

# Lymphocyte subsets and MHC molecules

# Lecture outline

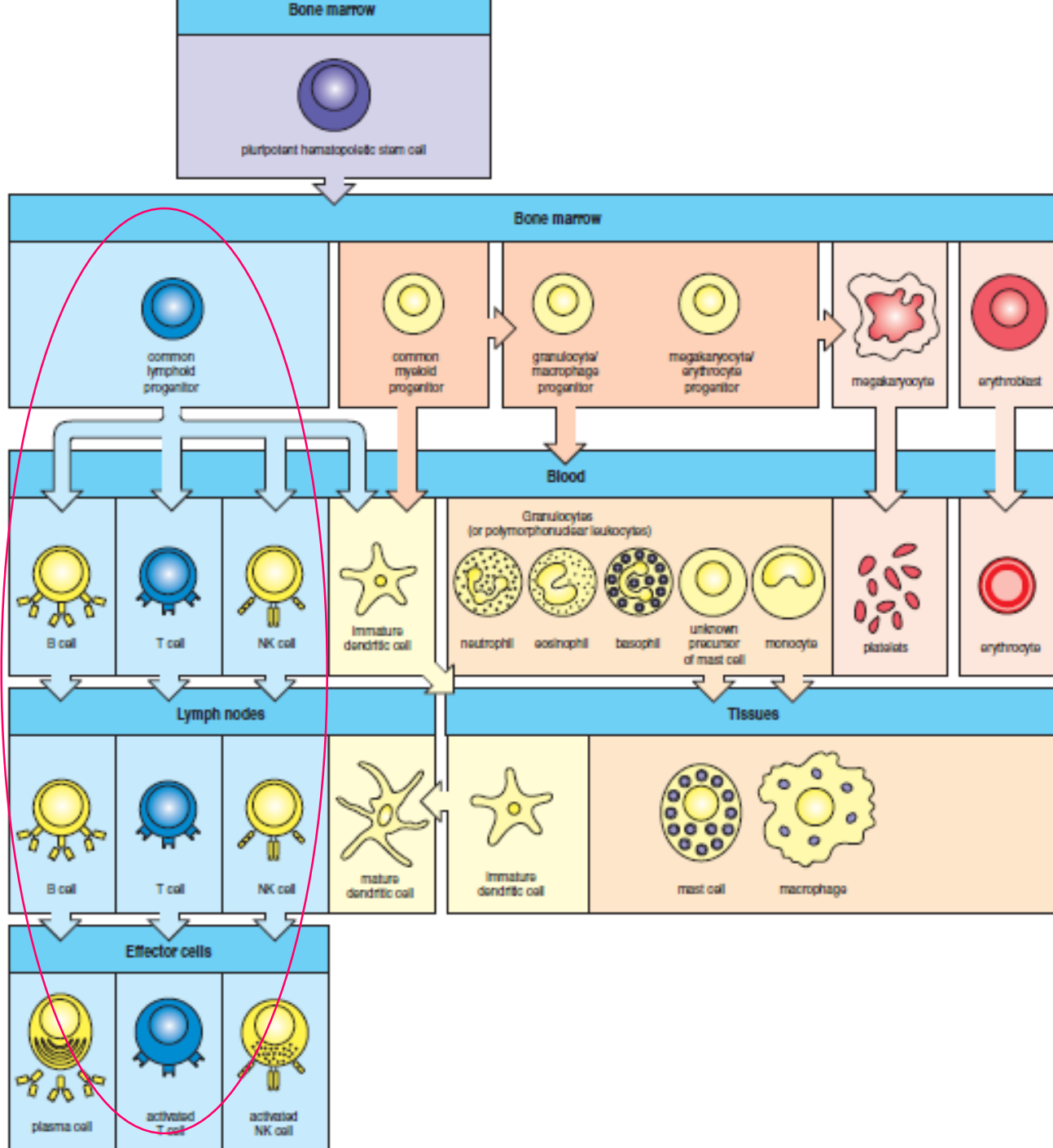
- ▶ Lymphocytes
- ▶ Lymphocyte subsets
- ▶ Antigen
- ▶ Structure & function of MHC
- ▶ Presentation of protein antigens through MHC

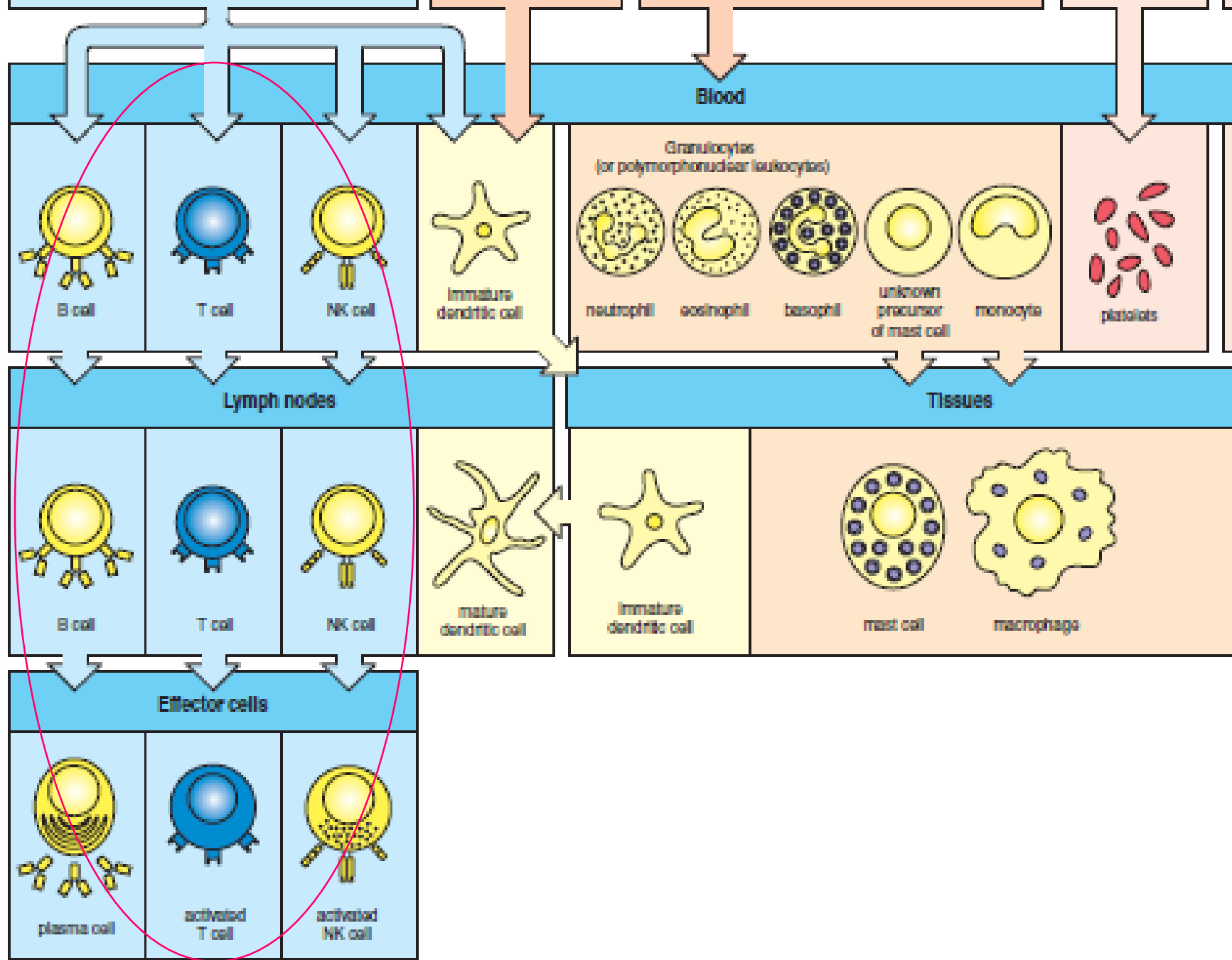
# Components of the IIS

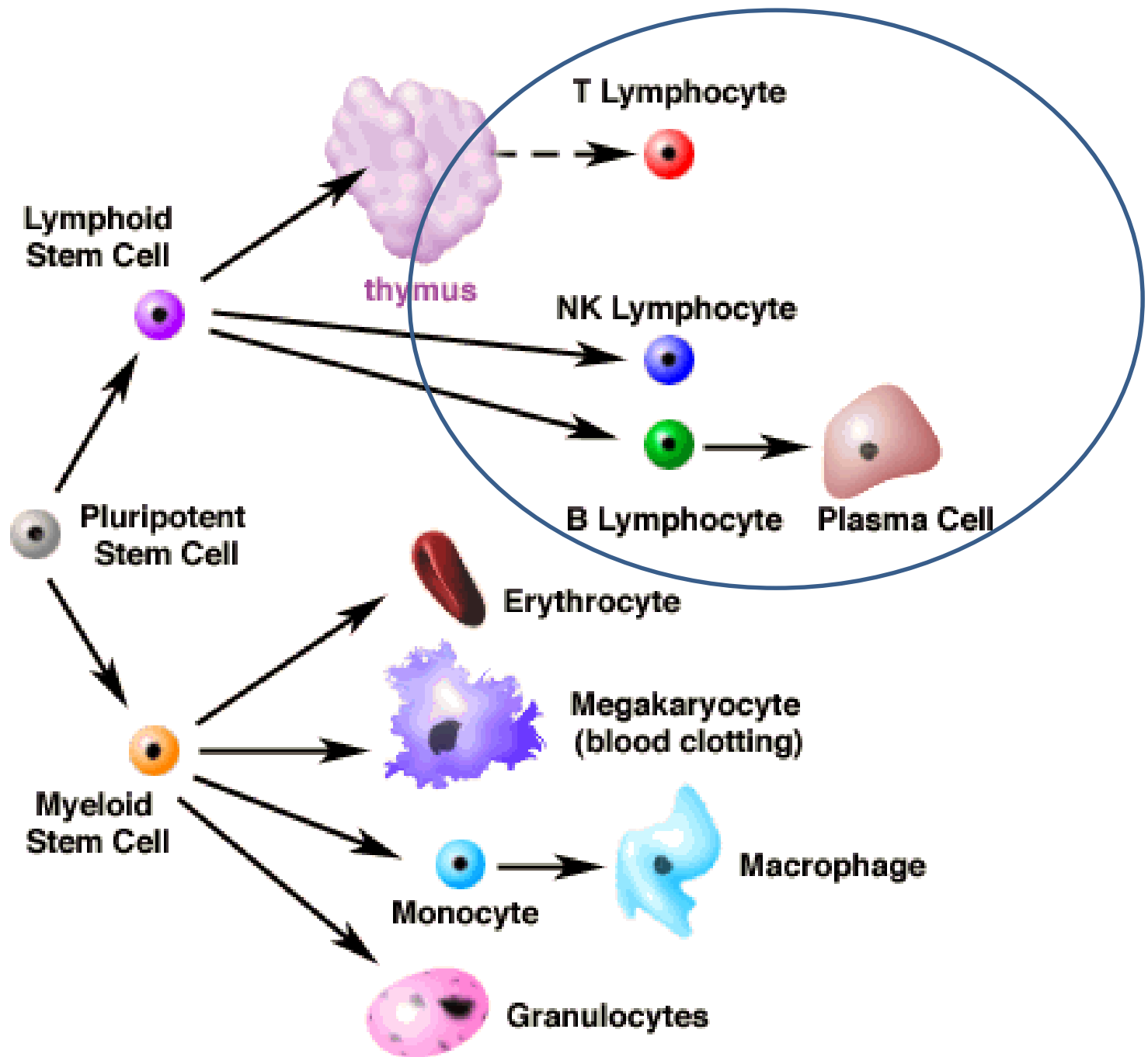
- Epithelia - barrier to infection
- Cells ( in circulation and tissues)
- Proteins
  - APP
  - Compliments

# Cells of the immune system

- ▶ Lymphocytes
- ▶ Antigen presenting cells (APC)
- ▶ Effector cells

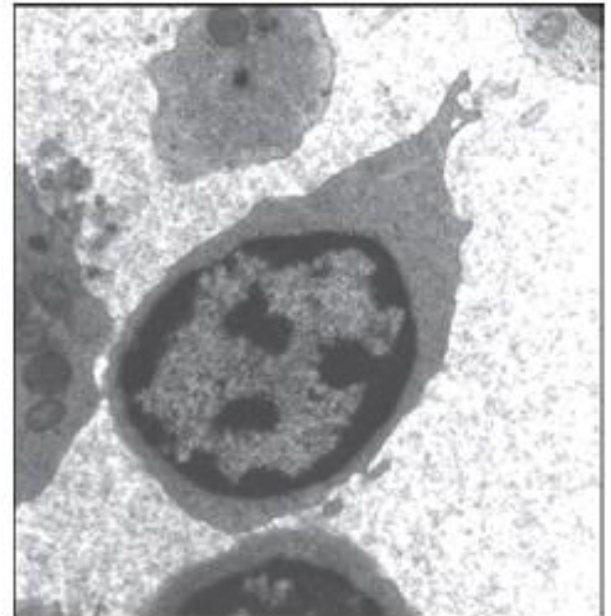
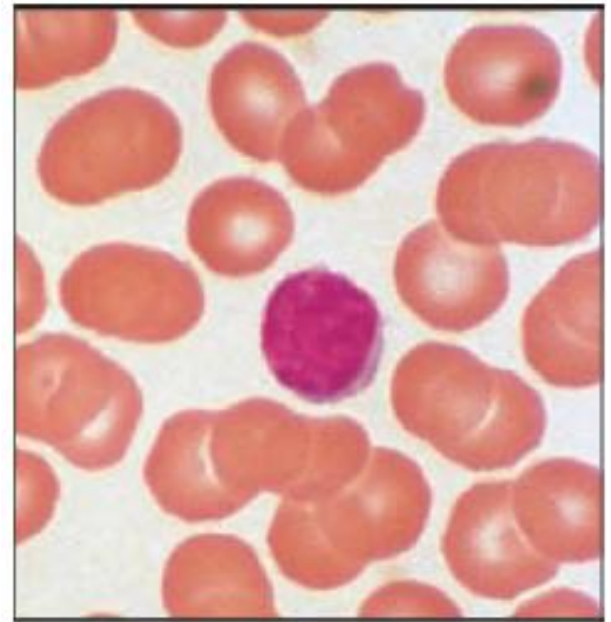






