molecules play key roles in presenting lipid antigens (see Chapter 8). Studies using mice engineered to lack Qa-1-restricted $CD8^+$ T_{REG} cells showed that these animals develop aggressive autoimmune reactions against self antigens, suggesting that this population is involved in regulating $CD4^+$ T-cell responses to self antigens to maintain peripheral tolerance. In various in vitro experimental systems, $CD8^+$ iT_{REG} cells have been found to express inhibitory cytokines, including IL-10 and TGF-β, although whether these cells are actually using any of these cytokines in vivo to suppress immune responses is still an open question.

Autoimmunity

Simply stated, autoimmune disease is caused by failure of the tolerance processes described above to protect the host from the action of self-reactive lymphocytes. These diseases result from the destruction of self proteins, cells, and organs by auto-antibodies or self-reactive T cells. For example, auto-antibodies are the major offender in Hashimoto's thyroiditis, in which antibodies reactive with thyroid-specific antigens cause severe tissue destruction. On the other hand, many autoimmune diseases are characterized by tissue destruction mediated directly by T cells. A well-known example is *r*heumatoid *a*rthritis (RA), in which self-reactive T cells attack the tissue in joints, causing an inflammatory response that results in swelling and tissue destruction. Other examples of T-cell-mediated autoimmune disease include *i*nsulin-*d*ependent or Type 1 *d*iabetes *m*ellitus (T1DM) and *m*ultiple *s*clerosis (MS). Table 16-1 lists several of the more common autoimmune disorders, as well as their primary immune mediators.

Autoimmune disease is estimated to affect between 3% and 8% of individuals in the industrialized world, making this a rising problem in terms of morbidity and mortality

TABLE 16-1 Some autoimmune diseases in humans

Disease	Self antigen/Target gene	Immune effector
	ORGAN-SPECIFIC AUTOIMMUNE DISEASES	
Addison's disease	Adrenal cells	Auto-antibodies
Autoimmune hemolytic anemia	RBC membrane proteins	Auto-antibodies
Goodpasture's syndrome	Renal and lung basement membranes	Auto-antibodies
Graves' disease	Thyroid-stimulating hormone receptor	Auto-antibody (stimulating)
Hashimoto's thyroiditis	Thyroid proteins and cells	T_H1 cells, auto-antibodies
Idiopathic thrombocytopenia purpura	Platelet membrane proteins	Auto-antibodies
Type 1 diabetes mellitus	Pancreatic beta cells	T_H1 cells, auto-antibodies
Myasthenia gravis	Acetylcholine receptors	Auto-antibody (blocking)
Myocardial infarction	Heart	Auto-antibodies
Pernicious anemia	Gastric parietal cells; intrinsic factor	Auto-antibody
Poststreptococcal glomerulonephritis	Kidney	Antigen-antibody complexes
Spontaneous infertility	Sperm	Auto-antibodies
	SYSTEMIC AUTOIMMUNE DISEASES	
Ankylosing spondylitis	Vertebrae	Immune complexes
Multiple sclerosis	Brain or white matter	T_H1 cells and T_C cells, auto-antibodies
Rheumatoid arthritis	Connective tissue, IgG	Auto-antibodies, immune complexes
Scleroderma	Nuclei, heart, lungs, gastrointestinal tract, kidney	Auto-antibodies
Sjögren's syndrome	Salivary gland, liver, kidney, thyroid	Auto-antibodies
Systemic lupus erythematosus (SLE)	DNA, nuclear protein, RBC and platelet membranes	Auto-antibodies, immune complexes
*I*mmune dysregulation *p*olyendocrinopathy *e*nteropathy *X*-linked (IPEX)	Multiorgan, loss of *FoxP3* gene	Missing regulatory T cells
*A*utoimmune *p*oly*e*ndocrinopathy-candidiasis-*e*ctodermal *d*ystrophy (APECED)	Multiorgan, loss of *aire* gene	Defective central tolerance

TABLE 16-2 Experimental animal models of autoimmune diseases

Animal model	Possible human disease counterpart	Inducing antigen	Disease transferred by T cells
	SPONTANEOUS AUTOIMMUNE DISEASES		
*N*onobese *d*iabetic (NOD) mouse	Insulin-dependent diabetes mellitus (1)	Unknown	Yes
(NZB X NZW) F_1 mouse	Systemic lupus erythematosus (SLE)	Unknown	Yes
Obese-strain chicken	Hashimoto's thyroiditis	Thyroglobulin	Yes
	EXPERIMENTALLY INDUCED AUTOIMMUNE DISEASES*		
*E*xperimental *a*utoimmune *m*yasthenia *g*ravis (EAMG)	Myasthenia gravis	Acetylcholine receptor	Yes
Experimental autoimmune encephalomyelitis (EAE)	*M*ultiple *s*clerosis (MS)	*M*yelin *b*asic *p*rotein (MBP); *p*roteo*l*ipid *p*rotein (PLP)	Yes
*A*utoimmune *a*rthritis (AA)	*R*heumatoid *a*rthritis (RA)	*M. tuberculosis* (proteoglycans)	Yes
*E*xperimental *a*utoimmune *t*hyroiditis (EAT)	Hashimoto's thyroiditis	Thyroglobulin	Yes

* These diseases can be induced by injecting appropriate animals with the indicated antigen in complete Freund's adjuvant. Except for autoimmune arthritis, the antigens used correspond to the self antigens associated with the human disease counterpart. Rheumatoid arthritis involves reaction to proteoglycans, which are self antigens associated with connective tissue.

around the globe. These diseases are often categorized as either organ-specific or systemic, depending on whether they affect a single organ or multiple systems in the body. Another method of grouping involves the immune component that does the bulk of the damage: T cells versus antibodies. In this section, we describe several examples of both organ-specific and systemic autoimmune disease. In each case, we discuss the antigenic target (when known), the causative process (either cellular or humoral), and the resulting symptoms. When available, examples of animal models used to study these disorders are also considered (Table 16-2). Finally, we touch on the factors believed to be involved in induction or control of autoimmunity, and the treatments for these conditions.

Some Autoimmune Diseases Target Specific Organs

Autoimmune diseases are caused by immune stimulatory lymphocytes or antibodies that recognize self components, resulting in cellular lysis and/or an inflammatory response in the affected organ. Gradually, the damaged cellular structure is replaced by connective tissue (fibrosis), and the function of the organ declines. In an organ-specific autoimmune disease, the immune response is usually directed to a target antigen unique to a single organ or gland, so that the manifestations are largely limited to that organ. The cells of the target organs may be damaged directly by humoral or cell-mediated effector mechanisms. Alternatively, anti-self antibodies may overstimulate or block the normal function of the target organ.

Hashimoto's Thyroiditis

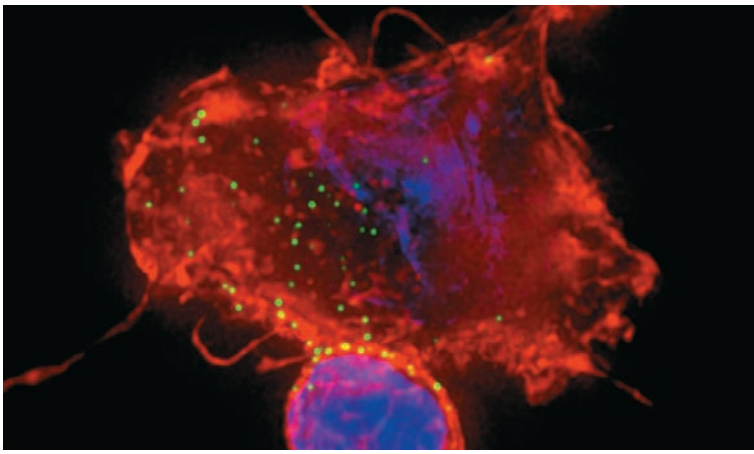
In Hashimoto's thyroiditis, an individual produces autoantibodies and sensitized T_H1 cells specific for thyroid antigens. This disease is much more common in women, often striking in middle-age (see Clinical Focus Box 16-2). Antibodies are formed to a number of thyroid proteins, including thyroglobulin and thyroid peroxidase, both of which are involved in the uptake of iodine. Binding of the auto-antibodies to these proteins interferes with iodine uptake, leading to decreased thyroid function and hypothyroidism (decreased production of thyroid hormones). The resulting *d*elayed-*t*ype *h*ypersensitivity (DTH) response is characterized by an intense infiltration of the thyroid gland by lymphocytes, macrophages, and plasma cells, which form lymphocytic follicles and germinal centers. (See Chapter 15 for a description of the DTH response.) The ensuing inflammatory response causes a goiter, or visible enlargement of the thyroid gland, a physiological response to hypothyroidism.

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) or insulin-dependent diabetes, affects almost 2 in 1000 children in the U.S.; roughly double the incidence observed just 20 years ago. It is seen mostly in youth under the age of 14 and is less common than Type 2, or non-insulin dependent diabetes mellitus. T1DM is caused by an autoimmune attack against insulin-producing

18

Immunodeficiency Disorders



Interaction between dendritic cell and T cell indicating passage of HIV-1 (green dots) between the cells. *[Courtesy of Thomas J. Hope, Northwestern University.]*

- Primary Immunodeficiencies
- Secondary Immunodeficiencies

Like any complex multicomponent system, the immune system can be subject to failures of some or all of its parts. These failures can have dire consequences. When the system loses its sense of self and begins to attack the host's own cells, the result is **autoimmunity**, described in Chapter 16. When the system errs by failing to protect the host from disease-causing agents, the result is **immunodeficiency**, the subject of this chapter.

Immunodeficiency resulting from an inherited genetic or developmental defect in the immune system is called a **primary immunodeficiency**. In such a condition, the defect is present at birth, although it may not manifest until later in life. These diseases can be caused by defects in virtually any gene involved in immune development or function, innate or adaptive, humoral or cell mediated, plus genes not previously associated with immunity. As one can imagine, the nature of the component(s) that fail(s) determines the degree and type of the immune defect; some immunodeficiency disorders are relatively minor, requiring little or no treatment, although others can be life threatening and necessitate major intervention.

Secondary immunodeficiency, also known as acquired immunodeficiency, is the loss of immune function that results from exposure to an external agent, often an infection. Although several external factors can affect immune function, by far the most well-known secondary immunodeficiency is ***a*cquired *i*mmuno*d*eficiency *s*yndrome (AIDS)**, which results from infection with the **human immunodeficiency virus (HIV)**. A global summary of the AIDS epidemic conducted by the Joint United Nations Programme on HIV/AIDS (UNAIDS) shows that by the end of 2011 (the most recent data available) over 34 million people were living with HIV and 2.5 million new infections occurred in just that year (330,000 of them in children under age 15 years). In 2011, AIDS killed approximately 1.7 million people. The good news is that, largely thanks to increased access to antiretroviral drugs, this was roughly a 24% decrease in the rate of AIDS-related deaths as compared to just 6 years earlier. People with AIDS, like individuals with severe inherited immunodeficiency, are at risk of **opportunistic infections**, caused by microorganisms that healthy individuals can easily eradicate but that cause disease and even death in those with significantly impaired immune function.

