Immunity lecture 2

*In this lecture we will be talking about:

1) Cells: basophils & mast cells, monocytes, dendritic cells, lymphocytes, NK cells

2)tissues: bone marrow, thymus ,lymph nodes

Cells

1) Basophil & Mast cell:

-These cells are very similar and they diverge very early in development ,you can say that they develop separately ,they are not exactly the same (one doesn't change to another)

-they diverge, the basophil stays in the blood and the mast cells leave the blood and inhabits the tissues (specially connective tissue)

-they constitute less than 1% of WBCs

-they have got receptors on their surfaces which are for IgE

*If you have these cells with IgE on their surface, an antigen comes and sticks to the immunoglobulin E, this will induce the cell to release its granules (degranulation) into the surrounding (the granules are basophilic which means that the contents are acidic)

*what is the main content of the granules of mast cells and basophils?

Histamine (it's a very potent mediator of inflammation),there is also heparin and serotonin

*what induces these cells and causes release of their granules?

1)binding of an antigen to IgE

2) Breakdown products of complement activation like C5A&C3A

3) Trauma and pressure

*what does histamine do?

-It's a mediator of inflammation

-vasodilatation

-constriction of smooth muscles

-increases the permeability of smooth muscles

-it irritates the nerve endings to produce pain and itching

-it results in the cardinal signs of inflammation: rubor (redness), tumor (swelling), calor (heat), functio laesa (loss of function) might be temporary or permanent

*histamine is a very short acting mediator ,it is released quickly when activated because it's already preformed in the granules ,but its effect is very short lasting and it's not good enough for prolonged reaction of the inflammation

Another function of basophils and mast cells :production of long acting mediators of inflammation and this is through arachidonic acid metabolites(metabolites of lipids in the plasma membranes), the lipoxygenase and the cyclooxygenase (these two are pathways of arachidonic acid metabolism)

*prostaglandins and leukotrienes are long acting mediators of inflammation, they work almost like histamine but they take some time to be produced because they are not already in the granules, they have to be synthesized in de novo and then when they are released their action lasts for hours and this prolongs the action of inflammation after stimulation of mast cells in the tissues.

*cyclooxygenase produces prostaglandins.

*lipoxygenase produces leukotrienes.

2)Monocytes

-sometimes they are known as mononuclear phagocytic cells

-their cytoplasm is not granular(maybe few granules are found but not many)

-they are large,15 or 18 microns in diameter

-kidney shaped nucleus

-In the blood they are known as monocytes and they constitute about 7% or 8% of the WBCs in the blood

-monocytes in the blood then migrate into different tissues and there they change their morphology according to the microenvironment which they live in; if they go to the liver they change into kupffer cells, if they go to the nervous system they become microglia, if the go to the bone they become osteoclasts, in other places they are known as phagocytic cells or macrophages depending on the tissue that they reside in, but all of them do the same function

*what is their function?

Same as neutrophils, they recognize non –specifically any foreign material in the body and they phagocytosis it into phagosome then the phagosome fuses with lysosome forming phagolysosome

-Unlike neutrophils that once they phagocytose and release their enzymes they die quickly, these monocytes don't die ,they are more refined ,live longer and after taking up the antigens & bacteria they break it down to small pieces(small peptides) then these peptides are transported to the surface of the cell and presented for the benefit of T-lymphocytes

Lymphocytes recognize antigens ;B- lymphocytes can recognize antigens in its native form ,while T-cells they really need to have the antigen processed for them and then presented on antigen presenting cell (i.e.: dendritic cell and macrophages) so they can recognize the antigen.

-These macrophages besides being phagocytic cells they serve as antigen presenting cells for the benefit of T-cells (B-cells can recognize the antigen as it is).

-macrophages cut the big antigen or bacteria into pieces and then these pieces are displayed on the surface for the benefit of T-lymphocytes(antigen presentation), so antigen presentation is an important function of the macrophages

3) Dendritic cells

-they are called dendritic because they have dendrites but when they are immature we find that the cytoplasmic projections or extensions look like a folds/veil ,so these cells when they are immature they are called veil cells but once they become mature they will develop these dendrites and they will extend all over the place.

