SHEET NO.

3

IMMUNOLOGY

DOCTOR 2019 | MEDICINE | JU

DONE BY : Doctor 2018

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

-This lecture will give us a knowledge about antigen representing cells APCs (dendritic cells) which link the two part of Immune system, and lymphocytes (T cells, B cells (as a part of adaptive immune system)and Natural killer cells) .

At first

- **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 (especially T-cells as they can't bind microbes directly) >>> and provide signals that stimulate the proliferation and differentiation of the lymphocytes.

***As you note, APCs link responses of the innate immune system to responses of the adaptive immune system, and therefore they may be considered components of both systems.

Dendritic cells, macrophages and B cells are examples of APCs which activate T cells as they recognize the presented antigens on APCs' surface. **"Dendritic cells are the most important ones".**

✓ **Dendritic cells (DCs):**

Dendritic cells are the most important APCs for **activating naive T Cells** , which originated from Monocytes from bone marrow.

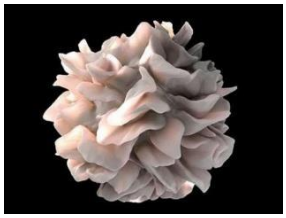
-Found in areas where we find a lot of Microbes such as skin, mucosal epithelium and GIT.

-Also,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. (**A more detailed explanation for this procedure :** some fluid leaks from blood into tissues , and undoubtedly

it needs to go back to blood , unfortunately this won't be poi I left until the fluid is resterilized as it gets contaminated in the tissue , so the fluid (and of its contents including dendritic cells) leaves the tissue as part of the lymph and travels through lymph vessels until reaching lymph nodes where it can be sterilized by lymphocytes)

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



✓ **Follicular Dendritic Cells (FDCs):**

They are a type of antigen presenting cells. Although they are called **follicular dendritic,**
they are not dendritic cells. What are them?

- 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 recognize >>> this process helps in maturate B cells

Here is a comparison between DCs and FDCS.

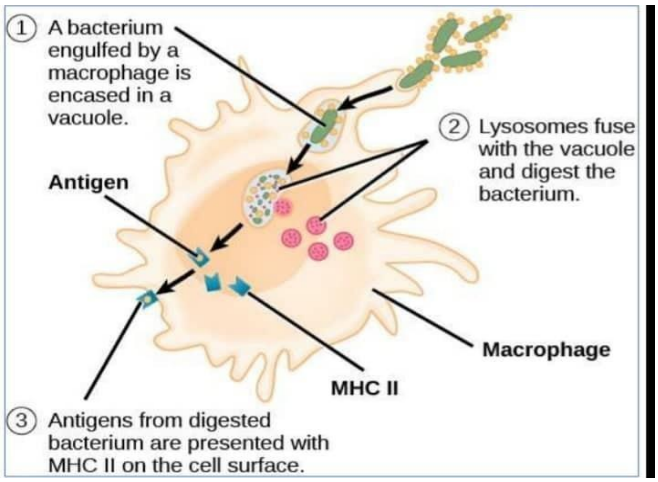
	DCs	FDCs
Precursor	Monocytes- bone marrow-	Mesenchymal stem cells
mobility	mobile	Immobile
present antigens to	T cells	B cells

***Notes

_DCs have many precursors but for simplicity we just mention monocytes

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

✓ **Macrophages**



A type of APCs which ingulf microbes- bacteria for example- 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.

✓ **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 cytotoxicT cells are subtypes of T- lymphocytes.

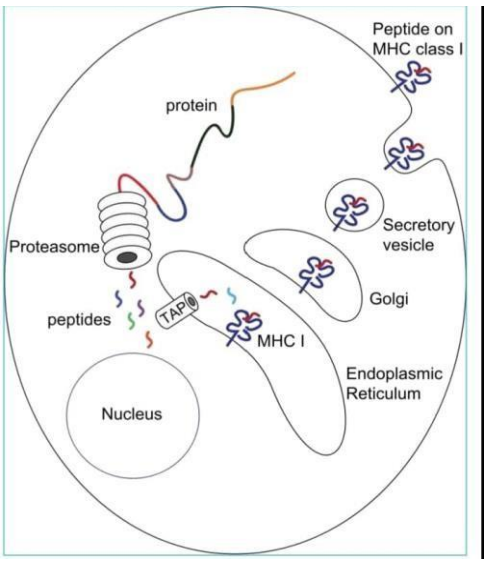
√ The proteasome is a macromolecule that consists of 28 subunits and do degradeproteinss.

