Corso di Immunologia - III anno
Prof. Paolini

Lezione 18/10/2024

"Processazione e presentazione dell'antigene"

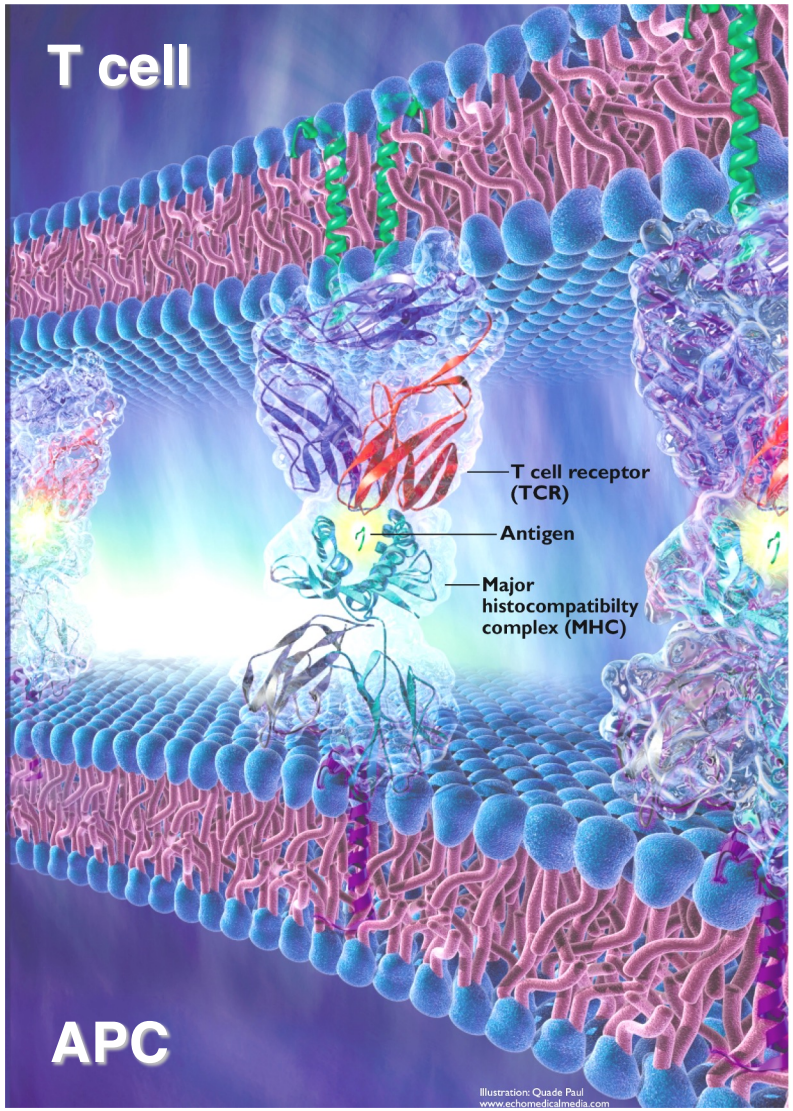
Antigen recognition of T cells

CELLS:

- T cells
- APC

MOLECULES:

- Antigen
- TCR
- MHC



Antigen recognition of T cells is SPECIFIC and (self) MHC-RESTRICTED

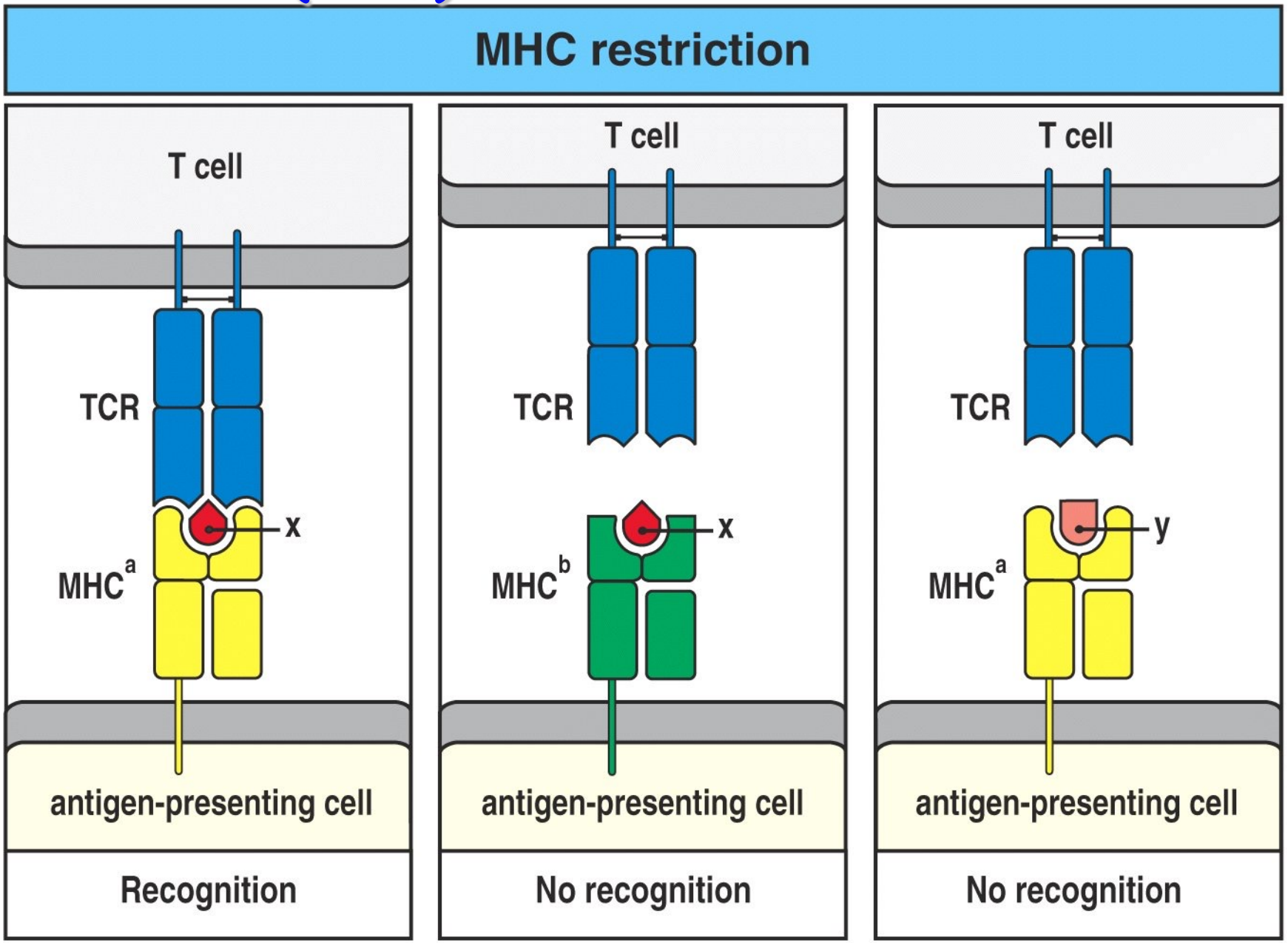
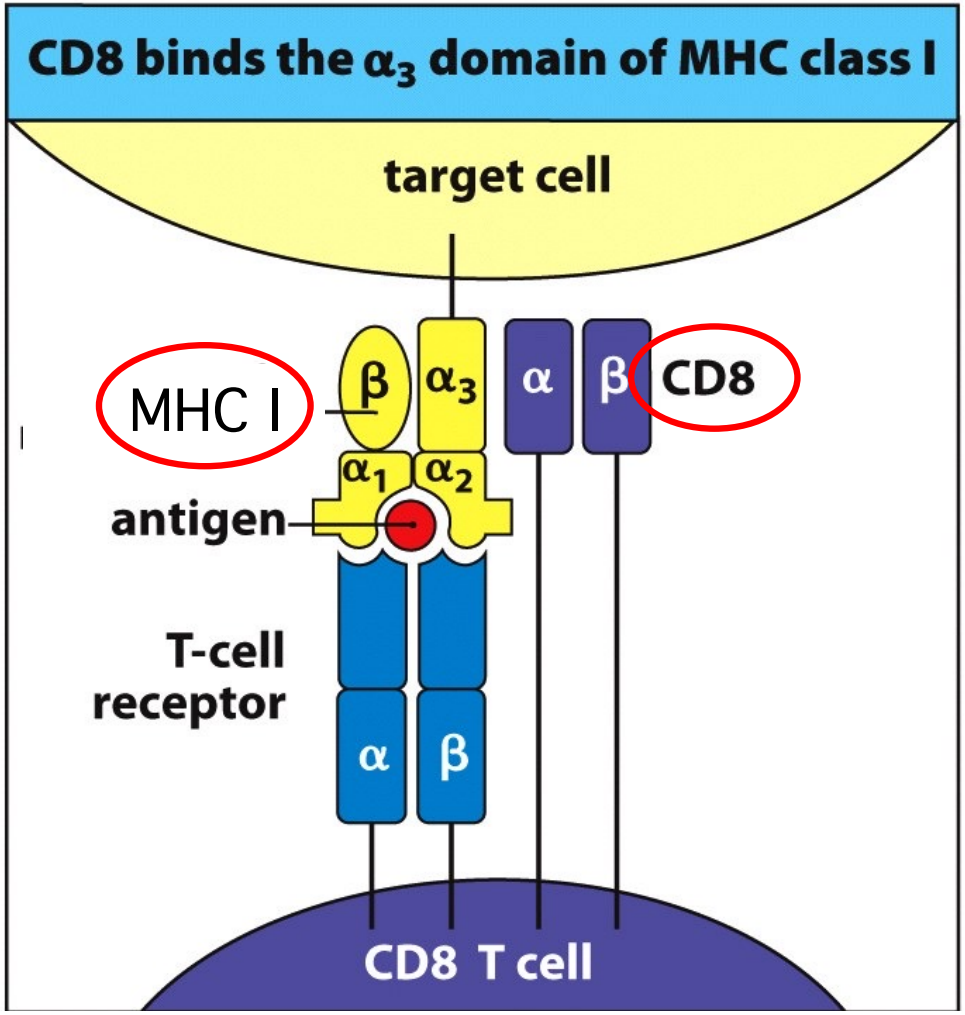
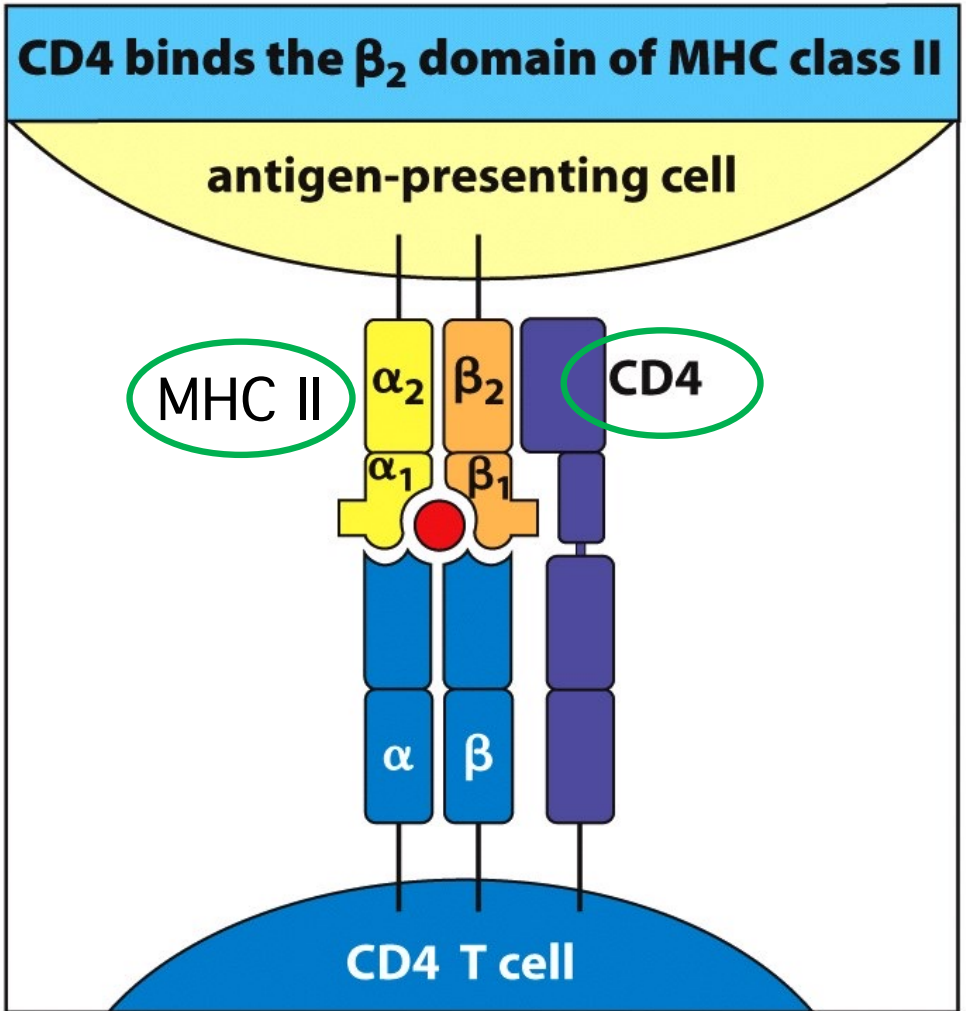


Figure 5-17 Immunobiology, 6/e. (© Garland Science 2005)

CD4 and CD8 are coreceptors for MHC II and MHC I and are alternatively expressed on different T cell subsets

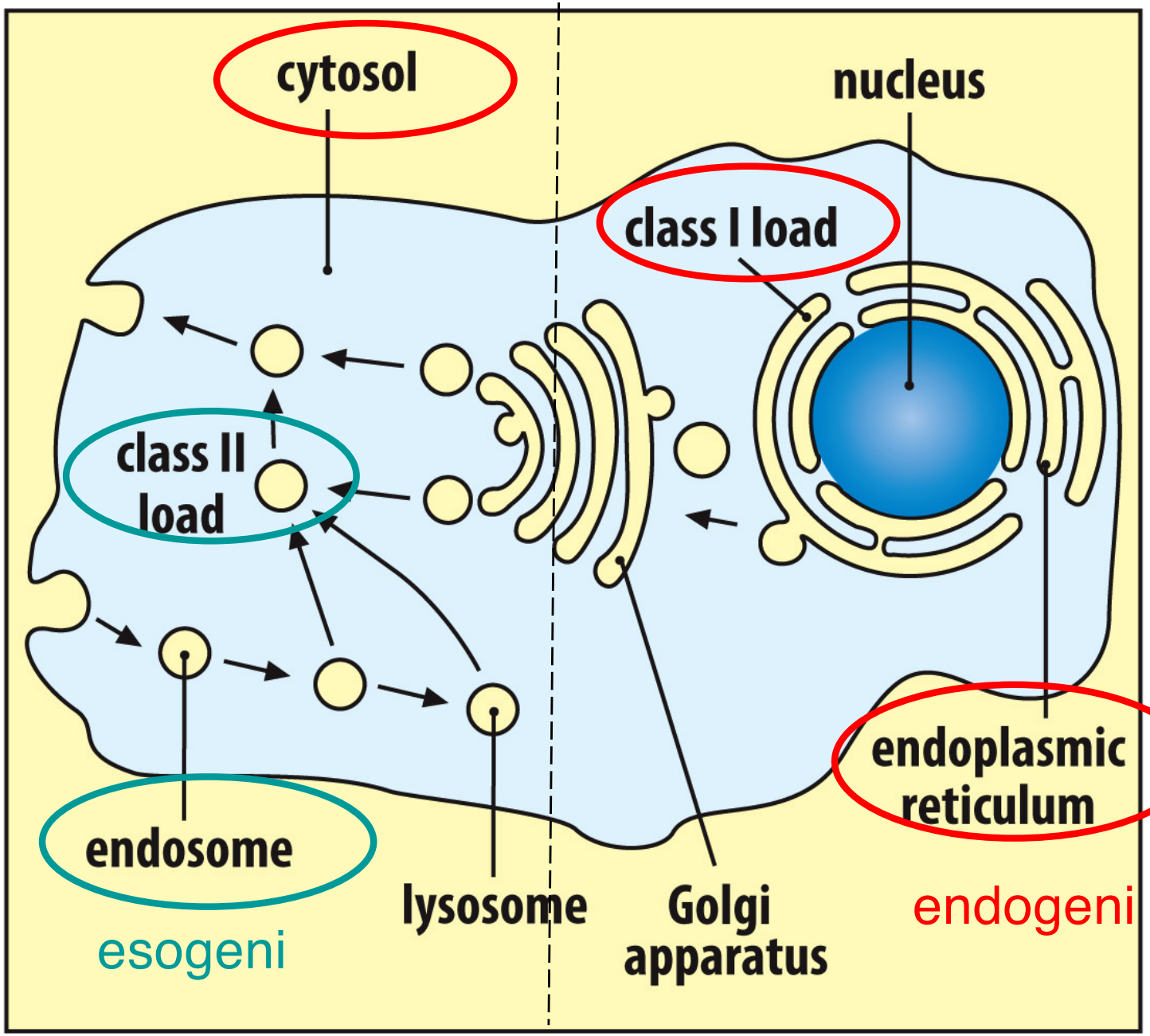


Cytotoxic T cells



Helper T cells

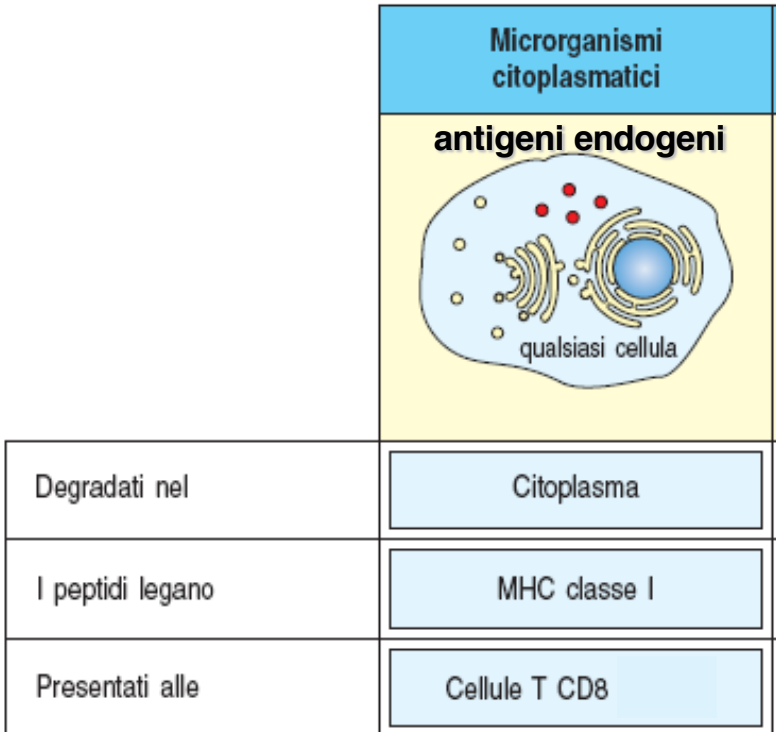
Antigenic peptides derived from OUTSIDE and INSIDE cells are presented by different MHC molecules

