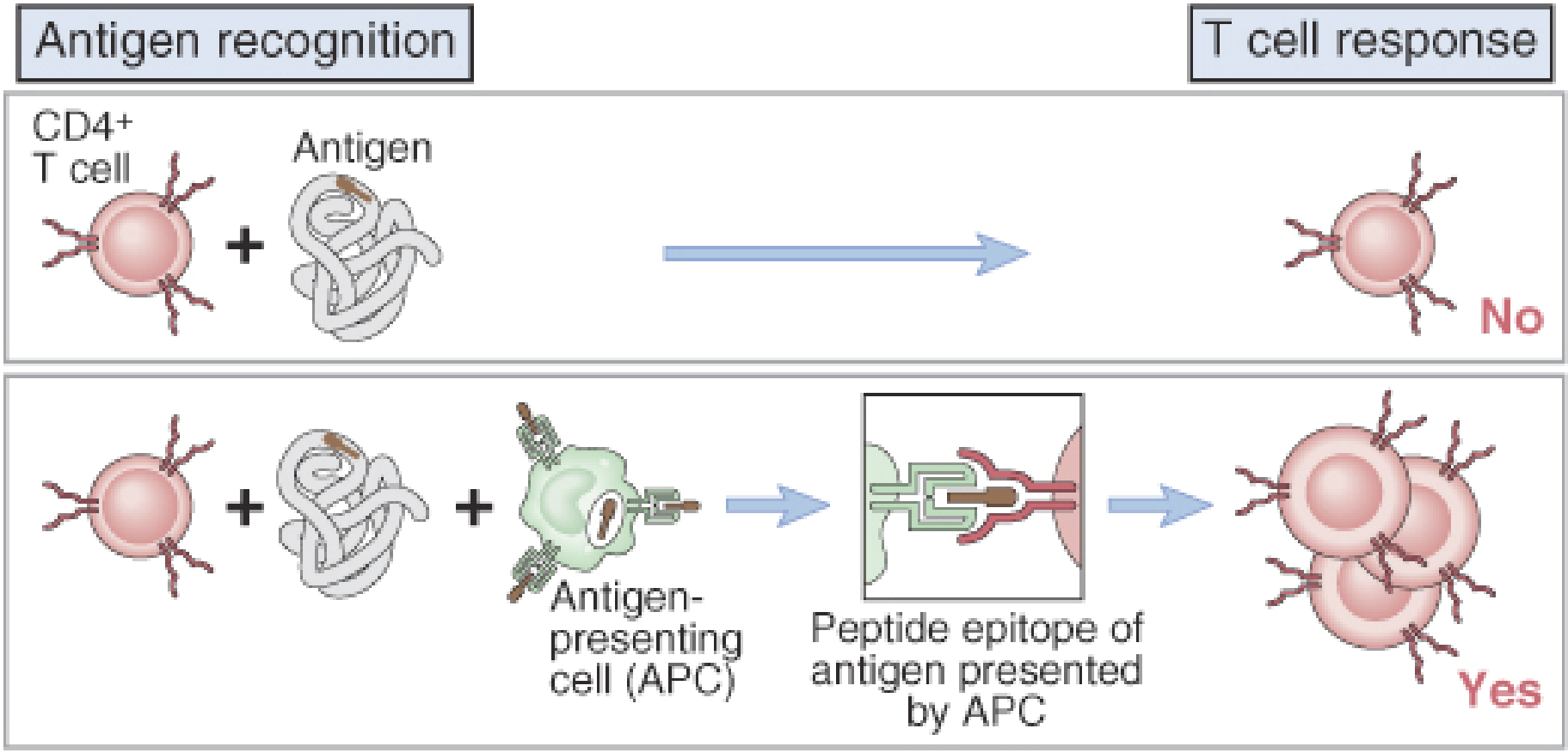
Antigen processing and presentation

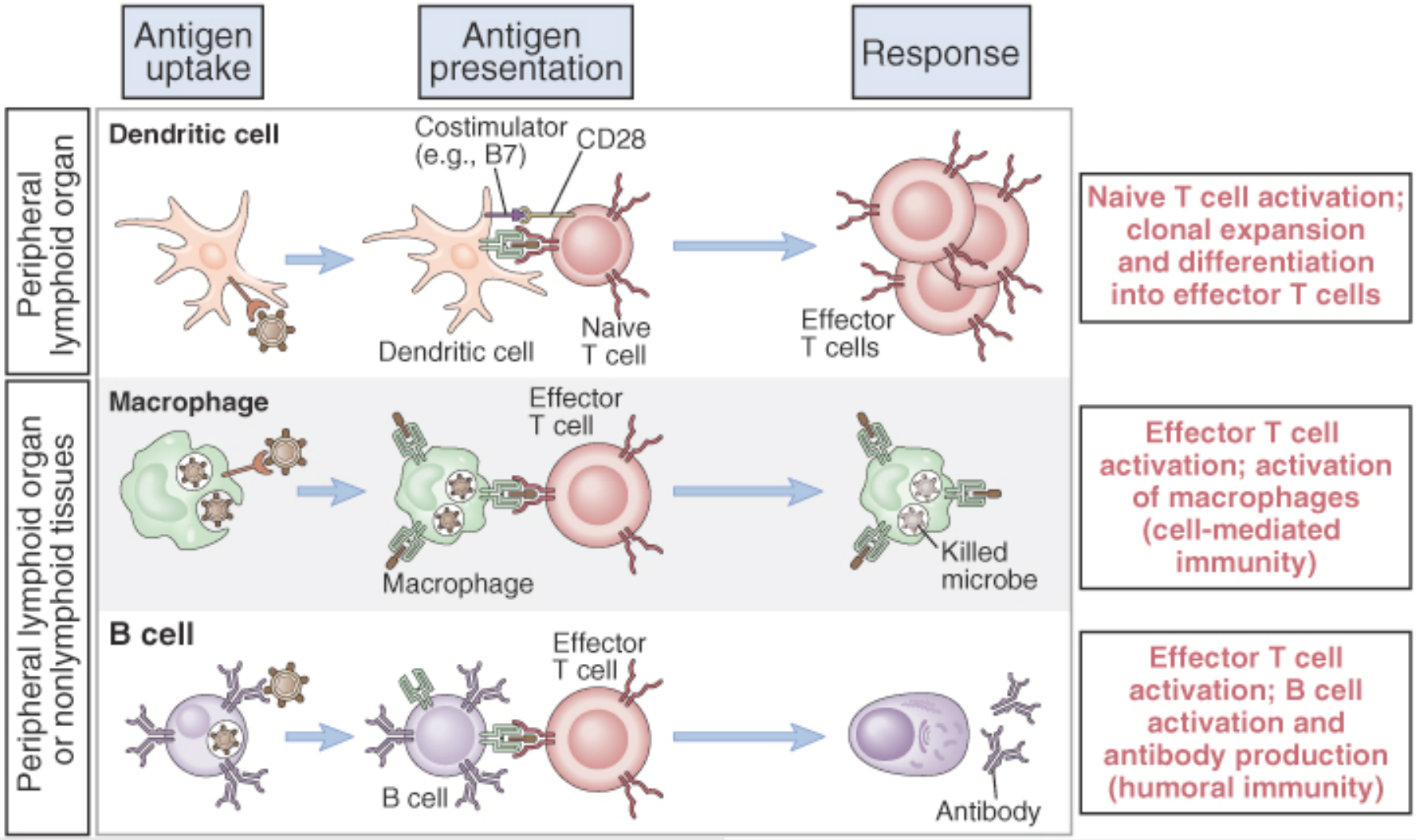
Requirement for Antigen Presenting Cells (APCs)



