Antigen Processing and Presentation

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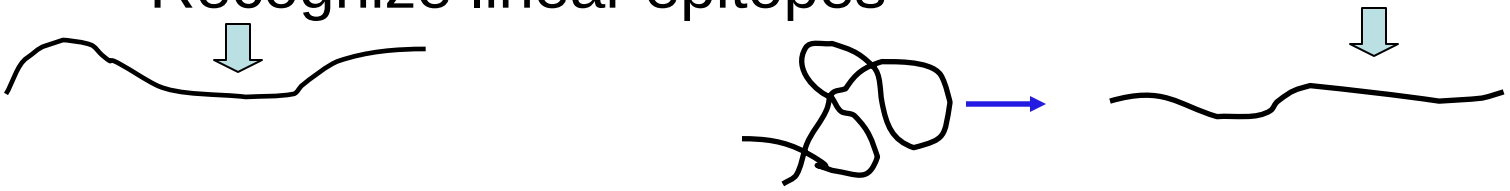
Antigen Recognition: how does the adaptive immune system “see” antigen?

- B cells:
  - Antibody on B cells or free antibody can recognize intact antigen (i.e. soluble antigens, and cell surface antigens).
  - Proteins, nucleic acids, polysaccharides, lipids, and small molecules are antigenic for B cells.
  - Can recognize conformational or linear epitopes.

- T cells:
  - Recognize protein antigens
  - Recognize linear epitopes



  - Recognize antigen only when it is bound to MHC

- $CD8^+$ cytotoxic cells "see" antigen complexed to MHC Class I and respond by killing the infected cell

- CD4+ helper cells "see" antigen complexed to MHC Class II and respond by proliferation and production of cytokines

Table 5–2. Differences in Antigen Recognition by T and B Lymphocytes

Primary immunization	Secondary antigen challenge	Secondary immune response	
		B cell response (Antibody production)	T cell response (Delayed-type hypersensitivity)
Native protein	Native protein	+	+
Denatured protein	Native protein	−	+
Native protein	Denatured protein	−	+
Denatured protein	Denatured protein	+	+

In an animal immunized with a protein antigen, B cells are specific for conformational determinants of the antigen and therefore distinguish between native and denatured antigens. In contrast, T cells do not distinguish between native and denatured antigens because T cells recognize linear epitopes on peptides derived from the native antigens.

T Cells do not Respond to “Free” Antigen

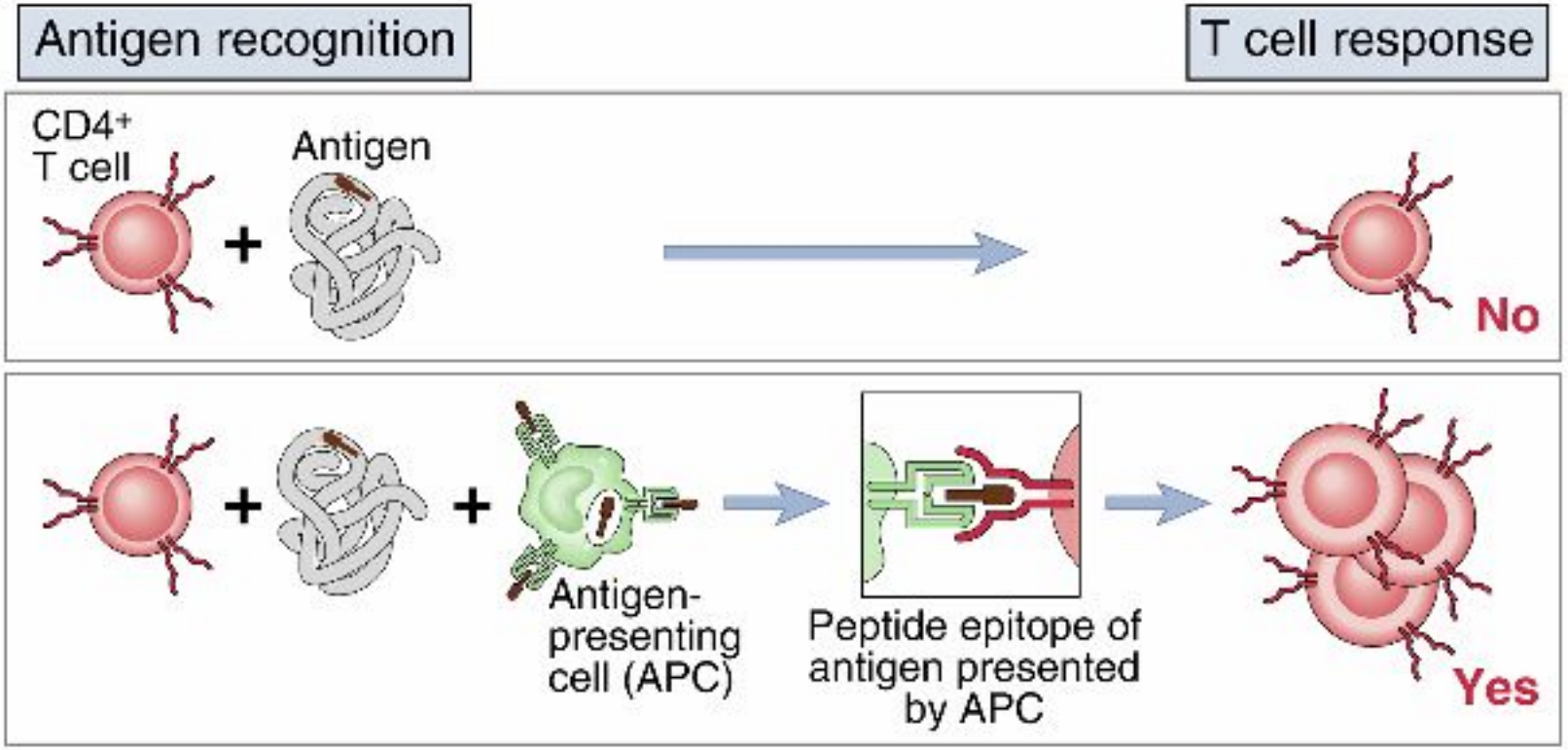


Fig. 5-2

MHC Restriction

APC must express MHC molecules recognized as self in order for the T cell to recognize and respond to a foreign protein antigen.

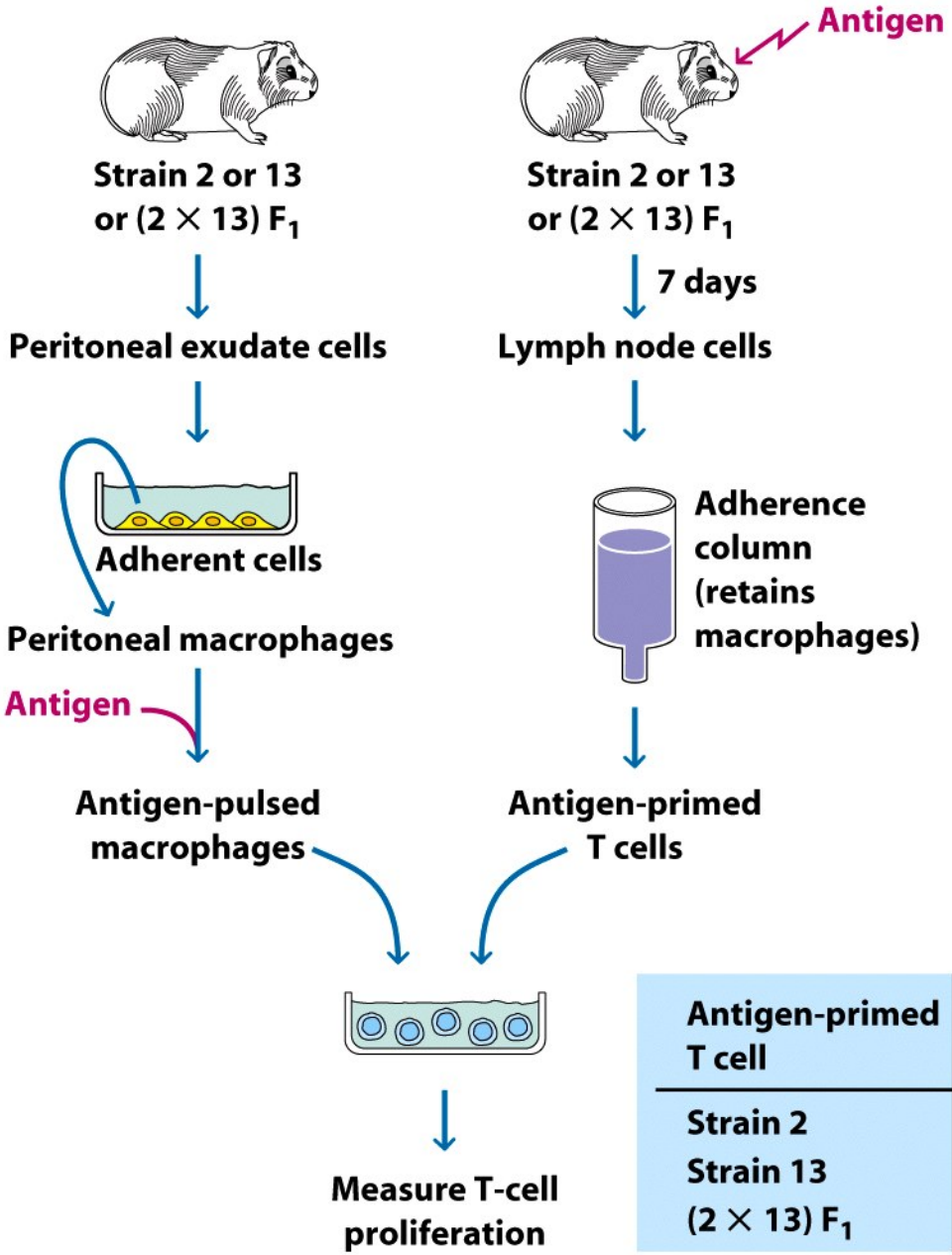
"Self" MHC are those MHC antigens that the T cell encountered during development in the thymus.

Both $CD4^+$ and $CD8^+$ cells show MHC restriction:

$CD4^+$ cells are restricted by MHC class II antigens

$CD8^+$ cells are restricted by MHC class I antigens

MHC Restriction of Th cells



Antigen-primed T cell	Antigen-pulsed macrophages		
	Strain 2	Strain 13	(2 × 13) F_1
Strain 2	+	−	+
Strain 13	−	+	+
(2 × 13) F_1	+	+	+

Figure 8-14
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MHC Restriction of $CD8^+$ CTL

