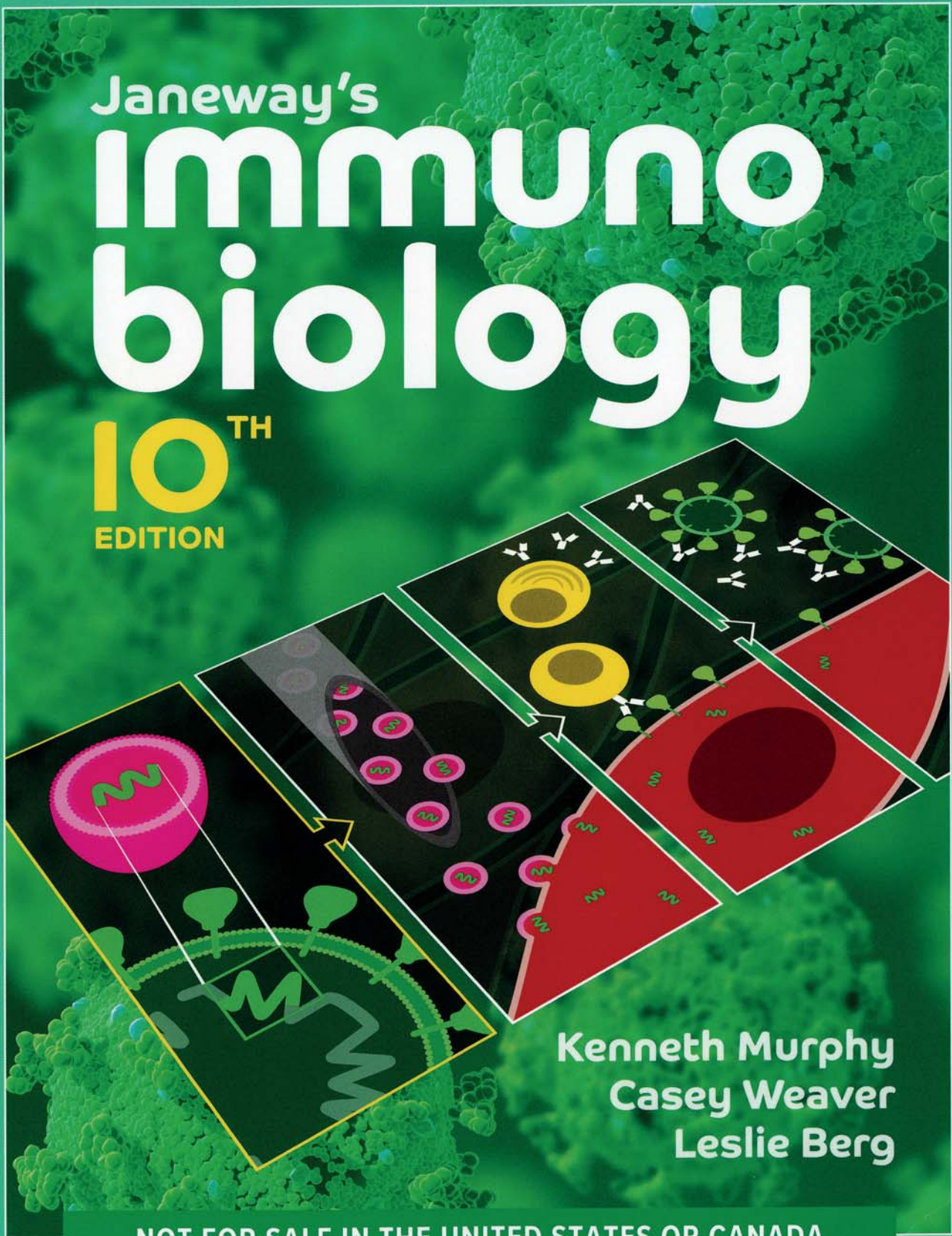


International Student Edition

Janeway's

Immunobiology

10TH
EDITION



Kenneth Murphy
Casey Weaver
Leslie Berg

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When a T cell first encounters an antigen that its receptor can bind, it proliferates and differentiates into one of several different functional types of **effector T lymphocytes**. When effector T cells subsequently detect antigen, they can manifest three broad classes of activity. **Cytotoxic T cells** kill other cells that are infected with viruses or other intracellular pathogens bearing the antigen. **Helper T cells** provide signals, often in the form of specific cytokines that activate the functions of other cells, such as B-cell production of antibody and macrophage killing of engulfed pathogens. **Regulatory T cells** suppress the activity of other lymphocytes and help to limit the possible damage of immune responses. We discuss the detailed functions of cytotoxic, helper, and regulatory T cells in Chapters 9, 11, 12, and 15.

