Antigen processing

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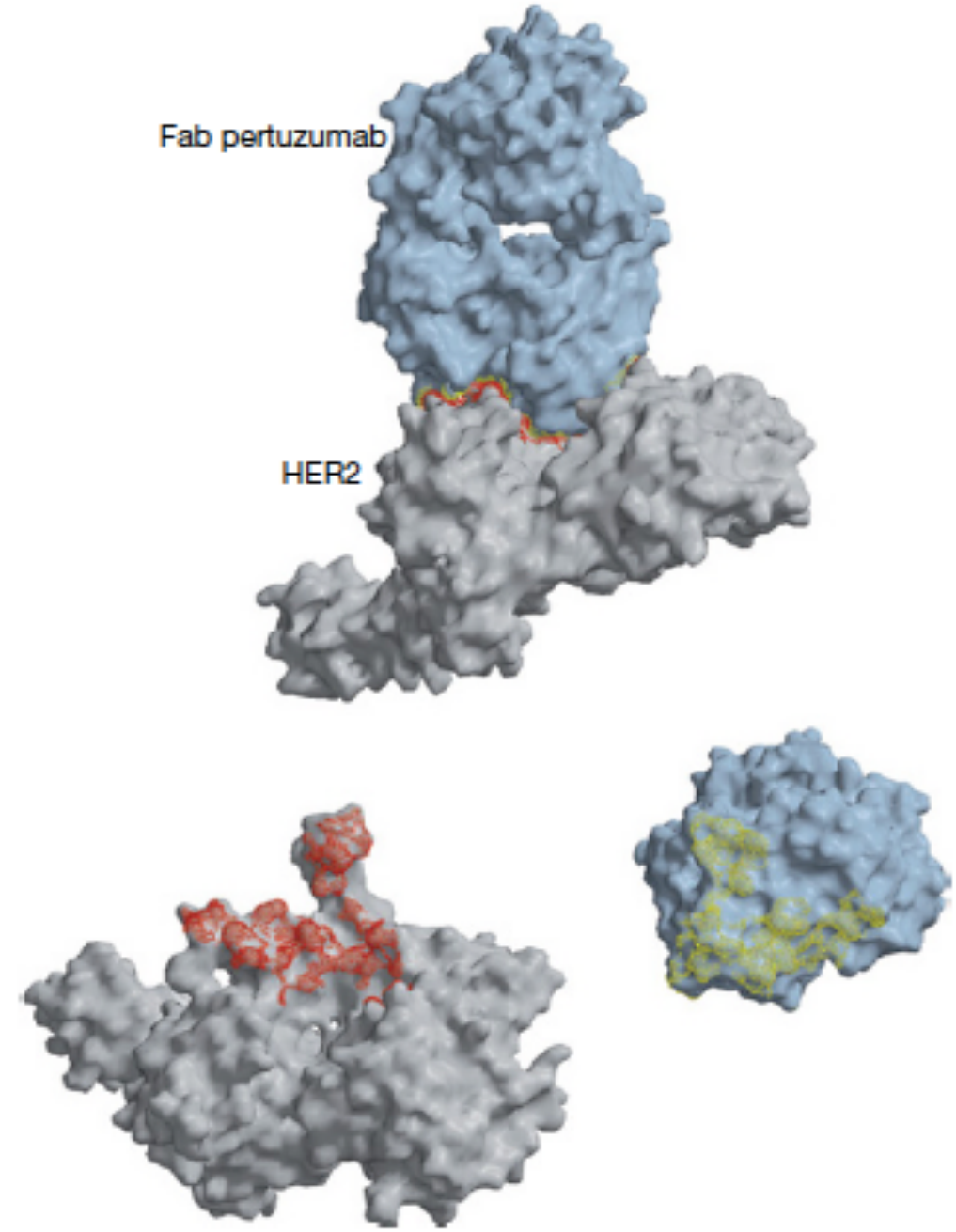
Introduction