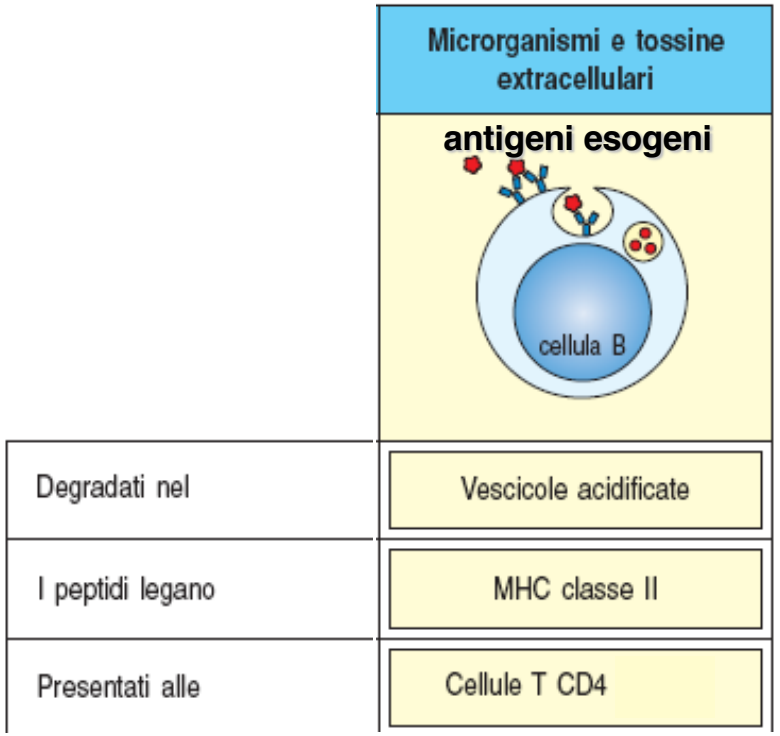


Cytoplasmic antigens are presented by MHC I

Extracellular antigens are presented by MHC II

MHC CLASS I AND II MOLECULES ASSOCIATE ANTIGENS OF DIFFERENT ORIGINS

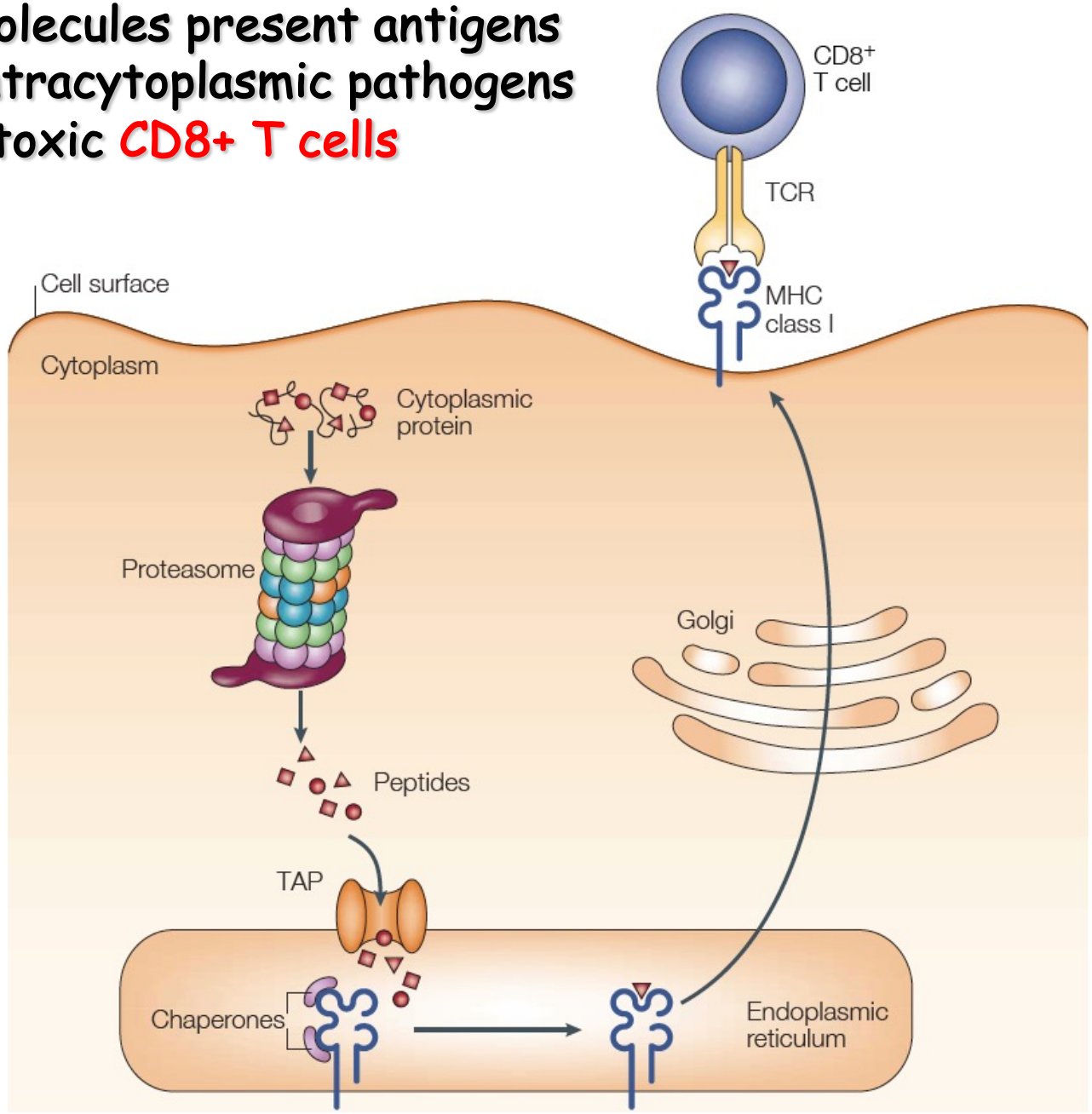




If the antigen derives from a protein synthesized inside the cell (endogenous antigen) the peptide will be "presented" in association with MHC I molecules and will be recognized by CD8 cells.

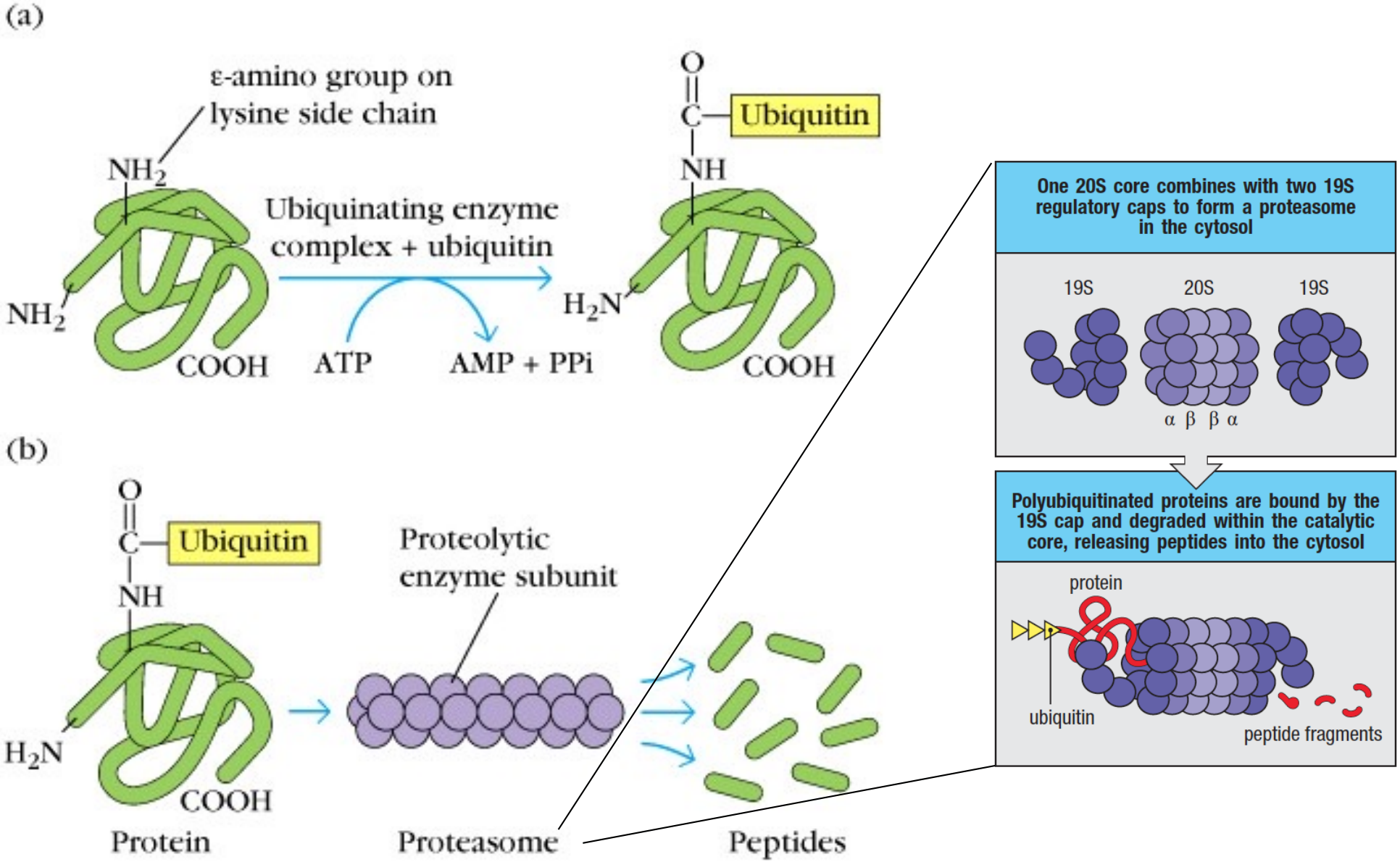
If the antigen is captured from the outside (exogenous antigen) it will be "presented" in association with MHC II molecules and will be recognized by CD4 cells.

MHC class I molecules present antigens derived from intracytoplasmic pathogens to cytotoxic CD8+ T cells

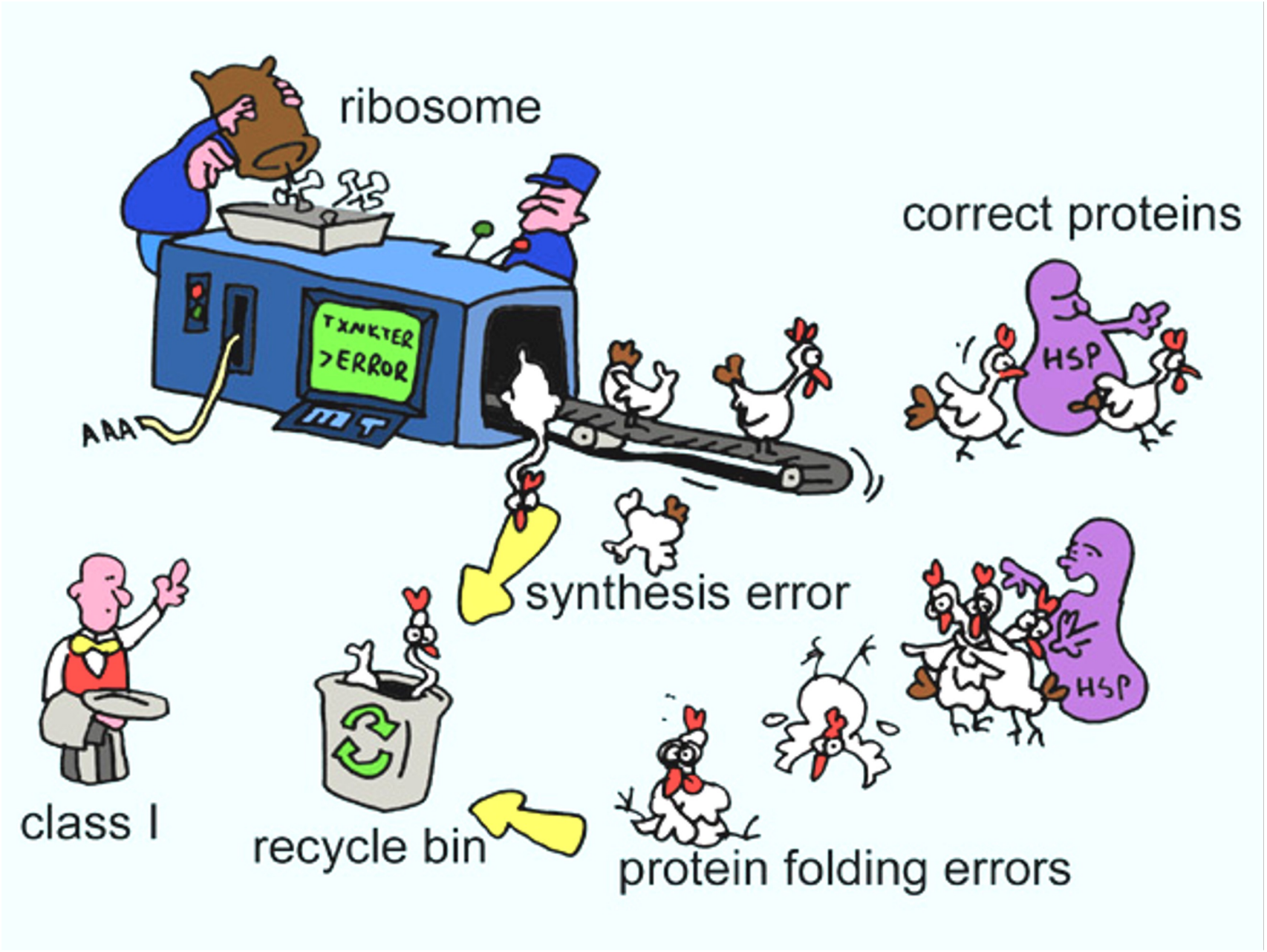


Nature Reviews Immunology 3, 952-961, 2003

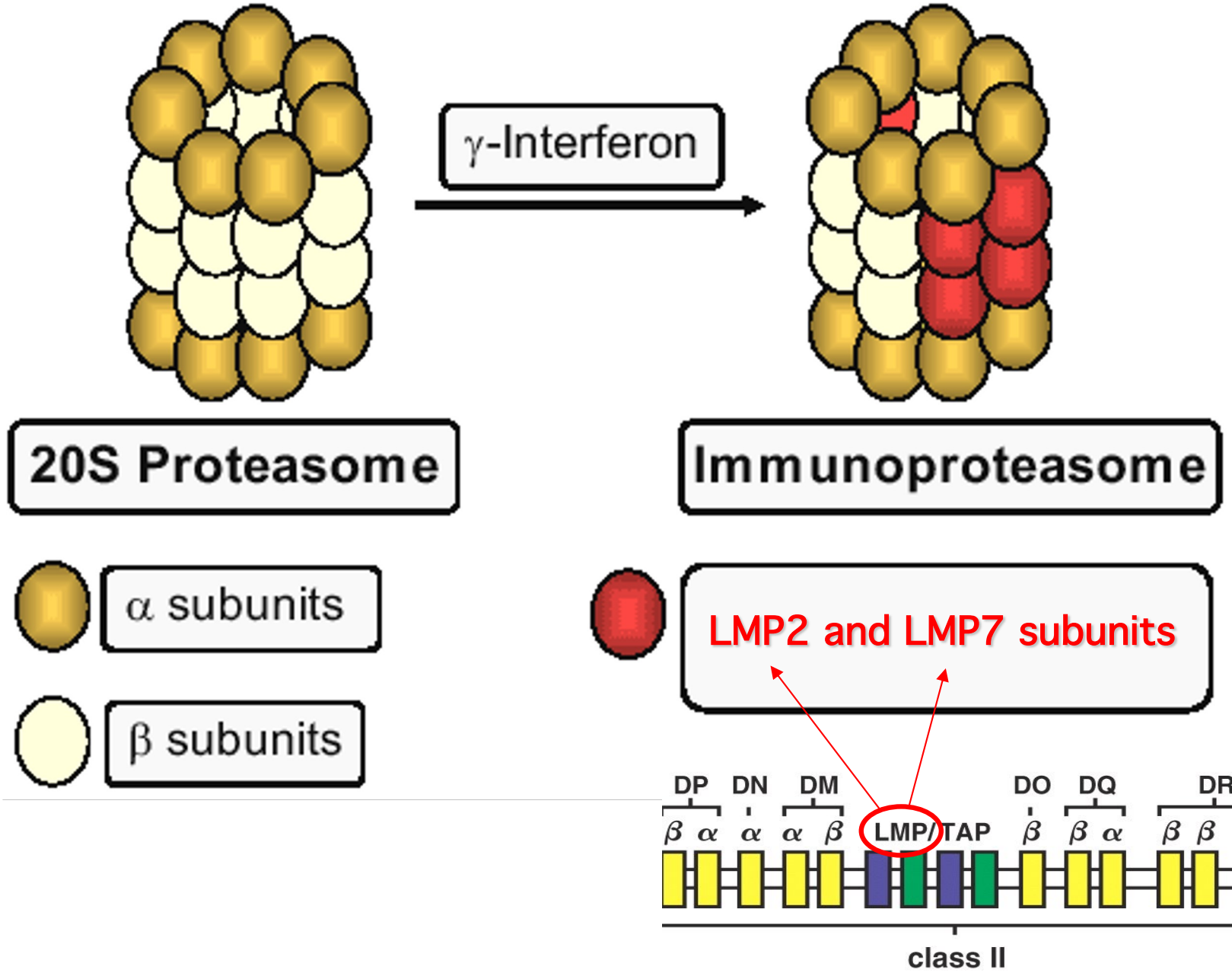
Proteasomal dependent degradation of intracelluar ubiquitinated proteins



