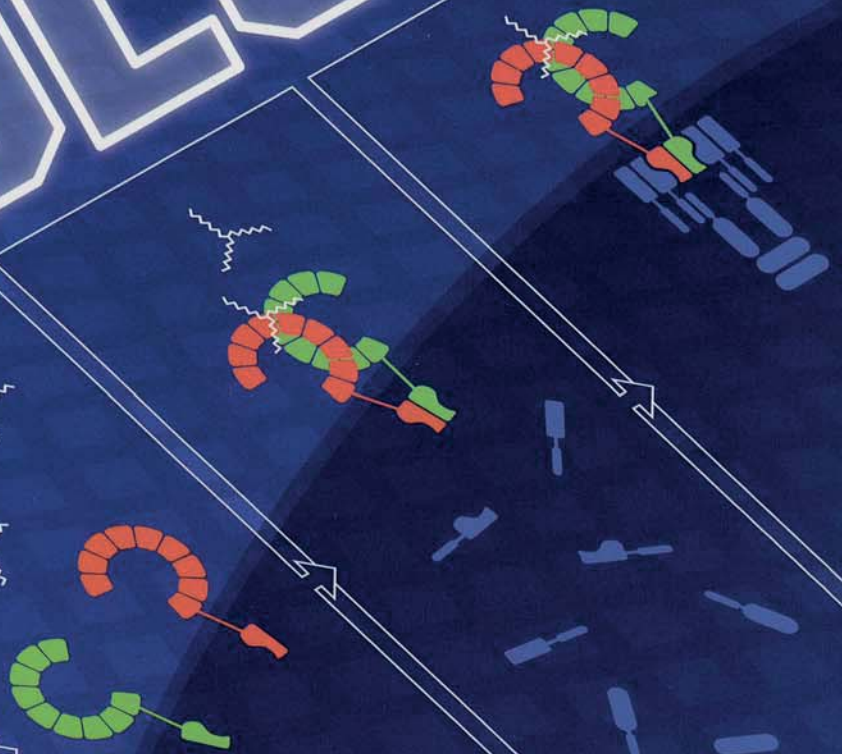
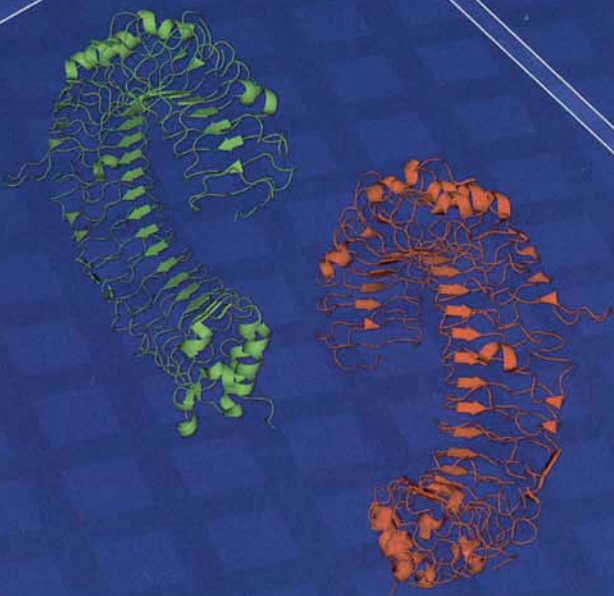


JANEWAY'S

8TH EDITION

IMMUNOLOGY



KENNETH MURPHY

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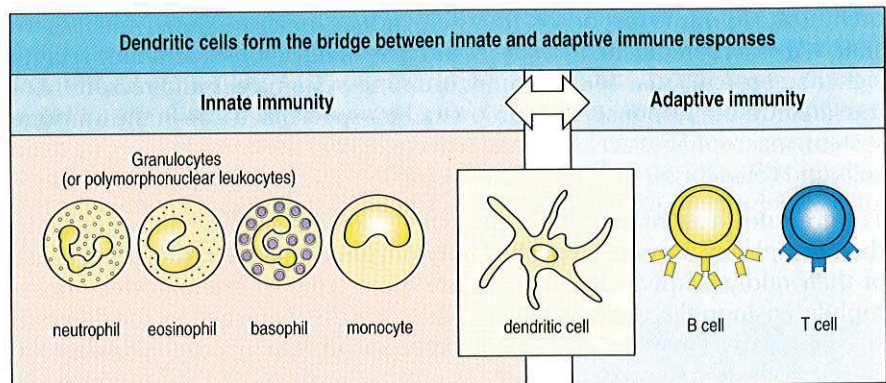
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Fig. 1.5 Dendritic cells form a key link between the innate immune system and the adaptive immune system.

Like the other cells of innate immunity, dendritic cells recognize pathogens via invariant cell-surface receptors for pathogen molecules, and are activated by these stimuli early in an infection. Dendritic cells in the tissues are phagocytic and are specialized to ingest a wide range of pathogens and to display their antigens at the dendritic cell surface in a form that can be recognized by T cells. As described later in the chapter, activated dendritic cells also produce molecules that enable T cells to be activated by antigen.



1-4 The lymphoid lineage comprises the lymphocytes of the adaptive immune system and the natural killer cells of innate immunity.

The **common lymphoid progenitor** in the bone marrow gives rise to the antigen-specific lymphocytes of the adaptive immune system and also to a type of lymphocyte that responds to the presence of infection but is not specific for antigen, and is thus considered to be part of the innate immune system. This latter is a large cell with a distinctive granular cytoplasm and is called a **natural killer cell (NK cell)** (Fig. 1.6). These cells can recognize and kill some abnormal cells, for example some tumor cells and cells infected with herpesviruses, and are thought to be important in holding viral infections in check before the adaptive immune response kicks in. Their functions in innate immunity are described in Chapter 3.

We come finally to the key components of adaptive immunity, the antigen-specific lymphocytes. Unless indicated otherwise, we shall use the term lymphocyte from now on to refer to the antigen-specific lymphocytes only. The immune system must be able to mount an immune response against any of the wide variety of different pathogens a person is likely to encounter during their lifetime. Lymphocytes collectively make this possible through the highly variable antigen receptors on their surface, by which they recognize and bind antigens. Each lymphocyte matures bearing a unique variant of a prototype antigen receptor, so that the population of lymphocytes expresses a huge repertoire of receptors that are highly diverse in their antigen-binding sites. Among the billion or so lymphocytes circulating in the body at any one time there will always be some that can recognize a given foreign antigen.

In the absence of an infection, most lymphocytes circulating in the body are small, featureless cells with few cytoplasmic organelles and much of the nuclear chromatin inactive, as shown by its condensed state (Fig. 1.7). This appearance is typical of inactive cells. It is hardly surprising that until the 1960s, textbooks described these cells, now the central focus of immunology, as having no known function. Indeed, these small lymphocytes have no functional activity until they encounter their specific antigen. Lymphocytes that have not yet been activated by antigen are known as **naive lymphocytes**; those that have met their antigen, become activated, and have differentiated further into fully functional lymphocytes are known as **effector lymphocytes**.

There are two types of lymphocytes—**B lymphocytes (B cells)** and **T lymphocytes (T cells)**—each with quite different roles in the immune system and distinct types of antigen receptors. After antigen binds to a **B-cell antigen receptor**, or **B-cell receptor (BCR)**, on the B-cell surface, the lymphocyte will proliferate and differentiate into **plasma cells**. These are the effector form of B lymphocytes and they produce antibodies, which are a secreted form of the B-cell receptor and have an identical antigen specificity. Thus the antigen that

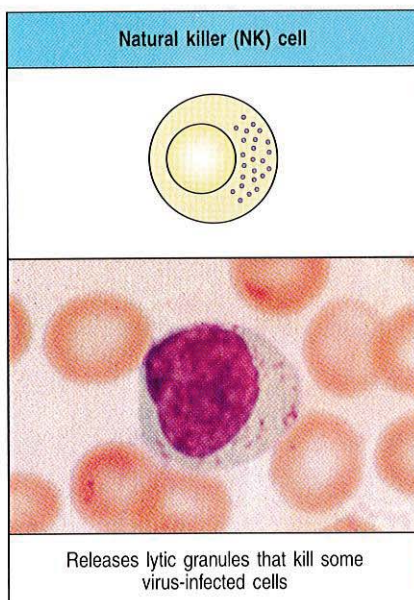


Fig. 1.6 Natural killer (NK) cells. These are large granular lymphoid-like cells with important functions in innate immunity, especially against intracellular infections, being able to kill other cells. Unlike lymphocytes, they lack antigen-specific receptors. Photograph courtesy of B. Smith.

activates a given B cell becomes the target of the antibodies produced by that cell's progeny. Antibody molecules as a class are known as **immunoglobulins (Ig)**, and so the antigen receptor of B lymphocytes is also known as **membrane immunoglobulin (mIg)** or **surface immunoglobulin (sIg)**.

The **T-cell antigen receptor**, or **T-cell receptor (TCR)**, is related to immunoglobulin but is quite distinct in its structure and recognition properties. After a T cell has been activated by its first encounter with antigen, it proliferates and differentiates into one of several different functional types of **effector T lymphocytes**. Effector T-cell functions fall into three broad classes: killing, activation, and regulation. **Cytotoxic T cells** kill cells that are infected with viruses or other intracellular pathogens. **Helper T cells** provide essential additional signals that influence the behavior and activity of other cells. Helper T cells provide signals to antigen-stimulated B cells that influence their production of antibody, and to macrophages that allow them to become more efficient at killing engulfed pathogens. We return to the functions of cytotoxic and helper T cells later in this chapter, and their actions are described in detail in Chapters 9 and 11. **Regulatory T cells** suppress the activity of other lymphocytes and help to control immune responses; they are discussed in Chapters 9, 11, 12, and 15.

