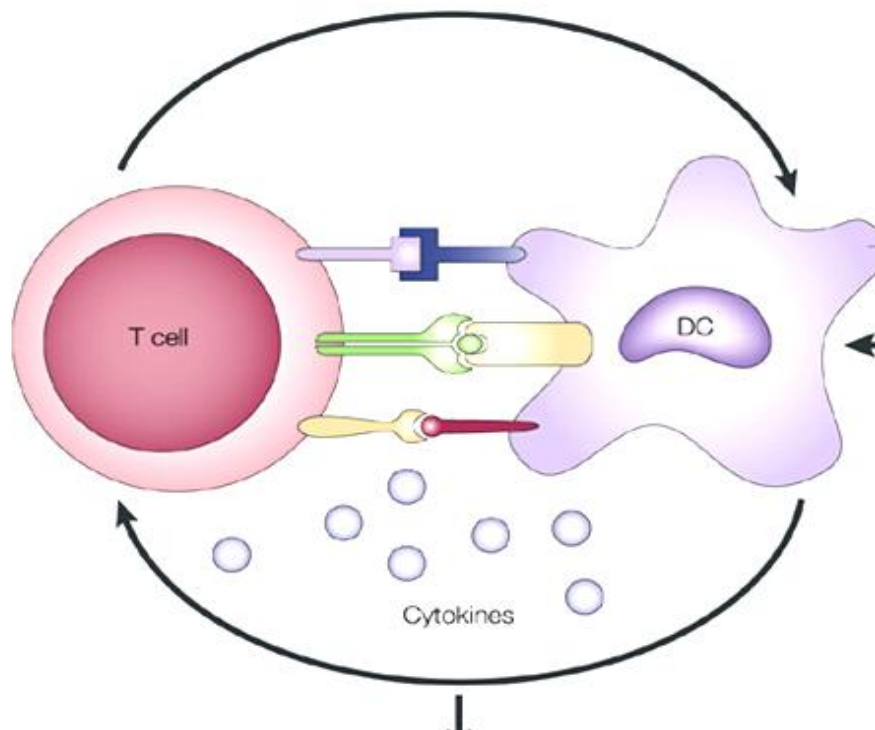


Presentation of Antigen and Recognition of Antigen in Acquired Immunity



Antigen uptake and antigen presentation to lymphocytes

Recognition of antigens in acquired immunity

Presentation of Antigens

What do lymphocytes see?

APC division; APC function

Function of MHC molecules

Processing and presentation of protein
antigens

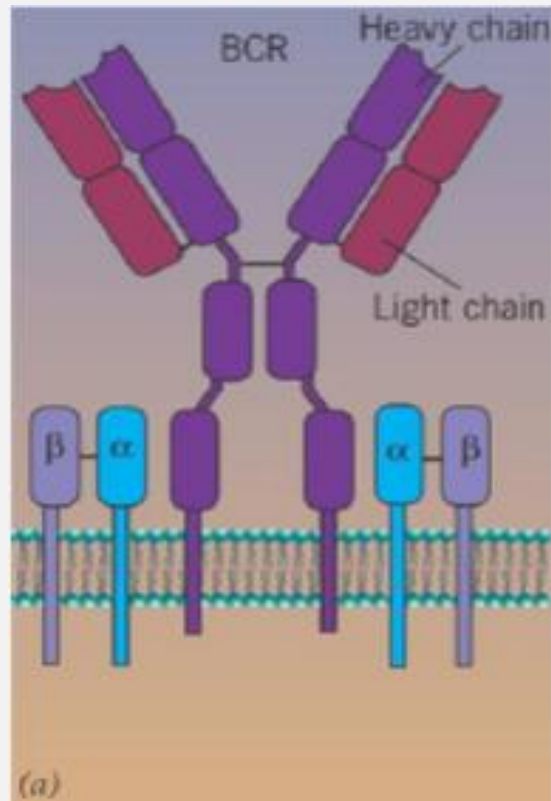
Adaptive (specific) immune response...

... it starts when
antigen receptors on lymphocytes
recognize (see) antigens.

Antigen Receptors of Lymphocytes

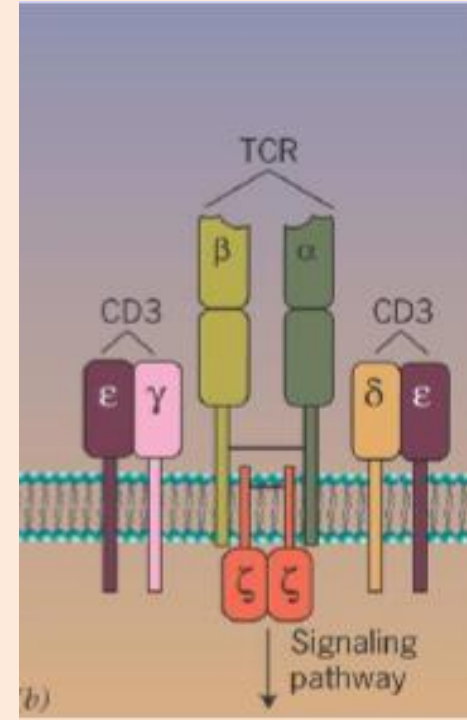
B cell receptor (BCR)

- BCR (membrane antibody) recognizes macromolecules (proteins, lipids, polysaccharides, lipopolysaccharides, nucleic acids), as well as small molecules in solution or on the surface of the corpuscular antigen.



T cell receptor (TCR)

- Most of the TCR recognizes only peptide fragments of protein antigens when displayed on the surface of the APC (Antigen Presenting Cells).
- These peptides are displayed on the membrane as part of special molecules specializing in peptide rendering (MHC).

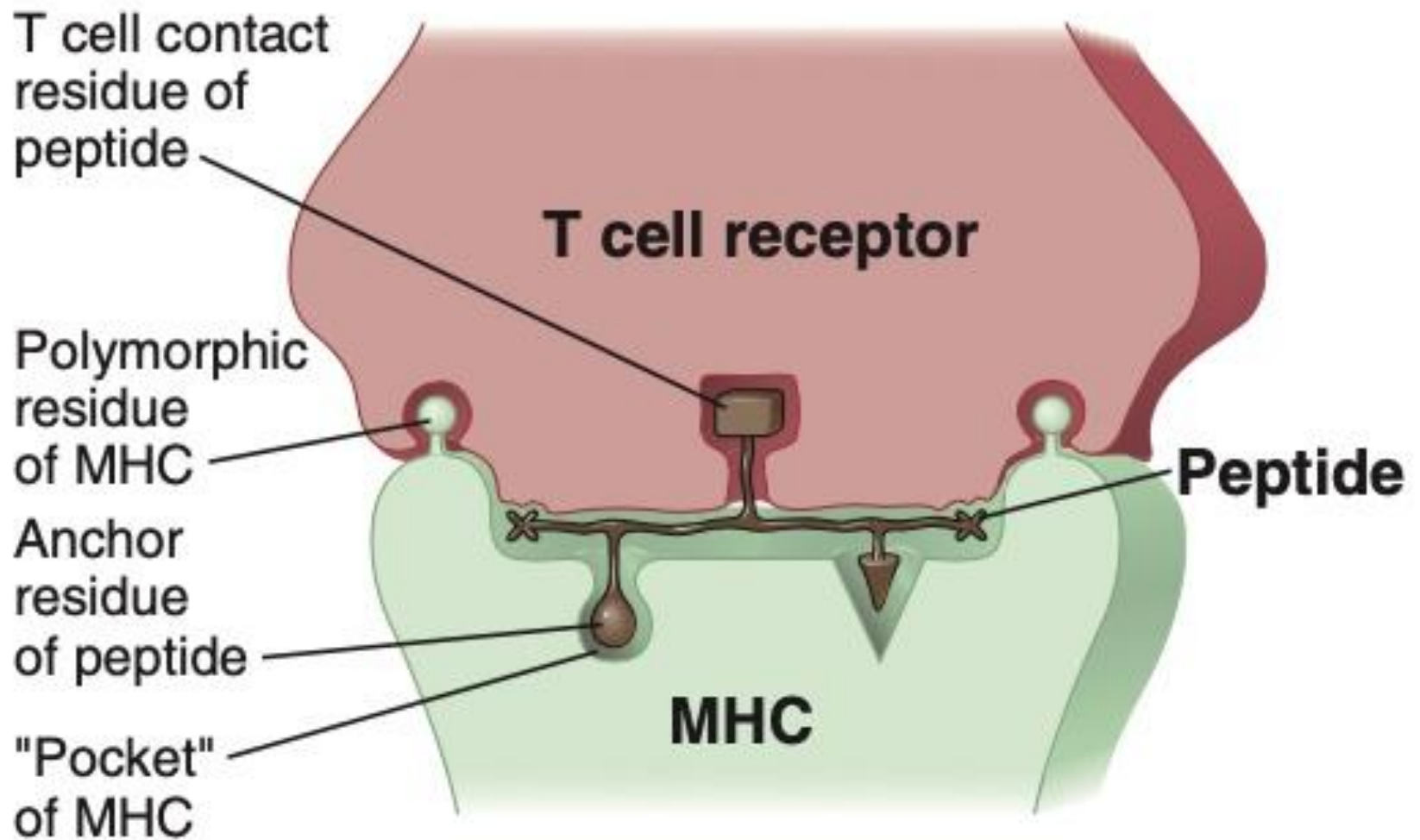


What do T lymphocytes see?

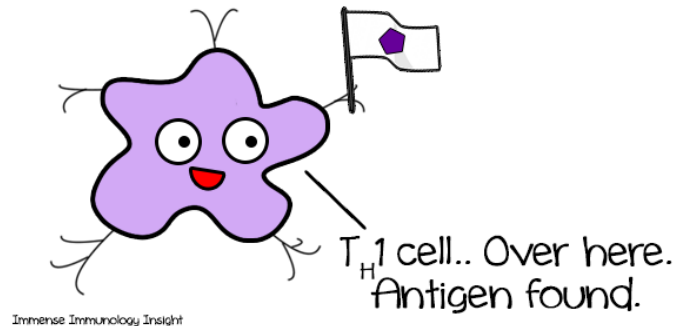
T lymphocytes only see (recognize) peptides attached to MHC molecules (Major Histocompatibility Complex) on the surface of the host cell.