- In acquired immune response, specific antigens are recognized by
  - Antibodies – soluble or transmembrane (BCR)
  - TCR
- Antibodies recognize antigens on the outside of pathogens or as soluble materials e.g. toxins
- TCR recognize peptides in the context of MHC molecules on the surface of host cells

Antigen recognition by antibodies/B cells

- Recognize molecular shapes (epitopes) on antigens
- Complementary to paratope on Ab
- Abs recognize the topographic surface of a protein Ag



Antigen recognition by T cells

- TCR sees peptide antigen associated with an MHC class I or II molecules on the surface of cells
- These T cells usually only respond when the APCs express the same MHC haplotype as the host from which the T cells were derived (**haplotype restriction**)
- Cytotoxic T cells recognize Ag in the context of class I MHC
- Helper T cells recognize Ag when it is associated with class II MHC
- T cells recognize a linear peptide sequence from the antigen

- T cells recognize peptide lying within the MHC peptide-binding groove
- These peptides are produced through **antigen processing**
  - Proteolytic cleavage of proteins into small fragments (antigen peptides) that can bind to MHC molecules on antigen presenting cells

Two compartments of the cell

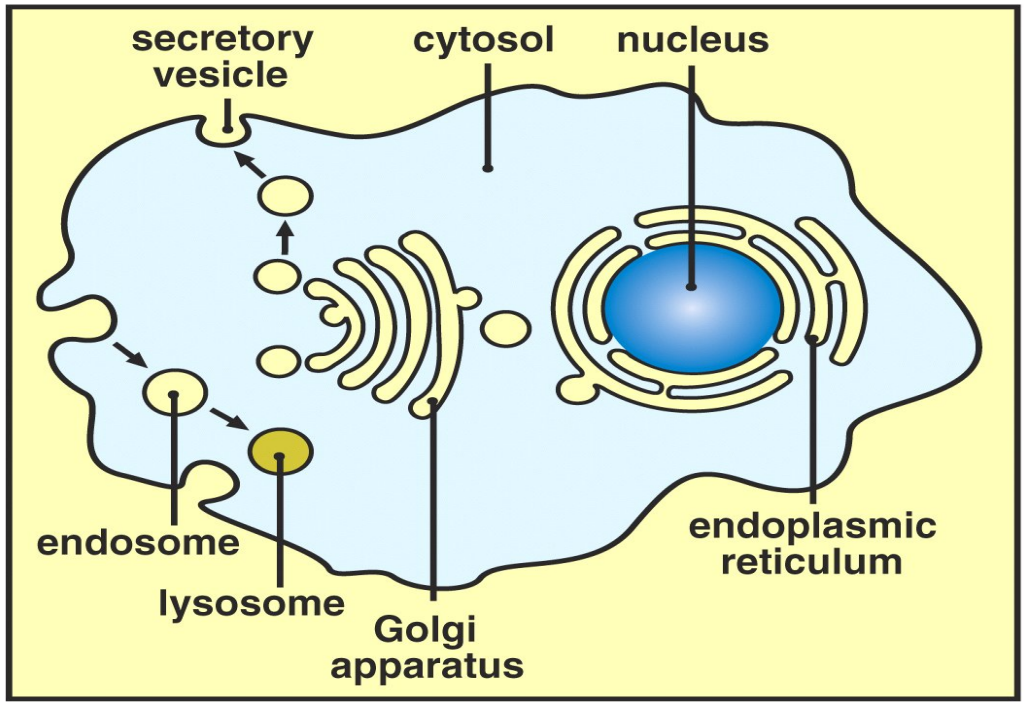


Figure 5-1 Immunobiology, 6/e. (© Garland Science 2005)

Cytosol: continuous with nucleus

Vesicular system (ER, golgi, endosomes, lysosomes): continuous with extracellular fluid

	Intracellular pathogens	Extracellular pathogens
Degraded in	Cytosol (endogenous)	Endocytic vesicles (exogenous)
Peptides bind to	Class I	Class II
Presented to	CD8 T cells	CD4 T cells

