Antigen presentation and T cells

23.04.2025

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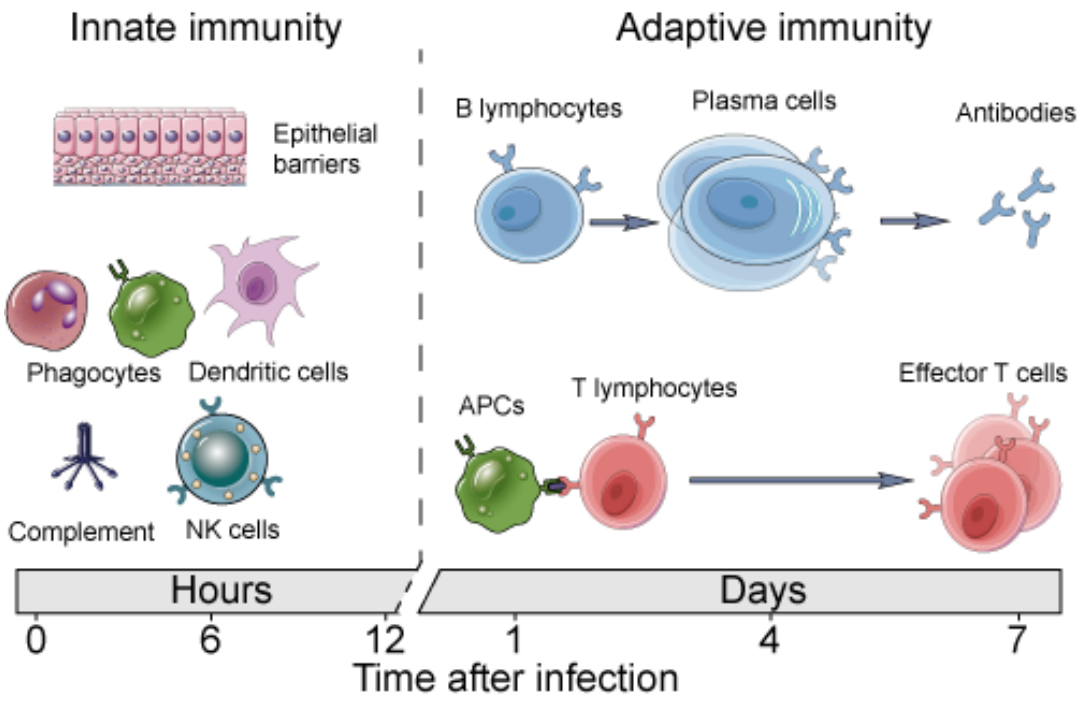
Molecular Immunology

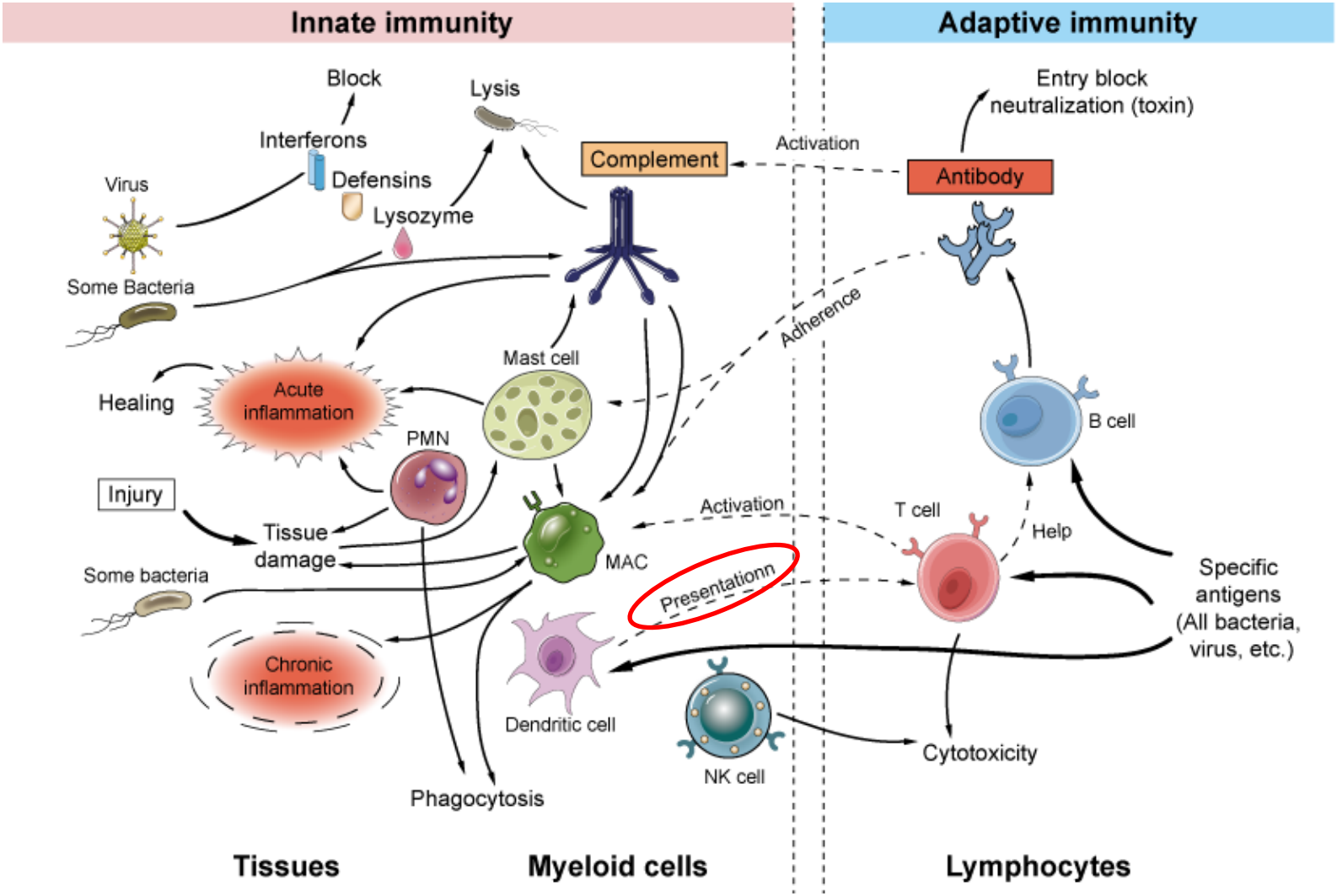
Agenda

- Antigen presentation and APCs
- Major Histocompatibility Complexes
- T cells:
  - Development
  - Subsets
  - Lineages
  - T cell receptor

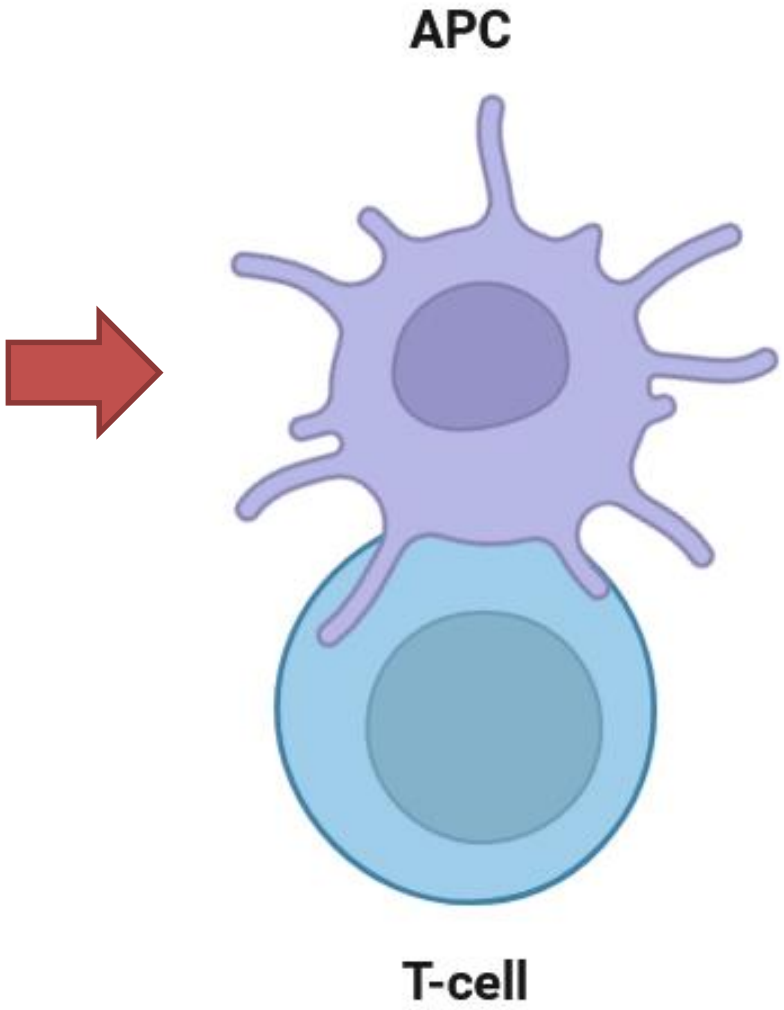
Antigen presentation



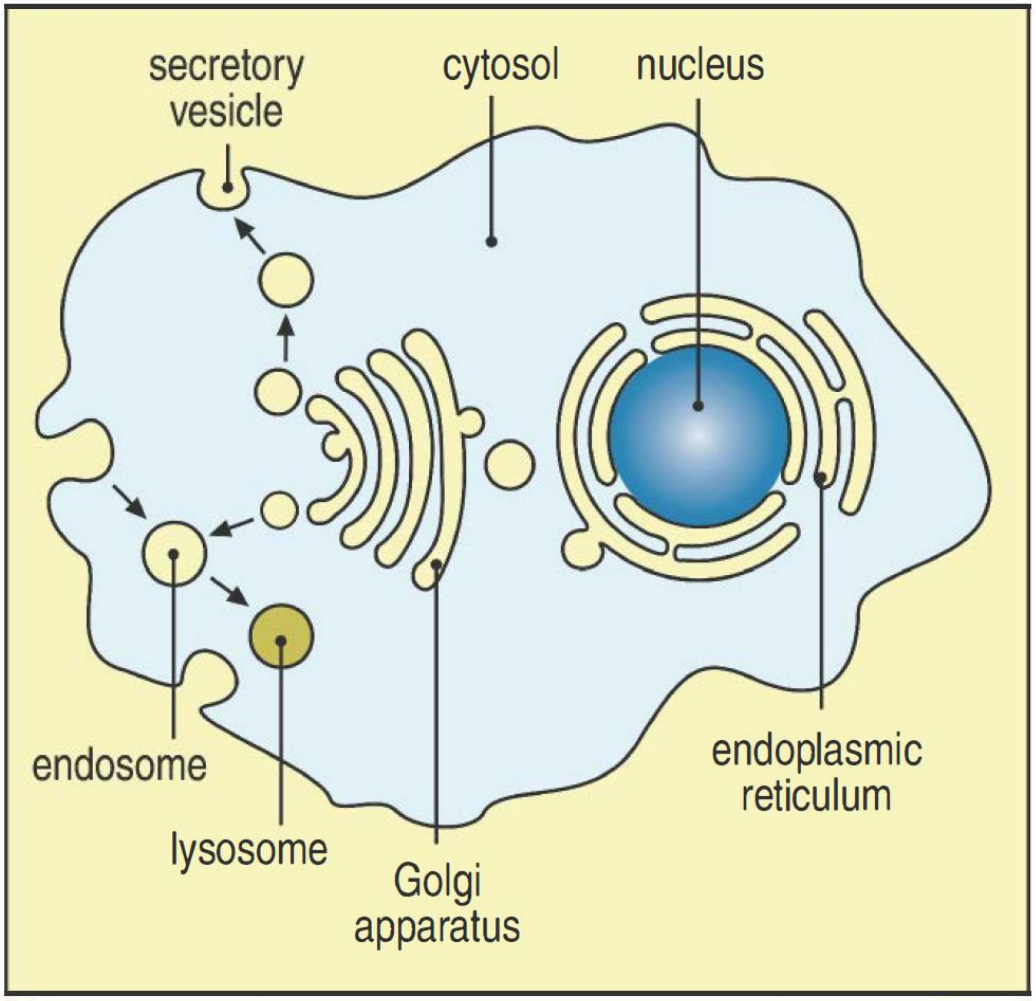
Antigen presentation



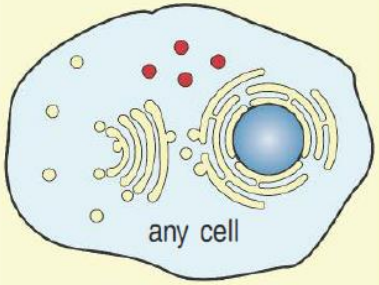
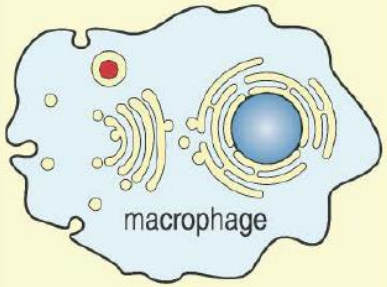
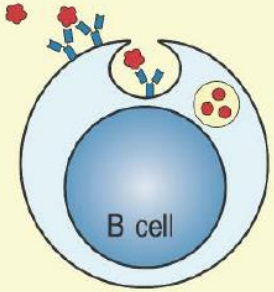
Innate – Adaptive Immune system



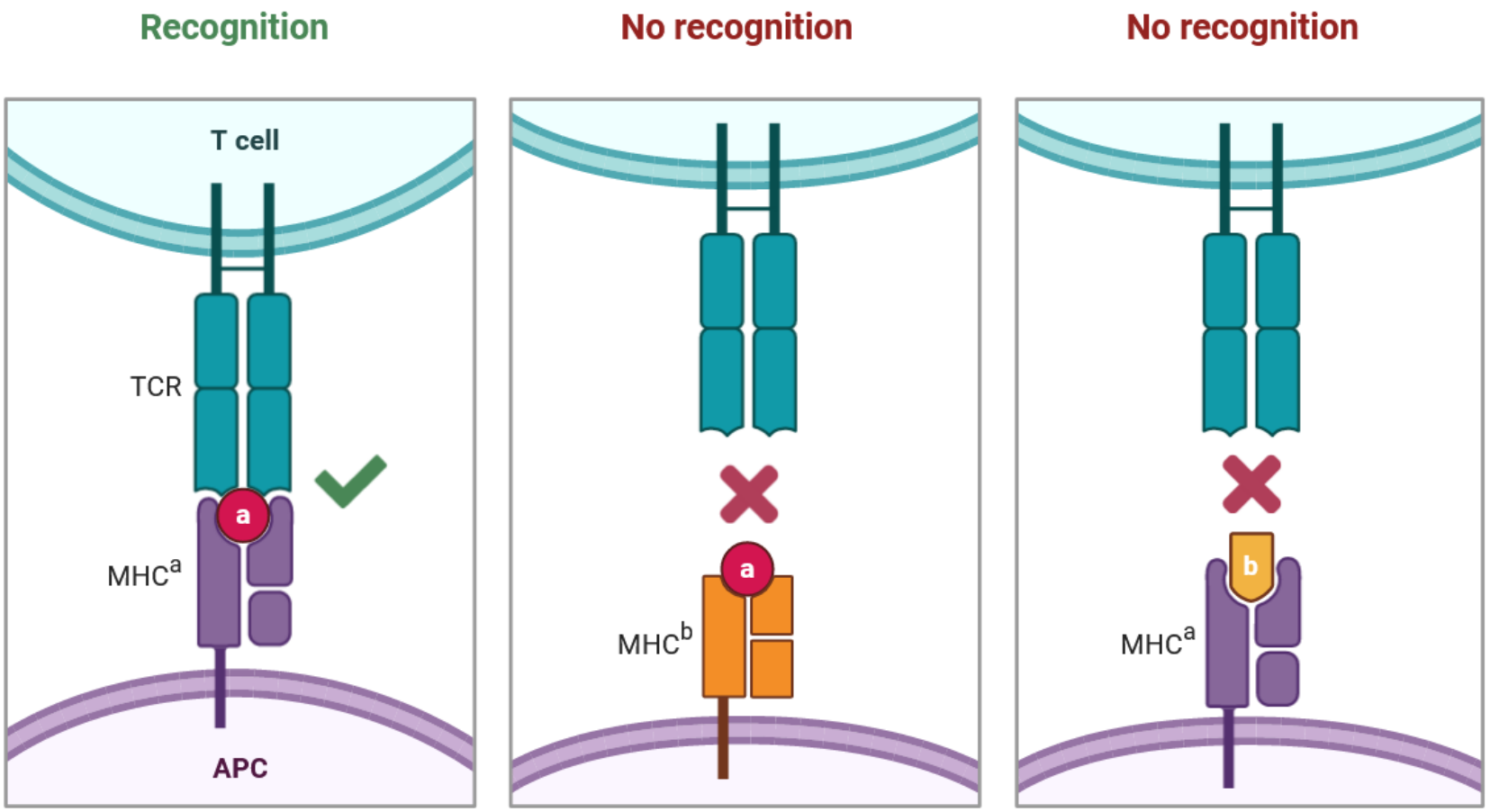
Intracellular compartments



Antigen presenting cells

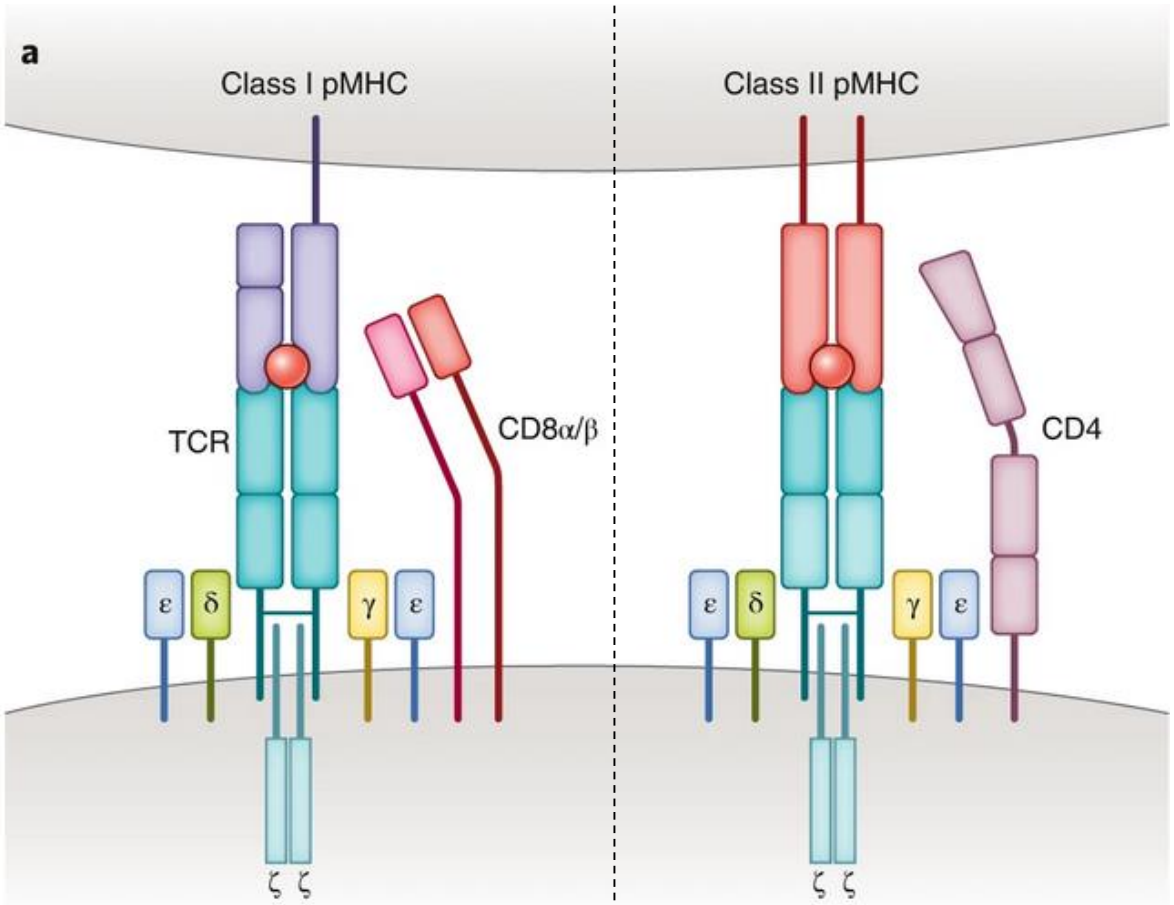
	Cytosolic pathogens	Intravesicular pathogens	Extracellular pathogens and toxins
			
