

Antigen presentation and T cells

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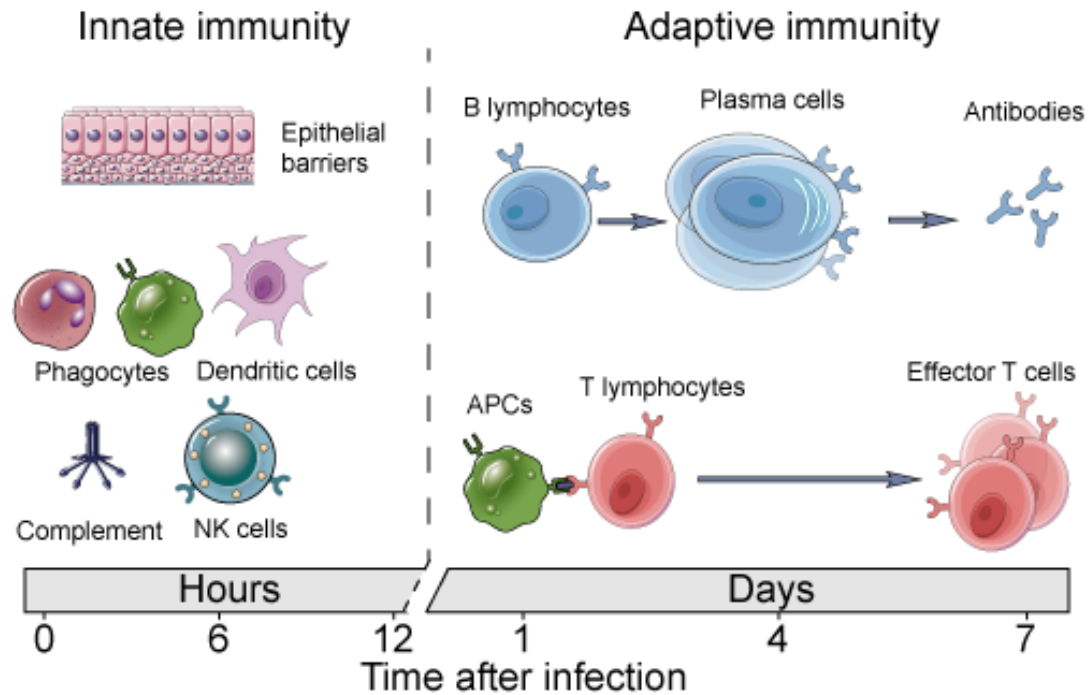


Molecular Immunology

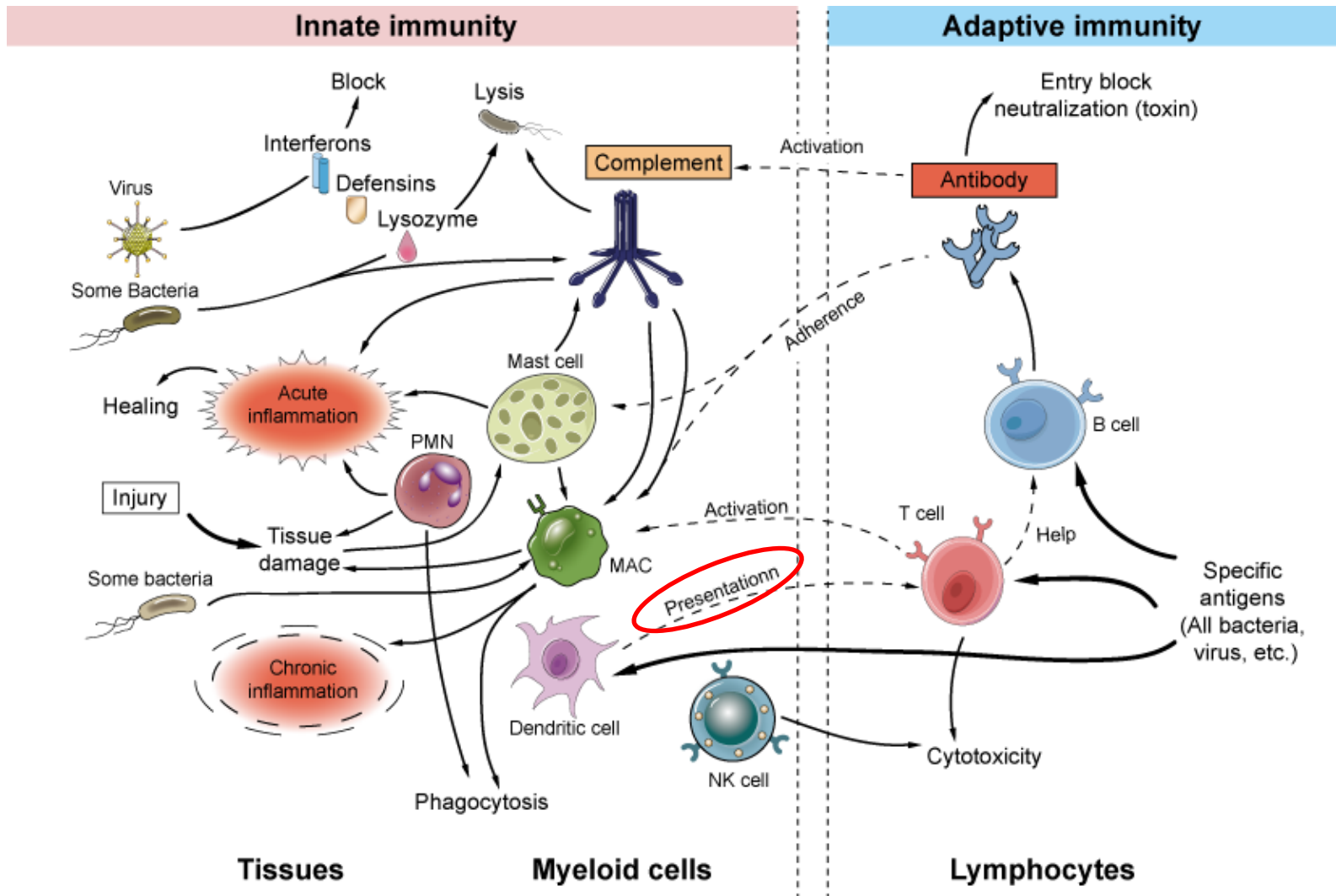
Agenda

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

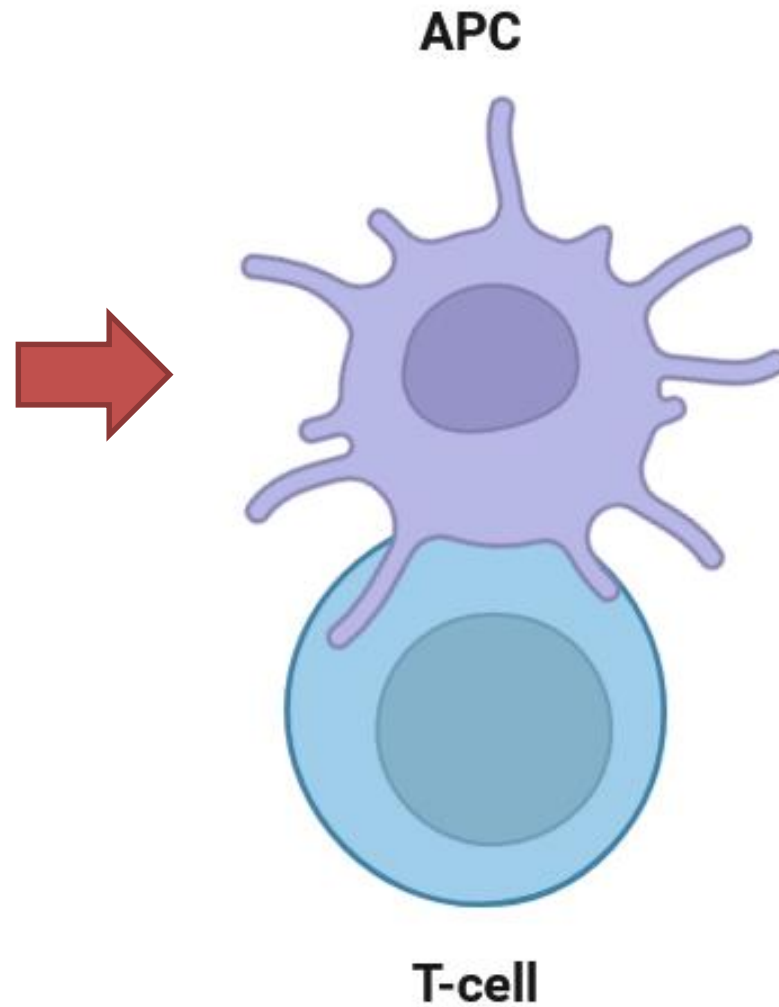
Antigen presentation



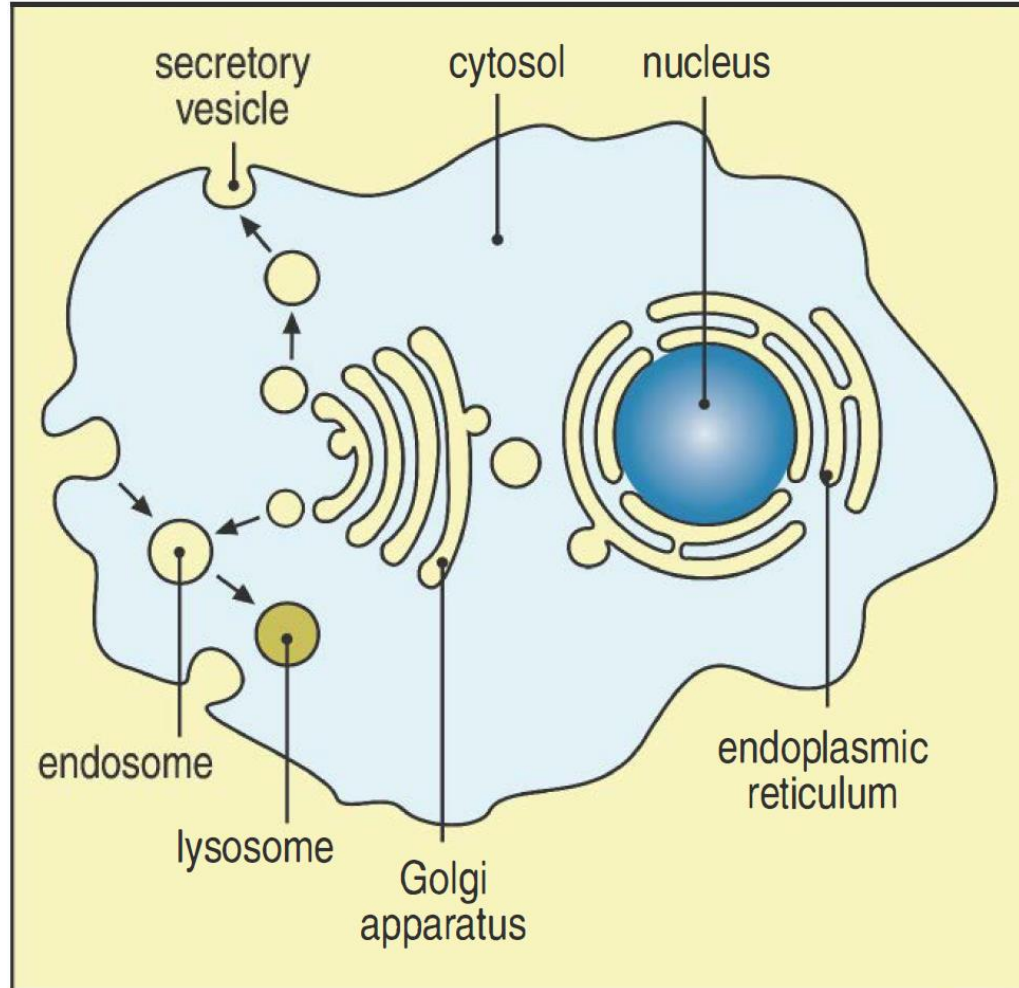
Antigen presentation



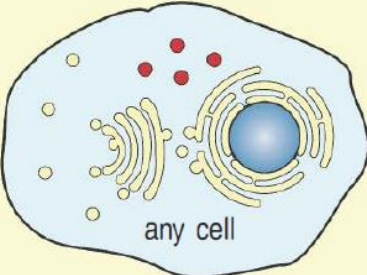
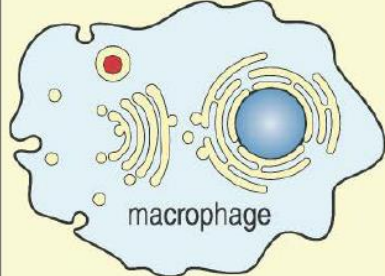
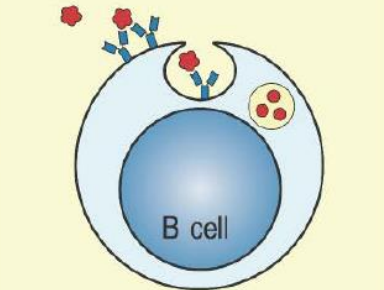
Innate – Adaptive Immune system



Intracellular compartments

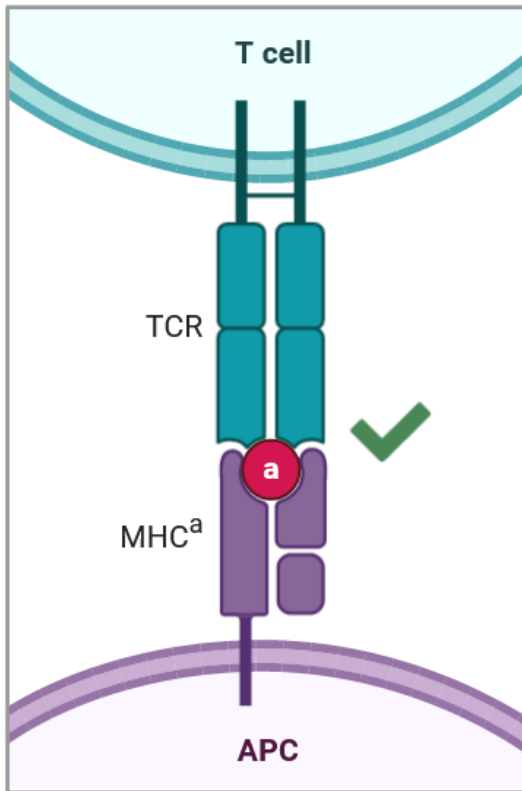


Antigen presenting cells

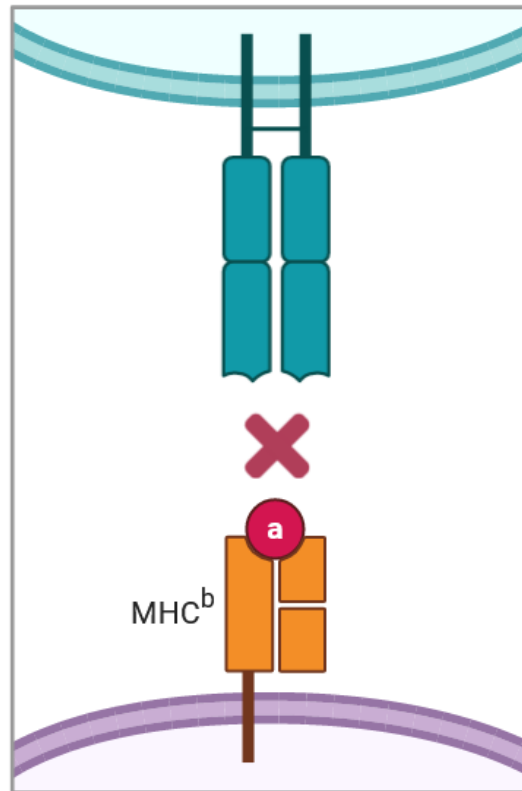
	Cytosolic pathogens	Intravesicular pathogens	Extracellular pathogens and toxins
	 <p>any cell</p>	 <p>macrophage</p>	 <p>B cell</p>
Degraded in	Cytosol	Endocytic vesicles (low pH)	Endocytic vesicles (low pH)
Peptides bind to	MHC class I	MHC class II	MHC class II
Presented to	Effector CD8 T cells	Effector 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

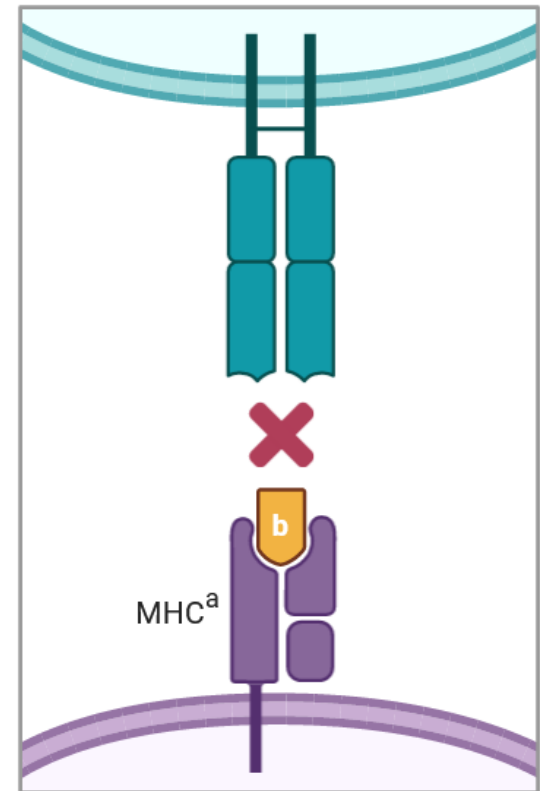
Recognition



No recognition



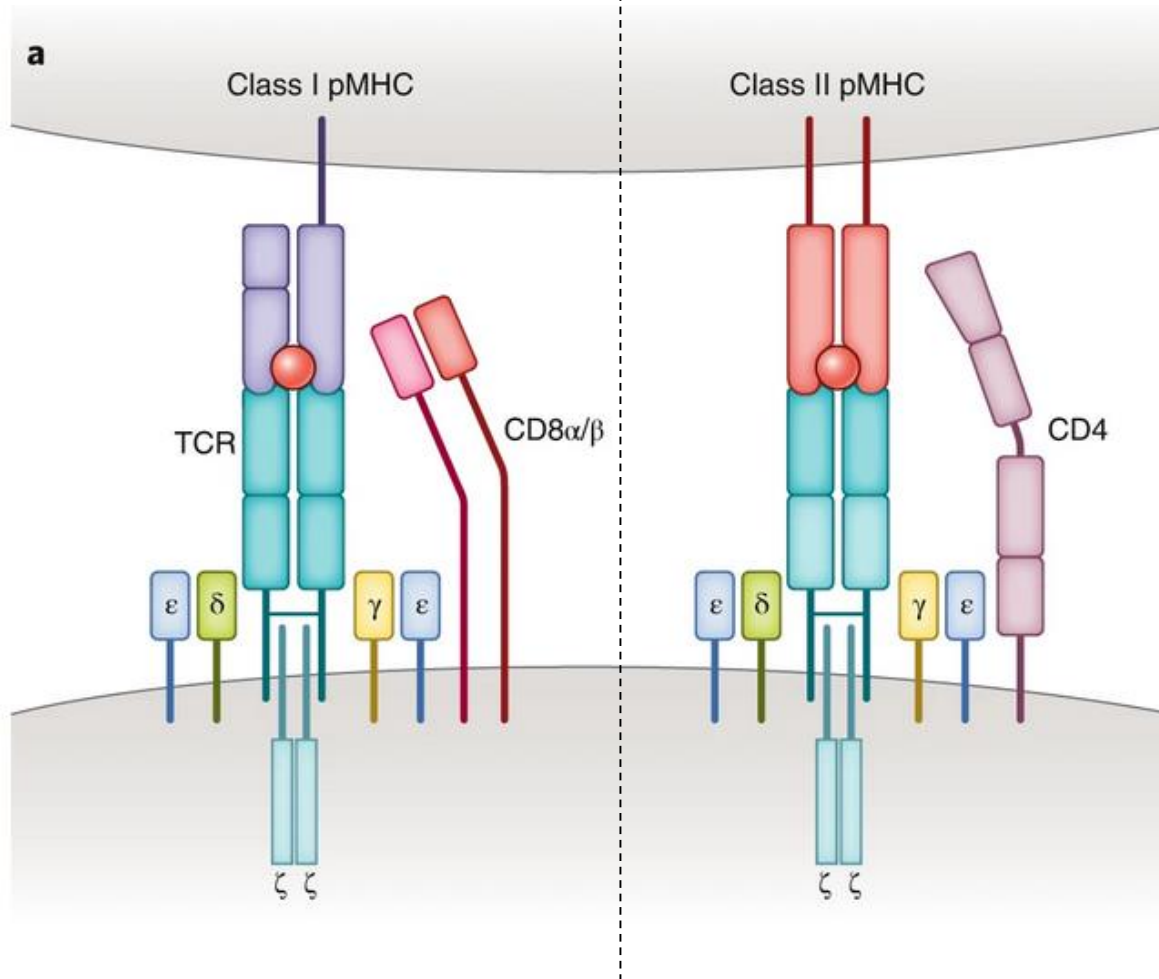
No recognition



Antigen presenting cells

Antigen presenting cell (APC)