Some of the B cells and T cells activated by antigen will 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.

1-9 Antibodies and T-cell receptors are composed of constant and variable regions that provide distinct functions.

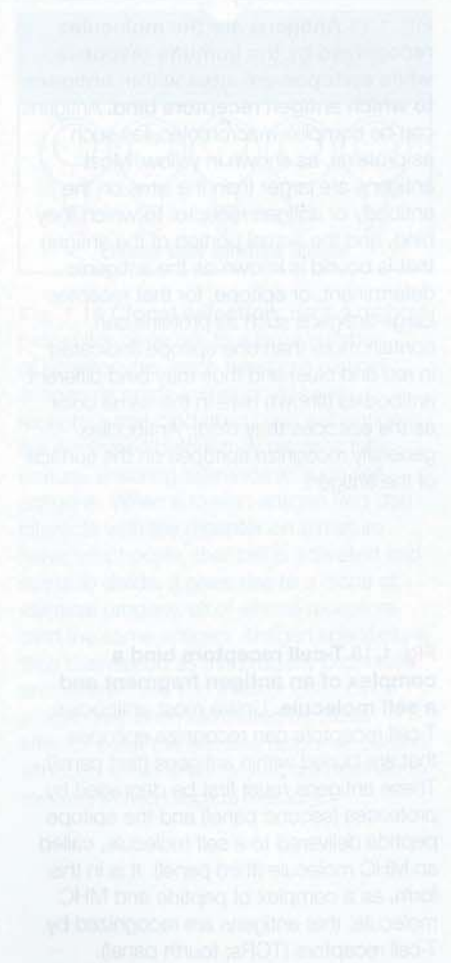
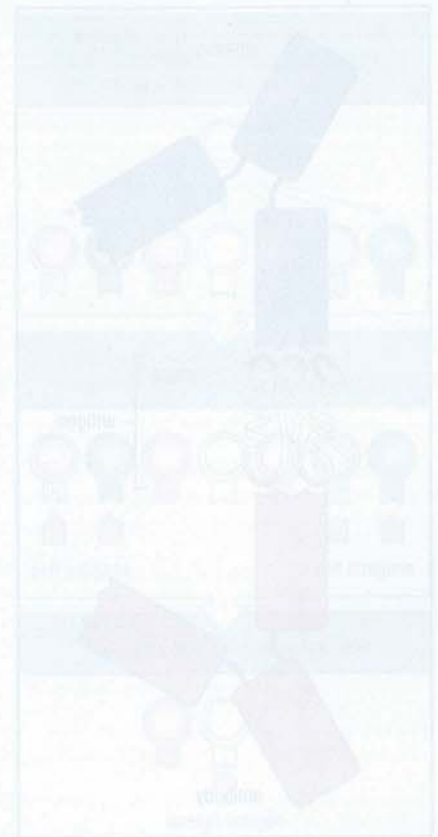
Antibodies were studied by traditional biochemical techniques long before recombinant DNA technology allowed the study of the membrane-bound forms of the antigen receptors on B and T cells. These early studies found that antibody molecules are composed of two distinct regions. One is a **constant region**, also called the **fragment crystallizable region**, or **Fc region**, which takes one of only five biochemically distinguishable forms (see Fig. 1.13). The **variable region** of different antibody molecules, by contrast, can be composed of a vast number of different amino acid sequences that allow antibodies to recognize an equally vast variety of antigens. The basic structure of antibody molecules was determined by Gerald Edelman and Rodney Porter, who shared the 1972 Nobel Prize for their work. These biochemical studies led to subsequent X-ray crystallographic determination of the structure of the antibody Fc region.

The antibody molecule is composed of two identical **heavy chain** and two identical **light chain** polypeptides. Heavy and light chains each have variable and constant regions. The variable regions of a heavy chain and a light chain combine to form an **antigen-binding site** that determines the antigen-binding specificity of the antibody. Thus, both heavy and light chains contribute to the antigen-binding specificity of the antibody molecule. Also, each antibody has two identical variable regions, and so has two identical antigen-binding sites. The constant region determines the effector function of the antibody; that is, how the antibody will interact with various immune cells to dispose of antigen once it is bound.