√ 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 Histocompitability 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 or 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 **proteosomes** 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.

_There are MHCI and MHCII

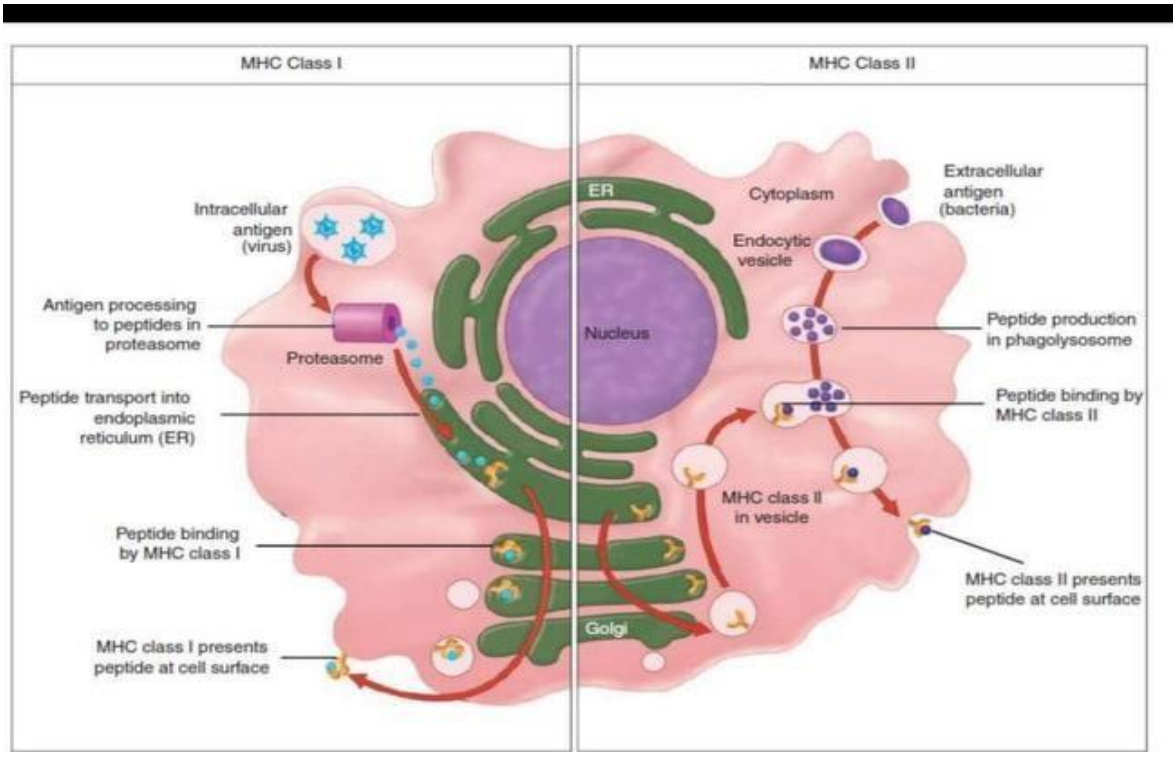
MHC I == Found in the most cells to check if the antigen it is self (cell's protein), or non- self (viral protein), but the antigen from inside cell not from outside the cell >>> It will be broken by proteasomes to small peptides >> then>> present in cell's surface.↑↑

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

MHC II == In 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). (↑↑ as the picture in page 2).

	MHC I	MHC II
Nature of Antigen Presentation	MHC class I presents endogenous antigens that originate from the cytoplasm. (foreign intracellular antigens, e.g : 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.

See the picture



We have finished talking about, phagocytes, granulocytes and antigen presenting cells
>>> now let's talk about lymphocytes.

- lymphocytes

* B and T cells have different function, 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 organ.

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

T cells:

>Their name come from **" Thymus gland"** where they matued

>They Originate in bone marrow and maturate in thymus gland.

- both of them get larger when activated.

