INTRODUCTION TO MEDICAL

IMMUNOLOGY

SLIDE SHEET

NUMBER	14
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Self tolerance and MHC restriction

In the previous lectures we talked about the innate and the adaptive immune systems, how they are activated and the restriction for both of them. Also we mentioned how to spare some stimuli and not react with them, such as food and gut bacteria. In today's lecture we'll answer the question; how the immune cells don't attack our own antigens "self antigens, or auto antigens"?

Two main concepts are discussed:

1- **Self tolerance**
Self tolerance is mainly how we educate T and B cells to differentiate between self and non-self antigens and attack only the non-self, leaving the self antigens with no attack!

2- **MHC restriction**
it's the ability to restrict T cells to recognize only antigens presented on MHC molecules. *"not any antigen- only those bound to MHC molecules"*

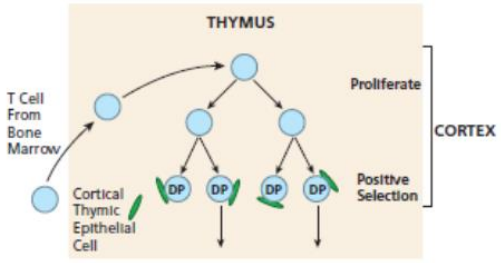
Failing in any self tolerance or MHC restriction tests, will induce apoptosis.

T cell tolerance

T cells originate from the Bone Marrow (BM) and travel to the thymus as **double negative T cells** (No expression for CD4, CD8, and CD3). As they go through the cortex and medulla they are being educated and only **non-auto reactive, single positive T cells** leave the thymus.

After a double negative T cell enters the thymus, proliferation and generation of double positive cells take place in the cortex. How is that done? Simply by producing the TCR first then the other CD molecules; V(D)G recombination for the alpha and beta receptors on T cells happens in the cortex. If this arrangement successful, the other molecules (CD4 and CD8) will be expressed to produce double positive T cells. Double positive cells highly express Fas- fas L molecules, and have low numbers of Bcl-2 molecules; thus these cells are very sensitive to apoptosis. This is important for the rapid killing of auto reactive cells.

Note1: Fas-fas L induces apoptosis
Note2: Bcl-2 molecules are anti apoptotic protein



These cells (double positive cells) will undergo the first stage of selection "the first test", which is positive selection.

Positive selection

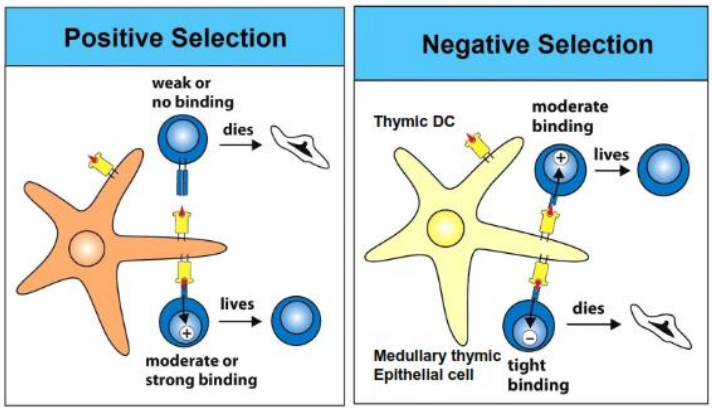
- Cortical thymic epithelial cells check if the double positive T cells have receptors that recognize one of their surface MHC molecules? If yes, the cell will live while if no, the cell will undergo apoptosis.
- The presentation in this selection happens on MHC1 or MHC2, MHC1 is usually presented by Bone marrow or thymic DC, while MHC2 molecules presented by thymic epithelial cells.
- In this selection, the aim is eliminating the weak and non-binding T cells, which couldn't recognize MHC molecules in order to keep only T cells that recognize processed presented antigens by moderate to strong binding.
- After positive selection, the cells will differentiate into single positive T cells. This process is determined by the strength of binding and affinity. If a cell binds more with MHC1 it will differentiate into cytotoxic T cell keeping the CD8 molecule and if it binds more with MHC2 it will differentiate into helper T cell keeping the CD4.
- Now the single positive T cell travel to medulla to undergo the second selection, "negative selection"

Q/Why we need positive selection, even though most of us live and die and will never see a foreign MHC molecule?
*We need it to **focus** the attention on the presented antigen only, also determining which T cell to react with the relevant antigen by focusing cytotoxic T cells or helper T cell specifically.*