During the course of an immune response, some of the B cells and T cells activated by antigen differentiate into **memory cells**, the lymphocytes that are responsible for the long-lasting immunity that can follow exposure to disease or vaccination. Memory cells will readily differentiate into effector cells on a second exposure to their specific antigen. Immunological memory is described in Chapter 11.

1-5 Lymphocytes mature in the bone marrow or the thymus and then congregate in lymphoid tissues throughout the body.

Lymphocytes circulate in the blood and the lymph and are also found in large numbers in **lymphoid tissues** or **lymphoid organs**, which are organized aggregates of lymphocytes in a framework of nonlymphoid cells. Lymphoid organs can be divided broadly into the **central** or **primary lymphoid organs**, where lymphocytes are generated, and the **peripheral** or **secondary lymphoid organs**, where mature naive lymphocytes are maintained and adaptive immune responses are initiated. The central lymphoid organs are the bone marrow and the **thymus**, an organ in the upper chest. The peripheral lymphoid organs comprise the **lymph nodes**, the **spleen**, and the **mucosal lymphoid tissues** of the gut, the nasal and respiratory tract, the urogenital tract, and other mucosa. The location of the main lymphoid tissues is shown schematically in Fig. 1.8, and we describe the individual peripheral lymphoid organs in more detail later in the chapter. Lymph nodes are interconnected by a system of lymphatic vessels, which drain extracellular fluid from tissues, through the lymph nodes, and back into the blood.

Both B and T lymphocytes originate in the bone marrow, but only the B lymphocytes mature there. The precursor T lymphocytes migrate to the thymus, from which they get their name, and mature there. The 'B' in B lymphocytes originally stood for the **bursa of Fabricius**, a lymphoid organ in young chicks in which lymphocytes mature; fortunately, it can stand equally well for bone marrow derived. Once they have completed maturation, both types of lymphocytes enter the bloodstream as mature naive lymphocytes. They circulate through the peripheral lymphoid tissues, in which an adaptive immune response is initiated if a lymphocyte meets its corresponding antigen. Before this, however, an innate immune response to the infection has usually occurred, and we now look at how this alerts the rest of the immune system to the presence of a pathogen.

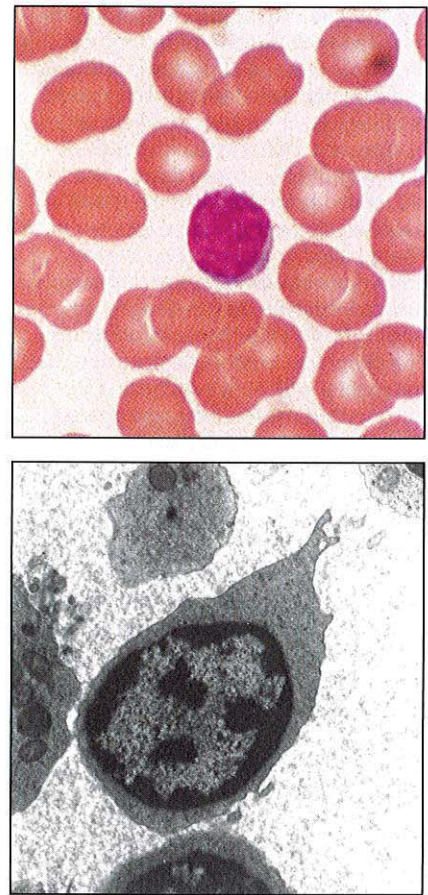


Fig. 1.7 Lymphocytes are mostly small and inactive cells. The upper panel shows a light micrograph of a small lymphocyte in which the nucleus has been stained purple by the hematoxylin and eosin dye, surrounded by red blood cells (which have no nuclei). Note the darker purple patches of condensed chromatin of the lymphocyte nucleus, indicating little transcriptional activity, the relative absence of cytoplasm, and the small size. The lower panel shows a transmission electron micrograph of a small lymphocyte. Again, note the evidence of functional inactivity: the condensed chromatin, the scanty cytoplasm, and the absence of rough endoplasmic reticulum. Photographs courtesy of N. Rooney.

Fig. 4.13 The crystal structure of an $\alpha\beta$ T-cell receptor resolved at 2.5 Å. In panels a and b the α chain is shown in pink and the β chain in blue. Disulfide bonds are shown in green. In panel a, the T-cell receptor is viewed from the side as it would sit on a cell surface, with the CDR loops that form the antigen-binding site (labeled 1, 2, and 3) arrayed across its relatively flat top. In panel b, the C_α and C_β domains are shown. The C_α domain does not fold into a typical Ig-like domain; the face of the domain away from the C_β domain is mainly composed of irregular strands of polypeptide rather than β sheet. The intramolecular disulfide bond joins a β strand to this segment of α helix. The interaction between the C_α and C_β domains is assisted by carbohydrate (colored gray and labeled on the figure), with a sugar group from the C_α domain making hydrogen bonds to the C_β domain. In panel c, the T-cell receptor is shown aligned with the antigen-binding sites from three different antibodies. This view is looking down into the binding site. The V_α domain of the T-cell receptor is aligned with the V_L domains of the antigen-binding sites of the antibodies, and the V_β domain is aligned with the V_H domains. The CDRs of the T-cell receptor and immunoglobulin molecules are colored, with CDRs 1, 2, and 3 of the TCR shown in red and the HV4 loop in orange. For the immunoglobulin V domains, the CDR1 loops of the heavy chain (H1) and light chain (L1) are shown in light and dark blue, respectively, and the CDR2 loops (H2, L2) in light and dark purple, respectively. The heavy-chain CDR3 loops (H3) are in yellow; the light-chain CDR3s (L3) are in bright green. The HV4 loops of the TCR (orange) have no hypervariable counterparts in immunoglobulins. Model structures courtesy of I.A. Wilson.

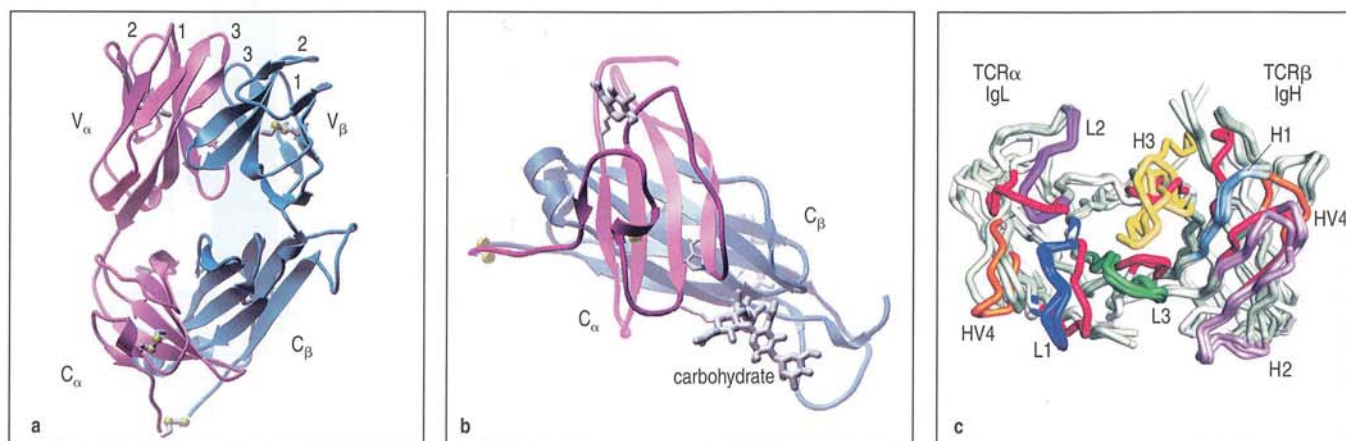
the heavy and light immunoglobulin chains first enabled prediction of the structural resemblance of the T-cell receptor heterodimer to a Fab fragment of immunoglobulin.

The three-dimensional structure of the T-cell receptor has since been determined by X-ray crystallography, and the two structures are indeed similar: the T-cell receptor chains fold in much the same way as those of a Fab fragment (Fig. 4.13a), although the final structure appears a little shorter and wider. There are, however, some distinct structural differences between T-cell receptors and Fab fragments. The most striking is in the C_α domain, where the fold is unlike that of any other Ig-like domain. The half of the domain that is juxtaposed with the C_β domain forms a β sheet similar to that found in other Ig-like domains, but the other half of the domain is formed of loosely packed strands and a short segment of α helix (Fig. 4.13b). In a C_α domain the intramolecular disulfide bond, which in Ig-like domains normally joins two β strands, joins a β strand to this segment of α helix.

There are also differences in the way in which the domains interact. The interface between the V and C domains of both T-cell receptor chains is more extensive than in most antibodies. The interaction between the C_α and C_β domains is distinctive as it might be assisted by carbohydrate, with a sugar group from the C_α domain making a number of hydrogen bonds to the C_β domain (see Fig. 4.13b). Finally, a comparison of the variable binding sites shows that, although the CDR loops align fairly closely with those of antibody molecules, there is some relative displacement (see Fig. 4.13c). This is particularly marked in the V_α CDR2 loop, which is oriented at roughly right angles to the equivalent loop in antibody V domains, as a result of a shift in the β strand that anchors one end of the loop from one face of the domain to the other. A strand displacement also causes a change in the orientation of the V_β CDR2 loop in some V_β domains whose structures are known. As relatively few crystallographic structures have been solved to this level of resolution, it remains to be seen to what degree all T-cell receptors share these features, and whether there are more differences to be discovered.

4-11 A T-cell receptor recognizes antigen in the form of a complex of a foreign peptide bound to an MHC molecule.