In other words: T lymphocytes see peptide parts of antigens only if they are presented in the context of MHC products that are expressed on our cells.

T lymphocytes of one individual recognize peptides only if they are presented within the MHC molecules characteristic of that individual – MHC restriction.



Cells That Display Antigen (APC, *Antigen Presenting Cells*)



- ✗ **Professional APC (APC in a narrow sense)**

- ✗ Show peptide antigens in the MHC II class, and also in the MHC I class.

These are: Dendritic cells, Mo/Mf Cells, B lymphocytes.

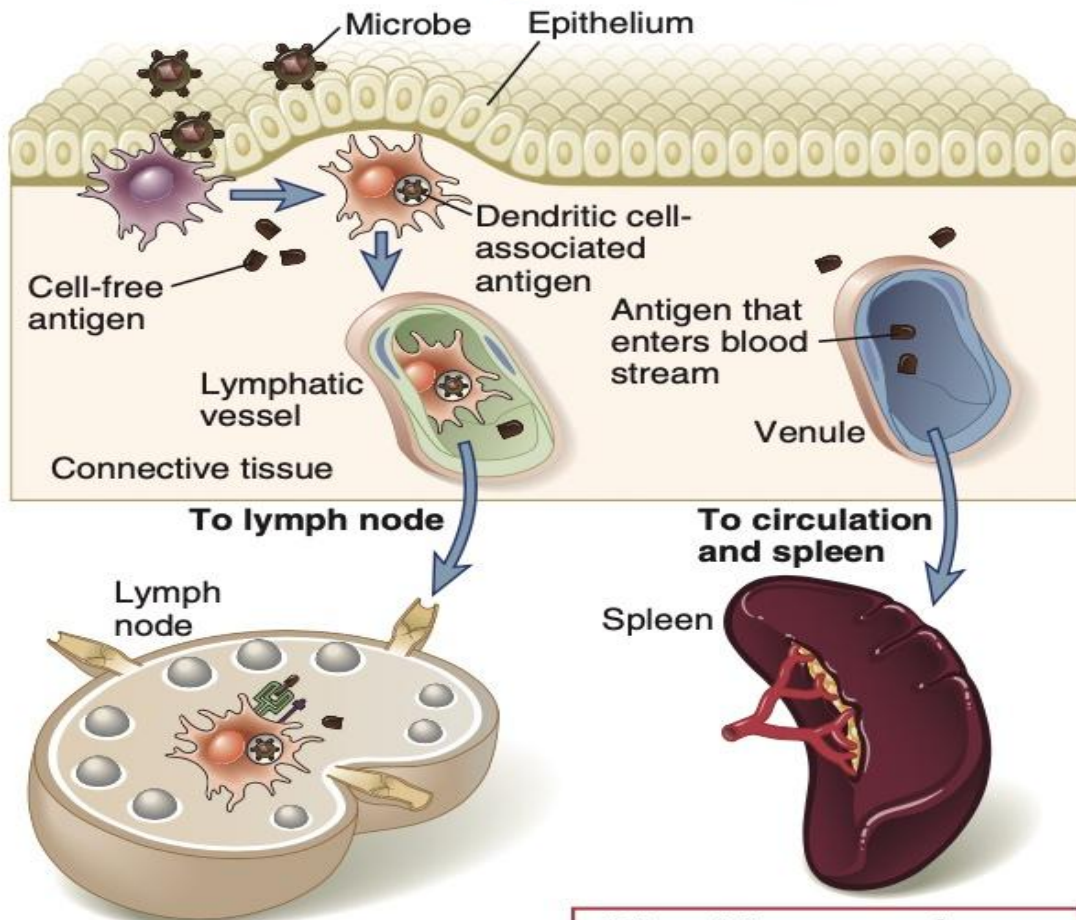
- ✗ **Non-professional APC (APC in a broad sense)**

Display peptide antigens, as part of class I MHC molecules
effector CD8 + T lymphocytes.

Exception: erythrocytes, sperm cells and trophoblast.

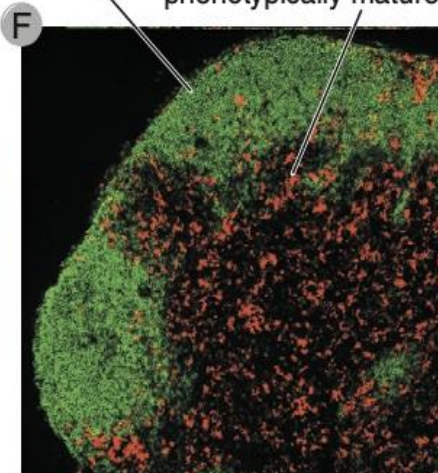
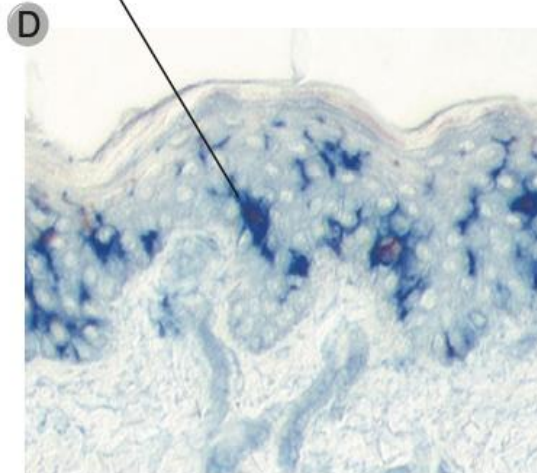
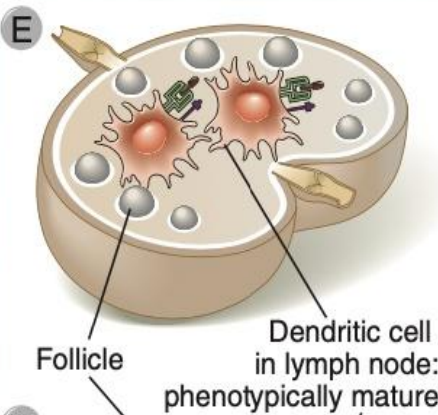
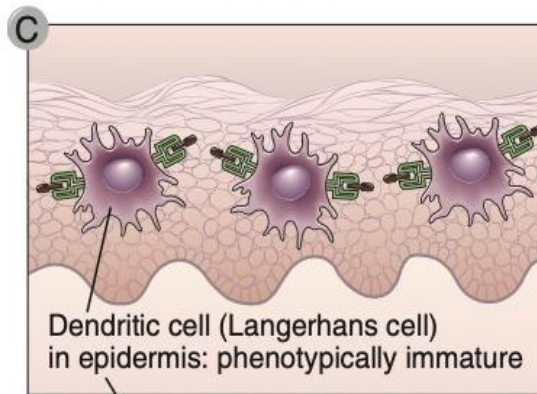
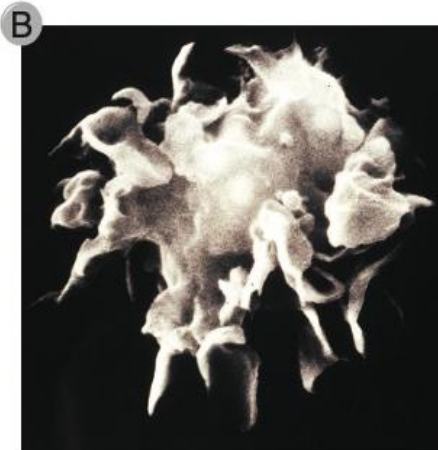
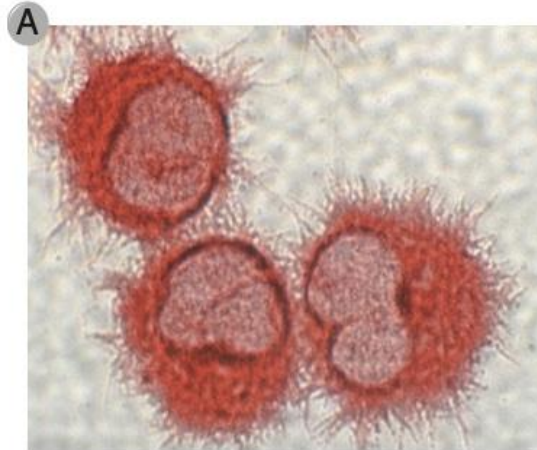
Antigen Presentation

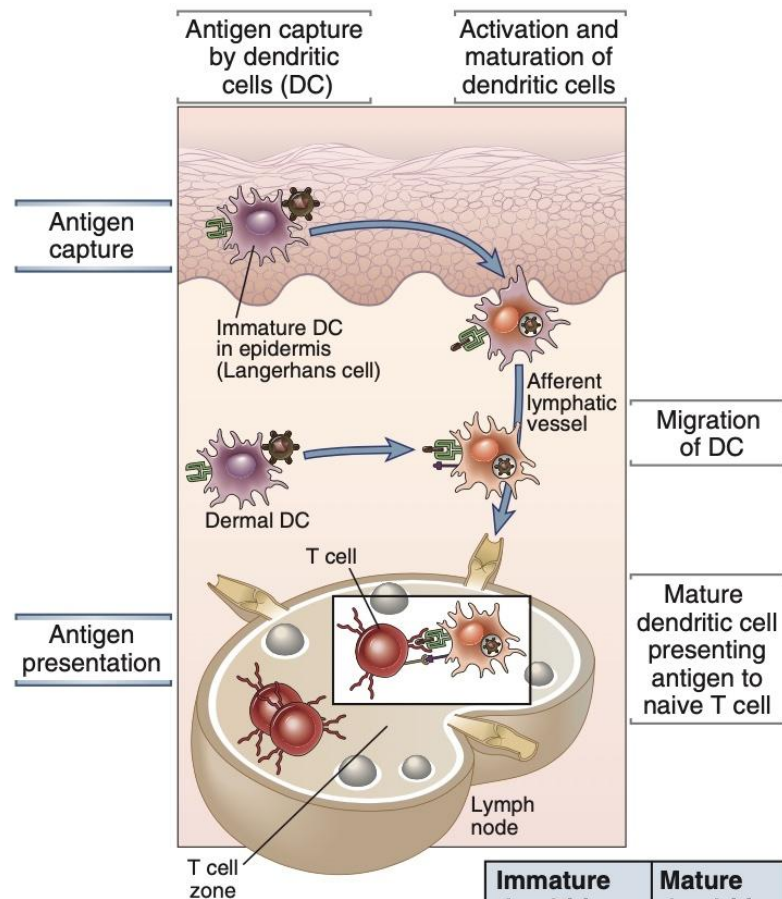
- To initiate immune responses, antigens are captured from their site of entry and concentrated in secondary (peripheral) lymphoid organs through which naïve T cells circulate constantly.
- T lymphocytes recognize and respond only to cell-associated antigens and not to soluble, cell-free antigens



