *Streptococcus pyogenes*. Although readily controlled by antibiotics, these recurrent infections lead to anatomical destruction, particularly of the lungs; chronic obstructive lung disease and bronchiectasis invariably result when proper prophylactic treatment is not undertaken. Boys with X-linked agammaglobulinemia may have persistent viremia and are at risk of acquiring paralytic poliomyelitis from live-virus vaccines. They are also susceptible to an unusual and potentially fatal form of persistent enterovirus (usually echovirus) infection that is associated with chronic meningoencephalitis and a syndrome resembling dermatomyositis. *Giardia lamblia* infestation leads to chronic diarrhea, weight loss, protein-losing enteropathy, and steatorrhea. About 35 percent of affected boys present with arthritis of the large joints; this symptom is usually controlled by immune globulin therapy. In many cases it is probably due to mycoplasma (*Ureaplasma urealyticum*).

During the past decade prophylaxis with intravenous immune globulin has become the standard therapy for X-linked agammaglobulinemia. With the use of this route it has been possible to administer large doses of immune globulin so that patients can lead relatively normal lives. The optimal dose and frequency of administration must be determined for each patient. Usually, a dose of 350 to 500 mg per kilogram of body weight is given each month, but it may be preferable to divide this dose for administration every other week. Some patients require as much as 600 mg of immune globulin per kilogram to maintain adequate prophylaxis. Immune globulin is a safe biologic product. Nevertheless, the risk of transmitting hepatitis C virus is ever present, and a few unfortunate outbreaks have occurred.⁸ This problem may soon be overcome with detergent treatment of immune globulin preparations. Attempts are also being made to pump immune globulin into subcutaneous tissue.

Typically, the serum of patients with X-linked agammaglobulinemia contains less than 100 mg of IgG per deciliter and no detectable IgM or IgA. The patients are incapable of making antibodies in response to standard antigenic provocations. B cells are virtually absent from the blood. Cell-mediated immunity is rel-

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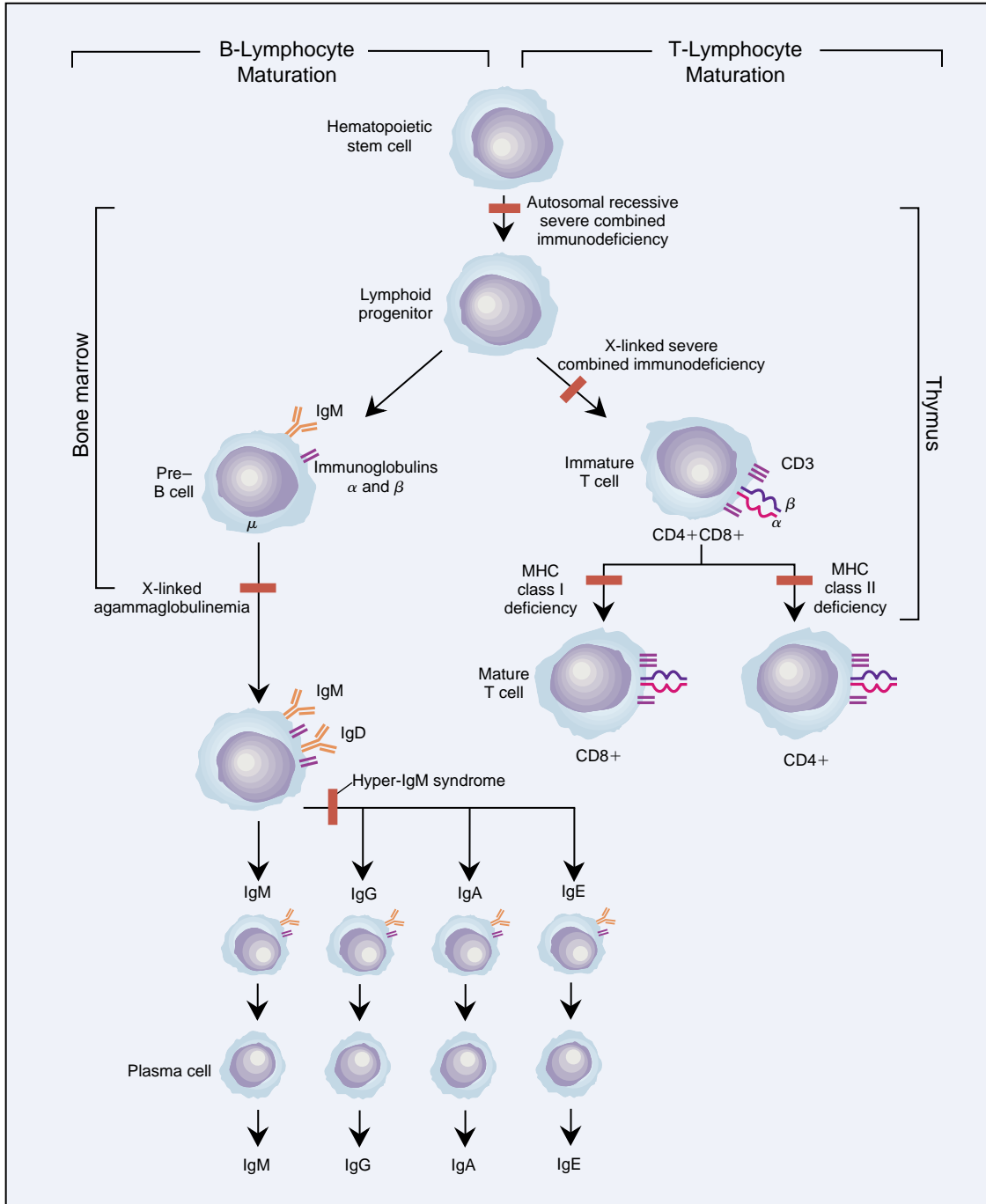


