Immunology

Lec.8

Major Histocompatibility Complex (MHC)

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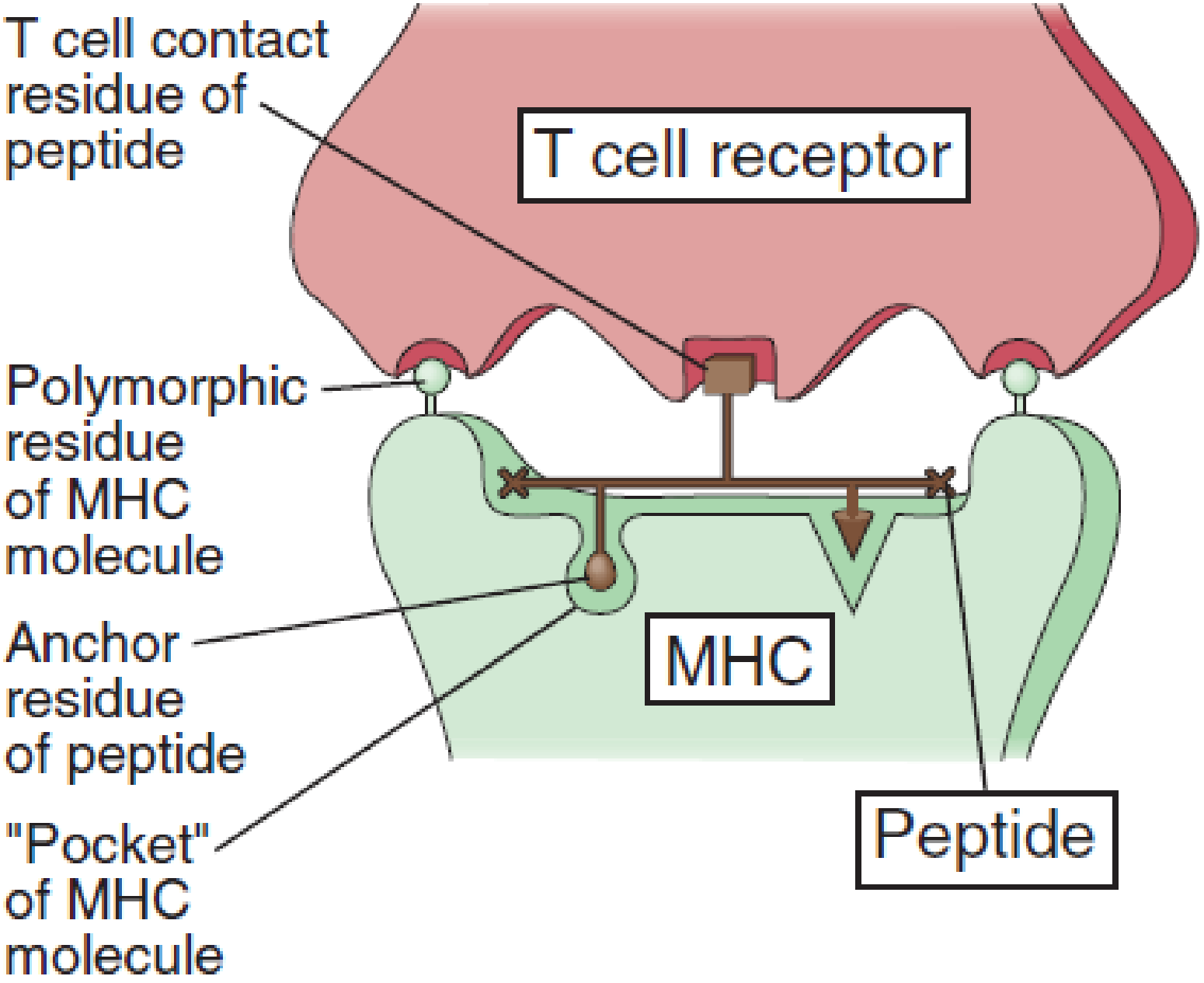
Major Histocompatibility Complex (MHC)

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


T cell contact residue of peptide
T cell receptor
Polymorphic residue of MHC molecule
Anchor residue of peptide
"Pocket" of MHC molecule
MHC
Peptide

