SAWA UNIVERSITY

المناعة 1

MAJOR HISTOCOMPATIBILITY COMPLEX

Sawa University — جامعـــــة ســـــــاوة الاهلية

College of health and medical techniques — كليـــــة التقنيـــات الصحيـة والطبيـة

Department of Medical Laboratories — قسم تقنيات المختبرات الطبية

Third Stage — المرحلـــــــــــة الثالثة

الجانب النظري

Theoretical

محاضرة رقم 6

Lecture No. 6

تدريسي المادة : د. زيدون حسين مهدي

Major histocompatibility complex

MHC I & MHCII:

Are membrane bounded glycoproteins that are closely related in structure and function.

MHCI bind to endogenous antigen processed by cytosolic pathway while **MHCII** bind to exogenous antigen processed by endocytic pathway.

- **MHC I** molecules are expressed on most nucleated cell that bind peptides and present them to CD8 T cell.

- **MHC II** molecules are expressed on antigen presented cell that bind peptides and present them to CD4 T cell.

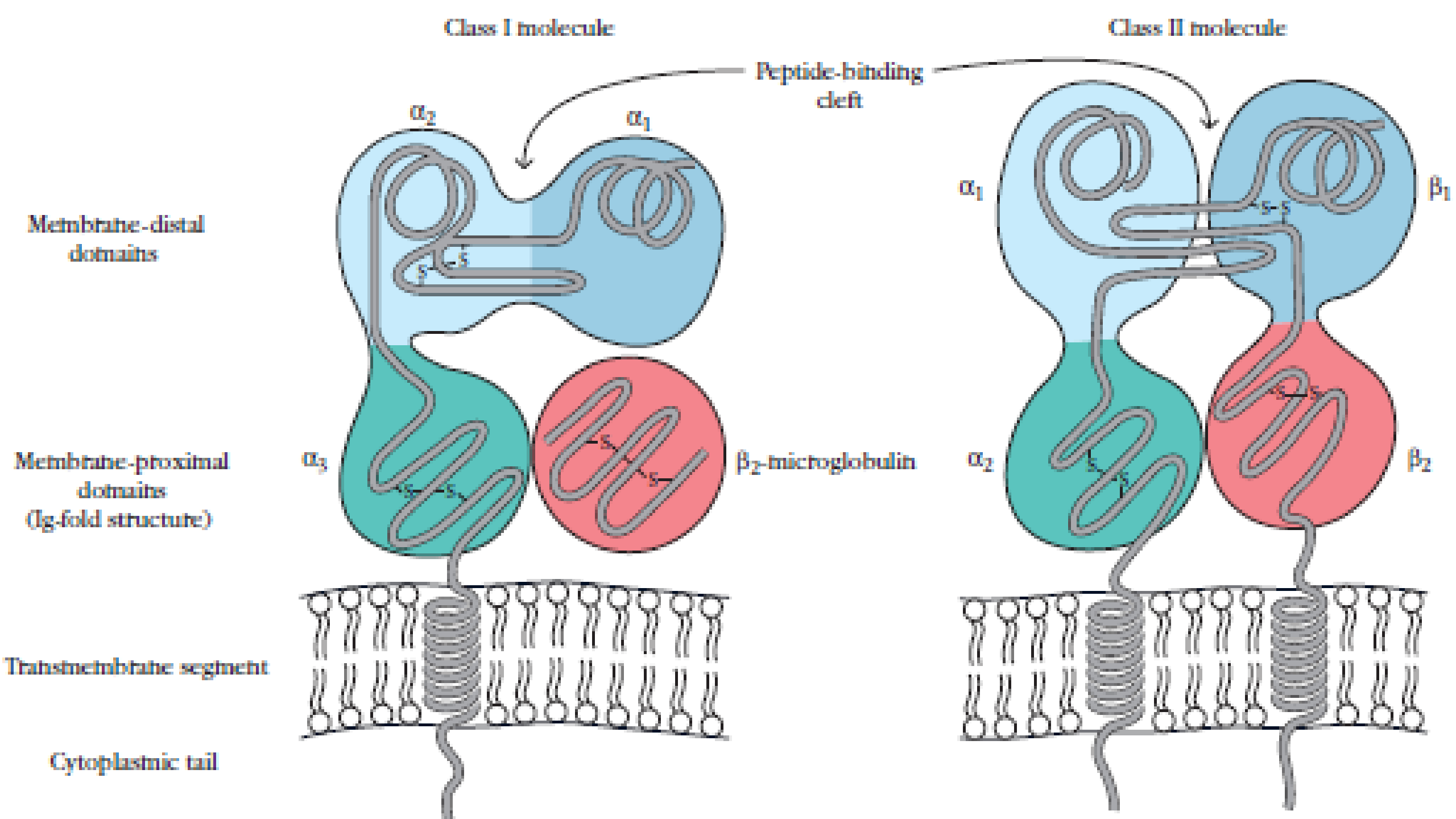
- **MHCIII** gene encode various secreted proteins

