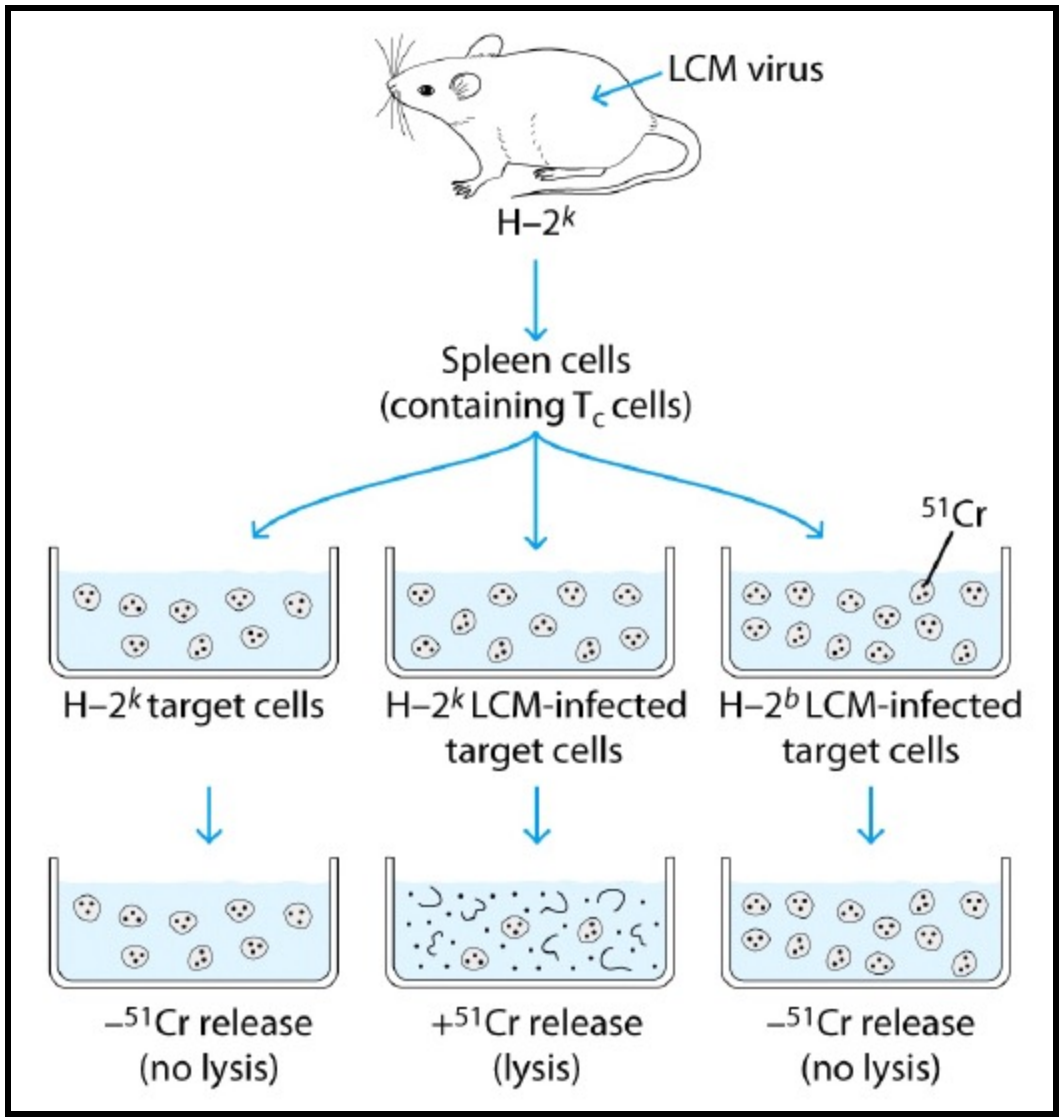
Lecture 16
6 Sept 2023

"Self-MHC I" restriction of (CD8) T_C cells



- T_C cells kill only syngeneic virally-infected target cells
- Both the T_C cell and the infected cell must share the same set of MHC genes
- Shown by Doherty & Zinkernagel (1974)