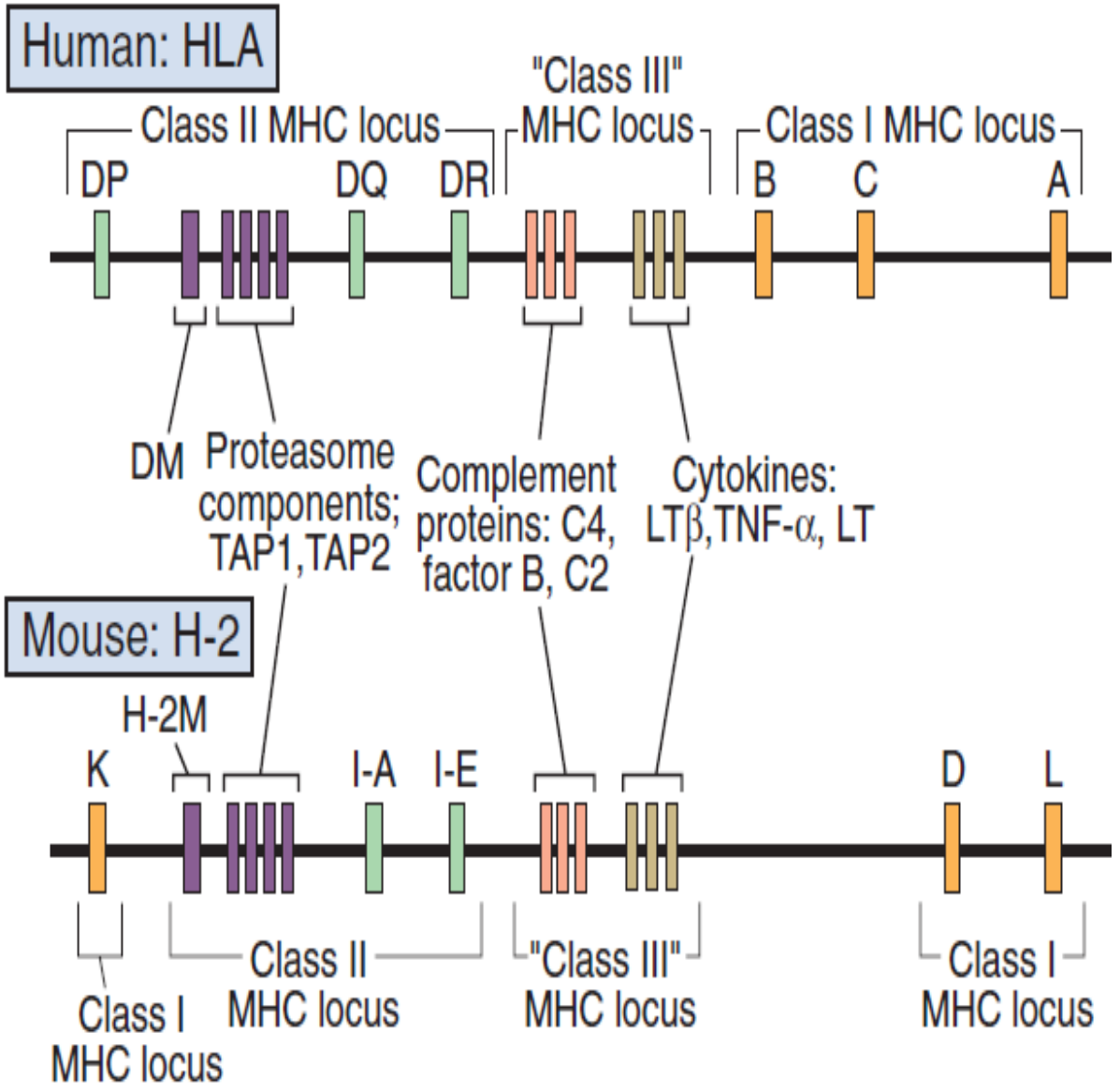