The T-cell receptor shows many similarities to the B-cell receptor and antibody (see Fig. 1.13). It is composed of two chains, the TCR α and β chains, that are roughly equal in size and which span the T-cell membrane. Like antibody, each TCR chain has a variable region and a constant region, and the combination of the α - and β -chain variable regions creates a single site for binding antigen. The structures of both antibodies and T-cell receptors are described in detail in Chapter 4, and functional properties of antibody constant regions are discussed in Chapters 4 and 10.

1-10 Antibodies and T-cell receptors recognize antigens by fundamentally different mechanisms.

In principle, almost any chemical structure can be recognized as an antigen by the adaptive immune system, but the usual antigens encountered in an infection are the proteins, glycoproteins, and polysaccharides of pathogens.



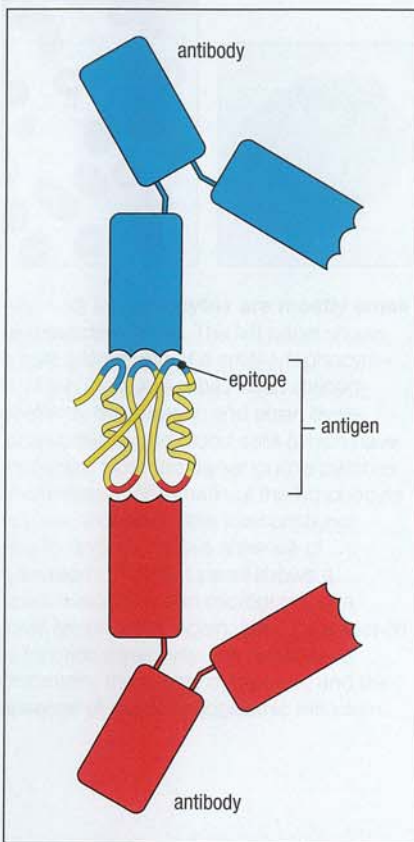


Fig. 1.14 Antigens are the molecules recognized by the immune response, while epitopes are sites within antigens to which antigen receptors bind. Antigens can be complex macromolecules such as proteins, as shown in yellow. Most antigens are larger than the sites on the antibody or antigen receptor to which they bind, and the actual portion of the antigen that is bound is known as the antigenic determinant, or epitope, for that receptor. Large antigens such as proteins can contain more than one epitope (indicated in red and blue) and thus may bind different antibodies (shown here in the same color as the epitopes they bind). Antibodies generally recognize epitopes on the surface of the antigen.

An individual antigen receptor or antibody recognizes a small portion of the antigen's molecular structure, and the part recognized is known as an **antigenic determinant**, or **epitope** (Fig. 1.14). Typically, proteins and glycoproteins have many different epitopes that can be recognized by different antigen receptors.

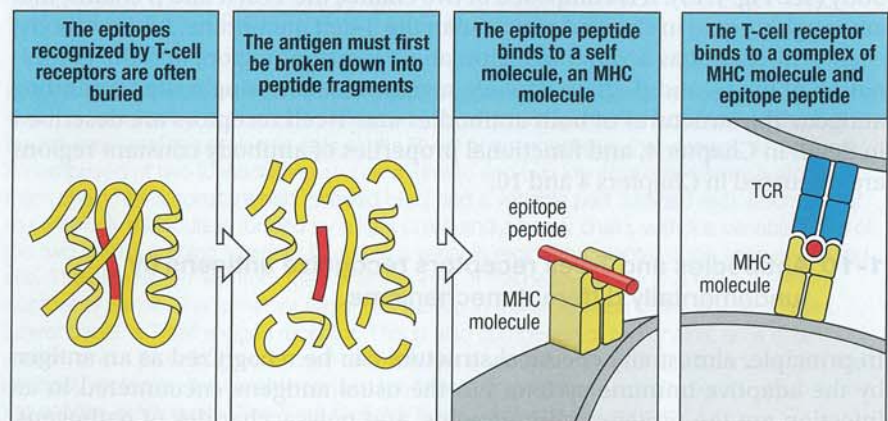
Antibodies and B-cell receptors directly recognize the epitopes of native antigen in the serum or the extracellular spaces. It is possible for different antibodies to simultaneously recognize an antigen by its different epitopes; such simultaneous recognition increases the efficiency of clearing or neutralizing the antigen.