Distinctions between MHC I and MHC II

MHC I

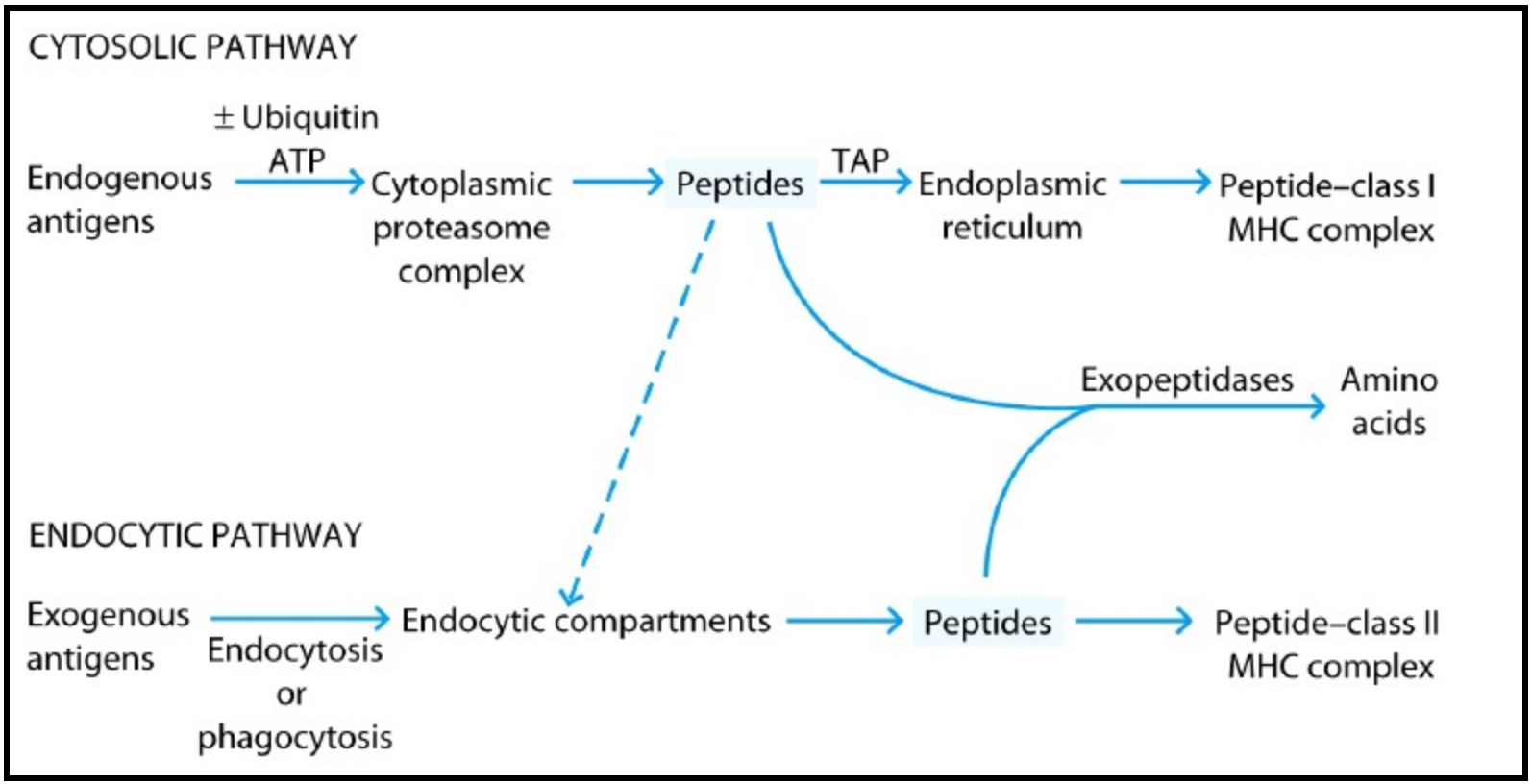
- Most cells (target cells) can present Ag w/ MHC I to T_C's
- Nearly all nucleated cells infected by microbes/virus, or abnormal proteins prod by cancer cells, aging cells, or by allogeneic cells from transplants
- Assoc w/ MHC I requires replication of foreign entity (i.e., abnormal protein synth) within the target cell

