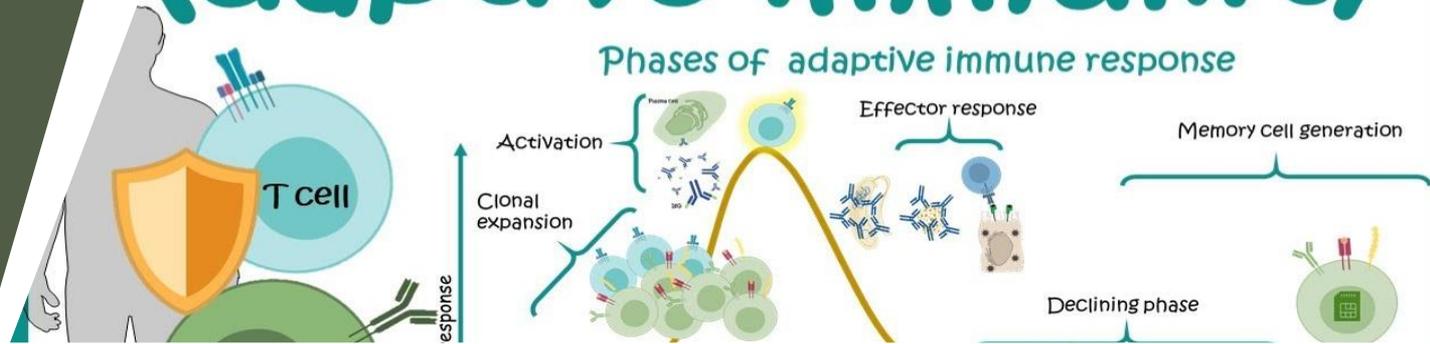


Adaptive immunity



and

MAJOR

**Histocompatibility
Complex (MHC)**



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Learning outcomes

- By the end of this lecture the students will be able to :

- Identify characters of adaptive immunity
- Define types of adaptive immunity
- Recognize functions of antibody isotypes
- Relate primary and secondary humoral immune response
- Categorize types of cell mediated immunity.
- Describe MHC and classify MHC
- Describe structure, distribution and functions of MHC molecules

lecture Outline

- Characters of adaptive immunity
- Types of adaptive immunity (humoral and cellular)
- Humoral immunity
- Primary and secondary humoral immune response
- Cell mediated immunity
- Major histocompatibility complex

Case scenario, Clinical Correlate, Practice points



An infant boy experiences multiple bacterial, viral, and fungal infections during his first of life. He has also been suffering diarrhea since birth. Tests are performed to determine the likely cause of his symptoms. Serum calcium levels are normal, and the patient's white blood cells change nitroblue tetrazolium clear to bright blue; however, his B- and T-lymphocyte counts are very low.

What is a possible mechanism accounting for his symptoms?

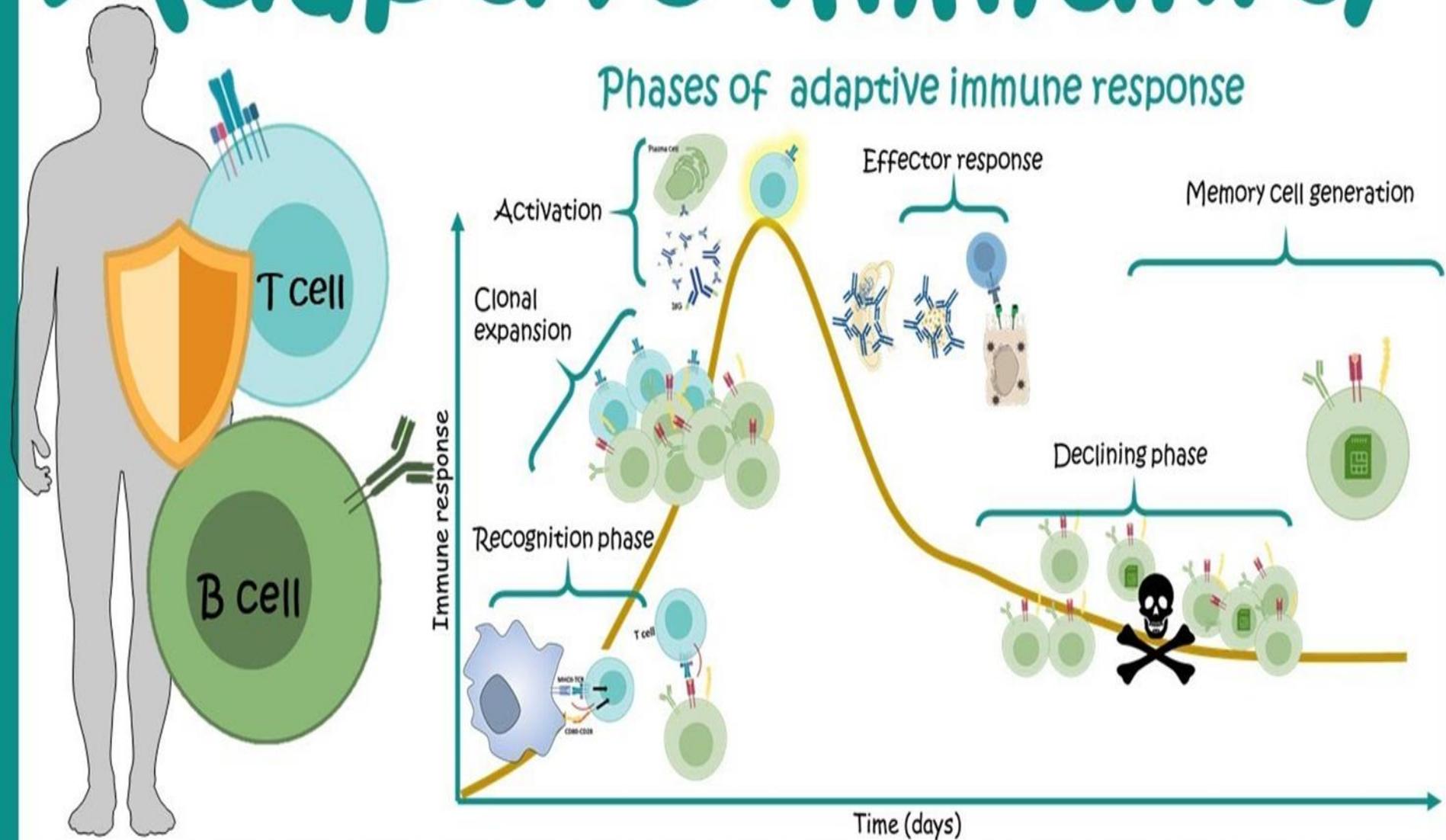
Adaptive immunity

Characters

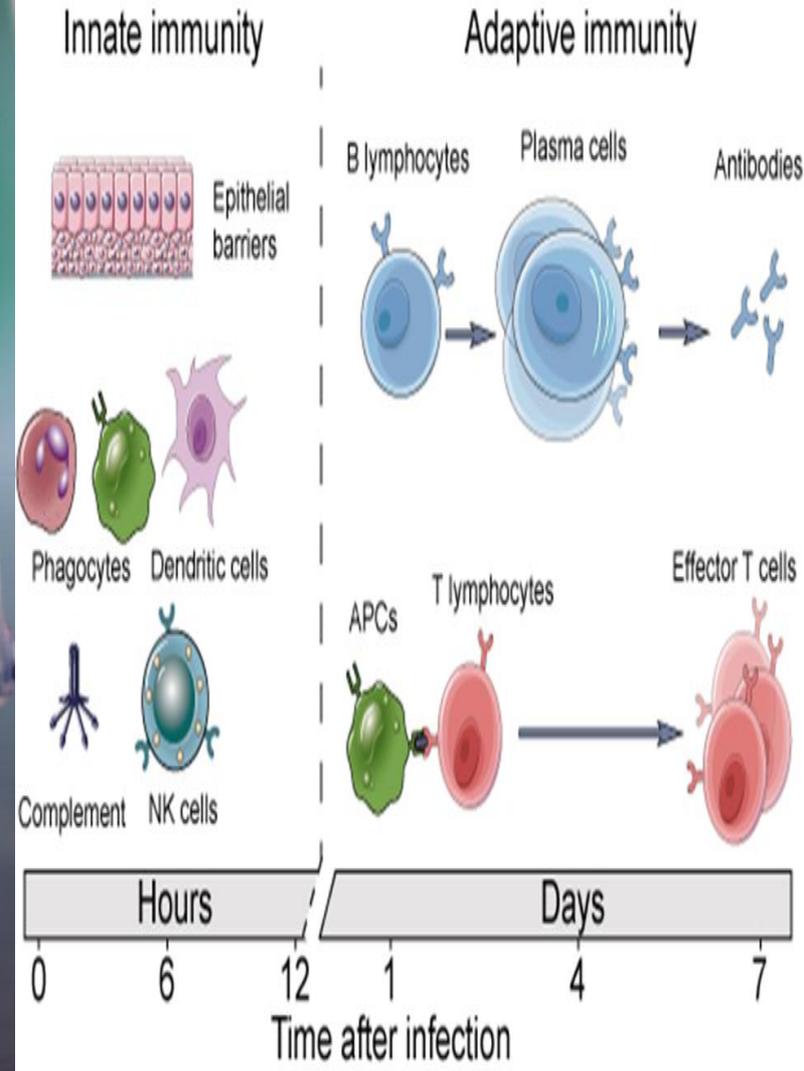
- Second line of defense.
- Develops as a response to infection.
- Specificity and memory are characteristic features of adaptive immunity:
 - Specificity: the immune response is specific for a certain antigen
 - Memory: is the ability to “remember” and respond more strongly to repeated exposure to the same microbe.

Adaptive immunity

Phases of adaptive immune response

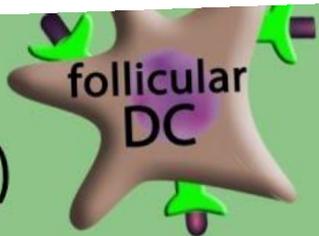


Types of adaptive immunity:
1- Humoral (Antibody - Mediated) Immunity. 2- Cell-Mediated Immunity.

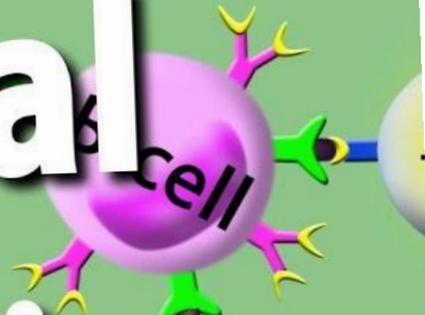
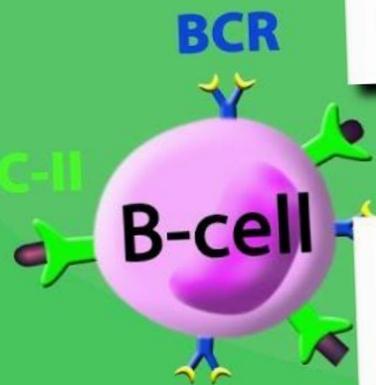


B-cell zone

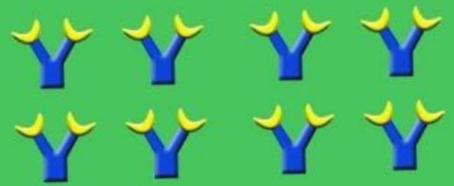
Germinal center (GC)



Humoral Immunity



IgM



1- Humoral (Antibody - Mediated) Immunity.

