an mRNA molecule for the complete L chain by linking the coding regions for the rearranged VJ unit with that for the C unit (Figure 33.16).

J genes are important contributors to antibody diversity because they encode part of the last hypervariable segment (CDR3). In forming a continuous variable-region gene, any of the 40 V genes can become linked to any of five J genes. Thus, somatic recombination of these gene segments amplifies the diversity already present in the germ line. The linkage between V and J is not precisely controlled. Recombination between these genes can take place at one of several bases near the codon for residue 95, generating additional diversity. A similar array of V and J genes encoding the λ light chain is present on human chromosome 22. This region includes 30 $V_\lambda$ gene segments and four $J_\lambda$ segments. In addition, this region includes four distinct C genes, in contrast with the single C gene in the κ locus.

In human beings, the genes encoding the heavy chain are present on chromosome 14. Remarkably, the variable domain of heavy chains is assembled from *three* rather than two segments. In addition to $V_H$ genes that encode residues 1 to 94 and $J_H$ segments that encode residues 98 to 113, this chromosomal region includes a distinct set of segments that encode residues 95 to 97 (Figure 33.17). These gene segments are called D for *d*iversity. Some 27 D segments lie between 51 $V_H$ and 6 $J_H$ segments. The recombination process first joins a D segment to a $J_H$ segment; a $V_H$ segment is then joined to $DJ_H$. A greater variety of antigen-binding patches and clefts can be formed by the H chain than by the L chain because the H chain is encoded by three rather than two gene segments. Moreover, CDR3 of the H chain is diversified by the action of terminal deoxyribonucleotidyl transferase, a special DNA polymerase that requires no template. This enzyme inserts extra nucleotides between $V_H$ and D. The *V(D)J recombination* of both the L and the H chains is executed by specific enzymes present in immune cells. These proteins, called *RAG-1* and *RAG-2*, recognize specific DNA sequences called *recombination signal sequences (RSSs)* adjacent to the V, D, and J segments and facilitate the cleavage and religation of the DNA segments.

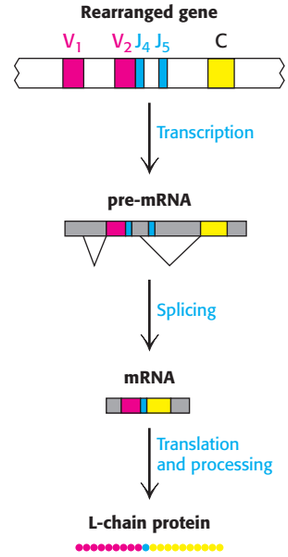



**FIGURE 33.16 Light-chain expression.** The light-chain protein is expressed by transcription of the rearranged gene to produce a pre-RNA molecule with the VJ and C regions separated. RNA splicing removes the intervening sequences to produce an mRNA molecule with the VJ and C regions linked. Translation of the mRNA and processing of the initial protein product produces the light chain.

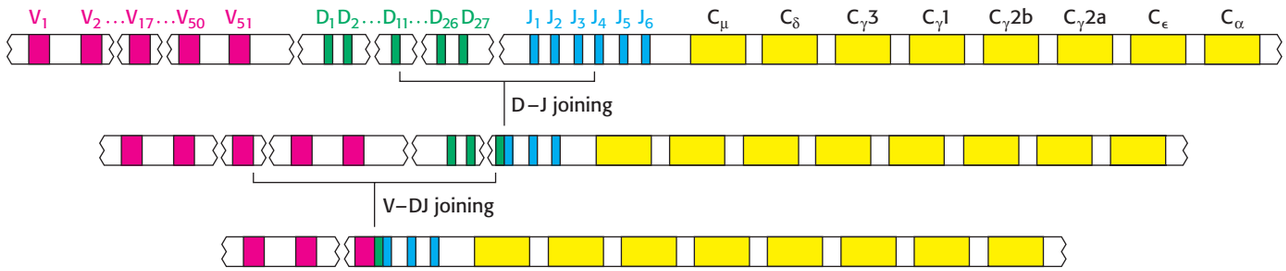



**FIGURE 33.17 V(D)J recombination.** The heavy-chain locus includes an array of 51 V segments, 27 D segments, and 6 J segments. Gene rearrangement begins with D–J joining, followed by further rearrangement to link the V segment to the DJ segment.

### 33.4.2 More Than $10^8$ Antibodies Can Be Formed by Combinatorial Association and Somatic Mutation

Let us recapitulate the sources of antibody diversity. The germ line contains a rather large repertoire of variable-region genes. For κ light chains, there are about 40 V-segment genes and five J-segment genes. Hence, a total of $40 \times 5 = 200$ kinds of complete $V_\kappa$ genes can be formed by the combinations of V and J. A similar analysis suggests that at least 120 different λ light chains can be generated. A larger number of heavy-chain genes can be formed because of the role of the D segments. For 51 V, 27 D, and 6 J gene segments, the number of complete $V_H$ genes that can be formed is 8262.

The association of 320 kinds of L chains with 8262 kinds of H chains would yield $2.6 \times 10^6$ different antibodies. Variability in the exact points of segment joining and other mechanisms increases this value by at least two orders of magnitude.

Even more diversity is introduced into antibody chains by *somatic mutation*—that is, the introduction of mutations into the recombined genes. In fact, a 1000-fold increase in binding affinity is seen in the course of a typical humoral immune response, arising from somatic mutation, a process called *affinity maturation*. The generation of an expanded repertoire leads to the selection of antibodies that more precisely fit the antigen. Thus, nature draws on each of three sources of diversity—a germ-line repertoire, somatic recombination, and somatic mutation—to form the rich variety of antibodies that protect an organism from foreign incursions.