Antigen presenting cell (APC)



T cell

T cell

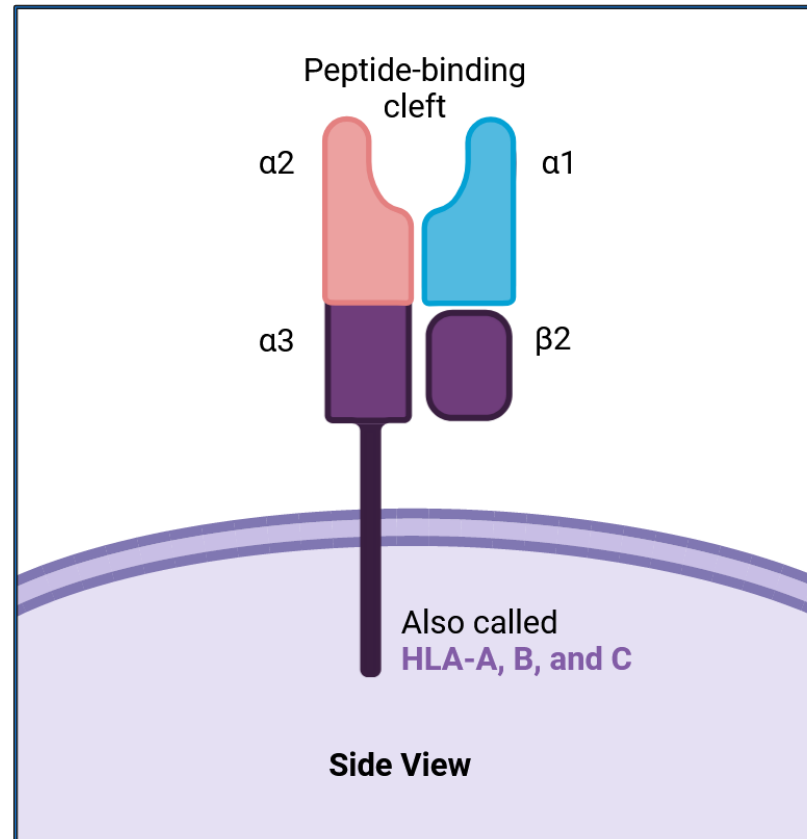
Antigen presenting cells

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	-	-

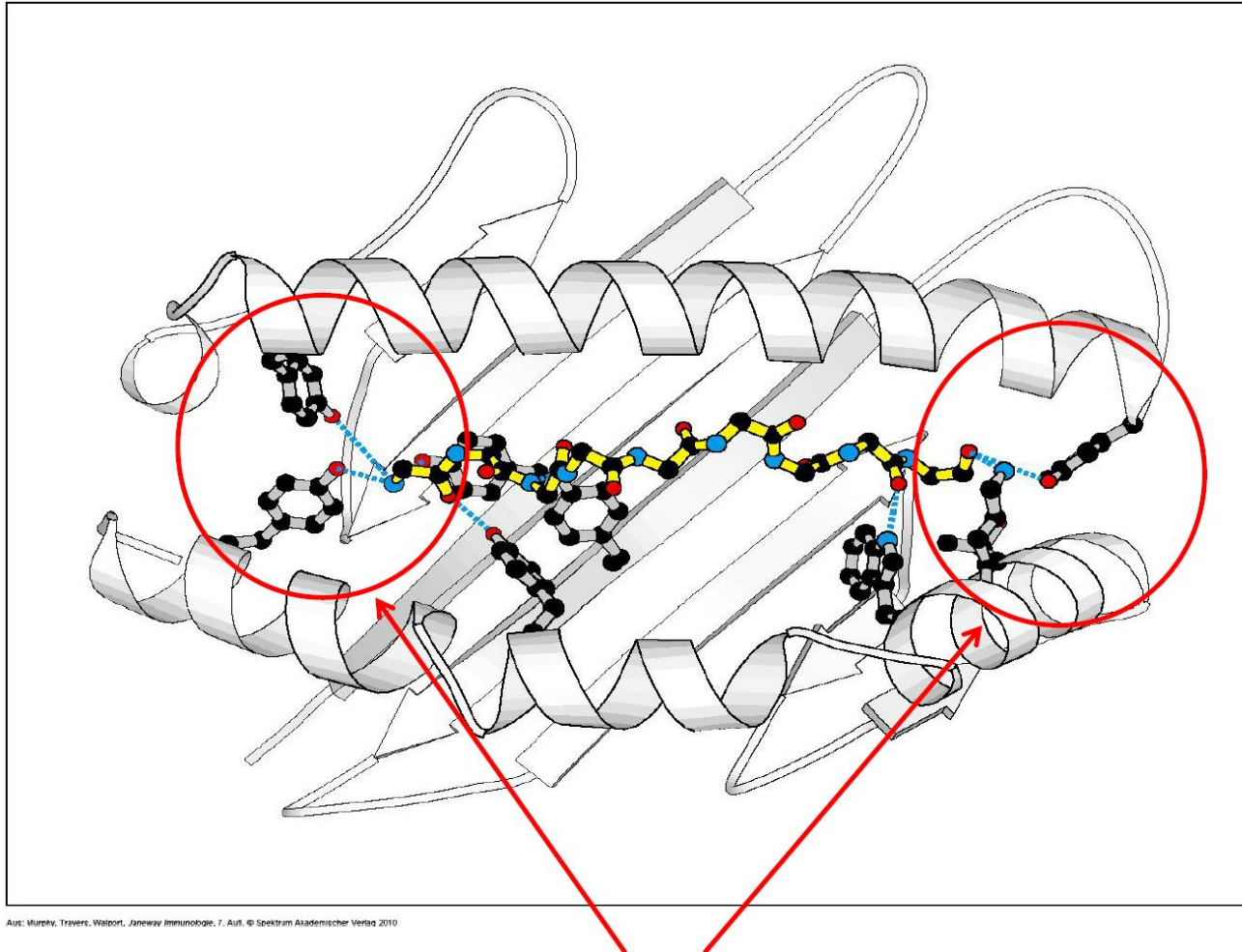
*activated T cells

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

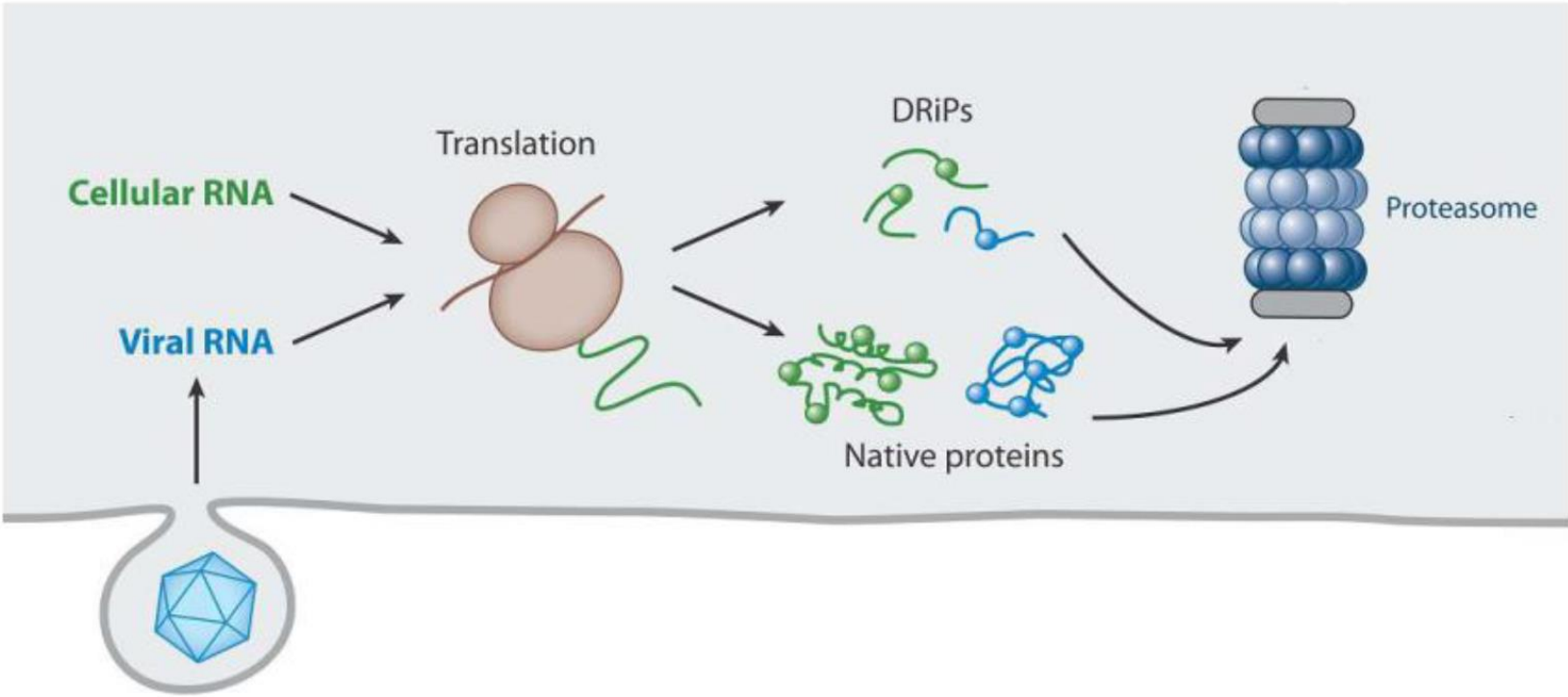


Major Histocompatibility Complex (MHC) I



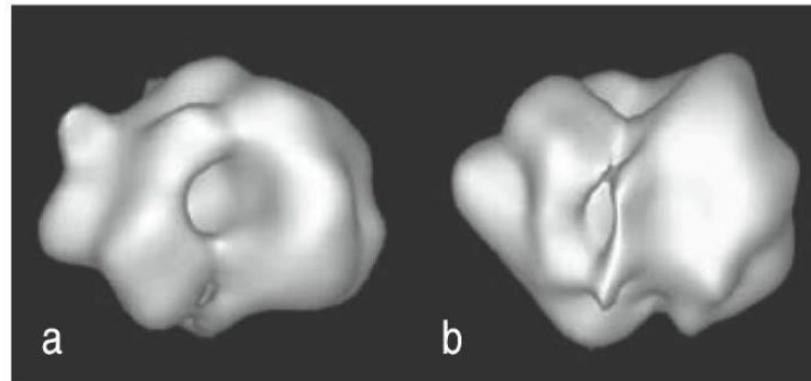
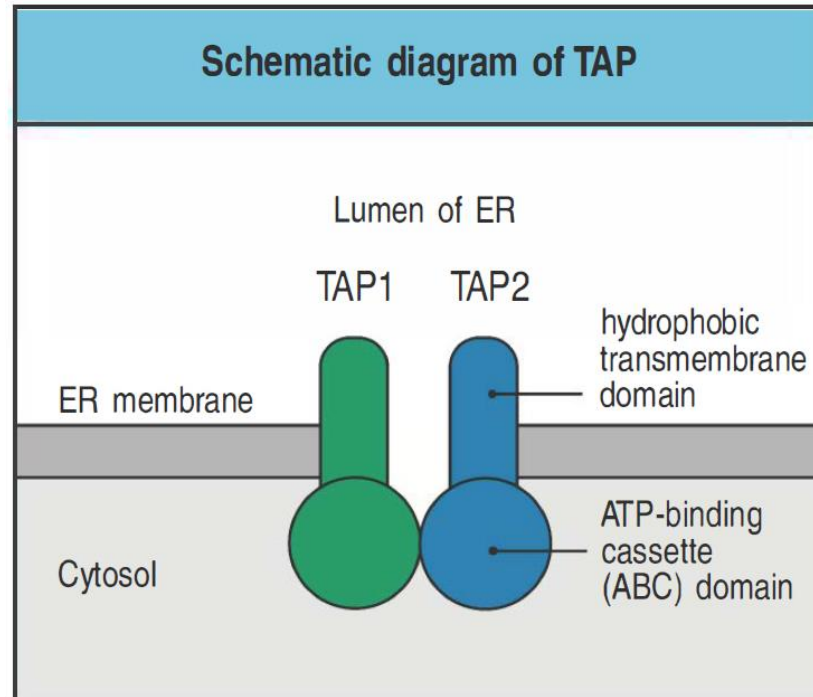
Coordination of the MHC1 binding peptide