- Humoral immunity is mediated by **secreted antibodies**
- Its physiologic function is defense against **extracellular microbes and microbial toxins**, also against **intracellular microbes** because antibodies can bind to them before they enter host cells **thus prevent infection**

HUMORAL IMMUNITY



Lymphocyte



Antibody



Antigen

Bacteria



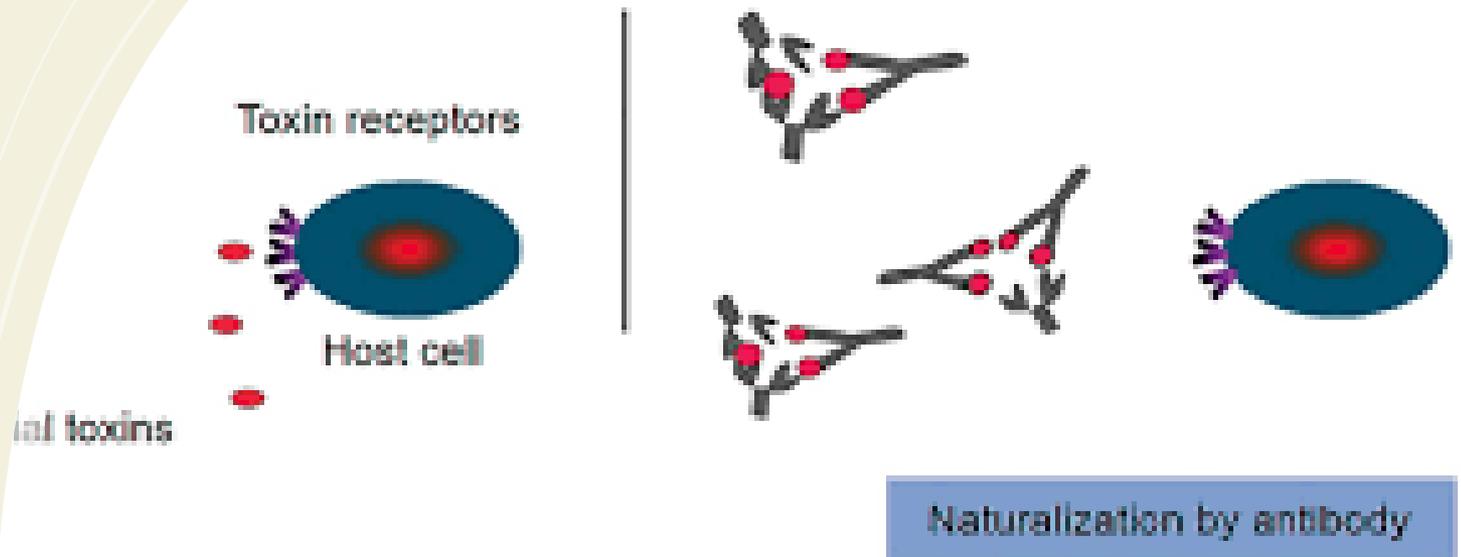
Antibody



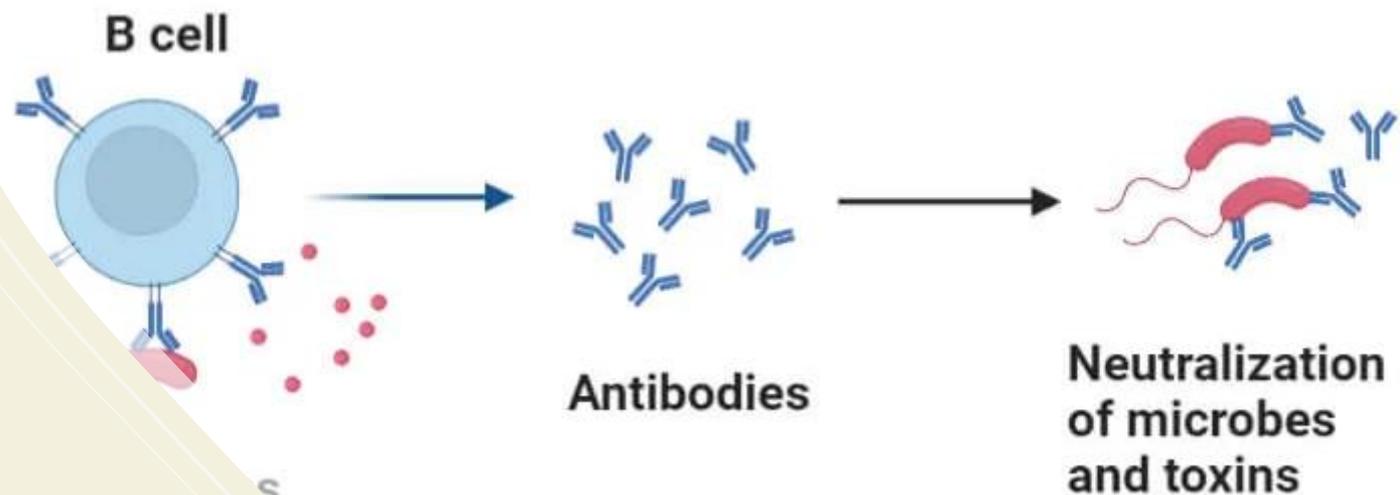
Functions of antibody isotypes:

1 Neutralization of microbes and microbial toxins

- Antibodies blocks and prevent binding of microbe to cells i.e. prevent infection of cells
- Antibodies inhibit the spread of microbes from an infected cell to an adjacent cell.
- Antibodies block binding of toxin to cellular receptors, and thus inhibit pathologic effects of the toxin.

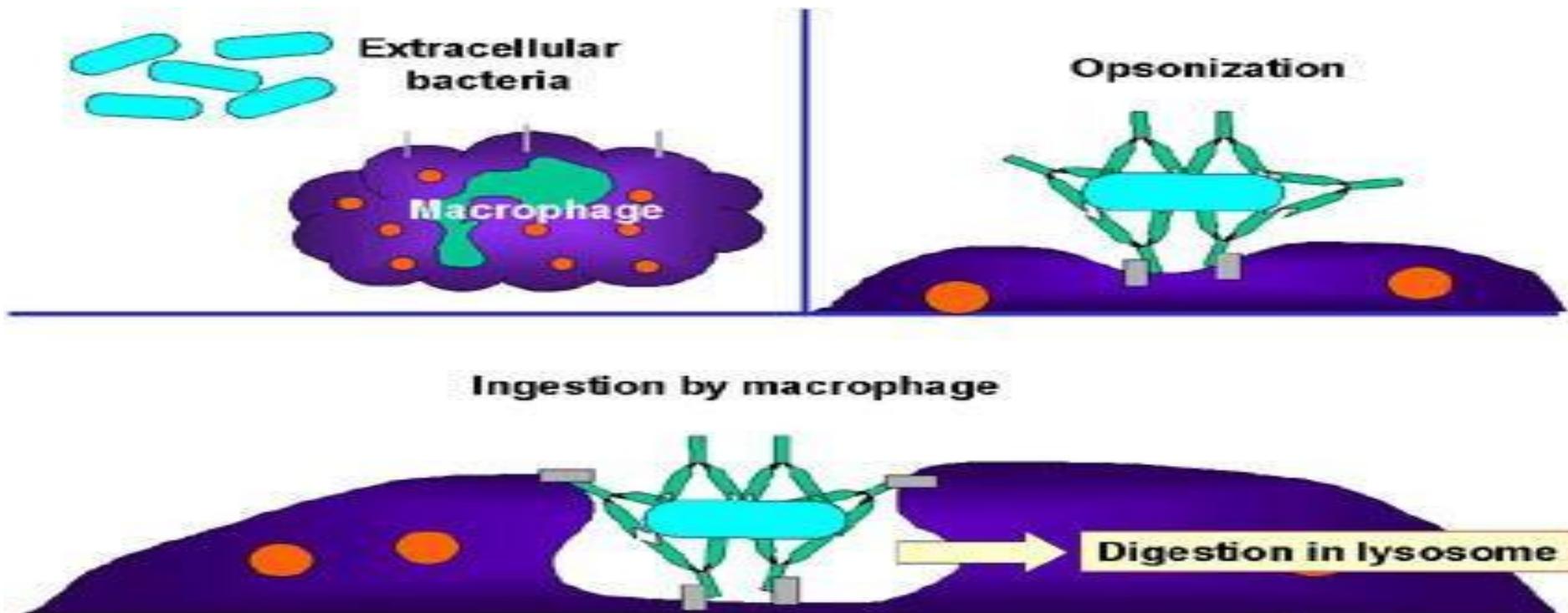


Neutralization



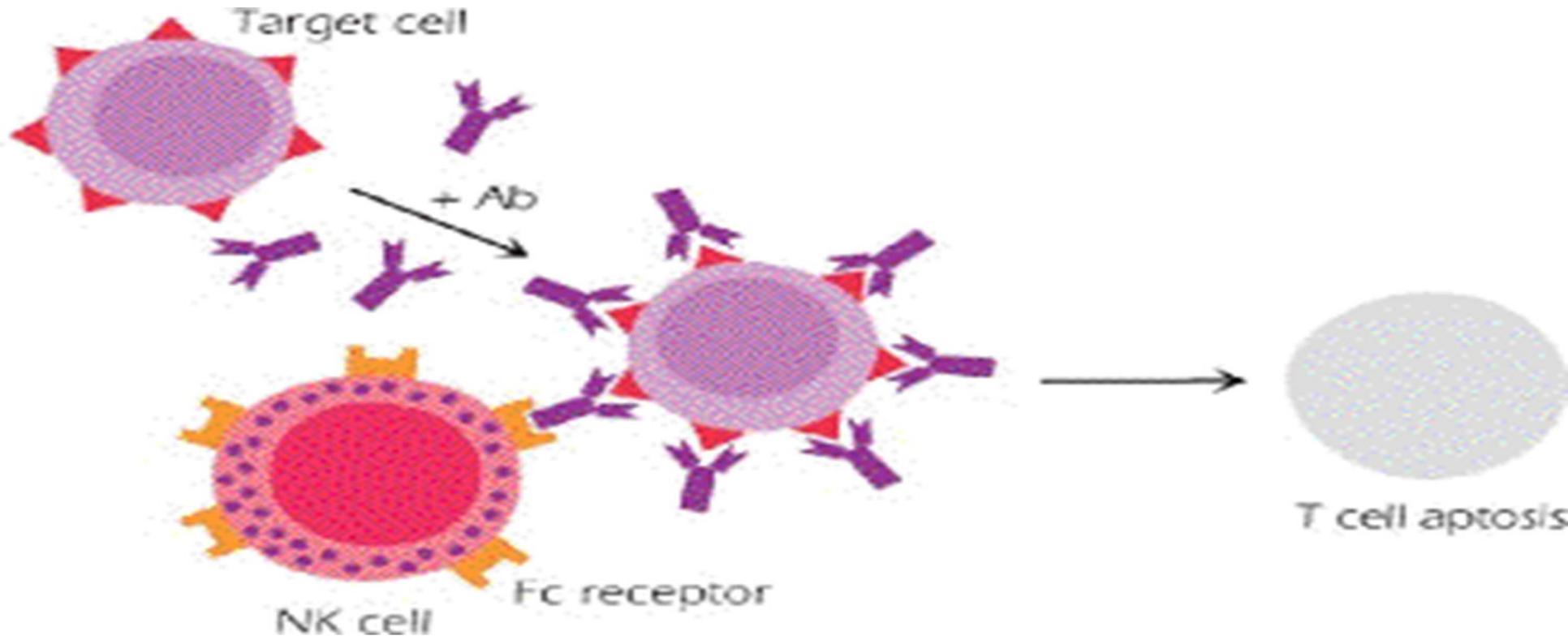
2- Opsonization and phagocytosis

- Antibodies of IgG isotype opsonize (coat) microbes and promote their phagocytosis by binding to Fc receptors on phagocytic cells (neutrophils and macrophages).