MHC II

- Only APC's can present Ag w/ MHC II to TH's
- APC's are of 2 categories:
  - **Professional APC's**
  - **Non-professional APC's**
- Assoc w/ MHC II does not require replication of entity w/i target cells
- Phagocytosis is important in Ag-processing

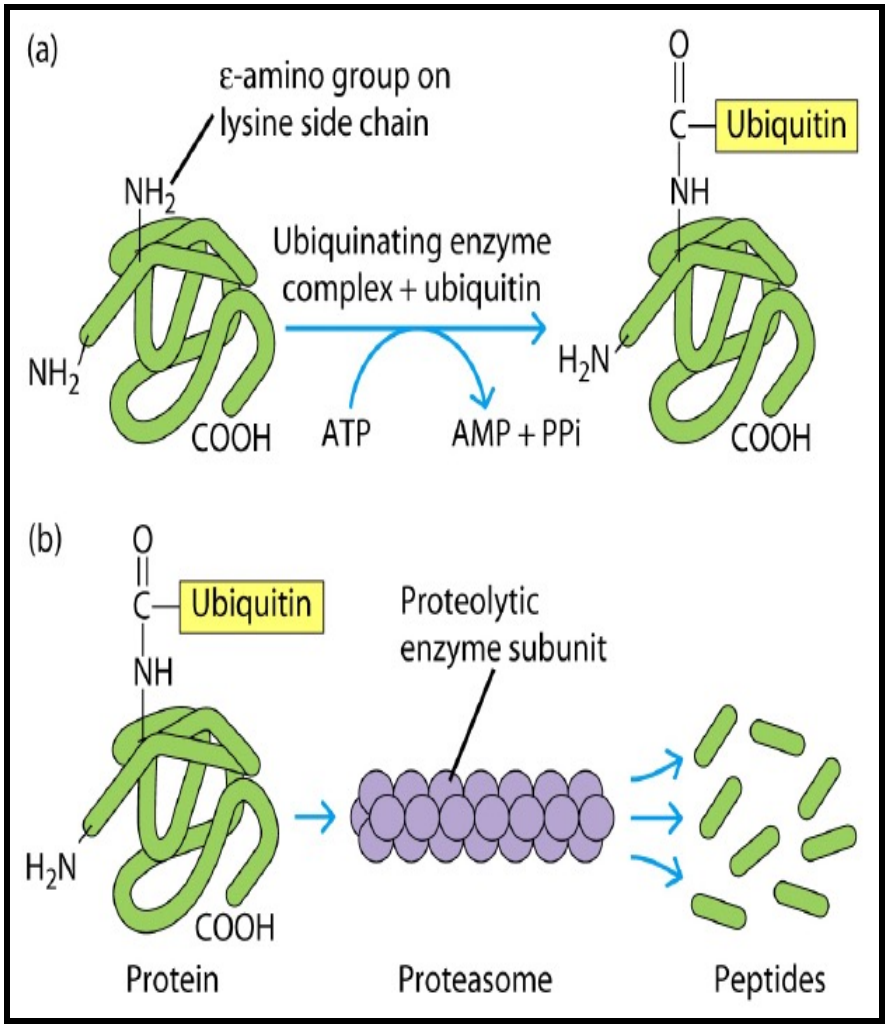
Ag is processed thru 2 separate pathways:

*MHC I interacts w/ peptides from **cytosolic** degradation
*MHC II interacts w/ peptides from **endocytic** degradation



