INTRODUCTION TO MEDICAL

IMMUNOLOGY

SLIDE SHEET

NUMBER	11
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Anything with double asterisks ** is mentioned in the handout but not the lecture.

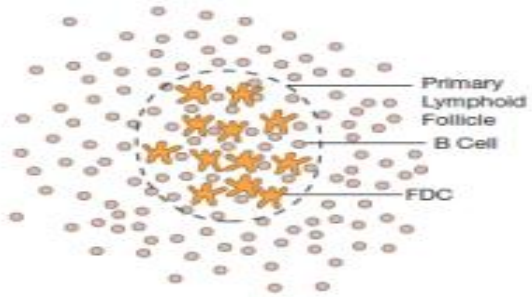
The adaptive immune system is mainly formed by B and T cells. B and T cells are both formed in the bone marrow but then they mature in the **primary lymphoid organs**: bone marrow (for B cells) and thymus (for T cells). After that, they settle in the **secondary lymphoid organs**: lymph nodes, spleen and mucosal-associated lymphoid tissue (MALT): (Peyer's patches, tonsils, appendix) waiting to be activated. It is true that the initial contact between the pathogen and the immune system happens at peripheral sites (e.g. skin, gut, etc.), but the real recognition of pathogens happens in the secondary lymphoid organs.

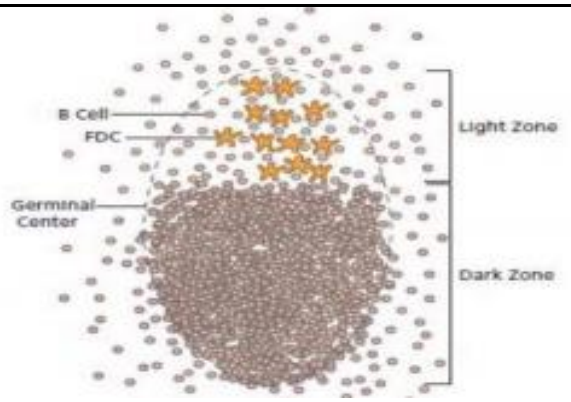
Lymphoid follicles:

Lymphoid follicles are common in all secondary lymphoid organs.
In the lymph node for example (seen bellow), the B cell zone is separated and before the adaptive immune system is activated, the follicle is called the **primary follicle**, containing naïve B cells and follicular dendritic cells (FDC). After the opsonized foreign body is presented by FDC to B cells, B cells are activated. Some B cells will undergo somatic hypermutation and class switching (class switching needs CD40L from Th cells*). This causes a difference in color and produces a dark zone (proliferating B cells) and a light zone (FDC and B cells) which are called together a **secondary lymphoid follicle** or **germinal center**. Affinity testing and restimulation is done with FDC and Th in light zone.

Other B cells will become plasma cells that leave the germinal center and go to the spleen or bone marrow to produce antibodies. Mature plasma cells stop expressing CD19 and CD20 and express CD27 (mature B cell marker) and CD138.

*People who have a deficiency in CD40L don't have germinal centers because Th cells can't properly activate B cells.





Notes:

-**FDC**: They are mostly previous skin, liver cells, etc. that take their position during embryonic development in the lymphoid follicles (they don't leave them) in order to capture opsonized antigens (opsonized by complement or antibodies) and present them to B-cells which have complement receptors and anti-Fc receptors that recognize complement proteins and antibodies opsonizing the pathogen respectively.

-**AP DC**: synthesized in the bone marrow, localized to tissues, and present antigens to T cells in lymph nodes.

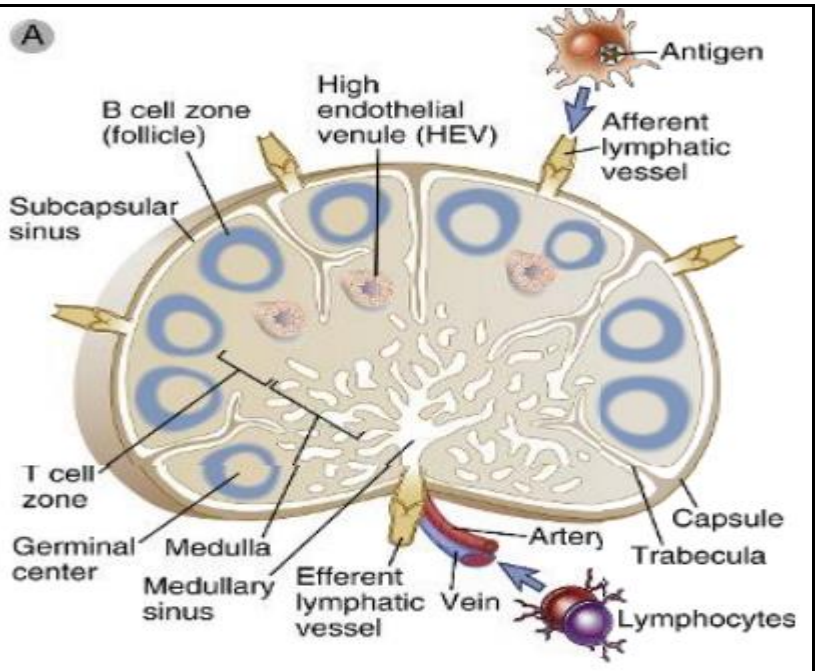
*So, secondary lymphoid organs depend on 2 types of cells for antigen presentation: FDCs which are already in the follicles filtering lymph, and AP DCs that migrate to lymph nodes to present the antigen.