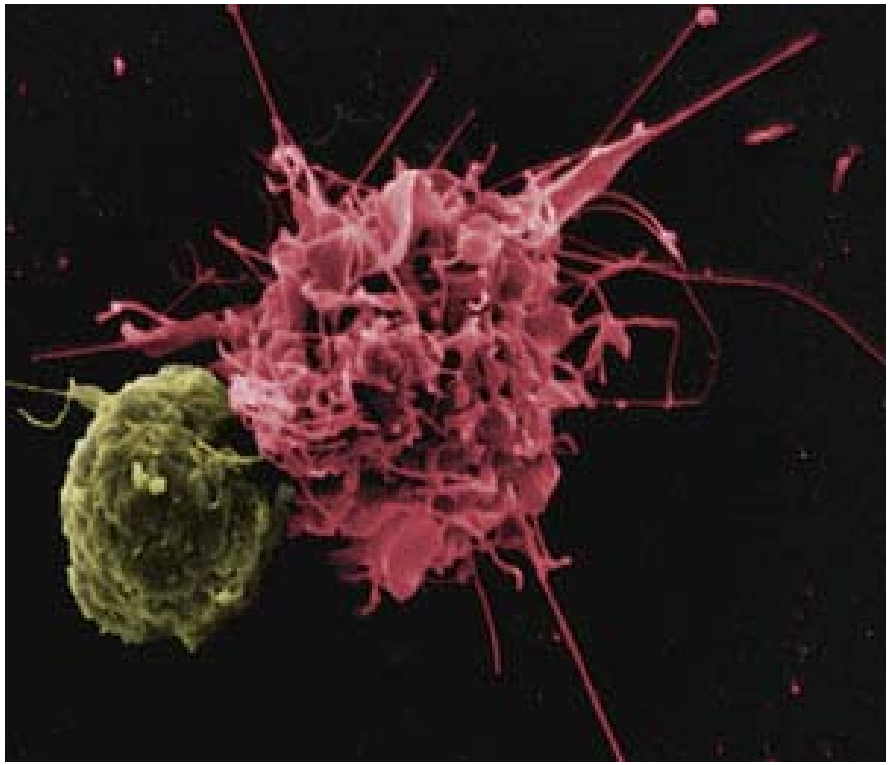
Properties and functions of APCs

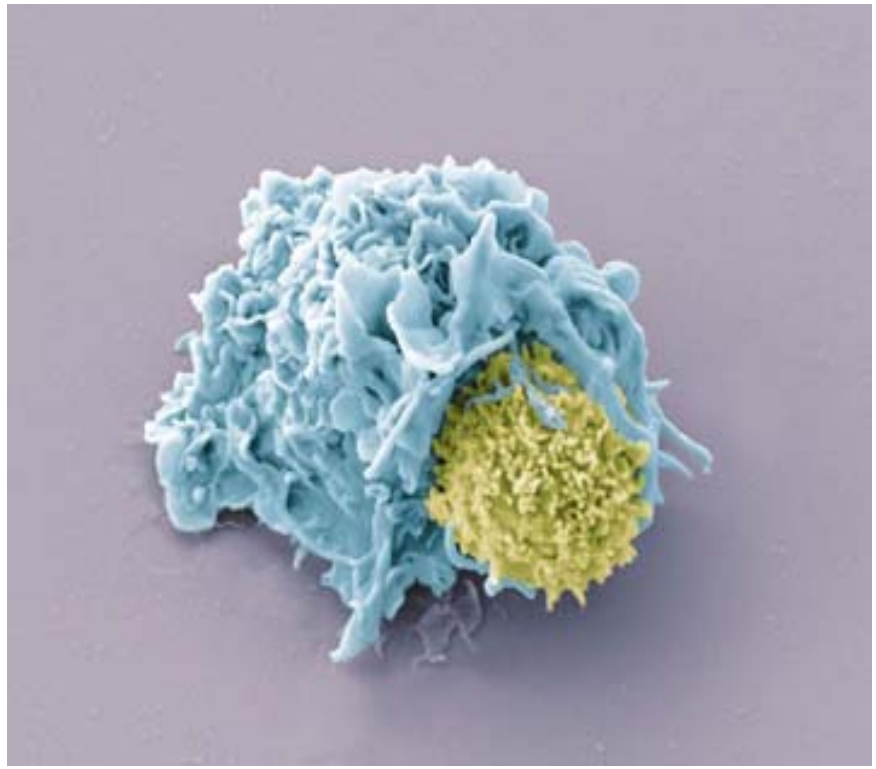
Cell type	Expression of		Principal function
	Class II MHC	Costimulators	
Dendritic cells	Constitutive; increases with maturation; increased by IFN-γ	Constitutive; increases with maturation; inducible by IFN-γ, CD40-CD40L interactions	Initiation of T cell responses to protein antigens (priming)
Macrophages	Low or negative; inducible by IFN-γ	Inducible by LPS, IFN-γ, CD40-CD40L interactions	Effector phase of cell-mediated immune responses
B lymphocytes	Constitutive; increased by IL-4	Induced by T cells (CD40-CD40L interactions), antigen receptor cross-linking	Antigen presentation to $CD4^+$ helper T cells in humoral immune responses (cognate T cell–B cell interactions)
Vascular endothelial cells	Inducible by IFN-γ; constitutive in humans	Constitutive (inducible in mice)	May promote activation of antigen-specific T cells at site of antigen exposure
Various epithelial and mesenchymal cells	Inducible by IFN-γ	Probably none	No known physiologic function