-these cells can be derived from the myeloid line or lymphoid line

-they are very well distributed in the body like lymph nodes, cells that are in the subcutaneous tissue they are sometimes called Langerhans cells (they are called so because they were discovered by somebody called Langerhans)

Note: Don't confuse them with the giant cells of the granulomas that are called langhans cells (giant multinucleated cells)

-these cells are called dendritic cells if they were found anywhere in the body, but if they were found in the skin they are called Langerhans cells (both are the same, but because Langerhans found them in the skin so they were called so according to his name)

-they are the professional antigen presenting cells(they have a little phagocytic activity) ,they sample the environment by taking molecules by endocytosis or pinocytosis but very little phagocytosis ,they take these samples of antigens and break them down and display them very quickly on the surface for the benefit of T-lymphocytes

-these cells are the main antigen presenting cells specially when the T-cell is being stimulated for the first time ,but once the cell has been stimulated it becomes memory cell and can be easily activated by macrophages

*dendritic cells are called excellent antigen presenting cell

-We are done with the cells that come from the myeloid lineage and are mainly involved in the non-specific/ innate/natural immunity (their recognition of foreign materials non-specific)-

4)Lymphocytes : T-lymphocytes & B-lymphocytes

-they constitute about 30% of WBCs , the majority of them are T-lymphocytes(60%) ,B-lymphocytes(20%),NK cells (10%)

-**B-lymphocytes** belong to the adaptive/specific/acquired immune response(this means that they are very specific),they have receptors on their surfaces that are only specific for one antigen in its native form so they can only recognize one antigen, If the antigen is present, B-cell interacts with it becoming active

*the first phase of immune response is recognition; B-cell has recognized its particular antigen then it becomes active, what does that mean?

There is enlargement of the cell(B-lymphocyte is mainly composed of nucleus and very small cytoplasm around it),so what happens is that it becomes larger because there is increase in the cytoplasm(genes are activated, proteins are synthesized & we need ER, Golgi apparatus) and it is known as **blast cell**, this blast cell starts dividing forming cells that are exactly similar to the mother cell (all the progeny of this blast cell are exactly similar to the mother cell & all of these cells are specific)

*clone: collection of all these B- cells that are proliferating, the blast cell is being copied continuously until it produces a large number of cells that are exactly similar to the mother cell

This takes a few days for the cells to be functional (it might take about 7 days), so there is a delay from the recognition to the effect

Natural immunity: recognition then immediately we have an action For example: - mast cell recognizes an antigen and releases the granules straight away -neutrophil: does phagocytosis straight away.

*what happens to this clone?

Suppose that the clone contains one million cells ,half of them will become 1) effector cells (cells that produce an effect)

How does the B-cell do that? By becoming a plasma cell that secretes antibodies which will go and attack the antigens and get rid of it

the others will revert and become 2)small lymphocytes as they were before & they are known as memory cells ,these memory cells are specific for a particular antigen(specific for one epitope),they hide and stay dormant, they are very long living

*Naïve cells: B-cells which have not been subjected or didn't meet their own antigen

*If a B-cell doesn't encounter an antigen within few weeks it dies ,but once it encounters its own antigen it will be activated and produce a clone then the clone produces effector cells which die after doing their job (plasma cells live a couple of months then they die),but the memory cells are very long living(they can live 20 years or more)

*what happens if the same antigen or bacteria came again?

We have got millions or hundreds of thousands of cells that can recognize it, very quickly they produce effector cells and get rid of the antigen, so in the **first encounter** one B-cell recognize one antigen, this took about 7 days to produce effector cells, antibodies and then memory cells this is known as the **primary response** (when you have the first exposure of the B-cell to the antigen) recognition then there is a delay (proliferative phase) then effector cell production

*what happens in the **second encounter**?

We have millions of these cells so they act quickly, it will only take one or two days, so the response is shorter and the produced antibodies are of a better quality (more refined)

	Primary response	Secondary response
Delay	Present(more)	Less
Magnitude	less	More
Response	-	Better quality

*B-cell encounters an antigen, it takes some time to produce a response which is followed by antibody production then plasma cells die after a while

*If you are exposed again to the antigen, you respond very quickly and you produce antibodies ***If we were exposed to antigen A & B what will happen?**

There will be a secondary response for antigen A and a primary response for antigen B

- **T-cells** :there are 2 kinds of T-cells:CD4(helper T- lymphocytes)& CD8(cytotoxic T-lymphocytes)

-they only recognize antigens that have been presented to them by antigen presenting cells, they are only specific to one antigen, then the cell is activated and it becomes a blast cell then the blast cell will divide producing a clone which will divide into two parts; one becomes memory cells & the other becomes effector cells (effector cells don't change their morphology like B-cells which change their morphology completely and become plasma cells)

*how do they work?

