Antigen Processing And Presentation

by

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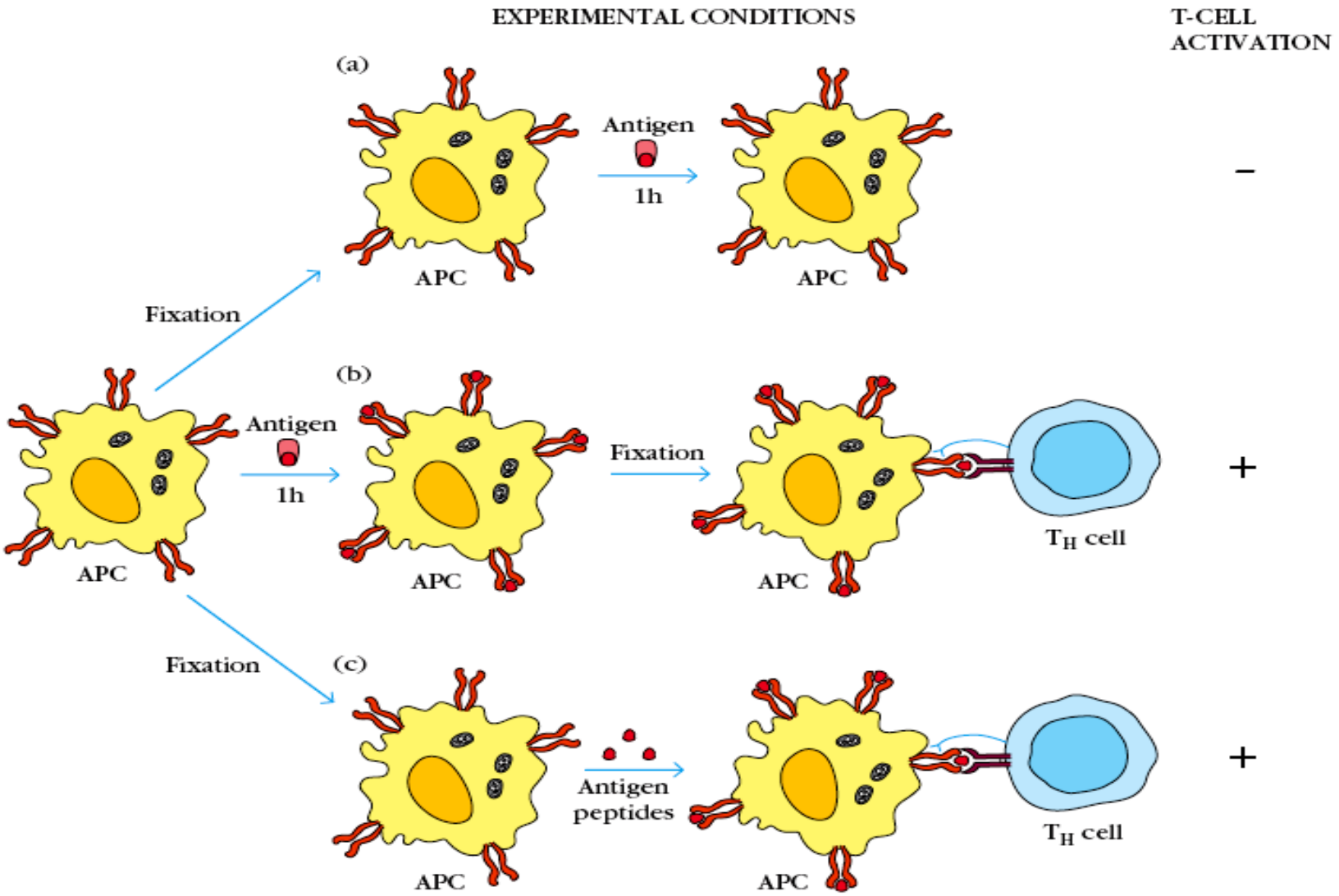
Comparison of Antigen Recognition by BCR and TCR

- B cells
  - Soluble or cell associated
    - Proteins (conformational and sequence determinants)
    - Polysaccharides
    - Nucleic acids
    - Some lipids
    - Small chemicals (haptens)
- T cells
  - Only fragments of proteins associated with MHC molecules on the surface of cells
    - Th cells recognize peptide associated with class II MHC
    - Tc recognize peptides associated with class I MHC



Experimental demonstration that antigen processing is necessary for T_H-cell activation. (a) When antigen-presenting cells (APCs) are fixed before exposure to antigen, they are unable to activate T_H cells. (b) In contrast, APCs fixed at least 1 h after antigen exposure can activate T_H cells. (c) When APCs are fixed before antigen exposure and incubated with peptide digests of the antigen (rather than native antigen), they also can activate T_H cells.

- **Recognition of foreign antigen protein by a T cell requires that peptides derived from the antigen be displayed within the cleft of an MHC molecule on the membrane of a cell.**