The first part of this chapter describes the most common primary immunodeficiencies, examines progress in identifying new defects that can lead to these types of disorders, and considers approaches to their study and treatment. The rest of the chapter describes acquired immunodeficiency, with a focus on HIV infection and AIDS, along with the current status of therapeutic and prevention strategies for combating this often fatal disorder.

Primary Immunodeficiencies

To date, over 150 different types of primary, or inherited, immunodeficiency have been identified. Theoretically, any component important to immune function that is defective can lead to some form of immunodeficiency. Collectively, *p*rimary *i*mmunodeficiency *d*isorders (PIDs) have helped immunologists to appreciate the importance of specific cellular events or proteins that are required for proper immune system function. Most of these disorders are monogenic, or

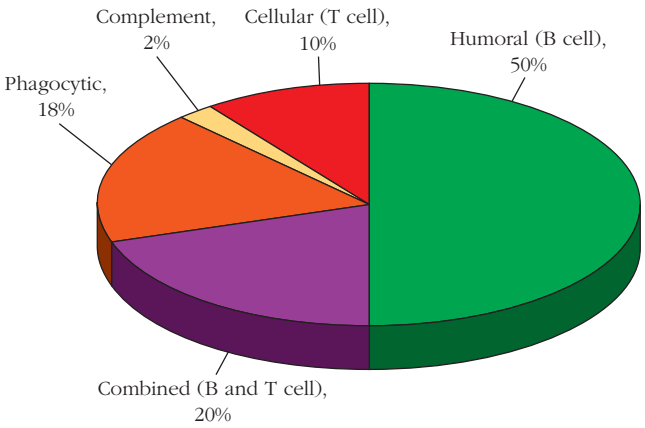


FIGURE 18-1 Distribution of primary immunodeficiencies by type. Primary immunodeficiency can involve either innate processes (phagocytosis, complement, or other defects) or the adaptive immune response (humoral, cellular, or both). Of these categories, adaptive immune disruptions are the most common, with antibody defects making up the largest portion of these. *[Song et al., 2011*, Clinical and Molecular Allergy ***9:****10. doi:10.1186/1476-7961-9-10]*

caused by defects in a single gene, and are extremely rare. Primary immunodeficiency diseases vary in severity from mild to nearly fatal. They can be loosely categorized as affecting either innate immunity or adaptive responses, and are often grouped by the specific components of the immune system most affected (Figure 18-1). The most common forms of primary immunodeficiency, and frequently the least severe, are those that impair one or more antibody isotype. However, due to the complex interconnections of the immune response, defects in one pathway can also manifest in other arms of the immune response, and different gene defects can produce the same phenotype, making strict categorization complicated.

The cellular consequences of a particular gene disruption depend on the specific immune system component involved and the severity of the disruption (Figure 18-2). Defects that interrupt early hematopoietic cell development affect everything downstream of this step, as is the case for reticular dysgenesis, a disease in which all hematopoietic cell survival is impaired. Defects in more highly differentiated downstream compartments of the immune system, such as in selective immunoglobulin deficiencies, have consequences that tend to be more specific and usually less severe. In some cases, the loss of a gene not specifically associated with immunity has been found to have undue influence on cells of the hematopoietic lineage, such as the lymphoid cell destruction seen in *a*denosine *d*eaminase *d*eficiency (ADA), which disables both B and T cells, leading to a form of severe combined immunodeficiency. Decreased production of phagocytes, such as neutrophils, or the inhibition of phagocytic processes typically manifest as increased susceptibility to bacterial or fungal infections, as seen in defects that affect various cells within the myeloid lineage (Figure 18-2, orange). In general, defects in the T-cell components of the immune system tend to have a greater overall impact on the immune response than genetic mutations that affect only B cells or innate responses. This is due to the pivotal role of T cells in directing downstream immune events, and occurs because defects in this cell type often affect both humoral and cell-mediated responses.

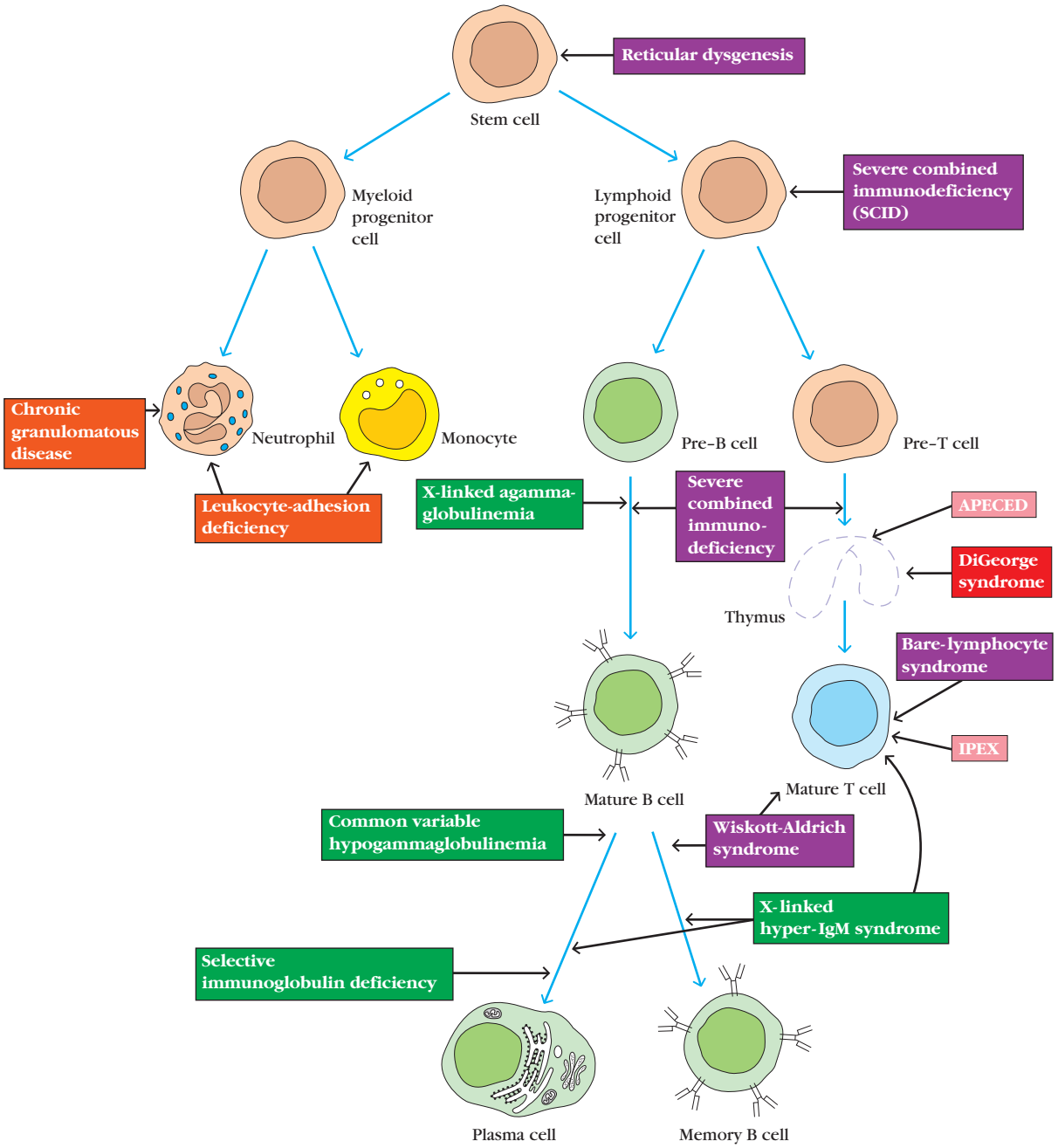
Immunodeficiency disorders can also stem from developmental defects that alter a specific organ. This is most commonly seen in sufferers of DiGeorge syndrome, where T-cell development is hindered by a congenital defect that blocks growth of the thymus. Since many B-cell responses require T-cell help, most of the adaptive immune response is compromised in patients who suffer the complete form of the disease in which little or no thymic tissue is present, even though B cells are intact. Finally, a more recent category of immunodeficiency syndrome has come to light, illustrating the importance of immune regulation, or "the brakes" of the immune system. APECED and IPEX are both immunodeficiency disorders that result in *overactive* immune responses, or autoimmunity, due to the dysregulation of self-reactive T cells. Some of the most well-characterized primary immunodeficiency disorders with known genetic causes are listed in Table 18-1, along with the specific gene defect and resulting immune impairment.

The nature of the immune defect will determine which groups of pathogens are most challenging to individuals who inherit these immunodeficiency disorders (Table 18-2). Inherited defects that impair B cells, resulting in depressed expression of one or more of the antibody classes, are typically characterized by recurring bacterial infections. These symptoms are similar to those exhibited by some of the individuals who inherit mutations in genes that encode complement components. Phagocytes are so important for the removal of fungi and bacteria that individuals with disruptions of phagocytic function suffer from more of these types of infections. Finally, the pivotal role of the T cell in orchestrating the direction of the immune response means that disruptions to the performance of this cell type can have wide-ranging effects, including depressed antibody production, dysregulation of cytokine expression, and impaired cellular cytotoxicity. In some instances, such as when T- and B-cell responses to self are not properly regulated, autoimmunity can become the primary symptom.

The first part of this section on primary immunodeficiency diseases looks at defects within adaptive immunity, starting with the most extreme cases, characterized by defects to T cells, B cells, or both. This is followed by a discussion of disruptions to innate responses, including cells of the myeloid lineage, receptors important for innate immunity, and complement defects. The autoimmune consequences stemming from dysregulation of the immune system are also described. Finally, we look at the current treatment options available to affected individuals and the use of animal models of primary immunodeficiency in basic immunology research.

OVERVIEW FIGURE 18-2

Primary Immunodeficiencies Result from Congenital Defects in Specific Cell Types



Orange = phagocytic deficiencies, green = humoral deficiencies, red = cell-mediated deficiencies, pink = regulatory cell deficiencies, and purple = combined immunodeficiencies, or defects that affect more than one cell lineage. APECED = *a*utoimmune *p*olyendo*c*rinopathy and *e*ctodermal *d*ystrophy. IPEX = *i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked syndrome.

