

the cellular genome. Viral gene transcription and viral reproduction are stimulated by signals that normally activate the host cell. Production of virus is accompanied by cell death.

- **CD4⁺ T cell depletion in HIV-infected individuals** is due to direct cytopathic effects of the virus, toxic effects of viral products such as shed gp120, and indirect effects such as activation-induced cell death or CTL killing of infected CD4⁺ cells.
- Several reservoirs of HIV exist in infected individuals, including short-lived activated CD4⁺ T cells, longer lived macrophages, and very long lived, latently infected resting T cells.
- **HIV-induced depletion of CD4⁺ T cells** results in greatly increased susceptibility to infection by a number of opportunistic microorganisms. In addition, HIV-infected patients have an increased incidence of tumors, particularly Kaposi's sarcoma and EBV-associated B cell lymphomas, and encephalopathy frequently develops, the mechanism of which is not fully understood.
- **HIV has a high mutation rate**, which allows the virus to evade host immune responses as well as drug therapies. Genetic variability also poses a problem for the design of an effective vaccine against HIV. HIV infection can be treated by a combination of inhibitors of viral enzymes.

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Appendix I

Glossary

$\alpha\beta$ T cell receptor ($\alpha\beta$ TCR). The most common form of TCR, expressed on both CD4⁺ and CD8⁺ T cells. The $\alpha\beta$ TCR recognizes peptide antigen bound to an MHC molecule. Both α and β chains contain highly variable (V) regions that together form the antigen-binding site as well as constant (C) regions. TCR V and C regions are structurally homologous to the V and C regions of Ig molecules.

ABO blood group antigens. Glycosphingolipid antigens present on many cell types, including red blood cells. These antigens differ between different individuals, depending on inherited alleles encoding the enzymes required for synthesis of the antigens. The ABO antigens act as alloantigens responsible for blood transfusion reactions and hyperacute rejection of allografts.

Accessory molecule. A lymphocyte cell surface molecule distinct from the antigen receptor complex that mediates adhesive or signaling functions important for activation or migration of the lymphocyte.

Acquired immunodeficiency. A deficiency in the immune system that is acquired after birth, usually because of infection (e.g., AIDS), and that is not related to a genetic defect.

Acquired immunodeficiency syndrome (AIDS). A disease caused by human immunodeficiency virus (HIV) infection that is characterized by depletion of CD4⁺ T cells leading to a profound defect in cell-mediated immunity. Clinically, AIDS includes opportunistic infections, malignant tumors, wasting, and encephalopathy.

Activation protein-1 (AP-1). A family of DNA-binding transcription factors composed of dimers of two proteins that bind to one another through a shared structural motif called a leucine zipper. The best characterized AP-1 factor is composed of the proteins Fos and Jun. AP-1 is involved in transcriptional regulation of many different genes important in the immune system, such as cytokine genes.

Active immunity. The form of adaptive immunity that is induced by exposure to a foreign antigen and activation of lymphocytes and in which the immunized individual plays an active role in responding to the antigen. This type contrasts with passive immunity, in which an individual receives antibodies or lymphocytes

from another individual who was previously actively immunized.

Acute-phase reactants. Proteins, mostly synthesized in the liver, whose plasma concentrations increase shortly after infection as part of the systemic inflammatory response syndrome. Examples include C-reactive protein, fibrinogen, and serum amyloid A protein. Hepatic synthesis of these molecules is up-regulated by inflammatory cytokines, especially IL-6 and TNF. The acute-phase reactants play various roles in the innate immune response to microbes.

Acute-phase response. The increase in plasma concentrations of several proteins, called acute-phase reactants, that occurs as part of the early innate immune response to infections.

Acute rejection. A form of graft rejection involving vascular and parenchymal injury mediated by T cells, macrophages, and antibodies that usually begins after the first week of transplantation. Differentiation of effector T cells and production of antibodies that mediate acute rejection occur in response to the graft, thus the delay in onset.

Adapter protein. Proteins involved in lymphocyte signal transduction pathways by serving as bridge molecules or scaffolds for the recruitment of other signaling molecules. During lymphocyte activation, adapter molecules may be phosphorylated on tyrosine residues to enable them to bind other proteins containing Src homology 2 (SH2) domains. Adapter molecules involved in T cell activation include LAT, SLP-76, and Grb-2.

Adaptive immunity. The form of immunity that is mediated by lymphocytes and stimulated by exposure to infectious agents. In contrast to innate immunity, adaptive immunity is characterized by exquisite specificity for distinct macromolecules and memory, which is the ability to respond more vigorously to repeated exposure to the same microbe. Adaptive immunity is also called specific immunity.

Addressin. Molecules expressed on endothelial cells in different anatomic sites that bind to counter-receptors on lymphocytes called homing receptors and that direct organ-specific lymphocyte homing. Mucosal addressin cell adhesion molecule-1 (MAdCAM-1) is an example of an addressin expressed in Peyer's patch in

the intestinal wall that binds to the integrin $\alpha_4\beta_7$ on gut-homing T cells.

Adhesion molecule. A cell surface molecule whose function is to promote adhesive interactions with other cells or the extracellular matrix. Leukocytes express various types of adhesion molecules, such as selectins, integrins, and members of the Ig superfamily, and these molecules play crucial roles in cell migration and cellular activation in innate and adaptive immune responses.

Adjuvant. A substance, distinct from antigen, that enhances T cell activation by promoting the accumulation and activation of other leukocytes, called accessory cells, at a site of antigen exposure. Adjuvants enhance accessory cell expression of T cell-activating costimulators and cytokines and may also prolong the expression of peptide-MHC complexes on the surface of APCs.

Adoptive transfer. The process of transferring lymphocytes from one, usually immunized, individual into another individual. Adoptive transfer is used in research to define the role of a particular cell population (e.g., CD4⁺ T cells) in an immune response. Clinically, adoptive transfer of tumor-reactive T lymphocytes is used in experimental cancer therapy.

Affinity. The strength of the binding between a single binding site of a molecule (e.g., an antibody) and a ligand (e.g., an antigen). The affinity of a molecule X for a ligand Y is represented by the dissociation constant (K_d), which is the concentration of Y that is required to occupy the combining sites of half the X molecules present in a solution. A smaller K_d indicates a stronger or higher affinity interaction, and a lower concentration of ligand is needed to occupy the sites.

Affinity chromatography. A technique used to purify an antigen from a solution by passing it through a column packed with antibody that binds the antigen and is attached to a solid support such as agarose beads.

Affinity maturation. The process that leads to increased affinity of antibodies for a particular protein antigen as a humoral response progresses. Affinity maturation is the result of somatic mutation of Ig genes, followed by selective survival of the B cells producing the highest affinity antibodies.

Allele. One of different forms of a gene present at a particular chromosomal locus. An individual who is heterozygous at a locus has two different alleles, each on a different member of a pair of chromosomes, one inherited from the mother and one from the father. If a particular gene in a population has many different alleles, the gene or locus is said to be polymorphic. The MHC locus is extremely polymorphic.

Allelic exclusion. The exclusive expression of only one of two inherited alleles encoding Ig heavy and light chains and TCR β chains. Allelic exclusion occurs when the protein product of one productively recombined antigen receptor locus on one chromosome blocks rearrangement of the corresponding locus on the other chromosome. This property ensures that all the antigen receptors expressed by one clone of lymphocytes will have the identical antigen specificities. Because the

TCR α chain locus does not show allelic exclusion, some T cells do express two different types of TCR.

Allergen. An antigen that elicits an immediate hypersensitivity (allergic) reaction. Allergens are proteins or chemicals bound to proteins that induce IgE antibody responses in atopic individuals.

Allergy. A form of atopy or immediate hypersensitivity disease, often referring to the type of antigen that elicits the disease, such as food allergy, bee sting allergy, and penicillin allergy. All these conditions are related to antigen-induced mast cell or basophil activation.

Alloantibody. An antibody specific for an alloantigen (i.e., an antigen present in some individuals of a species but not in others).

Alloantigen. A cell or tissue antigen that is present in some members of a species and not in others and that is recognized as foreign on an allograft. Alloantigens are usually products of polymorphic genes.

Alloantisera. The alloantibody-containing serum of an individual who has previously been exposed to one or more alloantigens.

Allogeneic graft. An organ or tissue graft from a donor who is of the same species but genetically nonidentical to the recipient (also called an allograft).

Alloreactive. Reactive to alloantigens; describes T cells or antibodies from one individual that will recognize antigens on cells or tissues of another genetically nonidentical individual.

Allotype. The property of a group of antibody molecules defined by their sharing a particular allotope; that is, antibodies that share a particular allotope belong to the same allotype. Allotype is also often used synonymously with allotope, which refers to an antigenic determinant found on the antibodies of some individuals but not others.

Altered peptide ligands (APLs). Peptides with altered TCR contact residues that elicit responses different from the responses to native peptide ligands. Altered peptide ligands may be important in the regulation of T cell activation in physiologic, pathologic, or therapeutic situations.

Alternative pathway of complement activation. An antibody-independent pathway of activation of the complement system that occurs when the C3b protein binds to microbial cell surfaces. The alternative pathway is a component of the innate immune system and mediates inflammatory responses to infection as well as direct lysis of microbes.

Anaphylactic shock. Cardiovascular collapse occurring in the setting of a systemic immediate hypersensitivity reaction.

Anaphylatoxins. The C5a, C4a, and C3a complement fragments that are generated during complement activation. The anaphylatoxins bind specific cell surface receptors and promote acute inflammation by stimulating neutrophil chemotaxis and activating mast cells. At high concentrations, anaphylatoxins activate enough mast cells to mimic anaphylaxis.

Anaphylaxis. An extreme systemic form of immediate hypersensitivity in which mast cell or basophil mediators cause bronchial constriction, massive tissue edema, and cardiovascular collapse.

Anchor residues. The amino acid residues of a peptide whose side chains fit into pockets in the peptide-binding cleft of an MHC molecule. The side chains bind to complementary amino acids in the MHC molecule and therefore serve to anchor the peptide in the cleft of the MHC molecule.

Anergy. A state of unresponsiveness to antigenic stimulation. Clinically, anergy describes the lack of T cell-dependent cutaneous delayed-type hypersensitivity reactions to common antigens. Lymphocyte anergy (also called clonal anergy) is the failure of clones of T or B cells to react to antigen and may be a mechanism of maintaining immunologic tolerance to self.

Angiogenesis. New blood vessel formation regulated by a variety of protein factors elaborated by cells of the innate and adaptive immune systems and often accompanying chronic inflammation.

Antagonist peptide. Variant peptide ligands of a TCR in which one or two TCR contact residues have been changed and in which negative signals are delivered to specific T cells that inhibit responses to native peptides.

Antibody. A type of glycoprotein molecule, also called immunoglobulin (Ig), produced by B lymphocytes that binds antigens, often with a high degree of specificity and affinity. The basic structural unit of an antibody is composed of two identical heavy chains and two identical light chains. N-terminal variable regions of the heavy and light chains form the antigen-binding sites, whereas the C-terminal constant regions of the heavy chains functionally interact with other molecules in the immune system. Every individual has millions of different antibodies, each with a unique antigen-binding site. Secreted antibodies perform various effector functions, including neutralizing antigens, activating complement, and promoting leukocyte-dependent destruction of microbes.

Antibody-dependent cell-mediated cytotoxicity (ADCC). A process by which NK cells are targeted to IgG-coated cells, resulting in lysis of the antibody-coated cells. A specific receptor for the constant region of IgG, called Fc γ RIII (CD16), is expressed on the NK cell membrane and mediates binding to the IgG.

Antibody feedback. The down-regulation of antibody production by secreted IgG antibodies that occurs when antigen-antibody complexes simultaneously engage B cell membrane Ig and Fc γ receptors (Fc γ RII). Under these conditions, the cytoplasmic tails of the Fc γ receptors transduce inhibitory signals inside the B cell.

Antibody repertoire. The collection of different antibody specificities expressed in an individual.

Antibody-secreting cell. A B lymphocyte that has undergone differentiation and produces the secretory form of Ig. Antibody-secreting cells are produced in response to antigen and reside in the spleen and lymph nodes as well as in the bone marrow.

Antigen. A molecule that binds to an antibody or a TCR. Antigens that bind to antibodies include all classes of molecules. TCRs bind only peptide fragments of proteins complexed with MHC molecules; both the peptide ligand and the native protein from which it is derived are called T cell antigens.

Antigen presentation. The display of peptides bound by MHC molecules on the surface of an APC that permits specific recognition by TCRs and activation of T cells.

Antigen processing. The intracellular conversion of protein antigens derived from the extracellular space or the cytosol into peptides and loading of these peptides onto MHC molecules for display to T lymphocytes.

Antigen-presenting cell (APC). A cell that displays peptide fragments of protein antigens, in association with MHC molecules, on its surface and activates antigen-specific T cells. In addition to displaying peptide-MHC complexes, APCs must also express costimulatory molecules to activate T lymphocytes optimally.

Antiserum. Serum from an individual previously immunized against an antigen that contains antibody specific for that antigen.

Apoptosis. A process of cell death characterized by DNA cleavage, nuclear condensation and fragmentation, and plasma membrane blebbing that leads to phagocytosis of the cell without inducing an inflammatory response. This type of cell death is important in lymphocyte development, regulation of lymphocyte responses to foreign antigens, and maintenance of tolerance to self antigens.

Arthus reaction. A localized form of experimental immune complex-mediated vasculitis induced by injection of an antigen subcutaneously into a previously immunized animal or into an animal that has been given intravenous antibody specific for the antigen. Circulating antibodies bind to the injected antigen and form immune complexes that are deposited in the walls of small arteries at the injection site and give rise to a local cutaneous vasculitis with necrosis.

Atopy. The propensity of an individual to produce IgE antibodies in response to various environmental antigens and to develop strong immediate hypersensitivity (allergic) responses. People who have allergies to environmental antigens, such as pollen or house dust, are said to be atopic.

Autoantibody. An antibody produced in an individual that is specific for a self antigen. Autoantibodies can cause damage to cells and tissues and are produced in excess in systemic autoimmune diseases, such as systemic lupus erythematosus.

Autocrine factor. A molecule that acts on the same cell that produces the factor. For example, IL-2 is an autocrine T cell growth factor that stimulates mitotic activity of the T cell that produces it.

Autoimmune disease. A disease caused by a breakdown of self-tolerance such that the adaptive immune system responds to self antigens and mediates cell and tissue damage. Autoimmune diseases can be organ specific (e.g., thyroiditis or diabetes) or systemic (e.g., systemic lupus erythematosus).

Autoimmunity. The state of adaptive immune system responsiveness to self antigens that occurs when mechanisms of self-tolerance fail.

Autologous graft. A tissue or organ graft in which the donor and recipient are the same individual. Autol-

ogenous bone marrow and skin grafts are commonly performed in clinical medicine.

Avidity. The overall strength of interaction between two molecules, such as an antibody and antigen. Avidity depends on both the affinity and the valency of interactions. Therefore, the avidity of a pentameric IgM antibody, with 10 antigen-binding sites, for a multivalent antigen may be much greater than the avidity of a dimeric IgG molecule for the same antigen. Avidity can be used to describe the strength of cell-cell interactions, which are mediated by many binding interactions between cell surface molecules.

B cell tyrosine kinase (Btk). A tyrosine kinase of the Src family that plays an essential role in B cell maturation. Mutations in the gene encoding Btk cause X-linked agammaglobulinemia, a disease characterized by failure of B cells to mature beyond the pre-B cell stage.

B lymphocyte. The only cell type capable of producing antibody molecules and therefore the central cellular component of humoral immune responses. B lymphocytes, or B cells, develop in the bone marrow, and mature B cells are found mainly in lymphoid follicles in secondary lymphoid tissues, in bone marrow, and in low numbers in the circulation.

B lymphocyte antigen receptor (BCR) complex. A multiprotein complex expressed on the surface of B lymphocytes that recognizes antigen and transduces activating signals into the cell. The BCR includes membrane Ig, which is responsible for binding antigen, and Igα and Igβ proteins, which initiate signaling events.

Bare lymphocyte syndrome. An immunodeficiency disease characterized by a lack of class II MHC molecule expression that leads to defects in antigen presentation and cell-mediated immunity. The disease is caused by mutations in genes encoding factors that regulate class II MHC gene transcription.

Basophil. A type of bone marrow–derived, circulating granulocyte with structural and functional similarities to mast cells that has granules containing many of the same inflammatory mediators as mast cells and expresses a high-affinity Fc receptor for IgE. Basophils that are recruited into tissue sites where antigen is present may contribute to immediate hypersensitivity reactions.

Biogenic amines. Low molecular weight, nonlipid compounds, such as histamine, that share the structural feature of an amine group, are stored in and released from the cytoplasmic granules of mast cells, and mediate many of the biologic effects of immediate hypersensitivity (allergic) reactions. (Biogenic amines are sometimes called vasoactive amines.)

Biologic response modifiers. Molecules, such as cytokines, used clinically as modulators of inflammation, immunity, and hematopoiesis.

Bone marrow. The central cavity of bone that is the site of generation of all circulating blood cells in adults, including immature lymphocytes, and the site of B cell maturation.

Bone marrow transplantation. The transplantation of bone marrow, including stem cells that give rise to all mature blood cells and lymphocytes; it is performed

clinically to treat hematopoietic or lymphopoietic disorders and malignant diseases and is also used in various immunologic experiments in animals.

Bronchial asthma. An inflammatory disease usually caused by repeated immediate hypersensitivity reactions in the lung that leads to intermittent and reversible airway obstruction, chronic bronchial inflammation with eosinophils, and bronchial smooth muscle cell hypertrophy and hyperreactivity.

Burkitt's lymphoma. A malignant B cell tumor that is defined by histologic features but almost always carries a reciprocal chromosomal translocation involving Ig gene loci and the cellular myc gene on chromosome 8. Many cases of Burkitt's lymphoma are associated with Epstein-Barr virus infection.

