Antigen Presentation

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Section 15 Antigen Presentation

Chapter 1 Antigen Presenting Cells

Antigen presenting cells:
capture, process, and present the antigen to T cells and B cells. Since all cells expressing either class I or class II MHC molecules can present peptides to T cells, strictly speaking they all could be designated as antigen-presenting cells.

Target cells:
By convention, cells that display peptides associated with class I MHC molecules to cells are referred to as target cells. Virus-infected or intracellular microorganism-infected cells, cancer cells, aging body cells, allogeneic cells from a graft.

APCs:
The cells that display peptides associated with class II MHC molecules to cells are called antigen-presenting cells (APCs) .

Professional APCs:
They constitutively express class II MHC proteins and co-stimulatory molecules.

Dendritic cells, macrophages, and B lymphocytes

These cells differ in their mechanisms of antigen uptake, in whether they constitutively express class II MHC molecules, and in their co-stimulatory activity:

--Dendritic cells are the most effective of the antigen presenting cells. Because these cells constitutively express a high level of class II MHC molecules and co-stimulatory activity, they can activate naive T cells.

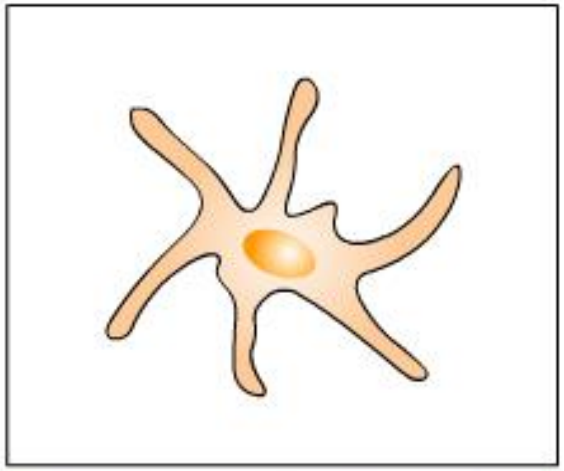
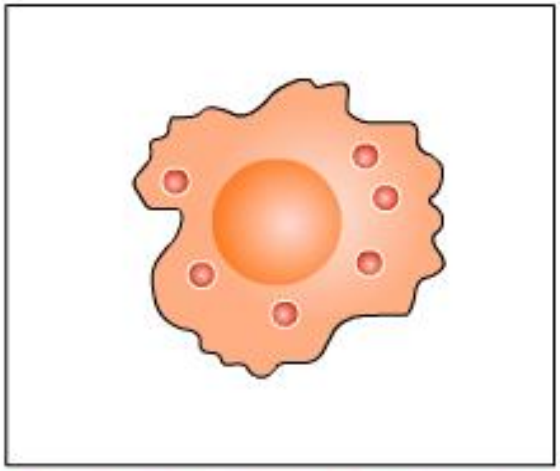
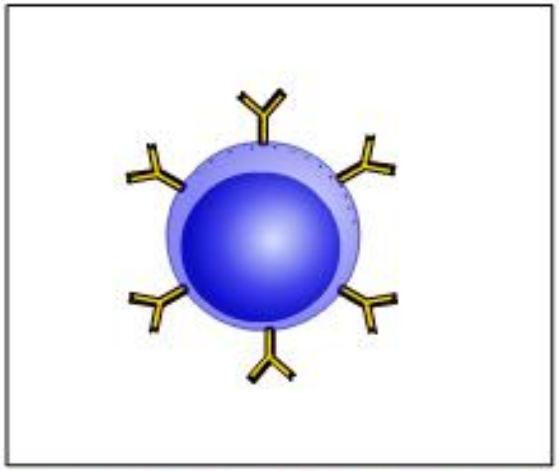
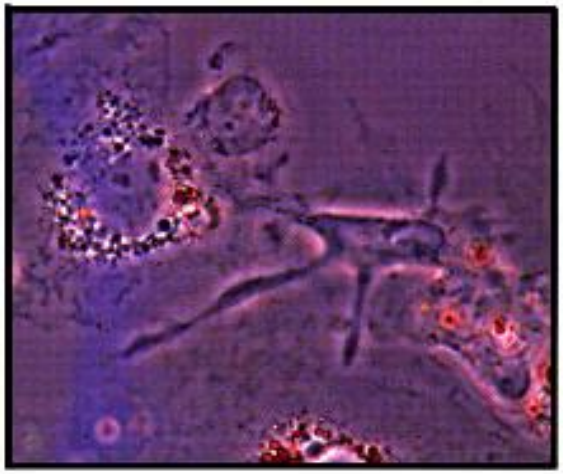
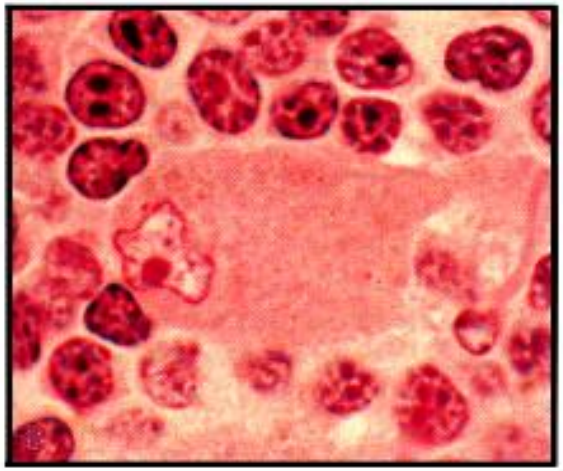
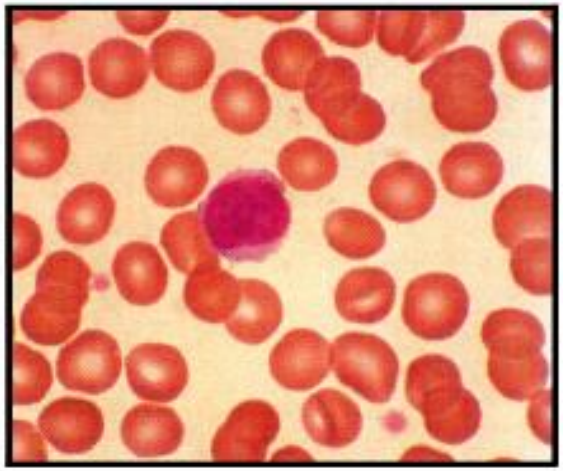
--Macrophages must be activated by phagocytosis of microorganisms before they express class II MHC molecules or the co-stimulatory B7 membrane molecule.

--B cells constitutively express class II MHC molecules but must be activated before they express the co-stimulatory B7 molecule.