TABLE 18-1 Some primary human immunodeficiency diseases and underlying genetic defects

Immunodeficiency disease	Specific defect	Impaired function	Inheritance mode*
Severe combined immunodeficiency (SCID)	*RAG1/RAG2* deficiency	No TCR or Ig gene rearrangement	AR
	ADA deficiency	Toxic metabolite in T and B cells	AR
	PNP deficiency		AR
	JAK-3 deficiency	Defective signals from IL-2, -4, -7, -9, -15, -21	AR
	IL-2Rγ deficiency		XL
	ZAP-70 deficiency	Defective signal from TCR	AR
Bare-lymphocyte syndrome (BLS)	Defect in class II MHC gene promoter	No class II MHC molecules	AR
Wiskott-Aldrich syndrome (WAS)	Cytoskeletal protein (WASP)	Defective T-cells and platelets	XL
Mendelian susceptibility to mycobacterial diseases (MSMD)	IFN-γR IL-12/IL-12R STAT1	Impaired immunity to mycobacteria	AR or AD
DiGeorge syndrome	Thymic aplasia	T-cell development	AD
Gammaglobulinemias	X-linked agammaglobulinemia	Bruton's tyrosine kinase (Btk); no mature B cells	XL
	X-linked hyper-IgM syndrome	Defective CD40 ligand	XL
	Common variable immunodeficiency	Low IgG, IgA; variable IgM	Complex
	Selective IgA deficiency	Low or no IgA	Complex
Chronic granulomatous disease	$gp91^{phox}$	No oxidative burst for phagocytic killing	XL
	$p67^{phox}$, $p47^{phox}$, $p22^{phox}$		AR
Chediak-Higashi syndrome	Defective intracellular transport protein (LYST)	Inability to lyse bacteria	AR
Leukocyte adhesion defect	Defective integrin β2 (CD18)	Leukocyte extravasation	AR
Autoimmune polyendocrinopathy and ectodermal dystrophy (APECED)	AIRE defect	T-cell tolerance	AR
Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome	FoxP3 defect	Absence of T_{REG} cells	XL

* AR = autosomal recessive; AD = autosomal dominant; XL= X linked; "Complex" inheritance modes include conditions for which precise genetic data are not available and that may involve several interacting loci.

TABLE 18-2 Patterns of infection and illness associated with primary immunodeficiency diseases

Disorder	Disease	
	OPPORTUNISTIC INFECTIONS	OTHER SYMPTOMS
Antibody	Sinopulmonary (pyogenic bacteria) Gastrointestinal (enterovirus, giardia)	Autoimmune disease (autoantibodies, inflammatory bowel disease)
Cell-mediated immunity	Pneumonia (pyogenic bacteria, *Pneumocystis carinii*, viruses) Gastrointestinal (viruses), mycoses of skin and mucous membranes (fungi)	
Complement	Sepsis and other blood-borne infections (streptococci, pneumococci, neisseria)	Autoimmune disease (systemic lupus erythematosus, glomerulonephritis)
Phagocytosis	Skin abscesses, reticuloendothelial infections (staphylococci, enteric bacteria, fungi, mycobacteria)	
Regulatory T cells	N/A	Autoimmune disease

Source: Adapted from H. M. Lederman, 2000, The clinical presentation of primary immunodeficiency diseases, Clinical Focus on Primary Immune Deficiencies. *Towson, MD: Immune Deficiency Foundation* ***2****(1):1.*

Combined Immunodeficiencies Disrupt Adaptive Immunity

Among the most severe forms of inherited immunodeficiency are a group of disorders termed ***c*ombined *i*mmuno*d*eficiences (CIDs)**: diseases resulting from an absence of T cells or significantly impaired T-cell function, combined with some disruption of antibody responses. Defects within the T-cell compartment generally also affect the humoral system because T_H cells are typically required for complete B-cell activation, antibody production, and isotype switching. Therefore, some depression in the level of one or more antibody isotypes and an associated increase in susceptibility to bacterial infection are common with CIDs. T-cell impairment can lead to a reduction in both delayed-type hypersensitivity responses and cell-mediated cytotoxicity, resulting in increased susceptibility to almost all types of infectious agents, but especially viruses, protozoa, and fungi. For instance, infections with species of *Mycobacteria* are common in CID patients, reflecting the importance of T cells in eliminating intracellular pathogens. Likewise, viruses that are otherwise rarely pathogenic (such as cytomegalovirus or even live, attenuated measles vaccine) may be life threatening for individuals with CIDs. The following section first discusses the most severe CIDs, such as when there is an absence of both T and B cells, followed by less severe forms of the disease, in which more minor disruptions to particular components of the T- and B-cell compartments are observed.

Severe Combined Immunodeficiency (SCID)

The most extreme forms of CID make up a family of disorders termed ***s*evere *c*ombined *i*mmuno*d*eficiency (SCID)**. These stem from genetic defects that lead to a virtual or absolute lack of functional T cells in the periphery. As a general rule, these defects target steps that occur early in T-cell development or that affect the stem cells that feed the lymphoid lineage. The four general categories of events that have been found to result in SCID include the following:

1. Defective cytokine signaling in T-cell precursors, caused by mutations in certain cytokines, cytokine receptors, or regulatory molecules that control their expression
2. Premature death of the lymphoid lineage due to accumulation of toxic metabolites, caused by defects in the purine metabolism pathways
3. Defective V(D)J rearrangement in developing lymphocytes, caused by mutations in the genes for RAG1 and RAG2, or other proteins involved in the rearrangement process
4. Disruptions in pre-TCR or TCR signaling during development, caused by mutations in tyrosine kinases, adapter molecules, downstream messengers, or transcription factors involved in TCR signaling

Depending on the underlying genetic defect, an individual with SCID may have a loss of only T cells (T^-B^+) or both T and B cells (T^-B^-). In either case, both cellular and humoral immunity are either severely depressed or absent. Clinically, SCID is characterized by a very low number of circulating lymphocytes and a failure to mount immune responses mediated by T cells. In many cases, the thymus will not fully develop without a sufficient number of T cells, and the few circulating T cells present in some SCID patients

often do not respond to stimulation by mitogens, indicating that they cannot proliferate in response to antigens. In many cases, myeloid and erythroid cells (red-blood-cell precursors) appear normal in number and function, indicating that only lymphoid cells are affected.

Infants born with SCID experience severe recurrent infections that, without early, aggressive treatment, can quickly prove fatal. Although both the T and B lineages may be affected, the initial manifestation in these infants is typically infection by fungi or viruses that are normally dealt with by cellular immune responses. This is because antibody deficits can be masked in the first few months of life by the presence of passive antibodies derived from transplacental circulation or breast milk. Infants with SCID often suffer from chronic diarrhea, recurrent respiratory infections, and a general failure to thrive. The life span of these children can be prolonged by preventing contact with all potentially harmful microorganisms—for example, by confinement in a sterile atmosphere. However, extraordinary effort is required to prevent contact with all opportunistic microorganisms; any object, including food, that comes in contact with the sequestered SCID patient must first be sterilized. Such isolation is feasible only as a temporary measure, pending replacement therapy treatments and/or bone marrow transplantation (more on these below).

The immune system is so compromised in SCID patients that common microbes and even live-attenuated vaccines can cause persistent infection and life-threatening disease. For this reason, it is important to diagnose SCID early, especially prior to the administration of live vaccines, such as the rotavirus vaccine, which is recommended at 2 months of age (see Chapter 17). A screening test for SCID has been developed that utilizes the standard blood samples collected from neonates via heel or finger pricks. This rapid *p*olymerase *c*hain *r*eaction (PCR)-based assay looks for evidence of gene recombination as in excised DNA from the TCR or BCR locus, called *T*-cell *r*eceptor *e*xcision *c*ircles (TRECs) and κ-*d*eleting *r*ecombination *e*xcision *c*ircles (KRECs). In 2010, recommendations to screen every newborn for SCID were approved. To date, approximately half of the babies born in the United States receive standard newborn screening for SCID, before live vaccines are administered and when the implementation of aggressive therapy is most beneficial.

Deficiency in cytokine signaling is at the root of the most common forms of SCID, and defects in the gene encoding the common gamma (γ) chain of the IL-2 receptor (*IL2RG*; see Figure 4-8) are the most frequent culprits. This particular form of immunodeficiency is often referred to as *X*-linked *SCID* (or SCIDX1) because the affected gene is located on the X chromosome, and the disorder is thus more common in males. Defects in this chain impede signaling not only through IL-2R but also through receptors for IL-4, -7, -9, -15, and -21, all of which use this chain in their structures. This leads to widespread defects in B-, T-, and NK-cell development. Although this chain was first identified as a part of the IL-2 receptor, impaired IL-7 signaling is likely the source

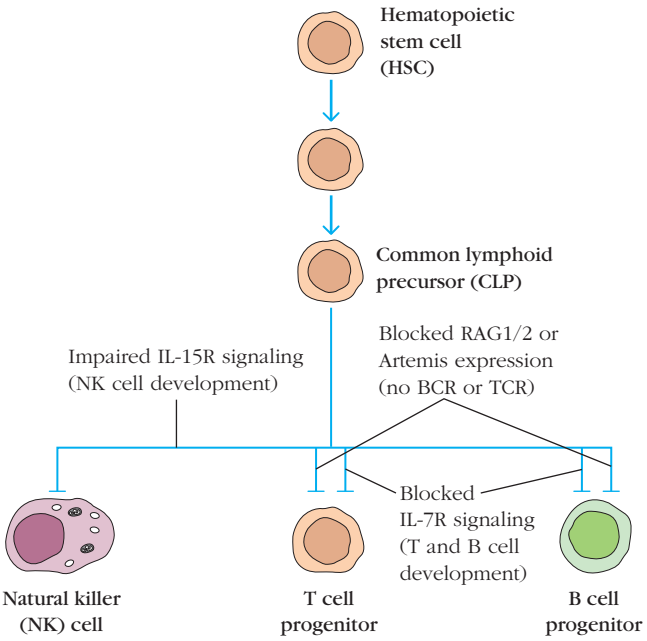


FIGURE 18-3 Defects in lymphocyte development and signaling can lead to severe combined immunodeficiency (SCID). SCID may result from defects in the recombination-activating genes (*RAG1* and *RAG2*) or the DNA excision-repair pathway (e.g., *Artemis*) required for synthesis of the functional immunoglobulins and T-cell receptors in developing lymphocytes. Likewise, defects in the common γ chain of receptors for IL-2, -4, -7, -9, and -15, required for the hematopoietic development of lymphocytes, or JAK-3, which transduces these signals (not shown), can also lead to SCID.

of both T-and B-cell developmental defects, while lack of IL-15 signaling is believed to account for the block to NK cells (Figure 18-3). Deficiency in the kinase JAK-3, which associates with the cytoplasmic region of the common gamma (γ) chain, can produce a phenotype similar to X-linked SCID, as this enzyme is required for the intracellular signaling cascade utilized by all of these cytokine receptors (see Chapter 4).

Defects in the pathways involved in the recombination events that produce immunoglobulin and T-cell receptors highlight the importance of early signaling through these receptors for lymphocyte survival. Mutations in the *r*ecombinase *a*ctivating *g*enes (*RAG1* and *RAG2*) and genes encoding proteins involved in the DNA excision-repair pathways employed during gene rearrangement (e.g., *Artemis*) can also lead to SCID (see Figure 18-3). In these cases, production of antigen-specific receptors is blocked at the pre-T- and pre-B-cell receptor stages of development, leading to a virtual absence of functioning T and B cells, while leaving the numbers and function of NK cells largely intact (see Clinical Focus Box 7-3).