Figure 1. Maturation of T and B Lymphocytes.

Progenitor cells derived from hematopoietic stem cells enter the thymus and undergo several stages of maturation, during which the α and β chains of the T-cell receptor and the five chains of CD3 are expressed.¹ Immature T cells transiently express both CD4 and CD8. The interaction of CD4 with MHC class II molecules or of CD8 with MHC class I molecules on thymic stromal cells is instrumental in determining whether the cells will survive to become mature CD4+ or CD8+ T cells.²

Lymphoid progenitor B cells interact with neighboring stromal cells in bone marrow to give rise to a population of pre-B cells.³ Pre-B cells first express μ heavy chains in their cytoplasm and then an IgM-receptor complex. The transmembrane immunoglobulin α and β signal-transduction unit, which is analogous to T-cell CD3, is also expressed.⁴ The pre-B cells subsequently express κ and λ light chains to become IgM-bearing mature B cells committed to an antibody specificity that they and their mature plasma-cell progeny will produce.⁵ On leaving the bone marrow, IgM-bearing B cells acquire surface IgD. These mature B cells can respond positively to an antigen and to help from CD4 T cells by undergoing proliferation and differentiation; ultimately, they secrete antibody of all the immunoglobulin classes.

The red bars indicate where maturation is blocked in autosomal recessive and X-linked severe combined immunodeficiency, X-linked agammaglobulinemia, MHC class I and II deficiencies, and the hyper-IgM syndrome.

actively normal in affected male patients; they have normal numbers of circulating T cells, which can respond appropriately to specific and nonspecific mitogens. It has recently been recognized, since the identification of the genetic defect, that these laboratory findings define X-linked agammaglobulinemia too narrowly⁹; this diagnosis should be suspected in all young boys with recurrent pyogenic infections, decreased immunoglobulin levels, or low numbers of B cells.

Standard linkage analysis was used to map the gene for X-linked agammaglobulinemia to the long arm of the X chromosome at position Xq21.2–22, and X-linked agammaglobulinemia exhibited no crossovers with a polymorphic DNA marker.¹⁰ A candidate signal-transducing molecule encoded by a tyrosine kinase gene called *bt*k was identified and cloned.^{6,7} Missense and nonsense mutations in *bt*k, as well as splice-site mutations, have been identified.^{6,7,9,11–17} The gene is called *bt*k for Bruton's, or B-cell, tyrosine kinase and is expressed early in B-cell development, but not in T cells or plasma cells.^{18,19} It is expressed in myeloid cells, where its role is obviously less crucial than in B cells, because granulocyte defects are rarely seen in X-linked agammaglobulinemia. Early B cells are generated in the bone marrow of affected male patients.^{20,21} However, these early B cells mature at an extremely low rate. The *bt*k gene must therefore have a vital but as yet undetermined role in the maturation of B-lineage cells.

