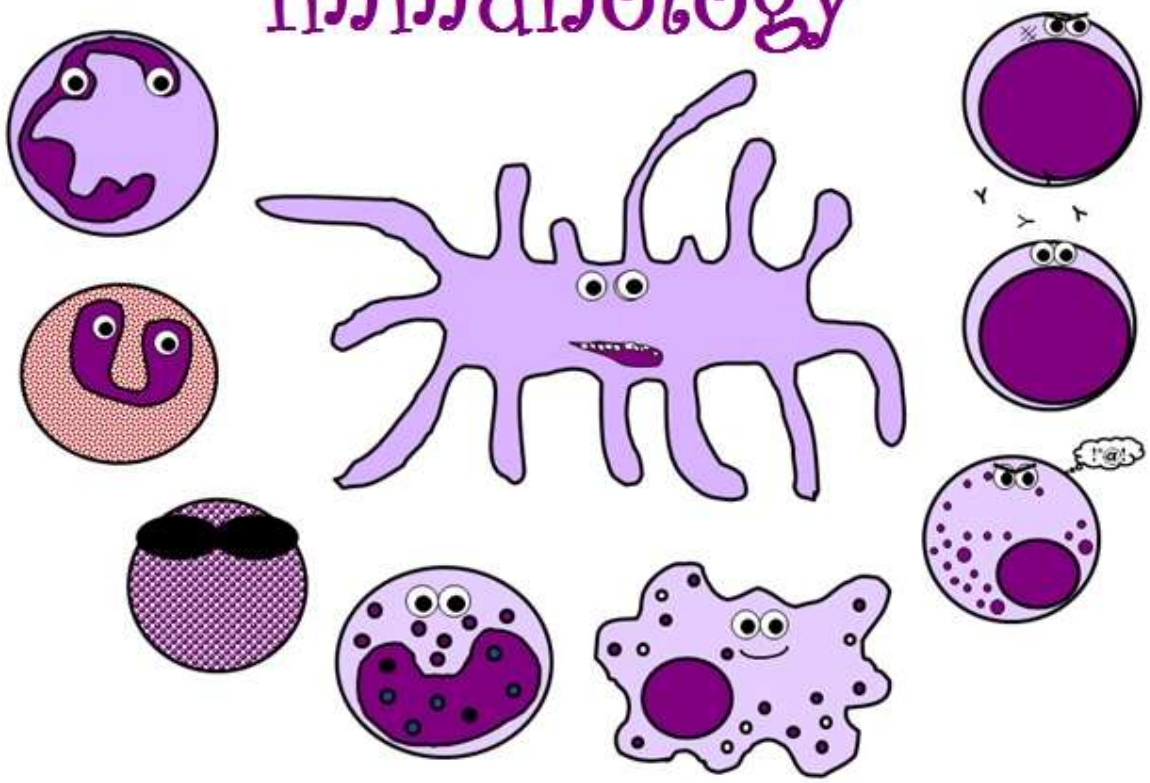
Immunology



Sheet Slides

Number: 14

Subject: Self Tolerance & MHC Restriction

Done by: Tala Ashour

Corrected by: Omar Mahafza

Doctor: Issa Abu-Dayyeh

.....

.....

- This sheet was written according to the record that belongs to section 2.
- This is the last topic included in our midterm exam.
- Wish you all the best:D

Self Tolerance and MHC Restriction

By the end of this sheet we should be able to "hopefully" answer these two questions:

1. How do we teach B and T cells not to recognize self antigens as dangerous?
2. How do we restrict T cells to recognize only antigens presented on a self MHC molecule?

- **Brief summary to what we must know by now:**

Our adaptive immune system is very regulated, in a very sophisticated way, these cells are originally produced by the bone marrow, they are naïve, B cells continue their maturation in the bone marrow while T cells migrate to the thymus, the cells in these two central (primary) lymphoid organs are maturating and becoming immunocompetent, then they fight pathogens in the secondary lymphoid tissue, after the battle the immune system must shut down in order to prevent hyperinflammation & autoimmune disease.

