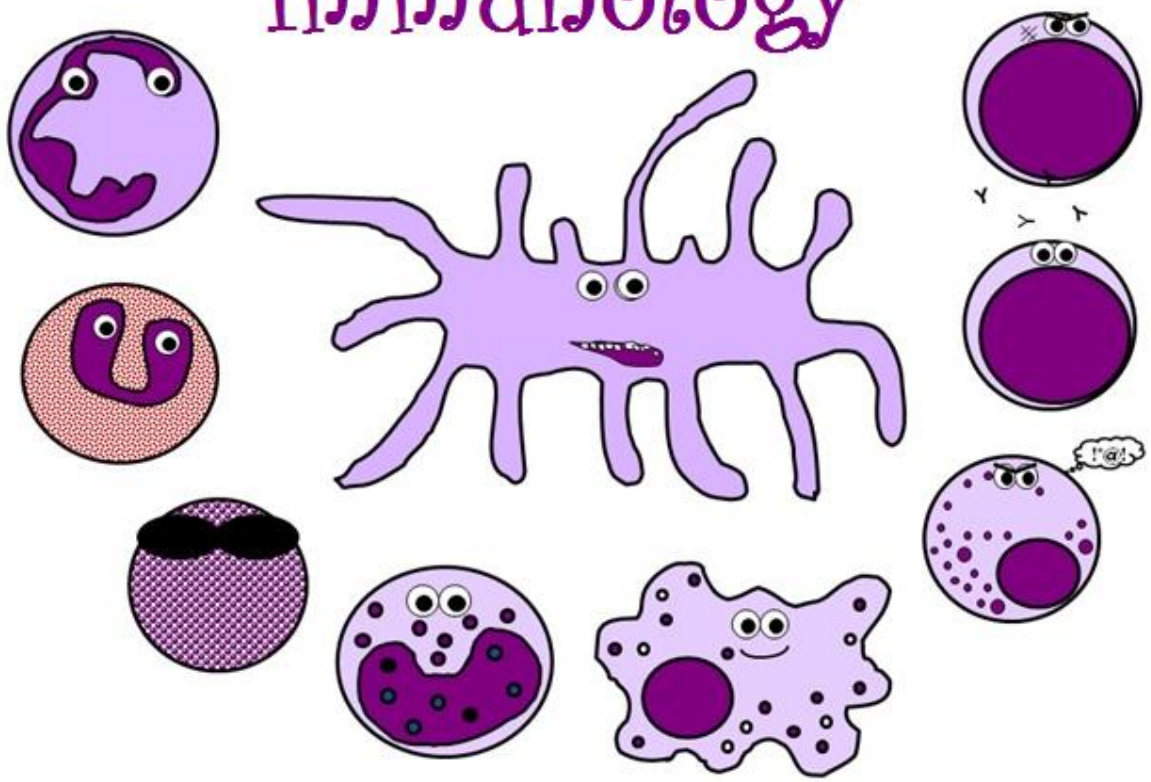
Immunology



◉Sheet ○Slides

Number: 10

Subject: lymphoid organs and trafficking

Done by: sohaib fahmawi

Corrected by: .....

Doctor: .....

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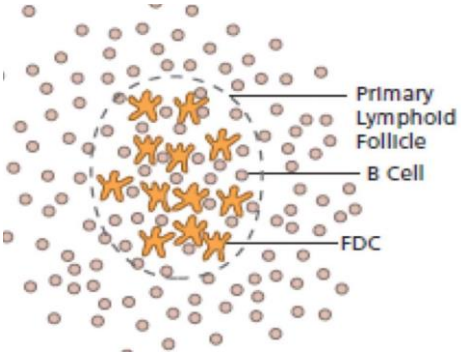
❖ Introduction