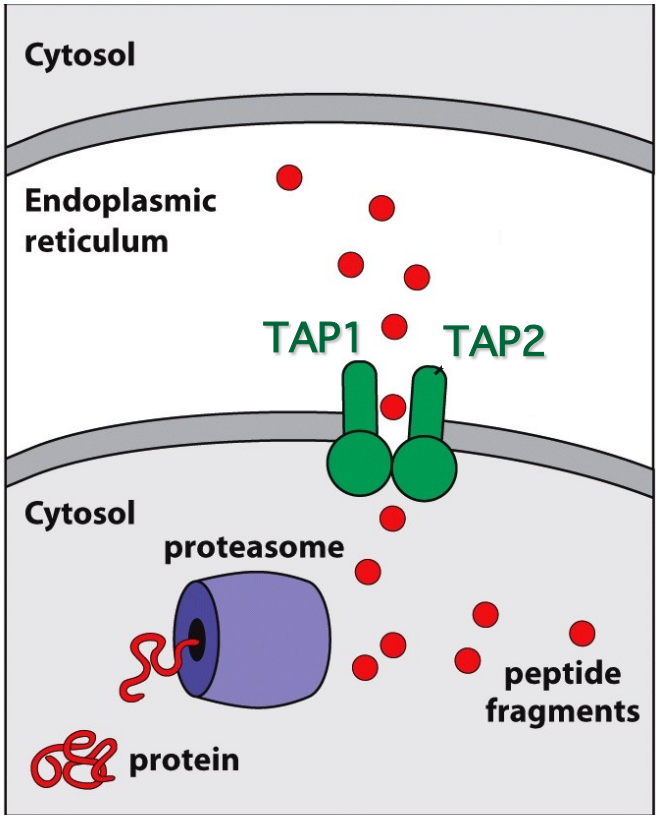
Which proteins are digested by the proteasome?

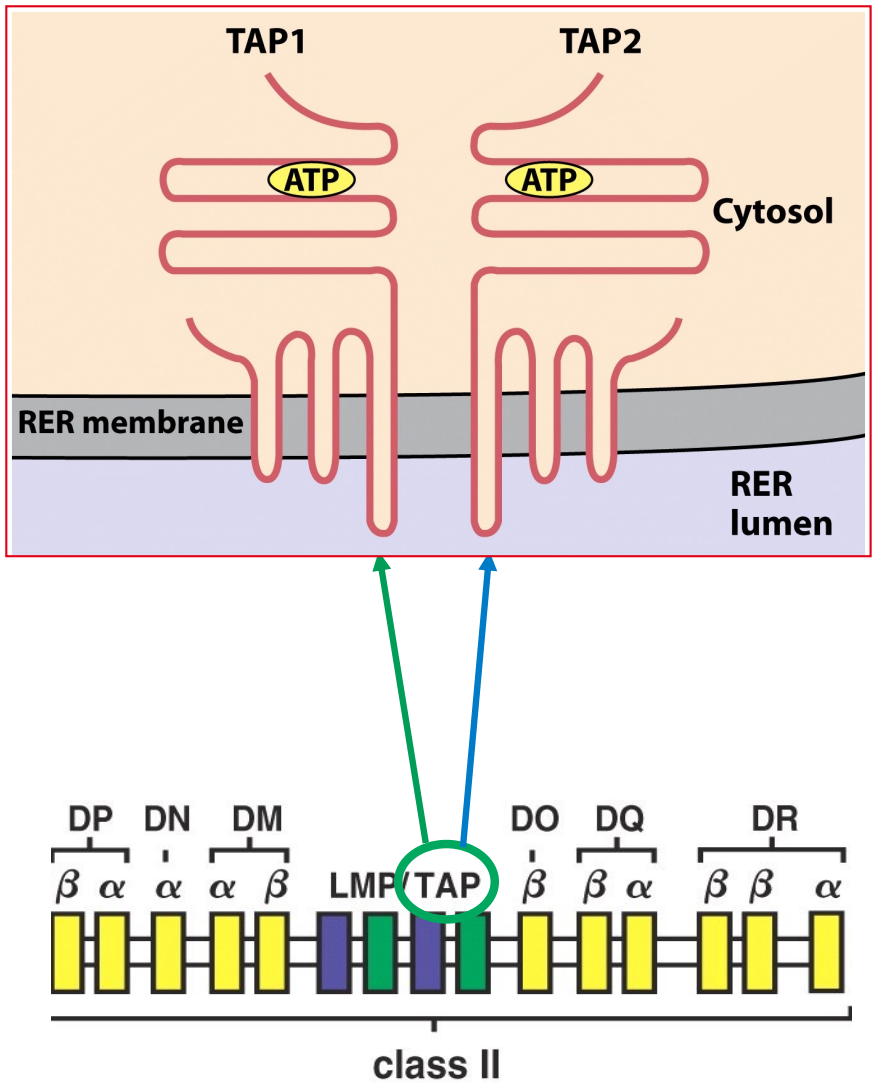


IMMUNOPROTEASOME



Proteasome-derived peptides are transported into the lumen of the endoplasmic reticulum by TAP1/2 transporters





- TAP1/TAP2 transport peptides of approximately 8-13 amino acids.
- Peptides with basic or hydrophobic residues at the C terminus are transported more efficiently

The genes for TAP1/2 map in the MHC locus

The MHC class I pathway for the processing and presentation of cytoplasmic antigens

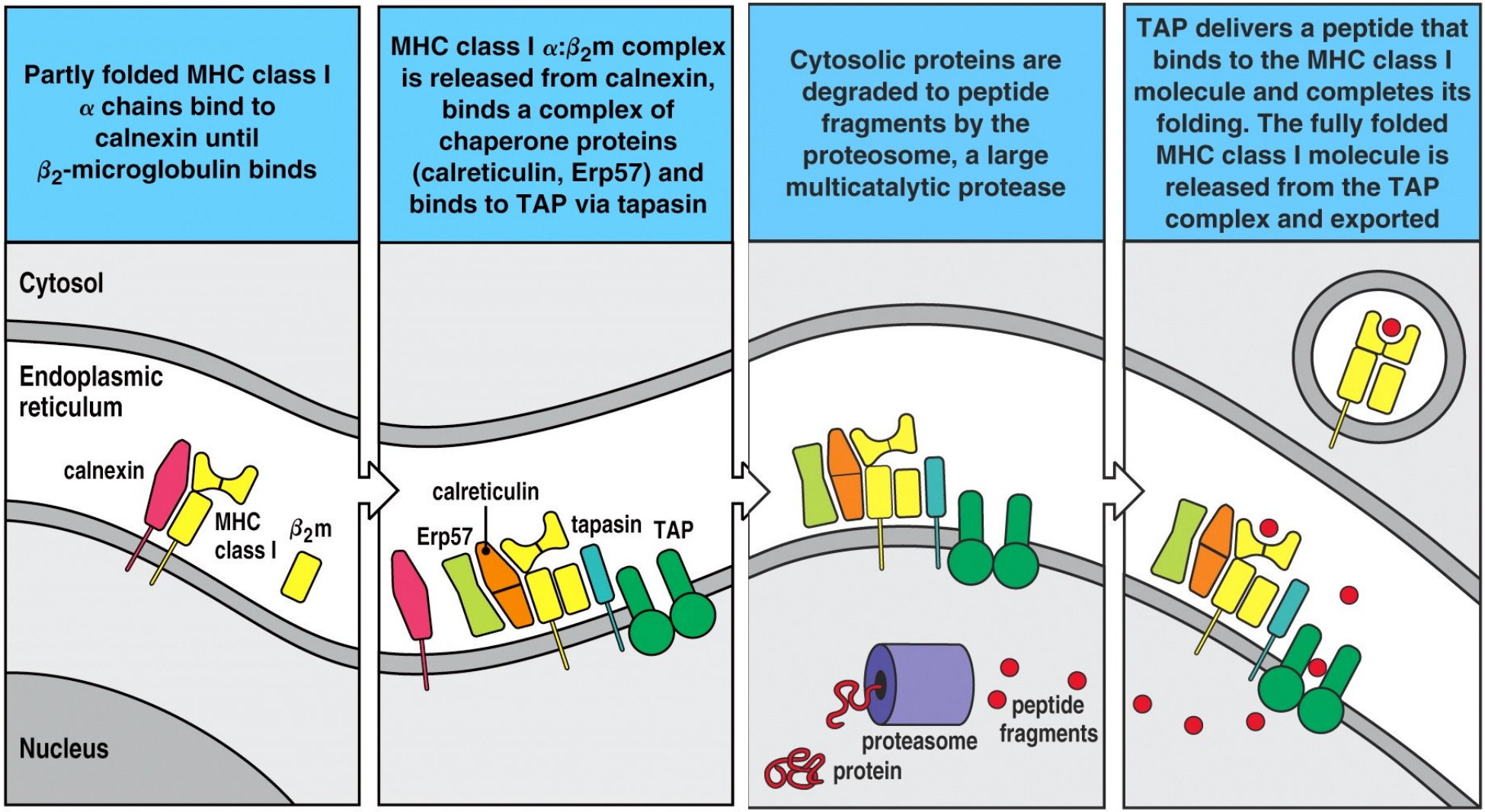
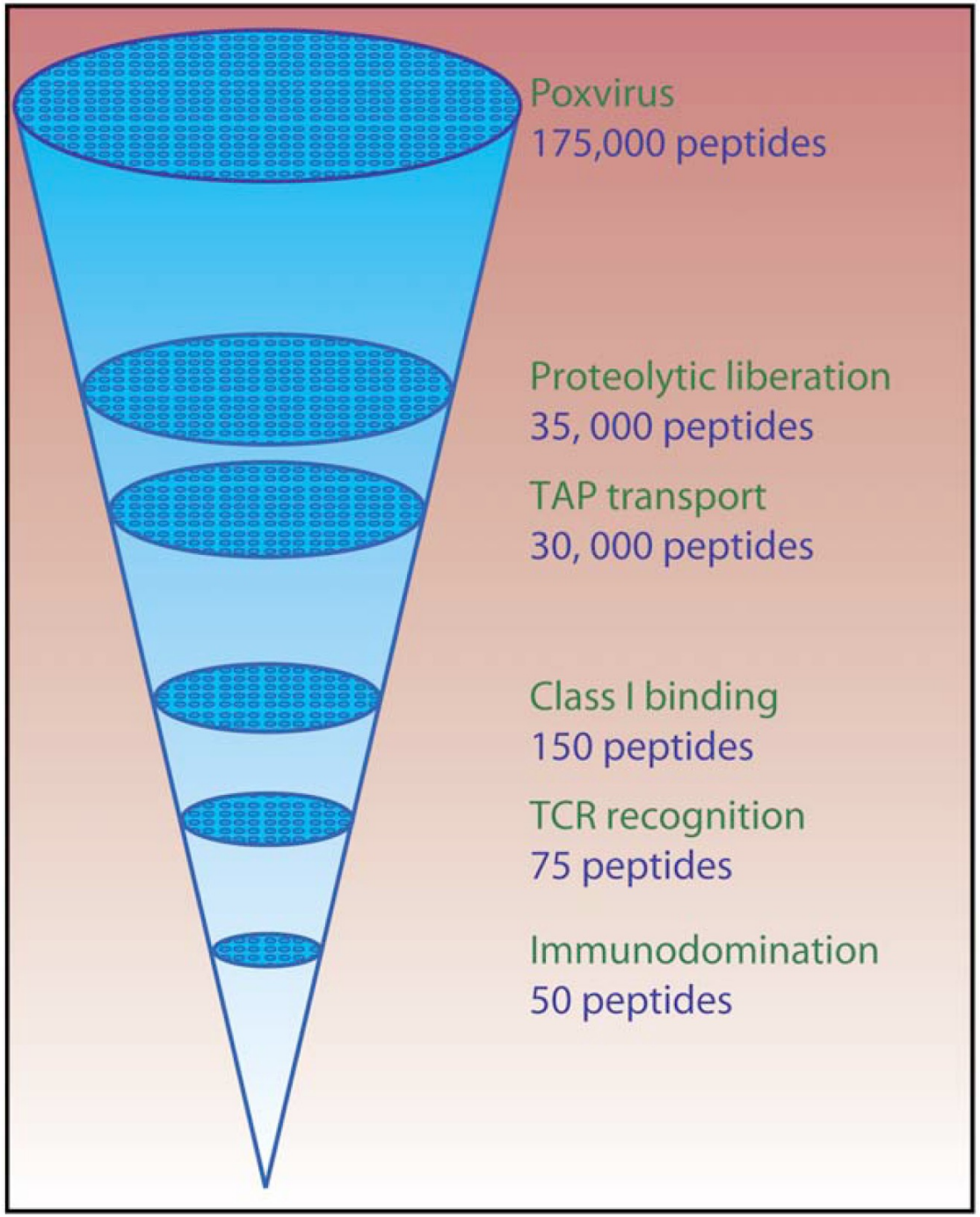