Antigen recognition by T-cell receptors clearly differs from recognition by B-cell receptors and antibodies. The immunoglobulin on B cells binds directly to the intact antigen and, as discussed in Section 4-8, antibodies typically bind to the surface of protein antigens, contacting amino acids that are discontinuous in the primary structure but are brought together in the folded protein. T cells, in contrast, respond to short continuous amino acid



sequences. These sequences are often buried within the native structure of the protein and thus cannot be recognized directly by T-cell receptors unless the protein is unfolded and processed into peptide fragments (Fig. 4.14). We shall see in Chapter 6 how this occurs.

The nature of the antigen recognized by T cells became clear with the realization that the peptides that stimulate T cells are recognized only when bound to an MHC molecule. The ligand recognized by the T cell is thus a complex of peptide and MHC molecule. The evidence for involvement of the MHC in T-cell recognition of antigen was at first indirect, but it has been proved conclusively by stimulating T cells with purified peptide:MHC complexes. The T-cell receptor interacts with this ligand by making contacts with both the MHC molecule and the antigen peptide.

4-12 There are two classes of MHC molecules with distinct subunit compositions but similar three-dimensional structures.

There are two classes of MHC molecules—**MHC class I** and **MHC class II**—which differ in both their structure and in their expression pattern in the tissues of the body. As shown in Figs 4.15 and 4.16, MHC class I and MHC class II molecules are closely related in overall structure but differ in their subunit compositions. In both classes, the two paired protein domains nearest to the membrane resemble immunoglobulin domains, whereas the two domains furthest away from the membrane fold together to create a long cleft, or groove, which is the site at which a peptide binds. Purified peptide:MHC class I and peptide:MHC class II complexes have been characterized structurally, allowing us to describe in detail both the MHC molecules themselves and the way in which they bind peptides.

MHC class I molecules (see Fig. 4.15) consist of two polypeptide chains. One chain, the α chain, is encoded in the MHC (on chromosome 6 in humans) and is noncovalently associated with a smaller chain, β_2 -microglobulin, which is not polymorphic and is encoded on a different chromosome—chromosome 15 in humans. Only the class I α chain spans the membrane. The complete molecule has four domains, three formed from the MHC-encoded α chain, and one contributed by β_2 -microglobulin. The α_3 domain and β_2 -microglobulin closely resemble Ig-like domains in their folded structure. The folded α_1 and α_2 domains form the walls of a cleft on the surface of the molecule; this is where the peptide binds and is known as the **peptide-binding cleft** or **peptide-binding groove**. The MHC molecules are highly polymorphic and the major differences between the different forms are located in the peptide-binding cleft, influencing which peptides will bind and thus the specificity of the dual antigen presented to T cells.

An MHC class II molecule consists of a noncovalent complex of two chains, α and β , both of which span the membrane (see Fig. 4.16). The MHC class II α chain is a different protein from the class I α chain. The MHC class II α and β chains are both encoded within the MHC. The crystallographic structure of the MHC class II molecule shows that it is folded very much like the MHC class I molecule, but the peptide-binding cleft is formed by two domains from different chains, the α_1 and β_1 domains. The major differences lie at the ends of the peptide-binding cleft, which are more open in MHC class II molecules than in MHC class I molecules. Consequently, the ends of a peptide bound to an MHC class I molecule are substantially buried within the molecule, whereas the ends of peptides bound to MHC class II molecules are not. In both MHC class I and class II molecules, bound peptides are sandwiched between the two α -helical segments of the MHC molecule (Fig. 4.17). The T-cell receptor interacts with this compound ligand, making contacts with both the MHC molecule and the peptide antigen. The sites of major polymorphism in MHC class II molecules are again located in the peptide-binding cleft.

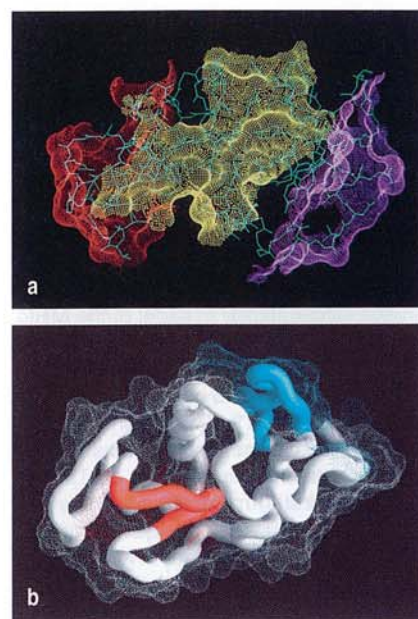
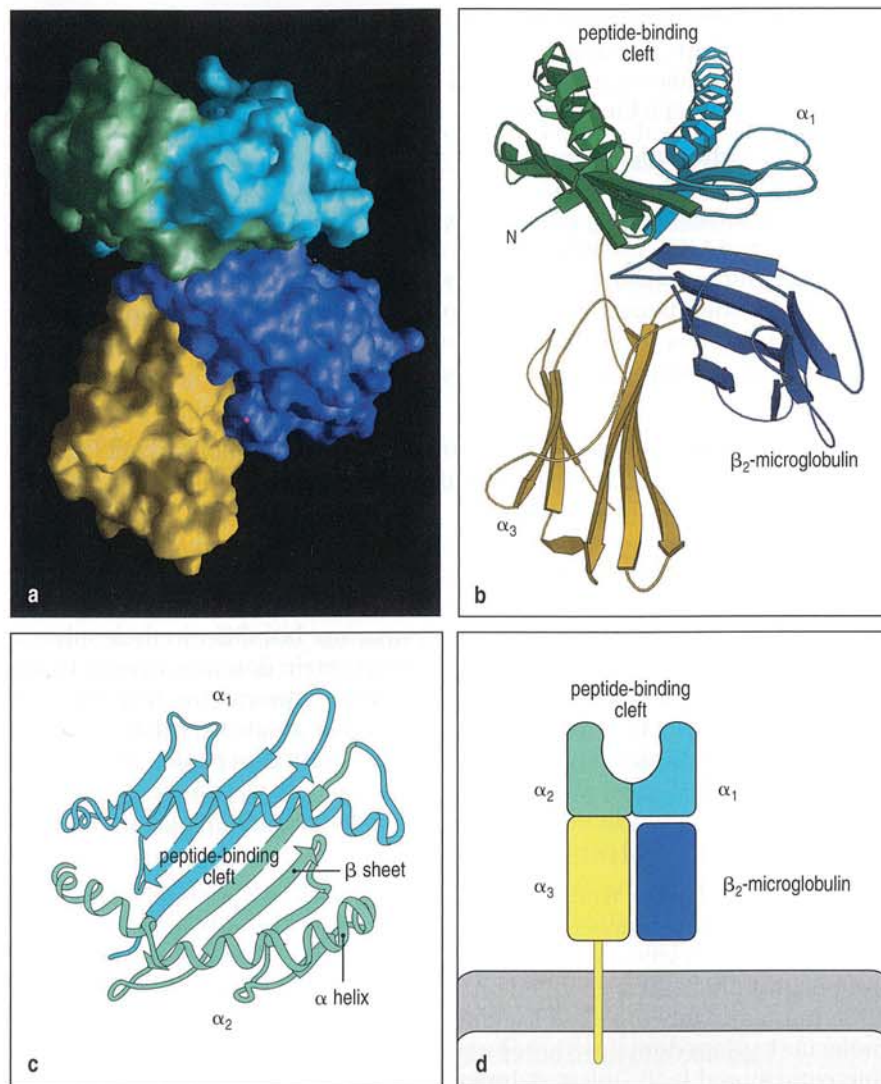


Fig. 4.14 Differences in the recognition of hen egg-white lysozyme by immunoglobulins and T-cell receptors.

Antibodies can be shown by X-ray crystallography to bind epitopes on the surface of proteins, as shown in panel a, where the epitopes for three antibodies are shown in different colors on the surface of hen egg-white lysozyme (see also Fig. 4.10). In contrast, the epitopes recognized by T-cell receptors need not lie on the surface of the molecule, because the T-cell receptor recognizes not the antigenic protein itself but a peptide fragment of the protein. The peptides corresponding to two T-cell epitopes of lysozyme are shown in panel b. One epitope, shown in blue, lies on the surface of the protein but a second, shown in red, lies mostly within the core and is inaccessible in the folded protein. For this residue to be accessible to the T-cell receptor, the protein must be unfolded and processed. Panel a courtesy of S. Sheriff.

Fig. 4.15 The structure of an MHC class I molecule determined by X-ray crystallography. Panel a shows a computer graphic representation of a human MHC class I molecule, HLA-A2, which has been cleaved from the cell surface by the enzyme papain. The surface of the molecule is shown, colored according to the domains shown in panels b–d and described below. Panels b and c show a ribbon diagram of that structure. Shown schematically in panel d, the MHC class I molecule is a heterodimer of a membrane-spanning α chain (molecular weight 43 kDa) bound noncovalently to β_2 -microglobulin (12 kDa), which does not span the membrane. The α chain folds into three domains: α_1 , α_2 , and α_3 . The α_3 domain and β_2 -microglobulin show similarities in amino acid sequence to immunoglobulin C domains and have similar folded structures, whereas the α_1 and α_2 domains fold together into a single structure consisting of two separated α helices lying on a sheet of eight antiparallel β strands. The folding of the α_1 and α_2 domains creates a long cleft or groove, which is the site at which peptide antigens bind to the MHC molecules. The transmembrane region and the short stretch of peptide that connects the external domains to the cell surface are not seen in panels a and b because they have been removed by the digestion with papain. As can be seen in panel c, looking down on the molecule from above, the sides of the cleft are formed from the inner faces of the two α helices; the β -pleated sheet formed by the pairing of the α_1 and α_2 domains creates the floor of the cleft.



4-13 Peptides are stably bound to MHC molecules, and also serve to stabilize the MHC molecule on the cell surface.