Degraded in	Cytosol	Endocytic vesicles (low pH)	Endocytic vesicles (low pH)
Peptides bind to	MHC class I	MHC class II	MHC class II
Presented to	Effector CD8 T cells	Effector CD4 T cells	Effector CD4 T cells
Effect on presenting cell	Cell death	Activation to kill intravesicular bacteria and parasites	Activation of B cells to secrete Ig to eliminate extracellular bacteria/toxins

Antigen presenting cells



Antigen presenting cells

Antigen presenting cell (APC) | **Antigen presenting cell (APC)**



T cell | **T cell**

https://doi.org/10.1038/s41592-020-0867-z

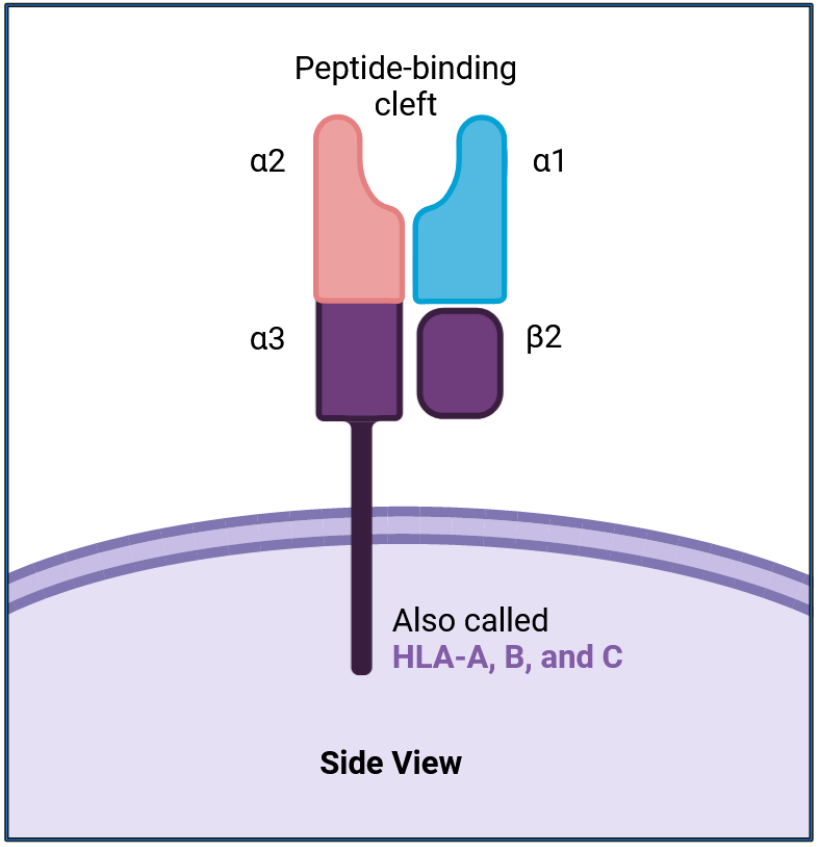
Antigen presenting cells

Tissue	MHC class I	MHC class II
Lymphatic tissue		
T cells	+++	+*
B cells	+++	+++
macrophages	+++	++
Dendritic cells	+++	+++
Corticoepithelial cells (thymus)	+	+++
Other tissues		
Neutrophils	+++	–
Hepatocytes	+	–
Kidney cells	+	–
Neurons	+	–**
Blood		
Red blood cells	–	–

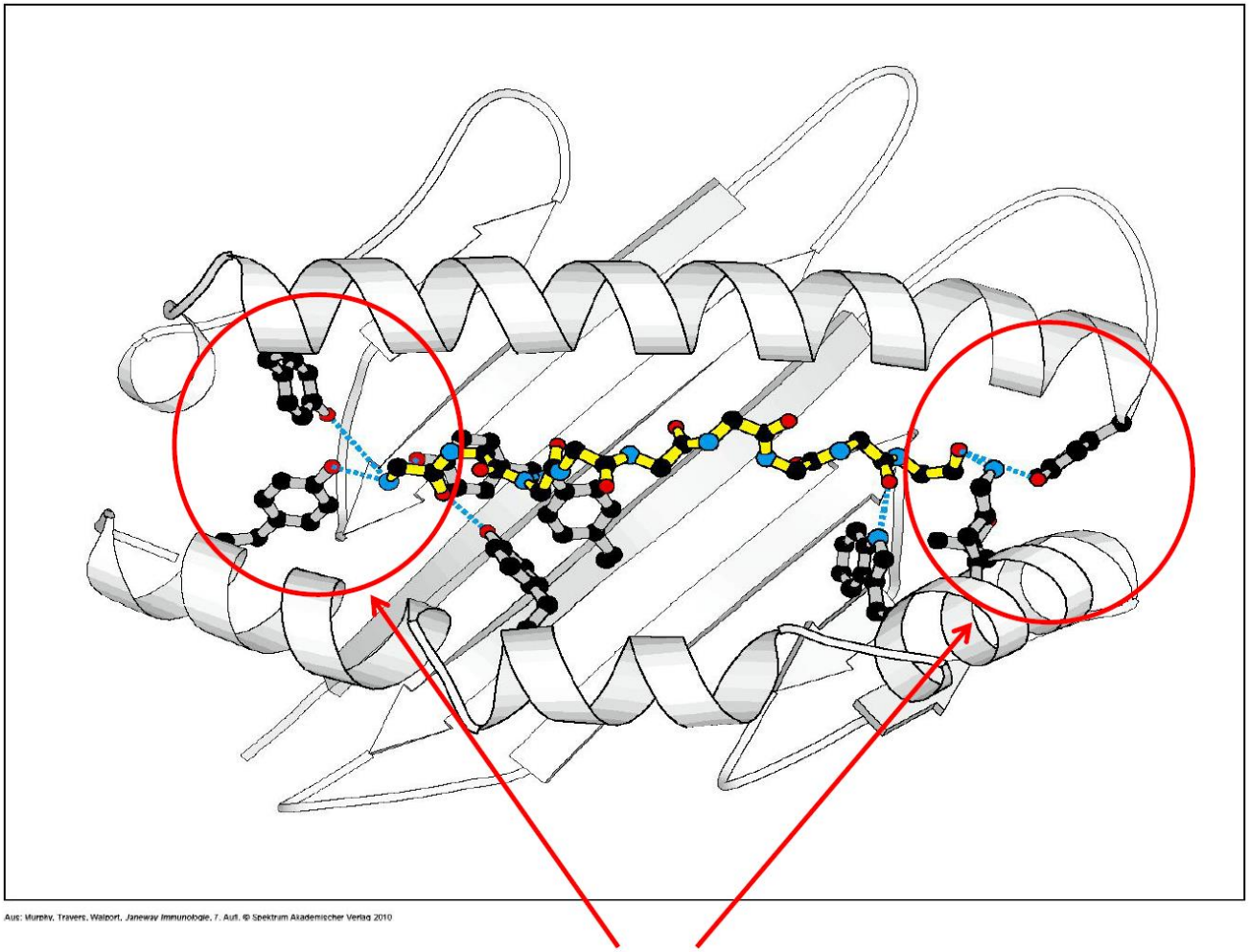
*activated T cells

Major Histocompatibility Complex (MHC) I

- Expressed in all nucleated cells
- Gen loci: HLA-A, HLA-B, HLA-C
- Location: Endoplasmic reticulum
- Interaction: CD8+ T cells

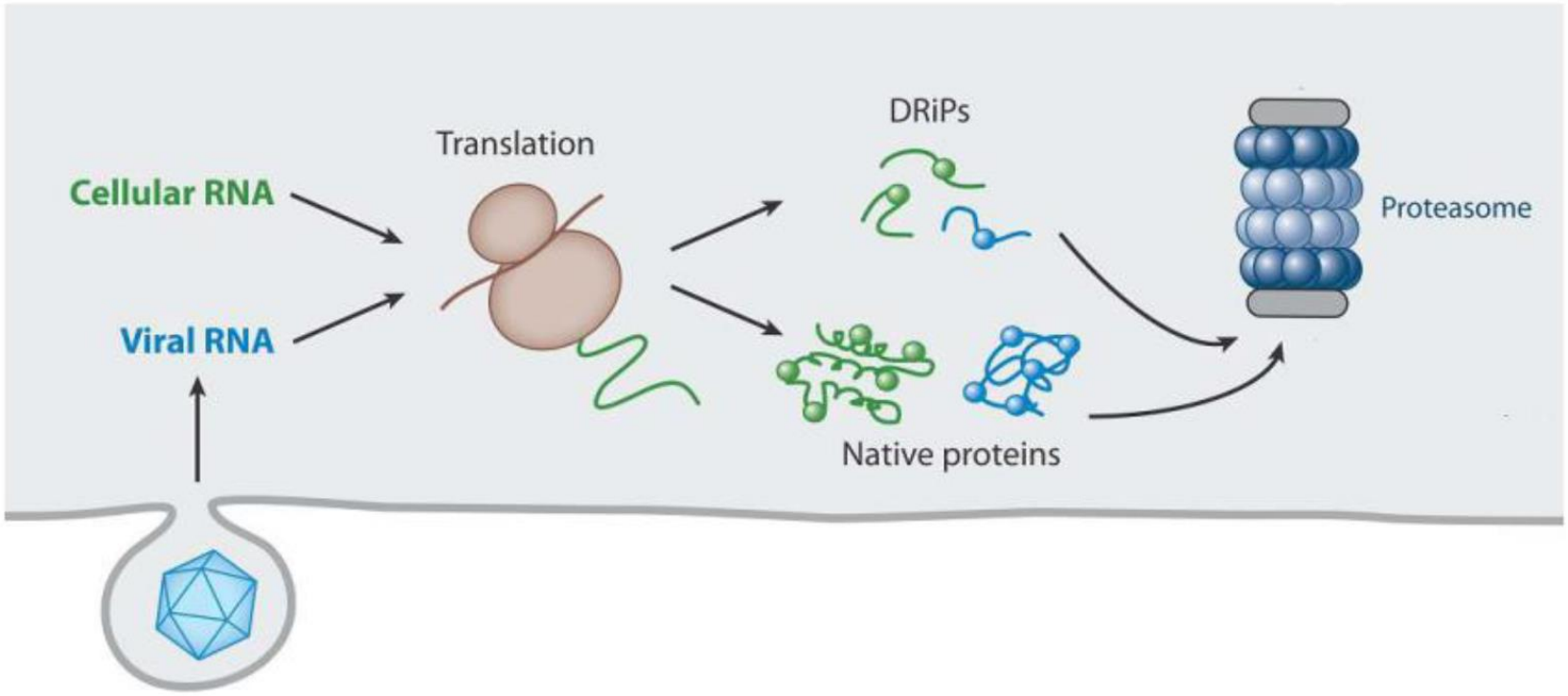


Major Histocompatibility Complex (MHC) I



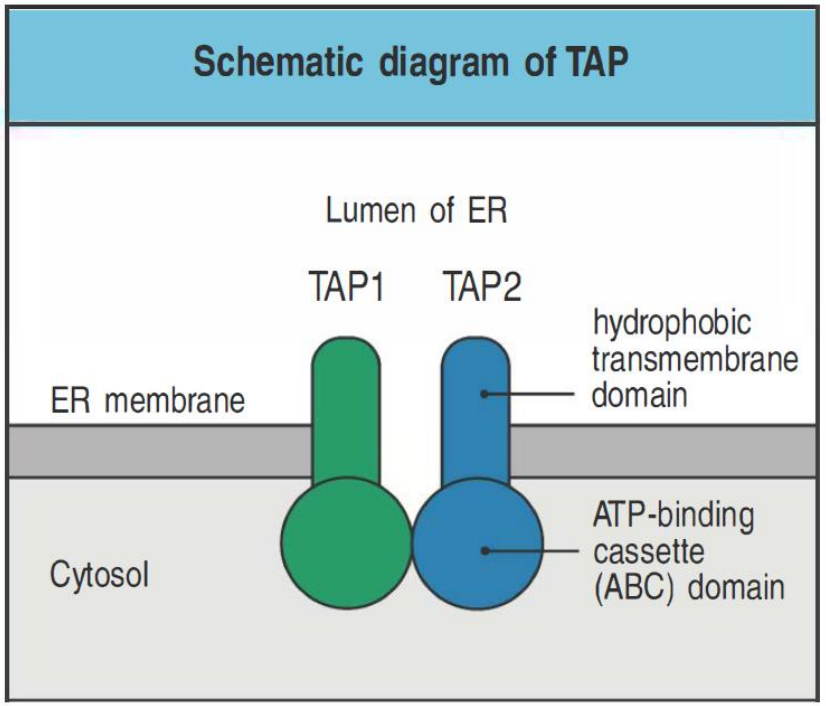
Coordination of the MHC1 binding peptide