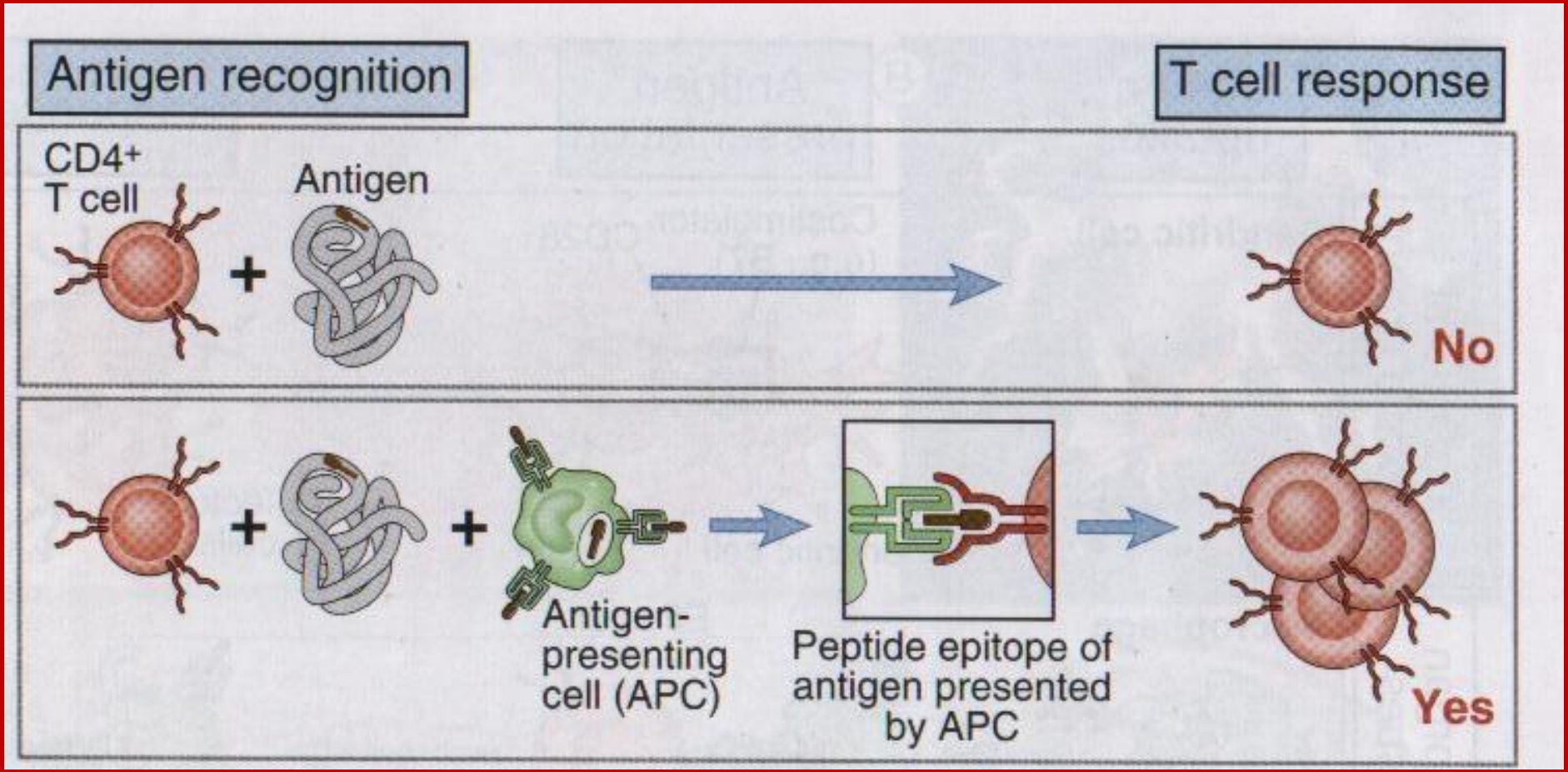
- **The formation of these peptide-MHC complexes requires that a protein antigen be degraded into peptides by a sequence of events called antigen processing.**

- **The degraded peptides then associate with MHC molecules within the cell interior, and the peptide-MHC complexes are transported to the membrane, where they are displayed (antigen presentation).**

- **Class I MHC molecules bind peptides derived from endogenous antigens that have been processed within the cytoplasm of the cell (e.g., normal cellular proteins, tumor proteins, or viral and bacterial proteins produced within infected cells).**

- **Class II MHC molecules bind peptides derived from exogenous antigens that are internalized by phagocytosis or endocytosis and processed within the endocytic pathway**

Discovery of antigen-presenting cells and their role in immune response



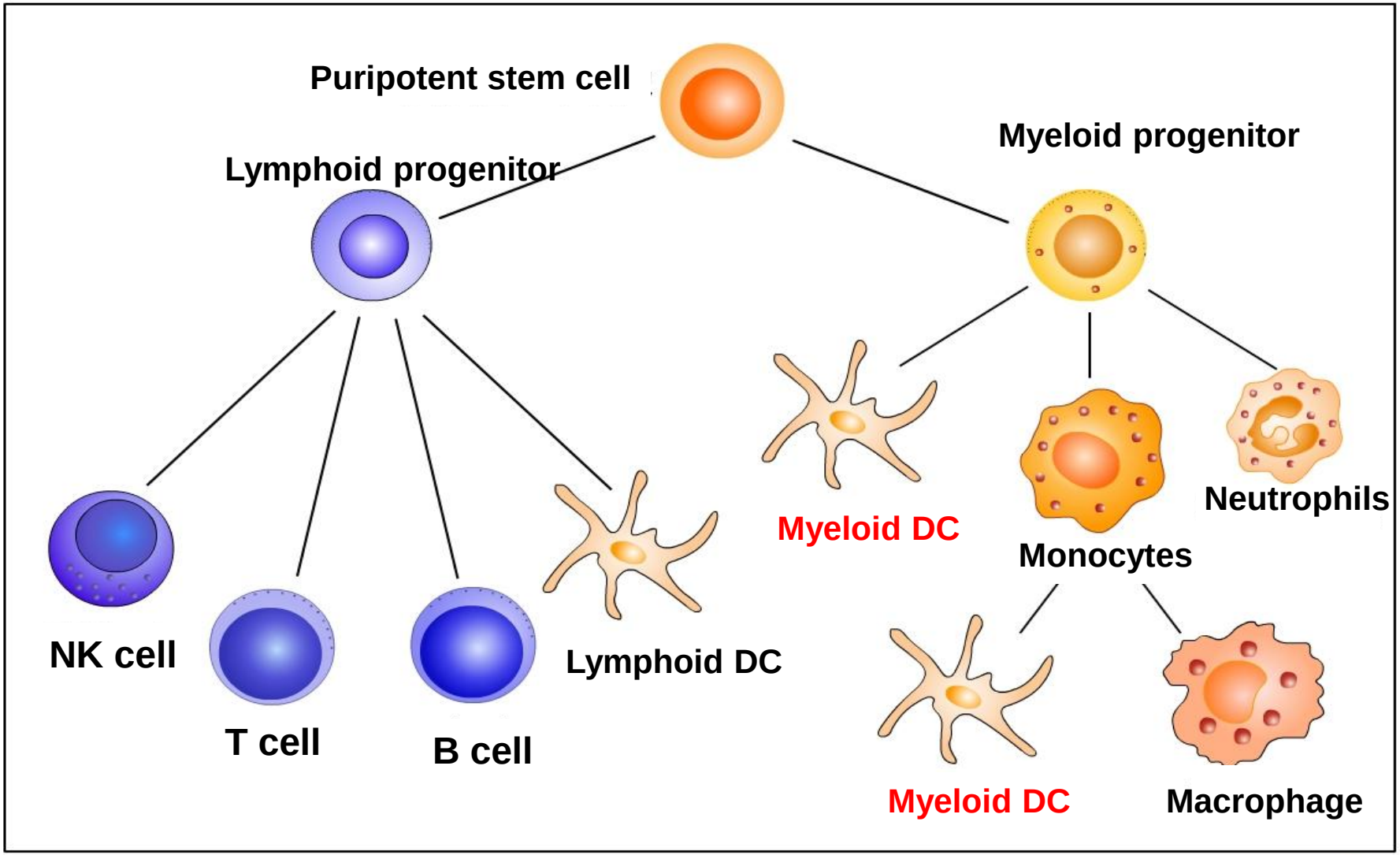
Points Concerning Antigen Processing and Presentation

