

Antigen Capture and Presentation to T Lymphocytes

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Features of Antigens Recognized by T Lymphocytes

- The antigen receptors of most T lymphocytes, can see **only peptide fragments** of protein antigens, and **only when these peptides are presented by specialized molecules** that bind peptides generated inside a host cell and then display them on the cell surface.
- Therefore, T cell–mediated immune responses may be generated only against protein antigens that are either produced in or taken up by host cells.
- The cells that capture microbial antigens and display them for recognition by T lymphocytes are called **antigen-presenting cells (APCs)**.

- **The majority of T lymphocytes recognize peptide antigens that are bound to and displayed by major histocompatibility complex (MHC) molecules of antigen-presenting cells.**
- In every individual, different clones of CD4+ and CD8+ T cells can see peptides only when these peptides are displayed by that individual's MHC molecules. **MHC restriction**

- The T cell receptor (TCR) recognizes some amino acid residues of the peptide antigen and simultaneously also recognizes residues of the MHC molecule that is displaying that peptide.

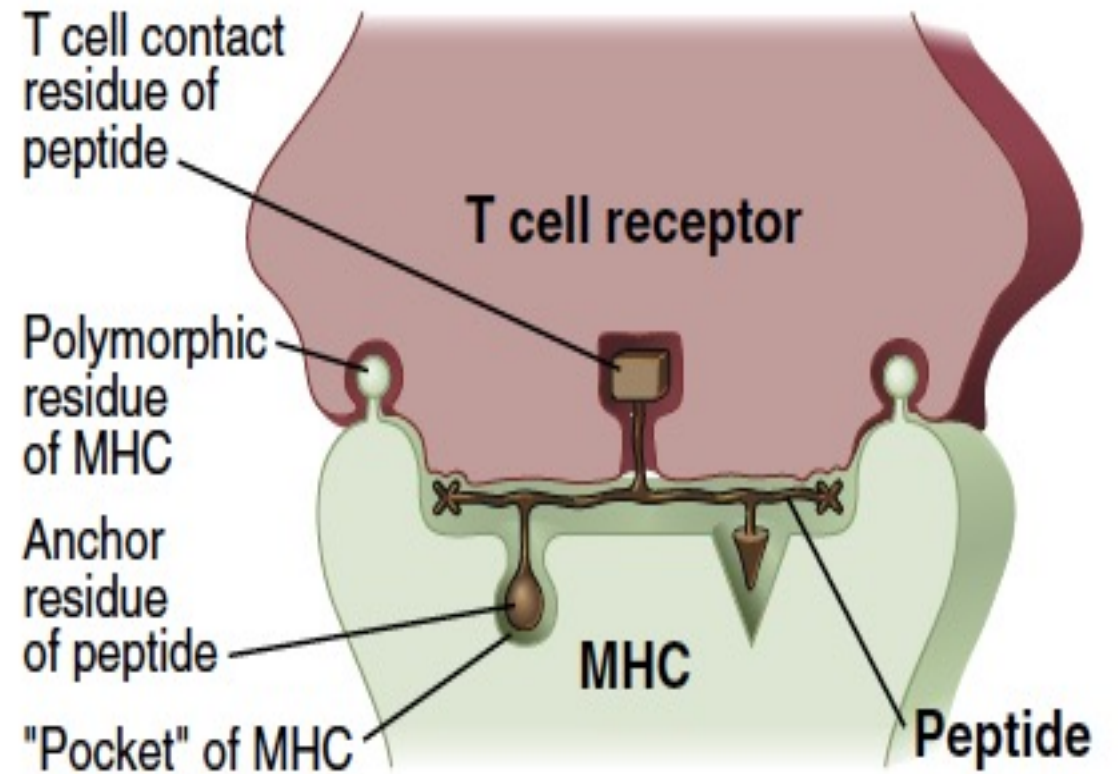


TABLE 6–1 Features of Antigens Recognized by T Lymphocytes

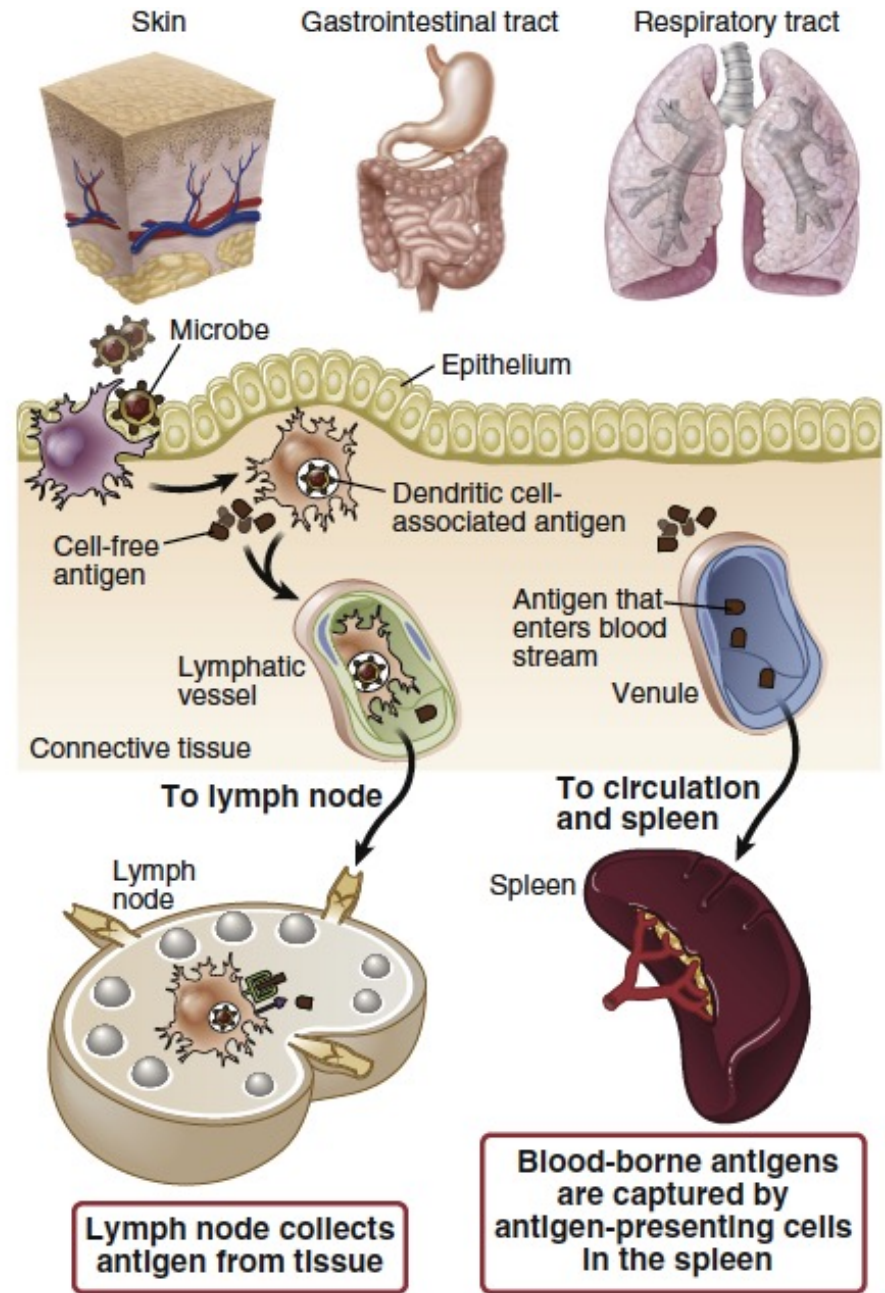
Features of Antigens Recognized by T Cells	Explanation
Most T cells recognize peptides and no other molecules.	Only peptides bind to MHC molecules.
T cells recognize linear peptides and not conformational determinants of protein antigens.	Linear peptides bind to clefts of MHC molecules, and protein conformation is lost during the generation of these peptides.
T cells recognize cell-associated and not soluble antigens.	T cell receptors recognize only MHC-like shapes, and MHC molecules are membrane proteins that display stably bound peptides on cell surfaces.
CD4 ⁺ and CD8 ⁺ T cells preferentially recognize antigens sampled from the extracellular and cytosolic pools, respectively.	Pathways of assembly of MHC molecules ensure that class II molecules display peptides that are derived from extracellular proteins and taken up into vesicles in APCs and that class I molecules present peptides from cytosolic proteins; CD4 and CD8 bind to nonpolymorphic regions of class II and class I MHC molecules, respectively.