An individual can be infected by a wide variety of pathogens, whose proteins will not generally have peptide sequences in common. If T cells are to be alerted to all possible infections, the MHC molecules on each cell (both class I and class II) must be able to bind stably to many different peptides. This behavior is quite distinct from that of other peptide-binding receptors, such as those for peptide hormones, which usually bind only a single type of peptide. The crystal structures of peptide:MHC complexes have helped to show how a single binding site can bind peptides with high affinity while retaining the ability to bind a wide variety of different peptides.

An important feature of the binding of peptides to MHC molecules is that the peptide is bound as an integral part of the MHC molecule's structure, and MHC molecules are unstable when peptides are not bound. Stable peptide binding is important, because otherwise peptide exchanges occurring at the cell surface would prevent peptide:MHC complexes from being reliable indicators of infection or of uptake of a specific antigen. When MHC molecules are purified from cells, their stably bound peptides co-purify with them, and this has enabled the peptides bound by particular MHC molecules to be

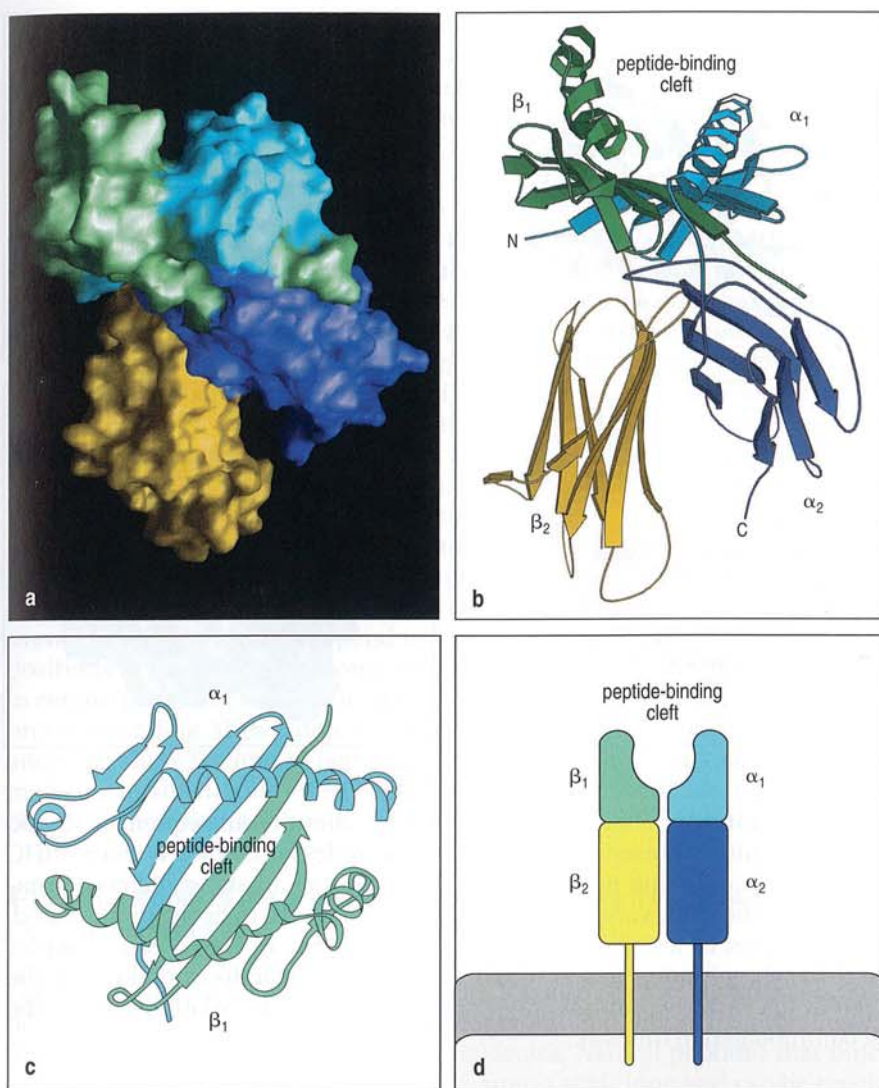


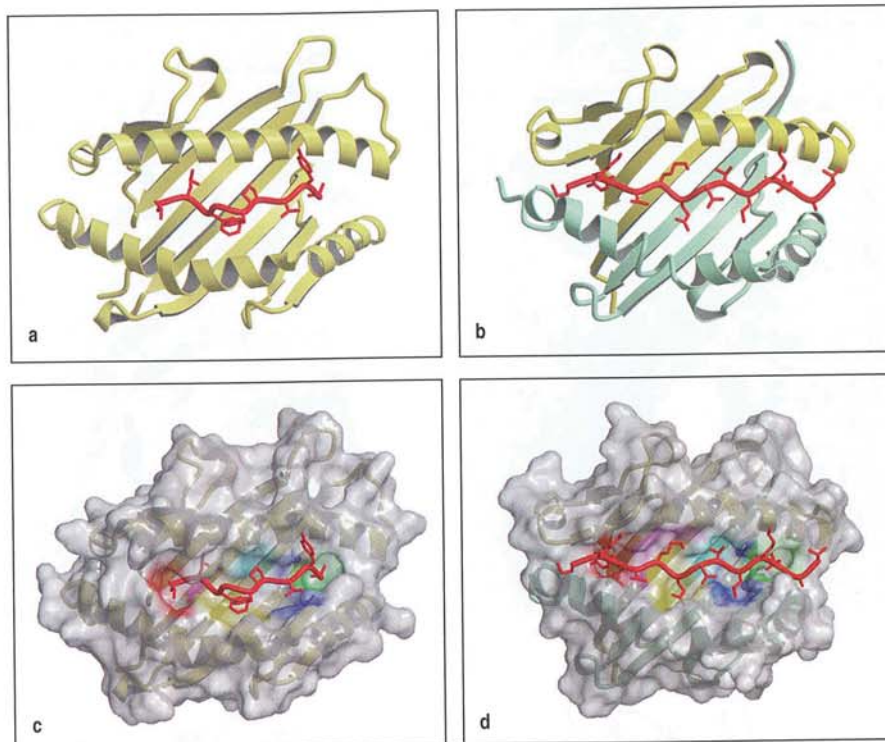
Fig. 4.16 MHC class II molecules resemble MHC class I molecules in overall structure. The MHC class II molecule is composed of two transmembrane glycoprotein chains, α (34 kDa) and β (29 kDa), as shown schematically in panel d. Each chain has two domains, and the two chains together form a compact four-domain structure similar to that of the MHC class I molecule (compare with panel d of Fig. 4.15). Panel a shows a computer graphic representation of the surface of the MHC class II molecule, in this case the human protein HLA-DR1, and panel b shows the equivalent ribbon diagram. N, amino terminus; C, carboxy terminus. The α_2 and β_2 domains, like the α_3 and β_2 -microglobulin domains of the MHC class I molecule, have amino acid sequence and structural similarities to immunoglobulin C domains; in the MHC class II molecule the two domains forming the peptide-binding cleft are contributed by different chains and are therefore not joined by a covalent bond (see panels c and d). Another important difference, not apparent in this diagram, is that the peptide-binding groove of the MHC class II molecule is open at both ends.

analyzed. Peptides are released from the MHC molecules by denaturing the complex in acid, and they are then purified and sequenced. Pure synthetic peptides can also be incorporated into empty MHC molecules and the structure of the complex determined, revealing details of the contacts between the MHC molecule and the peptide. From such studies a detailed picture of the binding interactions has been built up. We first discuss the peptide-binding properties of MHC class I molecules.

4-14 MHC class I molecules bind short peptides of 8–10 amino acids by both ends.

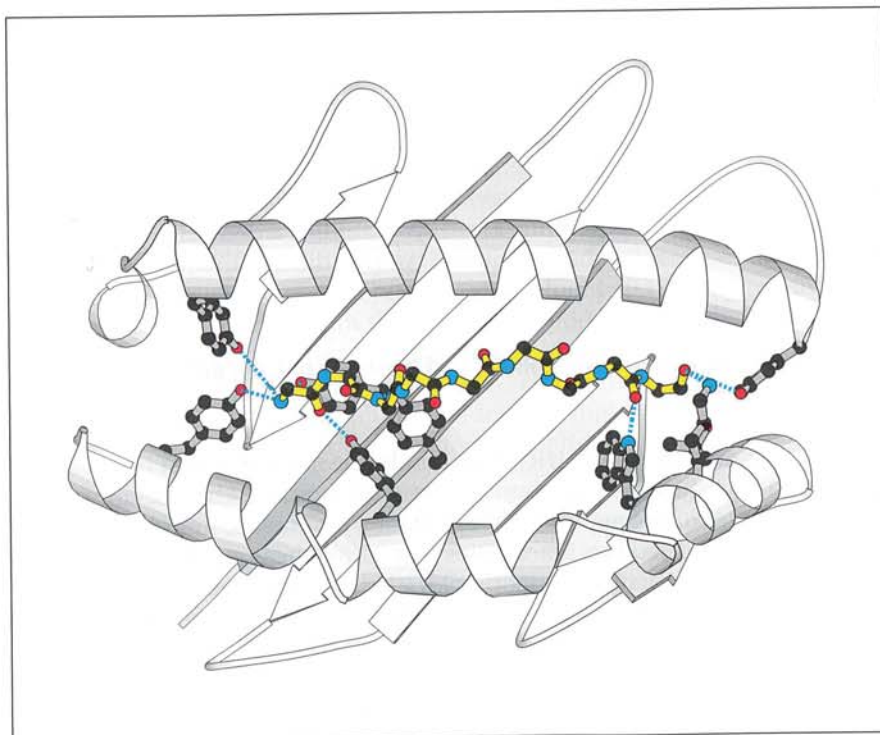
Binding of a peptide to an MHC class I molecule is stabilized at both ends of the peptide-binding cleft by contacts between atoms in the free amino and carboxy termini of the peptide and invariant sites that are found at each end of the cleft in all MHC class I molecules (Fig. 4.18). These are thought to be the main stabilizing contacts for peptide:MHC class I complexes, because synthetic peptide analogs lacking terminal amino and carboxyl groups fail to bind stably to MHC class I molecules. Other residues in the peptide serve as additional anchors. Peptides that bind to MHC class I molecules are usually 8–10 amino acids long. Longer peptides are thought to bind, however, particularly