Protein degradation

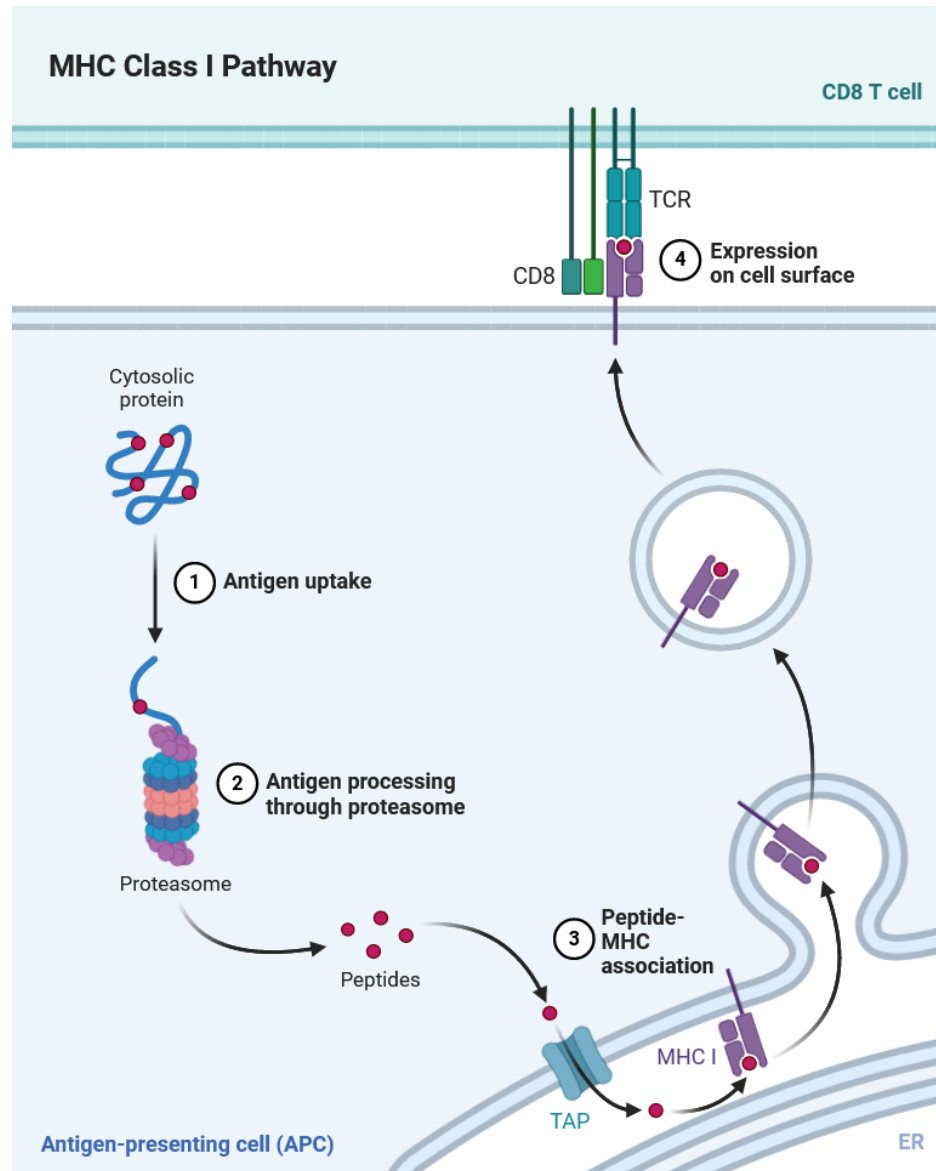


DRiP: Defective ribosomal product

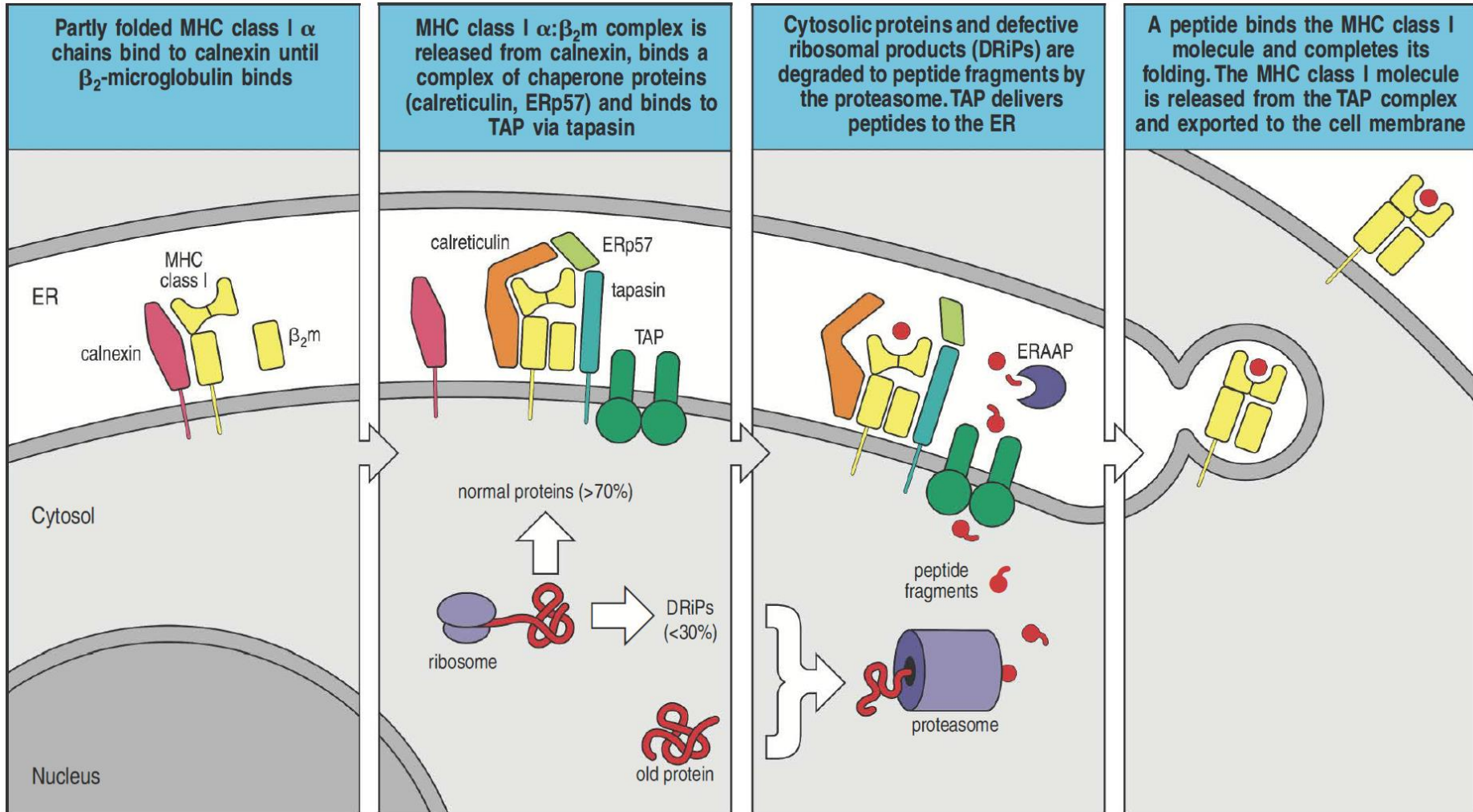
Peptide transport from cytosol to ER



MHC I peptide load



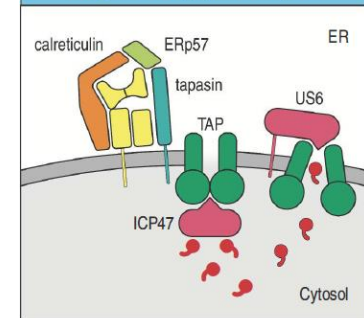
MHC I peptide load



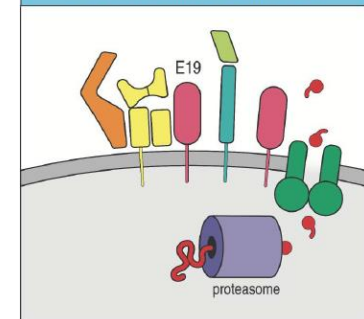
Immuno evasion

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

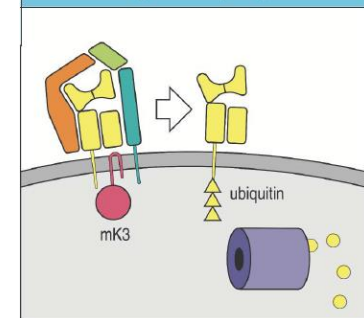
Viral evasins US6 and ICP47 block antigen presentation by preventing peptide movement through the TAP peptide transporter



Adenovirus protein E19 competes with tapasin and inhibits peptide loading onto nascent MHC class I proteins

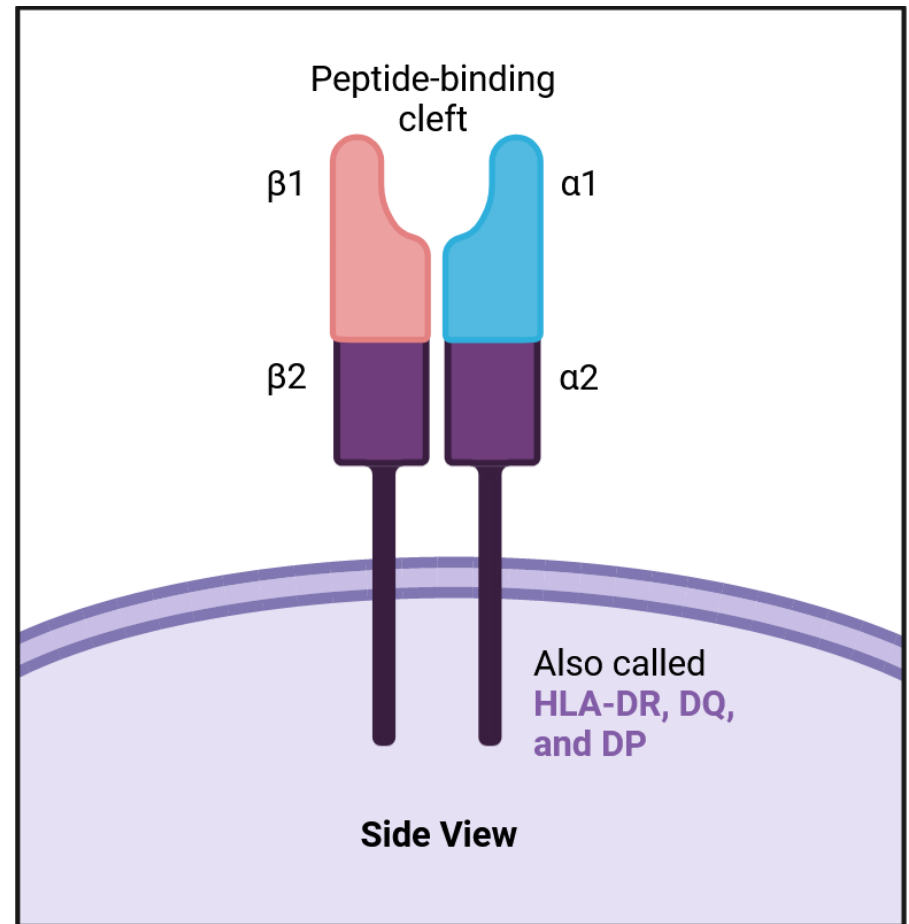


The mK3 protein of murine γ herpes virus is an E3-ubiquitin ligase, targeting MHC class I for degradation by the proteasome

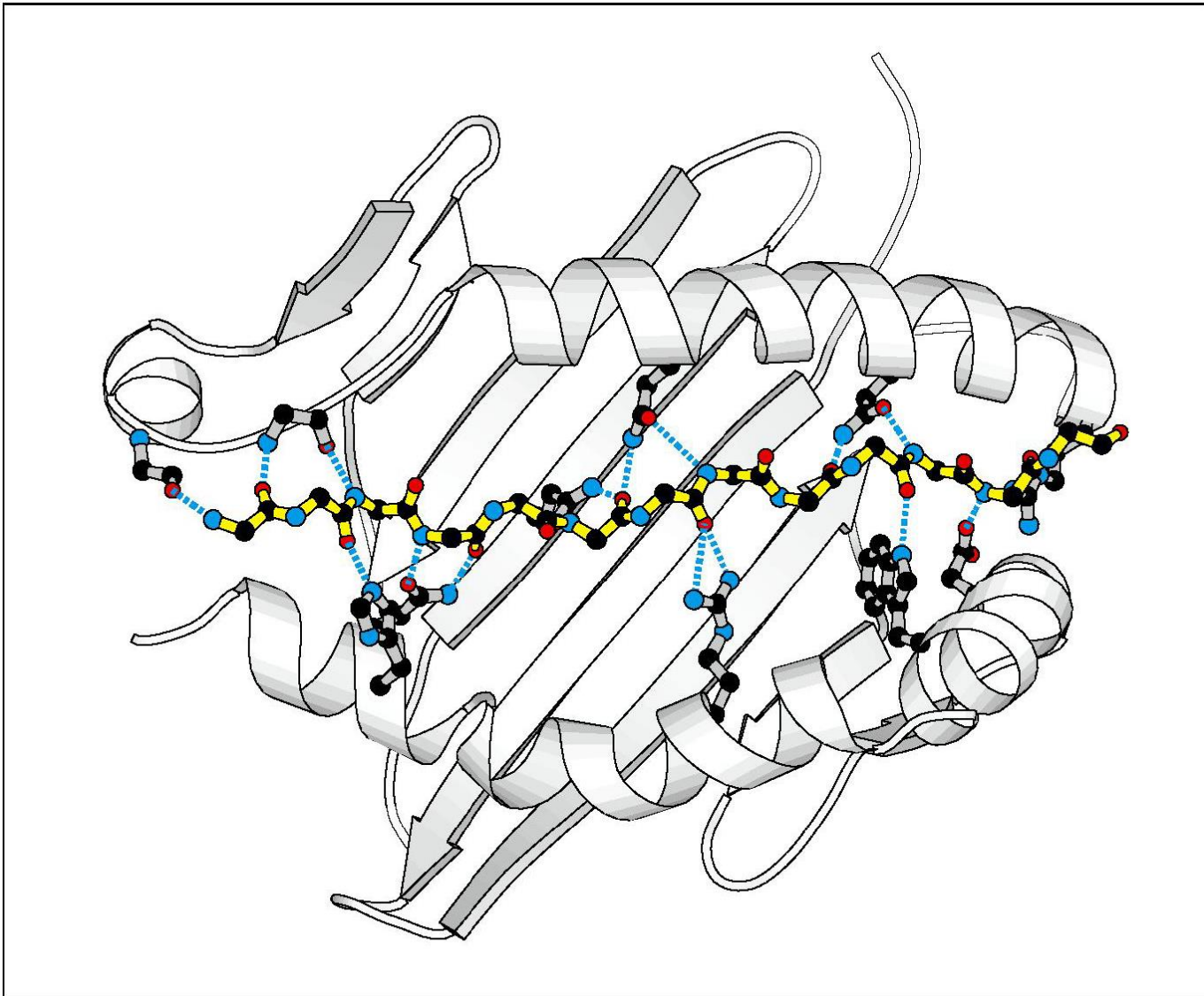


Major Histocompatibility Complex (MHC) II

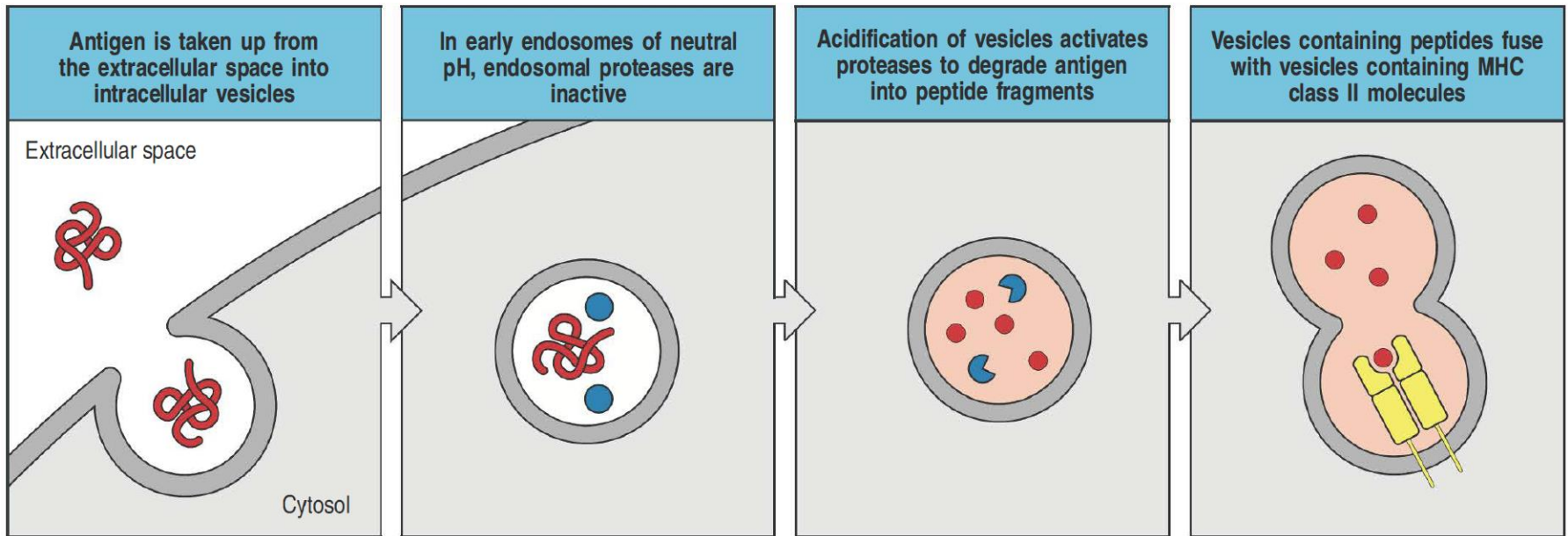
- Expressed in particular antigen-presenting cells
- Gen loci: HLA-DR, HLA-DQ, HLA-DP
- Location: Endosomes
- Interaction: CD4+ T cells