C (constant region) gene segments. The DNA sequences in the Ig and TCR gene loci that encode the nonvariable portions of Ig heavy and light chains and TCR α, β, γ, and δ chains.

C1. A serum complement system protein composed of several polypeptide chains that initiates the classical pathway of complement activation by attaching to the Fc portions of IgG or IgM antibody that has bound antigen.

C1 inhibitor (C1 INH). A plasma protein inhibitor of the classical pathway of complement activation. C1 INH is a serine protease inhibitor (serpin) that mimics the normal substrates of the C1r and C1s components of C1. A genetic deficiency in C1 INH causes the disease hereditary angioneurotic edema.

C3. The central and most abundant complement system protein; it is involved in both the classical and alternative pathway cascades. C3 is proteolytically cleaved during complement activation to generate a C3b fragment, which covalently attaches to cell or microbial surfaces, and a C3a fragment, which has various proinflammatory activities.

C3 convertase. A multiprotein enzyme complex generated by the early steps of either the classical or alternative pathway of complement activation. C3 convertase cleaves C3, which gives rise to two proteolytic products called C3a and C3b.

C5 convertase. A multiprotein enzyme complex generated by C3b binding to C3 convertase. C5 convertase cleaves C5 and initiates the late steps of complement activation leading to formation of the membrane attack complex and lysis of cells.

Calcineurin. A cytoplasmic serine/threonine phosphatase that dephosphorylates and thereby activates the transcription factor NFAT. Calcineurin is activated by calcium signals generated through TCR signaling in response to antigen recognition, and the immunosuppressive drugs cyclosporine and FK-506 work by blocking calcineurin activity.

Carcinoembryonic antigen (CEA, CD66). A highly glycosylated membrane protein; increased expression of CEA in many carcinomas of the colon, pancreas, stomach, and breast results in a rise in serum levels. The level of serum CEA is used to monitor the persistence or recurrence of metastatic carcinoma after treatment. Because CEA expression is normally high in many tissues during fetal life but is suppressed in adults

except in tumor cells, it is called an oncofetal tumor antigen.

Caspases. Intracellular proteases with cysteines in their active sites that cleave substrates at the C-terminal sides of aspartic acid residues and are components of enzymatic cascades that cause apoptotic death of cells. Lymphocyte caspases may be activated by two pathways; one is associated with mitochondrial permeability changes in growth factor–deprived cells, and the other is associated with signals from death receptors in the plasma membrane.

Cathepsins. Thiol and aspartyl proteases with broad substrate specificities. The most abundant proteases of endosomes in APCs, cathepsins probably play an important role in generating peptide fragments from exogenous protein antigens that bind to class II MHC molecules.

CD molecules. Cell surface molecules expressed on various cell types in the immune system that are designated by the "cluster of differentiation" or CD number. See Appendix II for a list of CD molecules.

Cell-mediated immunity (CMI). The form of adaptive immunity that is mediated by T lymphocytes and serves as the defense mechanism against microbes that survive within phagocytes or infect nonphagocytic cells. CMI responses include CD4⁺ T cell–mediated activation of macrophages that have phagocytosed microbes and CD8⁺ CTL killing of infected cells.

Central tolerance. A form of self-tolerance induced in generative (central) lymphoid organs as a consequence of immature self-reactive lymphocytes recognizing self antigens and subsequently leading to their death or inactivation. Central tolerance prevents the emergence of lymphocytes with high-affinity receptors for the ubiquitous self antigens that are likely to be present in the bone marrow or thymus.

Chédiak-Higashi syndrome. A rare autosomal recessive immunodeficiency disease caused by a defect in the cytoplasmic granules of various cell types that affects the lysosomes of neutrophils and macrophages as well as the granules of CTLs and NK cells. Patients show reduced resistance to infection with pyogenic bacteria.

Chemokine receptors. Cell surface receptors for chemokines that transduce signals stimulating the migration of leukocytes. These receptors are members of the seven-transmembrane α-helical, G protein–linked family of receptors.

Chemokines. A large family of structurally homologous, low molecular weight cytokines that stimulate leukocyte movement and regulate the migration of leukocytes from the blood to tissues.

Chemotaxis. Movement of a cell directed by a chemical concentration gradient. The movement of lymphocytes, polymorphonuclear leukocytes, monocytes, and other leukocytes into various tissues is often directed by gradients of low molecular weight cytokines called chemokines.

Chromosomal translocation. A chromosomal abnormality in which a segment of one chromosome is transferred to another. Many malignant diseases of lymphocytes are associated with chromosomal trans-

locations involving an Ig or TCR locus and a chromosomal segment containing a cellular oncogene.

Chronic granulomatous disease. A rare inherited immunodeficiency disease caused by a defect in the gene encoding a component of the phagocyte oxidase enzyme that is needed for microbial killing by polymorphonuclear leukocytes and macrophages. The disease is characterized by recurrent intracellular bacterial and fungal infections, often accompanied by chronic cell-mediated immune responses and the formation of granulomas.

Chronic rejection. A form of allograft rejection characterized by fibrosis with loss of normal organ structures occurring during a prolonged period. In many cases, the major pathologic event in chronic rejection is graft arterial occlusion, which is caused by proliferation of intimal smooth muscle cells and is called graft arteriosclerosis.

c-Kit ligand (stem cell factor). A protein required for hematopoiesis, early steps in T cell development in the thymus, and mast cell development. c-Kit ligand is produced in membrane-bound and soluble forms by stromal cells in the bone marrow and thymus and binds to the c-Kit tyrosine kinase membrane receptor on pluripotent stem cells.

Class I major histocompatibility complex (MHC) molecule. One of two forms of polymorphic, heterodimeric membrane proteins that bind and display peptide fragments of protein antigens on the surface of APCs for recognition by T lymphocytes. Class I MHC molecules usually display peptides derived from the cytoplasm of the cell.

Class II-associated invariant chain peptide (CLIP). A peptide remnant of the invariant chain that sits in the class II MHC peptide-binding cleft and is removed by action of the HLA-DM molecule before the cleft becomes accessible to peptides produced from extracellular protein antigens.

Class II major histocompatibility complex (MHC) molecule. One of two forms of polymorphic, heterodimeric membrane proteins that bind and display peptide fragments of protein antigens on the surface of APCs for recognition by T lymphocytes. Class II MHC molecules usually display peptides derived from extracellular proteins that are internalized into phagocytic or endocytic vesicles.

Class II vesicle (CIIV). A membrane-bound organelle identified in murine B cells that is important in the class II MHC pathway of antigen presentation. The CIIV is similar to the MHC class II compartment (MIIC) identified in other cells and contains all the components required for the formation of complexes of peptide antigens and class II MHC molecules, including the enzymes that degrade protein antigens, class II molecules, invariant chain, and HLA-DM.

Classical pathway of complement activation. The pathway of activation of the complement system that is initiated by binding of antigen-antibody complexes to the C1 molecule and induces a proteolytic cascade involving multiple other complement proteins. The classical pathway is an effector arm of the humoral immune system that generates inflammatory mediators,

opsonins for phagocytosis of antigens, and lytic complexes that destroy cells.

Clonal anergy. A state of antigen unresponsiveness of a clone of T lymphocytes experimentally induced by recognition of antigen in the absence of additional signals (costimulatory signals) required for functional activation. Clonal anergy is considered a model for one mechanism of tolerance to self antigens and may be applicable to B lymphocytes as well.

Clonal deletion. A mechanism of lymphocyte tolerance in which an immature T cell in the thymus or an immature B cell in the bone marrow undergoes apoptotic death as a consequence of recognizing an abundant antigen in the generative organ.

Clonal expansion. The increase in number of lymphocytes specific for an antigen that results from antigen stimulation and proliferation of naive T cells. Clonal expansion occurs in lymphoid tissues and is required to generate enough antigen-specific effector lymphocytes from rare naive precursors to eradicate infections.

Clonal ignorance. A form of lymphocyte unresponsiveness in which self antigens are ignored by the immune system even though lymphocytes specific for those antigens remain viable and functional.

Clonal selection hypothesis. A fundamental tenet of the immune system (no longer a hypothesis) stating that every individual possesses numerous clonally derived lymphocytes, each clone having arisen from a single precursor and being capable of recognizing and responding to a distinct antigenic determinant. When an antigen enters, it selects a specific preexisting clone and activates it.

c-myc. A cellular proto-oncogene that encodes a nuclear factor involved in cell cycle regulation. Translocations of the *c-myc* gene into Ig gene loci are associated with B cell malignant neoplasms.

Collectins. A family of proteins, including mannose-binding lectin, that are characterized by a collagen-like domain and a lectin (i.e., carbohydrate-binding) domain. Collectins play a role in the innate immune system by acting as microbial pattern recognition receptors, and they may activate the complement system by binding to C1q.

Colony-stimulating factors (CSFs). Cytokines that promote the expansion and differentiation of bone marrow progenitor cells. CSFs are essential for the maturation of red blood cells, granulocytes, monocytes, and lymphocytes. Examples of CSFs are granulocyte-monocyte colony-stimulating factor (GM-CSF), c-Kit ligand, IL-3, and IL-7.

Combinatorial diversity. Combinatorial diversity describes the many different combinations of variable, diversity, and joining segments that are possible as a result of somatic recombination of DNA in the Ig and TCR loci during B cell or T cell development. Combinatorial diversity is one mechanism for the generation of large numbers of different antigen receptor genes from a limited number of DNA gene segments.

Complement. A system of serum and cell surface proteins that interact with one another and with other molecules of the immune system to generate important

effectors of innate and adaptive immune responses. The classical and alternative pathways of the complement system are activated by antigen-antibody complexes or microbial surfaces, respectively, and consist of a cascade of proteolytic enzymes that generate inflammatory mediators and opsonins. Both pathways lead to the formation of a common terminal cell lytic complex that is inserted in cell membranes.

Complement receptor type 1 (CR1). A high-affinity receptor for the C3b and C4b fragments of complement. Phagocytes use CR1 to mediate internalization of C3b- or C4b-coated particles. CR1 on erythrocytes serves in the clearance of immune complexes from the circulation. CR1 is also a regulator of complement activation.

Complement receptor type 2 (CR2). A receptor expressed on B cells and follicular dendritic cells that binds proteolytic fragments of the C3 complement protein, including C3d, C3dg, and iC3b. CR2 functions to stimulate humoral immune responses by enhancing B cell activation by antigen and by promoting the trapping of antigen-antibody complexes in germinal centers. CR2 is also the receptor for Epstein-Barr virus.

Complementarity-determining region (CDR). Short segments of Ig and TCR proteins that contain most of the sequence differences among different antibodies or TCRs and that make contact with antigen. Three CDRs are present in the variable domain of each antigen receptor polypeptide chain and six CDRs in an intact Ig or TCR molecule. These hypervariable segments assume loop structures that together form a surface that is complementary to the three-dimensional structure of the bound antigen.

Congenic mouse strains. Inbred mouse strains that are identical to one another at every genetic locus except the one for which they are selected to differ; such strains are created by repetitive back-crossbreeding and selection for a particular trait. Congenic strains that differ from one another only at a particular MHC allele have been useful in defining the function of MHC molecules.

Constant (C) region. The portion of Ig or TCR polypeptide chains that does not vary in sequence among different clones and is not involved in antigen binding.

Contact sensitivity. The propensity for a T cell-mediated, delayed-type hypersensitivity reaction to develop in the skin on contact with a particular chemical agent. Chemicals that elicit contact hypersensitivity bind to and modify self proteins or molecules on the surfaces of APCs, which are then recognized by CD4⁺ or CD8⁺ T cells.

Coreceptor. A lymphocyte surface receptor that binds to an antigen complex at the same time that membrane Ig or TCR binds the antigen and delivers signals required for optimal lymphocyte activation. CD4 and CD8 are T cell coreceptors that bind nonpolymorphic parts of an MHC molecule concurrently with the TCR binding to polymorphic residues and the bound peptide. CR2 is a coreceptor on B cells that binds to complement-opsonized antigens at the same time that membrane Ig binds another part of the antigen.

Costimulator. A molecule on the surface of or secreted by an APC that provides a stimulus (or second signal) required for the activation of naive T cells, in addition to antigen. The best defined costimulators are the B7 molecules on professional APCs that bind to the CD28 molecule on T cells.

CpG nucleotides. Unmethylated cytidine-guanine sequences found in bacterial DNA that have adjuvant properties in the mammalian immune system and may be important to the efficacy of DNA vaccines.

C-reactive protein (CRP). A member of the pentraxin family of plasma proteins involved in innate immune responses to bacterial infections. CRP is an acute-phase reactant, and it binds to the capsule of pneumococcal bacteria. CRP also binds to C1q and may thereby activate complement or act as an opsonin by interacting with phagocyte C1q receptors.

Crossmatching. A screening test performed to minimize the chance of graft rejection in which a patient in need of an allograft is tested for the presence of preformed antibodies against donor cell surface antigens (usually MHC antigens). The test involves mixing the recipient serum with leukocytes from potential donors, adding complement, and observing whether cell lysis occurs.

Cross-priming. A mechanism by which a professional APC activates (or primes) a naive CD8⁺ CTL specific for the antigens of a third cell (e.g., avirus-infected or tumor cell). Cross-priming occurs, for example, when an infected (often apoptotic) cell is ingested by a professional APC and the microbial antigens are processed and presented in association with class I MHC molecules, just like any other phagocytosed antigen. The professional APC also provides costimulation for the T cells. Also called cross-presentation.

Cutaneous immune system. The components of the innate and adaptive immune system found in the skin that function together in a specialized way to detect and respond to environmental antigens. Components of the cutaneous immune system include keratinocytes, Langerhans cells, intraepithelial lymphocytes, and dermal lymphocytes.

Cyclosporine. An immunosuppressive drug used to prevent allograft rejection that functions by blocking T cell cytokine gene transcription. Cyclosporine (also called cyclosporin A) binds to a cytosolic protein called cyclophilin, and cyclosporine-cyclophilin complexes bind to and inhibit calcineurin, thereby inhibiting activation and nuclear translocation of the transcription factor NFAT.

Cytokines. Proteins produced by many different cell types that mediate inflammatory and immune reactions. Cytokines are principal mediators of communication between cells of the immune system.

Cytolytic (or cytotoxic) T lymphocyte (CTL). A type of T lymphocyte whose major effector function is to recognize and kill host cells infected with viruses or other intracellular microbes. CTLs usually express CD8 and recognize microbial peptides displayed by class I MHC molecules. CTL killing of infected cells involves the release of cytoplasmic granules whose contents include membrane pore-forming proteins and enzymes.

Cytopathic effect of viruses. Harmful effects of viruses on host cells that are caused by any of a variety of biochemical or molecular mechanisms and are independent of the host immune response to the virus. Some viruses have little cytopathic effect but still cause disease because the immune system recognizes and destroys the infected cells.

Defensins. Cysteine-rich peptides present in the skin and in neutrophil granules that act as broad-spectrum antibiotics to kill a wide variety of bacteria and fungi. The synthesis of defensins is increased in response to inflammatory cytokines such as IL-1 and TNF.

Delayed-type hypersensitivity (DTH). An immune reaction in which T cell-dependent macrophage activation and inflammation cause tissue injury. A DTH reaction to the subcutaneous injection of antigen is often used as an assay for cell-mediated immunity (e.g., the purified protein derivative skin test for immunity to *Mycobacterium tuberculosis*). DTH is a frequent accompaniment of protective cell-mediated immunity against microbes.

Delayed xenograft rejection. A frequent form of rejection of xenografts that occurs within 2 to 3 days of transplantation and is characterized by intravascular thrombosis and fibrinoid necrosis of vessel walls. Delayed xenograft rejection is likely to be caused by antibody- and cytokine-mediated endothelial activation and damage.

Dendritic cells. Bone marrow-derived immune accessory cells found in epithelial and lymphoid tissues that are morphologically characterized by thin membranous projections. Dendritic cells function as APCs for naive T lymphocytes and are important for initiation of adaptive immune responses to protein antigen.

Desensitization. A method of treating immediate hypersensitivity disease (allergies) that involves repetitive administration of low doses of an antigen to which individuals are allergic. This process often prevents severe allergic reactions on subsequent environmental exposure to the antigen, but the mechanisms are not well understood.

Determinant. The specific portion of a macromolecular antigen to which an antibody binds. In the case of a protein antigen recognized by a T cell, the determinant is the peptide portion that binds to an MHC molecule for recognition by the TCR. Synonymous with epitope.

Determinant selection model. A model to explain MHC-linked immune responses that was proposed before the demonstration of peptide-MHC molecule binding. The model states that the products of MHC genes in each individual select which determinants of protein antigens will be immunogenic in that individual.

Diacylglycerol (DAG). A membrane-bound signaling molecule generated by phospholipase C (PLC γ 1)-mediated hydrolysis of the plasma membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP₂) during antigen activation of lymphocytes. The main function of DAG is to activate an enzyme called

protein kinase C that participates in the generation of active transcription factors.

DiGeorge syndrome. A selective T cell deficiency caused by a congenital malformation that results in defective development of the thymus, parathyroid glands, and other structures that arise from the third and fourth pharyngeal pouches.

Direct antigen presentation (or direct allorecognition). Presentation of cell surface allogeneic MHC molecules by graft cells to a graft recipient's T cells that leads to T cell activation, with no requirement for processing. Direct recognition of foreign MHC molecules is a cross-reaction in which a normal TCR that recognizes a self MHC molecule plus foreign peptide cross-reacts with an allogeneic MHC molecule plus peptide. Direct presentation is partly responsible for strong T cell responses to allografts.

Diversity. The existence of a large number of lymphocytes with different antigenic specificities in any individual (i.e., the lymphocyte repertoire is large and diverse). Diversity is a fundamental property of the adaptive immune system and is the result of variability in the structures of the antigen-binding sites of lymphocyte receptors for antigens (antibodies and TCRs).