- **Lymphoid organs are divided into**

1. **primary lymphoid organs :**
   A. bone marrow : where T and B lymphocytes are synthesized , and where B-cells mature.
   B.thymus : where T-cells mature , and where autoreactive T-cells and the cells that doesnt recognize MHC are killed.
2. **secondary lymphoid organs : the first places to involve the adaptive immune sys. (the doc. didnt say adaptive but i guess he meant that)**
   A.lymph nodes. *deals with the invaders found in the tissue (the invader goes to the node draining that certain tissue).*
   B.spleen. *deals with invaders found in the blood*
   C.MALT (Mucosal Associated Lymphoid Tissue) : e.g. payers patches (in the intestines), tonsils, and appendix. *deals with invaders found in the GI tract.*

❖The structure of sec. lymphoid organs

- ✓ **Before discussing each organ, there are two common structures in almost all the sec. lymphoid organs :1-The lymphoid follicles**
  2-The high endothelial venules



➢ Lymphoid follicles

1. **primary follicles**:
   -found when there is no stimulation of B cells.
   -Consist of Follicular <u>Dendritic Cells (FDC)</u>, and <u>B-cells</u>.

FDC vs Antigen Presenting Denritic cells(AP DC) :

FDC : They are mostly previous skin, liver cells that take their position during embryonic development in the <u>lymphoid follicles</u> (they don't leave them) in order to capture opsonized antigens (by complement or Antibodies) and <u>present them to B-cells</u>

AP DC : synthesized in the <u>bone marrow</u> , localized to <u>tissues</u>, and <u>present antigens to T cells</u> in lymph nodes.

<u>Primary</u> follicle ⟶ FDC activates B-cells after presenting an opsonized antigen

↓

<u>Secondary</u> follicle ⟵ B-cell proliferation

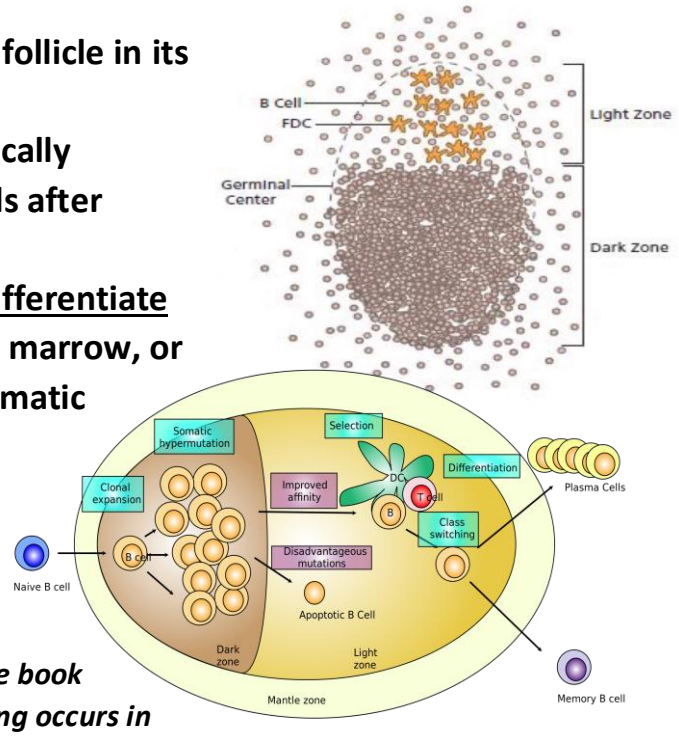
(co-stimulation by TH is needed)

2. Secondary follicles (germinal center):

-Divided into two zones

>light zone: similar to the primary follicle in its structure(FDC and B cells).

>dark zone: appears dark histologically because of the huge num. of B-cells after activation and proliferation.



