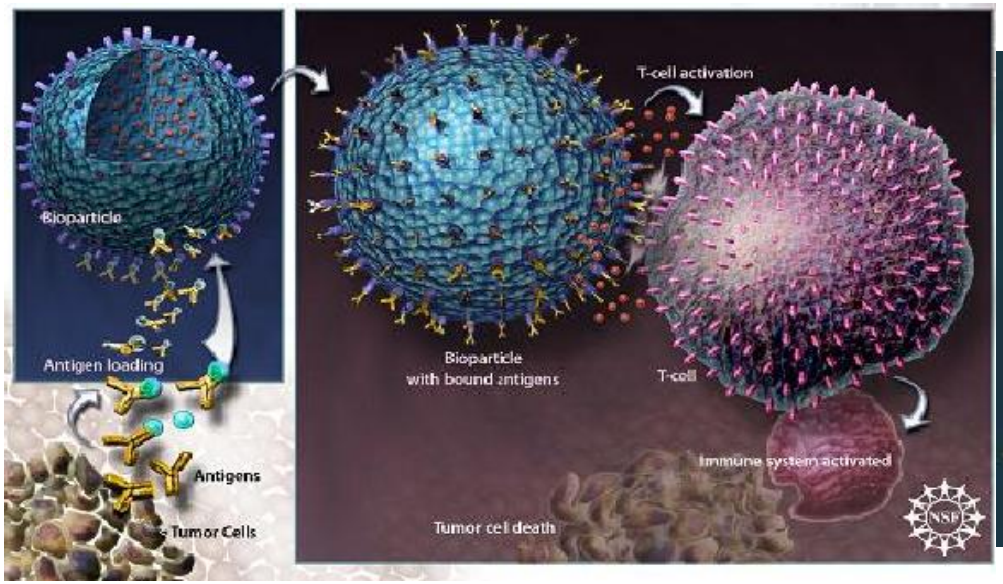
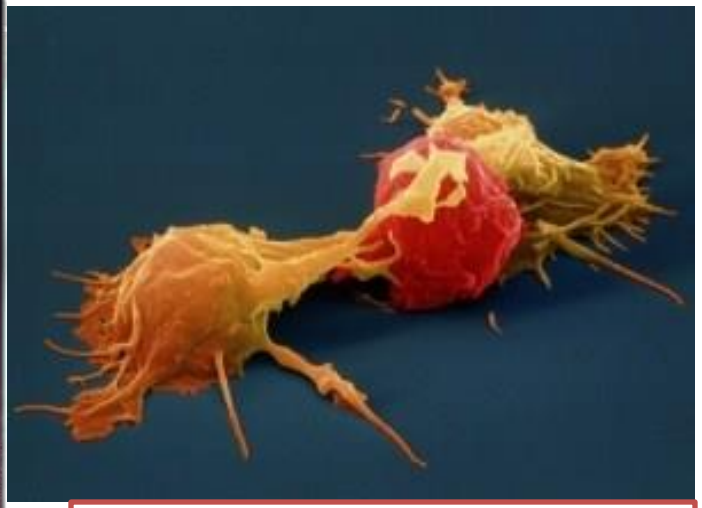
Cell Mediated Immunity

(adaptive immunity)





Dr. Raghed M. Jassem

Antigen-Presenting Cells (APCs):-

1- Dendritic Cells

2- Macrophages

3-B-lymphocytes

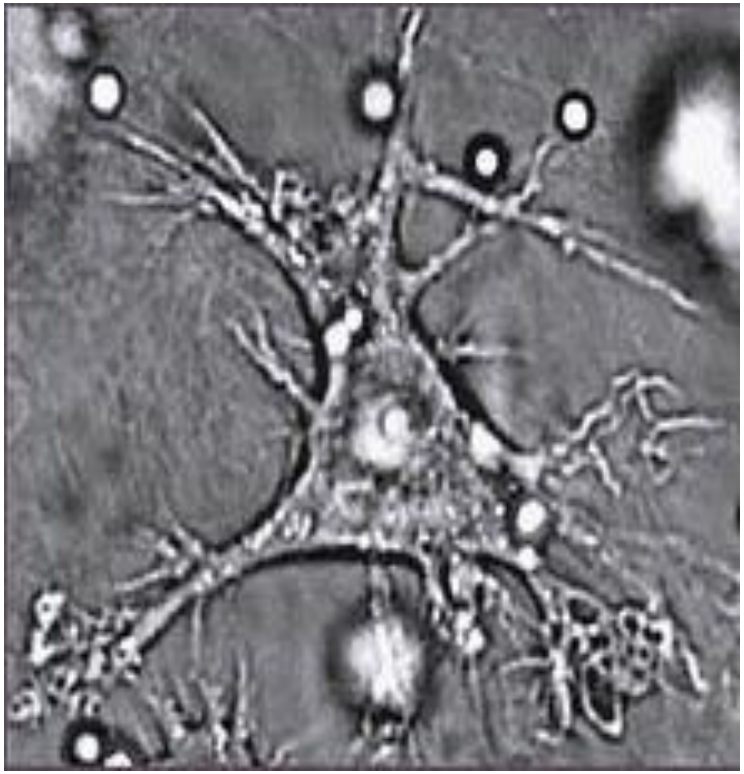
They express both MHC-I and MHC-II molecules .They serve two major functions during adaptive immunity:

a. They capture and process antigens for presentation to T-lymphocytes

b. They produce signals required for the proliferation and differentiation of lymphocytes

Denderitic cells These cells are mostly found in the skin and mucosal epithelium, where they are referred to as Langerhan's cells.