# Lymphocytes

- ▶ T lymphocyte
- ▶ B lymphocyte
- ▶ Natural Killer (NK) cells

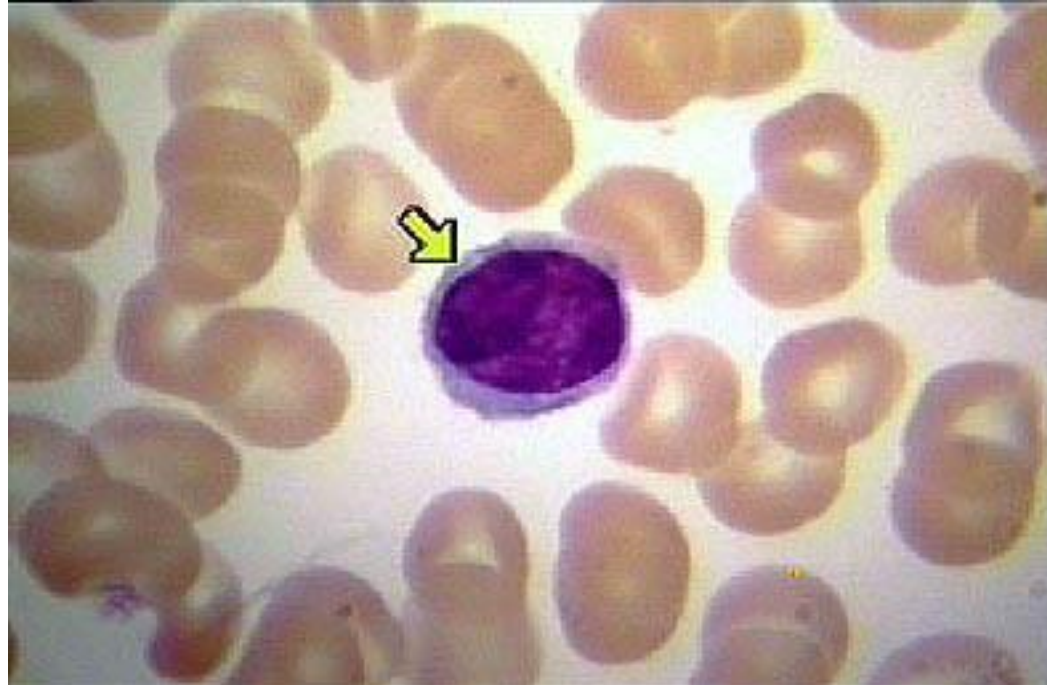


**Fig. 1.7** Lymphocytes are mostly small and inactive cells. The upper panel



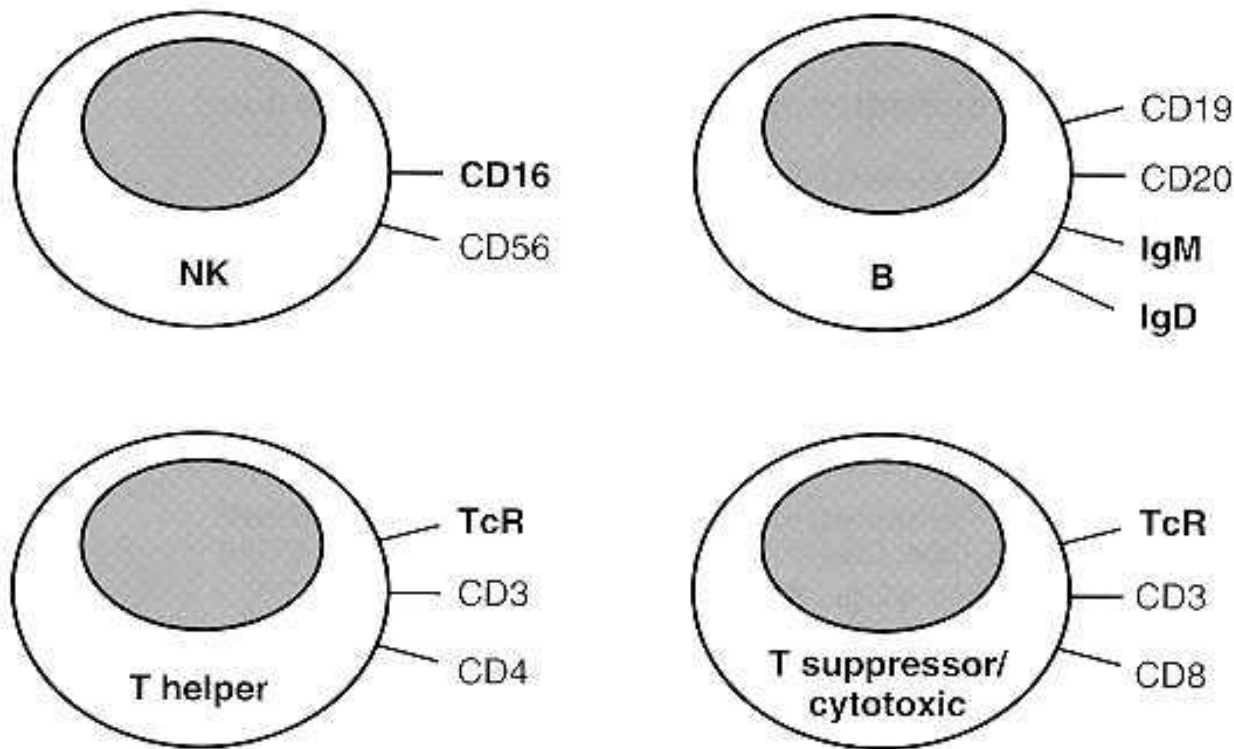
# Lymphocytes

- ▶ Key cell in adaptive immunity
- ▶ 20-40% of WBC in blood
- ▶ Extravasate - tissues - return in lymph
- ▶ little visible cytoplasm around their nucleus.



# Lymphocytes

- ▶ T and B lymphocytes - not distinguishable morphologically
- ▶ Different lineages - distinguish by **CD** molecules



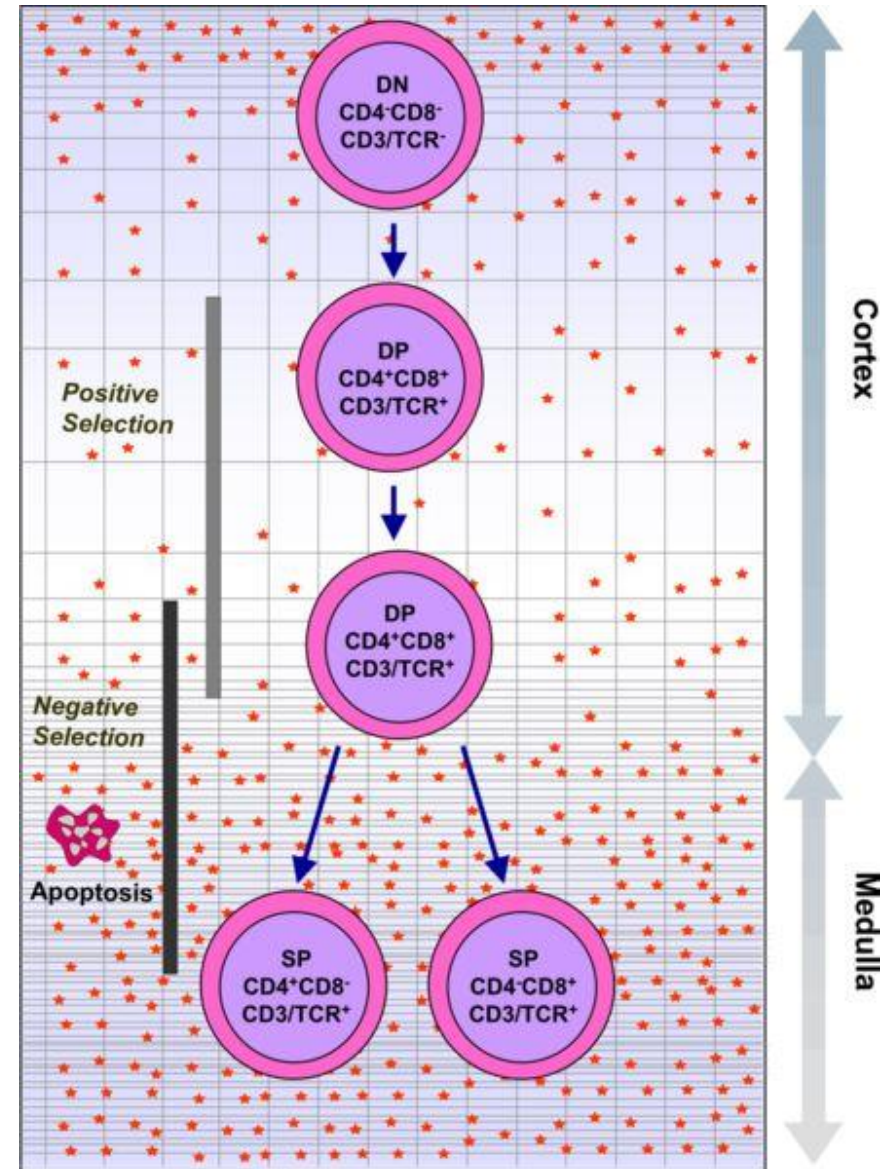
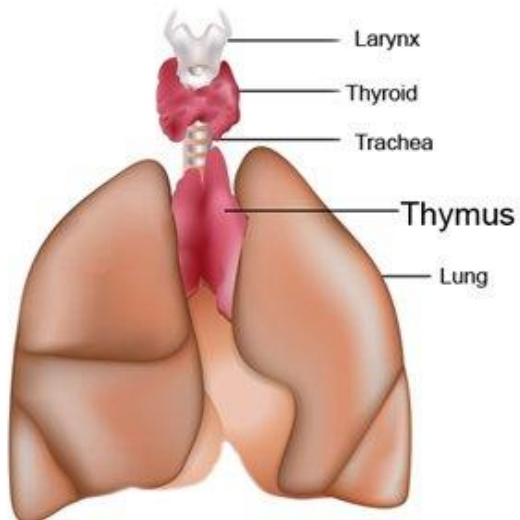
# Identifying Cell Using the CD Nomenclature

Over 300 CD markers

- ▶ T cells, CD4 or CD8 and CD3
- ▶ B cells, CD19
- ▶ NK cells, CD56
- ▶ Monocytes / Macrophages CD14
- ▶ Dendritic Cells, CD1c