In X-linked agammaglobulinemia, mutations have been found in all parts of the *bt*k gene.^{6,7,9,11–17} There is no apparent correlation between the phenotype and the different mutations, although there can be marked phenotypic differences among affected male patients in a single kindred. A point mutation has been found in *bt*k in male CBA/N mice with a mild humoral immunodeficiency (called *Xid* for X-linked immunodeficiency).^{22–24} Recently, it has been possible to disrupt *bt*k in mice. The severity of the phenotype in these mice depends on their genetic background. This may provide an excellent model for experimental gene therapy.²⁵

Female carriers of X-linked agammaglobulinemia, who are immunologically normal, have two populations of B-cell precursors. The Lyon hypothesis, which states that one X chromosome in every female cell is randomly inactivated, predicts that half of the early B cells in such persons would have an active X chromosome bearing normal *bt*k and that the other half would have the defective *bt*k. Consequently, cells bearing the mutated *bt*k on the active X chromosome would not mature into B cells; only the cells containing the active X chromosome bearing the normal gene would mature. This prediction turns out to be correct. An examination of the X chromosome in the B cells of normal female subjects reveals random inactivation of one of the two X chromosomes. However, the B cells of obligate female carriers of the gene for X-linked agammaglobulinemia exhibit nonrandom inactivation of the X chromosome, in that only the B cells with the normal X chromosome survive; all other cells have random inactivation of the X chromosome.^{26–28} This observation

not only allows the identification of carriers but was also of considerable importance before the discovery of *bt*k because it suggested that the defect was confined to the B-cell lineage. This kind of analysis can also be applied to other X-linked diseases to determine which cell lineages are affected by the genetic defect.

HYPER-IGM SYNDROME

In 1961 two boys with a syndrome that resembled X-linked agammaglobulinemia clinically were found to have elevated serum concentrations of IgM but no IgA and very low concentrations of IgG.²⁹ This new defect was presumed to be inherited as an X-linked recessive trait. Then, two female patients with the same clinical phenotype were identified.^{30,31}

Many patients with this syndrome have since been described, approximately 70 percent of whom have the X-linked form of the hyper-IgM syndrome.³² The mode of inheritance in the remaining patients is not clear-cut. The genetic defect in the X-linked form has recently been discovered and reveals new facets of collaboration between T and B lymphocytes.

Male patients with X-linked hyper-IgM syndrome have a clinical history of pyogenic infections that resembles that encountered in male patients with X-linked agammaglobulinemia. In addition, they are susceptible to opportunistic infections, particularly those due to *Pneumocystis carinii*. They also are prone to autoimmune diseases involving the formed elements of the blood — autoimmune hemolytic anemia, thrombocytopenic purpura, and most important of all, recurrent, often severe, and prolonged neutropenia. The neutropenia responds well to immune globulin and granulocyte-macrophage colony-stimulating factor. In these patients administration of intravenous immune globulin in the same doses as are used in X-linked agammaglobulinemia is recommended. This therapy usually results in a decrease in the serum IgM concentration. In the second decade of life there may be uncontrollable proliferation of IgM-producing plasma cells, which extensively invade the gastrointestinal tract, liver, and gallbladder. Although the proliferating cells always exhibit polyclonality, the cellular infiltrates may be so extensive as to prove fatal. Patients with X-linked hyper-IgM syndrome also have an increased risk of abdominal cancers.

The serum of patients with X-linked hyper-IgM syndrome usually contains undetectable amounts of IgA and IgE and very low concentrations of IgG (<150 mg per deciliter). However, IgM concentrations may be in the high normal range, and may even be 1000 mg per deciliter or more; IgD concentrations are also elevated. The blood contains a normal number of B lymphocytes, but they have only surface IgM and IgD.^{33,34} As in X-linked agammaglobulinemia, there is no germinal-center development in the lymph nodes and spleen despite the presence of normal numbers of B cells and T cells.

In an immune response IgM and IgD antibodies are produced first. As the immune response progresses,

IgG antibodies appear, followed by IgA antibodies and finally by IgE antibodies. The sequential appearance of different classes of immunoglobulins is called class switching. It was possible to induce class switching to IgG and IgA in B cells from patients with X-linked hyper-IgM syndrome by incubating B cells with activated CD4+ T cells from a woman with the Sézary syndrome.³⁵ Studies of class switching in normal B cells show that two signals are required for the B cell to switch from synthesizing and secreting IgM to synthesizing and secreting IgE: the binding of interleukin-4 secreted by T cells to the interleukin-4 receptor on B cells and the interaction of CD40 on the B-cell surface with the CD40 ligand, which is expressed on activated T cells.^{36,37} This observation led to the discovery that T cells of patients with X-linked hyper-IgM syndrome could not synthesize the CD40 ligand.