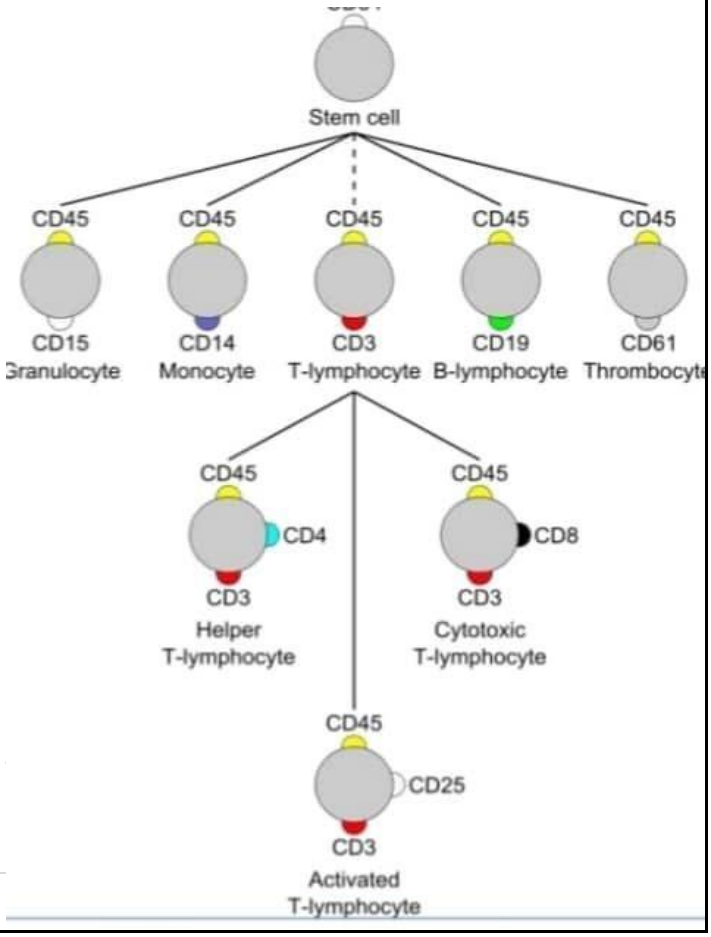
As we can't distinguish them morphologically, we used their membrane proteins as a phenotypic marker.

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

CD molecules have different functions, they can be ligands, receptors or adhesion molecules.

Look at the next photo and try to differentiate between different cells.

For example: helper T lymphocytes have CD3, CD45 and**CD4**. And cytotoxic T lymphocytes haveCD3, CD45 and**CD8**.



To have a look at their functions we start

1- B lymphocytes:

- 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.
  - 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.

Fortunately, this will be discussed later.

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

2- T lymphocytes, two subtybes-:

- They are the cells of **cell-mediated immunity**, recognize the antigen to intracellular microbes. They either help phagocytes to destroy these microbes, **(helper)**, or kill them directly (**cytotoxic**).
- Don't produce antibodies.
- Their antigen receptors are distinct membrane molecules but structurally related antibodies.

1* Helper T cells - cells >> that are specialized in binding to MHCII-**.**
When macrophages digest microbes and present their proteins on **MHCII** helper **T- lymphocytes** bind to them and secrete **CYTOKINES**.
These cytokines have many functions. One of them is helping **macrophages** to get rid of bacteria inside. Why?

Because sometimes bacteria resist killing.(some bacterial cells are capable of

escaping from phagosomes and sometimes lysosomes)

- **MHC II** >> because the antigen is extracellularly.