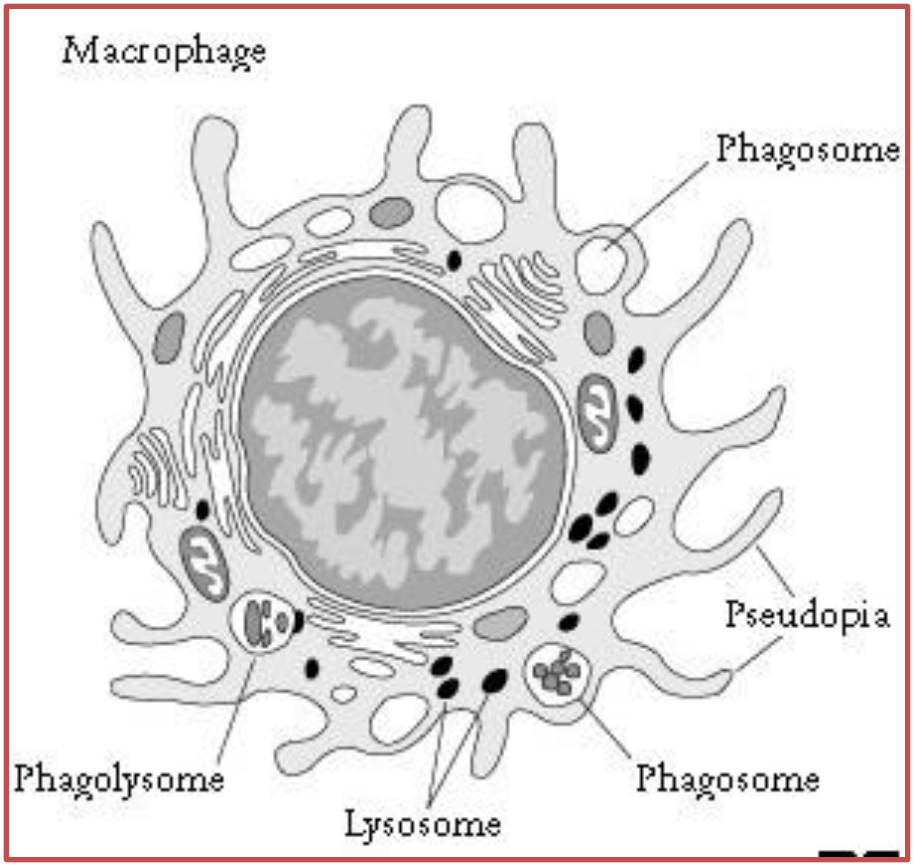
Upon recognition of infectious particles, these cells migrate through the lymphatics to the nearest lymph node .In the follicles of the lymph node they come into close contact with naive T cells and B cells to initiate the adaptive immune response..



Macrophage These cells are part of the innate response. Unlike T and B cells, they do not contain any specific receptors. Macrophages continuously phagocytose self-proteins and cells in their surrounding area, during normal tissue repair and aging (e.g. old red blood cells).

Macrophage takes different names in tissue :-

1-Kupffer cells in the liver
2- Alveolar macrophage in the lung
3-Splenic macrophages in the white pulp
4- peritoneal macrophage , free floating in peritoneal fluid
5- Microglial cells , in the central nervous tissue

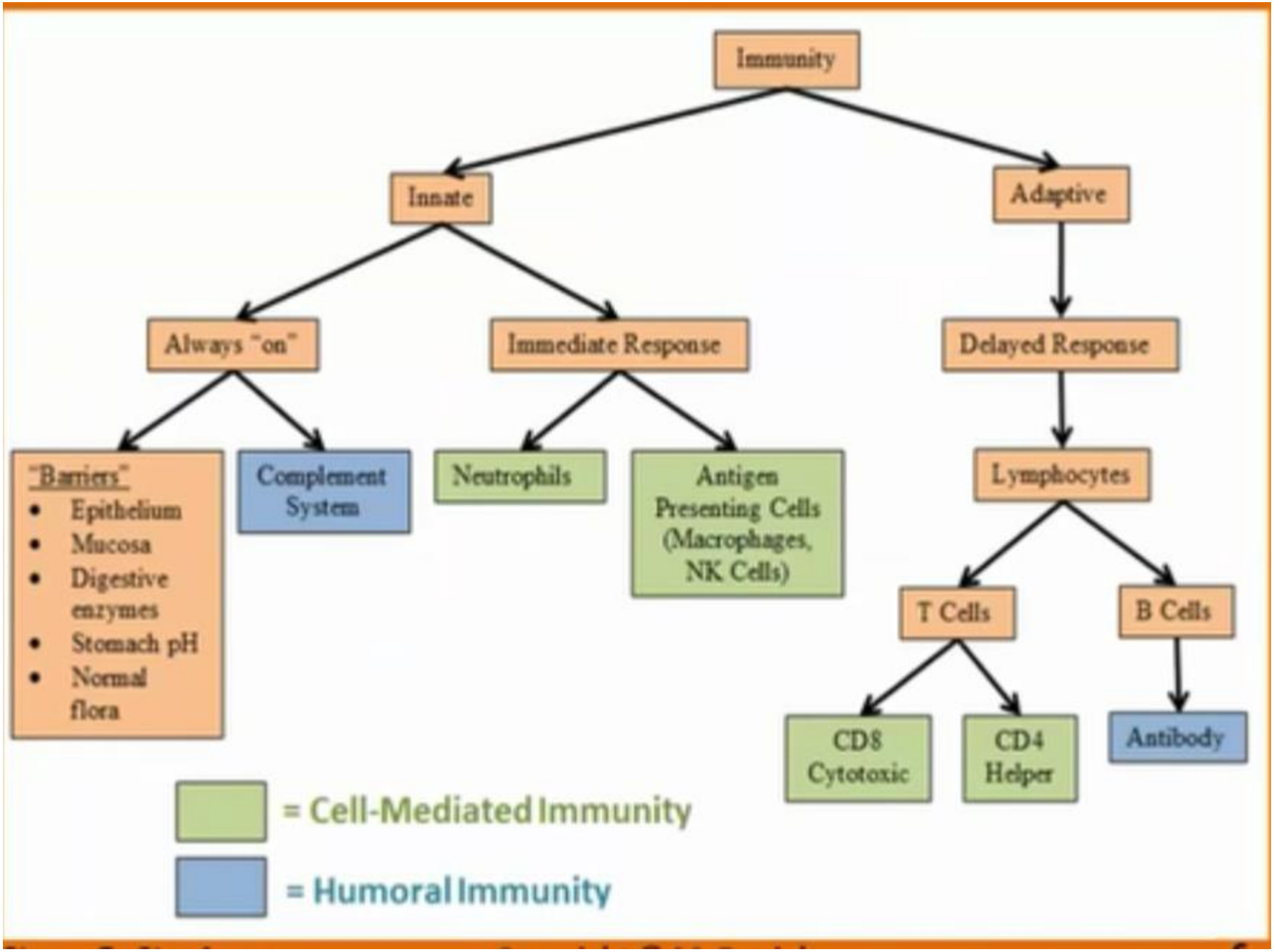


B cells are the least efficient antigen presenting cells. Unlike the other two APC's, they possess specific antigen receptors, surface immunoglobulins.