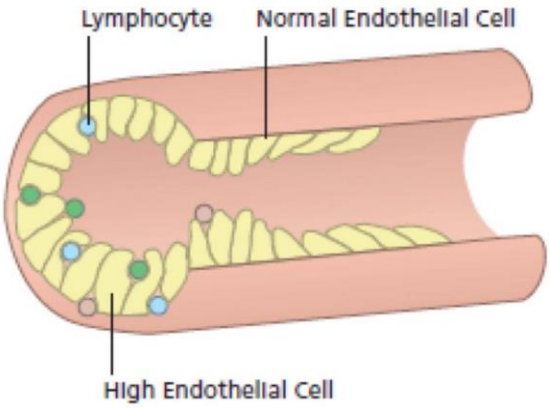
-The activated B-cells will either <u>differentiate to plasma cells</u> and go to the bone marrow, or stay in the follicle and undergo somatic hypermutation*(to create an antibody with higher affinity to the Ag)* and class switching*(to produce the Ab isotype needed)..what the doc. said is a bit different from whats in the pic. As didn't mention anything about it and the book he uses as a reference says class switching occurs in the dark zone.*

-In the light zone , <u>affinity testing</u>*(to test the affinity of new Ab produced by the somatic hypermutation)* ,and <u>restimulation</u> by FDC and TH cells occurs*(if we didn't restimulate them, they will die by apoptosis)*.

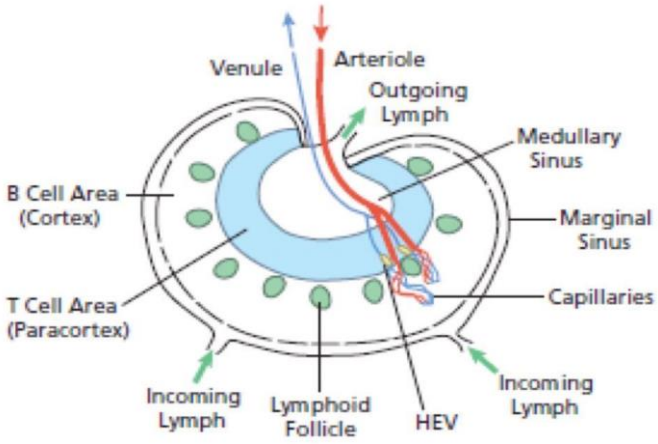
➢ High endothelial venules(HEV)

-Found in all sec. lymphoid organs except in the spleen.

-The endothelial cells here are made of more elongated cells (like a column), and they are loose , making it easier for immune cells to extravasate between them and enter the organ.



➢ Lymph nodes



-As u can see from the figure, the lymph node consists of:

1- The cortex : which contains lymphoid follicles(B-cells).

2- The paracortex : contains T-cells.

3- blood vessels: entering arteriole, exiting venules and the HEV between them.

4-incoming and outgoing lymphatics

5-Sinuses : *e.g.* The marginal sinus which contains a large number of macrophage that act as a filter for incoming lymph.

**** <u>The immune cells</u> enter the lymph nodes either through the HEV or with the incoming lymph**

**** <u>Antigens</u> enter the lymph nodes either presented by AP dendritic cells or as an opsonized Ag with the incoming lymph(and is captured by the FDC).**

- ## Sequence of events (after infection for e.g.)

1- In the lymph node, a Th cell encounters a DC presenting its cognate antigen.

2- Over the following few days, the T cells gets activated and proliferates.

3-To make sure we are fighting the invader everywhere in the body(not only in this lymph node), the Th cell<u>s</u> exit the lymph node, circulate through the blood and enter other lymph node<u>s</u> via HEV in less than a day.

4- Proliferation and recirculation are key events that make sure that there are enough of the right T cell in secondary lymphoid organs to meet other immune cells (B cells) and provide them with help.

5- Once T and B cells are activated, some continue to stimulate and be stimulated in lymph nodes, others go to body tissues to do their defensive job *(e.g. we need Th cells in the site of infection to secrete cytokines)*.

