DOCTOR 2020 | JU

IMMUNOLOGY

WRITER : Belal Al-hamaideh .

CORRECTOR : Sham Al-Salim.

DOCTOR: Anas Abu Humaidan.

HELLO EVERY ONE

In the last lecture we talked about phagocytes and Granulocytes as a part of the innate immune system

This lecture will give us a knowledge about

1- (Dendritic cells)

Which link the two parts of the Immune system and lymphocytes (T cells, B cells)

2- (Natural killer cells)

APCs : (dendritic cells)

link the two part of Immune system

(INNATE AND ADAPTIVE)

REMEMBER :

- Phagocytes
- Mast Cells, Basophils, Eosinophils (we put them together because they have similarity in the function and shape).
- Antigen-Presenting Cells.
- Lymphocytes.

1- Antigen presenting cells – APCs :

They are a population of cells that are specialized for capture microbes and other antigens (foreign bodies) → degrade them and present them on their surfaces using **MHC** proteins (we will discuss them later) → in order to display them to lymphocytes (T-cells (in specific) they can't bind to microbes directly) → and provide signals that stimulate the proliferation and differentiation of the lymphocytes.

APCs link responses of the innate immune system with the adaptive immune system, therefore they may be considered a components of both systems.

Some Notes Here

Lymphocytes can't work without **APCs.** It is necessary for presenting the antigen.

Dendritic cells, Macrophages and B cells

examples of **APCs** which activate T cells as they recognize the presented antigens on APCs' surface.

"Dendritic cells are the most important ones".

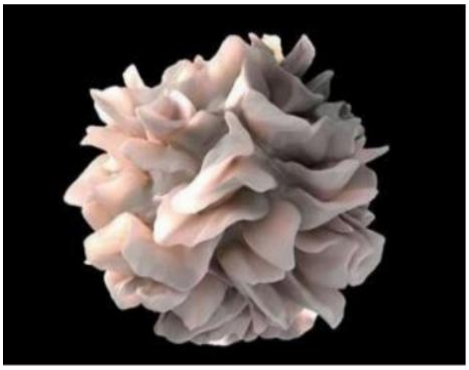
1- Dendritic cells :

The most important APCs for activating naive T Cells , which originated from Monocytes from the bone marrow .

- Found in areas where we find a lot of Microbes such as skin, mucosal epithelium and GIT.

- They have long membranous projections and phagocytic Capabilities.

Once Dendritic cells find an antigen, they become activated and mobile, and they carry the antigen through lymph vessels to the lymphatics where we can find T cells .



Refer to the microscopic image to see how **keratinocytes** are interspersed by dendritic cells (darkly stained particles)

some fluid leaks from blood into tissues , and undoubtedly it needs to go back to blood ,as it gets contaminated in the tissue , so the fluid and its contents including dendritic cells leave the tissue as part of the lymph and travels through lymph vessels until reaching lymph nodes where it can be sterilized by lymphocytes.

Similar to the dendritic cells , we have what is call :

Follicular Dendritic Cells (FDCs):

They are not dendritic cells. What are they ?

- cells with membranous projections that are found intermingled in specific regions in lymphoid follicles of the lymph nodes, spleen, and mucosal lymphoid tissues, called **germinal centers**, which are a specialized collections of activated B cells (this region for maturation (activation) of B cells).

FDCs are immobile, so their function is catching free antigens and presenting them on their surfaces in order for B cells to be recognized

This process helps in maturate B cells .

Here is a comparison between DCs and FDCS :

	DCs	**FDCs**
Precursor	Monocytes- bone marrow	Mesenchymal stem cells
mobility	mobile	Immobile
present antigens to	T cells	B cells

***Notes

1- DCs have many precursors but for simplicity we just mention monocytes.