The helper T-cells become effective by the production of chemical messengers that work like hormones (we don't call them hormones, we call them cytokines)

*cytokines: messenger molecules secreted by the helper T-cells, they go and help other cells to do their job (that's why they are called helper T-cells)

*cytokines work like hormones, so they have autocrine, paracrine and endocrine actions

*these cytokines that are produced can act on the same cell, for example the helper T-cell can produce IL-2 which is a cytokine that comes out and then goes back into the cell and act on the same cell to make it divide and grow ,this is known as autocrine action of the cytokine, or maybe this helper T-cell will produce IFNγ which goes to the phagocytic cells and make them do their job better, this is known as paracrine because it is produced by one cell and acts on a nearby cell, there are also other cytokines that work on distant organs as IL-1 or TNF they travel to the hypothalamus for example, and act on the heat center there to produce heat and elevate the body temperature (pyrexia: elevation of body temperature),IL-6 might be produced by some helper T-cells which will go and work on the liver to make it produce more proteins that are needed for the immune response(acute phase proteins)

So these are the 3 modes of action of the cytokines(autocrine,paracrine,endocrine)

*after the helper T-cells do their job ,the helper effector cells die ,but of course we still have the memory cells and again if we are exposed to the same antigen we will find that the antigen is dealt with very quickly because of the memory cells, this memory is actually a property of the adaptive immune response(we don't have memory with other cells , we only have it with T-cells & B-cells which are members of the adaptive/specific immune response)

*CD8: again the same story, they are activated by antigen presenting cells-blast formation-clone formation-memory cells & effector cells

*the effector cells of the cytotoxic T-cells are sometimes called **armed cells,** their function is to search for the cells that are diseased and kill them, they find the infected cell(intracellular pathogen, virus inside the cell, tumor cell) ,so they come to this cell, stick to it & kill it **HOW?** By injecting chemicals inside the cell, these chemicals can be perforins (they perforate the plasma membrane, this leads to swelling of the cell followed by death), it also injects chemicals known as granzymes which activate the caspases in the cell which are responsible of the apoptosis (suicidal death of the cell) then these cells are taken up by phagocytic cells & cleared away

This is how cytotoxic armed T-cells do their job, and then these cells die & we still have the memory cells

5) NK cell

-belongs to natural/non-specific immune response

-this cell recognizes any cell any that is abnormal(it doesn't differentiate between cell infected with a virus or tumor cell)

-It attacks the cells non- specifically and kills them

-it's the first line of defense against diseases

*how does it do its job?

Same as cytotoxic T-cell, by injecting perforins and granzymes

-We are done with the cells, we will move to the tissues-

Tissues

1)Bone marrow

-it looks like a mess ,you see cells everywhere

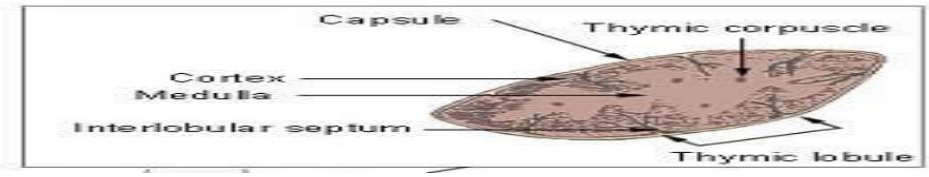
-when you look at it you will find niches; cells of each niche will produce same type of cells

-although when you look at the histology it looks disorganized ,it is actually organized ,there are compartments and each compartment is going to produce a particular line of cells ,

What makes them stay there?

The adhesion molecules between the cells and the matrix and also the cytokines which are involved in development of these cells

2) Thymus



-thymus is a retrosternal organ that develops from the 3rd and 4th branchial pouches during embryological life

-its maximal activity is at the time of birth ,by the time you reach adolescence it evolutes,if you examine cadavers and look behind the sternum usually there is only some fat ,there is no thymus

*what happens after adolescence?

T-lymphocytes have to go and develop in the thymus, so if we lose our thymus what will happen to our lymphocytes as our lymphocytes are being continuously regenerated?