Diversity (D) segments. Short coding sequences between the variable (V) and constant (C) gene segments in the Ig heavy chain and TCR β and γ loci that together with J segments are somatically recombined with V segments during lymphocyte development. The resulting recombined VDJ DNA codes for the carboxyl terminal ends of the antigen receptor V regions, including the third hypervariable (CDR) regions. Random use of D segments contributes to the diversity of the antigen receptor repertoire.

DNA vaccine. A vaccine composed of a bacterial plasmid containing a complementary DNA encoding a protein antigen. DNA vaccines presumably work because professional APCs are transfected *in vivo* by the plasmid and express immunogenic peptides that elicit specific responses. Furthermore, the plasmid DNA contains CpG nucleotides that act as potent adjuvants. DNA vaccines may elicit strong CTL responses.

Double-negative thymocyte. A subset of developing T cells (thymocytes) in the thymus that express neither CD4 nor CD8. Most double-negative thymocytes are at an early developmental stage and do not express antigen receptors. They will later express both CD4 and CD8 during the intermediate double-positive stage before further maturation to single-positive T cells expressing only CD4 or CD8.

Double-positive thymocyte. A subset of developing T cells (thymocytes) in the thymus at an intermediate developmental stage that express both CD4 and CD8. Double-positive thymocytes also express TCRs and are subject to selection processes, the survivors of which mature to single-positive T cells expressing only CD4 or CD8.

Ectoparasite. Parasites that live on the surface of an animal, such as ticks and mites. Both the innate and adaptive immune systems may play a role in protection against ectoparasites, often by destroying the larval stages of these organisms.

Effector cells. The cells that perform effector functions during an immune response, such as secreting cytokines (e.g., helper T cells), killing microbes (e.g., macrophages), killing microbe-infected host cells (e.g., CTLs), or secreting antibodies (e.g., differentiated B cells).

Effector phase. The phase of an immune response, after the recognition and activation phases, in which a foreign antigen is actually destroyed or inactivated. For example, in a humoral immune response, the effector phase may be characterized by antibody-dependent complement activation and phagocytosis of antibody- and complement-opsonized bacteria.

Endosome. An intracellular membrane-bound vesicle into which extracellular proteins are internalized during antigen processing. Endosomes have an acidic pH and contain proteolytic enzymes that degrade proteins into peptides that bind to class II MHC molecules. A subset of class II MHC-rich endosomes, called MIIC, play a special role in antigen processing and presentation by the class II pathway.

Endotoxin. A component of the cell wall of gram-negative bacteria, also called **lipopolysaccharide (LPS)**, that is released from dying bacteria and stimulates many innate immune responses, including the secretion of cytokines, induction of microbicidal activities of macrophages, and expression of leukocyte adhesion molecules on endothelium. Endotoxin contains both lipid components and carbohydrate (polysaccharide) moieties.

Enhancer. A regulatory nucleotide sequence in a gene that is located either upstream or downstream of the promoter, binds transcription factors, and increases the activity of the promoter. In cells of the immune system, enhancers are responsible for integrating cell surface signals that lead to induced transcription of genes encoding many of the effector proteins of an immune response, such as cytokines.

Envelope glycoprotein (Env). A membrane glycoprotein encoded by a retrovirus that is expressed on the plasma membrane of infected cells and on the host cell-derived membrane coat of viral particles. Env proteins are often required for viral infectivity. The Env proteins of HIV include gp41 and gp120, which bind to CD4 and chemokine receptors, respectively, on human T cells and mediate fusion of the viral and T cell membranes.

Enzyme-linked immunosorbent assay (ELISA). A method of quantifying an antigen immobilized on a solid surface by use of a specific antibody with a covalently coupled enzyme. The amount of antibody that binds the antigen is proportional to the amount of antigen present and is determined by spectrophotometrically measuring the conversion of a clear substrate to a colored product by the coupled enzyme.

Eosinophil. A bone marrow-derived granulocyte that is abundant in the inflammatory infiltrates of immediate hypersensitivity late-phase reactions and that contributes to many of the pathologic processes in allergic diseases. Eosinophils are important in defense against extracellular parasites, including helminths.

Epitope. The specific portion of a macromolecular antigen to which an antibody binds. In the case of a protein antigen recognized by a T cell, an epitope is the peptide portion that binds to an MHC molecule for recognition by the TCR. Synonymous with **determinant**.

Epstein-Barr virus (EBV). A double-stranded DNA virus of the herpesvirus family that is the etiologic agent of infectious mononucleosis and is associated with some B cell malignant tumors and nasopharyngeal carcinoma. EBV infects B lymphocytes and some epithelial cells by specifically binding to CR2 (CD21).

Equilibrium dialysis. A method of determining the affinity of interaction between a macromolecule such as an antibody and a small ligand such as a hapten. A solution of the macromolecule, at a defined concentration, is confined within a semipermeable membrane and immersed in a solution containing the small ligand. The membrane does not permit the macromolecule to pass through, but the small ligand can pass across the membrane freely. The concentration of the small ligand in solution at equilibrium is used to calculate the affinity of binding to the macromolecule.

Experimental autoimmune encephalomyelitis. An animal model of autoimmune demyelinating disease of the central nervous system (e.g., multiple sclerosis) that is induced in rodents by immunization with components of the myelin sheath (e.g., myelin basic protein) of nerves, mixed with an adjuvant. The disease is mediated in large part by cytokine-secreting CD4⁺ T cells specific for the myelin sheath proteins.

Extravasation. Escape of the fluid and cellular components of blood from a blood vessel into tissues.

Fab (fragment, antigen-binding). A proteolytic fragment of an IgG antibody molecule that includes one complete light chain paired with one heavy chain fragment containing the variable domain and only the first constant domain. Fab fragment retains the ability to monovalently bind an antigen but cannot interact with IgG Fc receptors on cells or with complement. Therefore, Fab preparations are used in research and therapeutic applications when antigen binding is desired without activation of effector functions. (Fab' fragment retains the hinge region of the heavy chain.)

F(ab')₂ fragment. A proteolytic fragment of an IgG molecule that includes two complete light chains but only the variable domain, first constant domain, and hinge region of the two heavy chains. F(ab')₂ fragments retain the entire bivalent antigen-binding region of an intact IgG molecule but cannot bind complement or IgG Fc receptors. They are used in research and therapeutic applications when antigen binding is desired without antibody effector functions.

Fas (CD95). A member of the TNF receptor family that is expressed on the surface of T cells and many other cell types and initiates a signaling cascade leading to apoptotic death of the cell. The death pathway is initiated when Fas binds to Fas ligand expressed on activated T cells. Fas-mediated killing of T cells, called activation-induced cell death, is important for the maintenance of self-tolerance. Mutations in the Fas gene cause systemic autoimmune disease.

Fas ligand (CD95 ligand). A membrane protein that is a member of the TNF family of proteins expressed on activated T cells. Fas ligand binds to Fas, thereby stimulating a signaling pathway leading to apoptotic cell death of the Fas-expressing cell. Mutations in the Fas ligand gene cause systemic autoimmune disease in mice.

Fc (fragment, crystalline). A proteolytic fragment of IgG that contains only the disulfide-linked carboxyl terminal regions of the two heavy chains. Fc is also used to describe the corresponding region of an intact Ig molecule that mediates effector functions by binding to cell surface receptors or the C1q complement protein. (Fc fragments are so named because they tend to crystallize out of solution.)

Fc receptor. A cell surface receptor specific for the carboxyl terminal constant region of an Ig molecule. Fc receptors are typically multichain protein complexes that include signaling components and Ig-binding components. Several types of Fc receptors exist, including those specific for different IgG isotypes, IgE, and IgA. Fc receptors mediate many of the cell-dependent effector functions of antibodies, including phagocytosis of antibody-bound antigens, antigen-induced activation of mast cells, and targeting and activation of NK cells.

Fc ϵ RI. A high-affinity receptor for the carboxyl terminal constant region of IgE molecules that is expressed on mast cells and basophils. Fc ϵ RI molecules on mast cells are usually occupied by IgE, and antigen-induced cross-linking of these IgE-Fc ϵ RI complexes activates the mast cell and initiates immediate hypersensitivity reactions.

Fc γ receptor (Fc γ R). A specific cell surface receptor for the carboxyl terminal constant region of IgG molecules. There are several different types of Fc γ receptors, including a high-affinity Fc γ RI that mediates phagocytosis by macrophages and neutrophils, a low-affinity Fc γ RIIB that transduces inhibitory signals in B cells, and a low-affinity Fc γ RIIA that mediates targeting and activation of NK cells.

First-set rejection. Allograft rejection in an individual who has not previously received a graft or otherwise been exposed to tissue alloantigens from the same donor. First-set rejection usually takes about 7 to 10 days.

FK-506. An immunosuppressive drug used to prevent allograft rejection that functions by blocking T cell cytokine gene transcription, similar to cyclosporine. FK-506 binds to a cytosolic protein called FK-506-binding protein, and the resulting complex binds to calcineurin, thereby inhibiting activation and nuclear translocation of the transcription factor NFAT.

Flow cytometry. A method of analysis of the phenotype of cell populations requiring a specialized instrument (flow cytometer) that can detect fluorescence on individual cells in a suspension and thereby determine the number of cells expressing the molecule to which a fluorescent probe binds. Suspensions of cells are incubated with fluorescently labeled antibodies or other probes, and the amount of probe bound by each cell in the population is measured by passing the cells one at

a time through a fluorimeter with a laser-generated incident beam.

Fluorescence-activated cell sorter (FACS). An adaptation of the flow cytometer that is used for the purification of cells from a mixed population according to which and how much fluorescent probe the cells bind. Cells are first stained with fluorescently labeled probe, such as an antibody specific for a surface antigen of a cell population. The cells are then passed one at a time through a fluorimeter with a laser-generated incident beam and are differentially deflected by electromagnetic fields whose strength and direction are varied according to the measured intensity of the fluorescence signal.

Follicle. See **Lymphoid follicle**.

Follicular dendritic cells. Cells found in lymphoid follicles that express complement receptors, Fc receptors, and CD40 ligand and have long cytoplasmic processes that form a meshwork integral to the architecture of a lymphoid follicle. Follicular dendritic cells display antigens on their surface for B cell recognition and are involved in the activation and selection of B cells expressing high-affinity membrane Ig during the process of affinity maturation.

N-Formylmethionine. An amino acid that initiates all bacterial proteins and no mammalian proteins (except those synthesized within mitochondria) and serves as a signal to the innate immune system of infection. Specific receptors for N-formylmethionine-containing peptides are expressed on neutrophils and mediate activation of the neutrophils.

G protein-coupled receptor family. A diverse family of receptors for hormones, lipid inflammatory mediators, and chemokines that use associated trimeric G proteins for intracellular signaling.

G proteins. Proteins that bind guanyl nucleotides and act as exchange molecules by catalyzing the replacement of bound guanosine diphosphate (GDP) by guanosine triphosphate (GTP). G proteins with bound GTP can activate a variety of cellular enzymes in different signaling cascades. Trimeric GTP-binding proteins are associated with the cytoplasmic portions of many cell surface receptors, such as chemokine receptors. Other small soluble G proteins, such as Ras and Rac, are recruited into signaling pathways by adapter proteins.

$\gamma\delta$ T cell receptor ($\gamma\delta$ TCR). A form of TCR that is distinct from the more common $\alpha\beta$ TCR and is expressed on a subset of T cells found mostly in epithelial barrier tissues. Although structurally similar to the $\alpha\beta$ TCR, the forms of antigen recognized by $\gamma\delta$ TCRs are poorly understood; they do not recognize peptide complexes bound to polymorphic MHC molecules.

Generative lymphoid organ. Organs in which lymphocytes develop from immature precursors. The bone marrow and thymus are the major generative lymphoid organs in which B cells and T cells develop, respectively.

Germinal center. A lightly staining region within a lymphoid follicle in spleen, lymph node, or mucosal lymphoid tissue that forms during T cell-dependent humoral immune responses and is the site of B cell affinity maturation.

Germline organization. The inherited arrangement of variable, diversity, joining, and constant region gene segments of the antigen receptor loci in nonlymphoid cells or in immature lymphocytes. In developing B or T lymphocytes, the germline organization is modified by somatic recombination to form functional Ig or TCR genes.

Glomerulonephritis. Inflammation of the renal glomeruli, often initiated by immunopathologic mechanisms such as deposition of circulating antigen-antibody complexes in the glomerular basement membrane or binding of antibodies to antigens expressed in the glomerulus. The antibodies can activate complement and phagocytes, and the resulting inflammatory response can lead to renal failure.

Graft. A tissue or organ that is removed from one site and placed in another site, usually in a different individual.

Graft arteriosclerosis. Occlusion of graft arteries caused by proliferation of intimal smooth muscle cells. This process is evident within 6 months to a year after transplantation and is responsible for chronic rejection of vascularized organ grafts. The mechanism is likely to be a result of a chronic immune response to vessel wall alloantigens. Graft arteriosclerosis is also called accelerated arteriosclerosis.

Graft rejection. A specific immune response to an organ or tissue graft that leads to inflammation, damage, and possibly graft failure.

Graft-versus-host disease. A disease occurring in bone marrow transplant recipients that is caused by the reaction of mature T cells in the marrow graft with alloantigens on host cells. The disease most often affects the skin, liver, and intestines.

Granulocyte colony-stimulating factor (G-CSF). A cytokine made by activated T cells, macrophages, and endothelial cells at sites of infection that acts on bone marrow to increase the production of and mobilize neutrophils to replace those consumed in inflammatory reactions.

Granulocyte-monocyte colony-stimulating factor (GM-CSF). A cytokine made by activated T cells, macrophages, endothelial cells, and stromal fibroblasts that acts on bone marrow to increase the production of neutrophils and monocytes. GM-CSF is also a macrophage-activating factor and promotes the differentiation of Langerhans cells into mature dendritic cells.

Granuloma. A nodule of inflammatory tissue composed of clusters of activated macrophages and T lymphocytes, often with associated necrosis and fibrosis. Granulomatous inflammation is a form of chronic delayed-type hypersensitivity, often in response to persistent microbes, such as *Mycobacterium tuberculosis* and some fungi, or in response to particulate antigens that are not readily phagocytosed.

Granzyme. A serine protease enzyme found in the granules of CTLs and NK cells that is released by exocytosis, enters target cells mainly through perforin-created membrane "holes," and proteolytically cleaves and activates caspases, which in turn cleave several substrates and induce target cell apoptosis.

H-2 molecule. An MHC molecule in the mouse. The mouse MHC was originally called the H-2 locus.

Haplotype. The set of MHC alleles inherited from one parent and therefore on one chromosome.

Hapten. A small chemical that can bind to an antibody but must be attached to a macromolecule (carrier) to stimulate an adaptive immune response specific for that chemical. For example, immunization with dinitrophenol (DNP) alone will not stimulate an anti-DNP antibody response, but immunization with a protein with covalently bonded DNP hapten will.

Heavy chain class (isotype) switching. The process by which a B lymphocyte changes the class, or isotype, of the antibodies that it produces, from IgM to IgG, IgE, or IgA, without changing the antigen specificity of the antibody. Heavy chain class switching is regulated by helper T cell cytokines and CD40 ligand and involves recombination of B cell VDJ segments with downstream heavy chain gene segments.

Helminth. A parasitic worm. Helminthic infections often elicit T_H2 -regulated immune responses characterized by eosinophil-rich inflammatory infiltrates and IgE production.

Helper T cells. The functional subset of T lymphocytes whose main effector functions are to activate macrophages in cell-mediated immune responses and to promote B cell antibody production in humoral immune responses. These effector functions are mediated by secreted cytokines and by T cell CD40 ligand binding to macrophage or B cell CD40. Most helper T cells express the CD4 molecule.

Hematopoiesis. The development of mature blood cells, including erythrocytes, leukocytes, and platelets, from pluripotent stem cells in the bone marrow and fetal liver. Hematopoiesis is regulated by several different cytokine growth factors produced by bone marrow stromal cells, T cells, and other cell types.

Hematopoietic stem cell. An undifferentiated bone marrow cell that divides continuously and gives rise to additional stem cells and cells of multiple different lineages. A hematopoietic stem cell in the bone marrow will give rise to cells of the lymphoid, myeloid, and erythrocytic lineage.

High endothelial venule (HEV). Specialized venules that are the sites of lymphocyte extravasation from the blood into the stroma of a peripheral lymph node or mucosal lymphoid tissue. HEVs are lined by plump endothelial cells that protrude into the vessel lumen and express unique adhesion molecules involved in binding naive T cells.

Highly active antiretroviral therapy (HAART). Combination chemotherapy for HIV infection consisting of reverse transcriptase inhibitors and a viral protease inhibitor. HAART can reduce plasma virus titers to below detectable levels for more than 1 year and slow the progression of HIV disease.

Hinge region. A region of Ig heavy chains between the first two constant domains that can assume multiple conformations, thereby imparting flexibility in the orientation of the two antigen-binding sites. Because of the hinge region, an antibody molecule can simultane-

ously bind two epitopes that are anywhere within a range of distances from one another.

Histamine. A biogenic amine stored in the granules of mast cells that is one of the important mediators of immediate hypersensitivity. Histamine binds to specific receptors in various tissues and causes increased vascular permeability and contraction of bronchial and intestinal smooth muscle.

HLA. See **Human leukocyte antigens**.

HLA-DM. A peptide exchange molecule that plays a critical role in the class II MHC pathway of antigen presentation. HLA-DM is found in the specialized MHC endosomal compartment and facilitates removal of the invariant chain-derived CLIP peptide and the binding of other peptides to class II MHC molecules. HLA-DM is encoded by a gene in the MHC and is structurally similar to class II MHC molecules, but it is not polymorphic.