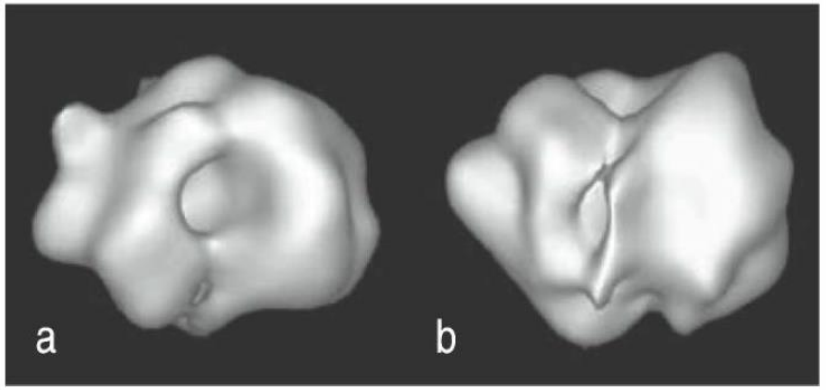
Protein degradation



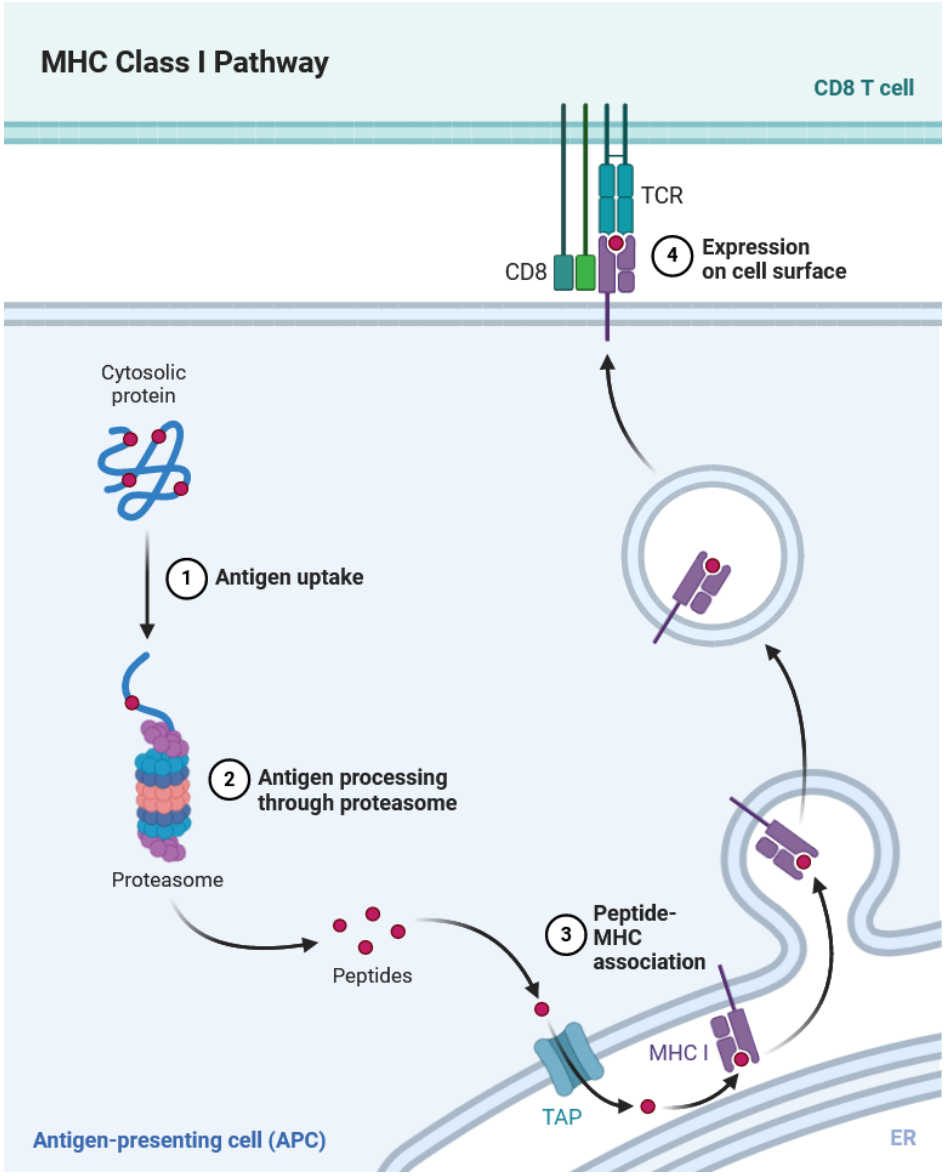
DRiP: Defective ribosomal product

Peptide transport from cytosol to ER

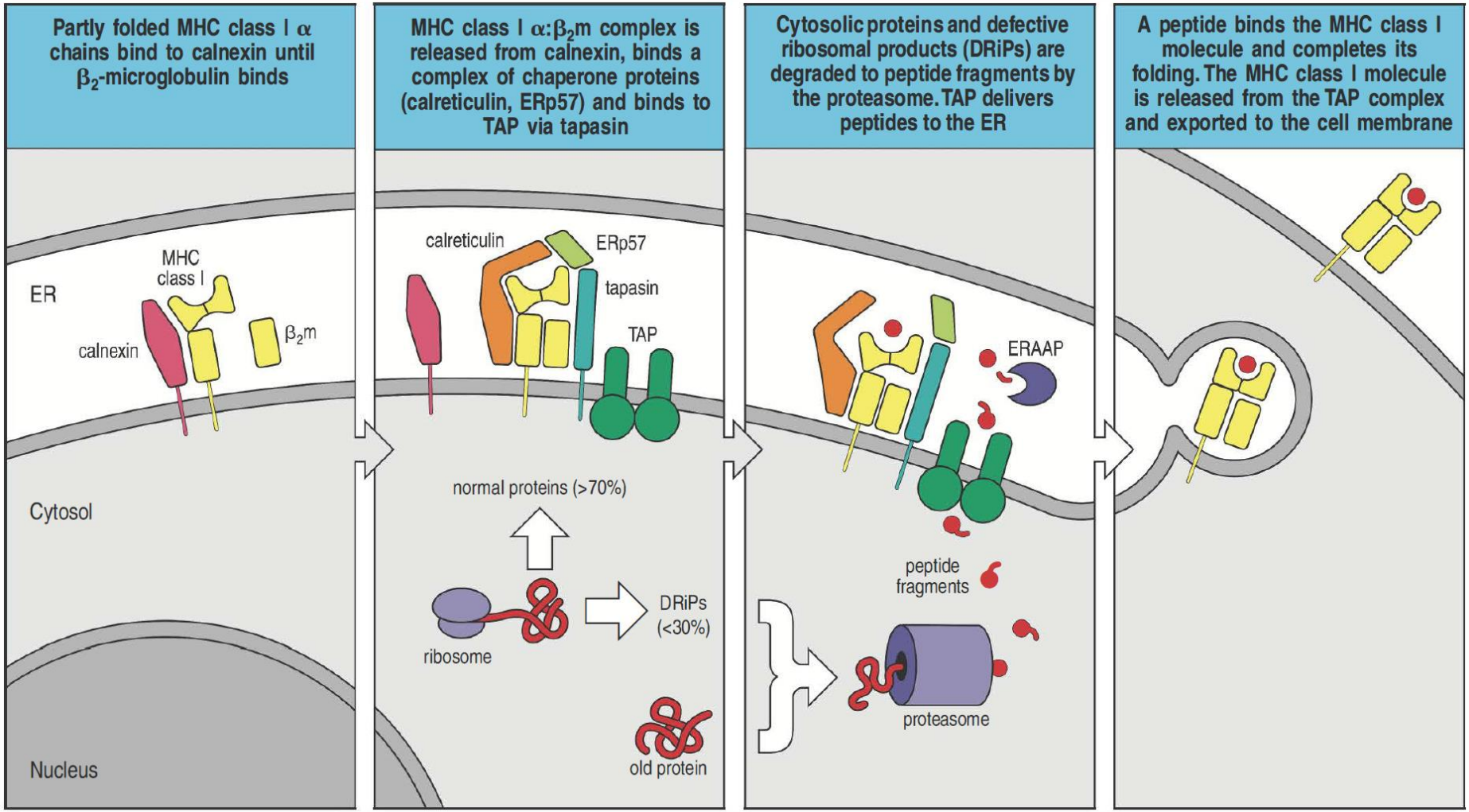




MHC I peptide load

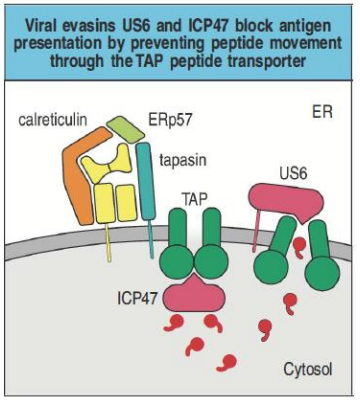


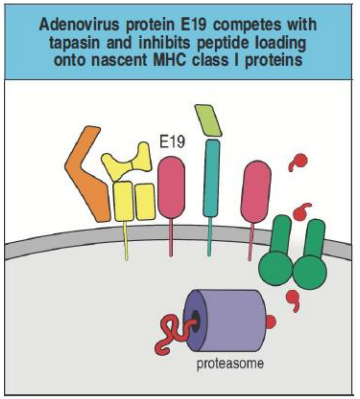
MHC I peptide load

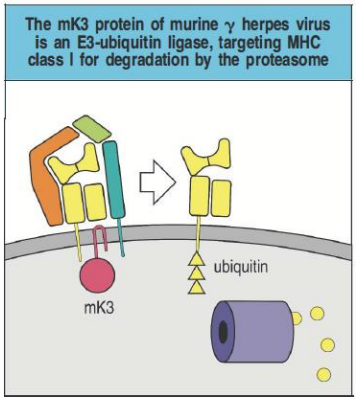


Immuno evasion

Virus	Protein	Category	Mechanism
Herpes simplex virus 1	ICP47	Blocks peptide entry to endoplasmic reticulum	Blocks peptide binding to TAP
Human cytomegalovirus (HCMV)	US6		Inhibits TAP ATPase activity and blocks peptide release into endoplasmic reticulum
Bovine herpes virus	UL49.5		Inhibits TAP peptide transport
Adenovirus	E19	Retention of MHC class I in endoplasmic reticulum	Competitive inhibitor of tapasin
HCMV	US3		Blocks tapasin function
Murine cytomegalovirus (CMV)	M152		Unknown
HCMV	US2	Degradation of MHC class I (dislocation)	Transports some newly synthesized MHC class I molecules into cytosol
Murine gamma herpes virus 68	mK3		E3-ubiquitin ligase activity
Murine CMV	m4	Binds MHC class I at cell surface	Interferes with recognition by cytotoxic lymphocytes by an unknown mechanism

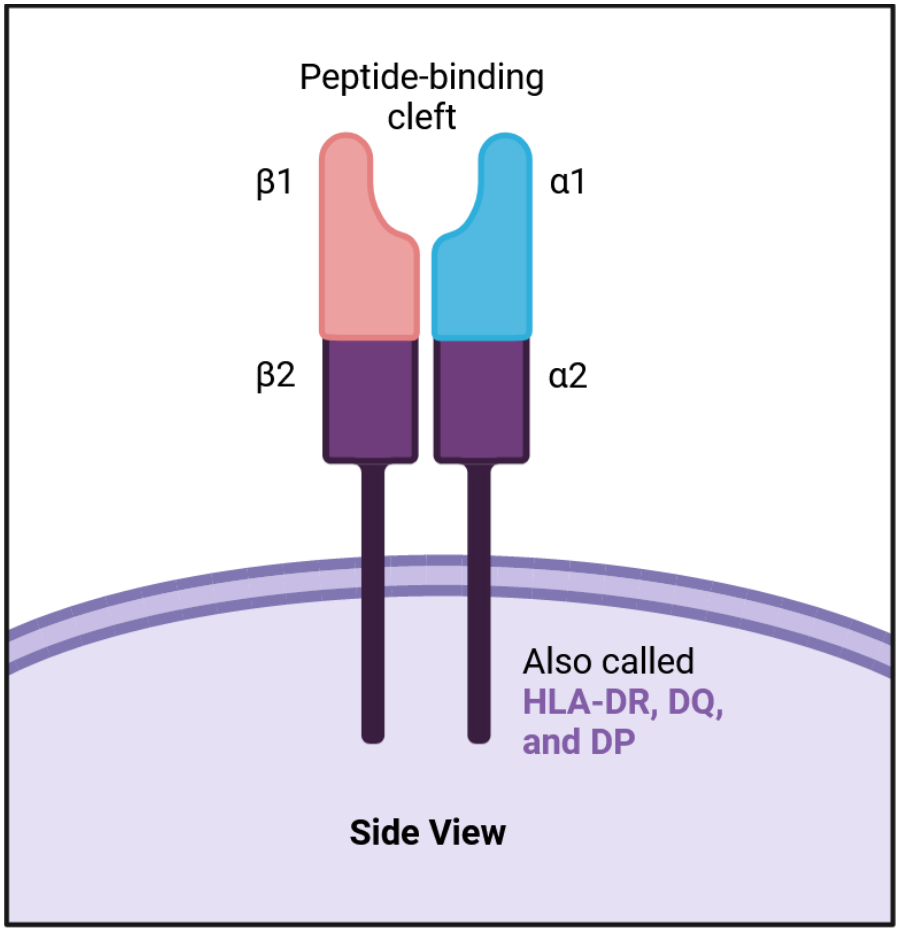




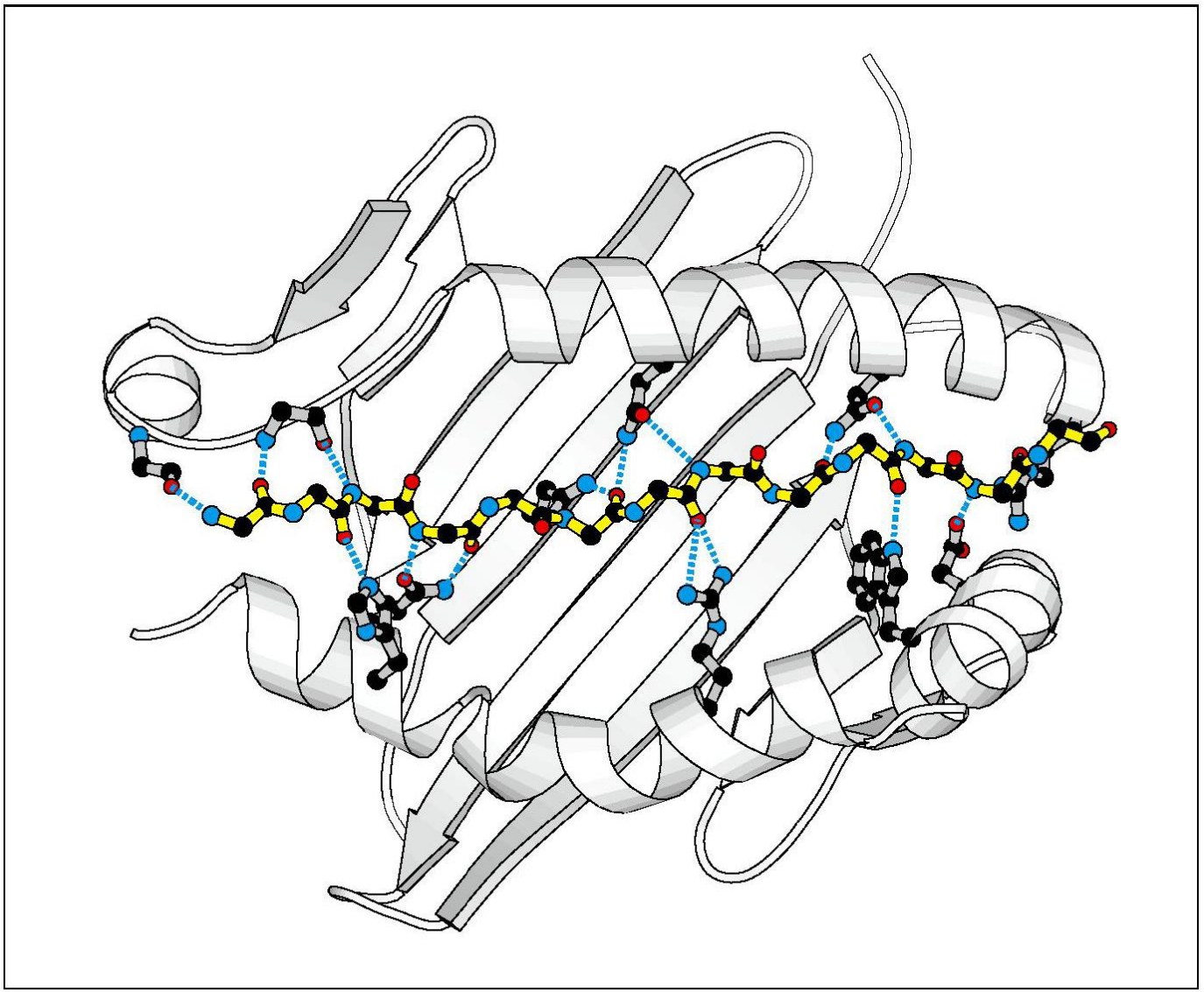


Major Histocompatibility Complex (MHC) II

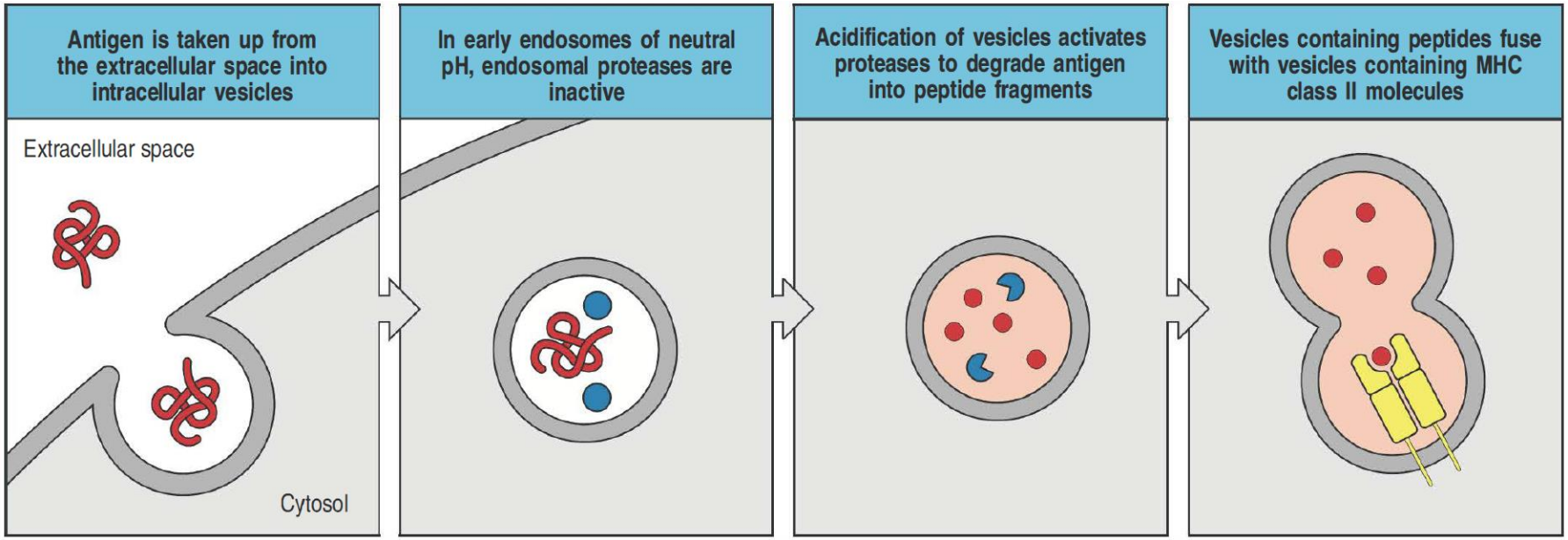
- Expressed in particular antigen-presenting cells
- Gen loci: HLA-DR, HLA-DQ, HLA-DP
- Location: Endosomes
- Interaction: CD4+ T cells



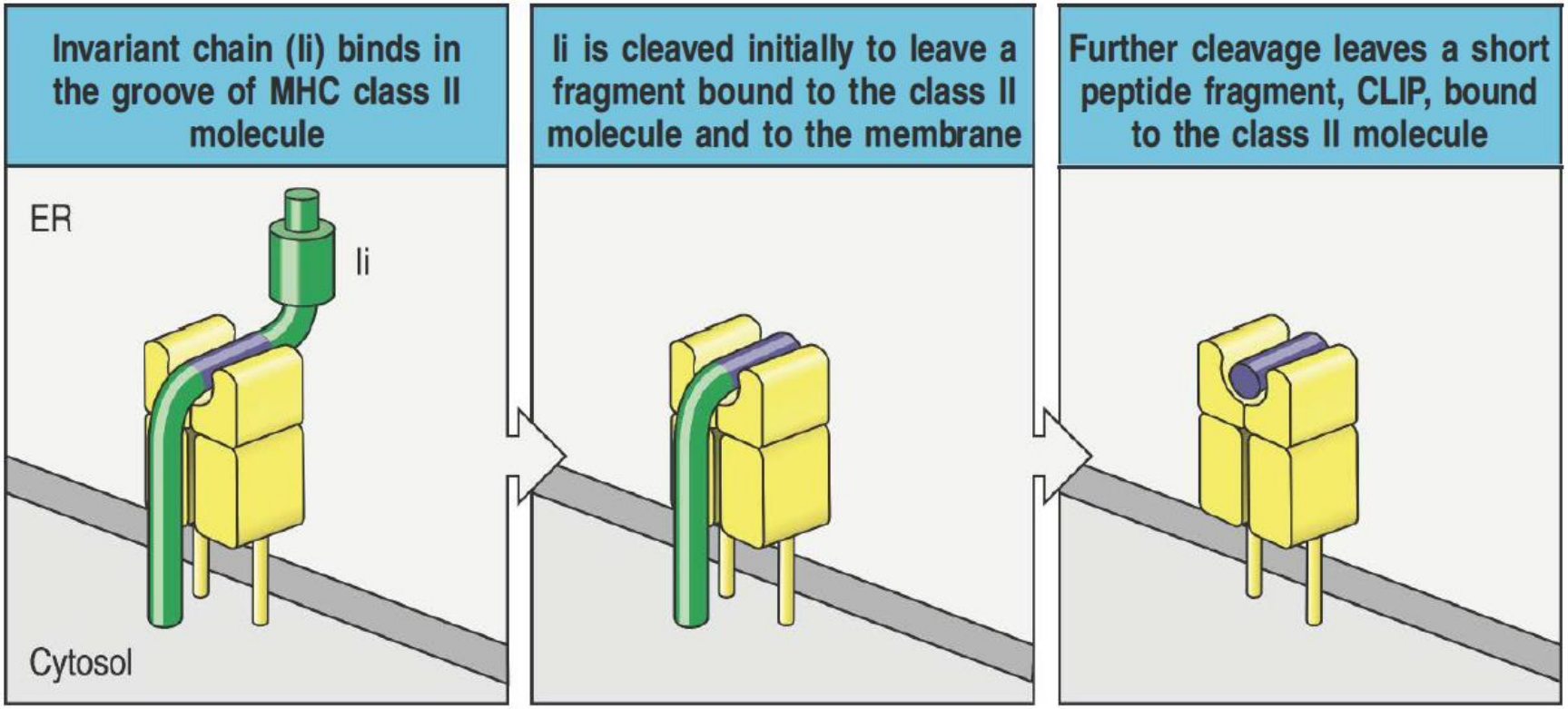
MHC II



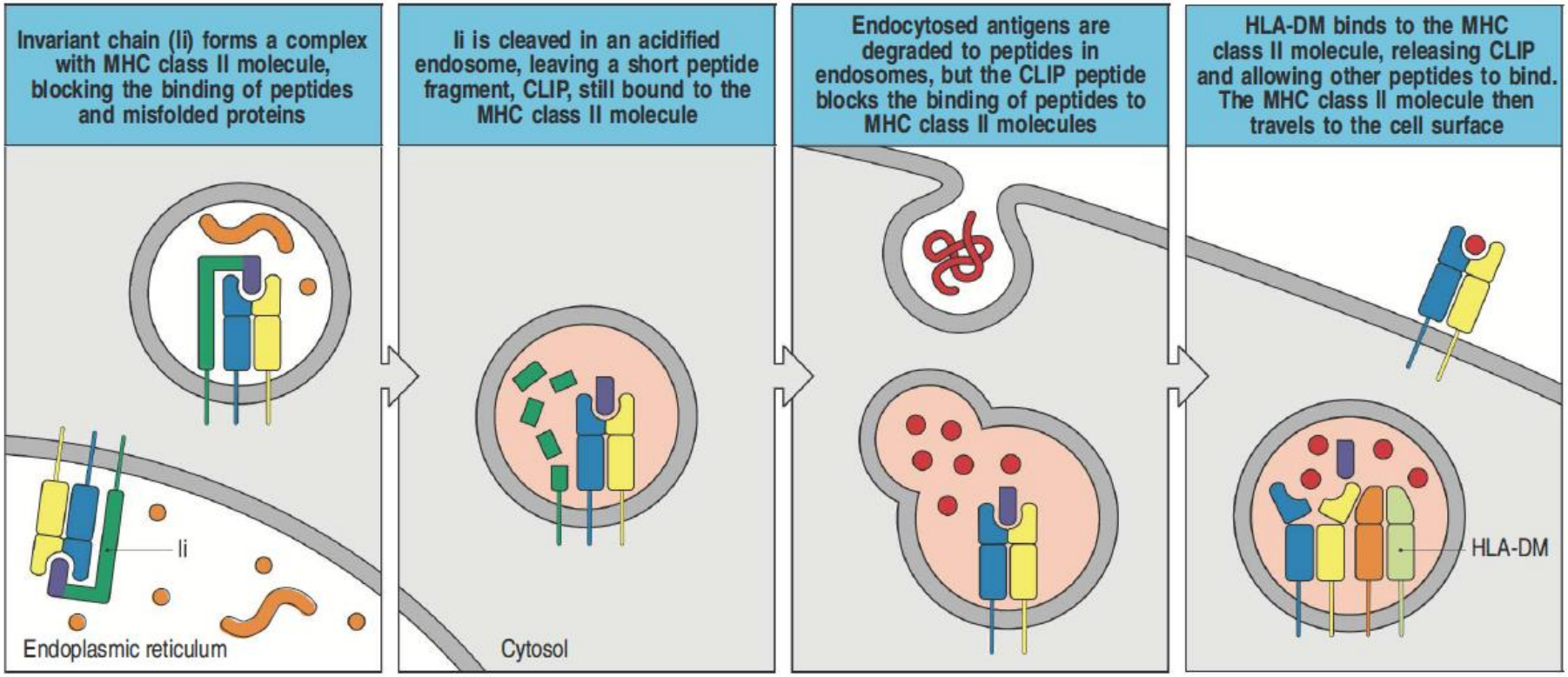
MHC II


Antigen is taken up from the extracellular space into intracellular vesicles
Extracellular space
Cytosol
In early endosomes of neutral pH, endosomal proteases are inactive
Acidification of vesicles activates proteases to degrade antigen into peptide fragments
Vesicles containing peptides fuse with vesicles containing MHC class II molecules