- Peptides from both self and non-self proteins can associate with MHC class I and class II MHC molecules
  - T cells capable of recognizing self peptides are eliminated during development (Clonal Selection Postulate)
- Chemical nature of MHC groove determines which peptides will bind

Antigen Presenting Cells (APCs)

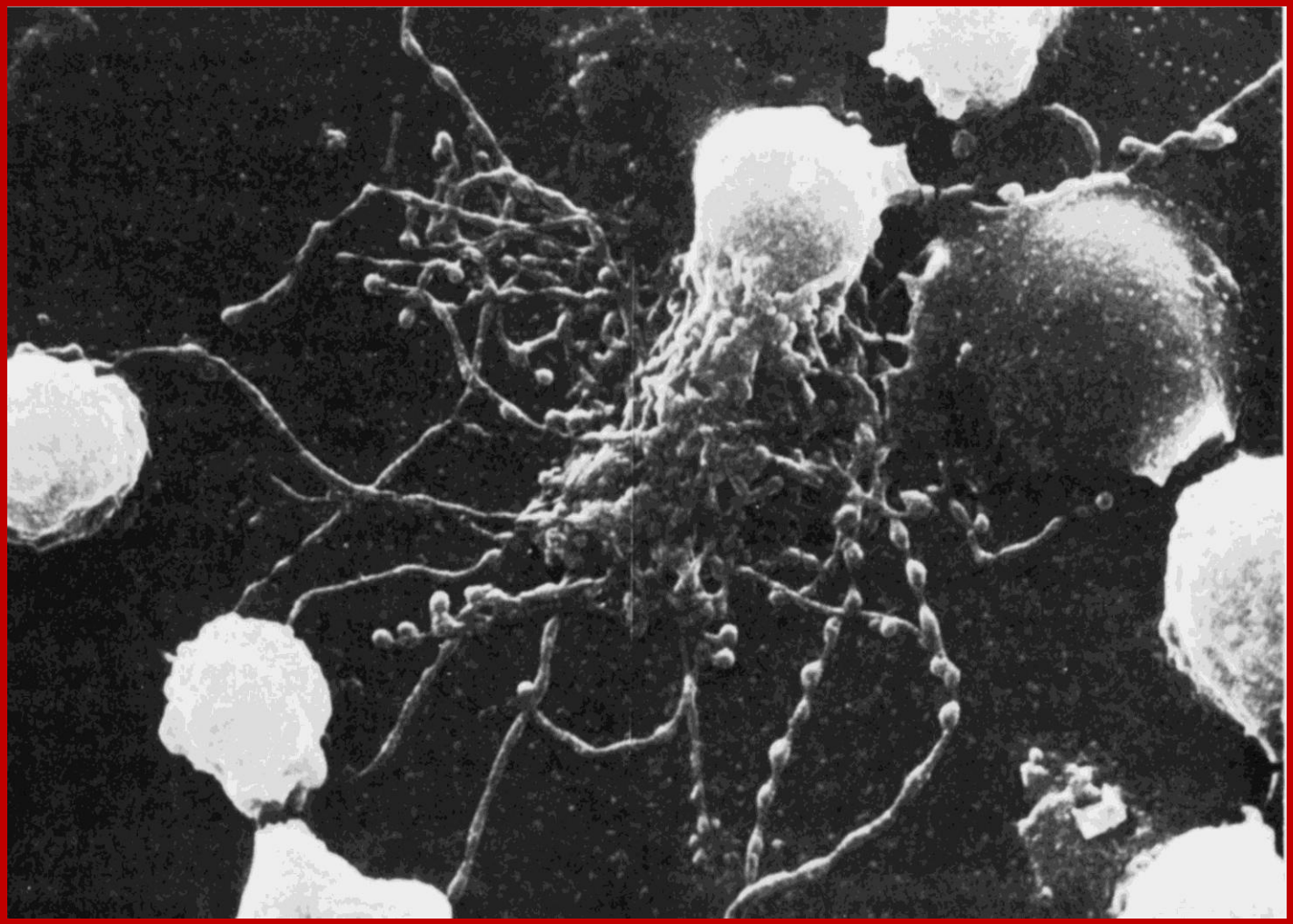
- Three main APC
  - Dendritic cells (DCs)
  - Macrophages
  - B cells

(2) Origin and distribution



Dendritic cells are derived from different lineages

Interdigitating DC (IDC)



IDC express high levels of MHC molecules, and are more potent antigen-presenting cells than others

Antigen Presenting Cells - Macrophages

- Ingest antigens by phagocytosis
- Not as effective as DCs in activating “naïve” T cells
- Effective in activating memory T cells

Antigen Presenting Cells - B cells

- Bind antigen by surface Ig
- Ingest antigens by endocytosis
- Not as effective as DCs in activating “naïve” T cells
- Effective in activating memory T cells
- Very effective APCs when antigen concentration are low

Self-MHC Restriction of T Cells

- **Both CD4 and CD8 T cells can recognize antigen only when it is presented by a self-MHC molecule, an attribute called *self-MHC restriction*.**

- ***Beginning in the mid-1970s, experiments* conducted by a number of researchers demonstrated self-MHC restriction in T-cell recognition.**

- **A. Rosenthal and E.Shevach, for example, showed that the CD4 T_H cell is activated and proliferates only in the presence of antigen-pulsed macrophages that share class II MHC alleles.**

- **Thus, antigen recognition by the CD4 Th cell is *class II MHC restricted*.**

- **In 1974 *R. Zinkernagel and P. Doherty* demonstrated the self-MHC restriction of CD8 Tc cells.**

- **They showed that the Tc cell and the virus-infected target cell must share class I molecules encoded by the K or D regions of the MHC.**

- **Thus, antigen recognition by CD8 T_C cells is *class I MHC restricted. In 1996, Doherty and Zinkernagel were awarded* the Nobel prize for their major contribution to the understanding of cell-mediated immunity.**