The gene for X-linked hyper-IgM syndrome was mapped to Xq26 on the long arm of the X chromosome.^{38,39} The gene encoding the CD40 ligand was cloned and mapped to the same location.⁴⁰ Several groups simultaneously discovered that the defect in X-linked hyper-IgM syndrome resides in mutations in the gene for the CD40 ligand.⁴¹⁻⁴⁶ Missense as well as nonsense mutations and deletions have been found in the CD40 ligand gene in patients with X-linked hyper-IgM syndrome.

This syndrome illustrates the importance of physical contact between B cells and T cells through CD40 and its ligand in the activation of B cells and in germinal-center formation and immunoglobulin class switching.^{47,48} Further work is required to explain the high frequency of autoimmune disease and neutropenia, susceptibility to opportunistic infections, and the lymphoproliferative complications in X-linked hyper-IgM syndrome. Because the CD40 ligand molecule is not required for the normal development of T lymphocytes, female obligate heterozygous carriers of X-linked hyper-IgM syndrome, unlike carriers of X-linked agammaglobulinemia, have random inactivation of the X chromosome in lymphocytes. A polymorphic region at the 3' end of the CD40 ligand gene makes prenatal diagnosis of X-linked hyper-IgM syndrome possible.⁴⁹

COMMON VARIABLE IMMUNODEFICIENCY

The term "common variable immunodeficiency" is used to designate a group of as yet undifferentiated syndromes. All are characterized by defective antibody formation. The diagnosis is based on the exclusion of other known causes of humoral immune defects.⁵⁰ As would be expected in a heterogeneous group of undifferentiated diseases, several patterns of inheritance (autosomal recessive, autosomal dominant, and X-linked) have been noted. Sporadic cases are, however, most common.

Among populations of European origin, common variable immunodeficiency is the most frequent of the primary specific immunodeficiency diseases.⁵¹ It affects men and women equally. The usual age at presentation is the second or third decade of life. The terms "late-onset hypogammaglobulinemia," "adult-onset hypogam-

maglobulinemia," and "acquired immunodeficiency," which were used in the past, are no longer appropriate.

The clinical presentation of common variable immunodeficiency disease is generally that of recurrent pyogenic sinopulmonary infections. Appropriate early investigation and diagnosis are important; many cases are only identified after serious chronic obstructive lung disease and bronchiectasis have developed. A few patients with common variable immunodeficiency present with infections involving unusual organisms such as *P. carinii*, mycobacteria, or various fungi.⁵¹ Recurrent attacks of herpes simplex are common, and herpes zoster develops in about one fifth of patients.⁵² As in patients with X-linked agammaglobulinemia, some patients with common variable immunodeficiency have unusual enteroviral infections with a chronic meningoencephalitis and a syndrome resembling dermatomyositis. The patients are also highly prone to infection with enteric pathogens, such as chronic *G. lamblia* infection.

There is an unusually high incidence of malignant lymphoreticular and gastrointestinal conditions in common variable immunodeficiency.⁵³ A 50-fold increase in gastric carcinoma has been observed. Lymphoma is about 300 times more frequent in women with common variable immunodeficiency than in affected men.⁵⁴ In contrast to patients with X-linked agammaglobulinemia, many patients with common variable immunodeficiency have diffuse lymphadenopathy and often splenomegaly. The lymph nodes and spleen show a striking reactive follicular hyperplasia.⁵⁵ The gastrointestinal tract is also commonly involved in the process, with nodular lymphoid hyperplasia. As in celiac disease, malabsorption with weight loss, diarrhea, and associated findings such as hypoalbuminemia and vitamin deficiencies is seen. Inflammatory bowel diseases are more frequent. Patients with common variable immunodeficiency are also prone to a variety of other autoimmune disorders (e.g., pernicious anemia, hemolytic anemia, thrombocytopenia, and neutropenia). Noncaseating (sarcoid-like) granulomas occur in the skin, the gut, and other viscera.