General properties of APCs for CD4+ T lymphocytes.

- Different cell types function as APCs to activate naïve and previously differentiated effector T cells.
- Dendritic cells, macrophages, and B lymphocytes express class II MHC molecules and other molecules involved in stimulating T cells and are therefore capable of activating CD4+ T lymphocytes.
- APCs display peptide-MHC complexes for recognition by T cells and also provide additional stimuli to the T cells that are required for the full responses of the T cells.

CAPTURE OF PROTEIN ANTIGENS BY ANTIGEN- PRESENTING CELLS

- **Protein antigens of microbes that enter the body are captured mainly by dendritic cells and concentrated in the peripheral lymphoid organs, where immune responses are initiated .**
- Microbes usually enter the body through the skin (by contact), the gastrointestinal tract (by ingestion), and the respiratory tract (by inhalation).
- Some insect-borne microbes may be injected into the bloodstream as a result of insect bites, and some infections are acquired through the genitourinary tract.
- Microbial antigens can also be produced in any infected tissue



Lymph node collects antigen from tissue

Blood-borne antigens are captured by antigen-presenting cells in the spleen

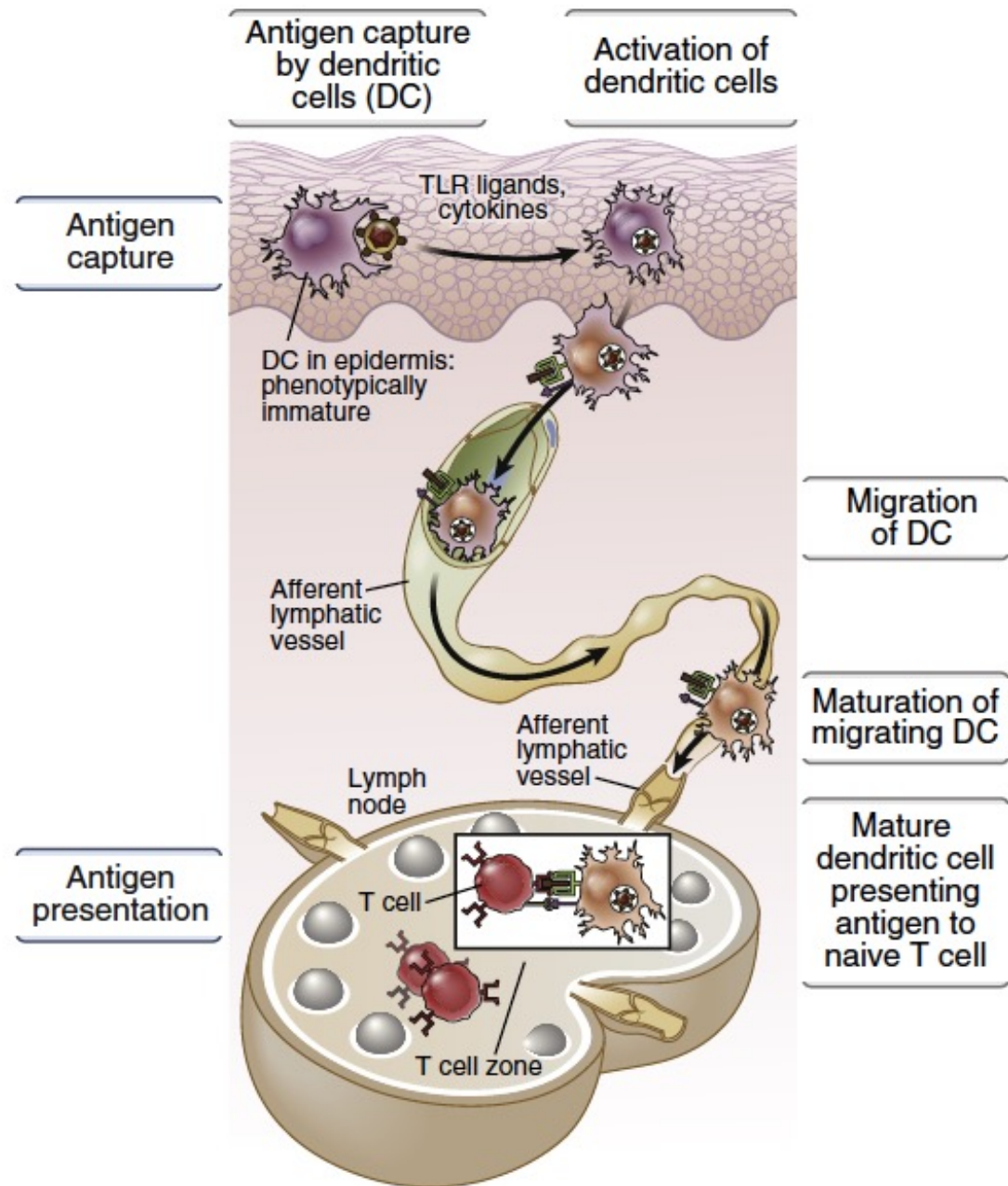
Morphology and Populations of Dendritic Cells

