

6

Antigen Presentation to T Lymphocytes

Vertebrate adaptive immune cells possess two types of antigen receptors: the immunoglobulins that serve as antigen receptors on B cells, and the T-cell receptors. While immunoglobulins can recognize native antigens, T cells recognize only antigens that are displayed by MHC complexes on cell surfaces. The conventional **α : β T cells** recognize antigens as peptide:MHC complexes (see Section 4-13). The peptides recognized by α : β T cells can be derived from the normal turnover of self proteins, from intracellular pathogens, such as viruses, or from products of pathogens taken up from the extracellular fluid. Various tolerance mechanisms normally prevent self peptides from initiating an immune response; when these mechanisms fail, self peptides can become the target of autoimmune responses, as discussed in Chapter 15. Other classes of T cells, such as **MAIT cells** and **γ : δ T cells** (see Sections 4-18 and 4-20), recognize different types of surface molecules whose expression may indicate infection or cellular stress.

The first part of this chapter describes the cellular pathways used by various types of cells to generate peptide:MHC complexes recognized by α : β T cells. This process participates in adaptive immunity in at least two different ways. In somatic cells, peptide:MHC complexes can signal the presence of an intracellular pathogen for elimination by armed effector T cells. In dendritic cells, which may not themselves be infected, peptide:MHC complexes serve to activate antigen-specific effector T cells. We will also introduce mechanisms by which certain pathogens defeat adaptive immunity by blocking the production of peptide:MHC complexes.

The second part of this chapter focuses on the MHC class I and II genes and their tremendous variability. The MHC molecules are encoded within a large cluster of genes that were first identified by their powerful effects on the immune response to transplanted tissues and were therefore called the **major histocompatibility complex (MHC)**. There are several different MHC molecules in each class, and each of their genes is highly polymorphic, with many variants present in the population. MHC polymorphism has a profound effect on antigen recognition by T cells, and the combination of multiple genes and polymorphism greatly extends the range of peptides that can be presented to T cells in each individual and in populations as a whole, thus enabling individuals to respond to the wide range of potential pathogens they will encounter. The MHC also contains genes other than those for the MHC molecules; some of these genes are involved in the processing of antigens to produce peptide:MHC complexes.

The last part of the chapter discusses the ligands for unconventional classes of T cells. We will examine a group of proteins similar to MHC class I molecules that have limited polymorphism, some encoded within the MHC and others encoded outside the MHC. These so-called **nonclassical MHC class I proteins** serve various functions, some acting as ligands for γ : δ T-cell receptors and MAIT cells, or as ligands for NKG2D expressed by T cells and NK cells. In addition, we will introduce a special subset of α : β T cells known as invariant NKT cells that recognize microbial lipid antigens presented by these proteins.

IN THIS CHAPTER

The generation of α : β T-cell receptor ligands.

The major histocompatibility complex and its function.

Generation of ligands for unconventional T-cell subsets.

The generation of $\alpha:\beta$ T-cell receptor ligands.

The protective function of T cells depends on their recognition of cells harboring intracellular pathogens or that have internalized their products. As we saw in Chapter 4, the ligand recognized by an $\alpha:\beta$ 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 peptide display 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, or groove, on their outer surface (see Sections 4-13 to 4-16). We will now look at how peptides are generated from the proteins derived from pathogens and how they are loaded onto MHC class I or MHC class II molecules.

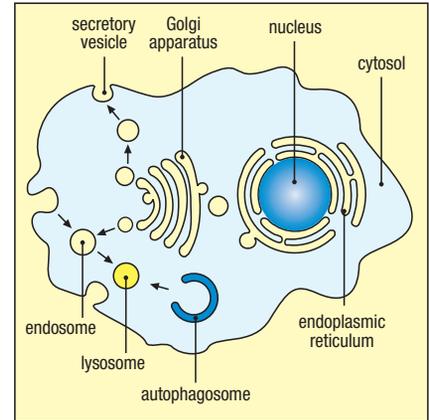
6-1 Antigen presentation functions both in arming effector T cells and in triggering their effector functions to attack pathogen-infected cells.