That have immune function theses include complement C4,C2 and factor B and several inflammatory cytokines including TNF.

- The MHC is a closely linked complex of genes located in chromosome no. 6 they are usually inherited as a complete set called haplotype from each parent.

- It is composed of six major groups of classical HLAs: HLA-A, HLA-B, HLA-C which represent **MHCI** while HLA-DR, HLA-DQ, HLA-DP represent **MHC II**.

- It is highly polymorphic (e.g. multiple alleles occurring at a single HLA locus).
- It is **codominant** in expression, when individual is heterozygous for particular HLA locus, both alleles at that locus are expressed, in contrast homozygous individual the alleles of the locus are identical so only one HLA is specified.


Class I molecule
Class II molecule
Peptide-binding cleft
α_2
α_1
α_1
β_1
Membrane-distal domains
S–S
S–S
Membrane-proximal domains (Ig-fold structure)
α_3
β_2-microglobulin
α_2
β_2
Transmembrane segment
Cytoplasmic tail

Antigen processing

- **There are 2 type of antigens :**

1. Endogenous antigen include :

viral proteins, proteins from bacteria which invade cells, parasites & normal cellular constituents)

- process through cytosolic pathway
- Bind to MHC I

- Endogenous protein degraded through cytosolic proteolytic system called proteasome (20s) after binding to small protein (ubiquitin) render them liable for proteolysis .
- Its ATP dependent proteolysis

- **There are 2 type of proteasome :**
- Standard (20s) resident in all cells
- Immuneproteasome : the same size of standard proteasome but has some unique component that can be induce by exposure to TNFα & INFγ.
- LMP2 &LMP7 gene are located within class I region responsible for replacement of catalytic protein subunit convert standard proteasomes to immunonoproteasomes after exposure to TNFα & INFγ.
- Immuneproteasome increasing production of peptides that bind efficiently to MHC class I