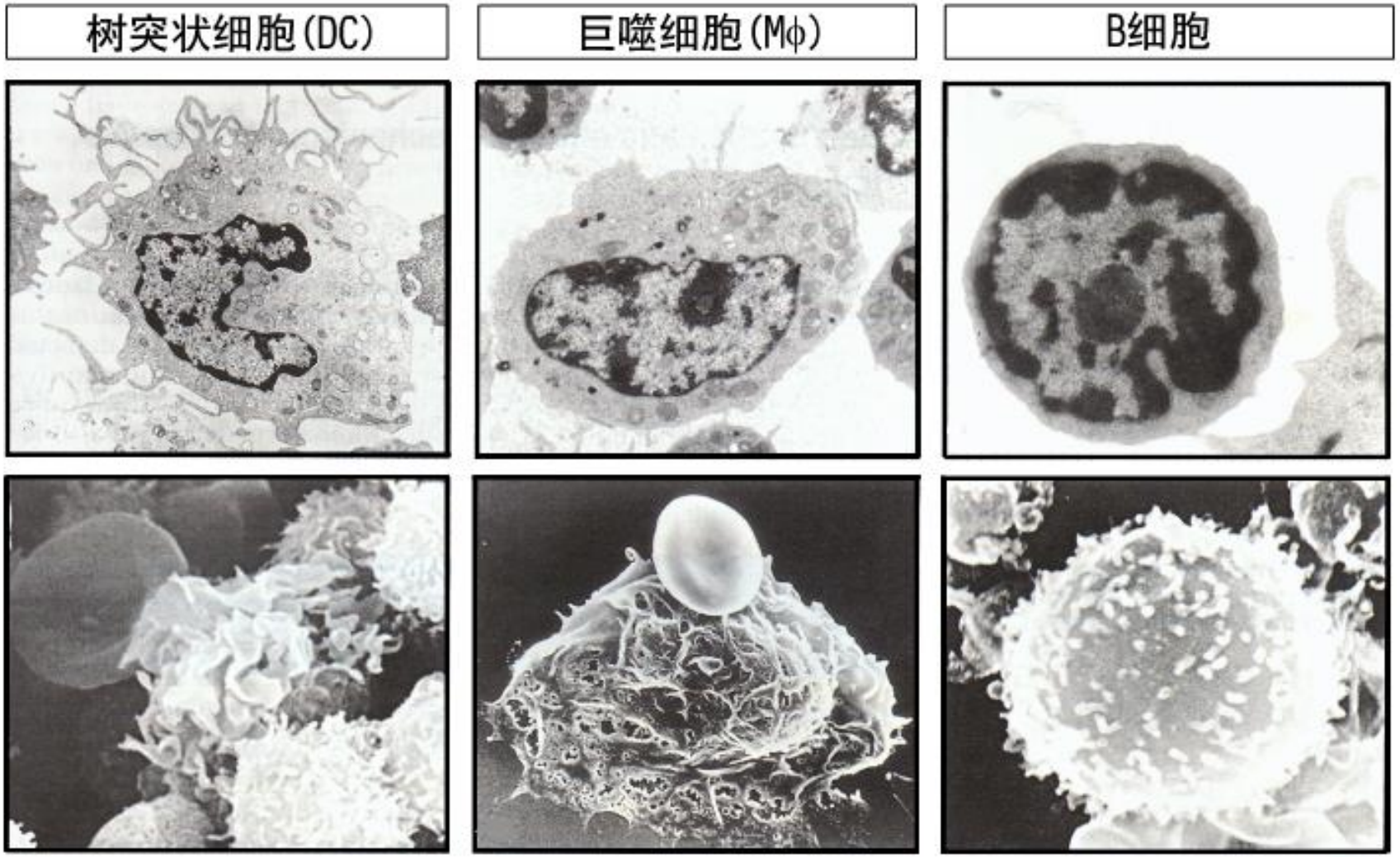
No-professional APCs:
They can be induced to express class II MHC proteins and co-stimulatory molecules.

Several other cell types, classified as nonprofessional antigen-presenting cells, can be induced to express class II MHC molecules or a co-stimulatory signal. Many of these cells function in antigen presentation only for short periods of time during a sustained inflammatory response.

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

树突状细胞(DC)	巨噬细胞(Mϕ)	B细胞
		
		

抗原提呈细胞(APC)染色



抗原提呈细胞(APC)电镜照片

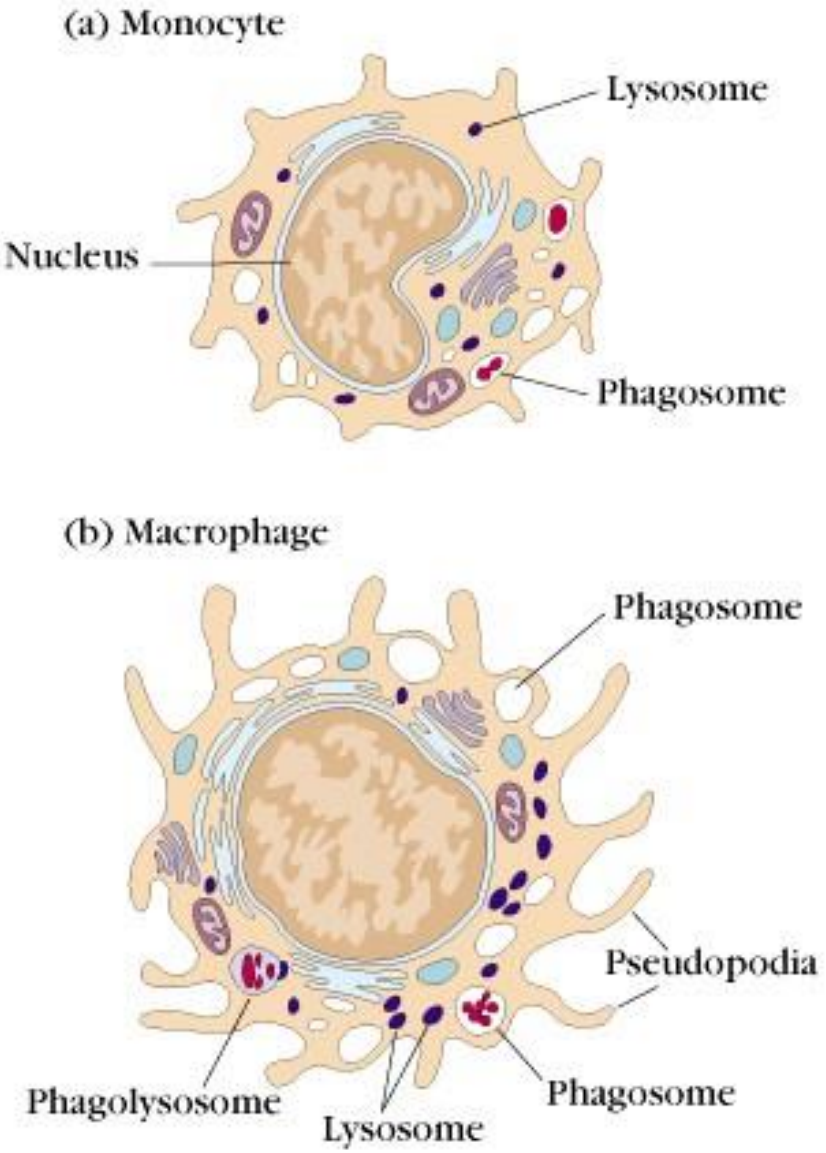
Immunology

MPS

Mononuclear phagocyte system (MPS) :
consists of pre-monocytes in bone marrow, monocytes circulating in peripheral blood and macrophages in tissues.