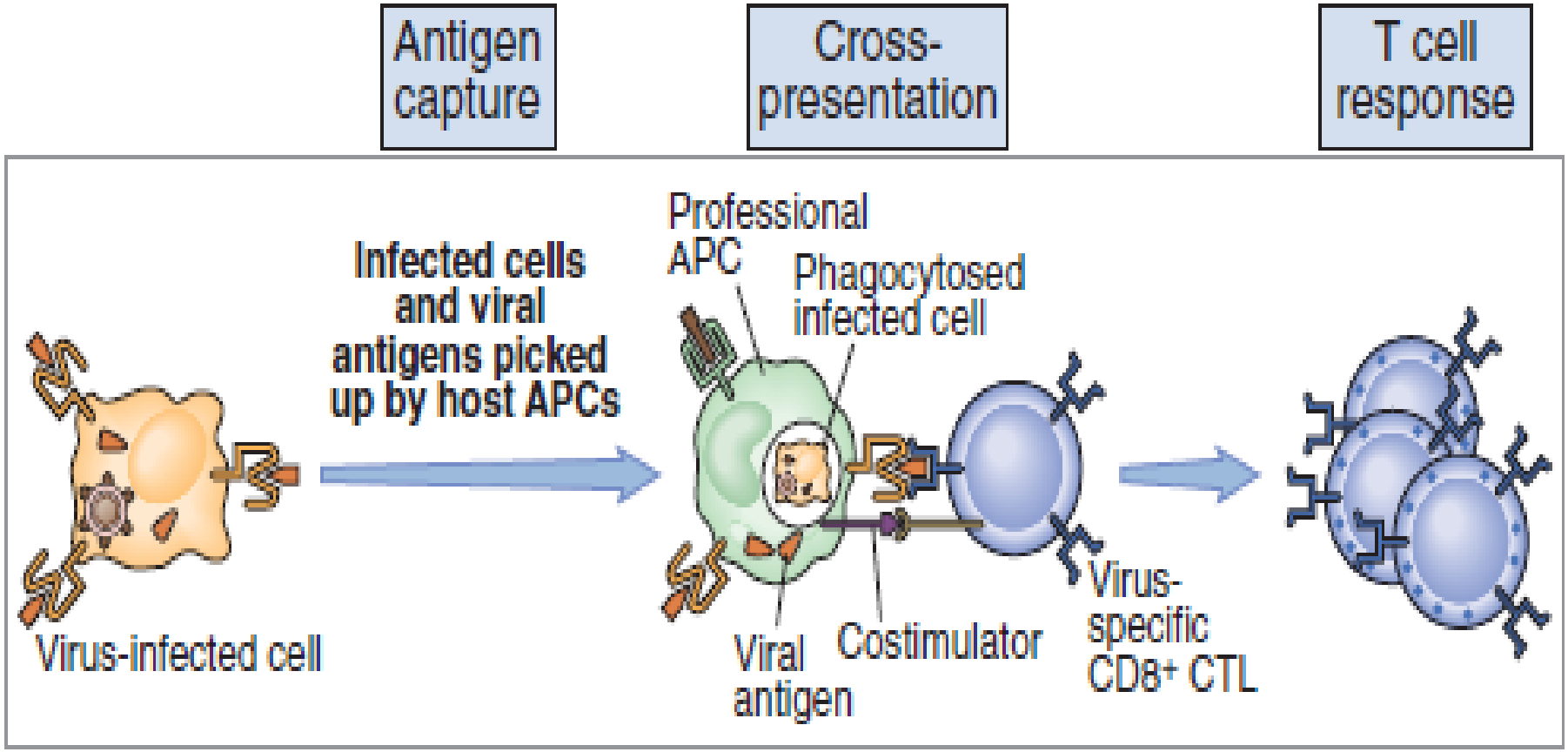