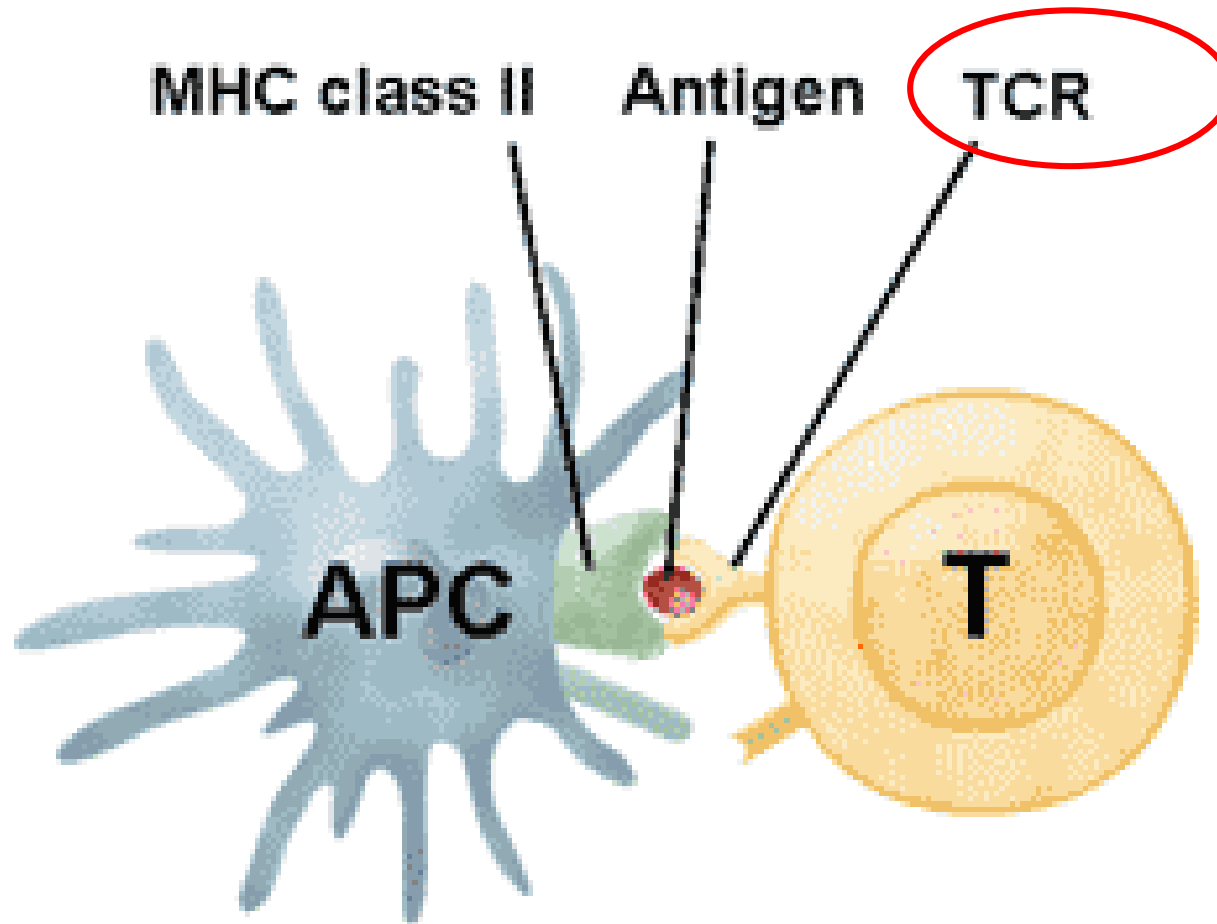
# T Lymphocytes

T cell maturation occur in thymus



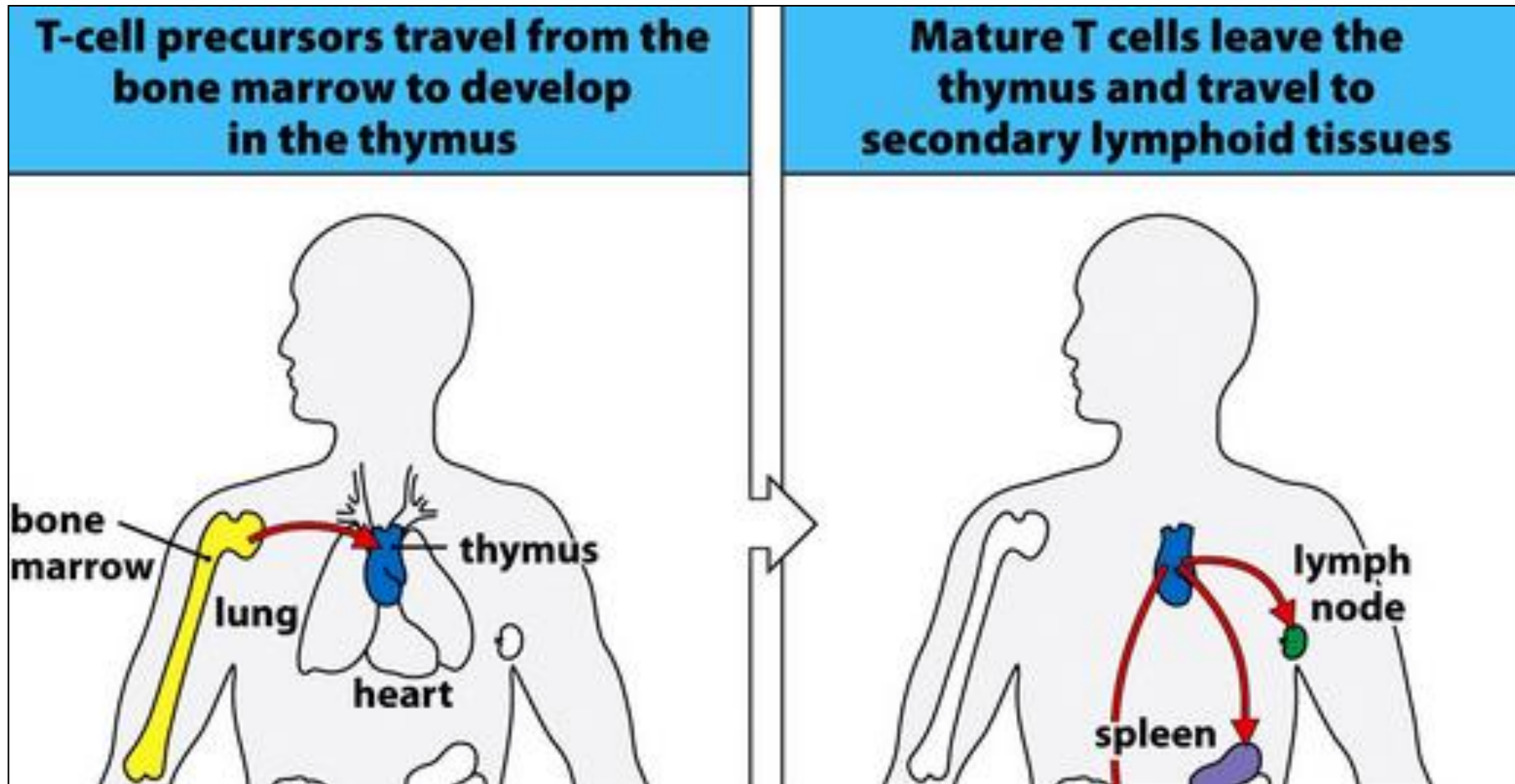
# T Lymphocytes

- During maturation T cells acquire T cell receptor (TCR)



# T Lymphocytes

- Mature T cells travel to secondary lymphoid tissues





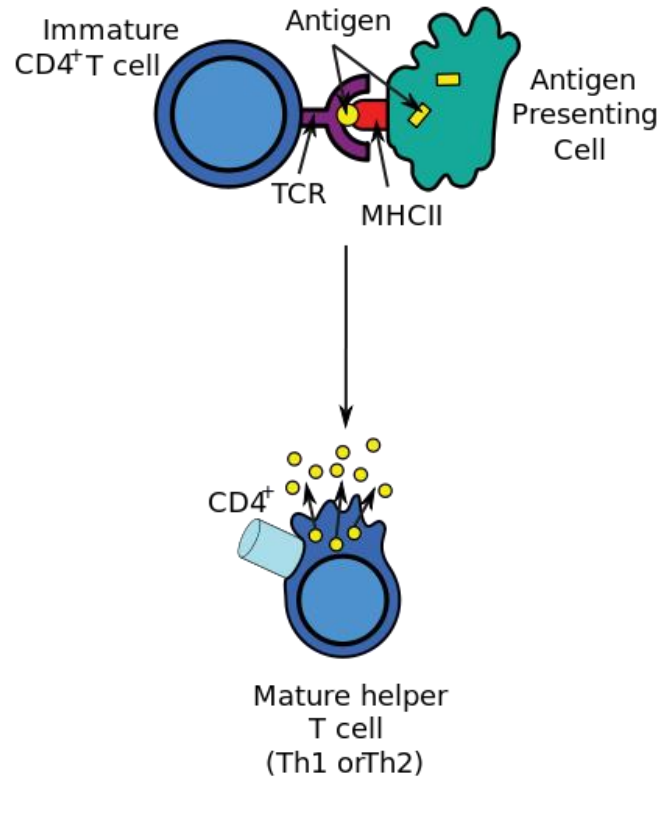
# T Lymphocytes

- Helper T cell (CD4+)

Th1

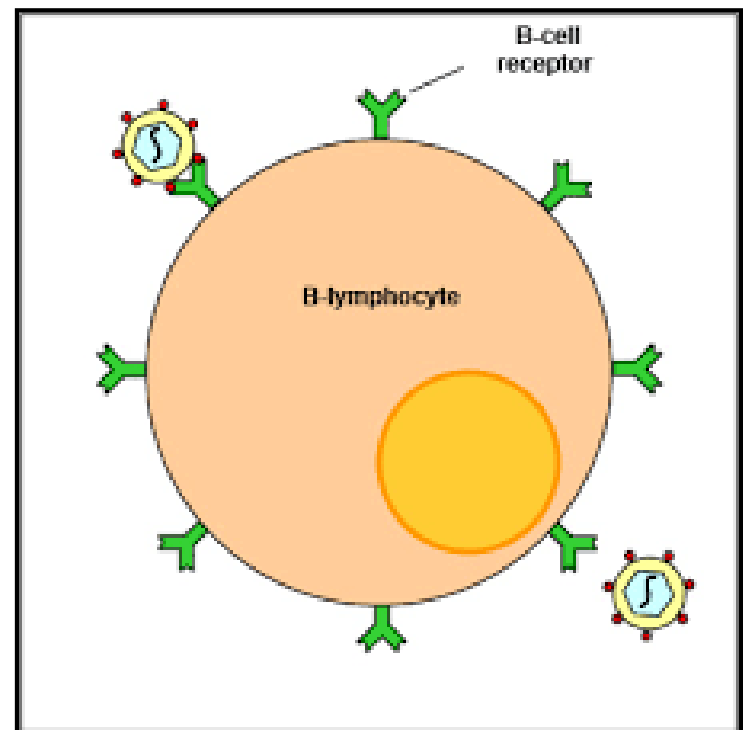
Th2

- Cytotoxic T cells (CD8+)

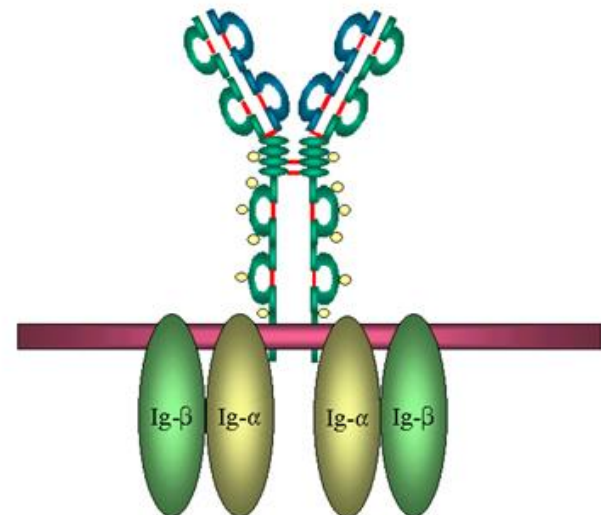


# B lymphocytes

- Mature in BM
- Major function - production of antibodies
- B cell - has receptor (BCR) membrane form of antibodies

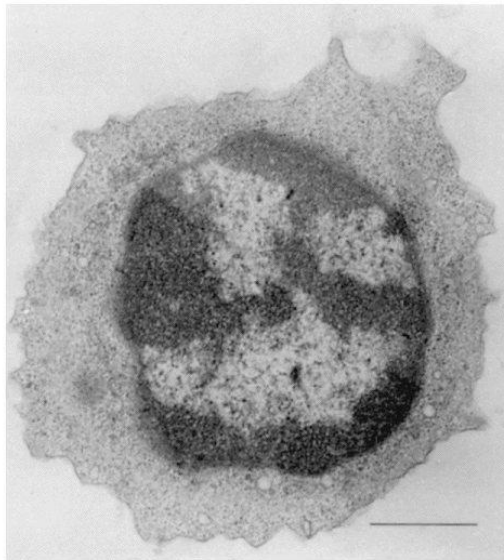


B Cell Antigen Receptor (BcR)





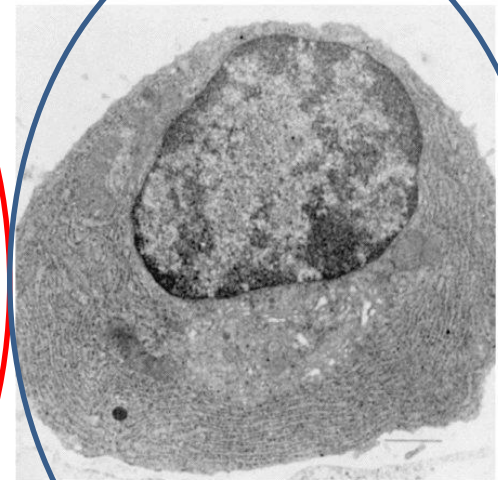
- ▶ Once stimulated with antigen, lymphocyte enlarges ( $15\mu\text{m}$ ) into a blast cell.
- ▶ Lymphoblasts further differentiate into effector cells (plasma cell) or memory cells.