Negative selection

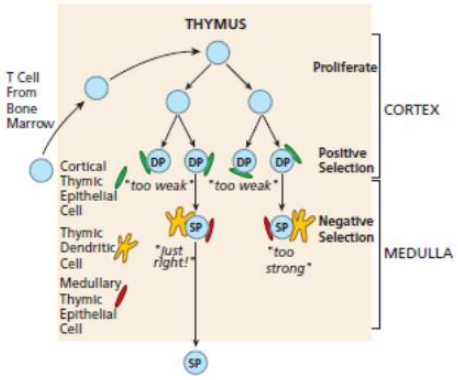
- Negative selection occurs in the medulla of the thymus, mostly by medullary thymic epithelial cells. These cells express lots of self molecules (such as antigens from the liver, heart, lung, and so on) through the transcription factor, Aire.
- If the single positive T cell binds strongly to these antigens it will undergo apoptosis.
  Note: Aire is a transcription factor that up regulates expression of tissue specific antigen

**The positive and negative selection need 2 weeks to be completed in the thymus, and the pass rate is 3-5%. It's a very complicated process and we don't know all the details, since thymus also like spleen, doesn't have high endothelial venules, HEV **



Q/ don't positive and negative selection contraindicate with each other?

No, we only need a perfect, right binding!! (Too weak (positive selection) or too strong (negative selection) binding cells will be eliminated).



And because there is flexibility in choosing the right one, we are at high risk of making mistakes, such as auto reactive T cells that leave the thymus. And the evidence for that are the autoimmune diseases.

Q/Do only autoimmune patients have auto reactive T cells leaving the thymus?

No, all of us have auto reactive T cells, but at the same time we have many layers of regulation that prevent these auto reactive T cells from acting and elicit an immune reaction.

How can an auto reactive T cell escape the negative selection from the thymus?

1- This cell may recognize a rare antigen for example, not found in high numbers in the thymus, thus will not be presented during the education and selection process. So a T cell might have receptor to this antigen but because it didn't show up, no negative selection occurred to this T cell.
2- This cell may have a receptor for auto antigen, but the binding affinity between the receptor and self antigen is low. So during selection the binding happened but it was weak, so the body thought it's the right binding!

These two scenarios allow an auto reactive T cell to leave the thymus. So we need to have regulatory and protection mechanisms to prevent the autoimmune reaction.

Mechanisms to prevent the autoimmune reaction:

1- **Central Tolerance in the thymus** which is the negative selection. T cells that recognize abundant self antigen in the thymus are eliminated

2- **Traffic Pattern** -remember the lecture about 2ry lymphoid organ- , naïve lymphocyte can't enter the tissue; they are only able to enter 2ry lymphoid organs, for example, lymph nodes. And the profile of the 2ry lymphoid tissue is very similar to that in thymus, so a rare antigen in thymus is also a rare antigen in 2ry lymphoid organ. Ando by this, the auto reactive T cell will not find its antigen and it will die "relatively short half life"

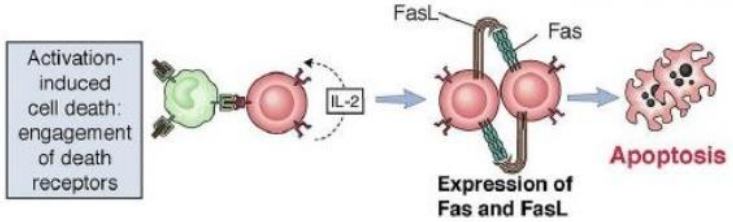
3- What if the antigen for that auto reactive T cell is rare in thymus and this allowed it to leave to go the 2ry lymphoid organ, and simultaneously, an injury took place which led to elevated levels of that rare antigen to a level that is sufficient for an interaction!! So we need a further protection mechanism! This is in this case, **naturally occurring regulatory T cells (FOXP3 + cells)**.
Naturally occurring T_{reg} cells recognize self antigen in thymus but they are not killed, they are spared to go to the lymph nodes and other organ, in order to suppress any immune reaction toward self antigens. So they suppress the function of auto reactive T cell.

*** T_{reg} cells mechanisms of suppression are a lot, of these:

a- *Cell-cell dependent:* the interaction between T_{reg} cell and APC prevent the APC from expression co-stimulatory molecules. So the auto reactive T cell sees its antigen and gets activated. But fortunately no other co-stimulation signal is found.
b- cell independent: T_{reg} cells are able to release anti inflammatory cytokines such as IL10, TGF-beta and these also suppress the immune reaction.
Note: Naturally occurring T reg cells help in the protection from autoimmunity, while induced T reg cells restrain the immune system.