Defective antibody formation is accompanied by decreased serum IgG concentrations and usually by decreased serum IgA and IgM concentrations. There is no convincing evidence of any intrinsic B-cell defects. Although the number of B cells may be reduced, with appropriate stimulation they can produce and secrete immunoglobulins.^{56,57} However, the B cells are immature. The findings in common variable immunodeficiency are consistent with insufficient *in vivo* stimulus for B-cell activation rather than an intrinsic failure of B cells to differentiate.

Relatives of patients with common variable immunodeficiency have an unusually high incidence of IgA deficiency⁵⁸ and an increased incidence of autoimmune disorders,⁵⁹ autoantibodies (including antilymphocyte antibodies),⁵⁹ and malignant conditions. Families whose members include persons with common variable immunodeficiency and IgA deficiency often have certain fixed haplotypes in the MHC.⁶⁰⁻⁶⁴ One or more genes in the

MHC may be involved in the pathogenesis of common variable immunodeficiency and IgA deficiency.

Since immature B cells in common variable immunodeficiency appear to be functionally intact, the defect might logically reside in the T-cell component of the interaction between B cells and T cells requisite for B-cell maturation. However, it is often difficult to interpret studies of T cells in common variable immunodeficiency, because of the activation of T cells that is probably a result of recurrent or chronic infections⁶⁵ or infusions of intravenous immune globulin.⁶⁶

In most patients with common variable immunodeficiency, stimulation of T-cell receptors⁶⁷ produces diminished responses and there is decreased gene transcription of cytokines such as interleukin-2, interleukin-4, interleukin-5, and interferon- γ .^{68,69} Decreased production of interleukin-2 after direct stimulation of T-cell receptors⁷⁰ is correlated with diminished expression of CD40 ligand⁷¹ and may reflect an abnormality in CD4+ T cells in common variable immunodeficiency.^{72,73} This abnormality of T-cell triggering can be bypassed by direct activation of signal transduction.^{74,75}

Thus, many patients with common variable immunodeficiency appear to have defective interactions between T cells and B cells. Defective T-cell signal transduction could contribute to the diminished humoral immunity found in these disorders in the presence of immature but otherwise potentially normal B cells. In the absence of appropriate T-cell signaling, B cells would fail not only to produce antibody, but also to proliferate and differentiate, which would result in both the decreased numbers and the arrested maturation of B cells seen frequently in common variable immunodeficiency.

SEVERE COMBINED IMMUNODEFICIENCY

In contrast to X-linked agammaglobulinemia and X-linked hyper-IgM syndrome, severe combined immunodeficiency has many genetic causes even though the phenotype is fairly uniform. Usually, affected infants are ill by three months of age with persistent thrush or an extensive rash in the diaper area due to monilia. They may have intractable diarrhea or a persistent pertussis-like cough due to interstitial pneumonia caused by *P. carinii*. Although growth and development may have proceeded normally for the first three months of life, growth and weight gain subsequently fall off, and failure to thrive becomes a striking feature. Sometimes these infants have a morbilliform rash shortly after birth, due to transplacental passage of maternal lymphocytes, which mount a graft-versus-host reaction. The rash becomes hyperpigmented. Death from varicella, herpes, adenovirus, or cytomegalovirus may occur very rapidly after infection. Giant-cell pneumonia has resulted from measles infection and live-measles vaccine, and progressive vaccinia has occurred after smallpox vaccination; both were uniformly fatal. A diagnosis of severe combined immunodeficiency represents a medical emergency; this immunodeficiency can be rapidly fatal if affected infants are not rendered im-

munocompetent by bone marrow transplantation in a timely fashion.

Infants with severe combined immunodeficiency almost invariably have profound lymphopenia (<1000 lymphocytes per cubic millimeter). The number of natural killer cells may be normal or high. In the X-linked form of severe combined immunodeficiency the number of B cells is normal or elevated, but these B cells fail to mature and function normally. CD3+ T cells, when present, may be of maternal origin. These infants are not capable of cell-mediated immunity. Lymphocytes do not respond in vitro to nonspecific mitogens such as phytohemagglutinin and concanavalin A. They also do not respond to an allogeneic stimulus or to specific antigens such as tetanus toxoid, which may have been used as an immunogen. The failure of the thymus to become a lymphoid organ is a common feature. The thymic shadow cannot be seen on a chest film. The serum immunoglobulin concentrations are all low. Rarely, an M component may be present in the serum, and in an infant this is virtually diagnostic of severe combined immunodeficiency.