Functions of different APCs

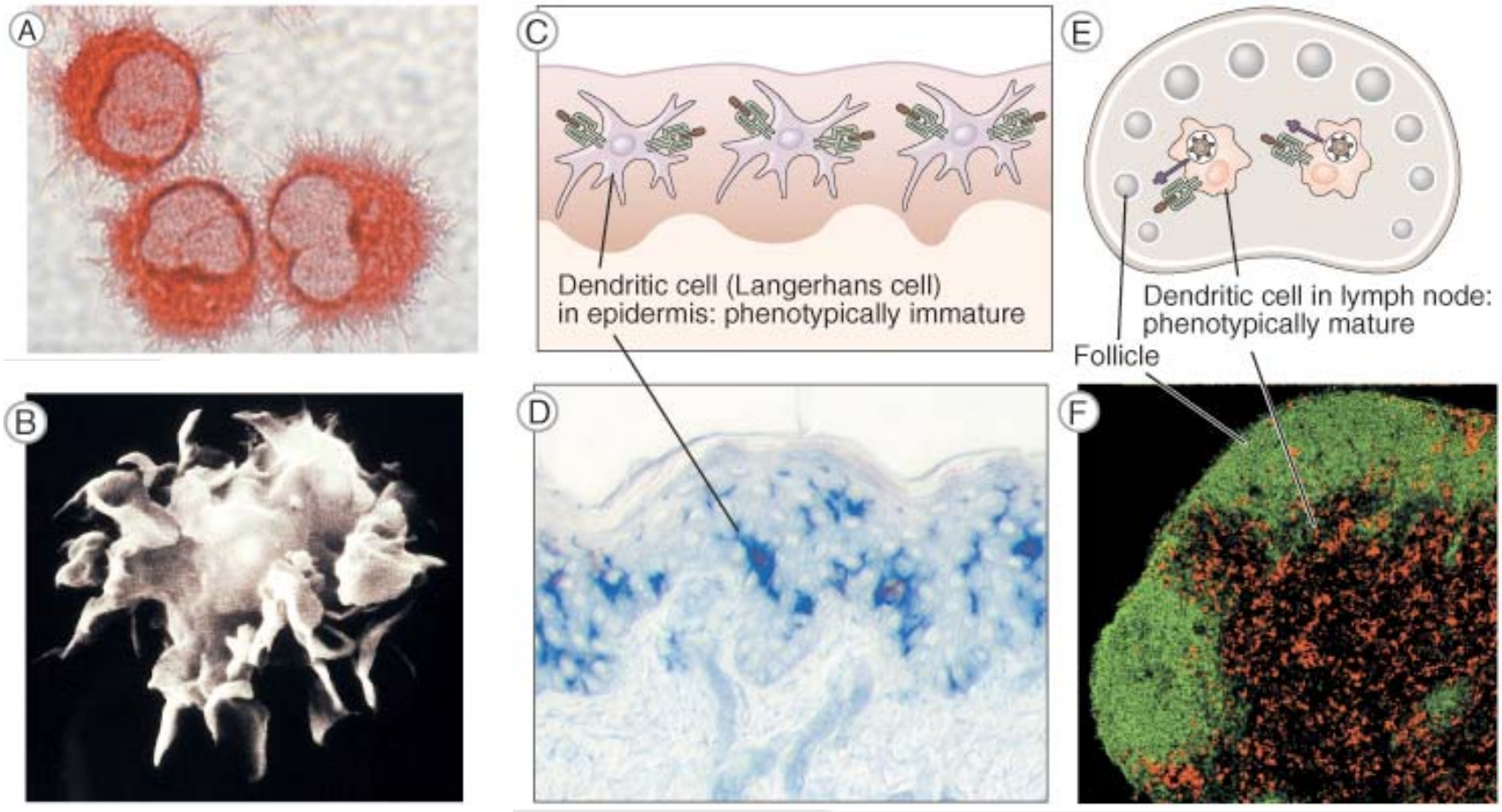


Dendritic cell - T cell interactions

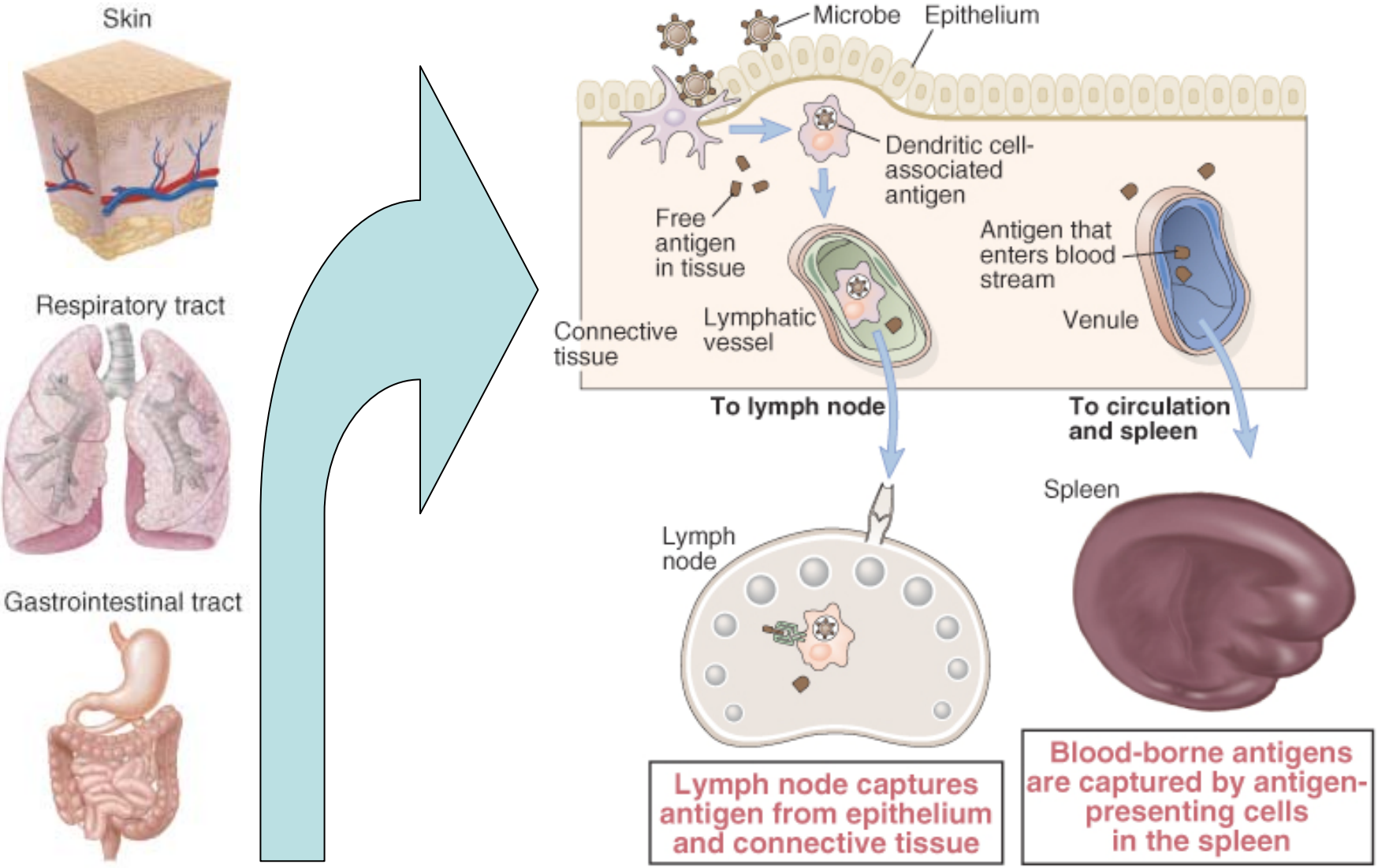




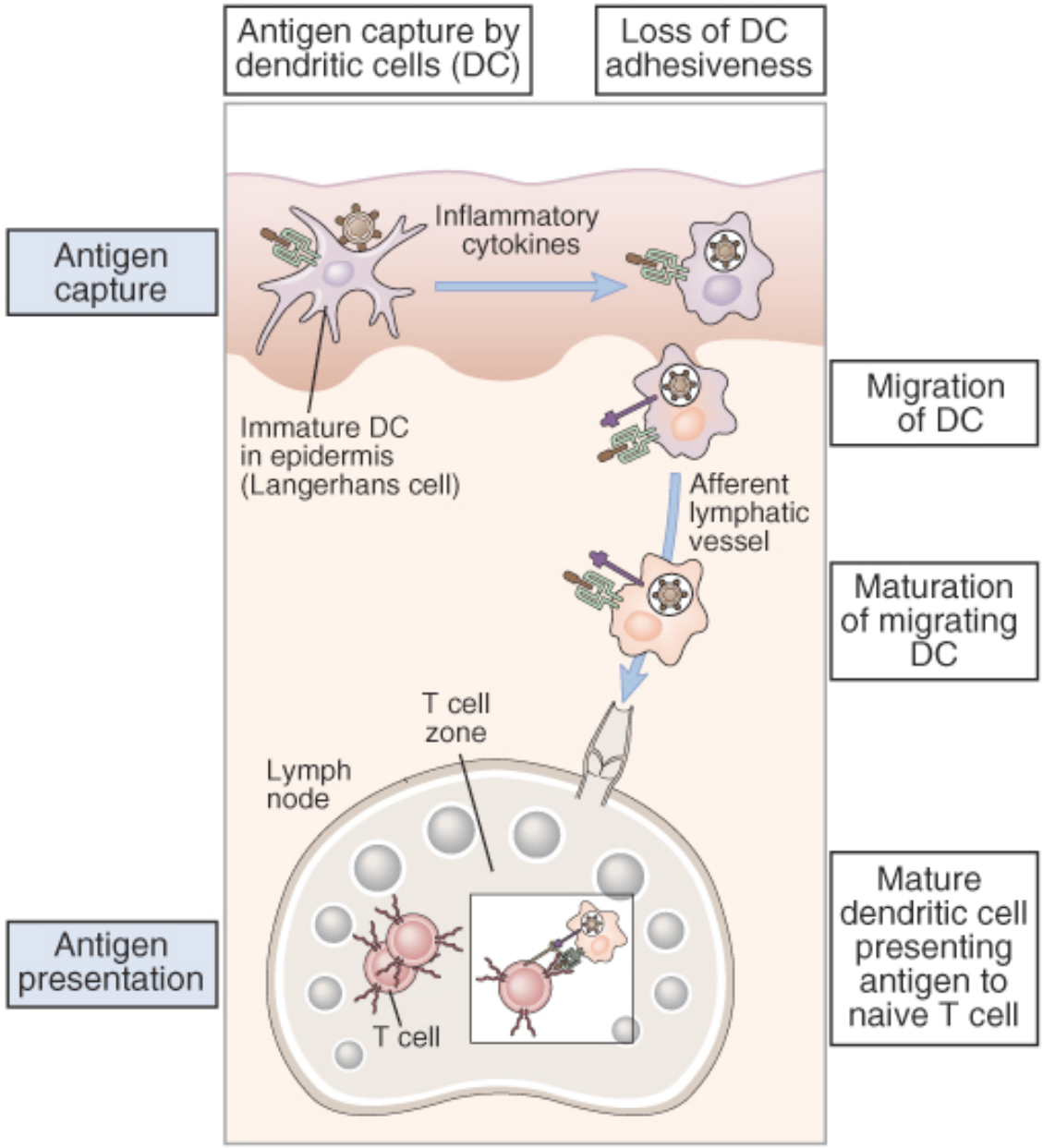
Human Dendritic Cells



Routes of antigen entry