Homeostasis. In the adaptive immune system, the maintenance of a constant number and diverse repertoire of lymphocytes, despite the emergence of new lymphocytes and tremendous expansion of individual clones that may occur during responses to immunogenic antigens. Homeostasis is achieved by several regulated pathways of lymphocyte death and inactivation.

Homing receptor. Adhesion molecules expressed on the surface of lymphocytes that are responsible for the different pathways of lymphocyte recirculation and tissue homing. Homing receptors bind to ligands (addressins) expressed on endothelial cells in particular vascular beds.

Human immunodeficiency virus (HIV). The etiologic agent of AIDS. HIV is a retrovirus that infects a variety of cell types, including CD4-expressing helper T cells, macrophages, and dendritic cells, and causes chronic progressive destruction of the immune system.

Human leukocyte antigens (HLA). MHC molecules expressed on the surface of human cells. Human MHC molecules were first identified as alloantigens on the surface of white blood cells (leukocytes) that bound serum antibodies from individuals previously exposed to other individuals' cells (e.g., mothers or transfusion recipients).

Humanized antibody. A monoclonal antibody encoded by a recombinant hybrid gene and composed of the antigen-binding sites from a murine monoclonal antibody and the constant region of a human antibody. Humanized antibodies are less likely than mouse monoclonal antibodies to induce an anti-antibody response in humans; they are used clinically in the treatment of tumors and transplant rejection.

Humoral immunity. The type of adaptive immune response mediated by antibodies produced by B lymphocytes. Humoral immunity is the principal defense mechanism against extracellular microbes and their toxins.

Hybridoma. A cell line derived by cell fusion, or somatic cell hybridization, between a normal lymphocyte and an immortalized lymphocyte tumor line. B cell hybridomas created by fusion of normal B cells of defined antigen specificity with a myeloma cell line are

used to produce monoclonal antibodies. T cell hybridomas created by fusion of a normal T cell of defined specificity with a T cell tumor line are commonly used in research.

Hyperacute rejection. A form of allograft or xenograft rejection that begins within minutes to hours after transplantation and that is characterized by thrombotic occlusion of the graft vessels. Hyperacute rejection is mediated by preexisting antibodies in the host circulation that bind to donor endothelial antigens, such as blood group antigens or MHC molecules, and activate the complement system.

Hypersensitivity diseases. Disorders caused by immune responses. Hypersensitivity diseases include autoimmune diseases, in which immune responses are directed against self antigens, and diseases that result from uncontrolled or excessive responses against foreign antigens, such as microbes and allergens. The tissue damage that occurs in hypersensitivity diseases is due to the same effector mechanisms used by the immune system to protect against microbes.

Hypervariable loop (hypervariable region). Short segments of about 10 amino acid residues within the variable regions of antibody or TCR proteins that form loop structures that contact antigen. Three hypervariable loops, also called CDRs, are present in each antibody heavy chain and light chain and in each TCR chain. Most of the variability between different antibodies or TCRs is located within these loops.

Idiotype. The property of a group of antibodies or TCRs defined by their sharing a particular idiotope; that is, antibodies that share a particular idiotope belong to the same idiotype. Idiotype is also used to describe the collection of idiotopes expressed by an Ig molecule, and it is often used synonymously with idiotope.

Idiotypic network. A network of complementary interactions involving idiotypes and anti-idiotypic antibodies (or T cells) that, according to the network hypothesis, reach a steady state at which the immune system is at homeostasis. Theoretically, when one or a few clones of lymphocytes respond to a foreign antigen, their idiotypes are expanded and anti-idiotypic responses are triggered that function to shut off the antigen-specific response.

Iga and Igβ. Proteins that are required for surface expression and signaling functions of membrane Ig on B cells. Iga and Igβ pairs are disulfide linked to one another, noncovalently associated with the cytoplasmic tail of membrane Ig, and form the BCR complex. The cytoplasmic domains of Iga and Igβ contain ITAMs that are involved in early signaling events during antigen-induced B cell activation.

IL-1 receptor antagonist (IL-1ra). A natural inhibitor of IL-1 produced by mononuclear phagocytes that is structurally homologous to IL-1 and binds to the same receptors but is biologically inactive. Attempts to use IL-1 inhibitors to reduce inflammation in diseases such as rheumatoid arthritis are ongoing.

Immature B lymphocyte. A membrane IgM⁺, IgD⁺ B cell, recently derived from marrow precursors, that does not proliferate or differentiate in response to

antigens but rather may undergo apoptotic death or become functionally unresponsive. This property is important for the negative selection of B cells that are specific for self antigens present in the bone marrow.

Immediate hypersensitivity. The type of immune reaction responsible for allergic diseases and dependent on IgE plus antigen-mediated stimulation of tissue mast cells and basophils. The mast cells and basophils release mediators that cause increased vascular permeability, vasodilation, bronchial and visceral smooth muscle contraction, and local inflammation.

Immune complex. A multimolecular complex of antibody molecules with bound antigen. Because each antibody molecule has a minimum of two antigen-binding sites and many antigens are multivalent, immune complexes can vary greatly in size. Immune complexes activate effector mechanisms of humoral immunity, such as the classical complement pathway and Fc receptor-mediated phagocyte activation. Deposition of circulating immune complexes in blood vessel walls or renal glomeruli can lead to inflammation and disease.

Immune complex disease. An inflammatory disease caused by the deposition of antigen-antibody complexes in blood vessel walls resulting in local complement activation and phagocyte recruitment. Immune complexes may form because of overproduction of antibodies to microbial antigens or as a result of autoantibody production in the setting of an autoimmune disease such as systemic lupus erythematosus. Immune complex deposition in the specialized capillary basement membranes of renal glomeruli can cause glomerulonephritis and impair renal function. Systemic deposition of immune complexes in arterial walls can cause thrombosis and ischemic damage to various organs.

Immune deviation. The conversion of a T cell response associated with one set of cytokines, such as T_H1 cytokines that stimulate cell-mediated immunity, to a response associated with other cytokines, such as T_H2 cytokines that stimulate the production of selected antibody isotypes.

Immune inflammation. Inflammation that is a result of an adaptive immune response to antigen. The cellular infiltrate at the inflammatory site may include cells of the innate immune system such as neutrophils and macrophages, which are recruited as a result of the actions of T cell cytokines.

Immune response. A collective and coordinated response to the introduction of foreign substances in an individual mediated by the cells and molecules of the immune system.

Immune response (Ir) genes. Originally defined as genes in inbred strains of rodents that were inherited in a dominant mendelian manner and that controlled the ability of the animals to make antibodies against simple synthetic polypeptides. We now know that Ir genes are polymorphic MHC genes that encode peptide-binding molecules required for the activation of T lymphocytes and are therefore also required for helper T cell-dependent B cell (antibody) responses to protein antigens.

Immune surveillance. The concept that a physiologic function of the immune system is to recognize and destroy clones of transformed cells before they grow into tumors and to kill tumors after they are formed. The term *immune surveillance* is sometimes used in a general sense to describe the function of T lymphocytes to detect and destroy any cell, not necessarily a tumor cell, that is expressing foreign (e.g., microbial) antigens.

Immune system. The molecules, cells, tissues, and organs that collectively function to provide immunity, or protection, against foreign organisms.

Immunity. Protection against disease, usually infectious disease, mediated by a collection of molecules, cells, and tissues collectively called the immune system. In a broader sense, immunity refers to the ability to respond to foreign substances, including microbes or molecules.

Immunoblot. An analytical technique in which antibodies are used to detect the presence of an antigen bound to (i.e., blotted on) a solid matrix such as filter paper (also known as a Western blot).

Immunodominant epitope. A linear amino acid sequence of a multideterminant protein antigen for which most of the responding T cells in any individual are specific. Immunodominant epitopes correspond to the peptides proteolytically generated within APCs that bind most avidly to MHC molecules and are most likely to stimulate T cells.

Immunofluorescence. A technique in which a molecule is detected by use of an antibody labeled with a fluorescent probe. For example, in immunofluorescence microscopy, cells that express a particular surface antigen can be stained with a fluorescein-conjugated antibody specific for the antigen and then visualized with a fluorescent microscope.

Immunogen. An antigen that induces an immune response. Not all antigens are immunogens. For example, small molecular weight compounds may not stimulate an immune response unless they are linked to macromolecules.

Immunoglobulin domain. A three-dimensional globular structural motif found in many proteins in the immune system, including Igs, TCRs, and MHC molecules. Ig domains are about 110 amino acid residues in length, include an internal disulfide bond, and contain two-layers of β-pleated sheet, each layer composed of three to five strands of antiparallel polypeptide chain. Ig domains are classified as V-like or C-like on the basis of closest homology to either the Ig V or C domains.

Immunoglobulin superfamily. A large family of proteins that contain a globular structural motif called an Ig domain, or Ig fold, originally described in antibodies. Many proteins of importance in the immune system, including antibodies, TCRs, MHC molecules, CD4, and CD8, are members of this superfamily.

Immunoglobulin (Ig). Synonymous with antibody (see Antibody).

Immunoglobulin heavy chain. One of two types of polypeptide chains in an antibody molecule. The basic structural unit of an antibody includes two identical, disulfide-linked heavy chains and two identical light

chains. Each heavy chain is composed of a variable (V) Ig domain and three or four constant (C) Ig domains. The different antibody isotypes, including IgM, IgD, IgG, IgA, and IgE, are distinguished by structural differences in their heavy chain constant regions. The heavy chain constant regions also mediate effector functions, such as complement activation or engagement of phagocytes.

Immunoglobulin light chain. One of two types of polypeptide chains in an antibody molecule. The basic structural unit of an antibody includes two identical light chains, each disulfide linked to one of two identical heavy chains. Each light chain is composed of one variable (V) Ig domain and one constant (C) Ig domain. There are two light chain isotypes, called κ and λ, both functionally identical. About 60% of human antibodies have κ light chains and 40% have λ light chains.

Immunohistochemistry. A technique to detect the presence of an antigen in histologic tissue sections by use of an enzyme-coupled antibody that is specific for the antigen. The enzyme converts a colorless substrate to a colored insoluble substance that precipitates at the site where the antibody and thus the antigen are localized. The position of the colored precipitate, and therefore the antigen, in the tissue section is observed by conventional light microscopy. Immunohistochemistry is a routine technique in diagnostic pathology and various fields of research.

Immunologic tolerance. See Tolerance.

Immunologically privileged site. A site in the body that is inaccessible to or constitutively suppresses immune responses. The anterior chamber of the eye, the testes, and the brain are examples of immunologically privileged sites.

Immunoperoxidase technique. A common immunohistochemical technique in which a horseradish peroxidase-coupled antibody is used to identify the presence of an antigen in a tissue section. The peroxidase enzyme converts a colorless substrate to an insoluble brown product that is observable by light microscopy.

Immunoprecipitation. A technique for the isolation of a molecule from a solution by binding it to an antibody and then rendering the antigen-antibody complex insoluble, either by precipitation with a second antibody or by coupling the first antibody to an insoluble particle or bead.

Immunoreceptor tyrosine-based activation motif (ITAM). A conserved motif composed of two copies of the sequence tyrosine-X-X-leucine (where X is an unspecified amino acid) found in the cytoplasmic tails of various membrane proteins in the immune system that are involved in signal transduction. ITAMs are present in the ζ and CD3 proteins of the TCR complex, in Iga and Igβ proteins in the BCR complex, and in several Ig Fc receptors. When these receptors bind their ligands, the tyrosine residues of the ITAMs become phosphorylated and form docking sites for other molecules involved in propagating cell-activating signal transduction pathways.

Immunoreceptor tyrosine-based inhibition motif (ITIM). A six-amino acid (isoleucine-X-tyrosine-X-X-

leucine) motif found in the cytoplasmic tails of various inhibitory receptors in the immune system, including FcγRIIB on B cells and killer cell Ig-like receptors (KIR) on NK cells. When these receptors bind their ligands, the ITIMs become phosphorylated on their tyrosine residue and form a docking site for protein tyrosine phosphatases, which in turn function to inhibit other signal transduction pathways.

Immunosuppression. Inhibition of one or more components of the adaptive or innate immune system as a result of an underlying disease or intentionally induced by drugs for the purpose of preventing or treating graft rejection or autoimmune disease. A commonly used immunosuppressive drug is cyclosporine, which blocks T cell cytokine production.

Immunotherapy. The treatment of a disease with therapeutic agents that promote or inhibit immune responses. Cancer immunotherapy, for example, involves promoting active immune responses to tumor antigens or administering anti-tumor antibodies or T cells to establish passive immunity.

Immunotoxins. Reagents that may be used in the treatment of cancer and consist of covalent conjugates of a potent cellular toxin, such as ricin or diphtheria toxin, with antibodies specific for antigens expressed on the surface of tumor cells. It is hoped that such reagents can specifically target and kill tumor cells without damaging normal cells, but safe and effective immunotoxins have yet to be developed.

Inbred mouse strain. A strain of mice created by repetitive mating of siblings that is characterized by homozygosity at every genetic locus. Every mouse of an inbred strain is genetically identical (syngeneic) to every other mouse of the same strain.

Indirect antigen presentation (or indirect allorecognition). In transplantation immunology, a pathway of presentation of donor (allogeneic) MHC molecules by recipient APCs that involves the same mechanisms used to present microbial proteins. The allogeneic MHC proteins are processed by recipient professional APCs, and peptides derived from the allogeneic MHC molecules are presented, in association with recipient (self) MHC molecules, to host T cells. In contrast to indirect antigen presentation, direct antigen presentation involves recipient T cell recognition of unprocessed allogeneic MHC molecules on the surface of graft cells.

Inflammation. A complex reaction of the innate immune system in vascularized tissues that involves the accumulation and activation of leukocytes and plasma proteins at a site of infection, toxin exposure, or cell injury. Inflammation is initiated by changes in blood vessels that promote leukocyte recruitment. Local adaptive immune responses can promote inflammation. Although inflammation serves a protective function in controlling infections and promoting tissue repair, it can also cause tissue damage and disease.

Inflammatory bowel disease (IBD). A group of disorders, including ulcerative colitis and Crohn's disease, characterized by chronic inflammation in the gastrointestinal tract. The etiology of IBD is not known, but some evidence indicates that immune mechanisms may

be involved. IBD develops in gene knockout mice lacking IL-2, IL-10, or the TCR α chain.

Innate immunity. Protection against infection that relies on mechanisms that exist before infection, are capable of a rapid response to microbes, and react in essentially the same way to repeated infections. The innate immune system includes epithelial barriers, phagocytic cells (neutrophils, macrophages), NK cells, the complement system, and cytokines, largely made by mononuclear phagocytes, that regulate and coordinate many of the activities of the cells of innate immunity.

Inositol 1,4,5-triphosphate (IP₃). A cytoplasmic signaling molecule generated by phospholipase C (PLCγ1)-mediated hydrolysis of the plasma membrane phospholipid PIP₂ during antigen activation of lymphocytes. The main function of IP₃ is to stimulate the release of intracellular stores of calcium from membrane-bound compartments such as the endoplasmic reticulum.

Insulin-dependent diabetes mellitus. A disease characterized by a lack of insulin that leads to various metabolic and vascular abnormalities. The insulin deficiency results from autoimmune destruction of the insulin-producing β cells of the islets of Langerhans in the pancreas, usually during childhood. CD4⁺ and CD8⁺ T cells, antibodies, and cytokines have been implicated in the islet cell damage. Also called type 1 diabetes mellitus.

Integrins. Heterodimeric cell surface proteins whose major functions are to mediate the adhesion of leukocytes to other leukocytes, endothelial cells, and extracellular matrix proteins. Integrins are important for T cell interactions with APCs and for migration of leukocytes from blood into tissues. The ligand-binding affinity of the integrins can be regulated by various stimuli, and the cytoplasmic domains of integrins bind to the cytoskeleton. There are two main subfamilies of integrins; the members of each family express a conserved β chain (β_1 , or CD29, and β_2 , or CD18) associated with different α chains. VLA-4 (very late activation protein-4) is a β_1 integrin expressed on T cells, and LFA-1 (leukocyte function-associated antigen-1) is a β_2 integrin expressed on T cells and phagocytes.

Interferon- γ (IFN- γ). A cytokine produced by T lymphocytes and NK cells whose principal function is to activate macrophages in both innate immune responses and adaptive cell-mediated immune responses. (IFN- γ is also called immune or type II interferon.)

Interleukin (IL). Another name for a cytokine originally used to describe a cytokine made by leukocytes that acts on leukocytes. The term is now generally used with a numerical suffix to designate a structurally defined cytokine regardless of its source or target.

Interleukin-1 (IL-1). A cytokine produced mainly by activated mononuclear phagocytes whose principal function is to mediate host inflammatory responses in innate immunity. The two forms of IL-1 (α and β) bind to the same receptors and have identical biologic effects, including induction of endothelial cell adhesion molecules, stimulation of chemokine production by endothelial cells and macrophages, stimulation of the synthesis of acute-phase reactants by the liver, and fever.

Interleukin-2 (IL-2). A cytokine produced by antigen-activated T cells that acts in an autocrine manner to stimulate T cell proliferation and also potentiates the apoptotic cell death of antigen-activated T cells. Thus, IL-2 is required for both the induction and self-regulation of T cell-mediated immune responses. IL-2 also stimulates the proliferation and effector functions of NK cells and B cells.

Interleukin-3 (IL-3). A cytokine produced by CD4⁺ T cells that promotes the expansion of immature marrow progenitors of all known mature blood cell types. IL-3 is also known as multilineage colony-stimulating factor.

Interleukin-4 (IL-4). A cytokine produced mainly by the T_H2 subset of CD4⁺ helper T cells whose functions include induction of differentiation of T_H2 cells from naive CD4⁺ precursors, stimulation of IgE production by B cells, and suppression of IFN- γ -dependent macrophage functions.

Interleukin-5 (IL-5). A cytokine produced by CD4⁺ T_H2 cells and activated mast cells that stimulates the growth and differentiation of eosinophils and activates mature eosinophils.