The processing and presentation of pathogen-derived antigens has two distinct purposes: inducing the development of armed effector T cells, and triggering the effector functions of these armed cells at sites of infection. MHC class I molecules bind peptides that are recognized by CD8 T cells, and MHC class II molecules bind peptides that are recognized by CD4 T cells, a pattern of recognition determined by specific binding of the CD8 or CD4 molecules to the respective MHC molecules (see Section 4-18). The importance of this specificity of recognition lies in the different distributions of MHC class I and class II molecules on cells throughout the body. Nearly all somatic cells (except red blood cells) express MHC class I molecules. Consequently, the CD8 T cell is primarily responsible for pathogen surveillance and cytolysis of somatic cells. Also called **cytotoxic T cells**, their function is to kill the cells they recognize. CD8 T cells are therefore an important mechanism in eliminating sources of new viral particles and bacteria that live only in the cytosol, and thus freeing the host from infection.

By contrast, MHC class II molecules are expressed primarily only on cells of the immune system, and particularly by dendritic cells, macrophages, and B cells. Thymic cortical epithelial cells and activated, but not naive, T cells can express MHC class II molecules, which can also be induced on many cells in response to the cytokine IFN- γ . Thus, CD4 T cells can recognize their cognate antigens during their development in the thymus, on a limited set of 'professional' antigen-presenting cells, and on other somatic cells under specific inflammatory conditions. **Effector CD4 T cells** comprise several subsets with different activities that help eliminate the pathogens. Importantly, naive CD8 and CD4 T cells can become armed effector cells only after encountering their cognate antigen once it has been processed and presented by activated dendritic cells.

In considering antigen processing, it is important to distinguish between the various cellular compartments from which antigens can be derived (**Fig. 6.1**). These compartments, which are separated by membranes, include the **cytosol** and the various **vesicular compartments** involved in endocytosis and secretion. Peptides derived from the cytosol are transported into the endoplasmic reticulum and directly loaded onto newly synthesized MHC class I molecules on the same cell for recognition by T cells, as we will discuss below in greater detail. Because viruses and some bacteria replicate in the cytosol or in the contiguous nuclear compartment, peptides from their components can be loaded onto MHC class I molecules by this process (**Fig. 6.2**, first upper panel).

Fig. 6.1 There are two categories of major intracellular compartments, separated by membranes. One compartment is the cytosol, which communicates with the nucleus via 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 being 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. Extracellular material is taken up by endocytosis or phagocytosis into endosomes or phagosomes, respectively. The fusion of incoming and outgoing vesicles is important both for pathogen destruction in cells such as neutrophils and for antigen presentation. Autophagosomes surround components in the cytosol and deliver them to lysosomes in a process known as autophagy.



This pathway of recognition is sometimes referred to as **direct presentation**, and can identify both somatic and immune cells that are infected by a pathogen.

Certain pathogenic bacteria and protozoan parasites survive ingestion by macrophages and are able to replicate inside the intracellular vesicles of the endosomal-lysosomal system (Fig. 6.2, second panel). Other pathogenic bacteria proliferate outside cells, and can be internalized, along with their toxic products, by phagocytosis, receptor-mediated endocytosis, or macropinocytosis into endosomes and lysosomes, where they are broken down by digestive enzymes. For example, receptor-mediated endocytosis by B cells can efficiently internalize extracellular antigens through 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.

Some pathogens may infect somatic cells but not directly infect phagocytes such as dendritic cells. In this case, dendritic cells must acquire antigens from exogenous sources in order to process and present antigens to T cells. For example, to eliminate a virus that infects only epithelial cells, activation of CD8 T cells will require that dendritic cells load MHC class I molecules with peptides derived from viral proteins taken up from virally infected cells. This exogenous pathway of loading MHC class I molecules is called **cross-presentation**, and is carried out very efficiently by some specialized types of dendritic cells (Fig. 6.3). The activation of naive T cells by this pathway is called **cross-priming**.