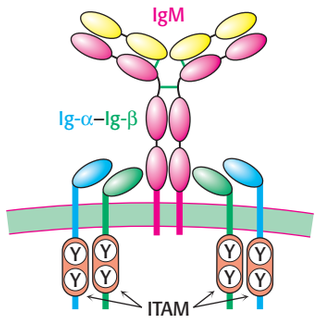



**FIGURE 33.18 B-cell receptor.** This complex consists of a membrane-bound IgM molecule noncovalently bound to two Ig-α–Ig-β heterodimers. The intracellular domains of each of the Ig-α and Ig-β chains include an immunoreceptor tyrosine-based activation motif (ITAM).

### 33.4.3 The Oligomerization of Antibodies Expressed on the Surface of Immature B Cells Triggers Antibody Secretion

The processes heretofore described generate a highly diverse set of antibody molecules—a key first step in the generation of an immune response. The next stage is the selection of a particular set of antibodies directed against a specific invader. How does this selection occur? Each immature B cell, produced in the bone marrow, expresses a monomeric form of IgM attached to its surface (Figure 33.18). Each cell expresses approximately $10^5$ IgM molecules, but *all of these molecules are identical in amino acid sequence and, hence, in antigen-binding specificity*. Thus, the selection of a particular immature B cell for growth will lead to the amplification of an antibody with a unique specificity. The selection process begins with the binding of an antigen to the membrane-bound antibody.

Associated with each membrane-linked IgM molecule are two molecules of a heterodimeric membrane protein called Ig-α–Ig-β (see Figure 33.18). Examination of the amino acid sequences of Ig-α and Ig-β is highly instructive. The amino terminus of each protein lies outside the cell and corresponds to a single immunoglobulin, and the carboxyl terminus, which lies inside the cell, includes a sequence of 18 amino acids called an *immunoreceptor tyrosine-based activation motif (ITAM)* (see Figure 33.18). As its name suggests, each ITAM includes key tyrosine residues, which are subject to phosphorylation by particular protein kinases present in immune-system cells.

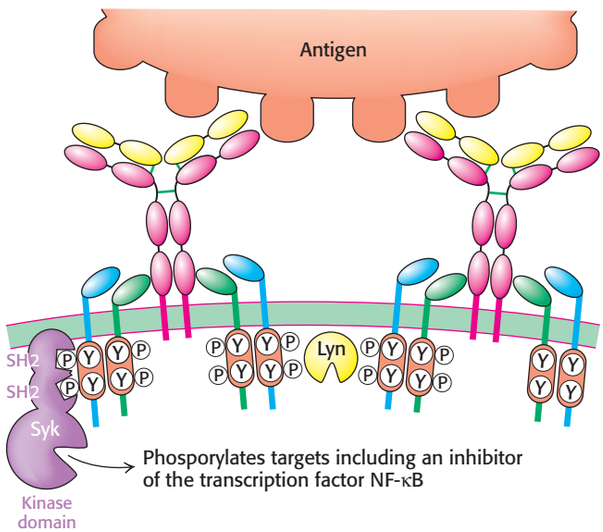
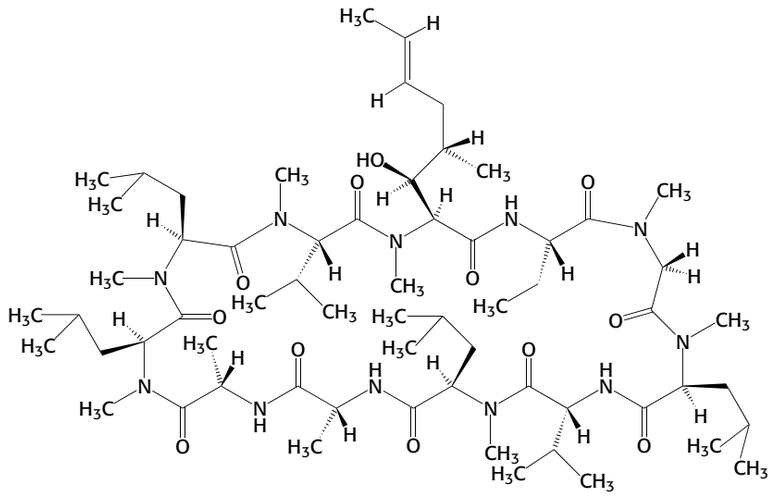



**FIGURE 33.19 B-cell activation.** The binding of multivalent antigen such as bacterial or viral surfaces links membrane-bound IgM molecules. This oligomerization triggers the phosphorylation of tyrosine residues in the ITAM sequences by protein tyrosine kinases such as Lyn. After phosphorylation, the ITAMs serve as docking sites for Syk, a protein kinase that phosphorylates a number of targets, including transcription factors.

A fundamental observation with regard to the mechanism by which the binding of antigen to membrane-bound antibody triggers the subsequent steps of the immune response is that *oligomerization or clustering of the antibody molecules is required* (Figure 33.19). The requirement for oligomerization is reminiscent of the dimerization of receptors triggered by growth hormone and epidermal growth factor encountered in Sections 15.4 and 15.4.1; indeed, the associated signaling mechanisms appear to be quite similar. The oligomerization of the membrane-bound antibodies results in the phosphorylation of the tyrosine residues within the ITAMs by protein tyrosine kinases including Lyn, a homolog of Src (Section 15.5). The phosphorylated ITAMs serve as docking sites for a protein kinase termed spleen tyrosine *k*inase (Syk), which has two SH2 domains that interact with the pair of phosphorylated tyrosines in each ITAM.