Interleukin-6 (IL-6). A cytokine produced by many cell types, including activated mononuclear phagocytes, endothelial cells, and fibroblasts, that functions in both innate and adaptive immunity. IL-6 stimulates the synthesis of acute-phase proteins by hepatocytes as well as the growth of antibody-producing B lymphocytes.

Interleukin-7 (IL-7). A cytokine secreted by bone marrow stromal cells that stimulates survival and expansion of immature, but lineage-committed, precursors of B and T lymphocytes.

Interleukin-10 (IL-10). A cytokine produced by activated macrophages and some helper T cells whose major function is to inhibit activated macrophages and therefore to maintain homeostatic control of innate and cell-mediated immune reactions.

Interleukin-12 (IL-12). A cytokine produced by mononuclear phagocytes and dendritic cells that serves as a mediator of the innate immune response to intracellular microbes and is a key inducer of cell-mediated immune responses to these microbes. IL-12 activates NK cells, promotes IFN- γ production by NK cells and T cells, enhances the cytolytic activity of NK cells and CTLs, and promotes the development of T_H1 cells.

Interleukin-15 (IL-15). A cytokine produced by mononuclear phagocytes and other cells in response to viral infections whose principal function is to stimulate the proliferation of NK cells. It is structurally similar to IL-2.

Interleukin-18 (IL-18). A cytokine produced by macrophages in response to LPS and other microbial products that functions together with IL-12 as an inducer of cell-mediated immunity. IL-18 synergizes with IL-12 in stimulating the production of IFN- γ by NK cells and T cells. IL-18 is structurally homologous to but functionally different from IL-1.

Intracellular bacterium. A bacterium that survives or replicates within cells, usually in endosomes. The principal defense against intracellular bacteria, such as *Mycobacterium tuberculosis*, is cell-mediated immunity.

Intraepidermal lymphocytes. T lymphocytes found within the epidermal layer of the skin. In the mouse, most of the intraepidermal T cells express the $\gamma\delta$ form of TCR (see **Intraepithelial T lymphocytes**).

Intraepithelial T lymphocytes. T lymphocytes present in the epidermis of the skin and in mucosal epithelia that typically express a limited diversity of antigen receptors. Some of these lymphocytes may recognize microbial products, such as glycolipids, associated with nonpolymorphic class I MHC-like molecules. Intraepithelial T lymphocytes may be considered effector cells of innate immunity and function in host defense by secreting cytokines and activating phagocytes and by killing infected cells.

Invariant chain (I_i). A nonpolymorphic protein that binds to newly synthesized class II MHC molecules in the endoplasmic reticulum. The invariant chain prevents loading of the class II MHC peptide-binding cleft with peptides present in the endoplasmic reticulum, and such peptides are left to associate with class I molecules. The invariant chain also promotes folding and assembly of class II molecules and directs newly formed class II molecules to the specialized endosomal MHC compartment, where peptide loading takes place.

Isotype. One of five types of antibodies, determined by which of five different forms of heavy chain are present. Antibody isotypes include IgM, IgD, IgG, IgA, and IgE, and each isotype performs a different set of effector functions. Additional structural variations characterize distinct subtypes of IgG and IgA.

J chain. A small polypeptide that is disulfide bonded to the tail pieces of multimeric IgM and IgA antibodies.

JAK/STAT signaling pathway. A signaling pathway initiated by cytokine binding to type I and type II cytokine receptors. This pathway sequentially involves activation of receptor-associated Janus kinase (JAK) tyrosine kinases, JAK-mediated tyrosine phosphorylation of the cytoplasmic tails of cytokine receptors, docking of signal transducers and activators of transcription (STATs) to the phosphorylated receptor chains, JAK-mediated tyrosine phosphorylation of the associated STATs, dimerization and nuclear translocation of the STATs, and STAT binding to regulatory regions of target genes causing transcriptional activation of those genes.

Janus kinases (JAK kinases). A family of tyrosine kinases that associate with the cytoplasmic tails of several different cytokine receptors, including the receptors for IL-2, IL-4, IFN- γ , IL-12, and others. In response to cytokine binding and receptor dimerization, JAKs phosphorylate the cytokine receptors to permit the binding of STATs, and then the JAKs phosphorylate and thereby activate the STATs. Different JAK kinases associate with different cytokine receptors.

Joining (J) segments. Short coding sequences, between the variable (V) and constant (C) gene segments in all the Ig and TCR loci, that together with D segments are somatically recombined with V segments during lymphocyte development. The resulting recombined VDJ DNA codes for the carboxyl terminal ends of the antigen receptor V regions, including the third hypervariable (CDR) regions. Random use of different

J segments contributes to the diversity of the antigen receptor repertoire.

Functional diversity. The diversity in antibody and TCR repertoires that is attributed to the random addition or removal of nucleotide sequences at junctions between V, D, and J gene segments.

Kaposi's sarcoma. A malignant tumor of vascular cells that frequently arises in patients with AIDS. Kaposi's sarcoma is associated with infection by the Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8).

Killer Ig-like receptors (KIRs). Ig superfamily receptors expressed by NK cells that recognize different alleles of HLA-A, HLA-B, and HLA-C molecules. Some KIRs have signaling components with ITIMs in their cytoplasmic tails, and these deliver inhibitory signals to inactivate the NK cells. Some members of the KIR family have short cytoplasmic tails without ITIMs, and these function as activating receptors.

Knockout mouse. A mouse with a targeted disruption of one or more genes that is created by homologous recombination techniques. Knockout mice lacking functional genes encoding cytokines, cell surface receptors, signaling molecules, and transcription factors have provided extensive information about the roles of these molecules in the immune system.

Langerhans cells. Immature dendritic cells found as a continuous meshwork in the epidermal layer of the skin whose major function is to trap and transport protein antigens to draining lymph nodes. During their migration to the lymph nodes, Langerhans cells mature into lymph node dendritic cells, which can efficiently present antigen to naive T cells.

Large granular lymphocyte. Another name for an NK cell based on the morphologic appearance of this cell type in the blood.

Late-phase reaction. A component of the immediate hypersensitivity reaction that ensues 2 to 4 hours after mast cell and basophil degranulation and that is characterized by an inflammatory infiltrate of eosinophils, basophils, neutrophils, and lymphocytes. Repeated bouts of this late-phase inflammatory reaction can cause tissue damage.

Lck. An Src family nonreceptor tyrosine kinase that noncovalently associates with the cytoplasmic tails of CD4 and CD8 molecules in T cells and is involved in the early signaling events of antigen-induced T cell activation. Lck mediates tyrosine phosphorylation of the cytoplasmic tails of CD3 and ζ proteins of the TCR complex.

Lectin pathway of complement activation. A pathway of complement activation triggered, in the absence of antibody, by the binding of microbial polysaccharides to circulating lectins such as MBL. MBL is structurally similar to C1q and activates the C1r–C1s enzyme complex (like C1q) or activates another serine esterase, called mannose-binding protein–associated serine esterase. The remaining steps of the lectin pathway, beginning with cleavage of C4, are the same as the classical pathway.

Leishmania. An obligate intracellular protozoan parasite that infects macrophages and can cause a

chronic inflammatory disease involving many tissues. *Leishmania* infection in mice has served as a model system for study of the effector functions of several cytokines and the helper T cell subsets that produce them. T_H1 responses to *Leishmania major* and associated IFN- γ production control infection, whereas T_H2 responses with IL-4 production lead to disseminated lethal disease.

Lethal hit. A term used to describe the events that result in irreversible damage to a target cell when a CTL binds to it. The lethal hit includes CTL granule exocytosis, perforin polymerization in the target cell membrane, and entry of calcium ions and apoptosis-inducing enzymes (granzymes) into the target cell cytoplasm.

Leukemia. A malignant disease of bone marrow precursors of blood cells in which large numbers of leukemic cells usually occupy the bone marrow and often circulate in the blood stream. Lymphocytic leukemias are derived from B or T cell precursors, myelogenous leukemias are derived from granulocyte or monocyte precursors, and erythroid leukemias are derived from red blood cell precursors.

Leukocyte adhesion deficiency (LAD). One of a rare group of immunodeficiency diseases with infectious complications that is caused by defective expression of the leukocyte adhesion molecules required for tissue recruitment of phagocytes and lymphocytes. LAD-1 is due to mutations in the gene encoding the CD18 protein, which is part of β_2 integrins. LAD-2 is caused by mutations in a gene that encodes a fucose transporter involved in the synthesis of leukocyte ligands for endothelial selectins.

Leukotrienes. A class of arachidonic acid–derived lipid inflammatory mediators produced by the lipoxygenase pathway in many cell types. Mast cells make abundant leukotriene C_4 (LTC $_4$) and its degradation products LTD $_4$ and LTE $_4$, which bind to specific receptors on smooth muscle cells and cause prolonged bronchoconstriction. Leukotrienes contribute to the pathologic processes of bronchial asthma. Collectively, LTC $_4$, LTD $_4$, and LTE $_4$ constitute what was once called a slow-reacting substance of anaphylaxis.

Lipopolysaccharide. Synonymous with endotoxin.

Live viral vaccine. A vaccine composed of a live but nonpathogenic (attenuated) form of a virus. Attenuated viruses carry mutations that interfere with the viral life cycle or pathogenesis. Because live virus vaccines actually infect the recipient cells, they can effectively stimulate immune responses, such as the CTL response, that are optimal for protecting against wild-type viral infection. A commonly used live virus vaccine is the Sabin poliovirus vaccine, and there is much interest in development of an attenuated live virus vaccine to protect against HIV infection.

LMP-2 and LMP-7. Two catalytic subunits of the proteasome, the organelle that degrades cytosolic proteins into peptides in the class I MHC pathway of antigen presentation. LMP-2 and LMP-7 are encoded by genes in the MHC, are up-regulated by IFN- γ , and are particularly important for generating class I MHC-binding peptides.

Lymph node. Small nodular, encapsulated aggregates of lymphocyte-rich tissue situated along lymphatic channels throughout the body where adaptive immune responses to lymph-borne antigens are initiated.

Lymphatic system. A system of vessels throughout the body that collects tissue fluid called lymph, originally derived from the blood, and returns it, through the thoracic duct, to the circulation. Lymph nodes are interspersed along these vessels and trap and retain antigens present in the lymph.

Lymphocyte homing. The directed migration of subsets of circulating lymphocytes into particular tissue sites. Lymphocyte homing is regulated by the selective expression of adhesion molecules, called homing receptors, on the lymphocytes and the tissue-specific expression of endothelial ligands for these homing receptors, called addressins, in different vascular beds. For example, some T lymphocytes preferentially home to intestinal lymphoid tissue (e.g., Peyer's patches), and this directed migration is regulated by binding of the VLA-4 integrin on the T cells to the MadCAM addressin on Peyer's patch endothelium.

Lymphocyte maturation. The process by which pluripotent bone marrow precursor cells develop into mature, antigen receptor–expressing naive B or T lymphocytes that populate peripheral lymphoid tissues. This process takes place in the specialized environments of the bone marrow (for B cells) and the thymus (for T cells).

Lymphocyte migration. The movement of lymphocytes from the blood stream into peripheral tissues.

Lymphocyte recirculation. The continuous movement of lymphocytes through the blood stream and lymphatics, between the lymph nodes or spleen, and, if activated, to peripheral inflammatory sites.

Lymphocyte repertoire. The complete collection of antigen receptors and therefore antigen specificities expressed by the B and T lymphocytes of an individual.

Lymphoid follicle. A B cell–rich region of a lymph node or the spleen that is the site of antigen-induced B cell proliferation and differentiation. In T cell–dependent B cell responses to protein antigens, a germinal center forms within the follicles.

Lymphokine. An old name for a cytokine (soluble protein mediator of immune responses) produced by lymphocytes.

Lymphokine-activated killer (LAK) cell. NK cells with enhanced cytolytic activity for tumor cells as a result of exposure to high doses of IL-2. LAK cells generated *in vitro* have been adoptively transferred back into patients with cancer to treat their tumors.

Lymphoma. A malignant tumor of B or T lymphocytes usually arising in and spreading between lymphoid tissues but that may spread to other tissues. Lymphomas often express phenotypic characteristics of the normal lymphocytes from which they were derived.

Lymphotoxin (LT, TNF- β). A cytokine produced by T cells that is homologous to and binds to the same receptors as TNF. Like TNF, LT has proinflammatory effects, including endothelial and neutrophil activation. LT is also critical for the normal development of lymphoid organs.

Lysosome. A membrane-bound, acidic organelle abundant in phagocytic cells that contains proteolytic enzymes that degrade proteins derived both from the extracellular environment and from within the cell. Lysosomes are involved in the class II MHC pathway of antigen processing.

M cells. Specialized epithelial cells overlying Peyer's patches in the gut that play a role in delivering antigens to Peyer's patches.

Macrophage. A tissue-based phagocytic cell derived from blood monocytes that plays important roles in innate and adaptive immune responses. Macrophages are activated by microbial products such as endotoxin and by T cell cytokines such as IFN- γ . Activated macrophages phagocytose and kill microorganisms, secrete proinflammatory cytokines, and present antigens to helper T cells. Macrophages may assume different morphologic forms in different tissues, including the microglia of the central nervous system, Kupffer cells in the liver, alveolar macrophages in the lung, and osteoclasts in bone.

Major histocompatibility complex (MHC). A large genetic locus (on human chromosome 6 and mouse chromosome 17) that includes the highly polymorphic genes encoding the peptide-binding molecules recognized by T lymphocytes. The MHC locus also includes genes encoding cytokines, molecules involved in antigen processing, and complement proteins.

Major histocompatibility complex (MHC) molecule. A heterodimeric membrane protein encoded in the MHC locus that serves as a peptide display molecule for recognition by T lymphocytes. Two structurally distinct types of MHC molecules exist. Class I MHC molecules are present on most nucleated cells, bind peptides derived from cytosolic proteins, and are recognized by CD8 $^+$ T cells. Class II MHC molecules are restricted largely to professional APCs, bind peptides derived from endocytosed proteins, and are recognized by CD4 $^+$ T cells.

Mannose receptor. A carbohydrate-binding receptor (lectin) expressed by macrophages that binds-mannose and fucose residues on microbial cell walls and mediates phagocytosis of the organisms.

Mannose-binding lectin (MBL). A plasma protein that binds to mannose residues on bacterial cell walls and acts as an opsonin by promoting phagocytosis of the bacterium by macrophages. Macrophages express a surface receptor for C1q that can also bind MBL and mediate uptake of the opsonized organisms.

Marginal zone. A peripheral region of splenic lymphoid follicles containing macrophages that are particularly efficient at trapping polysaccharide antigens. Such antigens may persist for prolonged periods on the surfaces of marginal zone macrophages, where they are recognized by specific B cells, or they may be transported into follicles.

Mast cell. The major effector cell of immediate hypersensitivity (allergic) reactions. Mast cells are derived from the marrow, reside in most tissues adjacent to blood vessels, express a high-affinity Fc receptor for IgE, and contain numerous mediator-filled granules. Antigen-induced cross-linking of IgE bound

to the mast cell Fc receptors causes release of their granule contents as well as new synthesis and secretion of other mediators, leading to an immediate hypersensitivity reaction.

Mature B cell. IgM- and IgD-expressing, functionally competent naive B cells that represent the final stage of B cell maturation in the bone marrow and that populate peripheral lymphoid organs.

Membrane attack complex (MAC). A lytic complex of the terminal components of the complement cascade, including multiple copies of C9, that forms in the membranes of target cells. The MAC causes lethal ionic and osmotic changes in cells.

Memory. The property of the adaptive immune system to respond more rapidly, with greater magnitude, and more effectively to a repeated exposure to an antigen, compared with the response to the first exposure.

Memory lymphocytes. B or T lymphocytes that mediate rapid and enhanced (i.e., memory or recall) responses to second and subsequent exposures to antigens. Memory B and T cells are produced by antigen stimulation of naive lymphocytes and survive in a functionally quiescent state for many years after the antigen is eliminated.

MHC class II (MHC) compartment. A subset of endosomes (membrane-bound vesicles involved in cell trafficking pathways) found in macrophages and human B cells that are important in the class II MHC pathway of antigen presentation. The MHC contains all the components required for formation of peptide-class II MHC molecule complexes, including the enzymes that degrade protein antigens, class II molecules, invariant chain, and HLA-DM.

MHC restriction. The characteristic of T lymphocytes that they recognize a foreign peptide antigen only when it is bound to a particular allelic form of an MHC molecule.

MHC-tetramer. A reagent used to identify and enumerate T cells that specifically recognize a particular MHC-peptide complex. The reagent consists of four recombinant, biotinylated MHC molecules (usually class I) bound to a fluorochrome-labeled avidin molecule and loaded with a peptide. T cells that bind the MHC-tetramer can be detected by flow cytometry.

β_2 -Microglobulin. The light chain of a class I MHC molecule. β_2 -Microglobulin is an extracellular protein encoded by a nonpolymorphic gene outside the MHC, is structurally homologous to an Ig domain, and is invariant among all class I molecules.

Mitogen-activated protein (MAP) kinase cascade. A signal transduction cascade initiated by the active form of the Ras protein and involving the sequential activation of three serine/threonine kinases, the last one being MAP kinase. MAP kinase in turn phosphorylates and activates other enzymes or transcription factors. The MAP kinase pathway is one of several signal pathways activated by antigen binding to the TCR.

Mixed leukocyte reaction (MLR). An *in vitro* reaction of alloreactive T cells from one individual against MHC antigens on blood cells from another individual. The MLR involves proliferation of and cytokine secretion

by both CD4⁺ and CD8⁺ T cells and is used as a screening test to assess the compatibility of a potential graft recipient with a potential donor.

Microbial mimicry. A postulated mechanism of autoimmunity triggered by infection with a microbe containing antigens that cross-react with self antigens. Immune responses to the microbe result in reactions against self tissues.