TAP: Transporter protein asso. with antigen processing

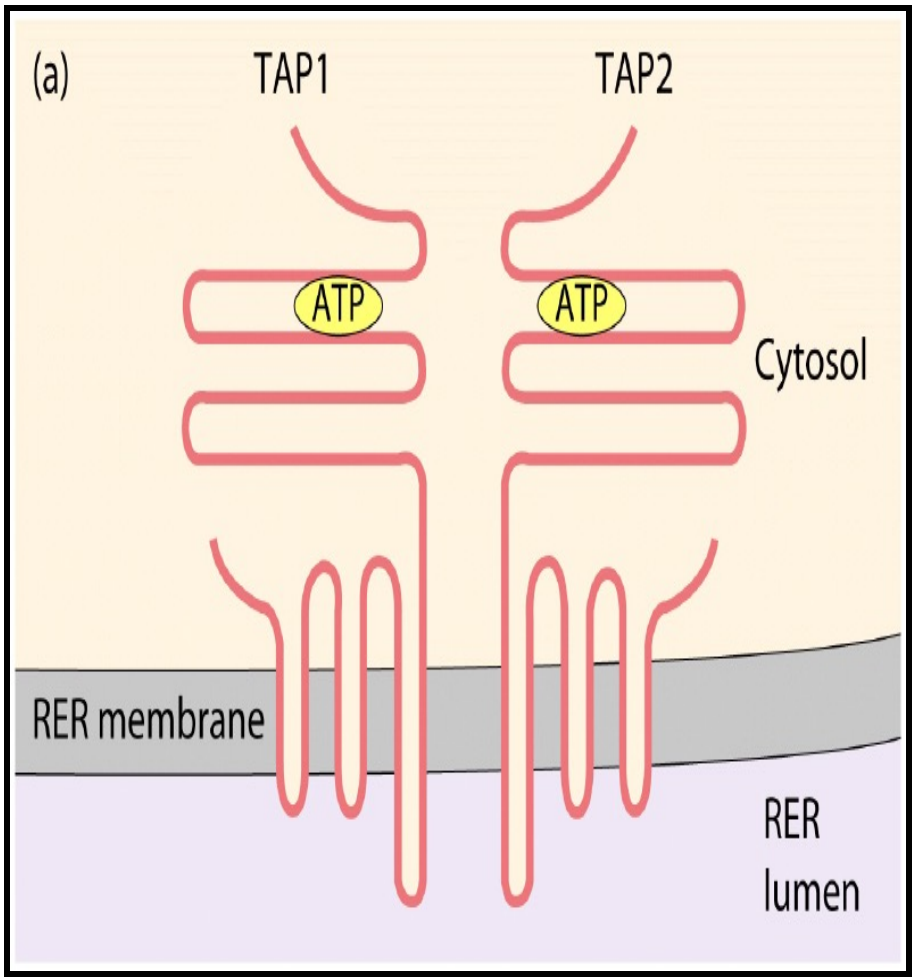
Endogenous Ag processing…



Peptide generation

- Proteins targeted for lysis combine w/ a small protein → **ubiquitin**
- **Ubiquitin-protein complex** is degraded by a proteosome
- Specific proteosomes generate peptides which can bind to MHC I