Severe combined immunodeficiency is three times as common in boys as in girls, because the most common form — accounting for 50 to 60 percent of the cases — is X-linked. It has been mapped to Xq13.⁷⁶⁻⁷⁸ The genetic defect in X-linked severe combined immunodeficiency has recently been identified as a mutation of the gamma chain of the interleukin-2 receptor,⁷⁹ which had been cloned earlier.⁸⁰ Mutations were found in the gamma chain of the interleukin-2 receptor in a number of patients with X-linked severe combined immunodeficiency. The disorder has also been found in basset hounds, and these dogs also have a mutation in the gamma chain of the interleukin-2 receptor.^{81,82}

At first this finding was very surprising because it did not seem likely that such a profound immunodeficiency could result from mutations in the gamma chain of the interleukin-2 receptor. It was soon discovered that the gamma chain is a component of several interleukin receptors — namely, receptors for interleukin-4, interleukin-7, interleukin-11, and interleukin-15.⁸³⁻⁸⁷ Thus, the early lymphoid progenitor cells in X-linked severe combined immunodeficiency, lacking intact interleukin receptors, fail to be stimulated by all these growth factors that are vital to the normal development and differentiation of T cells and the late phases of B-cell development. The T cells, natural killer cells, and late-stage B cells of obligate female heterozygous carriers of X-linked severe combined immunodeficiency exhibit nonrandom X-chromosome inactivation⁸⁶⁻⁸⁸; only cells with the normal X chromosome survive.

The remainder of the cases of severe combined immunodeficiency result from autosomal recessive inheritance. The most common causes of the autosomal recessive form are inherited deficiencies of the purine-degradation enzymes adenosine deaminase and nucleoside phosphorylase. Deficiencies of both these enzymes have been extensively reviewed.^{89,90} Many patients with adenosine deaminase deficiency have benefited from

regular injections of adenosine deaminase conjugated to polyethylene glycol.⁹¹ Adenosine deaminase deficiency was also the underlying problem treated in the first successful gene therapy.⁹²

In 1968 the first successful bone marrow transplantation in an infant with X-linked severe combined immunodeficiency was performed.⁹³ Subsequently, scores of these infants have been treated successfully with bone marrow transplantation from histoidentical related donors as well as from unrelated donors and from donors with one or more HLA mismatches whose bone marrow was depleted of T cells.⁹⁴ These bone marrow transplantations should be performed as quickly as possible, since X-linked severe combined immunodeficiency is invariably fatal. In families with a previously affected infant, prenatal diagnosis is now possible so that preparations for transplantation can be made in advance of the birth.

In a few rare instances, cases of severe combined immunodeficiency have been reported as a result of defective interleukin-1 receptors, mutated interleukin-2 genes, failure of signal transduction in T cells, or defective T-cell-specific promoters.⁹⁵⁻¹⁰¹ In these cases, the lymphocyte counts may be normal but the T cells are not functional.

DEFECTS IN THE EXPRESSION OF THE MHC

Defects in the expression of the MHC were originally called the "bare lymphocyte syndrome." Use of this unfortunate term should be dropped since it fails to differentiate the several distinct types of MHC class I and class II defects that have been described. The MHC class II molecules are constitutively expressed on antigen-presenting cells such as B lymphocytes, dendritic cells, and cells of monocyte or macrophage lineage¹⁰² and on thymic epithelial cells, where they have an important role in the maturation of CD4+ T cells.¹⁰³ The MHC class II molecules are also expressed on activated T cells. The chief function of these molecules is to bind and present antigenic fragments to the T-cell receptor on CD4+ T cells and thereby activate them. This interaction is vital to both cell-mediated immunity and humoral immunity. In contrast, MHC class I molecules are expressed on virtually all cells. They bind and present antigenic peptides to the T-cell receptor of CD8+ T cells and activate their cytotoxic function. Class I molecules also have a vital role in the intrathymic maturation of CD8+ T cells.