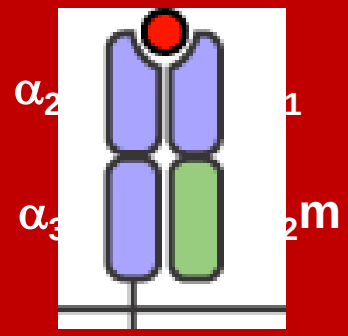
Antigen Processing and Presentation

- **Cytosolic (endogenous) pathway**
- **Endocytic (exogenous) pathway**

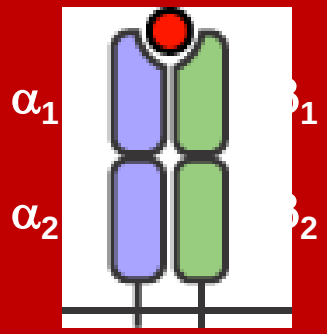
Ag processing: degradation of proteins into peptides

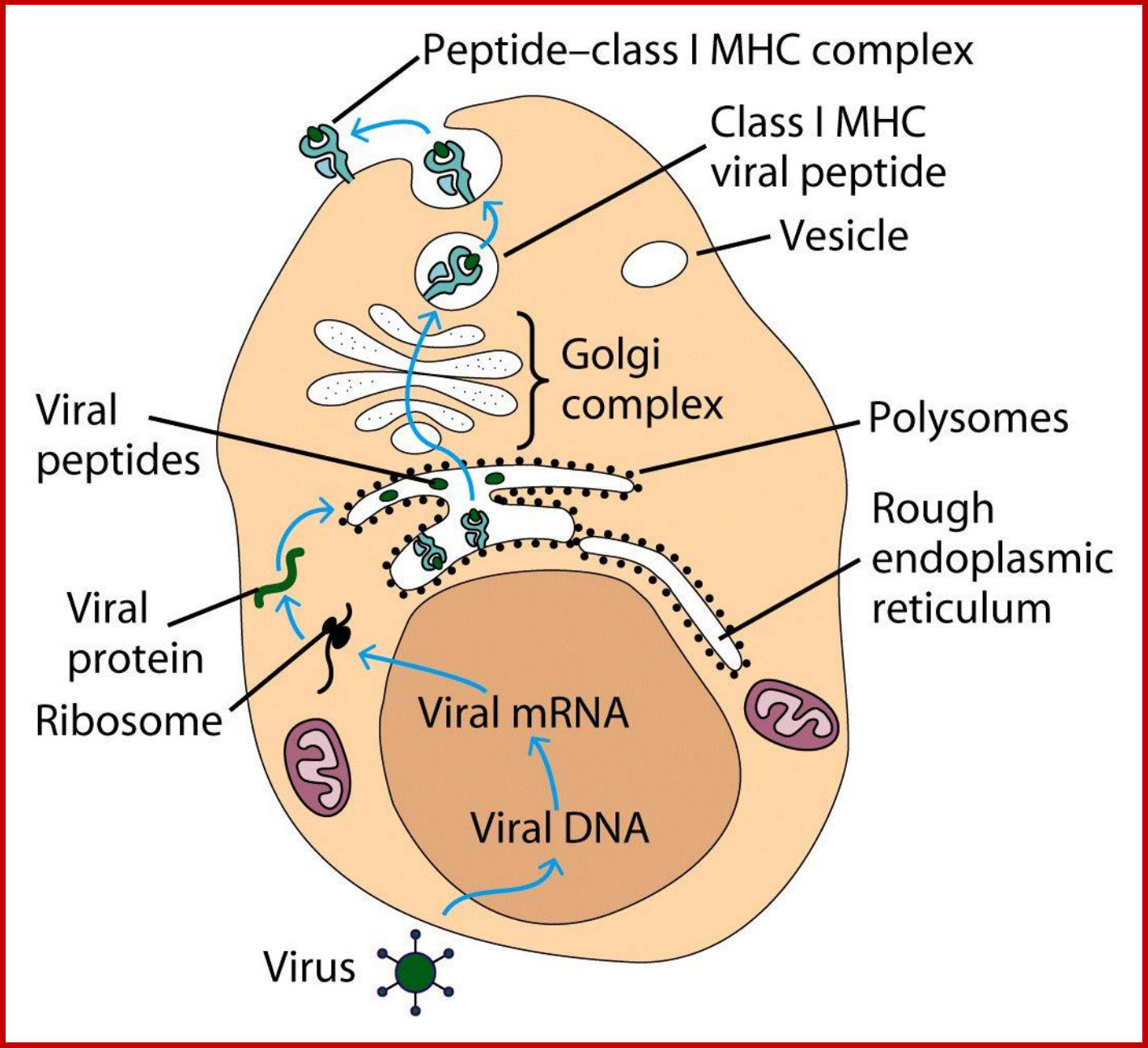
Ag presentation: binding of peptide by MHC molecule and displaying the complex on the cell surface