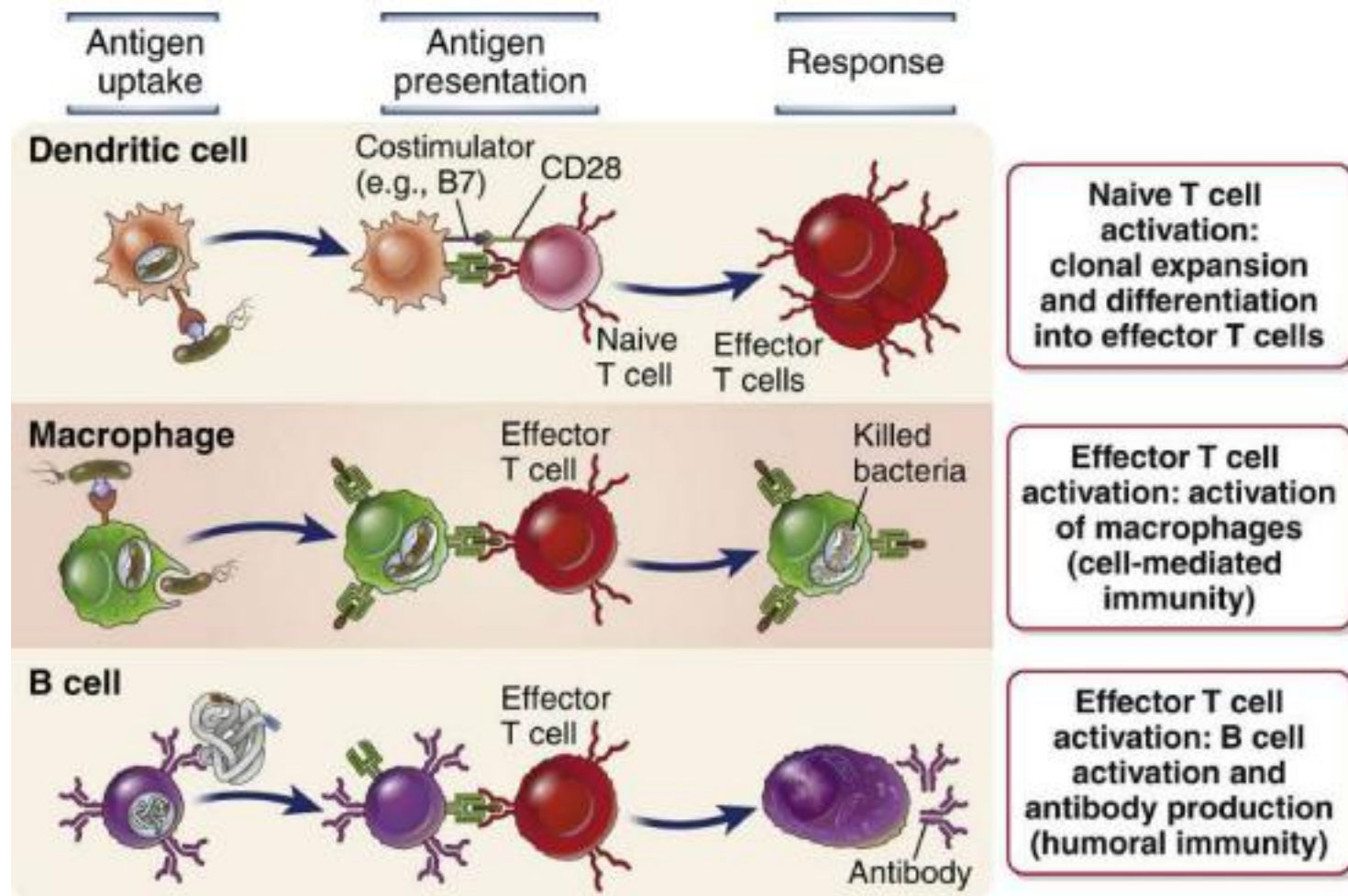
Lymph node collects antigen from epithelium and connective tissue

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





	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



How APC take protein Antigens?

- ✓ Microorganisms, which have entered the body, are taken over by professional APCs. And they put them in the endosomes..
 - This event (as well as cytokines innate immunity – TNF и IL-1), activates dendritic cells.
- ✓ **Activated dendritic cells** they lose the ability to adhere to the epithelium and express receptors for those chemokines that are produced in lymph nodes (LN).
 - This leads them towards the regional LN In the paracortex. (T lymphocyte zone).
- ✓ **During migration, dendritic cells change further: they become mature** (they show co-stimulating molecules) and capable of activating T lymphocytes.

Let's remember...

**In addition to dendritic cells, there are
other
professional APC!!!**

Professional APC

1. Dendritic cells are most potent in activating naïve CD4+ T lymphocytes.

They can also direct the differentiation of naïve CD4+ T lymphocytes in different directions.

Dendritic cells display peptide antigens to CD8 + T lymphocytes also as part of Class I MHC molecules – CROSS PRESENTATION.

2. Mo/Mφ are important APC in the effector phase of cellular immune response.

They present antigens to effector CD4+ T lymphocytes.

3. B Lymphocytes are the dominant APC in the humoral immune response.

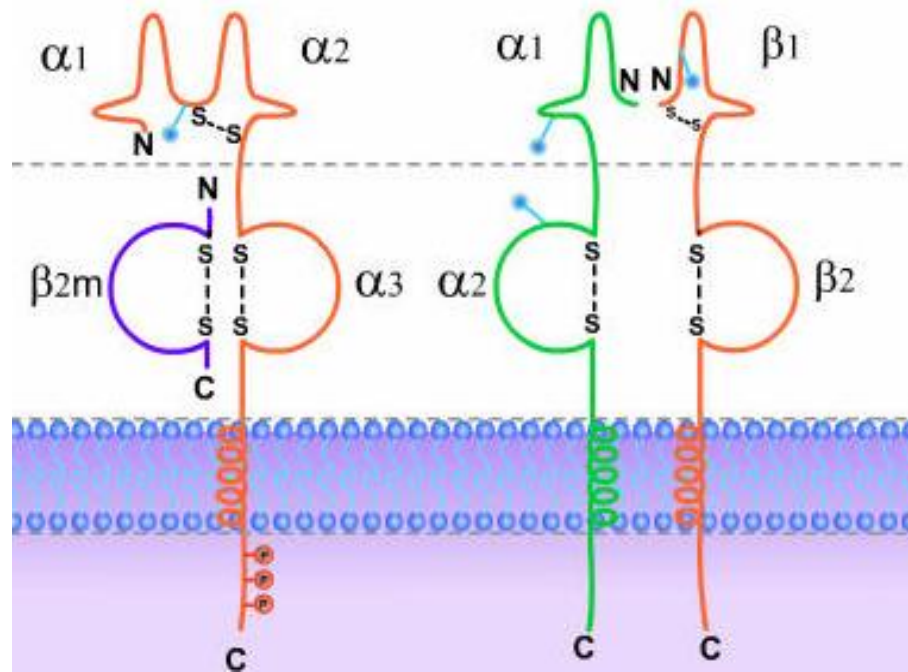
Other Functions of APC

In addition to the presentation of antigens, APC provide T lymphocytes so-called The second activation signal...

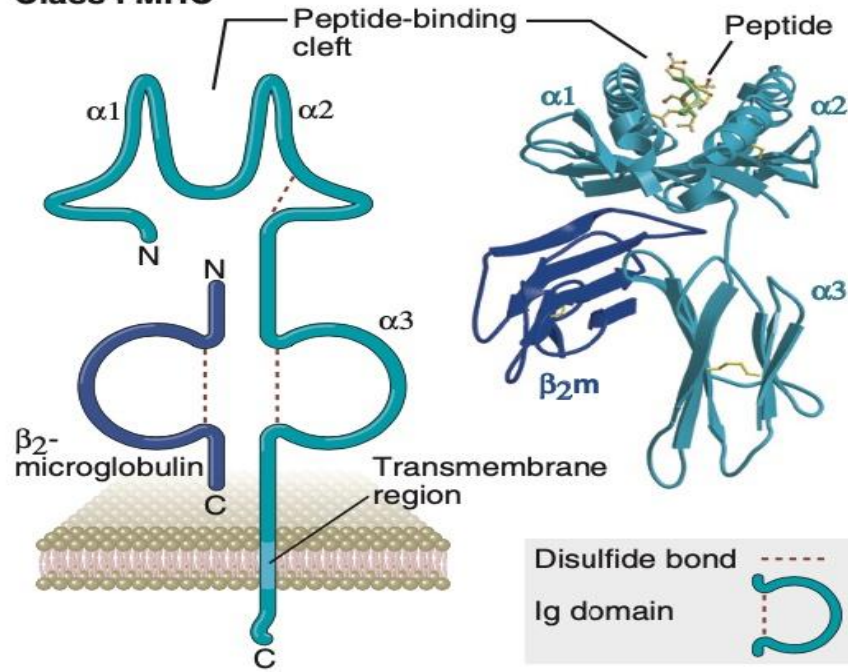
*...The second signal is provided by **co-stimulating membrane proteins and cytokines.***

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.	Most T cell receptors recognize only peptide-MHC complexes, and MHC molecules are membrane proteins that display stably bound peptides on cell surfaces.
CD4⁺ and CD8⁺ T cells preferentially recognize antigens ingested from the extracellular environment into vesicles and antigens present in the cytosol, respectively.	Pathways of assembly of MHC molecules ensure that class II MHC molecules display peptides that are proteolytically degraded in vesicles in APCs and class I MHC molecules present peptides from cytosolic proteins that are degraded by cytosolic proteasomes.