FIGURE 3-6 The genes of the major histocompatibility complex (MHC) locus. Schematic maps of the human MHC (called the HLA complex) and the mouse MHC (called the H-2 complex) are shown, illustrating the major genes that code for molecules involved in immune responses. Sizes of genes and intervening DNA segments are not shown to scale. Class II loci are shown as single blocks but each consists of at least two genes. Class III MHC locus refers to genes that encode molecules other than peptide display molecules; this term is not used commonly. There are also multiple class I–like genes and pseudogenes *(not shown)*. HLA, human leukocyte antigen; LT, lymphotoxin; TAP, transporter associated with antigen processing; TNF, tumor necrosis factor.

- **Genes of MHC Organized In 3 Classes**
  - Class I MHC genes
    - Glycoproteins expressed on all nucleated cells
    - Major function to present processed Ags to T-Cytotoxic (T_C)
  - Class II MHC genes
    - Glycoproteins expressed on B lymphocytes, a proportion of macrophages and monocytes, skin associated (Langerhans) cells, dendritic cells and occasionally on other cells.
    - Major function to present processed Ags to T-helper (T_{H})
  - Class III MHC genes
    - Products that include secreted proteins that have immune functions. Ex. Complement system, inflammatory molecules.


Antigen capture
Cross-presentation
T cell response
Infected cells and viral antigens picked up by host APCs
Professional APC
Phagocytosed infected cell
Virus-infected cell
Viral antigen
Costimulator
Virus-specific CD8+ CTL