- There are two major populations of dendritic cells, called classical and plasmacytoid, which differ in their locations and responses .

Feature	Classical dendritic cells	Plasmacytoid dendritic cells
Surface markers	CD11c high CD11b high	CD11c low CD11b negative B220 high
Major location	Tissues	Blood and tissue
Expression of Toll-like receptors	TLRs 4, 5, 8 high	TLRs 7, 9 high
Major cytokines produced	TNF, IL-6, IL-12	Type I interferons
Postulated major functions	Induction of T cell responses against most antigens	Antiviral innate immunity and induction of T cell responses against viruses

Antigen Capture and Transport by Dendritic Cells

- DCs that are resident in epithelia and tissues capture protein antigens and transport the antigens to draining lymph nodes.
- The activated DCs (also called mature DCs) lose their adhesiveness for epithelia or tissues and migrate into lymph nodes. The DCs also begin to express a chemokine receptor called **CCR7** that is specific for two chemokines, **CCL19** and **CCL21**, that are produced in the T cell zones of lymph nodes.
- DCs can ingest infected cells and present antigens from these cells to CD8+ T lymphocytes, **crosspresentation, or cross-priming**.



T cell zone

	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	~10 hr	>100 hr
Number of surface molecules	~10 ⁶	~7 x 10 ⁶

Different types of APC serve distinct functions in T cell–dependent immune responses

- ❖ Dendritic cells are the principal inducers of such responses, because these cells are located at sites of microbe entry and are the most potent APCs for activating naive T lymphocytes.
- ❖ One important type of APC for **effector T cells** is the **macrophage**, which is abundant in all tissues. In cell-mediated immune reactions, macrophages phagocytose microbes and display the antigens of these microbes to effector T cells, which activate the macrophages to kill the microbes
- ❖ **B lymphocytes** ingest protein antigens and display them to helper T cells within lymphoid tissues; this process is important for the development of humoral immune responses .
- ❖ All nucleated cells (MHC I) can present antigens derived from microbes in the cytoplasm to CD8+ T cells.