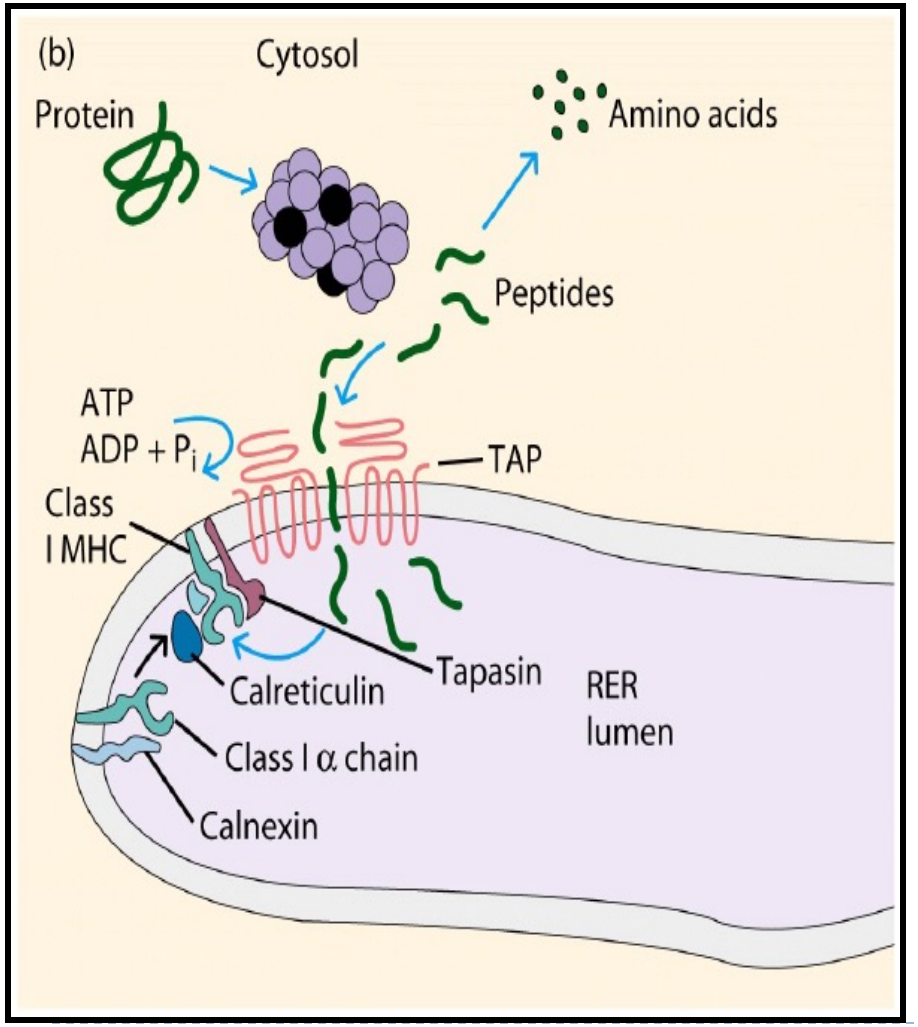
Endogenous Ag processing…



Transport to ER

- Peptides from proteolysis bind to a "**t**ransporter protein **a**ssoc w/ Ag **p**rocessing" (**TAP**)
- TAP is a heterodimer which uses ATP to help transport peptides (8-10 aa's) to lumen of ER