Fig. 4.17 MHC molecules bind peptides tightly within the cleft. When MHC molecules are crystallized with a single synthetic peptide antigen, the details of peptide binding are revealed. In MHC class I molecules (panels a and c) the peptide is bound in an elongated conformation with both ends tightly bound at either end of the cleft. In MHC class II molecules (panels b and d) the peptide is also bound in an elongated conformation but the ends of the peptide are not tightly bound and the peptide extends beyond the cleft. The upper surface of the peptide:MHC complex is recognized by T cells, and is composed of residues of the MHC molecule and the peptide. In representations c and d, the electrostatic potential of the MHC molecule surface is shown, with blue areas indicating a positive potential and red a negative potential. Structures courtesy of R.L. Stanfield and I.A. Wilson.



if they can bind at their carboxy terminus, but they are subsequently cleaved by exopeptidases present in the endoplasmic reticulum, which is where MHC class I molecules bind peptides. The peptide lies in an elongated conformation along the cleft; variations in peptide length seem to be accommodated, in most cases, by a kinking in the peptide backbone. However, two examples of MHC class I molecules in which the peptide is able to extend out of the cleft at the carboxy terminus suggest that some length variation can also be accommodated in this way.

Fig. 4.18 Peptides are bound to MHC class I molecules by their ends. MHC class I molecules interact with the backbone of a bound peptide (shown in yellow) through a series of hydrogen bonds and ionic interactions (shown as dotted blue lines) at each end of the peptide. The amino terminus of the peptide is to the left, the carboxy terminus to the right. Black circles are carbon atoms; red are oxygen; blue are nitrogen. The amino acid residues in the MHC molecule that form these bonds are common to all MHC class I molecules, and their side chains are shown in full (in gray) on a ribbon diagram of the MHC class I groove. A cluster of tyrosine residues common to all MHC class I molecules forms hydrogen bonds to the amino terminus of the bound peptide, while a second cluster of residues forms hydrogen bonds and ionic interactions with the peptide backbone at the carboxy terminus and with the carboxy terminus itself.

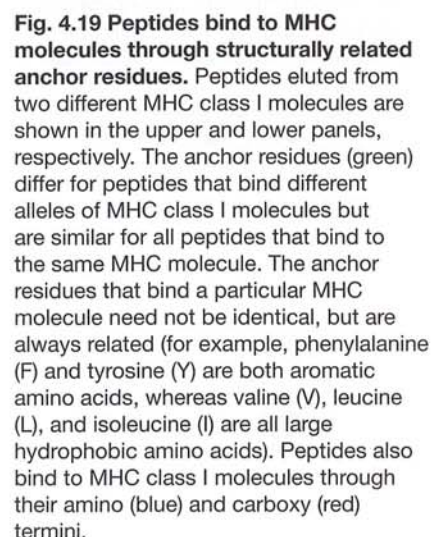


These interactions give MHC class I molecules a broad peptide-binding specificity. In addition, MHC molecules are highly polymorphic. There are hundreds of different versions, or **alleles**, of the MHC class I genes in the human population, and each individual carries only a small selection. The main differences between allelic MHC variants are found at certain sites in the peptide-binding cleft, resulting in different amino acids in key peptide-interaction sites. In consequence, the different MHC variants preferentially bind different peptides. The peptides that can bind to a given MHC variant have the same or very similar amino acid residues at two or three particular positions along the peptide sequence. The amino acid side chains at these positions insert into pockets in the MHC molecule that are lined by the polymorphic amino acids. Because this binding anchors the peptide to the MHC molecule, the peptide residues involved are called the **anchor residues**. Both the position and identity of these anchor residues can vary, depending on the particular MHC class I variant that is binding the peptide. However, most peptides that bind to MHC class I molecules have a hydrophobic (or sometimes basic) anchor residue at the carboxy terminus (Fig. 4.19). Whereas changing an anchor residue will in most cases prevent the peptide from binding, not every synthetic peptide of suitable length that contains these anchor residues will bind the appropriate MHC class I molecule, and so the overall binding must also depend on the nature of the amino acids at other positions in the peptide. In some cases, particular amino acids are preferred in certain positions, whereas in others the presence of particular amino acids prevents binding. These additional amino acid positions are called 'secondary anchors.' These features of peptide binding enable an individual MHC class I molecule to bind a wide variety of different peptides, yet allow different MHC class I allelic variants to bind different sets of peptides.

4-15 The length of the peptides bound by MHC class II molecules is not constrained.

Peptide binding to MHC class II molecules has also been analyzed by elution of bound peptides and by X-ray crystallography, and differs in several ways from peptide binding to MHC class I molecules. Natural peptides that bind to MHC class II molecules are at least 13 amino acids long and can be much longer. The clusters of conserved residues that bind the two ends of a peptide in MHC class I molecules are not found in MHC class II molecules, and the ends of the peptide are not bound. Instead, the peptide lies in an extended conformation along the peptide-binding cleft. It is held there both by peptide side chains that protrude into shallow and deep pockets lined by polymorphic residues and by interactions between the peptide backbone and side chains of conserved amino acids that line the peptide-binding cleft in all MHC class II molecules (Fig. 4.20). Structural data show that amino acid side chains at residues 1, 4, 6, and 9 of an MHC class II-bound peptide can be held in these binding pockets.

The binding pockets of MHC class II molecules accommodate a greater variety of side chains than those of MHC class I molecules, making it more difficult to define anchor residues and to predict which peptides will be able to bind a particular MHC class II variant (Fig. 4.21). Nevertheless, by comparing the sequences of known binding peptides it is usually possible to detect patterns of amino acids that permit binding to different MHC class II variants, and to model how the amino acids of this peptide sequence motif will interact with the amino acids of the peptide-binding cleft. Because the peptide is bound by its backbone and allowed to emerge from both ends of the binding groove, there is, in principle, no upper limit to the length of peptides that could bind to MHC class II molecules. However, it seems that longer peptides bound to MHC class II molecules are trimmed by peptidases to a length of around 13–17 amino acids in most cases. Like MHC class I molecules, MHC class II molecules that lack bound peptide are unstable.



and the products of many of these genes are involved in the production of peptide:MHC complexes. We shall also consider a group of proteins, encoded both within and outside the MHC, that are similar to MHC class I molecules but have limited polymorphism. They have various functions, such as activating T cells and NK cells by binding NKG2D (see Section 3-22) and the presentation of microbial lipid antigens to a special subset of $\alpha\beta$ T cells known as iNKT cells, which express a restricted repertoire of T-cell receptors.

The generation of T-cell receptor ligands.

The protective function of T cells depends on their ability to recognize cells that are harboring pathogens or that have internalized pathogens or their products. As we saw in Chapter 4, the ligand recognized by a T-cell receptor is a peptide bound to an MHC molecule and displayed on a cell surface. The generation of peptides from native proteins is commonly referred to as **antigen processing**, while the display of the peptide at the cell surface by the MHC molecule is referred to as **antigen presentation**. We have already described the structure of MHC molecules and seen how they bind peptide antigens in a cleft on their outer surface (see Sections 4-13 to 4-16). In this chapter we look at how peptides are generated from pathogen proteins present in two distinct intracellular compartments—the cytosol and the vesicular compartment (Fig. 6.1)—and how they are loaded onto MHC class I or MHC class II molecules, respectively.

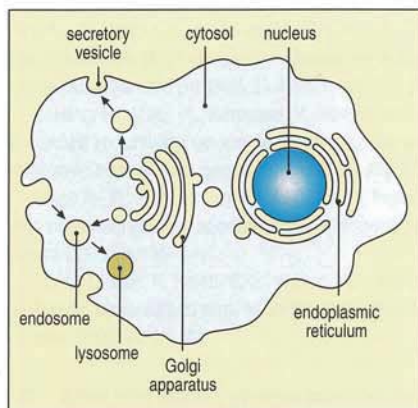


Fig. 6.1 There are two major intracellular compartments, separated by membranes. One compartment is the cytosol, which also communicates with the nucleus via the nuclear pores in the nuclear membrane. The other is the vesicular system, which comprises the endoplasmic reticulum, Golgi apparatus, endosomes, lysosomes, and other intracellular vesicles. The vesicular system can be thought of as continuous with the extracellular fluid. Secretory vesicles bud off from the endoplasmic reticulum and are transported via fusion with Golgi membranes to move vesicular contents out of the cell, whereas extracellular material is taken up by endocytosis or phagocytosis into endosomes or phagosomes, respectively. The inward and outward pathways can be linked by the fusion of incoming and outgoing vesicles, which is important both for pathogen destruction in specialized cells such as neutrophils and for antigen presentation, as we shall see in this chapter.

6-1 The MHC class I and class II molecules deliver peptides to the cell surface from two intracellular compartments.

Antigens from infectious agents get into the cytosolic or vesicular compartments of cells by various routes. Viruses and some bacteria replicate in the cytosol or in the contiguous nuclear compartment (Fig. 6.2, first panel). Microbial antigens enter the vesicular compartment in either of two ways. Certain pathogenic bacteria and protozoan parasites survive ingestion by macrophages and replicate inside the intracellular vesicles of the endosomal-lysosomal system (Fig. 6.2, second panel). Other pathogenic bacteria proliferate outside cells, where they cause tissue damage by secreting toxins and other proteins. These bacteria and their toxic products can be internalized by phagocytosis, receptor-mediated endocytosis, or macropinocytosis into endosomes and lysosomes, where they are broken down by digestive enzymes; illustrated here is the case of receptor-mediated endocytosis by B cells, which are very efficient at taking up and internalizing extracellular antigens by means of their antigen-specific B-cell receptors (Fig. 6.2, third panel). Virus particles and parasite antigens in extracellular fluids can also be taken up by these routes and degraded, and their peptides presented to T cells.