Whereas antibodies can recognize nearly any type of chemical structure, T-cell receptors usually recognize protein antigens and do so very differently from antibodies. The T-cell receptor recognizes a peptide epitope derived from a partially degraded protein, but only if the peptide is bound to specialized cell-surface glycoproteins called **MHC molecules** (Fig. 1.15). The members of this large family of cell-surface glycoproteins are encoded in a cluster of genes called the **major histocompatibility complex (MHC)**. The antigens recognized by T cells can be derived from proteins arising from intracellular pathogens, such as a virus, or from extracellular pathogens. A further difference from the antibody molecule is that there is no secreted form of the T-cell receptor; the T-cell receptor functions solely to signal to the T cell that it has bound its antigen, and the subsequent immunological effects depend on the actions of the T cells themselves. We will further describe how epitopes from antigens are placed on MHC proteins in Chapter 6 and how T cells carry out their subsequent functions in Chapter 9.

1-11 Antigen-receptor genes are assembled by somatic gene rearrangements of incomplete receptor gene segments.

The innate immune system detects inflammatory stimuli by means of a relatively limited number of sensors, such as the TLR and NOD proteins, numbering fewer than 100 different types of proteins. Antigen-specific receptors of adaptive immunity provide a seemingly infinite range of specificities and yet are encoded by a finite number of genes. The basis for this extraordinary range of specificity was discovered in 1976 by Susumu Tonegawa, for which he was awarded the 1987 Nobel Prize. Immunoglobulin variable regions are inherited as sets of **gene segments**, each encoding a part of the variable region of one of the immunoglobulin polypeptide chains. During B-cell development in the bone marrow, these gene segments are irreversibly joined by a process of DNA recombination to form a stretch of DNA encoding a complete variable region. A similar process of antigen-receptor gene rearrangement takes place for the T-cell receptor genes during development of T cells in the thymus.

Fig. 1.15 T-cell receptors bind a complex of an antigen fragment and a self molecule. Unlike most antibodies, T-cell receptors can recognize epitopes that are buried within antigens (first panel). These antigens must first be degraded by proteases (second panel) and the epitope peptide delivered to a self molecule, called an MHC molecule (third panel). It is in this form, as a complex of peptide and MHC molecule, that antigens are recognized by T-cell receptors (TCRs; fourth panel).



receptor chains fold in much the same way as the regions comprising the Fab fragment shown in Fig. 4.1a. 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 C_α 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. 4.19b). 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 carbohydrates, with a sugar group from the C_α domain making a number of hydrogen bonds to the C_β domain (see Fig. 4.19b). 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 (Fig. 4.19c). 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. These differences with antibodies influence the ability of the T-cell receptor to recognize their specific ligands, as we will discuss in the next section. In addition to the three hypervariable regions shared with immunoglobulins, the T-cell receptor has a fourth hypervariability region, HV4, in both of its chains (see Fig. 4.19c). These regions occur away from the antigen-binding face of the receptor and have been implicated in other functions of the TCR, such as superantigen binding, which we will describe in Section 6-14.

4-15 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 4-11, 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. In contrast, $\alpha\beta$ T cells respond to short, continuous amino acid sequences. As we described in Section 1-10, these peptide sequences are often buried within the native structure of the protein. Thus, antigens cannot be recognized directly by T-cell receptors unless the protein is unfolded and processed into peptide fragments (Fig. 4.20) and then presented by an MHC molecule (see Fig. 1.15). We will discuss this process in Chapter 6.

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

Fig. 4.20 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 (red, yellow, purple) on the surface of hen egg-white lysozyme (see also Fig. 4.11). 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. This indicates that T-cell receptors do not recognize their epitopes in the native protein.

