

# IMMUNOPATHOLOGY-I

# COMPETENCIES

- 9.1- Principles and Mechanisms involved in Immunity
- 9.2- Describe the mechanism of Hypersensitivity reactions
- 9.3- HLA system . Principles and mechanisms involved in transplantation and transplant rejection reaction.
- 9.4 Define autoimmunity. Enumerate autoimmune disorders
- 9.5 Define and describe pathogenesis of SLE
- 9.6 Define and describe pathogenesis of HIV and AIDS
- 9.7 Define and describe pathogenesis of common autoimmune disorders.

# **PA 9.1 - DESCRIBE THE PRINCIPLES AND MECHANISMS INVOLVED IN IMMUNITY**

## **TLM : SGD/Lecture – 1 hr**

9.1.1. Define innate immunity.

9.1.2. Describe the components and mechanism of innate immunity.

9.1.3. Define and enumerate the types of Adaptive immunity.

9.1.4. Describe the cells of the immune system and their role in immunity.

9.1.5. Describe the mechanism of humoral immunity.

9.1.6. Describe the mechanism of cell mediated immunity.

# IMMUNE SYSTEM-DOUBLE EDGED SWORD

- Normal defense mechanism
- Protects the body from infection and invasion by foreign substances
- To an extent has a limited role in fighting cancer cells

In-appropriate immune response-

TOO LESS  
TOO MUCH

# IMMUNE SYSTEM DERANGEMENTS

- Hypersensitivity
- Transplant rejection
- Autoimmunity
- Immunodeficiency

# THERE ARE 2 KINDS OF IMMUNITY:

INNATE

ADAPTIVE

CMI

HUMORAL

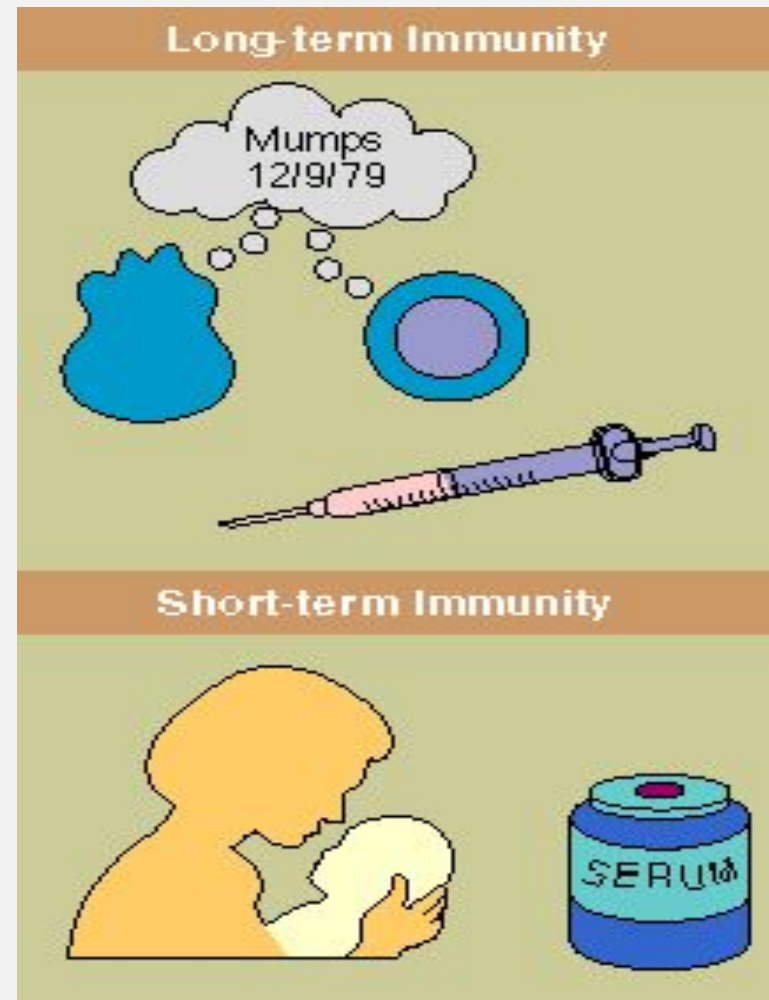
# ARTIFICIALLY ACQUIRED IMMUNITY

## LONG TERM:VACCINES

- giving a safe form of the antigen artificially causes the body to produce its own antibodies and develop memory cells

## SHORT TERM:ANTIBODY

- injecting antibody-containing serum or the injection of monoclonal antibodies



# IMMUNE SYSTEM

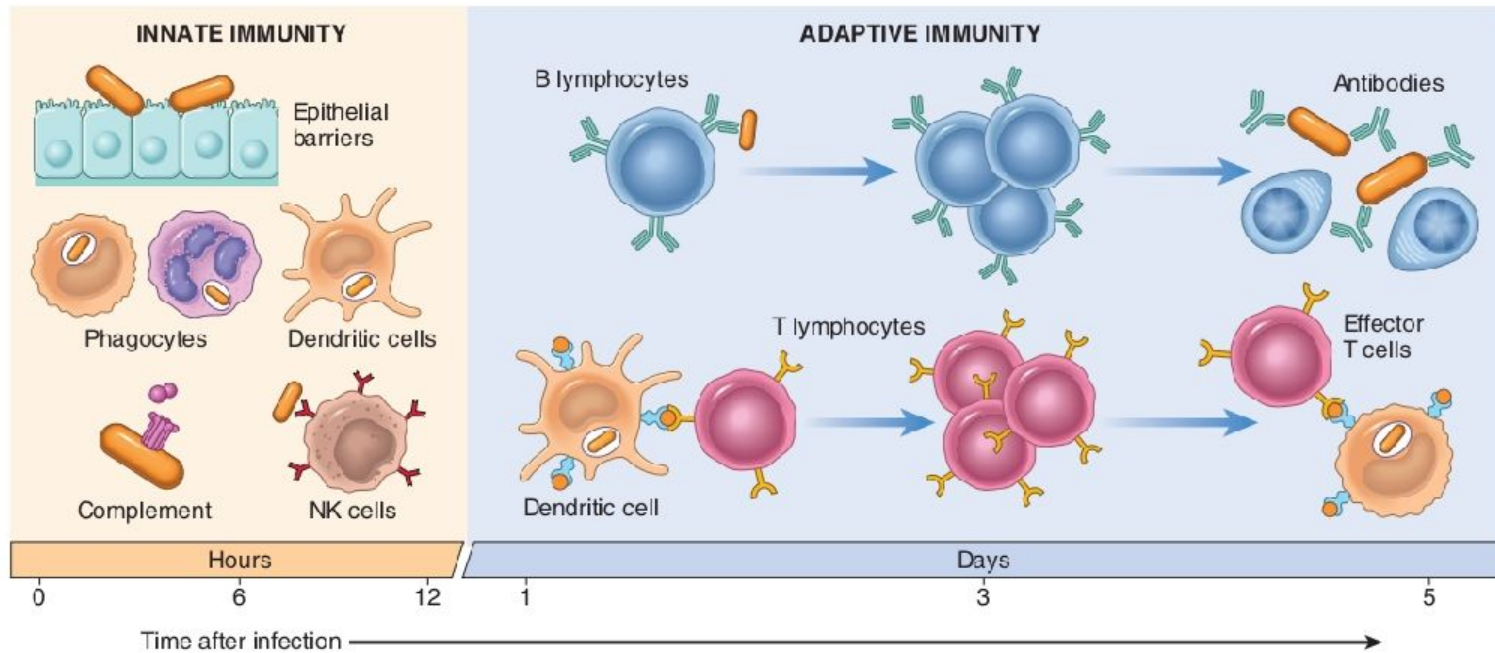


Fig. 5.1 The principal components and kinetics of response of the innate and adaptive immune systems. *NK cells*, Natural killer cells.