Class I

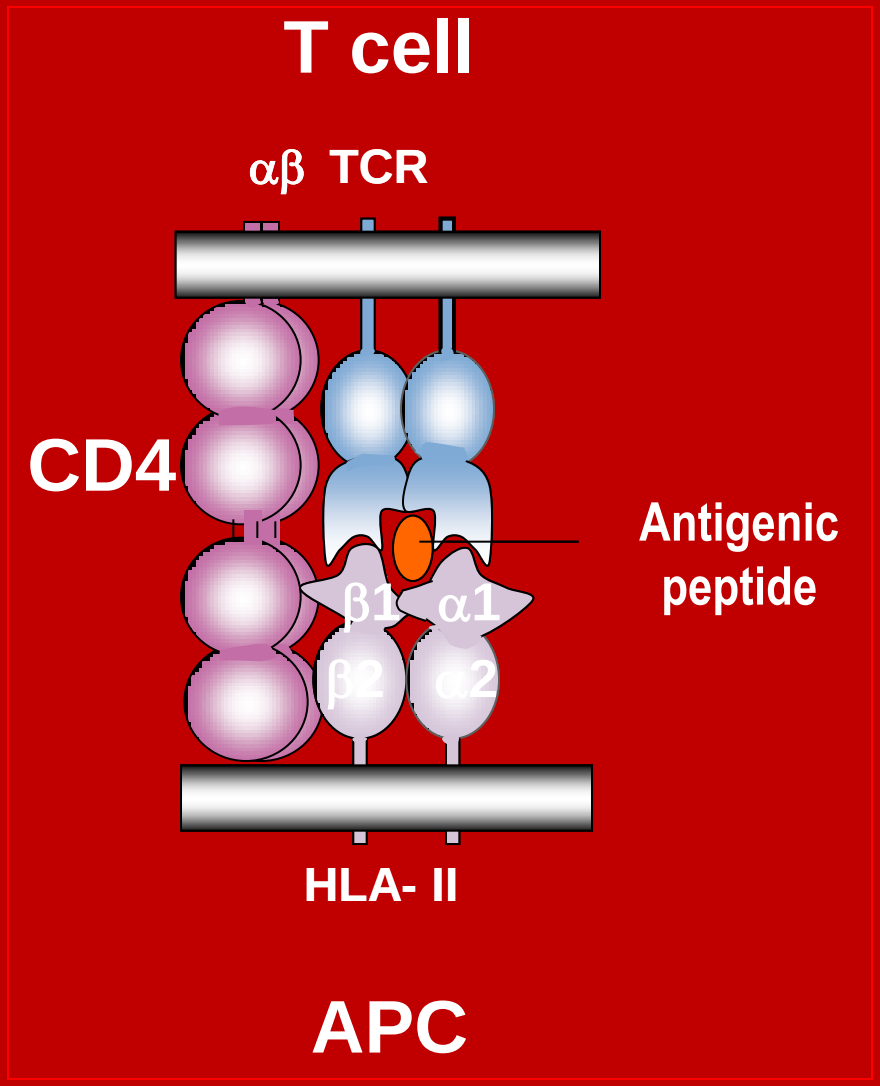


Class II

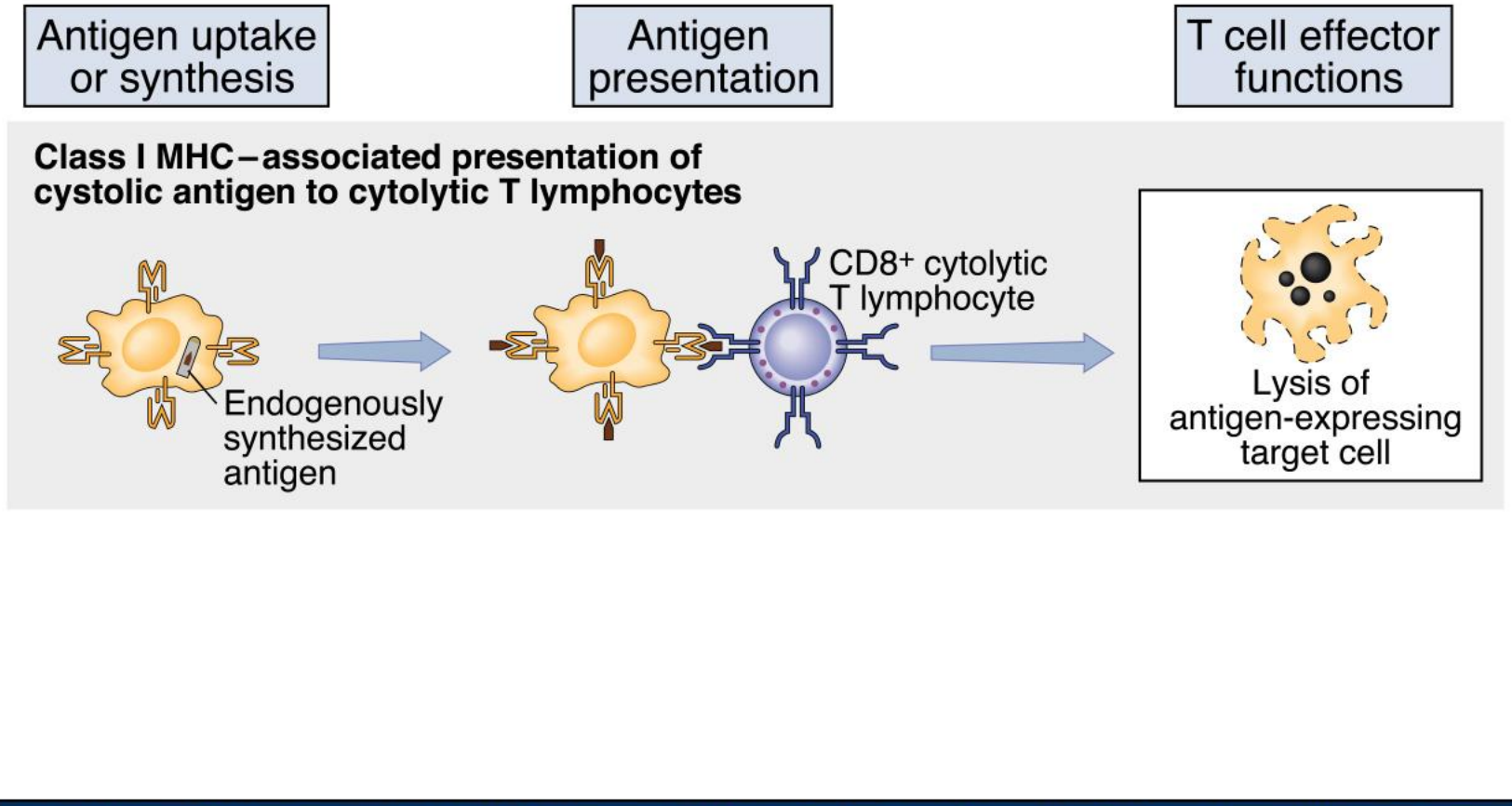



Peptide–class I MHC complex
Class I MHC viral peptide
Vesicle
Golgi complex
Viral peptides
Polysomes
Rough endoplasmic reticulum
Viral protein
Ribosome
Viral mRNA
Viral DNA
Virus