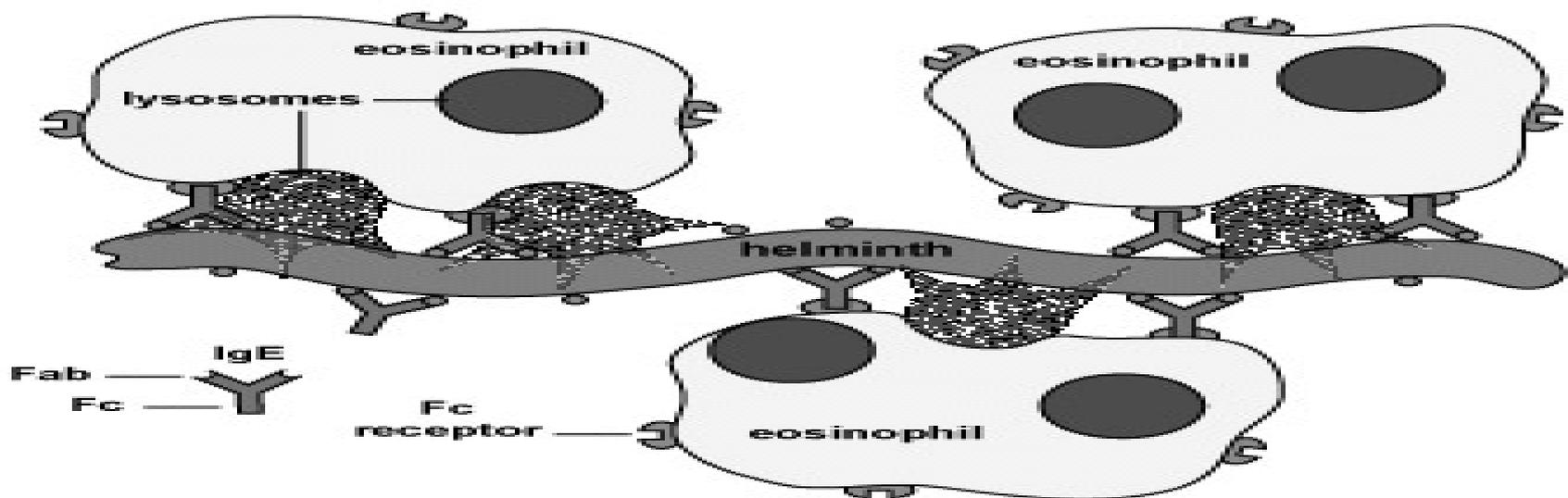
3- Antibody-dependent cell-mediated cytotoxicity (ADCC)

- **IgG** bind to infected cells by the Fab regions, and bind by Fc to Fc receptors on NK cells. The NK cells are activated and kill the cells.



3- Antibody-dependent cell-mediated cytotoxicity (ADCC)

- **IgE** bind to helminthic parasites by the Fab regions, and bind by Fc to Fc receptors on eosinophils. The eosinophils are activated to release their granule contents, which kill the parasites.



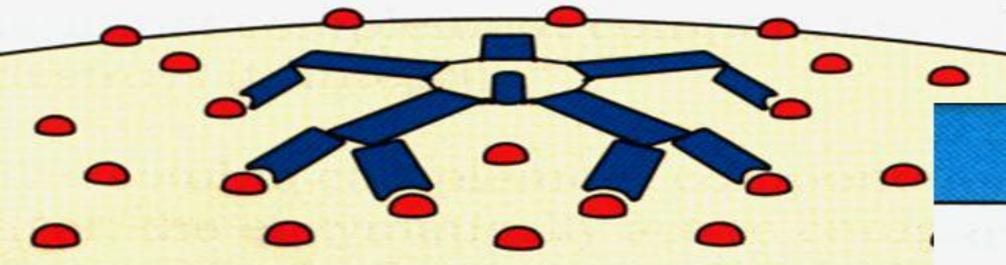
4- Activation of the complement by IgG and IgM:

Pentameric IgM molecules bind to antigens on bacterial surface and adopt 'staple' form

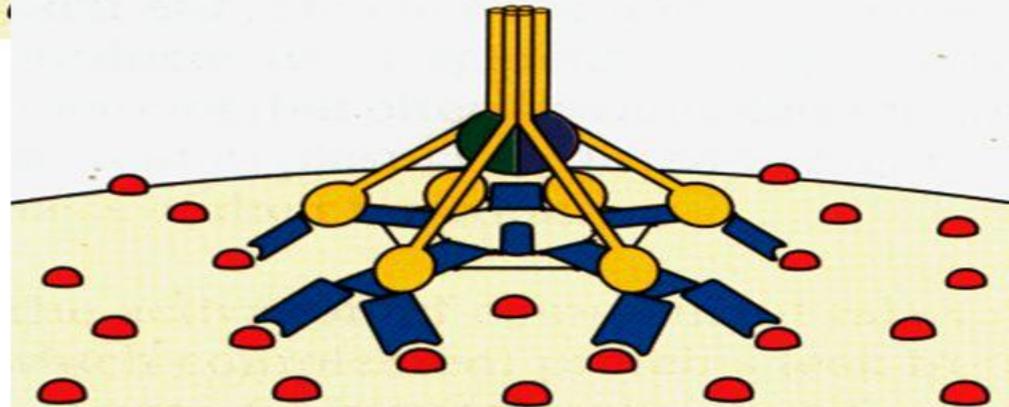


'planar' form of IgM

'staple' form of IgM



C1q binds to a single IgM molecule



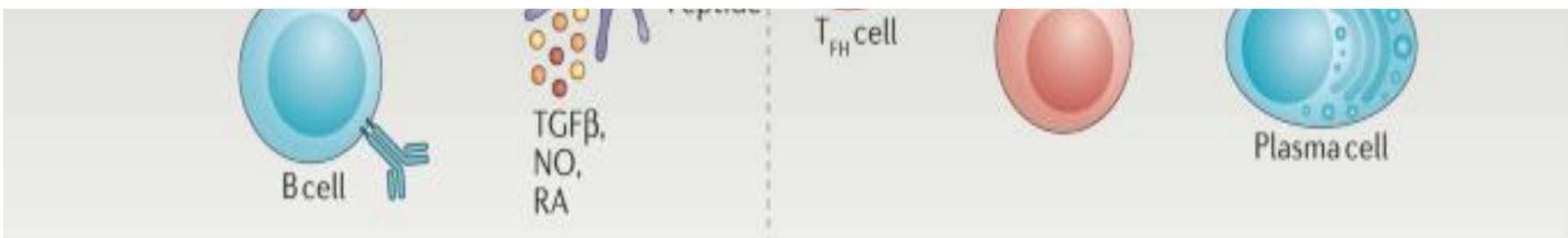
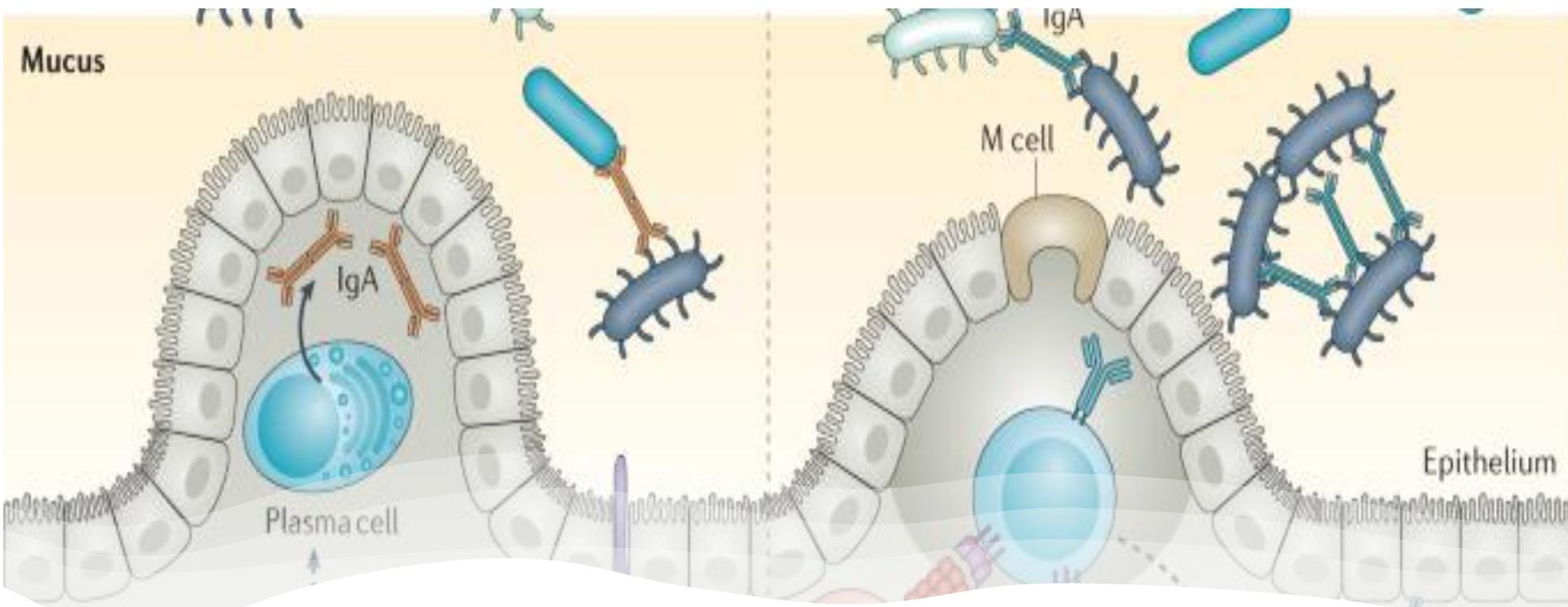
IgM is the best activator of complement.



5- Functions of antibodies at special sites:

Mucosal immunity: **IgA** is the major class that is produced by the mucosa-associated lymphoid tissues (**MALT**) in the GIT and RT and transported to the lumens of organs. In mucosal secretions, IgA binds to microbes and toxins present in the lumen and neutralize them by blocking their entry.

Neonatal immunity: neonates are protected from infection by maternal antibodies (**IgG**) transported across the **placenta** into the fetal circulation and by **antibodies in ingested milk** transported across the gut epithelium of newborns.