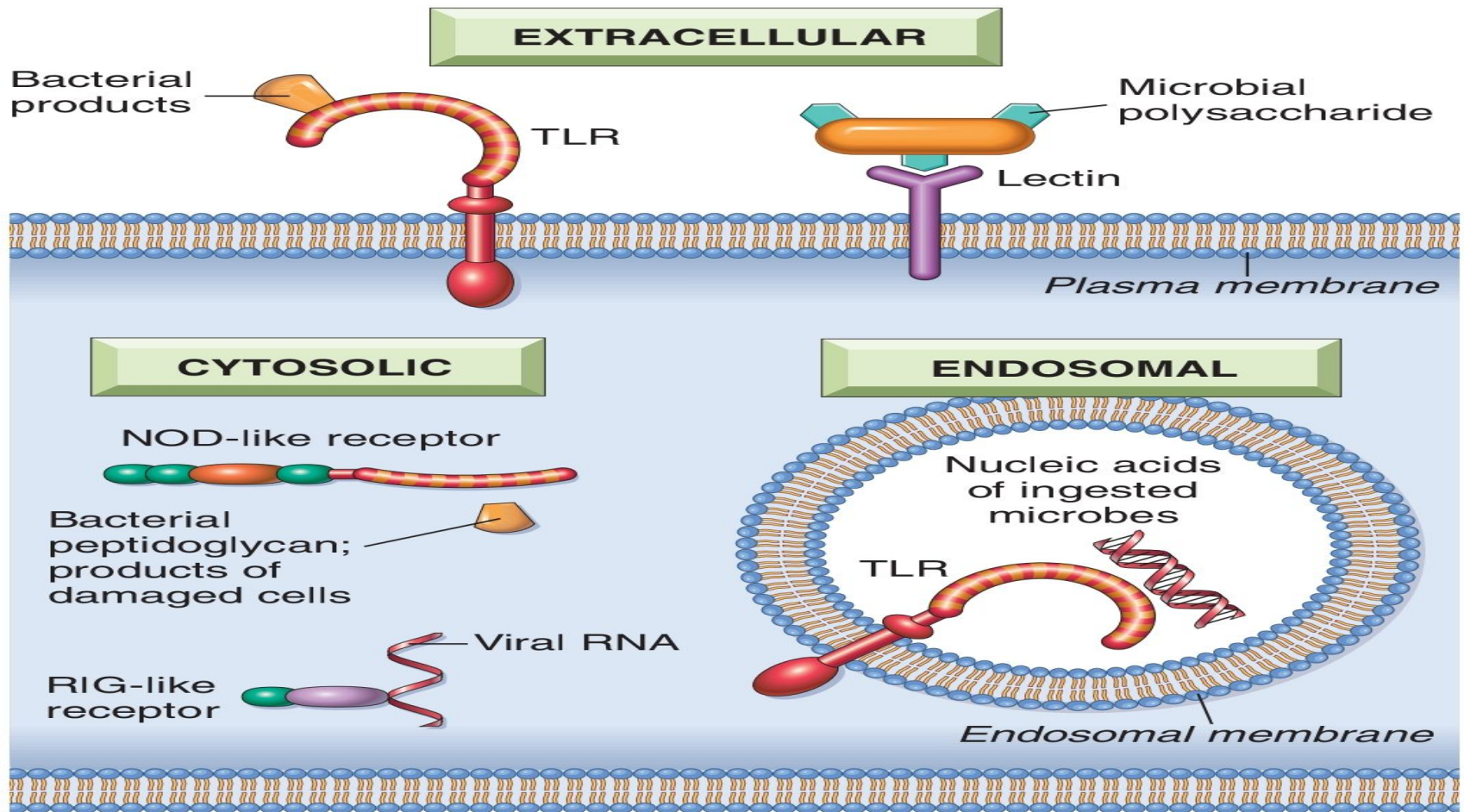
## INNATE IMMUNITY (NATURAL/ NATIVE)

- First line of defense present from birth
- Immediate initial protection
- Does not depend on prior contact
- Lacks specificity, but highly effective
- **Triggers the adaptive immune responses**

## **MAJOR COMPONENTS**

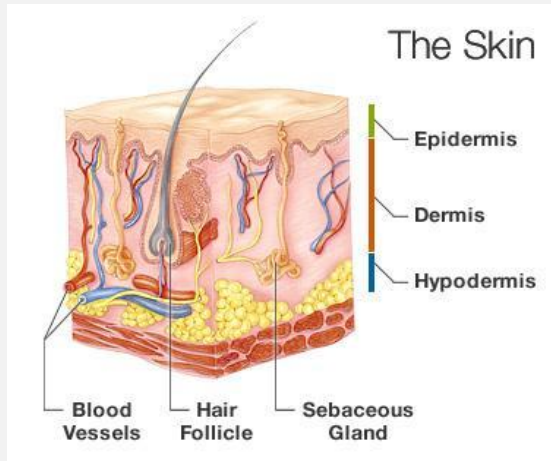
- **Physical/ anatomical barriers** – skin , GIT, Resp.T
- **Cellular defenses**
  - Phagocytic leukocytes ( Neutrophils & Macrophages)
  - NK cells
  - Dendritic cells
  - Mast cells
  - Innate lymphoid cells-IL-5, IL-17, IL-22, IF-r

- **Soluble mediators**
  - Proteins of complement system –C3a,C3b,C5a
  - Kinins- proinflammatory
  - CRP- Acute phase protein
- **Pattern-recognition receptors**
  - Toll- like receptors
  - NOD-like receptors
  - RIG-like receptors
  - C-type lectin receptors

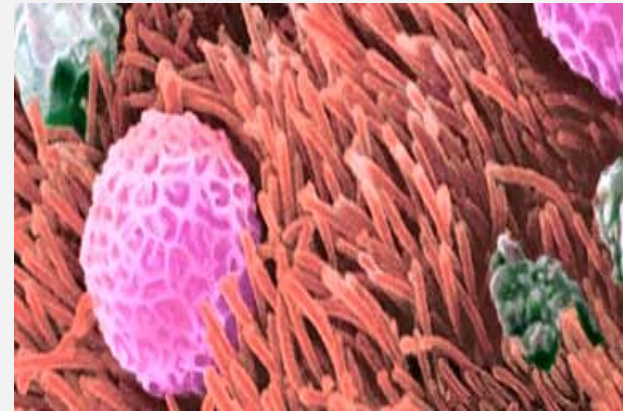


**Fig. 5.2** Cellular receptors for microbes and products of cell injury. Phagocytes, dendritic cells, and many types of epithelial cells express different classes of receptors that sense the presence of microbes and dead cells. Toll-like receptors (TLRs) located in different cellular compartments, as well as other cytoplasmic and plasma membrane receptors, recognize products of different classes of microbes. The major classes of innate immune receptors are TLRs, NOD-like receptors in the cytosol (NLRs), C-type lectin receptors, RIG-like receptors for viral RNA, named after the founding member RIG-I, and cytosolic DNA sensors.

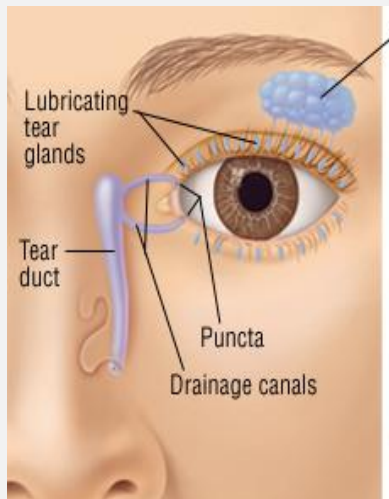
# ANATOMICAL BARRIERS - MECHANICAL FACTORS