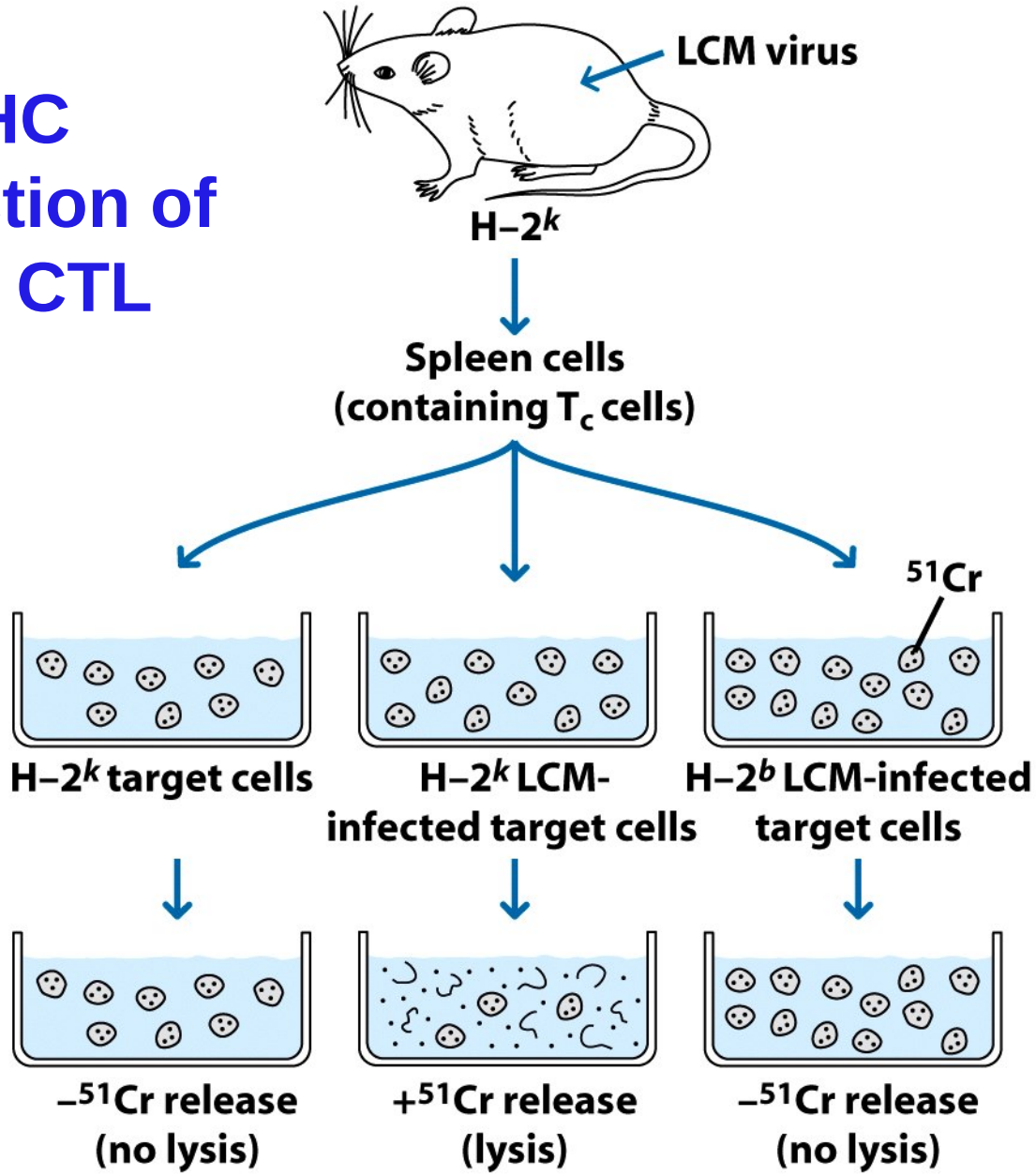

Figure 8-15
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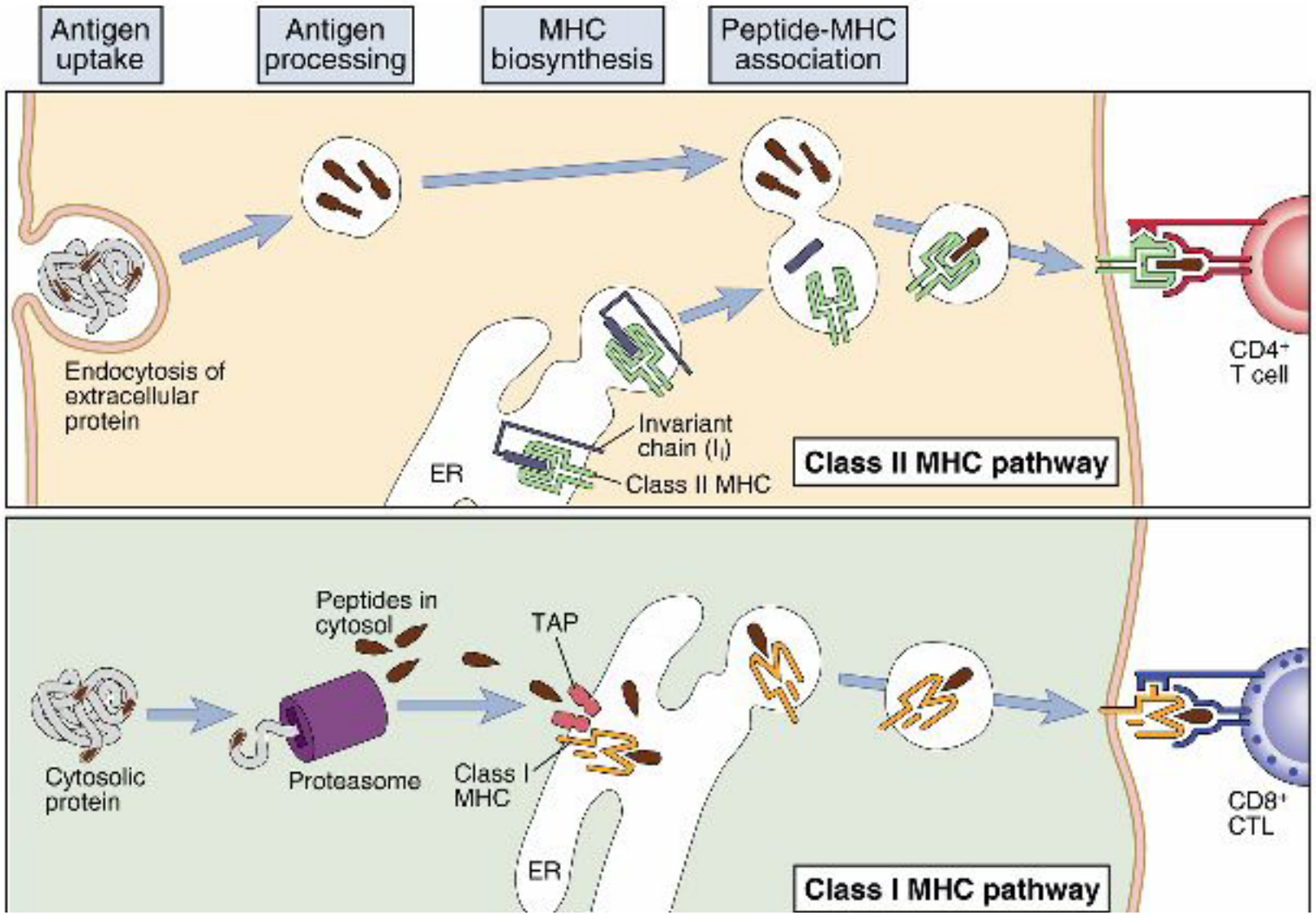
Nobel prize:
Zinkernagel and Doughtery

Two Pathways for Antigen Processing and Presentation:



CD4 Cells Recognize Exogenous Antigens

- **Exogenous** antigens are taken up by **antigen presenting cells (APC)**
- These antigens are processed and presented with **MHC Class II**
- The **$CD4^+$ T cells** respond with proliferation and cytokine production

“Professional”Antigen Presenting Cells

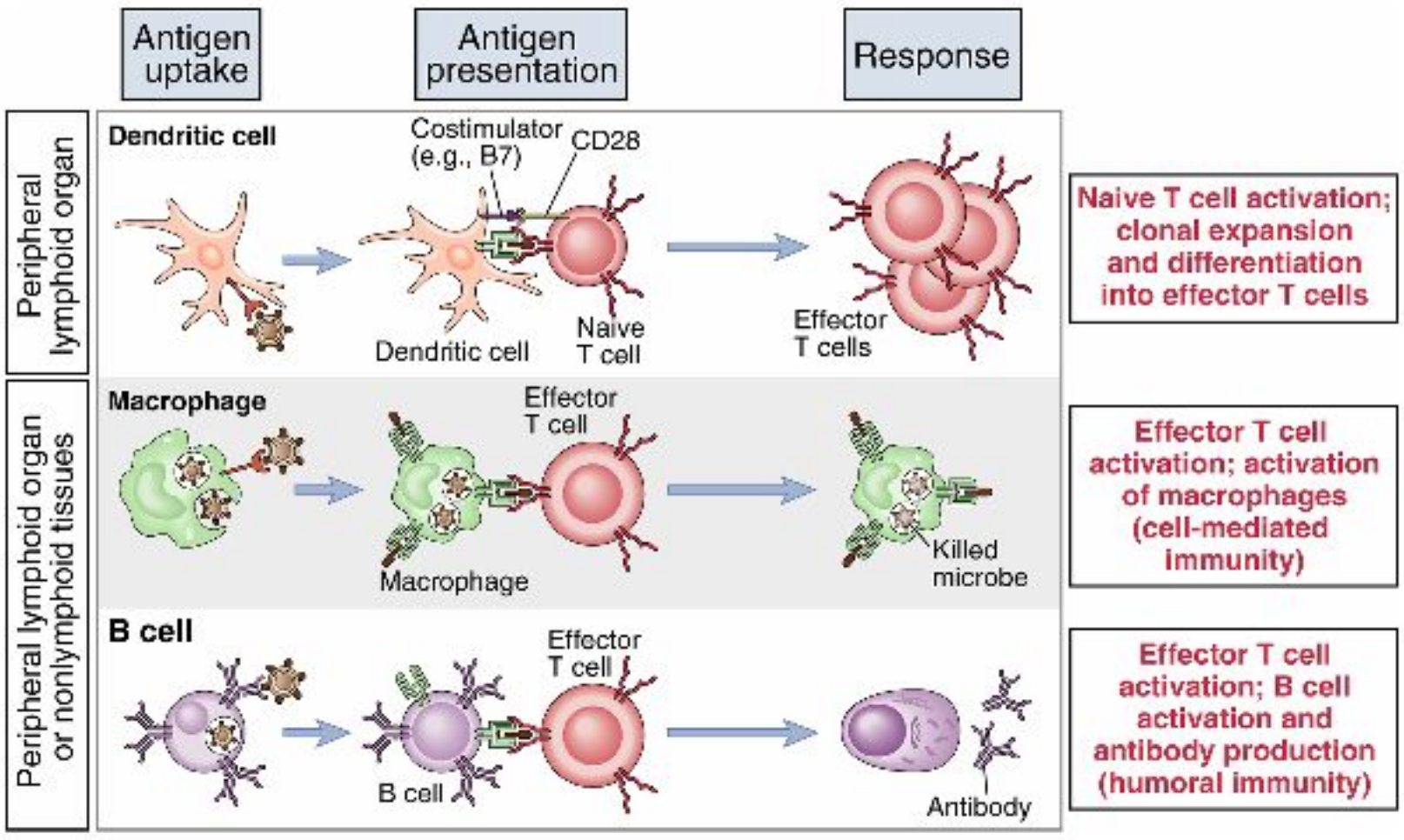
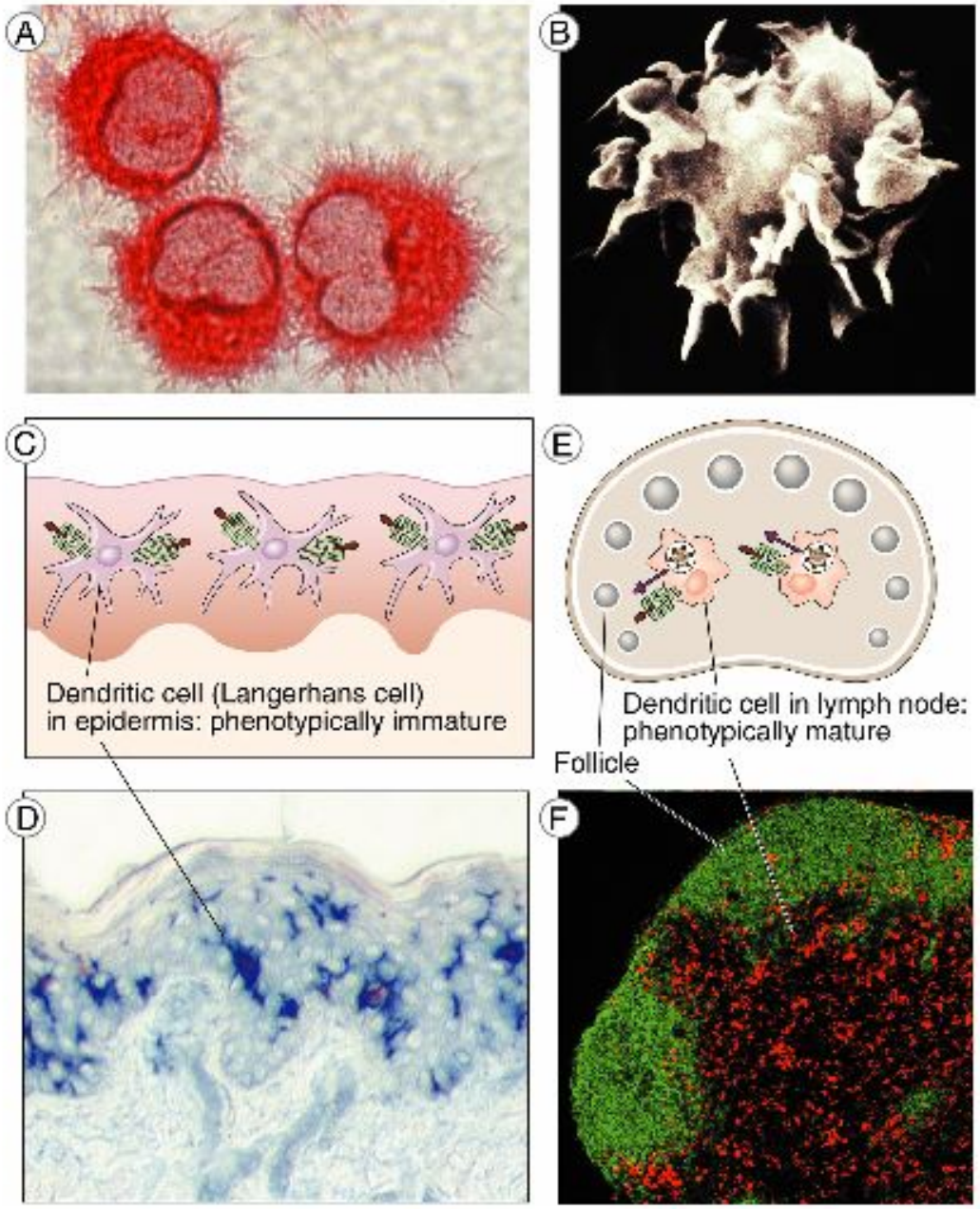