Presentation of protein antigens to $CD4^+$ T lymphocytes



Physiologic significance of class I-associated antigen presentation

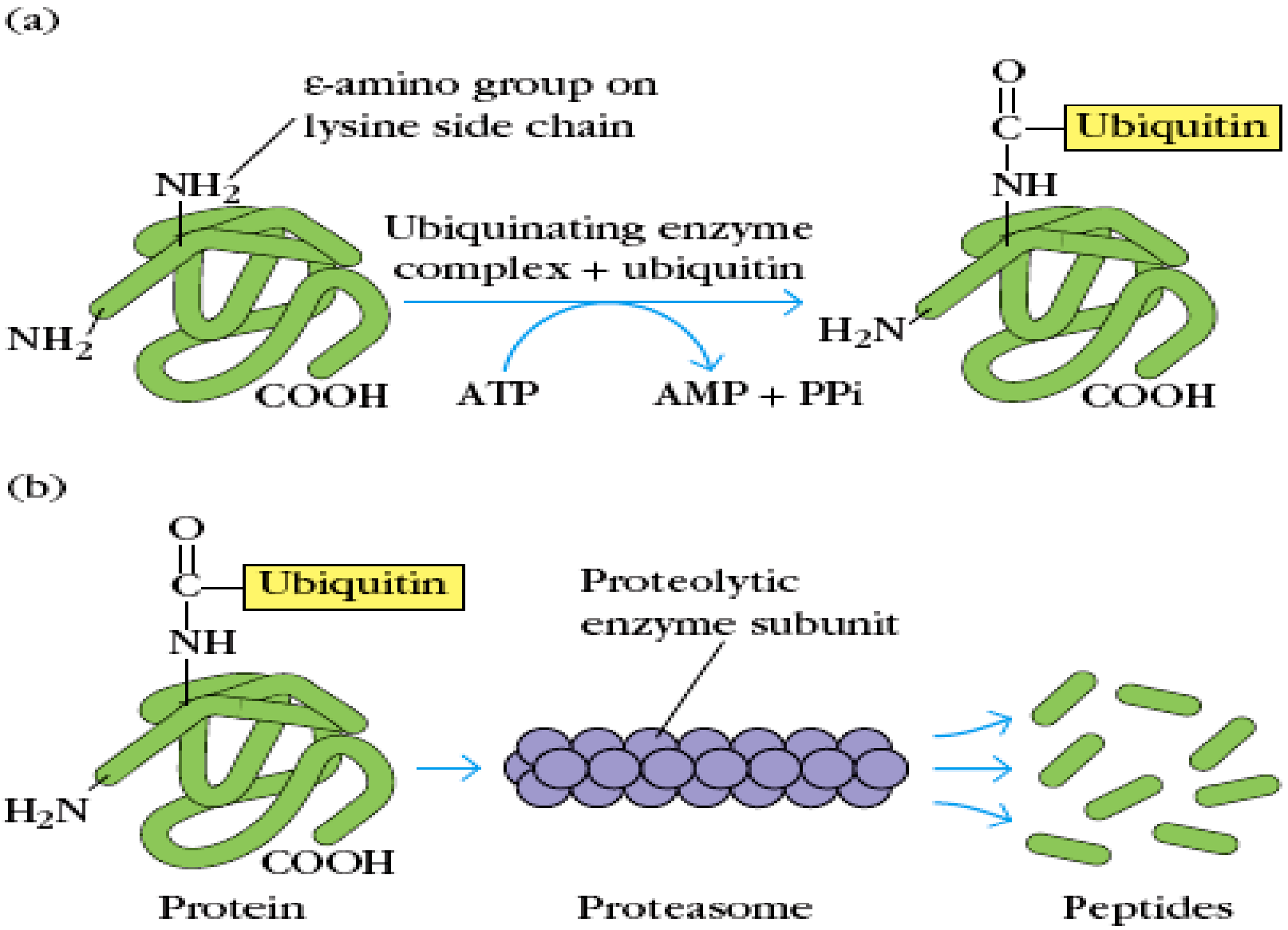


From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 5-14b

Endogenous Antigens:The Cytosolic Pathway

Peptides for Presentation Are Generated by Protease Complexes Called Proteasomes:

- **Intracellular proteins are degraded into short peptides by a cytosolic proteolytic system present in all cells. Those proteins targeted for proteolysis often have a small protein, called *ubiquitin,* attached to them .**
- ***Ubiquitin-protein* conjugates can be degraded by a multifunctional protease complex called a proteasome.**
- **Each proteasome is a large (26S), cylindrical particle consisting of four rings of protein subunits with a central channel of diameter 10–50 Å.**
- **A proteasome can cleave peptide bonds between 2 or 3 different amino acid combinations in an ATP-dependent process.**



Cytosolic proteolytic system for degradation of intracellular proteins. (a) Proteins to be degraded are often covalently linked to a small protein called ubiquitin. (b) Degradation of ubiquitin-protein complexes occurs within the central channel of proteasomes, generating a variety of peptides.

Peptides Are Transported from the Cytosol to the Rough Endoplasmic Reticulum:

- **Intracellular proteins are degraded into short peptides by a cytosolic proteolytic system present in all cells.**

- **Those proteins targeted for proteolysis often have a small protein, called *ubiquitin*, attached to them . *Ubiquitin-protein* conjugates can be degraded by a multifunctional protease complex called a proteasome.**

- **Each proteasome is a large (26S), cylindrical particle consisting of four rings of protein subunits with a central channel of diameter 10–50 Å. A proteasome can cleave peptide bonds between 2 or 3 different amino acid combinations in an ATP-dependent process.**

- **The transporter protein, designated TAP (for transporter associated with antigen processing) is a membrane-spanning heterodimer consisting of two proteins: TAP1 and TAP2 .**

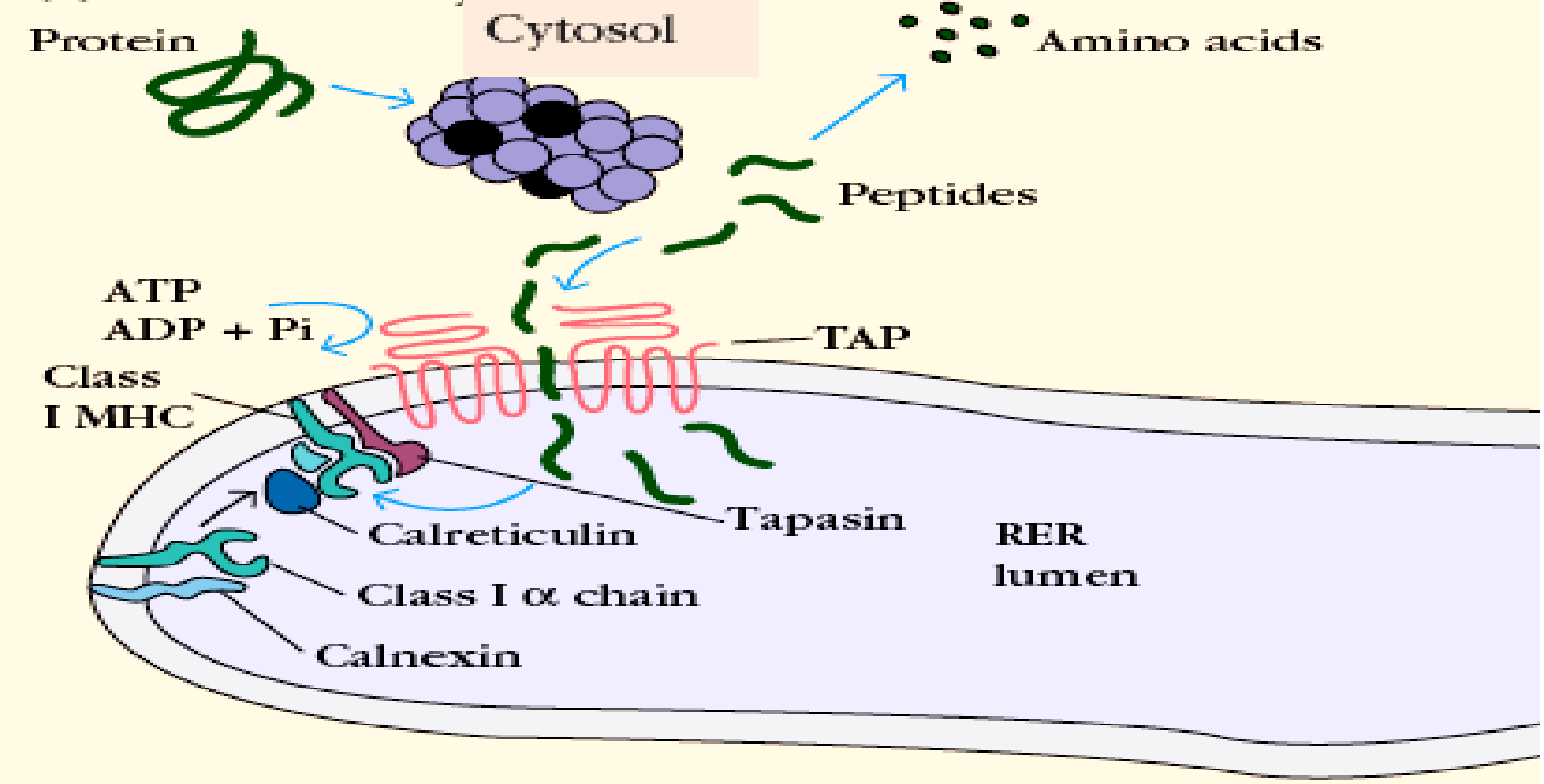
- **In addition to their multiple transmembrane segments, the TAP1 and TAP2 proteins each have a domain projecting into the lumen of the RER, and an ATP-binding domain that projects into the cytosol.**