Monoclonal antibody. An antibody that is specific for one antigen and is produced by a B cell hybridoma (a cell line derived by the fusion of a single normal B cell and an immortal B cell tumor line). Monoclonal antibodies are widely used in research and clinical diagnosis and therapy.

Monocyte. A type of bone marrow-derived circulating blood cell that is the precursor of tissue macrophages. Monocytes are actively recruited into inflammatory sites, where they differentiate into macrophages.

Monocyte colony-stimulating factor (M-CSF). A cytokine made by activated T cells, macrophages, endothelial cells, and stromal fibroblasts that stimulates the production of monocytes from bone marrow precursor cells.

Monokine. An old name for a cytokine produced by mononuclear phagocytes.

Mononuclear phagocytes. Cells with a common bone marrow lineage whose primary function is phagocytosis. These cells function as accessory cells in the recognition and activation phases of adaptive immune responses and as effector cells in innate and adaptive immunity. Mononuclear phagocytes circulate in the blood in an incompletely differentiated form called monocytes, and once they settle in tissues, they mature into macrophages.

Mucosa-associated lymphoid tissue. Lymphocytes and accessory cells within the mucosa of the gastrointestinal and respiratory tracts that are sites of adaptive immune responses to environmental antigens. Mucosa-associated lymphoid tissues include intraepithelial lymphocytes, mainly T cells, and organized collections of lymphocytes, often rich in B cells, below mucosal epithelia, such as Peyer's patches in the gut or pharyngeal tonsils.

Mucosal immune system. A part of the immune system that responds to and protects against microbes that enter the body through mucosal surfaces, such as the gastrointestinal and respiratory tracts. The mucosal immune system is composed of mucosa-associated lymphoid tissues, which are collections of lymphocytes and accessory cells in the epithelia and lamina propria of mucosal surfaces.

Multiple myeloma. A malignant tumor of antibody-producing B cells that often secretes Igs or parts of Ig molecules. The monoclonal antibodies produced by multiple myelomas were critical for early biochemical analyses of antibody structure.

Mycobacterium. A genus of aerobic bacteria, many species of which can survive within phagocytes and cause disease. The principal host defense against mycobacteria such as *M. tuberculosis* is cell-mediated immunity.

N nucleotides. The name given to nucleotides randomly added to the junctions between V, D, and J gene segments in Ig or TCR genes during lymphocyte development. The addition of up to 20 of these nucleotides, which is mediated by the enzyme terminal deoxynucleotidyl transferase, contributes to the diversity of the antibody and TCR repertoires.

Naive lymphocyte. A mature B or T lymphocyte that has not previously encountered antigen, nor is it the progeny of an antigen-stimulated mature lymphocyte. When naive lymphocytes are stimulated by antigen, they differentiate into effector lymphocytes, such as antibody-secreting B cells or helper T cells and CTLs. Naive lymphocytes have surface markers and recirculation patterns that are distinct from those of previously activated lymphocytes. ("Naive" also refers to an unimmunized individual.)

Natural antibodies. IgM antibodies, largely produced by B-1 cells, specific for bacteria that are common in the environment and gastrointestinal tract. Normal individuals contain natural antibodies without any evidence of infection, and these antibodies serve as a preformed defense mechanism against microbes that succeed in penetrating epithelial barriers. Some of these antibodies cross-react with ABO blood group antigens and are responsible for transfusion reactions.

Natural killer (NK) cells. A subset of bone marrow-derived lymphocytes, distinct from B or T cells, that function in innate immune responses to kill microbe-infected cells by direct lytic mechanisms and by secreting IFN- γ . NK cells do not express clonally distributed antigen receptors like Ig receptors or TCRs, and their activation is regulated by a combination of cell surface stimulatory and inhibitory receptors, the latter recognizing self MHC molecules.

Negative selection. The process by which developing lymphocytes that express self-reactive antigen receptors are eliminated, thereby contributing to the maintenance of self-tolerance. Negative selection of developing T lymphocytes (thymocytes) is best understood and involves high-avidity binding of a thymocyte to self MHC molecules with bound peptides on thymic APCs leading to apoptotic death of the thymocyte.

Neonatal Fc receptor (FcRn). An IgG-specific Fc receptor that mediates the transport of maternal IgG across the placenta and the neonatal intestinal epithelium. FcRn resembles a class I MHC molecule. An adult form of this receptor functions to protect plasma IgG antibodies from catabolism.

Neonatal immunity. Passive humoral immunity to infections in mammals in the first months of life, before full development of the immune system. Neonatal immunity is mediated by maternally produced antibodies transported across the placenta into the fetal circulation before birth or derived from ingested milk and transported across the gut epithelium.

Neutrophil (also polymorphonuclear leukocyte, PMN). A phagocytic cell characterized by a segmented lobular nucleus and cytoplasmic granules filled with degradative enzymes. PMNs are the most abundant type of circulating white blood cells and are the major cell

type mediating acute inflammatory responses to bacterial infections.

Nitric oxide. A biologic effector molecule with a broad range of activities that in macrophages functions as a potent microbicidal agent to kill ingested organisms.

Nitric oxide synthase. A member of a family of enzymes that synthesize the vasoactive and microbicidal compound nitric oxide from L-arginine. Macrophages express an inducible form of this enzyme on activation by various microbial or cytokine stimuli.

Nuclear factor κ B (NF- κ B). A family of transcription factors composed of homodimers or heterodimers of proteins homologous to the c-Rel protein. NF- κ B proteins are important in the transcription of many genes in both innate and adaptive immune responses.

Nuclear factor of activated T cells (NFAT). A transcription factor required for the expression of IL-2, IL-4, TNF, and other cytokine genes. The four different NFATs are each encoded by separate genes; NFATp and NFATc are found in T cells. Cytoplasmic NFAT is activated by calcium/calmodulin-dependent, calcineurin-mediated dephosphorylation that permits NFAT to translocate into the nucleus and bind to consensus binding sequences in the regulatory regions of IL-2, IL-4, and other cytokine genes, usually in association with other transcription factors such as AP-1.

Nude mouse. A strain of mice that lacks development of the thymus, and therefore T lymphocytes, as well as hair follicles. Nude mice have been used experimentally to define the role of T lymphocytes in immunity and disease.

Oncofetal antigen. Proteins that are expressed at high levels on some types of cancer cells and in normal developing (fetal) but not adult tissues. Antibodies specific for these proteins are often used in histopathologic identification of tumors or to monitor the progression of tumor growth in patients. CEA (CD66) and alpha-fetoprotein are two oncofetal antigens commonly expressed by certain carcinomas.

Opsonin. A macromolecule that becomes attached to the surface of a microbe and can be recognized by surface receptors of neutrophils and macrophages and that increases the efficiency of phagocytosis of the microbe. Opsonins include IgG antibodies, which are recognized by the Fc γ receptor on phagocytes, and fragments of complement proteins, which are recognized by CR1 (CD35) and by the leukocyte integrin Mac-1.

Opsonization. The process of attaching opsonins, such as IgG or complement fragments, to microbial surfaces to target the microbes for phagocytosis.

Oral tolerance. The suppression of systemic humoral and cell-mediated immune responses to an antigen after the oral administration of that antigen as a result of anergy of antigen-specific T cells or the production of immunosuppressive cytokines such as transforming growth factor- β . Oral tolerance is a possible mechanism for preventing immune responses to food antigens and to bacteria that normally reside as commensals in the intestinal lumen.

P nucleotides. Short inverted repeat nucleotide sequences in the VDJ junctions of rearranged Ig and

TCR genes that are generated by RAG-1- and RAG-2-mediated asymmetric cleavage of hairpin DNA intermediates during somatic recombination events. P nucleotides contribute to the junctional diversity of antigen receptors.

Paracrine factor. A molecule that acts on cells in proximity to the cell that produces the factor. Most cytokines act in a paracrine fashion.

Partial agonist. A variant peptide ligand of a TCR that induces only a subset of the functional responses by the T cell or responses entirely different from responses to the unaltered (native) peptide. For instance, a partial agonist may stimulate production of only some of the many cytokines that are induced by the native peptide or quantitatively smaller responses. Partial agonist peptides are usually synthetic peptides in which one or two TCR contact residues have been changed; they are also called APLs.

Passive immunity. The form of immunity to an antigen that is established in one individual by transfer of antibodies or lymphocytes from another individual who is immune to that antigen. The recipient of such a transfer can become immune to the antigen without ever having been exposed to or having responded to the antigen. An example of passive immunity is the transfer of human sera containing antibodies specific for certain microbial toxins or snake venom to a previously unimmunized individual.

Pathogenicity. The ability of a microorganism to cause disease. Multiple mechanisms may contribute to pathogenicity, including production of toxins, stimulation of host inflammatory responses, and perturbation of host cell metabolism.

Pattern recognition receptors. Receptors of the innate immune system that recognize frequently encountered structures called molecular patterns produced by microorganisms and that facilitate innate immune responses against the microorganisms. Examples of pattern recognition receptors include CD14 receptors on macrophages, which bind bacterial endotoxin leading to macrophage activation, and the mannose receptor on phagocytes, which binds microbial glycoproteins or glycolipids.

Pentraxins. A family of plasma proteins that contain five identical globular subunits; includes the acute-phase reactant C-reactive protein.

Peptide-binding cleft. The portion of an MHC molecule that binds peptides for display to T cells. The cleft is composed of paired α -helices resting on a floor made up of an eight-stranded β -pleated sheet. The polymorphic residues, which are the amino acids that vary among different MHC alleles, are located in and around this cleft.

Perforin. A pore-forming protein, homologous to the C9 complement protein, that is present as a monomer in the granules of CTLs and NK cells. When perforin monomers are released from the granules of activated CTLs or NK cells, they undergo polymerization in the lipid bilayer of the target cell plasma membrane and form a large aqueous channel. This channel can cause osmotic lysis of the target cell and serve as a

channel for the influx of enzymes derived from the CTL granules.

Periarteriolar lymphoid sheath (PALS). A cuff of lymphocytes surrounding small arterioles in the spleen, adjacent to lymphoid follicles. A PALS contains mainly T lymphocytes, about two thirds of which are CD4⁺ and one third CD8⁺. In humoral immune responses to protein antigens, B lymphocytes are activated at the interface between the PALS and follicles and then migrate into the follicles to form germinal centers.

Peripheral lymphoid organs and tissues. Organized collections of lymphocytes and accessory cells, including the spleen, lymph nodes, and mucosa-associated lymphoid tissues, in which adaptive immune responses are initiated.

Peripheral tolerance. Physiologic unresponsiveness to self antigens that are present in peripheral tissues and not usually in the generative lymphoid organs. Peripheral tolerance is induced by the recognition of antigens without adequate levels of the costimulators required for lymphocyte activation or by persistent and repeated stimulation by these self antigens.

Peyer's patches. Organized lymphoid tissue in the lamina propria of the small intestine in which immune responses to ingested antigens may be initiated. Peyer's patches are composed mostly of B cells, with smaller numbers of T cells and accessory cells, all arranged in follicles similar to those found in lymph nodes, often with germinal centers.

Phagocytosis. The process by which certain cells of the innate immune system, including macrophages and neutrophils, engulf large particles (>0.5 μ m in diameter) such as intact microbes. The cell surrounds the particle with extensions of its plasma membrane by an energy- and cytoskeleton-dependent process; this process results in the formation of an intracellular vesicle called a phagosome, which contains the ingested particle.

Phagosome. A membrane-bound intracellular vesicle that contains microbes or particulate material from the extracellular environment. Phagosomes are formed during the process of phagocytosis, and fusion with other vesicular structures such as lysosomes leads to enzymatic degradation of the ingested material.

Phosphatase (proteinphosphatase). An enzyme that removes phosphate groups from the side chains of certain amino acid residues of proteins. Protein phosphatases in lymphocytes, such as CD45 or calcineurin, regulate the activity of various signal transduction molecules and transcription factors. Some protein phosphatases may be specific for phosphotyrosine residues and others for phosphoserine and phosphothreonine residues.

Phospholipase C γ (PLC γ). An enzyme that catalyzes hydrolysis of the plasma membrane phospholipid PIP₂ to generate two signaling molecules, IP₃ and DAG. PLC γ becomes activated in lymphocytes by antigen binding to the antigen receptor.

Phytohemagglutinin (PHA). A carbohydrate-binding protein, or lectin, produced by plants that cross-links human T cell surface molecules, including the T cell

receptor, thereby inducing polyclonal activation and agglutination of T cells. PHA is frequently used in experimental immunology to study T cell activation. In clinical medicine, PHA is used to assess whether a patient's T cells are functional or to induce T cell mitosis for the purpose of generating karyotypic data.

Plasma cell. A terminally differentiated antibody-secreting B lymphocyte with a characteristic histologic appearance, including an oval shape, eccentric nucleus, and perinuclear halo.

Platelet-activating factor (PAF). A lipid mediator derived from membrane phospholipids in several cell types, including mast cells and endothelial cells. PAF can cause bronchoconstriction and vascular dilatation and leak and may be an important mediator in asthma.

Polyclonal activators. Agents that are capable of activating many clones of lymphocytes, regardless of their antigen specificities. Examples of polyclonal activators include anti-IgM antibodies for B cells and anti-CD3 antibodies, bacterial superantigens, and PHA for T cells.

Poly-Ig receptor. An Fc receptor expressed by mucosal epithelial cells that mediates the transport of IgA and IgM through the epithelial cells into the intestinal lumen.

Polymerase chain reaction (PCR). A rapid method of copying and amplifying specific DNA sequences up to about 1 kb in length that is widely used as a preparative and analytical technique in all branches of molecular biology. The method relies on the use of short oligonucleotide primers complementary to the sequences at the ends of the DNA to be amplified and involves repetitive cycles of melting, annealing, and synthesis of DNA.

Polymorphism. The existence of two or more alternative forms, or variants, of a gene that are present at stable frequencies in a population. Each common variant of a polymorphic gene is called an allele, and one individual may carry two different alleles of a gene, each inherited from a different parent. The MHC genes are the most polymorphic genes in the mammalian genome.

Polyvalency. The presence of multiple identical copies of an epitope on a single antigen molecule, cell surface, or particle. Polyvalent antigens, such as bacterial capsular polysaccharides, are often capable of activating B lymphocytes independent of helper T cells.

Positive selection. The process by which developing T cells in the thymus (thymocytes) whose TCRs bind to self MHC molecules are rescued from programmed cell death, whereas thymocytes whose receptors do not recognize self MHC molecules die by default. Positive selection ensures that mature T cells are self MHC restricted and that CD8⁺ T cells are specific for complexes of peptides with class I MHC molecules and CD4⁺ T cells for complexes of peptides with class II MHC molecules.

Pre-B cell. A developing B cell present only in hematopoietic tissues that is at a maturational stage characterized by expression of cytoplasmic Ig μ heavy chains and surrogate light chains but not Ig light

chains. Pre-B cell receptors composed of μ chains and surrogate light chains deliver signals that stimulate further maturation of the pre-B cell into an immature B cell.

Pre-B cell receptor. A receptor expressed on maturing B lymphocytes at the pre-B cell stage that is composed of an Ig μ heavy chain and an invariant surrogate light chain. The surrogate light chain is composed of two proteins, including the $\lambda 5$ protein, which is homologous to the λ light chain C domain, and the V pre-B protein, which is homologous to a V domain. The pre-B cell receptor associates with the Ig α and Ig β signal transduction proteins to form the pre-B cell receptor complex. Pre-B cell receptors are required for stimulating the proliferation and continued maturation of the developing B cell. It is not known whether the pre-B cell receptor binds a specific ligand.

Pre-cytolytic T lymphocyte (pre-CTL). A mature, naive CD8⁺ T lymphocyte that cannot perform effector functions but, on activation by antigen and costimulators, will differentiate into a CTL capable of lysing target cells and secreting cytokines.

Pre-T cell. A developing T lymphocyte in the thymus at a maturational stage characterized by expression of the TCR β chain, but not the α chain or CD4 or CD8. In pre-T cells, the TCR β chain is found on the cell surface as part of the pre-T cell receptor.

Pre-T cell receptor. A receptor expressed on the surface of pre-T cells that is composed of the TCR β chain and an invariant pre-T α protein. This receptor associates with CD3 and ζ molecules to form the pre-T cell receptor complex. The function of this complex is similar to that of the pre-B cell receptor in B cell development, namely, the delivery of signals that stimulate further proliferation, antigen receptor gene rearrangements, and other maturational events. It is not known whether the pre-T cell receptor binds a specific ligand.

Pre-Ta. An invariant transmembrane protein with a single extracellular Ig-like domain that associates with TCR β chain in pre-T cells to form the pre-T cell receptor.

Primary immune response. An adaptive immune response that occurs after the first exposure of an individual to a foreign antigen. Primary responses are characterized by relatively slow kinetics and small magnitude compared with the responses after a second or subsequent exposure.

Primary immunodeficiency. A genetic defect in which an inherited deficiency in some aspect of the innate or adaptive immune system leads to an increased susceptibility to infections. Primary immunodeficiency is frequently manifested early in infancy and childhood but is sometimes clinically detected later in life.

Pro-B cell. A developing B cell in the bone marrow that is the earliest cell committed to the B lymphocyte lineage. Pro-B cells do not produce Ig, but they can be distinguished from other immature cells by the expression of B lineage-restricted surface molecules such as CD19 and CD10.

Professional antigen-presenting cells (professional APCs). APCs for naive helper T lymphocytes, used to

refer to dendritic cells, mononuclear phagocytes, and B lymphocytes, all of which are capable of expressing class II MHC molecules and costimulators. The most important professional APCs for initiating primary T cell responses are dendritic cells.

Programmed cell death. A pathway of cell death by apoptosis that occurs in lymphocytes deprived of necessary survival stimuli, such as growth factors or costimulators. Programmed cell death, also called death by neglect or passive cell death, is characterized by the release of mitochondrial cytochrome *c* into the cytoplasm, activation of caspase-9, and initiation of the apoptotic pathway.