Fig. 5-3

Dendritic Cells: Professional APC



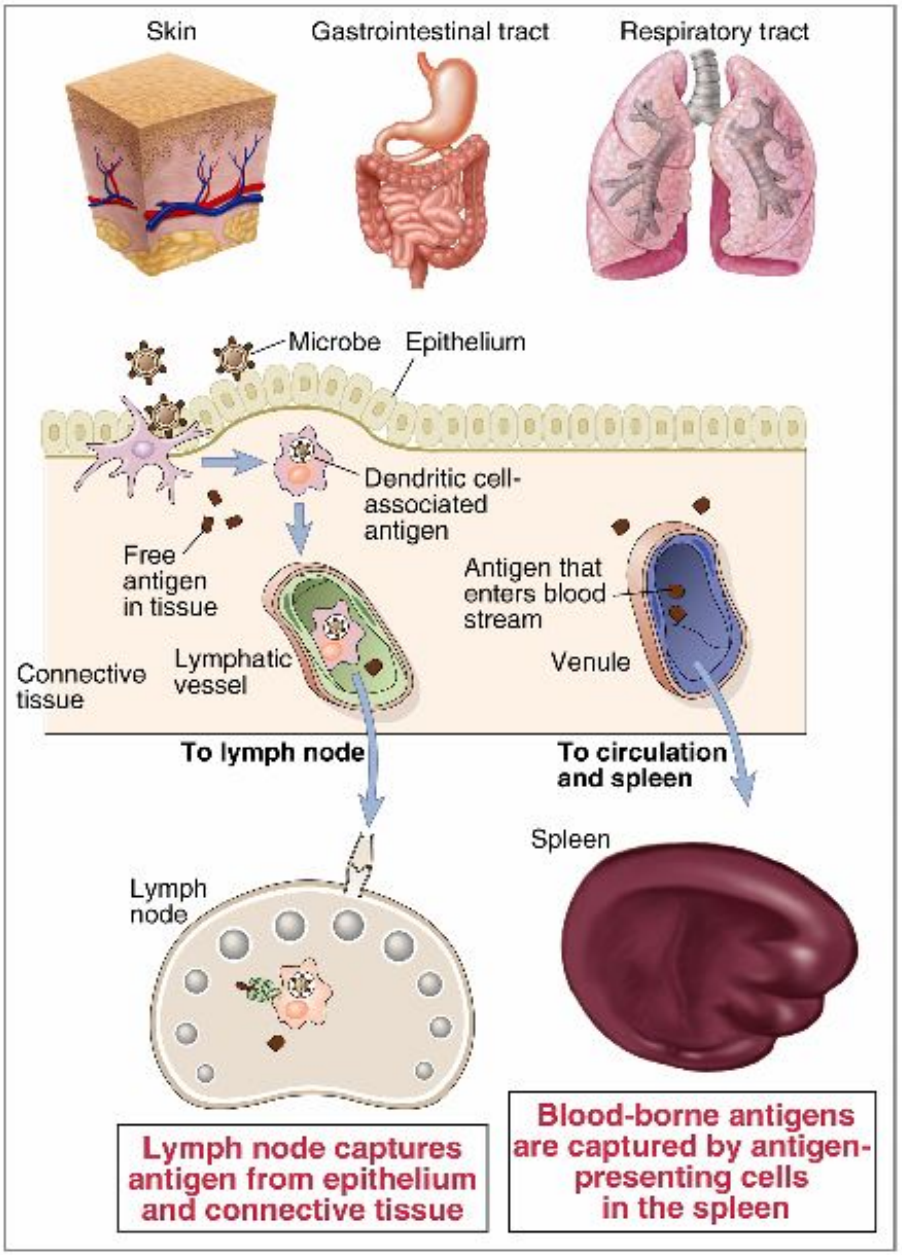
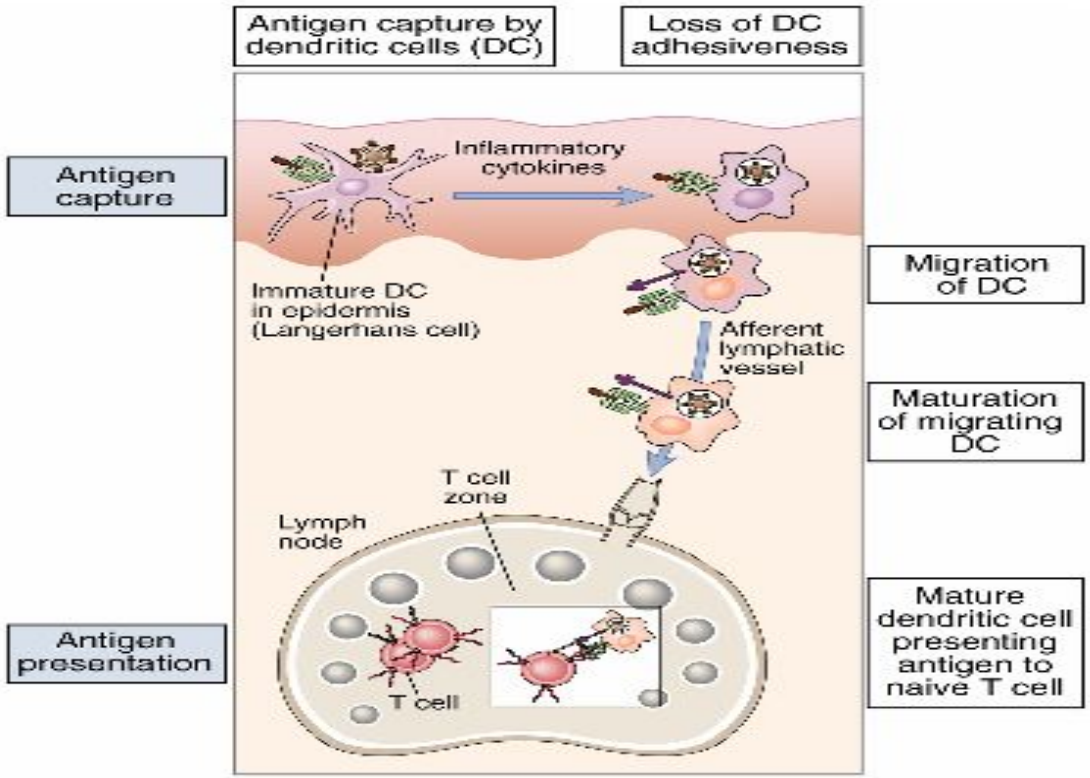


Fig 5-5



	Immature dendritic cell	Mature dendritic cell
Principal function	Antigen capture	Antigen presentation to T cells
Expression of Fc receptors, mannose receptors	++	—
Expression of molecules involved in T cell activation: B7, ICAM-1, IL-12	— or low	++
Class II MHC molecules		
Half-life on surface	~10 hr	>100 hr
Number of surface molecules	~10^5	~7×10^6

Fig 5-6

DC vs. B Cells as APC

- **DC** efficiently deliver both signals needed to activate T cells. They are the most efficient APC to function in the **primary immune response**.
- **B cells** that are specific for a given Ag are rare in primary response, but dramatically expand in secondary response. They are therefore efficient as APC in the **secondary response**

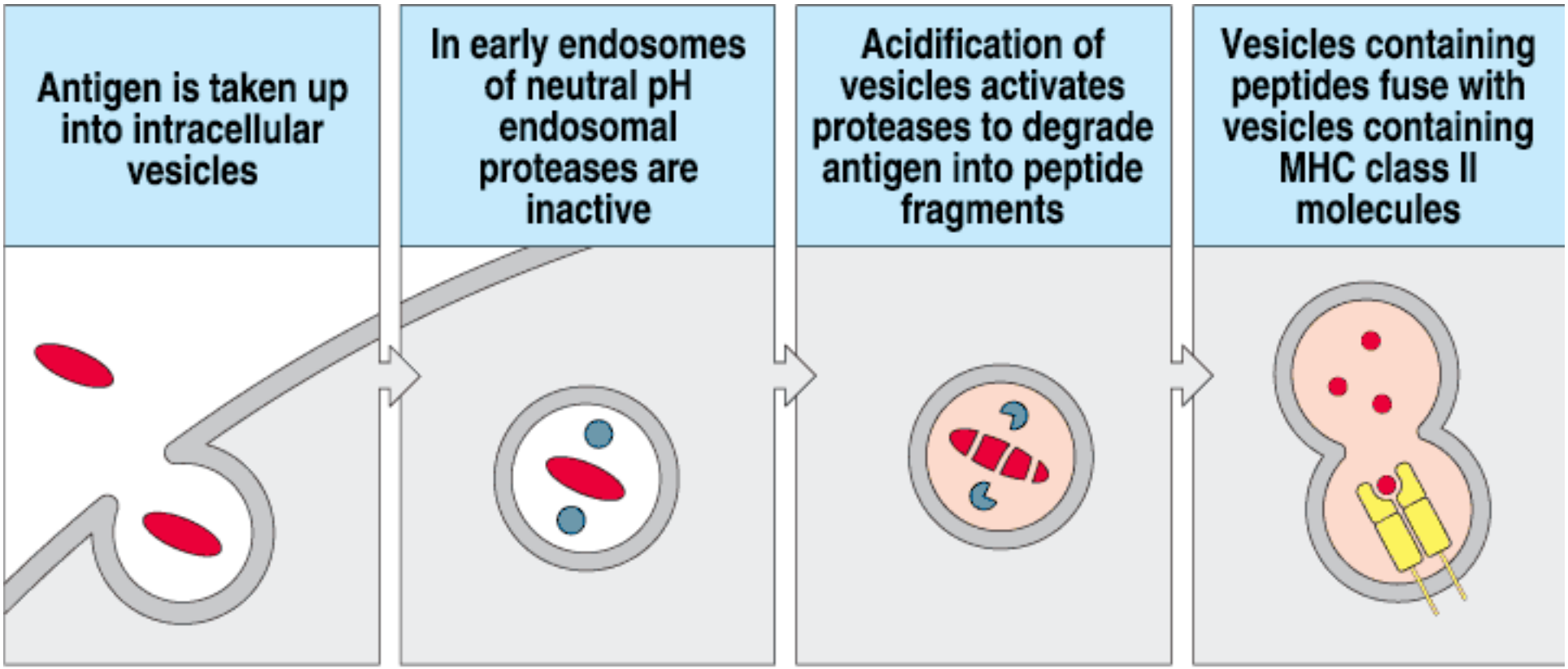
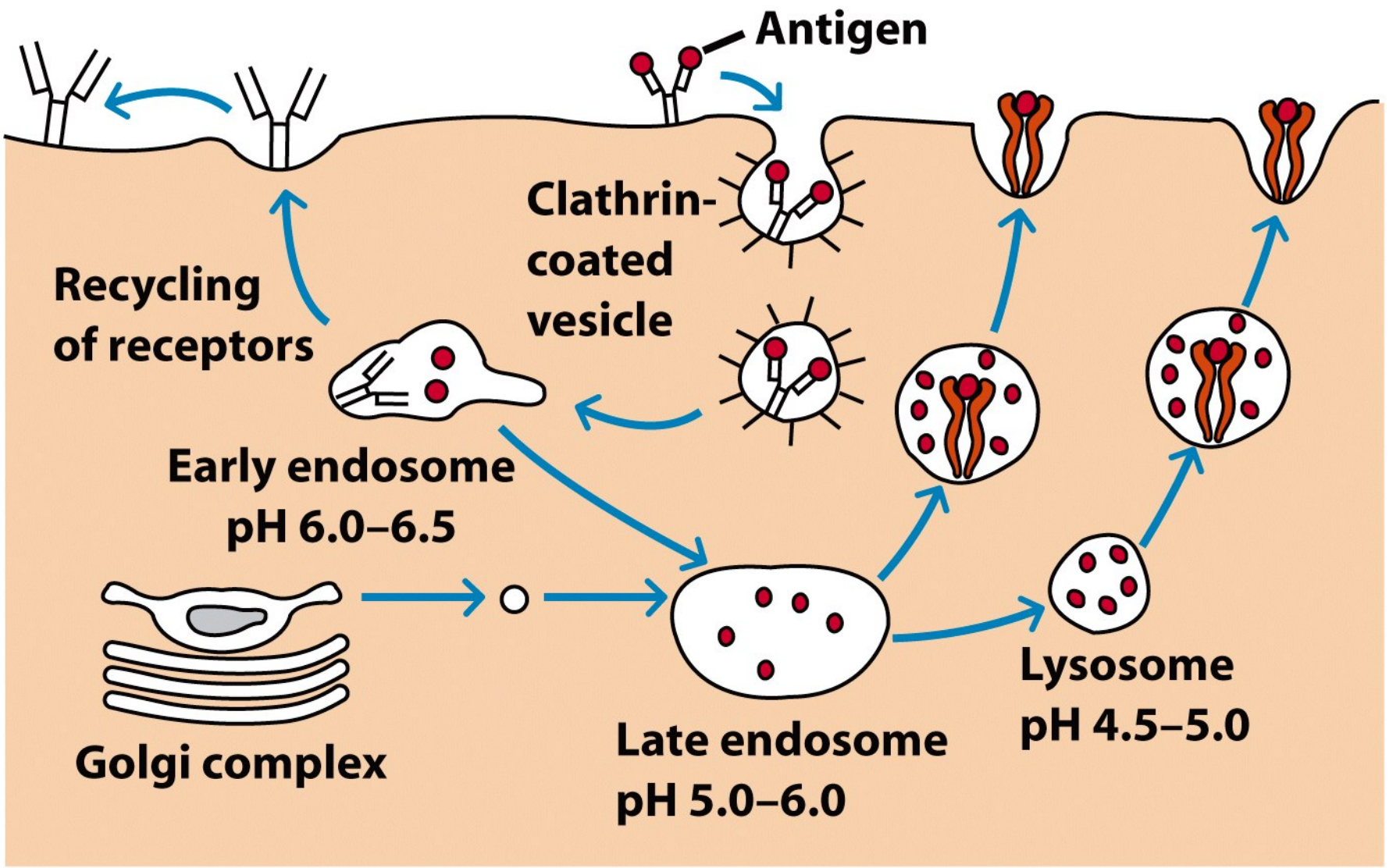