Figure 5-6 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

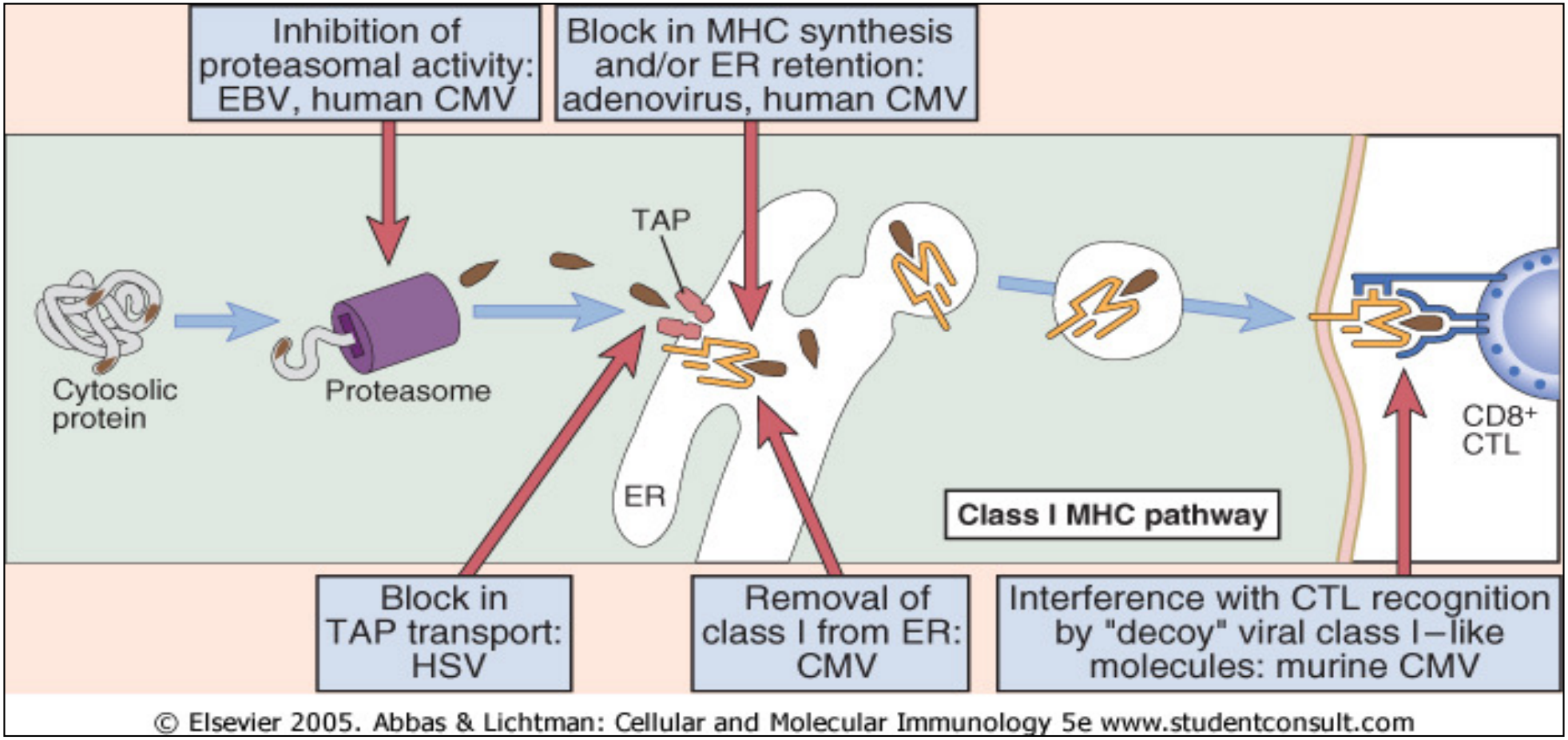
Immunodominant peptides

An entire viral genome
can generate ≅10^5 peptides

90% of CD8 T response
focuses on ≅50 peptides



Inhibition of endogenous antigen presentation by viruses

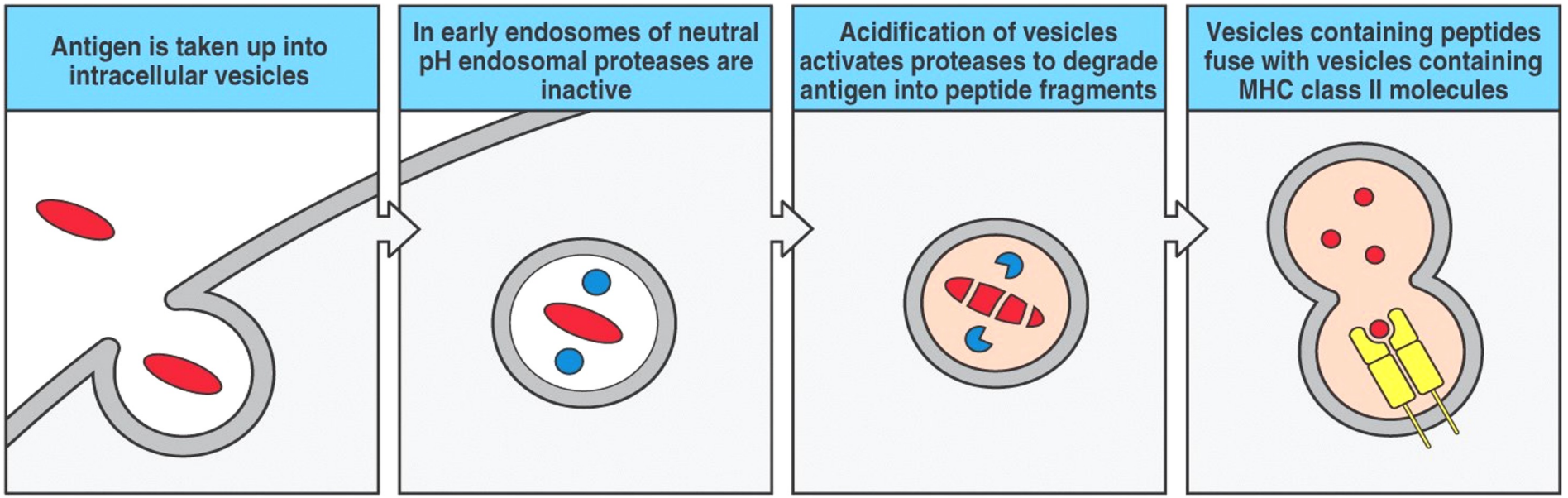


HSV= virus herpes simplex

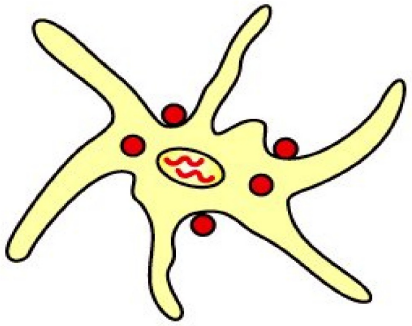
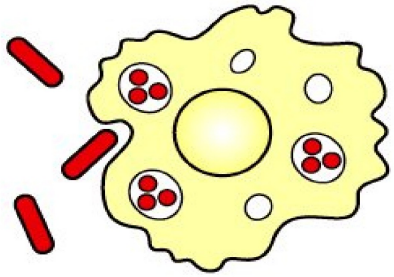
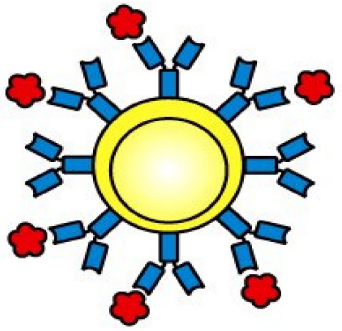
EBV= epstein barr

CMV= citomegalovirus

The exogenous antigen processing pathway



How exogenous antigens are taken up by the APC?

	Dendritic cells	Macrophages	B cells
			
Antigen uptake	+++ Macropinocytosis and phagocytosis by tissue dendritic cells Viral infection	Phagocytosis +++	Antigen-specific receptor (Ig) ++++
MHC expression	Low on tissue dendritic cells High on dendritic cells in lymphoid tissues	Inducible by bacteria and cytokines – to +++	Constitutive Increases on activation +++ to ++++

Immature dendritic cells take up antigens in the periphery

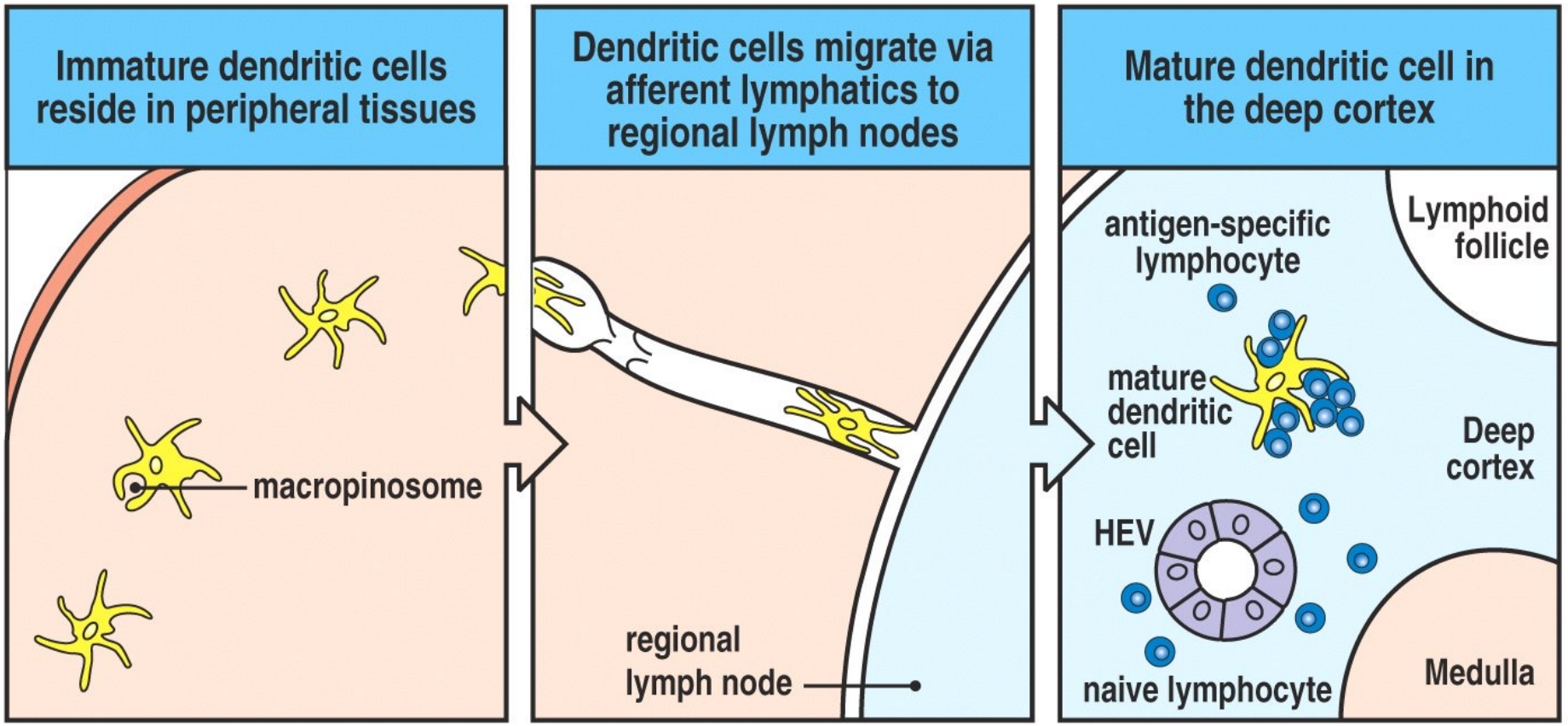
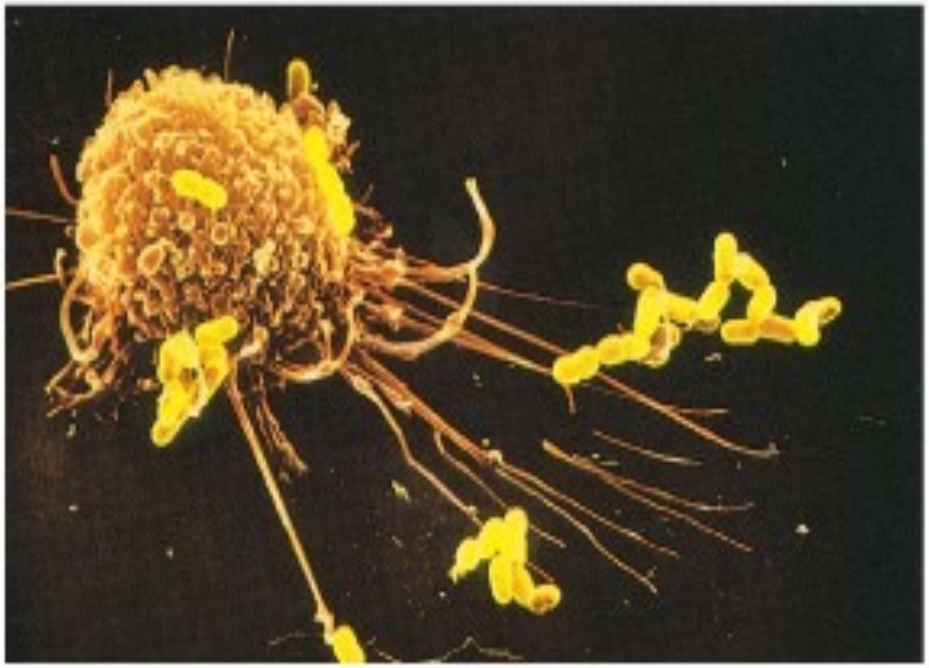


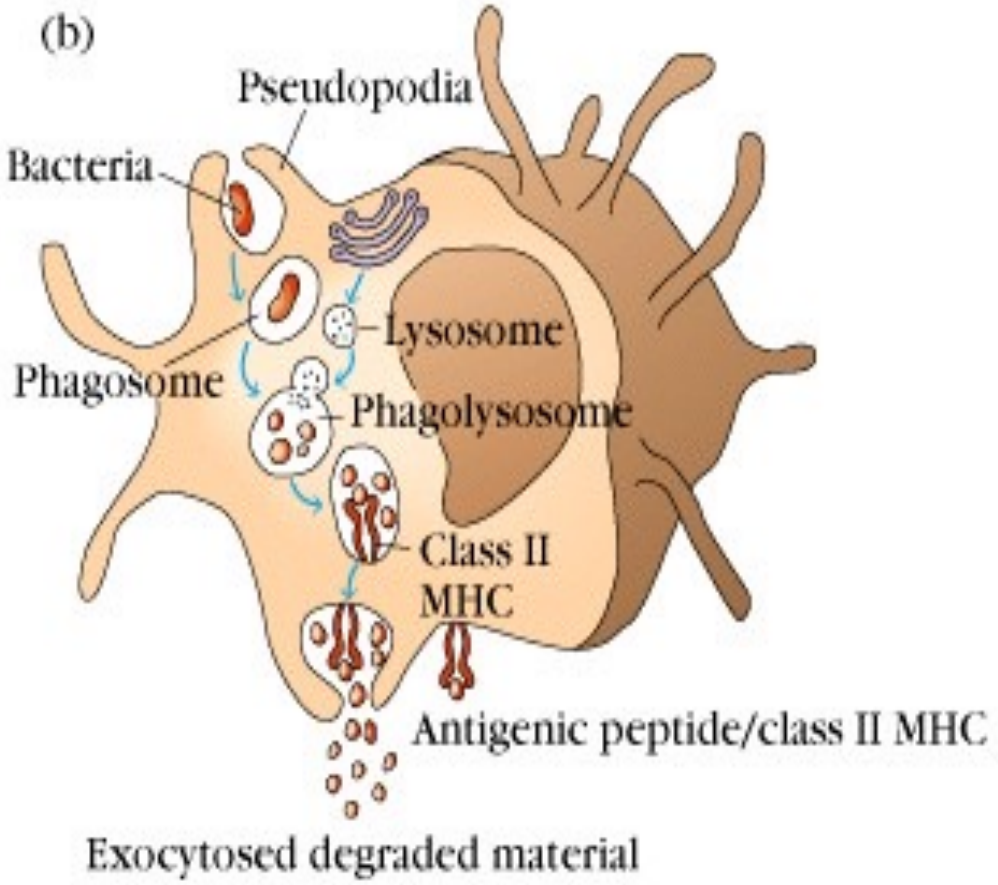
Figure 1-13 Immunobiology, 6/e. (© Garland Science 2005)

Macrophages present exogenous antigens obtained through phagocytosis

(a)



(b)



B lymphocytes present their specific antigen very efficiently

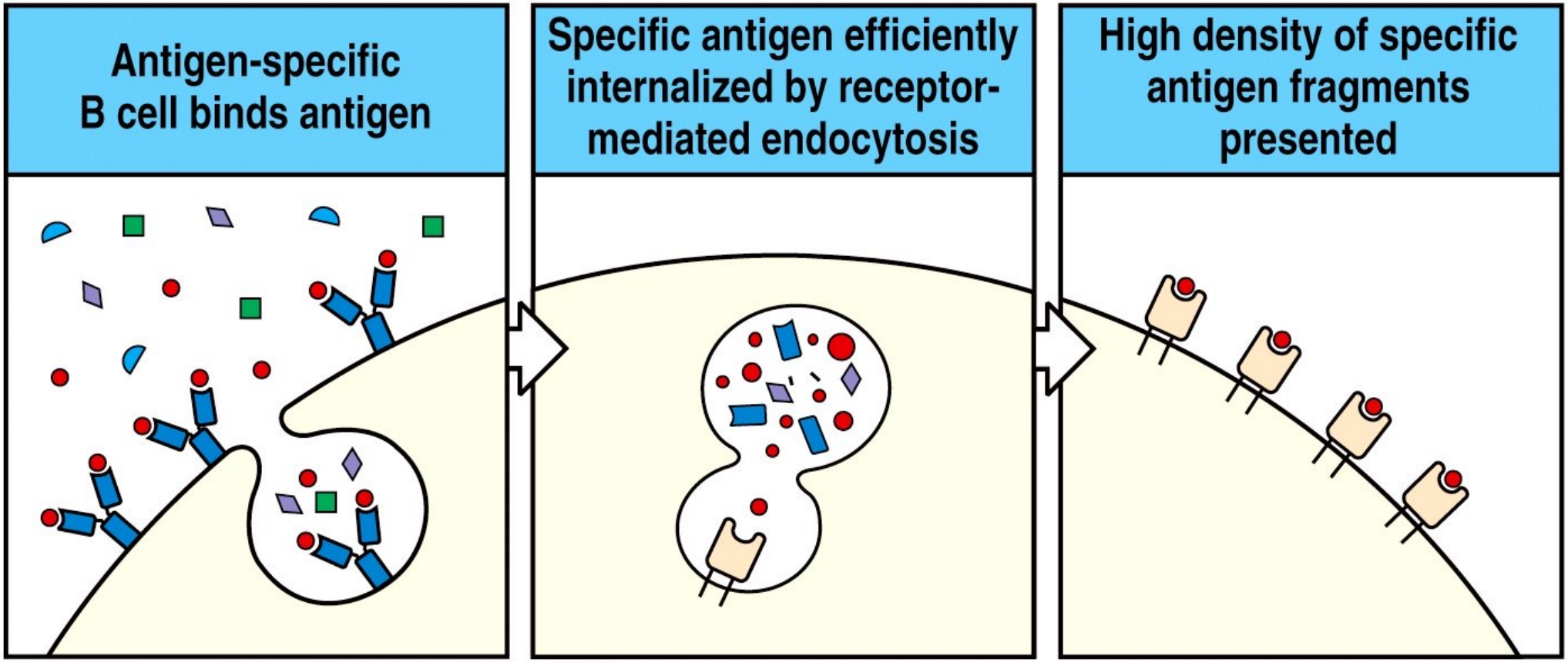


Figure 8-17 Immunobiology, 6/e. (© Garland Science 2005)

Endocytosed material meets MHC class II molecules in a low-pH vesicular compartment, with proteolytic enzymes