Syk, when activated by phosphorylation, proceeds to phosphorylate other signal-transduction proteins including an inhibitory subunit of a transcription factor called NF-κB and an isoform of phospholipase C. The signaling processes continue downstream to activate gene expression, leading to the stimulation of cell growth and initiating further B-cell differentiation.

Drugs that modulate the immune system have served as sources, of insight into immune-system signaling pathways. For example, *cyclosporin,* a powerful suppressor of the immune system, acts by blocking a phosphatase called *calcineurin*, which normally activates a transcription factor called NF-AT by dephosphorylating it.



**Cyclosporin A**

The potent immune supression that results reveals how crucial the activity of this transcription factor is to the development of an immune response. Without drugs such as cyclosporin, organ transplantation would be extremely difficult because transplanted tissue expresses a wide range of foreign antigens, which causes the immune system to reject the new tissue.

The role of oligomerization in the B-cell signaling pathway is illuminated when we consider the nature of many antigens presented by pathogens. The surfaces of many viruses, bacteria, and parasites are characterized by arrays of identical membrane proteins or membrane-linked carbohydrates. Thus, most pathogens present multiple binding surfaces that will naturally cause membrane-associated antibodies to oligomerize as they bind adjacent epitopes. In addition, the mechanism accounts for the observation that most small molecules do not induce an immune response; however, coupling multiple copies of the small molecule to a large oligomeric protein such as keyhole limpet hemocyanin (KLH), which has a molecular mass of close to 1 million daltons or more, promotes antibody oligomerization and, hence, the production of antibodies against the small-molecule epitope. The large protein is called the *carrier* of the attached chemical group, which is called a *haptenic determinant*. The small foreign molecule by itself is called a *hapten.* Antibodies elicited by attached haptens will bind unattached haptens as well.

### 33.4.4 Different Classes of Antibodies Are Formed by the Hopping of $V_H$ Genes

The development of an effective antibody-based immune response depends on the secretion into the blood of antibodies that have appropriate effector functions. At the beginning of this response, an alternative mRNA splicing

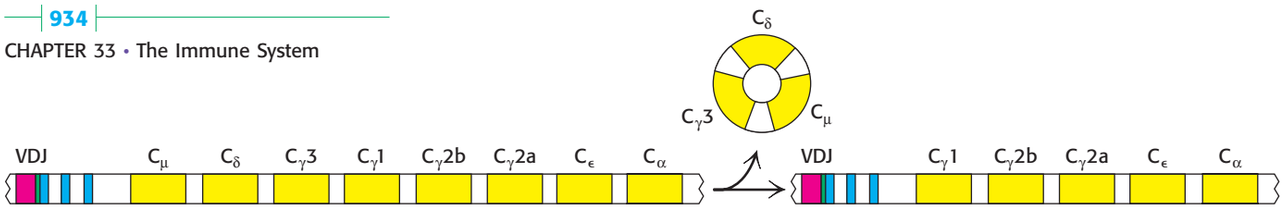



**FIGURE 33.20 Class switching.** Further rearrangement of the heavy-chain locus results in the generation of genes for antibody classes other than IgM. In the case shown, rearrangement places the VDJ region next to the $C\gamma1$ region, resulting in the production of IgG1. Note that no further rearrangement of the VDJ region takes place, so the specificity of the antibody is not affected.

pathway is activated so that the production of membrane-linked IgM is supplanted by the synthesis of secreted IgM. As noted in Section 33.1, secreted IgM is pentameric and has a relatively high avidity for multivalent antigens. Later, the antibody-producing cell makes either IgG, IgA, IgD, or IgE of the same specificity as the intially secreted IgM. In this switch, the light chain is unchanged, as is the variable region of the heavy chain. Only the constant region of the heavy chain changes. This step in the differentiation of an antibody-producing cell is called *class switching* (Figure 33.20). In undifferentiated cells, the genes for the constant region of each class of heavy chain, called $C_\mu$, $C_\delta$, $C_\gamma$, $C_\epsilon$, and $C_\alpha$, are next to each other. There are eight in all, including four genes for the constant regions of γ chains. A complete gene for the heavy chains of IgM antibody is formed by the translocation of a $V_H$ gene segment to a $DJ_H$ gene segment.

How are other heavy chains formed? Class switching is mediated by a gene-rearrangement process that moves a VDJ gene from a site near one C gene to a site near another C gene. Importantly, *the antigen-binding specificity is conserved in class switching because the entire $V_HDJ_H$ gene is translocated in an intact form*. For example, the antigen-combining specificity of IgA produced by a particular cell is the same as that of IgM synthesized at an earlier stage of its development. The biological significance of $C_H$ switching is that a whole recognition domain (the variable domain) is shifted from the early constant region ($C_\mu$) to one of several other constant regions that mediate different effector functions.