Fig 5.6 © 2001 Garland Science



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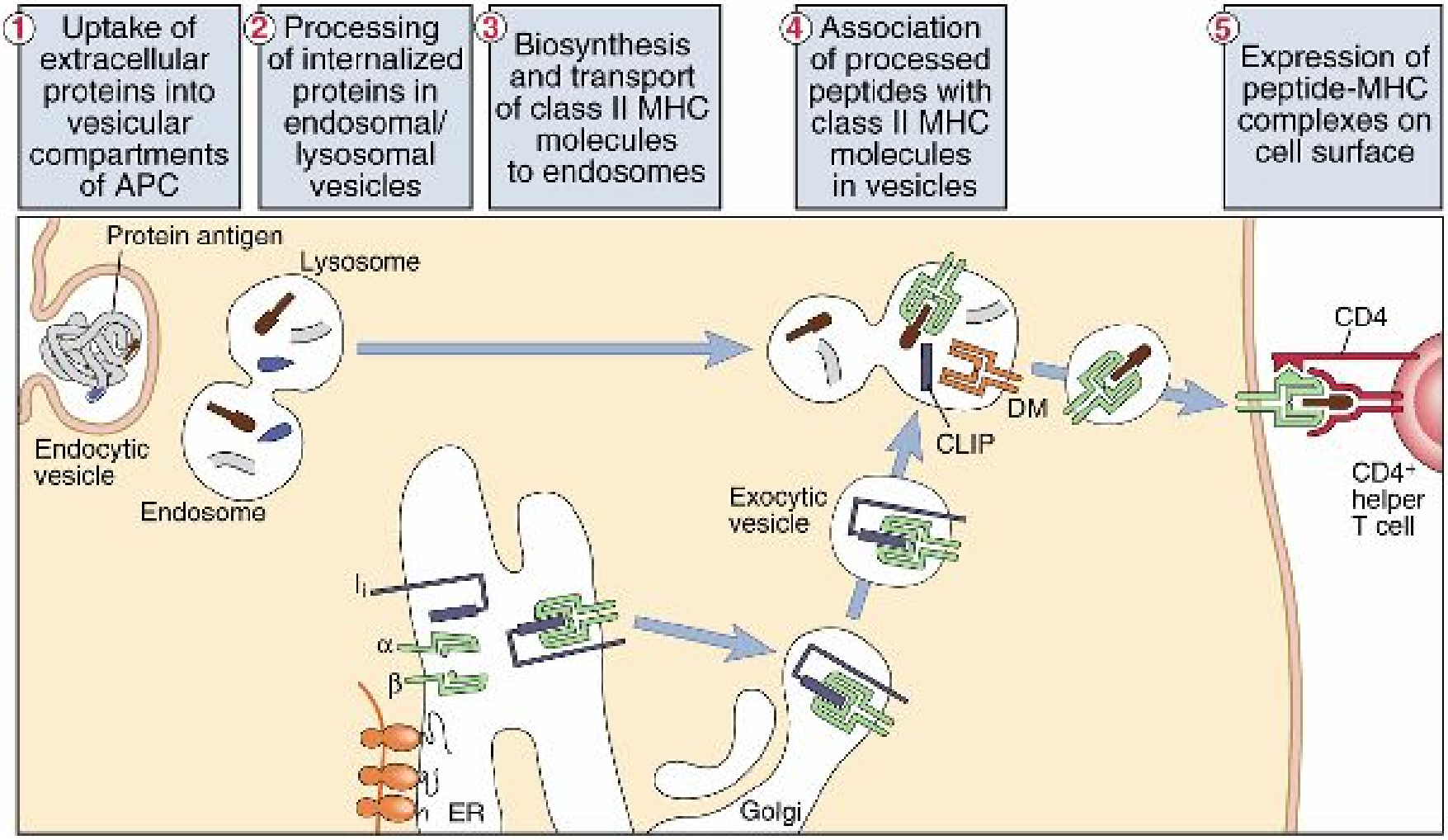
Antigen Processing for Exogenous (Extracellular) Antigens



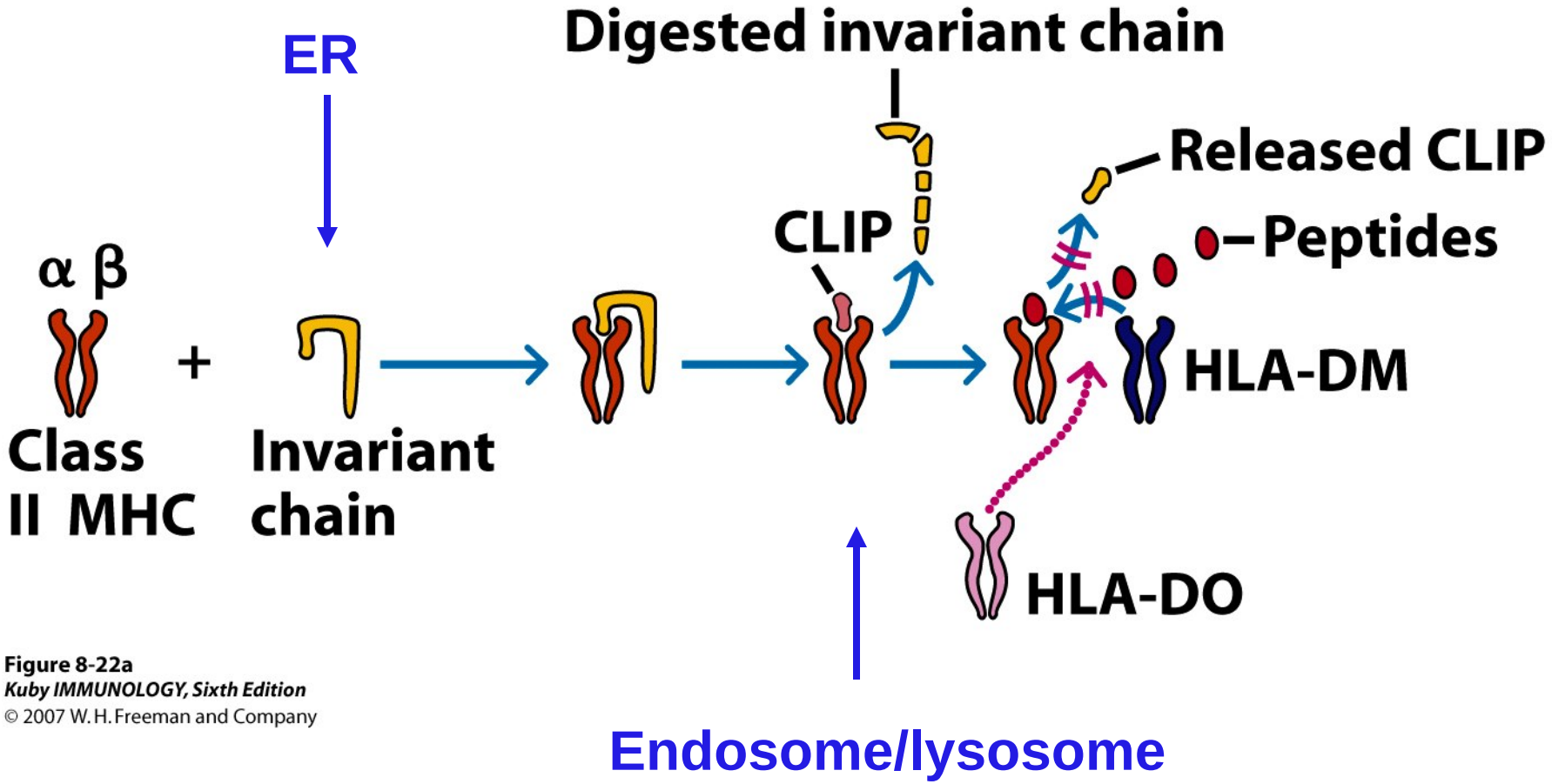


Figure 8-22a
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CD8+ Cytotoxic T Lymphocytes also see antigen on cells

- The antigen is endogenously expressed in the cytoplasm of the cell (e.g. viral infection)
- The endogenous antigen is processed and presented, this time with MHC class I
- The CTL recognizes the antigen and kills the infected cell
- Any cell that expresses MHC Class I can be a target for CTL

Presentation of Ag by MHC Class I

- Endogenous antigens - viral, tumor, self
- Cytoplasmic expressed antigen
- Processing in proteasome
- Presentation can occur for virtually any infected cell

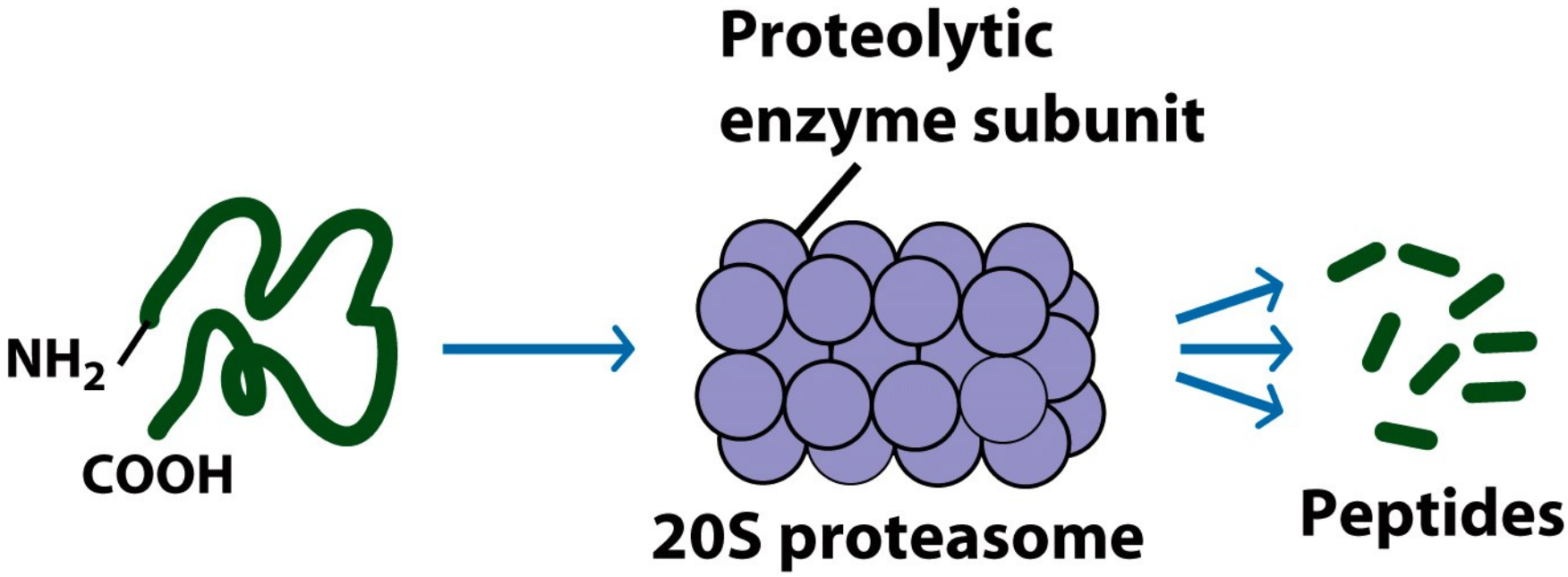

Figure 8-18a
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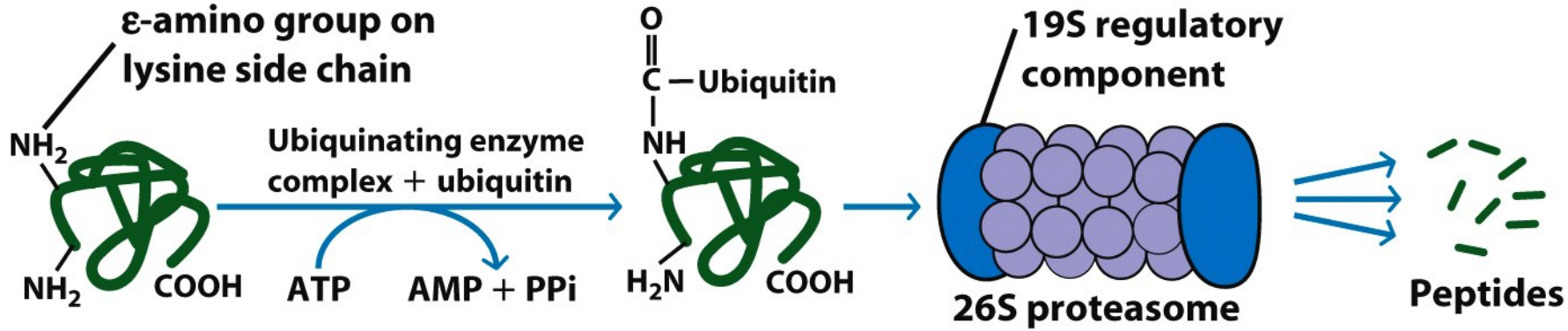

Figure 8-18b
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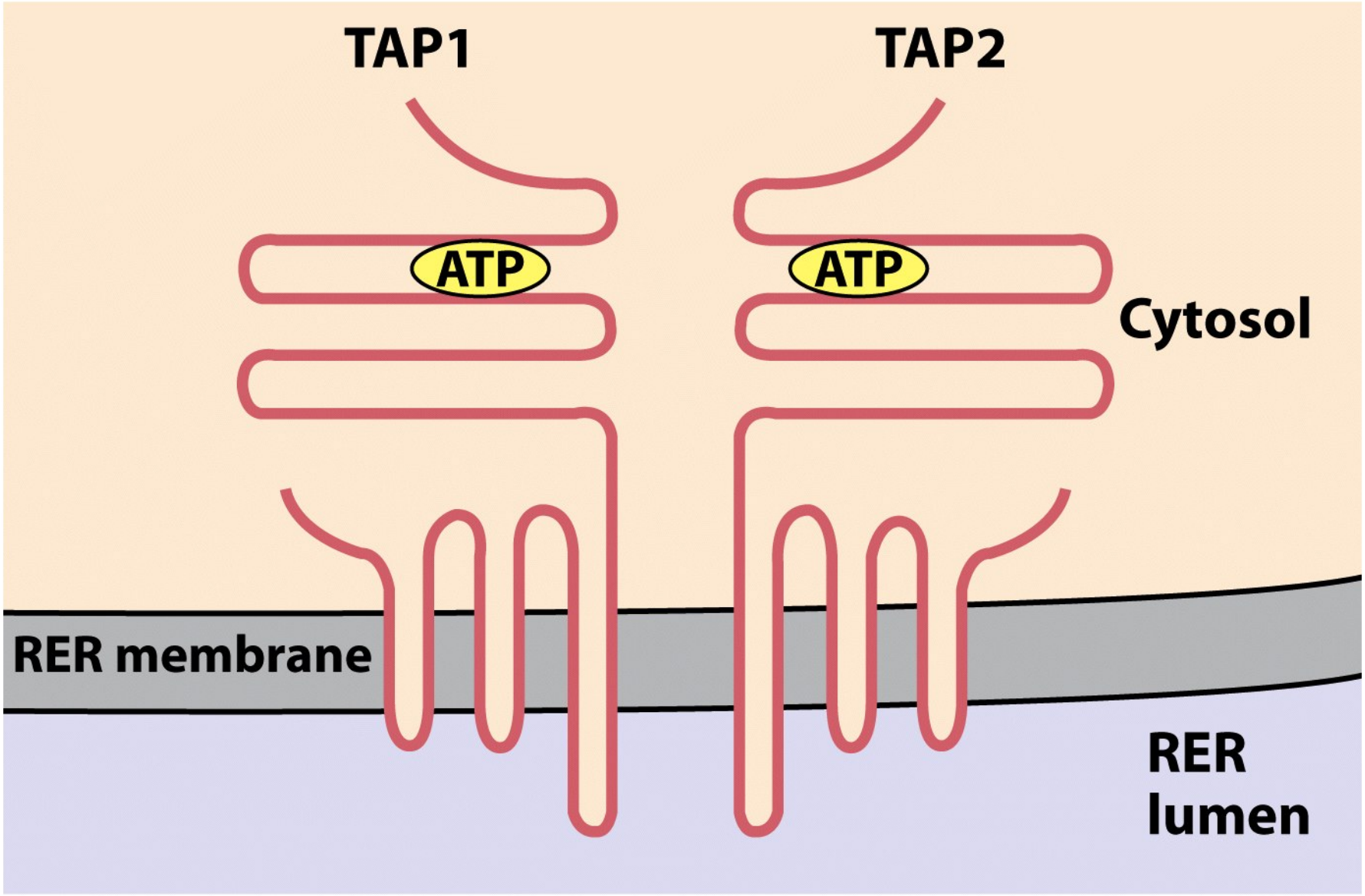