Monocytes: 1-6% of all nucleated blood cells, circulate in the blood stream for about one day, during which they enlarge and then migrate into the tissues and differentiate into macrophages.

Nearly all tissues, organs, and serosal cavities harbor a population of resident macrophages.



Surface marks of Macrophages

--Most types of macrophages express MHC proteins, their levels of MHC class II proteins, B7.1 and B7.2 expression increase when they become activated.

--express a family of very broad-specificity receptors, called scavenger receptors

--also have receptors for complement components, Fc of IgG, cytokines, and other opsonins.

--express LPS receptor called membrane CD14. It belong to Toll-like receptors, are especially important for activating macrophage.

Their many broad-specificity receptors enable macrophages to capture a wide range of pathogens, but their affinity for most ligands is low, so that most unopsonized immunogens must accumulate to relatively high local concentrations to be presented efficiently by macrophages.

Products of Macrophages

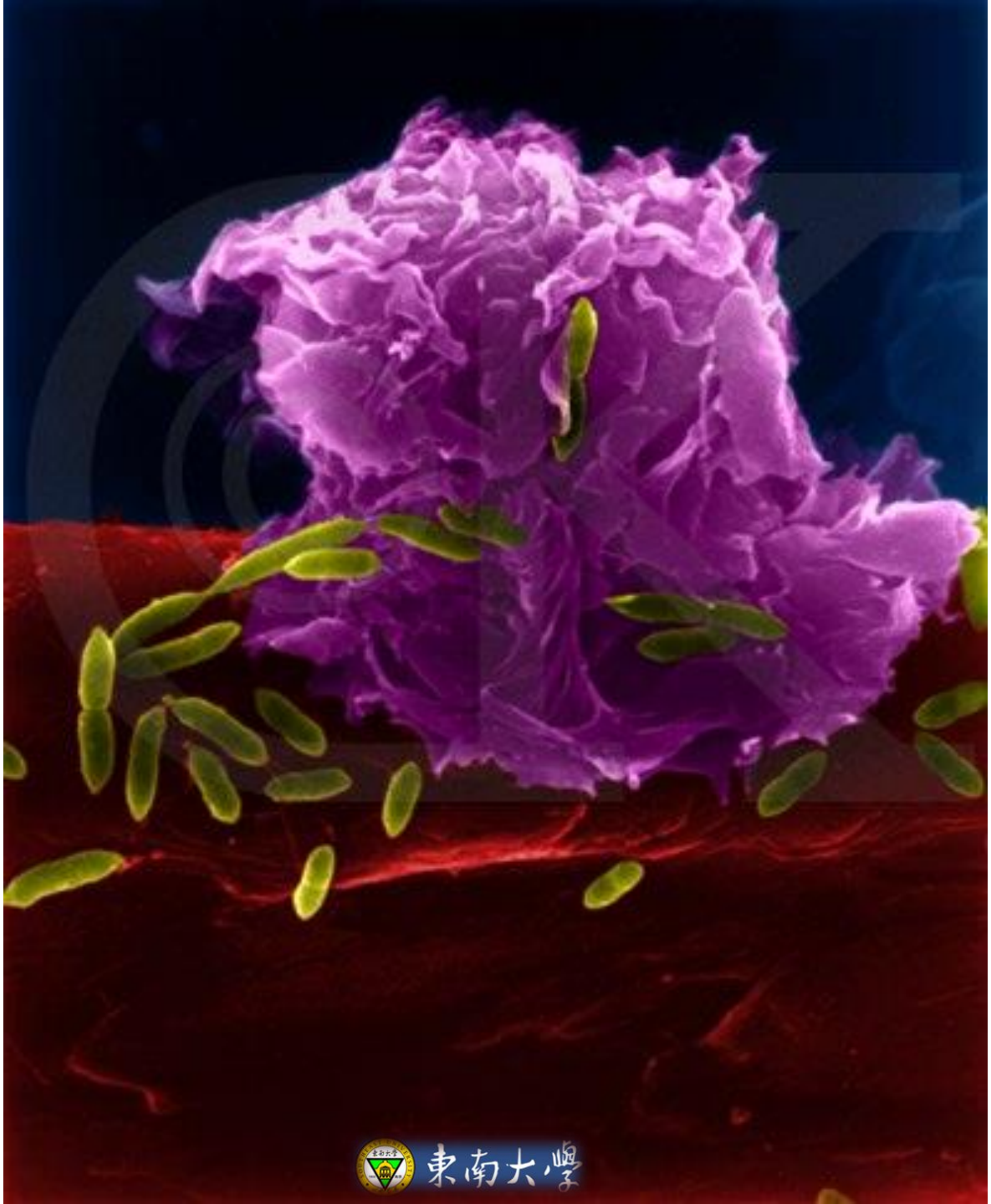
Activated macrophages not only function as phagocytes, but also specifically secrete an enormous variety of biologically active substances into the surrounding tissues.

Over 100 macrophage secretory products have been identified as far.

Lysozyme, complement components, hydrogen peroxide:
have anti-microbial activity

elatases, collagenases:
act to liquefy and remodel the extracellular matrix. These process facilitates cellular migration and helps clear the way for the healing process.

cytokines: colony-stimulating factors, IL-6, IL-2, IL-1, Fibroblast growth factors, prostaglandins chemokins: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Antigen processing and presentation by macrophages

Capture and process the antigen, they can intake the antigens by:

- Phagocytosis for particle antigens
- Pinocytosis for soluble antigens
- Receptor-mediated endocytosis

The processed foreign substances are then presented to $CD4^+$ T cells in complex with class II MHC proteins.

Dendritic cells (DC)

DC represents the class of APCs that initiates most immune responses.