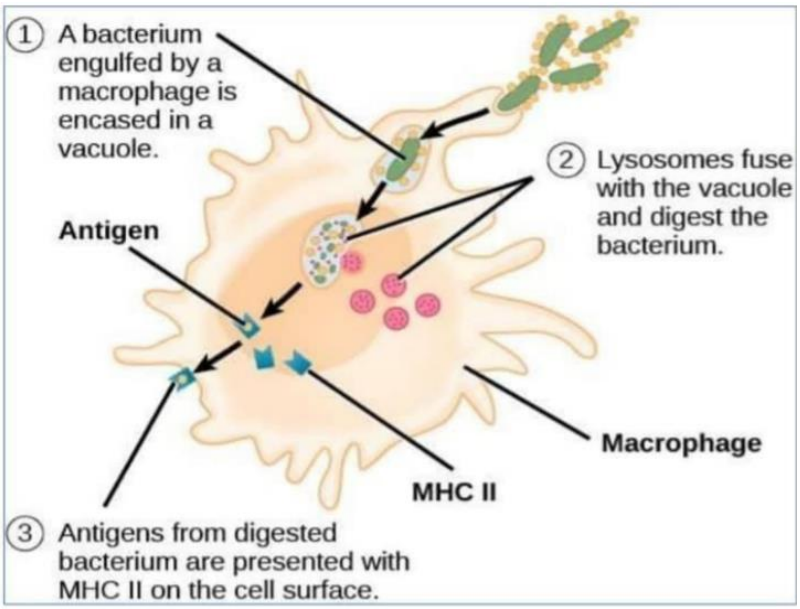
2- FDCs have a role in maturation of B cells - will be discussed latter - .

2- Macrophages :

A type of APCs which engulfs microbes and present them as antigens on its surface by **MHC II proteins.**

To be presented to Helper T lymphocytes at the sites of infection, which leads to helper T cell activation and production of molecules that further activate the macrophages.

This process is important for the eradication of microbes that are ingested by the phagocytes but resist killing.



Why the neutrophils can't play a role in presenting antigen like macrophages ?

Because they die after a short time when they finish their work.

-

3- B cells

Also, B cells are APCs, they present antigens to helper T cells in lymph nodes and spleen, which is a key step in the cooperation of helper T cells with B cells in **humoral immune responses to protein antigens .**

YOU SHOULD KNOW :

- Helper T cells and cytotoxic T cells are subtypes of T-lymphocytes
- The proteasome is a macromolecule that consists of 28 subunits and do degrade proteins.
- T cells can't deal with free antigens, so these antigens have to be bounded to proteins called MHC on the surface of APCs

---

WHAT ARE MHCS- Major Histocompatibility Complexes ?

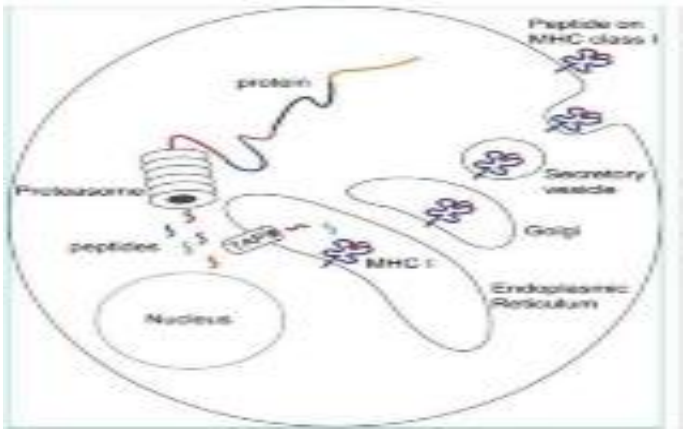
They are proteins that are used by cells to present degraded proteins on their surfaces.

HOW DO T CELLS DISTINGUISH BETWEEN NORMAL AND INFECTED CELLS?

One of the mechanisms by which immune system distinguishes self from non self cells is the representation of normally existing intracellular proteins fragments on the surface of normal cells (attached to MHC 1) and this indicates the presence of MHC 1 molecules on the surface of all cells not only APCs.