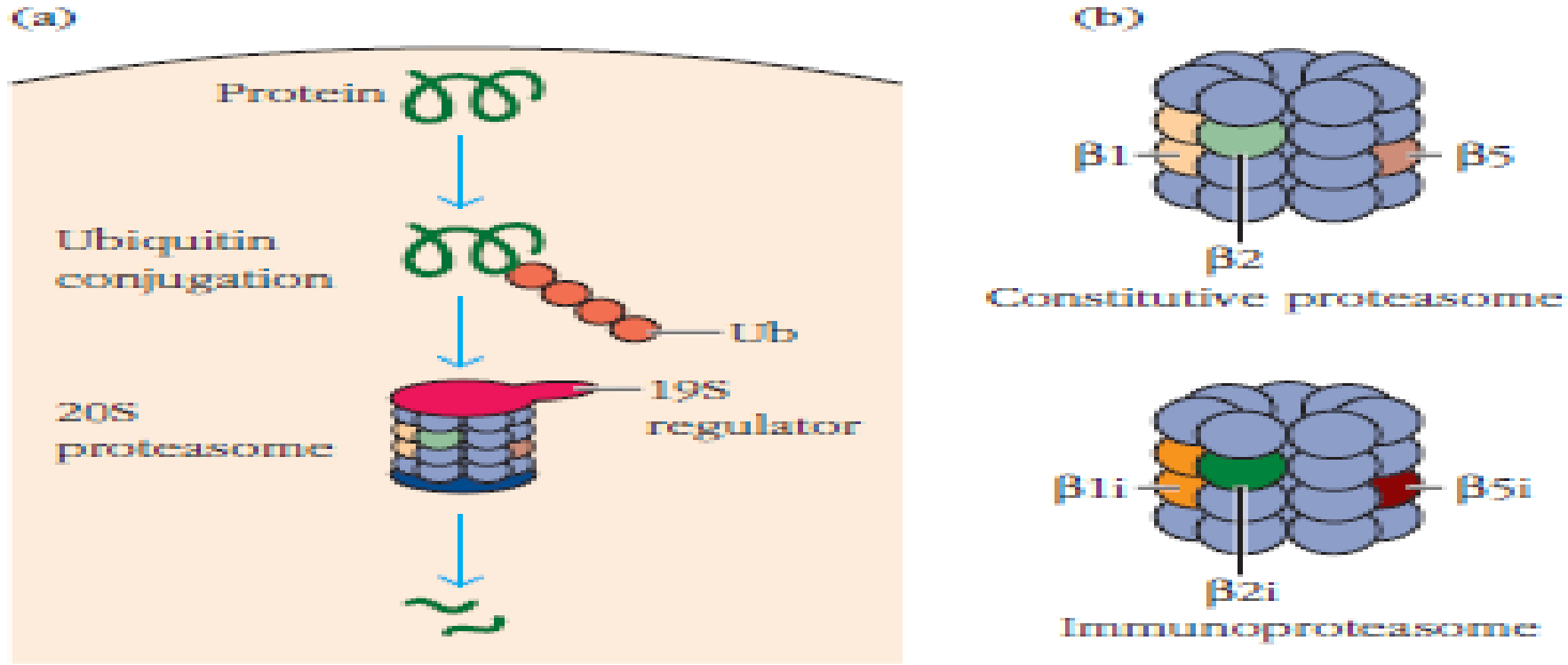


FIGURE 8-16 Cytosolic proteolytic system for degradation of intracellular proteins. (a) Endogenous proteins may be targeted for degradation by ubiquitin conjugation. These proteins are degraded by the 26S proteasome complex, which includes the 20S constitutive proteasome and a 19S regulator. (b) In activated APCs, several proteins in the constitutive proteasome (β1, β2, and β5) are replaced by proteins encoded by the LMP genes and specific to the immunoproteasome (β1i, β2i, and β5i). This immunoproteasome has increased proteolytic efficiency for creating peptides that can assemble with MHC class I molecules. *[Adapted from M. Groettrup et al. 2010. Proteasomes in immune cells: More than peptide producers.* Nature Reviews. Immunology *10:73–78. doi:10.1038/nri2687]*