Cell type	Expression of		Principal function
	Class II MHC	Costimulators	
Dendritic cells	Constitutive; increases with maturation; increased by IFN- γ	Constitutive; increases with maturation; increased by TLR ligands, IFN- γ , and T cells (CD40-CD40L interactions)	Antigen presentation to naive T cells in the initiation of T cell responses to protein antigens (priming)
Macrophages	Low or negative; inducible by IFN- γ	Low, inducible by TLR ligands, IFN- γ , and T cells (CD40-CD40L interactions)	Antigen presentation to CD4 ⁺ effector T cells in the effector phase of cell-mediated immune responses
B lymphocytes	Constitutive; increased by cytokines (e.g., IL-4)	Induced by T cells (CD40-CD40L interactions), antigen receptor cross-linking	Antigen presentation to CD4 ⁺ helper T cells in humoral immune responses (T cell–B cell interactions)

Peptide Binding to MHC Molecules

- **The peptide-binding clefts of MHC molecules bind peptides derived from protein antigens and display these peptides for recognition by T cells.**
- Each MHC molecule can present only one peptide at a time, because there is only one binding cleft.
- MHC molecules bind mainly peptides and not other types of antigens.
- MHC molecules acquire their peptide cargo during their biosynthesis, assembly, and transport inside cells. Therefore, MHC molecules display peptides derived from protein antigens that are inside host cells .
- In each individual, the MHC molecules can display peptides derived from the individual's own proteins, as well as peptides from foreign (i.e., microbial) proteins.

PROCESSING AND PRESENTATION OF PROTEIN ANTIGENS

- **Extracellular proteins that are internalized by specialized APCs (dendritic cells, macrophages, B cells) are processed in late endosomes and lysosomes and displayed by class II MHC molecules.**
- **Whereas proteins in the cytosol of any nucleated cell are processed in proteolytic structures called proteasomes and displayed by class I MHC molecules .**

Processing of Cytosolic Antigens for Display by Class I MHC Molecules

- Most cytosolic protein antigens are synthesized within cells, and some are phagocytosed and transported into the cytosol.
- *Proteolysis of cytosolic proteins.* **The peptides that bind to class I MHC molecules are derived from cytosolic proteins following digestion by the ubiquitin-proteasome (UPS) pathway .**
- Peptides generated in the cytosol are translocated by a specialized transporter into the ER, where newly synthesized class I MHC molecules are available to bind the peptides. **transporter associated with antigen processing (TAP).**
- *Binding of peptides to class I MHC molecules.* **In order to form peptide-MHC complexes, the peptides must be transported into the endoplasmic reticulum.**