- Skin



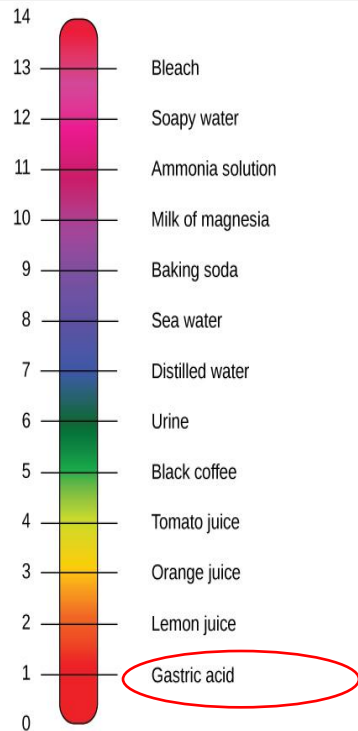
- Mucociliary escalator



- Flushing action of saliva, tears, urine

# ANATOMICAL BARRIERS – CHEMICAL FACTORS

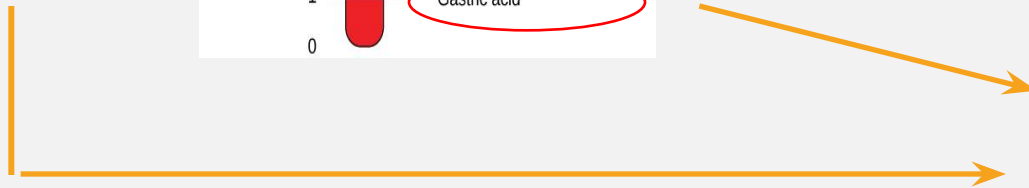
## HCl in stomach



Antimicrobial  
Peptides in sweat



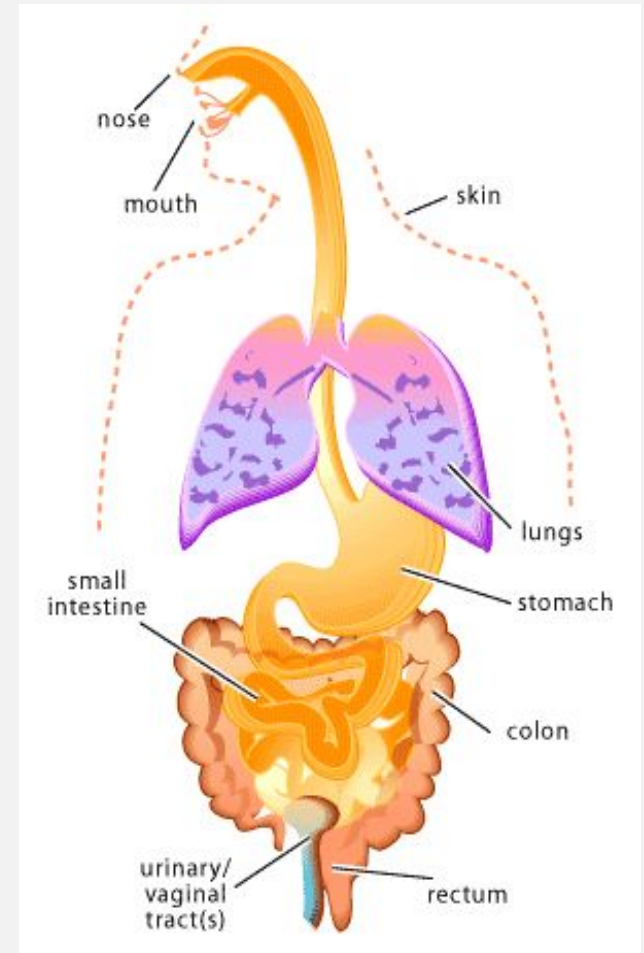
Lysozyme in tears  
/saliva



# ANATOMICAL BARRIERS – BIOLOGICAL FACTORS

Normal flora – microbes in many parts of the body

Normal flora – competes with pathogens for nutrients and space



# FUNCTIONS OF INNATE IMMUNITY

- Important in initial inflammatory response
- Antiviral role
- Initiation of subsequent adaptive immune response
- In born but lack memory

# ADAPTIVE IMMUNITY

- If innate immune system fails

## **GENERAL FEATURES**

- Second line of defense
- Recognize both microbial & non microbial substances
- Long standing protection
- Prior exposure to antigen is present
- Specificity, Diversity, memory

# MAJOR FUNCTIONS

recognition of self from nonself

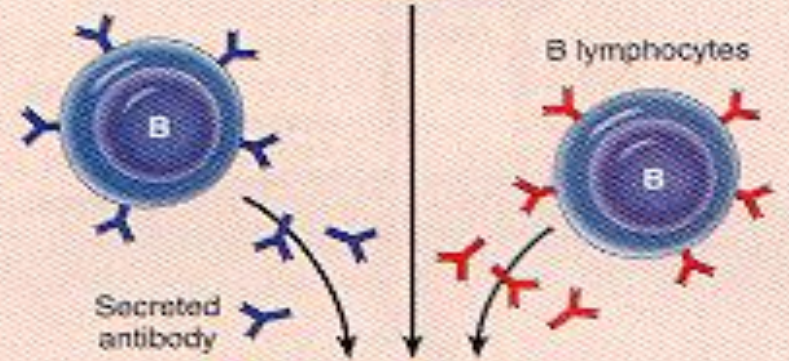
specific response

Production of Abs

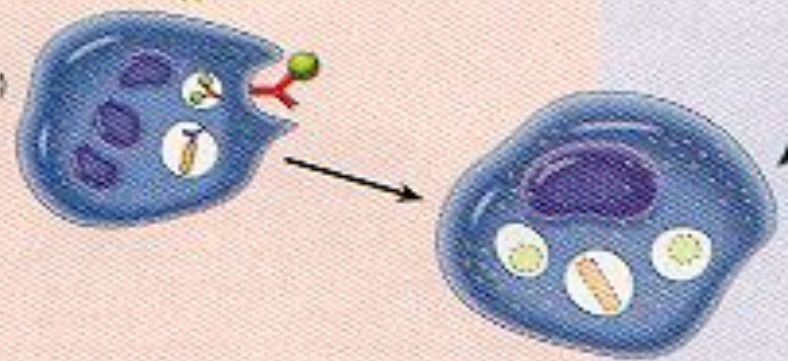
Dev of memory cells

### HUMORAL IMMUNITY

Extracellular microbe  
(e.g., bacteria)

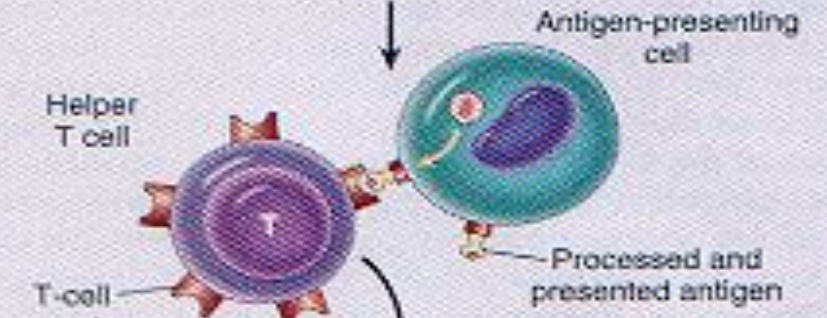


Neutralization  
Lysis (complement)  
Phagocytosis  
(PMN, macrophage)



### CELLULAR IMMUNITY

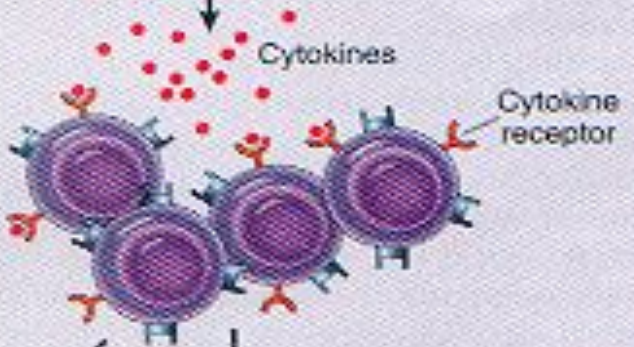
Intracellular microbe  
(e.g., viruses)