Cells always degrade proteins by proteasomes and present them on MHCs. if proteins were from the cell itself, T cells don't attack them. But when cells degrade a viral protein, T cells recognize these foreign proteins and do the immune response.

Look !!
Here to the
Proces .. →



THERE ARE MHC I AND MHC II

MHC I Found in the most cells to check if the antigen it is self (cell's protein), or non- self (viral protein), but the antigen from **inside** cell not from outside the cell .

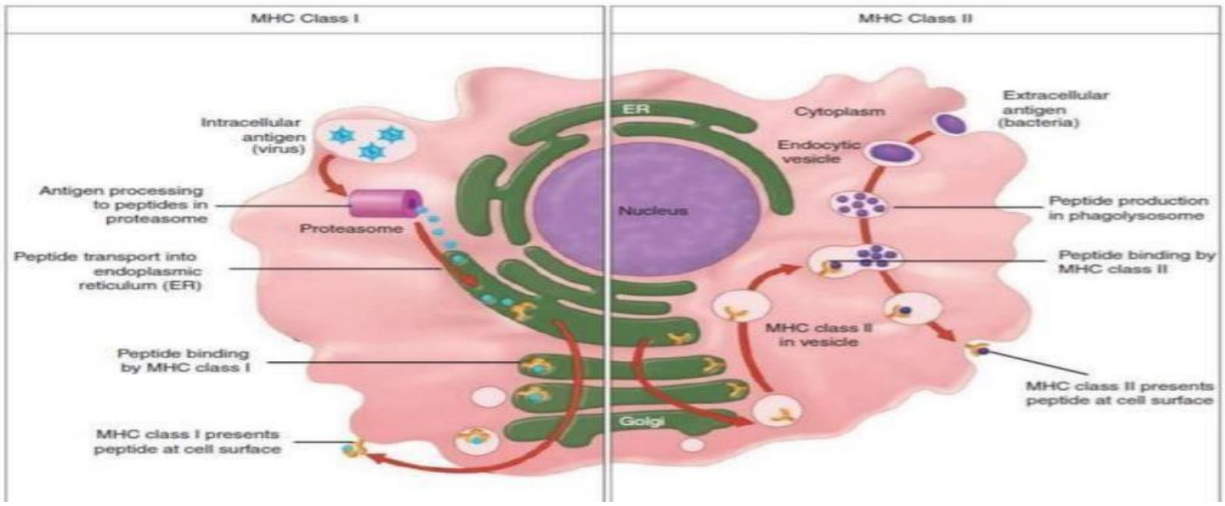
It will be broken by proteasomes to small peptides then present in cell's surface. ↑↑

After that : lymphocytes (which is cytotoxic T cell) will come and see if it's self or not ; to do their job

MHC II

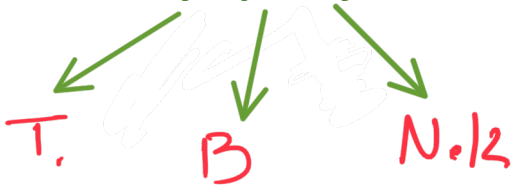
Is professional antigen-presenting cells (dendritic, macrophages, B cells and sometimes endothelial cells), and the antigens are originated from the **outside cells** (From ECM, not IC as).

	MHC I	MHC II
Nature of Antigen Presentation	MHC class I presents endogenous antigens that originate from the cytoplasm. (foreign intracellular antigens (Viruses).	MHC II presents exogenous antigens that originate extracellularly from foreign bodies such as bacteria. (foreign extracellular antigens)
Sources of Protein Antigens	Cytosolic proteins (mostly synthesized in the cell, may enter cytosol from phagosomes).	Endosomal / lysosomal proteins (mostly internalized from extracellular environment).
Enzymes Responsible for peptide generation	Cytosolic proteasomes .	Endosomal and lysosomal proteases.
Site of peptide loading of MHC	Endoplasmic reticulum.	Specialized vesicular compartment.
Responsive T Cells	Present antigen to cytotoxic T cell lymphocytes	Present antigen to Helper T cell lymphocytes.