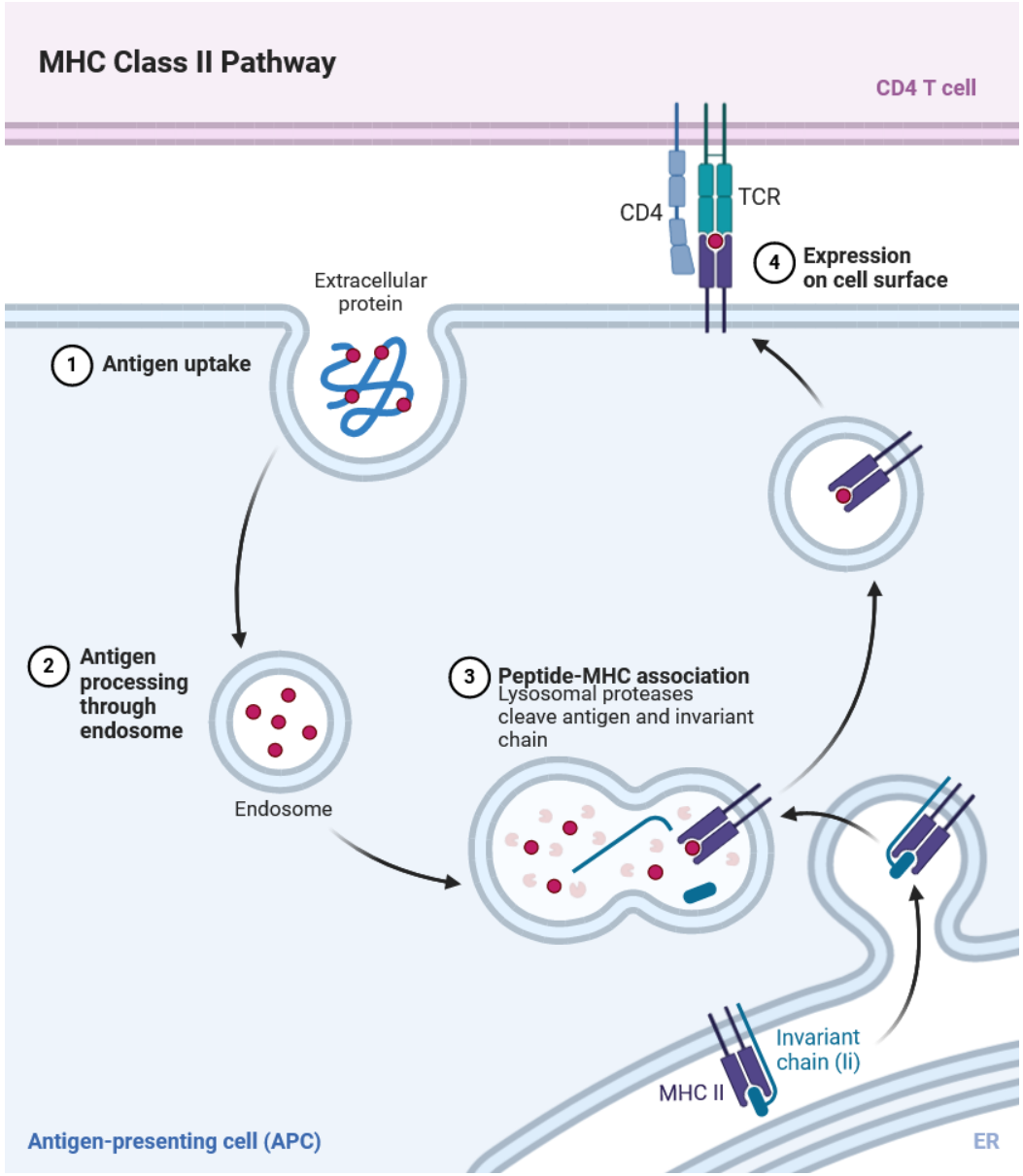
MHC II


Invariant chain (Ii) binds in the groove of MHC class II molecule
Ii is cleaved initially to leave a fragment bound to the class II molecule and to the membrane
Further cleavage leaves a short peptide fragment, CLIP, bound to the class II molecule
ER
Ii
Cytosol

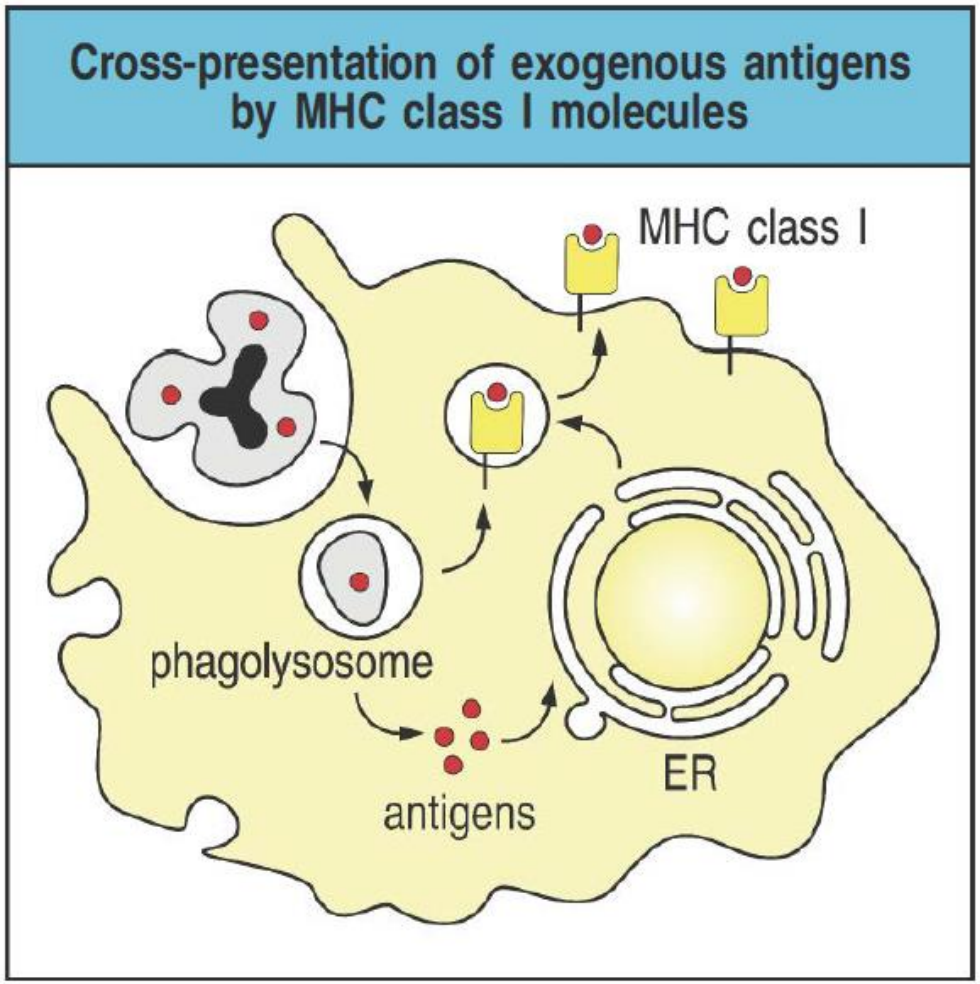
MHC II


Invariant chain (Ii) forms a complex with MHC class II molecule, blocking the binding of peptides and misfolded proteins
Ii
Endoplasmic reticulum
Ii is cleaved in an acidified endosome, leaving a short peptide fragment, CLIP, still bound to the MHC class II molecule
Cytosol
Endocytosed antigens are degraded to peptides in endosomes, but the CLIP peptide blocks the binding of peptides to MHC class II molecules
HLA-DM binds to the MHC class II molecule, releasing CLIP and allowing other peptides to bind. The MHC class II molecule then travels to the cell surface
HLA-DM

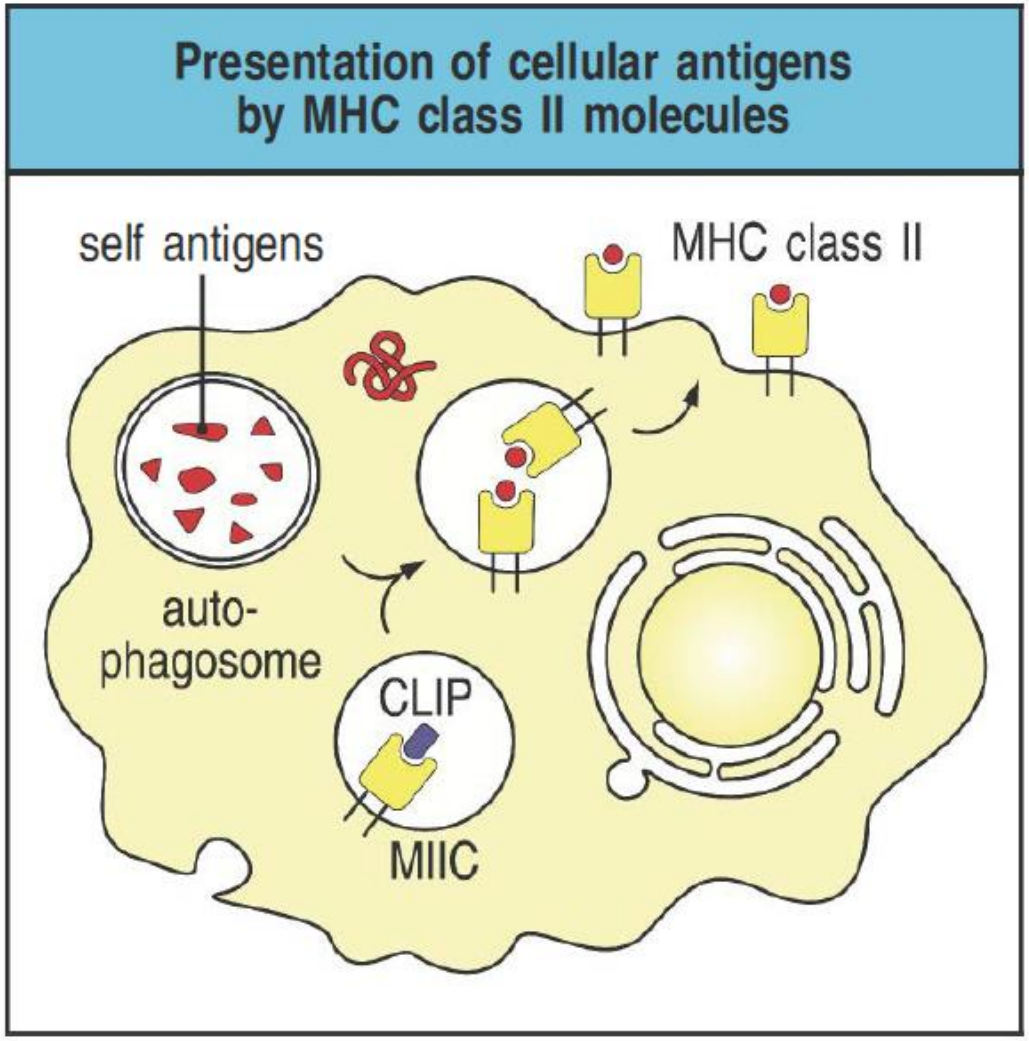
MHC II


MHC Class II Pathway
CD4 T cell
CD4
TCR
4 Expression on cell surface
Extracellular protein
1 Antigen uptake
2 Antigen processing through endosome
Endosome
3 Peptide-MHC association
Lysosomal proteases cleave antigen and invariant chain
Invariant chain (Ii)
MHC II
Antigen-presenting cell (APC)
ER

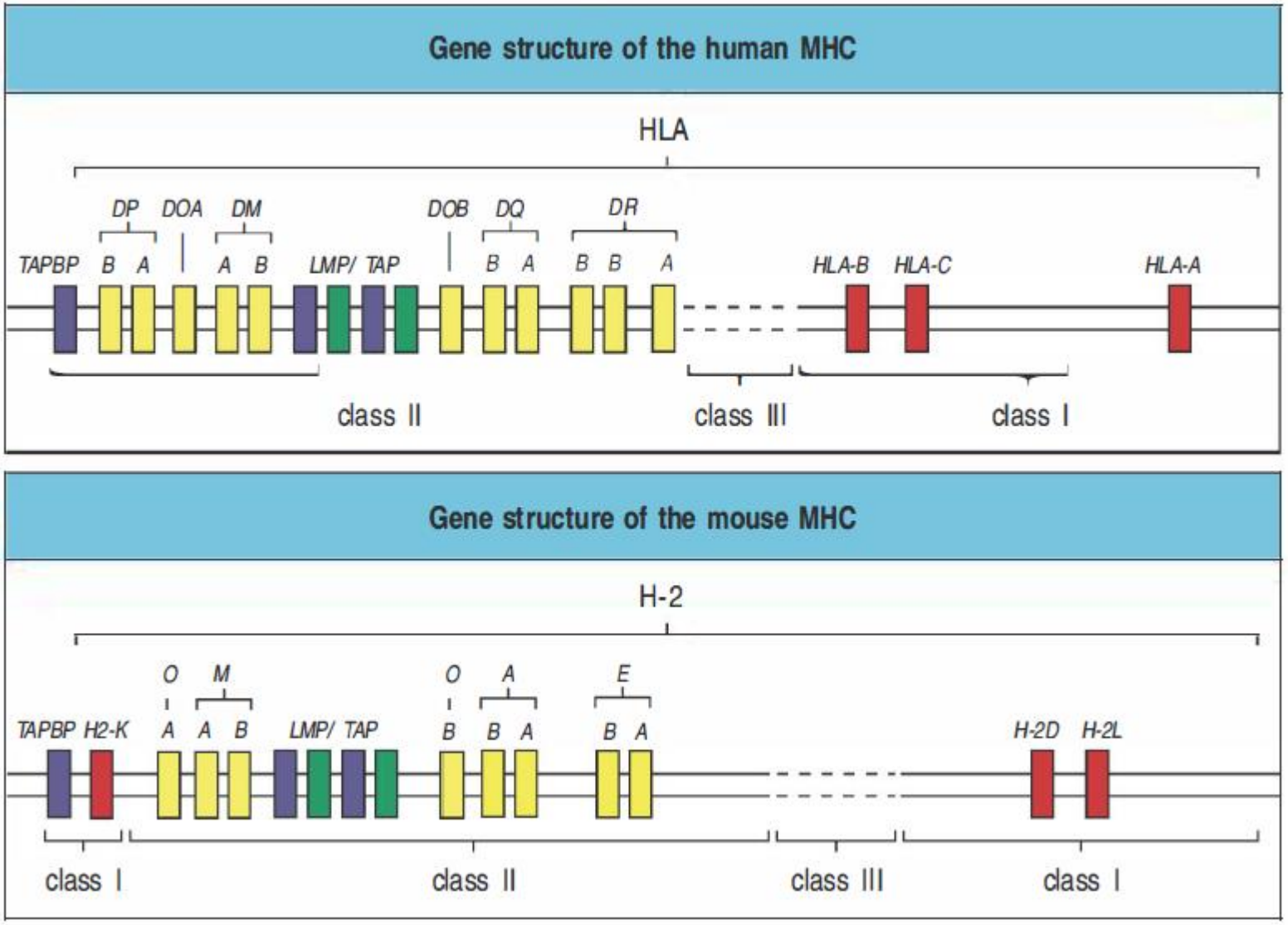
Cross-presentation



Cross-presentation

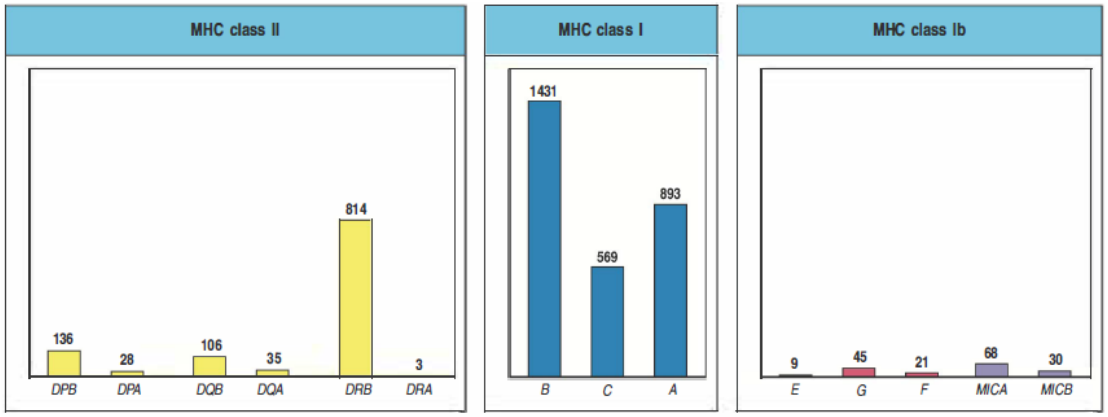


MHC genes

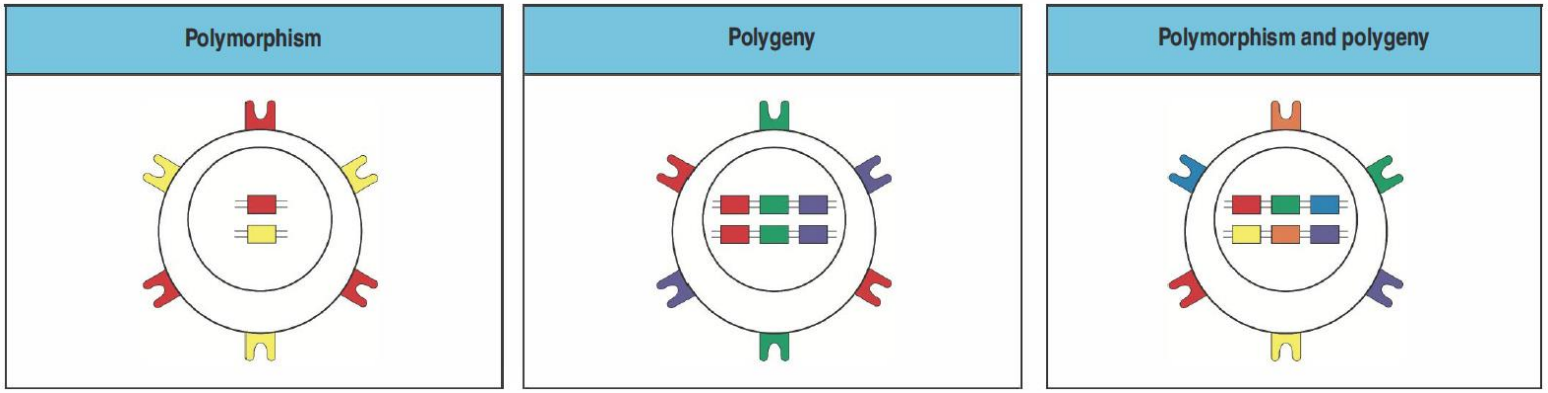

Gene structure of the human MHC
HLA
DP
DOA
DM
DOB
DQ
DR
TAPBP
B
A
A
B
LMP/ TAP
B
A
B
B
A
HLA-B
HLA-C
HLA-A
class II
class III
class I
Gene structure of the mouse MHC
H-2
O
M
O
A
E
TAPBP
H2-K
A
A
B
LMP/ TAP
B
B
A
B
A
H-2D
H-2L
class I
class II
class III
class I