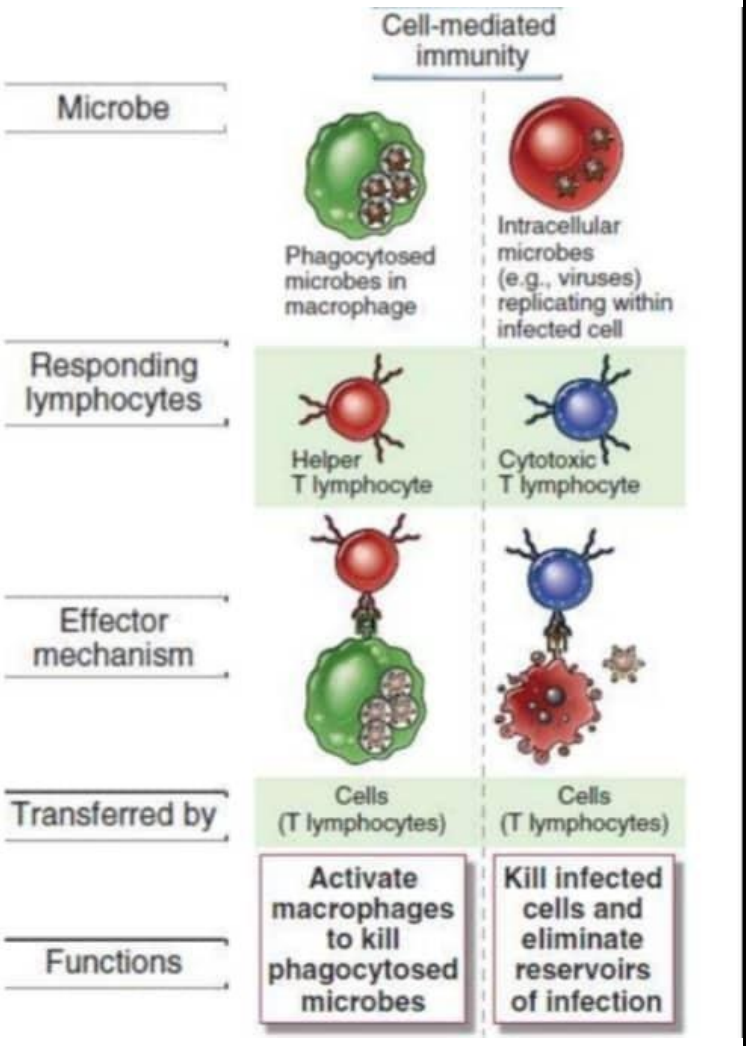
2*cytotoxic T-lymphocytes -toxic to cells-.

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).

Note that Helper T-cells have many functions other than activating macrophages such as: (in general , potentiate immune responses)

-potentiate inflammation

-sometimes they react with B cells and activate their differentiation and proliferation(both B and T cells) .



>> 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.

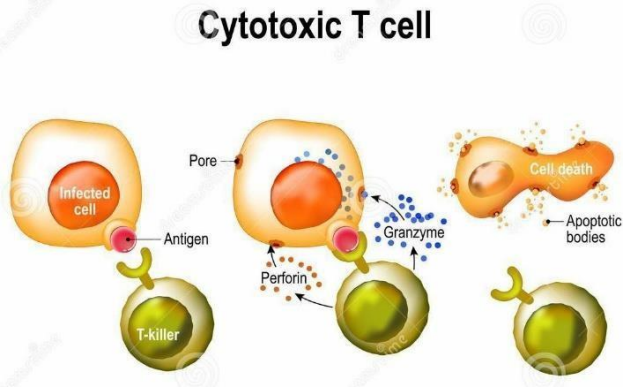
>>> Defense against such infections is a function of cell mediated immunity, which promotes the destruction of microbes residing in phagocytes or the killing of infected cells to eliminate reservoirs of infection >> Through the action of **perforin and granzymes.**

- Perforin and Granzyme.

-**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.



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. SEE THE FIGURE FROM SLIDE 16 .

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.

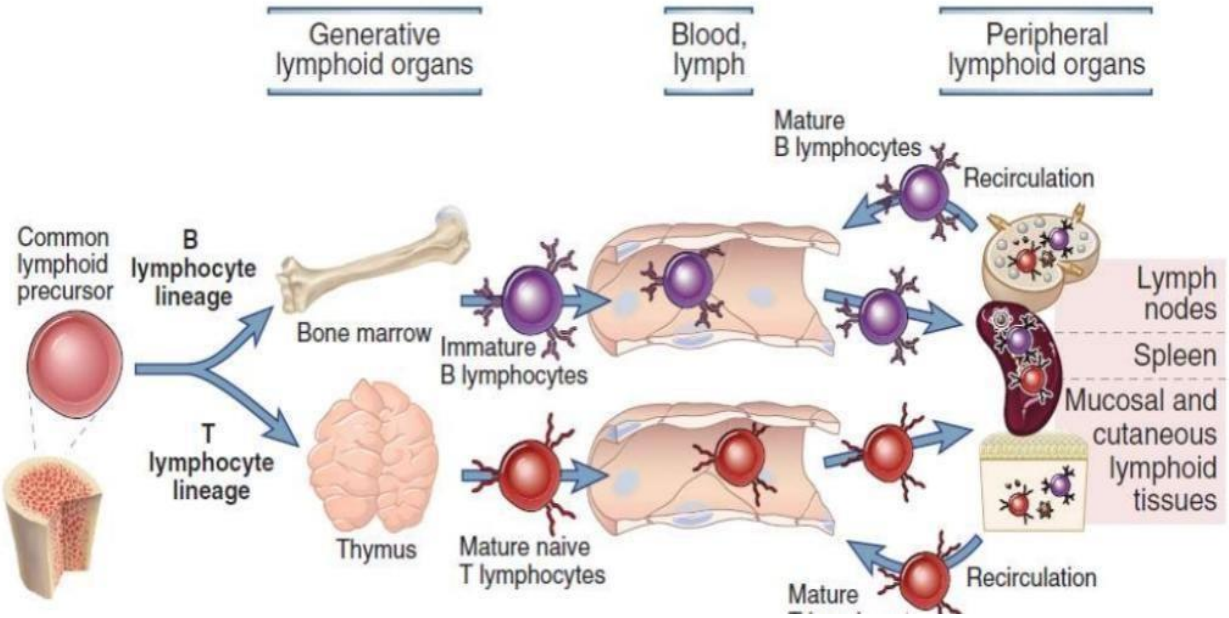
- T cells leave Thymus gland as mature cells, but they are naïve cells as they haven't been exposed to antigens yet.