Small lymphocyte (T or B)  
6  $\mu\text{m}$  diameter



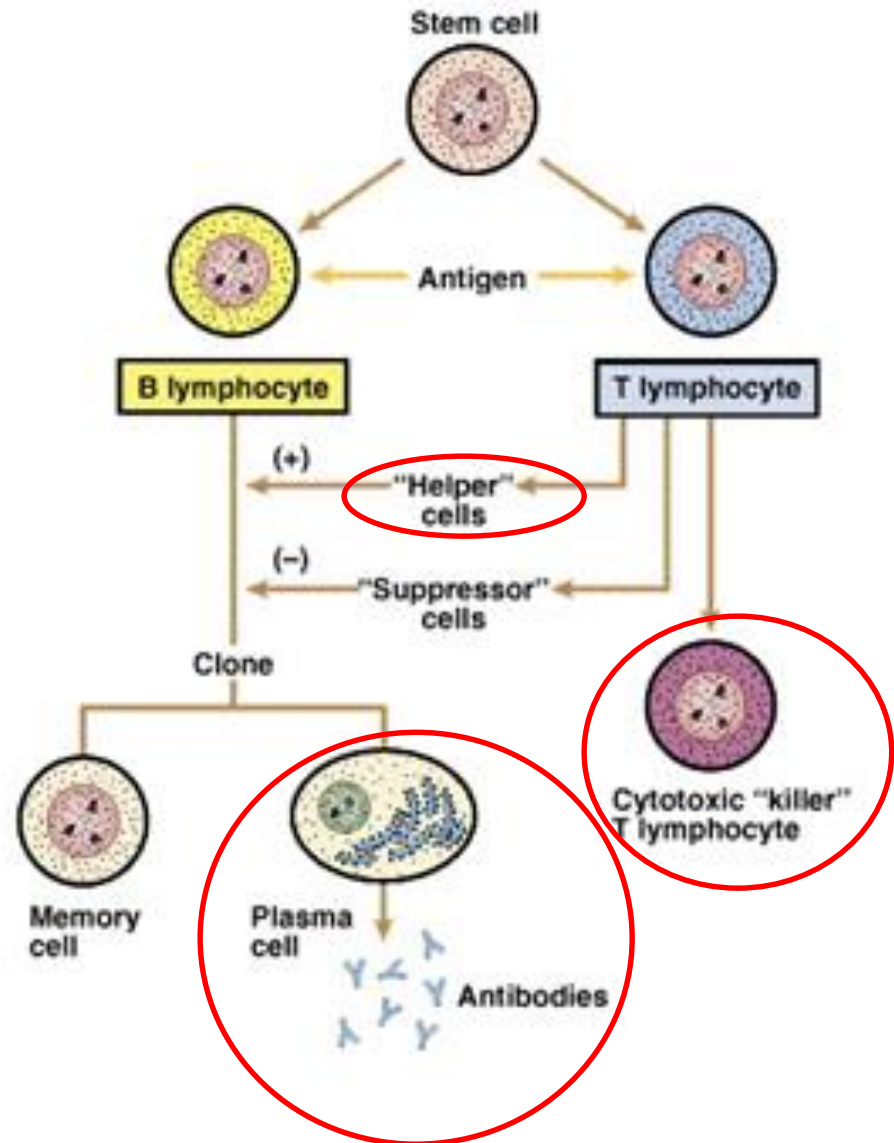
Blast cell (T or B)  
15  $\mu\text{m}$  diameter



Plasma cell (B)  
15  $\mu\text{m}$  diameter

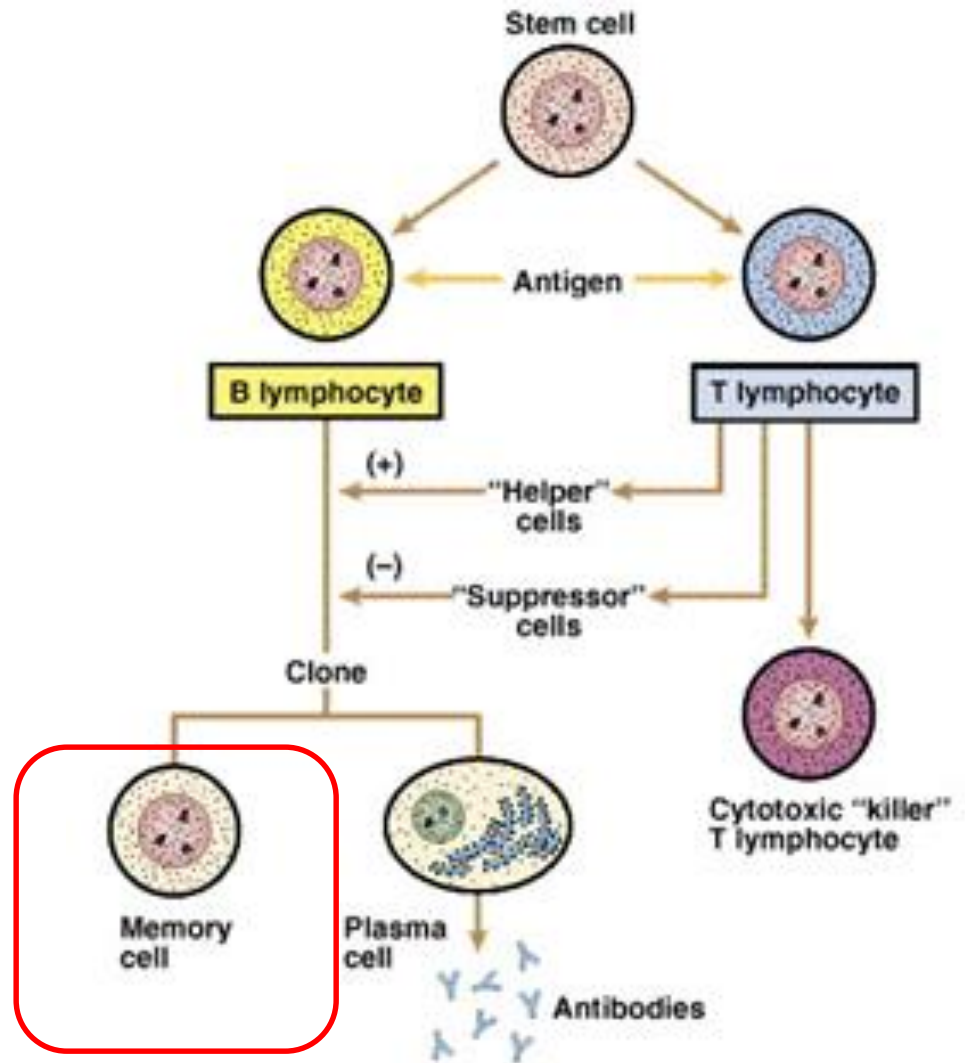
# Effector cells

- ▶ Functionally active
- ▶ Effector B cell - Antibody secreting cell - plasma cell
- ▶ Effector CD4 T cell (helper cell) - produce cytokines - help antibody production
- ▶ Effector CD8 T cell - kill infected host cell



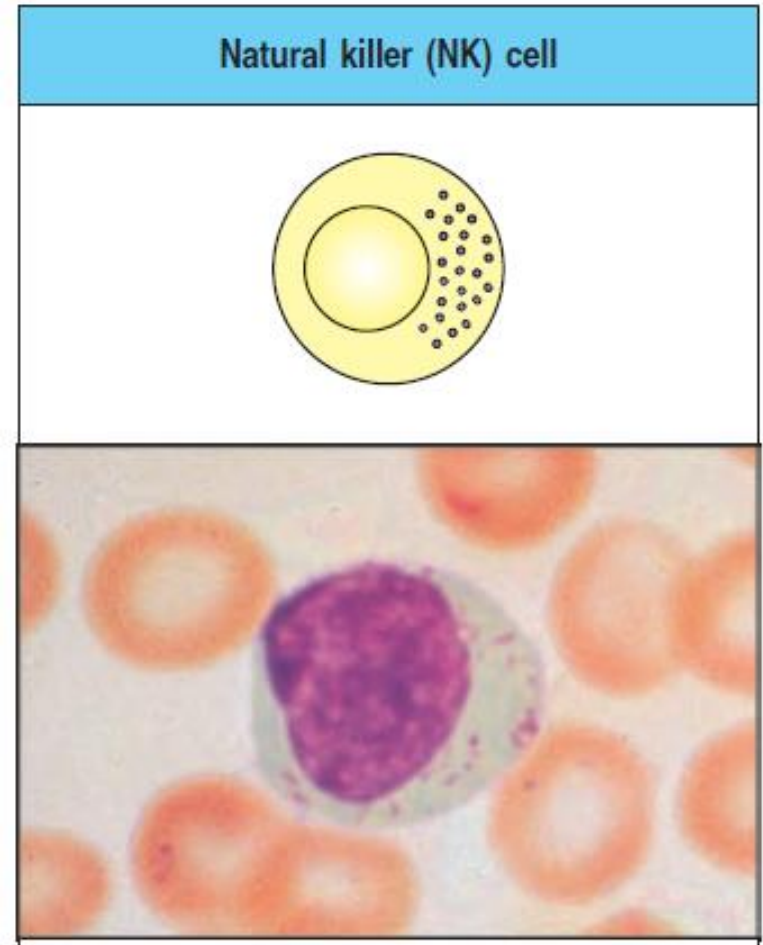
# Memory cells

- Long-lived cells
- Functionally inactive
- When encounter same antigen - start development



# NK cells

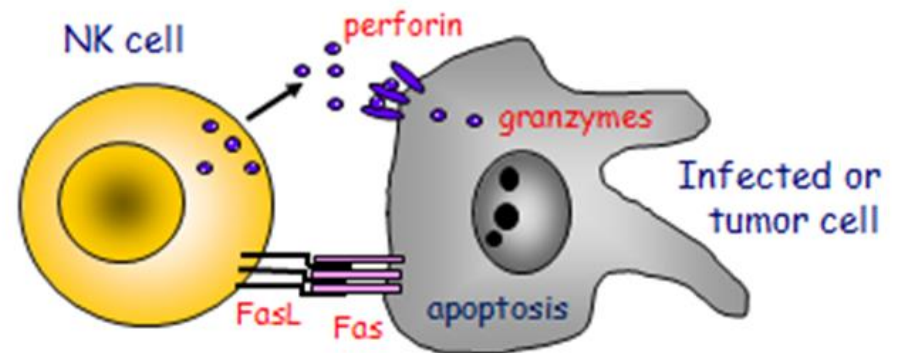
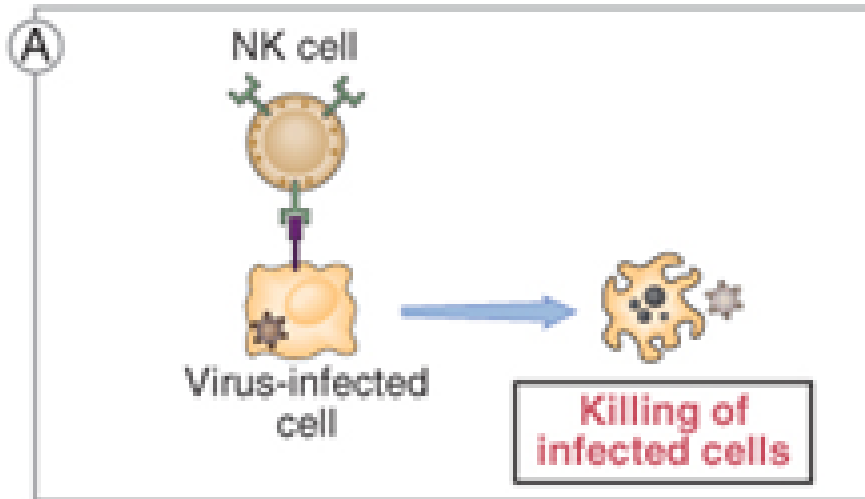
- Do Not express classical lymphocyte markers
- CD marker - CD56
- Role -
  - Eliminate tumor cells and virally infected cells
  - Activation of macrophages
  - Antibody Dependent Cell Cytotoxicity (ADCC)



# Role of NK cells in innate immunity

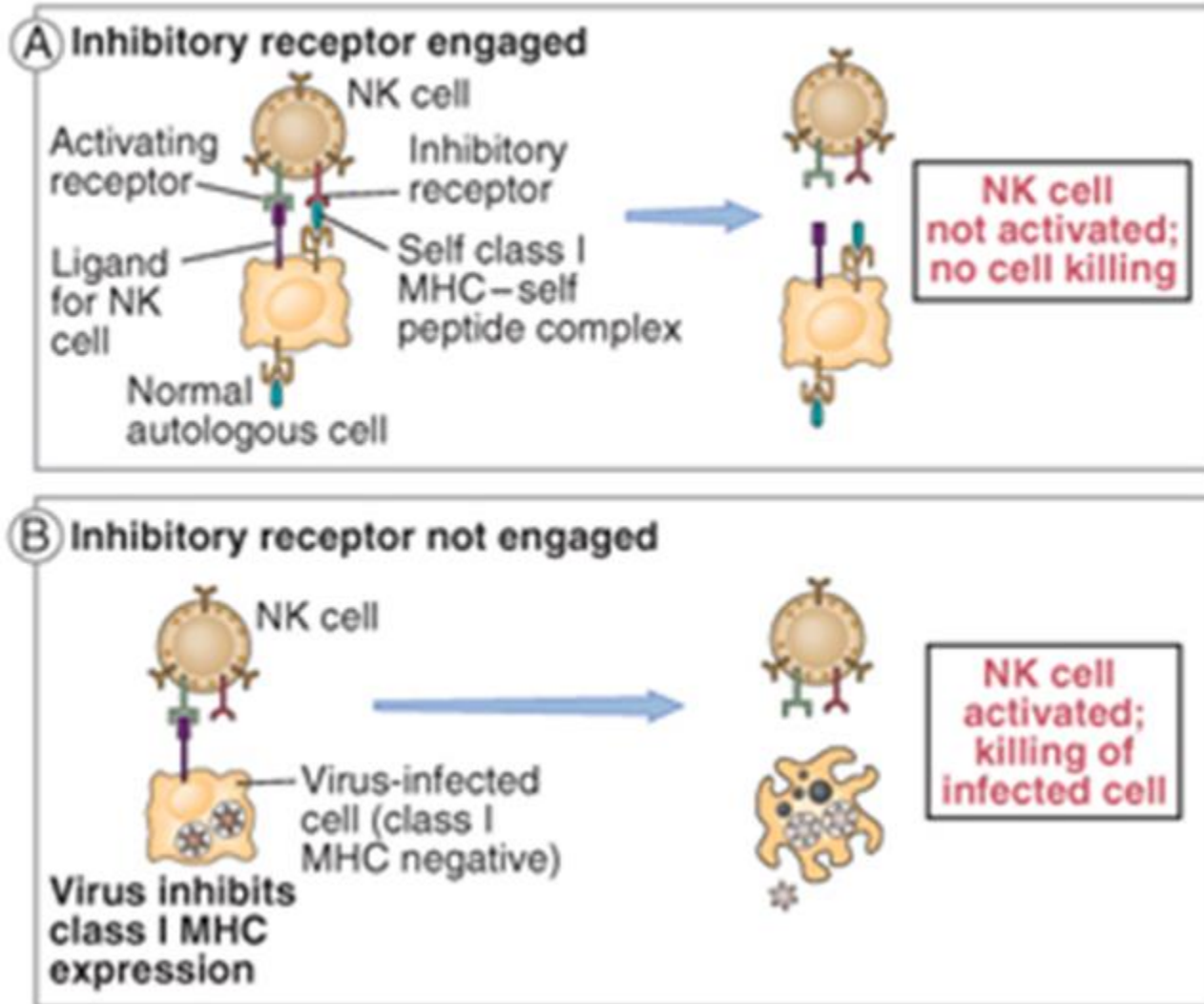
NK - Natural killer

Killing of cells infected by  
intracellular pathogens  
(eg. viruses) and  
tumor cells