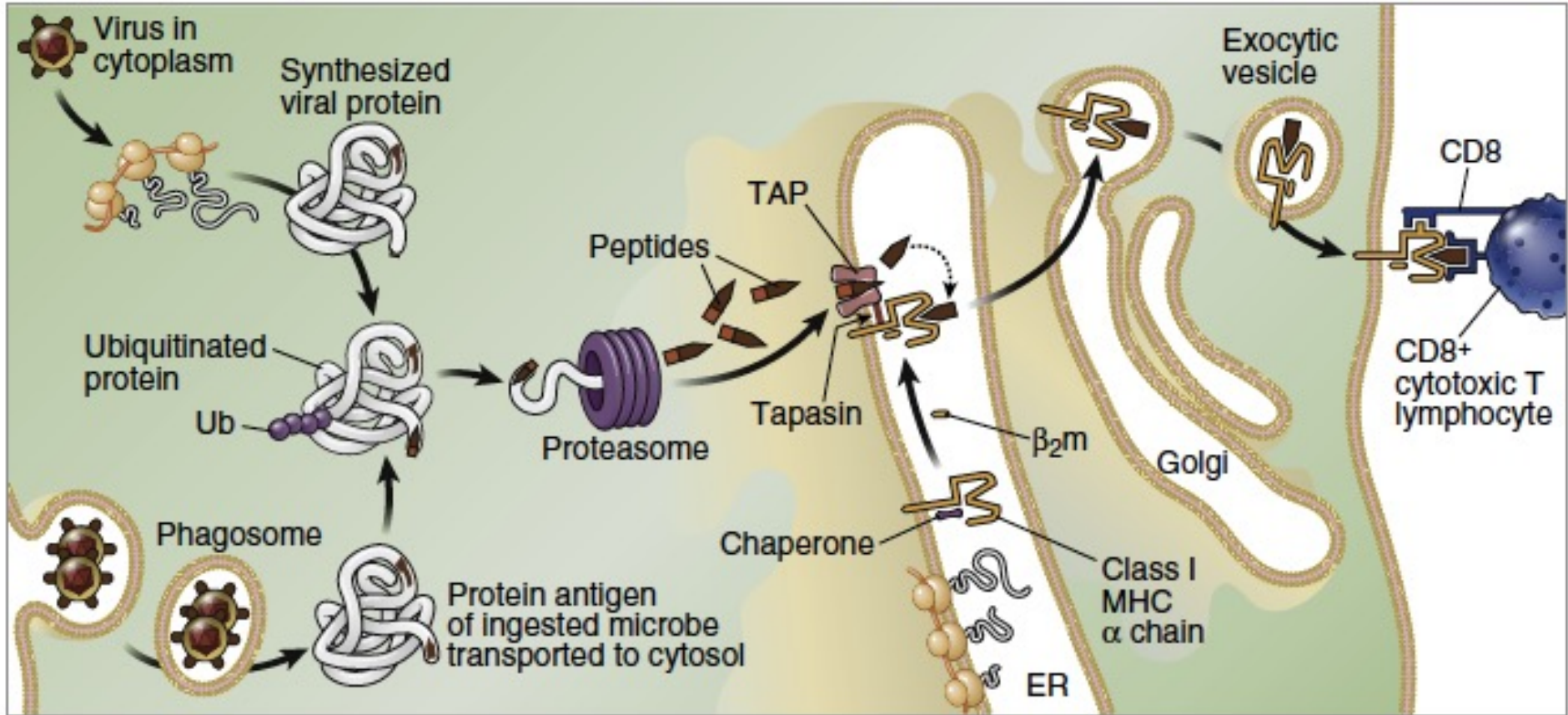
Production of proteins in the cytosol

Proteolytic degradation of proteins

Transport of peptides from cytosol to ER

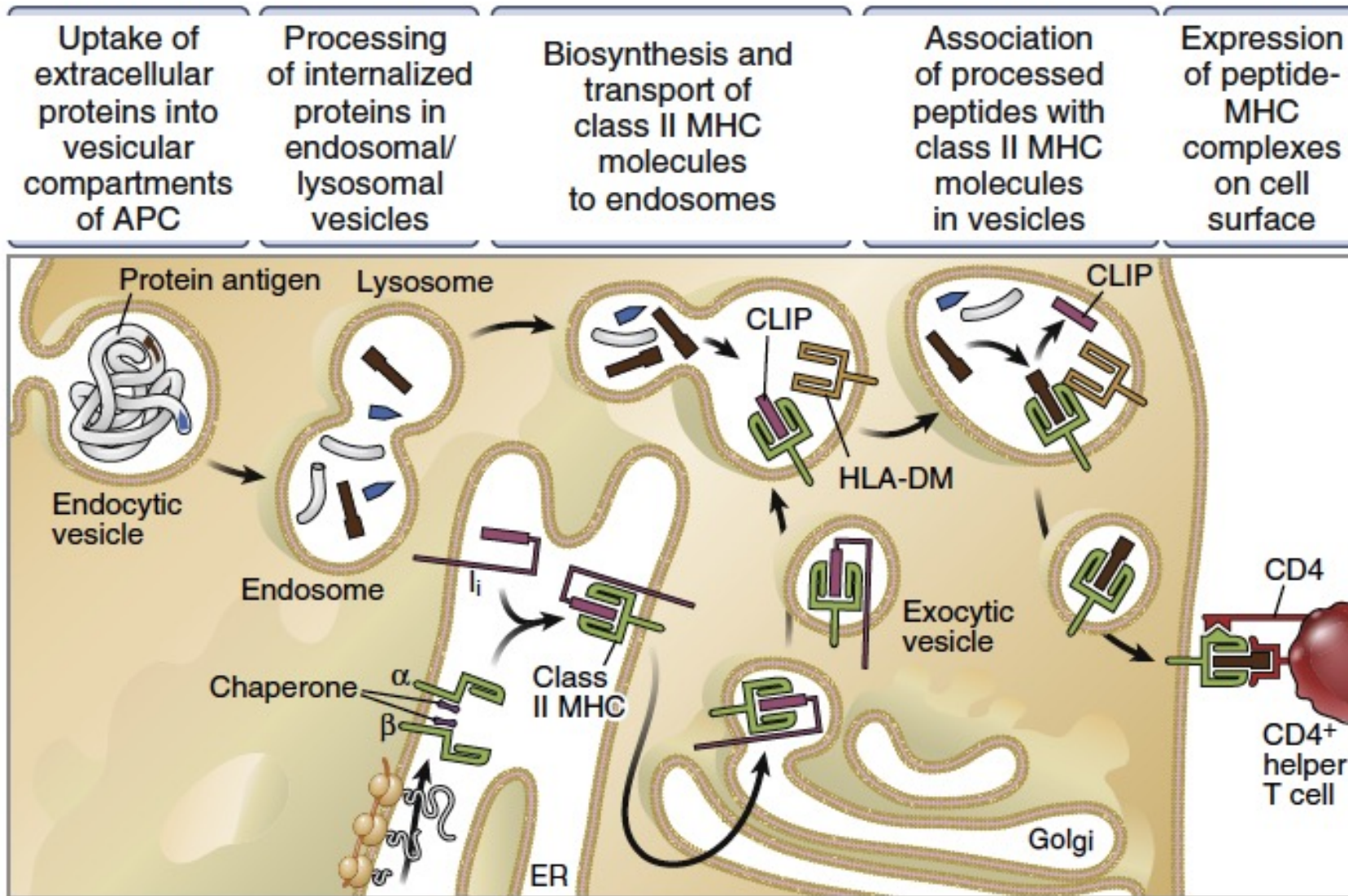
Assembly of peptide-class I complexes in ER

Surface expression of peptide-class I complexes



Processing of Cytosolic Antigens for Display by Class II MHC Molecules

- Most **class II**-associated peptides are derived from protein antigens that are captured from the **extracellular environment and internalized into endosomes** by specialized APCs.
- Internalized proteins are degraded enzymatically (cathepsins) in late endosomes and lysosomes to generate peptides that are able to bind to the peptide-binding clefts of class II MHC molecules.
- Class II MHC molecules are synthesized in the ER and transported to endosomes with an associated protein, the invariant chain (Ii), which occupies the peptide-binding clefts of the newly synthesized class II molecules.
- Within the endosomal vesicles, the Ii dissociates from class II MHC molecules by the combined action of proteolytic enzymes and the HLA-DM molecule, and antigenic peptides are then able to bind to the available peptide binding clefts of the class II molecules