✓ 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".

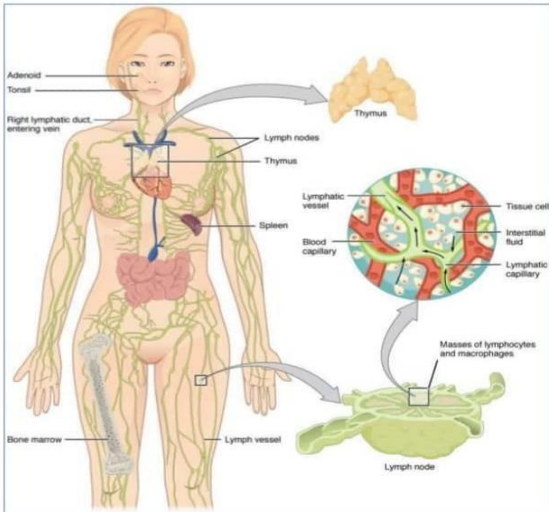


Here is the disttibution of lymphatics in adults body

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

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>>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.

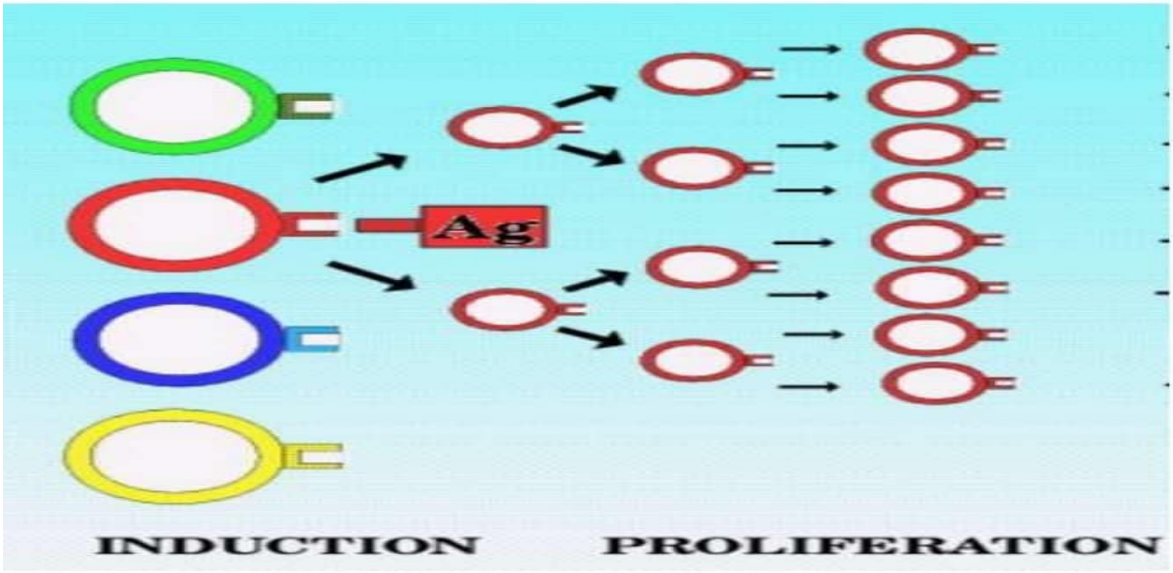
>>Another problem in adaptive immunity is that there is a limited number of lymphocytes that have the same receptor. This limited number is not enough to activate immune response.