B cells ingest soluble proteins by pinocytosis. B cells present antigen via MHC-II. But these cells do not express co-stimulatory molecules unless it was activated by Th2 cells

Summary table of Antigen Presenting Cells

	Macrophage	Dendritic Cell	B cell
MHC-II Expression	*Low levels. Induced by Bacteria and/or Cytokines*	*Always Expressed.*	*Always Expressed.*
Antigen type and presentation by MHC	*Extracellular Antigens: presentation via MHC-II*	*Intracellular & Extracellular Antigens: presentation via MHC-I & II*	*Extracellular Antigen binds to specific Ig receptors or Ags presentation via MHC-II*
Co-Stimulation (B7 expression)	*Low levels. Induced by Bacteria and/or Cytokines*	*Always expressed at high Levels*	*Low levels. Inducible upon Activation*
Location	*Lymphoid tissue Connective tissue Body Cavities*	*Lymphoid tissue Connective tissue Epithelium*	*Lymphoid tissues. Blood*


Immunity
Innate
Adaptive
Always "on"
Immediate Response
Delayed Response
"Barriers"
• Epithelium
• Mucosa
• Digestive enzymes
• Stomach pH
• Normal flora
Complement System
Neutrophils
Antigen Presenting Cells (Macrophages, NK Cells)
Lymphocytes
T Cells
B Cells
CD8 Cytotoxic
CD4 Helper
Antibody
= Cell-Mediated Immunity
= Humoral Immunity

Cellular Components of adaptive Immunity:

- **T cells are key cellular component of adaptive immunity** and it involves specialized set of lymphocytes that recognize foreign antigens on the surface of cells, organisms, or tissue.
- **Type of T cells are**
  - **Helper T cells (CD4+)** (turn on immune response) and it will present in two types either Th1 & Th2
  - **Suppressor T cells** (regulatory T cells (Tregs) – turn off immune response. Their major role is to :-

  1- Shut down T cell-mediated immunity toward the end of an immune reaction

  2- Suppress autoreactive T cells that escaped the process of negative selection in the thymus

  - **Cytotoxic T (CD8+)** cells directly attack antigen

Defense against:

- Bacteria and viruses that are inside host cells and are inaccessible to antibodies.
- Fungi, protozoa, and helminthes
- Cancer cells
- Transplanted tissue
- Pregnancy (accept of fetus)

	T Cell Activation	
	CD4 Helper T	CD8 Cytotoxic T
In response to	Extracellular Pathogen	Intracellular Pathogen
Presents Antigen	Dendritic Cell or Macrophage	Any infected nucleated Cell
"Signal 1a"	CD4-MHCII	CD8-MHCI
"Signal 1b"	TCR-Peptide	TCR-Peptide
"Signal 2" (Co-stimulatory)	CD28-B7	

T-cells development and maturation

T cells complete their maturation in thymus (Clonal deletion theory) deactivation of lymphocytes cells after expressed receptors for self-Ags and before they complete their development into full immunocompetent lymphocytes.

- **under go positive and negative selection .(learn how to recognize self MHC Ags)((CD4+ cells recognize MHCII and CD8+ recognize MHC I))**
- **T – cells react with self Ags undergo apoptosis**
- **It is so important as it protect from autoimmune disease and this process called selftolerance**

T cells have an antigen receptor (T cell receptor *CD*) that recognizes and reacts to a specific antigen.

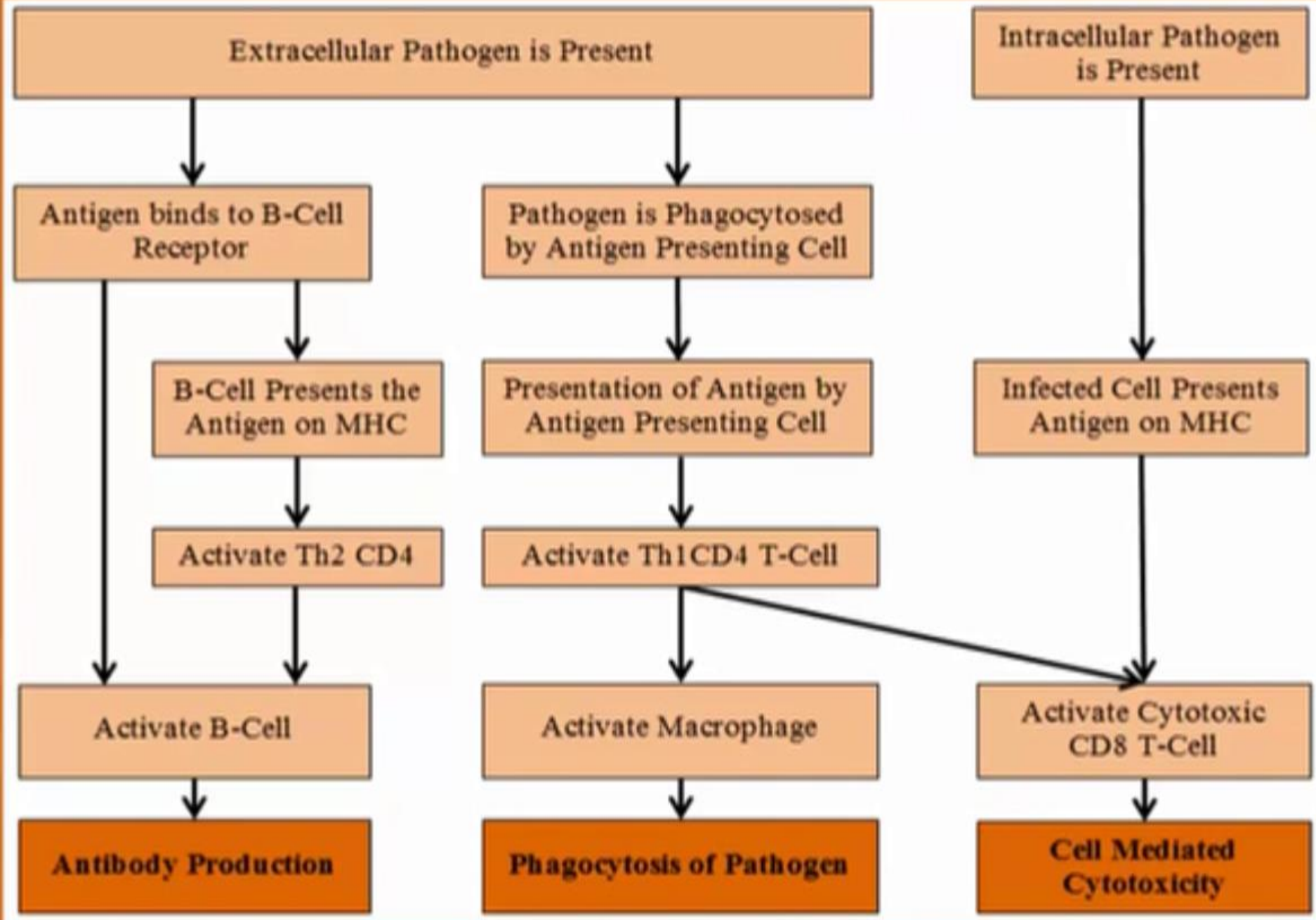
- **T cells respond to :-**

1- Antigens display on a cell's surface (antigen presenting cells (APC))