There are 3 explanations to this question:

1st: some people say that not all the thymus is gone, so you may find remnants that still do the job of thymus epithelial cells and maturing of the T-lymphocytes

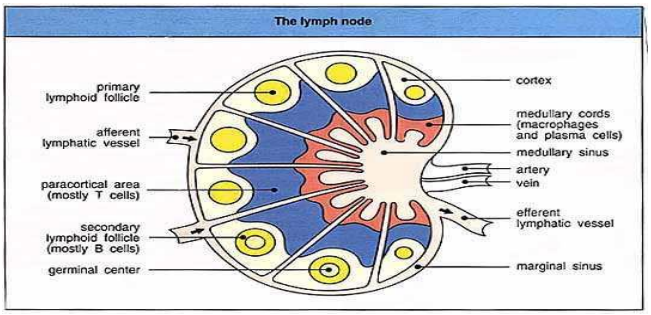
2nd:by the time we reach adolescence, we have a mass and large number of memory T-cells that should be enough for the rest of our lives (because memory cells live long about 20 years)

3rd:MALT specially in the GIT and some areas of the bone take over the function of the thymus after it evolutes

-the thymus has an outer area which is the **cortex** & inner area which is the **medulla**

*when T- lymphocytes leave the bone marrow, they are immature they go to the blood then to the thymus,the thymus blood vessels have high endothelial cells and have special receptors that attract the T-cells & the T-cells will go through to the thymus ,as they go through the will go to the cortex first ,in the cortex the cells are mainly thymic epithelial cells, macrophages & dendritic cells are also present, but the majority of the cells that belong to the thymus in the cortex are thymic epithelial cells , T-lymphocytes when they are passing through the thymus they are called thymocytes (Don't get confused, thymocytes don't belong to thymus,they are the T-lymphocytes that are passing through the thymus) ,these thymocytes will interact with the epithelial cells ,macrophages and dendritic cells then they start maturing and then they pass through the cortex to the medulla,in the medulla again we have thymic epithelial cells but the majority of the cells here are dendritic cells &macrophages ,nevertheless there are still thymic epithelial cells present in the medulla ,again the thymocytes interact with the cells of the medulla &then they become mature T-lymphocytes, some will become helper T-lymphocytes and others will be cytotoxic T-lymphocyte ,then they come out of the thymus into the blood then they will go and populate the secondary lymphoid tissues of the body

3)**Lymph nodes** : secondary lymphoid tissues



-they are found everywhere in the body

-kidney shaped

-they have a hilum and a capsule around them

-they collect lymph from the area that is drained by the lymph node

-lymphatics come in through the capsule, afferent lymphatics (brings in)

*for example :lymph node in the axilla probably gets lymphatics from the arm

Then it acts like a sieve, so the lymph circulates through the structure of the lymph node and then comes out through the efferent lymphatics ,eventually it will go to the thoracic duct & right left trunk then to the veins then to the blood circulation

*anatomy of the lymph node:

-the follicles are mainly made of B-cells

-if you look at the follicles, you will find that there is a dark zone and a light zone in the middle **WHY?**

If you look at an H&E section, you will find that the dark zone is made of cells that are not active (not dividing/resting T-cells) , they are mainly nuclei so they appear blue in color while in the light zone the cells are active (dividing /proliferating B-cells),they have more cytoplasm(the cytoplasm is not stained blue that's why they appear lighter in color)

*can we have a follicle that is completely blue/ not proliferating at all?

Yes ,if you haven't been exposed to an antigen like a newborn baby ,you will find that all follicles are blue because none of them have been activated

Primary follicles: follicles that have never been activated –naïve cells

Secondary follicles: activated follicles that have developed the light area (germinal center)

↔ We classify them depending on if they have been activated or not.

*around the B-cells we have paracortex (area for the T-cells, they reside there & scattered there we can find macrophages, dendritic cells and follicular dendritic cells) and in the medulla we have plasma cells

*follicular dendritic cells :they will be in the follicles of the lymph nodes (that's why they are called follicular)they look like dendritic cells but they are not dendritic & they come from the mesenchyme(not from the bone marrow) ,they have receptors for complement breakdown products and they keep these breakdown products with the antigen on their surface for a long time(when you get rid of an antigen,some antigens will form immune complexes on the surface of follicular dendritic cells ,the purpose of keeping a small amount of antigen is to keep the stimulation of B cells this is probably involved in the development of the memory cells and prolonging their action)

Note: B-cells are found in the follicles

*MALT: it is a disorganized lymph nodes , no capsule, no septa, no efferent & afferent lymphatics, there will only be T-lymphocytes and follicles in between which could be primary or secondary(in peyer's patches we see many T-lymphocytes & between them we also have follicles)

Sorry for any mistake!

GOOD LUCK ☺

Page 5: ** neutrophils are known as PMN not PNL
** Additional info mentioned in the lec: lysozymes destroy the bridges in peptidoglycan molecules resulting in killing gram +ve bacteria
Page 6: 6) monocytes not macrophages since monocytes only circulate in blood & upon reaching tissues they become macrophages which aren't present in blood

Page7: in 1 mm3 there is: *5million RBCs *4000-10,000 WBCs

Page9: note: CD4 is found on T-helper lymphocytes