Peptides originating in the different compartments are delivered to the cell surface by different classes of MHC molecules. MHC class I molecules deliver peptides originating in the cytosol, whereas MHC class II molecules deliver peptides originating in the vesicular system. The immune system has different strategies for eliminating pathogens replicating in the cytosol or in the endosomal system, and the MHC molecules ensure that the appropriate strategy is activated. Cells infected with viruses or cytosolic bacteria are detected and eliminated by **cytotoxic T cells**; these effector T cells are distinguished by the co-receptor molecule CD8, which binds to MHC class I molecules (see Section 4-17). The function of CD8 T cells is to kill the cells they recognize;

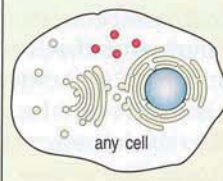
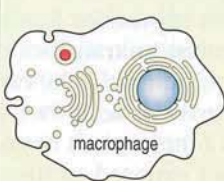
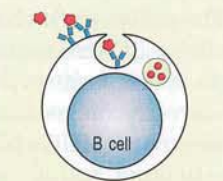
	Cytosolic pathogens	Intravesicular pathogens	Extracellular pathogens and toxins
			
Degraded in	Cytosol	Endocytic vesicles (low pH)	Endocytic vesicles (low pH)
Peptides bind to	MHC class I	MHC class II	MHC class II
Presented to	Effector CD8 T cells	Effector CD4 T cells	Effector CD4 T cells
Effect on presenting cell	Cell death	Activation to kill intravesicular bacteria and parasites	Activation of B cells to secrete Ig to eliminate extracellular bacteria/toxins

Fig. 6.2 Pathogens and their products can be found in either the cytosolic or the vesicular compartment of cells.

First panel: all viruses and some bacteria replicate in the cytosolic compartment. Their antigens are presented by MHC class I molecules to CD8 T cells. Second panel: other bacteria and some parasites are taken up into endosomes, usually by specialized phagocytic cells such as macrophages. Here they are killed and degraded, or in some cases are able to survive and proliferate within the vesicle. Their antigens are presented by MHC class II molecules to CD4 T cells. Third panel: proteins derived from extracellular pathogens may enter the intracellular vesicular system by binding to cell-surface receptors followed by endocytosis. This is illustrated here for antigens bound by the surface immunoglobulin (B-cell receptor) of B cells (the endoplasmic reticulum and Golgi apparatus have been omitted for simplicity). The B cells present these antigens to CD4 helper T cells, which can then stimulate the B cells to produce antibody. Other types of cells that bear receptors for the Fc regions of antibody molecules can also internalize antigens in this way and are able to activate T cells.

this is an important means of eliminating sources of new viral particles and bacteria that must live in the cytosol, and so freeing the host from infection.

Pathogens and their products in the vesicular compartment are detected by a different class of T cell, distinguished by the co-receptor molecule CD4, which binds to MHC class II molecules (see Section 4-17). **Effector CD4 T cells** comprise several different subsets, each of which has a distinct activity that helps to eliminate the pathogens against which it is targeted. Intravesicular pathogens are adapted to resist intracellular killing, and the macrophages in which they live have to be given an extra boost of activation to kill the pathogen: this is one of the roles of the T_H1 subset of CD4 T cells. Other CD4 T-cell subsets have roles in regulating other aspects of the immune response, and some CD4 T cells even have cytotoxic activity. The different activities of CD8 and CD4 T cells can largely be viewed as being adapted to deal with pathogens found in different cellular compartments; however, as we shall see later, there is significant cross-talk between these two pathways.

MHC class I and MHC class II molecules have distinct distributions on the cells of the body, and these reflect the different effector functions of the T cells that recognize them. MHC class I molecules are expressed by virtually all the cells of the body (except red blood cells), whereas the expression of MHC class II molecules is mainly restricted to immune-system cells—dendritic cells, macrophages, B cells, and T cells (the last in humans, but not in mice)—and thymic cortical epithelial cells, as described in Section 4-18 and Fig. 4.27. The cells illustrated in Fig. 6.2 are targets for already activated effector T cells. To initiate an adaptive immune response, however, antigen must be presented to naive T cells by specialized antigen-presenting cells, primarily conventional dendritic cells (see Section 3.12). Dendritic cells are highly specialized for this task and activate both CD8 and CD4 naive T cells. Macrophages and B cells can also act as antigen-presenting cells, albeit in a more limited way. Macrophages take up particulate material by phagocytosis and so mainly present pathogen-derived peptides on MHC class II molecules, activating the CD4 T cells that are needed to act back on the macrophage to clear pathogens living in its vesicles. By efficiently endocytosing specific antigen via their surface immunoglobulin and presenting the antigen-derived peptides on MHC class II molecules, B cells can activate CD4 T cells that will in turn serve as helper T cells for the production of antibodies against that antigen.

6-2 Peptides that bind to MHC class I molecules are actively transported from the cytosol to the endoplasmic reticulum.

The polypeptide chains of proteins destined for the cell surface, including the chains of MHC molecules, are translocated during synthesis into the lumen of the endoplasmic reticulum. Here, the two chains of each MHC molecule fold correctly and assemble with each other. This means that the peptide-binding site of the MHC class I molecule is formed in the lumen of the endoplasmic reticulum and is never exposed to the cytosol. The antigen fragments that bind to MHC class I molecules, however, are typically derived from proteins made in the cytosol. This raised the question: How are these peptides able to bind to MHC class I molecules and be delivered to the cell surface?

The answer is that peptides are continually being transported from the cytosol into the endoplasmic reticulum. The first clues to this delivery mechanism came from mutant cells with a defect in antigen presentation by MHC class I molecules. Although both chains of MHC class I molecules were synthesized normally, there were far fewer MHC class I proteins than normal on the cell surface. The defect could be corrected by the addition of synthetic peptides to the culture medium, suggesting that it was the supply of peptides to the MHC class I molecules that was being affected. This defect was also the first indication that MHC molecules are unstable in the absence of bound peptide and that peptide binding is required for the appearance and maintenance of MHC class I molecules at the cell surface. Analysis of the DNA of the mutant cells showed that the genes affected encoded members of the ATP-binding cassette (ABC) family of proteins and that these proteins were absent or non-functional in the mutant cells. ABC proteins mediate the ATP-dependent transport of ions, sugars, amino acids, and peptides across membranes. The two ABC proteins missing from the mutant cells are normally associated with the endoplasmic reticulum membrane and are called **transporters associated with antigen processing-1 and -2 (TAP1 and TAP2)**. Transfection of the mutant cells with the missing genes restored the presentation of peptides by the cell's MHC class I molecules. The two TAP proteins form a heterodimer in the membrane (Fig. 6.3), and mutations in either TAP gene can prevent antigen presentation by MHC class I molecules. The genes *TAP1* and *TAP2* map within the MHC (see Section 6-11) and are inducible by interferons, which are produced in response to viral infection; indeed, viral infection increases the delivery of cytosolic peptides into the endoplasmic reticulum.

In assays *in vitro* using fractions from nonmutant cells, microsomal vesicles that mimic the endoplasmic reticulum will internalize peptides, which bind to MHC class I molecules present in the microsome lumen. Vesicles from TAP1- or TAP2-deficient cells do not take up peptides. Peptide transport into normal microsomes requires ATP hydrolysis, confirming that the TAP1:TAP2 complex is an ATP-dependent peptide transporter. Similar experiments in

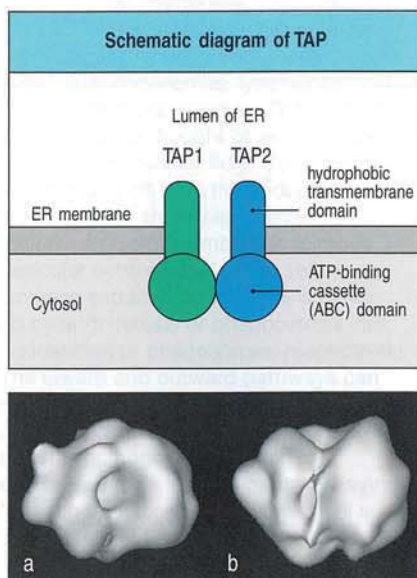


Fig. 6.3 TAP1 and TAP2 form a peptide transporter in the endoplasmic reticulum membrane. Upper panel: TAP1 and TAP2 are individual polypeptide chains, each with one hydrophobic and one ATP-binding domain. The two chains assemble into a heterodimer to form a four-domain transporter typical of the ATP-binding cassette (ABC) family. The hydrophobic transmembrane domains have multiple transmembrane regions (not shown here). The ATP-binding domains lie within the cytosol, whereas the hydrophobic domains project through the membrane into the lumen of the endoplasmic reticulum (ER) to form a channel through which peptides can pass. Lower panel: electron microscopic reconstruction of the structure of the TAP1:TAP2 heterodimer. Panel a shows the surface of the TAP transporter as seen from the lumen of the ER, looking down onto the top of the transmembrane domains, while panel b shows a lateral view of TAP in the plane of the membrane. The ATP-binding domains form two lobes beneath the transmembrane domains; the bottom edges of these lobes are just visible at the back of the lateral view. TAP structures courtesy of G. Velarde.

human cells show that the TAP complex has some specificity for the peptides it will transport. It prefers peptides of between 8 and 16 amino acids in length, with hydrophobic or basic residues at the carboxy terminus—the precise features of peptides that bind MHC class I molecules (see Section 4-14)—and has a bias against proline in the first three amino-terminal residues. The discovery of TAP explained how viral peptides from proteins synthesized in the cytosol gain access to the lumen of the endoplasmic reticulum and are bound by MHC class I molecules, but left open the question of how these peptides are generated.