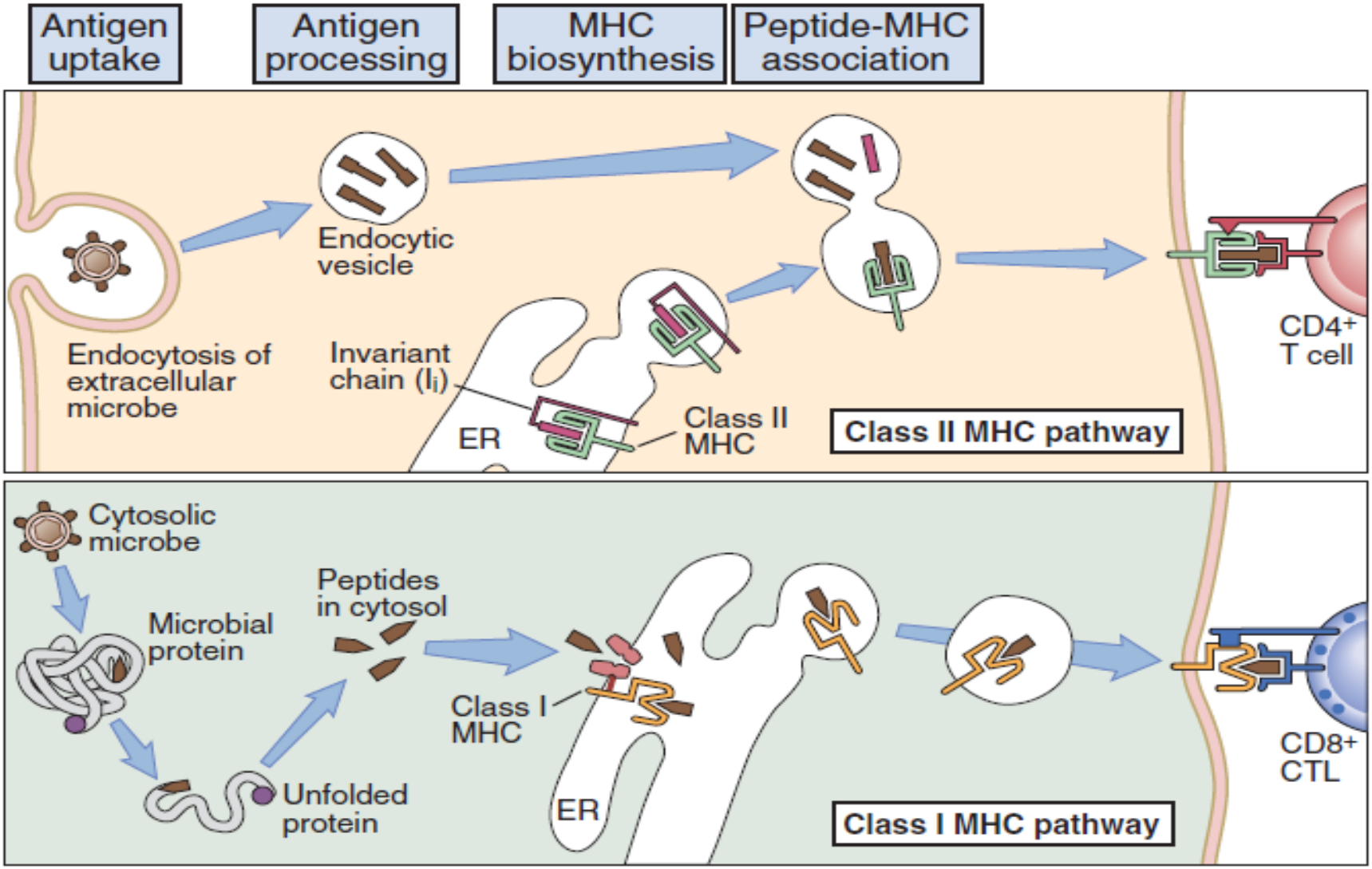


FIGURE 3-11 Pathways of intracellular processing of protein antigens. The class II MHC pathway converts protein antigens that are endocytosed into vesicles of antigen-presenting cells into peptides that bind to class II MHC molecules for recognition by CD4+ T cells. The class I MHC pathway converts proteins in the cytoplasm into peptides that bind to class I MHC molecules for recognition by CD8+ T cells. CTL, cytotoxic T lymphocyte; ER, endoplasmic reticulum; MHC, major histocompatibility complex.

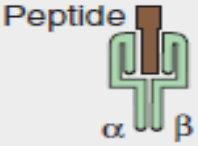
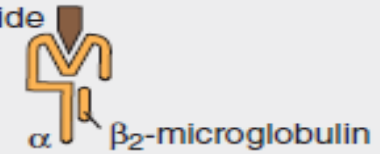
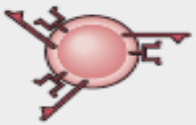
Feature	Class II MHC Pathway	Class I MHC pathway
Composition of stable peptide-MHC complex	Polymorphic α and β chains, peptide 	Polymorphic α chain, β_2-microglobulin, peptide 
Types of APCs	Dendritic cells, mononuclear phagocytes, B lymphocytes; some endothelial cells, thymic epithelium	All nucleated cells
Responsive T cells	$CD4^+$ T cells (helper T cells) 	$CD8^+$ T cells (CTLs) 
Source of protein antigens	Endosomal/lysosomal proteins (mostly internalized from extracellular environment)	Cytosolic proteins (mostly synthesized in the cell; may enter cytosol from phagosomes)
Enzymes responsible for peptide generation	Endosomal and lysosomal proteases (e.g., cathepsins)	Cytosolic proteasome
Site of peptide loading of MHC	Specialized vesicular compartment	Endoplasmic reticulum
Molecules involved in transport of peptides and loading of MHC molecules	Invariant chain, DM	TAP

FIGURE 3-12 Features of the pathways of antigen processing. APCs, antigen-presenting cells; CTL, cytotoxic T lymphocyte; MHC, major histocompatibility complex; TAP, transporter associated with antigen processing.