1. The lymph nodes:

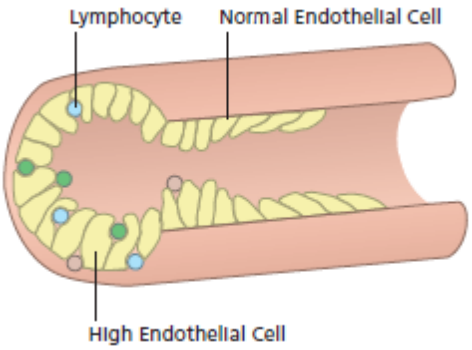
The innate immune system finds a foreign body, it can use compliment proteins or antibodies (IgG) to opsonize it or represent it on dendritic cells to warn the adaptive system. Lymph nodes are spread all around the body, for example: in the cervical, inguinal, and mesenteric regions, with the supraclavicular nodes being more important if they swell. The entrance to a lymph node is through the lymph.

The architecture of lymph nodes:

- Afferent lymphatic vessel through which lymph enters.
- Efferent lymphatic vessel through which lymph exits.
- Medullary sinus
- B cell zones
- T cell zones
- High endothelial venules:



The **high endothelial venules** (HEVs) are structures present in arterioles in certain locations. Here, endothelial cells are longer and have more spaces between them allowing lymphocytes and other cells to leave the circulation into the lymphoid tissue; they are doorways through which B and T cells enter secondary lymphoid organs from blood. High endothelial venules are common in all secondary lymphoid organs except the spleen.



Lymph nodes are centers of immune activation; they are the place where lymphocytes can meet the APC which is expressing its cognate antigen.

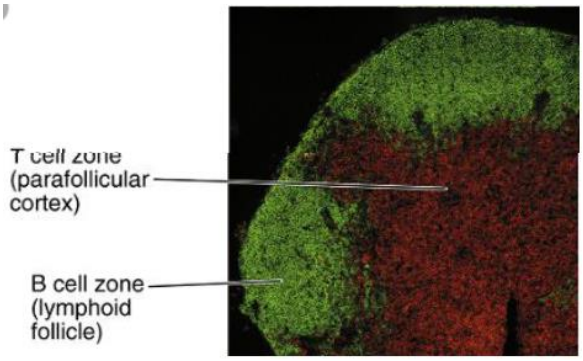
**When lymph enters a node, it percolates through holes in the marginal sinus through the cortex and paracortex, and finally into the medullary sinus – from where it exits the node via the outgoing lymphatic vessels.

**The walls of the marginal sinus (subcapsular sinus) are lined with macrophages which capture pathogens as they enter a lymph node. This substantially reduces the number of invaders that the adaptive immune system will need to deal with. So one of the functions of a lymph node is as a “lymph filter.”

**High endothelial venules are located in the paracortex, so B and T cells pass through this region of the node when they arrive from the blood. T cells tend to accumulate in the paracortex, being retained there by adhesion molecules. This accumulation of T cells makes sense, because dendritic cells also are found in the paracortex (so T cells can meet the APC they need!).

**On the other hand, B cells entering a lymph node accumulate in the cortex, the area where lymphoid follicles are located. This localization of B cells works well, because the follicular dendritic cells that display opsonized antigen to B cells are located in this region of the lymph node.

**So <u>each cell has a specific place</u> in the lymph node: T in paracortex, B in cortex, macrophages in sinuses. <u>This localization is mediated by chemokines</u> secreted inside the lymph node.
There are B cell-attracting chemokines and T cell-attracting chemokines that are recognized by B cells and T cells respectively.