We have finished talking about~~, phagocytes, granulocytes and antigen presenting cells~~

Now let's talk about **lymphocytes**.



B and T cells have different functions, but they are morphologically the same. So, we **can't** distinguish between them morphologically.

B cells :

Their name come from "**Bursa of fabricius** " Which cells like B cells found in birds (but not in humans) in a specialized organs.

They Originate and maturate (early maturation) in bone marrow .

T cells :

Their name come from " Thymus gland" where they matured .

They Originate in bone marrow and maturate in thymus gland.

Both of them get larger when activated.

As we can't distinguish them morphologically, we used their membrane proteins as a phenotypic marker .

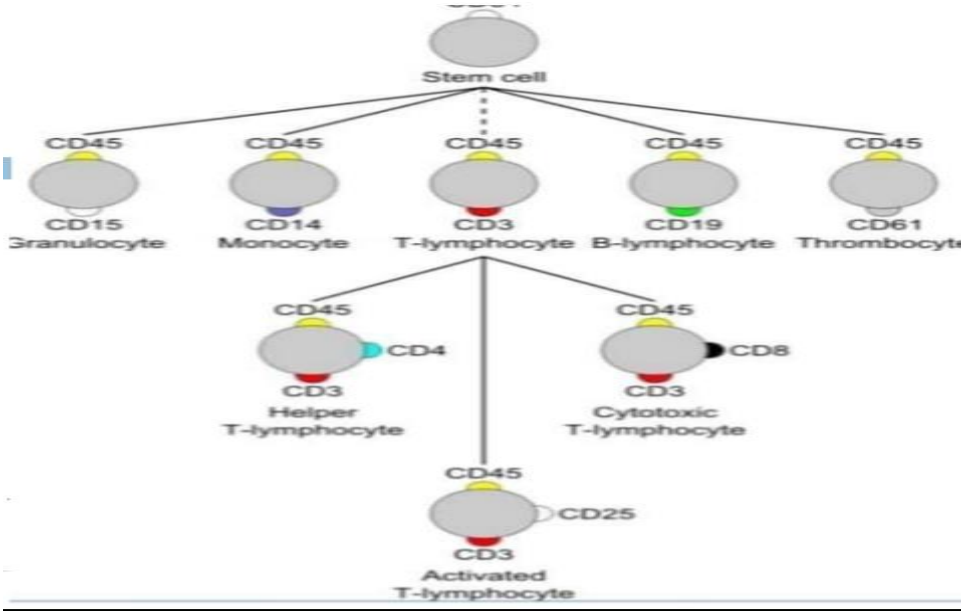
A protocol used for identification called **cluster of differentiation CD :**

CD molecules have different functions, they can be ligands, receptors or adhesion molecules For example:

Helper T lymphocytes have CD3, CD45 and CD4.

Cytotoxic T lymphocytes have CD3, CD45 and CD8.

important.!!!



Functions of **B Cells :**

They are the only cells that are capable of producing antibodies.

They recognize extracellular antigens (including cell surface) and differentiate into >> antibody-secreting plasma cells, thus functioning as mediators of humoral immunity → by secreting antibodies - humoral immunity is an immune response that depends on activating B cells to produce antibodies.

- Plasma cells are B lymphocytes in the last stages of maturation.

T cells :

1- They are the cells of cell-mediated immunity that , recognize the antigen (intracellular microbes.)

2- Don't produce antibodies .