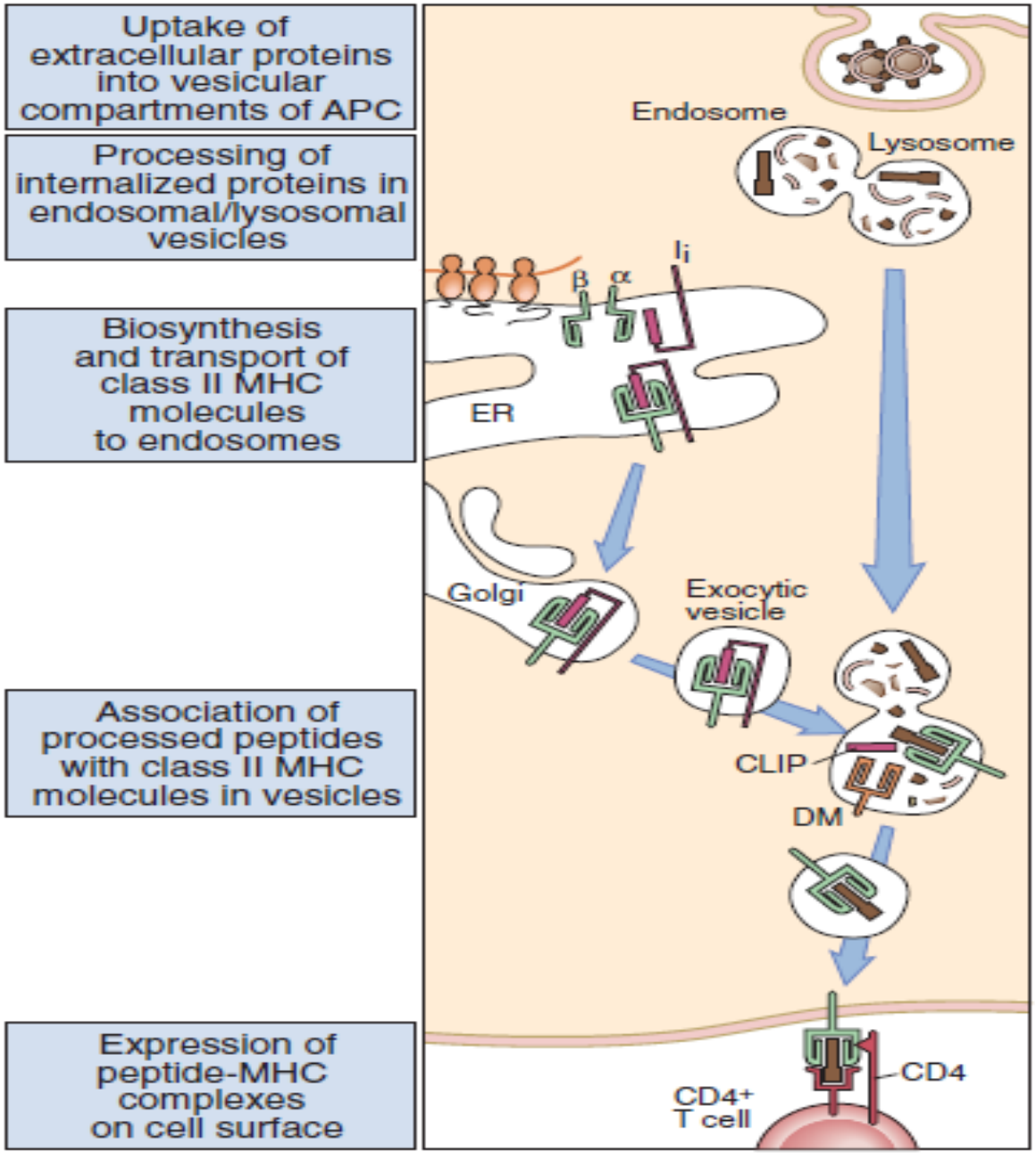


FIGURE 3-13 The class II major histocompatibility complex (MHC) pathway of processing of internalized vesicular antigens. Protein antigens are ingested by antigen-presenting cells (APCs) into vesicles, where they are degraded into peptides. Class II MHC molecules enter the same vesicles and lose the CLIP peptide that occupies the cleft of newly synthesized class II molecules. These class II molecules are able to bind peptides derived from the endocytosed protein. The DM molecule facilitates the removal of CLIP and subsequent binding of the antigenic peptide. The peptide–class II MHC complexes are transported to the cell surface and are recognized by $CD4^+$ T cells. ER, endoplasmic reticulum.