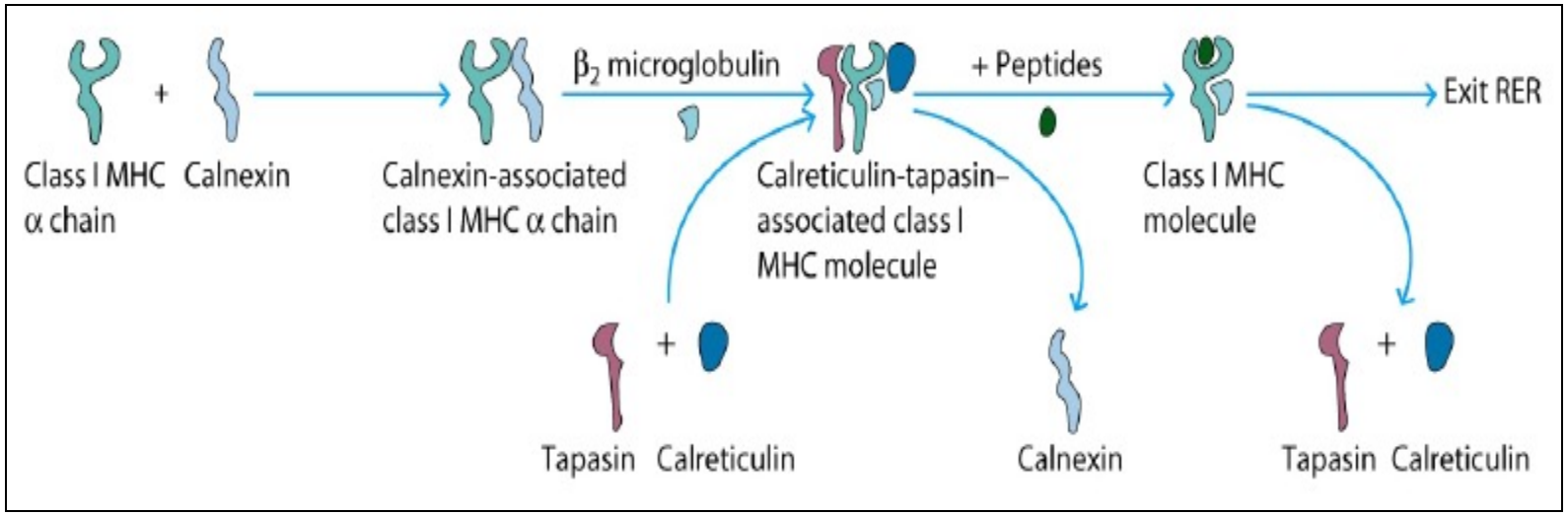
Endogenous Ag processing…



Peptide binding to MHC I

- MHC I assembly occurs w/ the aid of **chaperone proteins** to promote folding (**calnexin** + MHC I α chain)
- **Tapasin + calreticulin** brings TAP/ peptide close to MHC assembly
- Allows MHC I to bind to peptides
- **MHC I-Ag** exits ER to Golgi to plasma membrane

Assembly and stabilization of MHC I – Ag complex



Experimental demonstration that antigen processing is necessary for T helper cell activation