Cytokines

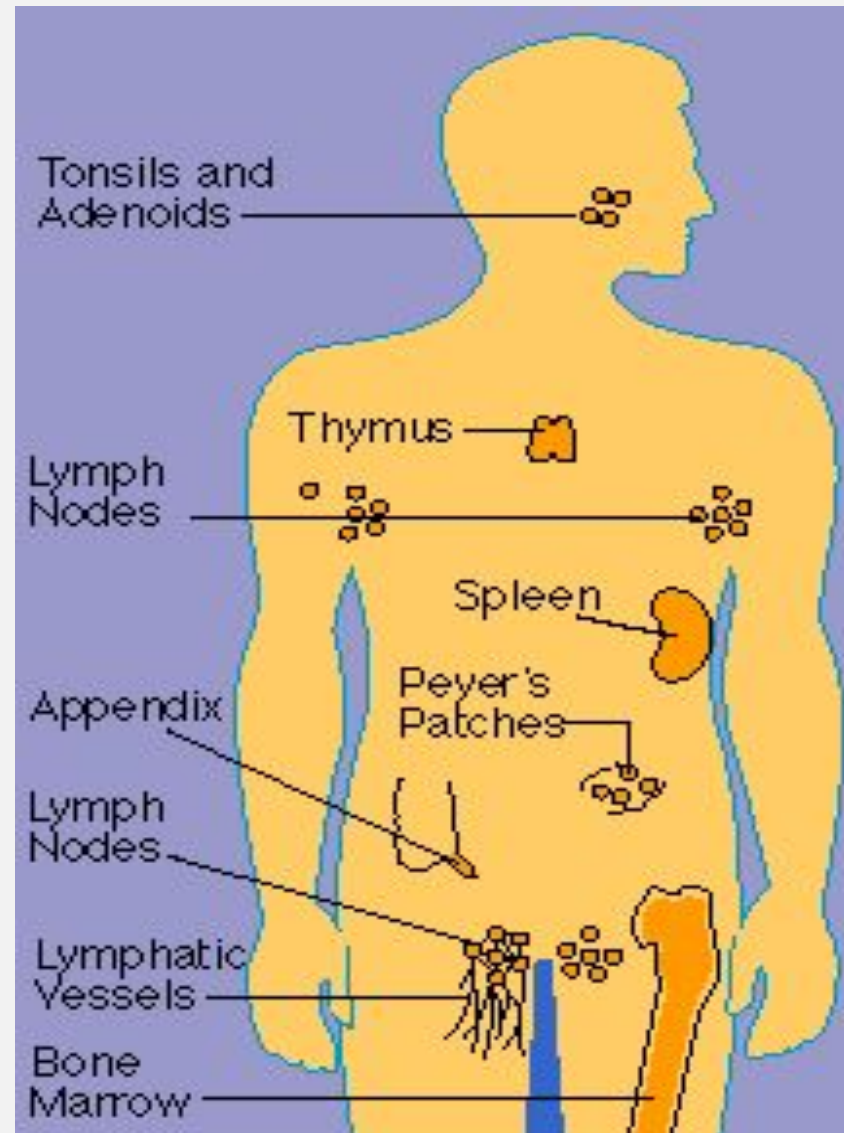
Cytokine receptor

Proliferation and activation of effector cells  
(macrophages, cytotoxic T cells)



# ORGANS OF THE IMMUNE SYSTEM

- Bone Marrow
- Thymus
- Spleen
- Lymph Nodes
- MALT



# CELLS OF IMMUNE SYSTEM

- Lymphoid cells

T lymphocytes

B lymphocytes

NK cells

- Cells of Mononuclear Phagocyte system

Macrophages

Dendritic cells

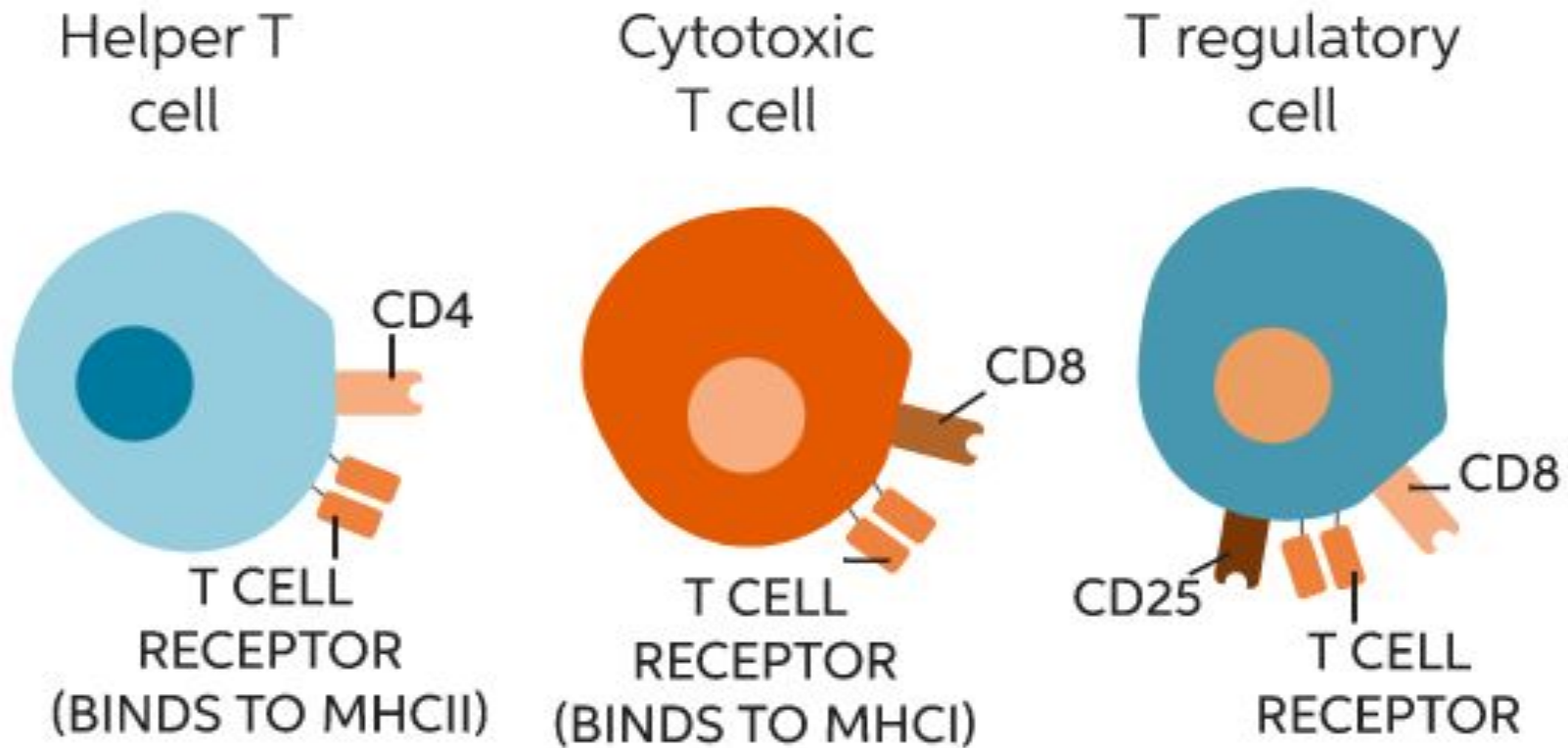
# T LYMPHOCYTES

- Paracortical LN
- Periarteriolar sheath spleen
- Thymus
- BM & p blood
- 60-70 %
- TCR –  $\alpha\beta$  ,  $\gamma\delta$
- CD4 60-70% , CD8 30-40%

# T LYMPHOCYTES

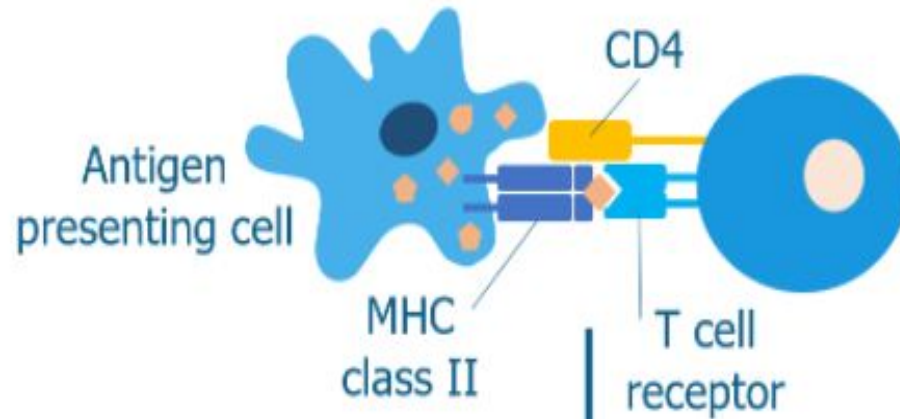
- Thymus derived
- Functions
  - Cellular immunity
  - Induce B cell derived humoral immunity
- Recognize Ag – only when presented by Ag presenting cells through MHC molecules
- T helper cells
- Cytotoxic T cells