A number of children, largely of North African origin, with a moderately severe immunodeficiency, were found to be unable to express MHC class II molecules. These children had severe, protracted diarrhea, frequently associated with candidiasis and cryptosporidiosis, and failure to thrive. Sclerosing cholangitis supervened in a number of them after prolonged gastrointestinal symptoms. Pneumonia, in addition to severe upper respiratory tract infections, was frequent. When given bacille Calmette-Guérin (BCG) in infancy, they survived, in contrast to infants with severe combined immunodeficiency, who invariably die of progressive bacille Cal-

mette-Guérin infection. Graft-versus-host disease does not develop after transfusion with whole blood, whereas it is the inevitable outcome of transfusion in infants with severe combined immunodeficiency.¹⁰⁴

MHC class II deficiency is inherited as an autosomal recessive trait, but the defect does not segregate with the MHC genes, which are encoded on chromosome 6.¹⁰⁵ As expected, children with MHC class II deficiency have insufficient numbers of CD4+ T cells but not of CD8+ T cells and cannot mount delayed hypersensitivity reactions. Although the number of B cells is normal, affected children have hypogammaglobulinemia. The *in vitro* responses to phytohemagglutinin and other non-specific mitogens are normal, but T cells fail to respond to specific antigens.¹⁰⁴

There are three major MHC class II molecules: HLA-DP, DQ, and DR. The coordinate expression of these molecules on the surface of B cells and macrophages is regulated in a complex way. At least three unique promoter boxes, called the Y, X, and S boxes, upstream of the MHC genes are involved in the regulation of transcription of MHC class II molecules.¹⁰² The regulation of this transcription is defective in MHC class II deficiency.

Complementation analysis has shown that there are several different types of MHC class II defects. B lymphocytes from patients with MHC class II deficiency were transformed with Epstein-Barr virus and maintained in culture. When transformed B cells from certain patients were fused, they corrected one another's defect to allow the expression of MHC class II molecules. This led to the identification of so-called complementation groups of MHC class II deficiency.^{106,107} Only cells within one complementation group do not cross-correct; cells from any two complementation groups cross-correct.

It is well known that interferon- γ induces the expression of MHC class II molecules after a considerable lag period.¹⁰⁸ However, interferon- γ fails to induce the expression of MHC class II molecules in patients with MHC class II deficiency.¹⁰⁹ During the lag period that follows exposure to interferon- γ the cells synthesize a new protein called class II transactivator,¹¹⁰ which does not itself bind to the Y, X, or S boxes but appears to coordinate the binding of the promoters that do. This intracellular protein is defective in one of the complementation groups. The gene encoding the class II transactivator maps to chromosome 15. In another group of patients there is a defect in the promoter protein that binds to the X box.^{111,112} This protein, called RFX5, maps to chromosome 2. Other transactivating factors have not yet been completely identified, and the pathogenesis of MHC class II deficiency promises to become more complex.

Although MHC class II deficiency is less clinically severe than the profound immunodeficiency of severe combined immunodeficiency, it is uniformly fatal in the first or second decade of life. Bone marrow transplantation has resulted in long-term survival.

Because the expression of MHC class I molecules

may be decreased in MHC class II deficiency, the identification of isolated MHC class I defects has been elusive. The molecular basis of MHC class I deficiency has recently been defined in a Moroccan family, in which two affected siblings had recurrent, severe bacterial pulmonary infections starting in late childhood.¹¹³ In this large kindred the MHC class I deficiency segregated with the MHC genes, unlike MHC class II deficiency. From this observation it was possible to define the defect. The assembly of MHC class I molecules in the Golgi apparatus proceeds successfully when the α chain of these molecules associates with beta₂-microglobulin and the complex is joined by antigenic peptides transported across the Golgi membrane by a transporter protein, called TAP. The unit then moves to the cell membrane (Fig. 2). If the assembly of the components cannot be completed, usually because no antigenic peptide is loaded onto the α chain, the MHC class I complex is destroyed in the cytoplasm of the cell. TAP is encoded by two genes in the MHC, *TAP1* and *TAP2*. The defect in the family studied results from a nonsense mutation in the *TAP2* gene.¹¹³ As expected, the affected children have a deficiency of CD8+ T cells.