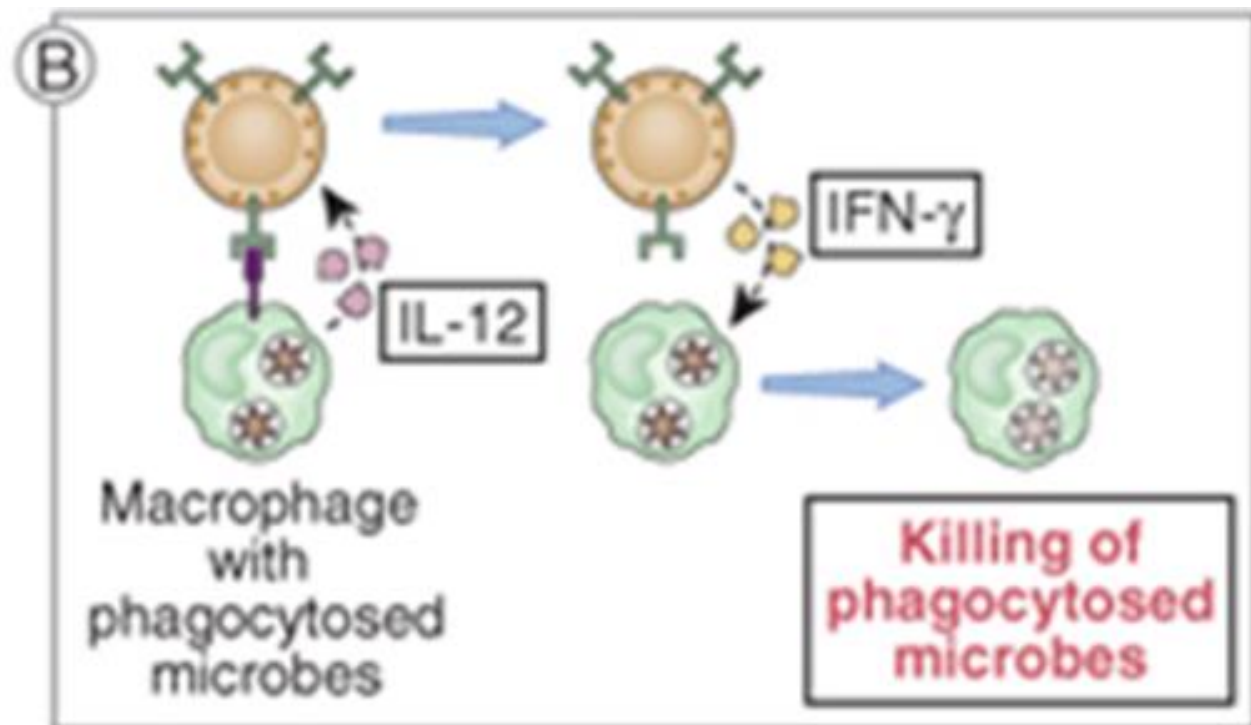
# How does NK cell kill?

## Mechanism of NK cell recognition



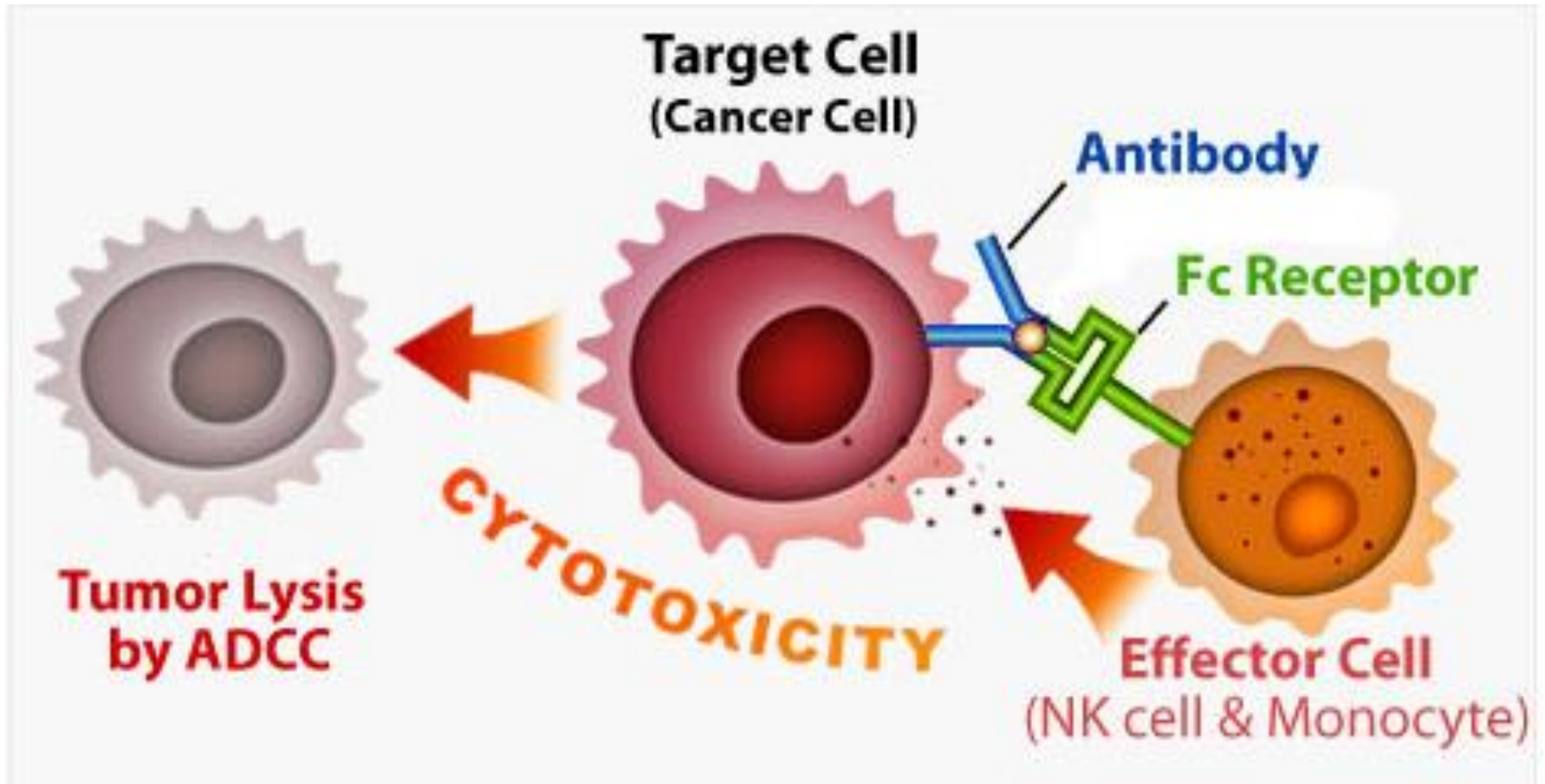


## Role of NK cells in innate immunity



Activation of  
macrophages (by IFN- $\gamma$ )

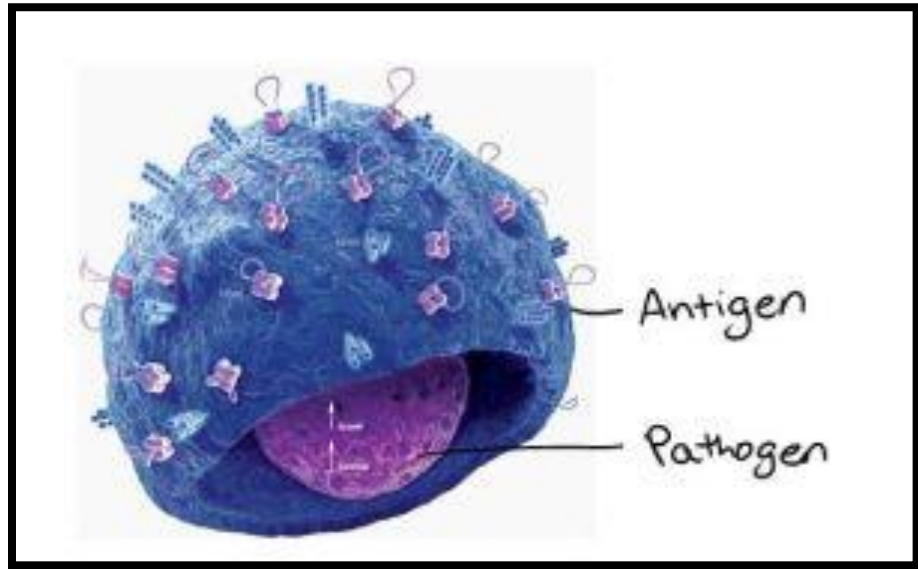
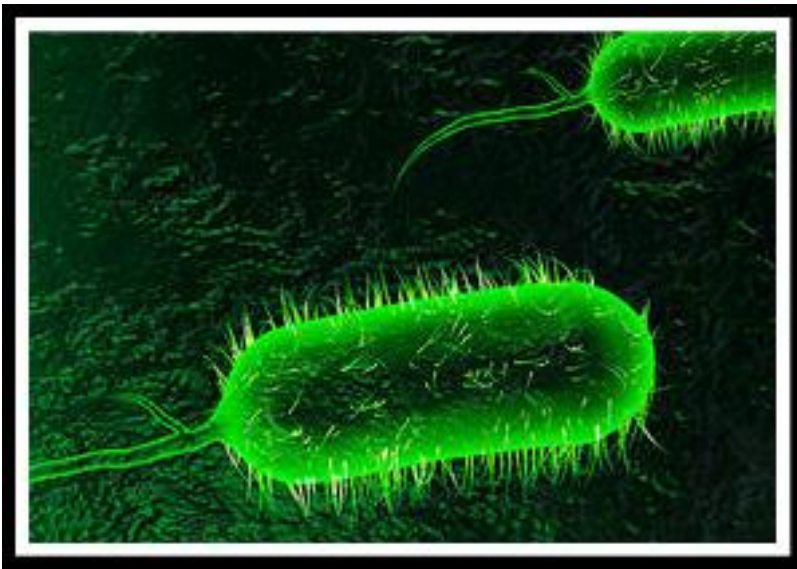
# Antibody Dependent Cell Cytotoxicity (ADCC)