2- Ags present on the surface of foreign cells ex:-cancer cells

3- Cells infected with intracellular pathogen (virus or bacteria)

When stimulated, they differentiate into effector T cells and undergo clonal selection increases number of T cells.

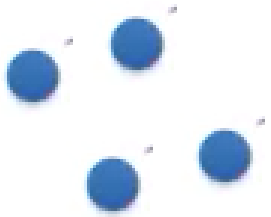


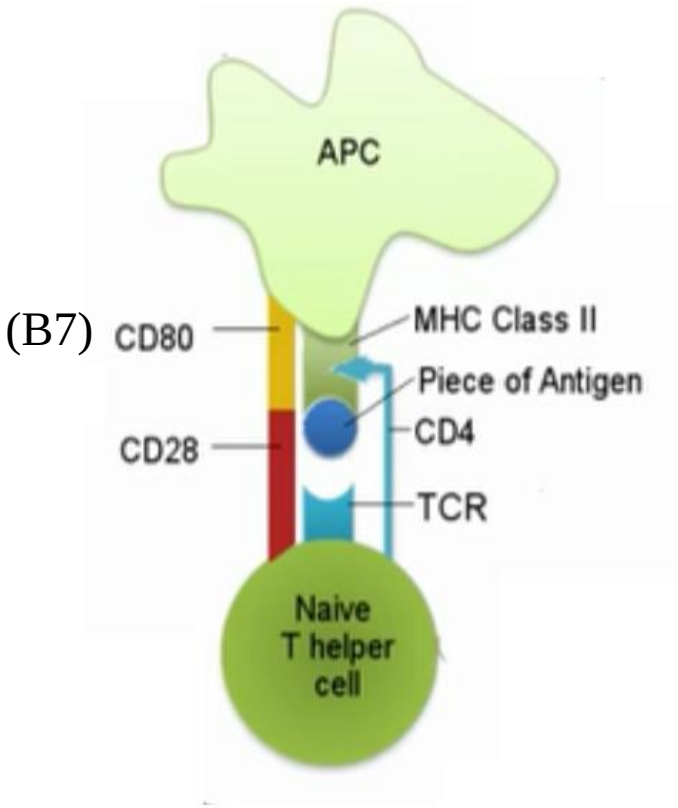
1- Activation of T-helper cells (T-cell response to antigens display on antigen presenting cells (APC))

Extracellular Antigen
(bacteria, protozoa, etc.)

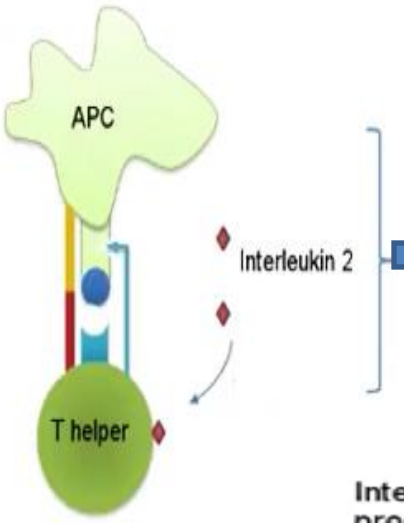
Step 1: An Antigen-Presenting Cell (APC), internalizes and processes an antigen to display on its surface using an MHC class II molecule.

Step 2: The APC presents the processed antigen with MHC class II to a Naive T helper (TH) cell. The TH cell will recognize the antigen and MHC class II with its antigen receptor and CD4 molecule. In addition, the TH cell uses its CD28 to recognize the CD80 on the APC.





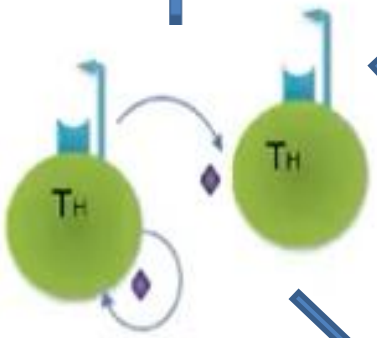
Step 3: Upon dual recognition (first signal: MHC:Antigen with TCR:CD4; second signal: CD80 with CD28) the naive T cell is activated.The TH cell binds to Interleukin-2 (IL-2). IL-2 causes T cells to undergo proliferation and differentiation.