- **Both TAP1 and TAP2 belong to the family of ATP-binding cassette proteins found in the membranes of many cells, including bacteria; these proteins mediate ATP-dependent transport of amino acids, sugars, ions, and peptides.**

- **Peptides generated in the cytosol by the proteasome are translocated by TAP into the RER by a process that requires the hydrolysis of ATP .**

- **TAP has the highest affinity for peptides containing 8–10 amino acids, which is the optimal peptide length for class I MHC binding.**

- **In addition, TAP appears to favor peptides with hydrophobic or basic carboxyl-terminal amino acids, the preferred residues for class I MHC molecules. Thus, TAP is optimized to transport peptides that will interact with class I MHC molecules.**



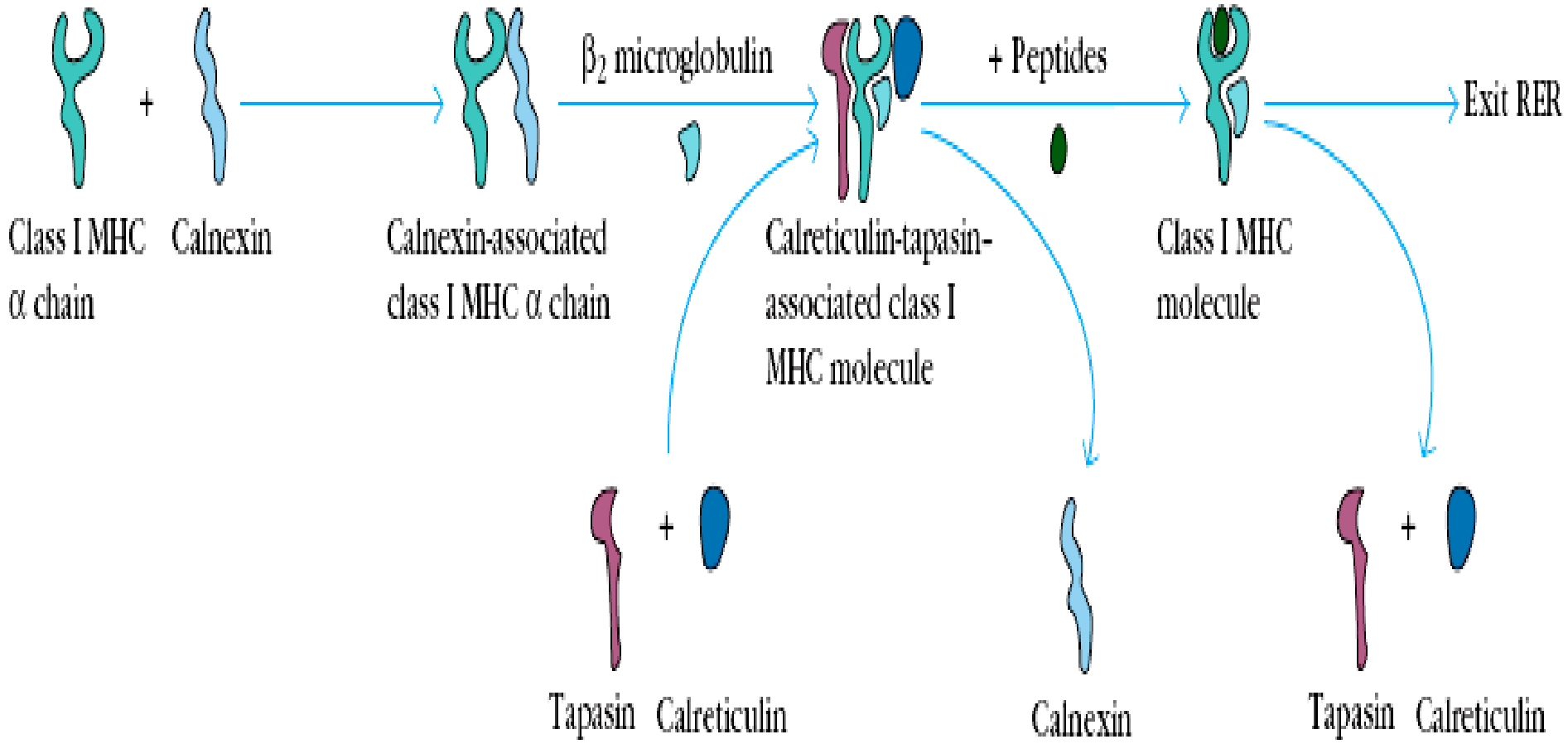
In the cytosol, association of LMP2, LMP7, and LMP10 (black spheres) with a proteasome changes its catalytic specificity to favor production of peptides that bind to class I MHC molecules. Within the RER membrane, a newly synthesized class Iα chain associates with calnexin until β-microglobulin binds to the chain. The class Iα chain/β_2-microglobulin heterodimer then binds to calreticulin and the TAP-associated protein tapasin. When a peptide delivered by TAP is bound to the class I molecule, folding of MHC class I is complete and it is released from the RER and transported through the Golgi to the surface of the cell.