- **Antibodies role in immune system:**

1. Blocking infections and extracellular microbes

. 2. They must be bounded to microbes in order to be phagocytosed by phagocytes (work as salt and pepper on food)

3. They activate the complement system.

>> Suggested video >> https://youtu.be/lrYlZJiuf18

Two subtypes:

1 - Helper T cell :

Helps phagocytes to destroy these microbes **.**

Specialized in binding to MHC II. When macrophages digest microbes and present their proteins on MHC II, helper T- lymphocytes bind with them and secrete CYTOKINES.

These cytokines have many functions. One of them is helping macrophages to get rid of the bacteria inside. Why?

Because sometimes bacteria resist killing .(some bacterial cells are capable of escaping from phagosomes and sometimes lysosomes) .

NOTE :

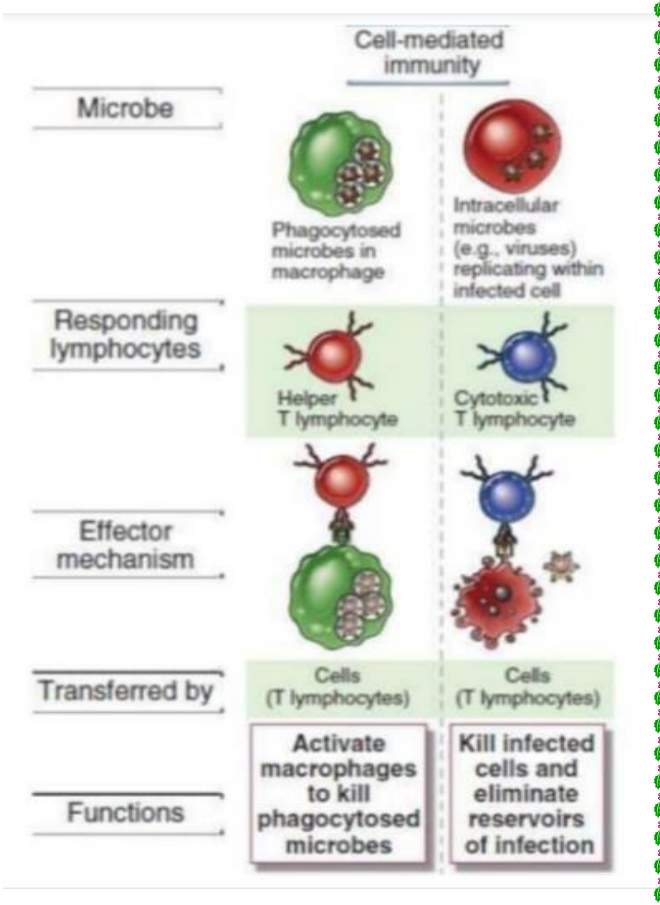
Helper T-cells have many functions other than activating macrophages such as: potentiate immune responses.

-potentiate inflammation

2- Cytotoxic T cell:

Kills microbes directly**,** When the cell present antigens of intracellular microbes - viruses for example- on MHCI they bind them and kill the infected cell directly by secreting some enzymes (we will talk about it).

In general, B cells are responsible for **humoral immunity** and T cells are responsible for **cell-mediated immunity.**



-Humoral immunity :

Occurs in the blood, fluid, as the immunity in the blood depends a lot on antibodies, produced by B cell → B cells are responsible for humoral immunity.

-Cell-mediated immunity :

Is the activation of phagocytes, cytotoxic T cells and the release of cytokines in response to antigen on MHCI.

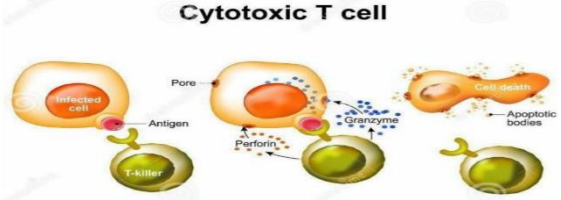
All of them are done by T cell.

Defense against such infections is a function of cell mediated immunity, which promotes the destruction of microbes residing in phagocytes or the killing of infected cells to eliminate reservoirs of infection through the action of perforin and granzymes.