Dendritic cells have numerous specialized features that make them extremely efficient at capturing and presenting antigens and at activating T cells.

DCs are responsible for launching most acquired immune responses, and particularly for primary responses.

Surface markers of DC

1 morphological feature: dendrites

2 the relative distinctive markers of human DC:

CD1a, CD11c, CD83

3 also express: MHC class II molecules, CD80/CD86, CD40,

CD44, CD54, FcR

4 secret cytokines: IL-1, IL-6, IL-8, IL-12, TNF-a, IFN-a

Identification of DC:

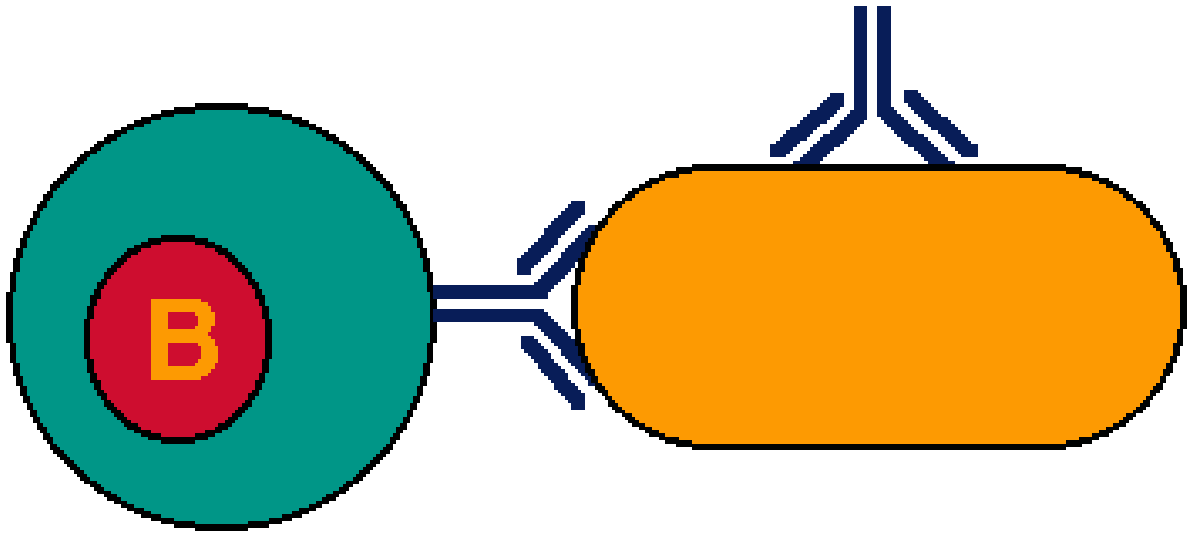
dendrites

CD1a, CD11c, CD83, MHC class II molecules,

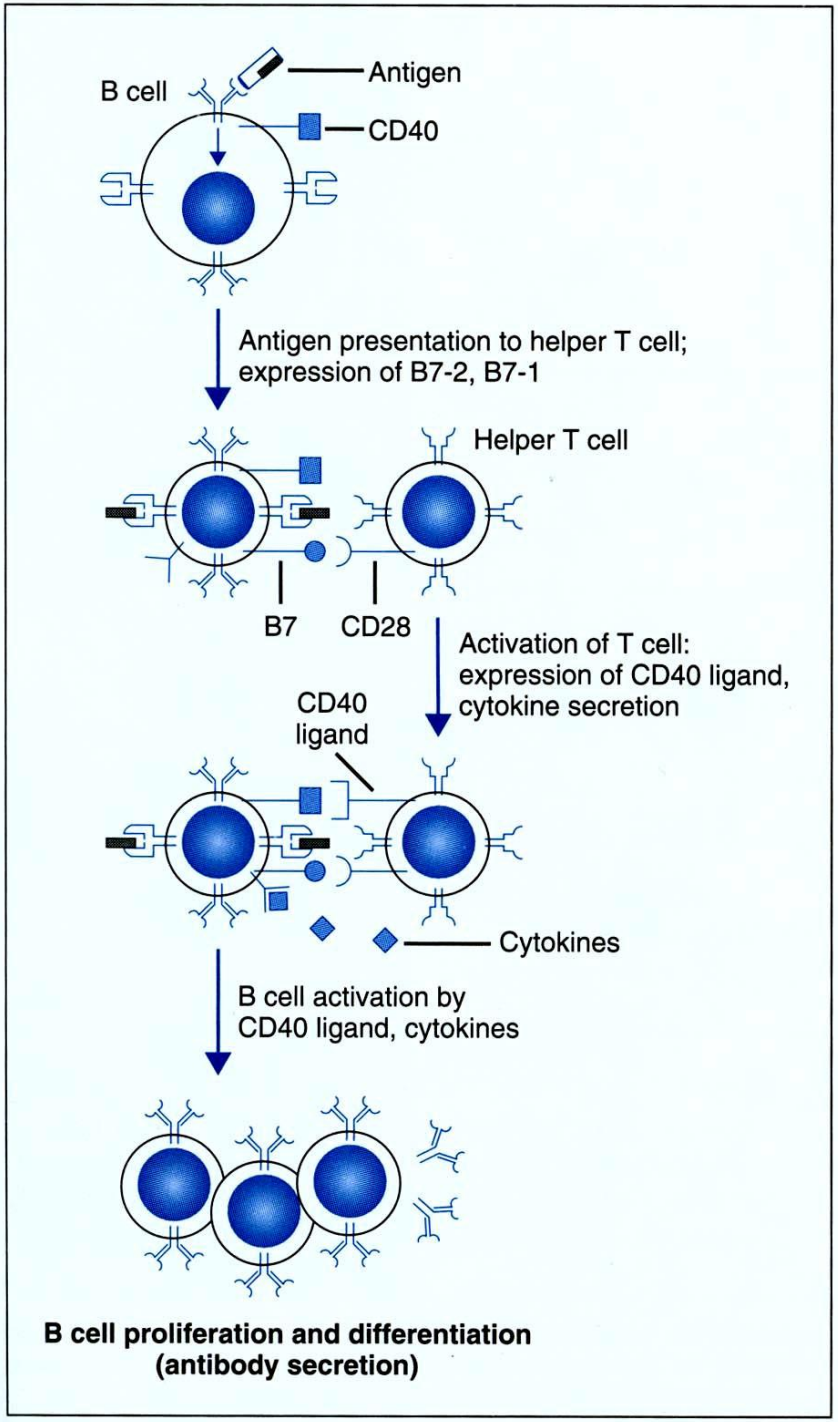
MLR: stimulate the naïve T cell proliferation