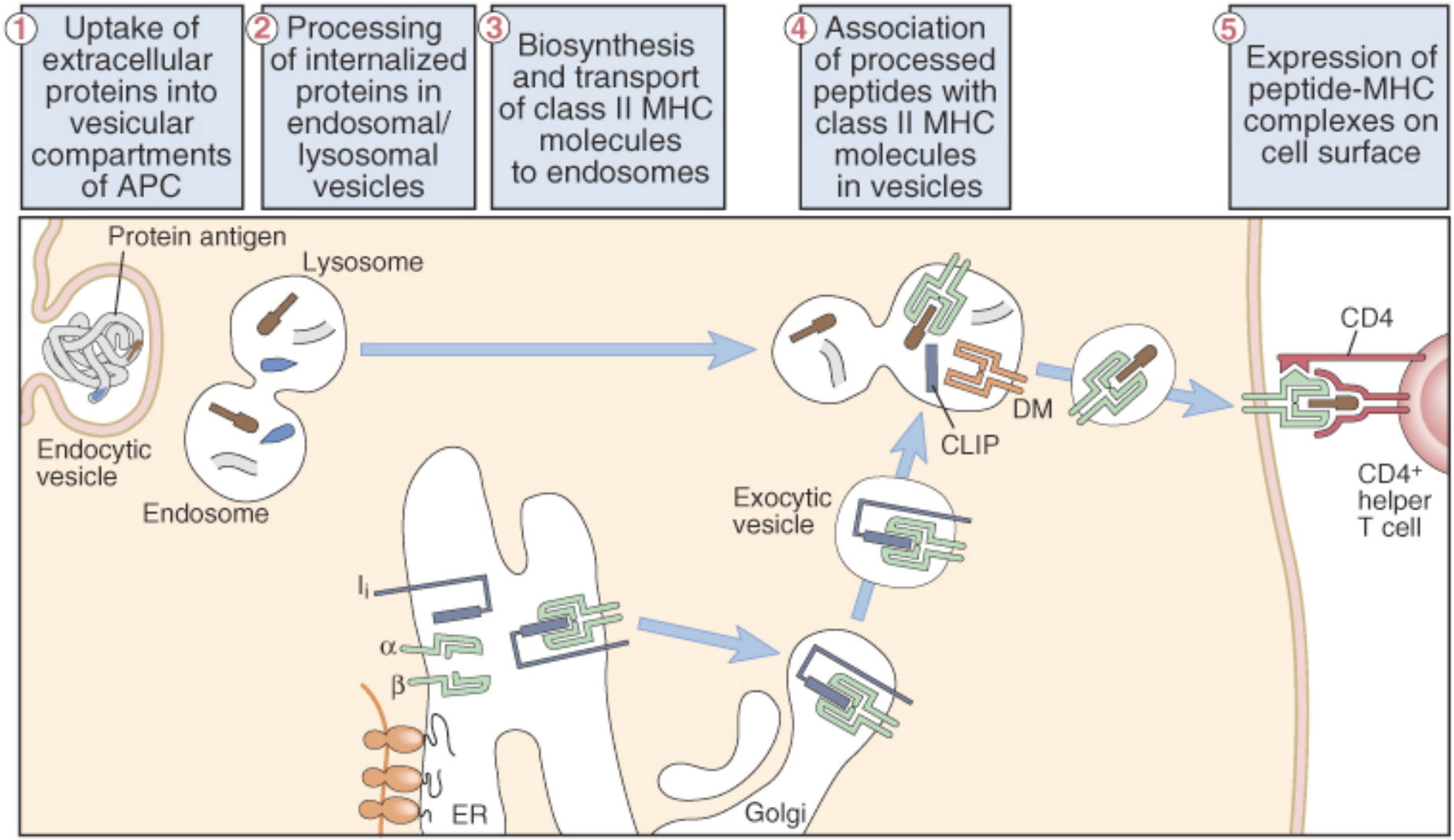
Maturation of dendritic cells



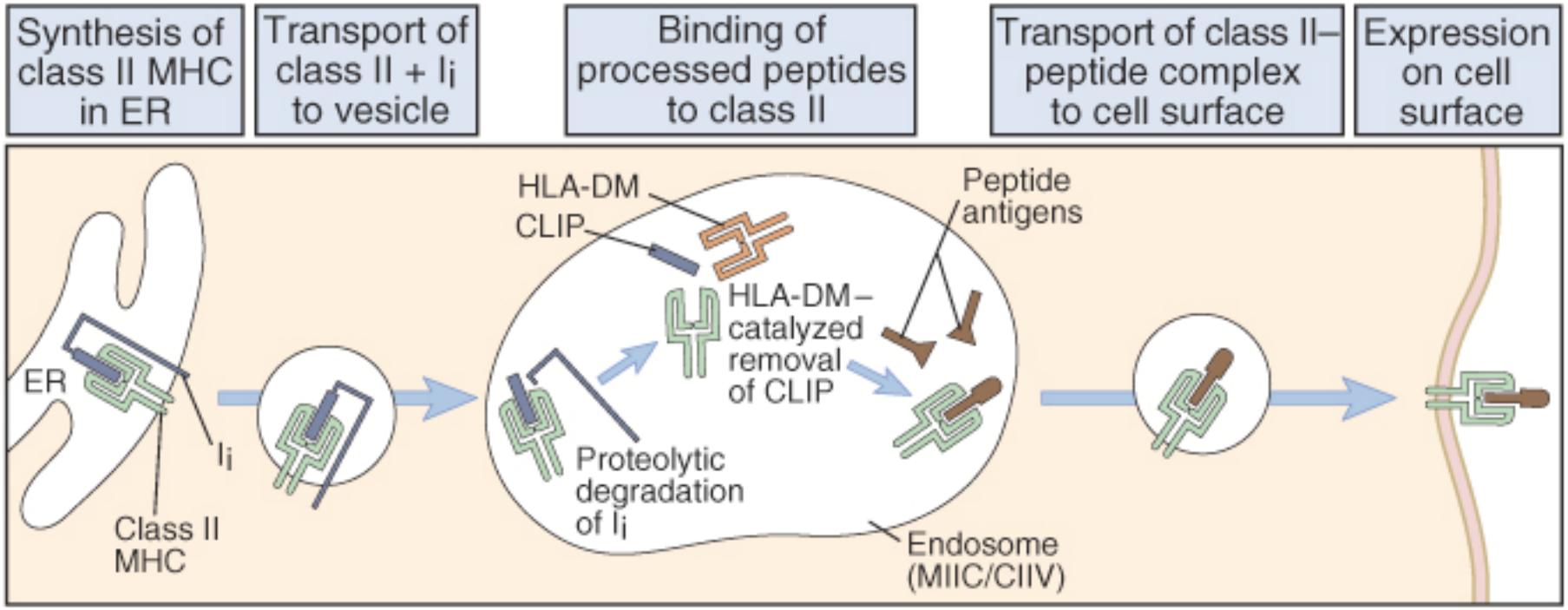
Immature vs. mature dendritic cells

	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	~10^6	~7 x 10^6

The class II MHC pathway of antigen presentation