Figure 8-19a
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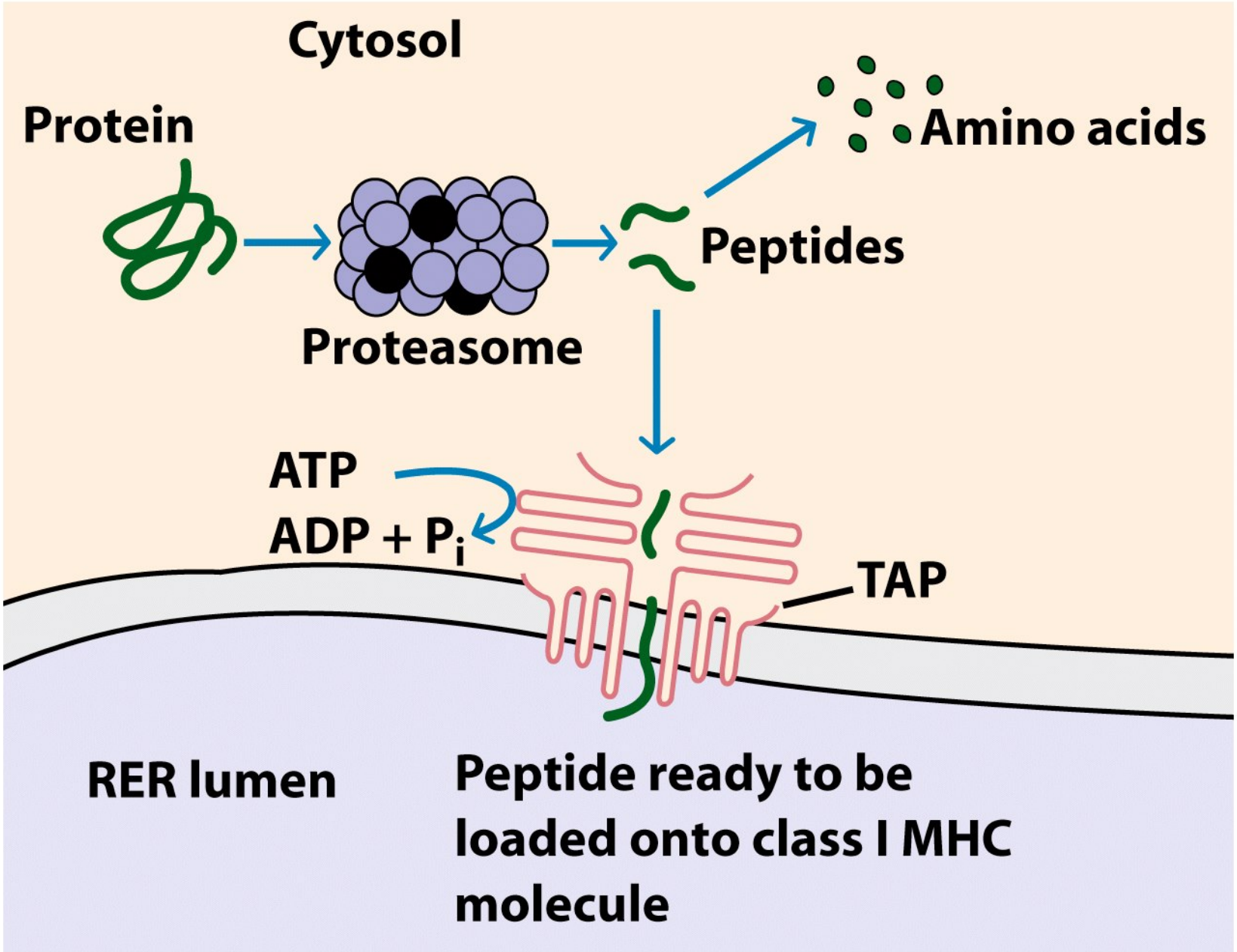

Figure 8-19b
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Assembly of MHC Class I/peptide complexes

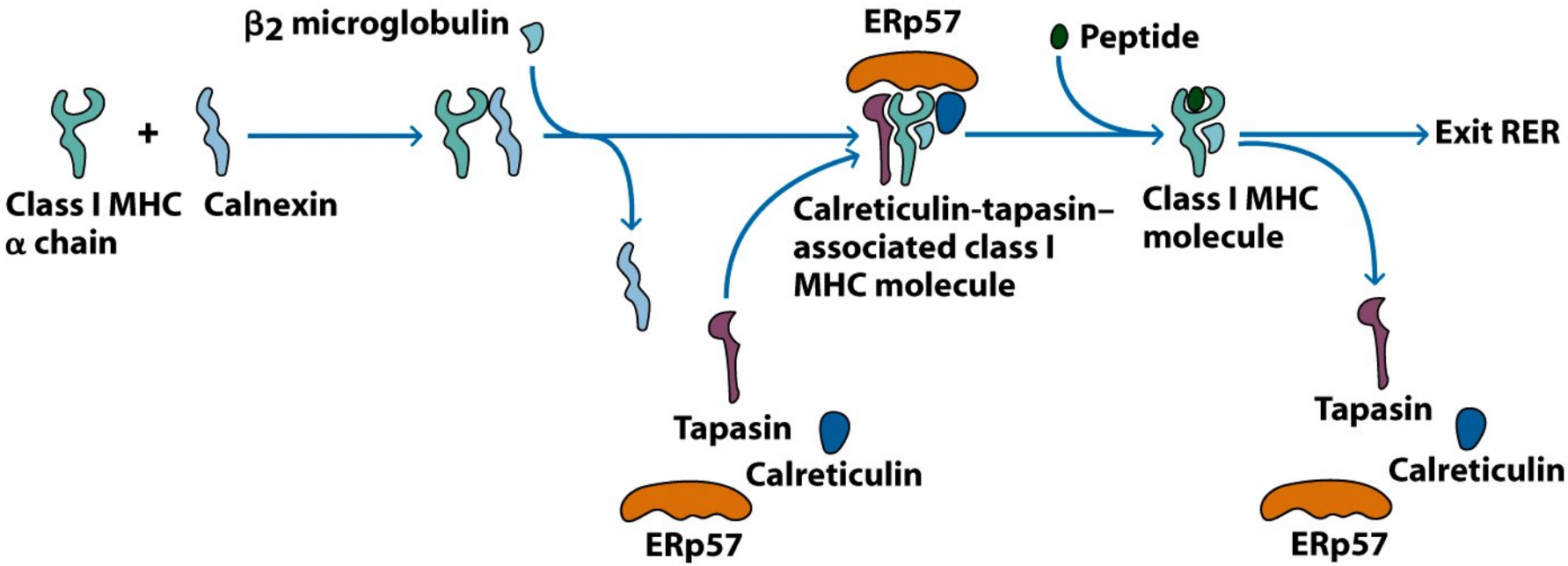

Figure 8-20
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Processing of Antigen in the Class I Pathway

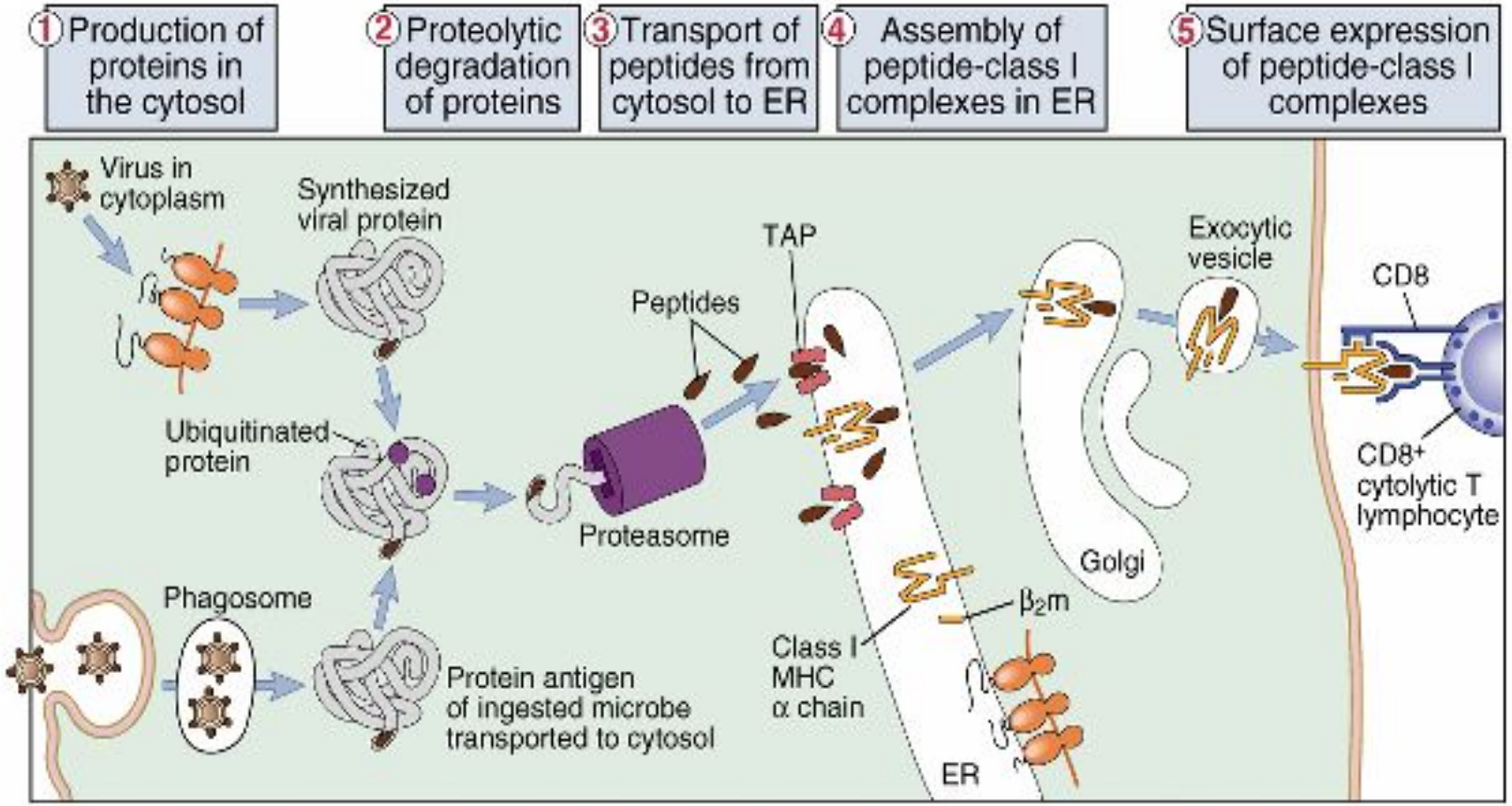


Fig 5-14

Invariant Chain (Ii) on MHC Class II Prevents Binding of Class I Peptides to Class II in the ER