B cell antigen recognition

The B cell antigen receptor is cell surface immunoglobulin (smIg)



Soluble antibodies and surface membrane immunoglobulin bind directly to native antigens



B cell proliferation and differentiation (antibody secretion)

Endocytic pathway(class II):

Exogenous antigens ⟶ peptide/MHC class II complexes ⟶ CD4+ T cell

(Phagocytosis, endocytosis, pinocytosis)

Cytosolic pathway(class I):

Endogenous antigens ⟶ peptide/MHC class I complexes ⟶ CD8+ T cell

(virus protein, intracellular bacteria, intracellular parasites)

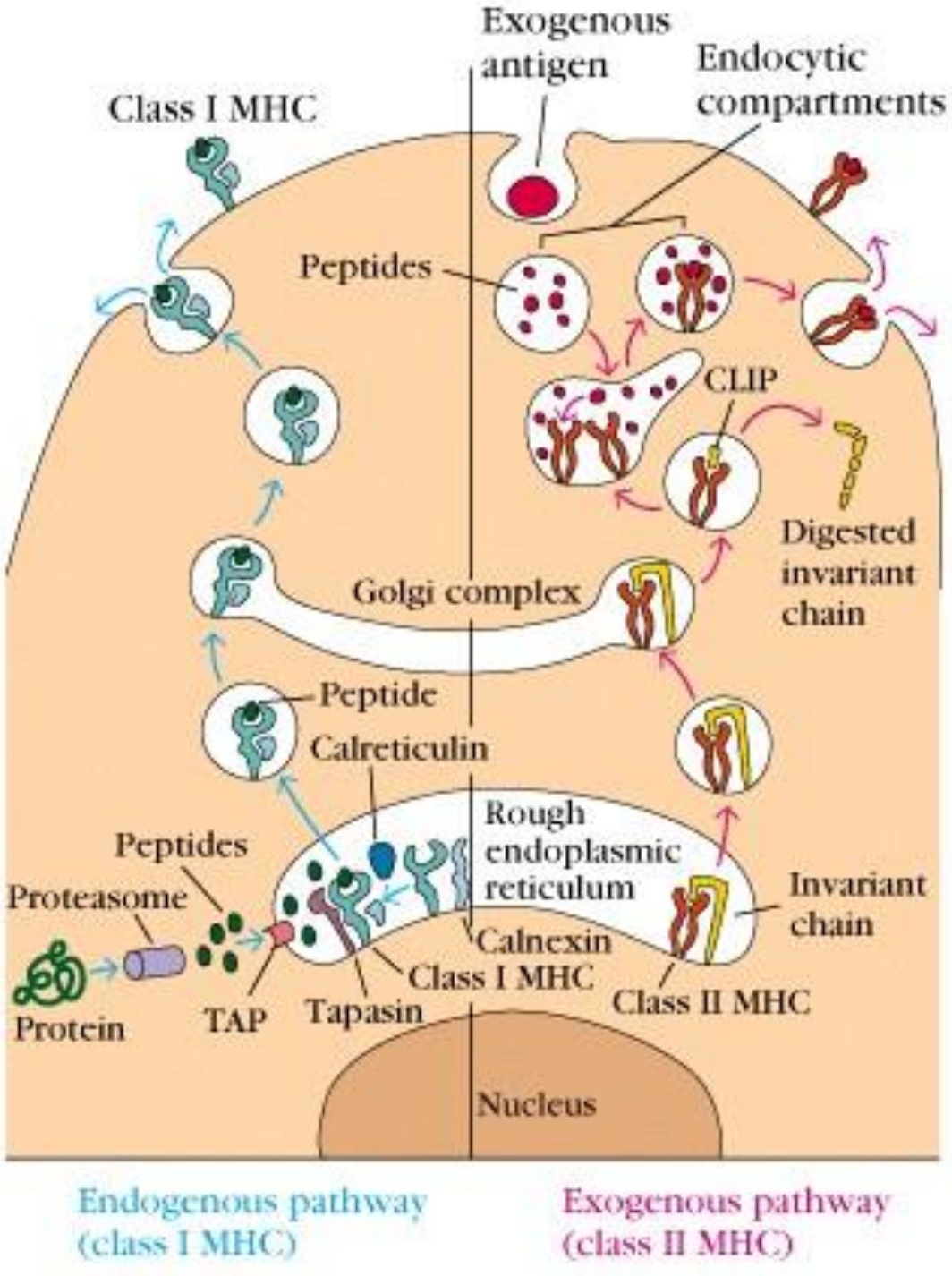
CD1 pathway:

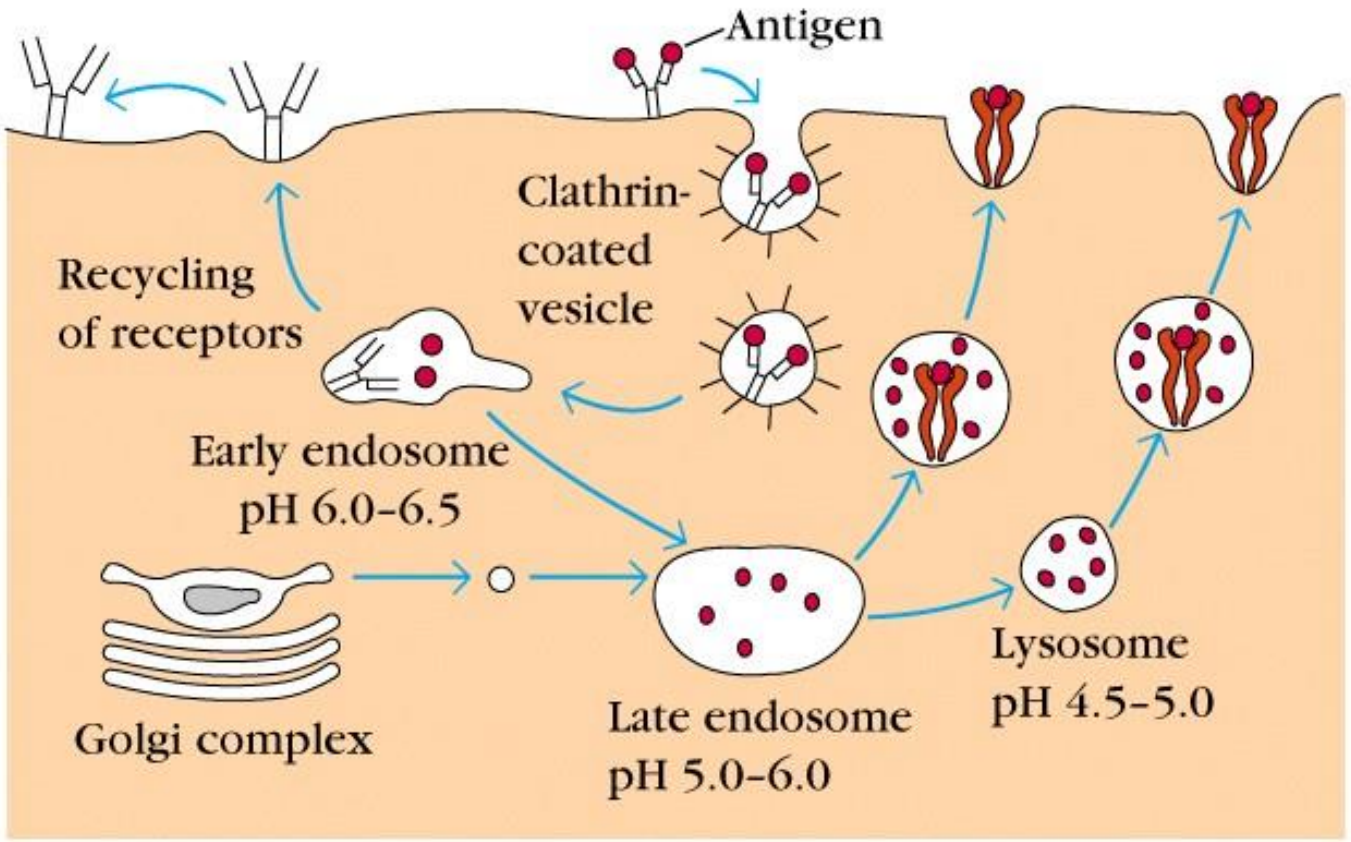
lipids, glycolipids ⟶ CD1d /lipid complexes ⟶ NKT cell