## 33.5 MAJOR-HISTOCOMPATIBILITY-COMPLEX PROTEINS PRESENT PEPTIDE ANTIGENS ON CELL SURFACES FOR RECOGNITION BY T-CELL RECEPTORS

Soluble antibodies are highly effective against extracellular pathogens, but they confer little protection against microorganisms that are predominantly intracellular, such as viruses and mycobacteria (which cause tuberculosis and leprosy). These pathogens are shielded from antibodies by the host-cell membrane (Figure 33.21). A different and more subtle strategy, *cell-mediated*

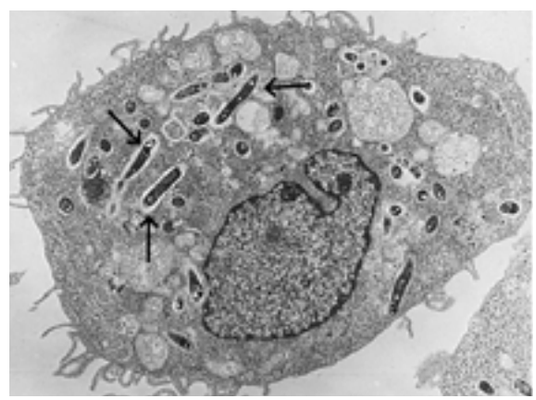


**FIGURE 33.21 Intracellular pathogen.** An electron micrograph showing mycobacteria (arrows) inside an infected macrophage. [Courtesy of Dr. Stanley Falkow.]

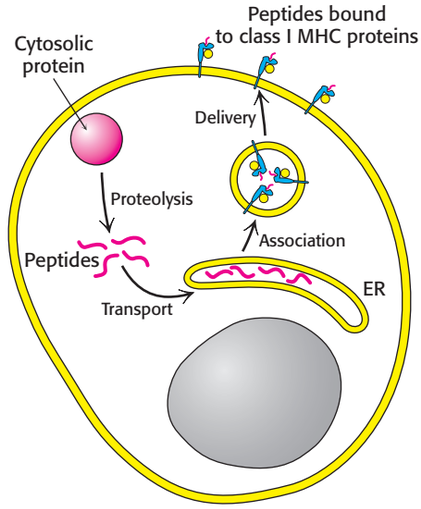



**FIGURE 33.22 Presentation of peptides from cytosolic proteins.** Class I MHC proteins on the surfaces of most cells display peptides that are derived from cytosolic proteins by proteolysis.

*immunity*, evolved to cope with intracellular pathogens. *T cells* continually scan the surfaces of all cells and kill those that exhibit foreign markings. The task is not simple; intracellular microorganisms are not so obliging as to intentionally leave telltale traces on the surface of their host. Quite the contrary, successful pathogens are masters of the art of camouflage. Vertebrates have devised an ingenious mechanism—cut and display—to reveal the presence of stealthy intruders. Nearly all vertebrate cells exhibit on their surfaces a sample of peptides derived from the digestion of proteins in their cytosol. These peptides are displayed by integral membrane proteins that are encoded by the *major histocompatibility complex (MHC)*. Specifically, peptides derived from cytosolic proteins are bound to *class I MHC proteins*.

How are these peptides generated and delivered to the plasma membrane? The process starts in the cytosol with the degradation of proteins, self proteins as well as those of pathogens (Figure 33.22). Digestion is carried out by proteasomes (Section 23.2.2). The resulting peptide fragments are transported from the cytosol into the lumen of the endoplasmic reticulum by an ATP-driven pump. In the ER, peptides combine with nascent class I MHC proteins; these complexes are then targeted to the plasma membrane.

MHC proteins embedded in the plasma membrane tenaciously grip their bound peptides so that they can be touched and scrutinized by T-cell receptors on the surface of a killer cell. Foreign peptides bound to class I MHC proteins signal that a cell is infected and mark it for destruction by cytotoxic T cells. An assembly consisting of the foreign peptide–MHC complex, the T-cell receptor, and numerous accessory proteins triggers a cascade that induces apoptosis in the infected cell. Strictly speaking, infected cells are not killed but, instead, are triggered to commit suicide to aid the organism.

### 33.5.1 Peptides Presented by MHC Proteins Occupy a Deep Groove Flanked by Alpha Helices

The three-dimensional structure of a large fragment of a human MHC class I protein, *human leukocyte antigen A2 (HLA-A2)*, was solved in 1987 by Don Wiley and Pamela Bjorkman. Class I MHC proteins consist of a 44-kd α chain noncovalently bound to a 12-kd polypeptide called $\beta_2$-*microglobulin*. The α chain has three extracellular domains ($\alpha_1$, $\alpha_2$, and $\alpha_3$), a transmembrane segment, and a tail that extends into the cytosol (Figure

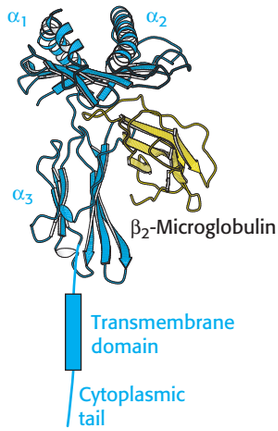



**FIGURE 33.23 Class I MHC protein.** A protein of this class consists of two chains. The α chain begins with two domains that include α helices ($\alpha_1$, $\alpha_2$), an immunoglobulin domain ($\alpha_3$), a transmembrane domain, and a cytoplasmic tail. The second chain, $\beta_2$-microglobulin, adopts an immunoglobulin fold.