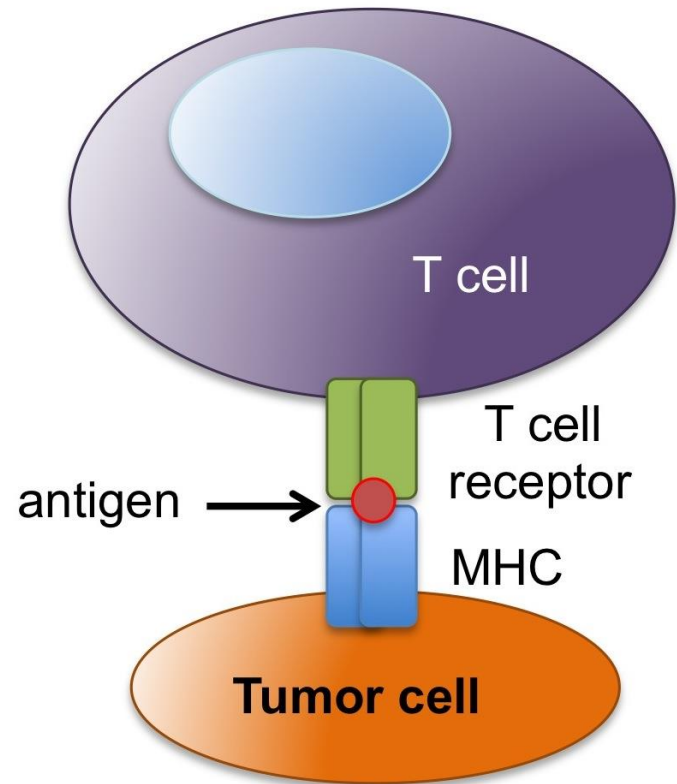
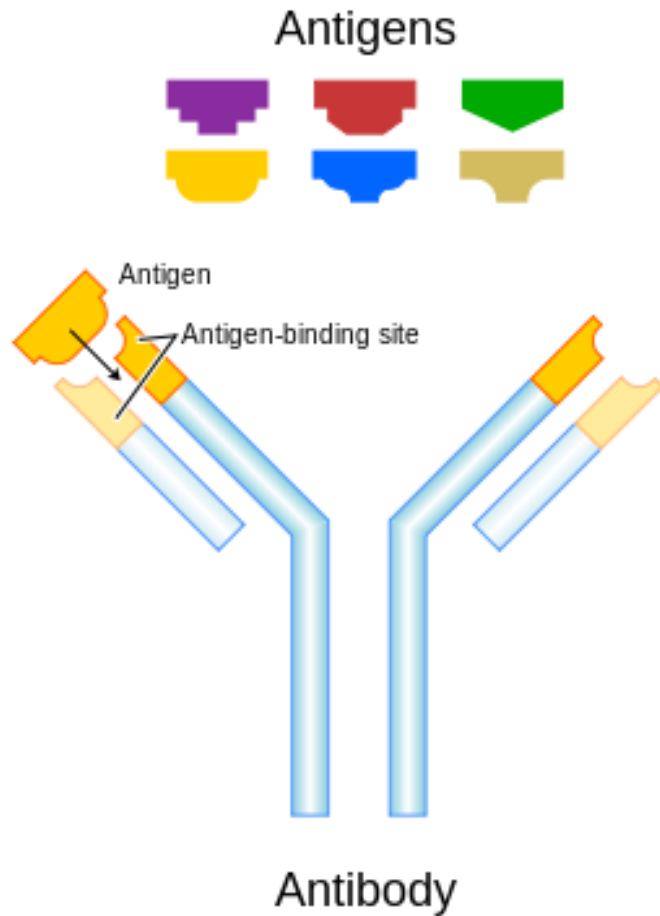
# Antigen

- All cells have antigens as a part of membrane / cell wall
- Can be protein, glycoprotein, lipoprotein or polysaccharide



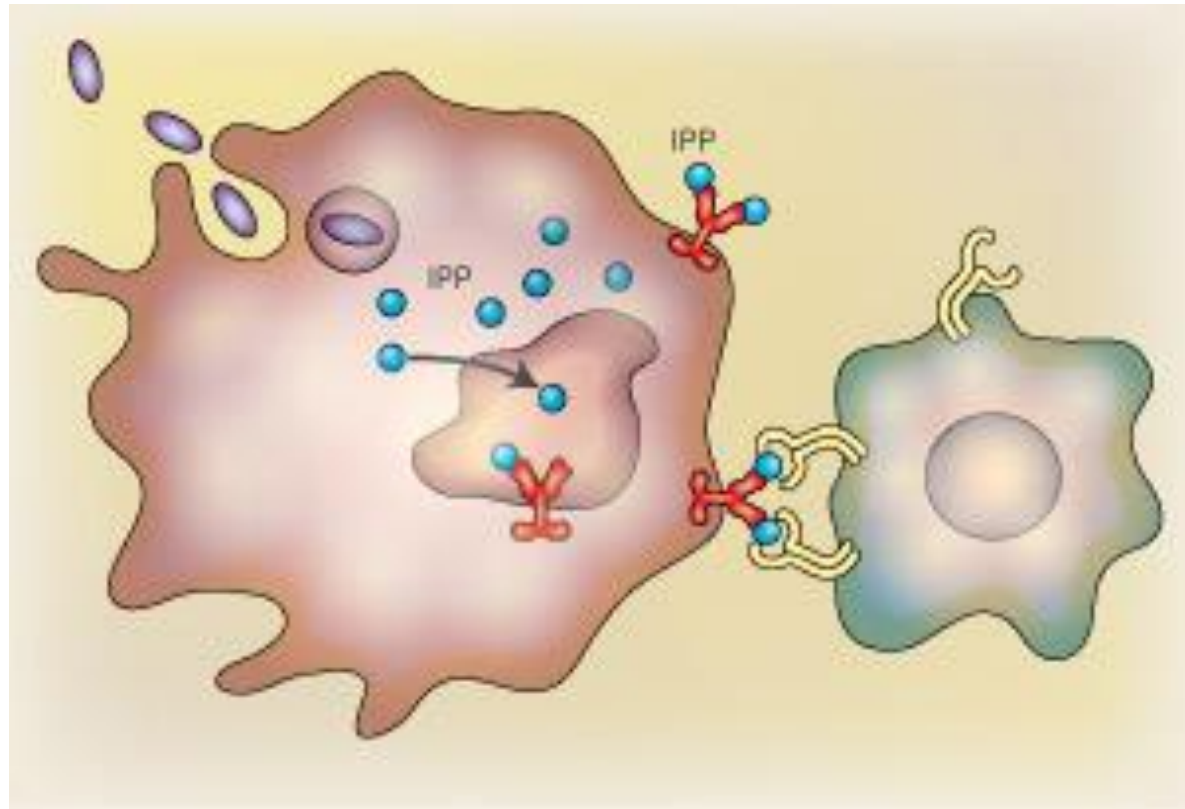
# Antigen.....

- A molecule that bind to an antibody or a TCR



# Antigen.....

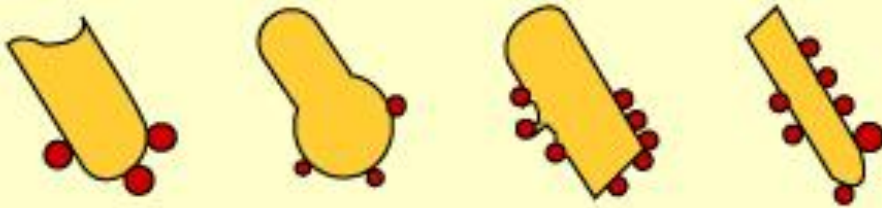
- Recognize by immune system- trigger immune response



# Antigen.....

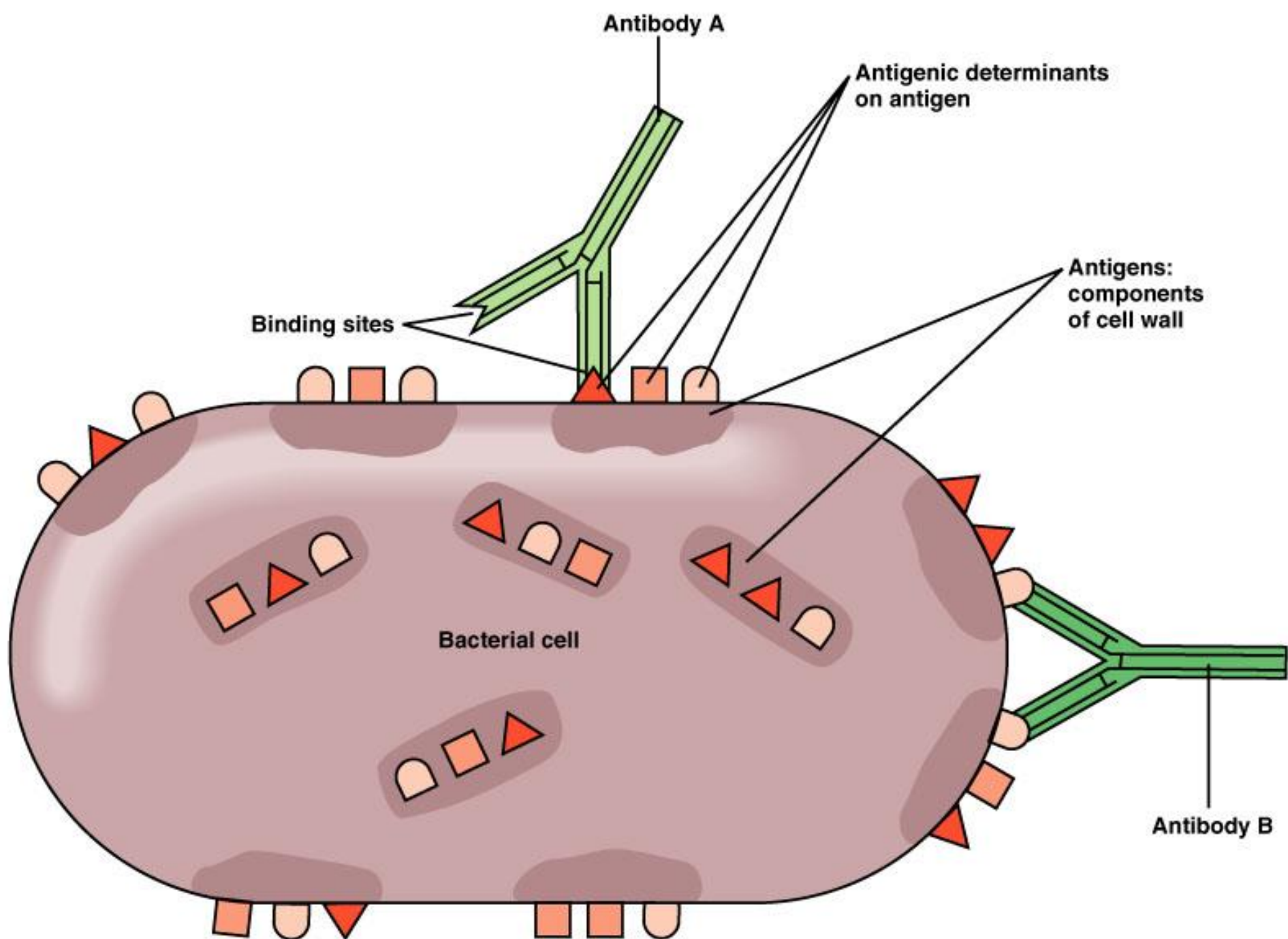
- Cells from different individuals have different antigens

Antigen



Antibody



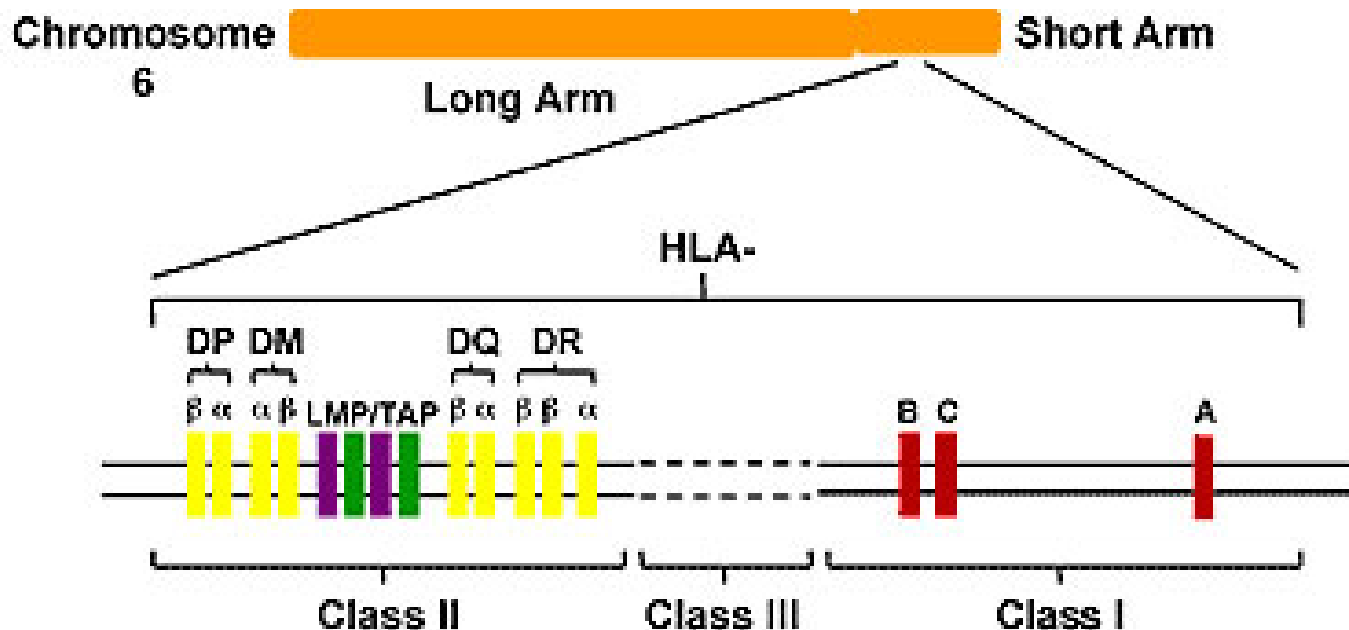


# Antigen.....

- Antigens are genetically controlled

# Major histocompatibility complex (MHC)

- ▶ A large genetic locus (on chromosome 6 of human genome) that include highly polymeric genes encoding the peptide binding molecules recognized by T lymphocytes