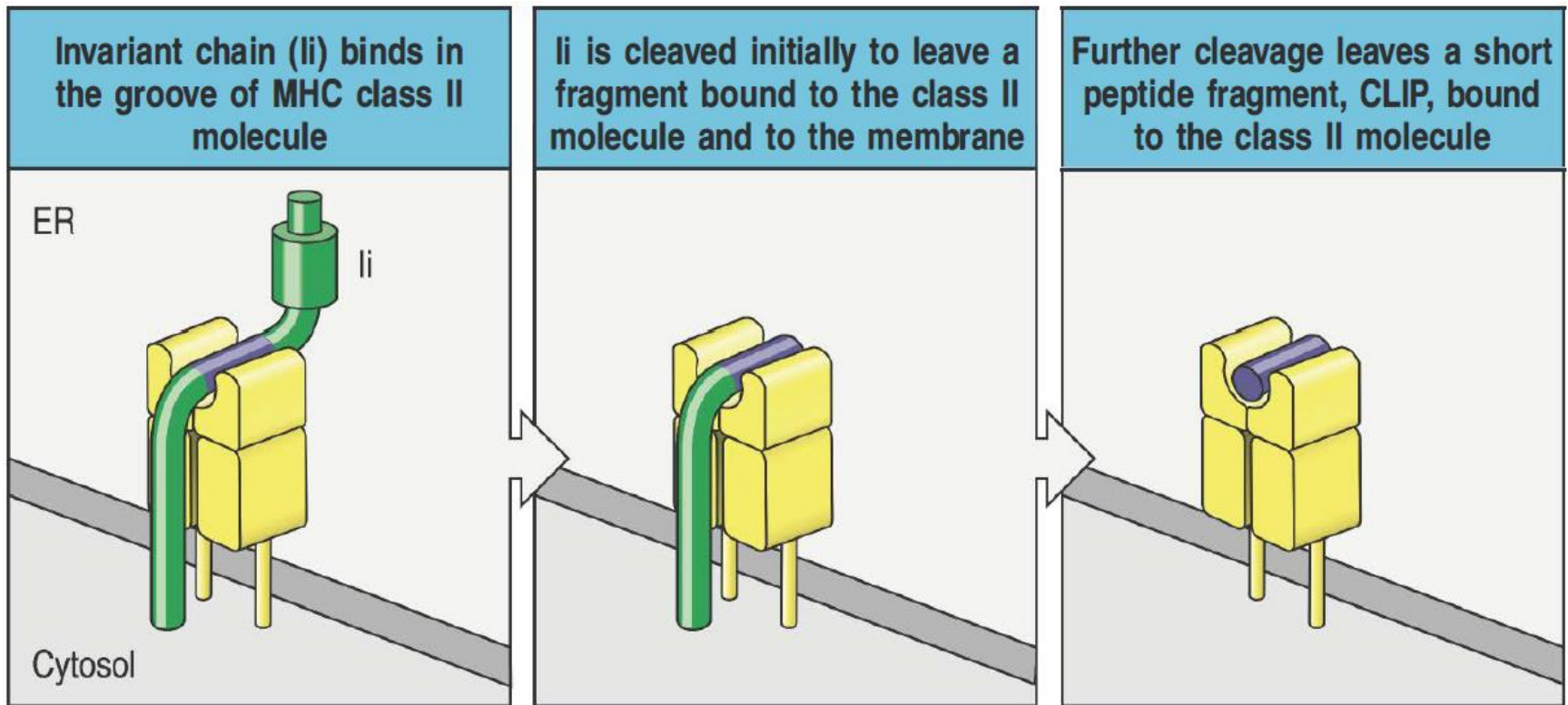
MHC II



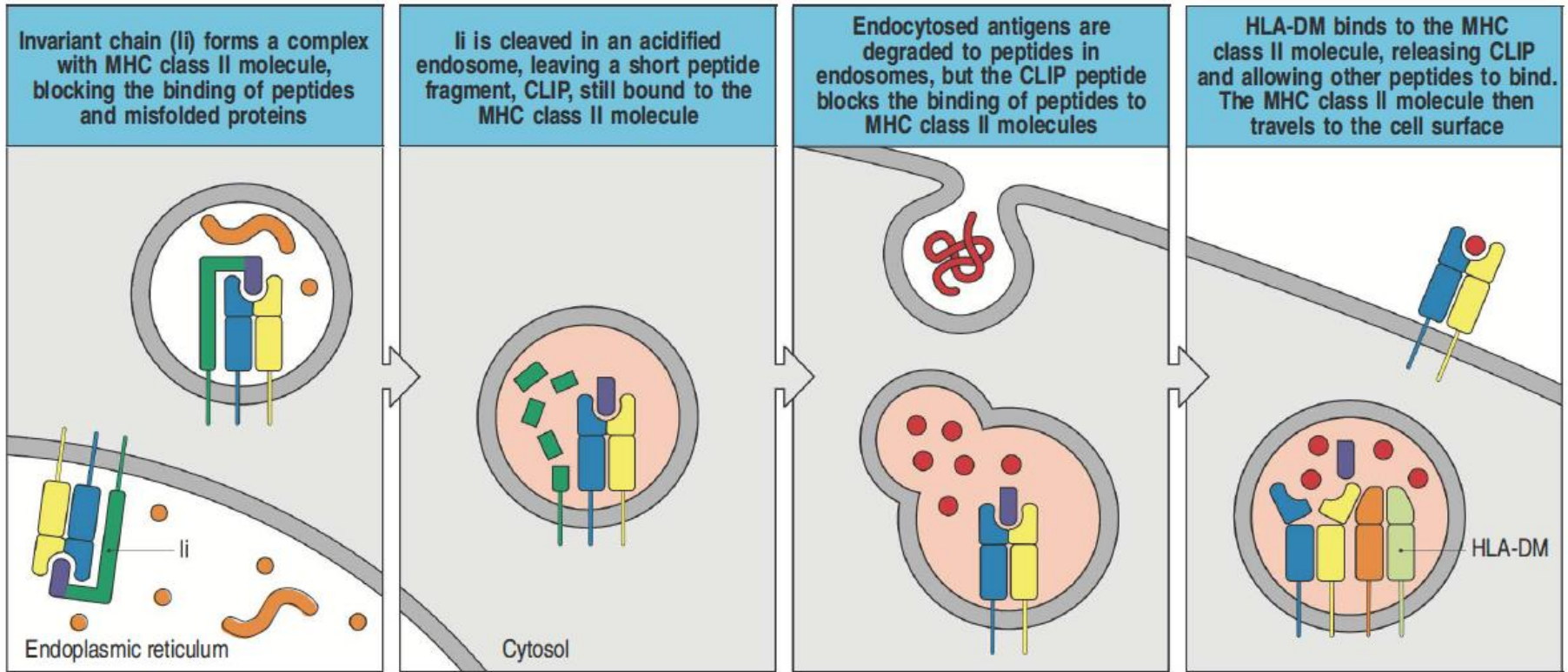
MHC II



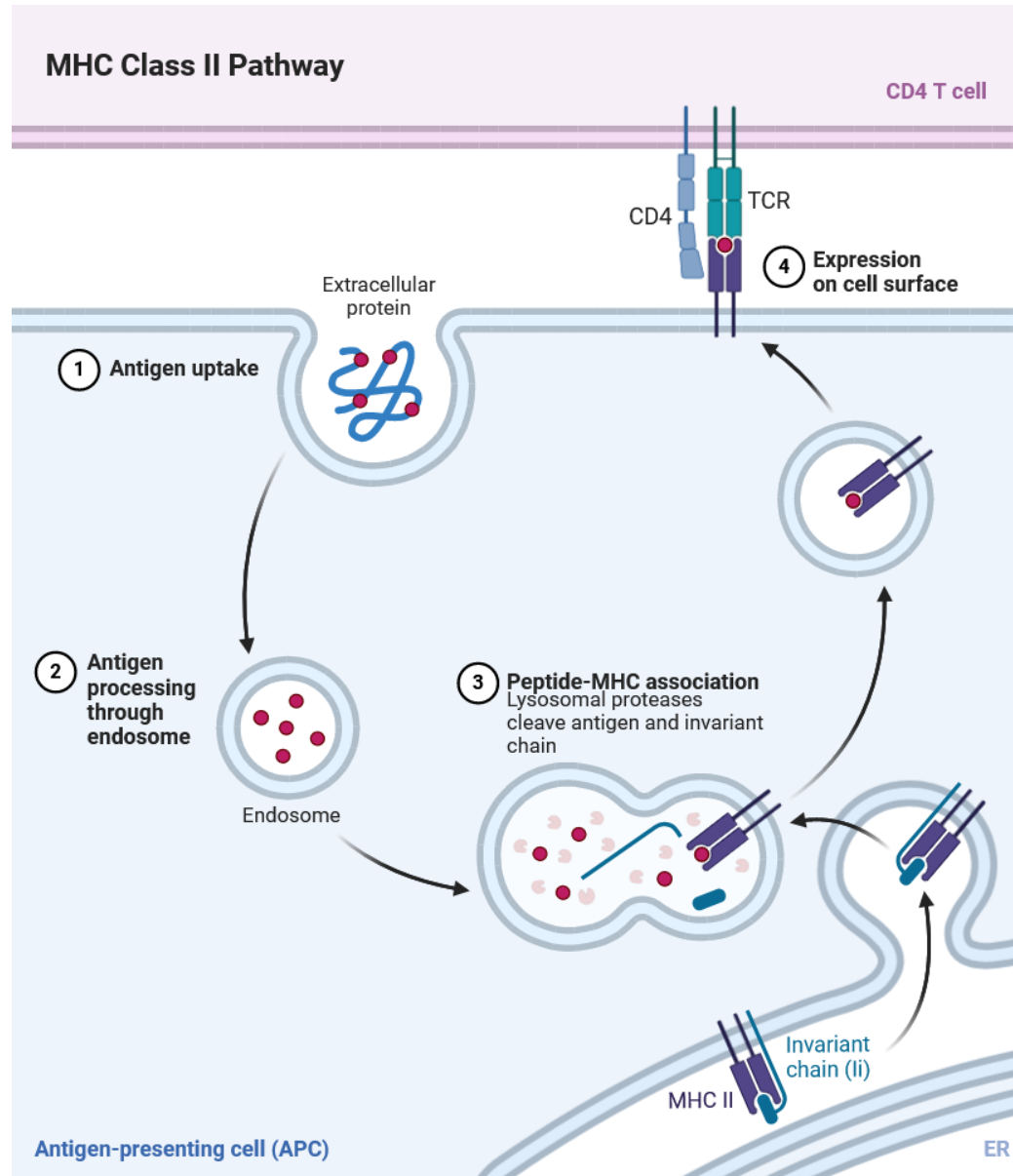
MHC II



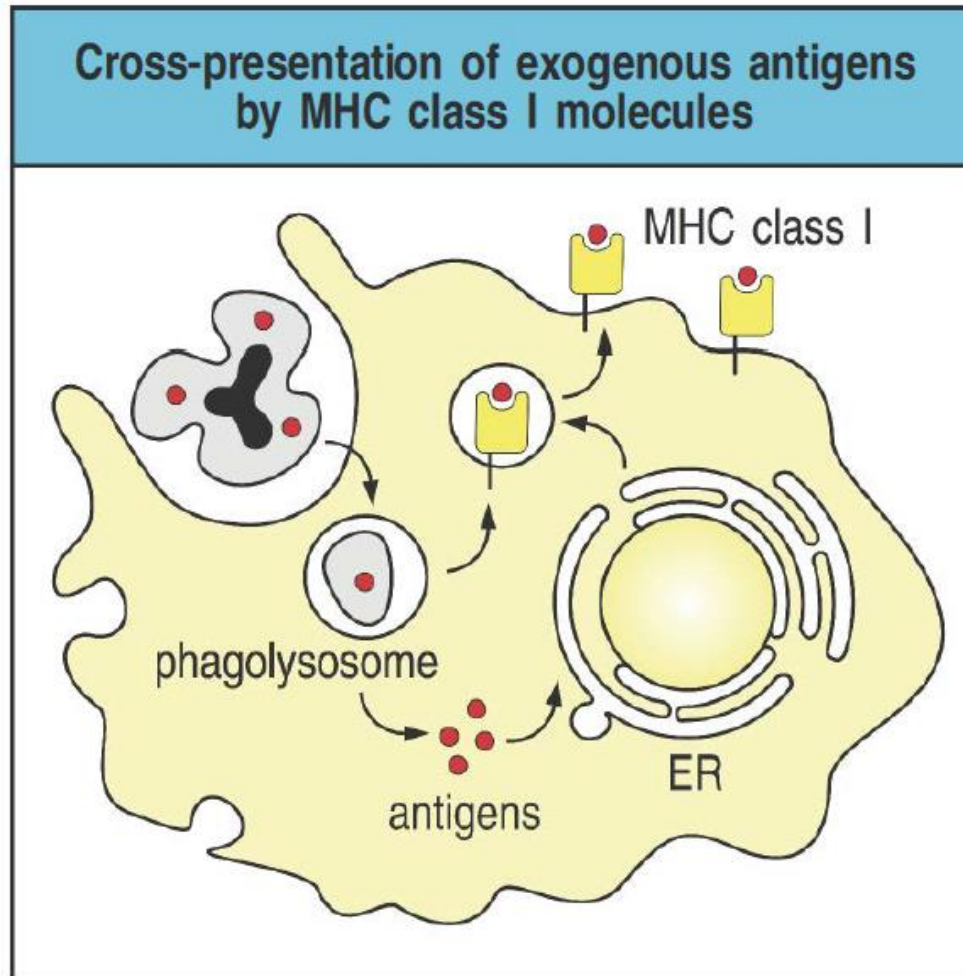
MHC II



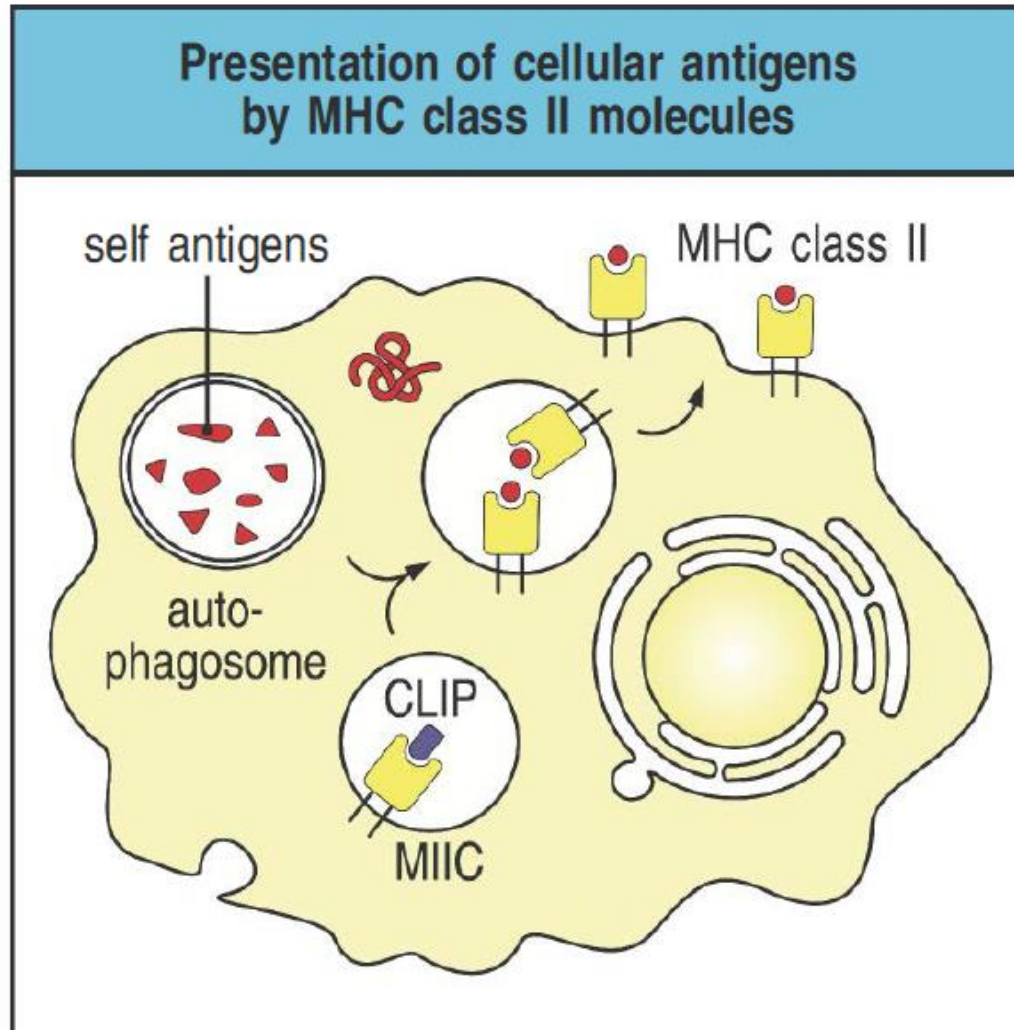
MHC II



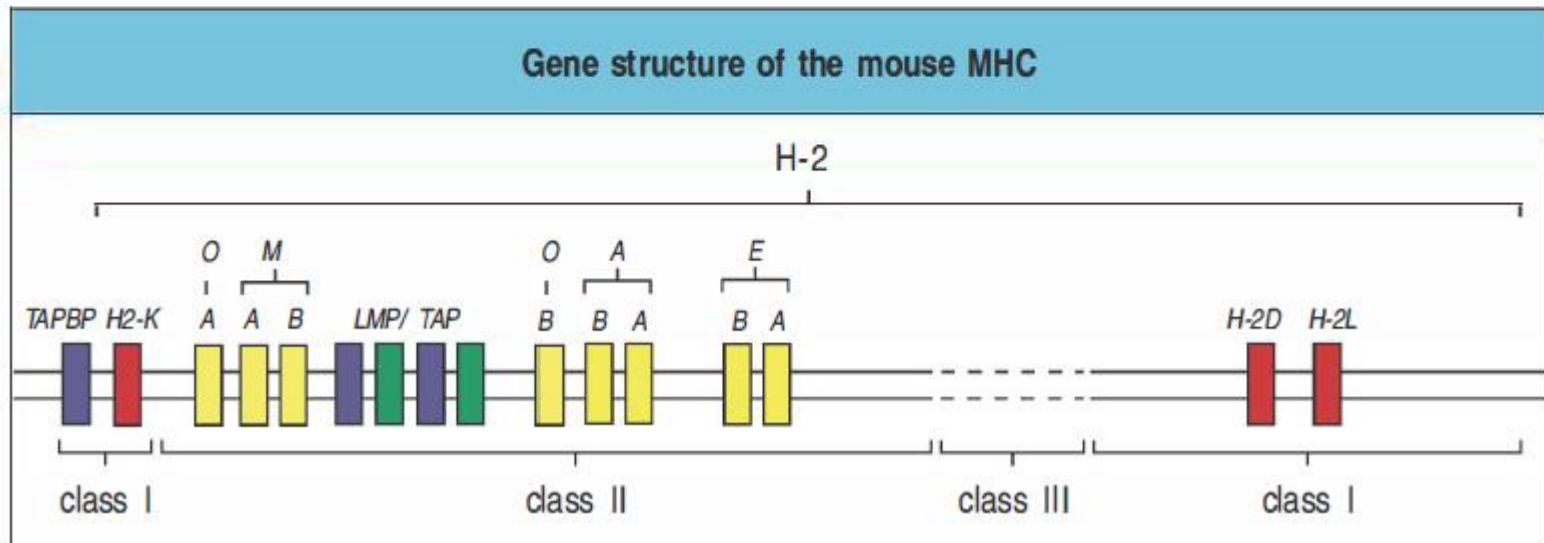
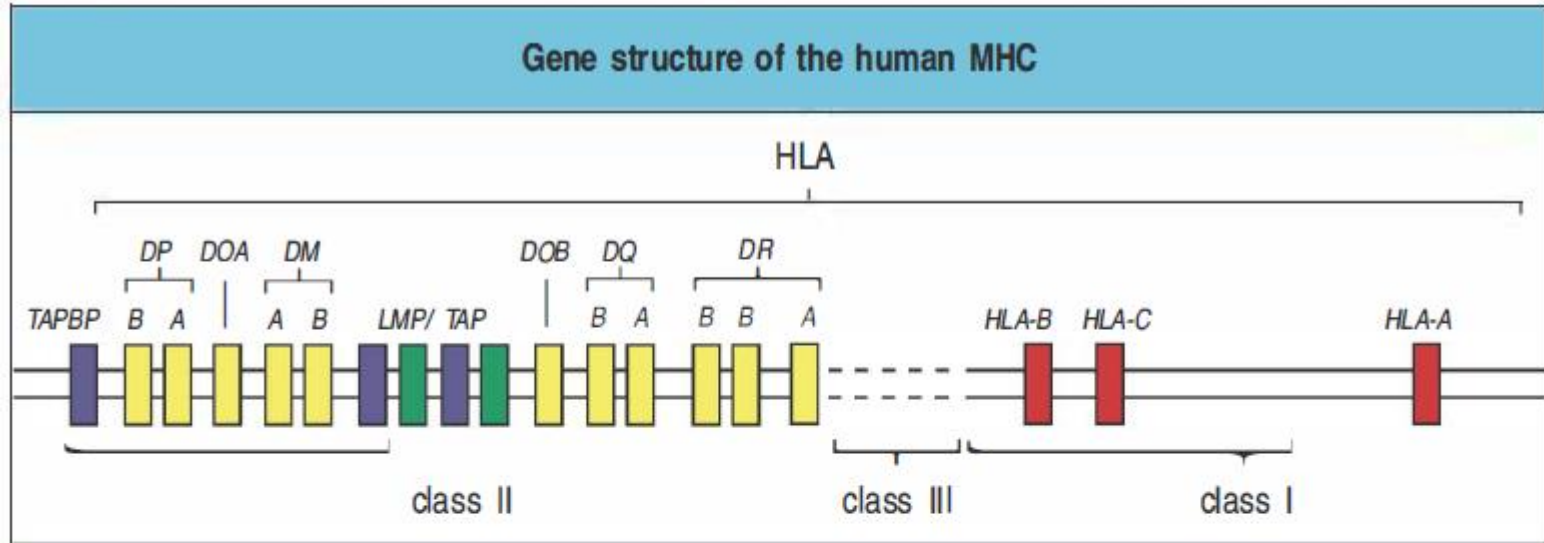
Cross-presentation