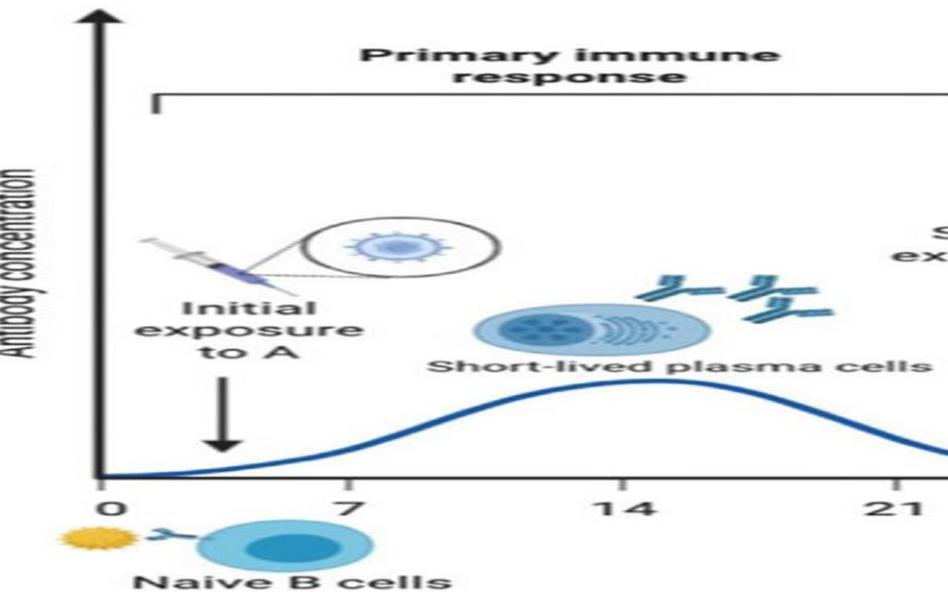
- **Mucosal immunity**

Primary and Secondary Immune Response

The primary response

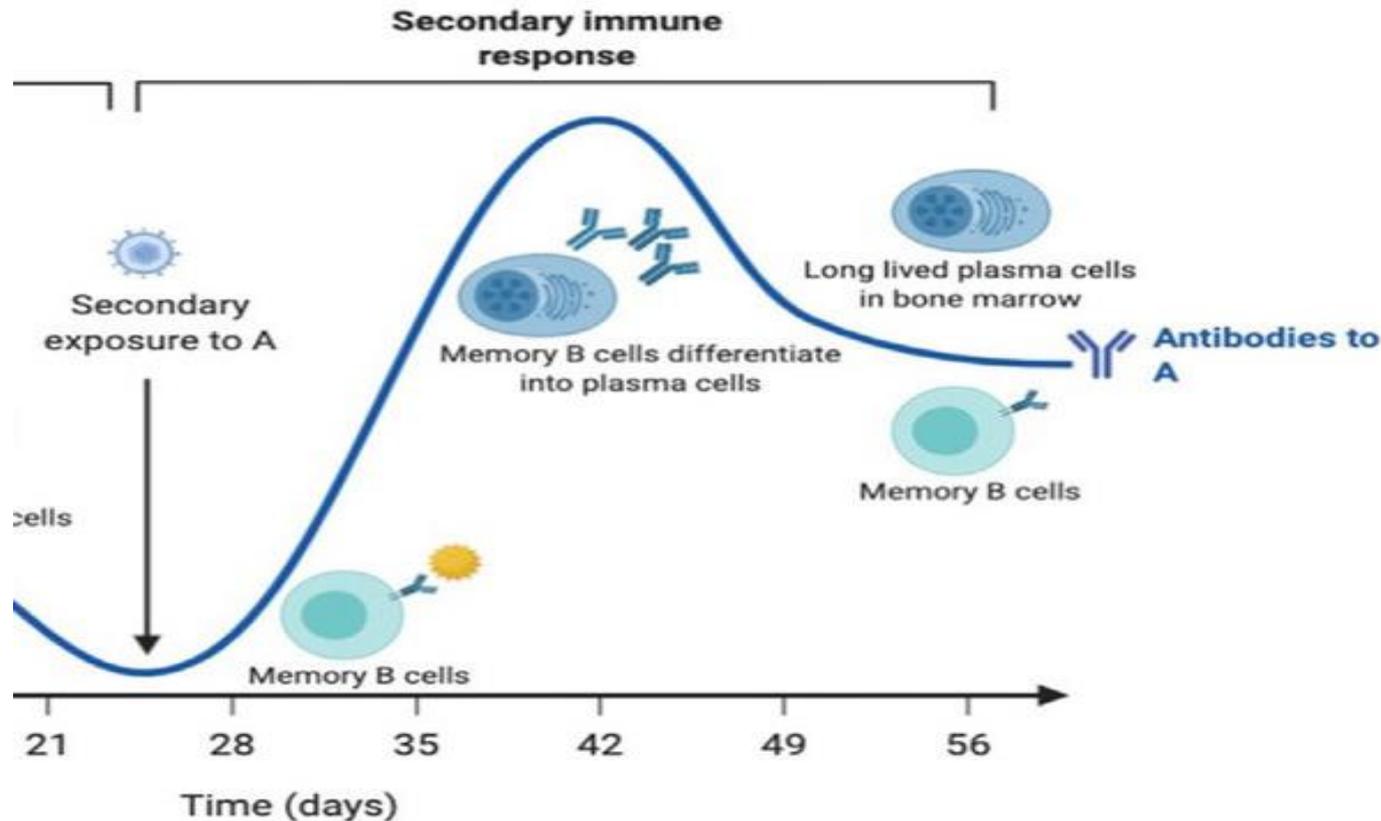
When we are exposed to an antigen for the first time:

- there is a lag of several days (10 days) before specific antibody becomes detectable.



The Secondary Response

- If at a later date we are re-exposed to the same antigen, there is more rapid appearance of antibody



- **This phenomenon is possible because the immune system possesses specific immunologic memory for antigens.**
- **During the primary response, some B lymphocytes, become memory cells which are long lived. Thus we can see that the secondary response requires the phenomenon known as **class switching (IgM to IgG)**.**

Primary Response

Secondary Response

Slow in Onset

Rapid in Onset

Low in Magnitude

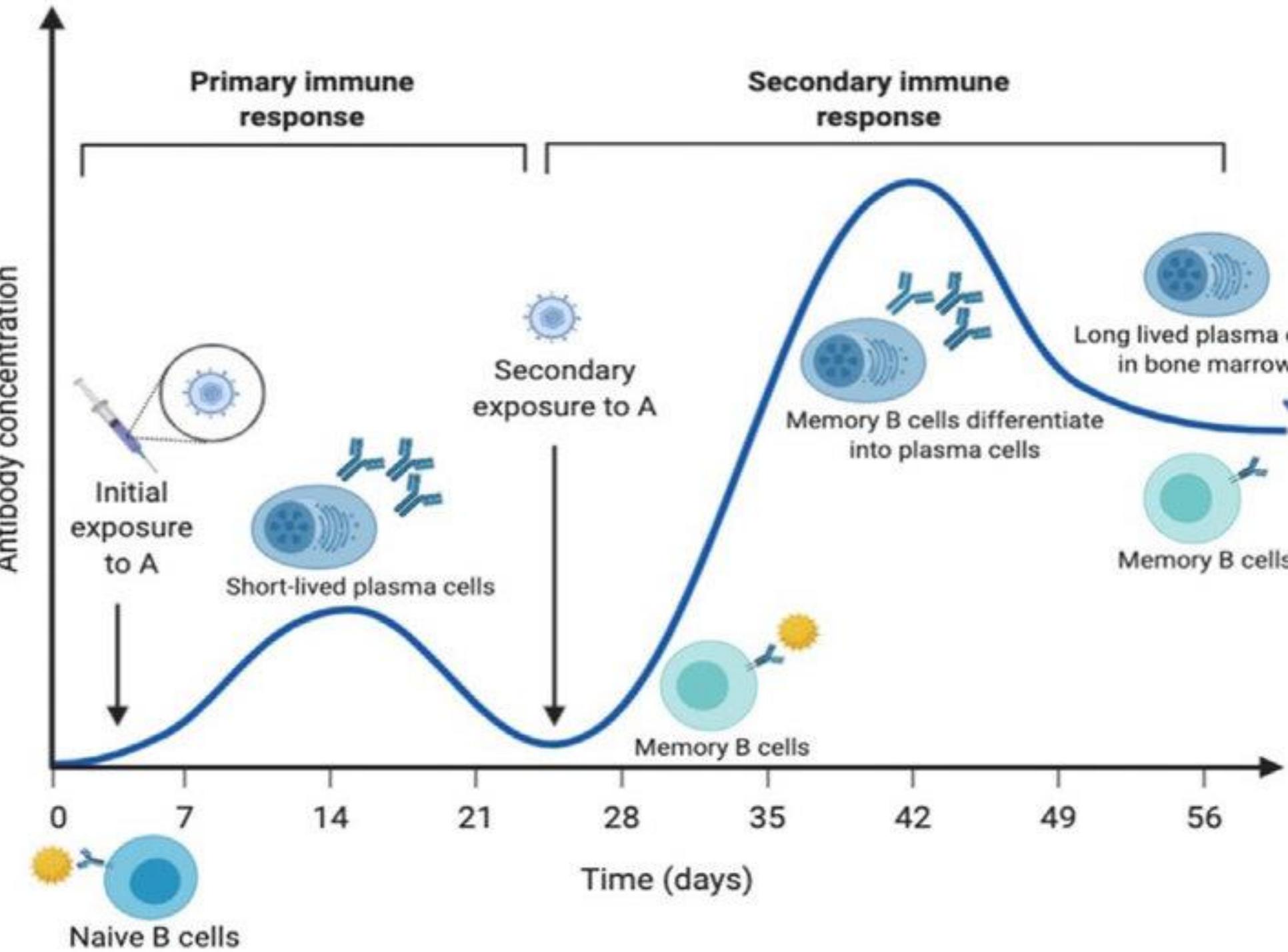
High in Magnitude

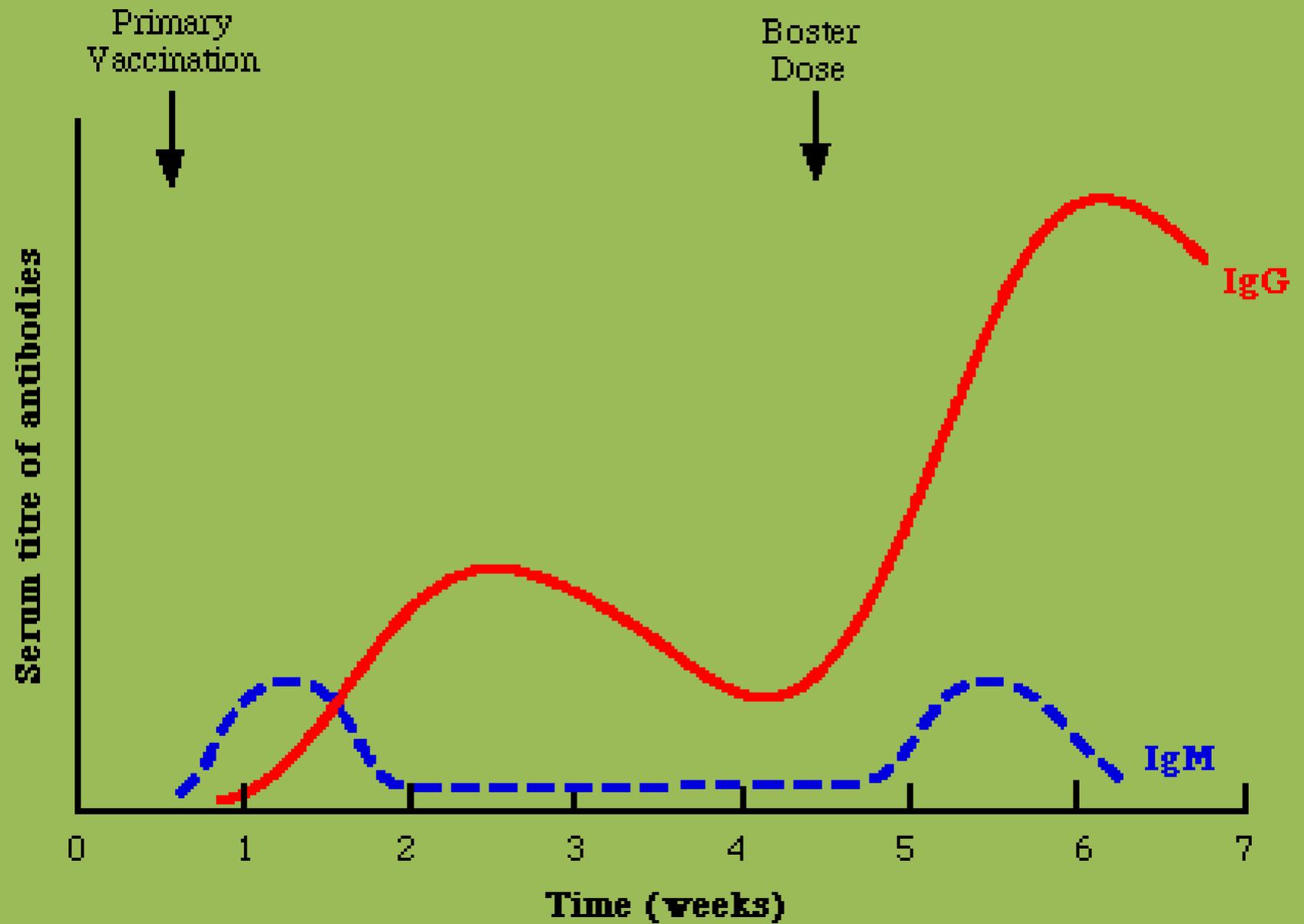
Short Lived

Long Lived

IgM

IgG (Or IgA, or IgE)