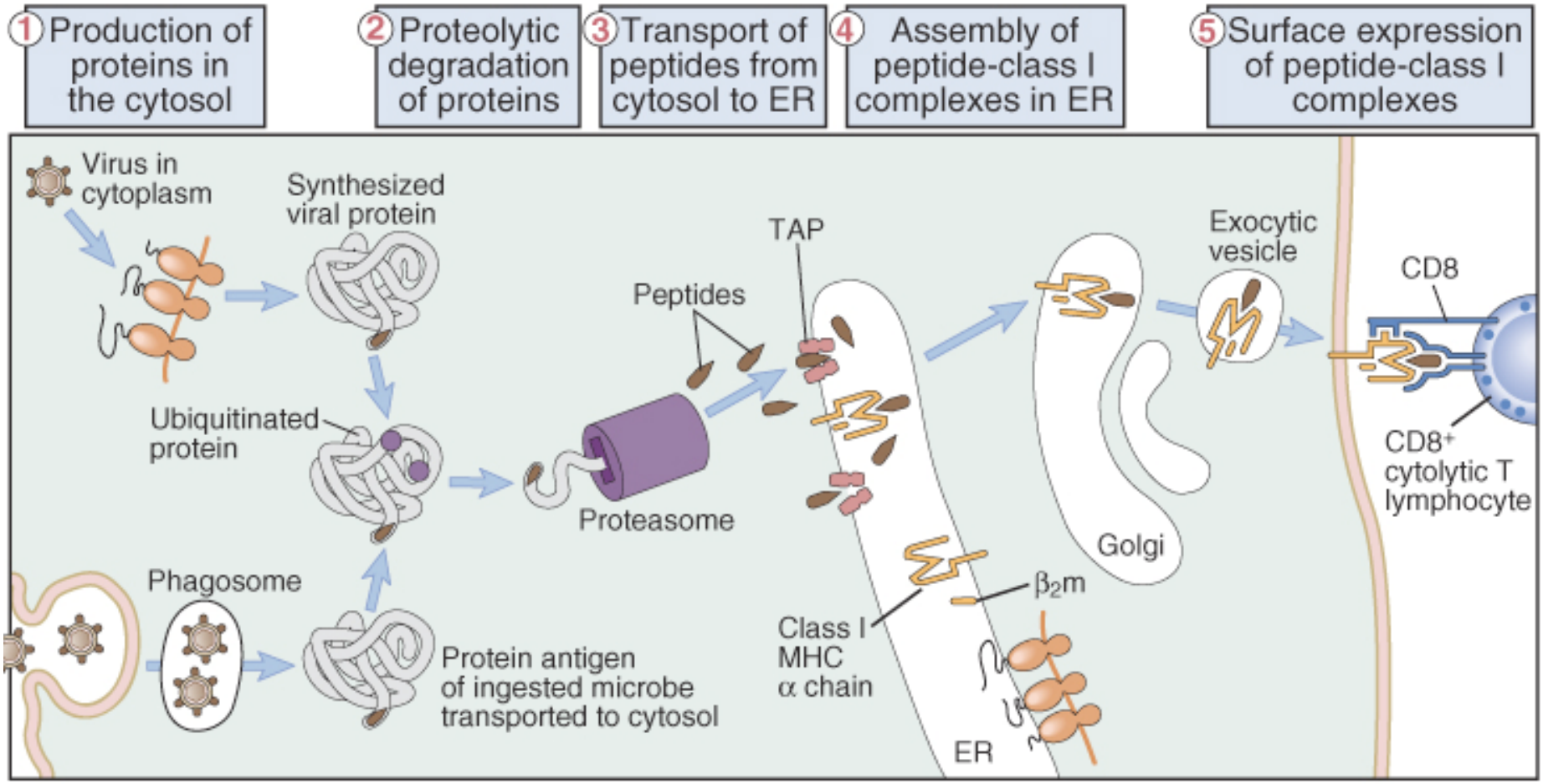


The functions of class II MHC-associated invariant chains and HLA-DM



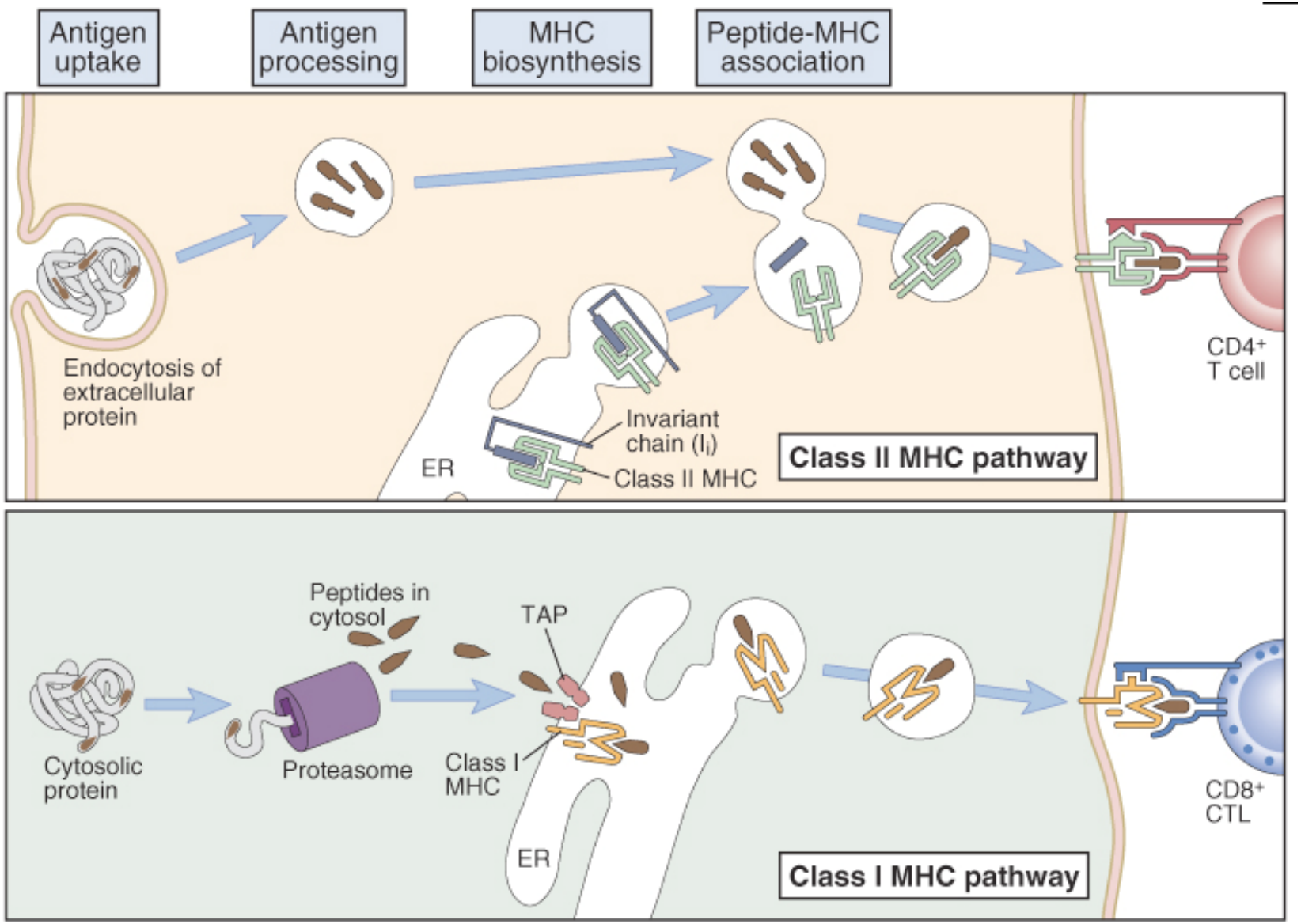
The invariant chain is a trimer made of three 30 kD subunits. The HLA DM a non-polymorphic Class-II like dimer.