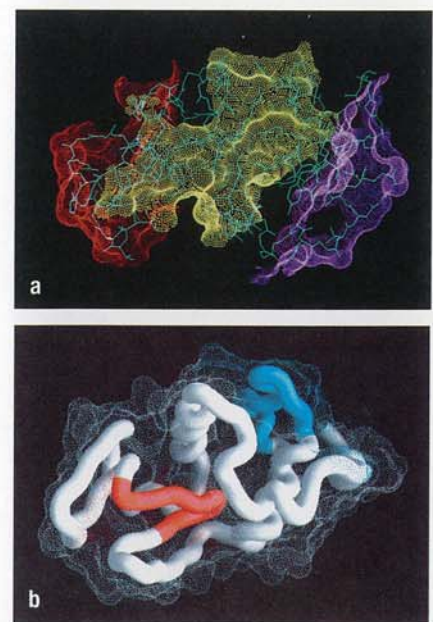
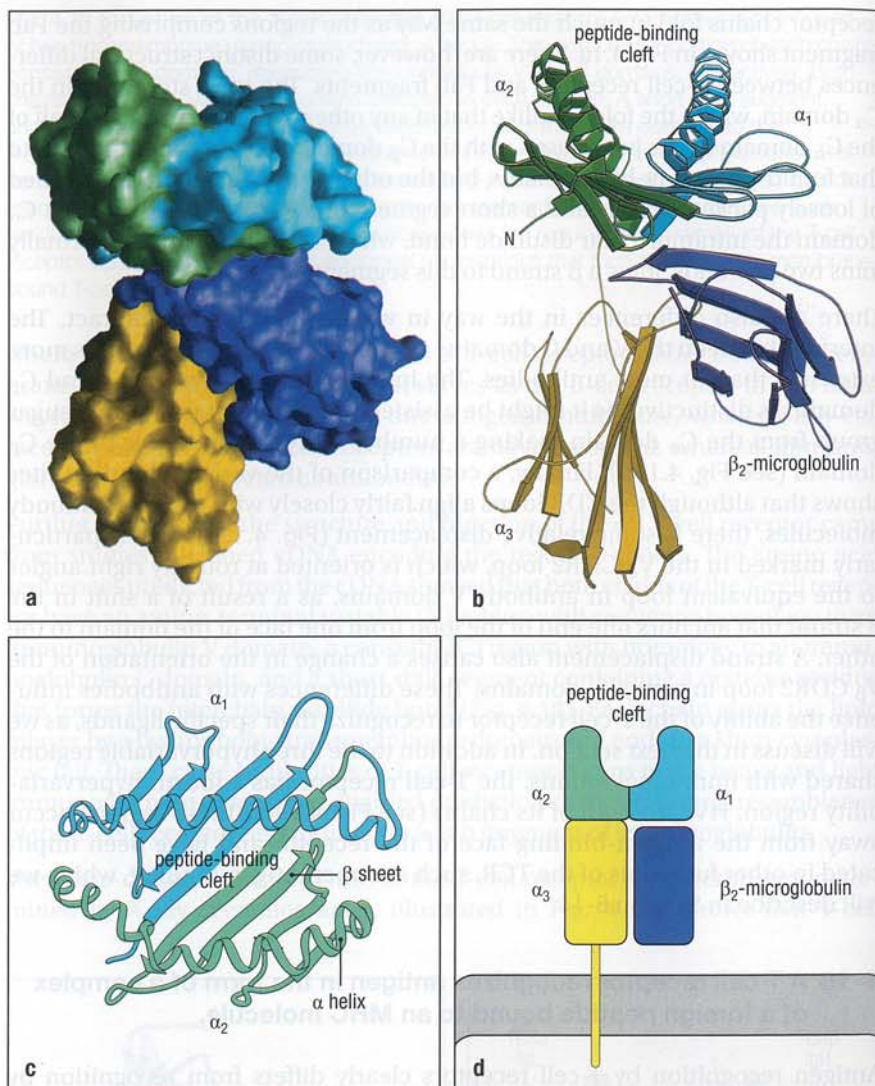


Fig. 4.21 The structure of an MHC class I molecule determined by X-ray crystallography. Panel a shows a computer-generated representation of a human MHC class I molecule, HLA-A2, which has been cleaved from the cell surface by the enzyme papain. The surface of the molecule is shown, colored according to the domains shown in panels b–d and described below. Panels b and c each show a ribbon diagram of the structure. Shown schematically in panel d, the MHC class I molecule is a heterodimer of a membrane-spanning α chain (molecular mass 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 are part of the same polypeptide and 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. For class I molecules, this groove is open at only one end. 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.



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 indirect at first, but it has been proven 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.

4-16 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**—and they differ in both their structure and their expression pattern in the tissues of the body. As shown in **Figs. 4.21** and **4.22**, MHC class I and MHC class II molecules are closely related in overall structure but differ in their subunit composition. 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.