# MHC

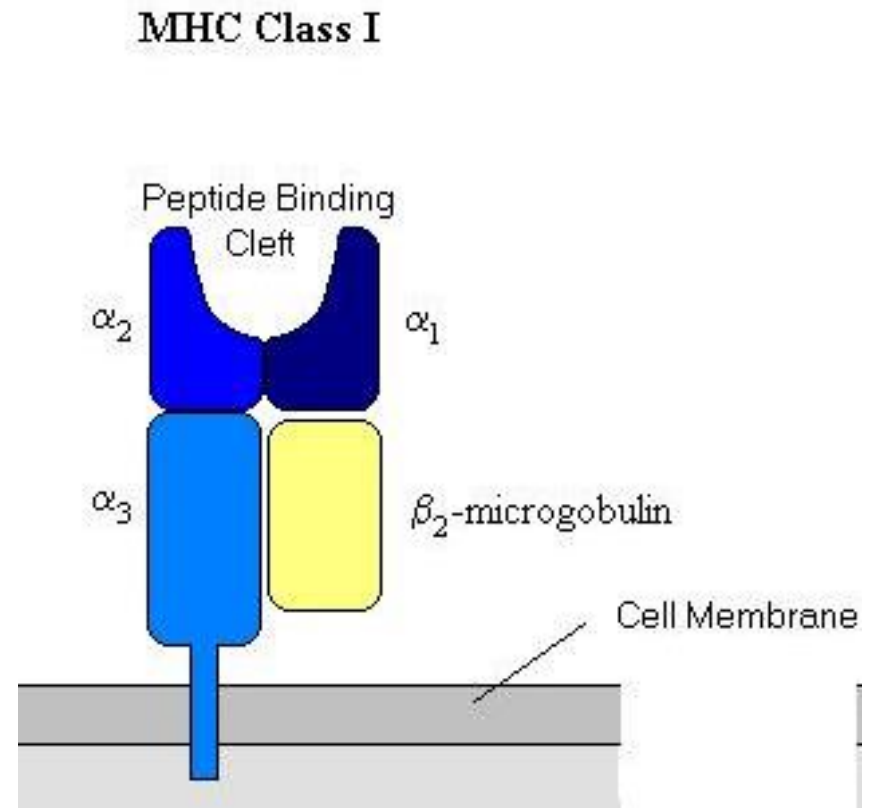
- Human MHC proteins are called human leucocyte antigens (HLA)
- Physiological function of MHC molecules is to display peptides derived from protein antigens to antigen specific T cells



# Major histocompatibility complex molecule

A membrane protein encoded by MHC locus that serves as a peptide display molecule for recognition by T cells.

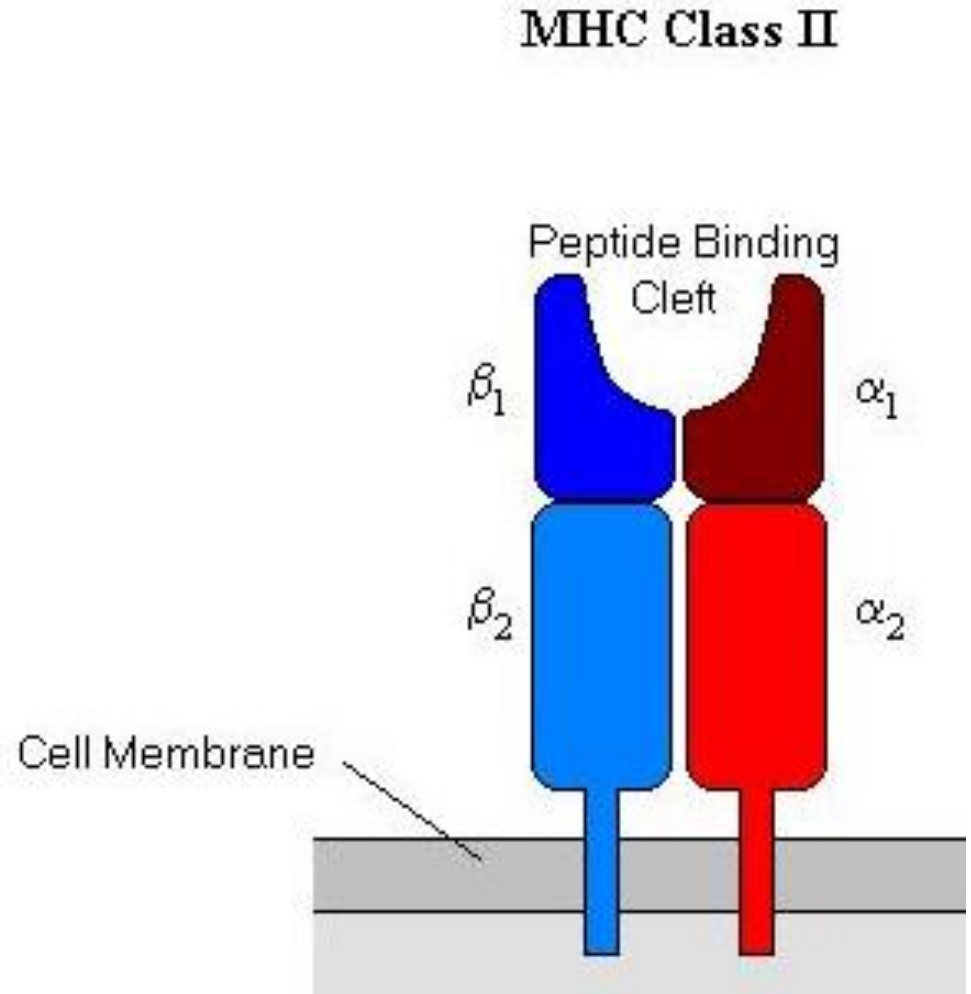
- Class 1 MHC -present on nucleated cells
- recognized by CD 8<sup>+</sup> T cells



# Major histocompatibility complex molecule

## Class II MHC -

- present on professional APC, MQ, B cells
- recognize by CD 4<sup>+</sup> T cells



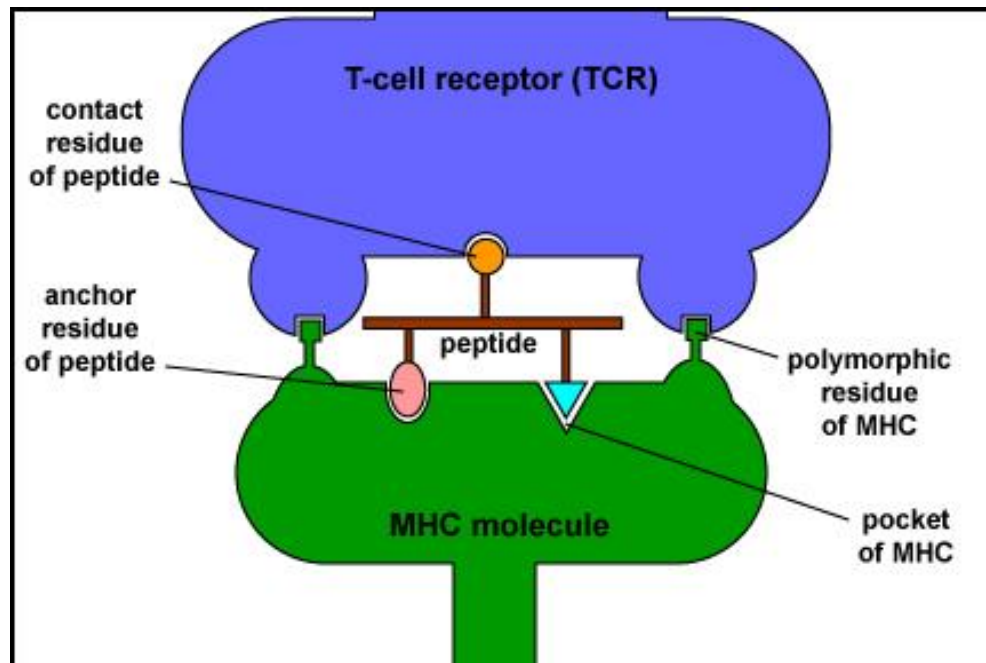
## Expression of MHC class I & II molecules

Tissue	MHC class I	MHC class II
T cells	+++	-
B cells	+++	++
Macrophages	+++	+++
Dendritic cells	+++	+++
Neutrophils	+++	-
Hepatocytes	+	-
Kidney	++	-
Brain	+	-
RBC	-	-

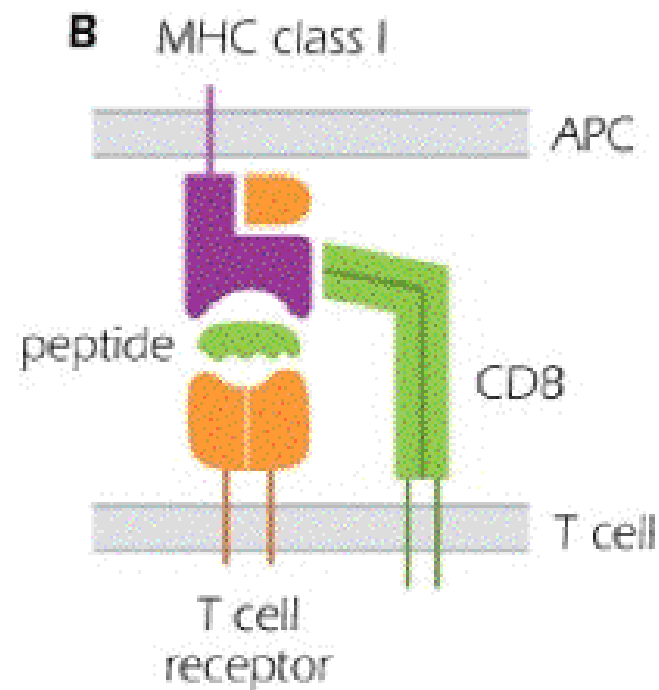
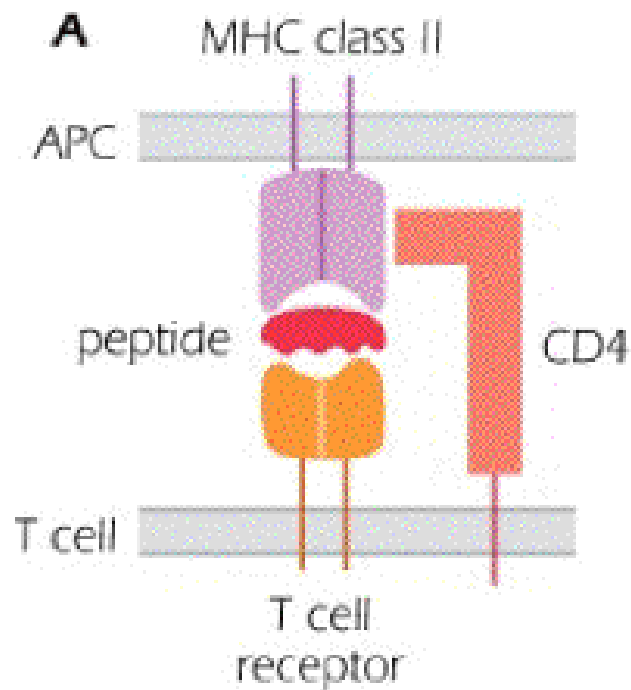
# MHC molecules

## How does it connect with TCR?

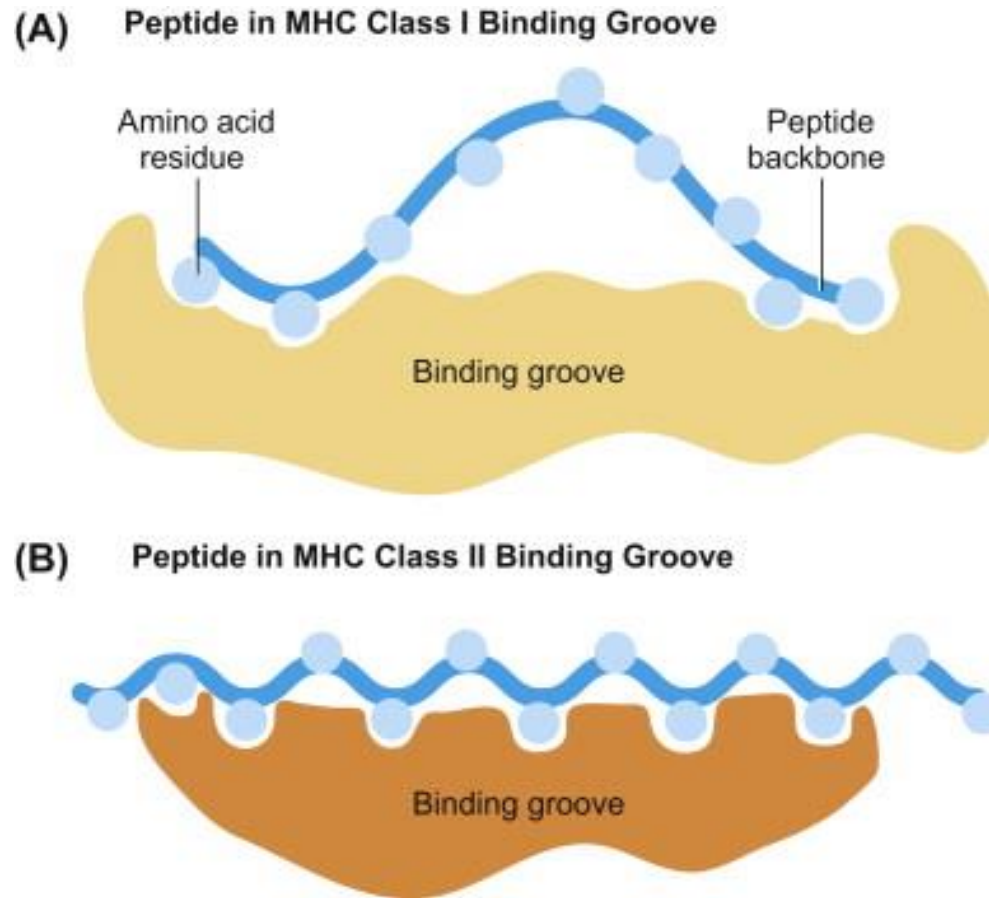
- ▶ Class I and class II MHC molecules contain peptide binding cleft (PBC)
- ▶ Flow of the PBC binds peptide and display to T cells
- ▶ Side and the top of the cleft bind with T cell receptor