Cross-presentation

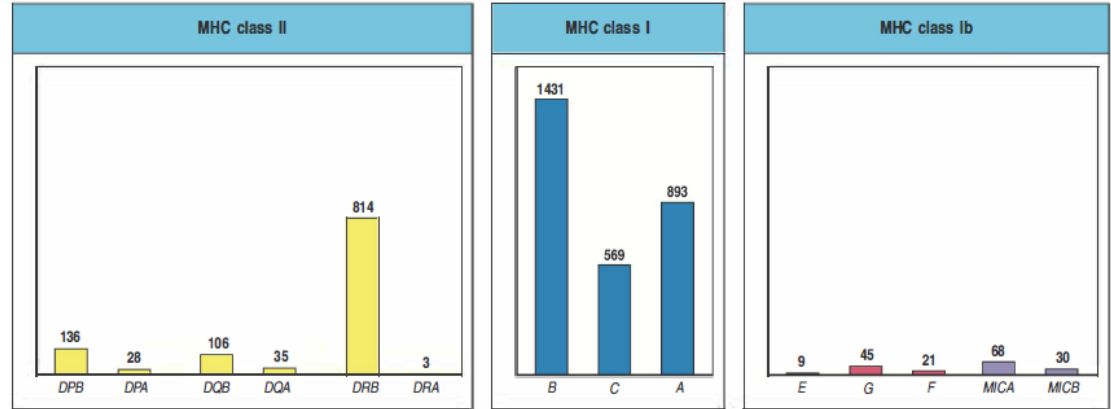


MHC genes

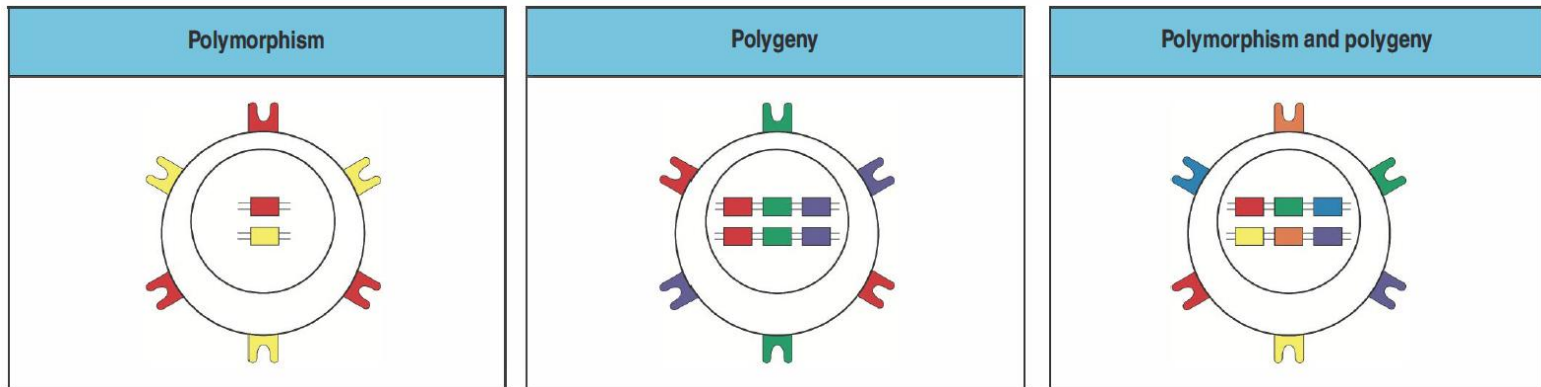


MHC genes

High polymorphic genes

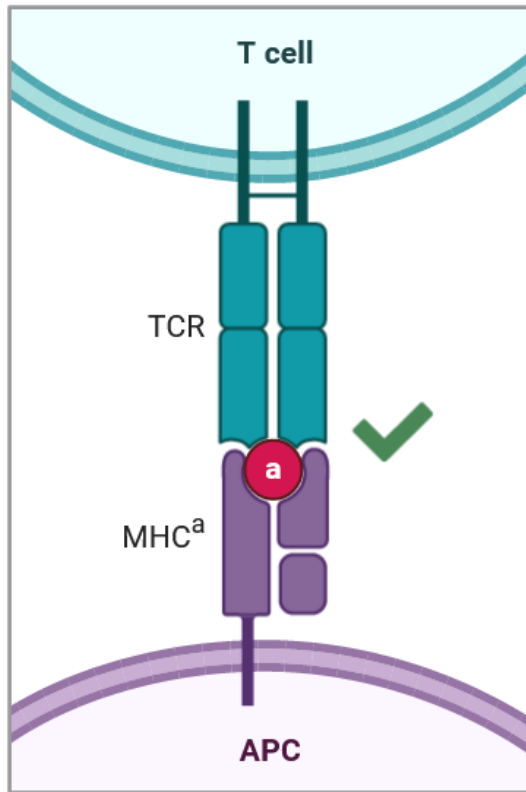


Co-dominant expression

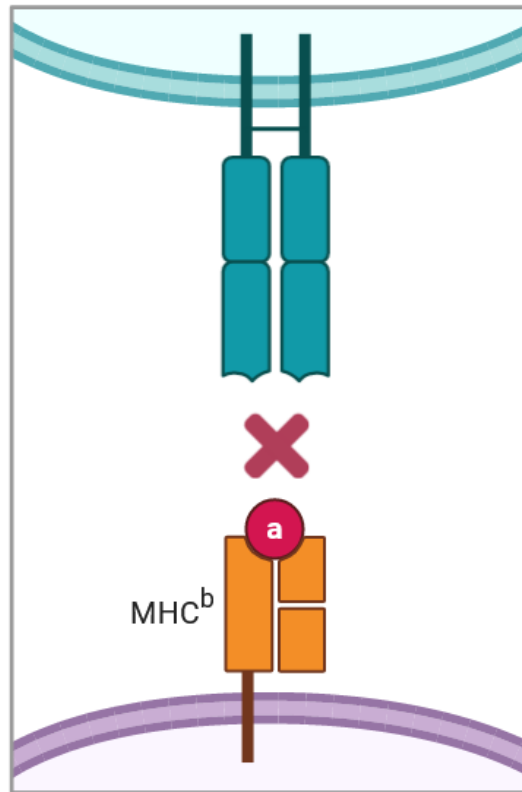


Antigen restriction

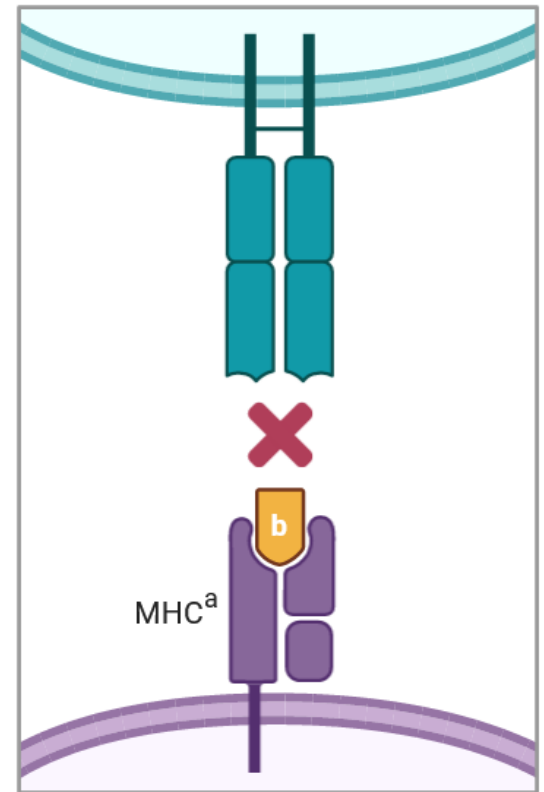
Recognition



No recognition



No recognition



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"

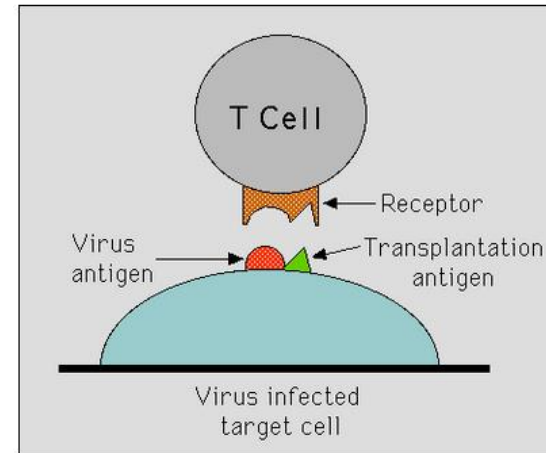
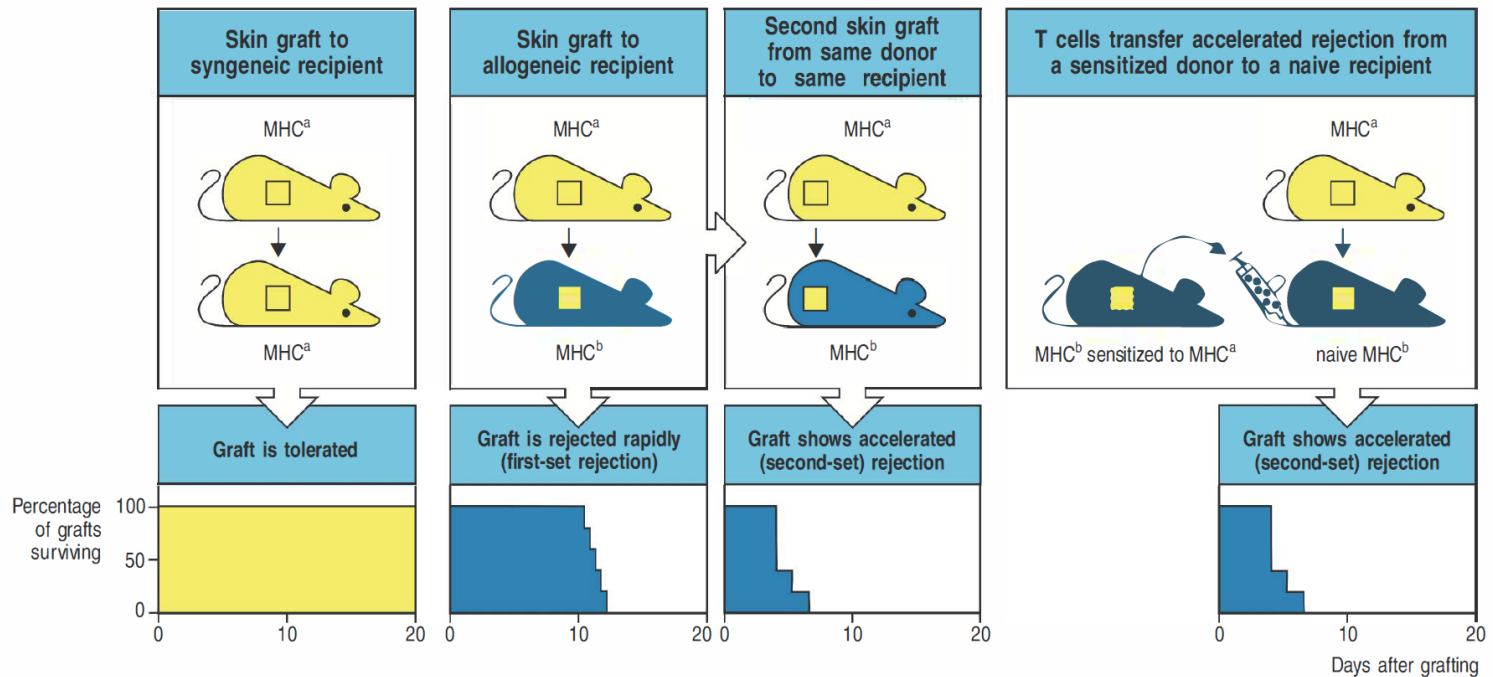


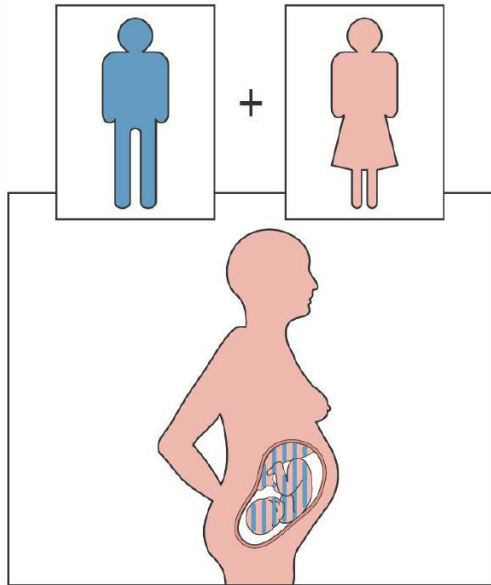
Figure legend: The figure describes how a killer T lymphocyte must recognize both the virus antigen and the self histocompatibility antigen molecule in order to kill a virus-infected target cell. The figure is a modification of the figure published by Zinkernagel and Doherty already 1974 (in Nature 251, 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 interface
- Secretion of TGF- β and IL-10

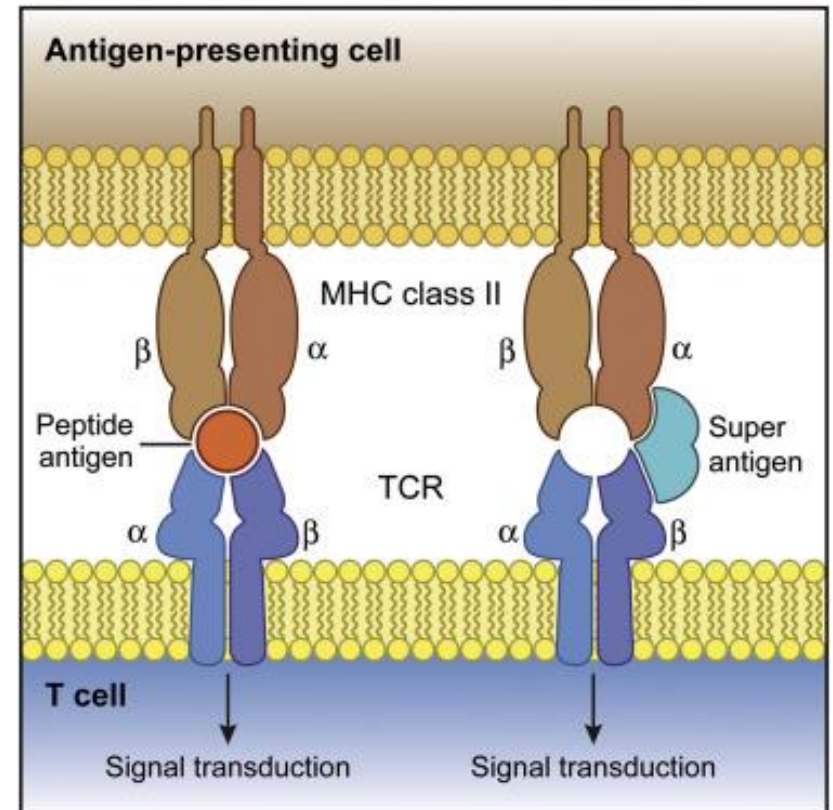
Superantigens

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

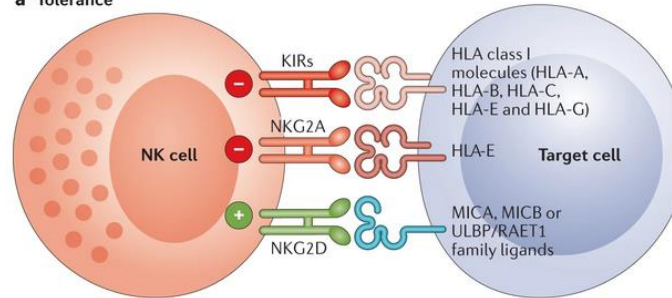
Massive production of cytokines by CD4 T cells:

- Systemic toxicity
- Suppression of the adaptive immune response

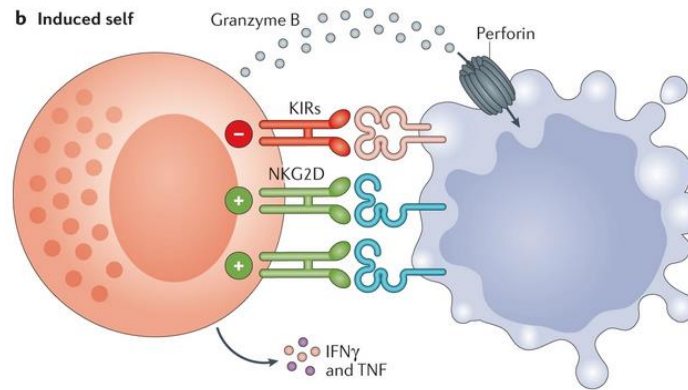


HLA and Natural-killer (NK) cells

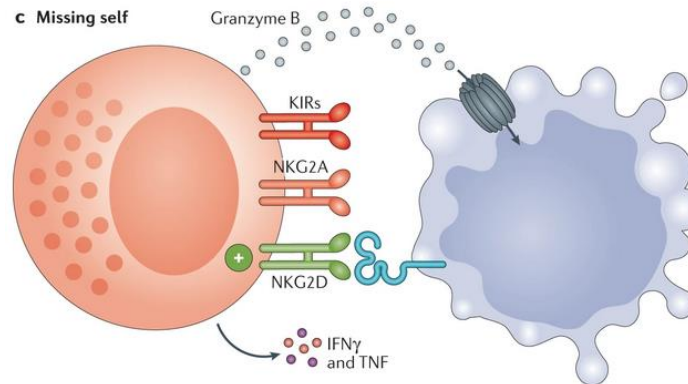
a Tolerance



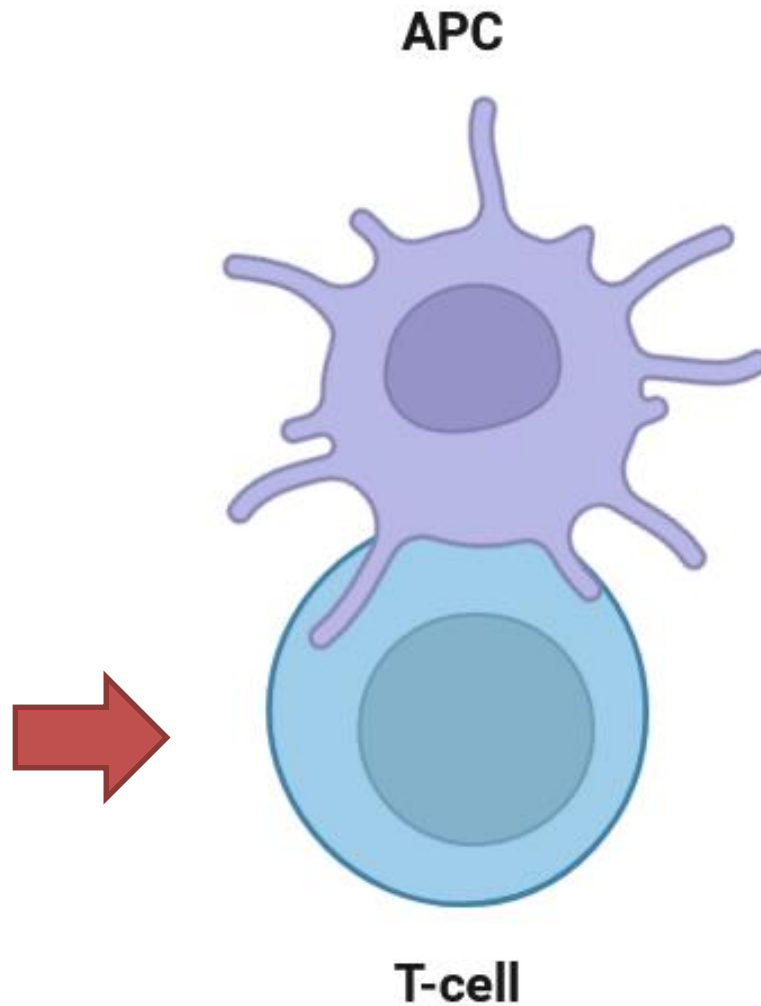
b Induced self

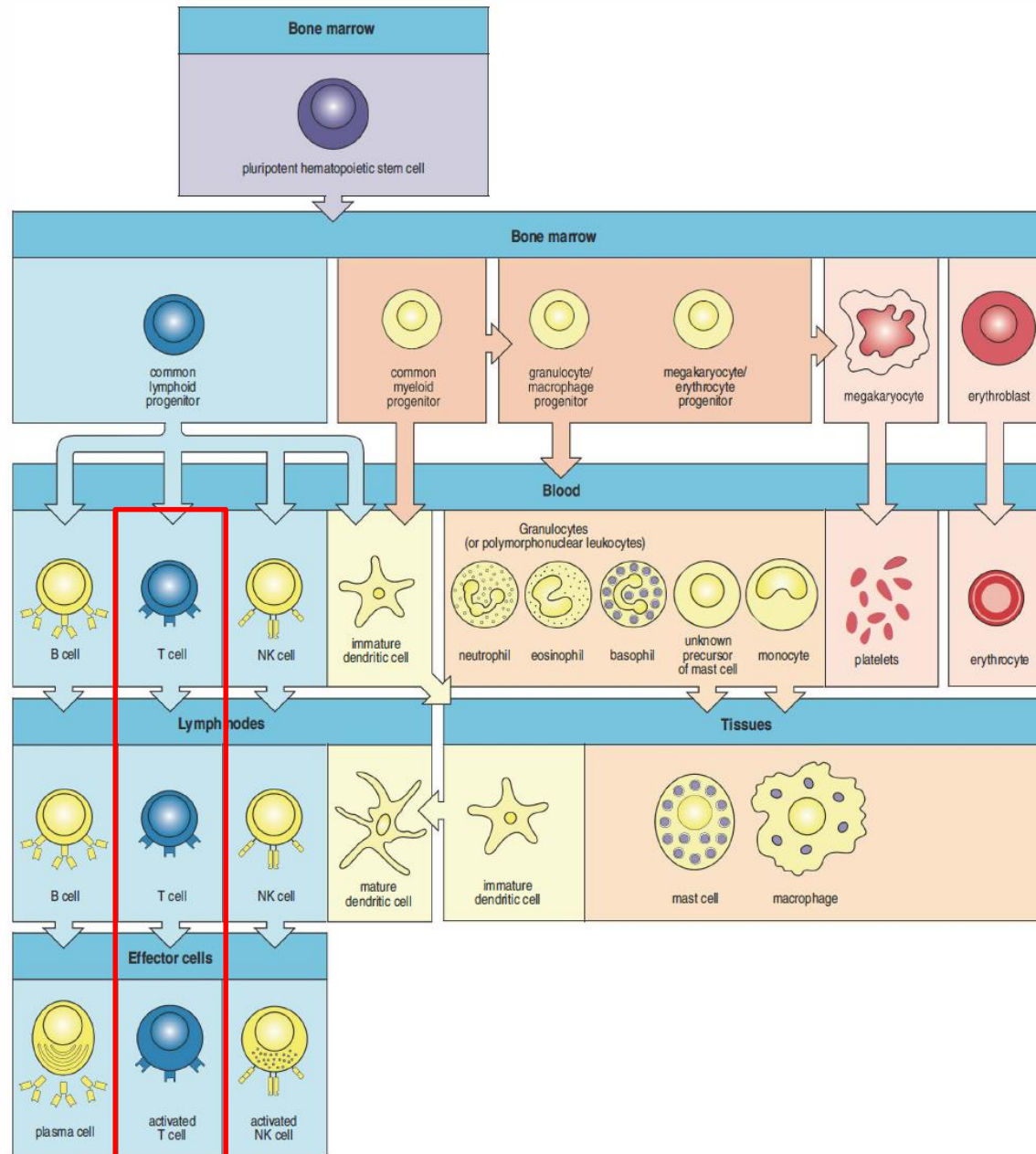


c Missing self

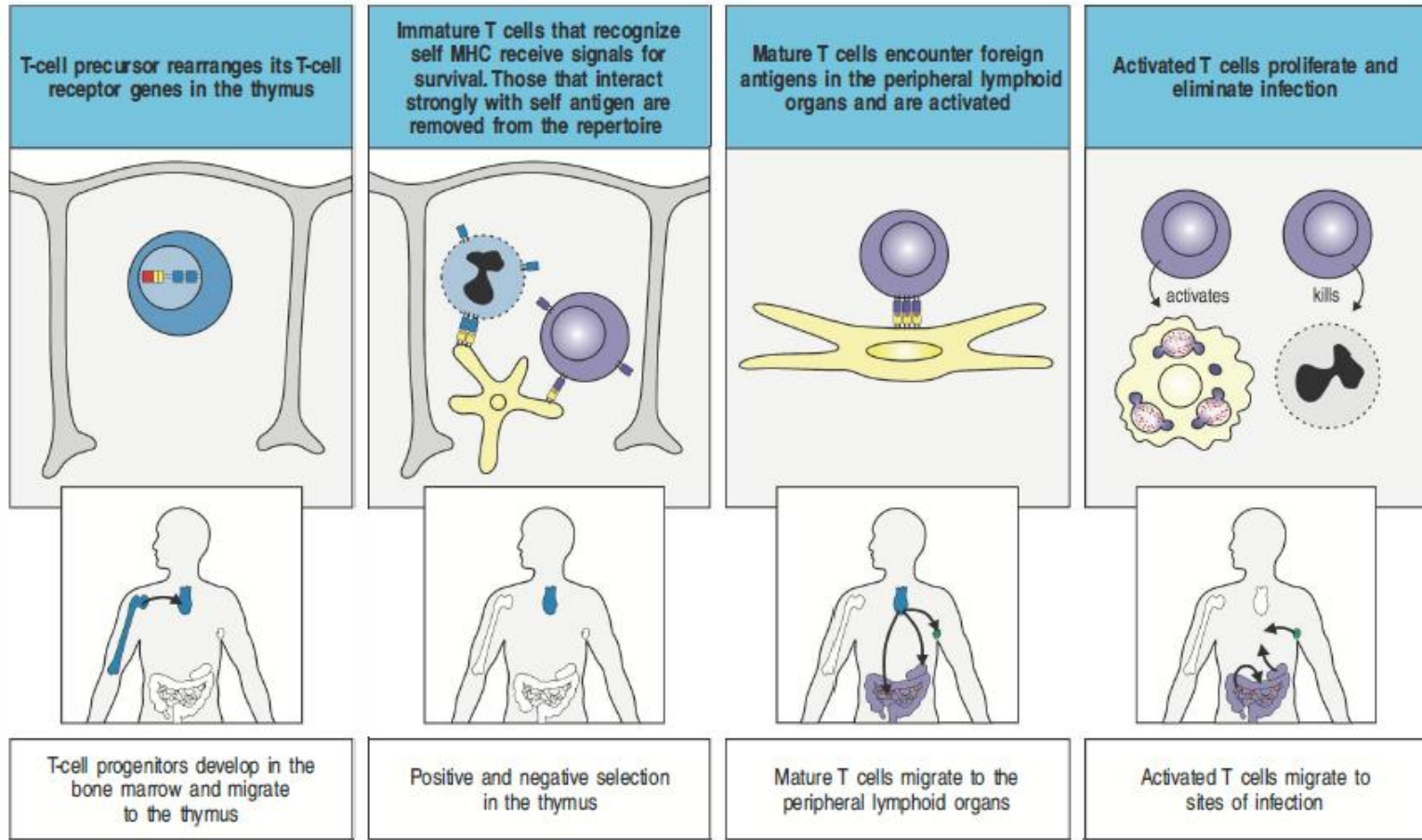


Innate – Adaptive Immune system

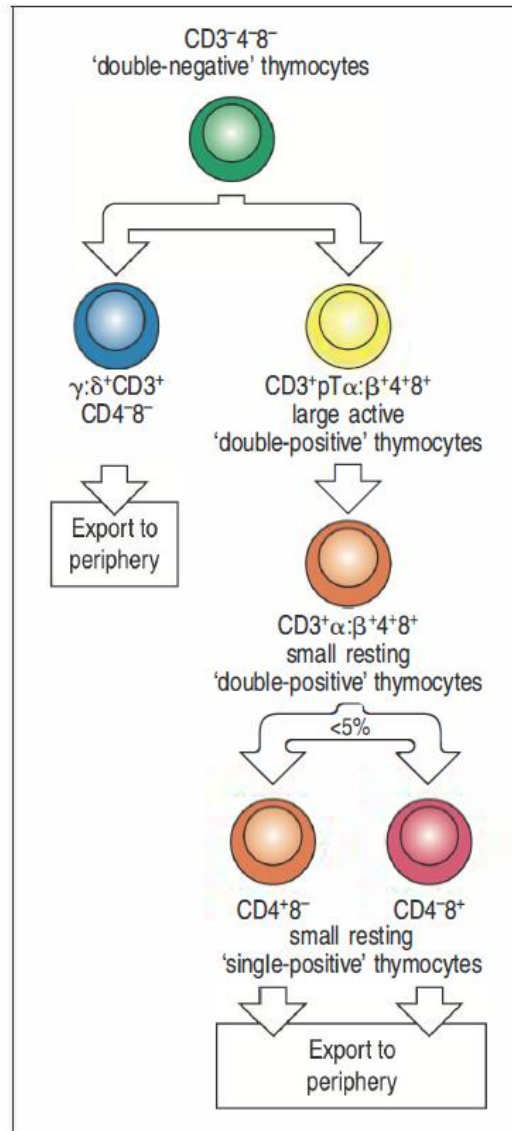




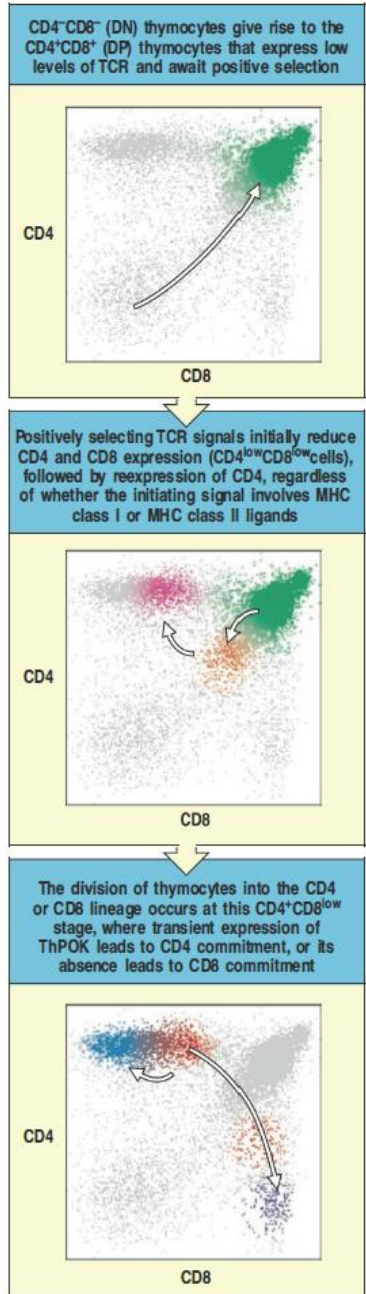
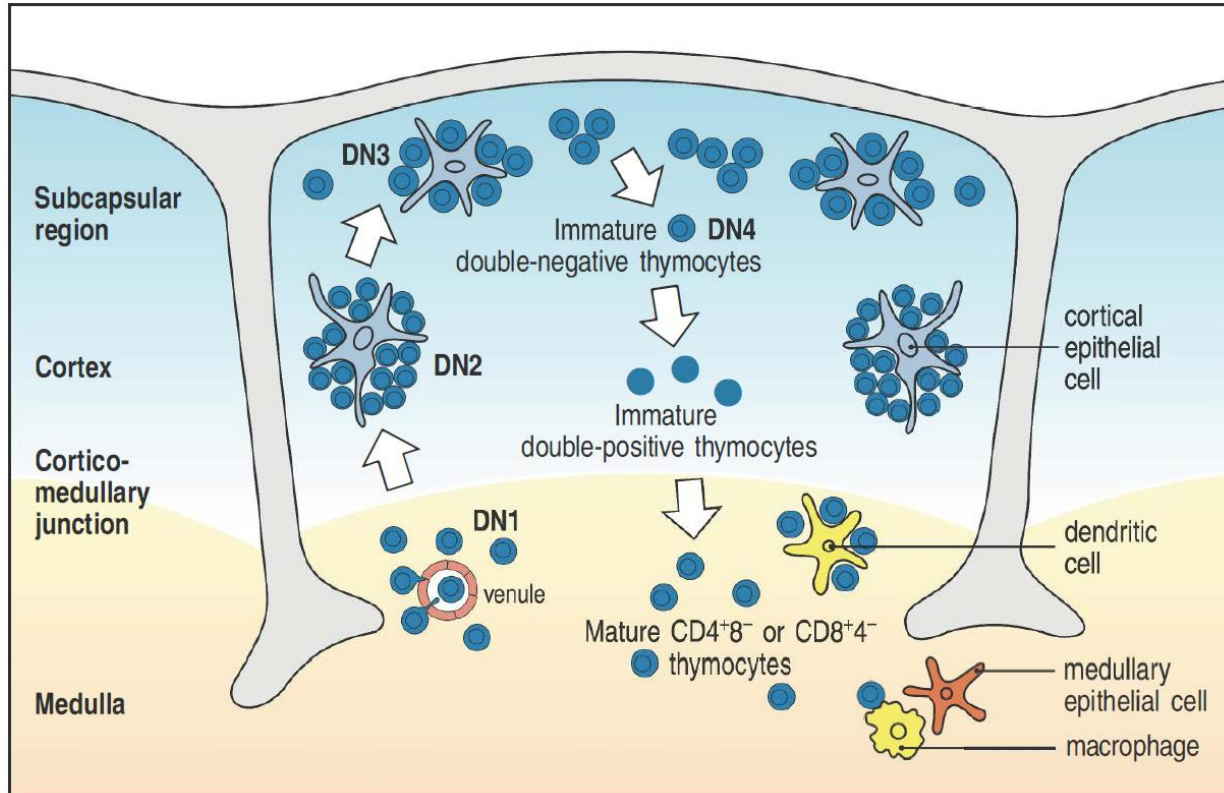
T cell development



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

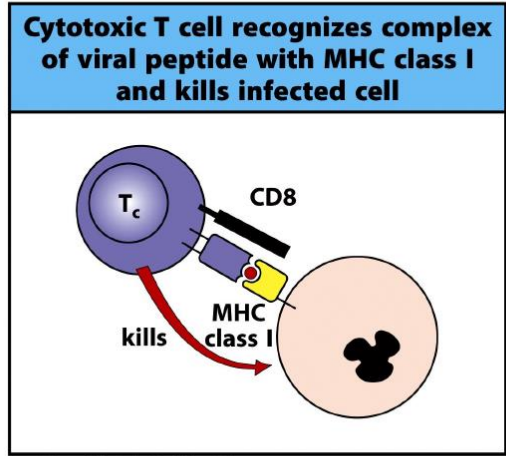


Figure 1-32 Immunobiology, 7ed. (© Garland Science 2008)

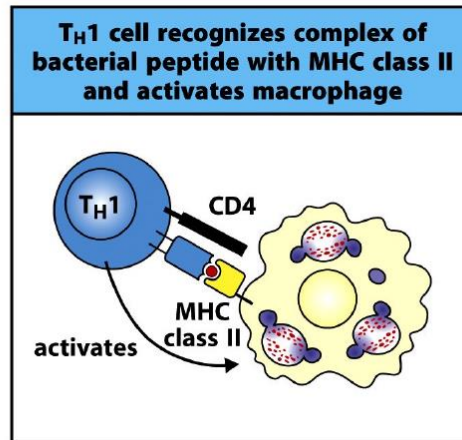
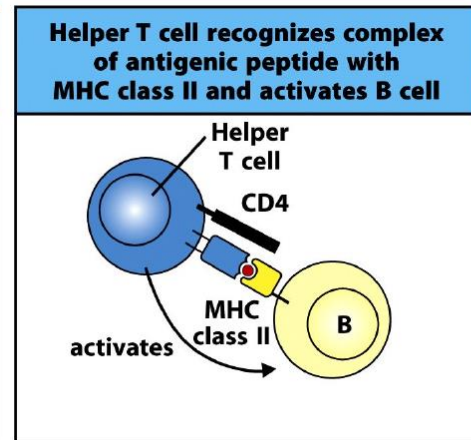


Figure 1-33 Immunobiology, 7ed. (© Garland Science 2008)