# T LYMPHOCYTES- TYPES

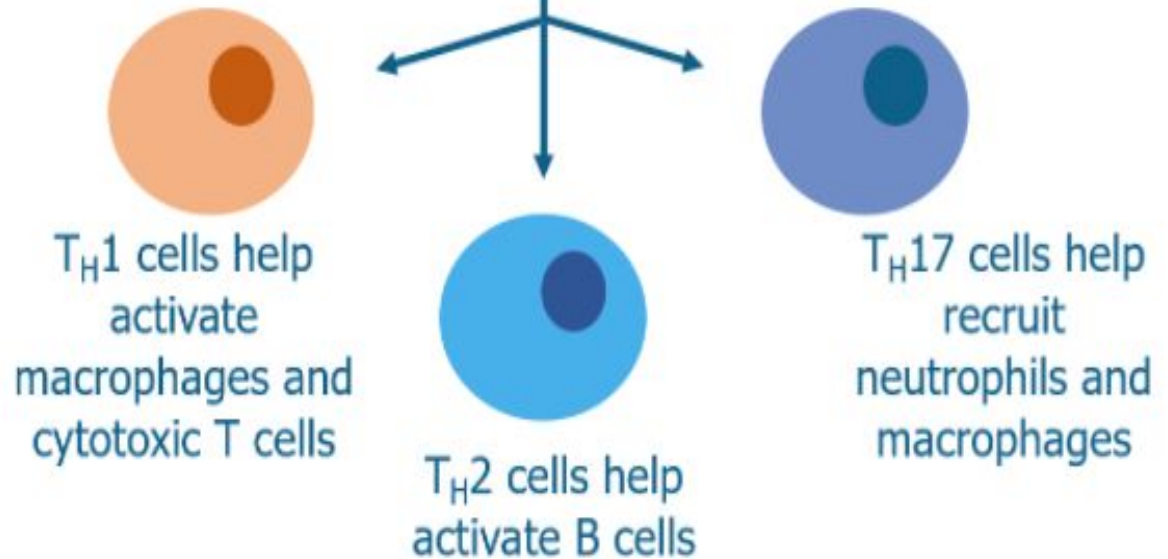


# HELPER T CELLS

1. The T cell receptor on a CD4+ T cell recognizes the pathogen peptide displayed on the surface of an antigen presenting cell

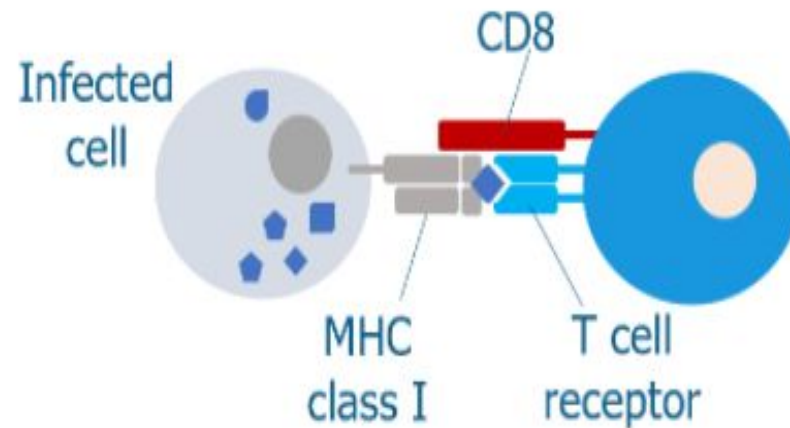


2. Different types of helper T cells ( $T_H$ ) are produced depending on the type of pathogen that is recognized

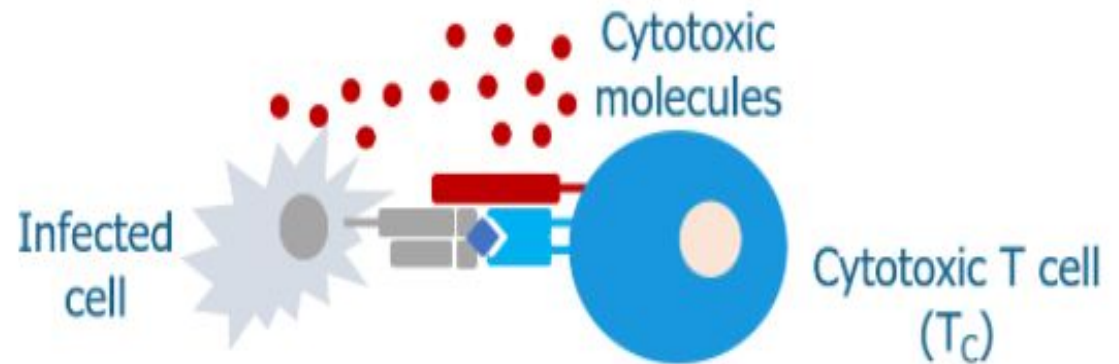


# CYTOTOXIC T LYMPHOCYTES

1. The T cell receptor on a CD8+ T cell recognizes the pathogen peptide displayed on the surface of an infected cell



2. The T cell releases cytotoxic molecules that kill the infected cell and stop the pathogen from spreading



# T cell receptors (TCR)

- Genetically programmed – unique peptide
- TCR diversity- somatic rearrangement of genes encoding chains of TCR
- **Marker for T cell lineage – TCR gene rearrangement**
- Polyclonal /monoclonal
- TCR-  $\alpha\beta$  chains (> 95%)
  - Variable region – bind to specific peptides
  - Constant region – interact with signaling molecules

- TCR –  $\gamma\delta$  chains (<5%) - mucosal surfaces (lung, GIT)
- TCR- noncovalent link – signaling proteins **CD3 protein & Zeta chains** – (no Ag binding, induce intracellular signals)