The class I MHC pathway of antigen presentation

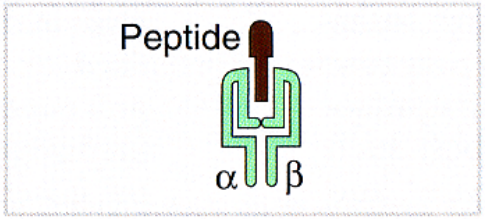
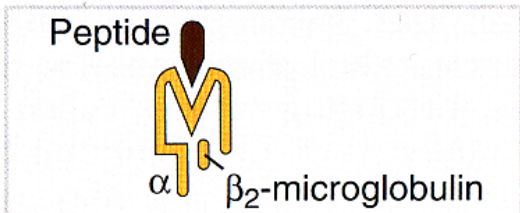


The proteasome responsible for the production of immunogenic peptides is a 1.500 kD complex made of several subunits. Two of them, LMP-2 and LMP7, are encoded within the MHC (within DP and DQ loci)

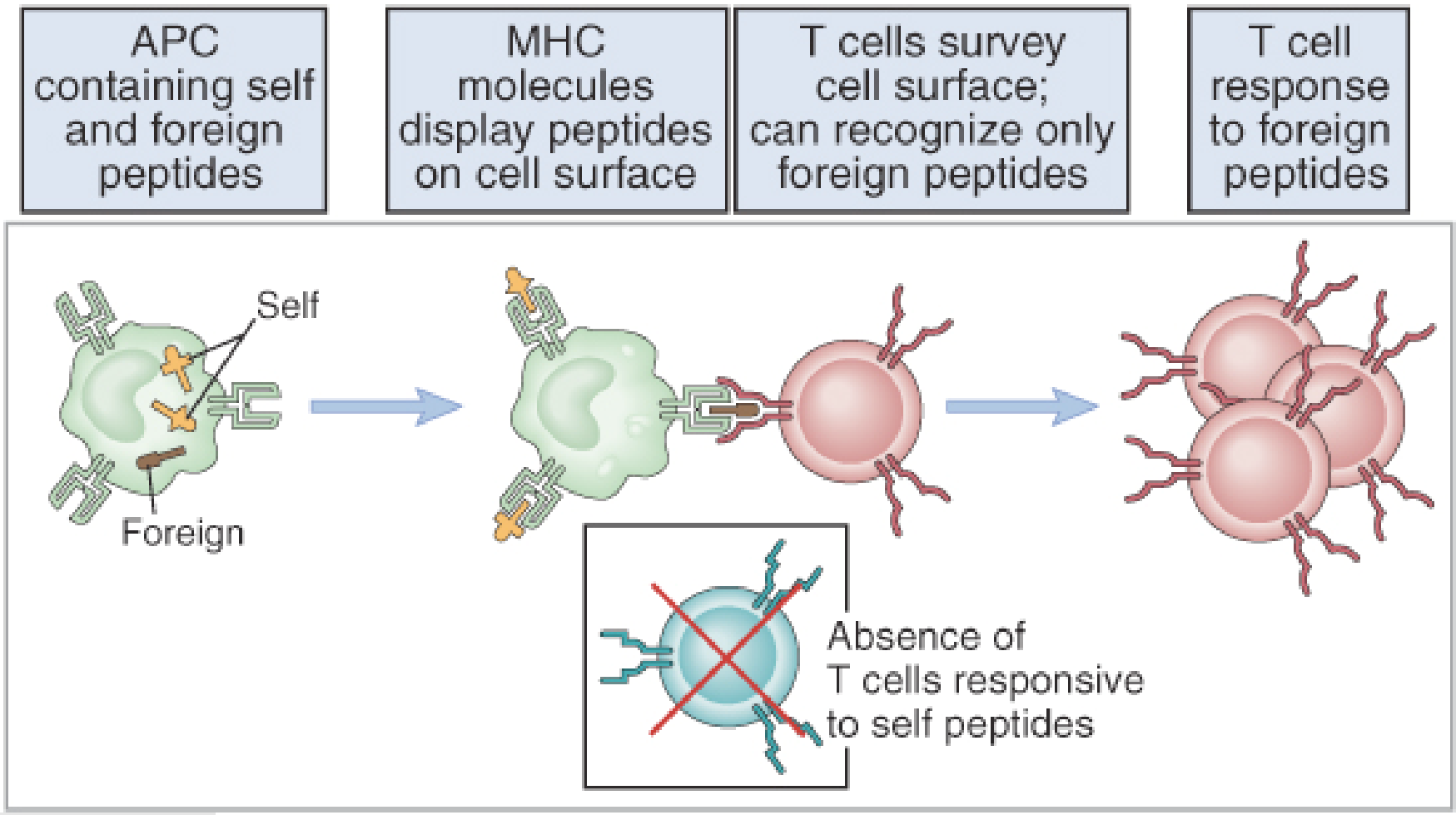
Pathways of antigen processing and presentation



Class I and Class II pathways compared

Feature	Class II MHC pathway	Class I MHC pathway
Composition of stable peptide-MHC complex	Polymorphic α and β chains, peptide 	Polymorphic α chain, β_2-microglobulin, peptide 
Types of APCs	Dendritic cells, mononuclear phagocytes, B lymphocytes; endothelial cells, thymic epithelium	All nucleated cells
Responsive T cells	$CD4^+$ T cells	$CD8^+$ T cells
Source of protein antigens	Endosomal/lysosomal proteins (mostly internalized from extracellular environment)	Cytosolic proteins (mostly synthesized in the cell; may enter cytosol from phagosomes)
Enzymes responsible for peptide generation	Endosomal and lysosomal proteases (e.g., cathepsins)	Cytosolic proteasome
Site of peptide loading of MHC	Specialized vesicular compartment	Endoplasmic reticulum
Molecules involved in transport of peptides and loading of MHC molecules	Calnexin in ER; invariant chain in ER, Golgi and MIIC/CIIV; DM	Calnexin, calreticulin, Tapasin, TAP in ER