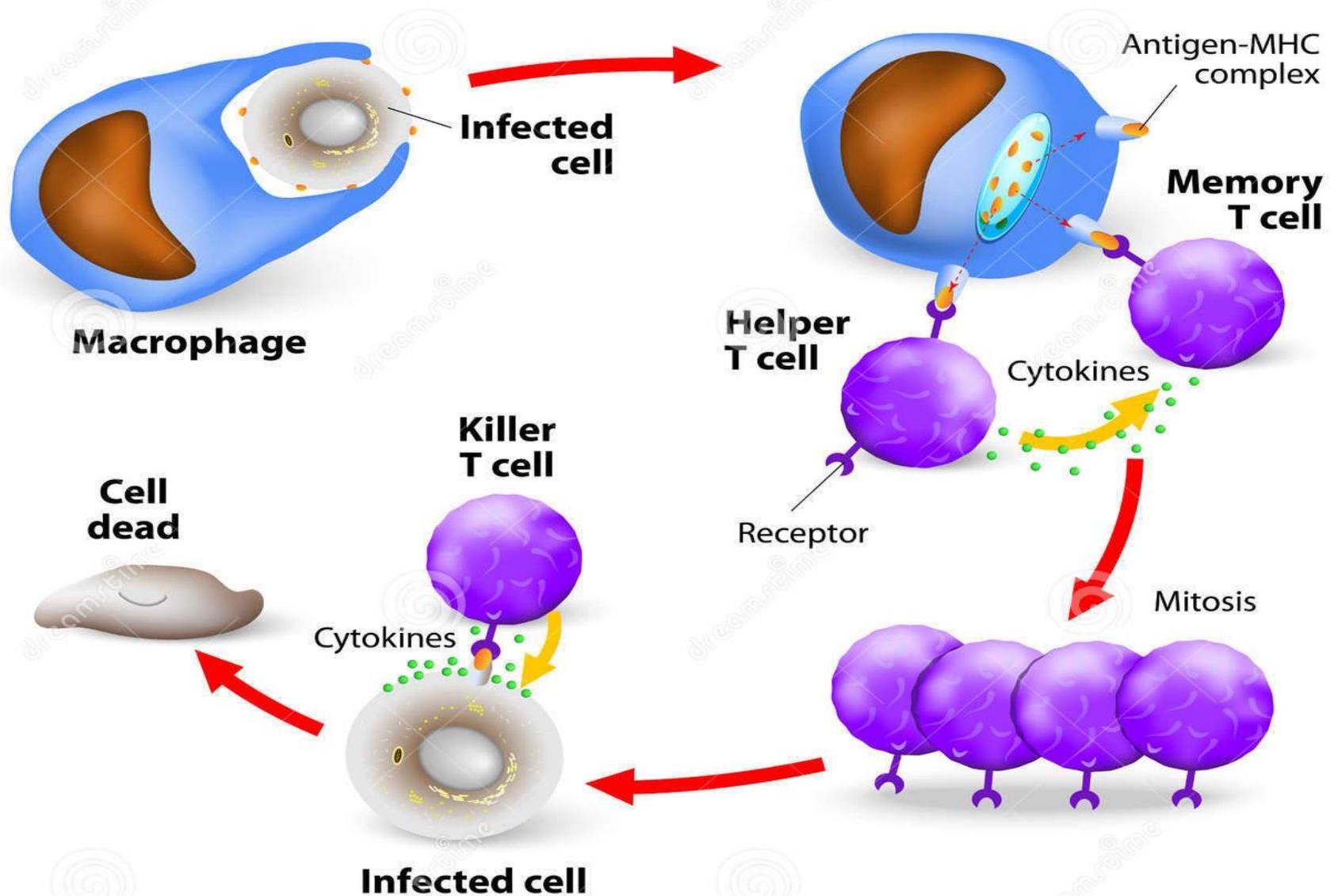




2- Cell-Mediated Immunity

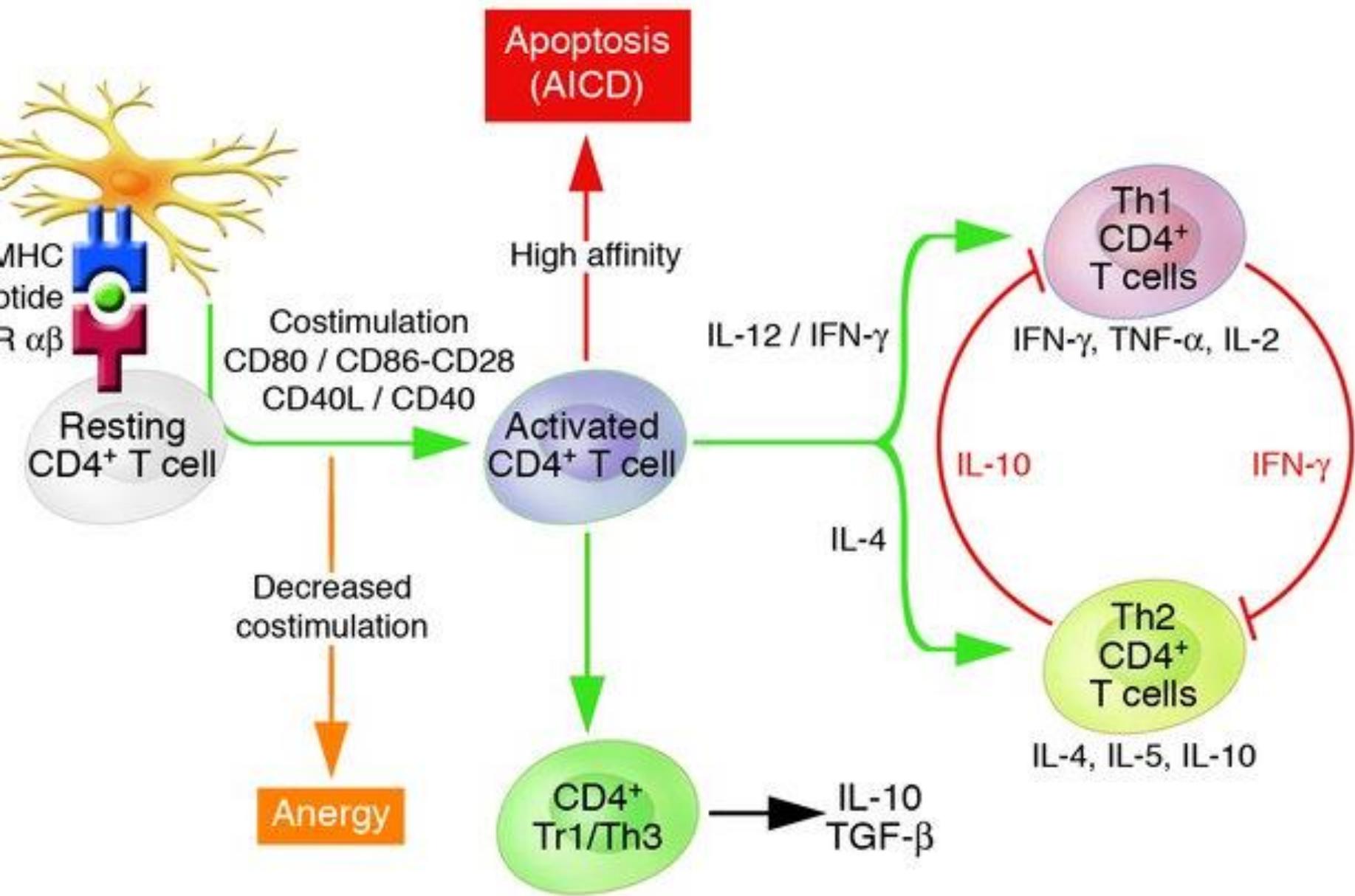
- **Eradicates infections by intracellular microbes.**
- **Consist of the activation of naïve T cells to proliferate and differentiate into effector cells (CD4+ T helper cells and CD8+ cytolytic cells; CTLs) and the elimination of the intracellular microbes.**

CELL-MEDIATED IMMUNE RESPONSE

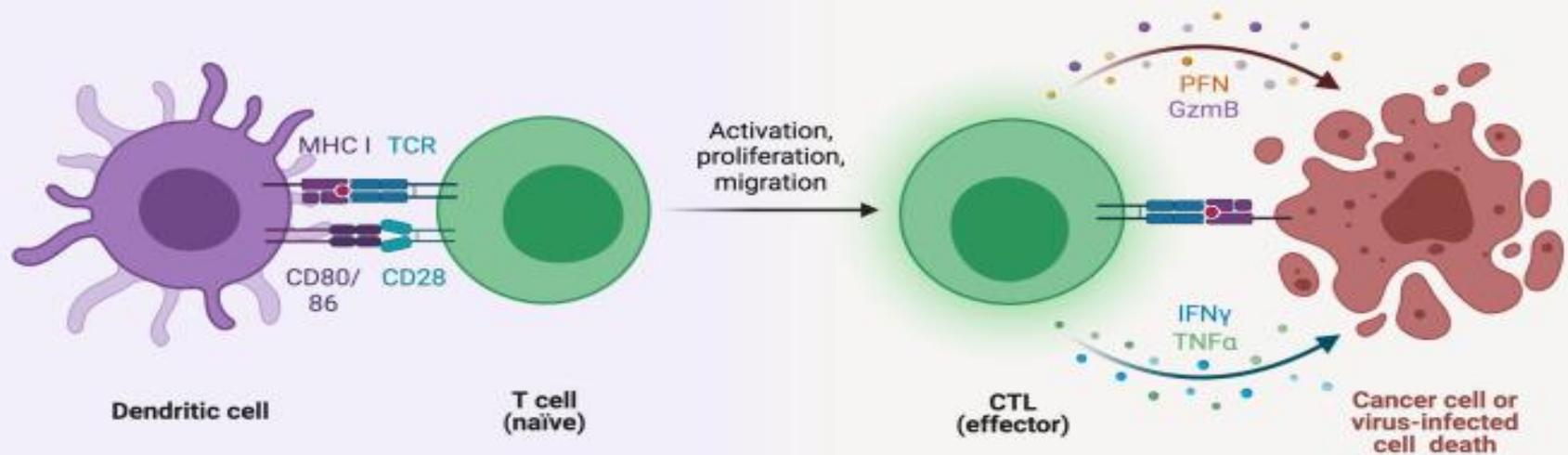


Types of cell-mediated immunity:

- **CD4+ T cells** : differentiate into 2 effector cells according to cytokine production by antigen presentig cell;
 - - IL-12 leads to Th1
 - - IL-4 leads to Th2
- a. **Th1** secretes IFN- γ activates phagocytes to kill microbes.
- b. **Th2** secretes IL-4 and IL-5 which stimulate eosinophil and mast cell degranulation in allergy and helminthic infection



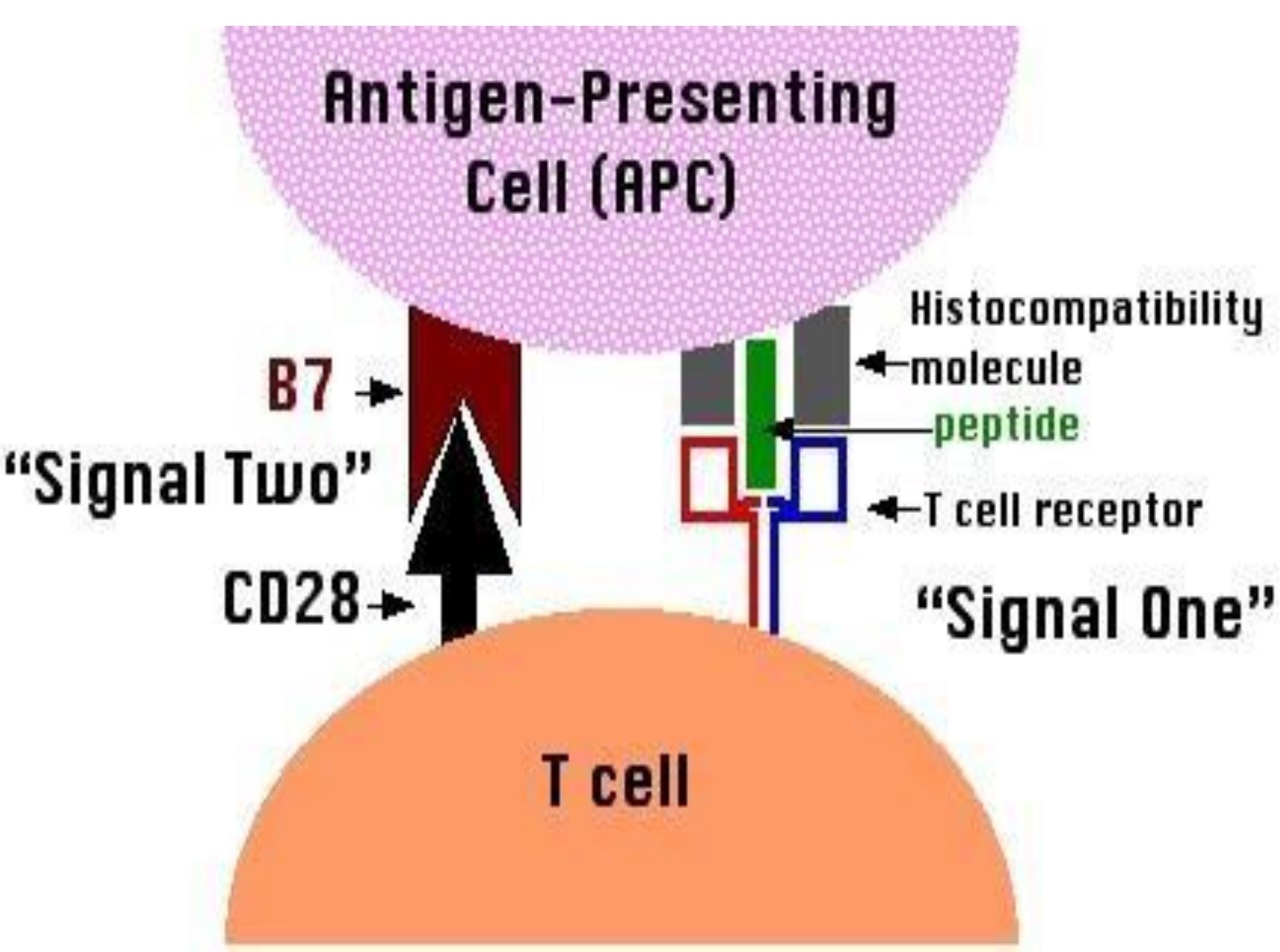
- CD8+ T cells
- kill any cell containing microbes or microbial proteins in the cytoplasm (intracellular) by direct cell cytotoxicity,; eliminating the reservoir of infection .



Activation of T cells:

Activated by two signals

- **The 1st signal:** peptide + MHC on the surface of APCs recognized by TCR-CD3.
- **The 2nd co-stimulatory signal:** is the interaction of B7 molecule on APCs with CD28 on T cells.
- **In absence of 2nd signal,** exposure of T cells to antigen lead to anergy (**unresponsiveness**).



Steps of killing of infected cells by CD8+ CTLs:

- 1- CTLs recognize class I MHC + peptides on the surface of infected “target” cell”.**
- 2 Formation of tight adhesions “conjugates” with these cells.**
- 3 CTLs are activated by IL-2 & IFN- γ to release their granule contents toward the target cell i.e. granule exocytosis.**

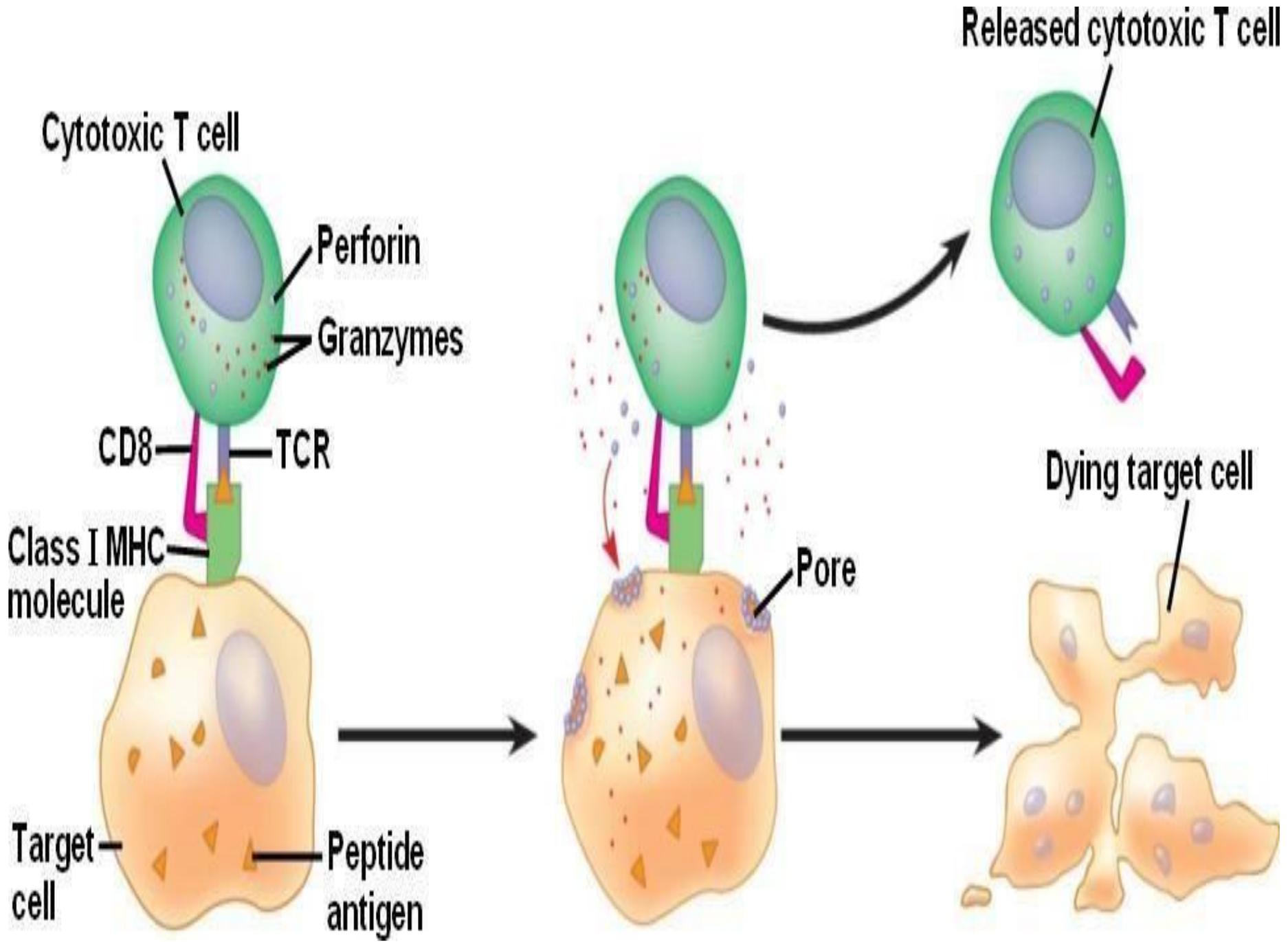
4- The granules contents include:

- Perforin, which form pores in the target cell membrane**
- Granzymes enter the target cells through these pores and induce apoptosis through the activation of caspases.**

5 Detachment of CTL from target cells to kill other target cell.

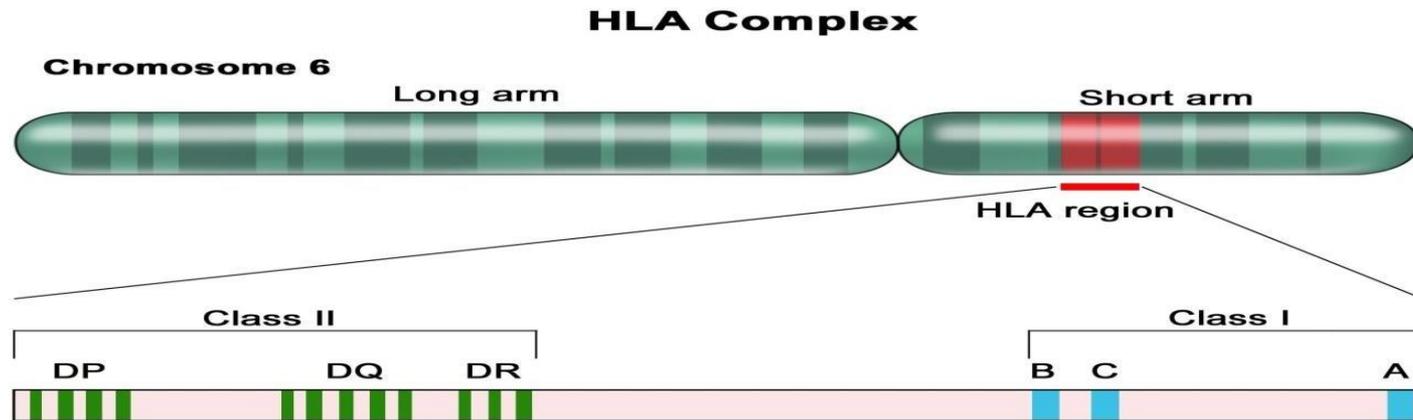
6 Death of target cell .