MHC genes

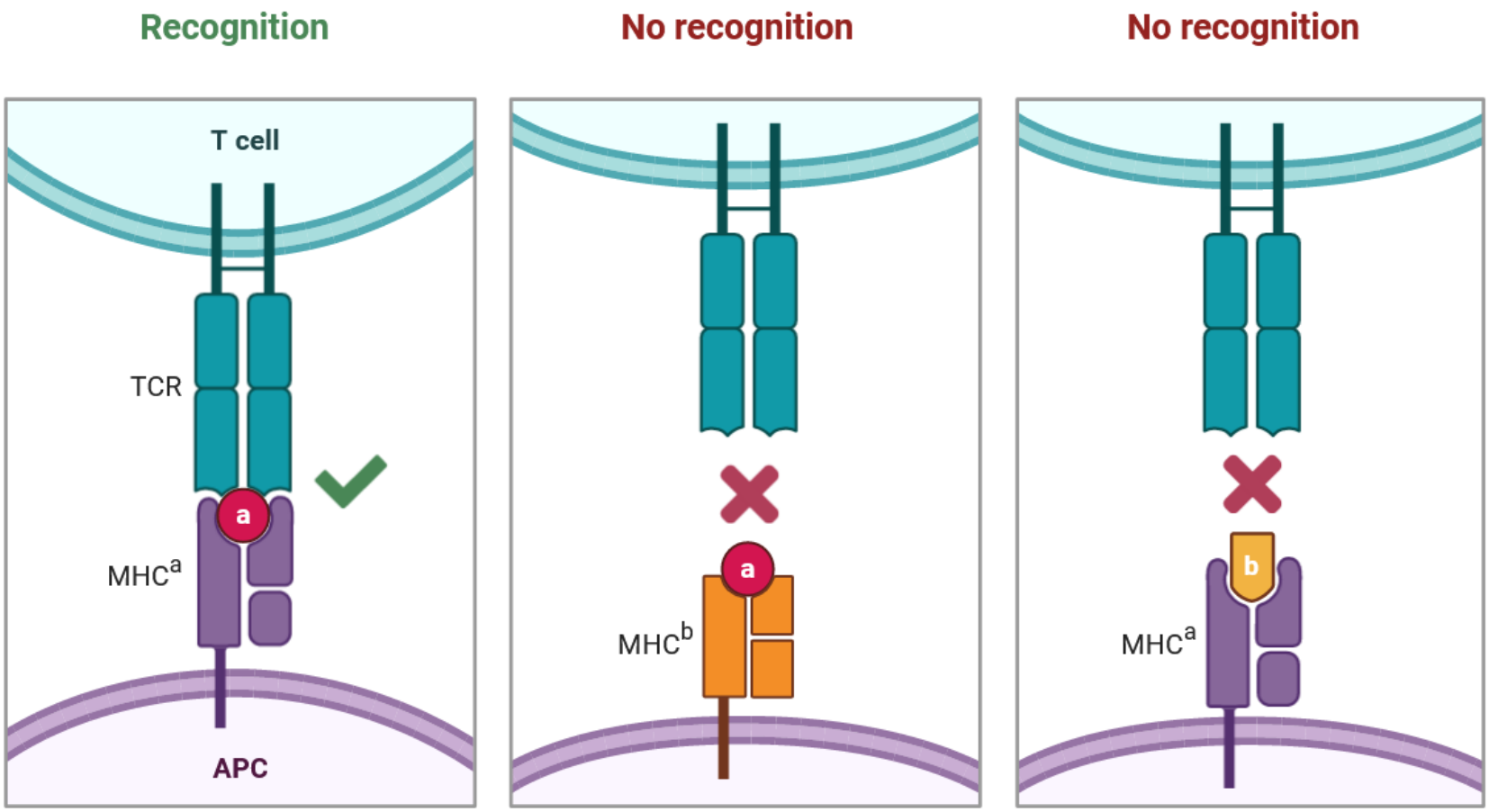
High polymorphic genes



Co-dominant expression



Antigen restriction



Antigen restriction

The Nobel Prize in Physiology or Medicine 1996

Photo from the Nobel Foundation archive.

Peter C. Doherty

Prize share: 1/2

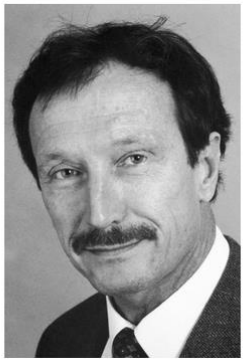


Photo from the Nobel Foundation archive.

Rolf M. Zinkernagel

Prize share: 1/2

The Nobel Prize in Physiology or Medicine 1996 was awarded jointly to Peter C. Doherty and Rolf M. Zinkernagel "for their discoveries concerning the specificity of the cell mediated immune defence"

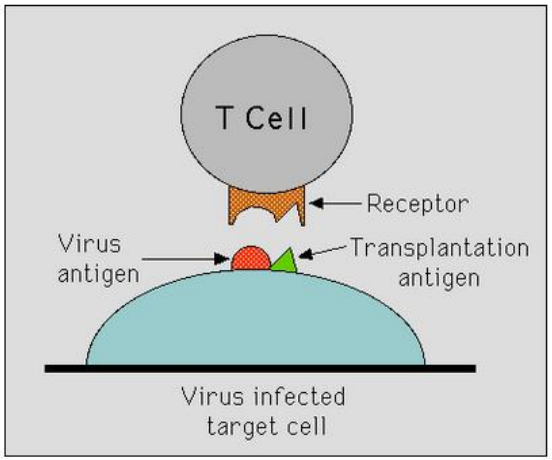
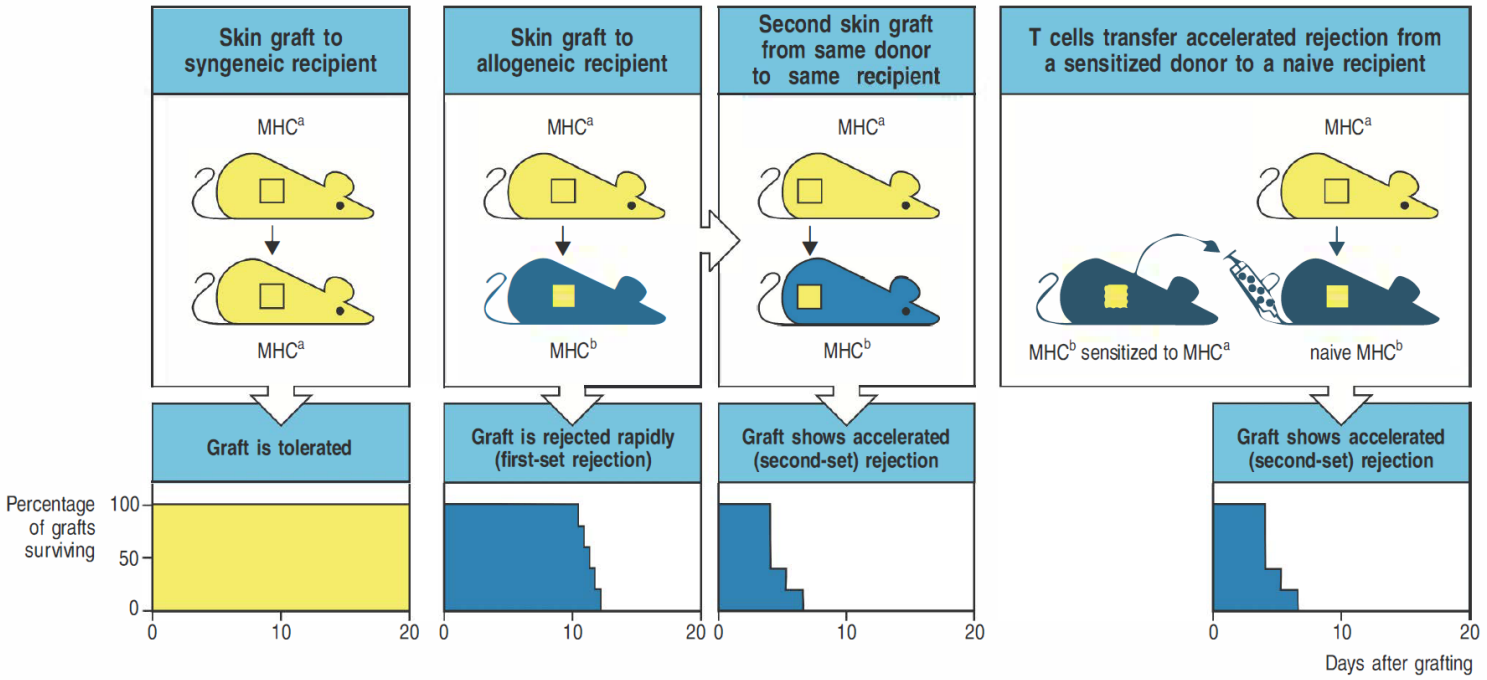


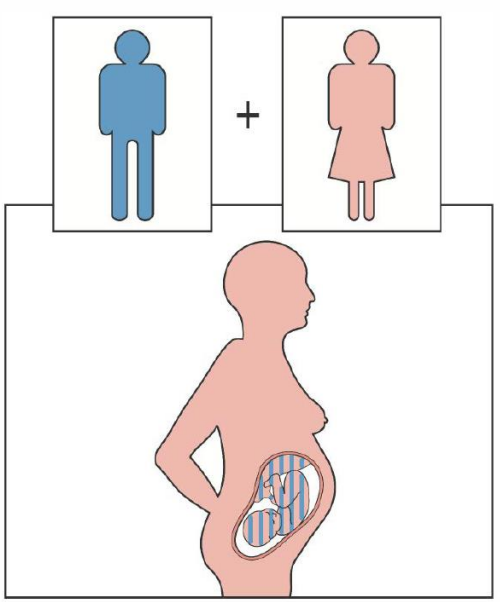
Figure legend: The figure describes how a killer T lymphocyte must recognize both the virus antigen and the self histocompatibility antigen molecule in order to kill a virus-infected target cell. The figure is a modification of the figure published by Zinkernagel and Doherty already 1974 (in Nature 251, p 547).

MHC/HLA and Transplants

Transplant rejection is caused by the immune response to non-self MHC molecules



MHC/HLA and Pregnancy



The fetus is an allograft that is not rejected

Suppression:

- Lack of MHC on trophoblast (outer membrane of the placenta)
- Expression of inhibitory HLA-G
- Expression of indoleamine
- 2,3-dioxygenase (IDO) at the maternal-fetal interphase
- Secretion of TGF-β and IL-10

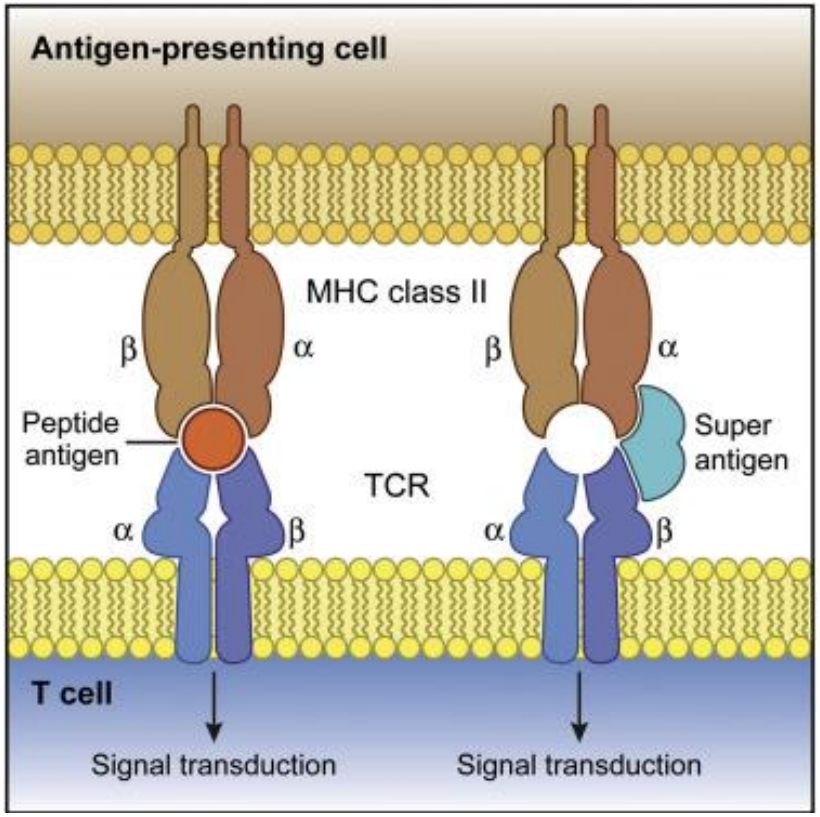
Superantigens

Different mode of binding to both MHC and TCR molecules that enables them to stimulate very large numbers of T cells

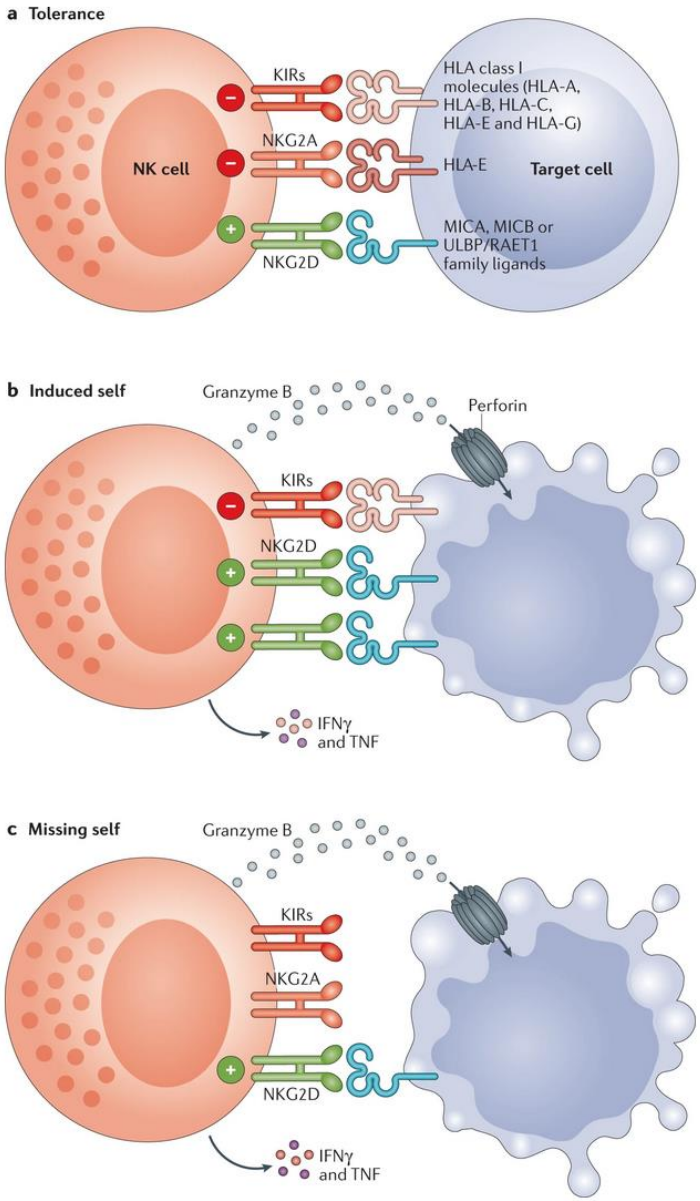
Recognized by T cells without being processed into peptides that are captured by MHC molecules

Massive production of cytokines by CD4 T cells:

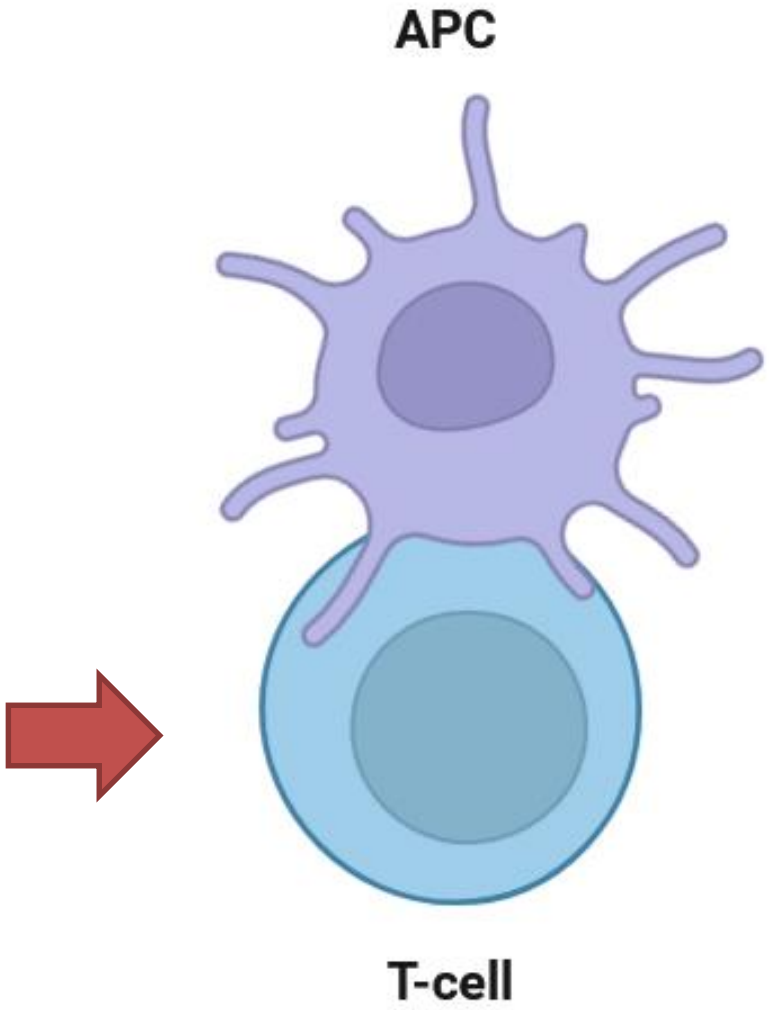
- Systemic toxicity
- Suppression of the adaptive immune response