What happens in the lymph node?

a. Once in the lymph node (such as in the first figure), the dendritic cell will represent the antigen to the T cells in the T cell zone.
b. Over the following few days, the naïve T cell gets activated and proliferates.
c. Then, the activated T cell will leave the lymph and circulate through the bloodstream to reach other lymph nodes and enter them via HEVs, taking almost a day to complete the process.
d. After that, T cells activate the B cells and antibodies start being produced.

It may seem to be a waste of time but proliferation and recirculation are key events that make sure that there is enough of the *right* T cell in secondary lymphoid organs; the T cells need to proliferate to increase their numbers for stronger activation of the B cells.

e. 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.
   High endothelial venules (have elongated cells) play an important part in recirculation. Naïve T cells express L-selectin (**binds to GlyCAM-1), or α4β7 (**binds toMadCAM-1). This allows naïve T cells to enter different secondary lymphoid tissues but not sites of inflammation. Whereas experienced T cells express different adhesion molecules and do the opposite by staying focused on entering the same type of lymphoid tissue it came from.

**Note that the Ag the B and T recognize are different, although they came from the same pathogen. B recognizes a certain epitope specific to BCR. But T recognizes a processed Ag that fits MHC molecule.

How do APCs and lymphocytes know where to go within a lymph node?
As seen, B cells, FDC and T cells are separated but need to interact in an order so what brings them closer to each other?

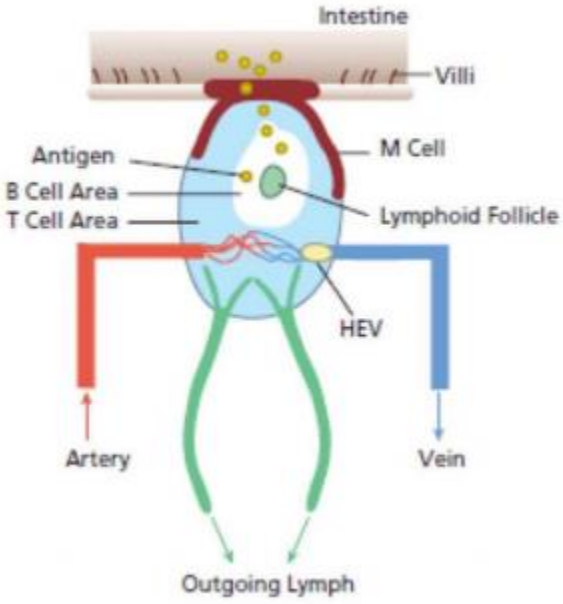
Through chemokines expressed on all these cell types starting with FDC that express CXCL13 which attracts naïve B cells that have CXCR5. After interacting with each other, CXCR5 is downregulated and CCR7 is upregulated in the B cell by transcriptional alterations. CCR7 allows the B cell to migrate to the border of the B cell zone to interact with T cells. (One way of remembering chemokines is that X attracts X and CR7 “Ronaldo” runs to the border).
Likewise, T cells that find their DC carrying their antigen migrate to the border of follicle to meet B cells, and later into the follicles to help in class switch and somatic hypermutation.

This whole process causes swelling of the lymph nodes. It is caused by the proliferation of lymphocytes and the increased amount of lymph in lymph nodes. Proliferation of lymphocytes can also cause blocking of the medullary sinus. Enlargement of lymph nodes can be a sign of inflammation or cancer metastasis.

2. Peyer's Patches:

Peyer's patches are an example of MALT [Mucosa Associated Lymphoid Tissue]. Their structure resembles that of lymph nodes like having high endothelial venules, lymphoid follicles, B and T zones but they don't have afferent lymphatic vessels (no ingoing lymph), rather antigen enters through **M cells**. This makes sense because they don't need to sample lymph, instead they sample intestinal material.

**These M cells are not coated with mucus, so they are easily accessible to microorganisms that inhabit the intestine. They are "sampling" cells which specialize in transporting antigen from the interior (lumen) of the small intestine into the tissues beneath the M cell. To accomplish this, M cells enclose intestinal antigens in vesicles (endosomes). These endosomes are then transported through the M cell, and their contents into the tissues that surround the small intestine. Except for its unusual method of acquiring antigen, a Peyer's patch is quite similar to a lymph node.