Processing of extracellular antigen by class II MHC

- Exogenous protein Ag is taken into the cells (endocytosis) by
  - Phagocytosis (macrophages)
    - Large particles such as microorganisms are ingested by macrophages into large endocytic vesicles called phagosomes
    - The phagosome subsequently fuses with a lysosome to form a phagolysosome
    - This compartment possesses a low pH coupled with lysosomal proteases which attack the phagocytosed particle
  - Pinocytosis (dendritic cells), or
  - Specific receptor-mediated uptake (B cells)

Processing of extracellular antigen by class II MHC

- Exogenous protein Ag is taken into the cells (endocytosis) by
  - Pinocytosis (dendritic cells)
    - Antigen uptake occurs by formation of small clathrin-coated pits at the plasma membrane
    - By internalization and formation of pinosomes, this mechanism mediates uptake of soluble proteins
    - Dendritic cells exhibit a specialized form of constitutive macropinocytosis, which make them particularly efficient at filtering the extracellular fluid
  - Specific receptor-mediated uptake (B cells)

Processing of extracellular antigen by class II MHC

- Exogenous protein Ag is taken into the cells (endocytosis) by
  - Specific receptor-mediated uptake (B cells)
    - Membrane-bound immunoglobulins (mIg) on the cell surface of B lymphocytes form the B-cell receptor (BCR)
    - An antigen that binds to the BCR is endocytosed via clathrin-coated pits
    - After leaving the plasma membrane, clathrin-coated vesicles lose their membrane coats and fuse with endocytic compartments
    - Antigen-derived epitopes are processed in B lymphocytes and presented in the context of the class II MHC to helper T lymphocytes
    - In turn, activated helper T lymphocytes activate the antigen specific B lymphocyte to produce antibodies

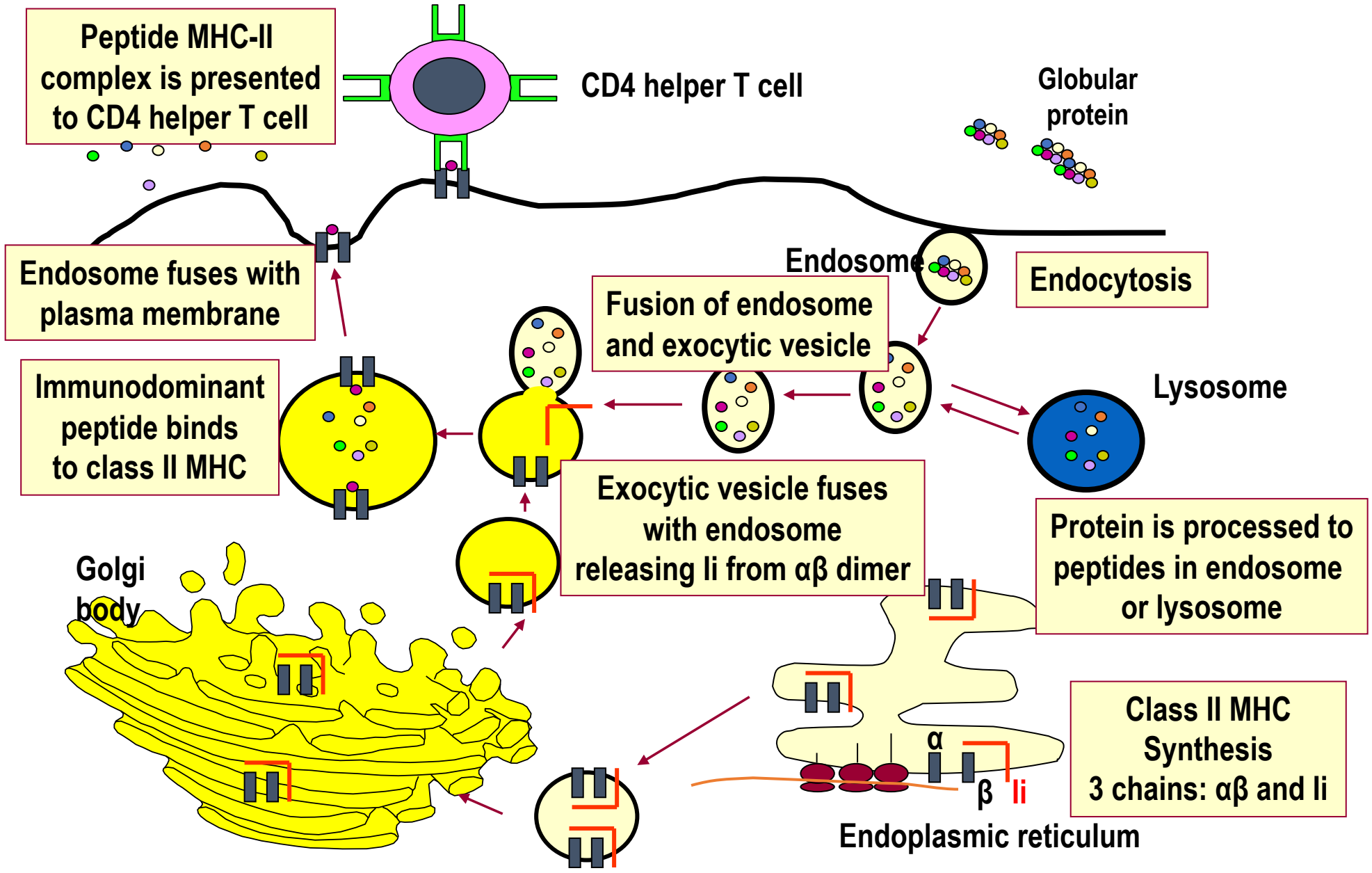
Processing of extracellular antigen by class II MHC