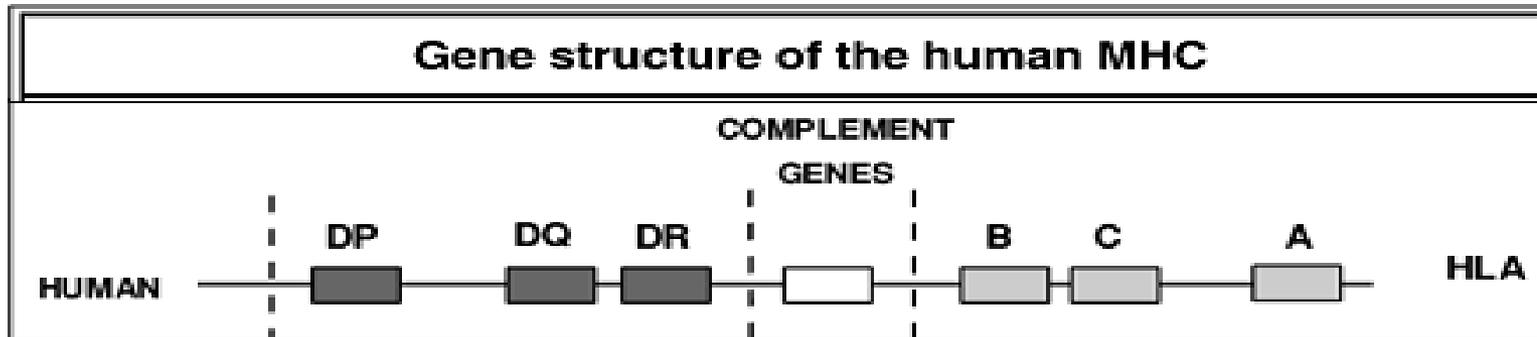
Major Histocompatibility Complex (MHC)

Def: group of genes on short arm of chromosome 6 which produce MHC molecules present on cell surfaces and responsible for display of protein Ag to T cell



Classification of genes

- **Class I MHC genes** → HLA-A & HLA-B & HLA-C
→ role in Ag presentation to Tc
- **Class II MHC genes** → HLA-D region (HLA-DR & HLA-DP & HLA-DQ) → role in Ag presentation to Th
- **Class III MHC genes** → lies between class I & II & not produce MHC but produce some complement components & TNF- α .

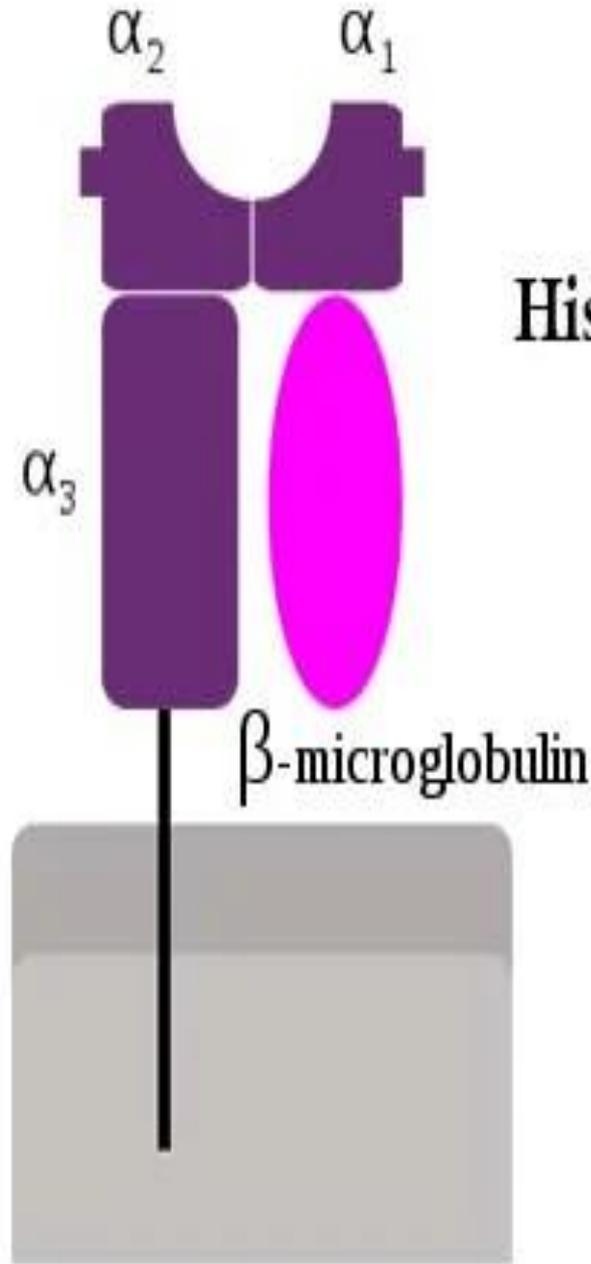
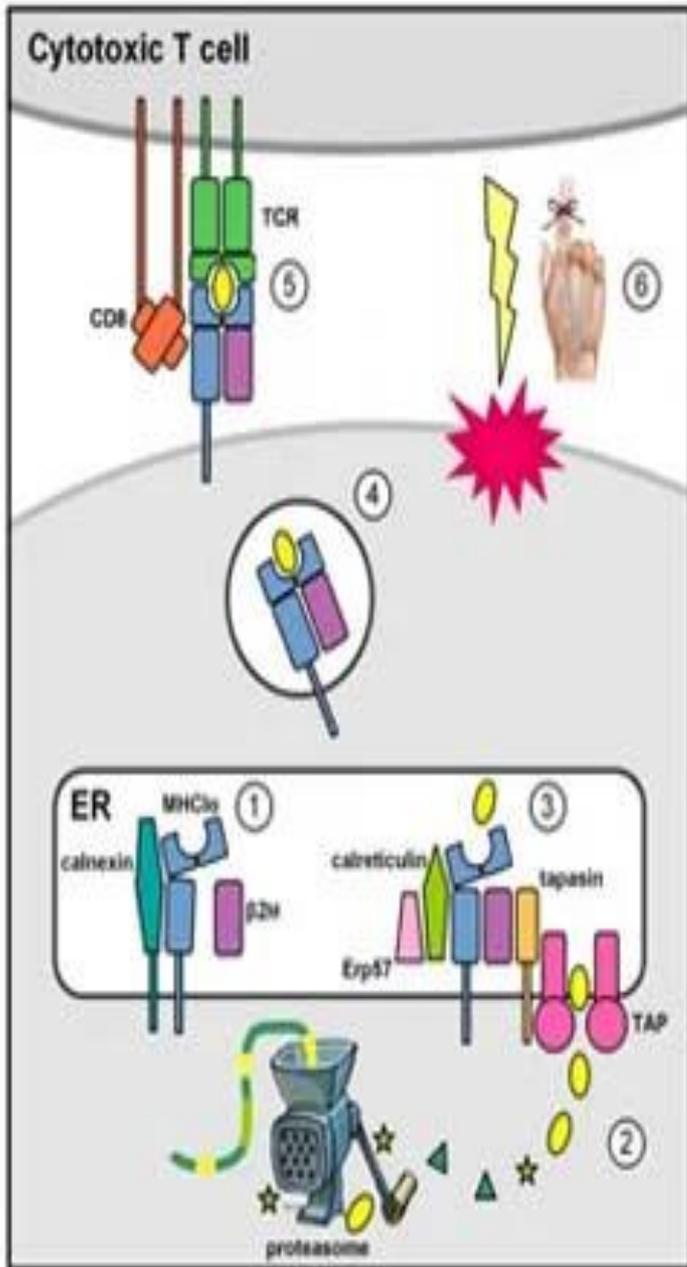


- **Structure and distribution of MHC molecules**

- **Are membrane proteins expressed on cells. Each class I & II molecule consist of extracellular part, a transmembrane and a cytoplasmic part to anchore the molecule to the cell.**

- Class I MHC molecules:

- 2 polypeptide chains, α chain formed of 3 domains ($\alpha 1$, $\alpha 2$, $\alpha 3$), attached to a polypeptide chain called β_2 microglobulin encoded by a gene outside MHC.
- $\alpha 1$ and $\alpha 2$ domains form the cleft or groove which bind peptide.
- Present antigen to CD8+ cells.
- Class I molecules are expressed on all nucleated cells.



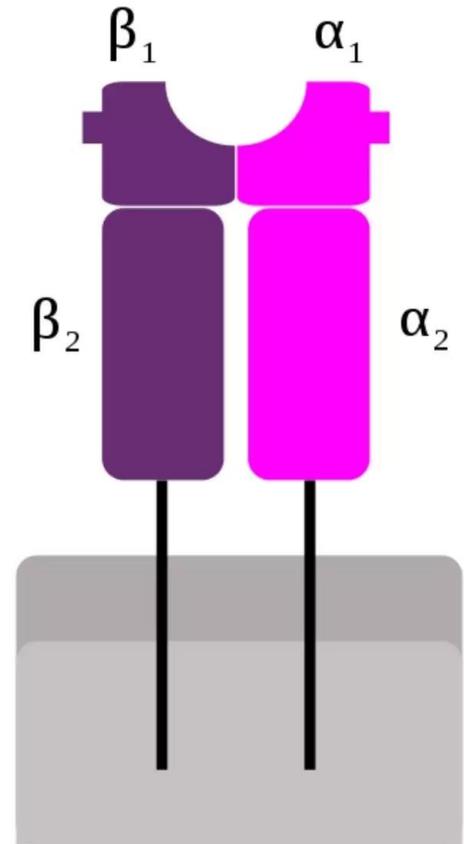
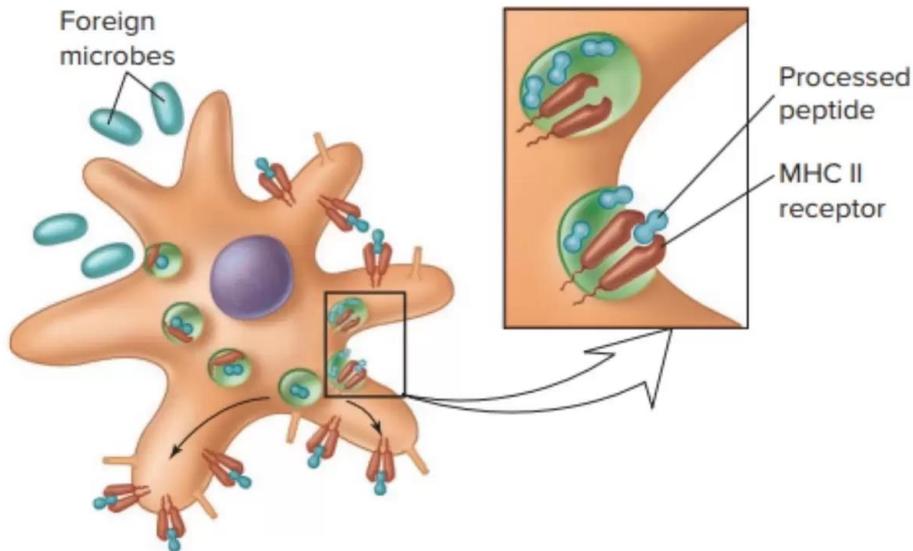
Major
Histocompatibility
Complex
I