Overview of cytosolic and endocytic pathways for processing antigen. The proteasome complex contains enzymes that cleave peptide bonds, converting proteins into peptides.

The antigenic peptides from proteasome cleavage and those from endocytic compartments associate with class I or class II MHC molecules, and the peptide-MHC complexes then are transported to the cell membrane. TAP (transporter of antigenic peptides) transports the peptides to the endoplasmic reticulum.

It should be pointed out that the ultimate fate of most peptides in the cell is neither of these pathways, but rather to be degraded completely into amino acids.

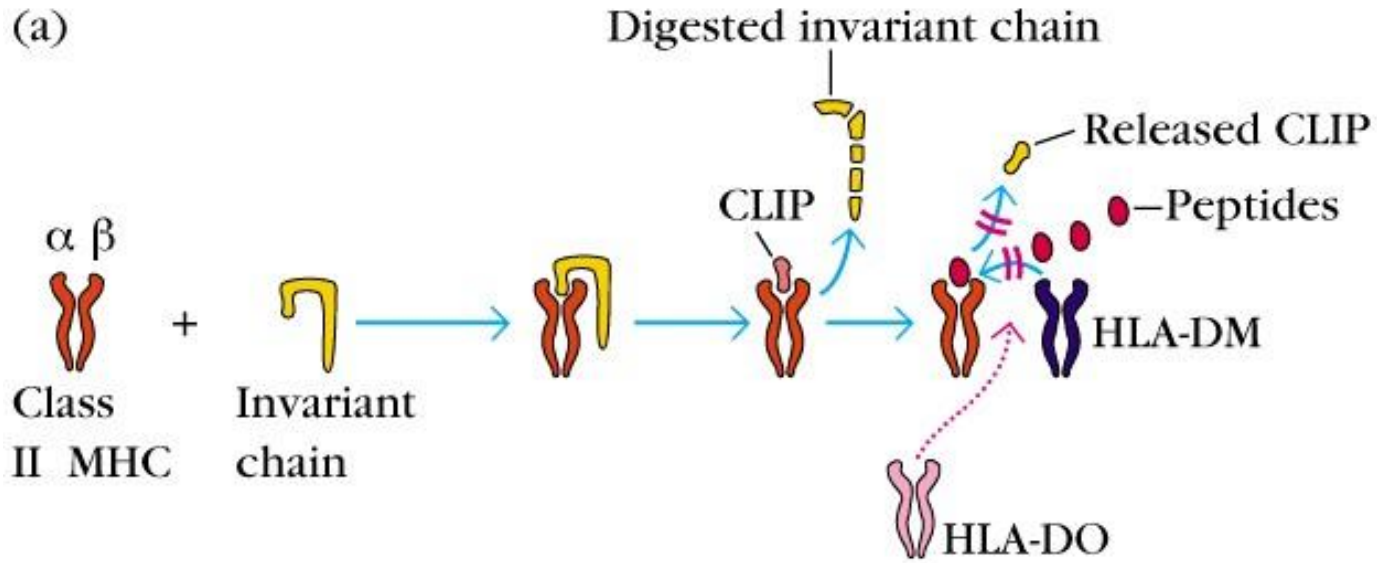




Generation of antigenic peptides in the endocytic processing pathway.

Internalized exogenous antigen moves through several acidic compartments, in which it is degraded into peptides that ultimately associate with class II MHC molecules transported in vesicles from the Golgi complex.

The cell shown here is a B cell, which internalizes antigen by receptor-mediated endocytosis, with the membrane-bound antibody functioning as an antigen-specific receptor.



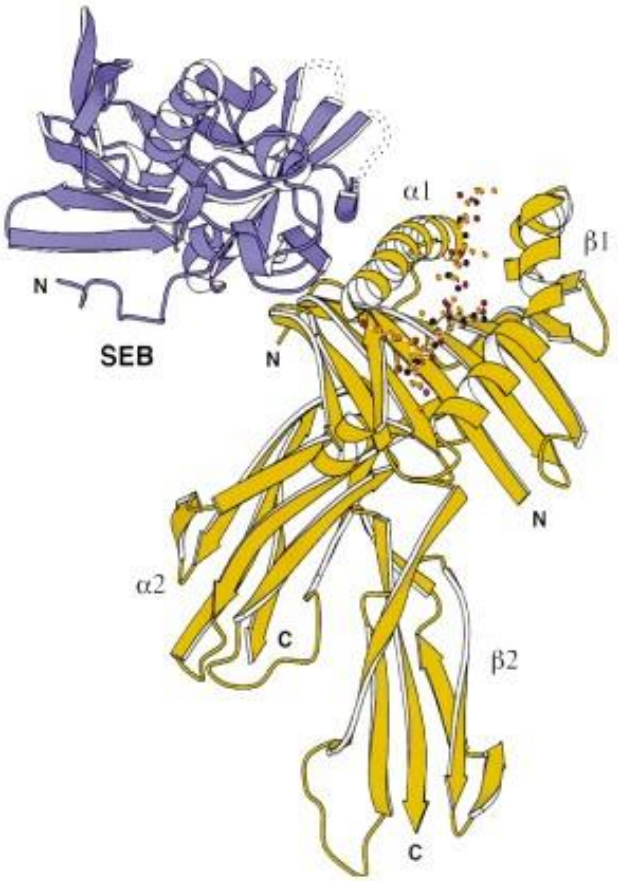
(a) Assembly of class II MHC molecules.