- A late endosome containing the antigen meets up with a trans-Golgi vesicle containing MHC II
- The MHC II are assembled in the ER in association with the transmembrane invariant chain **Ii**
  - Li acts as a chaperone to ensure correct folding of the nascent MHC I molecule
  - An internal sequence of the luminal portion of Ii sits in the MHC groove to inhibit precocious binding of peptides in the ER before the class II molecule reaches the endocytic compartment containing the antigen

- Proteins within the endosome are processed into peptides as the early endosome matures into a late endosome
- Late endosome fuses with the vacuole containing the class II-li complex
- Li is degraded, except for the part sitting in the MHC groove, which remains there as a peptide referred to as **CLIP** (class II-associated invariant chain peptide)
- An MHC-related heterodimeric molecule, DM, then catalyzes the removal of CLIP and keeps the groove open so that peptides generated in the endosome can be inserted

- The class II-peptide complexes are then transported to the membrane for presentation to T_H cells

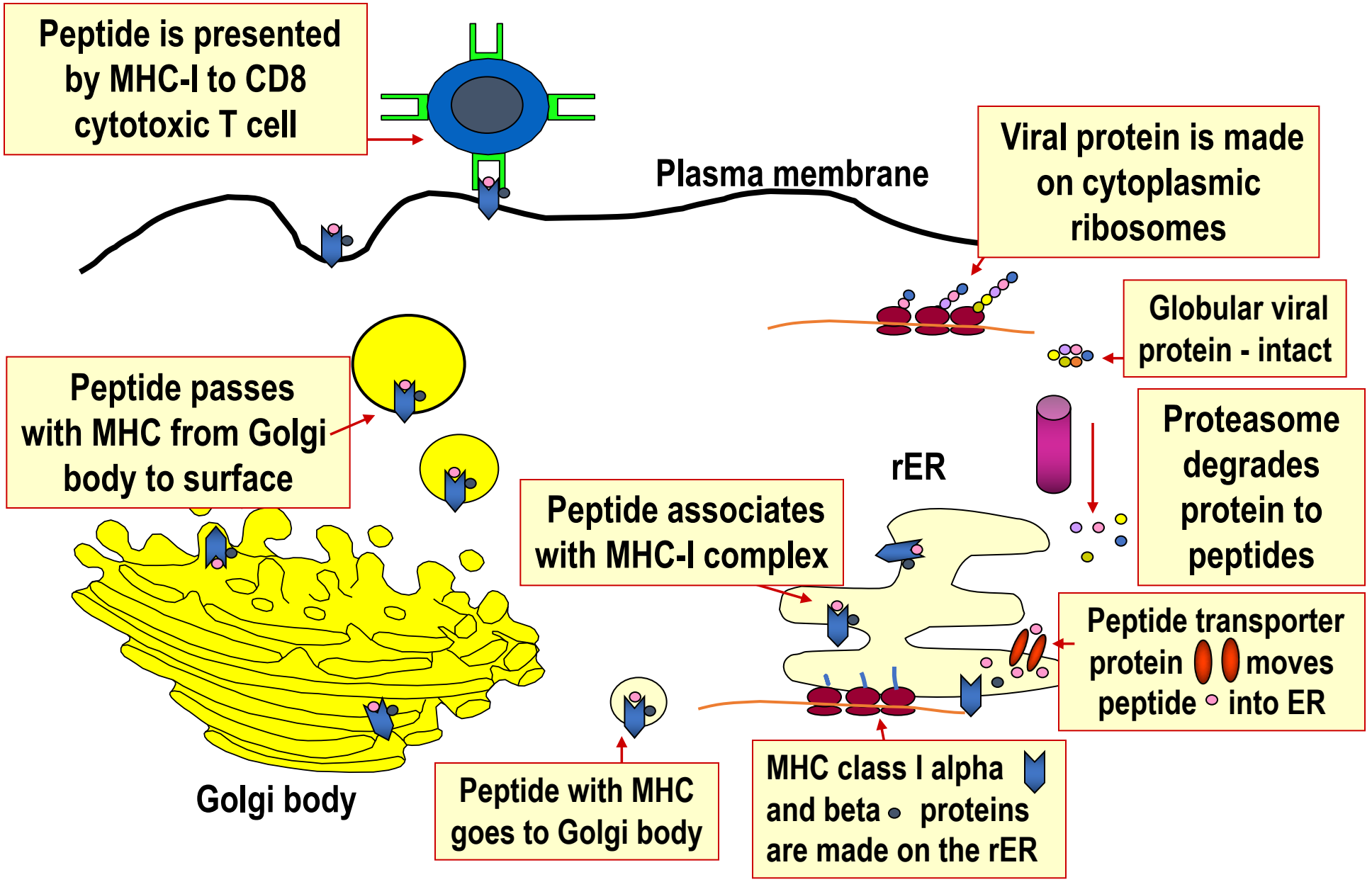
MHC class II pathway



Processing of intracellular antigen by class I MHC

- Peptides generated by a cytosolic multisubunit proteolytic complex called the **proteasome**
- The peptides are transported into the endoplasmic reticulum (ER) by the adenosine triphosphate-dependent transporters associated with antigen processing (TAPs), where they associate with MHC I
- When stably assembled, the complexes are transported to the cell surface via the ER and Golgi network

MHC class I pathway



Cross-presentation of antigens

- MHC I presents endogenous Ag
- MHC II presents exogenous Ag
- However, 10-30% of class I molecules present exogenous Ag, and a similar proportion of class II molecules present peptides derived from cytoplasmic or nuclear Ag
- Phagocytosed or endocytosed Ag can sneak out through channels in the vacuole into which they have been engulfed and gain entry onto the cytosol
- Once in the cytosol, they are subsequently degraded by the proteasome, followed by TAP-mediated transfer into the ER, and presentation by MHC I

- Autophagy – portions of the cytoplasm, which can contain peptides generated from the proteasome as well as intact proteins, are engulfed internally by structures known as autophagosomes
  - Occurs in professional APCs
  - The peptide-containing autophagosome can fuse with the MHC II containing MIIC, where proteolytic cleavage of any intact proteins could also take place
  - Peptide Ag is then presented through the exogenous pathway, with the peptides exchanging with CLIP, and transfer of the peptide-MHC to the cell surface