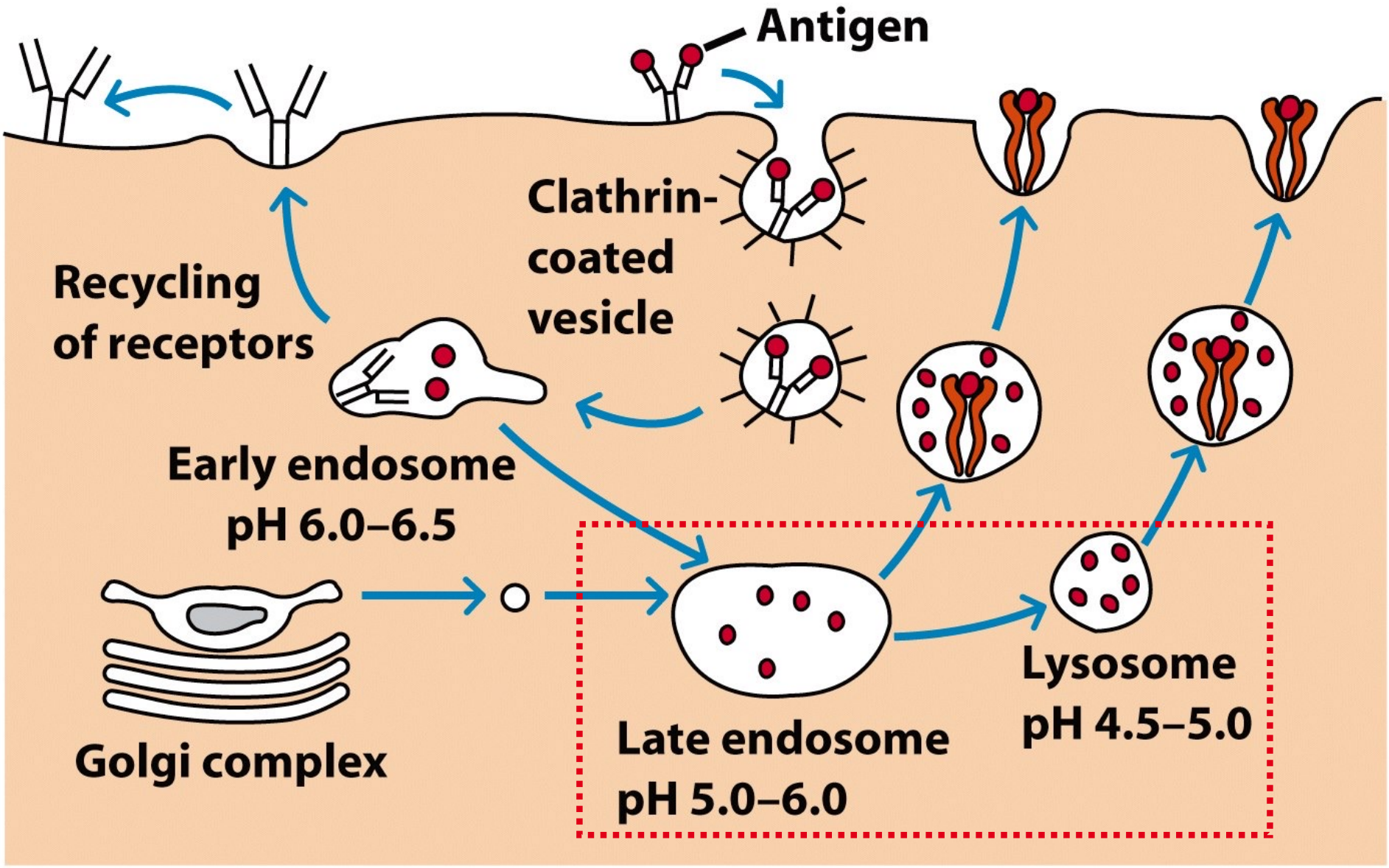
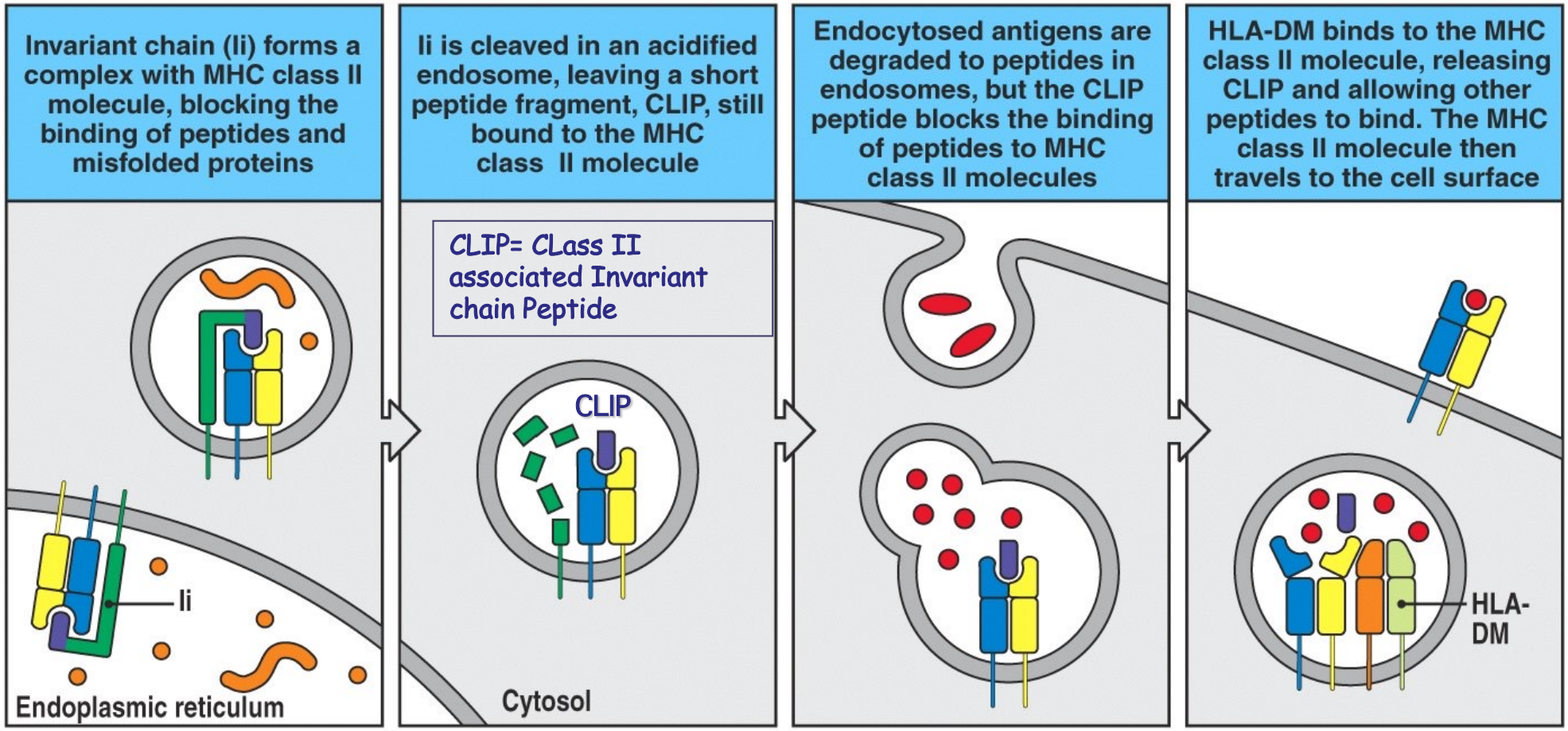


Figure 8-21
Kuby IMMUNOLOGY, Sixth Edition

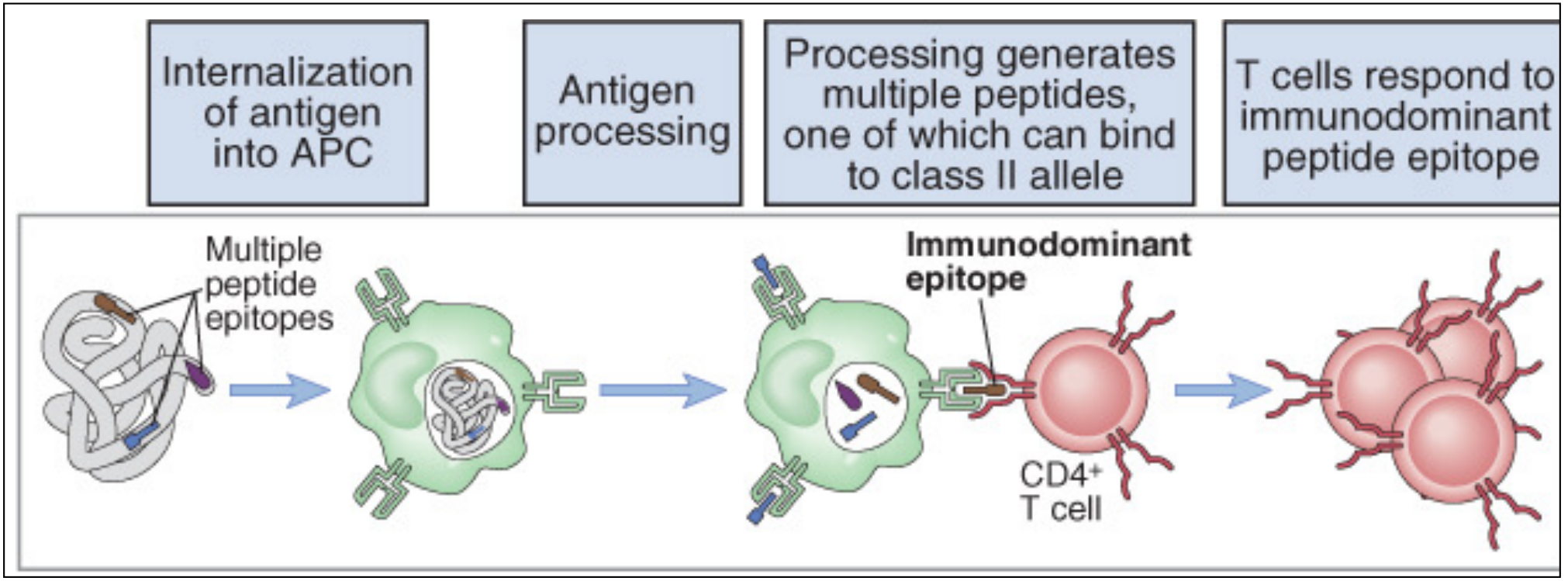
Nascent MHC class II molecules associate with the invariant chain (Ii) in the ER



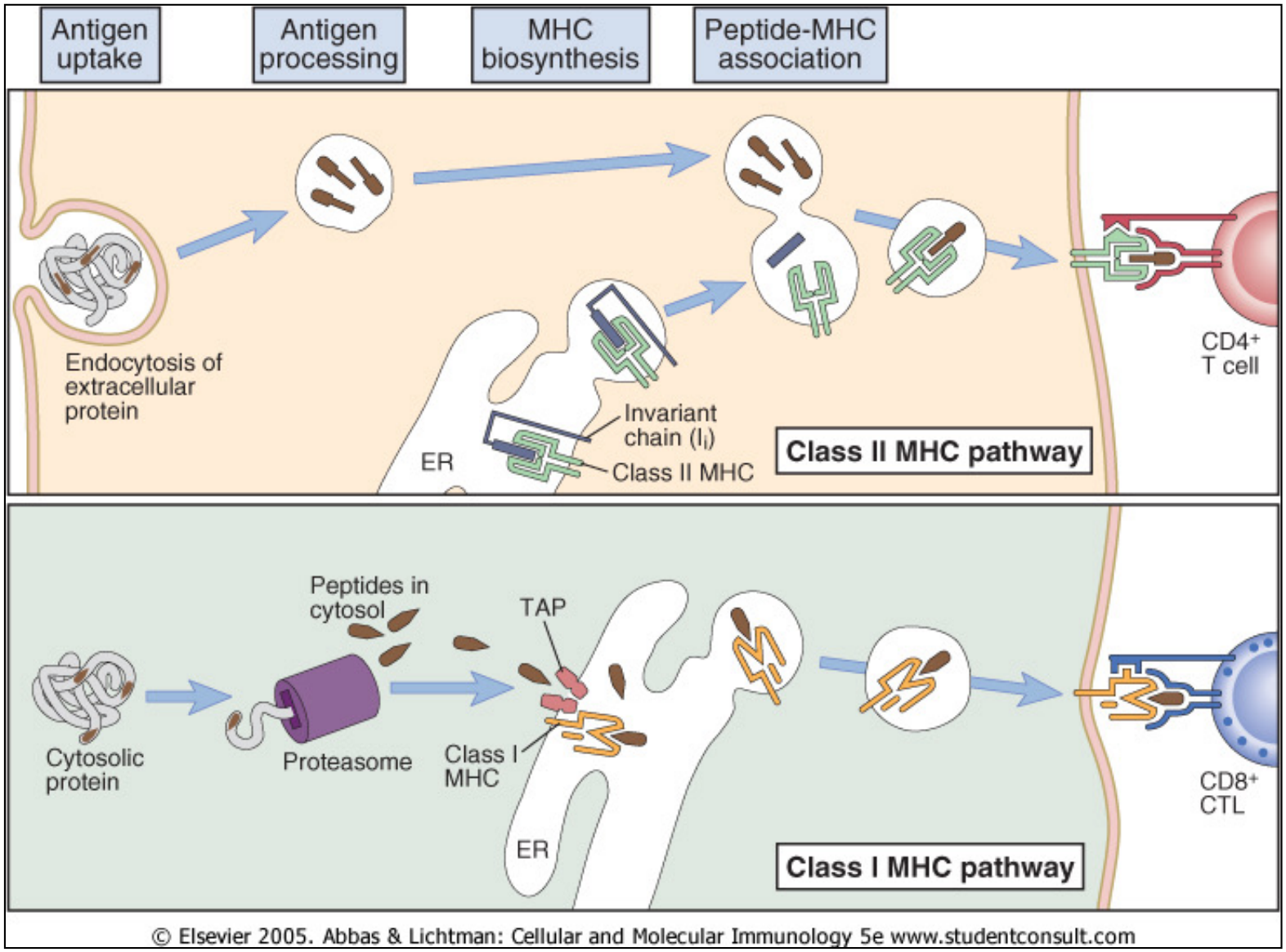
Ii has two roles:

1. to guide neosynthesized class II to the post Golgi compartment
2. to occupy the peptide groove, and to block the association with peptides present in the ER

Immunodominant peptides



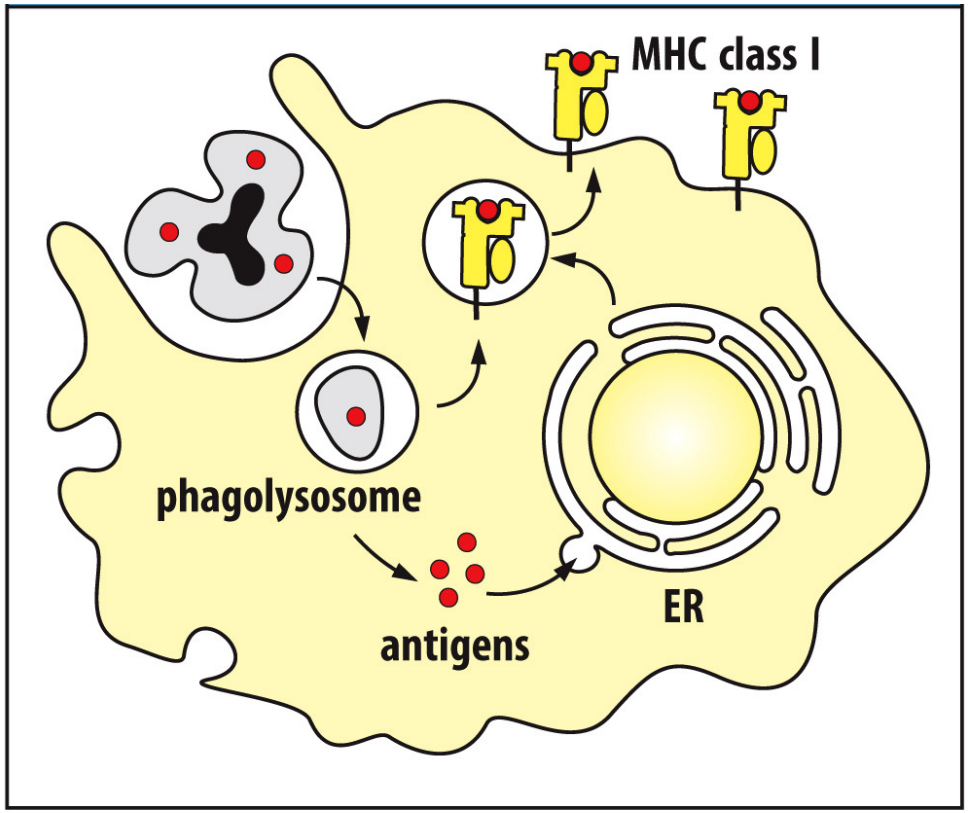
The two types of MHC (class I and class II) present antigens of different origin (endogenous and exogenous) to different T cell subsets (CD8+ and CD4+)



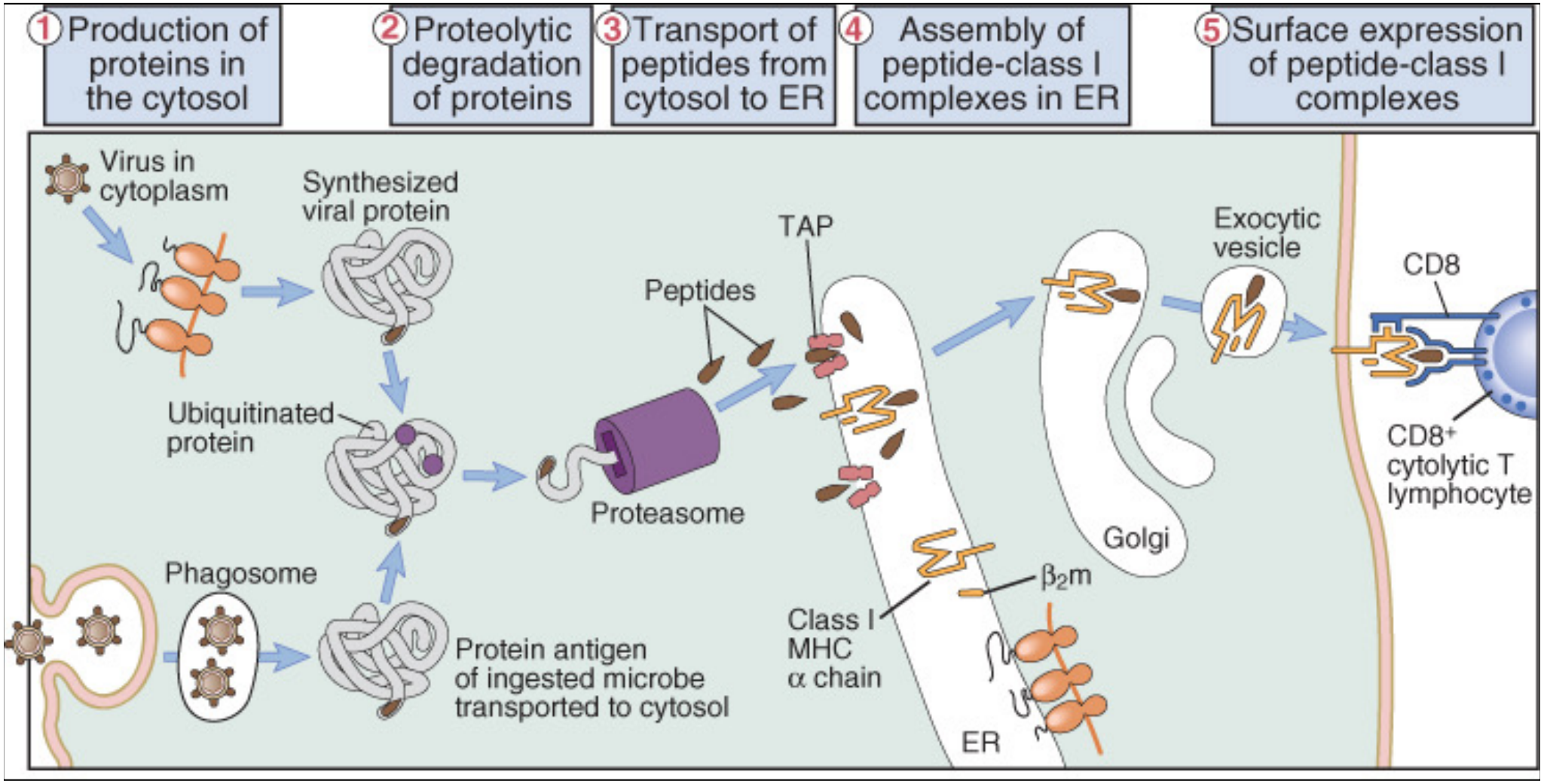
BUT……..