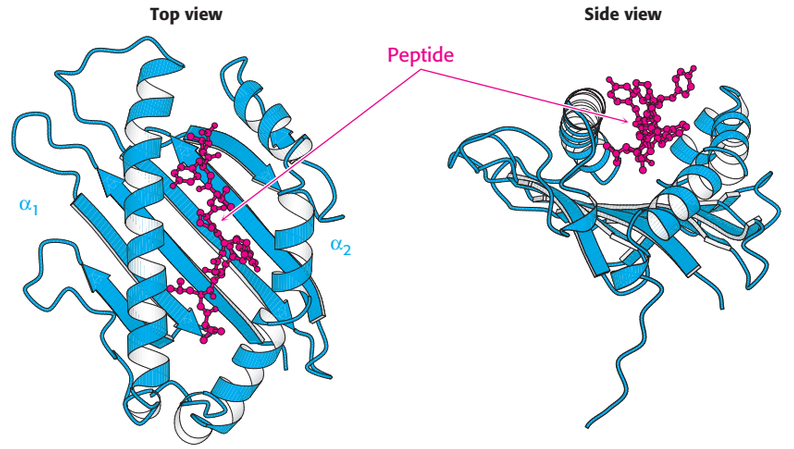
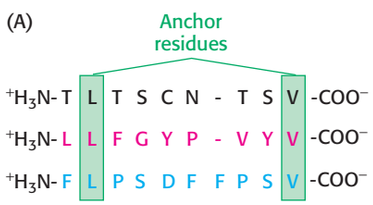


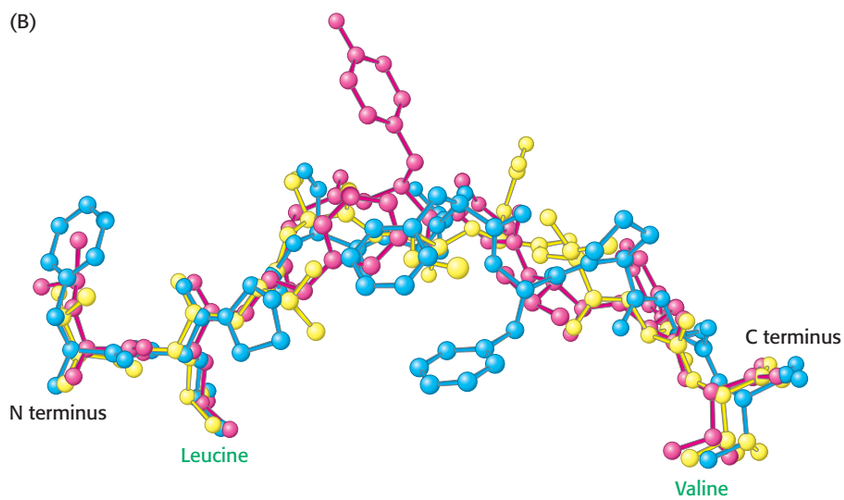

**FIGURE 33.24 Class I MHC peptide-binding site.** The $\alpha_1$ and $\alpha_2$ domains come together to form a groove in which peptides are displayed. The two views shown reveal that the peptide is surrounded on three sides by a β sheet and two α helices, but it is accessible from the top of the structure.

33.23). Cleavage by papain of the HLA α chain several residues before the transmembrane segment yielded a soluble heterodimeric fragment. The $\beta_2$-microglobulin subunit and the $\alpha_3$ domains have immunoglobulin folds, although the pairing of the two domains differs from that in antibodies. The $\alpha_1$ and $\alpha_2$ domains exhibit a novel and remarkable architecture. They associate intimately to form a deep groove that serves as the peptide-binding site (Figure 33.24). The floor of the groove, which is about 25 Å long and 10 Å wide, is formed by eight β strands, four from each domain. A long helix contributed by the $\alpha_1$ domain forms one side, and a helix contributed by the $\alpha_2$ domain forms the other side. *This groove is the binding site for the presentation of peptides.*

The groove can be filled by a peptide from 8 to 10 residues long in an extended conformation. As we shall see (Section 33.5.6), MHC proteins are remarkably diverse in the human population; each person expresses as many as six distinct class I MHC proteins and many different forms are present in different people. The first structure determined, HLA-A2, binds peptides that almost always have leucine in the second position and valine in the last position (Figure 33.25). Side chains from the MHC molecule in-

**FIGURE 33.25 Anchor residues.** (A) The amino acid sequences of three peptides that bind to the class I MHC protein HLA-A2 are shown. Each of these peptides has leucine in the second position and valine in the carboxyl-terminal position. (B) Comparison of the structures of these peptides reveals that the amino and carboxyl termini as well as the side chains of the leucine and valine residues are in essentially the same position in each peptide, whereas the remainder of the structures are quite different.



teract with the amino and carboxyl termini and with the side chains in these two key positions. These residues are often referred to as the *anchor residues*. The other residues are highly variable. Thus, many millions of different peptides can be presented by this particular class I MHC protein; the identities of only two of the nine residues are crucial for binding. Each class of MHC molecules requires a unique set of anchor residues. Thus, a tremendous range of peptides can be presented by these molecules. Note that *one face of the bound peptide is exposed to solution where it can be examined by other molecules, particularly T-cell receptors*. An additional remarkable feature of MHC–peptide complexes is their kinetic stability; once bound, a peptide is not released, even over a period of days.

### 33.5.2 T-Cell Receptors Are Antibody-like Proteins Containing Variable and Constant Regions

We are now ready to consider the receptor that recognizes peptides displayed by MHC proteins on target cells. The *T-cell receptor* consists of a 43-kd α chain ($T_\alpha$) joined by a disulfide bond to a 43-kd β chain ($T_\beta$; Figure 33.26). Each chain spans the plasma membrane and has a short carboxyl-terminal region on the cytosolic side. A small proportion of T cells express a receptor consisting of γ and δ chains in place of α and β. $T_\alpha$ and $T_\beta$, like immunoglobulin L and H chains, consist of *variable* and *constant* regions. Indeed, *these domains of the T-cell receptor are homologous to the V and C domains of immunoglobulins*. Furthermore, hypervariable sequences present in the V regions of $T_\alpha$ and $T_\beta$ form the binding site for the epitope.