Another relatively common defect resulting in SCID is **adenosine deaminase (ADA) deficiency**. Adenosine deaminase catalyzes conversion of adenosine or deoxyadenosine to inosine or deoxyinosine, respectively. Its deficiency results in

the intracellular accumulation of toxic adenosine metabolites, which interferes with purine metabolism and DNA synthesis. This housekeeping enzyme is found in all cells, so these toxic compounds also produce neurologic and metabolic symptoms, including deafness, behavioral problems, and liver damage. Defects in T, B, and NK cells are due to toxic metabolite-induced apoptosis of lymphoid precursors in primary lymphoid organs. Deficiency in another purine salvage pathway enzyme, *p*urine *n*ucleoside *p*hosphorylase (PNP), produces a similar phenotype via much the same mechanism.

In some instances, the genetic defects associated with SCID lead to perturbations in hematopoiesis. In ***r*eticular *d*ysgenesis (RD)**, the initial stages of hematopoietic cell development are blocked by defects in the *a*denylate *k*inase *2* gene (*AK2*), favoring apoptosis of myeloid and lymphoid precursors and resulting in severe reductions in circulating leukocytes (see Figure 18-2). The resulting general failure leads to impairment of both innate and adaptive immunity, resulting in susceptibility to infection by all types of microorganisms. Without aggressive treatment, babies with this very rare form of SCID usually die in early infancy from uncontrolled infection.

MHC Defects That Can Resemble SCID

A failure to express MHC molecules can lead to general failures of immunity that *resemble* SCID without directly impacting lymphocytes themselves. For example, without class II MHC molecules, positive selection of $CD4^+$ T cells in the thymus is impaired, and with it, peripheral T helper cell responses are impaired. This type of immunodeficiency is called **bare-lymphocyte syndrome** and is the topic of Clinical Focus Box 8-4. The important and ubiquitous role of class I MHC molecules is highlighted in patients with defective class I expression. This rare immunodeficiency disorder can be caused by mutations in the TAP genes, which are vital to antigen processing and presentation by class I MHC molecules (see Figure 8-17). This defect, which typically allows for some residual expression of class I molecules, results in impaired positive selection of $CD8^+$ T cells, depressed cell-mediated immunity, and heightened susceptibility to viral infection.

Developmental Defects of the Thymus

Some immunodeficiency syndromes affecting T cells are grounded in failure of the thymus to undergo normal development. These thymic malfunctions can have subtle to profound outcomes on T-cell function, depending on the nature of the defect. **DiGeorge syndrome (DGS)**, also called velocardiofacial syndrome, is one example. This disorder typically results from various deletions in a region on chromosome 22 containing up to 50 genes, with the *T-box* transcription factor (*TBX1*) thought to be most influential. This transcription factor is highly expressed during particular stages of embryonic development, when facial structures, heart, thyroid, parathyroid, and thymus tissues are forming (Figure 18-4). For this reason, the syndrome is sometimes also called the third and fourth pharyngeal pouch syndrome. Not surprisingly, DGS patients present with symptoms of immunodeficiency, hypoparathyroidism, and congenital heart anomalies, where the latter are typically the most critical. Although most DGS sufferers show some degree of immunodeficiency, the degree varies widely. In very rare cases of complete DGS, where no thymic tissue develops, severe depression of T-cell numbers and poor antibody responses due to lack of T-cell help leave patients susceptible to all types of opportunistic pathogens. Thymic transplantation and passive antibody treatment can be of value to these individuals, although severe heart disease can limit long-term survival even when the immune defects are corrected. In the majority of DGS patients, in which some residual thymic tissue develops and functional T cells are found in the periphery, treatments to avoid bacterial infection, such as antibiotics, are often sufficient to compensate for the immune defects.

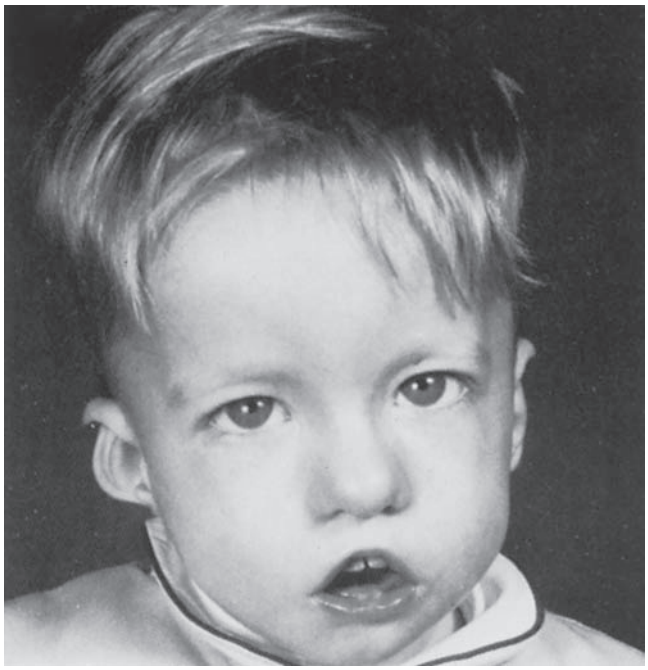


FIGURE 18-4 A child with DiGeorge syndrome showing characteristic dysplasia of ears and mouth and abnormally wide distance between the eyes. *[R. Kretschmer et al., 1968,* New England Journal of Medicine **279:***1295; photograph courtesy of F. S. Rosen.]*

Wiskott-Aldrich Syndrome (WAS)

Although SCID is caused by genetic defects that result in the loss of T cells or major T-cell impairment, a number of other CIDs can result from less severe disruptions to T-cell function. The defect in patients suffering from ***W*iskott-*A*ldrich *s*yndrome (WAS)** occurs in an X-linked gene named for this disease (*WASP*), which encodes a cytoskeletal protein highly

expressed in hematopoietic cells (see Table 18-1). The WAS protein (WASP) is required for assembly and reorganization of actin filaments in cells of the hematopoietic lineage, events critical to proper immune synapse formation and intracellular signaling. Clinical manifestations, which usually appear early in the first year of life, vary widely and severity depends on the specific mutation, but eczema and thrombocytopenia (low platelet counts and smaller than normal platelets, which can result in near fatal bleeding) are both common. Humoral defects, including lower than normal levels of IgM, as well as impaired cell-mediated immunity, are also common features. WAS patients often experience recurrent bacterial infections, especially by encapsulated strains such as *S. pneumoniae, H. influenzae* type b (Hib), and *S. aureus*. As the disease develops, autoimmunity and B-cell malignancy are not uncommon, suggesting that regulatory T-cell functions are also impaired. Mild forms of the disease can be treated by targeting the symptoms—transfusions for bleeding and passive antibodies or antibiotics for bacterial infections—but severe cases and long-term corrective measures require hematopoietic stem cell transfer.

Hyper IgM Syndrome

An inherited deficiency in CD40 ligand (CD40L or CD154) leads to impaired communication between T cells and *a*ntigen-*p*resenting *c*ells (APCs), highlighting the role of this surface molecule in this costimulatory process. In this X-linked disorder, T_H cells fail to express functional CD40L on their plasma membrane, which typically interacts with the CD40 molecule present on B cells and *d*endritic *c*ells (DCs). This costimulatory engagement is required for APC activation, and its absence in B cells interferes with class switching, B-cell responses to T-dependent antigens, and the production of memory cells (Figure 18-5). The B-cell response to T-*independent* antigens, however, is unaffected, accounting for the presence of IgM antibodies in these patients, which range from normal to high levels and give the disorder its common name, **hyper IgM syndrome (HIM)**. Without class switching or hypermutation, patients make very low levels of all other antibody isotypes and fail to produce germinal centers during a humoral response, which highlights the role of the CD40-CD40L interaction in the generation of these structures. Because CD40-CD40L interactions are also required for DC maturation and IL-12 secretion, defects in this pathway result in increased susceptibility to intracellular pathogens. Affected children therefore suffer from a range of recurrent infections, especially in the respiratory tract. Although this form of immunodeficiency results in alterations in antibody production and presents with symptoms similar to HIM variants seen in the next section on antibody deficiencies, it is classified as a CID. This is because the underlying deficiency is present in T cells, leading to a secondary defect in B-cell activation. Several other recessively inherited variants of HIM syndrome have been linked to downstream events, such as mutations in one of the enzymes involved in class switching, with the net result of depressed production of all antibody isotypes except IgM.

Hyper IgE Syndrome (Job Syndrome)

Another primary immunodeficiency is characterized by skin abscesses, recurrent pneumonia, eczema, and elevated levels of IgE, accompanied by facial abnormalities and bone fragility. This multisystem disorder, known as **hyper IgE syndrome (HIE)**, is most frequently caused by an autosomal dominant mutation in the *STAT3* gene. This gene is involved in the intracellular signaling cascade induced by IL-6 and TGF-β receptor ligation, and is important for T_H17 cell differentiation (see Figure 11-11). Its absence is thought to lead to dysregulation of T_H pathway development and may be the reason for overproduction of IgE. Patients with Job syndrome have lower-than-normal levels of circulating T_H17 cells, and naïve cells isolated from these individuals are not capable of producing IL-17 or IL-22 in response to antigenic stimulation. Depressed T_H17 responses, which are important for clearance of fungal and extracellular bacterial infections, explain the susceptibility of these patients to *C. albicans* and *S. aureus*. STAT3 defects also inhibit IL-10 signaling and the development of regulatory T cells, which is evident in the reduction of induced T_{REG} cells in these patients. Although STAT3 is involved in the signal transduction of many cytokines and therefore could play a role in the elevation of IgE in these patients, no clear mechanism for this has been defined.

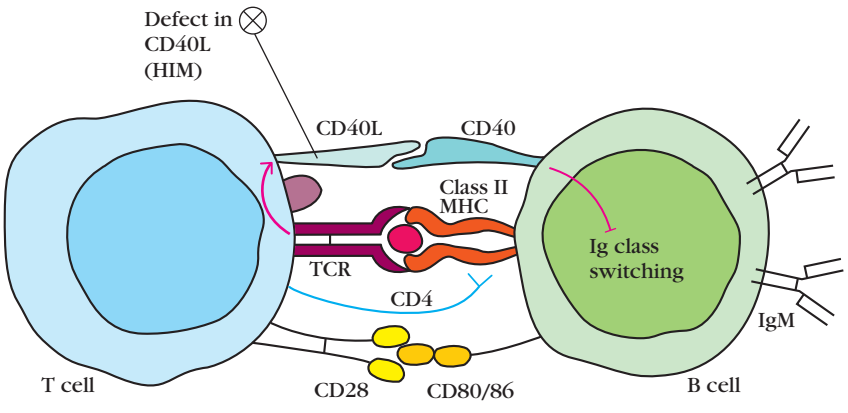


FIGURE 18-5 Defects in components of APC-T cell interactions can give rise to primary immunodeficiency. Defects in CD40/CD40L costimulation between T cells and APCs lead to a block in APC maturation. In B cells, this manifests as a defect in class switching, leading to elevated levels of IgM and no other isotypes (called hyperIgM syndrome, or HIM). In DCs, this blocks maturation and the secretion of costimulatory cytokines, such as IL-12, which are important for T-cell differentiation.