CD8+ cytotoxic T cells

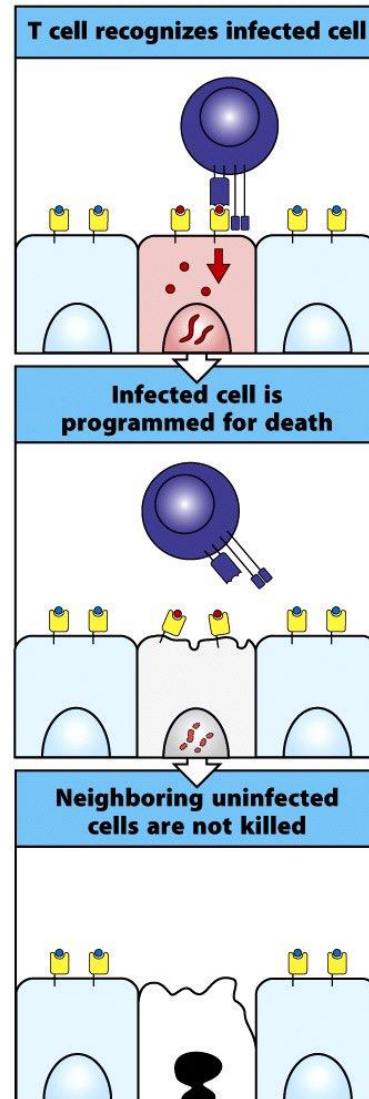
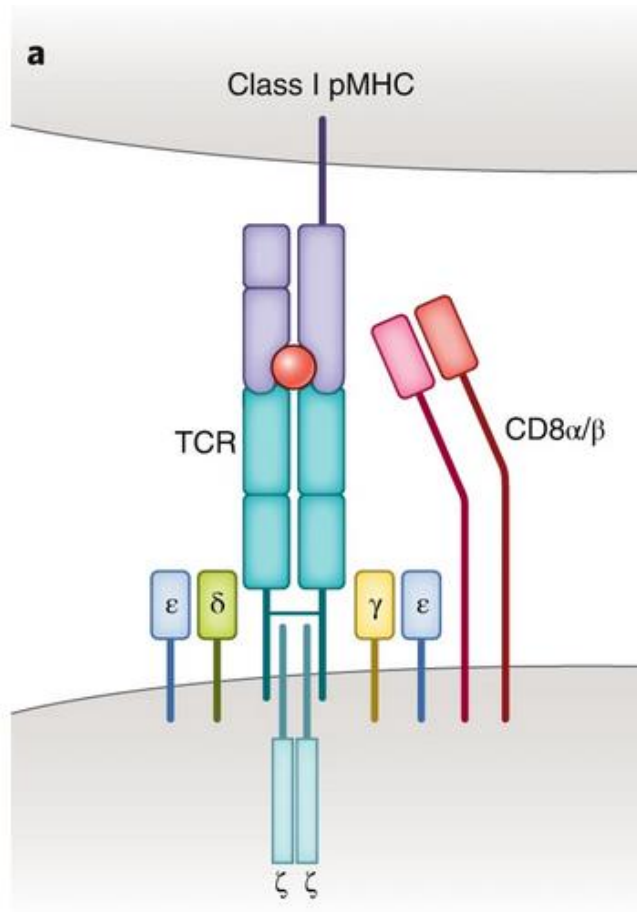
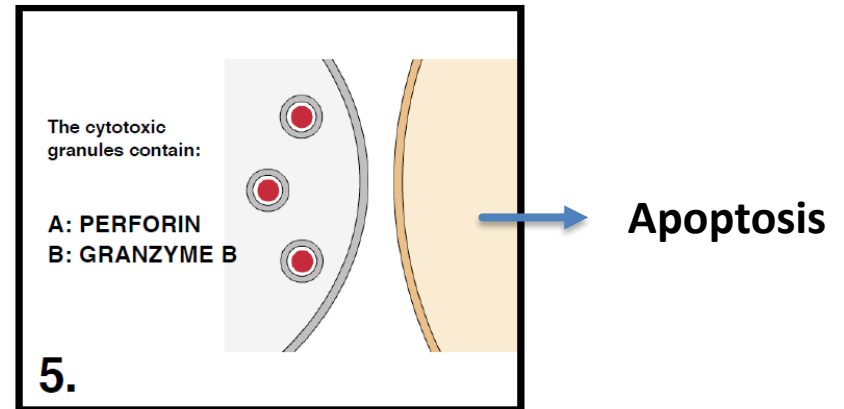
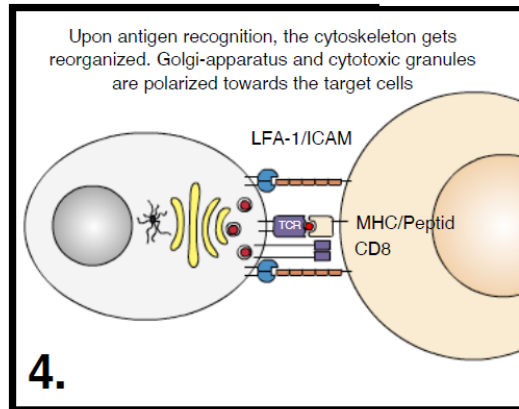
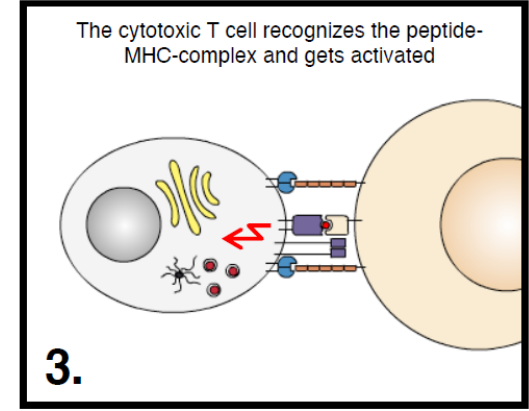
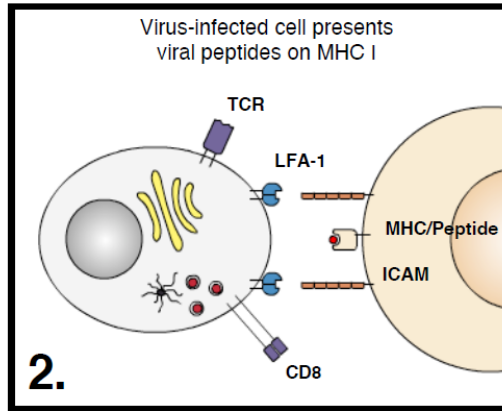
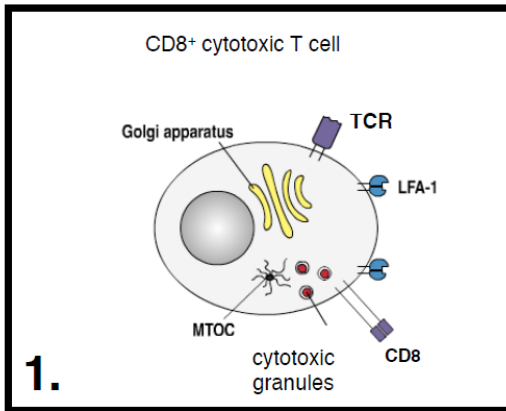
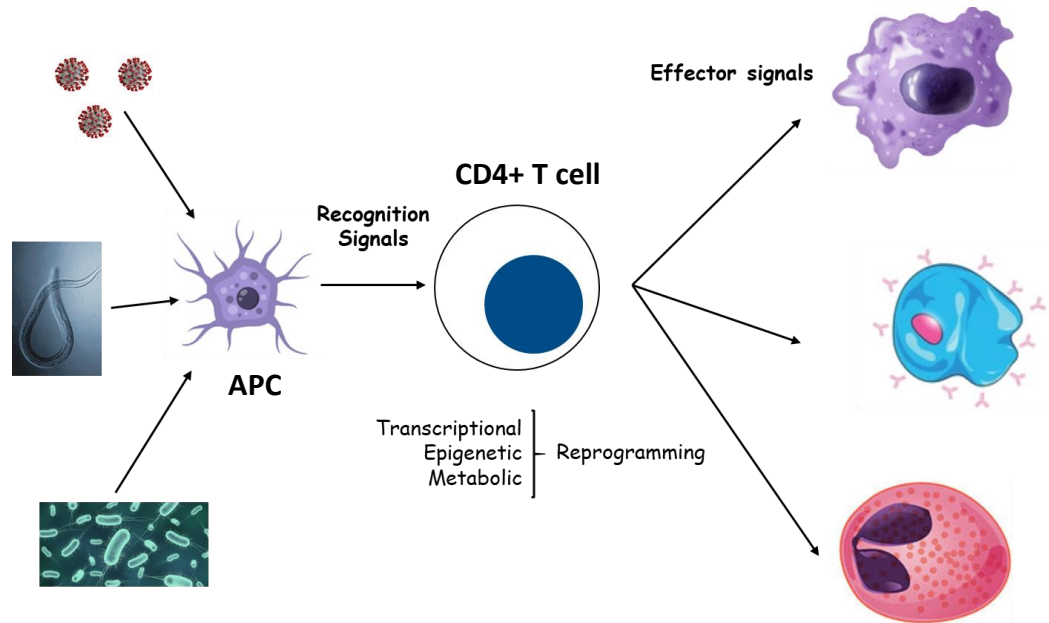
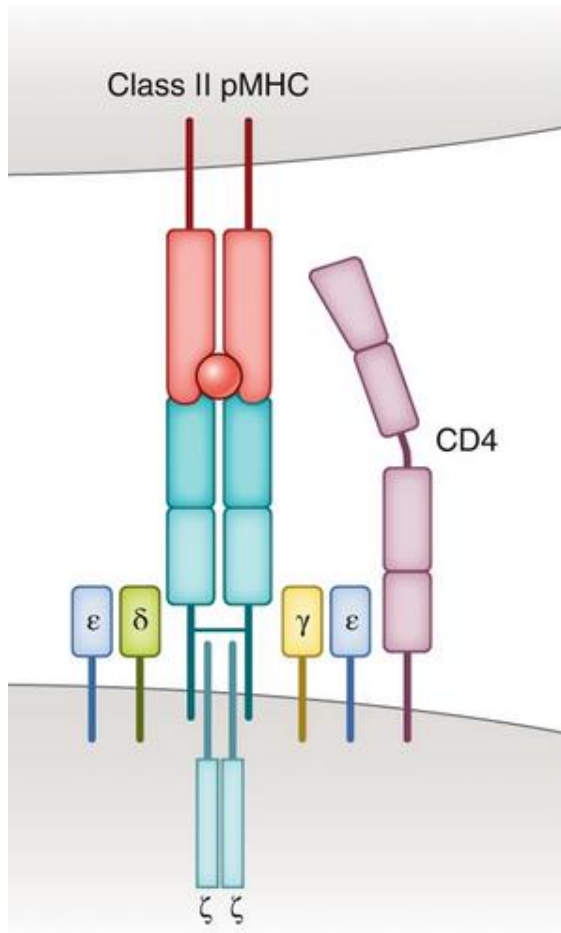


Figure 8-40 Immunobiology, 7ed. (© Garland Science 2008)

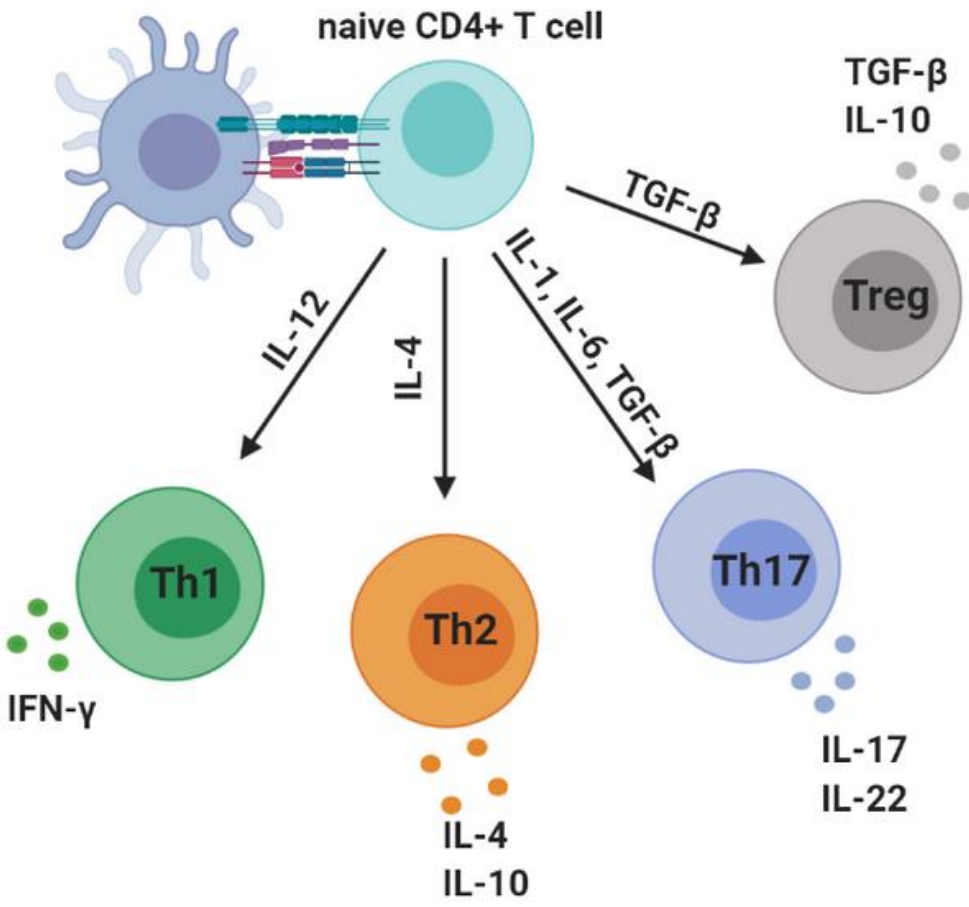
CD8+ cytotoxic T cells



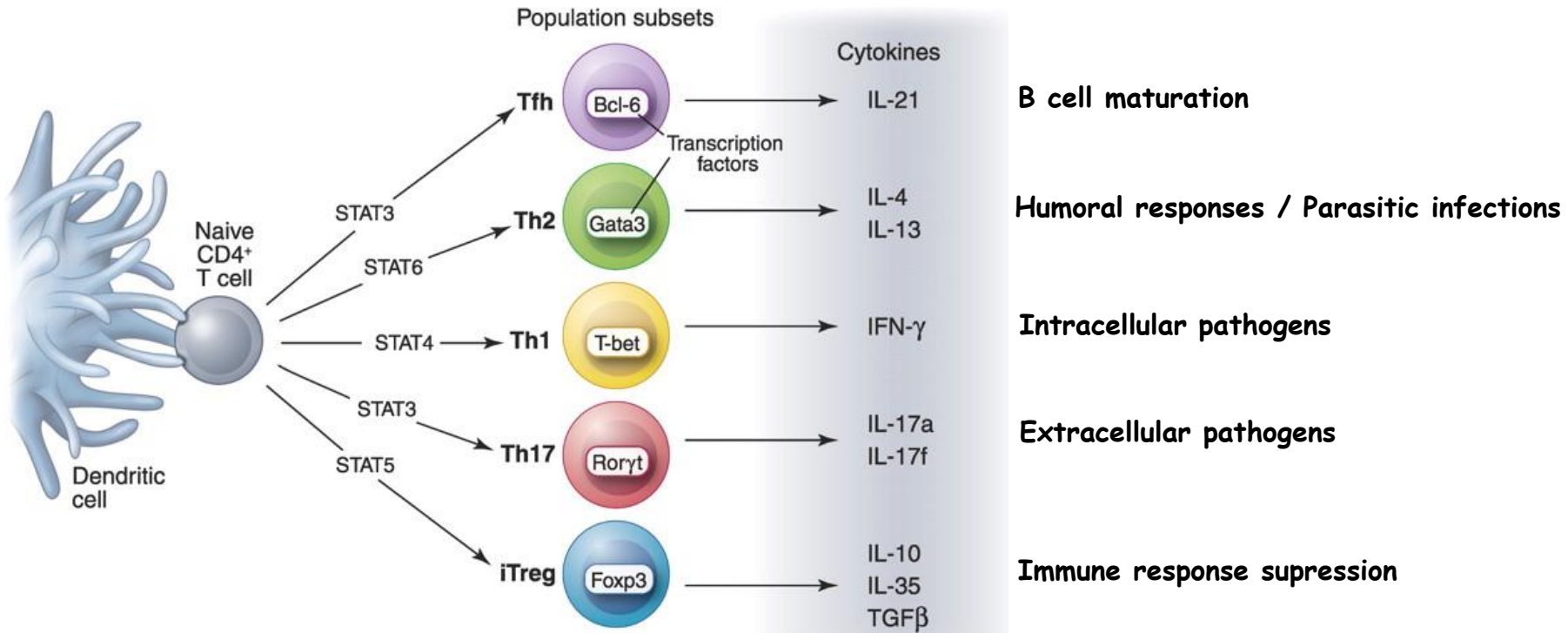
CD4+ helper T cells



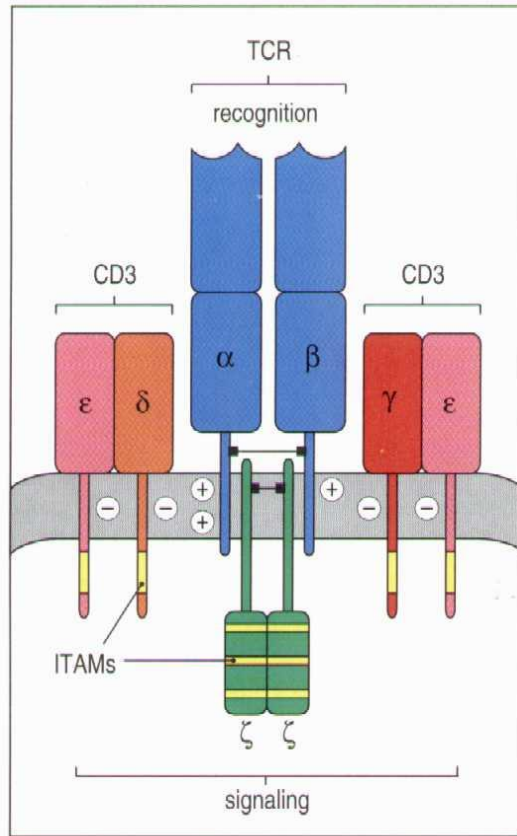
T helper lineages



T helper lineages



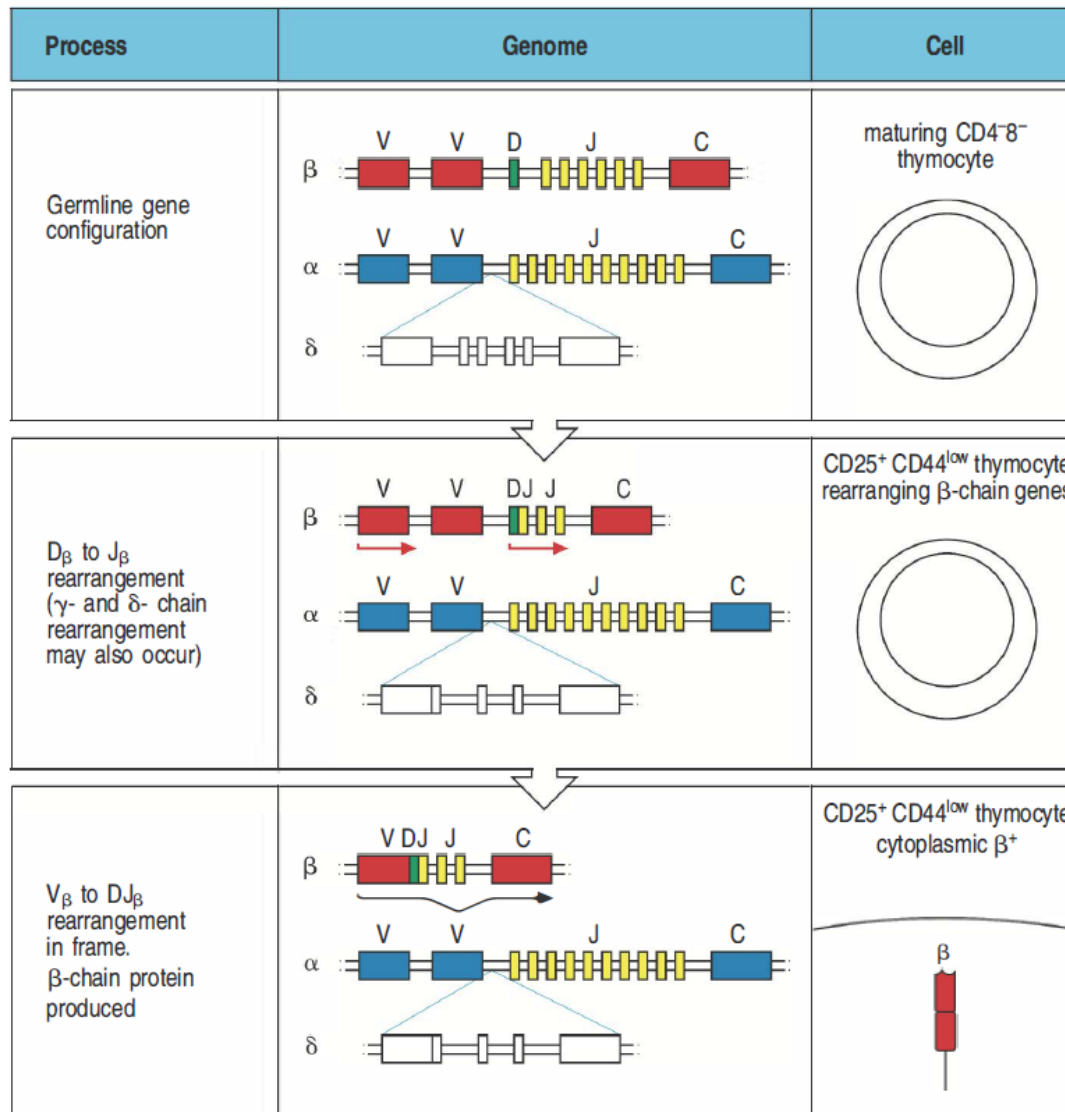
T cell receptor (TCR)