Within the rough endoplasmic reticulum, a newly synthesized class II MHC molecule binds an invariant chain. The bound invariant chain prevents premature binding of peptides to the class II molecule and helps to direct the complex to endocytic compartments containing peptides derived from exogenous antigens.

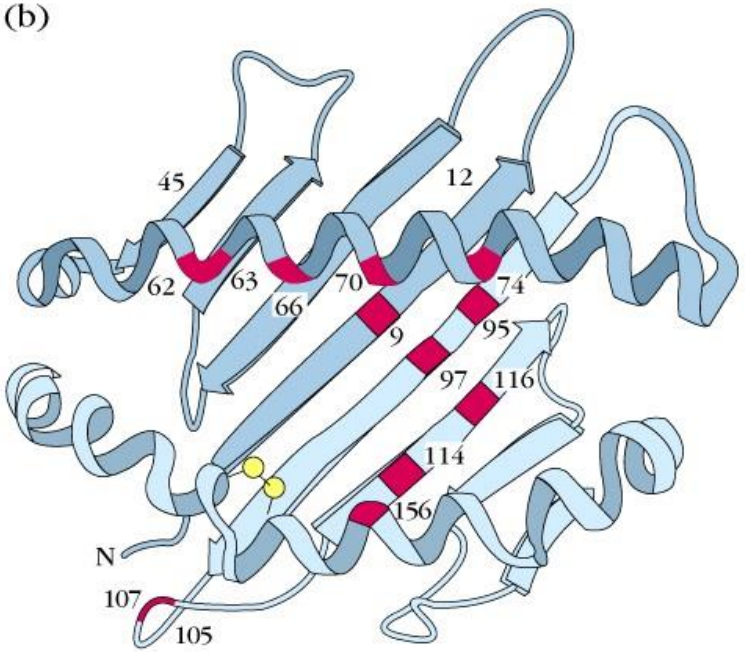
Digestion of the invariant chain leaves CLIP, a small fragment remaining in the binding groove of the class II MHC molecule. HLA-DM, a nonclassical MHC class II molecule expressed within endosomal compartments, mediates the exchange of antigenic peptides for CLIP.

The nonclassical class II molecule HLA-DO may act as a negative regulator of class II antigen processing by binding to HLA-DM and inhibiting its role in the dissociation of CLIP from class II molecules.

(c)


α1
β1
N
SEB
N
N
α2
C
β2
C

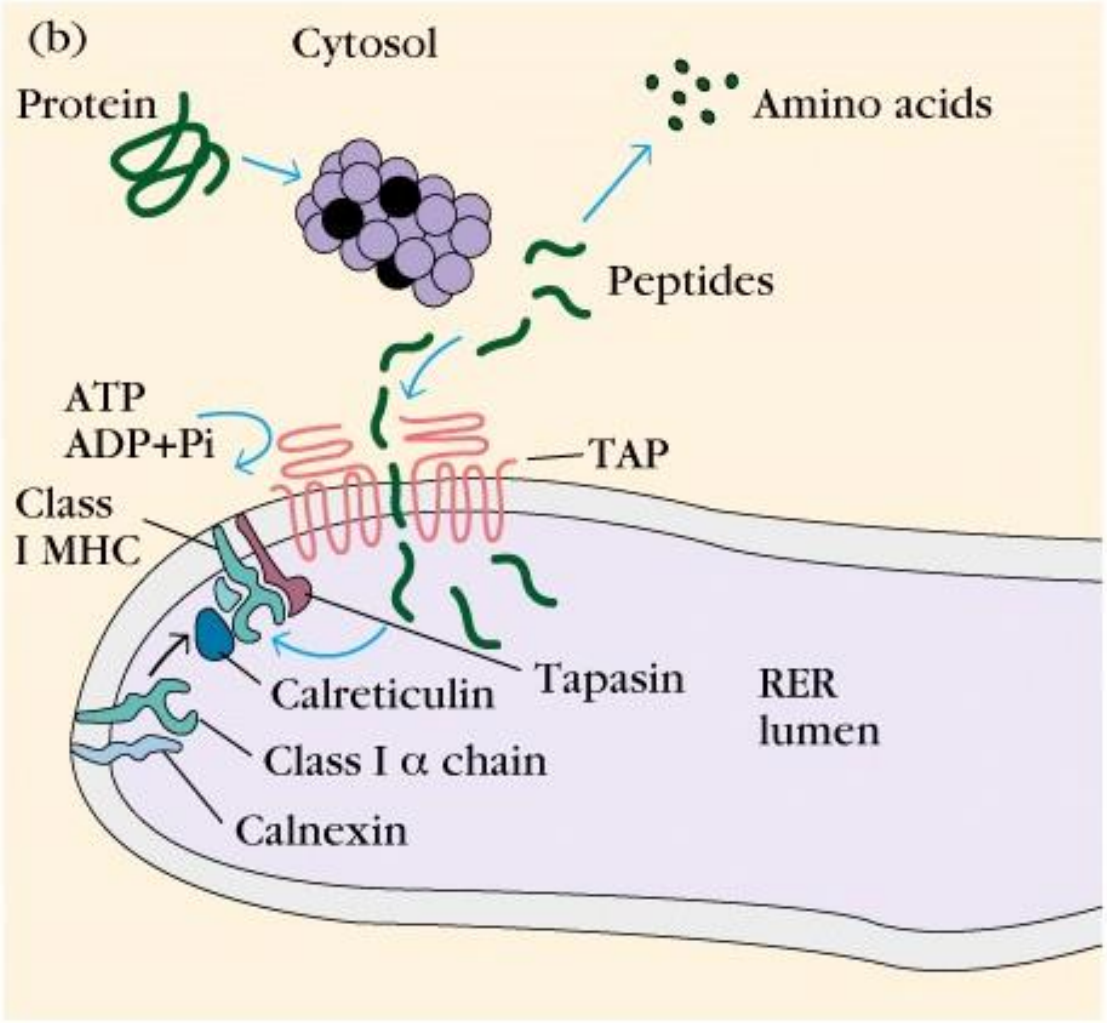
(b)