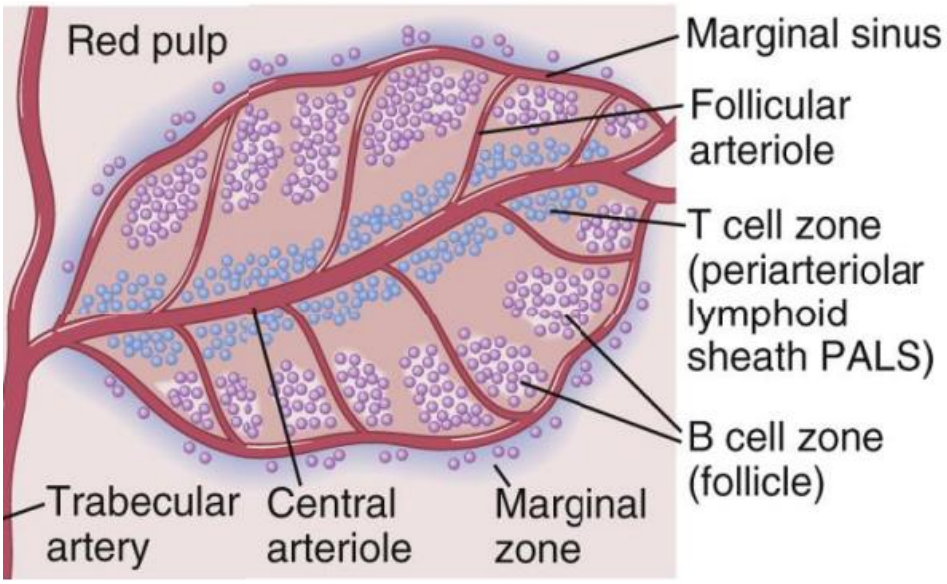
3. Spleen:

It is a secondary lymphoid organ that can filter blood in less than half an hour. It does not have high endothelial venules as the splenic artery is the entrance path to the spleen; it is screening *blood* directly.

By looking at the structure of the spleen, we see a central arteriole that branches into follicular arterioles.

The Marginal sinus contains macrophages (just like in the nodes) that phagocytose debris and invader. It also contains resident dendritic cells that present antigens to T cells.

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.



The Logic of Secondary Lymphoid Organs

Each secondary lymphoid organ is strategically positioned to intercept invaders that enter the body via different routes; lymph nodes are distributed all over the body, MALT in the GI tract and the spleen screens blood directly.

Naïve B and T cells circulate from one node to the other looking for the cognate antigen. Only B and T cells that find their cognate antigens remain in lymph nodes to complete their activation while others go on to circulate.

Once T cells stimulate B cells, they run out of CD40L after using it to activate B cells and their activity starts to decrease before the job ends, luckily B cells themselves are antigen presenting cells and they provide CD80 (B7-1) co-stimulation and **ICOS ligand (which binds to ICOS on T cells).

Recap:

Lymphocyte Trafficking

***important: Traffic patterns of naïve and experienced lymphocytes are *different*.

T cells originate in the bone marrow, get educated in the thymus, and then exit to circulation. **Naïve T cells** express an array of adhesion molecules (L-selectin, α4β7, etc.) that allows them to recognize molecules in HEV and therefore visit the different secondary lymphoid organs.

Once in secondary lymphoid organs, T cells pass through fields of APCs in T cell areas. If no cognate antigen is found, they return to blood whether through lymph or directly (Spleen). (Process continues for about six weeks!) T cells that encounter their cognate antigen become experienced T cells.

Experienced T cells will express adhesion molecules depending on WHERE these cells were activated. For example, if a T cell gets activated in a Peyer's patch it will express adhesion molecules that allow it to recirculate in Peyer's patches and so on. So, when activated cells re-circulate, they usually exit the blood and re-enter the same *type* of secondary lymphoid organ in which they originally encountered antigen.

Experienced T cells also express other adhesion molecules which direct them to exit the blood at places where invaders have started an infection. (Will not go round and round!)

Naive T cells have adhesion molecules that allow them to visit *all* secondary lymphoid organs but NOT sites of inflammation (naïve T cells will never enter the inflamed tissue).

Experienced T cells express restricted adhesion molecule to allow them to return to similar secondary lymphoid organs and exit to sites of inflammation to provide help to Tc and other immune cells.

Naive B cells behave similarly to T cells. Experienced B cells (plasma cells) tend not to migrate too much; they reside in bone marrow or secondary lymphoid organs (spleen) and secrete Abs!

Why mothers kiss their babies?

-Babies immune system is weak as they don't 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 and are irrelevant to the infant e.g. EBV Ab is given to the infant from the mother, but he/she won't face this virus at this time of his/her life.

-When the mother kisses her baby, she screen for what is 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 antibody production (against that specific pathogen on the baby) and will be secreted with milk.

The End