- **The arrangement of immune cells within lymph nodes**
  - ✓ **Immune cells (APCs, and lymphocytes) know where to go in a lymph nodes through Chemokines :**

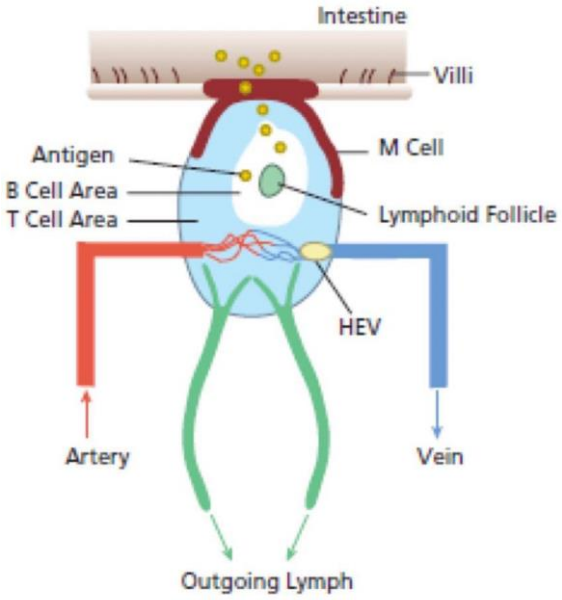
-FDCs produce CXCL13 which attracts B cells that express its receptor(and thats logical, because FDCs job is to present Ag to B cells so they must keep them in close proximity).
-If a B cell finds its cognate Ag, transcriptional alterations occur in the B cell so it downregulates CXCL13 receptor(because we dont need it near FDCs anymore) and upregulates CCR7 which mobilizes it to the border between the B and T cells areas (near the Th cells that will give it the co-stimulatory signal).
-Similar to B cells are the T cells that migrate to the border between the B and T cells areas upon activation by DC to meet B cells , and then into the follicles to help in class switching *(it needs CD40L to occur),* and somatic hypermutation.

  - ✓ **Swelling of lymph nodes occurs secondary to**

1-proliferation and accumulation of immune cells (specially macrophages) in the medullary sinus that blocks the efferent (outgoing) lymphatics after inflammation.
2- sometimes cancer metastasis to the draining lymph nodes of the primary cancer.
3- lymphomas *(There are no lab tests to diagnose lymphoma usually- except LDH might be elevated in some cases-)* .

➢ Payers patches

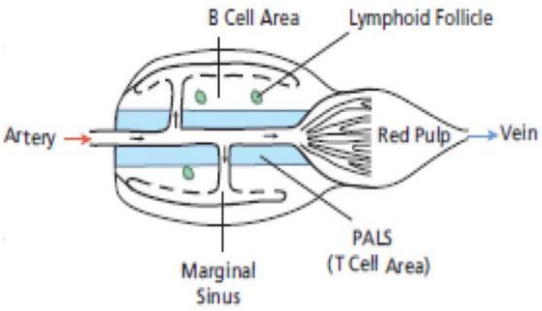
-Similar to lymph nodes in structure(they have lymphoid follicle , blood vessels,HEV and efferent lymphatics), and the only difference is that it doesnt contain an incoming lymphatic(afferent lymphatics), because Ag can directly reach them through M cells (allows certain molecules that can bind on its surface to enter from the GI tract), so it sample intestinal Ags that are able to bind the surface of intestinal cells.



Not mentioned :This selectivity makes perfect sense. The whole idea of the M cell and the Peyer's patch is to help initiate an immune response to pathogens that invade via the intes- tinal tract. But for a pathogen to be troublesome, it has to be able to bind to cells that line the intestines and gain entry into the tissues below. So the minimum requirement for a microbe to be dangerous is that it be able to bind to the surface of an intestinal cell. In contrast, most of the stuff we eat will just pass through the intestine in various stages of digestion without binding to anything.From how the immune sys. Works (the doc discusses the topics exactly as they are in this book).

➢ The spleen

-One of the differences between the spleen and lymph nodes is that it lacks HEV.(the doc. said its absent because all blood can go in and any thing can pass او زي ما حكى بصب صب الدم) . ***we took with dr.faraj that the marginal zone has the same function of HEV in the spleen, but according to cellular and molecular immunology by abbas neither is true, and it involves CCR7-binding chemokines :P***



-The Marginal sinus contains macrophages(just like in the nodes) that phagocytose debris and invaders, filtering the blood(the spleen is able to filter all our blood in half an hour).