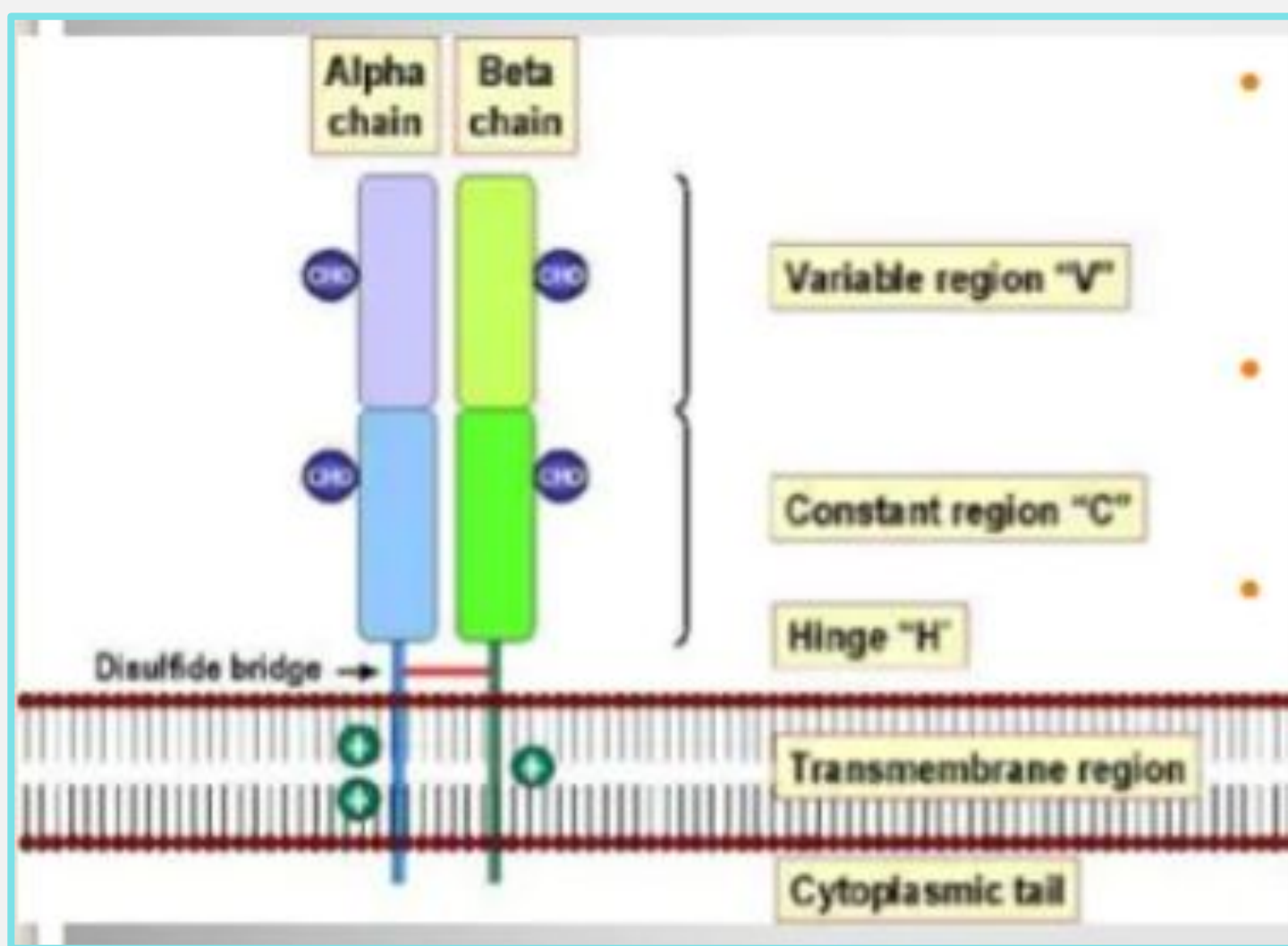
**CD4 & CD8 molecules- co-receptors**

**on distinct subset of T cells**

**CD4 – bind to Class II MHC molecules**

**CD8 – bind to Class I MHC molecules**

# T cell receptor

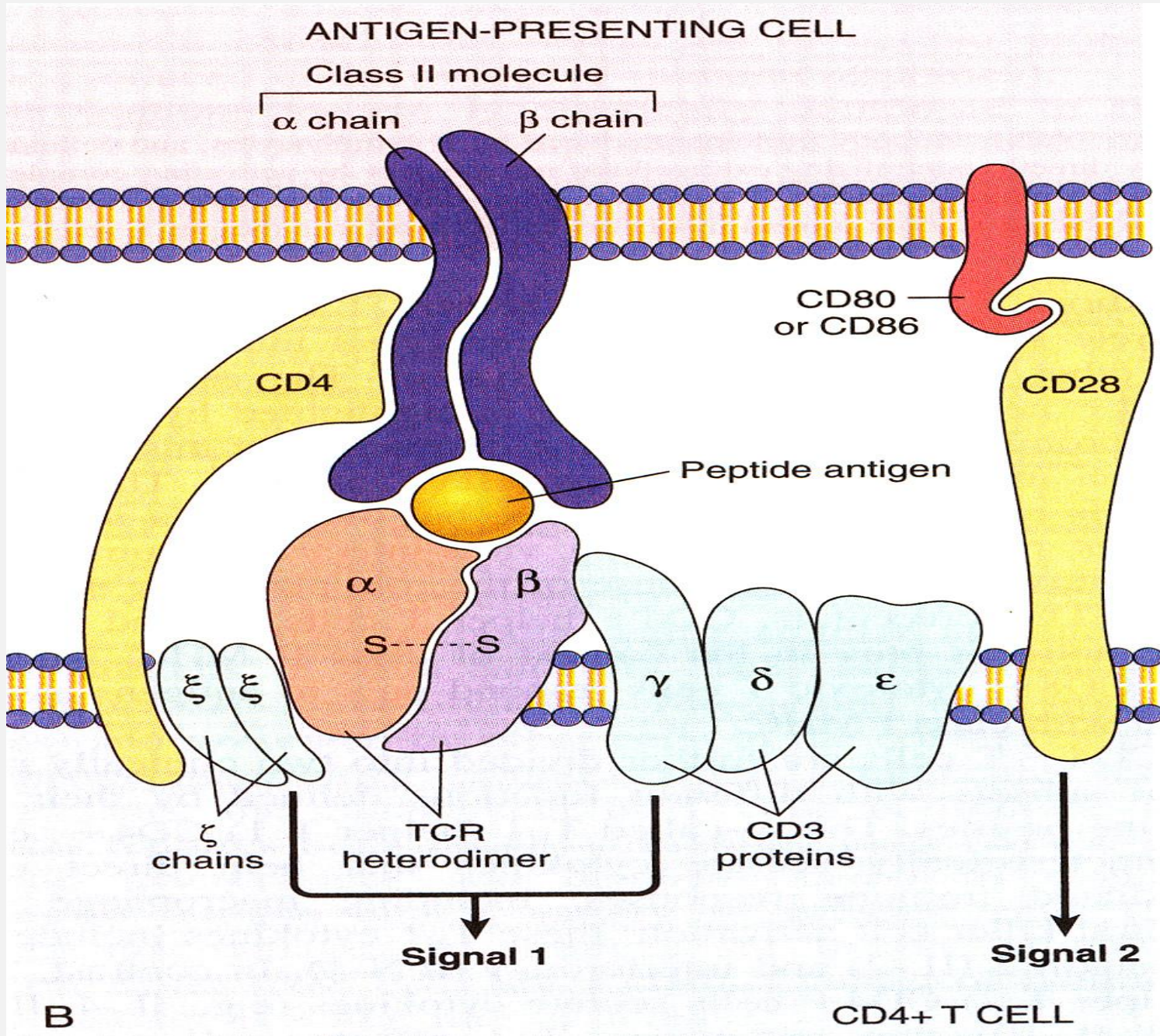


## Heterodimer

With  $\alpha$  and  $\beta$  chains.

Each have a **constant** and **variable** areas

TCR is closely related to a complex, **CD3** complex on its either side



- CD4 expression – 60% T cells
- CD8 expression – 30 %
- CD4 / CD 8 ratio 2:1

## CD4 + cells- Helper cells

- Has a central role
- Secrete cytokines & regulate all other cells of immune system
- $T_H1$  (Helper T1)
  - IL-2, IFN- $\gamma$  - direct CMI response,  
Macrophage & NK cell activation
- $T_H2$  – IL- 4, IL-5, IL-10  $\square$  Ig E