B-Cell Immunodeficiencies Exhibit Depressed Production of One or More Antibody Isotypes

Immunodeficiency disorders caused by B-cell defects make up a diverse spectrum of diseases ranging from the complete absence of mature recirculating B cells, plasma cells, and immunoglobulin, to the selective absence of only certain classes of immunoglobulins. Patients with inherited B-cell defects are usually subject to recurrent bacterial infections but display normal immunity to most viral and fungal infections because the T-cell branch of the immune system is largely unaffected. In patients with these types of immunodeficiencies, the most common infections are caused by encapsulated bacteria such as staphylococci, streptococci, and pneumococci, because antibody is critical for the opsonization and clearance of these organisms. Although the underlying defects have been identified for some of these conditions, several of the more common deficiencies, such as common variable immunodeficiency and selective IgA deficiency, appear to involve multiple genes and a continuum of phenotypes.

X-Linked Agammaglobulinemia

*X-l*inked *a*gammaglobulinemia (X-LA), or Bruton's hypogammaglobulinemia, is characterized by extremely low IgG levels and by the absence of other immunoglobulin classes. Babies born with this disorder have virtually no peripheral B cells (< 1%) and suffer from recurrent bacterial infections. X-LA is caused by a defect in Bruton's tyrosine kinase (Btk), which is required for signal transduction through the BCR (see Figure 3-28 and Clinical Focus Box 3-2). Without functional Btk, B-cell development in the bone marrow is arrested at the pro-B- to pre-B-cell stage, and the B lymphocytes in these patients remain in the pre-B stage, with heavy chains rearranged but light chains in their germ-line configuration. Present-day use of antibiotics and replacement therapy in the form of passively administered antibodies can make this disease quite manageable.

Common Variable Immunodeficiency Disorders

The defects underlying the complex group of diseases belonging to this category are more different than they are similar. However, sufferers of *c*ommon *v*ariable *i*mmunodeficiency *d*isorders (CVIDs) do share recurrent infection resulting from immunodeficiency, marked by reduction in the levels of one or more antibody isotype and impaired B-cell responses to antigen, all with no other known cause. This condition can manifest in childhood or later in life, when it is sometimes called late-onset hypogammaglobulinemia or, incorrectly, acquired hypogammaglobulinemia. Respiratory tract infection by common bacterial strains is the most common symptom, and can be controlled by administration of immunoglobulin. Most cases of CVID have undefined genetic causes, and most patients have normal numbers of B cells, suggesting that B-cell development is not the underlying defect in most cases. Reflecting the diversity of this set of diseases, inheritance can follow autosomal recessive or autosomal dominant patterns, although most cases are sporadic. Several different proteins involving various steps of the B-cell activation cascade have been implicated in recent years.

Selective IgA Deficiency

A number of immunodeficiency states are characterized by significantly lowered amounts of specific immunoglobulin isotypes. Of these, IgA deficiency is by far the most common, affecting approximately 1 in 700. Individuals with selective IgA deficiency typically exhibit normal levels of other antibody isotypes and may enjoy a full life span, troubled only by a greater-than-normal susceptibility to infections of the respiratory and genitourinary tracts, the primary sites of IgA secretion. Family-association studies have shown that IgA deficiency sometimes occurs in the same families as CVID, suggesting some overlap in causation. The spectrum of clinical symptoms of IgA deficiency is broad; most of those affected are asymptomatic (up to 70%), whereas others may suffer from an assortment of serious complications. Problems such as intestinal malabsorption, allergic disease, and autoimmune disorders can be associated with low IgA levels. The reasons for this variability in the clinical profile are not clear but may relate to the ability of some, but not all, patients to substitute IgM for IgA as a mucosal antibody. The defect in IgA deficiency is related to the inability of IgA-expressing B cells to undergo normal differentiation to the plasma-cell stage. A gene or genes outside of the immunoglobulin gene complex is suspected of being responsible for this fairly common syndrome.

Disruptions to Innate Components May Also Impact Adaptive Responses

Most innate immune defects are caused by problems in the myeloid-cell lineage or in complement (see Figure 18-2). Most of these defects result in depressed numbers of phagocytic cells or defects in the phagocytic process that are manifested by recurrent microbial infection of greater or lesser severity. The phagocytic processes may be faulty at several stages, including cell motility, adherence to and phagocytosis of organisms, and intracellular killing by macrophages.

Leukocyte Adhesion Deficiency

As described in Chapter 3, cell-surface molecules belonging to the integrin family of proteins function as adhesion molecules and are required to facilitate cellular interaction. Three of these, LFA-1, Mac-1, and gp150/95 (CD11a, b, and c, respectively), have a common β chain (CD18) and are variably present on different monocytic cells; CD11a is also expressed on B cells. An immunodeficiency related to dysfunction of the adhesion molecules is rooted in a defect

localized to the common β chain and affects expression of all three of the molecules that use this chain. This defect, called *l*eukocyte *a*dhesion *d*eficiency (LAD), causes susceptibility to infection with both gram-positive and gram-negative bacteria as well as various fungi. Impairment of adhesion of leukocytes to vascular endothelium limits recruitment of cells to sites of inflammation. Viral immunity is somewhat impaired, as would be predicted from the defective T–B-cell cooperation arising from the adhesion defect. LAD varies in its severity; some affected individuals die within a few years, whereas others survive into their forties. The reason for the variable disease phenotype in this disorder is not known.

Chronic Granulomatous Disease

Chronic granulomatous disease (CGD) is the prototype of immunodeficiency that impacts phagocytic function and arises in at least two distinct forms: an X-linked form in about 70% of patients and an autosomal recessive form found in the rest. This group of disorders is rooted in a defect in the *n*icotinamide *a*denine *d*inucleotide *ph*osphate (NADPH) oxidative pathway by which phagocytes generate superoxide radicals and other reactive compounds that kill phagocytosed pathogens. For this reason, CGD patients suffer from infection by bacterial and fungal pathogens, as well as excessive inflammatory responses that lead to the formation of granulomas (a small mass of inflamed tissue). Genetic causes have been mapped to several missing or defective *ph*agosome *ox*idase (phox) proteins that participate in this pathway (see Table 18-1). Standard treatment includes the use of antibiotics and antifungal compounds to control infection. Of late, the addition of IFN-γ to this regimen has been shown to improve CGD symptoms in both humans and animal models. Although the mechanism for this is still debated, in vitro studies have shown that IFN-γ treatment induces TNF-α and the production of *n*itric *o*xide (NO, another oxidative mediator) and enhances the uptake of inflammation-inducing apoptotic cells, which could play a role in inhibiting the formation of granulomas during inflammation in these patients.

Chediak-Higashi Syndrome

This rare autosomal recessive disease is an example of a lysosomal storage and transport disorder. *Chediak-Higashi syndrome* (CHS) is characterized by recurrent bacterial infections as well as defects in blood clotting, pigmentation, and neurologic function. Immunodeficiency hallmarks include neutropenia (depressed numbers of neutrophils) as well as impairments in T cells, NK cells, and granulocytes. CHS is associated with oculocutaneous albinism, or light-colored skin, hair, and eyes, accompanied by photosensitivity. The underlying cause has been mapped to mutations in the *lys*osomal *t*rafficking regulator (*LYST*) gene that cause defects in the LYST protein, which is important for transport of proteins into lysosomes as well as for controlling lysosome size, movement, and function. Disruption to this and related organelles, such as the melanosomes of skin cells (melanocytes), results in enlarged organelles and defective transport functions. Affected phagocytes produce giant granules, a diagnostic hallmark, but are unable to kill engulfed pathogens, and melanocytes fail to transport melanin (responsible for pigmentation). Similar enlarged lysosome-like structures in platelets and nerve cells are also thought to interfere with blood clotting and neurologic function, respectively. Exocytosis pathways are likewise affected, which could account for the defects in killing seen in T_C cells and NK cells, as well as impaired chemotactic responses. Without early antimicrobial therapy followed by bone marrow transplant, patients often die due to opportunistic infection before reaching 10 years of age. However, no therapies are currently available to treat the defects in other cells, so even when immune function is restored, neurologic and other complications continue to progress.

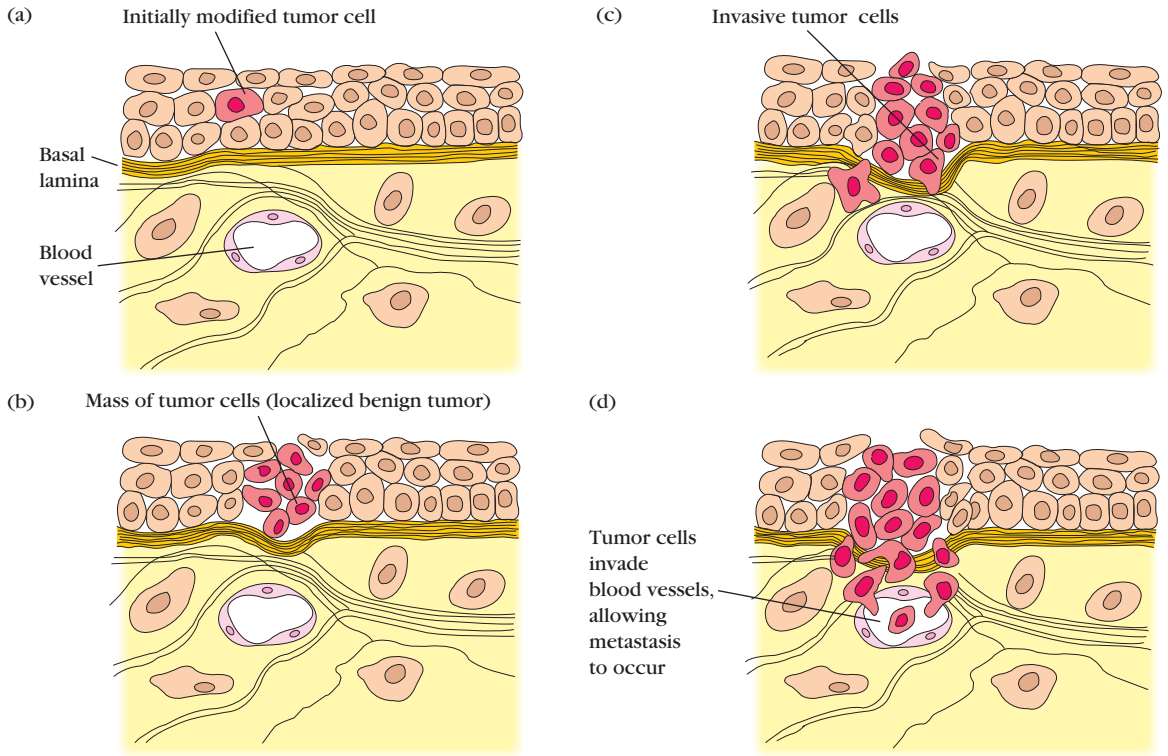
Mendelian Susceptibility to Mycobacterial Diseases

Recently, a set of immunodeficiency disorders has been grouped into a mixed-cell category based on the shared characteristic of single gene (*M*endelian) inheritance of *s*usceptibility to *m*ycobacterial *d*iseases (MSMD). Discovery of the underlying defects in MSMD highlights the connections between innate and adaptive immunity, as well as the key role played by IFN-γ in fighting infection by mycobacteria, intracellular organisms that can cause tuberculosis and leprosy. During natural mycobacterial infection, macrophages in the lung or DCs in the draining lymph node recognize these bacteria through *p*attern *r*ecognition *r*eceptors (PRRs), such as TLR2 and TLR4, which trigger migration to lymph nodes followed by APC activation and differentiation. In the presence of strong costimulation, such as engagement of CD40 on the APC with CD40L on the T cell, these activated APCs produce significant amounts of IL-12 and IL-23, which can bind to their receptors on T_H cells and NK cells, respectively. This leads to production of cytokines such as IFN-γ, IL-17, and TNF-α. In a positive feedback loop, T_H cells in this environment differentiate into T_H1-type cells, further producers of IFN-γ. Upon binding to the IFN-γR on APCs, this cytokine induces a signaling cascade, involving Janus kinases and STAT1, which results in enhanced phagocytosis and optimal phago-lysosomal fusion, effectively killing engulfed bacteria.