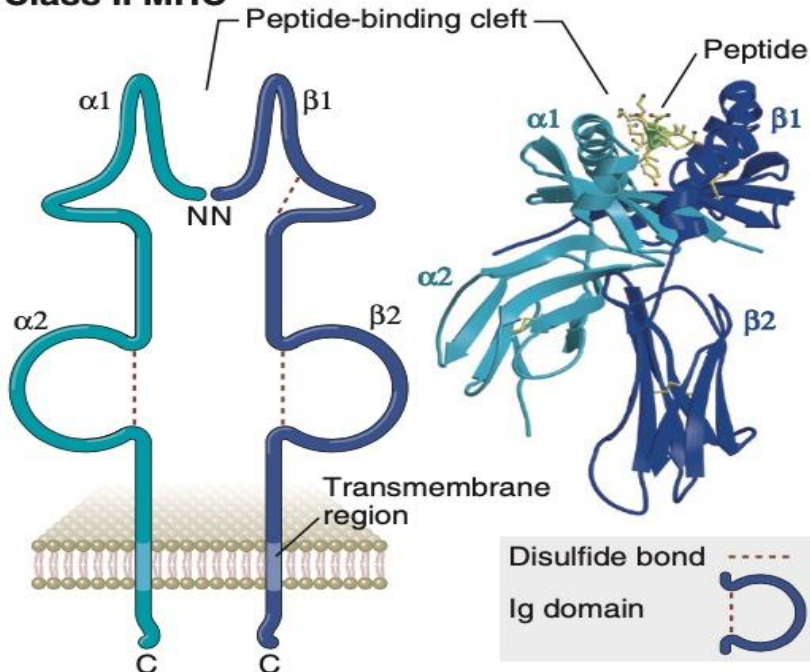
Genes and Products of MHC



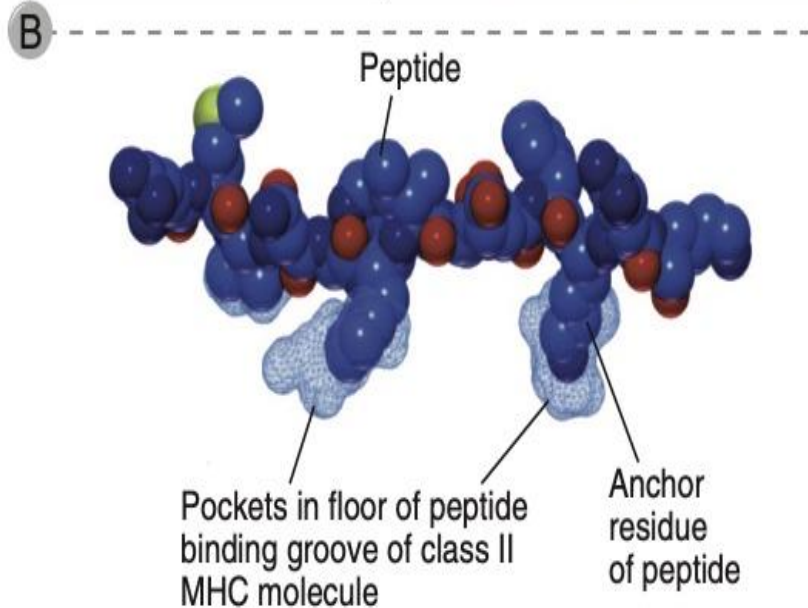
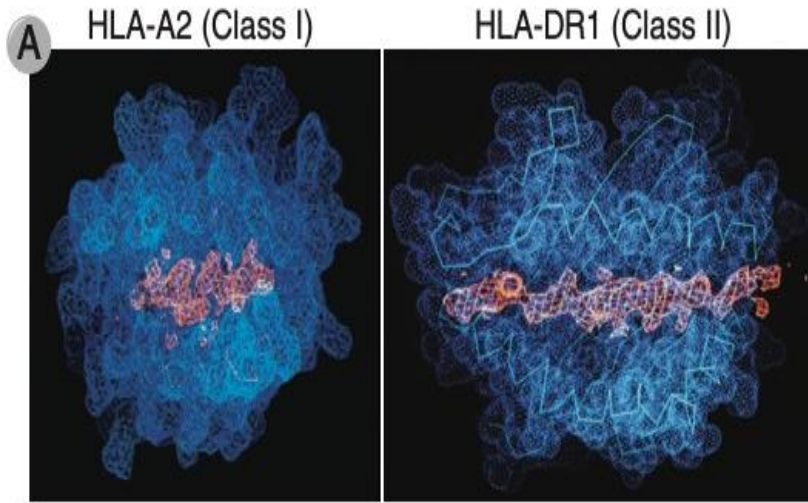
Class I MHC



Class II MHC



The molecules of MHC are membrane proteins whose function is to display peptides to the T lymphocytes.



MHC molecules at their N-end have a dent to the bottom of which peptides bind

Products of the I class MHC

- $\alpha 1$ and $\alpha 2$ domains* build an active site, that is, a dent whose bottom is formed by the most polymorphic parts of molecules, to which a peptide-sized peptide is bound by terminal amino acids 8-11 a. a.
- At the top of the dent there are less polymorphic parts of molecules that recognize T lymphocytes (Characteristic of each allele).
- the $\alpha 3$ domain is non-polymorphic (the same in alleles) and is the binding site of the T cell coreceptor CD8.

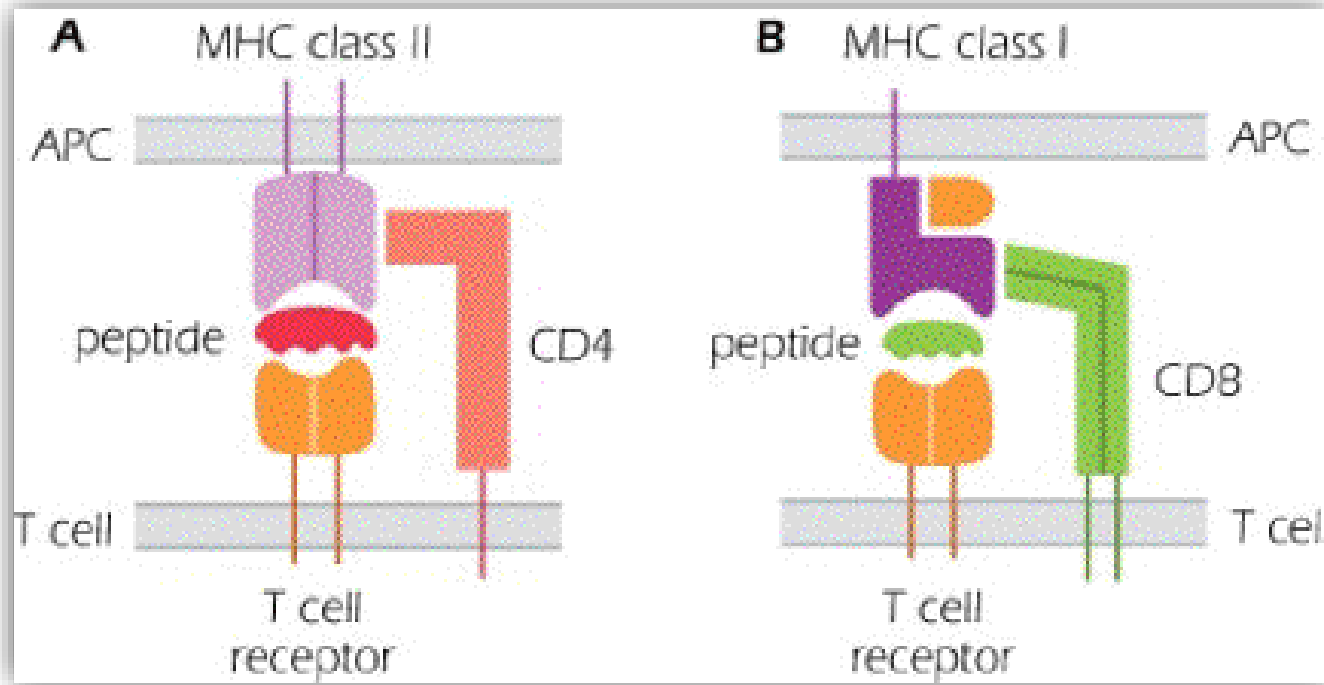
Products of the II class MHC

- the $\alpha 1$ and $\beta 1$ domains make up the walls of the dent large enough to accommodate a peptide size 10 – 30 a. a.
- **The bottom of the dent makes up the most polymorphic parts of the molecule.**
- At the top of the dent there are less polymorphic parts of molecules recognized by T lymphocytes (characteristic of each allele).
- $\beta 2$ is a non-polymorphic and is a place of binding of the T cell coreceptor CD4.

** The domain (loop, globule) consists of amino acids twisted around one S-S bond.*

Important!!!