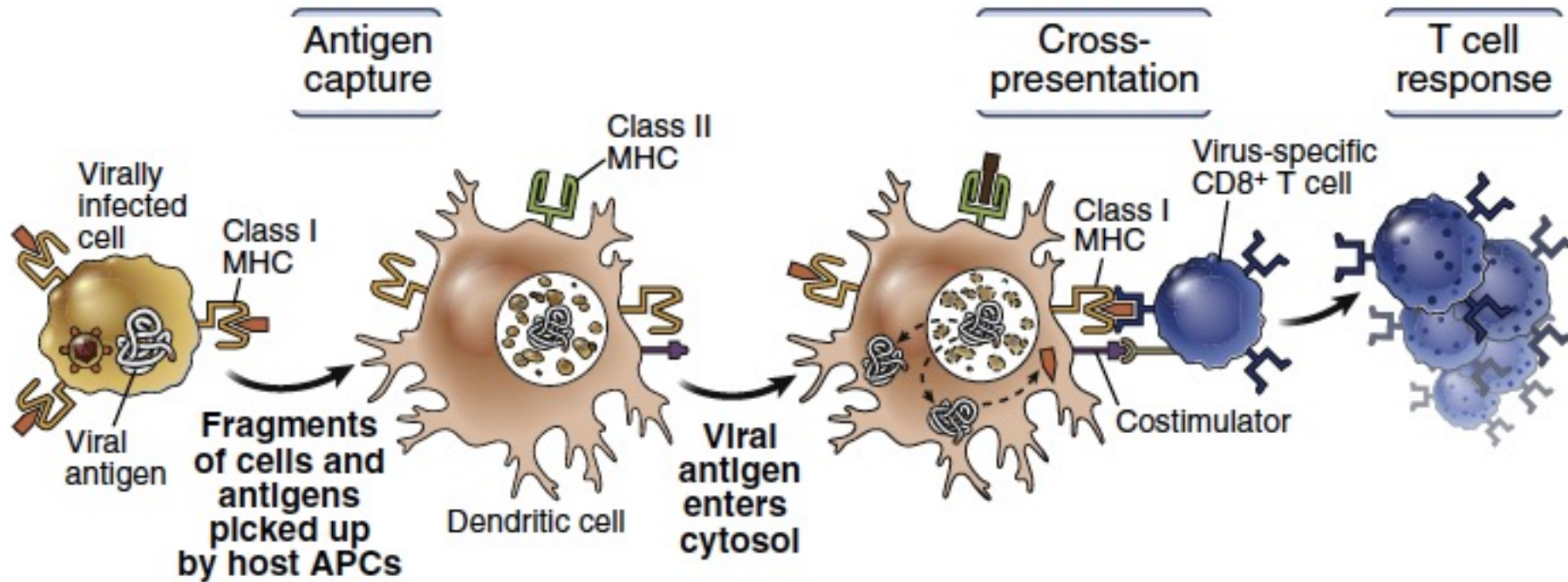
PRESENTATION OF NONPROTEIN ANTIGENS TO SUBSETS OF T CELLS

- Several small populations of T cells are able to recognize nonprotein antigens without the involvement of class I or class II MHC molecules, The best defined of these populations are NKT cells and $\gamma\delta$ T cells.
- NKT cells recognize lipids and glycolipids displayed by the class I-like “non-classical” MHC molecule called CD1.
- $\gamma\delta$ T cells are a small population of T cells that express antigen receptor proteins that are similar but not identical to those of CD4+ and CD8+ T cells
- $\gamma\delta$ T cells recognize many different types of antigens, including some proteins and lipids, as well as small phosphorylated molecules and alkyl amines. These antigens are not displayed by MHC molecules, and $\gamma\delta$ cells are not MHC restricted.

Cross-Presentation of Internalized Antigens to CD8⁺ T Cells

- **Some dendritic cells can present ingested antigens on class I MHC molecules to CD8⁺ T lymphocytes.**
- A subset of classical dendritic cells have the ability to ingest infected host cells, dead tumor cells, microbes, and microbial and tumor antigens and transport the ingested antigens into the cytosol, where they are processed by the proteasome. The antigenic peptides that are generated then enter the ER and bind to class I molecules, which display the antigens for recognition by CD8⁺ T lymphocytes. This process is called **cross-presentation** (or cross-priming), to indicate that one type of cell, dendritic cells, can present the antigens of other, infected or dying, cells or cell fragments, and prime (or activate) naive T lymphocytes specific for these antigens.
- Once the CD8⁺ T cells have differentiated into CTLs, they kill infected host cells or tumor cells without the need for dendritic cells or signals other than recognition of antigen.

Cross-Presentation



The End