Promoter. A DNA sequence immediately 5' to the transcription start site of a gene where the proteins that initiate transcription bind. The term *promoter* is often used to mean the entire 5' regulatory region of a gene, including enhancers, which are additional sequences that bind transcription factors and interact with the basal transcription complex to increase the rate of transcriptional initiation. Other enhancers may be located at a significant distance from the promoter, either 5' of the gene, in introns, or 3' of the gene.

Prostaglandins. A class of lipid inflammatory mediators derived from arachidonic acid in many cell types through the cyclooxygenase pathway. Activated mast cells make prostaglandin D₂ (PGD₂), which binds to receptors on smooth muscle cells and acts as a vasodilator and a bronchoconstrictor. PGD₂ also promotes neutrophil chemotaxis and accumulation at inflammatory sites.

Pro-T cell. A developing T cell in the thymic cortex that is a recent arrival from the bone marrow and does not express TCRs, CD3, ζ chains, or CD4 or CD8 molecules. Pro-T cells are also called double-negative thymocytes.

Protease. An enzyme that cleaves peptide bonds and thereby breaks proteins down into peptides. Different kinds of proteases have different specificities for bonds between particular amino acid residues. Proteases inside phagocytes are important for killing ingested microbes during innate immune responses, and proteases released from phagocytes at inflammatory sites can cause tissue damage. Proteases in APCs are critical for generating peptide fragments of protein antigens that bind to MHC molecules during T cell-mediated immune responses.

Proteasome. A large multiprotein enzyme complex with a broad range of proteolytic activity that is found in the cytoplasm of most cells and generates from cytosolic proteins the peptides that bind to class I MHC molecules. Proteins are targeted for proteasomal degradation by covalent linkage of ubiquitin molecules.

Protein kinase C (PKC). Any of several isoforms of an enzyme that mediates the phosphorylation of serine and threonine residues in many different protein substrates and thereby serves to propagate various signal transduction pathways leading to transcription factor activation. In T and B lymphocytes, PKC is activated by DAG, which is generated in response to antigen receptor ligation.

Protein tyrosine kinases (PTKs). Enzymes that mediate the phosphorylation of tyrosine residues in proteins and thereby promote phosphotyrosine-dependent protein-protein interactions. PTKs are involved in numerous signal transduction pathways in cells of the immune system.

Protozoa. Single-celled eukaryotic organisms, many of which are human parasites and cause diseases. Examples of pathogenic protozoa include *Entamoeba histolytica*, which causes amebic dysentery; *Plasmodium*, which causes malaria; and *Leishmania*, which causes leishmaniasis. Protozoa stimulate both innate and adaptive immune responses. It has proved difficult to develop effective vaccines against many of these organisms.

Provirus. A DNA copy of the genome of a retrovirus that is integrated into the host cell genome and from which viral genes are transcribed and the viral genome is reproduced. HIV proviruses can remain inactive for long periods and thereby represent a latent form of HIV infection that is not accessible to immune defense.

Purified antigen (subunit) vaccine. A vaccine composed of purified antigens or subunits of microbes. Examples of this type of vaccine include diphtheria and tetanus toxoids, pneumococcus and *Haemophilus influenzae* polysaccharide vaccines, and purified polypeptide vaccines against hepatitis B and influenza virus. Purified antigen vaccines may stimulate antibody and helper T cell responses, but they do not generate CTL responses.

Pyogenic bacteria. Bacteria, such as the gram-positive staphylococci and streptococci, that induce inflammatory responses rich in polymorphonuclear leukocytes (giving rise to pus). Antibody responses to these bacteria greatly enhance the efficacy of innate immune effector mechanisms to clear infections.

Rac. A small guanine nucleotide-binding protein that is activated by the GDP-GTP exchange factor Vav during the early events of T cell activation. GTP•Rac triggers a three-step protein kinase cascade that culminates in activation of the stress-activated protein (SAP) kinase, c-Jun N-terminal kinase (JNK), and p38 kinase, which are similar to the MAP kinases.

Radioimmunoassay. A highly sensitive and specific immunologic method of quantifying the concentration of an antigen in a solution that relies on a radioactively labeled antibody specific for the antigen. Usually, two antibodies specific for the antigen are used. The first antibody is unlabeled but attached to a solid support, where it binds and immobilizes the antigen whose concentration is being determined. The amount of the second, labeled antibody that binds to the immobilized antigen, as determined by radioactive decay detectors, is proportional to the concentration of antigen in the test solution.

Ras. A member of a family of 21-kD guanine nucleotide-binding proteins with intrinsic GTPase activity that are involved in many different signal transduction pathways in diverse cell types. Mutated *ras* genes are associated with neoplastic transformation. In T cell activation, Ras is recruited to the plasma membrane by tyrosine-phosphorylated adapter proteins, where it is activated by GDP-GTP exchange factors.

GTP•Ras then initiates the MAP kinase cascade, which leads to expression of the *fos* gene and assembly of the AP-1 transcription factor.

Reactive oxygen intermediates (ROIs). Highly reactive metabolites of oxygen, including superoxide anion, hydroxyl radical, and hydrogen peroxide, that are produced by activated phagocytes. ROIs are used by the phagocytes to form oxyhalides that damage ingested bacteria. ROIs may also be released from cells and promote inflammatory responses or cause tissue damage.

Reagin. IgE antibody that mediates an immediate hypersensitivity reaction.

Receptor editing. A process by which some immature B cells that recognize self antigens in the bone marrow may be induced to change their Ig specificities. Receptor editing involves reactivation of the RAG genes, additional light chain VJ recombinations, and new Ig light chain production, which allows the cell to express a different Ig receptor that is not self-reactive.

Recombination-activating gene 1 and 2 (RAG1 and RAG2). The genes encoding RAG1 and RAG2 proteins, which are the lymphocyte-specific components of V(D)J recombinase and are expressed in developing B and T cells. RAG proteins bind to recombination recognition sequences and are critical for DNA recombination events that form functional Ig and TCR genes. Therefore, RAG proteins are required for expression of antigen receptors and for the maturation of B and T lymphocytes.

Recombination signal sequences. Specific DNA sequences found adjacent to the V, D, and J segments in the antigen receptor loci and recognized by the RAG 1/RAG-2 component of V(D)J recombinase. The recognition sequences consist of a highly conserved stretch of 7 nucleotides, called the heptamer, located adjacent to the V, D, or J coding sequence, followed by a spacer of exactly 12 or 23 nonconserved nucleotides and a highly conserved stretch of 9 nucleotides, called the nonamer.

Red pulp. An anatomic and functional compartment of the spleen composed of vascular sinusoids, scattered among which are large numbers of erythrocytes, macrophages, dendritic cells, sparse lymphocytes, and plasma cells. Red pulp macrophages clear the blood of microbes, other foreign particles, and damaged red blood cells.

Regulatory T cells. A population of T cells that regulates the activation of other T cells and may be necessary to maintain peripheral tolerance to self antigens. Regulatory T cells are CD4⁺ and express activation markers.

Respiratory burst. The process by which reactive oxygen intermediates such as superoxide anion, hydroxyl radical, and hydrogen peroxide are produced in macrophages and polymorphonuclear leukocytes. The respiratory burst is mediated by the enzyme phagocyte oxidase and is usually triggered by inflammatory mediators, such as LTB₄, PAF, and TNF, or by bacterial products, such as N-formylmethionyl peptides.

Reverse transcriptase. An enzyme encoded by retroviruses, such as HIV, that synthesizes a DNA copy of the

viral genome from the RNA genomic template. Purified reverse transcriptase is used widely in molecular biology research for purposes of cloning complementary DNAs encoding a gene of interest from messenger RNA. Reverse transcriptase inhibitors are used as drugs to treat HIV-1 infection.

Reverse transcriptase-polymerase chain reaction (RT-PCR). An adaptation of the polymerase chain reaction (PCR) used to amplify a complementary DNA (cDNA) of a gene of interest. In this method, RNA is isolated from a cell expressing the gene, and cDNAs are synthesized by use of the reverse transcriptase enzyme. The cDNA of interest is then amplified by conventional PCR techniques with gene-specific primers.

Rh blood group antigens. A complex system of protein alloantigens expressed on red blood cell membranes that are the cause of transfusion reactions and hemolytic disease of the newborn. The most clinically important Rh antigen is designated D.

Rheumatoid arthritis. An autoimmune disease characterized primarily by inflammatory damage to joints and sometimes inflammation of blood vessels, lungs, and other tissues. CD4⁺ T cells, activated B lymphocytes, and plasma cells are found in the inflamed joint lining (synovium), and numerous proinflammatory cytokines, including IL-1 and TNF, are present in the synovial (joint) fluid.

RNase protection assay. A sensitive method of detecting and quantifying messenger RNA (mRNA) copies of particular genes based on hybridization of the mRNA to radiolabeled RNA probes and digestion of unhybridized RNA with the enzyme RNase. The double-stranded RNA duplexes created during the hybridization reaction resist degradation by RNase and are of a particular size determined by the length of the probe. They can be separated by gel electrophoresis and are detected and quantitated by radioautography.

Scavenger receptors. A family of cell surface receptors expressed on macrophages, originally defined as receptors that mediate endocytosis of oxidized or acetylated low-density lipoprotein particles but that also bind and mediate the phagocytosis of a variety of microbes.

SCID mouse. A mouse strain in which B and T cells are absent because of an early block in maturation from bone marrow precursors. SCID mice carry a mutation in a component of the enzyme DNA-dependent protein kinase, which is required for double-stranded DNA break repair. Deficiency of this enzyme results in abnormal joining of Ig and TCR gene segments during recombination and therefore failure to express antigen receptors.

Secondary immune response. An adaptive immune response that occurs on second exposure to an antigen. A secondary response is characterized by more rapid kinetics and greater magnitude relative to the primary immune response, which occurs on first exposure.

Second-set rejection. Allograft rejection in an individual who has previously been sensitized to the donor's tissue alloantigens by having received another graft or transfusion from that donor. In contrast to first-set rejection, which occurs in an individual who has not previously been sensitized to the donor alloantigens,

second-set rejection is rapid and occurs in 2 to 3 days as a result of immunologic memory.

Secretory component. The proteolytically cleaved portion of the extracellular domain of the poly-Ig receptor that remains bound to an IgA molecule in mucosal secretions.

Selectin. Any one of three separate but closely related carbohydrate-binding proteins that mediate adhesion of leukocytes to endothelial cells. Each of the selectin molecules is a single-chain transmembrane glycoprotein with a similar modular structure, including a non-extracellular calcium-dependent lectin domain. The selectins include L-selectin (CD62L), expressed on leukocytes; P-selectin (CD62P), expressed on platelets and activated endothelium; and E-selectin (CD62E), expressed on activated endothelium.

Selective immunoglobulin deficiency. Immunodeficiencies characterized by a lack of only one or a few Ig classes or subclasses. Selective IgA deficiency is the most common selective Ig deficiency, followed by IgG3 and IgG2 deficiencies. Patients with these disorders may be at increased risk for bacterial infections, but many are normal.

Self MHC restriction. The limitation (or restriction) of antigens that can be recognized by an individual's T cells to complexes of peptides bound to major histocompatibility complex (MHC) molecules that were present in the thymus during T cell maturation (i.e., self MHC molecules). The T cell repertoire is self MHC restricted as a result of the process of positive selection.

Self-tolerance. Unresponsiveness of the adaptive immune system to self antigens, largely as a result of inactivation or death of self-reactive lymphocytes induced by exposure to those self antigens. Self-tolerance is a cardinal feature of the normal immune system, and failure of self-tolerance leads to autoimmune diseases.

Septic shock. An often lethal complication of severe gram-negative bacterial infection with spread to the blood stream (sepsis) that is characterized by vascular collapse, disseminated intravascular coagulation, and metabolic disturbances. This syndrome is due to the effects of bacterial LPS and cytokines, including TNF, IL-12, and IL-1. Septic shock is also called endotoxin shock.

Seroconversion. The production of detectable antibodies in the serum specific for a microorganism during the course of an infection or in response to immunization.

Serology. The study of blood (serum) antibodies and their reactions with antigens. The term serology is often used to refer to the diagnosis of infectious diseases by detection of microbe-specific antibodies in the serum.

Serotype. An antigenically distinct subset of a species of an infectious organism that is distinguished from other subsets by serologic (i.e., serum antibody) tests. Humoral immune responses to one serotype of microbes (e.g., influenza virus) may not be protective against another serotype.

Serum. The cell-free fluid that remains when blood or plasma forms a clot. Blood antibodies are found in the serum fraction.

Serum amyloid A (SAA). An acute-phase protein whose serum concentration rises significantly in the setting of infection and inflammation, mainly because of IL-1- and TNF-induced synthesis by the liver. SAA activates leukocyte chemotaxis, phagocytosis, and adhesion to endothelial cells.

Serum sickness. A disease caused by the injection of large doses of a protein antigen into the blood and characterized by the deposition of antigen-antibody (immune) complexes in blood vessel walls, especially in the kidneys and joints. Immune complex deposition leads to complement fixation and leukocyte recruitment and subsequently to glomerulonephritis and arthritis. Serum sickness was originally described as a disorder that occurred in patients receiving injections of serum containing antitoxin antibodies to prevent diphtheria.

Severe combined immunodeficiency (SCID). Immunodeficiency diseases in which both B and T lymphocytes do not develop or do not function properly, and therefore both humoral and cell-mediated immunity are impaired. Children with SCID usually have infections during the first year of life and succumb to these infections unless the immunodeficiency is treated. SCID has several different genetic causes.

Shwartzman reaction. An experimental model of the pathologic effects of bacterial LPS and TNF in which two intravenous injections of LPS are administered to a rabbit 24 hours apart. After the second injection, the rabbit suffers disseminated intravascular coagulation and neutrophil and platelet plugging of small blood vessels.

Signal transducer and activator of transcription (STAT). A member of a family of proteins that function as signaling molecules and transcription factors in response to binding of cytokines to type I and type II cytokine receptors. STATs are present as inactive monomers in the cytoplasm of cells and are recruited to the cytoplasmic tails of cross-linked cytokine receptors, where they are tyrosine phosphorylated by JAKs. The phosphorylated STAT proteins dimerize and move to the nucleus, where they bind to specific sequences in the promoter regions of various genes and stimulate their transcription. Different STATs are activated by different cytokines.

Simian immunodeficiency virus. A lentivirus closely related to HIV-1 that causes disease similar to AIDS in monkeys.

Single-positive thymocyte. A maturing T cell precursor in the thymus that expresses CD4 or CD8 molecules but not both. Single-positive thymocytes are found mainly in the medulla and have matured from the double-positive stage, during which thymocytes express both CD4 and CD8 molecules.

Smallpox. A disease caused by variola virus. Smallpox was the first infectious disease shown to be preventable by vaccination and the first disease to be completely eradicated by a worldwide vaccination program.

Somatic hypermutation. High-frequency point mutations in Ig heavy and light chains that occur in germinal center B cells. Mutations that result in increased affinity of antibodies for antigen impart a selective survival advantage to the B cells producing those antibodies and lead to affinity maturation of a humoral immune response.

Somatic recombination. The process of DNA recombination by which the functional genes encoding the variable regions of antigen receptors are formed during lymphocyte development. A relatively limited set of inherited, or germline, DNA sequences that are initially separated from one another are brought together by enzymatic deletion of intervening sequences and religation. This process occurs only in developing B or T lymphocytes. This process is sometimes referred to as somatic rearrangement.

Southern blot. A technique used to determine the organization of genomic DNA around a particular gene. The DNA is cut into fragments by restriction endonucleases, different-sized fragments are electrophoretically separated in a gel, and the DNA is then immobilized (blotted) onto a sheet of nitrocellulose or nylon. The position and therefore the size of a particular DNA fragment can then be detected by use of a radioactively labeled DNA probe with a homologous sequence. (See Appendix III for a detailed description.)

Specificity. A cardinal feature of the adaptive immune system, namely, that immune responses are directed toward and able to distinguish between distinct antigens or small parts of macromolecular antigens. This fine specificity is attributed to lymphocyte antigen receptors that may bind to one molecule but not to another with only minor structural differences from the first.

Spleen. A secondary lymphoid organ in the left upper quadrant of the abdomen. The spleen is the major site of adaptive immune responses to blood-borne antigens. The red pulp of the spleen is composed of blood-filled vascular sinusoids lined by active phagocytes that ingest opsonized antigens and damaged red blood cells. The white pulp of the spleen contains lymphocytes and lymphoid follicles where B cells are activated.

Src homology 2 (SH2) domain. A three-dimensional domain structure of about 100 amino acid residues present in many signaling proteins that permits specific noncovalent interactions with other proteins by binding to phosphotyrosines. Each SH2 domain has a unique binding specificity that is determined by the amino acid residues adjacent to the phosphotyrosine on the target protein. Several proteins involved in early signaling events in T and B lymphocytes interact with one another through SH2 domains.

Src homology 3 (SH3) domain. A three-dimensional domain structure of about 60 amino acid residues present in many signaling proteins that mediates protein-protein binding. SH3 domains bind to proline residues and function cooperatively with the SH2 domains of the same protein. For instance, Sos, the

guanine nucleotide exchange factor for Ras, contains both SH2 and SH3 domains, and both are involved in Sos binding to the adapter protein Grb-2.

Stem cell. An undifferentiated cell that divides continuously and gives rise to additional stem cells and to cells of multiple different lineages. For example, all blood cells arise from a common hematopoietic stem cell.

Superantigens. Proteins that bind to and activate all the T cells in an individual that express a particular set or family of V β TCR genes. Superantigens are presented to T cells by binding to nonpolymorphic regions of class II MHC molecules on APCs, and they interact with conserved regions of TCR V β domains. Several staphylococcal enterotoxins are superantigens. Their importance lies in their ability to activate many T cells, which results in large amounts of cytokine production and a clinical syndrome that is similar to septic shock.