The genetic architecture of these proteins is similar to that of immunoglobulins. The variable region of $T_\alpha$ is encoded by about 50 V-segment genes and 70 J-segment genes. $T_\beta$ is encoded by two D-segment genes in addition to 57 V and 13 J-segment genes. Again, the diversity of component genes and the use of slightly imprecise modes of joining them increase the number of distinct proteins formed. *At least $10^{12}$ different specificities could arise from combinations of this repertoire of genes*. Thus, T-cell receptors, like immunoglobulins, can recognize a very large number of different epitopes. All the receptors on a particular T cell have the same specificity.

How do T cells recognize their targets? The variable regions of the α and β chains of the T-cell receptor form a binding site that recognizes a combined epitope–foreign peptide bound to an MHC protein (Figure 33.27). Neither the foreign peptide alone nor the MHC protein alone forms a complex with the T-cell receptor. Thus, fragments of an intracellular pathogen are presented in a context that allows them to be detected, leading to the initiation of an appropriate response.

### 33.5.3 CD8 on Cytotoxic T Cells Acts in Concert with T-Cell Receptors

The T-cell receptor does not act alone in recognizing and mediating the fate of target cells. Cytotoxic T cells also express a protein termed *CD8* on their surfaces that is crucial for the recognition of the class I MHC–peptide complex. The abbreviation CD stands for *cluster of differentiation*, referring to a cell-surface marker that is used to identify a lineage or stage of differentiation. Antibodies specific for particular CD proteins have been invaluable

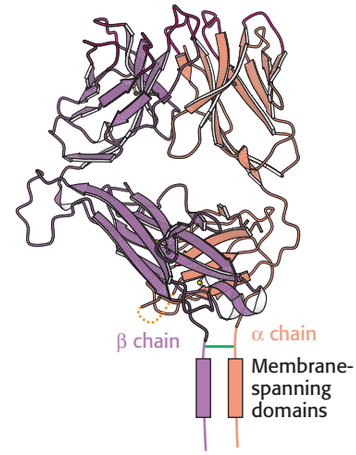



**FIGURE 33.26 T-cell receptor.** This protein consists of an α chain and a β chain, each of which consists of two immunoglobulin domains and a membrane-spanning domain. The two chains are linked by a disulfide bond.

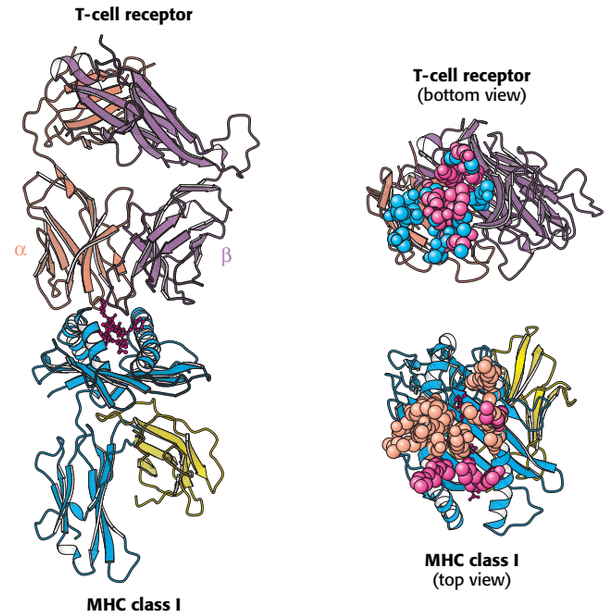



**FIGURE 33.27 T-cell receptor–Class I MHC complex.** The T-cell receptor binds to a class I MHC protein containing a bound peptide. The T-cell receptor contacts both the MHC protein and the peptide as shown by surfaces exposed when the complex is separated (right). These surfaces are colored according to the chain that they contact.

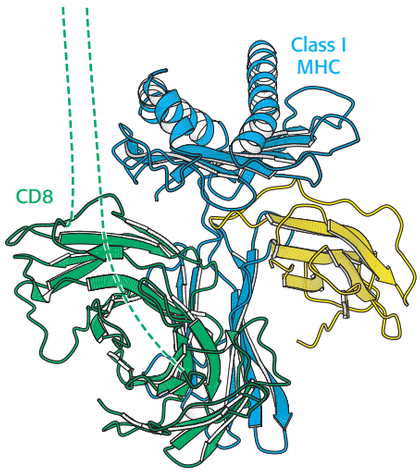



**FIGURE 33.28 The coreceptor CD8.** This dimeric protein extends from the surface of a cytotoxic T cell and binds to class I MHC molecules that are expressed on the surface of the cell that is bound to the T cell. The dashed lines represent extended polypeptide chains that link the immunoglobulin domain of CD8 to the membrane.

in following the development of leukocytes and in discovering new interactions between specific cell types.

Each chain in the CD8 dimer contains a domain that resembles an immunoglobulin variable domain (Figure 33.28). CD8 interacts primarily with the relatively constant $\alpha_3$ domain of class I MHC proteins. This interaction further stabilizes the interactions between the T cell and its target. The cytosolic tail of CD8 contains a docking site for Lck, a cytosolic tyrosine kinase akin to Src. The T-cell receptor itself is associated with six polypeptides that form the CD3 complex (Figure 33.29). The γ, δ, and ϵ chains of CD3 are homologous to Ig-α and Ig-β associated with the B-cell receptor (Section 33.4.3); each chain consists of an extracellular immunoglobulin domain and an intracellular ITAM region. These chains associate into CD3 γϵ and CD3 δϵ heterodimers. An additional component, the CD3 ζ chain, has only a small extracellular domain and a larger intracellular domain containing three ITAM sequences.