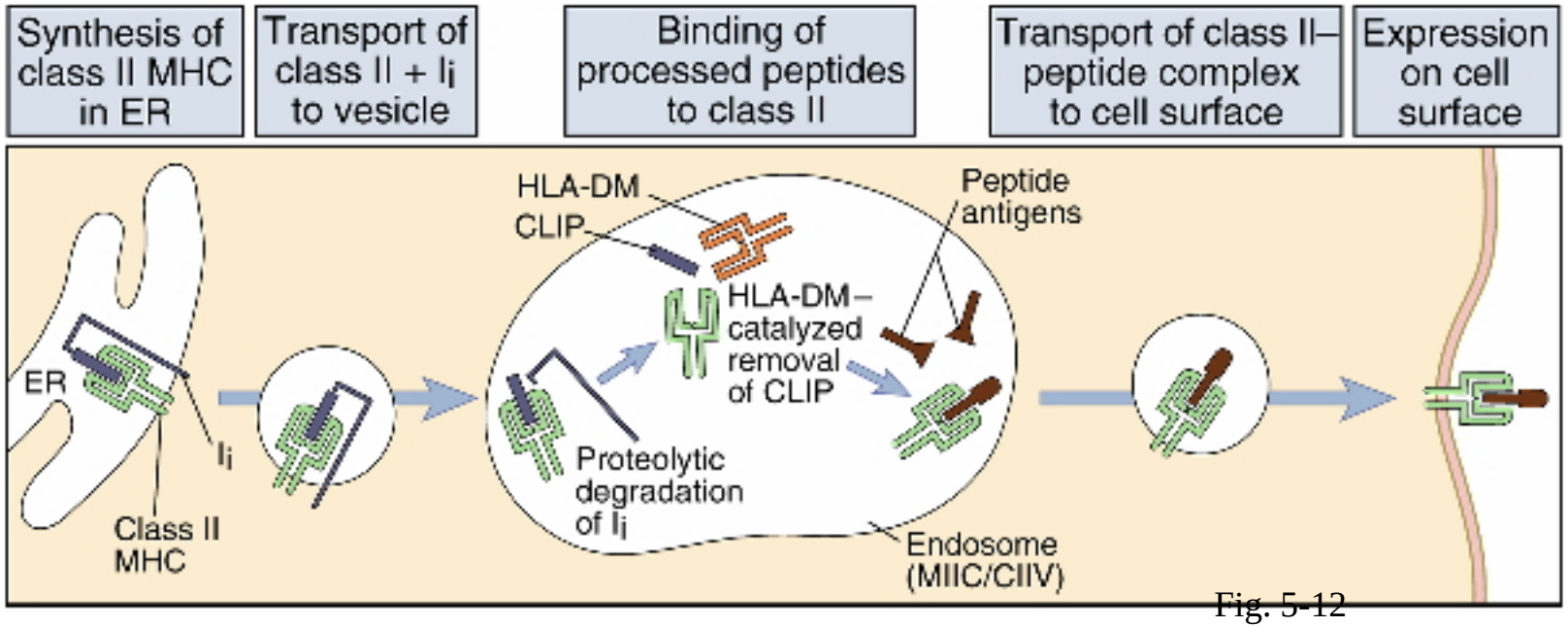


Fig. 5-12

The Route of Entry of Antigen Can Determine Outcome

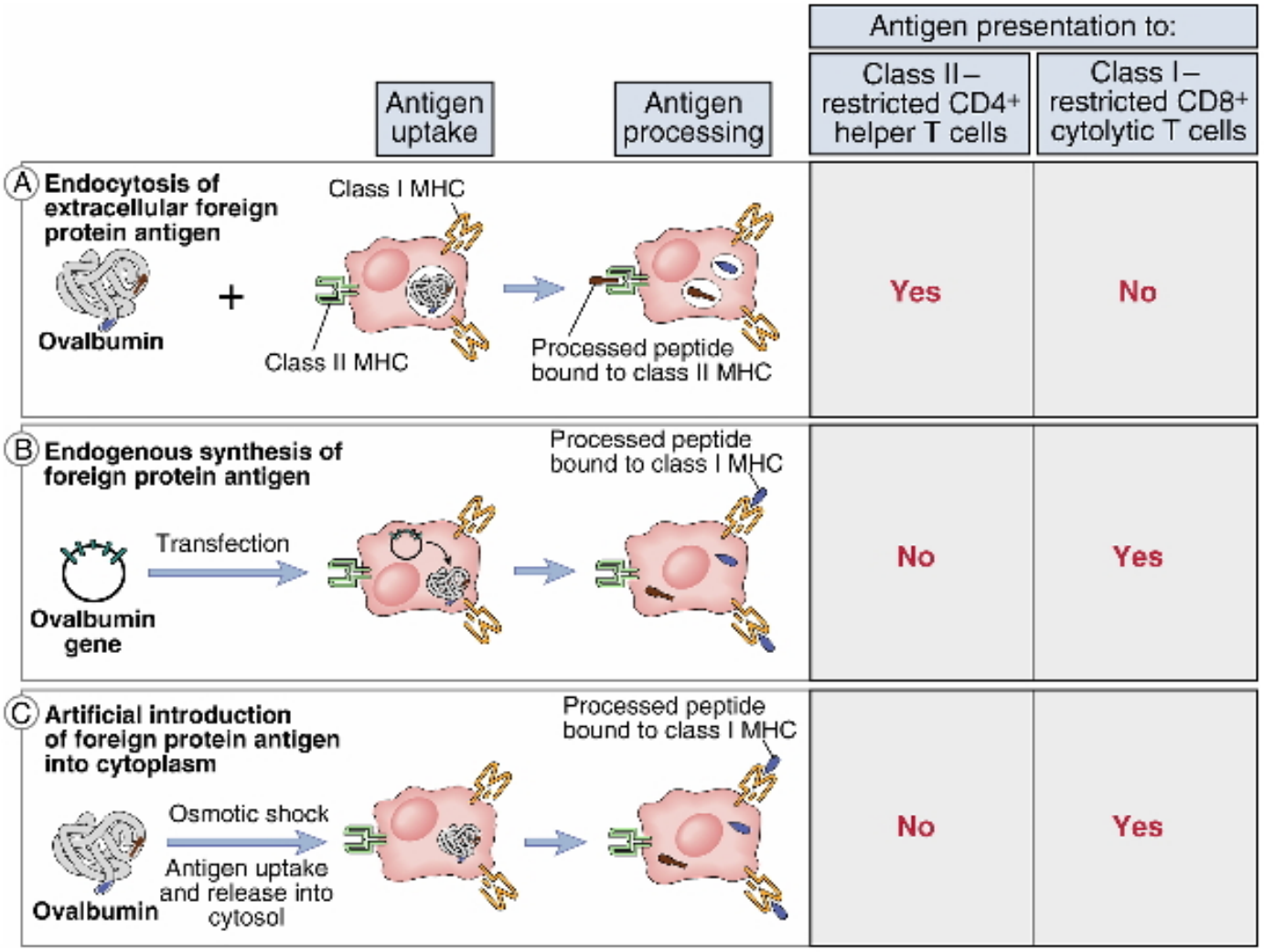


Fig. 5-9

T Cells Survey APCs for Foreign Peptides

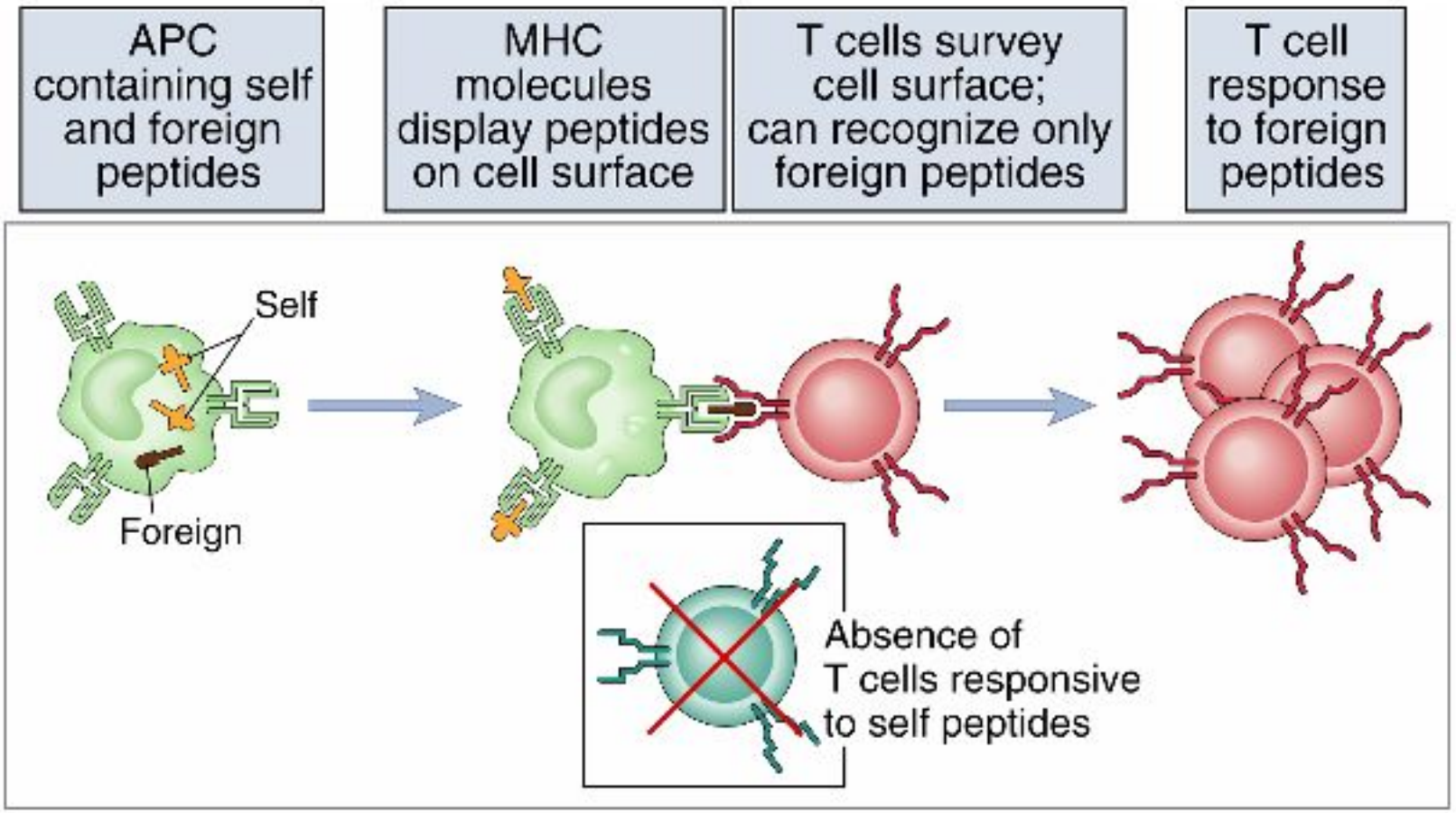


Fig. 5-16

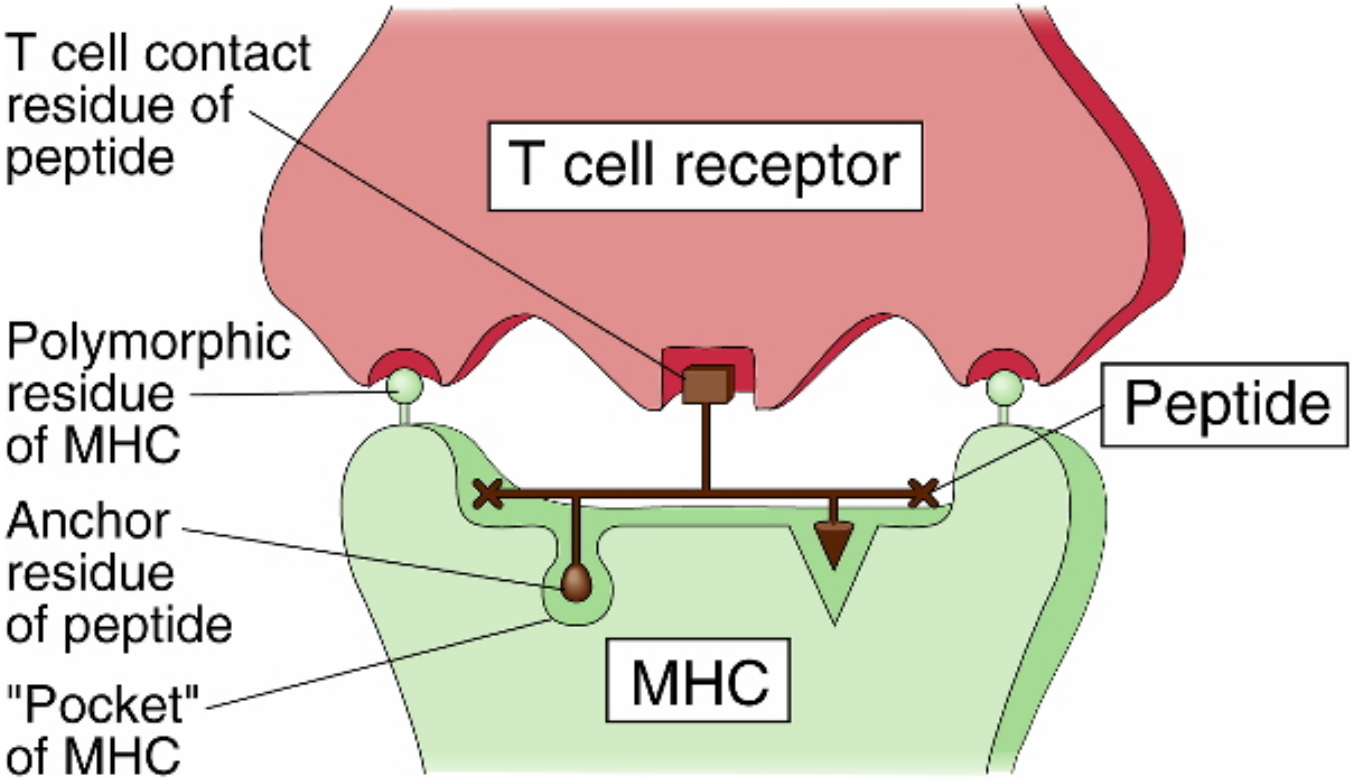
Immunogenicity of Protein Antigens

- **Immunodominant epitopes** are peptides which bind most avidly to MHC.

- Expression of particular MHC Class II alleles determines the ability of that individual to respond to particular antigens. Immune responses (Ir) genes - control immune responsiveness. For example, HLA-B8, DR3, DQw2a individuals are low responders to hepatitis B antigens.

- Adenovirus E19 protein can blocked nascent MHC Class I movement from ER by binding to it. Lowers Class I expression and therefore immune recognition. Many viruses can do this by a variety of different mechanisms.