Peptides Assemble with Class I MHC Aided by Chaperone Molecules:

- **The first molecular chaperone involved in class I MHC assembly is *calnexin, a* resident membrane protein of the endoplasmic reticulum.**

- **Calnexin associates with the free class I chain and promotes its folding. When β_2-microglobulin binds to the chain, calnexin is released and the class I molecule associates with the chaperone *calreticulin and with tapasin.***

- **Tapasin (TAP-associated protein) brings the TAP transporter into proximity with the class I molecule and allows it to acquire an antigenic peptide .**



Newly formed class I chains associate with calnexin, a molecular chaperone, in the RER membrane. Subsequent binding to β_2-microglobulin releases calnexin and allows binding to the chaperonin calreticulin and to tapasin, which is associated with the peptide transporter TAP. This association promotes binding of an antigenic peptide, which stabilizes the class I molecule–peptide complex, allowing its release from the RER.

Exogenous Antigens: The Endocytic Pathway

Peptides Are Generated from Internalized Molecules in Endocytic Vesicles:

- **Once an antigen is internalized, it is degraded into peptides within compartments of the endocytic processing pathway.**

- **The endocytic pathway appears to involve three increasingly acidic compartments: early endosomes (pH 6.0–6.5); late endosomes, or endolysosomes (pH 5.0–6.0); and lysosomes (pH 4.5–5.0).**

- **Internalized antigen moves from early to late endosomes and finally to lysosomes, encountering hydrolytic enzymes and a lower pH in each compartment.**

- **Lysosomes, for example, contain a unique collection of more than 40 acid-dependent hydrolases, including proteases, nucleases, glycosidases, lipases, phospholipases, and phosphatases.**

- **Within the compartments of the endocytic pathway, antigen is degraded into oligopeptides of about 13–18 residues, which bind to class II MHC molecules**

The Invariant Chain Guides Transport of Class II MHC Molecules to Endocytic Vesicles:

- **When class II MHC molecule are synthesized within the RER, three pairs of class II chains associate with a preassembled trimer of a protein called invariant chain (Ii, CD74).**

- **This trimeric protein interacts with the peptide-binding cleft of the class II molecules, preventing any endogenously derived peptides from binding to the cleft while the class II molecule is within the RER.**

Peptides Assemble with Class II MHC Molecules by Displacing CLIP:

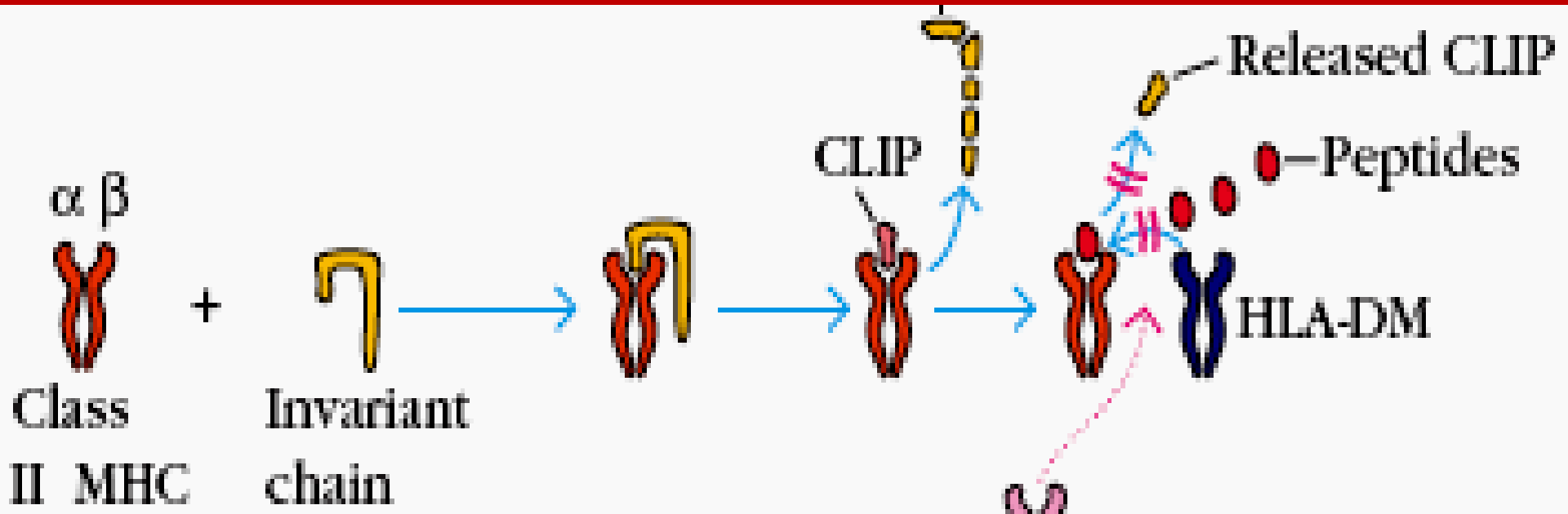
- **Recent experiments indicate that most class II MHC–invariant chain complexes are transported from the RER, where they are formed, through the Golgi complex and trans-Golgi network, and then through the endocytic pathway, moving from early endosomes to late endosomes, and finally to lysosomes.**

- **As the proteolytic activity increases in each successive compartment, the invariant chain is gradually degraded.**

- **However, a short fragment of the invariant chain termed *CLIP (for class II–associated invariant chain peptide) remains* bound to the class II molecule after the invariant chain has been cleaved within the endosomal compartment.**

- **A non-classical class II MHC molecule called *HLA-DM is* required to catalyze the exchange of CLIP with antigenic peptides .**

- **Like other class II MHC molecules, HLA-DM is a heterodimer of α and β chains. HLA-DM is not expressed at the cell membrane but is found predominantly within the endosomal compartment.**



Presentation of Nonpeptide Antigens

- **It is well known that nonprotein antigens also are recognized by the immune system.**
- **More recent reports indicate that T cells express TCR that react with glycolipid antigens derived from bacteria such as *Mycobacterium tuberculosis.***
- **These non-protein antigens are presented by members of the CD1 family of non-classical class I molecules.**

Acknowledgements

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