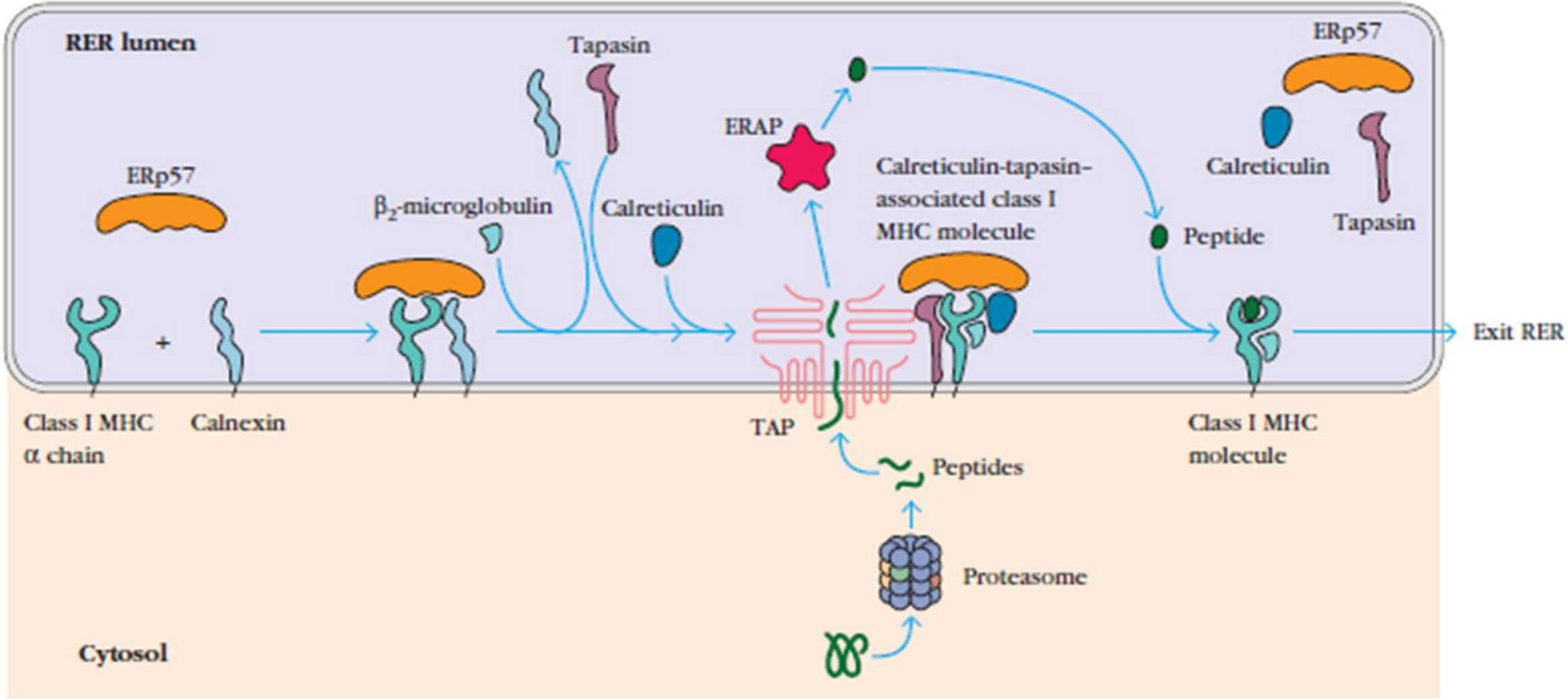


FIGURE 8-18 Assembly and stabilization of class I MHC molecules. Within the rough endoplasmic reticulum (RER) membrane, a newly synthesized class I α chain associates with calnexin, a molecular chaperone, and ERp57 until β_2-microglobulin binds to the α chain. The binding of β_2-microglobulin releases calnexin and allows binding to calreticulin and to tapasin, which is associated with the peptide transporter TAP. This association promotes binding of an antigenic peptide. Antigens in the ER can be further processed via exopeptidases such as ERAP1, producing fragments ideally suited for binding to class I. Peptide association stabilizes the class I molecule-peptide complex, allowing it to be transported from the RER to the plasma membrane.

2. Exogenous antigen

The antigen is introduced into cell by phagocytosis or endocytosis (receptor mediated or pinocytotic).