CROSS-PRESENTATION or CROSS-PRIMING

DC are also capable of presenting exogenous antigens in association with MHC class I molecules



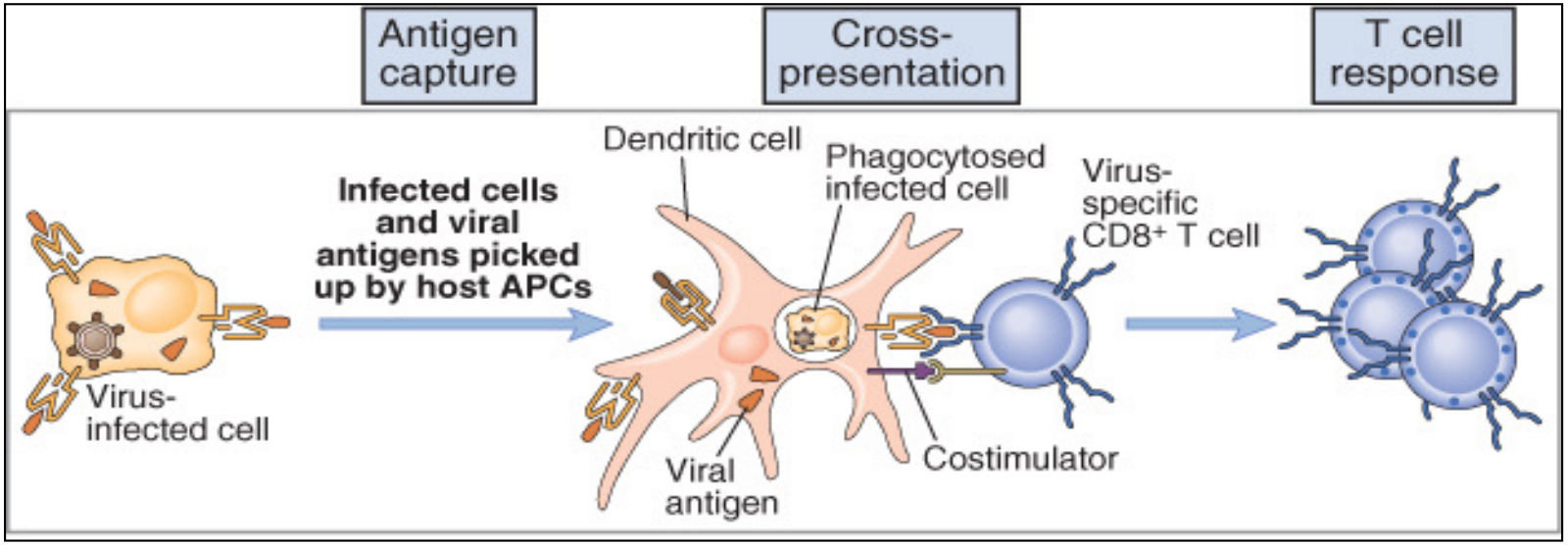
Cross-presentation of exogenous antigens in the MHC class I pathway



Dendritic cells and cross-presentation

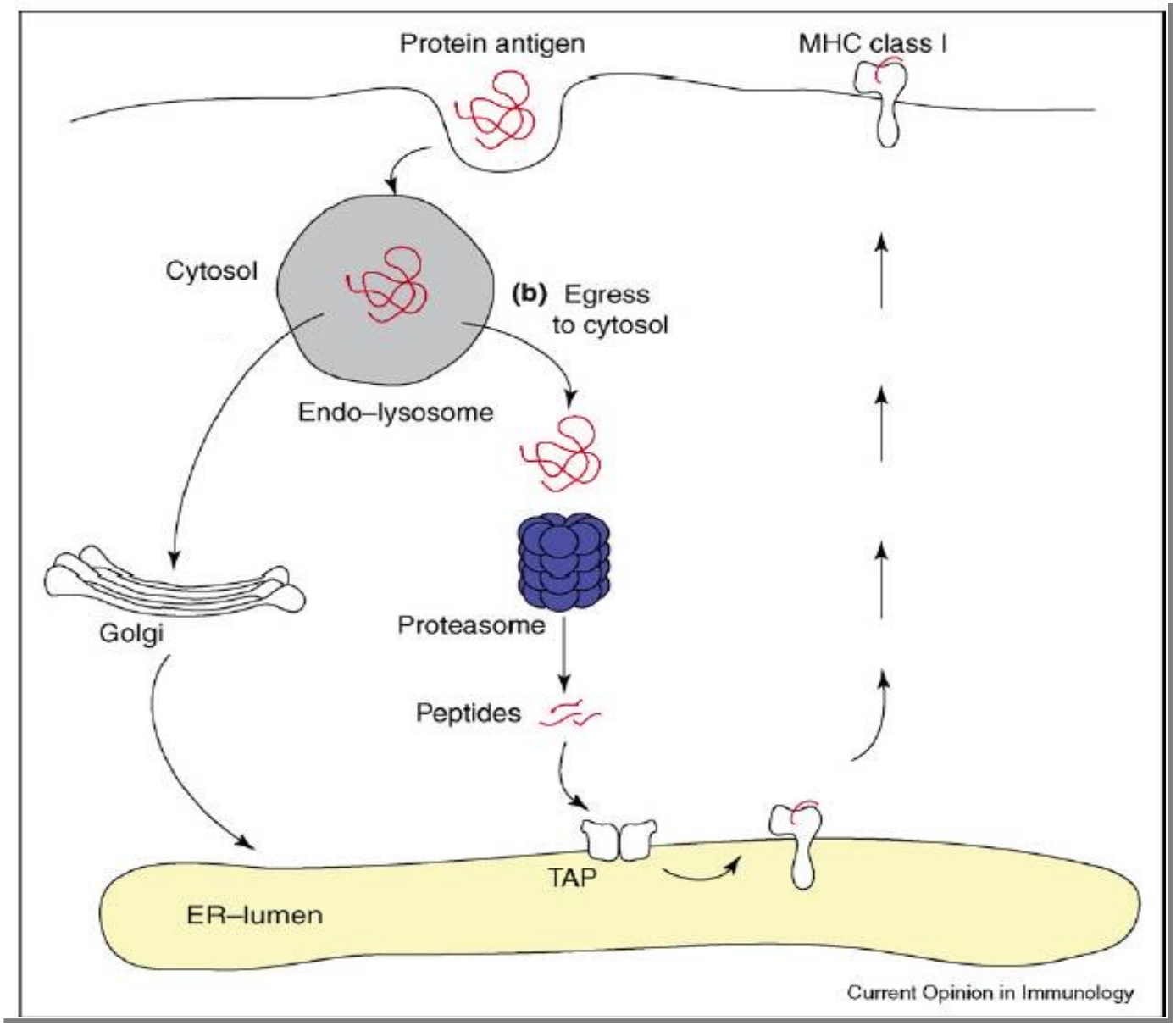
(exogenous antigens are presented in association with MHC I molecules)

- Dendritic cells are the only APCs (so far) to exhibit this activity in vivo.
- **Exogenous antigens** are redirected to the **endogenous presentation pathway.**
- This allows for their presentation on MHC class I molecules, priming $CD8^+$ T-cell responses.

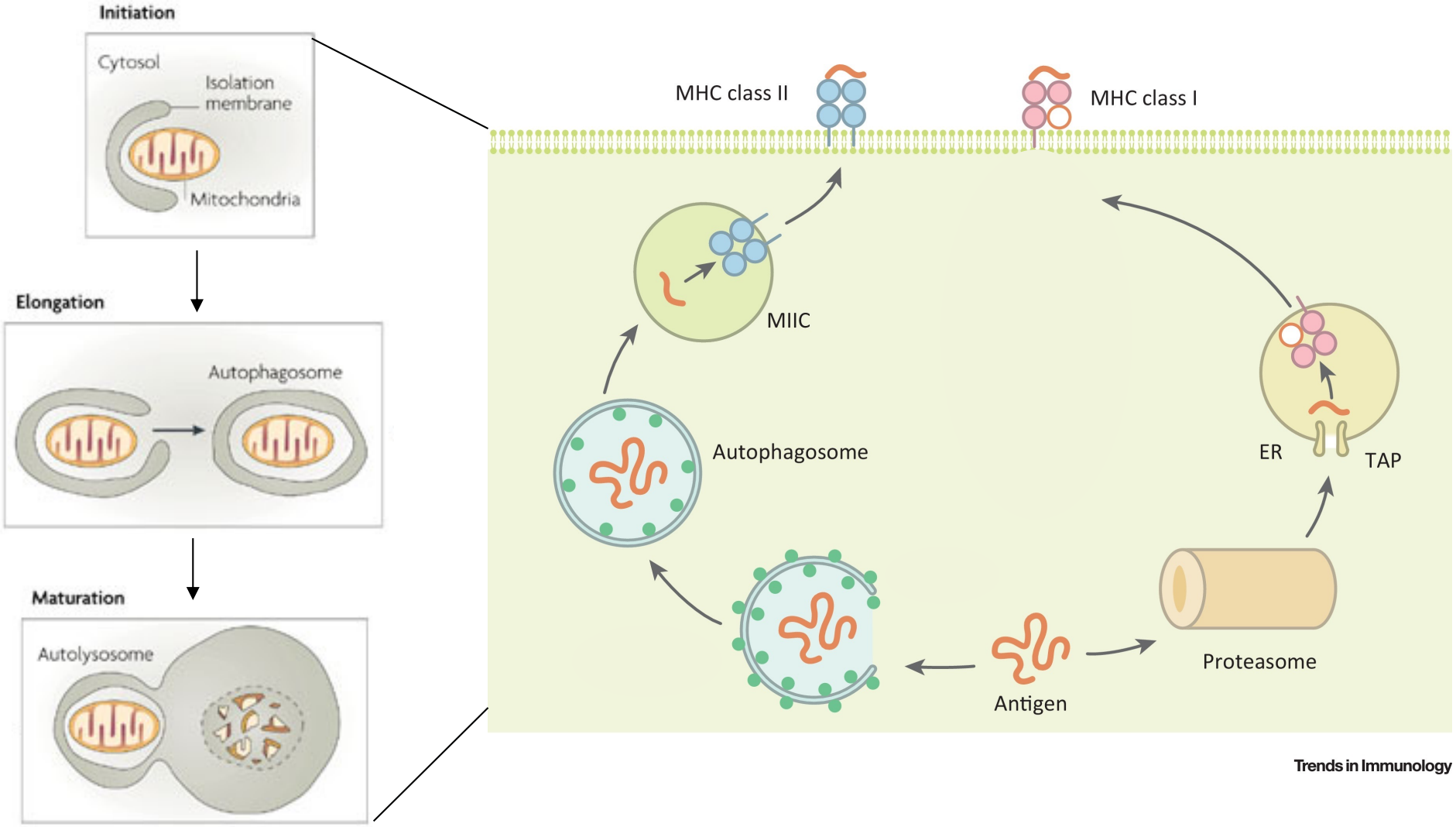


MECHANISMS OF CROSS-PRESENTATION:

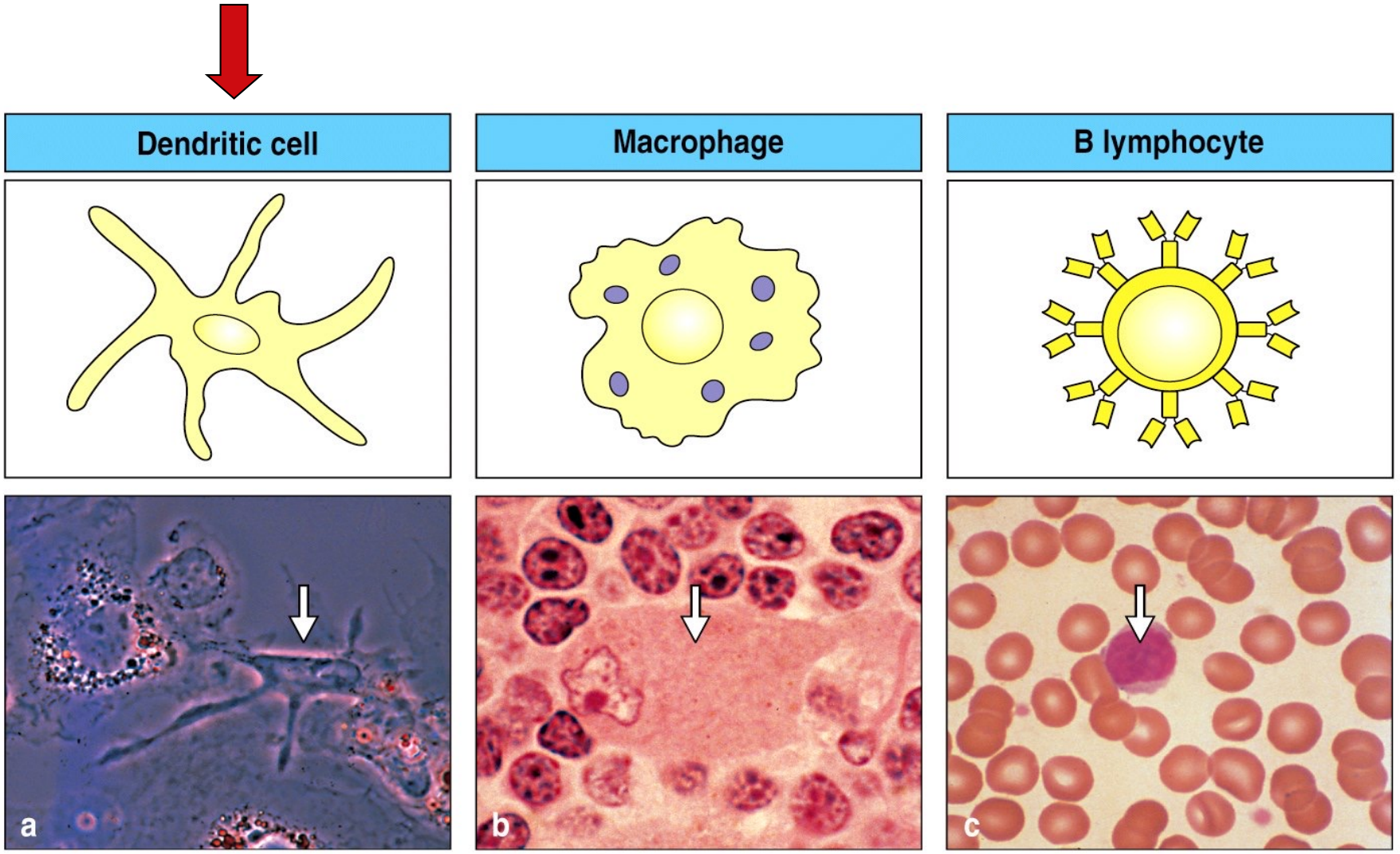
exogen antigens escape to the cytosol and reach the ER



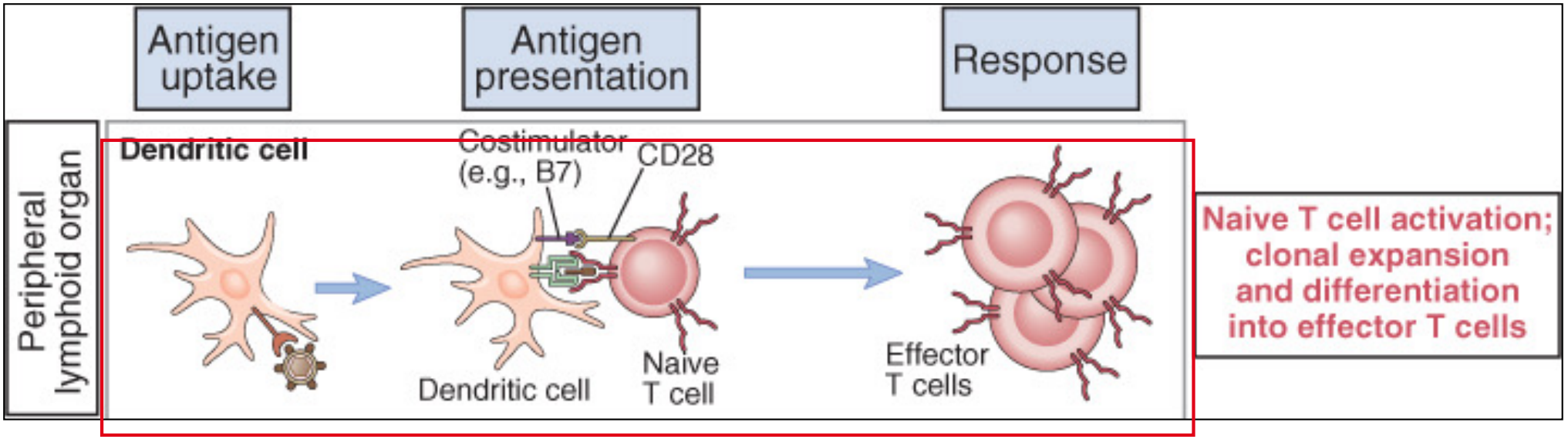
Cytoplasmic proteins can be presented in association with MHC II molecules ⟶ AUTOPHAGY