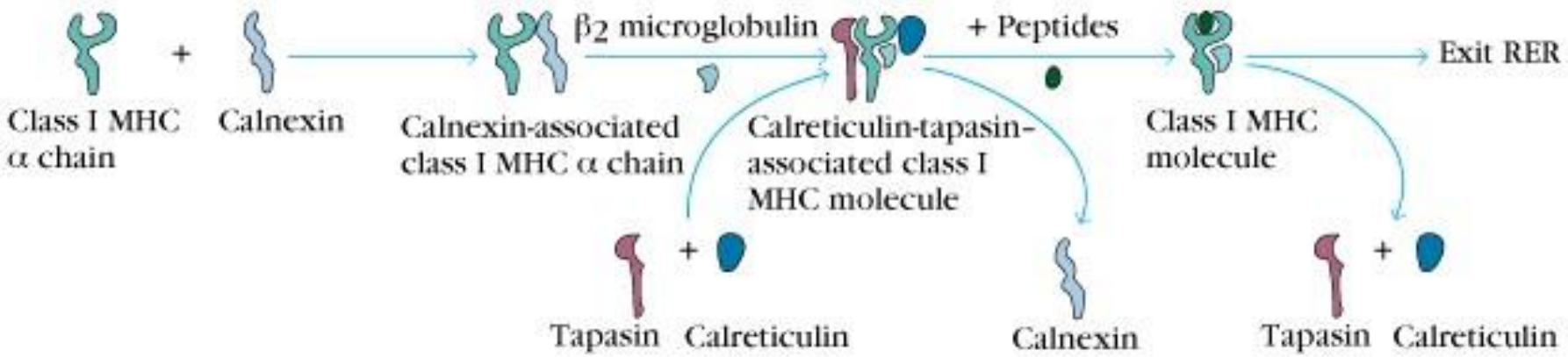

45
12
62
63
66
70
74
9
95
97
116
114
156
N
107
105

Generation of antigenic peptide–class I MHC complexes in the cytosolic pathway.

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, newly synthesized class I chain associates with calnexin until binds to the chain. The class I chain–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.




+
Class I MHC α chain
Calnexin
Calnexin-associated class I MHC α chain
β2 microglobulin
Calreticulin-tapasin-associated class I MHC molecule
+ Peptides
Class I MHC molecule
Exit RER
+
Tapasin
Calreticulin
Calnexin
+
Tapasin
Calreticulin

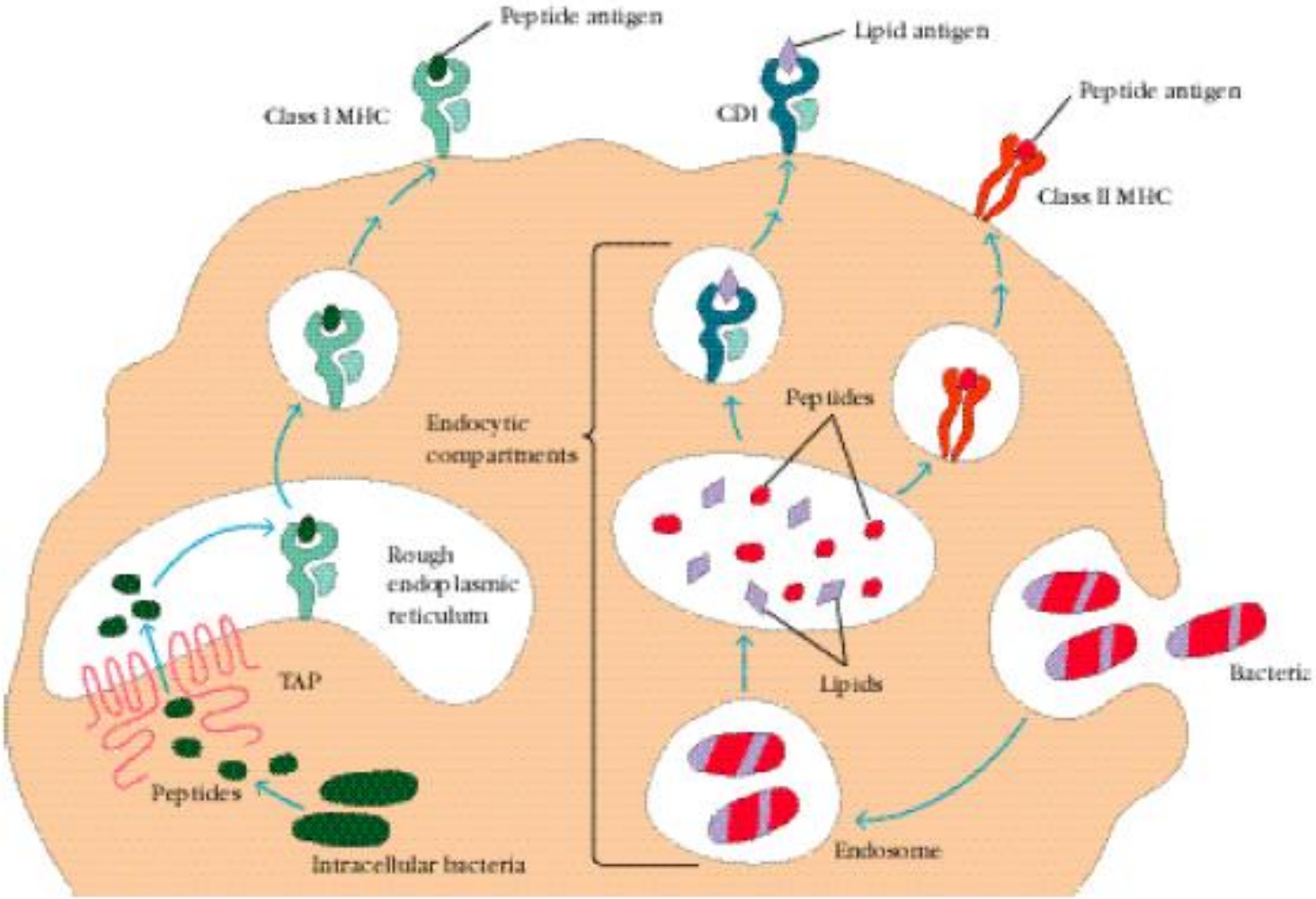


FIGURE 8-11 A role for the class I–like CD1 molecules in presentation of nonpeptide antigens from bacteria. CD1 molecules, which are not encoded within the MHC, have been shown to present lipid and glycolipid antigens from *Mycobacterium tuberculosis* and *Mycobacterium leprae*. A proposed scheme for the action of CD1 comparable to class I and II presentation of peptides is shown. Details of the CD1 pathway remain obscure. [Adapted from Melian et al. 1996. *Curr. Opin. Immunol.* 8:82–88.]