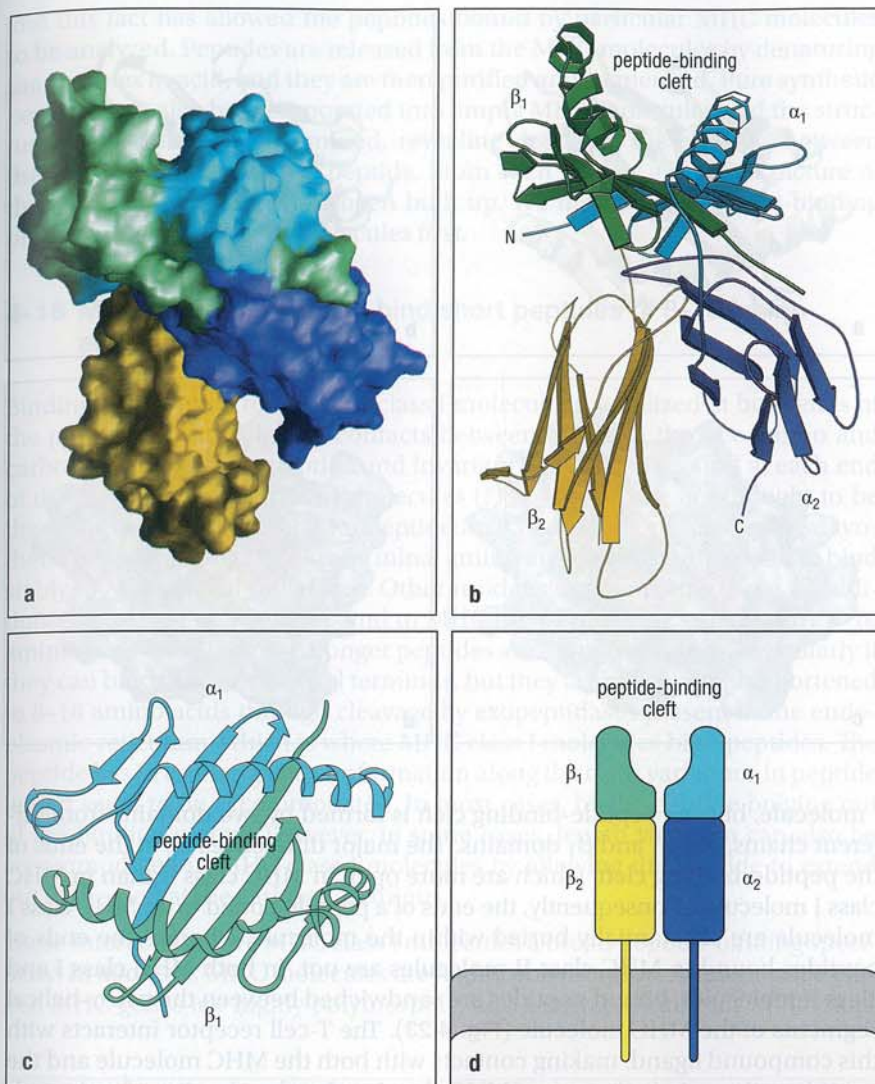


Fig. 4.22 MHC class II molecules resemble MHC class I molecules in overall structure. The MHC class II molecule is composed of two transmembrane glycoprotein chains, α (34 kDa) and β (29 kDa), as shown schematically in panel d. Each chain has two domains, and the two chains together form a compact four-domain structure similar to that of the MHC class I molecule (compare with panel d of Fig. 4.21). Panel a shows a computer-generated 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, carboxyl 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.

MHC class I molecules (see Fig. 4.21) 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 encoded on a different chromosome—chromosome 15 in humans. Only the class I α chain spans the membrane. The complete MHC class I 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; because this is where the peptide binds, this part of the MHC molecule is known as the **peptide-binding cleft** or **peptide-binding groove**. The MHC molecules are highly polymorphic, and the major differences between the different allelic forms are located in the peptide-binding cleft, influencing which peptides will bind and thus the specificity of the peptide:MHC antigen presented to T cells. By contrast, β_2 -microglobulin, which does not contribute directly to peptide binding, is not polymorphic.

An MHC class II molecule consists of a noncovalent complex of two chains, α and β , both of which span the membrane (see Fig. 4.22). 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