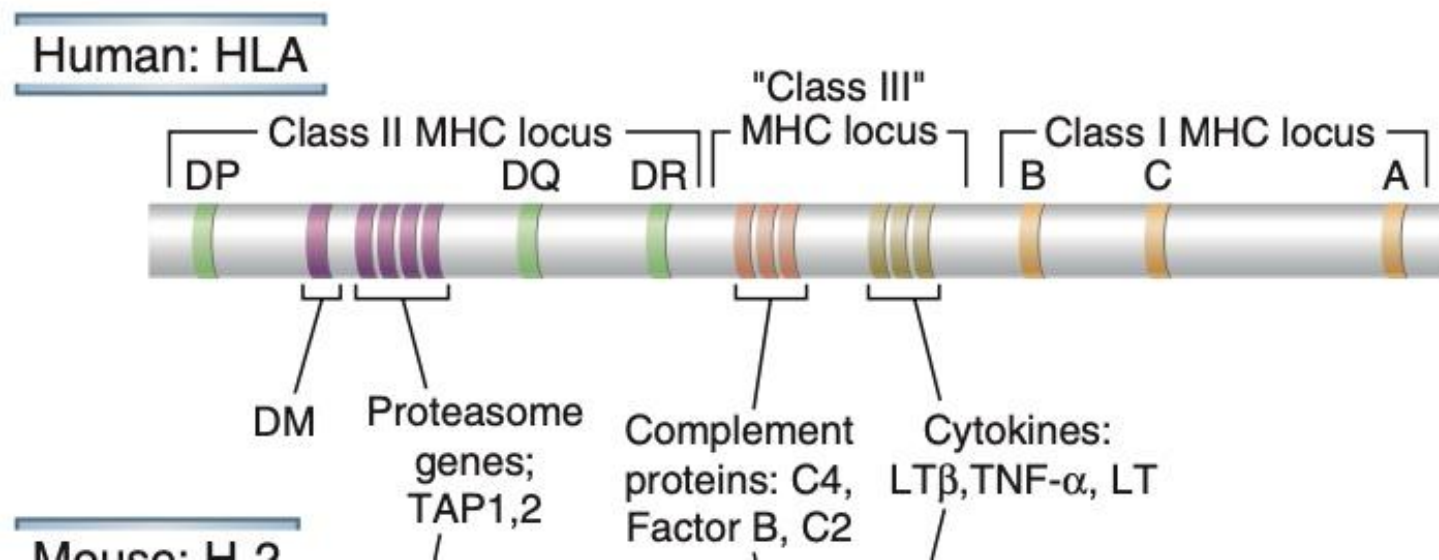
(1) Class I of MHC present antigens to CD8 + T lymphocytes



(2) Class II of MHC present antigens to CD4 + T lymphocytes

MHC Genes

- Polymorphism
- Coupled inheritance (in block)
- Codominant expression
- MHC locus (a set of coupled genes on one chromosome)
 - MHC = HLA
- Genes of I and Class II MHC



Characteristics of HLA(MHC) Genes

1. Codominant expression...

... the simultaneous expression of inherited alleles from the paternal and maternal chromosomes is mandatory.

a combination of alleles on one of the chromosomes called
The MHC haplotype.

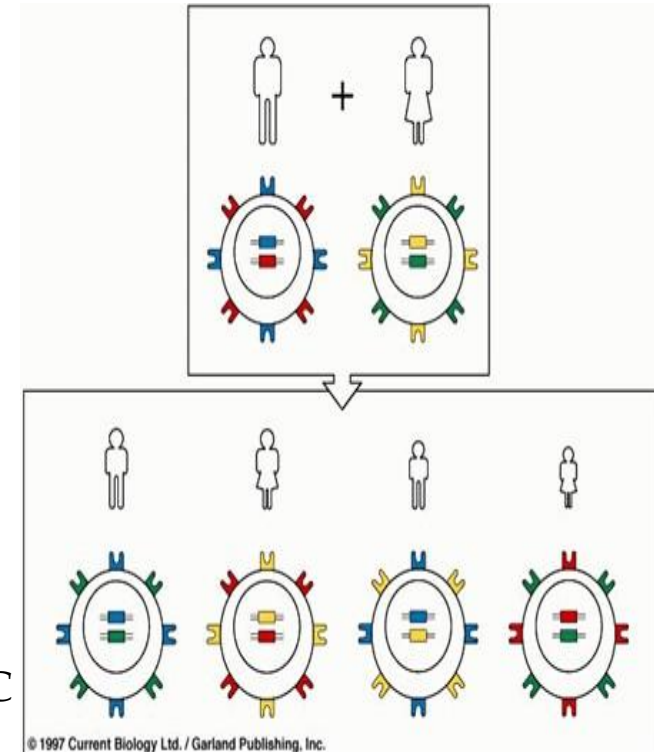
NUMBER of products reported:

- ✓ There are three genes – HLA-A, HLA-B, HLA-C for α chain I class on each of the chromosomes:

$3 \times 2 = 6$ class I MHC in/on each cell..

- ✓ There are three genes –HLA-DP, HLA-DQ, HLA-DR for α chain and three or four genes for β chain (which can be combined) II class on both Chromosomes:

$3 \times 3 \times 2 = 18$ class II MHC products on every professional APC



2. The Inheritance...

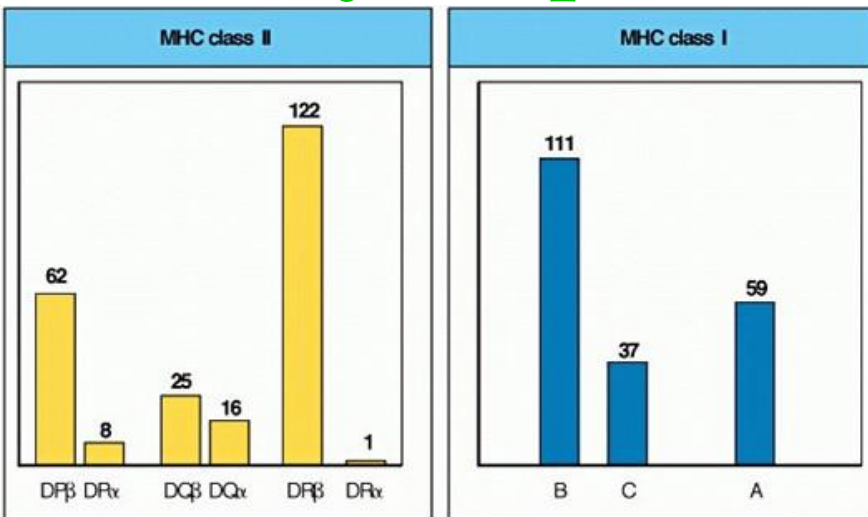
... "In the block" means that:

There is not *crossing over*.

This means that it is inherited.

one father and one mother's haplotype as a whole
(one mother's and one father's combination).

3. Polymorphism...



... It has a large number of alleles.

Each of these genes

At the level of the population.

It's not a result of genes.

recombination

they are already encoded by inherited genes.
It is important for selection within the population..

Characteristics of MHC molecules

Each MHC molecule binds peptides derived from protein antigens and displays them to the T lymphocytes that recognize them with their TCR.

Each MHC molecule can display only one peptide at a time, but it is capable of displaying a large number of different peptides at different times (it is widely specific).

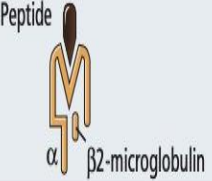

MHC molecules are constantly synthesized.

MHC molecules bind peptides during their synthesis and assembly within the cell.

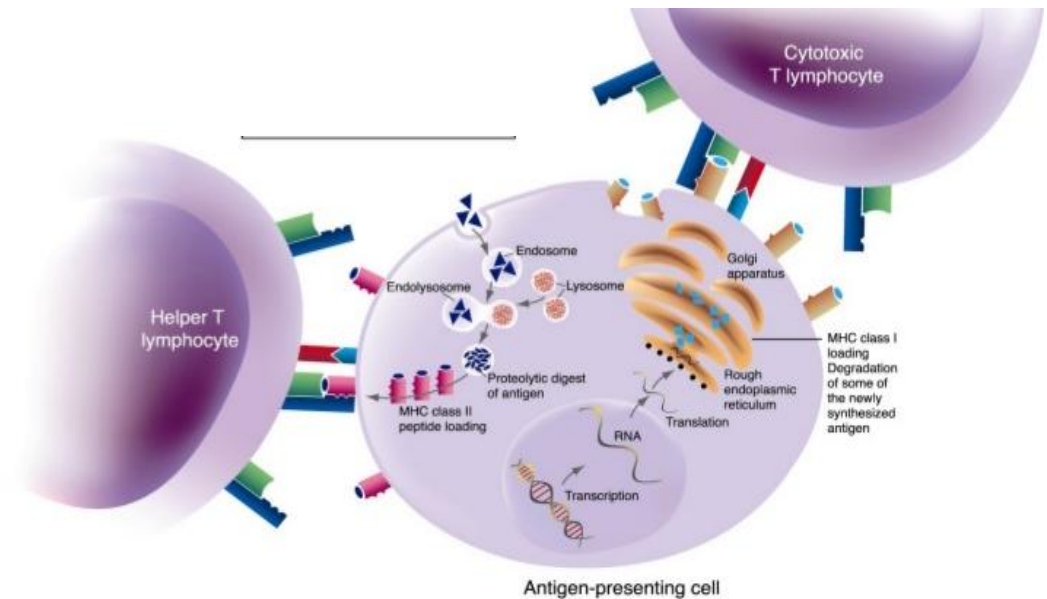
MHC molecules are extremely unstable – they stabilize, survive and can reach the membrane of the cell only when they bind the peptide.

At any given moment, a huge number of MHC molecules are expressed on the cells.

MHC molecules also show peptides that originate from the proteins of that individual itself.