On the basis of these components, a model for T-cell activation can be envisaged that is closely parallel to the pathway for B-cell activation (Section 33.3; Figure 33.30). The binding of the T-cell receptor with the class I MHC–peptide complex and the concomitant binding of CD8 from the T-cell with the MHC molecule results in the association of the kinase Lck with the ITAM substrates of the components of the CD3 complex. Phosphorylation of the tyrosine residues in the ITAM sequences generates docking sites for a protein kinase called ZAP-70 (for 70-kd *z*eta-*a*ssociated *p*rotein) that is homologous to Syk in B cells. Docked by its two SH2 domains, ZAP-70 phosphorylates downstream targets in the signaling cascade. Additional molecules, including a membrane-bound protein phosphatase called CD45 and a cell-surface protein called CD28, play ancillary roles in this process.

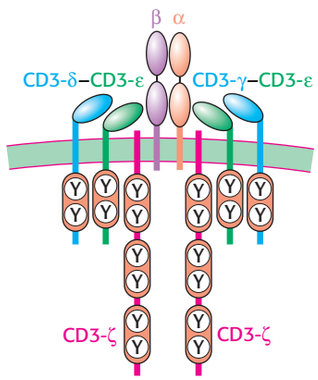



**FIGURE 33.29 T-cell receptor complex.** The T-cell receptor is associated with six CD3 molecules: a CD3-γ–CD3-ϵ heterodimer, a CD3-δ–CD3-ϵ heterodimer, and two chains of CD3-ζ. Single ITAM sequences are present in the cytoplasmic domains of CD3-γ, CD3-δ, and CD3-ϵ whereas three such sequences are found in each CD3-ζ chain.

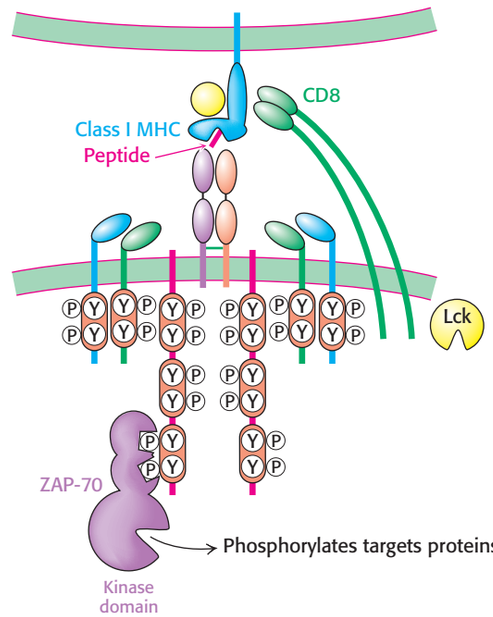



**FIGURE 33.30 T-cell activation.** The interaction between the T-cell receptor and a class I MHC–peptide complex results in the binding of CD8 to the MHC protein, the recruitment of the protein tyrosine kinase Lck, and the phosphorylation of tyrosine residues in the ITAM sequences of the CD3 chains. After phosphorylation, the ITAM regions serve as docking sites for the protein kinase ZAP-70, which phosphorylates protein targets to transmit the signal.

T-cell activation has two important consequences. First, the activation of cytotoxic T cells results in the secretion of *perforin*. This 70-kd protein makes the cell membrane of the target cell permeable by polymerizing to form transmembrane pores 10 nm wide (Figure 33.31). The cytotoxic T cell then secretes proteases called *granzymes* into the target cell. These enzymes initiate the pathway of apoptosis (Section 18.6.6), leading to the death of the target cell and the fragmentation of its DNA, including any viral DNA that may be present. Second, after it has stimulated its target cell to commit suicide, the activated T cell disengages and is stimulated to reproduce. Thus, additional T cells that express the same T-cell receptor are generated to continue the battle against the invader after these T cells have been identified as a suitable weapon.

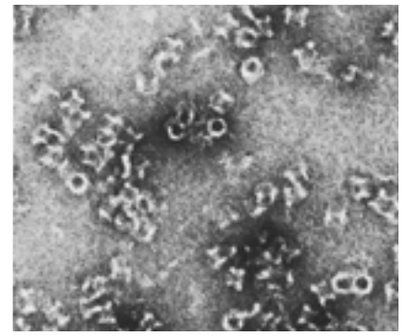


**FIGURE 33.31 Consequences of cytotoxic-T-cell action.** An electron micrograph showing pores in the membrane of a cell that has been attacked by a cytotoxic T cell. The pores are formed by the polymerization of perforin, a protein secreted by the cytotoxic T cell. [Courtesy of Dr. Eckhard Podock.]

### 33.5.4 Helper T Cells Stimulate Cells That Display Foreign Peptides Bound to Class II MHC Proteins

Not all T cells are cytotoxic. *Helper T cells, a different class, stimulate the proliferation of specific B lymphocytes and cytotoxic T cells and thereby serve as partners in determining the immune responses that are produced*. The importance of helper T cells is graphically revealed by the devastation wrought by AIDS, a condition that destroys these cells. Helper T cells, like cytotoxic T cells, detect foreign peptides that are presented on cell surfaces by MHC proteins. However, the source of the peptides, the MHC proteins that bind them, and the transport pathway are different.