Fig. 6.2 Cells become targets of T-cell recognition by acquiring antigens from either the cytosolic or the vesicular compartments. Top, first panel: viruses and some bacteria replicate in the cytosolic compartment. Their antigens are presented by MHC class I molecules to activate killing by cytotoxic 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 activate cytokine production by CD4 T cells. Third panel: proteins derived from extracellular pathogens may bind to cell-surface receptors and enter the vesicular system by endocytosis, illustrated here for antigens bound by the surface immunoglobulin of B cells. These antigens are presented by MHC class II molecules to CD4 helper T cells, which can then stimulate the B cells to produce antibody.

	Cytosolic pathogens	Intravesicular pathogens	Extracellular pathogens and toxins
	 any cell	 macrophage	 B cell
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

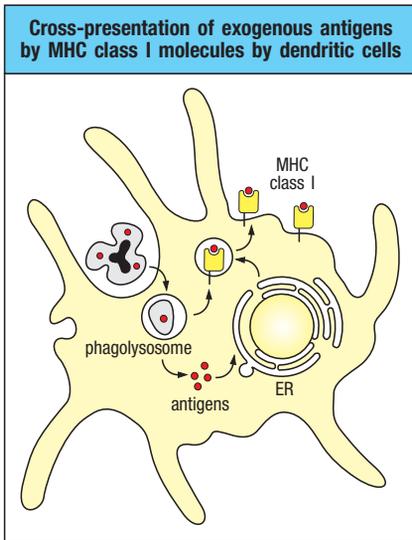


Fig. 6.3 Cross-presentation of extracellular antigens on MHC class I molecules by dendritic cells. Certain subsets of dendritic cells are efficient in capturing exogenous proteins and loading peptides derived from them onto MHC class I molecules. There is evidence that several cellular pathways may be involved. One route may involve the translocation of ingested proteins from the phagolysosome into the cytosol for degradation by the proteasome, with the resultant peptides then passing through TAP (see Section 6-3) into the endoplasmic reticulum, where they load onto MHC class I molecules in the usual way. Another route may involve direct transport of antigens from the phagolysosome into a vesicular loading compartment—without passage through the cytosol—where peptides are allowed to be bound to mature MHC class I molecules.

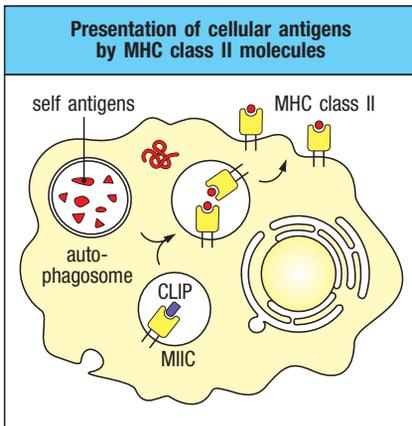


Fig. 6.4 Autophagy pathways can deliver cytosolic antigens for presentation by MHC class II molecules. In the process of autophagy, portions of the cytoplasm are taken into autophagosomes, specialized vesicles that are fused with endocytic vesicles and eventually with lysosomes, where the contents are catabolized. Some of the resulting peptides of this process can be bound to MHC class II molecules and presented on the cell surface. In dendritic cells and macrophages, this can occur in the absence of activation, so that immature dendritic cells may express self peptides in a tolerogenic context, rather than inducing T-cell responses to self antigens.