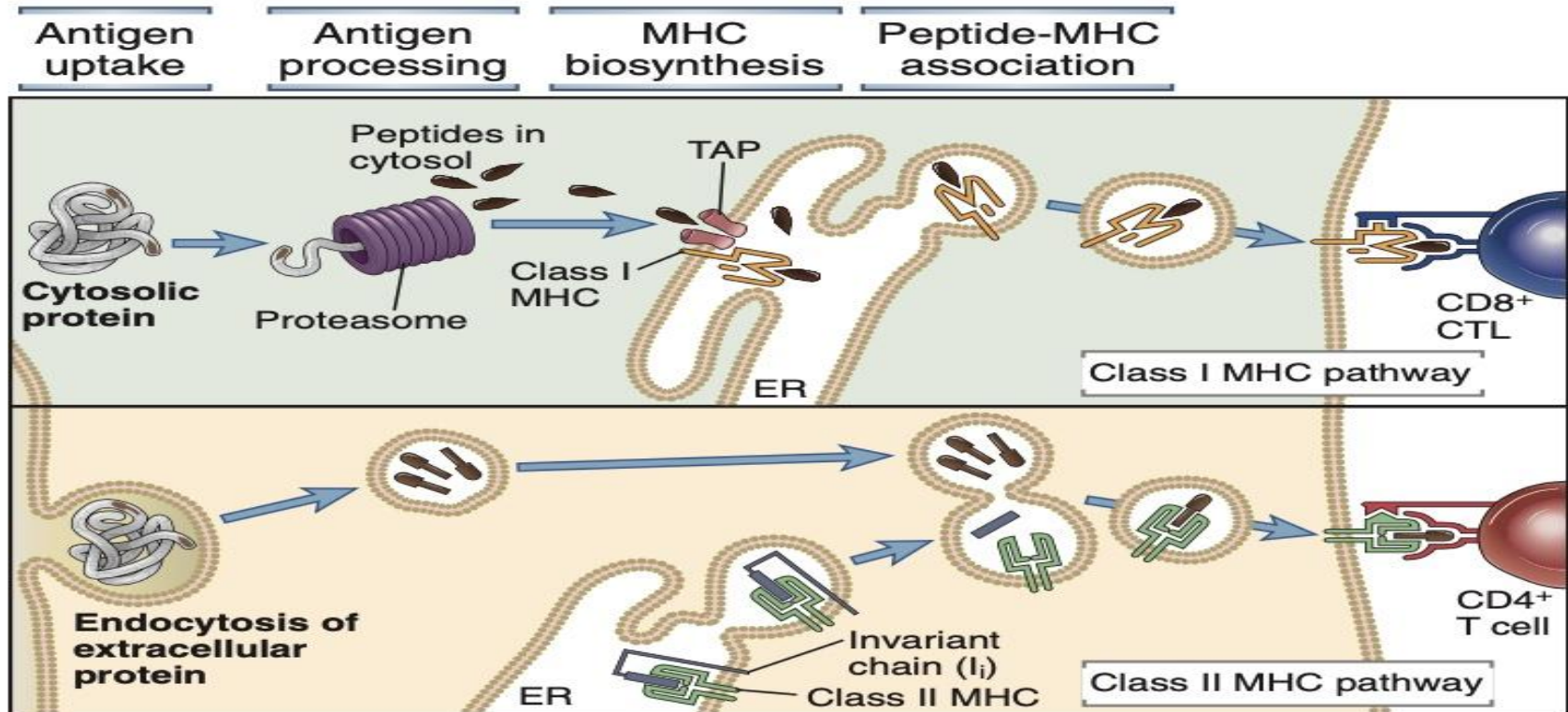
TABLE 6-5 Comparative Features of Class I and Class II MHC Pathways of Antigen Processing and Presentation		
Feature	Class I MHC Pathway	Class II MHC Pathway
Composition of stable peptide-MHC complex	Polymorphic α chain, β_2 -microglobulin, peptide 	Polymorphic α and β chains, peptide 
Types of APCs	All nucleated cells	Dendritic cells, mononuclear phagocytes, B lymphocytes; endothelial cells, thymic epithelium
Responsive T cells	CD8 ⁺ T cells	CD4 ⁺ T cells
Source of protein antigens	Cytosolic proteins (mostly synthesized in the cell; may enter cytosol from phagosomes)	Endosomal and lysosomal proteins (mostly internalized from extracellular environment)
Enzymes responsible for peptide loading of MHC	Cytosolic proteasome	Endosomal and lysosomal proteases (e.g., cathepsins)
Site of peptide loading of MHC	Endoplasmic reticulum	Specialized vesicular compartment
Molecules involved in transport of peptides and loading of MHC molecules	Chaperones, TAP in ER	Chaperones in ER; invariant chain in ER, Golgi and MIIC/CIIV; DM
APC, antigen-presenting cell; CIIV, class II vesicle; ER, endoplasmic reticulum; MHC, major histocompatibility complex; MIIC, MHC class II compartment; TAP, transporter associated with antigen processing.		

Processing and Presentation of Protein Antigens



Depending on the origin of the protein, there are two pathways of its processing for displaying T lymphocytes:

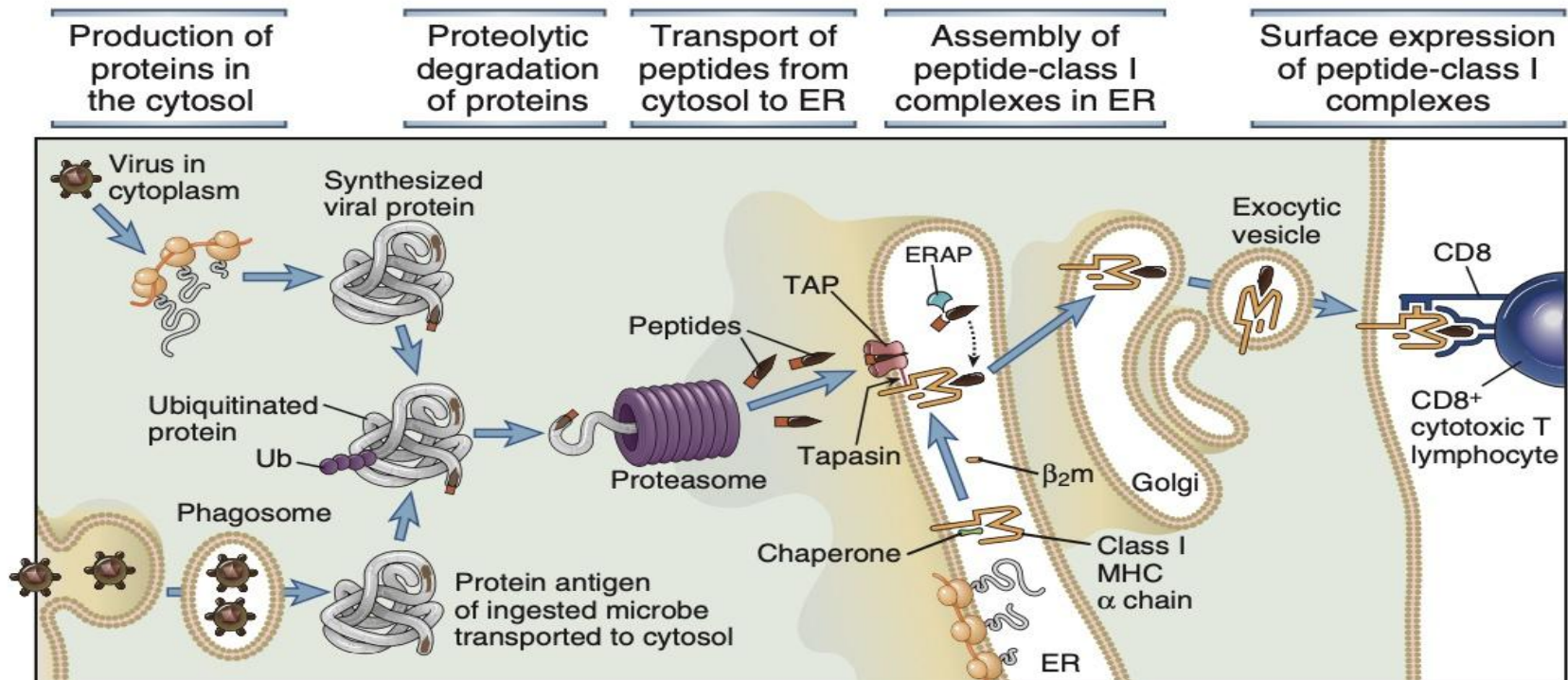
- Protein antigens synthesized outside our cells, and then introduced into the vesicles of professional APCs, are processed and presented to the CD4 + T lymphocytes as part of class II products of MHC.
- Protein antigens synthesized in any of our cells are presented to the CD8 + T lymphocytes in the context of class I products of MHC.



Processing and Presentation of Antigens **Within I Class** **Molecules of MHC**

Protein antigens in the cytoplasm are derived from:
viruses that multiply in the cytoplasm;
phagocytic microbes escaped from vesicles;
oncoproteins derived from altered genes.

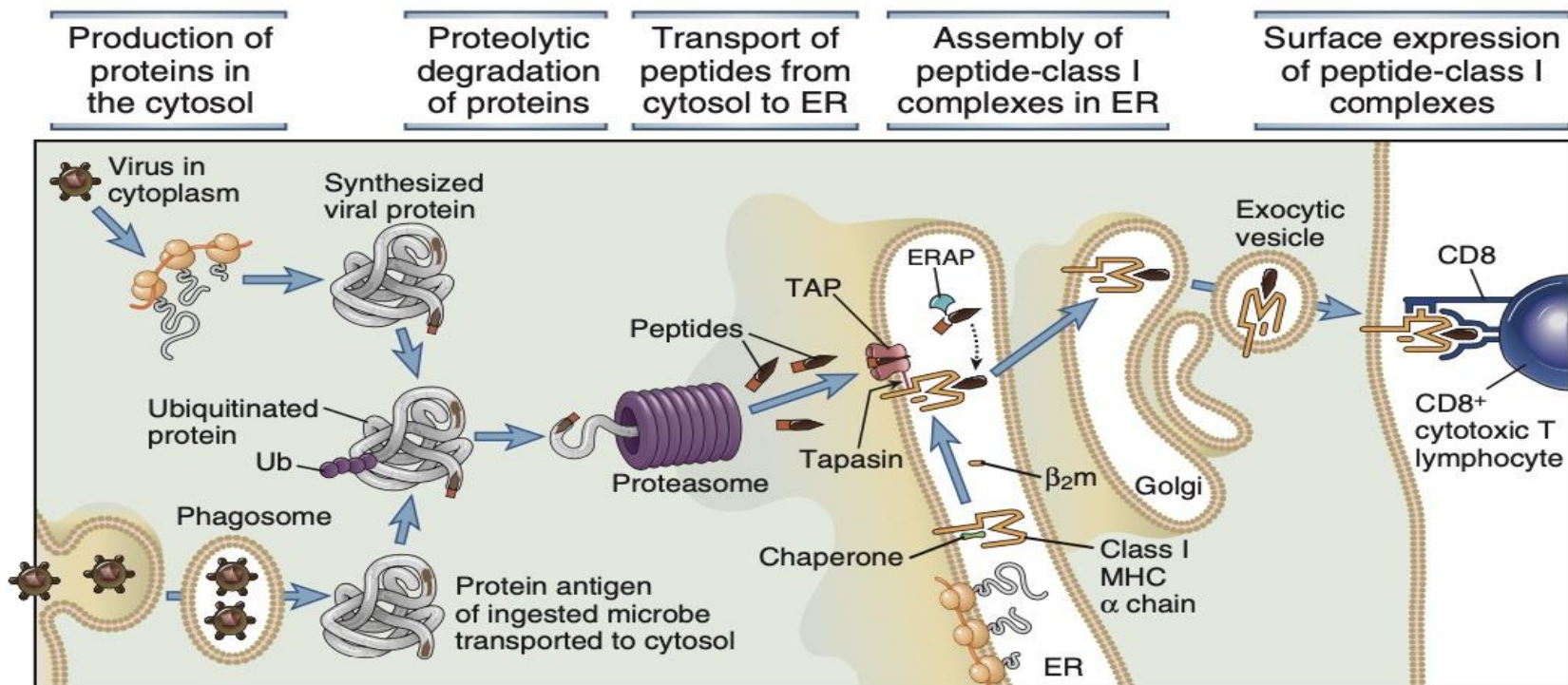
All these proteins (as well as the aging and worn-out proteins of the cell itself) are proteolytically decomposed...