Anchor Residues and TCR Binding Portions of Peptides



Immunodominant Epitopes

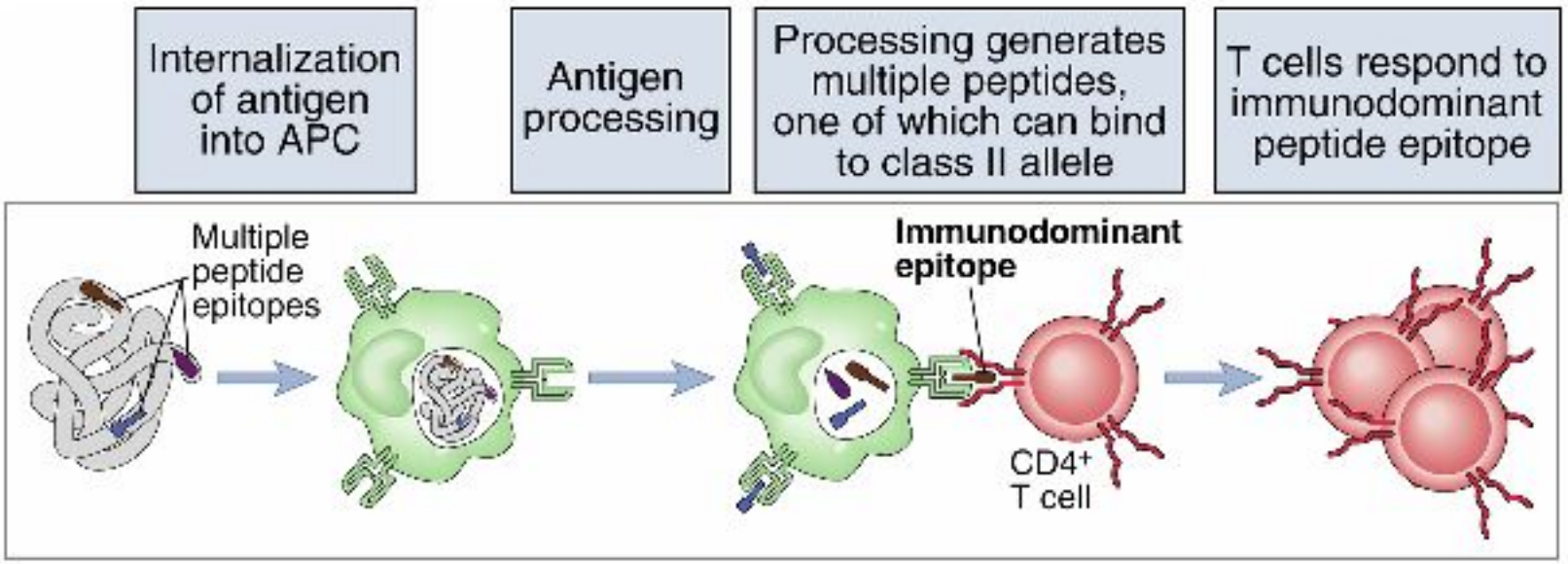


 Fig 5-18

Type of Presentation Influences Outcome:

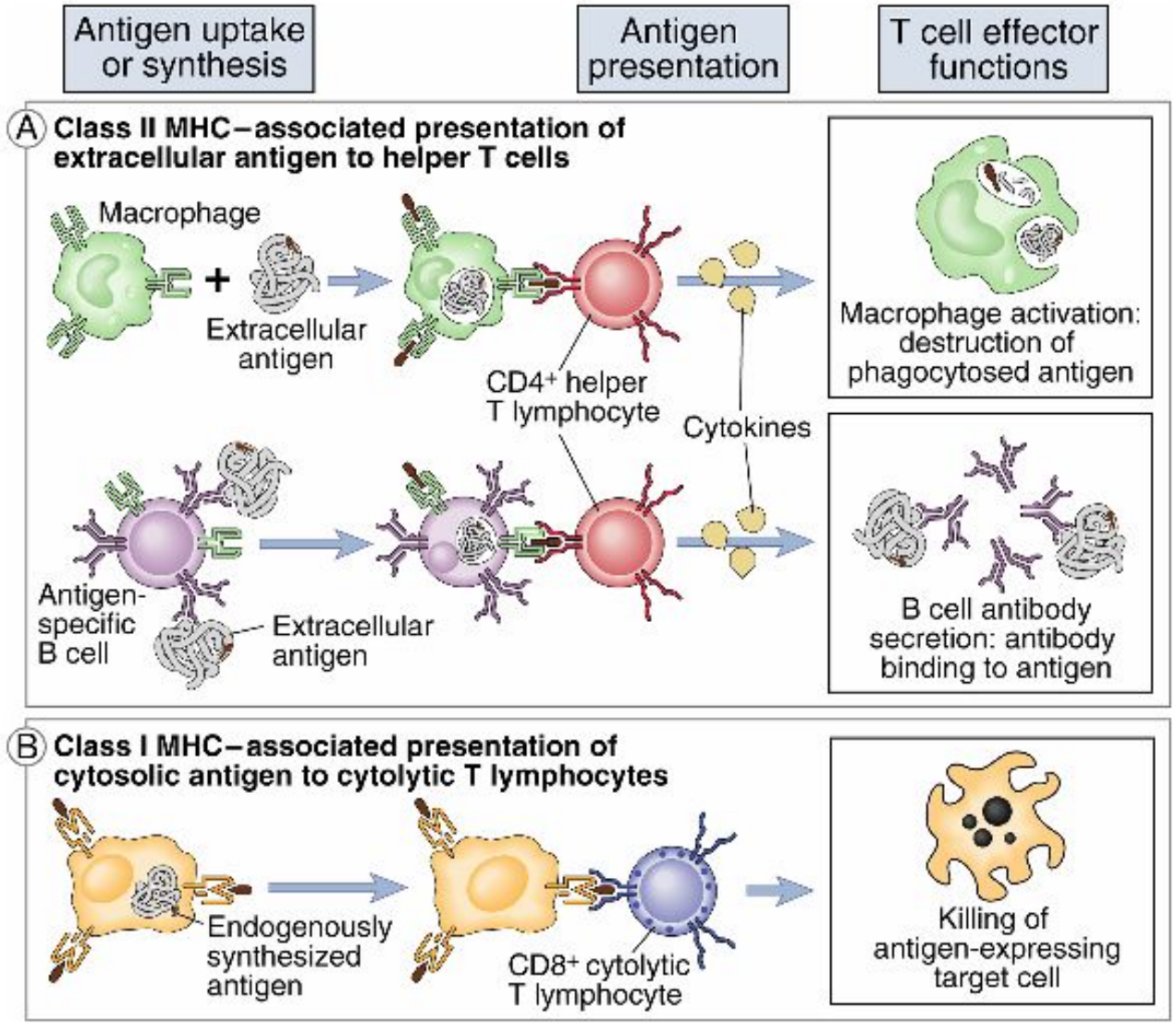


Fig. 5-17

Cross-Presentation by Dendritic Cells

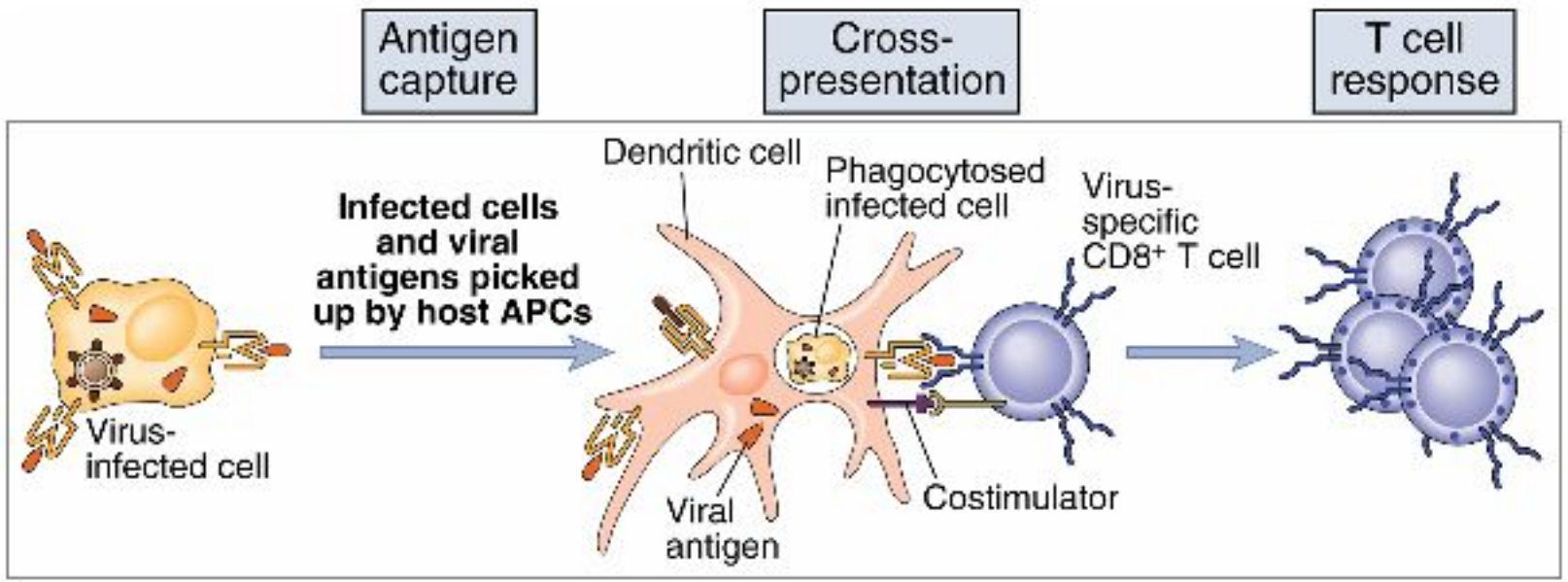


Fig. 5-7

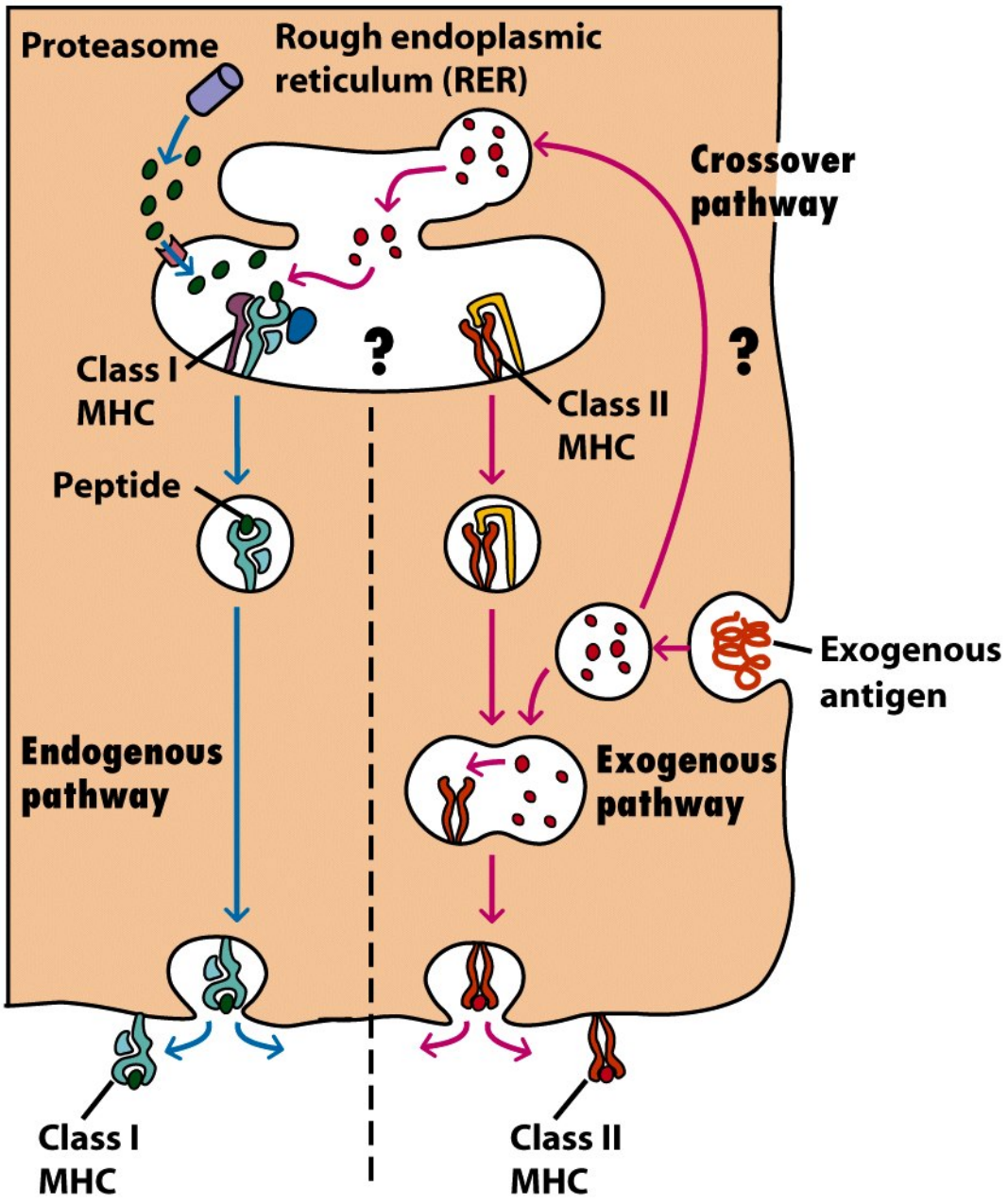


Figure 8-24
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Presentation of Antigen by CD1 (or, more exceptions to the rule)

- **CD1** is a non-polymorphic MHC-like molecule.
- Maps outside of MHC region.
- Like MHC Class I, associates with ß2-microglobulin.
- Capable of presenting **mycolic acid and lipoarabinomannan (lipid and glycolipid)** from mycobacteria to T cells. Source of antigen is **exogenous**.
- In mouse, CD1 on APC such as dendritic cells, thymic cortical cells is able to present certain antigens (e.g. cerebrosides) to a population of CD4 T cells that express NK1.1 or to some conventional T cells. These T cells make cytokines, which help shape the immune response.