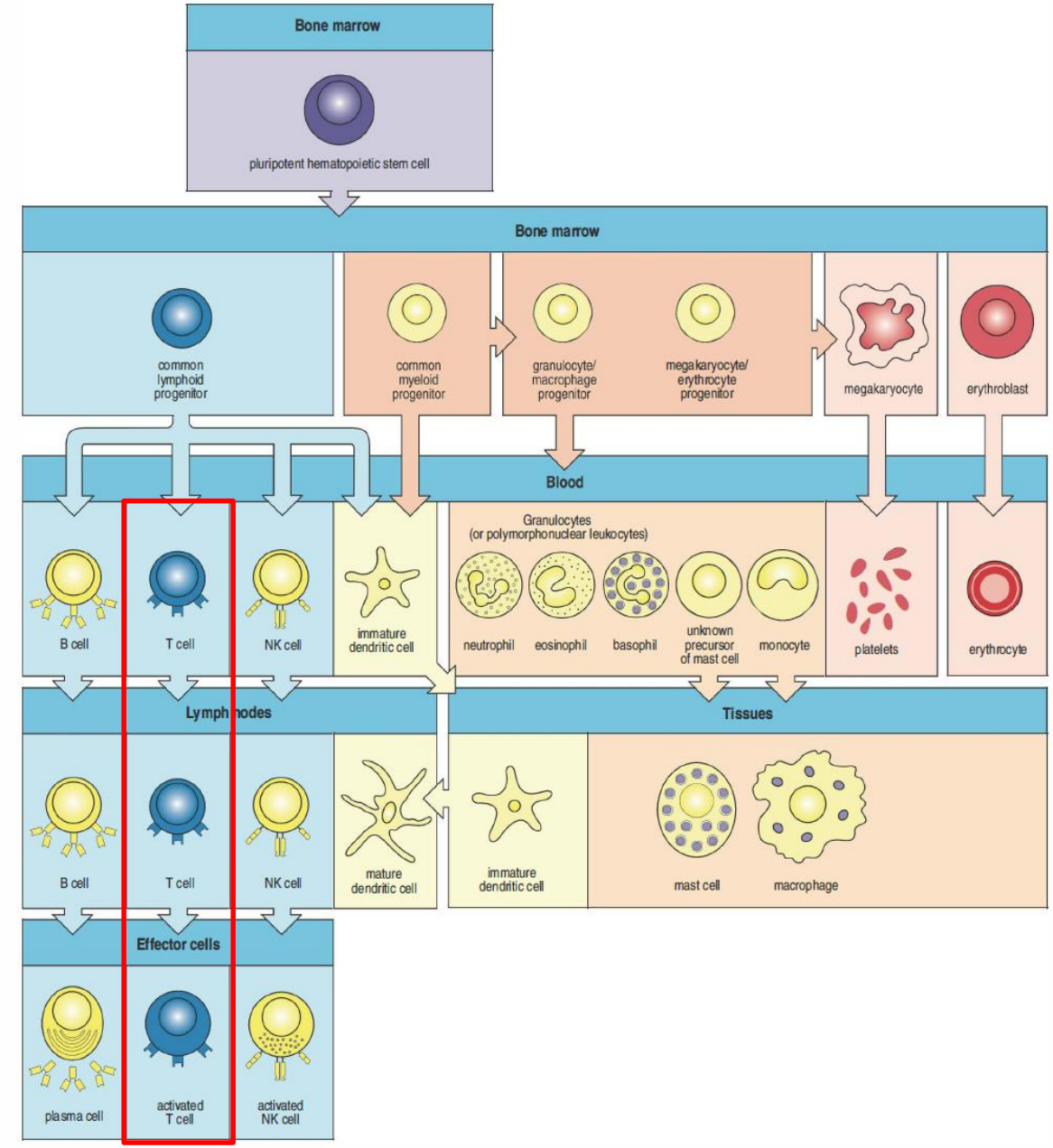


HLA and Natural-killer (NK) cells

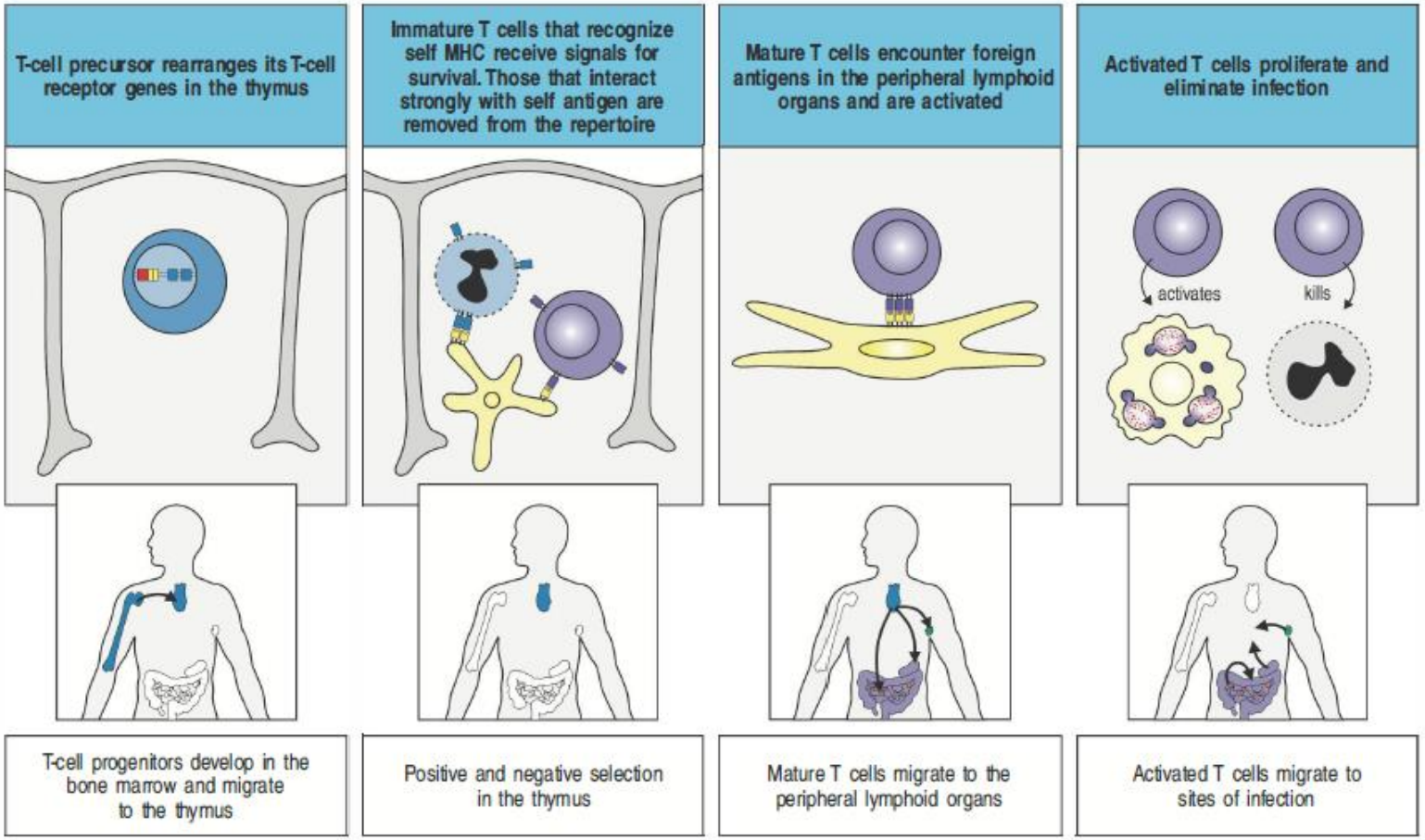


Innate – Adaptive Immune system

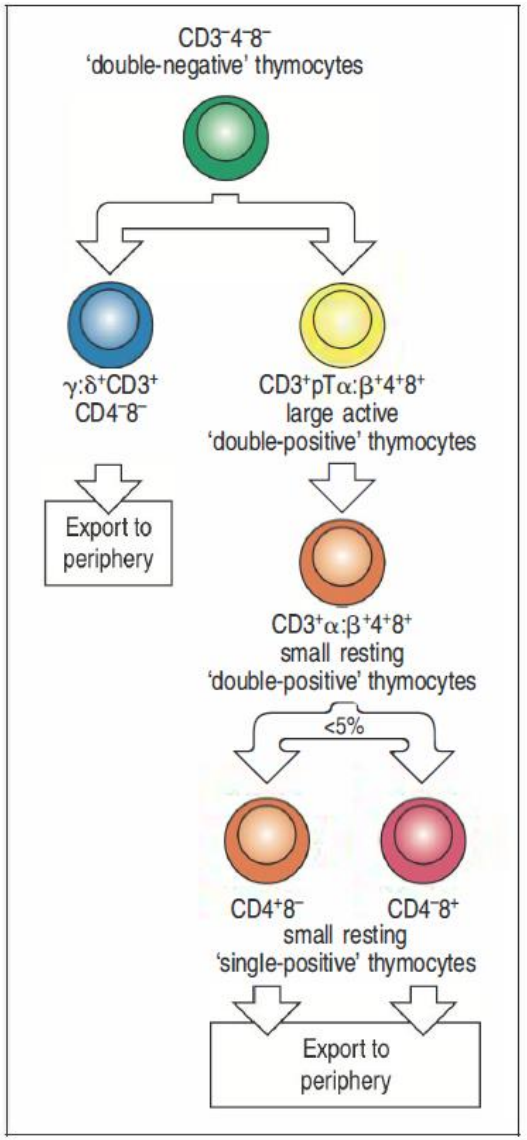



Bone marrow
pluripotent hematopoietic stem cell
Bone marrow
common lymphoid progenitor
common myeloid progenitor
granulocyte/ macrophage progenitor
megakaryocyte/ erythrocyte progenitor
megakaryocyte
erythroblast
Blood
B cell
T cell
NK cell
immature dendritic cell
Granulocytes (or polymorphonuclear leukocytes)
neutrophil
eosinophil
basophil
unknown precursor of mast cell
monocyte
platelets
erythrocyte
Lymph nodes
Tissues
B cell
T cell
NK cell
mature dendritic cell
immature dendritic cell
mast cell
macrophage
Effector cells
plasma cell
activated T cell
activated NK cell

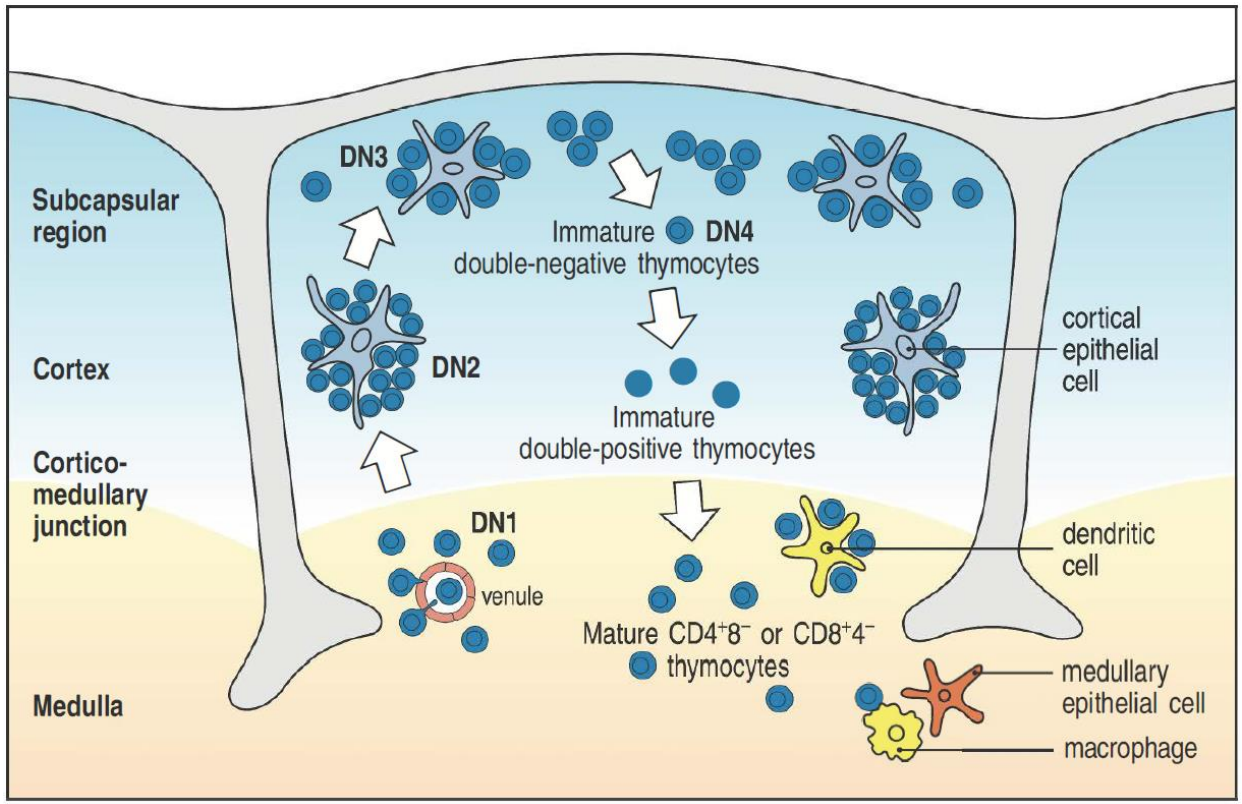
T cell development

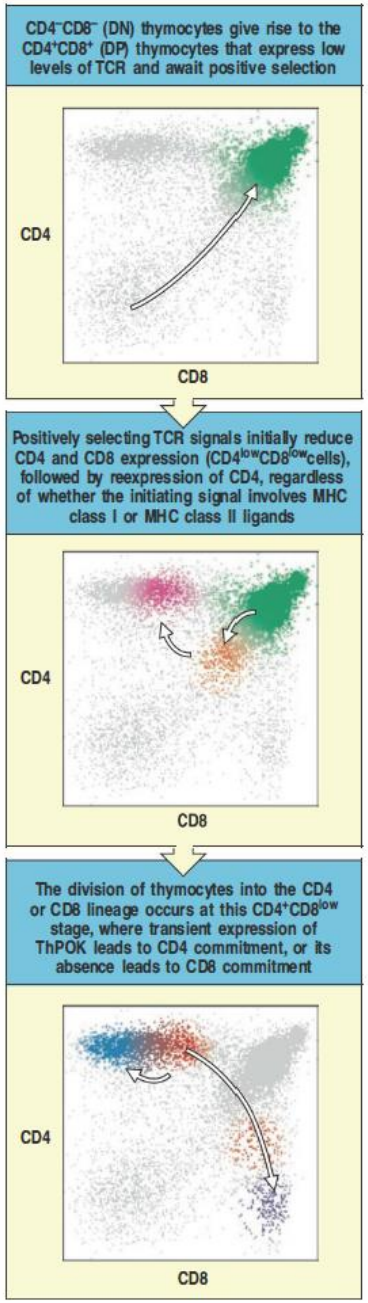


T cell development



T cell development





T cell subsets

1. Selection and Differentiation in the thymus into CD8+ or CD4+ T cells

CD4 T cells: peptide + MHC class II

2. Polarization of CD4+ T cells in the periphery into Th1 or Th2

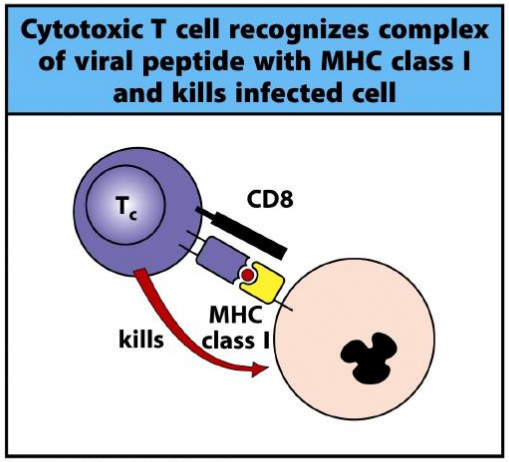
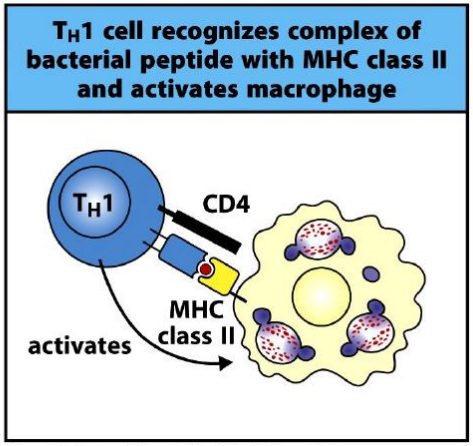


Figure 1-32 Immunobiology, 7ed. (© Garland Science 2008)



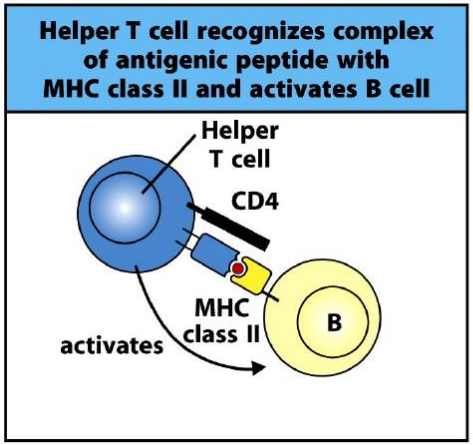
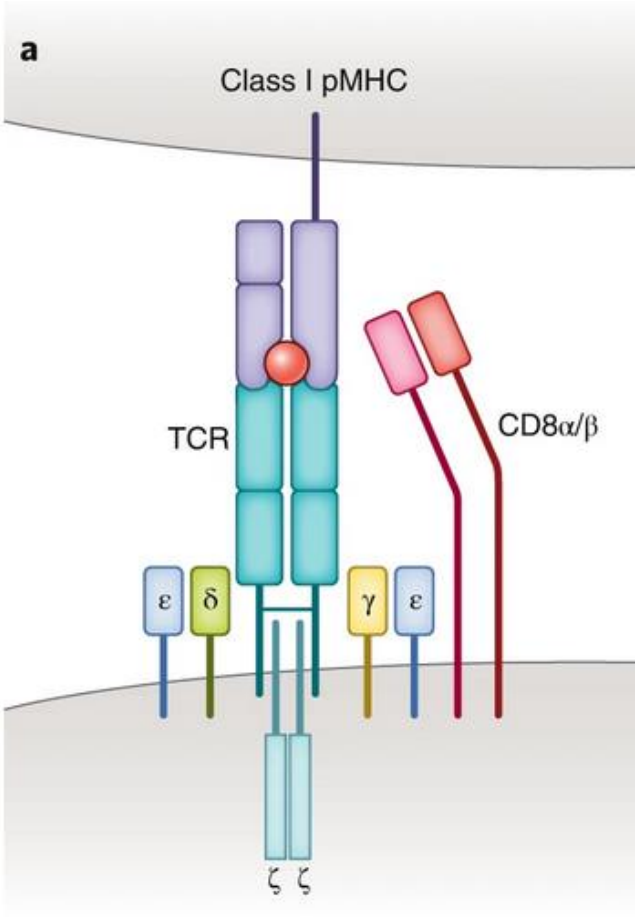