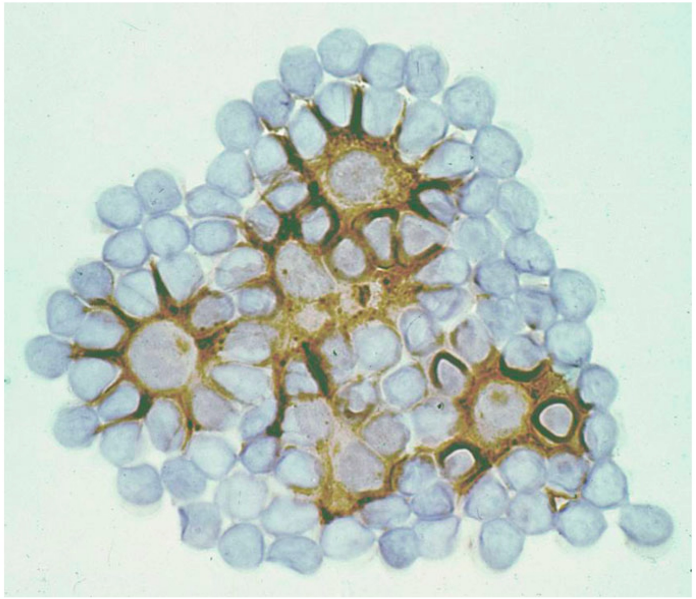


THE "SPECIALIZED" ANTIGEN-PRESENTING CELLS



Mature dendritic cells are the most efficient APC for naive T cells



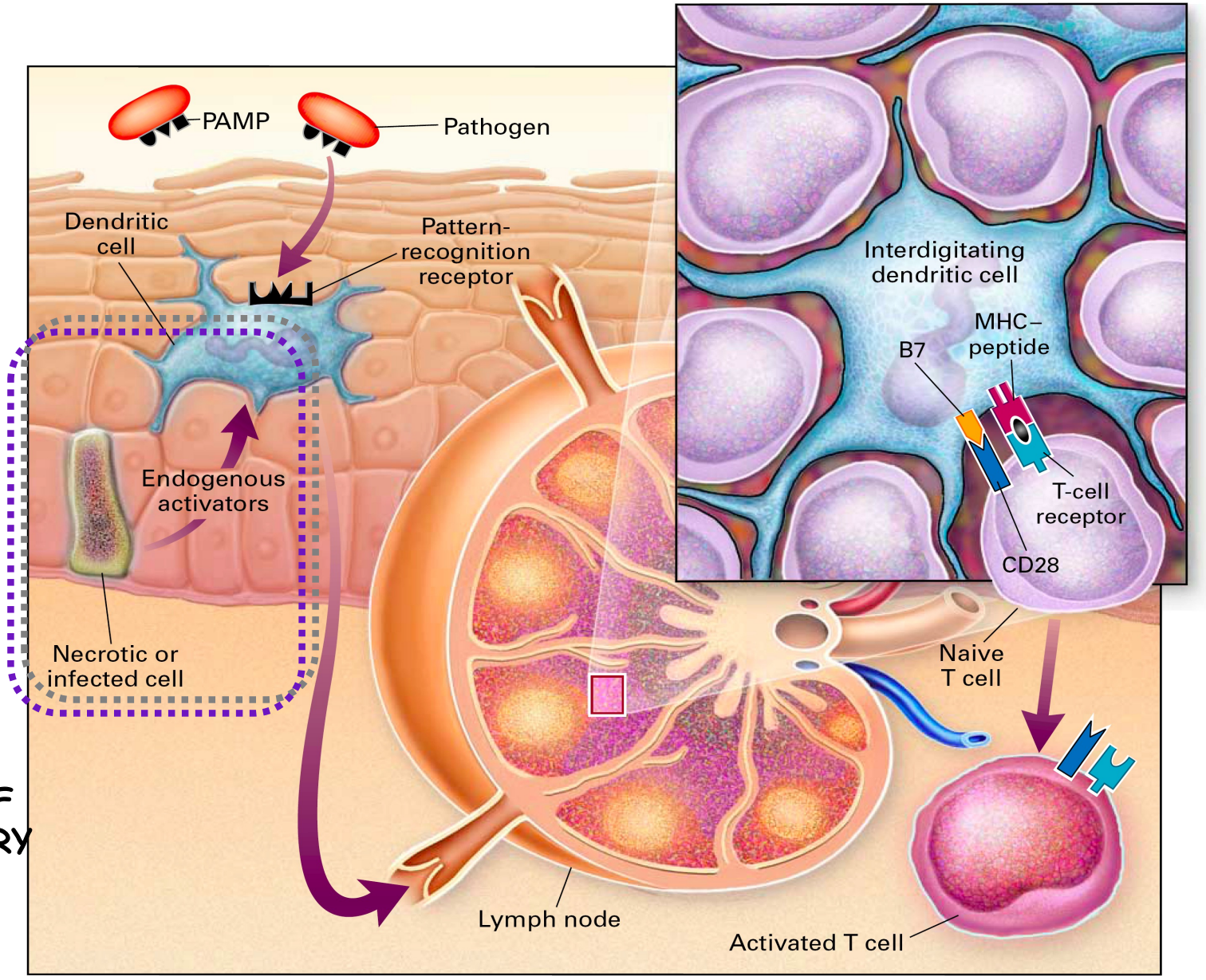


DC maturation is induced upon pathogen recognition or tissue injury

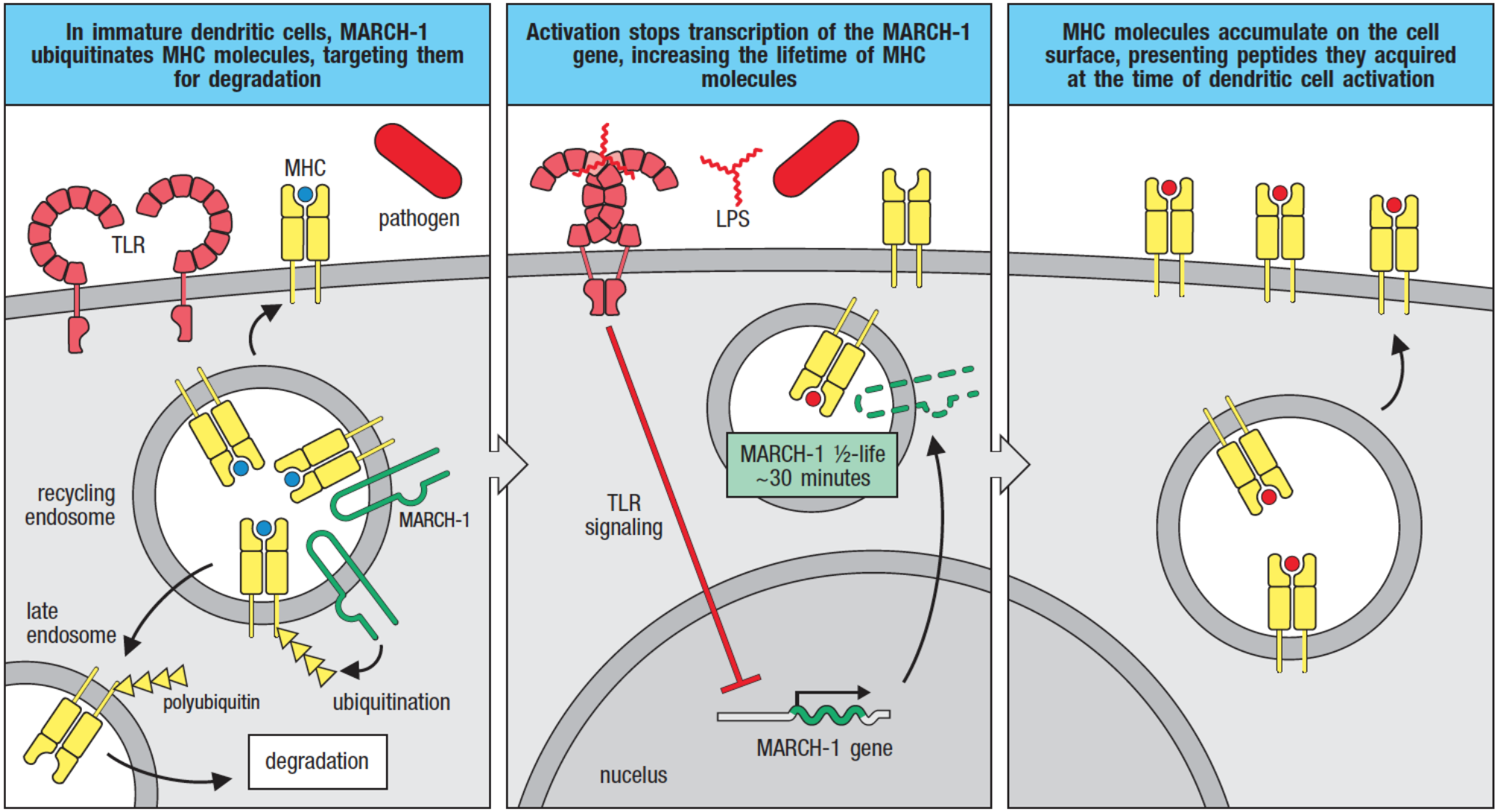
PATHOGEN COMPONENTS ACTIVATE IMMATURE DC STIMULATING:

MIGRATION

EXPRESSION OF COSTIMULATORY MOLECULES

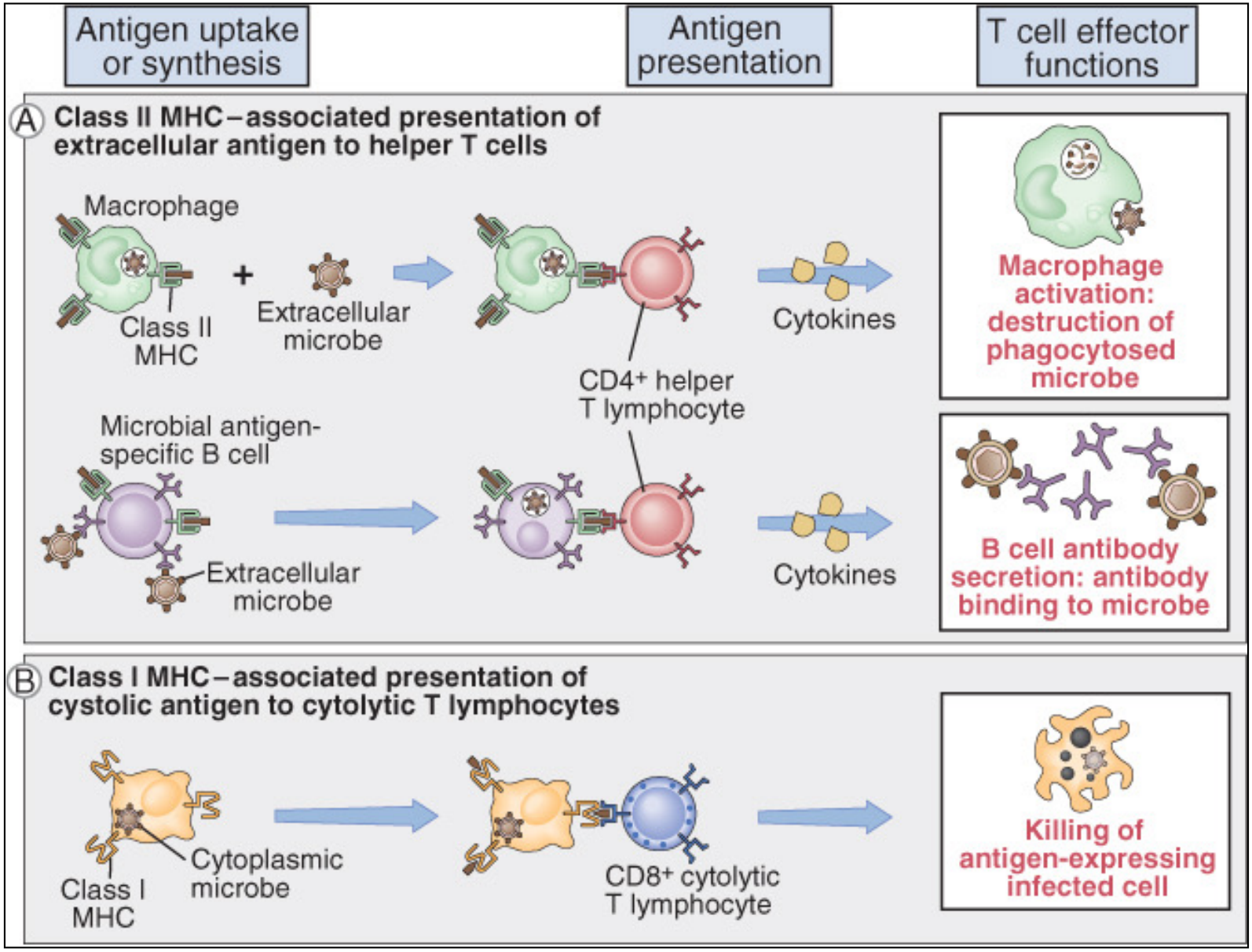


MHC class II molecules accumulate in mature DCs activated by pathogens via TLRs



MARCH-1 ligase regulates the expression of MHC molecules

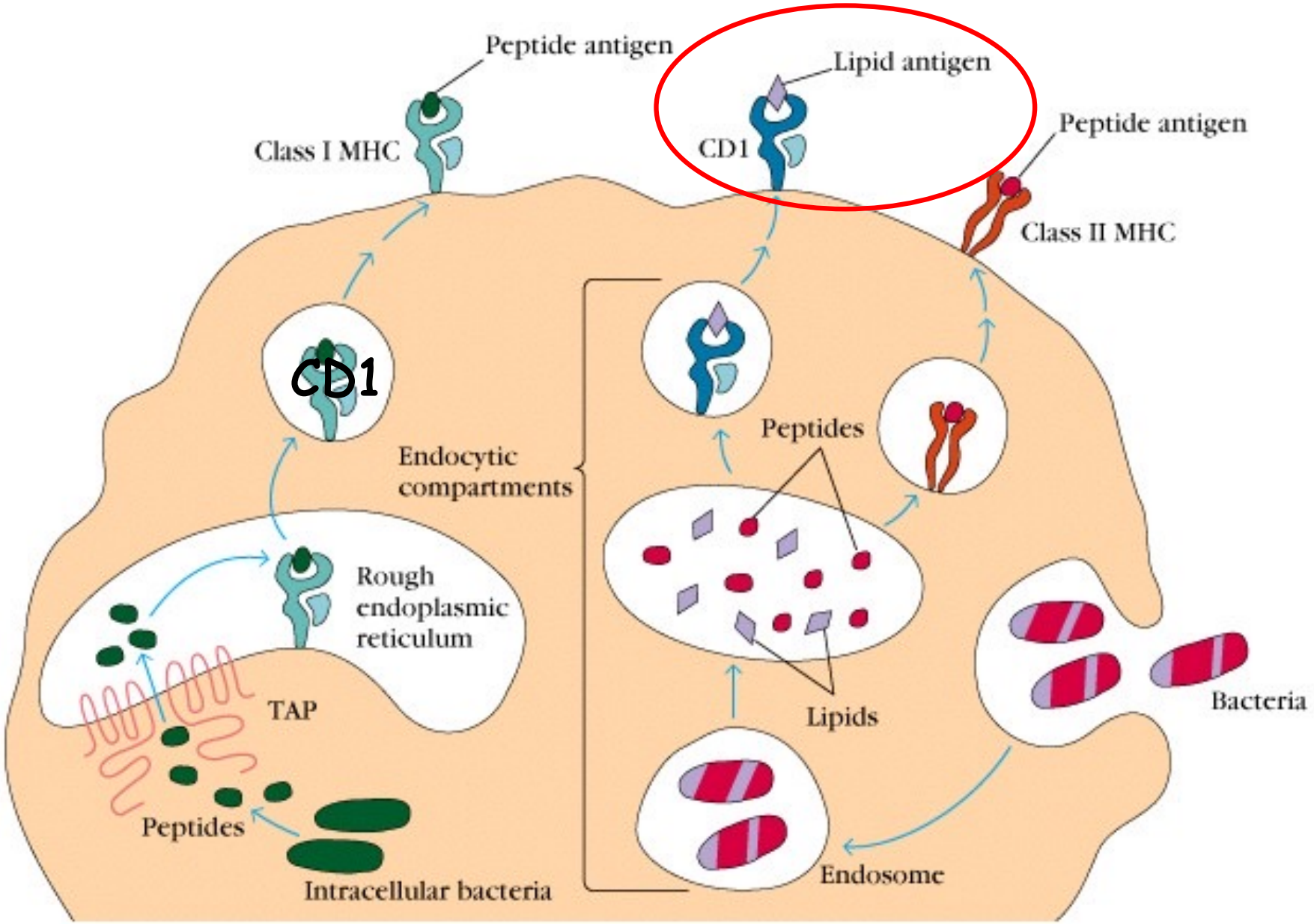
Effector T cells at the site of infection recognize the antigen: eradication of the infection



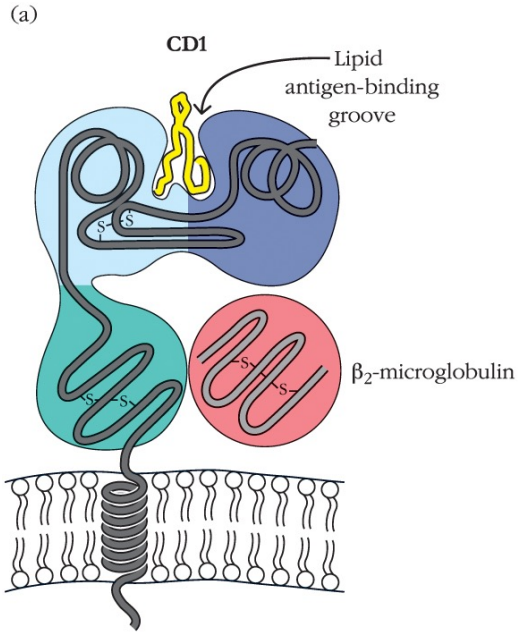
Presentation of Nonpeptide Antigens

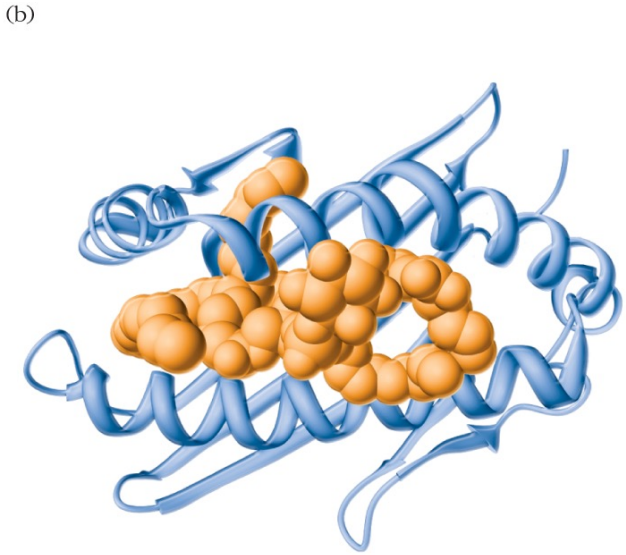
- Some nonprotein antigens can be recognized by T cells.
  - Lipid
  - Lipid-linked molecules
- Presentation occurs via **nonclassical MHC molecules**: **CD1**
- Genes are located outside the MHC locus and five human CD1 gene are known.
- Very little polymorphism is displayed.
- Most function similarly to MHC class II molecules.