Tolerance to self-antigens:

- Production of cells that are not auto-reactant (don't fight our own cells)
- This is very important to protect us from auto-immune-diseases
- Here, we are not restraining and inactivating our immune response, we are concerned about how to prepare our response from the very beginning not to react toward our self antigen

Tolerance in T-cells

❖ **Tolerance is further divided into :**

1. Central tolerance.
2. Peripheral (tissues) tolerance.

What's the difference between the two?

	Central tolerance	Peripheral tolerance
Occurrence	Primary lymphoid tissues (BM & thymus) & Secondary lymphoid tissues (When we talk about the central tolerance we mainly refer to the thymus, the thymus is the site at which the maturation of T cells occur)	Peripheral tissues (e.g. Kidney, limbs, etc..)
	It is the main process by which the lymphocyte that are believed to be immunocompetant and not reacting toward our self-antigens are allowed to be released to the circulation (initial)	Mechanism by which the lymphocytes that are autoreactant and unfortunately happened to reach the circulation, are prevented from causing auto-immune disease

Central tolerance

Thymus:

- The thymus remains a very mysterious organ: many processes that take place within the thymus are not fully understood of these for example:
  The entry of T cells after leaving the bone marrow since we know that there's no lymphatic's entering the thymus, only blood!

In the spleen we said that there are highly endothelial venules (HEVs) that allow cells to migrate from the blood, but in the thymus there was no evidence for the presence of such cells!

⇨ Tolerance in the thymus occur in two places: Cortex, then the medulla.

- **Steps for T cells tolerance**

1- Entry of the naïve cells:
   - When the nieve T cell leave the bone marrow we refer to it as **double negative** T cell.
   - Double negative T cells: they have no CD3 nor CD4/CD8 and no TCR.
   - It enters the thymus and reach the cortex.

2- Proliferation:
   - Once they enter the cortex, they start to proliferate to increase the number (the maturation start).
   - Once the proliferation starts, the re-arrangement of the alpha and beta chains (TCR) starts, **VDJ recombination** (most T cells are traditional have alpha and beta but there are also delta and gamma, and the rearrangement start here).
   - If the TCR rearrangement and production was successful the **expression of the CD3** start (marker for T cells in general) and the other CD4 and CD8. The cell now is referred to as **double positive** (DP) cells
   - DP cells have BOTH CD4 and CD8!
   - In DP cells, FAS is highly expressed & low BCL2 expression ➔ so these cells are very sensitive to apoptosis, thus if they fail any further tests (self tolerance and MHC restriction), they easily die out by apoptosis

P.S.) "Bcl-2" is anti-apoptotic as it stabilizes the mitochondria

3- ***Positive selection*** (The first test for DP cells)

- cortical thymic epithelial cell that has on its surface MHCs (produced from our cells, BOTH class 1 & class 2)
- The test:
  If T-cells **recognize** an MHC molecule by moderate or strong binding then these cells **survive**, if their binding is weak or they don't bind at all the T-cells die by apoptosis.

Why MHC Restriction?? A person would probably live an entire normal life without the need of organ transplant and thus never reacting with foreign surface antigens, so why do we consider these MHC molecules important??

- Because we want T cells to **focus**:3 and not to react with any surrounding antigen, thus restricting it to MHC make this possible, or else, the whole principle of antigen-resenting will be meaningless.
- MHC also stabilize the complex for CD4 or CD8, so MHC1 is recognized by Cytotoxic T cells, while MHC2 is recognized by T helper.