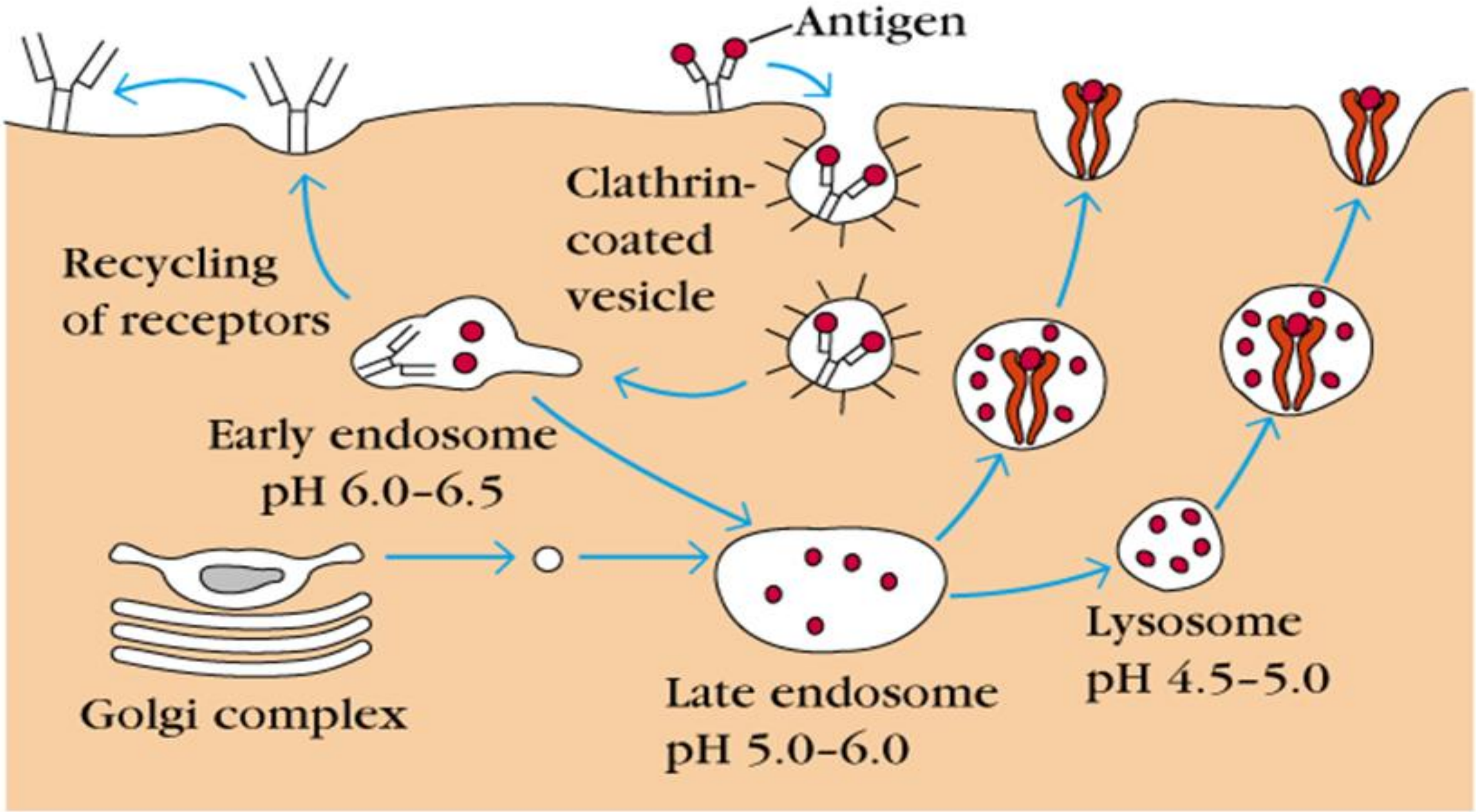
The Ag passes through a series of vesicles that have increasing acidity :