Figure 1-33 Immunobiology, 7ed. (© Garland Science 2008)

CD8+ cytotoxic T cells



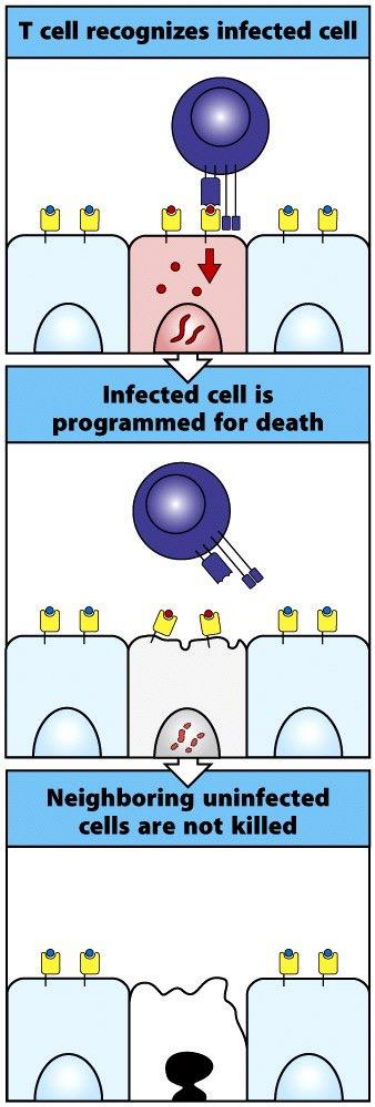
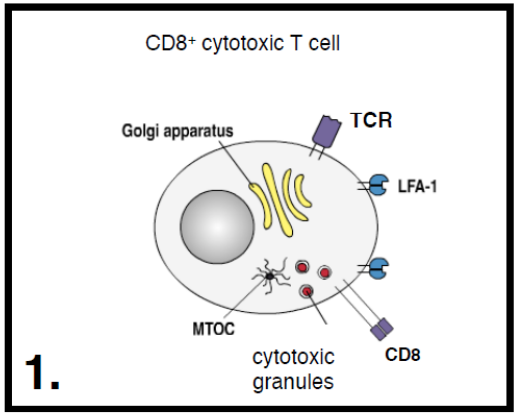
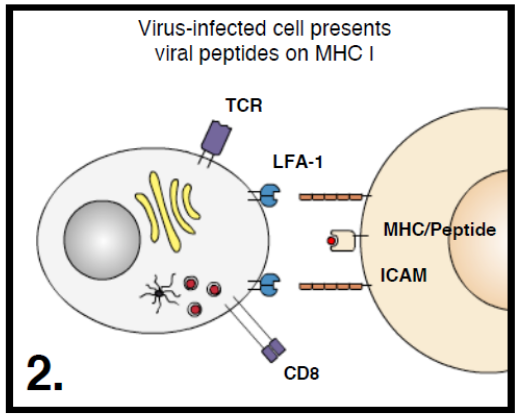
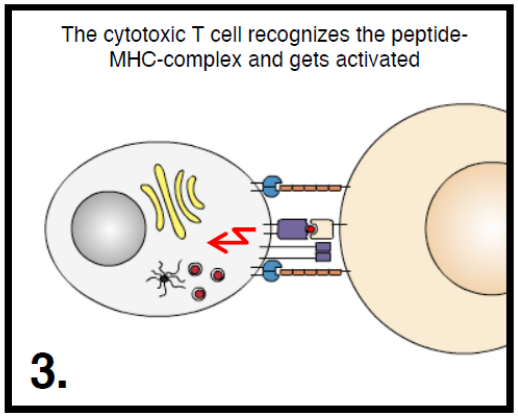


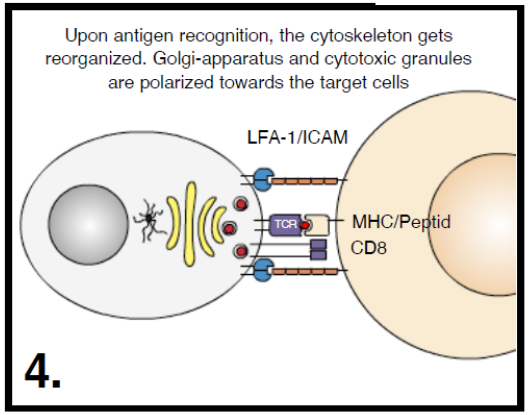
Figure 8-40 Immunobiology, 7ed. (© Garland Science 2008)

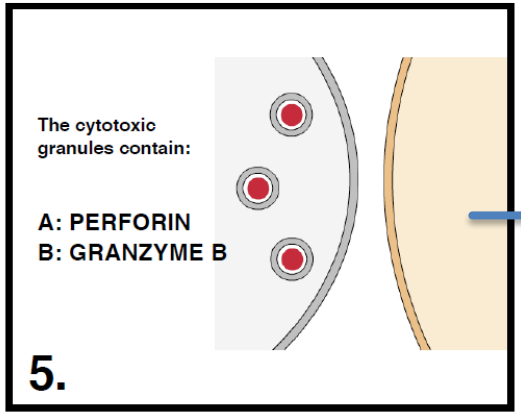
CD8+ cytotoxic T cells





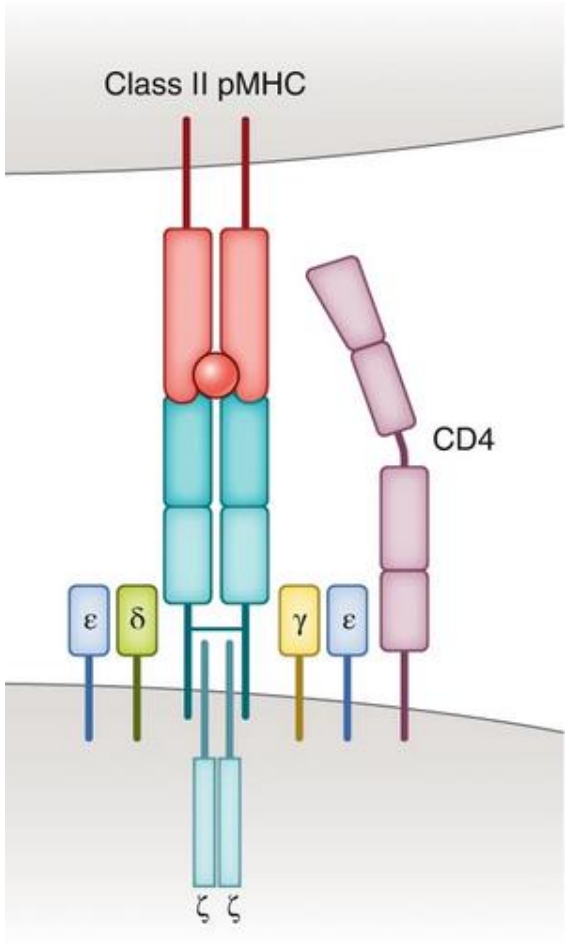


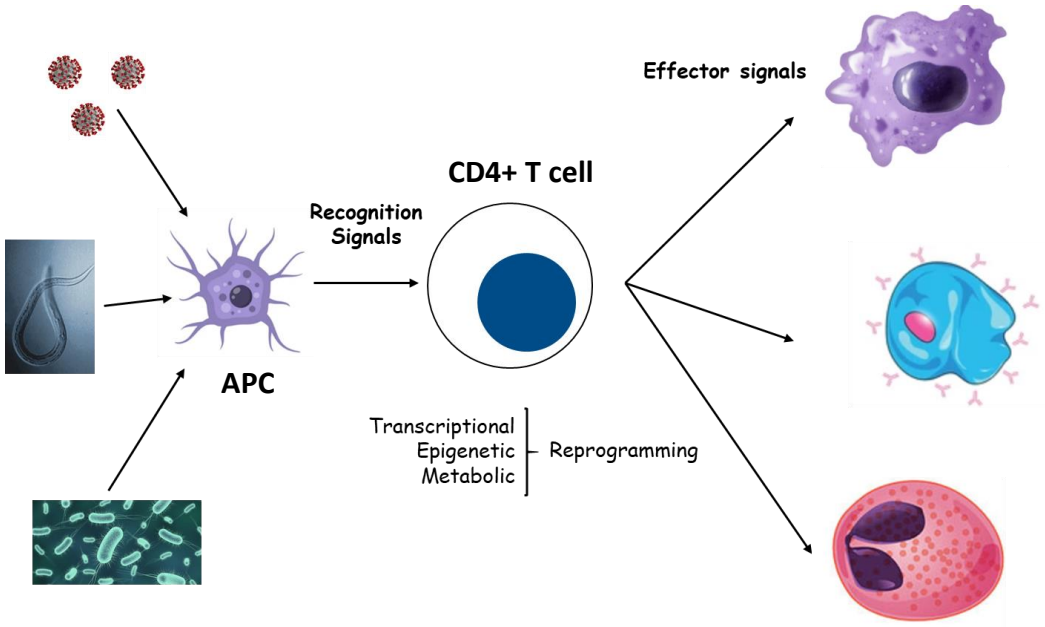




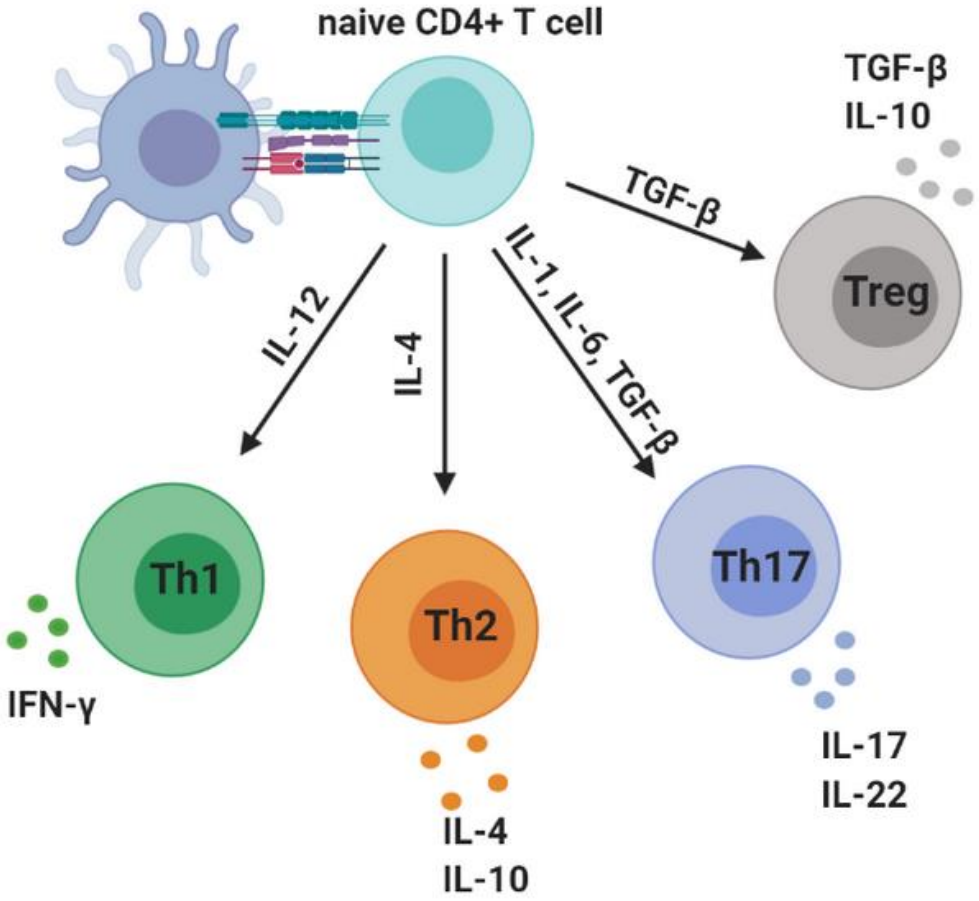
Apoptosis

CD4+ helper T cells

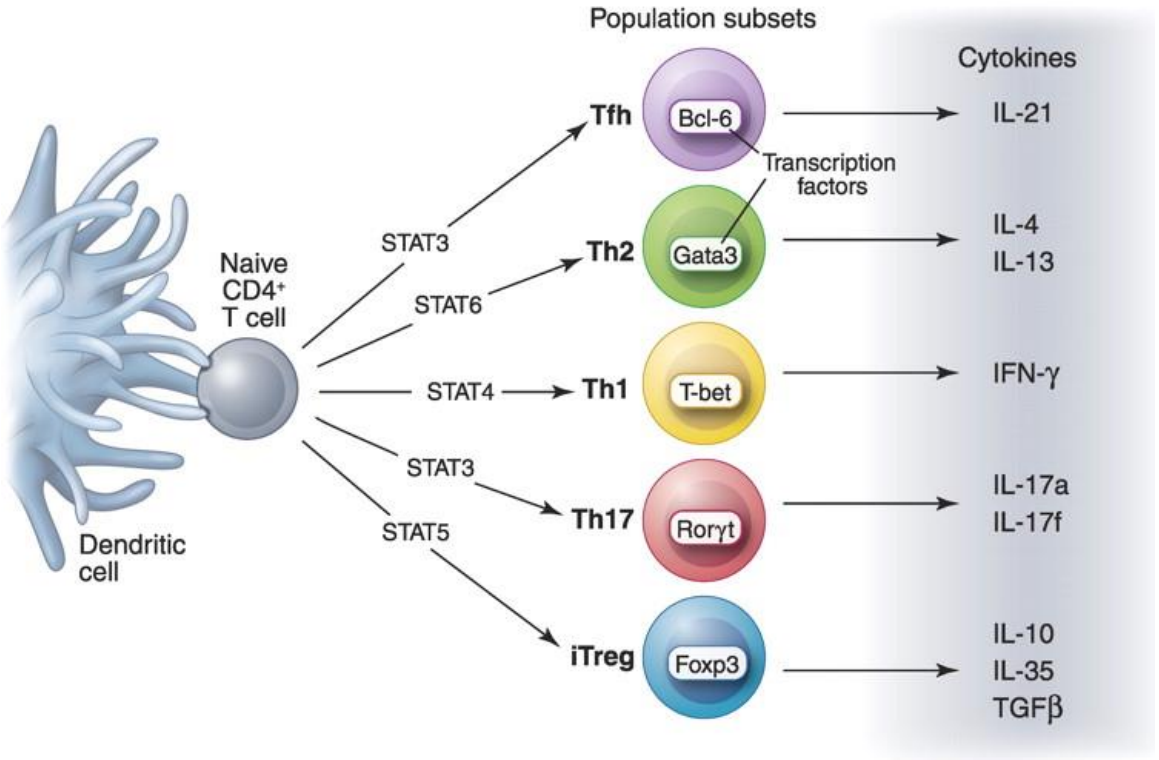




T helper lineages



T helper lineages



B cell maturation

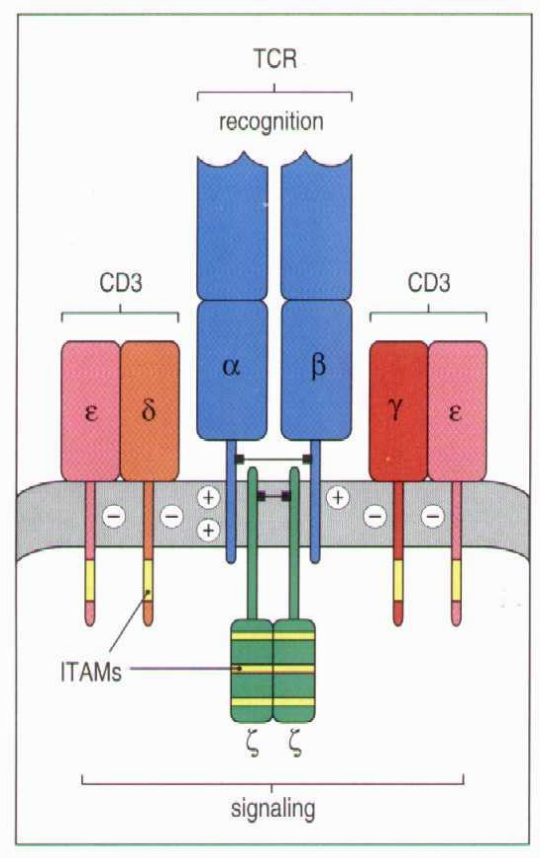
Humoral responses / Parasitic infections

Intracellular pathogens

Extracellular pathogens

Immune response supression

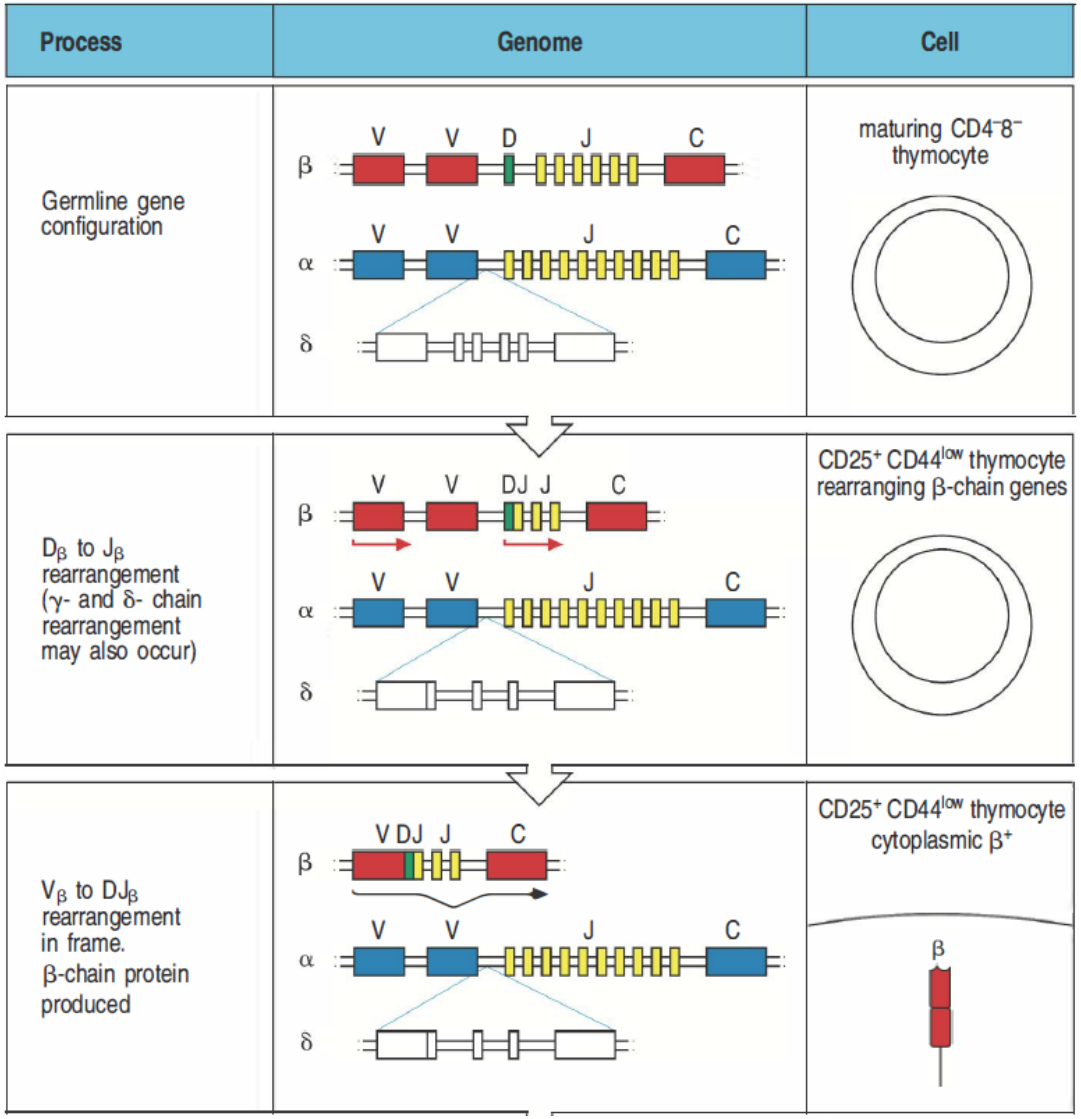
T cell receptor (TCR)