Further maturation:

- During or slightly after passing the positive selection test, the cells become single positive (SP) cells (by down regulating CD4 and becoming CD8+ only, or down regulating CD8 and becoming CD4+ only)
- These cells will leave the cortex and reach the medulla, where the negative selection test occur

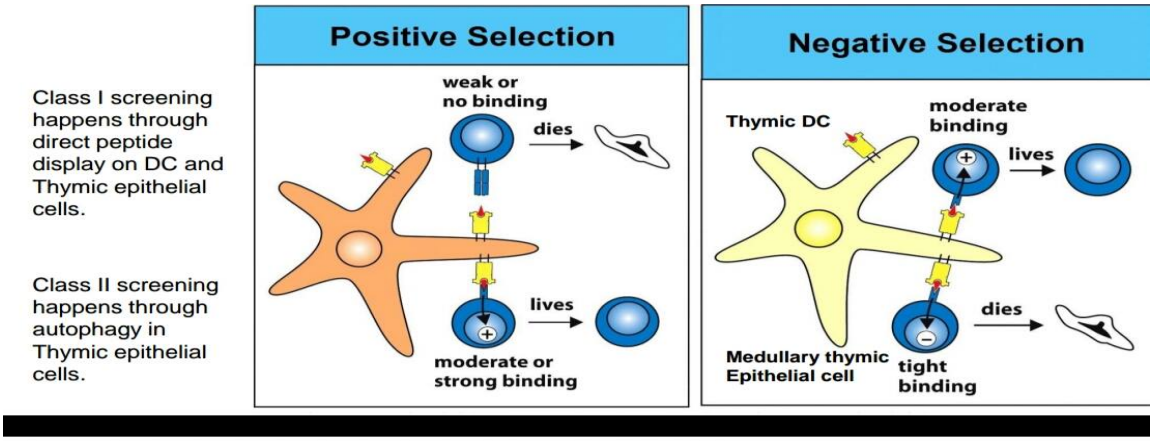
✓ MHC class I presentation by thymic epithelial cells & dendritic cells (proteosomal pathway and self antigens are already present within cells)**.**

✓ MHC class 2 presenting here is bit tricky because we said that the source for these antigens are external, by lysosomal pathway, because phagosytosis is a bit complicated in the thymus we have autophagy.

- ✓ **Autophagy** is process by which the cells eats its own old organelles through lysosomes and present them on MHC2 and thus testing the ability for our DP to recognize them.

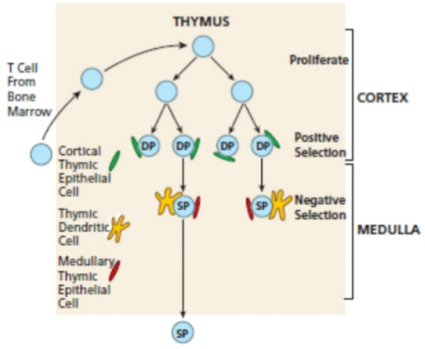
4- Negative selection

- If the cell are capable of recognizing our self-antigens and react with them by tight binding they die.
- If the binding is moderate and not tight, this signal the cell to survive and exit to periphery



Only 3% of the naïve T cells pass central tolerance, the whole process takes around two weeks.

Graduation



- ✓ So, we are getting rid of the cells the are very weak in binding in the positive selection test and of the cells that are very strongly binding in the negative selection test, those that are in between are surviving.

Peripheral tolerance

- ✓ Some T cells manage to escape the negative selection test and reach the periphery (these cells can strongly bind to our self-antigens)

How would these cells escape the test?

- Maybe these cells recognize rare self-antigens in tissues, and this rare antigen wasn't presented to them in the thymus so these will escape the negative selection.
- Maybe the initial binding of the cell to these antigens was weak in the thymus for some defects in the T-cell receptors, so these escape the negative selection and reach for the periphery.

⇨ **We have mechanism to deal with such situation, or otherwise, we all would have auto-immune disease;**

❖ **Tolerance by ignorance**

We make sure that these cells are not in contact with the rare Ag! How?

Lymphoid trafficking: Remember, naïve B cells and T cells do not reach the tissues! they are restricted to circulate in secondary lymphatic tissues from one site to another to screen for the foreign pathogen, so, again, virgin cells are only allowed to reach secondary lymph and not to the tissues.