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 antigensthat 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 be Ouse of the similarities between these receptors and antibodies in morphology and binding strategy)**

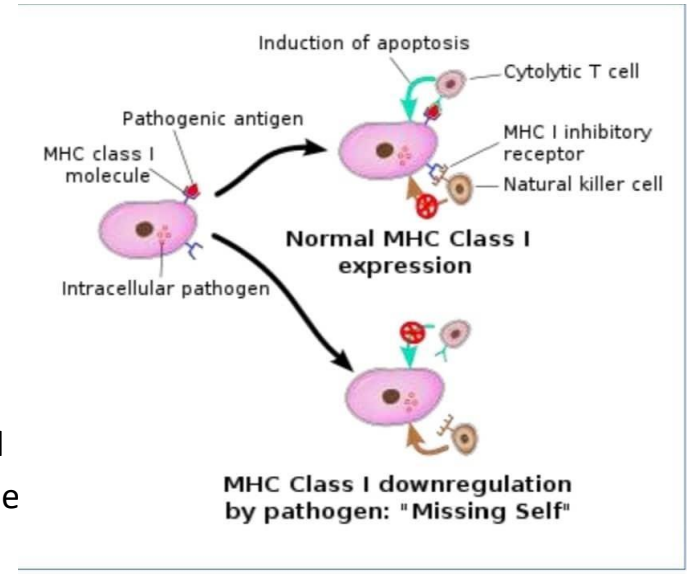


B cells, T cells and Natural killers are all lymphatic cells

3- Natural Killer NK cells are lymphatic cells that play a role in the **innate response**, mainly **against intracellular bacteria and viruses.**

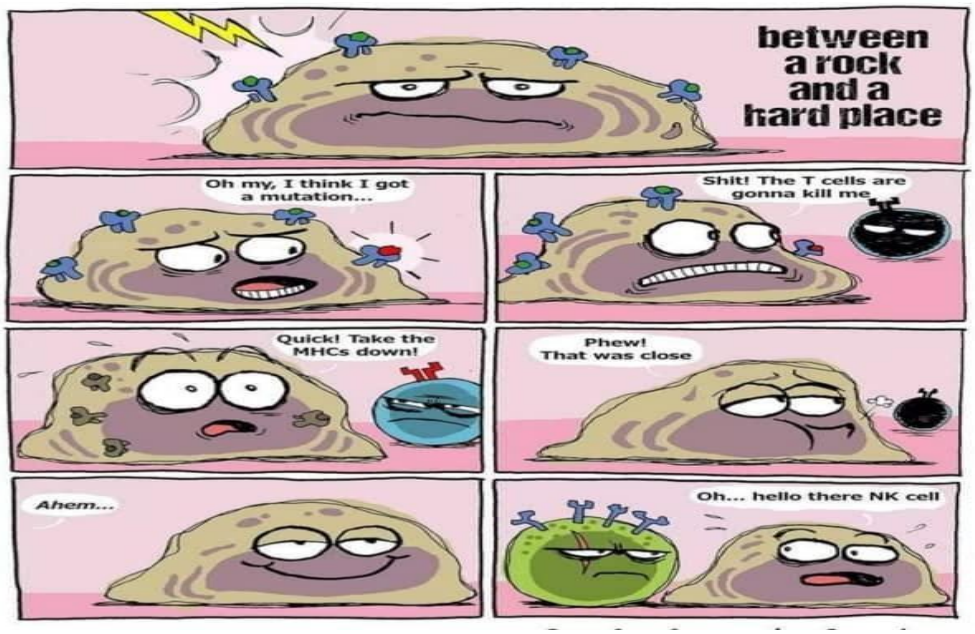
- these cells are capable of performing their functions without the need to **clonal expansion** and **differentiation**.

Before we talk about their function remember:



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) There are 2 main types of neutrophils:
Conventional: specialized in AP (capture , process , present)
Plasmacytoid : specialized in the synthesis and release of type 1 interferon
3) neutropenia is an abnormally low concentration of neutrophils in the blood (it can be congenital or acquired (e.g cancer treatment, autoimmune diseases)
4) 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
5) B-cells only bind to unprocessed antigens which means that both macrophages and dendritic cells don't present antigens for B-cells

Nice video memories the immune cells >> https://youtu.be/yjAZXlMpw3k

(skip the first minute)

~Good luck~