Helper T cells recognize peptides bound to MHC molecules referred to as class II. Their helping action is focused on B cells, macrophages, and dendritic cells. *Class II MHC proteins* are expressed only by these *antigen-presenting cells*, unlike class I MHC proteins, which are expressed on nearly all cells. The peptides presented by class II MHC proteins do not come from the cytosol. Rather, *they arise from the degradation of proteins that have been internalized by endocytosis*. Consider, for example, a virus particle that is captured by membrane-bound immunoglobulins on the surface of a B cell (Figure 33.32). This complex is delivered to an endosome, a membrane-enclosed acidic compartment, where it is digested. The resulting peptides become associated with class II MHC proteins, which move to the cell surface. Peptides from the cytosol cannot reach class II proteins, whereas peptides from endosomal compartments cannot reach class I proteins. This segregation of displayed peptides is biologically critical. The association of

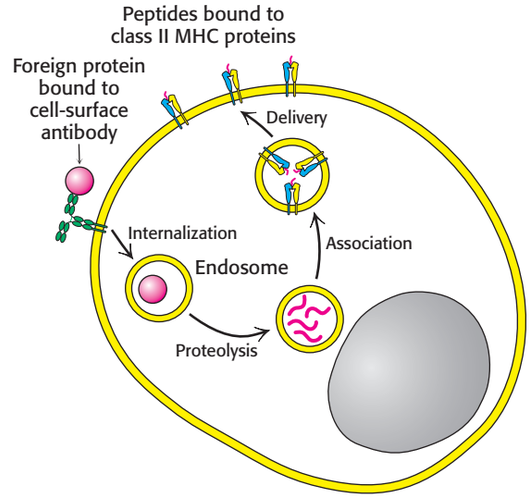



**FIGURE 33.32 Presentation of peptides from internalized proteins.** Antigen-presenting cells bind and internalize foreign proteins and display peptides that are formed from the digestion of these proteins in Class II MHC proteins.

a foreign peptide with a class II MHC protein signals that a cell has *encountered* a pathogen and serves as a call for *help*. In contrast, association with a class I MHC protein signals that a cell has *succumbed* to a pathogen and is a call for *destruction*.

### 33.5.5 Helper T Cells Rely on the T-Cell Receptor and CD4 to Recognize Foreign Peptides on Antigen-Presenting Cells

The overall structure of a class II MHC molecule is remarkably similar to that of a class I molecule. Class II molecules consist of a 33-kd α chain and a noncovalently bound 30-kd β chain (Figure 33.33).

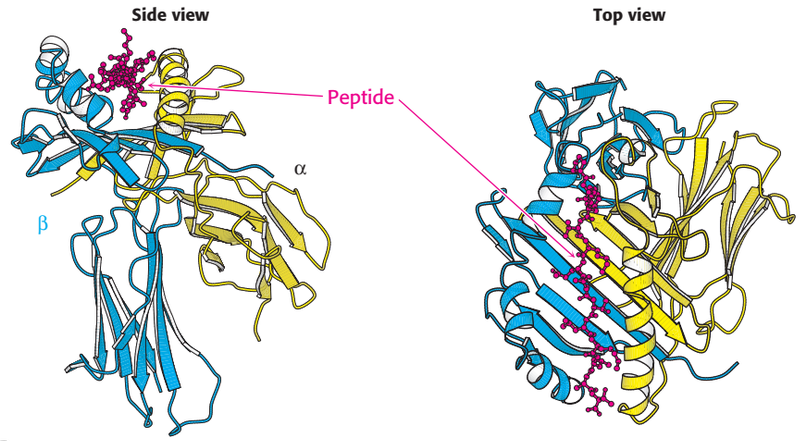



**FIGURE 33.33 Class II MHC protein.** A class II MHC protein consists of homologous α and β chains, each of which has an amino-terminal domain that constitutes half of the peptide-binding structure, as well as a carboxyl-terminal immunoglobulin domain. The peptide-binding site is similar to that in class I MHC proteins except that it is open at both ends, allowing class II MHC proteins to bind longer peptides than those bound by class I.

Each contains two extracellular domains, a transmembrane segment, and a short cytosolic tail. The peptide-binding site is formed by the $\alpha_1$ and $\beta_1$ domains, each of which contributes a long helix and part of a β sheet. Thus, the same structural elements are present in class I and class II MHC molecules, but they are combined into polypeptide chains in different ways. Class II MHC molecules appear to form stable dimers, unlike class I molecules, which are monomeric. The peptide-binding site of a class II molecule is open at both ends, and so this groove can accommodate longer peptides than can be bound by class I molecules; typically, peptides between 13 and 18 residues long are bound. The peptide-binding specificity of each class II molecule depends on binding pockets that recognize particular amino acids in specific positions along the sequence.

Helper T cells express T-cell receptors that are produced from the same genes as those on cytotoxic T cells. These T-cell receptors interact with class II MHC molecules in a manner that is analogous to T-cell-receptor interaction with class I MHC molecules. Nonetheless, helper T cells and cytotoxic T cells are distinguished by other proteins that they express on their surfaces. In particular, helper T cells express a protein called CD4 instead of expressing CD8. *CD4* consists of four immunoglobulin domains that extend from the T-cell surface, as well as a small cytoplasmic region (Figure 33.34). The amino-terminal immunoglobulin domains of CD4 interact with the base on the class II MHC molecule. Thus, helper T cells bind cells expressing class II MHC specifically because of the interactions with CD4 (Figure 33.35).


**FIGURE 33.34 Coreceptor CD4.** This protein comprises four tandem immunoglobulin domains that extend from the surface of helper T cells.