Interleukin 2

Interleukin-2 stimulates production of clone T-cells

Step 4: T cells proliferate into a



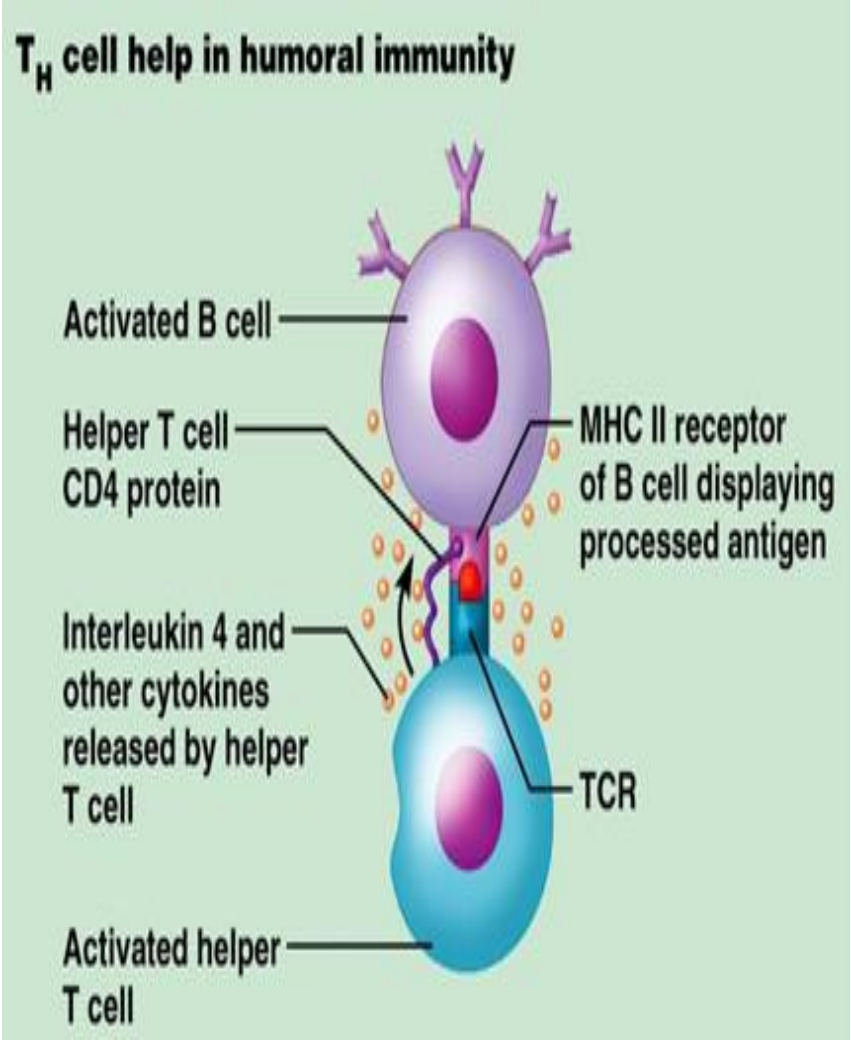
TH1 cells interact with macrophages and other effector cells to heighten immune reactions

TH2 cells are used for activated B cells and the humoral response

Regulatory T cells regulate the inflammation reaction and help regulate the immune reaction.

Memory T cells are distributed to immune tissues for long-term immune protection.

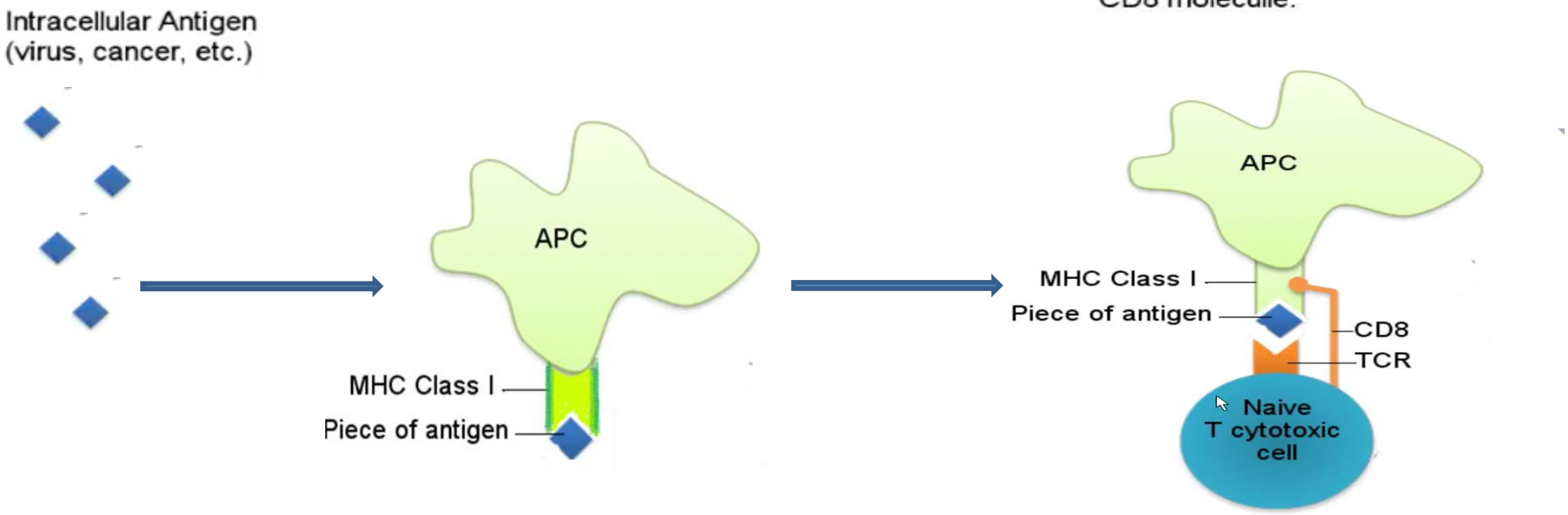
- T_{H2} cells interact directly with B cells that have antigen fragments on their surfaces bound to MHC Class II receptors
- T_{H2} cells stimulate B cells to divide more rapidly and begin antibody formation
- Most antigens, however, require T_{H2} co-stimulation to activate B cells



2- Activation of Cytotoxic T- cells to the intracellular Ags (A)