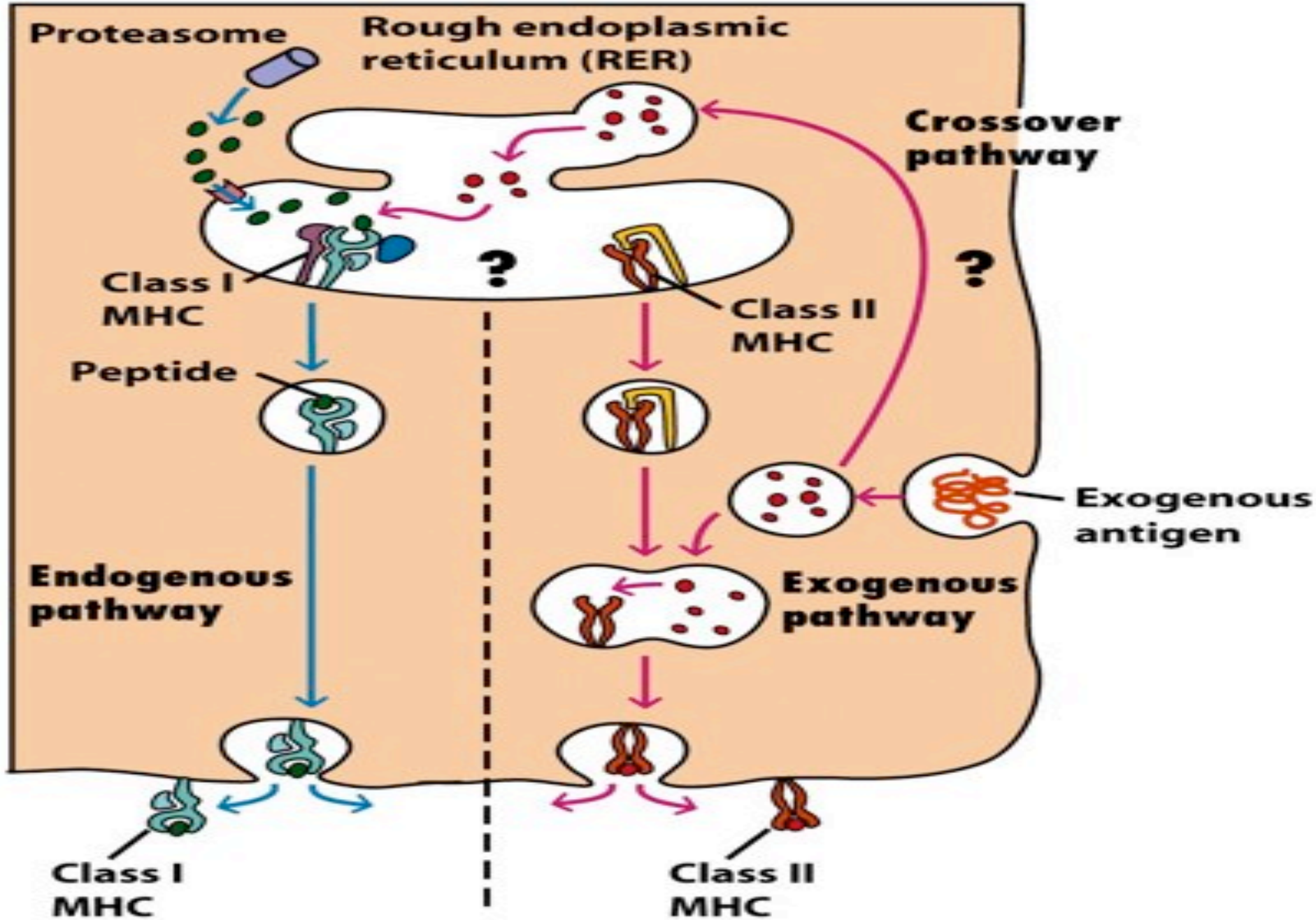


Figure 8-24
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