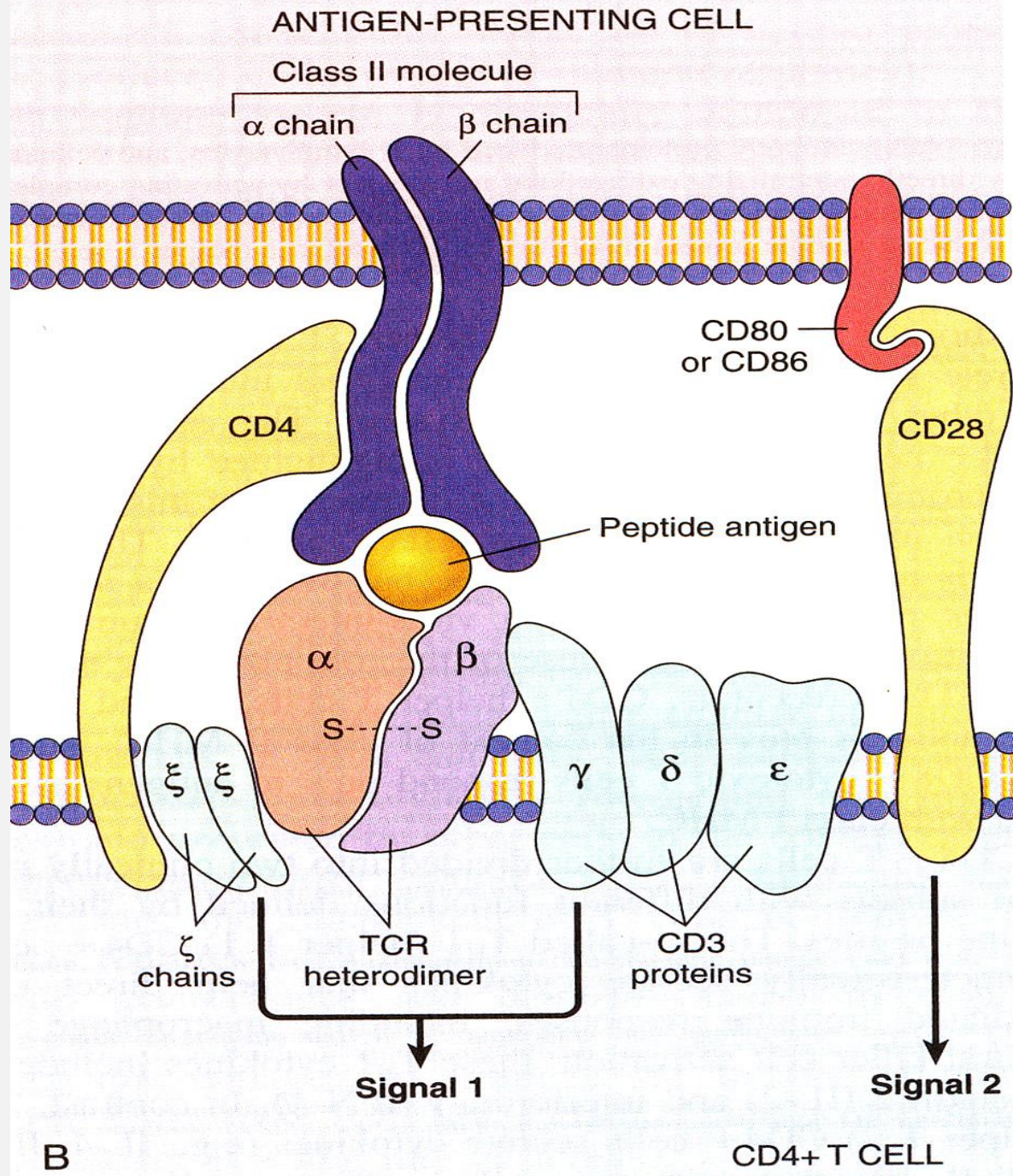
## Activation of T cells

- 2 signals
- **Signal 1** – TCR + Sp.Ag.- MHC complex  
CD4 & CD8 enhance this signal
- **Signal 2** – CD 28 + costimulatory molecules  
(CD80 or B7-1; CD86 or B7-2)

### In the absence of Signal 2

T cells  apoptosis

become unreactive (anergy)



# B LYMPHOCYTES

- BM derived
- 10- 20 %
- BM, LN, spleen, tonsil, GIT
- Germinal center
- B cells □ plasma cells □ Ig (Ab)
- Humoral immunity
- Directly neutralize extra cellular pathogens or activate complement / effector cells (N, Ma)

# B LYMPHOCYTES

- Antigen recognition
  - Ig M on BCR
  - BCR – unique specificity
- B cells & Ab –directly bind to free Ag
  
- Functions
  - ab mediated immune response
  - Transformation to plasma cells
  - Ig secretion

- IgG, IgM, IgA – 95%
- IgE, IgD – very low
- IgA – mucosal immunity
- IgE – allergic responses
- Marker for B cell lineage- Ig gene rearrangement, CD19,CD20,CD21,CD23
- Polyclonal/ monoclonal

- **Signaling proteins**

CD40- CD 154 on activated T cells → B cell maturation → secretion of Ig Ab-A,G,D

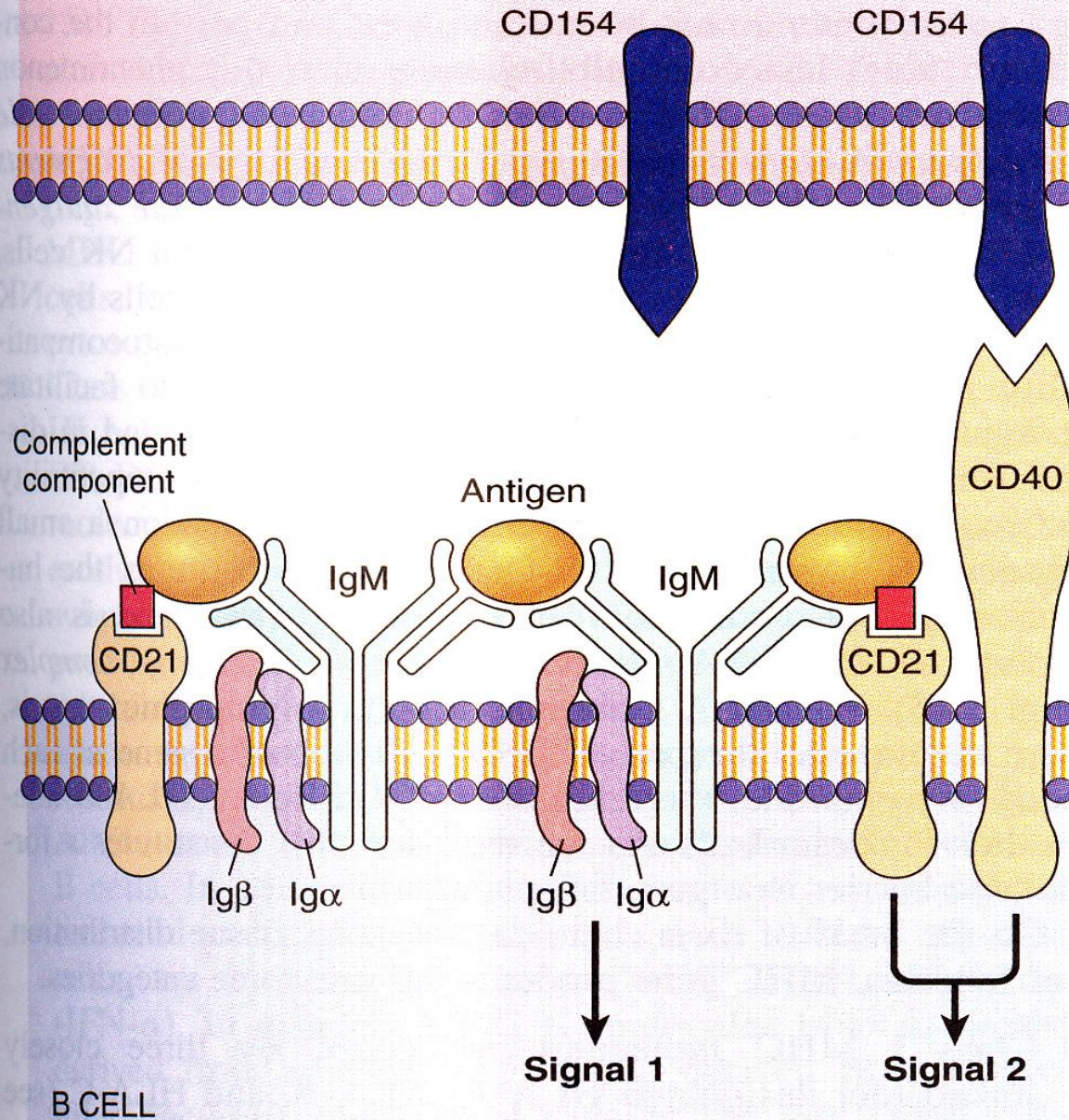
- Mutation in CD154 → only IgM → Ig-immunodeficiency ( X linked hyper IgM syndrome)

- **Costimulatory molecule**

CD21 (CR2 complement receptor)

EBV

# ACTIVATED T CELL



# NK CELLS

- 10-15 %
- Fc receptor of Ig G
- Virus infected / tumor cells
- CD16 , CD 56
- **ADCC** (antibody dependent cellular cytotoxicity)

## NK CELLS

- Larger than small lymphocytes
- 10 – 15 %
- Azurophilic granules
- Lyse Tr. cells, viral infected cells & some normal cells  
**without prior sensitisation**
- First line of defense
- Part of innate immunity
- No TCR & CD3