This story of mycobacterial infection makes the defective genes or proteins now implicated in MSMD no great surprise (Figure 18-6). To date, six genes within the IFN-γ/IL-12/IL-23 pathways have been linked to MSMD, including those encoding IL-12, IL-12R, IFN-γR (both chains), STAT1, and a kinase downstream of IL-12 signaling (TYK2). Another gene linked to MSMD, called *NEMO*, controls the behavior of the signal transduction molecule NF-κB (see Figure 3-17), which can affect CD40-dependent induction of IL-12. However, most mutations in *NEMO* lead to more widespread immune defects and susceptibility patterns than are seen in typical MSMD patients. The specific gene and type of mutation

OVERVIEW FIGURE 19-1

Tumor Growth and Metastasis



(a) A single cell develops altered growth properties at a tissue site. (b) The altered cell proliferates, forming a mass of localized tumor cells, or a benign tumor. (c) The tumor cells become progressively more invasive, spreading to the underlying basal lamina. The tumor is now classified as malignant. (d) The malignant tumor metastasizes by generating small clusters of cancer cells that dislodge from the tumor and are carried by the blood or lymph to other sites in the body. *[Adapted from J. Darnell et al., 1990,* Molecular Cell Biology, *2nd ed., Scientific American Books.]*

in the United States. Leukemias proliferate as single detached cells, whereas lymphomas and myelomas tend to grow as tumor masses. **Sarcomas**, which arise less frequently (around 1% of the incidence of cancer in the United States), are derived from mesodermal connective tissues, such as bone, fat, and cartilage.

Historically, the leukemias were classified as acute or chronic according to the clinical progression of the disease. The acute leukemias appeared suddenly and progressed rapidly, whereas the chronic leukemias were much less aggressive and developed slowly as mild, barely symptomatic diseases. These clinical distinctions apply to untreated leukemias; with current treatments, the acute leukemias often have a good prognosis, and permanent remission is possible. Now the major distinction between acute and chronic leukemias is the maturity of the cell involved. Acute leukemias tend to arise in less mature cells, whereas chronic leukemias arise in mature cells, although each can arise from lymphoid or myeloid lineages. The acute leukemias include **acute lymphocytic leukemia (ALL)** and **acute myelogenous leukemia (AML)**. These diseases can develop at any age and have a rapid onset. The chronic leukemias include **chronic lymphocytic leukemia (CLL)** and **chronic myelogenous leukemia (CML)**, which develop more slowly and are seen primarily in adults.

Malignant Transformation of Cells

Much has been learned about cancer from in vitro studies of primary cells. Treatment of normal cultured cells with specific chemical agents, irradiation, and certain viruses can alter their morphology and growth properties. In some cases, this process leads to unregulated growth and produces cells capable of growing as tumors when they are injected into animals. Such cells are said to have undergone **transformation**, or

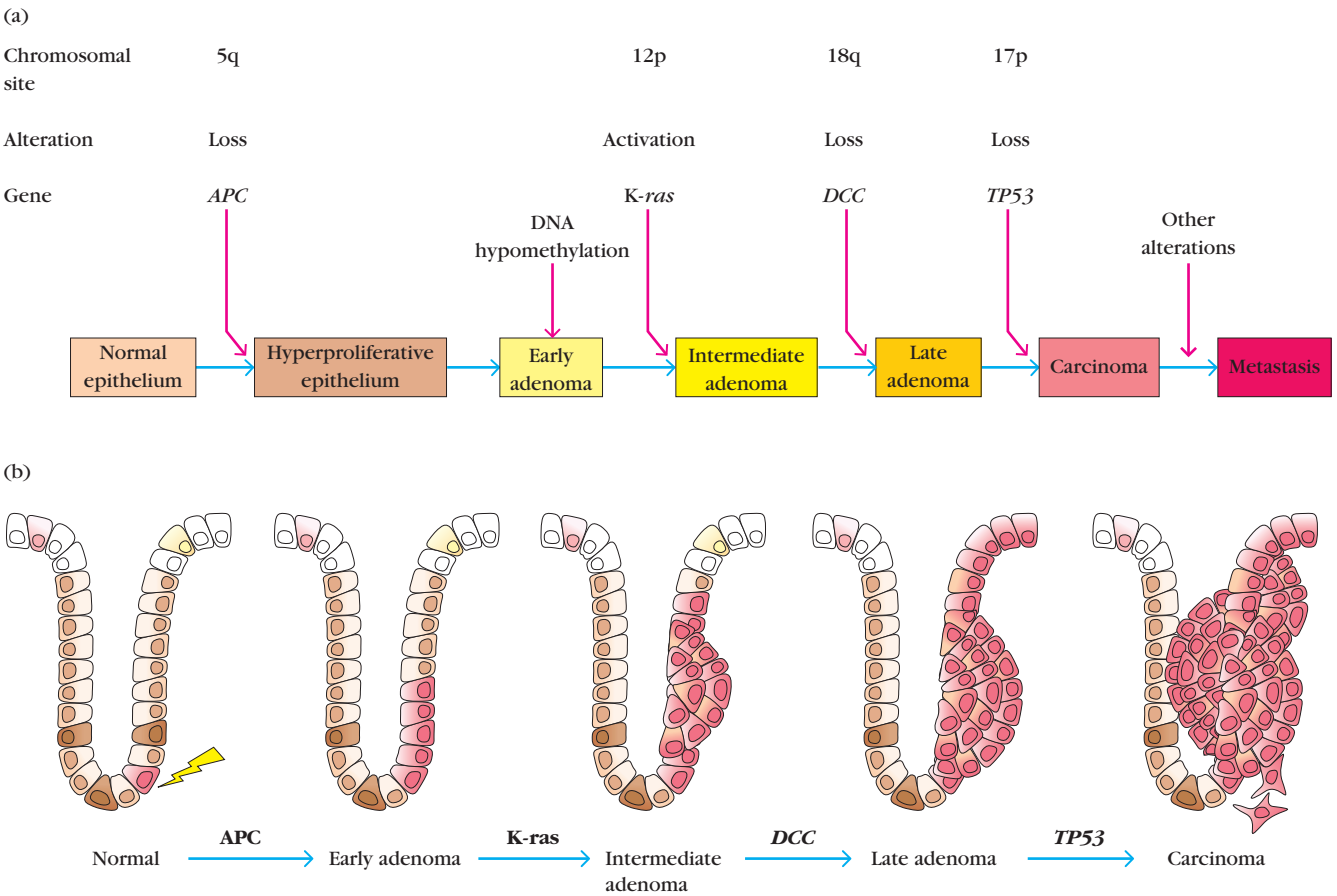


FIGURE 19-4 Model of sequential genetic alterations leading to metastatic colon cancer. Each of the stages indicated in (a) is morphologically distinct, as illustrated in (b), allowing researchers to determine the sequence of genetic alterations. In this sequence, benign colorectal polyps progress to carcinoma following mutations resulting in the inactivation or loss of three tumor-suppressor genes (*APC*, *DCC*, and *TP53*) and the activation of one oncogene linked to cellular proliferation (*K-ras*). *[(a) Adapted from B. Vogelstein and K. W. Kinzler, 1993, The multistep nature of cancer,* Trends in Genetics *9:138. (b) Adapted from P. Rizk and N. Barker, 2012, Gut stem cells in tissue renewal and disease: Methods, markers, and myths,* Systems Biology and Medicine ***4:****5, 475–496.]*

cutaneous cells of young children with XP leads to random genomic alterations, including to genes involved in regulating normal cell growth and division. This leads to unregulated growth of some cells, allowing further DNA mutations to occur and promoting the development of neoplasms, such as malignant melanoma or squamous cell carcinoma, the most common forms of skin cancer in XP patients. The mean age of skin cancer in children with XP is age 8, as compared to 60+ years of age in the general population. Figure 19-5 shows a child with the early skin manifestations common to XP.

Accumulating data from several recent studies suggest that within a growing tumor, not all cells have equal potential for unlimited growth. Clinical studies of at least three different types of tumors, including those originating in the gut, brain, and skin, all suggest that a subset of cells within a tumor may be the true engines of tumor growth. This subset (called cancer stem cells) displays true unlimited regenerative potential, and is the major producer of the other cancer cells, populating the mass of the tumor by sharing this unrestrained ability to divide. If these new discoveries prove valid and can be applied more broadly, future therapies will undoubtedly require that we hone in on these rare cancer stem cells, cutting off the source of tumor cell expansion and, potentially, providing hope for cancer eradication.

Tumor Antigens

Neoplastic cells are self cells and thus most of the antigens associated with them are subject to the tolerance-inducing processes that maintain homeostasis and inhibit the development of autoimmunity. However, unique or inappropriately expressed antigens can be found in many tumors and are frequently detected by the immune system. Some of these antigens may be the products of oncogenes, where

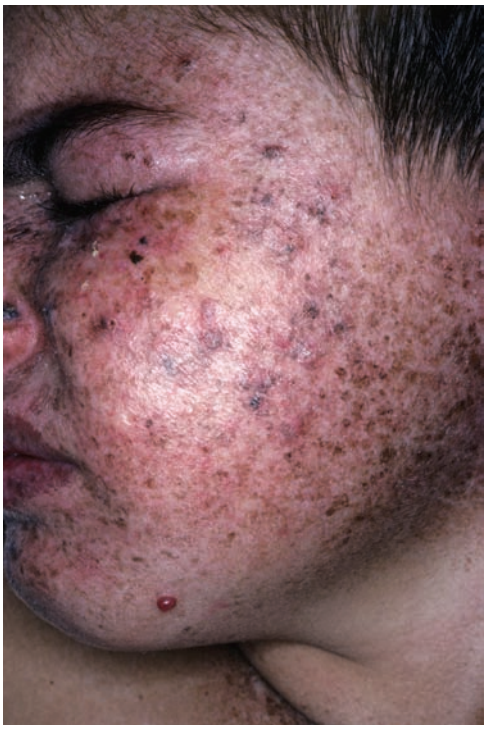


FIGURE 19-5 Xeroderma pigmentosum. This rare autosomal-recessive inherited disorder arises from mutations to one of several genes involved in DNA repair. This disorder is characterized by extreme skin sensitivity to ultraviolet light, abnormal skin pigmentation, and a high frequency of skin cancers, especially on sun-exposed skin of the face, neck and arms. *[CID/ISM/Phototake]*

there is no qualitative difference between the oncogene and proto-oncogene products; instead, it is merely increased levels of the oncogene product that can be recognized by the immune system.