-The T cells are located in the Periarteriolar lymphocyte sheath (PALS), and the B cells are located in the lymphoid follicles between the marginal sinuses and the PALS.
-They contain resident DCs in the marginal sinuses that present Ags to T cells.
****To be continued in the next case study :P**

➢ The logic of secondary lymphoid organs

-As we noted before, every secondary lymphoid organ intercept invaders that enter the body via different routes:
Spleen --> screens the <u>blood</u>.
MALT --> screens the Ags in the <u>GI tract</u>.
Lymph nodes -->screens all other tissues by draining lymph that might contain invaders from them.
- Only B and T cells that have found their cognate Ags remain in lymph nodes while others go on to circulate, because we need them to look for their Ags(the role of compartmentalization).
-Once T cells stimulate B cells, they run out of CD40L because after using it to co-stimulate B cells , Th cells rapidly endocytose it and degrade it *(according to How immune system works book ,butthe doc. said they endocytose it and reuse it :/)* , and in order to be able to express CD40L back, the Th cells needs to be restimulated ,but how that occurs when its far from the T cells area(far from DCs)?.. by B cells that express the Ag on MHCII molecules and have B7 which binds to CD28 on Th, giving the signal for Th cells to resynthesize CD40L and to present it.

❖Lymphoid trafficking

-Traffic patterns of naive and experienced lymphocytes are different.

-As we know, T cells originate from the bone marrow, get educated(matures) in the thymus, and then go to the blood, these cells express an array of adhesion molecules(L-selectin, α4β7) that allows them to recognize molecules in HEV so they migrate to secondary lymphoid organs but Not the site of inflammation.

Extra info…:
The adhesion molecules function as "passports" for travel to any of the secondary lymphoid organs. For example, virgin T cells have a molecule called L-selectin on their surface that can bind to its adhesion partner, GlyCAM-1, which is found on the high endothelial venules of lymph nodes. This is their "lymph node passport." Virgin T cells also express an integrin molecule, α4β7, whose adhesion partner, MadCAM-1, is found on the high endothelial venules of Peyer's patches and the lymph nodes that drain the tissues around the intestines (the mesenteric lymph nodes). From how immune system works…

-Once in the secondary lymphoid organs,Naive T cells screens APCs there looking for its Ags. If the cognate Ag is not found, they return to the blood whether through lymph or directly(spleen).

-Naive T cells that encounter their cognate Ag become experienced T cells, and will express adhesion molecules that allows them to:

1-return to the site of infection, so for e.g. the CTLs can kill infected cells and Th can provide cytokines .

2-go to the same type of secondary lymphoid organs it was stimulated in, meaning that if a T cell was stimulated in a lymph node it will not go to payers patches to activate immune cells that can help in the immune reaction (B cells to secrete more Ab and T cells to go to the site of infection).

The same type of secondary lymphoid organ means that for e.g. if a T cell were stimulated in a lymph node it can migrate to other lymph nodes ,but cant migrate to the spleen or payer patches ..etc

-Naive B cells behave similarly to Naive T cells, but Experienced B cells tend not to migrate to much, they reside in the bone marrow or secondary lymphoid organs to secrete Ab.

❖ Why mothers kiss their baby

-Babies immune system is weak as they dont produce IgG, they acquire IgG from their mothers through the placenta, and IgA through breast milk.
-These immunoglobulin represent infection the mother encountered, so most of them will not be of any use to the infant e.g. EBV Ab is given to the infant from the mother, but he/she wont face this virus at this time of his/her life.
-When the mother kisses her baby, she screen for whats on the baby,and picks up the pathogens on him/her, these pathogens will reactivate the B memory cells (that were produced in the mother upon previous infection) in the mother and these activated B cells will induce Ab production(against that specific pathogen on the baby) and will be secreted with milk.

Sorry for any mistake
thanks to Dr.ways :P