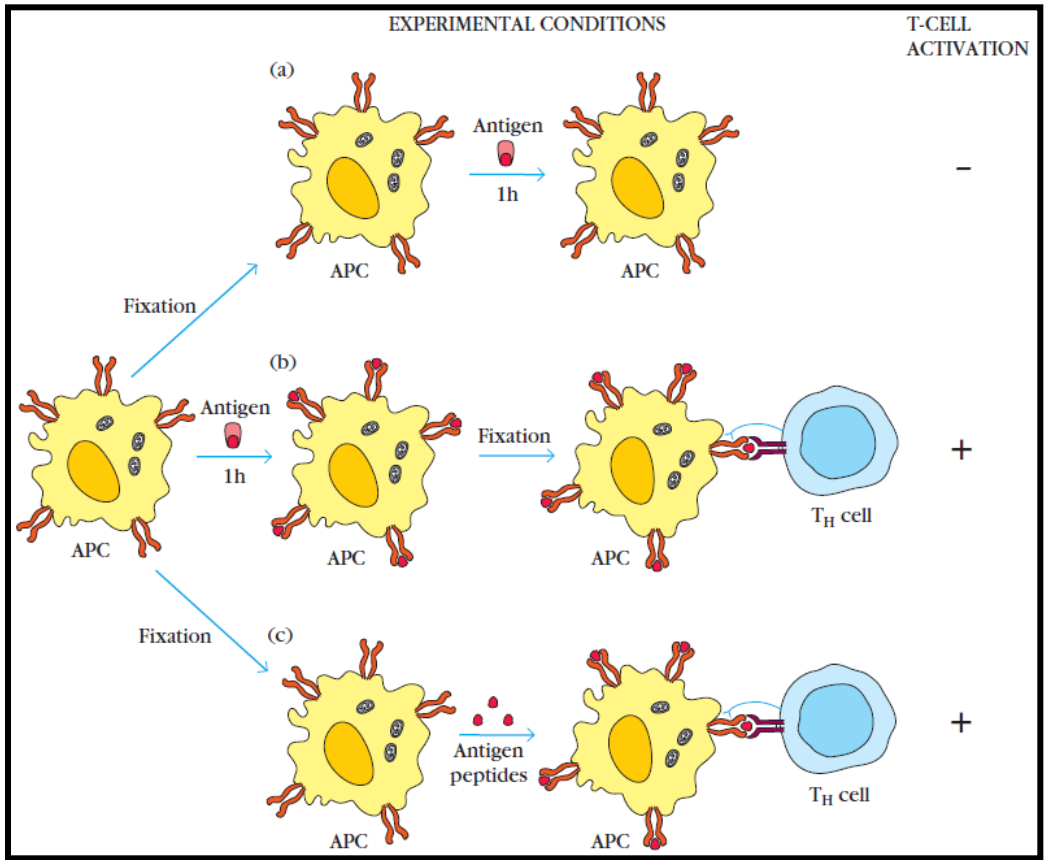


TABLE 8-1 Antigen-presenting cells

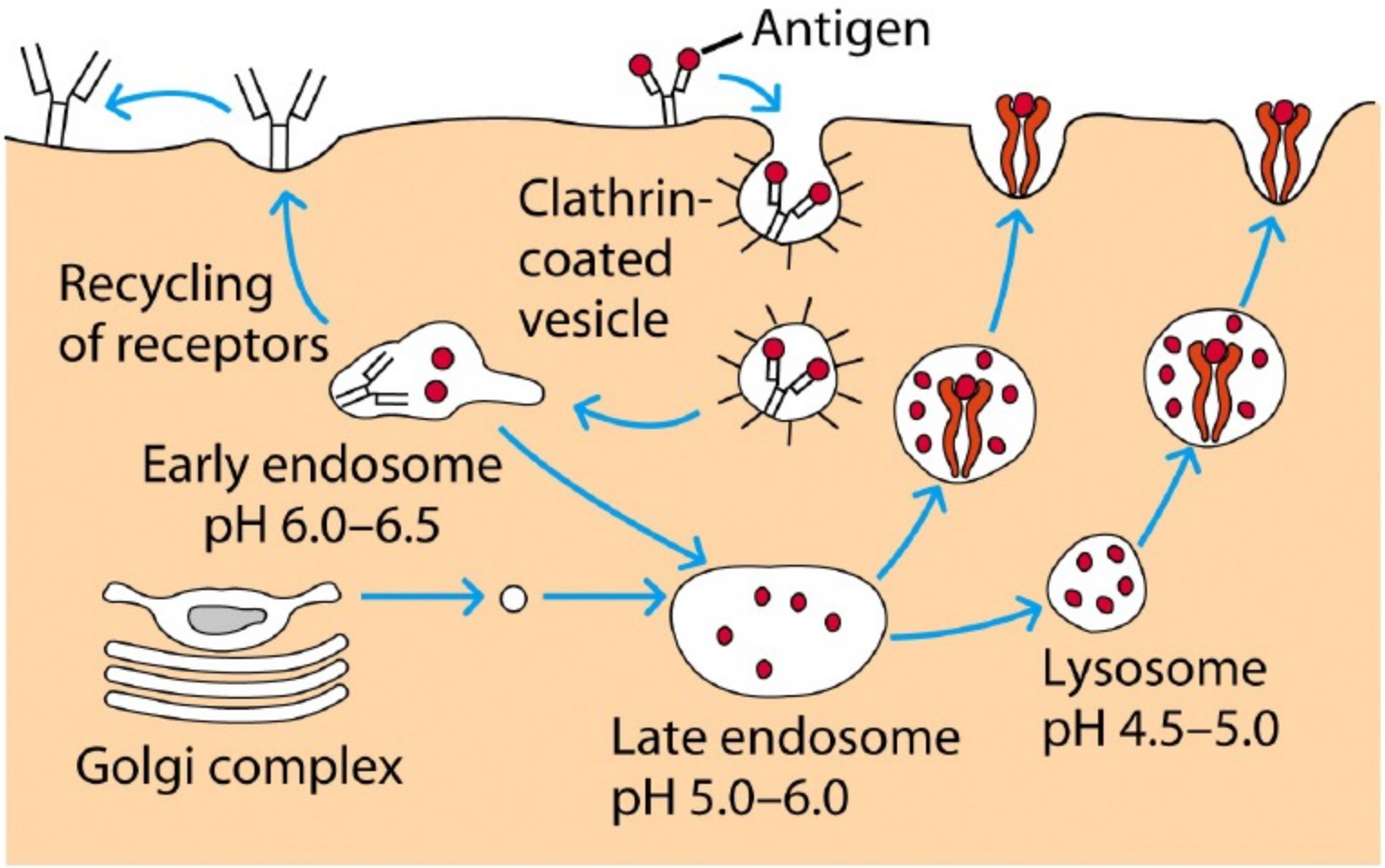
Professional antigen-presenting cells	Nonprofessional antigen-presenting cells	
Dendritic cells (several types)	Fibroblasts (skin)	Thymic epithelial cells
Macrophages	Glial cells (brain)	Thyroid epithelial cells
B cells	Pancreatic beta cells	Vascular endothelial cells