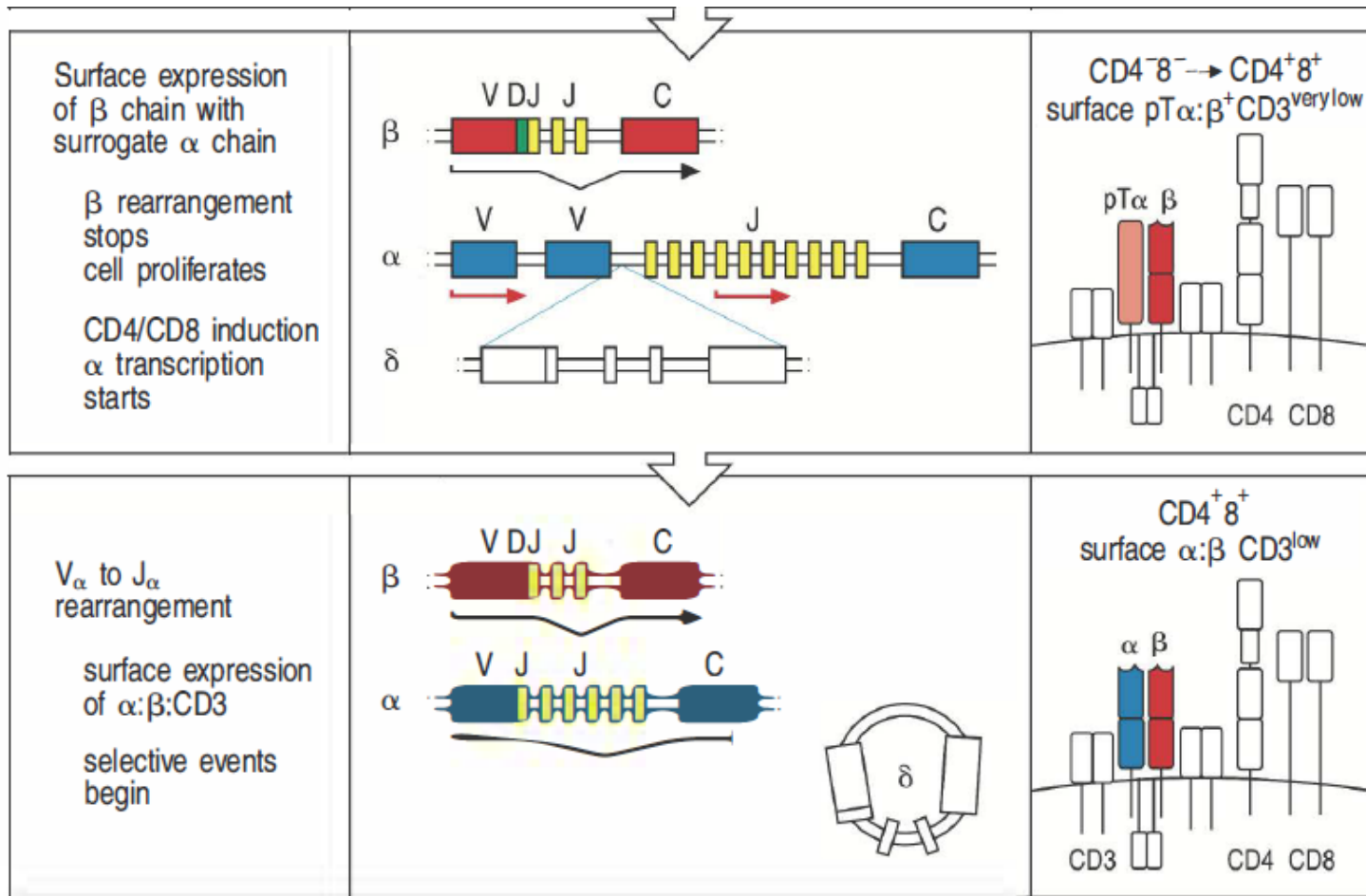
- T cell receptor
 - α and β chain heterodimer
 - antigen recognition
- CD3
 - transmembrane proteins with extracellular domains and cytoplasmic tails
 - two ϵ -chains
 - one δ -chain
 - one γ -chain
 - transmembrane/cytoplasmic ζ -homodimers

ITAM: immunoreceptor tyrosine-based activation motifs

T cell receptor (TCR) rearrangement



T cell receptor (TCR) rearrangement



Thymic T cell selection

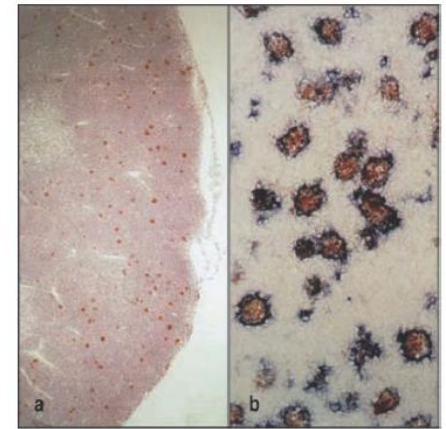
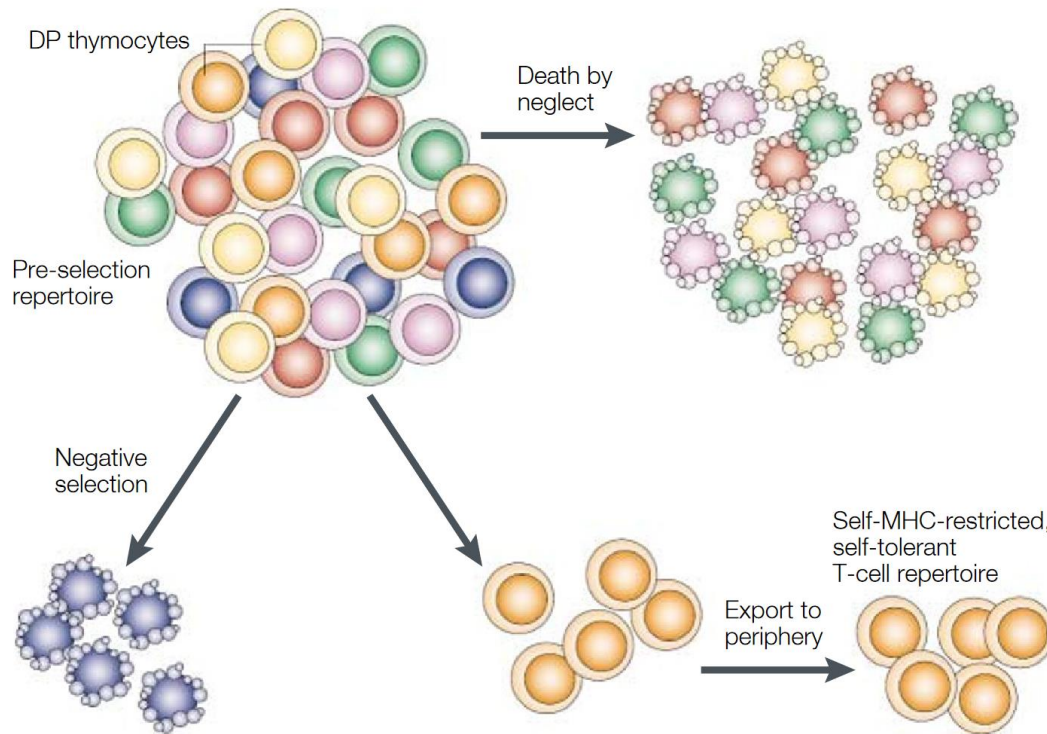
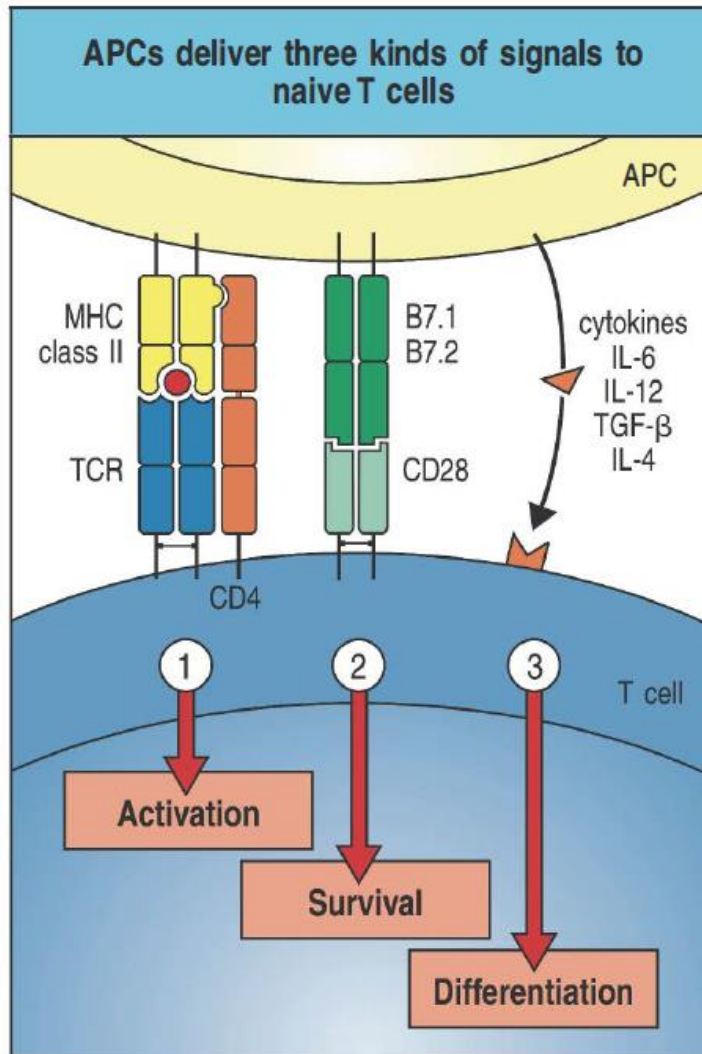


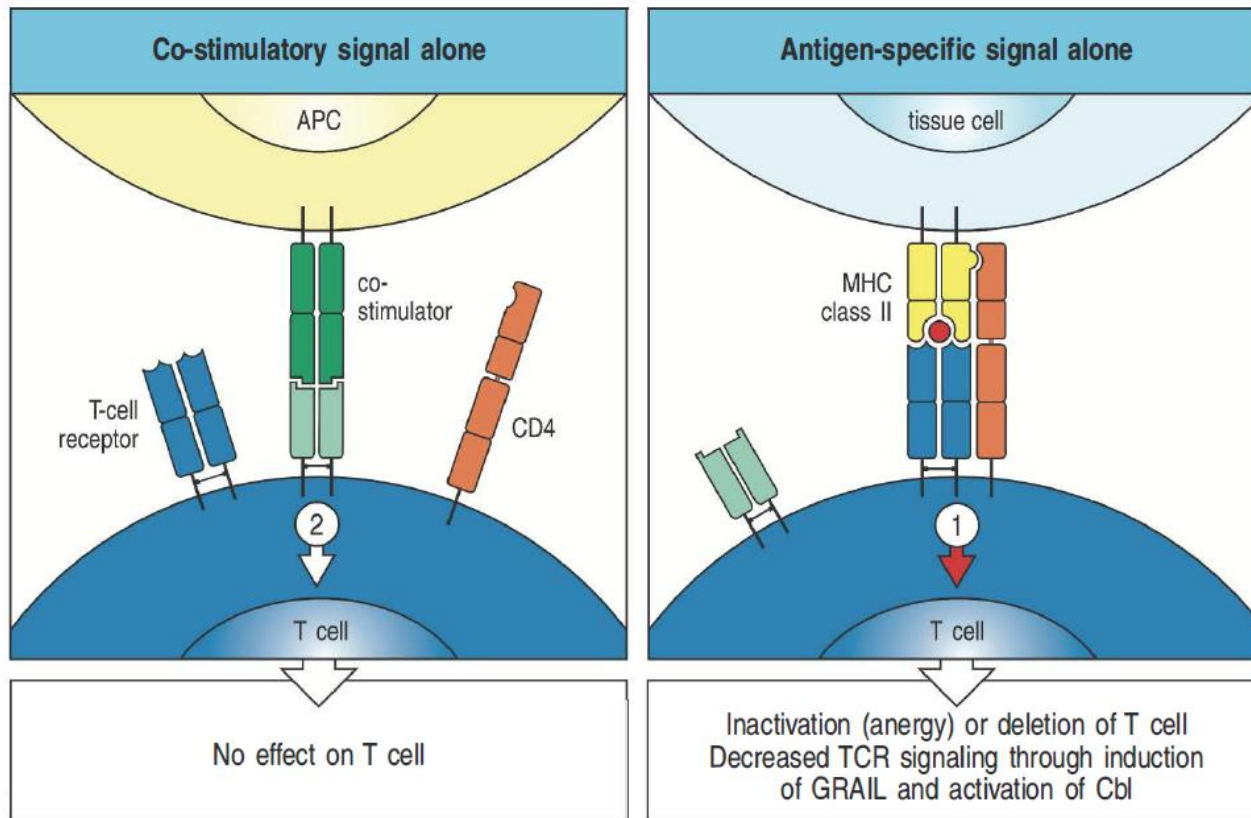
Fig. 8.18 Developing T cells that undergo apoptosis are ingested by macrophages in the thymic cortex.

More details in the lecture Immune regulation...

3 signals



T cell anergy



Anergy and immune regulation

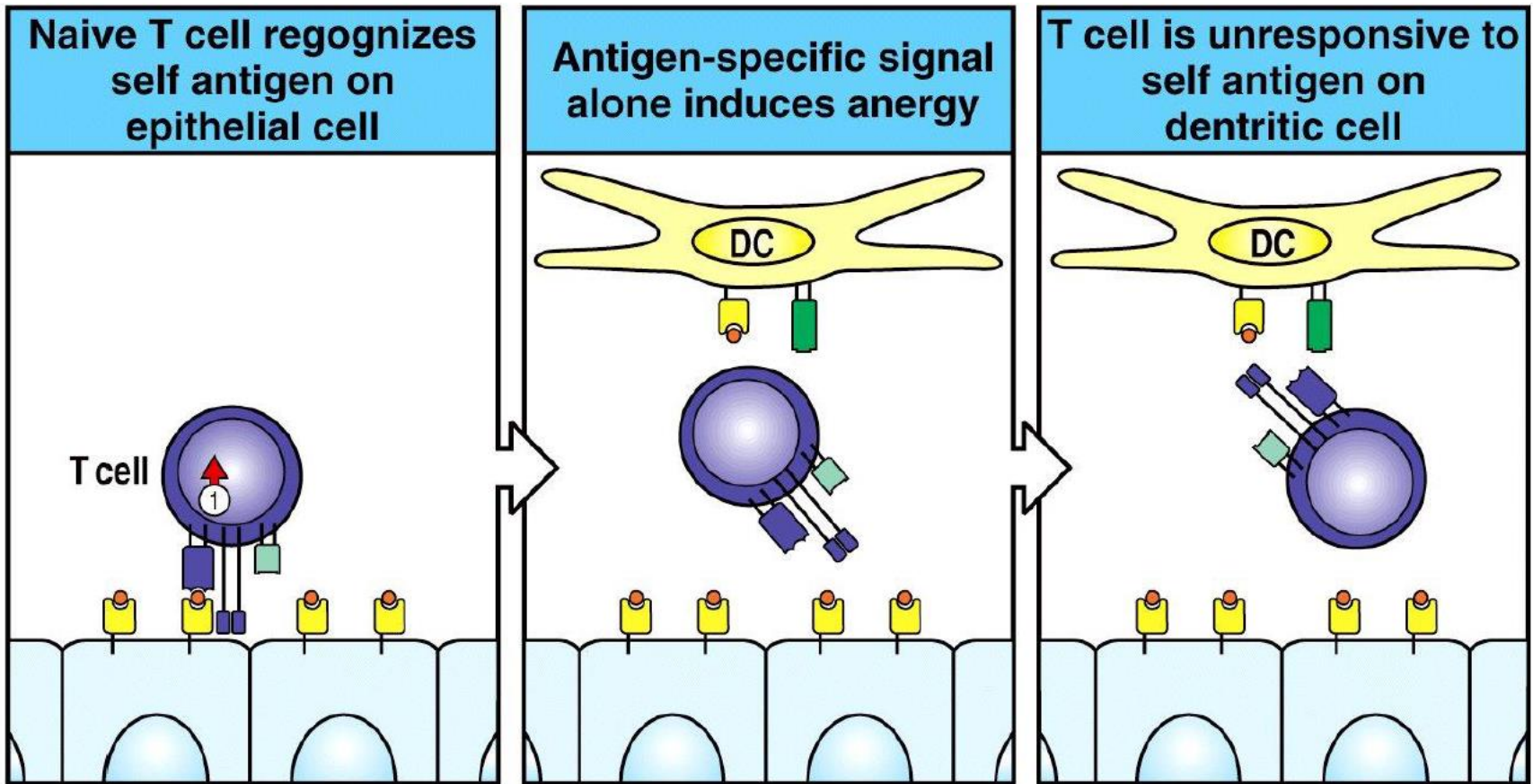


Figure 8-13 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Thank you for your attention!

Questions?

Please write to carlos.plazasirvent@rub.de