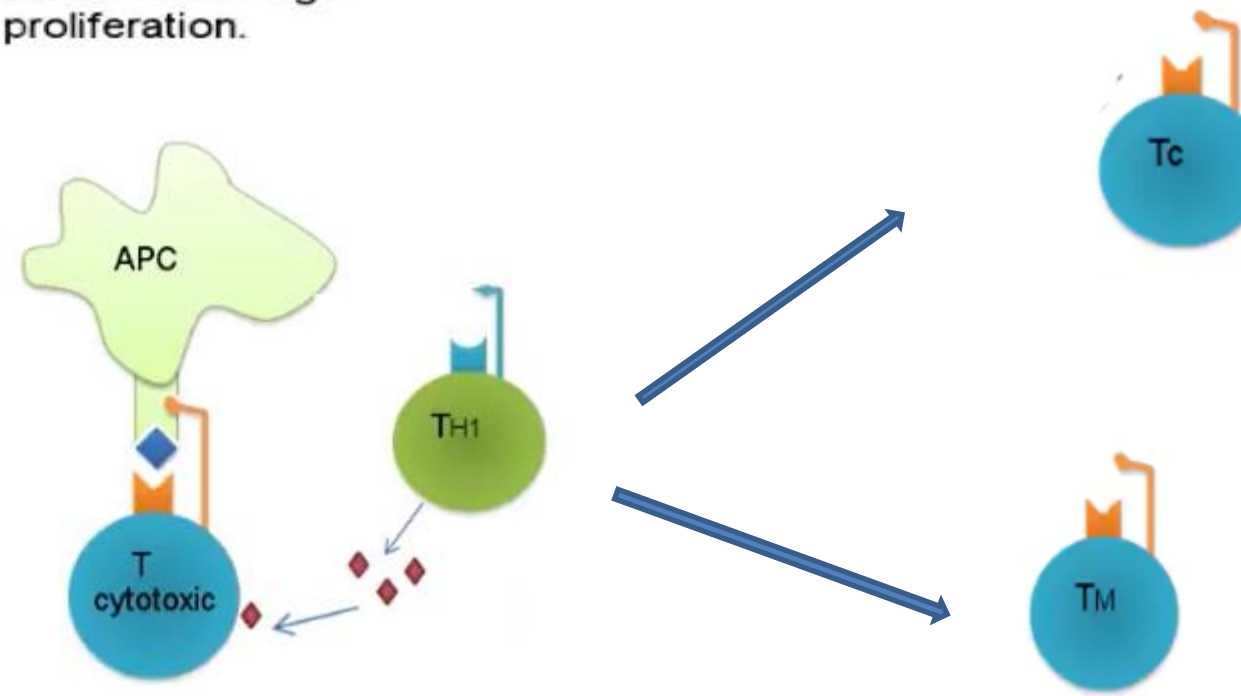
Step 1: An Antigen Presenting Cell (APC) internalizes and processes an antigen, then displays it on its surface using an MHC Class I molecule.

Step 2: The APC presents the processed antigen with the MHC Class I to a naive T cytotoxic (Tc) cell. The Tc cell will recognize the antigen piece and MHC Class I with its TCR and CD8 moleculle.



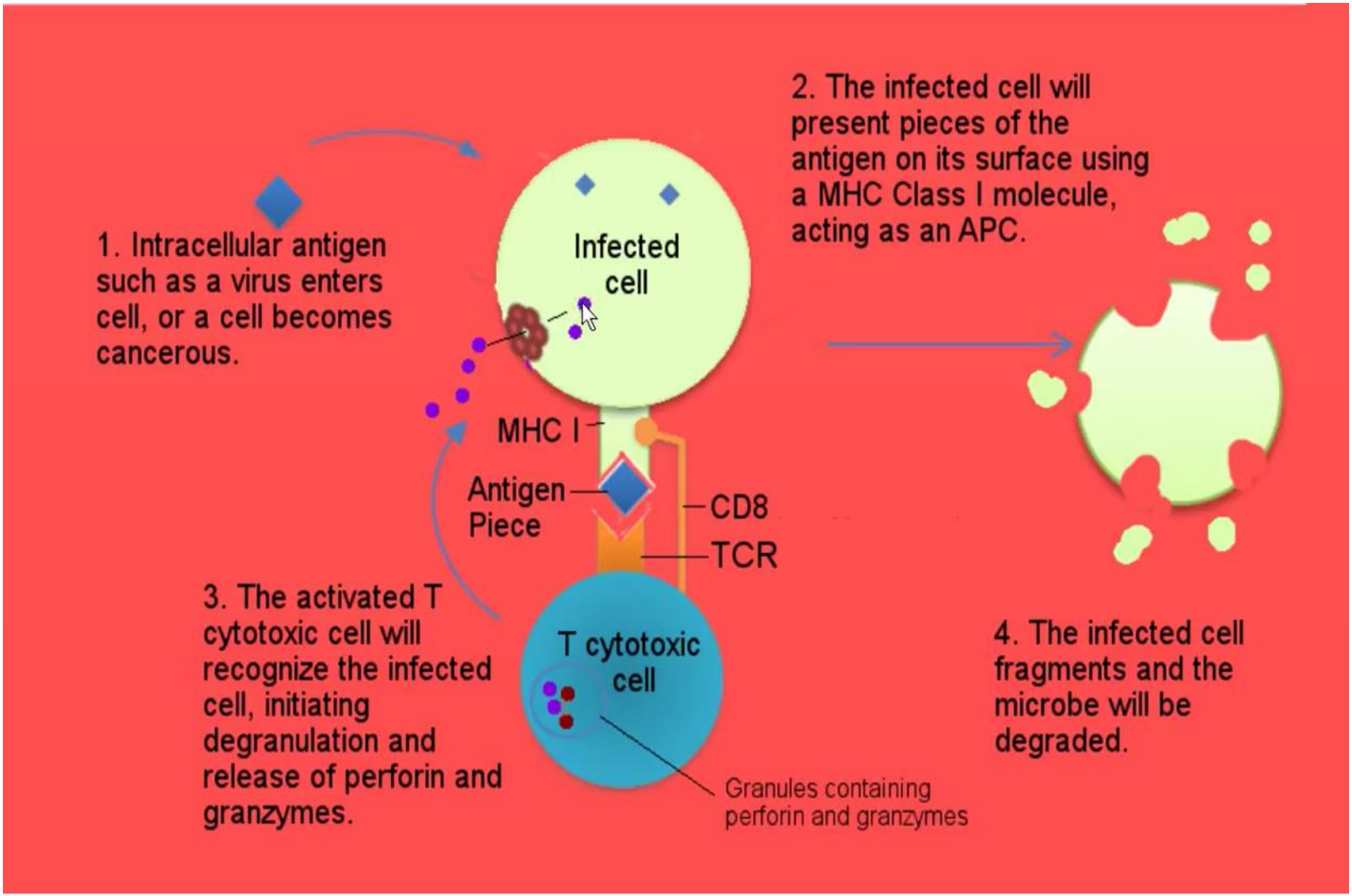
Step 3: Upon recognition of the MHC Class I by the CD8 on the Tc cell, and the piece of antigen by the TCR, interleukin 2 (IL-2) is released by TH1 causing the Tc to undergo proliferation.

Tc cells will interact with infected cells to destroy them.



T memory cells will be distributed to immune tissues for future protection.

2- Activation of Cytotoxic T- cells to the intracellular Ags (B)



T Lymphocyte Activity

- Primary T cell response usually peaks within a week
- T cells then undergo apoptosis within a month
- Reduced activity parallels elimination of antigen
- A few Memory T cells remain to respond to any future exposure to the same antigen

Suppressor T_s Lymphocytes

- T_S cells – immune regulatory cells which release cytokines that suppress the activity of both T cells and B cells

- T_S cells - generated when other specific T cell clones are generated

- Negative feedback control to bring the body back to normal after the “battle” has been won

Natural killer cells

- Natural Killer" cells are large granular lymphocytes which are an important part of innate immunity and typically constitute about 10% of total blood lymphocytes.