Most tumor antigens give rise to peptides that are recognized by the immune system following presentation by self *m*ajor *h*istocompatibility *c*omplex (MHC) molecules. In fact, many of these antigens have been identified by their ability to induce the proliferation of antigen-specific *c*ytotoxic *T l*ymphocytes (CTLs) or helper T cells. To date, tumor antigens recognized by human T cells fall into one of four groups based on their source:

- Antigens encoded by genes exclusively expressed by tumors (e.g., viral genes)
- Antigens encoded by variant forms of normal genes that are altered by mutation
- Antigens normally expressed only at certain stages of development
- Antigens that are overexpressed in particular tumors

Table 19-3 lists several categories of common antigens associated with tumors. As one can imagine, many clinical research studies aim to utilize these antigens as diagnostic or prognostic indicators, as well as therapeutic targets for tumor elimination. There are two main types of tumor antigens, categorized by their uniqueness: **tumor-specific antigens (TSAs)** and **tumor-associated antigens (TAAs)**. Originally these were designated as *t*ransplantation antigens (TSTAs and TATAs), stemming from studies in which these antigens were discovered by transplanting them into recipient animals, inducing a rejection immune response.

TABLE 19-3 Examples of common tumor antigens

Category	Antigen/s	Associated cancer types
Tumor-Specific Antigens (TSAs)		
Viral	HPV: L1, E6, E7	Cervical carcinoma
	HBV: HBsAg	Hepatocellular carcinoma
	SV40: Tag	Malignant pleural mesothelioma (cancer of the lung lining)
Tumor-Associated Antigens (TAAs)		
Overexpression	MUC1	Breast, ovarian
	MUC13/CA-125	Ovarian
	HER-2/neu	Breast, melanoma, ovarian, gastric, pancreatic
	MAGE	Melanoma
	PSMA	Prostate
	TPD52	Prostate, breast, ovarian
Differentiation Stage	CEA	Colon
	Gp100	Melanoma
	AFP	Hepatocellular carcinoma
	Tyrosinase	Melanoma
	PSA	Prostate
	PAP	Prostate

Abbreviations: SV40, simian virus 40; L, late gene; E, early gene; HBsAg, hepatitis B surface antigen; Tag, large tumor antigen; MUC, mucin; MAGE, melanoma-associated antigen; HER/neu, human epidermal receptor/neurological; PSMA, prostate-specific membrane antigen; TP, tumor protein; PSA, prostate-specific antigen; PAP, prostatic acid phosphatase.

Source: Adapted from Table 1 in J. F. Aldrich, et al., 2010. Vaccines and immunotherapeutics for the treatment of malignant disease, *Clinical and Developmental Immunology.*

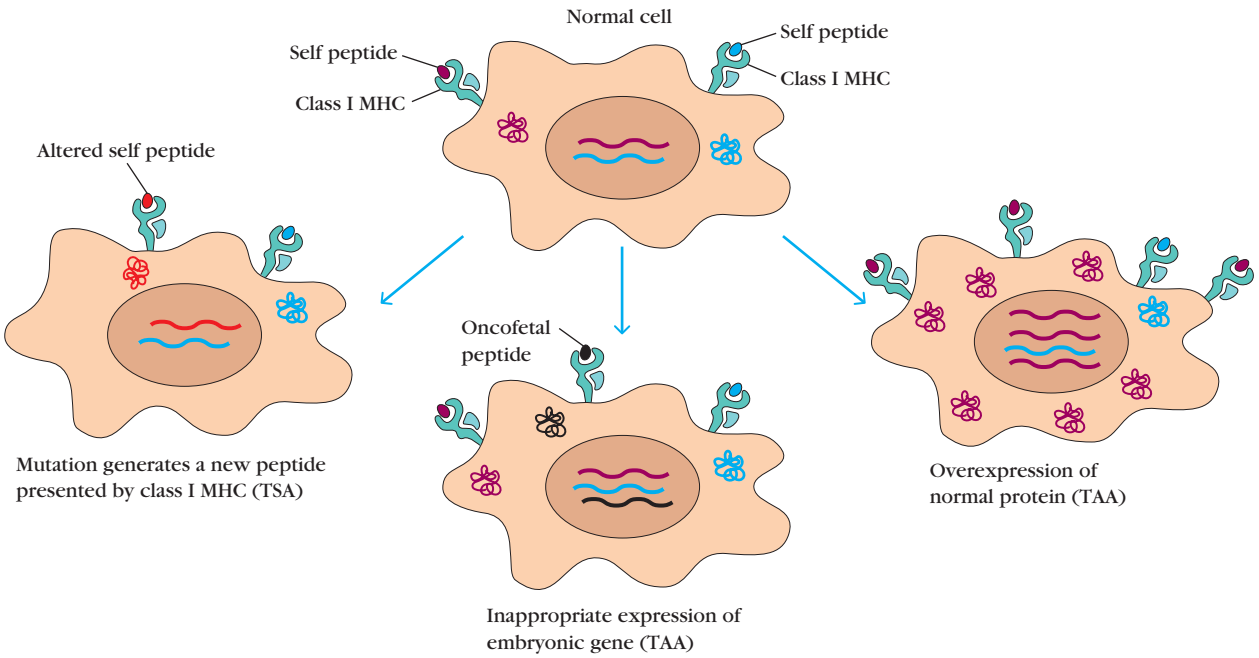


FIGURE 19-6 Different mechanisms generate tumor-specific antigens (TSAs) and tumor-associated antigens (TAAs). TSAs are unique to tumor cells, and can result from DNA mutations that lead to expression of altered self proteins or from expression of viral antigens (not shown) in transformed cells. TAAs are more common and represent normal cellular proteins displaying unique expression patterns, such as an embryonic protein expressed in the adult or overexpression of self proteins. Both types of tumor antigens can be detected by the immune system following presentation in class I MHC.

Tumor-Specific Antigens Are Unique to Tumor Cells

TSAs are unique proteins that may result from mutations in tumor cells that generate altered proteins and, therefore, new antigens. Cytosolic processing of these proteins then gives rise to novel peptides that are presented with class I MHC molecules (Figure 19-6), inducing a cell-mediated response by tumor-specific CTLs. TSAs have been identified on tumors induced with chemical or physical carcinogens, as well as on some virally induced tumors.

Demonstrating the presence of TSAs on spontaneously occurring or chemically induced tumors is particularly difficult. These antigens can be quite diverse and are only identified by their ability to induce T-cell-mediated rejection. The immune response to such tumors typically eliminates all of the tumor cells bearing sufficient numbers of these unique antigens, and thus selects for cells bearing few or none. Nonetheless, experimental methods have been developed to facilitate the characterization of TSAs, which have been shown to differ from normal cellular proteins by as little as a single amino acid. Further characterization of TSAs has demonstrated that many of these antigens are not cell membrane proteins; rather, they are short peptides derived from cytosolic proteins that have been processed and presented together with class I MHC molecules.

In contrast to chemically induced tumors, virally induced tumors express tumor antigens shared by all tumors induced by the same virus, making their characterization simpler. For example, when syngeneic mice are injected with killed cells from a particular polyoma virus-induced tumor, the recipients are protected against subsequent challenge with live cells from any polyoma-induced tumors. Likewise, when lymphocytes are transferred from mice with a virus-induced tumor into normal syngeneic recipients, the recipients reject subsequent transplants of all syngeneic tumors induced by the same virus, suggesting that lymphocytes recognize and kill cells expressing a virally derived TSA.

In some cases, the presence of virus-specific tumor antigens is an indicator of neoplastic transformation. In humans, Burkitt's lymphoma cells have been shown to express a nuclear antigen of the Epstein-Barr virus that may indeed be a tumor-specific antigen for this type of tumor. HPV E6 and E7 proteins are found in more than 80% of invasive cervical cancers, and they provide the clearest example of a virally encoded tumor antigen. In fact, the first clinically approved cancer vaccine is one used to prevent infection with HPV and block the emergence of cervical cancer (see Clinical Focus Box 19-1).

Tumor-Associated Antigens Are Normal Cellular Proteins with Unique Expression Patterns

In contrast to TSAs, TAAs are not unique to the cancer. Instead, these represent normal cellular proteins typically

recognize these cells lacking class I MHC. However, decreased expression of ligands that bind activating receptors on NK cells, also common among tumors, allows these cells to avoid NK cell-mediated killing.

Tumor Cell Subversion of Apoptosis Signals

The up-regulation of anti-apoptotic mediators and the expression of mutated or absent death receptors can lead to tumors that are resistant to programmed cell death signals. As mentioned earlier, faulty DNA repair mechanisms in transformed cells combined with immune-mediated pressures (e.g., selective destruction of cells expressing class I MHC) encourage the accumulation of tumor cells with these types of survival-enhancing mutations. In fact, the absence of MHC molecules on tumor cells is generally an indication of cancer progression and carries a poor prognosis.

Poor Costimulatory Signals Provided by Tumor Cells

As we know from Chapter 11, complete T-cell activation requires two signals: an activating signal, triggered by recognition of a peptide-MHC molecule complex by the T-cell receptor, and a costimulatory signal, triggered by the interaction of CD80/86 (B7) on *a*ntigen-*p*resenting *c*ells (APCs) with costimulatory molecules such as CD28 on T cells. Both signals are needed to induce IL-2 production and proliferation of T cells. By virtue of their status as self cells, tumors have fairly poor immunogenicity and tend to lack costimulatory molecules. Without sufficient numbers of APCs in the immediate vicinity of a tumor and with few stimulators to drive the activation of these cells, responding T cells may receive only a partial activating signal. This can lead to clonal anergy and immune tolerance. In fact, recently approved therapies for treating cancer specifically aim to enhance the costimulation provided to anti-tumor T cells.

Cancer Immunotherapy

Harnessing the immune system to fight cancer is not a new idea. In 1891, a bone carcinoma surgeon named William B. Coley first experimented with this approach, injecting bacteria directly into the inoperable tumor of one of his patients. This was an era prior to the development of chemotherapy or radiation treatment for cancer, and clinicians then had few choices. Based on success in this initial experimental treatment, Coley and other physicians continued this form of immunotherapy for many years, using bacteria or bacterial products that became known as "Coley's Toxins" to treat aggressive cancers. Published reports of remission and even elimination of tumors using this technique, however, met with much skepticism. This treatment was later replaced with chemo- and radiotherapy. Nonetheless, today we believe that Coley's observations were largely sound. His results were likely due to a boost to the patient's anticancer immune response as a result of a concurrent infection or presence of immunostimulatory bacterial products.