For loading peptides onto MHC class II molecules, dendritic cells, macrophages, and B cells are able to capture exogenous proteins via endocytic vesicles and through specific cell-surface receptors. For B cells, this process of antigen capture can include the B-cell receptor. The peptides that are derived from these proteins are loaded onto MHC class II molecules in specially modified endocytic compartments in these antigen-presenting cells, which we will discuss in more detail later. In dendritic cells, this pathway operates to activate naive CD4 T cells to become effector T cells. Macrophages take up particulate material by phagocytosis and so mainly present pathogen-derived peptides on MHC class II molecules. In macrophages, such antigen presentation may be used to indicate the presence of a pathogen within its vesicular compartment. Effector CD4 T cells, on recognizing antigen, produce cytokines that can activate the macrophage to destroy the pathogen. Some intravesicular pathogens have adapted to resist intracellular killing, and the macrophages in which they live require these cytokines 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. In B cells, antigen presentation may serve to recruit help from CD4 T cells that recognize the same protein antigen as the B cell. By efficiently endocytosing a 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.

Beyond the presentation of exogenous proteins, MHC class II molecules can also be loaded with peptides derived from cytosolic proteins by a ubiquitous pathway of **autophagy**, in which cytoplasmic proteins are delivered into the endocytic system for degradation in lysosomes (Fig. 6.4). This pathway can serve in the presentation of self-cytosolic proteins for the induction of tolerance to self antigens, and also as a means for presenting antigens from pathogens, such as herpes simplex virus, that have accessed the cell's cytosol.

6-2 Peptides are generated from ubiquitinated proteins in the cytosol by the proteasome.

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. 6.5). 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 around a hollow core. The two outer rings are composed of seven distinct α subunits and are noncatalytic. The two inner rings of the 20S proteasome core are composed of seven distinct β subunits. The constitutively expressed **proteolytic subunits** are $\beta1$, $\beta2$, and $\beta5$, which form the catalytic chamber. The 19S regulator is composed of a base containing nine subunits that binds directly to the α ring of the 20S

core particle and a lid that has up to 10 different subunits. The association of the 20S core with a 19S cap requires ATP as well as the ATPase activity of many of the caps' subunits. One of the 19S caps binds and delivers proteins into the proteasome, while the other keeps them from exiting prematurely.

Proteins in the cytosol are tagged for degradation via the **ubiquitin-proteasome system (UPS)**. This begins with the attachment of a chain of several ubiquitin molecules to the target protein, a process called **ubiquitination**. First, a lysine residue on the targeted protein is chemically linked to the glycine at the carboxy terminus of one ubiquitin molecule. Ubiquitin chains are then formed by linking the lysine at residue 48 (K48) of the first ubiquitin to the carboxy-terminal glycine of a second ubiquitin, and so on until at least 4 ubiquitin molecules are bound. This K48-linked type of ubiquitin chain is recognized by the 19S cap of the proteasome, which then unfolds the tagged protein so that it can be introduced into the proteasome's catalytic core. There the protein chain is degraded with a general lack of sequence specificity into short peptides, which are subsequently released into the cytosol. The general degradative functions of the proteasome have been co-opted for antigen presentation, so that MHC molecules have evolved to work with the peptides that the proteasome can produce.

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 constitutive $\beta 1$, $\beta 2$, and $\beta 5$ subunits of the catalytic chamber are sometimes replaced by three alternative catalytic subunits that are induced by interferons. These induced subunits are called **$\beta 1i$** (or **LMP2**), **$\beta 2i$** (or **MECL-1**), and **$\beta 5i$** (or **LMP7**). Both $\beta 1i$ and $\beta 5i$ are encoded by the *PSMB9* and *PSMB8* genes, which are located in the MHC locus, whereas $\beta 2i$ is encoded by *PSMB10* outside the MHC locus. Thus, the proteasome can exist both as both a constitutive proteasome present in all cells and as the **immunoproteasome**, which is present in cells stimulated with interferons. MHC class I proteins are also induced by 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.