6-3 Peptides for transport into the endoplasmic reticulum are generated in the cytosol.

Proteins in cells are continually being degraded and replaced with newly synthesized proteins. Much cytosolic protein degradation is carried out by a large, multicatalytic protease complex called the **proteasome** (Fig. 6.4). A typical proteasome is composed of one 20S catalytic core and two 19S regulatory caps, one at each end; both the core and the caps are multisubunit complexes of proteins. The 20S core is a large cylindrical complex of some 28 subunits, arranged in four stacked rings of seven subunits each. It has a hollow core lined by the active sites of the proteolytic subunits. Proteins are often tagged for degradation by the attachment of molecules of the protein ubiquitin. This modification targets them to the 19S cap, which recognizes ubiquitin and unfolds the tagged protein so that it can be introduced into the proteasome's catalytic core. There the protein chain is broken down into short peptides, which are subsequently released into the cytosol.

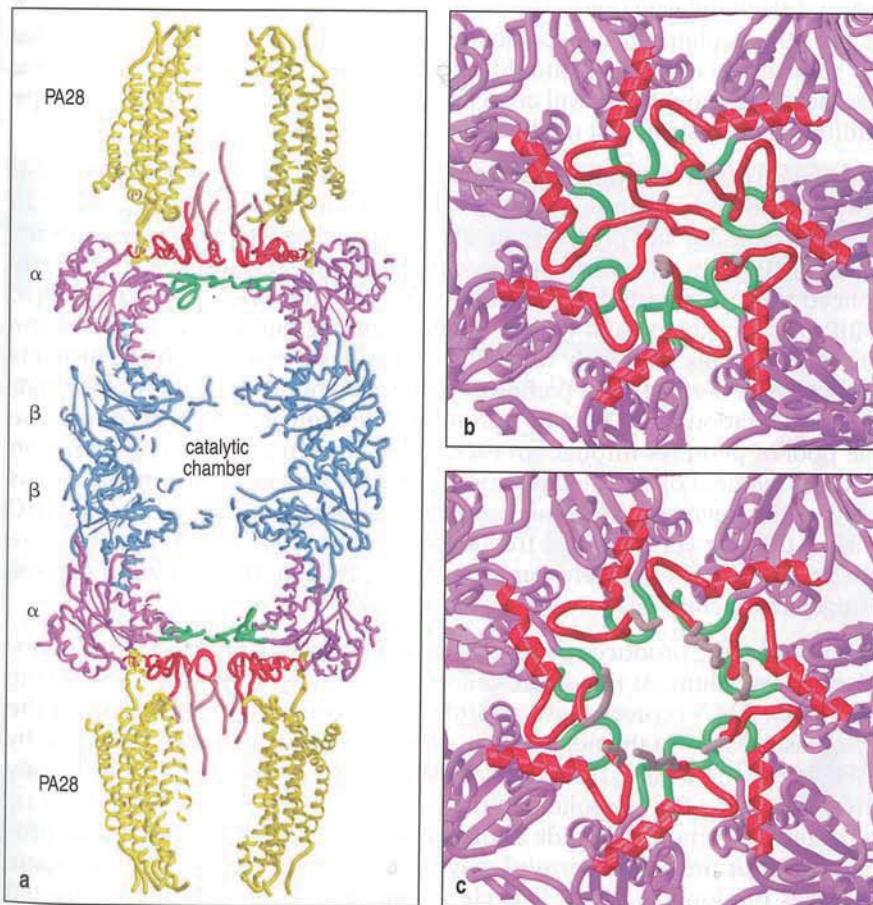


Fig. 6.4 The PA28 proteasome activator binds to either end of the proteasome.

Panel a: the heptamer rings of the PA28 proteasome activator (yellow) interact with the α subunits (pink) at either end of the core proteasome (the β subunits that make up the catalytic cavity of the core are in blue). Within this region is the α -annulus (green), a narrow ring-like opening that is normally blocked by other parts of the α subunits (shown in red). Panel b: close-up view of the α -annulus. Panel c: binding of PA28 (not shown, for simplicity) to the proteasome changes the conformation of the α subunits, moving those parts of the molecule that block the α -annulus, and opening the end of the cylinder. Structures courtesy of F. Whitby.

Various lines of evidence implicate the proteasome in the production of peptide ligands for MHC class I molecules. Experimentally tagging proteins with ubiquitin results in more efficient presentation of their peptides by MHC class I molecules, and inhibitors of the proteolytic activity of the proteasome inhibit antigen presentation by MHC class I molecules. Whether the proteasome is the only cytosolic protease capable of generating peptides for transport into the endoplasmic reticulum is not known.

The two inner rings of the 20S proteasome core are composed of constitutively expressed proteolytic subunits called $\beta 1$, $\beta 2$, and $\beta 5$, which form the catalytic chamber (see Fig. 6.4). These constitutive subunits are sometimes displaced by three alternative catalytic subunits, called LMP2 (PSMB9) and LMP7 (PSMB8), which are encoded within the MHC near *TAP1* and *TAP2*, and MECL-1, which is not encoded within the MHC. LMP2, LMP7, and MECL-1 are induced by interferons, similarly to MHC class I and TAP proteins. Thus, the proteasome can exist in two forms—as a constitutive proteasome present in all cells, and as the **immunoproteasome**, present in cells stimulated with interferons. The replacement of the β subunits by their interferon-inducible counterparts alters the enzymatic specificity of the proteasome such that there is increased cleavage of polypeptides after hydrophobic residues, and decreased cleavage after acidic residues. This produces peptides with carboxy-terminal residues that are preferred anchor residues for binding to most MHC class I molecules (see Chapter 4) and are also the preferred structures for transport by TAP.

The production of antigenic peptides of the right length is increased by a further modification of the proteasome induced by interferon- γ (IFN- γ). This is the binding to the proteasome of a protein complex called the PA28 proteasome-activator complex. PA28 is a six- or seven-membered ring composed of two proteins, PA28 α and PA28 β , both of which are induced by IFN- γ . A PA28 ring can bind to either end of the 20S proteasome core in place of the 19S regulatory cap, and acts to increase the rate at which peptides are released (see Fig. 6.4). In addition to simply providing more peptides, the increased rate of flow will allow potentially antigenic peptides to escape additional processing that might destroy their antigenicity.

Translation of self or pathogen-derived mRNAs in the cytoplasm generates not only properly folded proteins but also a significant quantity—possibly up to 30%—of peptides and proteins that are known as **defective ribosomal products (DRiPs)**. These include peptides translated from introns in improperly spliced mRNAs, translations of frameshifts, and improperly folded proteins. DRiPs are recognized and tagged by ubiquitin for rapid degradation by the proteasome. This seemingly wasteful process ensures that both self proteins and proteins derived from pathogens generate abundant peptides for eventual presentation by MHC class I proteins. The proteasome can also increase the pool of peptides through an excision-splicing mechanism, in which an internal segment of a protein is removed and the surrounding noncontiguous polypeptide segments are joined and used as the peptide presented by MHC class I. It is not yet clear how frequently excision-splicing occurs, but there are several examples of melanoma-specific CD8 T cells that recognize peptide antigens formed in this way.

The proteasome produces peptides that are ready for delivery into the endoplasmic reticulum. At this stage, cellular chaperones such as the TCP-1 ring complex (TRiC) protect these peptides from complete degradation in the cytoplasm. Many of the peptides are, however, longer than can be bound by MHC class I molecules. Thus, cleavage in the proteasome may not be the only processing step for cytosolic peptides. There is good evidence that the carboxy-terminal ends of peptide antigens are produced by cleavage in the proteasome, but the amino termini may be produced by another mechanism. Peptides too long to bind MHC class I molecules can still be transported