Processing of Exogenous Ag's:
the Endocytic pathway

- Exogenous Ag's are typically phagocytized/ endocytized by MØ and APC's
  - Foreign Ag is degraded w/i endocytic vacuole of endocytic pathway. The pathway includes:
    - Early endosomes (pH 6-6.5)
    - Late endosomes or endolysosome (pH 5-6)
    - Lysosomes (pH 4.5 – 5)
- Ag is degraded into 13-18 aa polypeptides which bind to MHC II
- Eventually endocytic vacuole returns to PM → recycling surface receptors

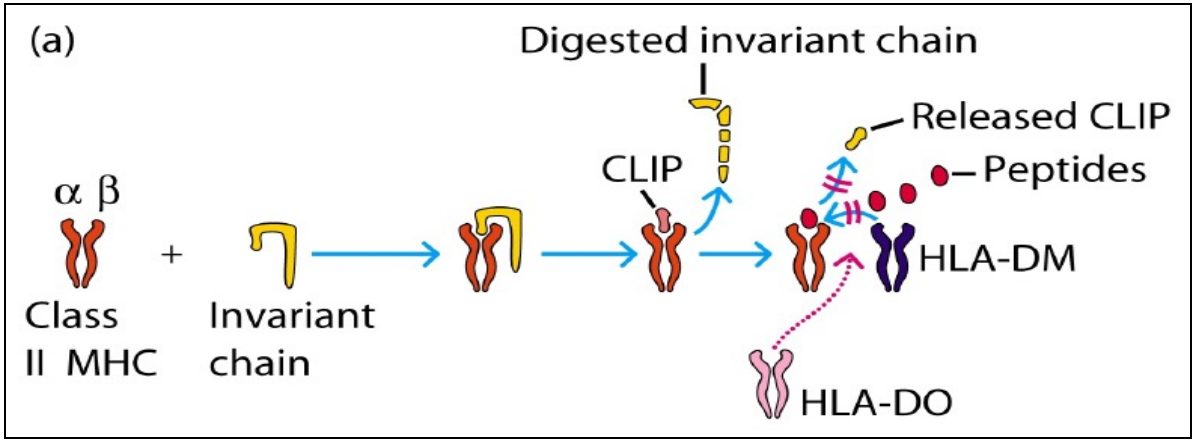
Processing of Exogenous Ag's:

the Endocytic pathway



Processing of Exogenous Ag's:

manufacture of MHC II



- w/i ER, α and β chains of MHC II combine w/ a protein – "**the invariant chain**" (Ii, CD74)
- the IC binds to MHC @peptide binding cleft + then exits the ER to Golgi apparatus
- as proteolytic activity continues, the IC is degraded to a small fragment (CLIP*)
- another MHC II (HLA-DM (found in endosomes)) substitutes Ag for CLIP w/i lysosome
- MHC II – Ag complex is transported to the PM

*CLIP = class II associated invariant chain peptide

Comparison of Ag-processing pathways