.... And that's by first unravelling, then connecting with ubiquitin and then running through the proteasome.

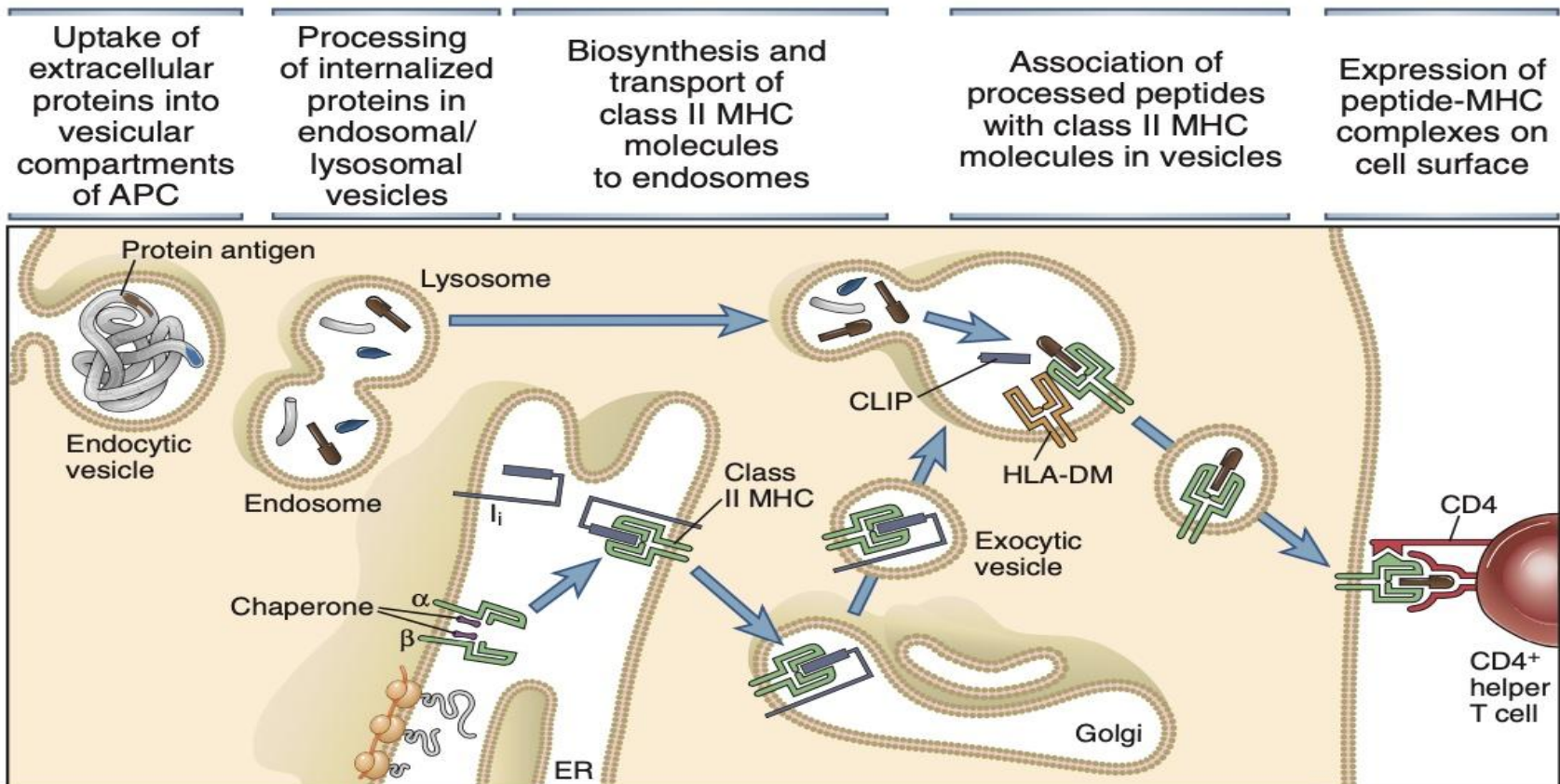
A proteasome is a proteolytic organelle in which proteins are cut into peptides suitable for bonding with class I molecules of MHC.

- **TAP** (*Transporter associated with Antigen Processing*) the active transport inserts peptides into the ER.
- MHC Class I molecules bind peptides in this way in the ER.
- **The exocytosis vesicle is transported to the membrane where they exhibit the bound peptide.**

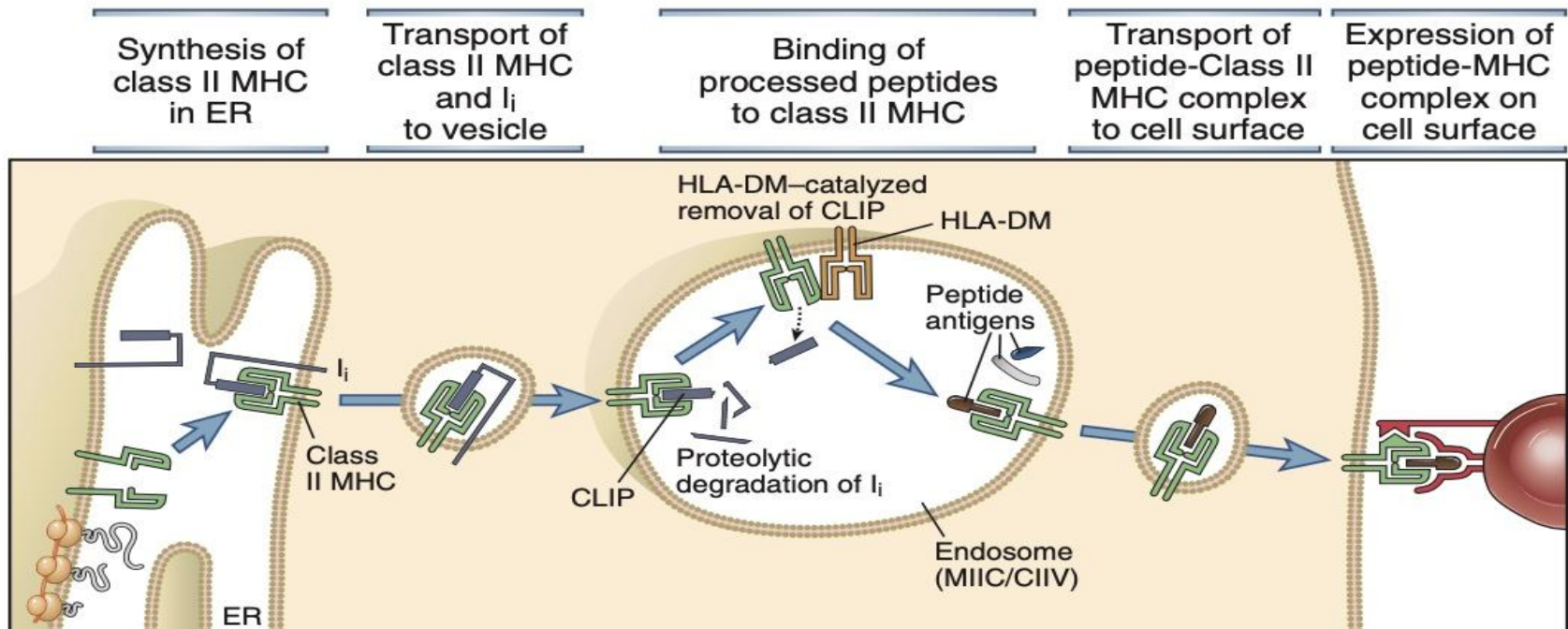


Processing and Presentation of Antigens **Within II Class Molecule MHC**

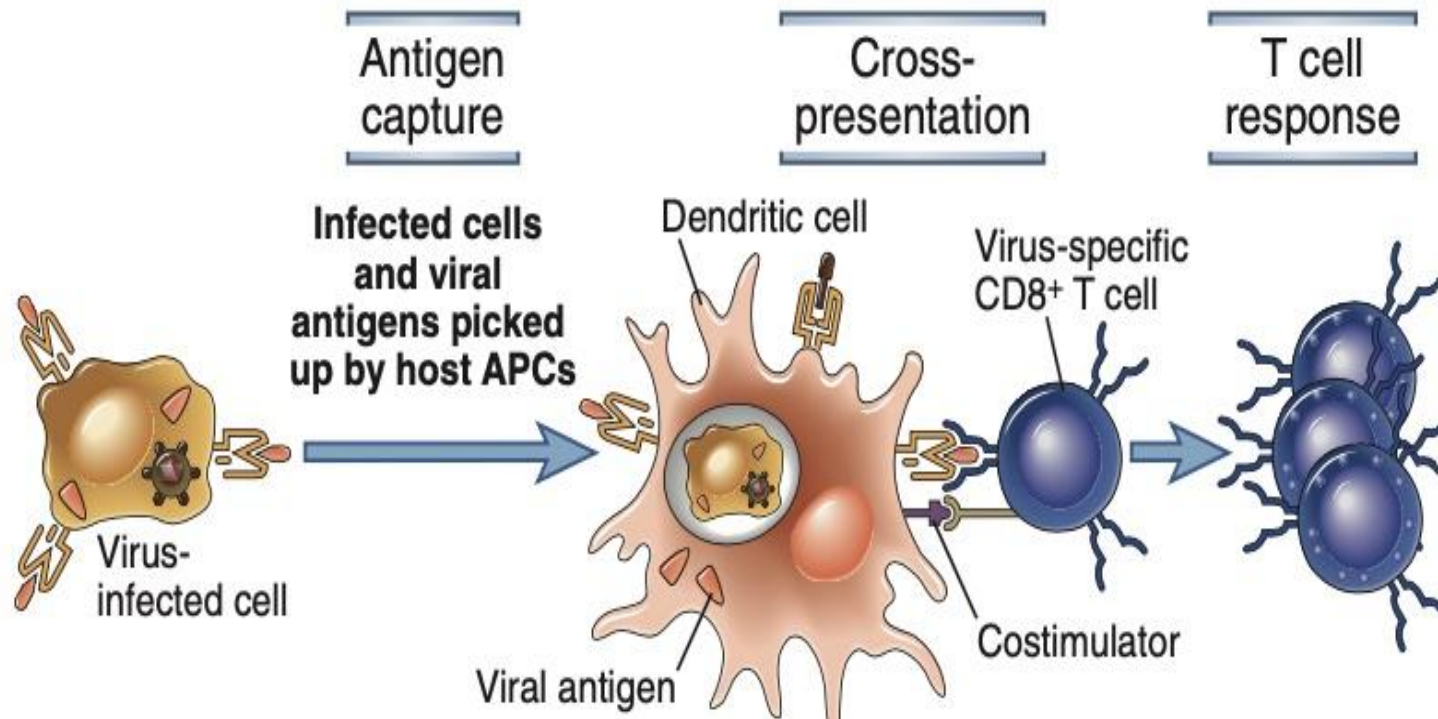
Professional APCs intake microorganisms into endosomes and phagosomes by various mechanisms, which then merge with lysosomes in which the proteins of microorganisms are enzymatically decomposed to peptides of different lengths.