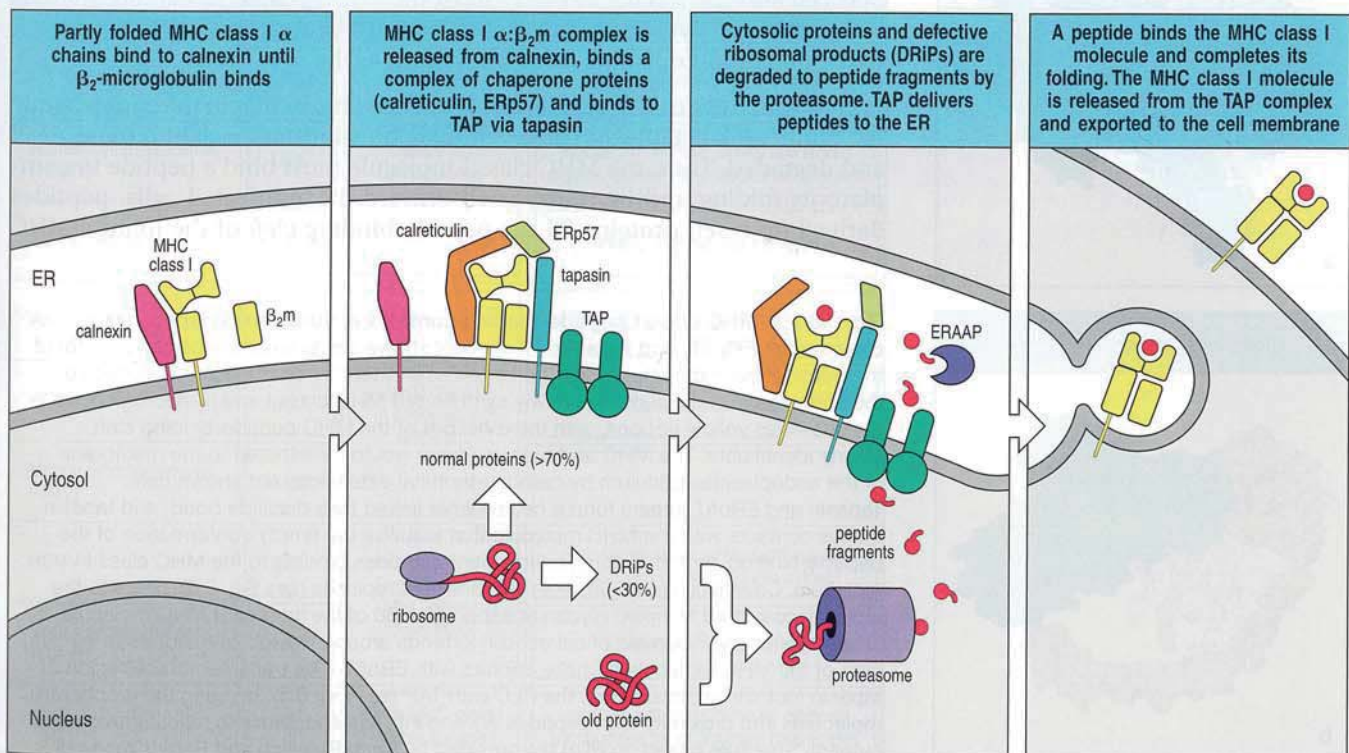
into the endoplasmic reticulum, where their amino termini can be trimmed by an aminopeptidase called the **endoplasmic reticulum aminopeptidase associated with antigen processing (ERAAP)**. Like other components of the antigen-processing pathway, ERAAP is upregulated by IFN- γ . Mice lacking ERAAP have an altered repertoire of peptides loaded onto MHC class I molecules. Although the loading of some peptides is not affected by the absence of ERAAP, other peptides fail to load normally, and many unstable and immunogenic peptides not normally present are found in complexes with MHC molecules on the cell surface. This causes cells from ERAAP-deficient mice to be immunogenic for T cells from wild-type mice, demonstrating that ERAAP is an important editor of the normal peptide:MHC repertoire.

6-4 Newly synthesized MHC class I molecules are retained in the endoplasmic reticulum until they bind a peptide.

Binding a peptide is an important step in the assembly of a stable MHC class I molecule. When the supply of peptides into the endoplasmic reticulum is disrupted, as in *TAP*-mutant cells, newly synthesized MHC class I molecules are held in the endoplasmic reticulum in a partly folded state. This explains why cells with mutations in *TAP1* or *TAP2* lack MHC class I molecules at the cell surface. The folding and assembly of a complete MHC class I molecule (see Fig. 4.17) depends on the association of the MHC class I α chain first with β_2 -microglobulin and then with peptide, and this process involves a number of accessory proteins with chaperone-like functions. Only after peptide has bound is the MHC class I molecule released from the endoplasmic reticulum and allowed to travel to the cell surface. This explains why the rare human patients that have been identified with immunodeficiency due to defects in *TAP-1* and *TAP-2* have few MHC class I molecules on their cell surfaces, a condition known as **MHC class I deficiency**.

Newly synthesized MHC class I α chains that enter the endoplasmic reticulum membranes bind to the chaperone protein **calnexin**, which retains the MHC class I molecule in a partly folded state (Fig. 6.5). Calnexin also associates with

Fig. 6.5 MHC class I molecules do not leave the endoplasmic reticulum unless they bind peptides. Newly synthesized MHC class I α chains assemble in the endoplasmic reticulum (ER) with the membrane-bound protein calnexin. When this complex binds β_2 -microglobulin (β_2m), the MHC class I α : β_2m dimer dissociates from calnexin, and the partly folded MHC class I molecule then binds to the peptide transporter TAP by interacting with one molecule of the TAP-associated protein tapasin. The chaperone molecules ERp57, which forms a heterodimer with tapasin, and calreticulin also bind to form the MHC class I peptide-loading complex. The MHC class I molecule is retained within the ER until released by the binding of a peptide, which completes the folding of the MHC molecule. Even in the absence of infection, there is a continual flow of peptides from the cytosol into the ER. Defective ribosomal products (DRiPs) and old proteins marked for destruction are degraded in the cytoplasm by the proteasome to generate peptides that are transported into the lumen of the endoplasmic reticulum by TAP. Some of these peptides will bind to MHC class I molecules. The aminopeptidase ERAAP trims the peptides at their amino termini, allowing peptides that are too long to bind, increasing the repertoire of potential peptides for presentation. Once a peptide has bound to the MHC molecule, the peptide:MHC complex leaves the endoplasmic reticulum and is transported through the Golgi apparatus and finally to the cell surface.



MHC Class I Deficiency



Movie 6.1

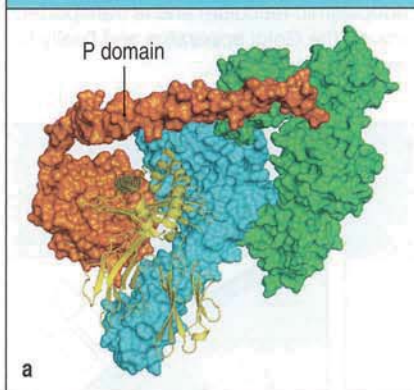


partly folded T-cell receptors, immunoglobulins, and MHC class II molecules, and so has a central role in the assembly of many immunological proteins. When β_2 -microglobulin binds to the α chain, the partly folded MHC class I α : β_2 -microglobulin heterodimer dissociates from calnexin and now binds to an assembly of proteins called the MHC class I **peptide-loading complex (PLC)**. One component of the PLC—**calreticulin**—is similar to calnexin and probably has a similar chaperone function. A second component of the complex is the TAP-associated protein **tapasin**, encoded by a gene within the MHC. Tapasin forms a bridge between MHC class I molecules and TAP, allowing the partly folded α : β_2 -microglobulin heterodimer to await the transport of a suitable peptide from the cytosol. A third component of this complex is the chaperone **ERp57**, a thiol oxidoreductase that may have a role in breaking and reforming the disulfide bond in the MHC class I α_2 domain during peptide loading (Fig. 6.6). ERp57 forms a stable disulfide-linked heterodimer with tapasin. Calnexin, ERp57, and calreticulin bind various other glycoproteins assembling in the endoplasmic reticulum and seem to be part of the cell's general quality-control machinery.

The final component of the PLC is the peptide-transporting TAP molecule itself. The other components seem to be essential to maintain the MHC class I molecule in a state receptive to a peptide and also to enable the exchange of low-affinity peptides bound to the MHC molecule for peptides of higher affinity, a process called **peptide editing**. *In vitro* binding studies suggest that the ERp57:tapasin heterodimer functions in editing peptides binding to MHC class I. Cells defective in either calreticulin or tapasin show defects in the assembly of MHC class I molecules, and those molecules that reach the cell surface are bound to suboptimal, low-affinity peptides. The binding of a peptide to the partly folded MHC class I molecule finally releases it from the loading complex. The fully folded MHC molecule and its bound peptide can now leave the endoplasmic reticulum and be transported to the cell surface. It is not yet clear whether the PLC actively loads peptides onto MHC class I molecules or whether binding to the PLC simply allows the MHC class I molecule to scan the peptides transported by TAP before they diffuse away. Most of the peptides transported by TAP will not bind to the MHC molecules in that cell and are rapidly cleared out of the endoplasmic reticulum; there is evidence that they are transported back into the cytosol by an ATP-dependent transport complex distinct from TAP, known as the Sec61 complex.

In cells with mutant *TAP* genes, the MHC class I molecules in the endoplasmic reticulum are unstable and are eventually translocated back into the cytosol and degraded. Thus, the MHC class I molecule must bind a peptide to complete its folding and be transported onward. In uninfected cells, peptides derived from self proteins fill the peptide-binding cleft of the mature MHC

Side view of the calreticulin, tapasin, ERp57, and MHC chaperone complex



Top view of chaperone complex

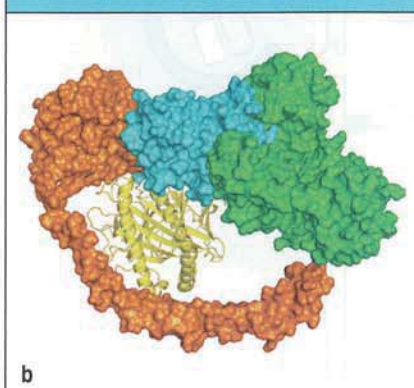


Fig. 6.6 The MHC class I peptide-loading complex includes the chaperones calreticulin, ERp57, and tapasin. This model shows a side view (a) and top view (b) of the peptide-loading complex (PLC) oriented as it extends from the luminal surface of the endoplasmic reticulum. The newly synthesized MHC class I and β_2 -microglobulin are shown as yellow ribbons, with the α helices of the MHC peptide-binding cleft clearly identifiable. The MHC and tapasin (cyan) would be tethered to the membrane of the endoplasmic reticulum by carboxy-terminal extensions not shown here. Tapasin and ERp57 (green) form a heterodimer linked by a disulfide bond, and tapasin makes contacts with the MHC molecule that stabilize the empty conformation of the peptide-binding cleft; they function in editing peptides binding to the MHC class I molecule. Calreticulin (orange), like the calnexin it replaces (see Fig. 6.5), binds to the monoglucosylated *N*-linked glycan at asparagine 86 of the immature MHC molecule. The long, flexible P domain of calreticulin extends around the top of the peptide-binding cleft of the MHC molecule to make contact with ERp57. The transmembrane region of tapasin (not shown) associates the PLC with TAP (see Fig. 6.5), bringing the empty MHC molecules into proximity with peptides arriving into the endoplasmic reticulum from the cytosol. Structure based on PDB file provided by Karin Reinisch and Peter Cresswell.