Another substitution for a β subunit in the catalytic chamber has been found to occur in cells in the thymus. Epithelial cells of the thymic cortex (**cTECs**) express a unique β subunit, called **$\beta 5t$** , that is encoded by *PSMB11*. In cTECs, $\beta 5t$ becomes a component of the proteasome in association with $\beta 1i$ and $\beta 2i$, and this specialized type of proteasome is called the **thymoproteasome**. Mice lacking expression of $\beta 5t$ have reduced numbers of CD8 T cells, indicating that the peptide:MHC complexes produced by the thymoproteasome are important in CD8 T-cell development in the thymus.

Interferon- γ (IFN- γ) can further increase the production of antigenic peptides by inducing expression of the **PA28 proteasome-activator complex** that binds to the proteasome. 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, which can bind to either end of the 20S proteasome core in place of the 19S regulatory cap, acts to increase the rate at which peptides are released (Fig. 6.6). In addition to simply providing more peptides, the increased rate of

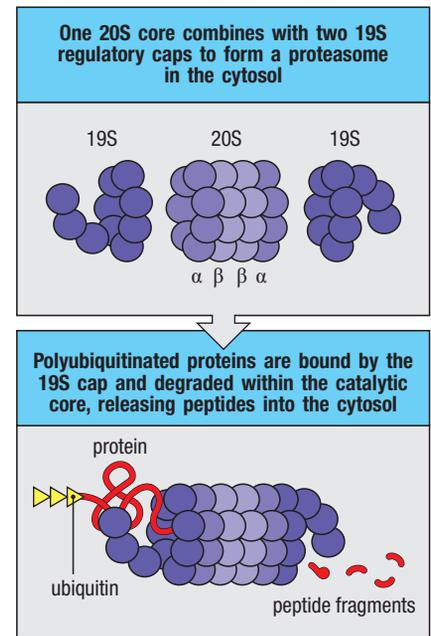
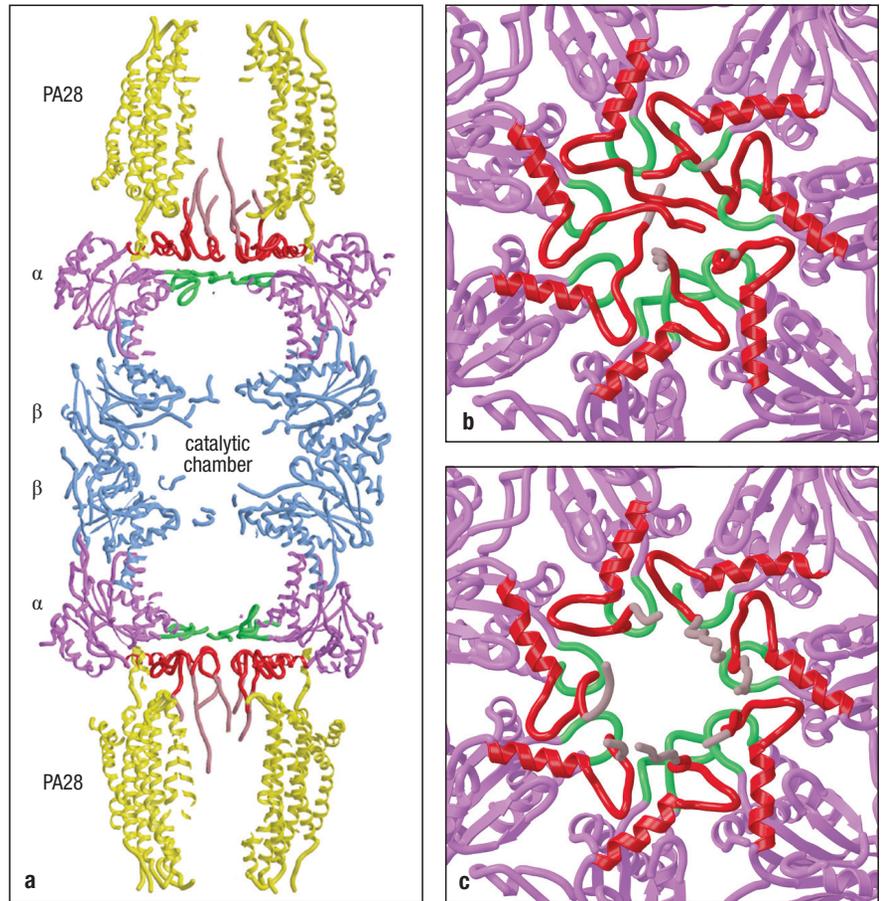