THE WISKOTT-ALDRICH SYNDROME

The Wiskott-Aldrich syndrome is inherited as an X-linked recessive disease.¹¹⁴ Wiskott was the first to report, in 1937, that affected male patients had recurrent bloody diarrhea and thrombocytopenia.¹¹⁵ The

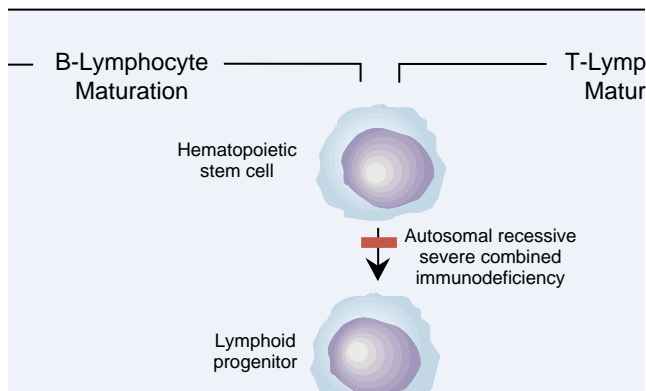


Figure 2. Pathway for the Assembly of MHC Class I Molecules. Antigens in the cytosol of cells are degraded by proteolytic enzymes in large organelles, called proteasomes. The antigen fragments are then transported across the membrane of the endoplasmic reticulum by transporter proteins, called TAP1 and TAP2. In the endoplasmic reticulum the antigenic fragments encounter MHC class I molecules that are in the process of assembling. The α chain of the MHC class I molecule and beta₂-microglobulin (β_2M) are held together by calnexin. Once the antigenic fragment is incorporated into the complex, the calnexin falls off and the rest of the complex is transported by the Golgi apparatus to the cell surface. In TAP2 deficiency, the antigenic-peptide fragments cannot be transported across the endoplasmic reticulum and the assembly of MHC class I molecules cannot be completed.

early onset of profound thrombocytopenia with small platelets is diagnostic. In addition, affected male patients have moderate-to-severe eczema and are susceptible to pyogenic and opportunistic infections. Serum IgM concentrations are low, but IgA and IgE concentrations are elevated and total IgG concentrations are normal. Affected patients do not make antibodies to polysaccharide antigens^{116,117} and have a poor response to protein antigens.¹¹⁸ The number of T cells progressively decreases, whereas the number of B cells progressively expands.¹¹⁸ In vitro tests of T-cell function yield extremely variable results, but the T cells consistently respond poorly or not at all to the mitogenic effects of antibodies to CD3.¹¹⁹ In the past, patients with the Wiskott-Aldrich syndrome generally died within the first decade of life of infection, bleeding, or malignant conditions, but improved management with splenectomy, intravenous immune globulin therapy, and other measures has improved their life expectancy.¹²⁰ In 1978 the first successful bone marrow transplantation for the Wiskott-Aldrich syndrome was reported, and subsequently, transplantation has resulted in complete bone marrow chimerism in many patients with the syndrome.¹²¹

The Wiskott-Aldrich syndrome maps to Xp11.23 on the short arm of the X chromosome¹²² (and Kwan S-P, et al.: unpublished data). In several kindreds isolated X-linked thrombocytopenia maps to the same locus and is probably a variant of the syndrome.¹²³⁻¹²⁶ Obligate female heterozygous carriers of the Wiskott-Aldrich syndrome, who are clinically normal, have nonrandom inactivation of their X chromosomes. Only the normal X chromosome survives in T and B lymphocytes, monocytes, and granulocytes.¹²⁷⁻¹³⁰ Precursor cells of these lineages exhibit nonrandom inactivation of X chromosomes early in the process of differentiation.¹³¹ A polymorphism in the DNA very close to the gene for the Wiskott-Aldrich syndrome facilitates prenatal diagnosis.¹³²

The blood elements that are most severely affected in the Wiskott-Aldrich syndrome are the platelets and T cells. The T cells in particular exhibit disorganization of the cytoskeleton and loss of microvilli.^{133,134} Scanning electron microscopy of fetal lymphocytes from the umbilical vein establishes the prenatal diagnosis. In addition, the cell-surface sialoglycoproteins, most notably CD43, are unstable, and their expression is decreased in the cell membranes of lymphocytes.^{135,136}

The gene that is defective in the Wiskott-Aldrich syndrome has recently been identified and encodes the Wiskott-Aldrich syndrome protein.¹³⁶ It has no relation to any known protein, and its function is unknown. Several nonsense and missense mutations, as well as deletions and insertions, have been found in this gene.^{132,137} It is extremely rich in proline residues and has long stretches of prolines. This suggests that it binds to the SH3 domains of tyrosine protein kinases, but the enigmatic role of this protein in the pathogenesis of the defect in the Wiskott-Aldrich syndrome remains to be determined.

We are indebted to Dr. Raif Geha for critical review of the manuscript and to Rachelle Rosenbaum for help in the preparation of the manuscript.

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