Present-day cancer treatment can take many forms. Beyond surgery and radiation treatment, which are most often employed in cases of larger, more discrete tumors, drug therapies can be used to target residual tumor cells and to attack dispersed cancers. Drug therapy for cancer falls loosely into four categories:

- Chemotherapies, aimed at blocking DNA synthesis and cell division
- Hormonal therapies, which interfere with tumor-cell growth
- Targeted therapies, such as small molecule inhibitors of cancer
- Immunotherapies, which induce or enhance the anti-tumor immune response

We will focus our attention here on immune-based therapies. These are designed to help eliminate a tumor by reviving, initiating, or supplementing the in vivo anti-tumor immune response or by neutralizing inhibitory pathways. Challenges in determining the efficacy of specific immunotherapies in clinical settings include the range of cancer cell types, tumor sizes, locations, and stages of disease, as well as questions of optimal dosing and schedule of treatment. The following sections describe several immunotherapeutic agents that have been licensed for use in humans, as well as some novel approaches that may yield clinically useful products to fight cancer in the future.

Monoclonal Antibodies Can Be Targeted to Tumor Cells

*M*onoclonal *anti*b*o*dies (mAbs) (see Clincal Focus Box 13-1 and Chapter 20) have long been used as experimental immunotherapeutic agents for treating cancer. At present, approximately 12 different mAbs are licensed for the treatment of cancer. Table 19-4 lists many of these, as well as the cancers for which they are approved. These mAbs may be used unmodified or can be conjugated with an agent to increase their efficacy. For instance, toxins, chemical agents, and radioactive particles can be attached to a mAb, which then delivers the conjugated substance to the target cell.

In one early success of mAb treatment, R. Levy and his colleagues successfully treated a 64-year-old man with terminal B-cell lymphoma that had metastasized to the liver, spleen, bone marrow, and peripheral blood. Because this was a B-cell cancer, the membrane-bound antibody on all the cancerous cells had the same idiotype (antigenic specificity). By the procedure outlined in Figure 19-9, these researchers produced mouse mAb specific for the B-lymphoma idiotype. When this mouse monoclonal anti-idiotype antibody was injected into the patient, it bound specifically to only the B-lymphoma cells that expressed that particular idiotype immunoglobulin. Since B-lymphoma cells are susceptible to complement-mediated lysis, the mAb activated the complement system and lysed the lymphoma cells without harming

TABLE 19-4 Monoclonal antibodies approved by the FDA and licensed for cancer treatment

mAb name	Trade name	Target	Used to treat	Approved in:
Rituximab	Rituxan	CD20	Non-Hodgkin's lymphoma Chronic lymphocytic leukemia (CLL)	1997 2010
Trastuzumab	Herceptin	HER2	Breast cancer Stomach cancer	1998 2010
Gemtuzumab ozogamicin[2]	Mylotarg	CD33	Acute myelogenous leukemia (AML)	2000[1]
Alemtuzumab	Campath	CD52	CLL	2001
Ibritumomab tiuxetan[2]	Zevalin	CD20	Non-Hodgkin's lymphoma	2002
^{131}I-Tositumomab[2]	Bexxar	CD20	Non-Hodgkin's lymphoma	2003
Cetuximab	Erbitux	EGFR	Colorectal cancer Head and neck cancers	2004 2006
Bevacizumab	Avastin	VEGF	Colorectal cancer Non-small cell lung cancer Breast cancer Glioblastoma and kidney cancer	2004 2006 2008 2009
Panitumumab	Vectibix	EGFR	Colorectal cancer	2006
Ofatumumab	Arzerra	CD20	CLL	2009
Denosumab	Xgeva	Rank ligand	Cancer spread to bone	2010
Ipilimumab	Yervoy	CTLA-4	Melanoma	2011
Brentuximab vedotin[2]	Adcetris	CD30	Hodgkin's lymphoma and one type of non-Hodgkin's lymphoma	2011

[1]General approval withdrawn in 2010 and now used only as a part of ongoing clinical trials

[2]Conjugated monoclonal antibodies

Source: American Cancer Society, www.cancer.org; and Table 2 from J. F. Aldrich et al., 2010, Vaccines and immunotherapeutics for the treatment of malignant disease, Clinical and Developmental Immunology, *doi:10.1155/2010/697158.*

other cells. After four injections with this anti-idiotype mAb, the tumors began to shrink and the patient entered an unusually long period of remission.

A custom approach targeting idiotypes like this is very costly and requires a specific reagent for each lymphoma patient. A more general mAb therapy for B-cell lymphoma is based on the fact that most B cells, whether normal or cancerous, bear lineage-distinctive antigens. For example, mAbs that target the B-cell marker CD20, such as Rituximab, are widely used to treat non-Hodgkin's lymphoma.

Some of the mAbs in clinical use can be coupled with radioactive isotopes, chemotherapy drugs, or potent toxins of biological origin. In such "guided missile" therapies, the toxic agents are delivered specifically to tumor cells. This ideally focuses the toxic effects on the tumor and spares normal tissues. Reagents known as **immunotoxins** have been constructed by coupling the inhibitor chain of a toxin (e.g., diphtheria toxin) to an antibody against a tumor-specific or tumor-associated antigen. In vitro studies have demonstrated that these "magic bullets" can kill tumor cells without harming normal cells, although none have yet been licensed for clinical use. Ibritumomab tiuxetan and ^{131}I-tositumomab are both examples of licensed radioisotope-conjugated mAbs for treating cancer. Each delivers a dose of radiation to cells bearing the CD20 cell-surface receptor, for which the mAb is specific, and can be used for the treatment of non-Hodgkin's lymphoma.

A variety of tumors express significantly increased levels of growth factors or their receptors, which are promising targets for anti-tumor mAbs. For example, in 25% to 30% of women with metastatic breast cancer, a genetic alteration of the tumor cells results in the increased expression of *h*uman

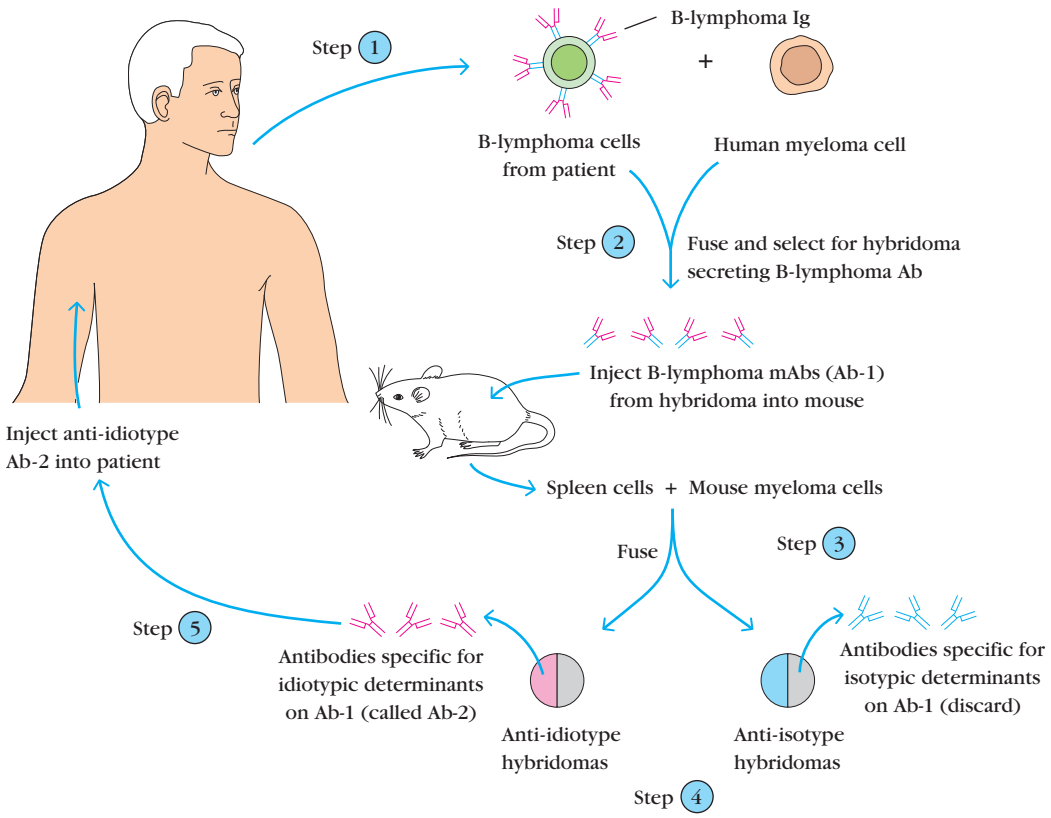


FIGURE 19-9 Development of a monoclonal antibody specific for idiotypic determinants on B-lymphoma cells. Because all the B-lymphoma cells in a patient are derived from a single transformed B cell, they all express the same membrane-bound antibody (Ab-1) with the same idiotype (i.e., the same antigenic specificity). In the procedure illustrated, a monoclonal anti-idiotypic antibody (Ab-2) against the B-lymphoma membrane-bound antibody is produced ex vivo (steps 1–4). This anti-idiotype antibody is then injected into the patient (step 5), where it binds selectively to the idiotypic determinants on the immunoglobulin of B-lymphoma cells, making these cells susceptible to complement-mediated lysis.

*e*pidermal-growth-factor–like *r*eceptor *2* (HER2) encoded by the *neu* gene and expressed in only trace amounts in normal adults. Because of this difference in protein levels, a humanized mAb against HER2 has been successfully used to treat HER2-expressing breast cancers, selectively eliminating cancer cells without damaging normal cells. Several other mAbs that target specific growth factors or their receptors have also been approved for clinical use and are included in Table 19-4.

Cytokines Can Be Used to Augment the Immune Response to Tumors

The isolation and cloning of the various cytokine genes has facilitated the large-scale production of cytokines for use in clinical settings. Several of these have been used either singly or in combination to augment the immune response against cancer in clinical trials. Among these are all three interferons (IFN-α, -β, and -γ), the *t*umor *n*ecrosis *f*actors (TNF-α and Lymphotoxin-α [TNF-β]), *g*ranulocyte-*m*acrophage *c*olony *s*timulating *f*actor (GM-CSF) and several interleukins (IL-2, -4, -6, and -12). Trials with some of these, either used in vivo or by treatment of cells ex vivo, have produced occasional encouraging results.

After some initially promising and long-lasting results in early trials, IL-2 was licensed for use in cancer therapy. Despite significant in vivo toxicity and the small fraction of patients impacted, many follow-up clinical trials incorporated IL-2 alone or in combination with other immunotherapies. Alas, many years of refinements with IL-2 regimens and combination drug testing have not shown this T-cell growth factor to be as effective as once hoped, and the mechanisms of action in those cases of durable response are still largely unknown. Today, IL-2 alone or in combination with IFN-α is still used for advanced kidney cancer and metastatic melanoma. One factor that may further complicate our understanding of the role of IL-2 in cancer is the impact of this cytokine on T_{REG} cells, a population that has been associated with both tumor-enhancing and tumor-inhibiting behaviors.

The major obstacles to in vivo cytokine therapy are the complexity of the cytokine network itself and systemic toxicity. This complexity makes it difficult to determine how a