Fig. 6.5 Cytosolic proteins are degraded by the ubiquitin-proteasome system into short peptides. The proteasome is composed of a 20S catalytic core, which consists of four multisubunit rings (see text), and two 19S regulatory caps on either end. Proteins (orange) that are targeted become covalently tagged with K48-linked polyubiquitin chains (yellow) through the actions of various E3 ligases. The 19S regulatory cap recognizes polyubiquitin and draws the tagged protein inside the catalytic chamber; there, the protein is degraded, giving rise to small peptide fragments that are released back into the cytoplasm.

Fig. 6.6 The PA28 proteasome activator binds to either end of the proteasome.

Panel a: in this side view cross-section, 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 ringlike opening that is normally blocked by other parts of the α subunits (shown in red). Panel b: a close-up view from the top, looking into the α -annulus without PA28 bound. Panel c: with the same perspective, the binding of PA28 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. For simplicity, PA28 is not shown. Structures courtesy of F. Whitby.



flow allows 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, which are tagged by ubiquitin for rapid degradation by the proteasome. This seemingly wasteful process provides another source of peptides and ensures that both self proteins and proteins derived from pathogens generate abundant peptide substrates for eventual presentation by MHC class I proteins.

- 6-3 Peptides from the cytosol are transported by TAP into the endoplasmic reticulum and further processed before binding to MHC class I molecules.**
- 6-4 Newly synthesized MHC class I molecules are retained in the endoplasmic reticulum until they bind a peptide.**
- 6-5 Dendritic cells use cross-presentation to present exogenous proteins on MHC class I molecules to prime CD8 T cells.**
- 6-6 Peptide:MHC class II complexes are generated in acidified endocytic vesicles from proteins obtained through endocytosis, phagocytosis, and autophagy.**

- 6-7** The invariant chain directs newly synthesized MHC class II molecules to acidified intracellular vesicles.
- 6-8** The MHC class II-like molecules HLA-DM and HLA-DO regulate exchange of CLIP for other peptides.
- 6-9** Cessation of antigen processing occurs in dendritic cells after their activation through reduced expression of the MARCH-1 E3 ligase.

Summary.

The major histocompatibility complex and its function.

- 6-10** Many proteins involved in antigen processing and presentation are encoded by genes within the MHC.
- 6-11** The protein products of MHC class I and class II genes are highly polymorphic.
- 6-12** MHC polymorphism affects antigen recognition by T cells by influencing both peptide binding and the contacts between T-cell receptor and MHC molecule.
- 6-13** Alloreactive T cells recognizing nonself MHC molecules are very abundant.
- 6-14** Many T cells respond to superantigens.
- 6-15** MHC polymorphism extends the range of antigens to which the immune system can respond.

Summary.

Generation of ligands for unconventional T-cell subsets.

- 6-16** A variety of genes with specialized functions in immunity are also encoded in the MHC.
- 6-17** Specialized MHC class I molecules act as ligands for the activation and inhibition of NK cells and unconventional T-cell subsets.
- 6-18** Members of the CD1 family of MHC class I-like molecules present microbial lipids to invariant NKT cells.
- 6-19** The nonclassical MHC class I molecule MR1 presents microbial folate metabolites to MAIT cells.
- 6-20** γ : δ T cells can recognize a variety of diverse ligands.

Summary.

Summary to Chapter 6.