NOTES :

-Perforin is a pore-forming protein, which form pores in plasma membrane of infected cells.

- Granzyme is a family of structurally related serine proteases stored within the cytotoxic granules of cytotoxic lymphocytes (CLS or T Killer).



-Perforin and granzyme induce target-cell apoptosis, granzyme is necessary for triggering caspase cascade, which lead to **apoptosis of target cells**.

Maturation of B and T cells :

–B and T cells have the same origin, common lymphoid precursor in the bone marrow.

–They leave it (common lymphoid precursor) as B and T cells, they are known if they are B or T lymphocytes then they will develop in Generative lymphoid organs (bone marrow and thymus)

–T cells leave it as immature cells and go to the Thymus to mature.

There is another type of T Cells called **regulatory T cells**,

Not well characterized, it regulates propagation of immune response. **HOW?**

Immune system works by propagation, each cell activates many cells, so if there was nothing to stop it, it will harm our body (by excessive release of cytokines) and that's **why immune response in all stages require tight regulation.**

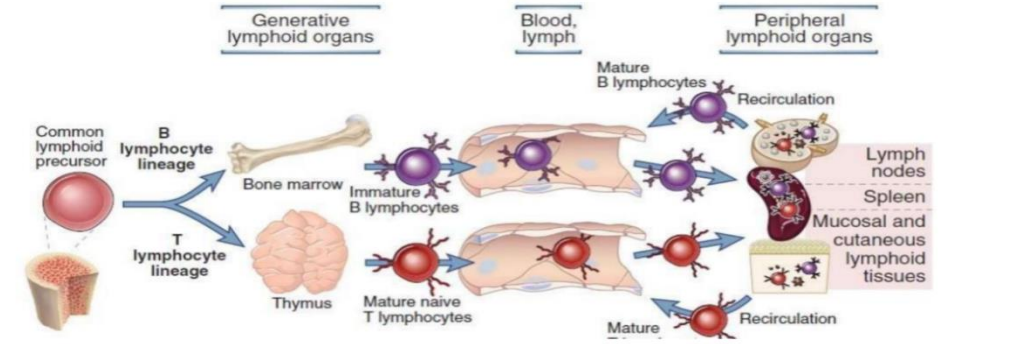
- T cells leave Thymus gland as mature cells, but they are naïve cells as they haven't been exposed to antigens yet.

In order to find antigens they leave to areas full of antigens. These areas are(spleen, lymph nodes and mucosal) and cutaneous lymph tissue>> peripheral lymphoid organs.

Each T cell have a specificity for a certain antigen.

- B cells leave bone marrow as immature cells. They get mature in the peripheral lymphoid organs where they become ready to find their first antigen.

Remember that " Early maturation of B cells happens in bone marrow ".

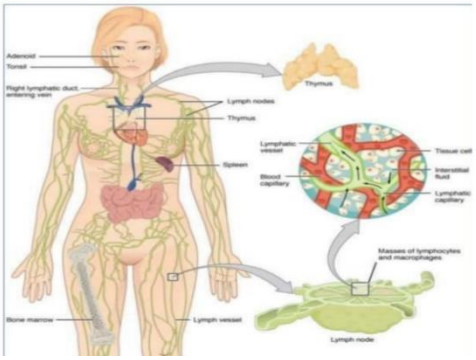


Here is the distributions of lymphatics in adults body :

Cells of the immune system / Lymphocytes

The total number of lymphocytes in a healthy adults about 5×10^{11}. Of these:

- ~2% are in the blood,
- ~10% in the bone marrow,
- ~15% in the mucosal lymphoid tissues of the gastrointestinal and respiratory tracts, and
- ~65% in lymphoid organs (mainly the lymph nodes and spleen)



Lymphoid tissue is found mostly in areas :

Where the pathogen could inter: like Adenoid, Tonsil and GI tract.