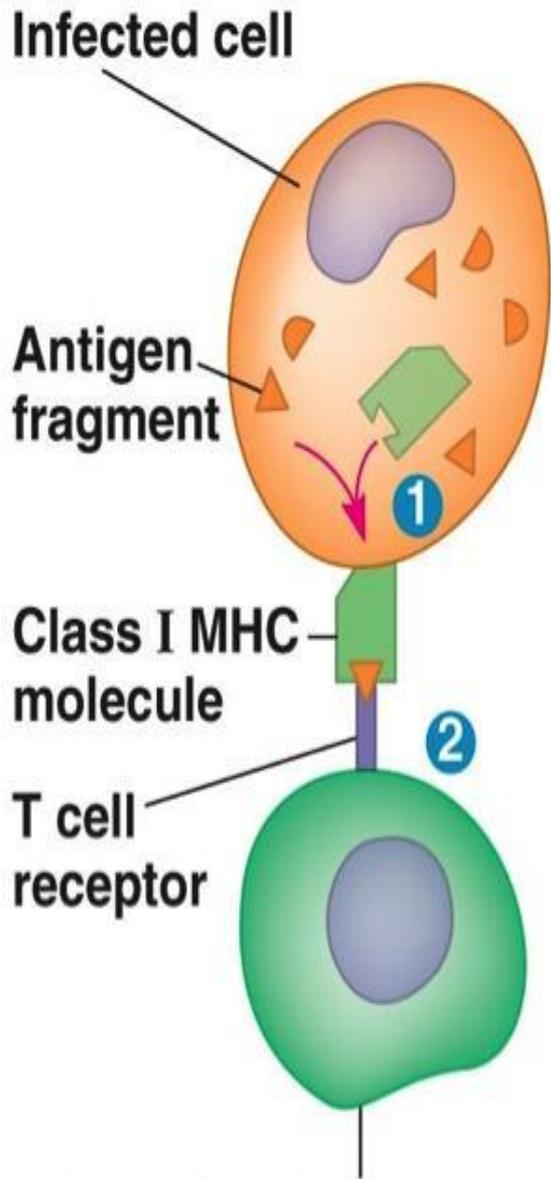
MHC
Class
1

- **Class II MHC molecules:**

- 2 polypeptide chains α chain ($\alpha 1$ & $\alpha 2$) and β chain ($\beta 1$ & $\beta 2$).
- $\alpha 1$ and $\beta 1$ domains form the peptide binding cleft.
- Present antigen to CD4+ cells.
- Class II is expressed on APCs only.

Structure and Functions of Major Histocompatibility Complex II

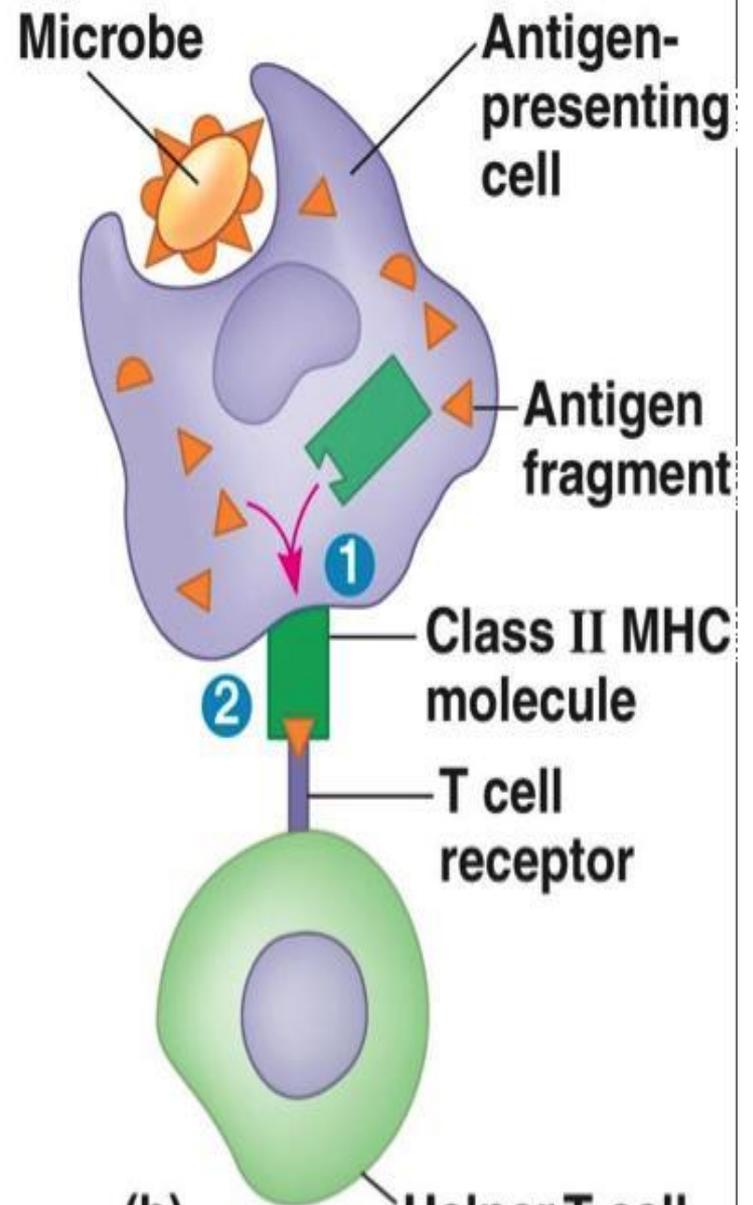




(a) Cytotoxic T cell

1 Antigen associates with MHC molecule

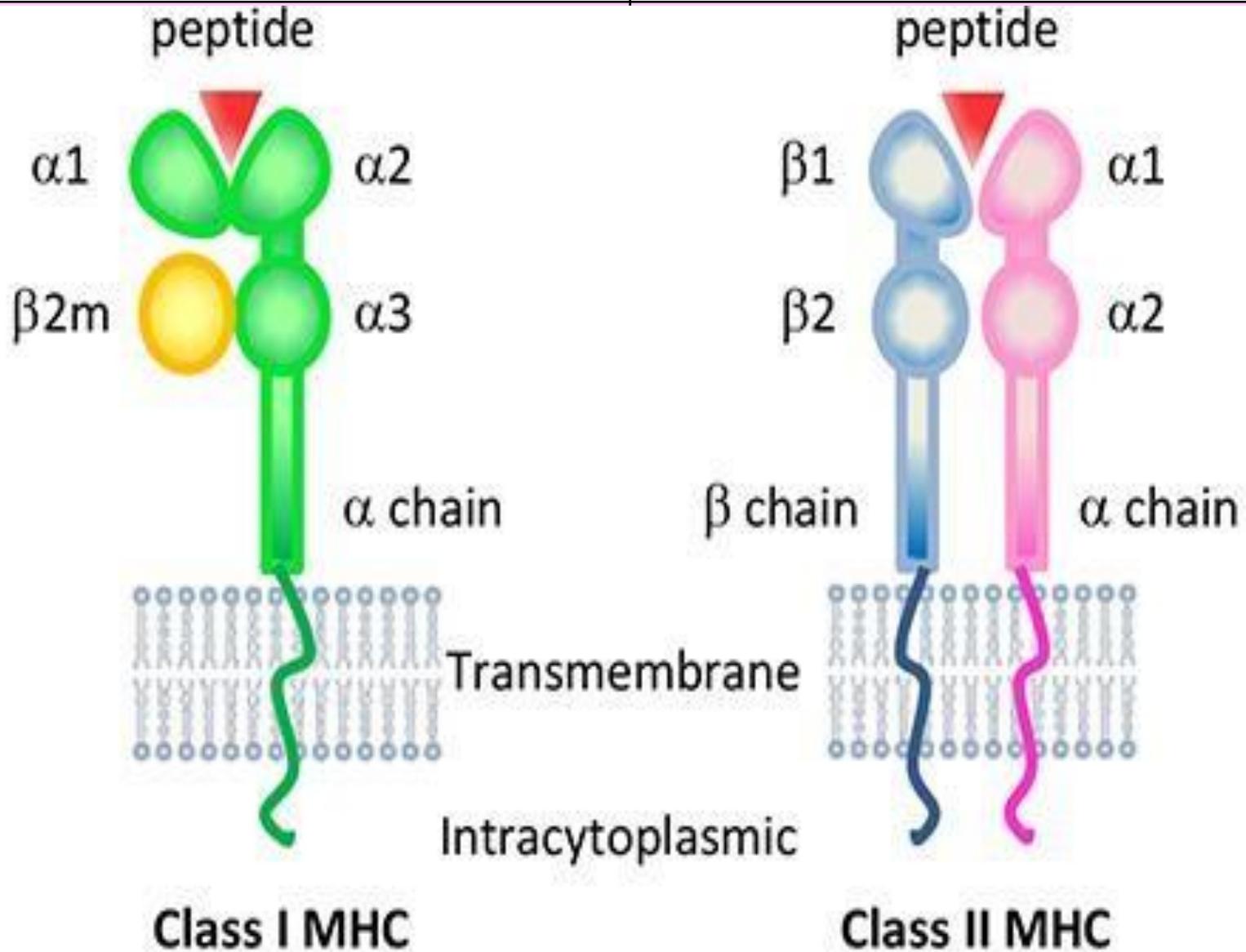
2 T cell recognizes combination



(b) Helper T cell

Class I molecules

Class II molecules

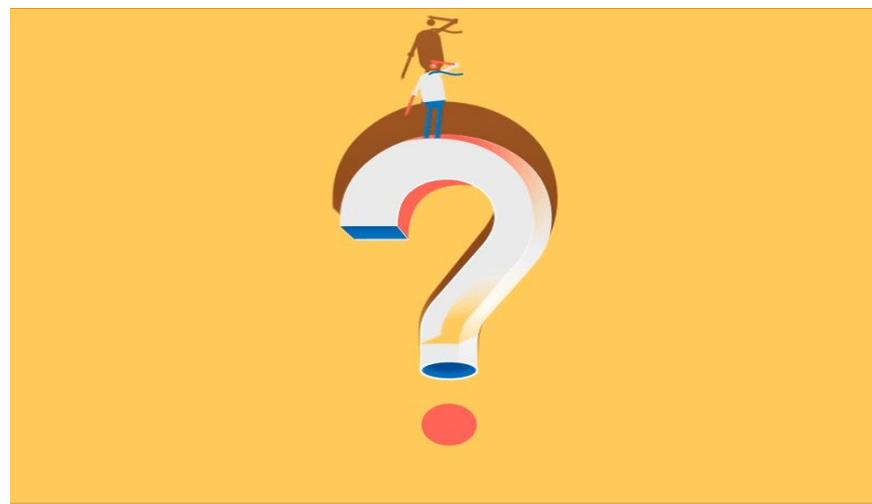


Case scenario, Clinical Correlate, Practice points



An infant boy experiences multiple bacterial, viral, and fungal infections during his first of life. He has also been suffering diarrhea since birth. Tests are performed to determine the likely cause of his symptoms. Serum calcium levels are normal, and the patient's white blood cells change nitroblue tetrazolium clear to bright blue; however, his B- and T-lymphocyte counts are very low.

What is a possible mechanism accounting for his symptoms?



- Class I MHC present antigen to:

- Th (CD4).
- NK.
- Tc (CD8).
- Monocytes.
- Macrophages



- The secondary immune response in antibody formation is characterized by:

- a. it means first exposure to antigen.
- b. it is usually formed of IgM
- c. it is slow in onset
- d. antibody levels increase rapidly
- e. the amount of antibody is low.



- During activation of T cells, the 2nd co-stimulatory signal is the interaction of:**
- a. B7 molecule on APCs with CD3 on T cells.
 - b. B7 molecule on APCs with CD28 on T cells.
 - c. B7 molecule on APCs with CD86 on T cells.
 - d. B7 molecule on APCs with CD4 on T cells.
 - e. B7 molecule on APCs with CD8 on T cells.

References or further readings

- Basic Immunology : functions and disorders of the immune system , fifth edition ; Abul K. Abbas, Andrew H. Lichtman and Shiv Pillai
- Immunology :7th edition ; David Male, Jonathan Brostoff, David Roth and Ivan Roitt

THANK

YOU