- ▶ Only the class I MHC molecule has co-receptor for CD 8 T cell, so MHC I bound peptides are only identified by CD8 T cells
- ▶ MHC II has co- receptor to bind with CD4 T cells. So, CD4 T cells can only respond to MHC II bound peptides



- ▶ MHC molecules bind only peptides and not other types of antigens



- ▶ Each MHC molecule can present only one peptide at a time but each MHC molecule can present many different peptides

# Capture of protein Ags by APCs

- Microbes usually enter to body through,
  - Skin ( contact)
  - Gastrointestinal tract ( by ingestion)
  - RT ( inhalation)

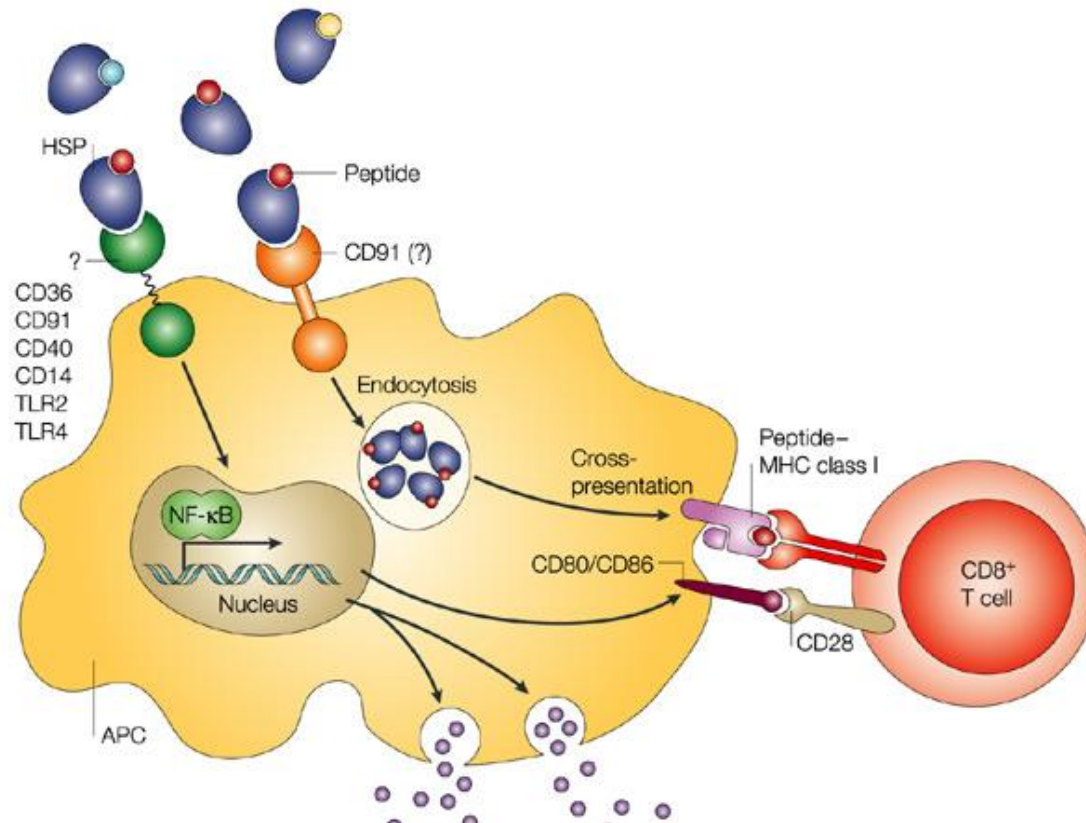
# Capture of protein Ags by APCs

- ▶ Protein antigen of microbes that enter the body are captured mainly by dendritic cells concentrated in peripheral lymphoid organs, where immune responses are initiated.



# Antigen presentation

- The display of peptides bound by MHC



# Processing of internalized antigens for display by class II MHC

Uptake of extracellular proteins into vesicular compartment of APC



Processing of internalized proteins in endosomal / lysosomal vesicles



Biosynthesis and transport of MHC II molecules to endosomes



Association of processed peptides with class II molecules in vesicles



Expression of peptide - MHC complexes on cell surface

# Processing of cytosolic antigens for display by class I MHC

Production of proteins in the cytosole ( eg by viruses)



Proteolytic degradation of cytosolic proteins



Transport of peptides from cytosole to ER with the aid of TAP (Transporter associated with antigen processing)



Assembly of peptide - class MHC I complexes in ER



Surface expression of peptide - class I complexes

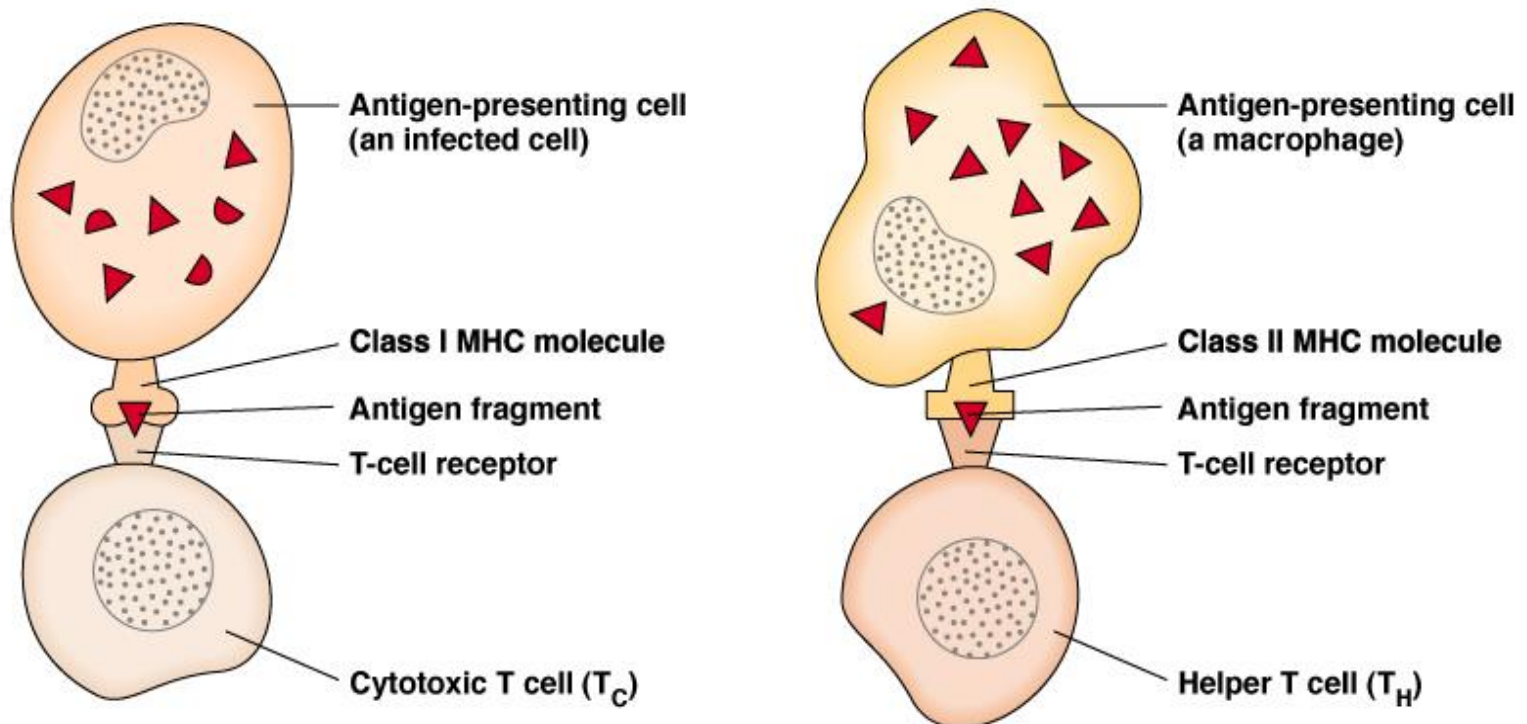
# Antigen Presenting Cells

## The physiologic significance of MHC associated Ag presentation

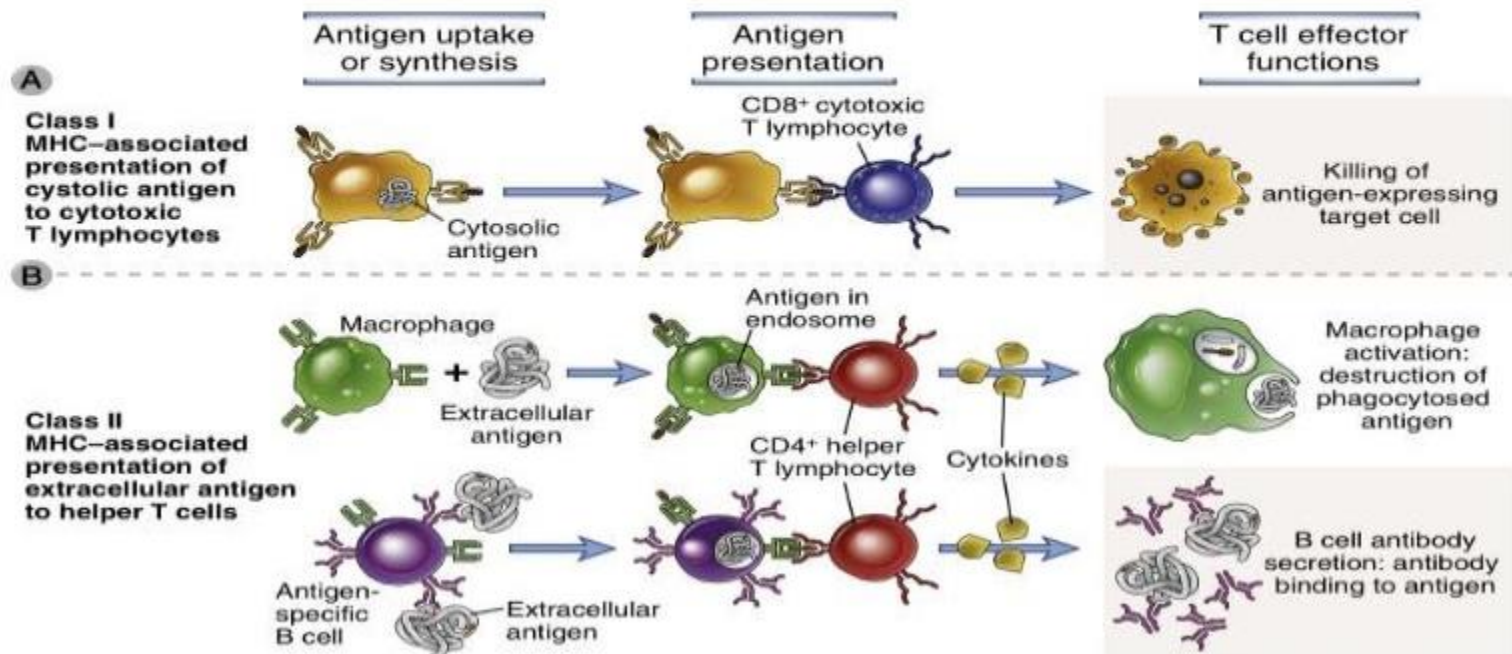
- The restriction of T cell recognition to MHC associated peptides ensure that T cells see and respond only to cell associated antigens

# The physiologic significance of MHC associated Ag presentation

- By segregating class I and class II pathways of antigen processing, the immune system is able to respond to intracellular and extracellular microbes in different ways



# Physiologic Significance of MHC-associated Antigen Presentation



**FIGURE 6-21 Presentation of extracellular and cytosolic antigens to different subsets of T cells.** **A**, Cytosolic antigens are presented by nucleated cells to CD8<sup>+</sup> CTLs, which kill (lyse) the antigen-expressing cells. **B**, Extracellular antigens are presented by macrophages or B lymphocytes to CD4<sup>+</sup> helper T lymphocytes, which activate the macrophages or B cells and eliminate the extracellular antigens.



# Summary

MHC I	MHC II
Composed of an $\alpha$ (or heavy) chain in a non-covalent complex with a $\beta$ 2-microglobulin	Contain two MHC-encoded polymorphic chains, an $\alpha$ chain and a $\beta$ chain.
Recognized by CD8+ T cells	Recognized by CD4+ T cells
Accommodate peptides that are 6 to 16 amino acid residues in length	Allows larger peptides (up to 30 amino acid residues in length or more) to bind
Expressed on all nucleated cells	Expressed mainly on specialized APCs
Cytosolic proteins are proteolytically degraded in the proteasome	Extracellular proteins are internalized into endosomes