This is important because **the environmental profile in secondary lymphoid organs is similar to that in the thymus!** So, since we have similar environment the rare antigens that they didn't see in the thymus won't be seen in the secondary lymphoid tissues.

~ Series of the " What Ifs ":p, let's make things a little bit harder, shall we??

❖ **What if** the rare antigen has suddenly increased in the blood and lymphatics (due to e.g. injury)?

⇨ Here comes the role of a special type of T reg cells; Naturally occurring regulatory T-cells (nTreg)

nTreg:

Remember we said that the inducible Tregs (iTregs) are the ones that play a role in restraining (inactivating) the immune response

- While it's being created in the bone marrow, it is distant to become a T-reg cell, and it is distant to roam around the secondary lymphoid organs.
- These also recognize the rare antigen, and escape the negative selection the exact same way the T cells did, thus they have TCR for the rare antigens.
- So, if the rare antigen present and the false (the one that escape) T cell come to react with the rare antigen the T reg recognize the antigen before it and prevent the reaction by competing for co-stimulation(The co-stimulatory signal will target mainly the nTreg and not the T cell).
- nTreg also secretes IL10 (anti-inflammatory/inhibitory).

But how would these cells know??

They don't, what happens is that this reaction is very localized, and the T cells that falsely recognize the rare self antigen are few in number, so the nTreg can control this and inhibit it. In our normal responses the reaction is very huge and generalized and overwhelm the ability of nTreg.

❖ **What if** this mechanism was insufficient and auto-reactive T-cells overcame the intervention of nTregs and passed to tissues?

- ✓ Remember that we have two key requirement rule! There must be costimulation in order for the activated T-cells to work.
- ✓ In the tissues we have APCs that are not good costimulants.
- ✓ They will not express high levels of MHC molecules, many of them won't express B7 molecules thus we reach a state of insufficient co-stimulation
- ✓ When we don't have enough co-stimulation, the cell will reach the state of anergy and then death.

❖ **What if** they manage to have co-stimulation? (MHC/B7 were high enough)

- ✓ Activation induced cell death (AICD) : hyperactivation of T-cells but the environment didn't push the reaction further → induce the expression of FAS and FAS ligand and make them susceptible to apoptosis. (fast response)

Tolerance in B-cells

- ❖ Because the B cell can sometimes react on its own, independent from T cell in some cases (incase of some non-protein Ags), it must have tolerance too.

- ❖ Mostly in BM when they are formed (central)

- ❖ Tolerance during VDJ recombination:

- ✓ Rag1 and Rag2 control recombination to produce receptors.
- ✓ If the recombinant can strongly bind a self-antigen, the cell is given another chance.
- ✓ Rearrangement and recombination again, the new BCR
- ✓ If the new BCR also recognize and strongly bind the self-antigen the cell die (only 1 chance :3).

  10% of the B cells produced actually pass this

  90% of the B cells die

- ⇨ The mechanism for peripheral tolerance and lymphatic trafficking mentioned before also apply to B cell

- ❖ **Maintenance of B cell Tolerance in Germinal Centres:-**

- In germinal centers we find B cells
- And these cells when activated will become plasma cells, these could do class switch and somatic hypermutation.

⇨ Somatic hypermutation: amount of mutations that edit the immunoglobulins, produce antibodies that can bind different antigens

❖ **What if** this induce antibodies that are auto-reactant?? (bind self-antigens)

- If initially the B cell recognize an antigen and co-stimulation by the T cell occur, but once this hypermutation occurs, the B cell now recognize the auto-antigen and the T cell won't induce co-stimulation anymore (بتتبرا منها) so, this B cell won't survive.
  (B cells in germinal centers are very fragile and they keep looking for self-antigens presented by follicular dendritic cells to stay alive, and require helper T cells for activation but since T cells won't recognize the new auto antigen the cell started to see, the cells die) ~ Very regulated mechanism! ~

Good luck ^^