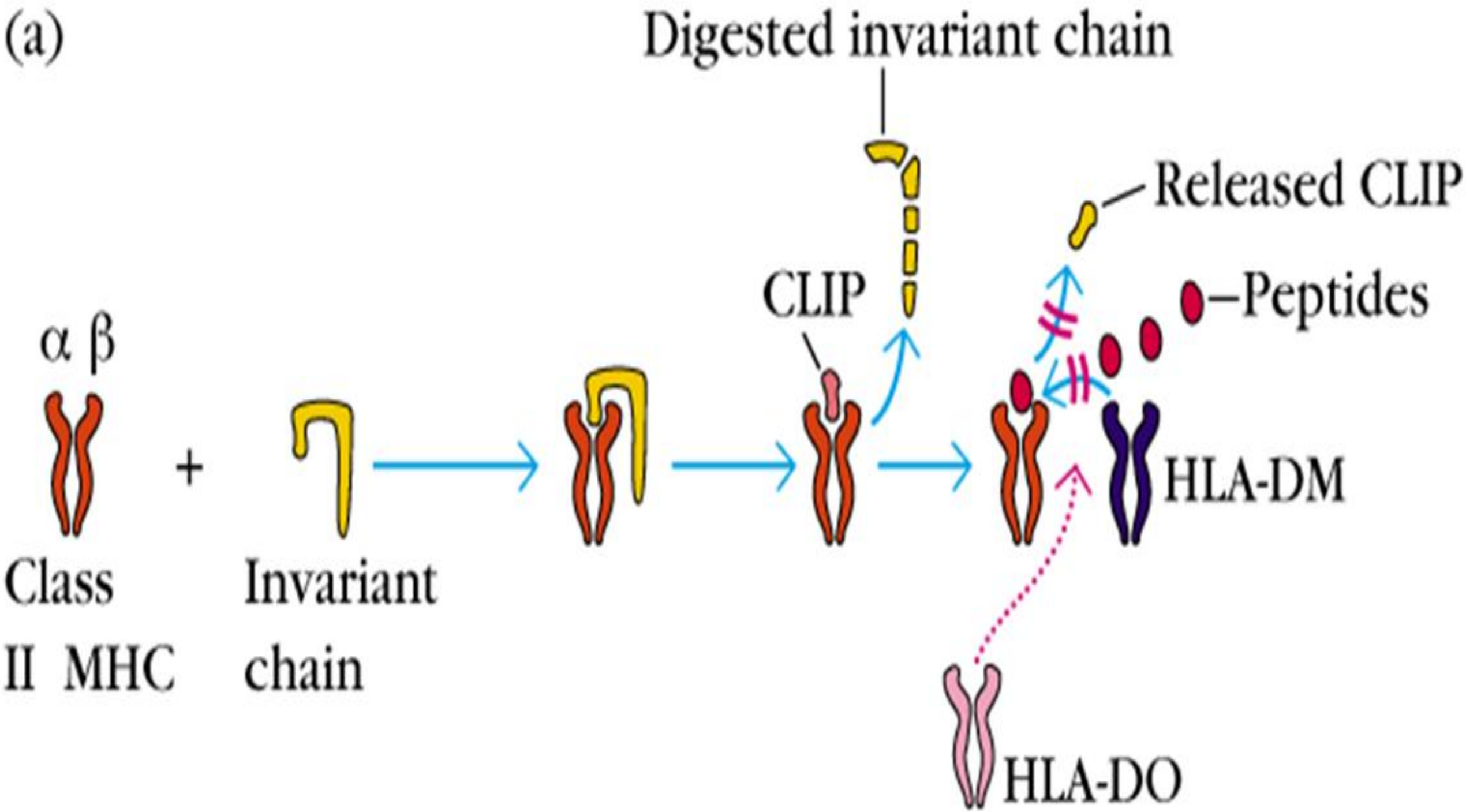
early endosomes (pH 6.0-6.5)

late endosomes (pH 5.0-6.0)

lysosome (pH 4.5-5.0).

Lysosomes contain ~140 acid dependent hydrolases including proteases, nucleases, lipases, glycosidases, phospholipases, phosphatases


Antigen
Clathrin-coated vesicle
Recycling of receptors
Early endosome pH 6.0–6.5
Golgi complex
Late endosome pH 5.0–6.0
Lysosome pH 4.5–5.0


(a)
Digested invariant chain
Released CLIP
CLIP
Peptides
α β
+
HLA-DM
Class II MHC
Invariant chain
HLA-DO

- Within the compartments endocytic pathway, antigen is degraded into oligopeptides of about 13 to 18 residues that meet up with and bind to class II MHC molecules in late endosomes.

TABLE 8-1 ANTIGEN-PRESENTING CELLS

Professional antigen-presenting cells	Nonprofessional antigen-presenting cells	
Dendritic cells (several types)	Fibroblasts (skin)	Thymic epithelial cells
Macrophages	Glial cells (brain)	Thyroid epithelial cells
B cells	Pancreatic beta cells	Vascular endothelial cells


Thank you!