T-cell receptors on conventional $\alpha:\beta$ T cells recognize peptides bound to MHC molecules. In the absence of infection, MHC molecules are occupied by self peptides, which do not normally provoke a T-cell response, because of various tolerance mechanisms. But during infections, pathogen-derived peptides become bound to MHC molecules and are displayed on the cell surface, where they can be recognized by T cells that have been previously activated and armed for the specific peptide:MHC complex. Naive T cells become activated when they encounter their specific antigen presented on activated dendritic cells. MHC class I molecules in most cells bind to peptides derived from proteins that have been synthesized and then degraded in the cytosol. Some dendritic cells can obtain and process exogenous antigens and present them on MHC class I molecules. This process of cross-presentation is important for priming CD8 T cells to many viral infections.

Through assembly with the invariant chain (Ii), MHC class II molecules bind peptides derived from proteins degraded in endocytic vesicles, but they can also acquire self antigens through autophagy. Stable peptides are bound after a process of peptide editing in the endocytic compartment involving HLA-DM and HLA-DO. CD8 T cells recognize peptide:MHC class I complexes and are activated to kill cells displaying foreign peptides derived from cytosolic pathogens, such as viruses. CD4 T cells recognize peptide:MHC class II complexes and are specialized to activate other immune effector cells, for example, B cells or macrophages, to act against the foreign antigens or pathogens that they have taken up.

For each class of MHC molecule, there are several genes arranged in clusters within a larger region known as the major histocompatibility complex (MHC). Within the MHC, the genes for the MHC molecules are closely linked to genes involved in the degradation of proteins into peptides, the formation of the complex of peptide and MHC molecule, and the transport of these complexes to the cell surface. Because the several different genes for the MHC class I and class II molecules are highly polymorphic and are expressed in a codominant fashion, each individual expresses a number of different MHC class I and class II molecules. Each different MHC molecule can bind stably to a range of different peptides, and thus the MHC repertoire of each individual can recognize and bind many different peptide antigens. Because the T-cell receptor binds a combined peptide:MHC ligand, T cells show MHC-restricted antigen recognition, such that a given T cell is specific for a particular peptide bound to a particular MHC molecule.

Unconventional T-cell subsets include iNKT cells, MAIT cells, and $\gamma:\delta$ T cells, which recognize nonpeptide ligands of various types. Some CD1 molecules bind self lipids and pathogen-derived lipid molecules and present them to iNKT cells. MAIT cells recognize vitamin metabolites that are specific to bacteria and yeast and that are presented by MR1. $\gamma:\delta$ T cells are activated by a diverse array of ligands, including MHC class Ib molecules and EPCR, that are induced by infection or cellular stress. These T-cell subsets function in the transitional area between innate and adaptive immunity, relying on a repertoire of receptors produced by somatic gene rearrangement but recognizing ligands in a manner somewhat similar to the way PAMPs are recognized by TLRs and other fully innate receptors.

Questions.