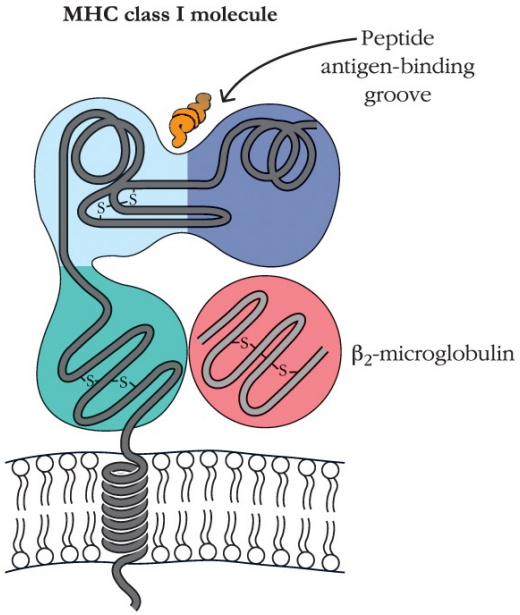
PRESENTATION OF LIPID ANTIGENS BY NON-CLASSICAL MHC → CD1

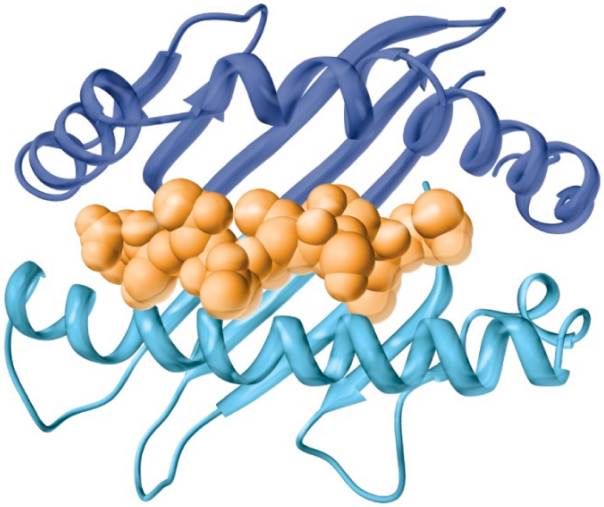


CD1 molecules are similar to MHC class I

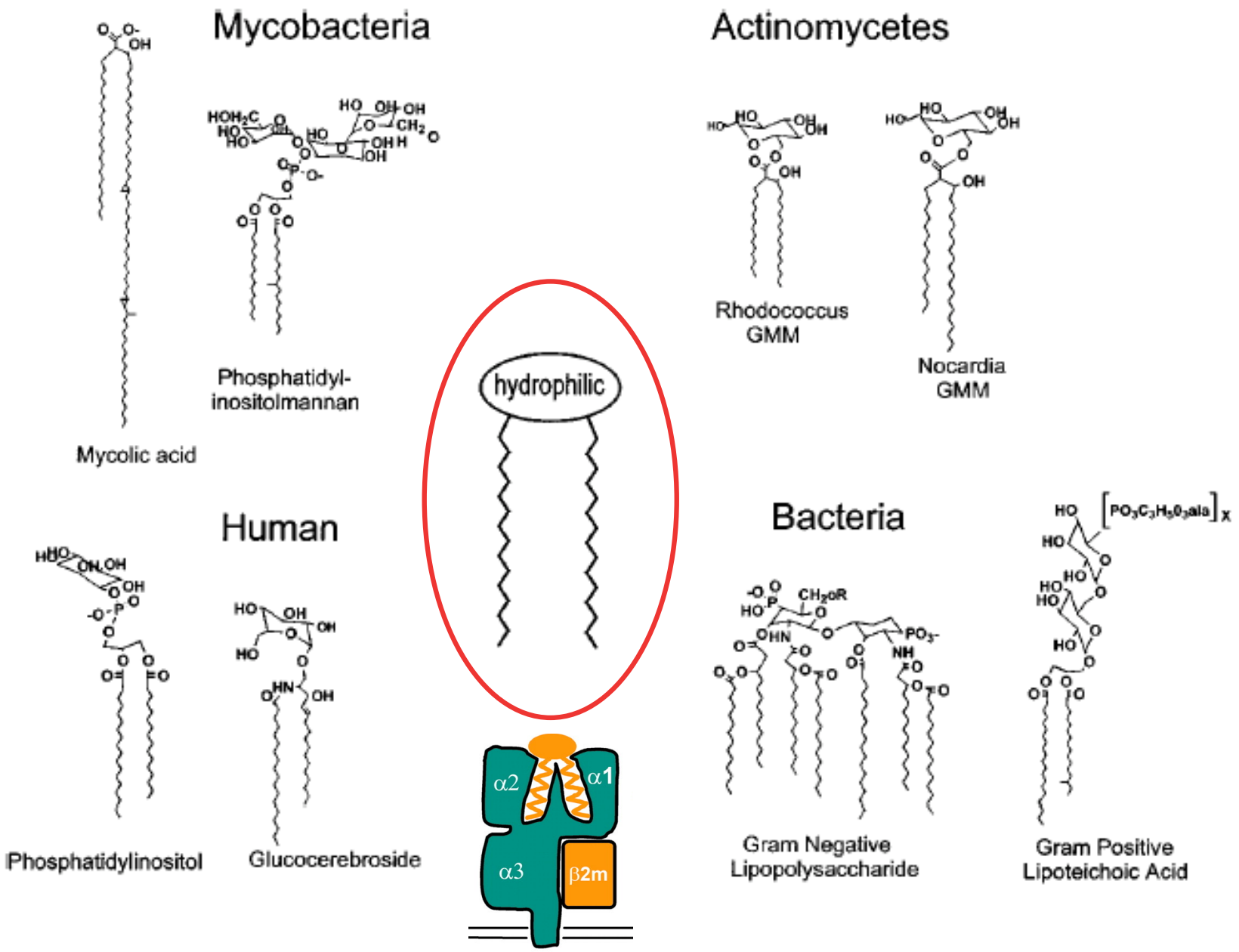








CD1 molecules can present self and non-self lipid antigens



Natural Killer (NK) T cells

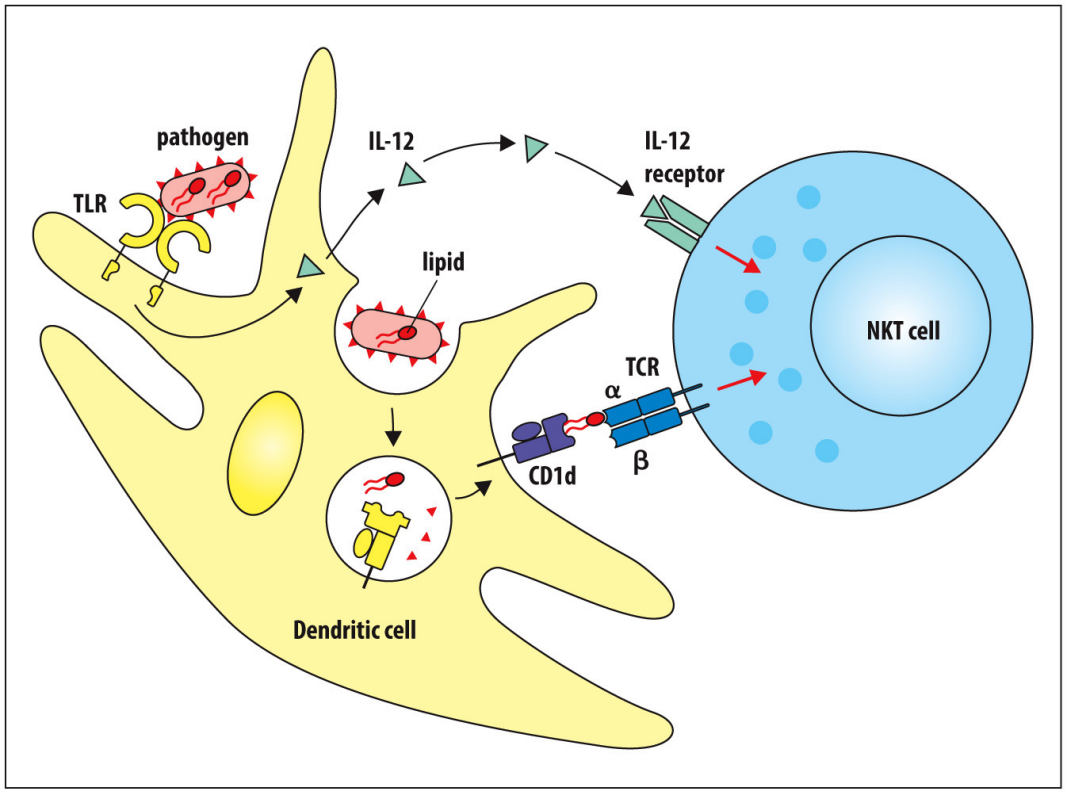
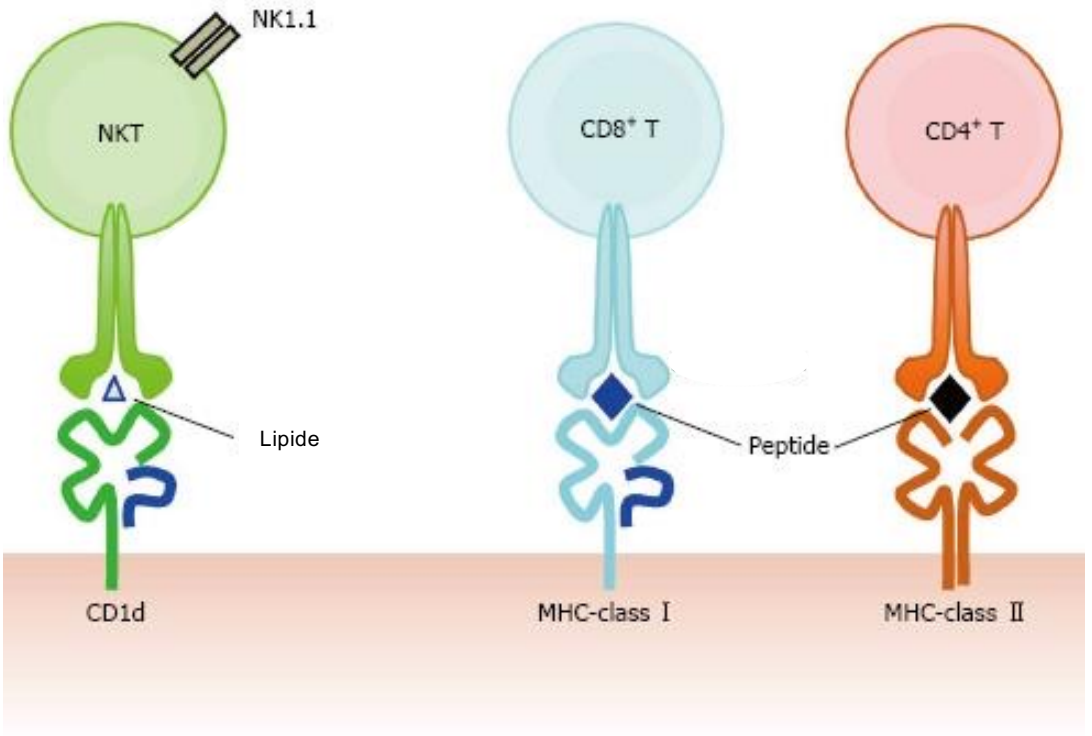


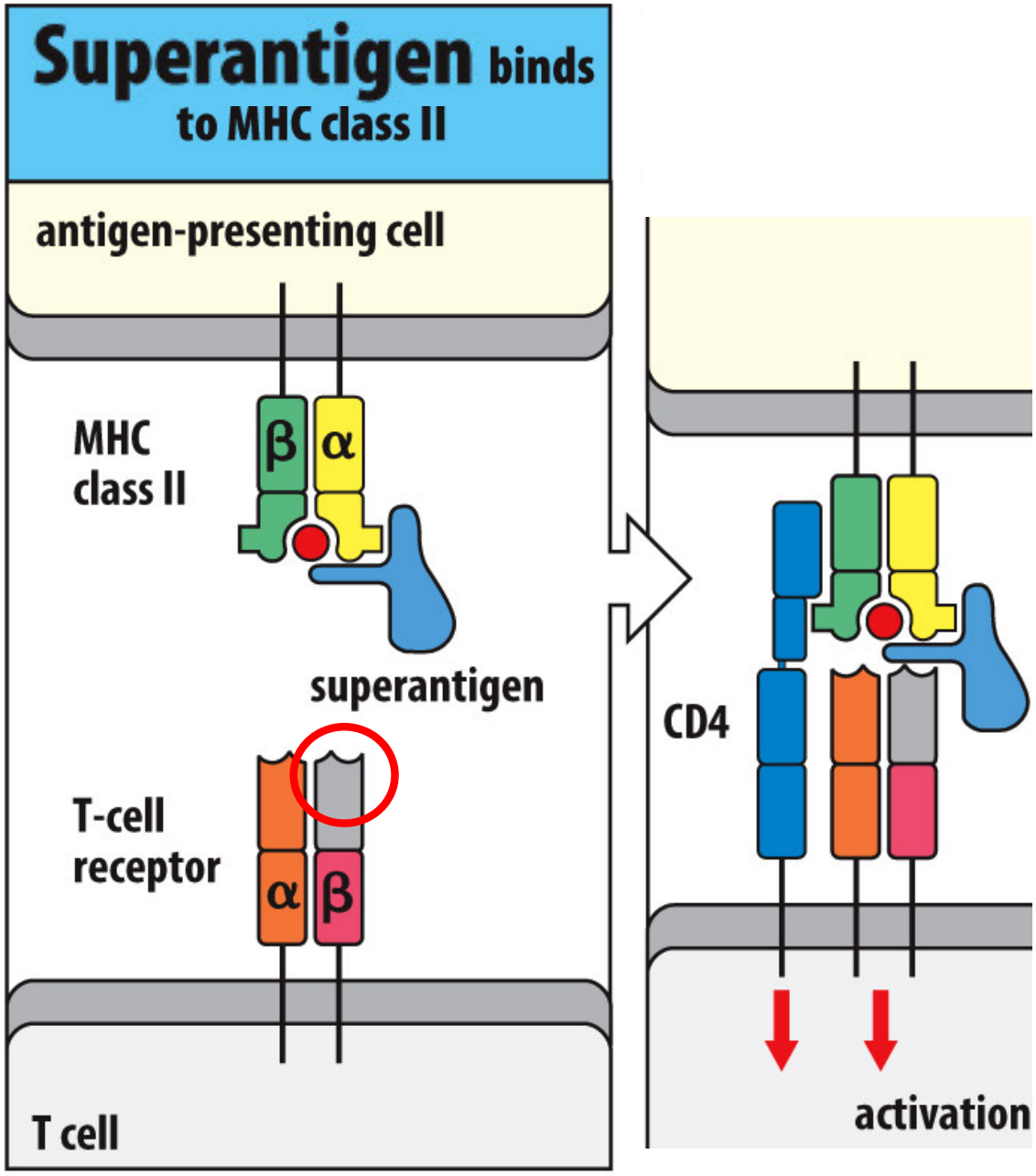
Figure 12.32 The Immune System, 4th ed. (© Garland Science 2015)

- They constitute 0.1-0.5% of circulating lymphocytes
- They express an invariant TCR: Vα24-Jα18/few Vβ
- They recognize lipids restricted by CD1d
- DN (CD4-, CD8-), co-express common markers to NK cells (CD56)
- They perform immunoregulatory functions (they enhance the effector response of B lymphocytes, NK cells and CTLs)

The 3 different routes of antigen presentation



Superantigens!



- They do not require processing
- They bind MHC II molecules: the binding site is outside the peptide pocket
- They cross-bind the hypervariable regions of Va of the TCR activating CD4 T cells
- They induce a massive production of cytokines

The responses they induce are more beneficial to pathogens than to the host