4- What if the antigen for that auto reactive T cell is rare in thymus and this allowed it to leave to go the 2ry lymphoid organ, and simultaneously, an injury took place which led to elevated levels of that rare antigen to a level that is sufficient for an interaction, and somehow the naturally occurring T_{reg} cells didn't prevent the reaction, thus the auto reactive T cell was able to escape to the tissue!! So there is a need for other protection mechanisms in peripheral. One of these mechanisms we've been mentioning it throughout the course all days which is the **two-key system**. The auto reactive T cell binds its antigen but no co-stimulatory signal can be found because it's not an inflamed tissue! So APC will not present anything to this cell and it will undergo a state of ANERGY, then apoptosis.

5- What if all the previous points happened, auto reactive T cell escaped the thymus, injury that led to elevation of that rare antigen and T_{reg} cells failed to control the reaction. Besides all that, the tissue itself that the auto reactive T cell went to is already inflamed!!!! In this case the auto reactive T cell will bind its antigen and will receive another co-stimulatory signal! Will this be the end? No, we have other protection levels such as **Activation Induced Cell Death (AICD)**. Hyper activation T cell will induce its apoptosis. Auto reactive T cells are few in number, so when they are hyper activated they will move toward their death and no other T cells can compensate.
Note: ALPS, autoimmune lymph proliferative syndrome, lead to autoimmune diseases because the high numbers of lymphocytes have some auto reactive lymphocytes and will not be killed by apoptosis.



B cell tolerance

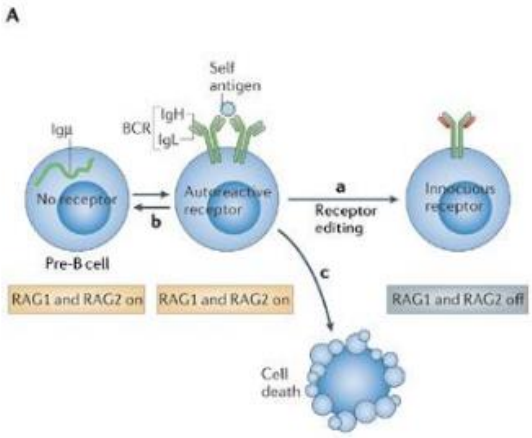
It was known from long time ago that B cells are getting activated by T cells. And by selection methods of T cell, we are automatically selecting B cells so there is no selection for B cells by themselves. But this is not the case.

In BM, RAG1 and RAG2 beside other enzymes make B cell receptor; this receptor can recognize auto-antigen. If a B cell recognized an auto-antigen during the education in BM, it will be given another chance for correction, by reactivation RAG1 and RAG2 and recombination to **LIGHT chain only**, the heavy chain will stay the same. And the test for auto-antigen is re-done. If it didn't see the self antigen it will live, but if it saw it will die by apoptosis. The rest of the trafficking patterns and protection mechanisms are the same as T cells.

B cells produced in the BM go to the secondary lymphoid organs. They settle in the primary follicle and after activation, germinal center develop. Germinal centers have activated B cells that undergo class switching and somatic hyper-mutation, which is a change in the antigen binding site to a site with better affinity, hopefully. Sometimes, this hyper-mutation can change the receptor into an autoimmune receptor! But this is very unlikely to happen because of two main things.

First of all, B cells in germinal centers are very fragile; they need constant stimulation of the antigen to stay active, otherwise they will die. So if the hyper-mutation process changed this receptor into an auto-antigen, its antigen doest present there to continue the re-stimulation.

Secondly, for the activation in the germinal centers to occur we need T cell stimulatory signal. (T cell and B cell should agree on seeing the same pathogen). If this B cell started seeing auto-antigen, the T cells won't give it another stimulatory signal.



Pass rate= **10% !**

So we have many levels of protection from the auto reactive T cell. And for an autoimmune disease to happen, there are certain conditions that will be discussed later. At the end always keep in mind that most of the autoimmune diseases that will be mentioned throughout the rest of the course are very rare because of the protection mechanisms discussed today.

Whoever is trying to bring you down is already below you!
GOODLUCK

ولأنه معي مجال بهاي الصفحة, رح أدعيلكم دعوة.. الله يوفقكم جميعًا و يجعل يومكم سعيد والله ينفع بعلمكم الأمه و ما تنسوه لما تكونوا بحاجته!