- Express 2 receptors

1. Activating receptor –

Recognise ill defined molecules

2. Killer inhibitor receptor(KIR)

Inhibits cytolysis – recognise self

Class I MHC

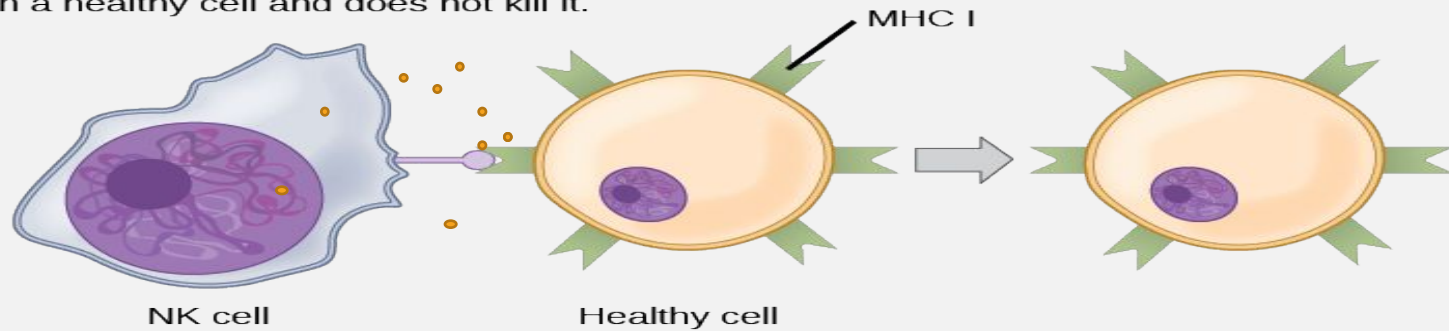
Do not lyse healthy nucleated cells

Viral infection & neoplastic transformation

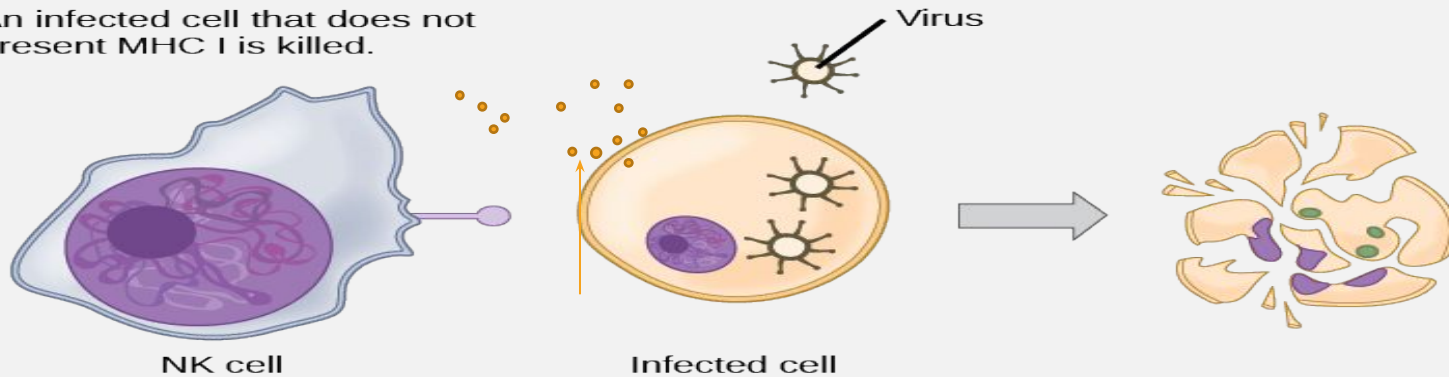
→ ↓ MHC I expression

# HOW DOES THE KILLER KILL ?

A natural killer (NK) cell recognizes MHC I on a healthy cell and does not kill it.



An infected cell that does not present MHC I is killed.



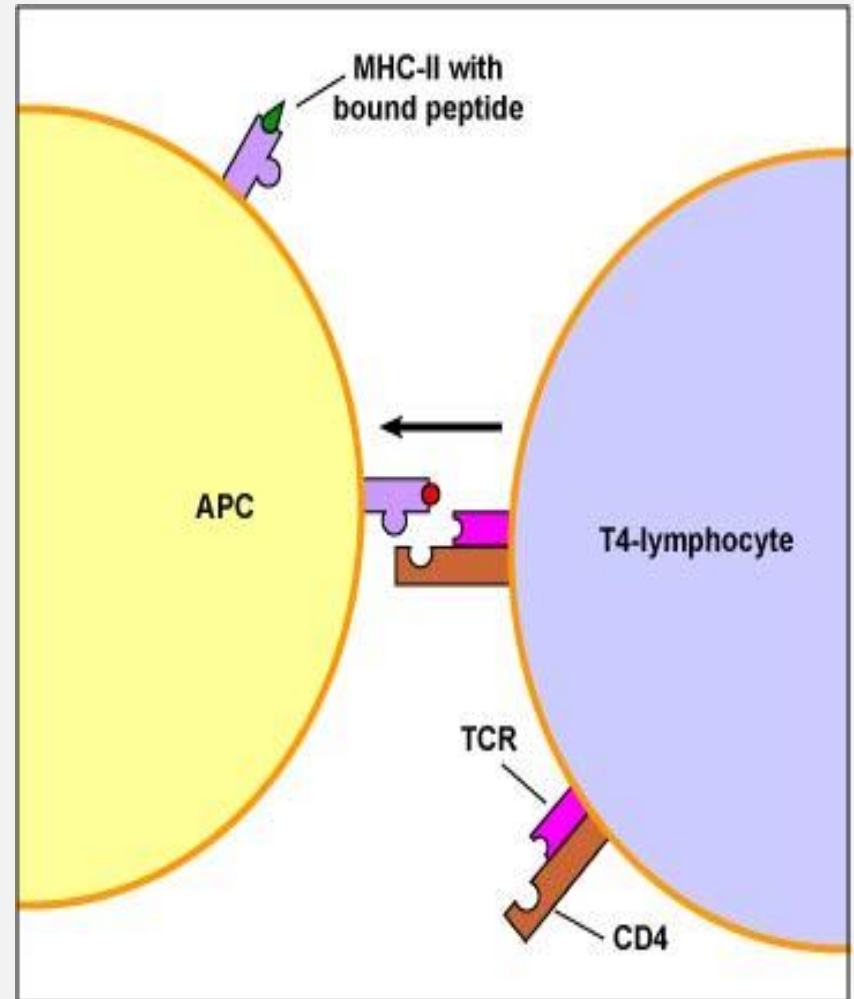
Kills both host cells and microbes

Release of granules with perforins and proteases(GRANZYMES)

# ANTIGEN PRESENTING CELLS

APCs serve two major functions :

- capture and process antigens for presentation to T-lymphocytes
- produce signals required for the proliferation and differentiation of lymphocytes
- APCs include
  - dendritic cells,
  - macrophages, and
  - B-lymphocytes



# DENDRITIC CELLS

- Follicular
- Interdigitating  
*Langerhans*

Dendritic  
cell



# MACROPHAGES

- Macrophages are derived from monocytes
- They are capable of capturing and presenting antigen to naive T-lymphocytes

# MACROPHAGES

- Express Class II MHC molecules

Present Ag to T cells

Central role in CMI

- Produce Cytokines

IL-1, IL-6, IL-12, TNF, PDGF, TGF-  $\beta$

- Phagocytosis of microbes

Humoral immunity

- Delayed HS

Actvtn of T cells to effector cells

# CYTOKINES

- Soluble signalling molecule

- Autocrine
- Paracrine
- Endocrine

Interferons

Interleukins

TNF

Chemokines

CSF /GF

***SSSS / Toxic shock syndrome***

## Categories of Cytokines

### I. THAT MEDIATE INNATE IMMUNITY

IL-1, IL-6, TNF, IFN-type I □ macrophage

Nonspe. proinflammatory  
responses

Acute phase reactants

viral infe.

### 2. THAT ACTIVATE INFL. CELLS

IFN- $\gamma$ , TNF, TNF- $\beta$  □ T cells

Activate Ag.nonspe. Effector cells

# THERAPEUTIC EFFECTS OF CYTOKINES

- Harmful effects of infl.& tissue damaging immune reactions can be controlled
- Recombinant cytokines- against Ca.& microbial infections

## DISEASES DUE TO CYTOKINE OVER PRODUCTION

a). Due to Super antigens

V $\beta$  region on TCR  $\rightarrow$  Sti.TCR  $\rightarrow$  polyclonal

T cell activation  $\longrightarrow$  excessive cytokine release (IL-2 , TNF)

cytokine storm