- NK cells (belonging to the group of innate lymphoid cells) are defined as large granular lymphocytes (LGL) and constitute the third kind of cells differentiated from the common lymphoid progenitor - generating B and T lymphocytes in the bone marrow , it complete development without the influence of the thymus.

Key surface markers (Receptors on the NK surface) :

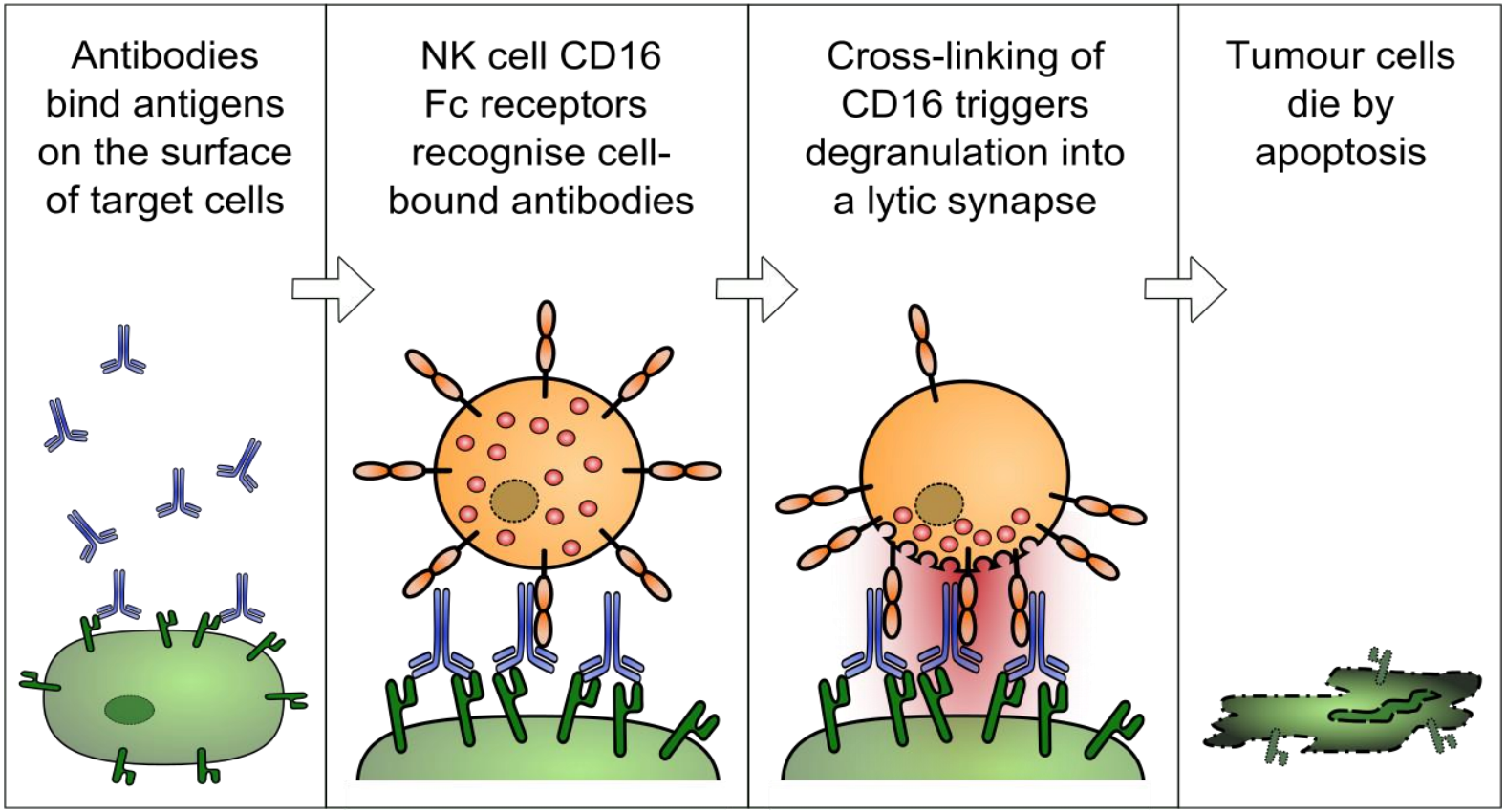
1- CD16 (FcγRIII), binds IgG and promotes the antibody-dependent cytotoxicity (ADCC) of NK cells

2- CD56 (adhesion molecule) Activation receptors, bind to signals from infected cells, enhance killing

3- Killer cell Immunoglobulin-like Receptor (KIR): recognize MHC class I molecules (HLA-A, B, C) delivers a *negative* signal to the NK cell (inhibit killing activity).

If a viral infection causes the target cell to express *reduced levels of HLA-A , B or C* molecules (several viruses can do this), then the negative signal to the NK cell is reduced and the target cell may be killed.

Alternatively, if the target cell expresses modified glycoproteins in its membrane (which can also result from viral infection, or from malignant transformation), then an increased *positive* signal may also result in target cell killing.



Key cytokines:

– Interleukin-15: required for NK cell development

– IL-12, IL-18 & IFN-γ : cause activation & cytotoxicity.

NK function

1- Surveillance function: NK cells are found in:

– Peripheral blood
– Secondary lymphoid organs: spleen and activated lymph nodes
– Peripheral tissue: liver, lung and the decidual lining of the uterus

2- Specific NK cell functions :-

1- Control of viral infections

2- Control of malignant cells

3- Role in hematopoeitic stem cell transplantation

4- NK cells has a role in maintain or lost of pregnancy

Cytokines: are immunomodulatory proteins representing a group of proteins and peptides that are used in organisms as signaling compounds allowing communication between the cells. **They are particularly important in both innate and adaptive immune responses.**

Due to their central role in the immune system, cytokines are involved in a variety of immunological, inflammatory and infectious diseases, also they are involved in several developmental processes during embryogenesis.