Suppressor T cell. T cells that block the activation and function of other effector T lymphocytes. Suppressor function may be attributed to a still poorly defined population of T cells currently called **regulatory T cells**.

Surrogate light chain. A complex of two nonvariable proteins that associate with Ig μ heavy chains in pre-B cells to form the pre-B cell receptor. The two surrogate light chain proteins include V pre-B protein, which is homologous to a light chain V domain, and $\lambda 5$, which is covalently attached to the μ heavy chain by a disulfide bond.

Switch recombination. The molecular mechanism underlying Ig isotype switching in which a rearranged VDJ gene segment in an antibody-producing B cell recombines with a downstream C gene and the intervening C gene is deleted. DNA recombination events in switch recombination are triggered by CD40 and cytokines and involve nucleotide sequences called switch regions located in the introns at the 5' end of each C H locus.

Syngeneic. Genetically identical. All animals of an inbred strain and monozygotic twins are syngeneic.

Syngeneic graft. A graft from a donor who is genetically identical to the recipient. Syngeneic grafts are not rejected.

Synthetic vaccine. Vaccines composed of recombinant DNA-derived antigens. Synthetic vaccines for hepatitis B virus and herpes simplex virus are now in use.

Systemic inflammatory response syndrome (SIRS). The systemic changes observed in patients who have disseminated bacterial infections. In its mild form, SIRS consists of neutrophilia, fever, and a rise in acute-phase reactants in the plasma. These changes are stimulated by bacterial products such as LPS and are mediated by cytokines of the innate immune system. In severe cases, SIRS may include disseminated intravascular coagulation, adult respiratory distress syndrome, and septic shock.

Systemic lupus erythematosus (SLE). A chronic systemic autoimmune disease that affects predominantly women and is characterized by rashes, arthritis,

glomerulonephritis, hemolytic anemia, thrombocytopenia, and central nervous system involvement. Many different autoantibodies are found in patients with SLE, particularly anti-DNA antibodies. Many of the manifestations of SLE are due to the formation of immune complexes composed of autoantibodies and their specific antigens, with deposition of these complexes in small blood vessels in various tissues. The underlying mechanism for the breakdown of self-tolerance in SLE is not understood.

T cell receptor (TCR). The clonally distributed antigen receptor on CD4⁺ and CD8⁺ T lymphocytes that recognizes complexes of foreign peptides bound to self MHC molecules on the surface of APCs. The most common form of TCR is composed of a heterodimer of two disulfide-linked transmembrane polypeptide chains, designated α and β , each containing one N-terminal Ig-like variable (V) domain, one Ig-like constant (C) domain, a hydrophobic transmembrane region, and a short cytoplasmic region. (Another less common type of TCR, composed of γ and δ chains, is found on a small subset of T cells and recognizes different forms of antigen.)

T cell receptor complex. A multiprotein plasma membrane complex on T lymphocytes that is composed of the highly variable, antigen-binding TCR heterodimer and the invariant signaling proteins CD3, ϵ , and ζ chain.

T lymphocyte. The cell type that mediates cell-mediated immune responses in the adaptive immune system. T lymphocytes mature in the thymus, circulate in the blood, populate secondary lymphoid tissues, and are recruited to peripheral sites of antigen exposure. They express antigen receptors (TCRs) that recognize peptide fragments of foreign proteins bound to self MHC molecules. Functional subsets of T lymphocytes include CD4⁺ helper T cells and CD8⁺ CTLs.

T-dependent antigen. An antigen that requires both B cells and helper T cells to stimulate an antibody response. T-dependent antigens are protein antigens that contain some epitopes recognized by T cells and other epitopes recognized by B cells. Helper T cells produce cytokines and cell surface molecules that stimulate B cell growth and differentiation into antibody-secreting cells. Humoral immune responses to T-dependent antigens are characterized by isotype switching, affinity maturation, and memory.

Th1 cells. A functional subset of helper T cells that secrete a particular set of cytokines, including IFN- γ , and whose principal function is to stimulate phagocyte-mediated defense against infections, especially with intracellular microbes.

Th2 cells. A functional subset of helper T cells that secrete a particular set of cytokines, including IL-4 and IL-5, and whose principal functions are to stimulate IgE and eosinophil/mast cell-mediated immune reactions and to down-regulate Th1 responses.

Thymic epithelial cells. Epithelial cells abundant in the cortical and medullary stroma of the thymus that play a critical role in T cell development. Thymic epithelial cells secrete factors, such as IL-7, that are required for the early stages of T cell development. In

the process of positive selection, maturing T cells must recognize self peptides bound to MHC molecules on the surface of thymic epithelial cells to be rescued from programmed cell death.

Thymocyte. A precursor of a mature T lymphocyte present in the thymus.

Thymus. A bilobed organ situated in the anterior mediastinum that is the site of maturation of T lymphocytes from bone marrow-derived precursors. Thymic tissue is divided into an outer cortex and an inner medulla and contains stromal thymic epithelial cells, macrophages, dendritic cells, and numerous T cell precursors (thymocytes) at various stages of maturation.

T-independent antigen. Nonprotein antigens, such as polysaccharides and lipids, that can stimulate antibody responses without a requirement for antigen-specific helper T lymphocytes. T-independent antigens usually contain multiple identical epitopes that can cross-link membrane Ig on B cells and thereby activate the cells. Humoral immune responses to T-independent antigens show relatively little heavy chain isotype switching or affinity maturation, two processes that require signals from helper T cells.

Tissue typing. The determination of the particular MHC alleles expressed by an individual for the purpose of matching allograft donors and recipients. Tissue typing, also called HLA typing, is usually done by testing whether sera known to be reactive with certain MHC gene products mediate complement-dependent lysis of an individual's lymphocytes. PCR techniques are now also used to determine whether an individual carries a particular MHC allele.

TNF receptor-associated factors (TRAFs). A family of adapter molecules that interact with the cytoplasmic domains of various receptors in the TNF receptor family, including TNF-R1, lymphotoxin (LT)- β receptor, and CD40. Each of these receptors contains a cytoplasmic motif that binds different TRAFs, which in turn engage other signaling molecules leading to activation of the transcription factors AP-1 and NF- κ B. A transforming gene product of Epstein-Barr virus encodes a protein with a domain that binds TRAFs, and therefore infection by the virus mimics TNF- or CD40-induced signals.

Tolerance. Unresponsiveness of the adaptive immune system to antigens, as a result of inactivation or death of antigen-specific lymphocytes, induced by exposure to the antigens. Tolerance to self antigens is a normal feature of the adaptive immune system, but tolerance to foreign antigens may be induced under certain conditions of antigen exposure.

Tolerogen. An antigen that induces immunologic tolerance, in contrast to an immunogen, which induces an immune response. Many antigens can be either tolerogens or immunogens, depending on how they are administered. Tolerogenic forms of antigens include large doses of the proteins administered without adjuvants, APLs, and orally administered antigens.

Toll-like receptors. Cell surface molecules on phagocytes and other cell types that are involved in recognition of microbial structures, such as endotoxin,

and the generation of signals that lead to the activation of innate immune responses. Toll-like receptors share structural homology and signal transduction pathways with the type I IL-1 receptor.

Toxic shock syndrome. An acute illness characterized by shock, skin exfoliation, conjunctivitis, and diarrhea that is associated with tampon use and caused by a *Staphylococcus aureus* superantigen.

Transforming growth factor- β (TGF- β). A cytokine produced by activated T cells, mononuclear phagocytes, and other cells whose principal actions are to inhibit the proliferation and differentiation of T cells, to inhibit the activation of macrophages, and to counteract the effects of proinflammatory cytokines.

Transfusion. Transplantation of circulating blood cells, platelets, or plasma from one individual to another. Transfusions are performed to treat blood loss from hemorrhage or to treat a deficiency in one or more blood cell types resulting from inadequate production or excess destruction.

Transfusion reactions. An immunologic reaction against transfused blood products, usually mediated by preformed antibodies in the recipient that bind to donor blood cell antigens, such as ABO blood group antigens or histocompatibility antigens. Transfusion reactions can lead to intravascular lysis of red blood cells and, in severe cases, kidney damage, fever, shock, and disseminated intravascular coagulation.

Transgenic mouse. A mouse that expresses an exogenous gene that has been introduced into the genome by injection of a specific DNA sequence into the pronuclei of fertilized mouse eggs. Transgenes insert randomly at chromosomal break points and are subsequently inherited as simple mendelian traits. By the design of transgenes with tissue-specific regulatory sequences, mice can be produced that express a particular gene only in certain tissues. Transgenic mice are used extensively in immunology research to study the functions of various cytokines, cell surface molecules, and intracellular signaling molecules.

Transplantation. The process of transferring cells, tissues, or organs (i.e., grafts) from one individual to another or from one site to another in the same individual. Transplantation is used to treat a variety of diseases in which there is a functional disorder of a tissue or organ. The major barrier to successful transplantation between individuals is immunologic reaction (rejection) to the transplanted graft.

Transporter associated with antigen processing (TAP). An adenosine triphosphate (ATP)-dependent peptide transporter that mediates the active transport of peptides from the cytosol to the site of assembly of class I MHC molecules inside the endoplasmic reticulum. TAP is a heterodimeric molecule composed of TAP-1 and TAP-2 polypeptides, both encoded by genes in the MHC. Because peptides are required for stable assembly of class I MHC molecules, TAP-deficient animals express few cell surface class I MHC molecules, which results in diminished development and activation of CD8⁺ T cells.

Tumor immunity. Protection against the development of tumors by the immune system. Although

immune responses to naturally occurring tumors can frequently be demonstrated, true immunity may occur only in the case of a subset of these tumors that express immunogenic antigens (e.g., tumors that are caused by oncogenic viruses and therefore express viral antigens). Research efforts are under way to enhance weak immune responses to other tumors by a variety of approaches, including infiltrating lymphocytes (TILs). Lymphocytes isolated from the inflammatory infiltrates present in and around surgical resection samples of solid tumors that are enriched with tumor-specific CTLs and NK cells. In an experimental mode of cancer treatment, TILs are grown *in vitro* in the presence of high doses of IL-2 and are then adoptively transferred back into patients with the tumor.

Tumor necrosis factor (TNF). A cytokine produced mainly by activated mononuclear phagocytes that functions to stimulate the recruitment of neutrophils and monocytes to sites of infection and to activate these cells to eradicate microbes. TNF stimulates vascular endothelial cells to express new adhesion molecules, induces macrophages and endothelial cells to secrete chemokines, and promotes apoptosis of target cells. In severe infections, TNF is produced in large amounts and has systemic effects, including induction of fever, synthesis of acute-phase proteins by the liver, and cachexia. The production of large amounts of TNF can cause intravascular thrombosis and shock. (TNF- β , or lymphotoxin, is a closely related cytokine with biologic effects identical to those of TNF- α but is produced by T cells.)

Tumor necrosis factor (TNF) receptors. Cell surface receptors for TNF- α and TNF- β (LT), present on most cell types. There are two distinct TNF receptors, TNF-R1 and TNF-R2, but most biologic effects of TNF are mediated by TNF-R1. TNF receptors are members of a family of homologous receptors with cysteine-rich extracellular motifs that include Fas and CD40.

Tumor-specific antigen. An antigen whose expression is restricted to a particular tumor and is not expressed by normal cells. Tumor-specific antigens may serve as target antigens for antitumor immune responses.

Tumor-specific transplantation antigen (TSTA). An antigen expressed on experimental animal tumor cells that can be detected by induction of immunologic rejection of tumor transplants. TSTAs were originally defined on chemically induced rodent sarcomas and shown to stimulate CTL-mediated rejection of transplanted tumors.

Two-signal hypothesis. A now proven hypothesis that states that the activation of lymphocytes requires two distinct signals, the first being antigen and the second either microbial products or components of innate immune responses to microbes. The requirement for antigen (so-called signal 1) ensures that the ensuing immune response is specific. The requirement for additional stimuli triggered by microbes or innate immune reactions (signal 2) ensures that immune responses are induced when they are needed, that is, against microbes and other noxious substances and not

against harmless substances, including self antigens. Signal 2 is referred to as costimulation and is often mediated by membrane molecules on professional APCs, such as B7 proteins.

Type I cytokine receptors. A family of cytokine receptors, also called hemopoietin receptors, that contain conserved structural motifs in their extracellular domains and bind cytokines that fold into four α -helical strands, including growth hormone, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-13, IL-15, GM-CSF, and GCSF. Some of these receptors consist of a ligand-binding chain and one or more signal-transducing chains, and all of these chains have the same structural motifs. Type I cytokine receptors are dimerized on binding their cytokine ligands, and they signal through JAK/STAT pathways.

Type I interferons (IFN- α , IFN- β). A family of cytokines, including several structurally related IFN- α proteins and a single IFN- β protein, all of which have potent antiviral actions. The major source of IFN- α is mononuclear phagocytes; IFN- β is produced by many cells, including fibroblasts. Both IFN- α and IFN- β bind to the same cell surface receptor and induce similar biologic responses. Type I IFNs inhibit viral replication, increase the lytic potential of NK cells, increase expression of class I MHC molecules on virus-infected cells, and stimulate the development of T_H1 cells, especially in humans.

Ubiquitination. Covalent linkage of several copies of a small polypeptide called ubiquitin to a protein. Ubiquitination serves to target the protein for proteolytic degradation by proteasomes, a critical step in the class I MHC pathway of antigen processing and presentation.

Urticaria. Localized transient swelling and redness of the skin caused by leakage of fluid and plasma proteins from small vessels into the dermis during an immediate hypersensitivity reaction.

V gene segments. A DNA sequence that encodes the variable domain of an Ig heavy chain or light chain or a TCR α , β , γ , or δ chain. Each antigen receptor locus contains many different V gene segments, any one of which may recombine with downstream D or J segments during lymphocyte maturation to form functional antigen receptor genes.

V(D)J recombinase. A collection of enzymes that together mediate the somatic recombination events that form functional antigen receptor genes in developing B and T lymphocytes. Some of the enzymes, such as RAG1 and RAG-2, are found only in developing lymphocytes, and others are ubiquitous DNA repair enzymes.

Vaccine. A preparation of microbial antigen, often combined with adjuvants, that is administered to individuals to induce protective immunity against microbial infections. The antigen may be in the form of live but avirulent microorganisms, killed microorganisms, purified macromolecular components of a microorganism, or a plasmid that contains a complementary DNA encoding a microbial antigen.

Variable region. The extracellular, N-terminal region of an Ig heavy or light chain or a TCR α , β , γ , or δ chain that contains variable amino acid sequences

that differ between every clone of lymphocytes and that are responsible for the specificity for antigen. The antigen-binding variable sequences are localized to extended loop structures or hypervariable segments.

Virus. A primitive obligate intracellular parasitic organism or infectious particle that consists of a simple nucleic acid genome packaged in a protein capsid, sometimes surrounded by a membrane envelope. Many pathogenic animal viruses cause a wide range of diseases. Humoral immune responses to viruses can be effective in blocking infection of cells, and NK cells and CTLs are necessary to kill cells already infected.

Western blot. An immunologic technique to determine the presence of a protein in a biologic sample. The method involves separation of proteins in the sample by electrophoresis, transfer of the protein array from the electrophoresis gel to a support membrane by capillary action (blotting), and finally detection of the protein by binding of an enzymatically or radioactively labeled antibody specific for that protein.

Wheal and flare reaction. Local swelling and redness in the skin at a site of an immediate hypersensitivity reaction. The wheal reflects increased vascular permeability and the flare results from increased local blood flow, both changes resulting from mediators such as histamine released from activated dermal mast cells.

White pulp. The part of the spleen that is composed predominantly of lymphocytes, arranged in periarteriolar lymphoid sheaths, and follicles and other leukocytes. The remainder of the spleen contains sinusoids lined with phagocytic cells and filled with blood, called the red pulp.

Wiskott-Aldrich syndrome. An X-linked disease characterized by eczema, thrombocytopenia (reduced blood platelets), and immunodeficiency manifested as susceptibility to bacterial infections. The defective gene encodes a cytosolic protein involved in signaling cascades and regulation of the actin cytoskeleton.

Xenoantigen. An antigen on a graft from another species.

Xenogeneic graft (xenograft). An organ or tissue graft derived from a species different from the recipient. Transplantation of xenogeneic grafts (e.g., from a pig) to humans is not yet practical because of special problems related to immunologic rejection.

Xenoreactive. Describing a T cell or antibody that recognizes and responds to an antigen on a graft from another species (a xenoantigen). The T cell may recognize an intact xenogeneic MHC molecule or a peptide derived from a xenogeneic protein bound to a self MHC molecule.

X-linked agammaglobulinemia. An immunodeficiency disease, also called Bruton's agammaglobulinemia, characterized by a block in early B cell maturation and absence of serum Ig. Patients suffer from pyogenic bacterial infections. The disease is caused by mutations or deletions in the gene encoding Btk, an enzyme involved in signal transduction in developing B cells.

X-linked hyper-IgM syndrome. A rare immunodeficiency disease caused by mutations in the CD40 ligand gene and characterized by failure of B cell heavy chain isotype switching and cell-mediated immunity. Patients

suffer from both pyogenic bacterial and protozoal infections.

Zeta-associated protein of 70 kD (ZAP-70). An Src family cytoplasmic protein tyrosine kinase that is critical for early signaling steps in antigen-induced T cell activation. ZAP-70 binds to phosphorylated tyrosines in the cytoplasmic tails of the ζ chain of the

TCR complex and in turn phosphorylates adapter proteins that recruit other components of the signaling cascade.

ζ Chain. A transmembrane protein expressed in T cells as part of the TCR complex that contains ITAMs in its cytoplasmic tail and binds the ZAP-70 protein tyrosine kinase during T cell activation.