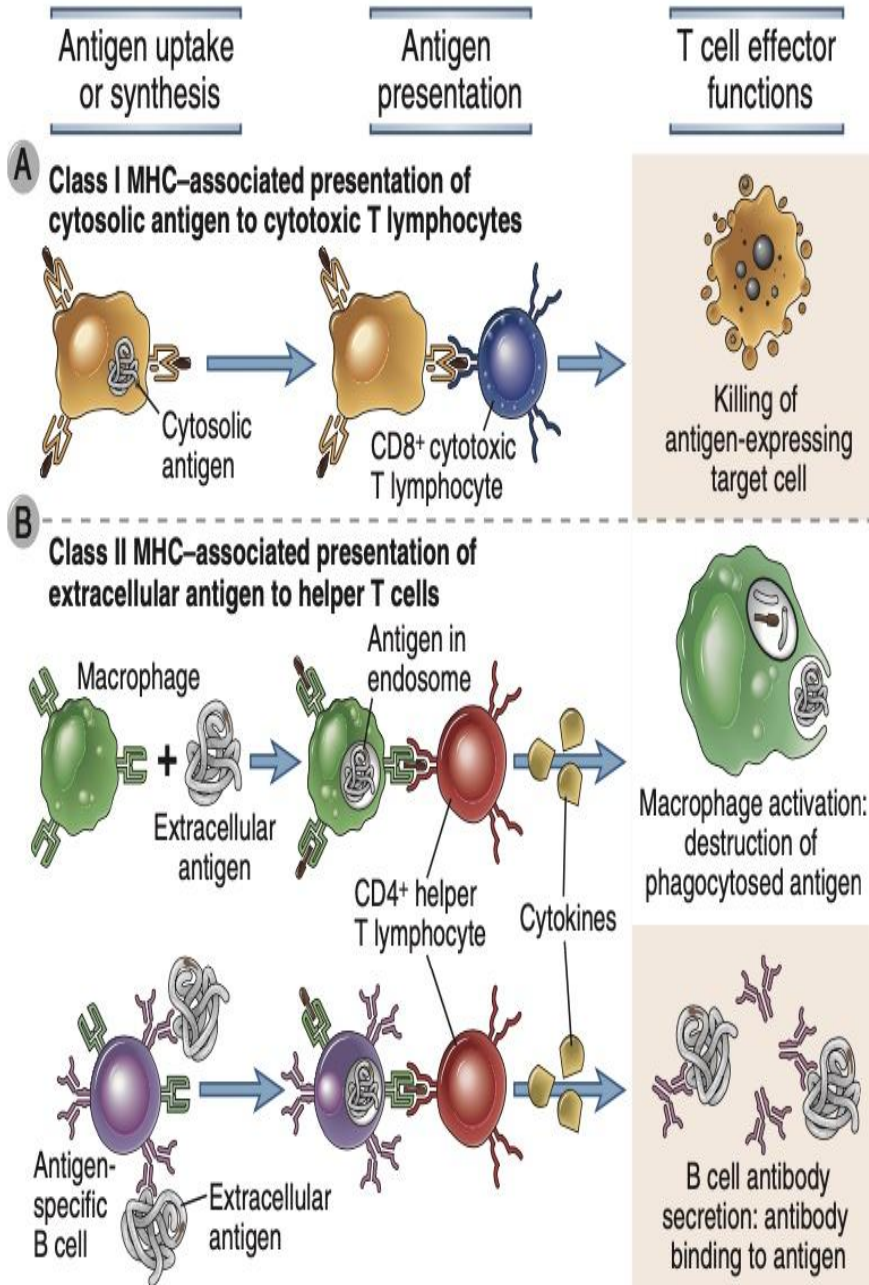
- MHC they are constantly synthesized in the ER in which they connect active place of MHC and **the unchangeable chain (CLIP – class II invariant chain peptide)**. CLIP temporarily stabilize MHC in a newly formed exosome that merges with an endosome. In the endosome there are peptides formed by decomposition.
- In the endosomal vesicles there is **DM** – a molecule similar to a class II product of MHC which now takes the CLIP and frees up the place for peptide binding, it permanently stabilizes the complex that is expressed on the membrane.



Cross Presentation



Physiological Significance of Antigen Presentation Within MHC

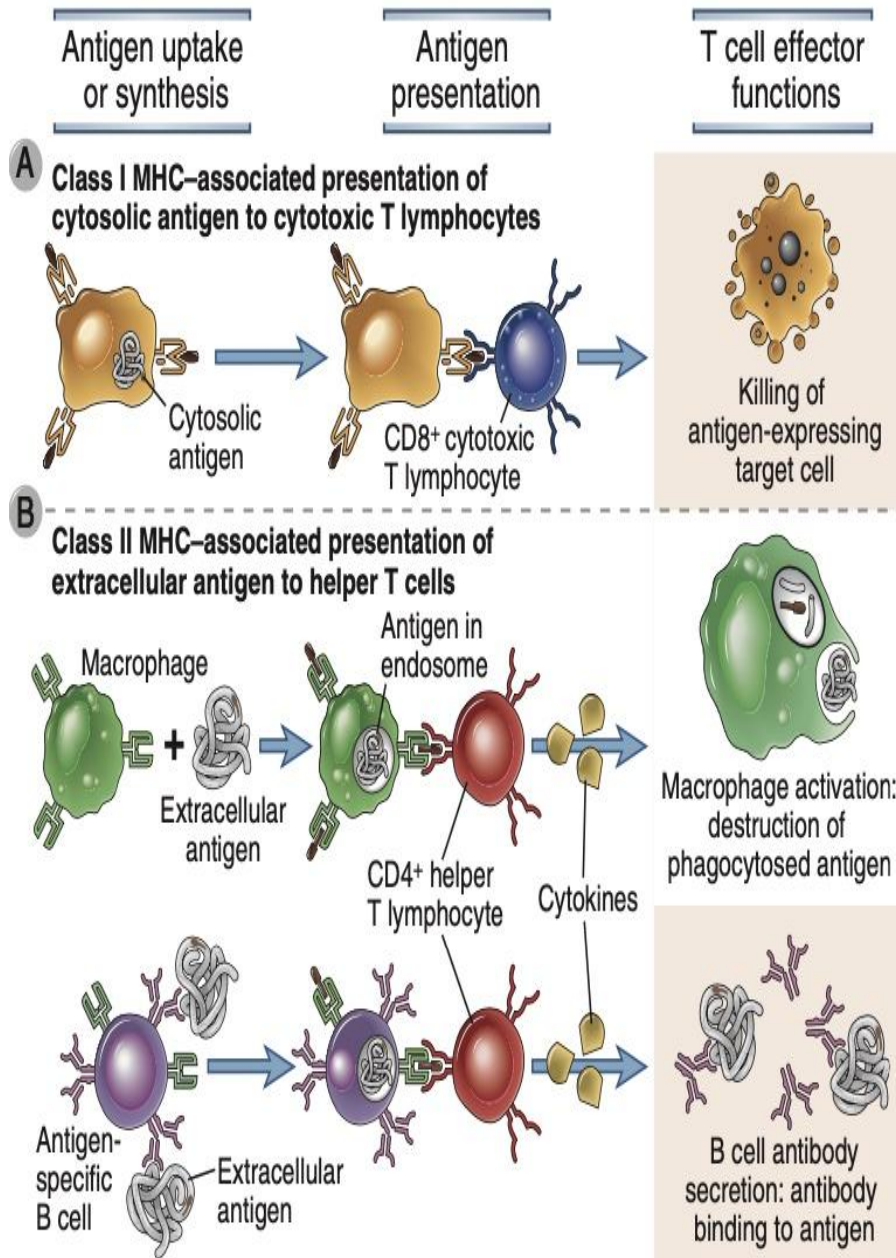


Extracellular microorganisms are taken over by professional APC and show their peptides within molecules II class **MHC**. This complex is recognized by CD4 + T lymphocytes.

CD4 + T lymphocytes with their cytokines mediate:

- B lymphocytes to produce antibodies
- Phagocytes to ingest and destroy the microorganism.

In this way, two of the most effective mechanisms for the elimination of extracellular and phagocytic microbes are activated.



...However:

Neither of these two mechanisms is effective against microorganisms (mainly viruses), which parasitize in the cytoplasm of infected cells.

Peptides of these cytoplasmic microorganisms are shown by class I molecules of MHC. This is recognized by CD8 + T lymphocytes that differentiate into CTL capable of killing the infected cell and thus removing the infection.

What do B lymphocytes see?

- B lymphocytes recognize antigens on the surface of microorganisms or soluble antigens.
- These antigens B lymphocytes see in their native form..