MHC is normally loaded with self peptides

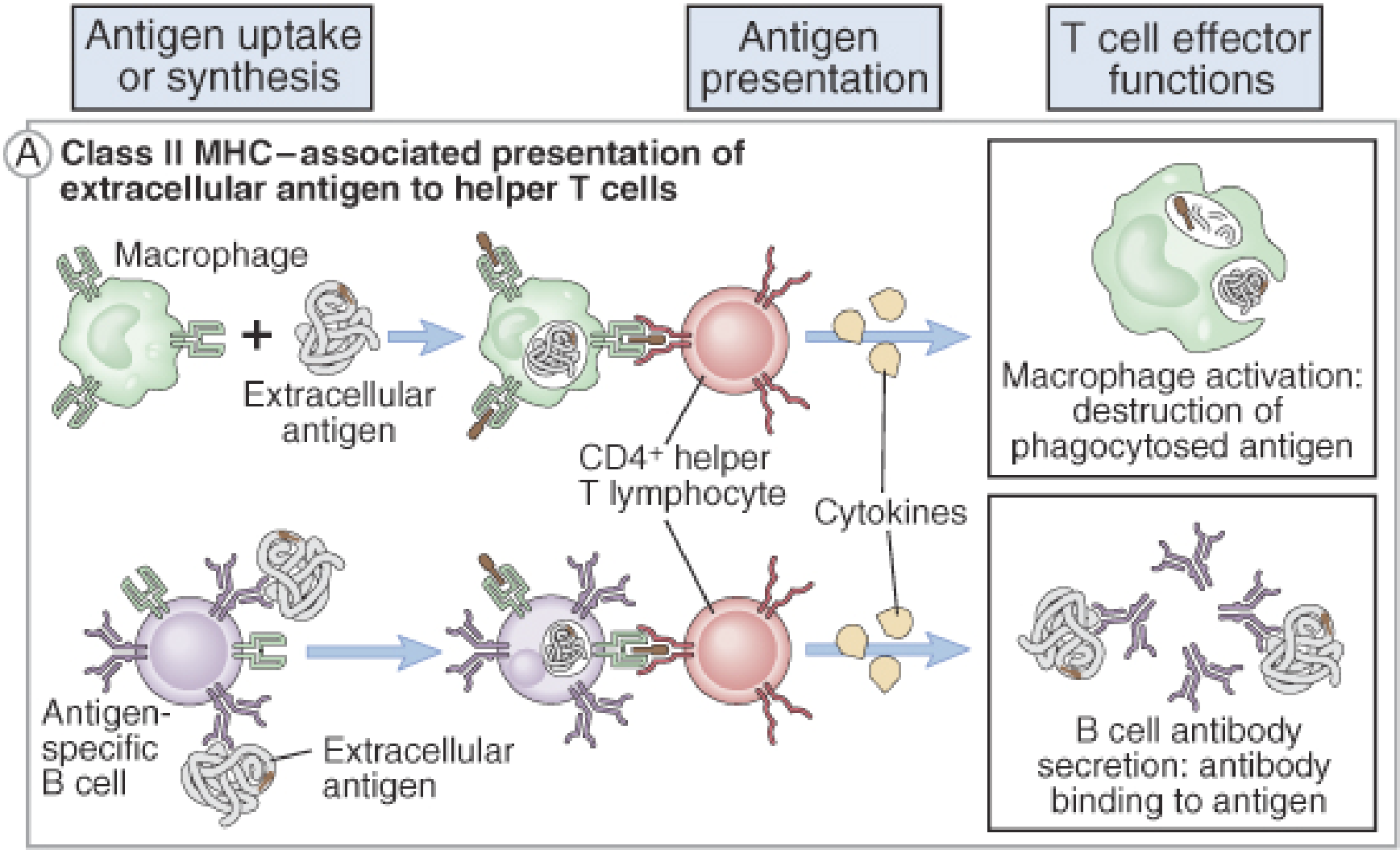


Binding of ~ 100 MHC molecules loaded with a specific non-self peptide is sufficient for a T cell to be activated

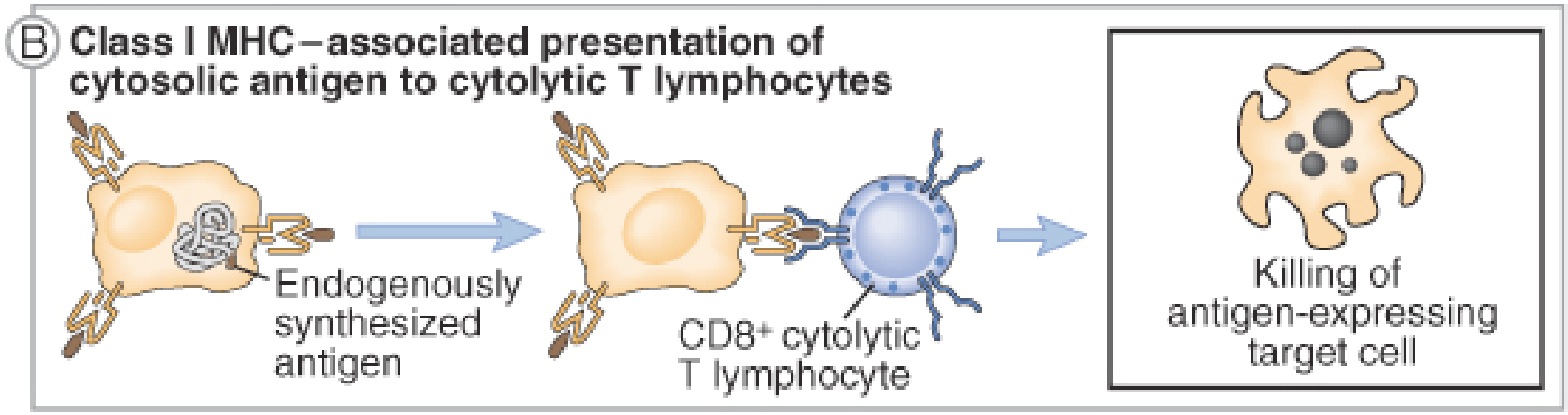
there are ~ 100.000 MHC molecules on the surface of each APC

Therefore, most of the MHC molecules of any APC remain occupied by self-peptides.