Cytokine -mediated effects

- **Cell growth**
- **Cell differentiation**
- **Cell death**
- **Induce non-responsiveness to other cytokines/cells**
- **Induce responsiveness to other cytokines/cells**
- **Induce secretion of other cytokines**

- They are produced by a variety of cells (both haemopoietic and non-haemopoietic) and same cytokine is even produced by different types of cells at the same time in response to any foreign particle

- Although various classifications for cytokines have been suggested on the basis of their mode of action, structure, receptors, etc. but depending on their inflammatory reactions, they are broadly categorized into :-

1- **Pro-inflammatory cytokines :- are produced by Th-1 , they are TNF-α, TNF-β, IFN-γ, IL-1, IL-2, etc. and they activated Tc and macrophages to stimulate cellular immunity and inflammation,**

2- **Anti-inflammatory cytokines :- are produced by Th-2 cells , they are IL-4, IL-5, IL-10, IL-12, etc. which stimulate antibody production by B cells.**

- **Interleukins:** **Communication between WBCs.**
- **Interferons:** **Protect against viral infections.**
- **Chemokines:** **Attract WBCs to infected areas.**

What are the differences between Ig and cytokines?

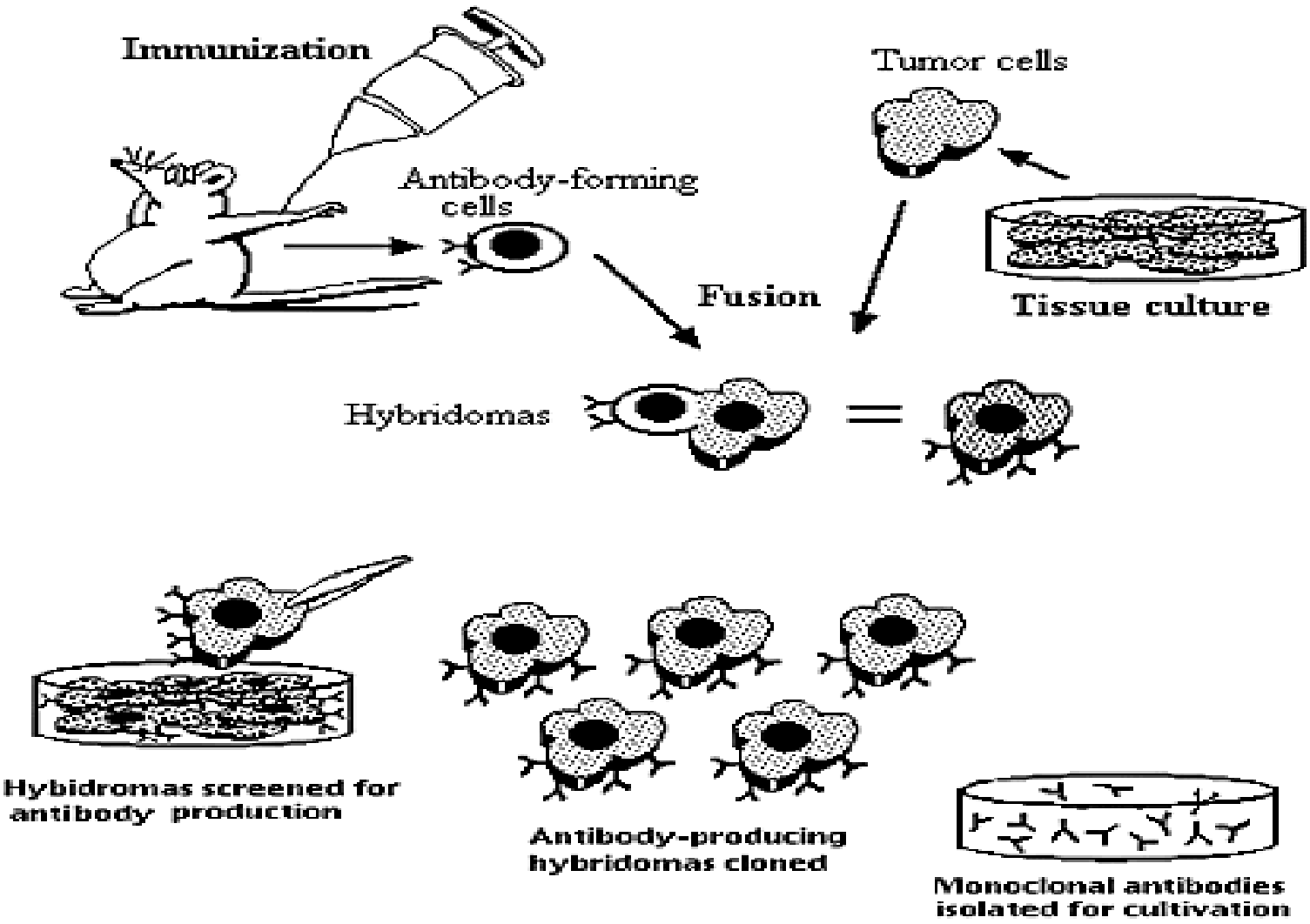
Cluster of differentiation (often abbreviated as **CD**) is a protocol used for the identification and investigation of cell surface molecules present on WBC, providing targets for immunophenotyping of cells.

Physiologically, CD molecules can act in numerous ways, often acting as receptors or ligands (the molecule that activates a receptor) important to the cell.

All T and B cells have about 10^5 = 100,000 molecules on their surface. **B** cells are coated withCD19, CD21, CD35,CD40, and CD45, while T cells express CD2, CD3, CD4, CD8, CD28, CD45R.

Monoclonal Antibody

MoAb :-Process by which large quantities of specific antibodies (targeted against a particular antigen) can be produced.



Monoclonal Antibody Production

Monoclonal Antibody Production

1- A mouse is immunized by injection of an antigen X to stimulate the production of antibodies targeted against X.
2- The antibody forming cells are isolated from the mouse's spleen.
3- Antibody-forming cells are fusing with tumor cells grown in culture. The resulting cell is called a **hybridoma**.
4- Each hybridoma produces relatively large quantities of identical antibody molecules.
5- hybridoma cells allowed to multiply in culture to produce a population of cells, each of which produces identical antibody molecules and these antibodies are called "**monoclonal antibodies**" because they are produced by the identical offspring of a single, cloned antibody producing cell.

Application

•Diagnostic tests like:- **Immunofluorescence** is a technique depend on using specific fluorescent dyse to identify specific bio-molecule within a cell allow visualization of the target molecule through the sample. Ex:- CD (MoAb), immunohistochemistry.

•Therapeutic treatment :- Ex:- Cancer treatment ;one possible treatment for cancer involves monoclonal antibodies that bind only to cancer cell and induce an immunological response against the target cancer cell