Note : there are 100-200 lymph nodes spread all over our bodies .

We have millions of antigens in our body, and our genome contains only 25000 genes.

So, how can our body produce sufficient receptors for these antigens from only 25000 genes?

While lymphocytes are maturing, their DNA is **recombined** so they can express a lot of receptors from this limited number of genes.

.

Another problem in adaptive immunity is that there is a limited number of lymphocytes that have the same receptor. This limited number is not enough to activate immune response.

In a mechanism called clonal expansion once the cell finds its antigen it undergoes clonal expansion and produce a lot of copies of it >> to be more efficient.

-when producing a wide variety of receptors from recombination of DNA segments during maturation of lymphocytes, some receptors will not have cells to combine with.

This will cause wastes, not all receptors will have cells to combine, but preserves responsiveness- increase the number of antigens that have antibodies .

The antigen receptors are basically antibodies bound to cell surface. **But we don't call them antibodies** because we use this term for secreted-not bounded- receptors.

(we refer to them as bound antibodies not because they really are but becuse of the similarities between these receptors and antibodies in morphology and binding strategy) .

REMEMBER : B cells, T cells and Natural killers are all lymphatic cells

3- Natural Killer NK cells

Are lymphatic cells that play a role in the innate response, mainly against intracellular bacteria and viruses.

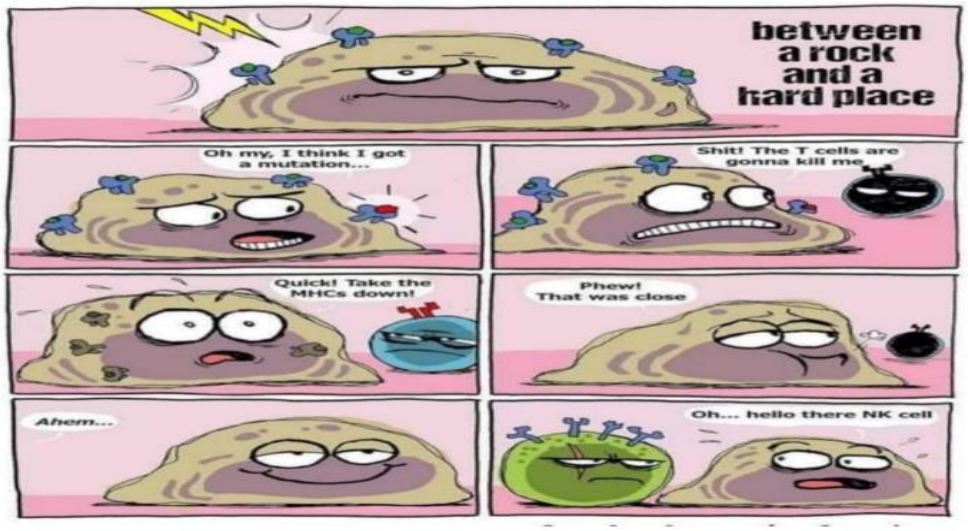
- These cells are capable of performing their functions without the need to clonal expansion and differentiation.

A) When MHCI is presented on a cell surface, cytotoxic T cells bind to it and kill the cell directly.

But there are some cells that hide their MHCI proteins in order to protect themselves. (Downregulate the production of MHCs)

B) NKs work by killing cells that hide their MHCI.

So, we can say that MHCI inhibits their work.



IMPORTANT: You won't find these things in the slides but they were explained and mentioned by the doctor in the live meeting.

1) Foreign bodies enter dendritic cells by either phagocytosis or micropinocytosis.

2) phagocytosis is done by both macrophages and dendritic cells but dendritic cells use it only for the sake of antigen presentation that's why when both macrophages and dendritic cells are present in a site of inflammation macrophages do phagocytosis in a much higher rate.

Nice video memories the immune cells >> https://youtu.be/yjAZXlMpw3k (skip the first minute)