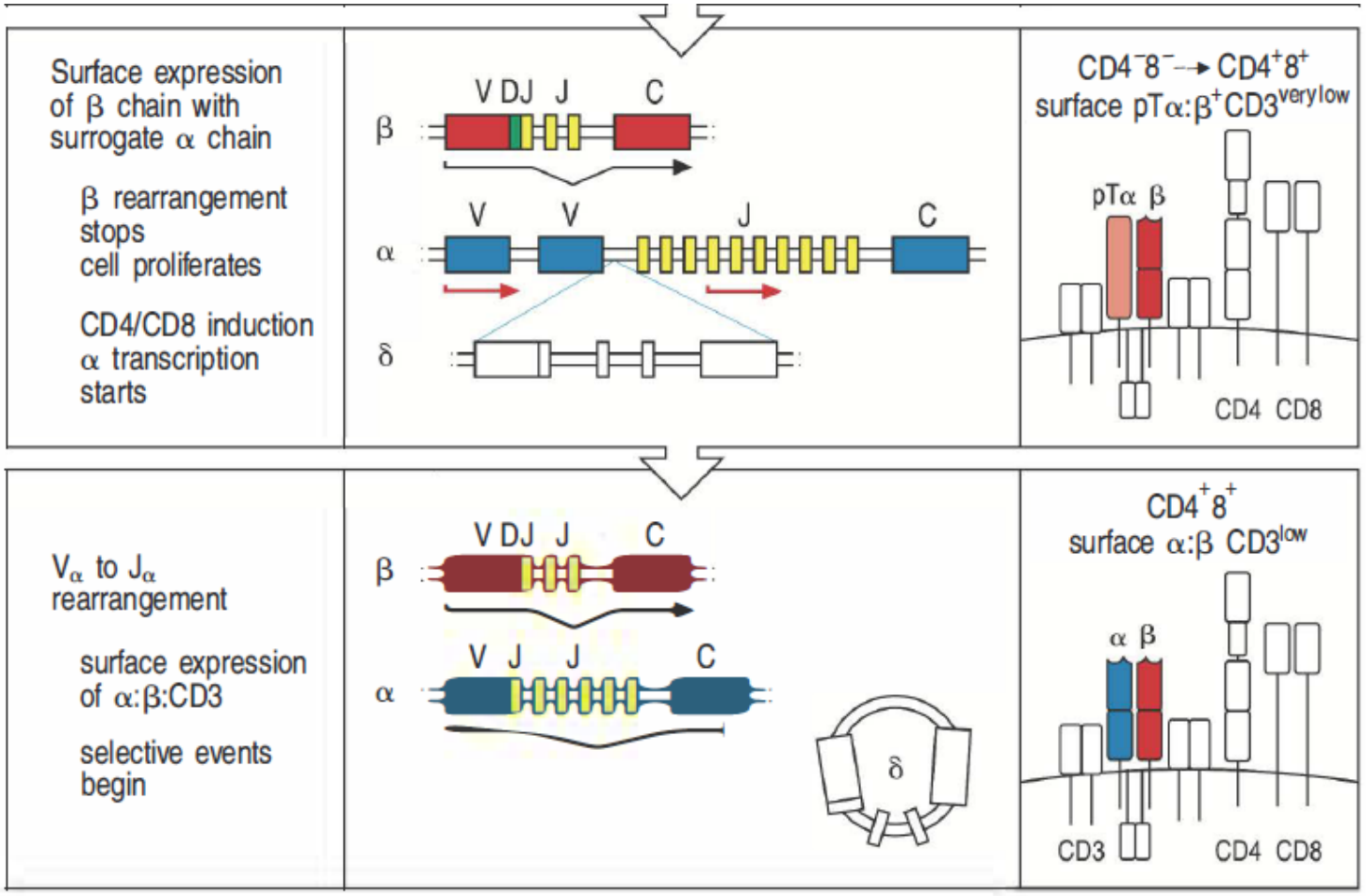
- T cell receptor
  - α and β chain heterodimer
  - antigen recognition
- CD3
  - transmembrane proteins with extracellular domains and cytoplasmic tails
    - two ε-chains
    - one δ-chain
    - one γ-chain
  - transmembrane/cytoplasmic ζ-homodimers

ITAM: immunoreceptor tyrosine-based activation motifs

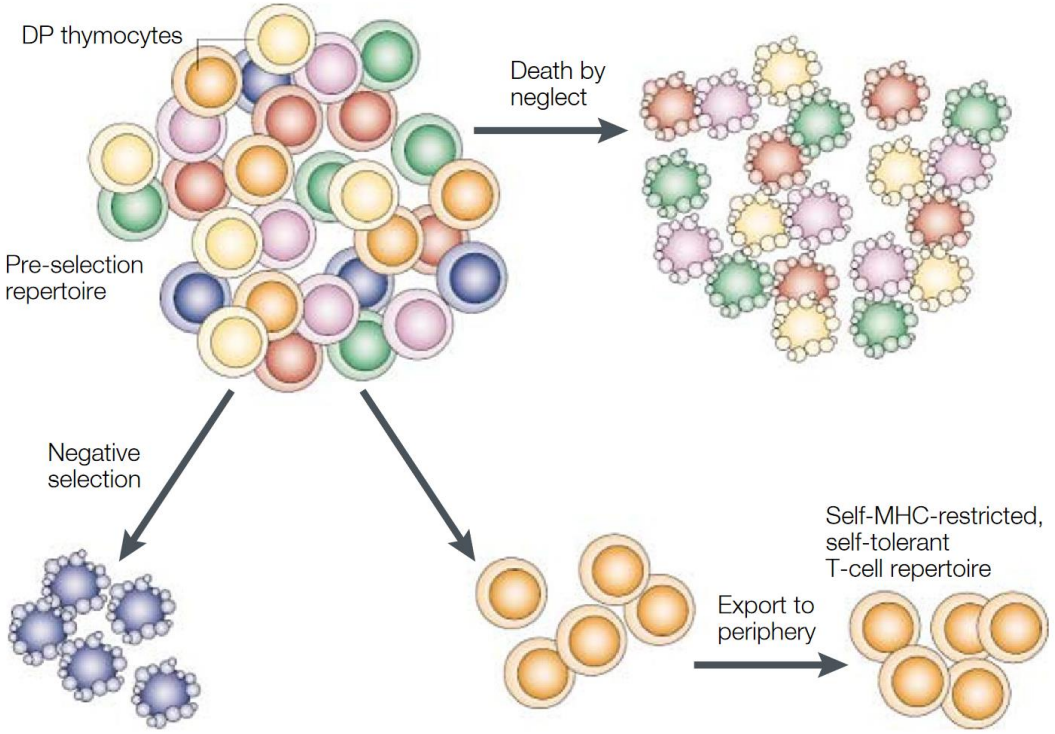
T cell receptor (TCR) rearrangement



T cell receptor (TCR) rearrangement



Thymic T cell selection



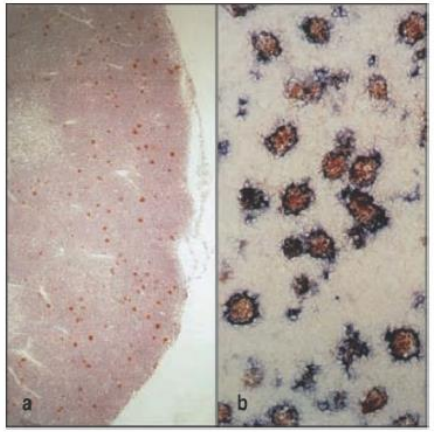
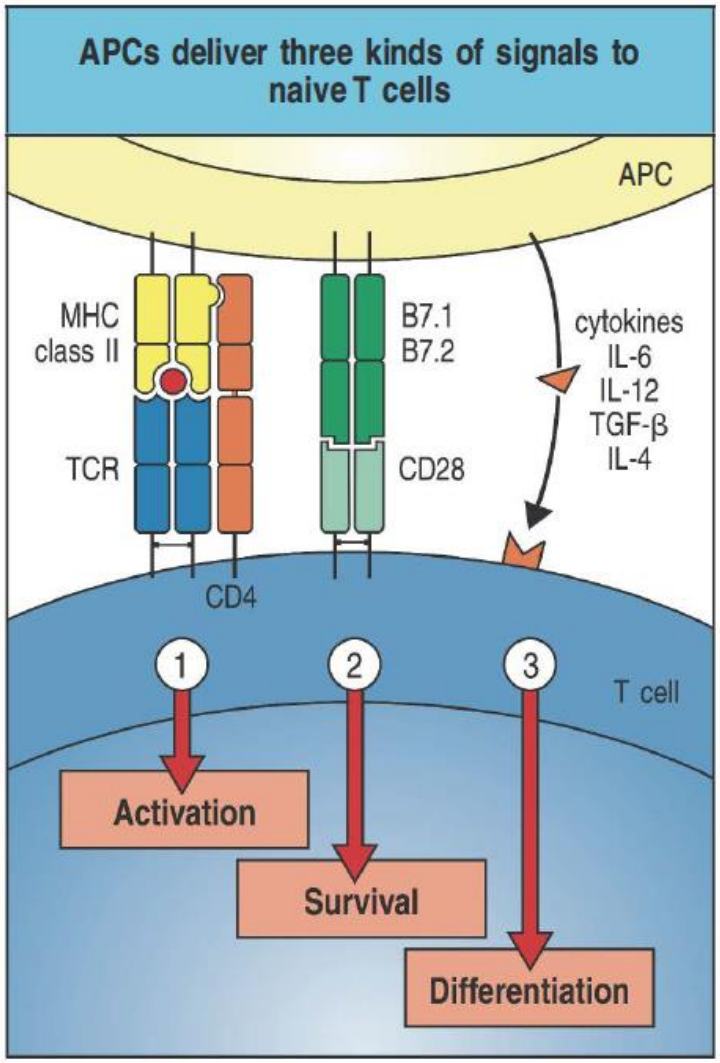


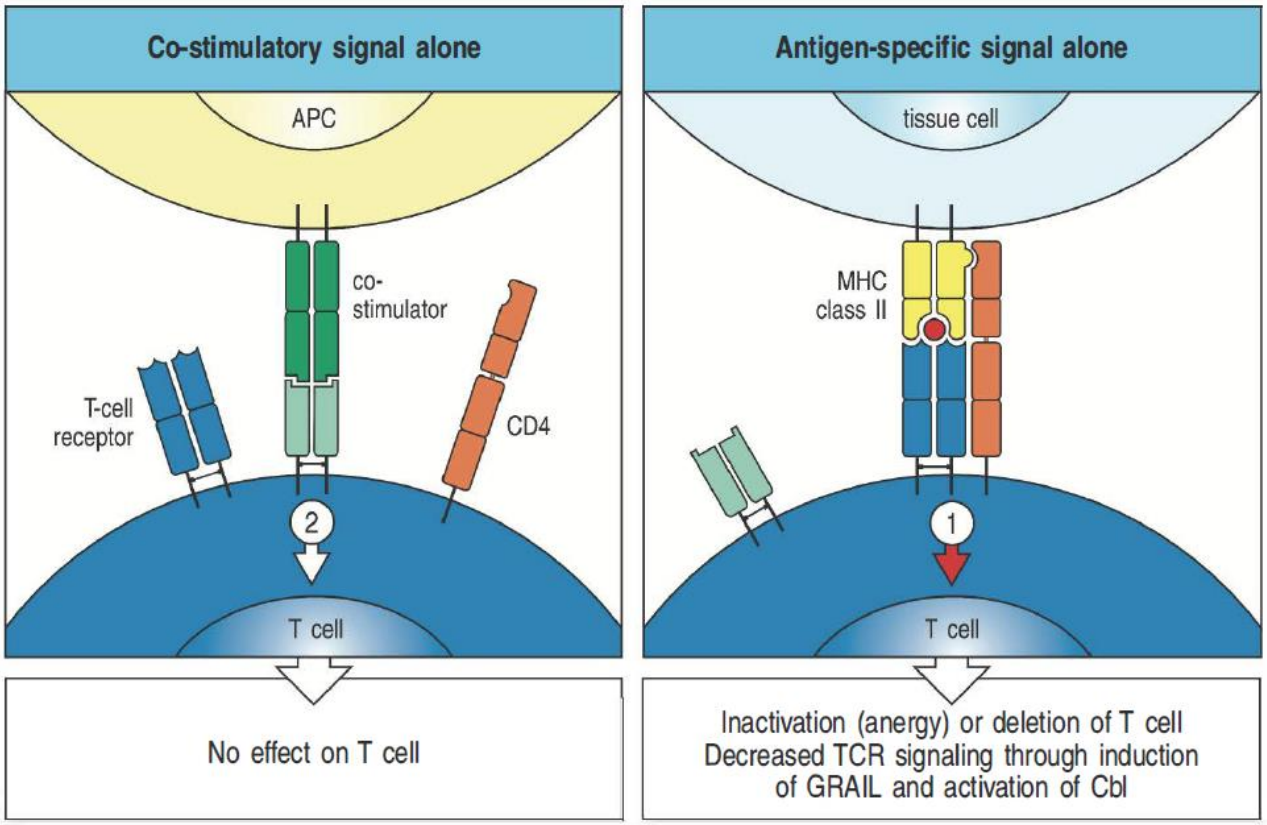
Fig. 8.18 Developing T cells that undergo apoptosis are ingested by macrophages in the thymic cortex.

More details in the lecture Immnue regulation…

3 signals


APCs deliver three kinds of signals to naive T cells
APC
MHC class II
TCR
CD4
B7.1
B7.2
CD28
cytokines
IL-6
IL-12
TGF-β
IL-4
1
2
3
T cell
Activation
Survival
Differentiation

T cell anergy



Anergy and immune regulation

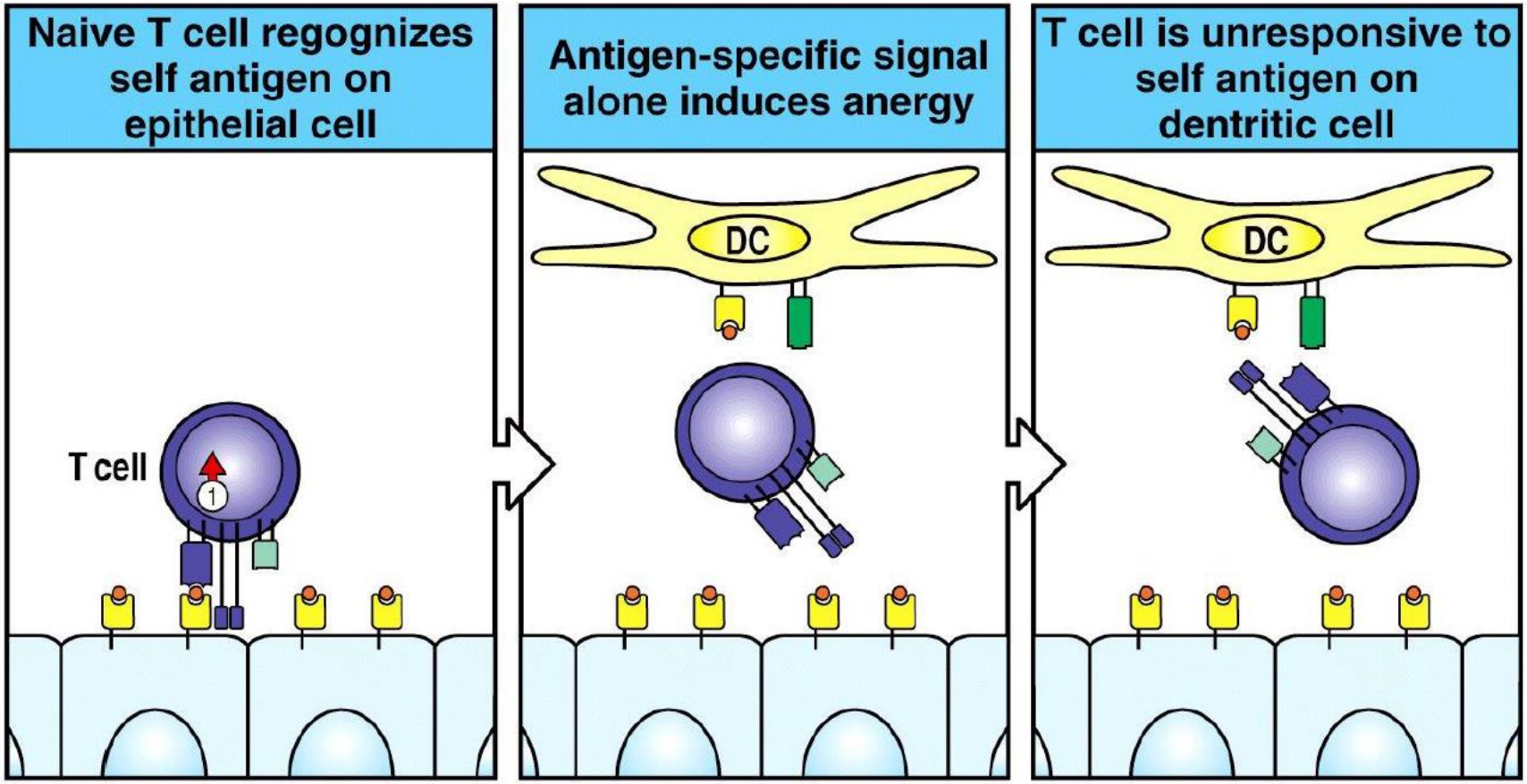


Figure 8-13 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Thank you for your attention!

Questions?

Please write to carlos.plazasirvent@rub.de