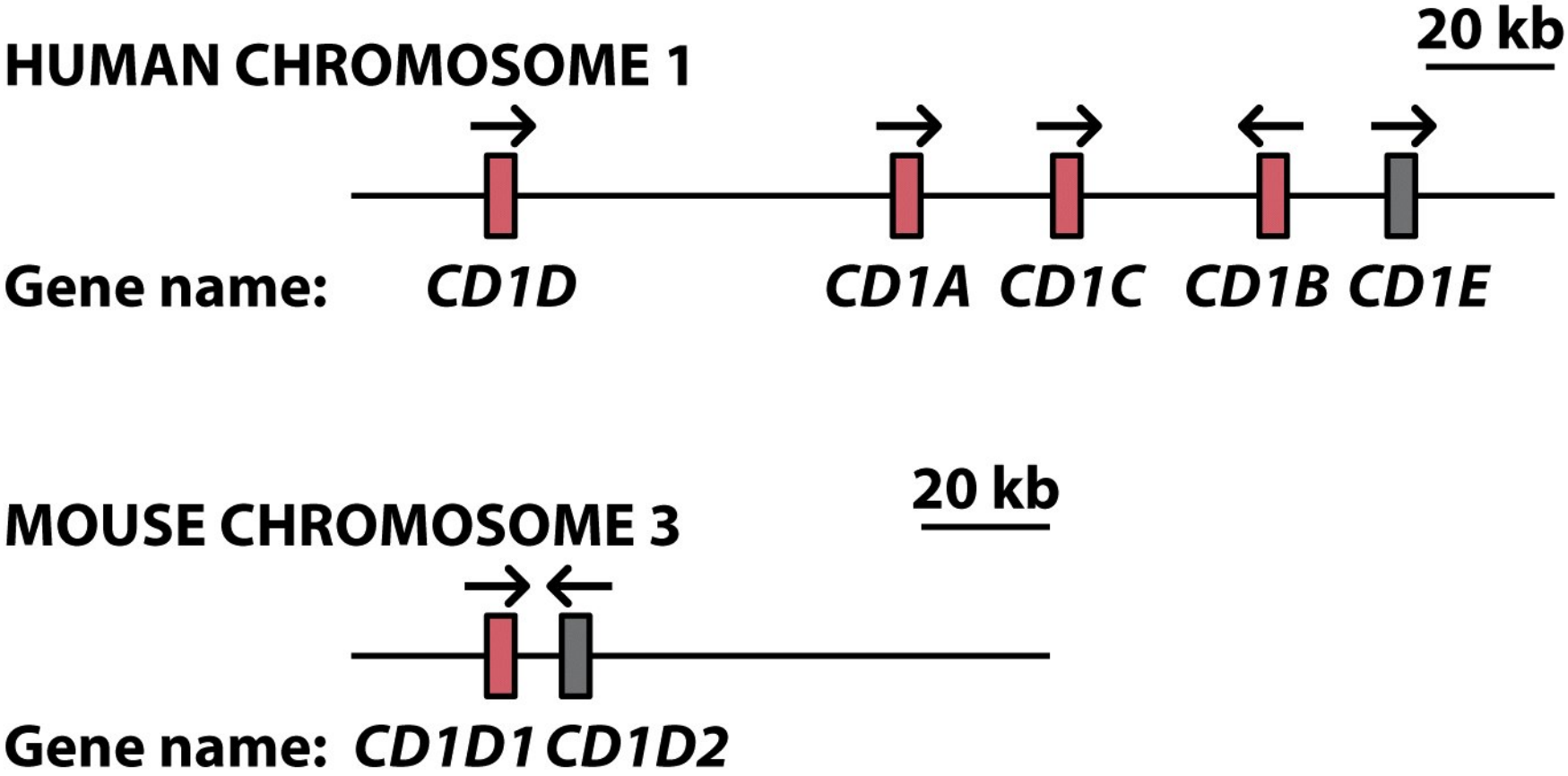

Figure 8-25a
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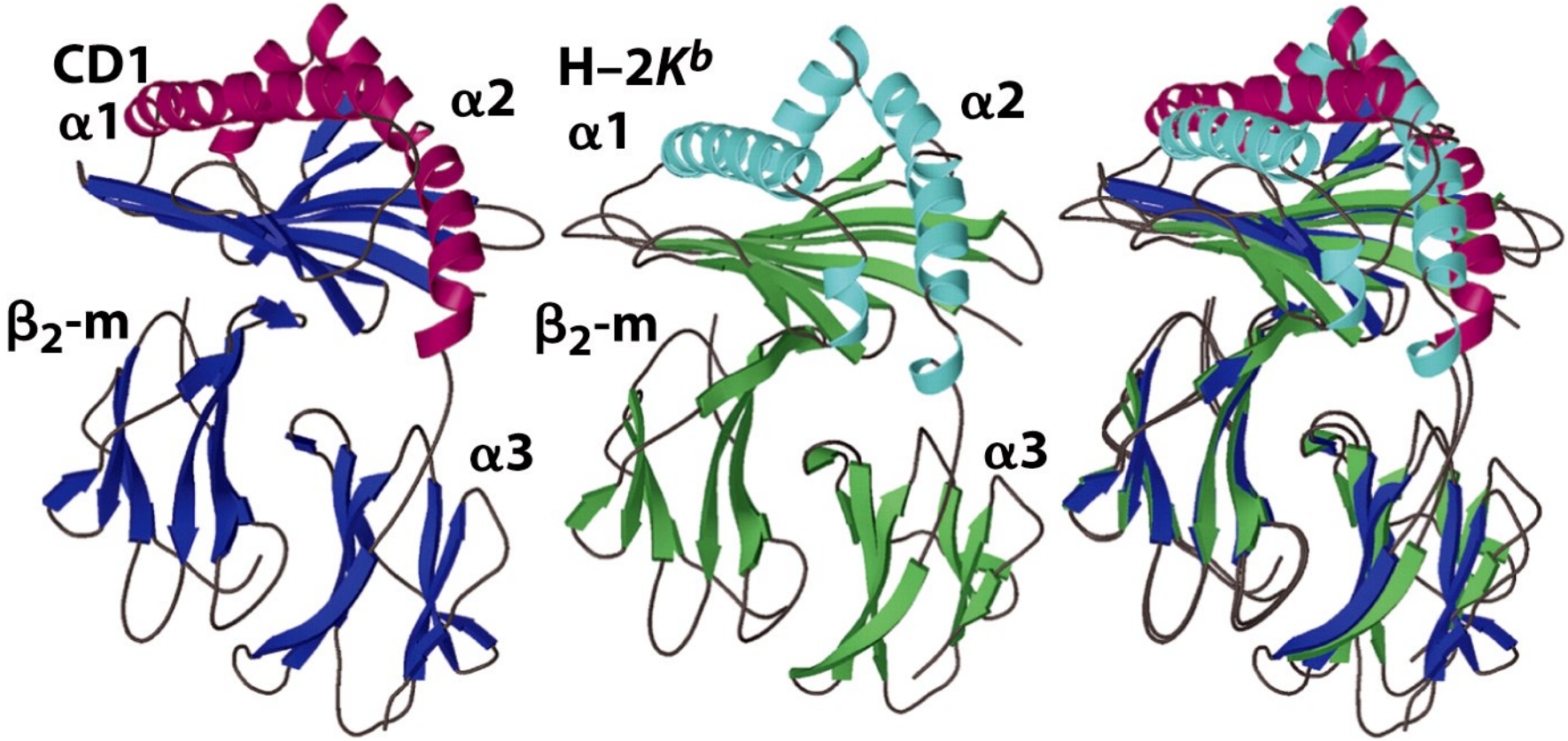

Figure 8-25b
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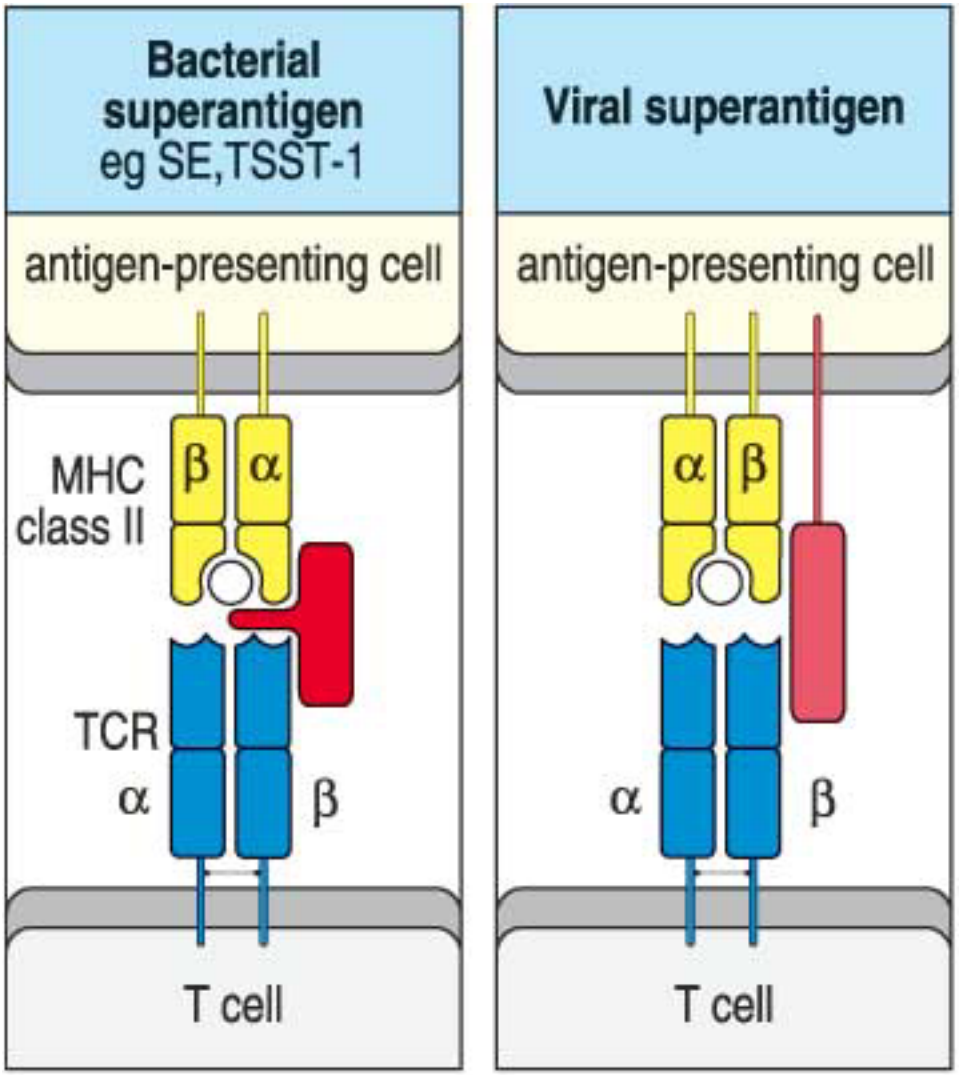
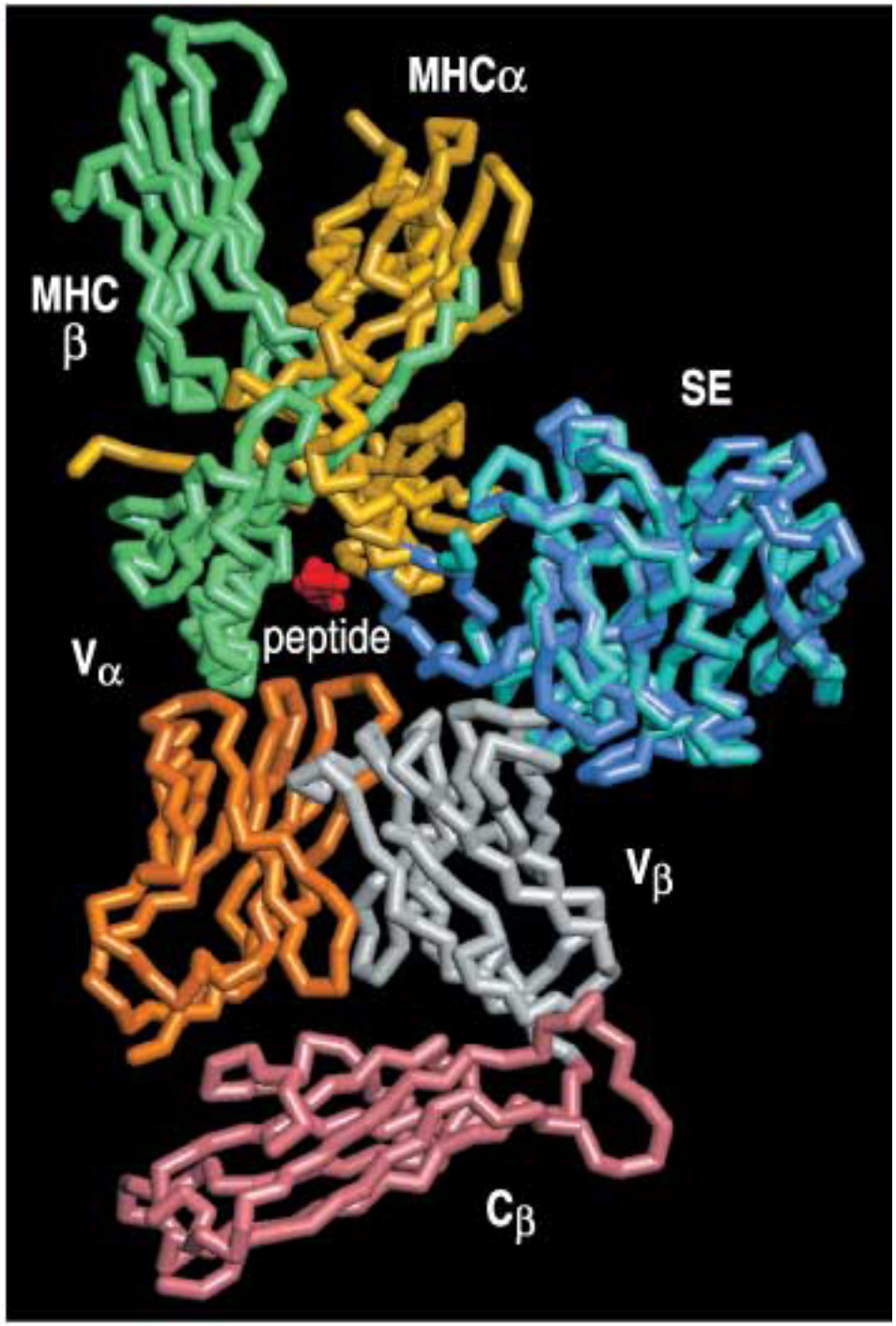

Bacterial superantigen
eg SE,TSST-1
antigen-presenting cell
MHC class II
β
α
TCR
α
β
T cell
Viral superantigen
antigen-presenting cell
α
β
α
β
T cell


MHCα
MHC β
SE
peptide
Vα
Vβ
Cβ

How is antigen presentation relevant to clinical medicine?

- **Transplantation** (organs, bone marrow, stem cells)
- **Transfusion**
- **Cancer:** can tumor antigens be presented?
- **Infectious disease:** upreg. and downreg. of MHC Class I
- **Autoimmunity**
- **Immunodeficiency**
- **Immunotherapy**
- **Vaccination**
  - What type of response am I aiming for? Antibody? CTL?
  - How can I get that vaccine into the right processing pathway?
  - Can the vacinee respond?