- 6.1 Short Answer:** Dendritic cells are capable of efficiently acquiring antigens from exogenous sources and presenting these them to T cells on MHC class I molecules. How is this different from every other cell in the body and why is it important?
- 6.2 Matching:** Match the following terms with the appropriate description:
- | | |
|------------------------|---|
| A. Proteasome | i. Displace the constitutive β subunits of the catalytic chamber as a response to interferons |
| B. 20S core | ii. Composed of one catalytic core and two 19S regulatory caps |
| C. LMP2, LMP7, MECL-1 | iii. Large cylindrical complex of 28 subunits arranged in four stacked rings |
| D. PA28 | iv. Targets protein for degradation |
| E. Lysine 48 ubiquitin | v. Binds the proteasome and increases the rate of protein release from the proteasome |
- 6.3 True or False:** MHC class I surface expression is not affected by the cell's capacity to transport peptides into the endoplasmic reticulum.
- 6.4 Fill-in-the-Blanks:** Cell membrane-destined polypeptides are translocated to the lumen of the endoplasmic reticulum, which is intriguing because the MHC class I presented peptides are found in the _____. Further research revealed that presentation of cytosolic peptides is possible due to a family of ABC transporters, _____, that mediate the ATP-dependent transport of peptides into the lumen of the _____. This transporter complex has limited specificities for the transported peptides; for example, peptides are generally _____ amino acids in length and transport is biased in favor of _____ residues in the carboxy terminus and against _____ residues within the first _____ amino-terminal residues.
- 6.5 Multiple Choice:** CD8 dendritic cells are uniquely capable of strongly cross-presenting antigens. Which of the following options correctly matches a transcription factor essential for CD8 dendritic cell development and a surface marker uniquely expressed by these cells?
- A. CIITA, CD74
 - B. BATF3, CD4
 - C. CIITA, CD94
 - D. BATF3, XCR1
- 6.6 Matching:** Match the following terms with the appropriate description:
- | | |
|-------------|--|
| A. TRiC | i. Retains the MHC class I molecule α chain in a partly folded state |
| B. ERAAP | ii. Protects peptides produced in the cytosol from complete degradation |
| C. Calnexin | iii. Forms a bridge between the MHC class I molecule and the TAP complex |
| D. ERp57 | iv. Trims the amino terminus of peptides that are too long for MHC binding |
| E. Tapasin | v. Breaks and re-forms disulfide bonds in the MHC class I α domain during peptide loading |
- 6.7 True or False:** Cytosolic antigens are not presented through MHC class II molecules.
- 6.8 Matching:** Order the following events in the sequence in which MHC class II processing happens in an antigen-presenting cell:
- ____ The CD74 trimerization domain is cleaved.
 - ____ MHC class II is translocated into the endoplasmic reticulum.
 - ____ Cathepsin S cleaves LIP22 and leaves the CLIP fragment on the MHC molecule.
 - ____ CD74 trimers bind non-covalently to MHC class II $\alpha:\beta$ heterodimers.
 - ____ HLA-DM catalyzes the release of CLIP and promotes peptide editing.
 - ____ MHC class II heterodimers are released from calnexin for transport to a low-pH endosomal compartment.
- 6.9 Multiple Choice:** Defective function of which of the following proteins will result in failed CD8 T-cell priming?
- A. HLA-DM
 - B. Cathepsin S
 - C. TAP1/2
 - D. CD74
- 6.10 Multiple Choice:** Defective function of which of the following proteins will result in decreased cytosolic peptide presentation on MHC class II?
- A. IRGM3
 - B. BATF3
 - C. MARCH-1
 - D. TAP1/2

6.11 True or False: Superantigens do not induce an adaptive immune response and are independent of peptide-specific MHC–TCR interactions.

6.12 Multiple Choice: Which of the following statements is *false*?

- A. Polymorphisms at each locus can potentially double the number of different MHC molecules expressed by an individual.
- B. Pathogens can evade the immune system by mutating the immunodominant epitope, which results in loss of affinity for the specific MHC allele.
- C. Pathogens do not cause evolutionary pressure to select MHC alleles that confer protection against them.
- D. The DR α chain and its mouse homolog, E α , are monomorphic.

6.13 True or False: Classical MHC class I molecules are highly polymorphic, as opposed to MHC class Ib, which are oligomorphic.

6.14 Matching: Match the following MHC class Ib genes with their appropriate description:

- | | |
|----------|---|
| A. H2-M3 | i. Presents microbial folate metabolites |
| B. MICA | ii. Binds α -GalCer |
| C. CD1d | iii. Presents <i>N</i> -formylated peptides |
| D. MR1 | iv. Binds NKG2D |

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6-1 Antigen presentation functions both in arming effector T cells and in triggering their effector functions to attack pathogen-infected cells.

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6-2 Peptides are generated from ubiquitinated proteins in the cytosol by the proteasome.

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