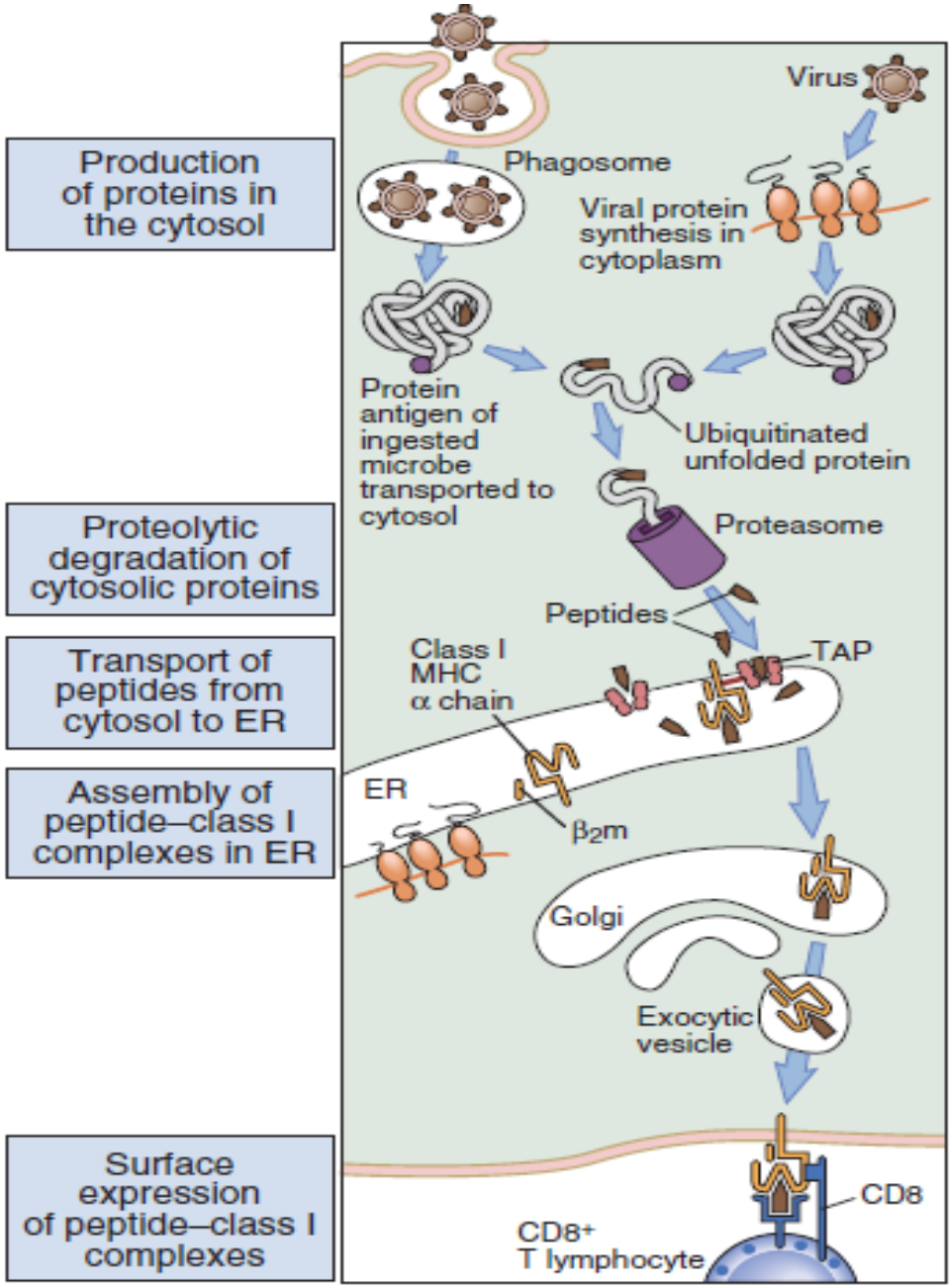
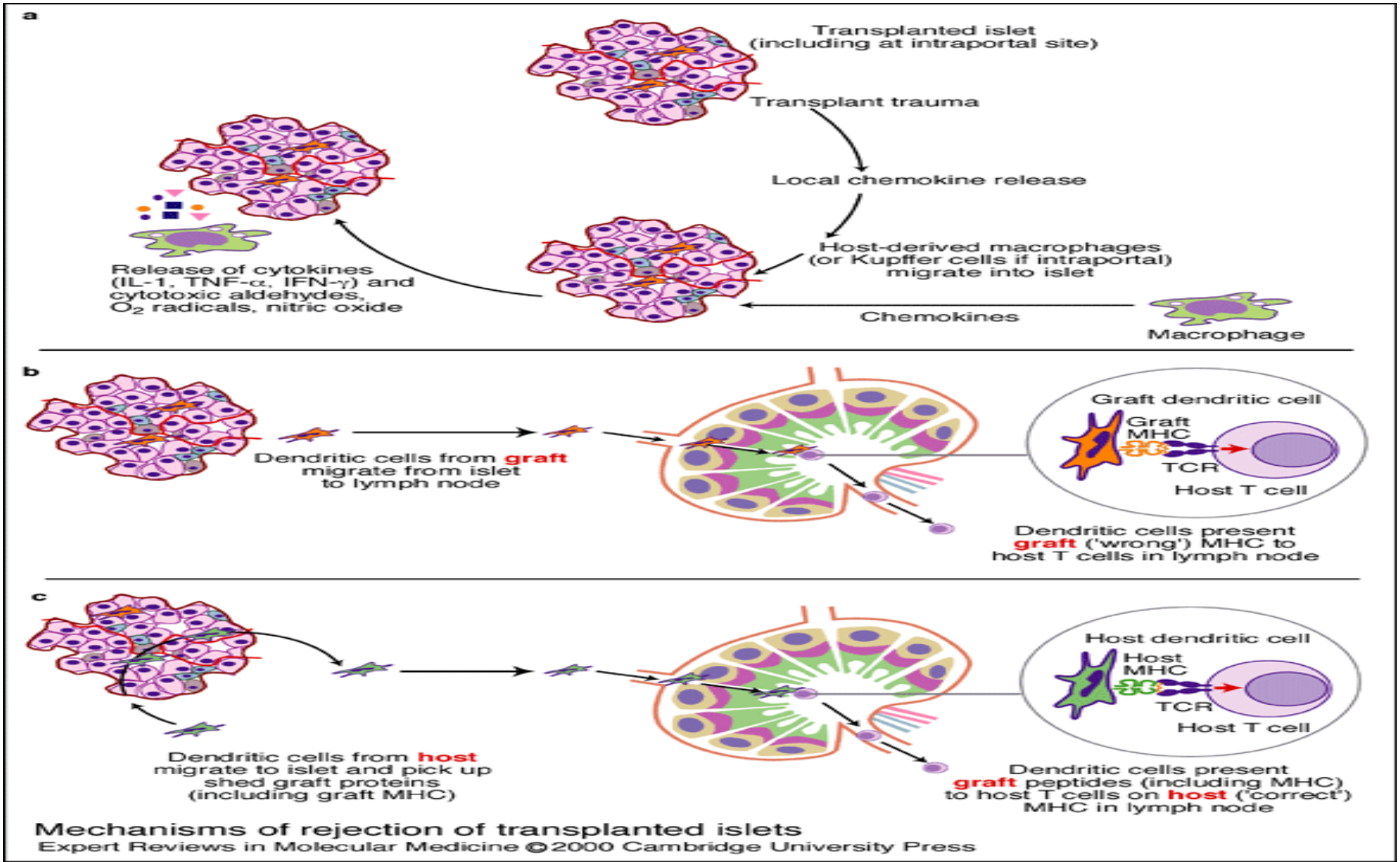


FIGURE 3-14 **The class I major histocompatibility complex (MHC) pathway of processing of cytosolic antigens.** Proteins enter the cytoplasm of cells either from phagocytosed microbes or from endogenous synthesis by microbes, such as viruses, that reside in the cytoplasm of infected cells. Cytoplasmic proteins are unfolded, ubiquitinated, and degraded in proteasomes. The peptides that are produced are transported by the transporter associated with antigen processing (TAP) into the endoplasmic reticulum (ER), where the peptides may be further trimmed by an ER-resident aminopeptidase and then bind to newly synthesized class I MHC molecules. The peptide–class I MHC complexes are transported to the cell surface and are recognized by CD8+ T cells.

Mechanisms of rejection of transplanted islets :-



Mechanisms of rejection of transplanted islets

- ***Q1:- What are MHC molecules? What are human MHC molecules called? How were they discovered, and what is their function?***

- ***Q2:- What are the differences between the antigens that are displayed by class I and class II MHC molecules?***