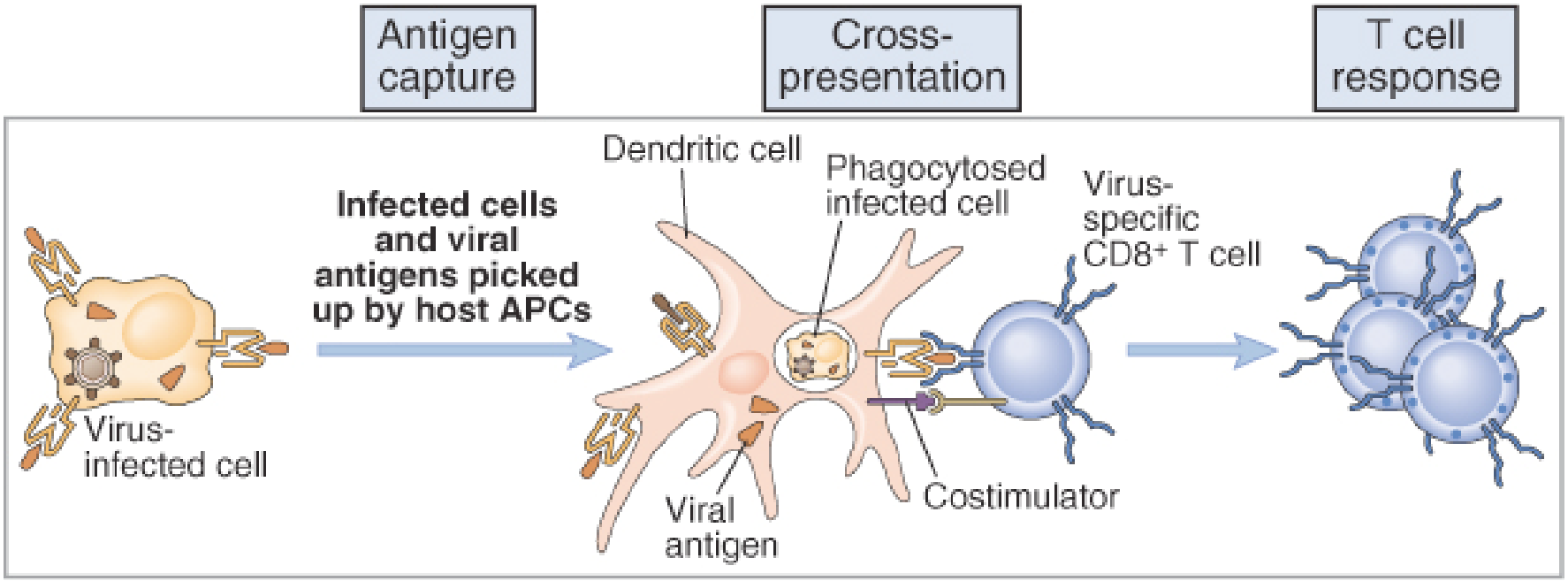
CD4 T cells effector functions



CD8 T cells effector functions

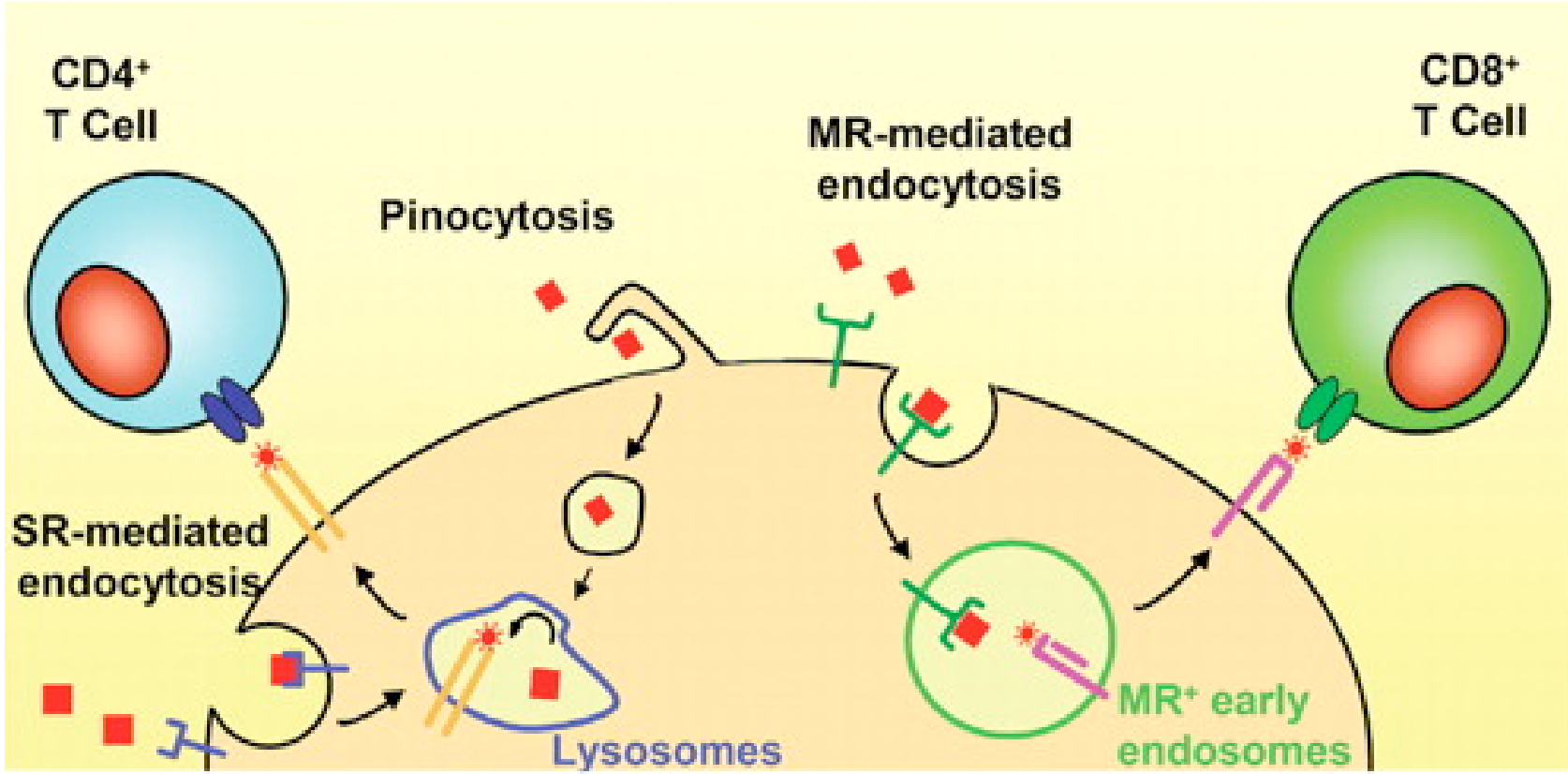


Cross-presentation of phagocytized antigens to CD8 T cells

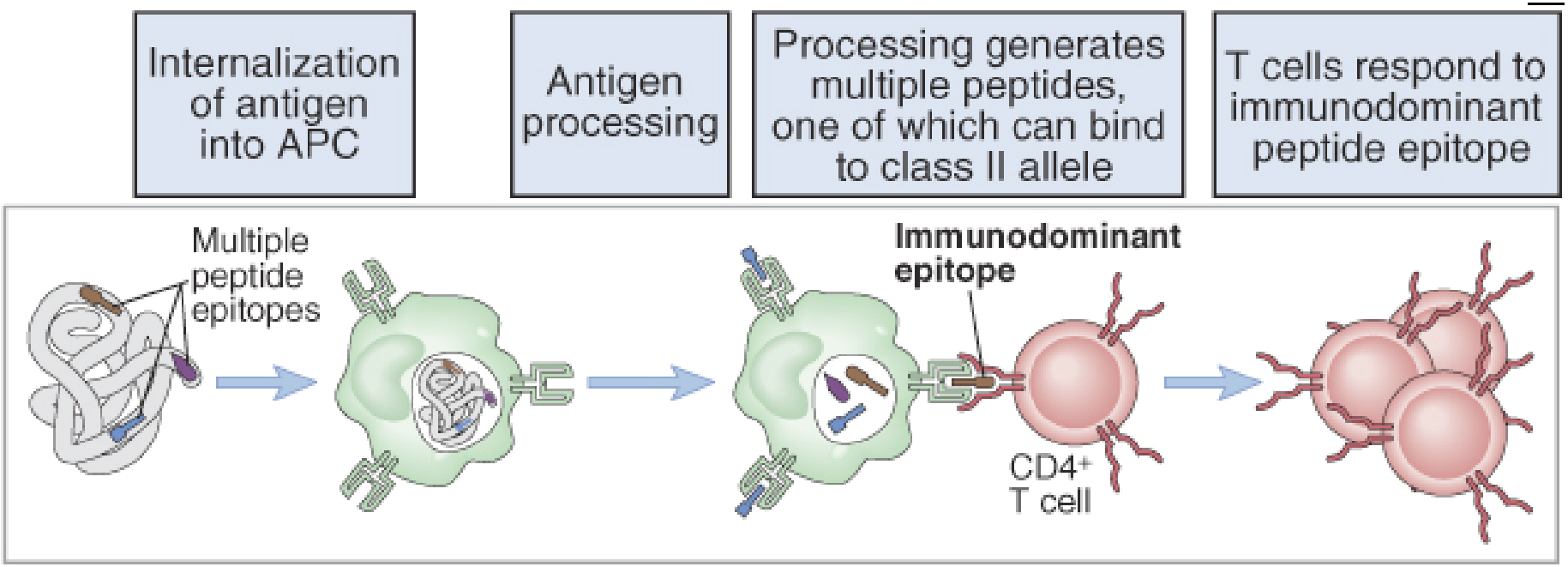


Cross presentation to CD4 T cells: endogenous proteins can access the endolysosome (autophagy, cell membrane proteins, even virus-derived).

Cross-presentation follows a Mannose Receptor-mediated endocytosis



Immunodominance of peptides



The specific MHC haplotype of an individual selects the peptides that will be immunodominant and immunogenic