

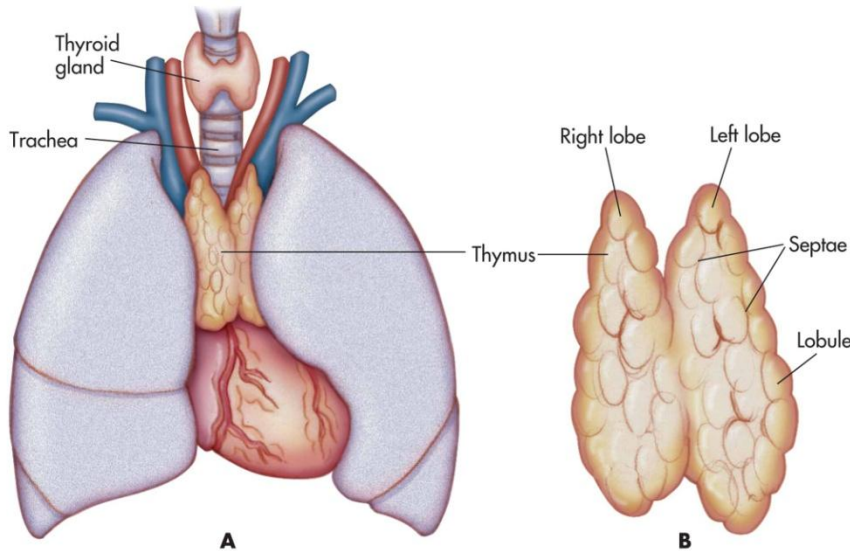
Self Tolerance and MHC Restriction

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How do we teach B and T cells not to recognise self antigens as dangerous?

How do we restrict T cells to recognise only Ags presented on a self MHC molecule?

Central Tolerance Induction



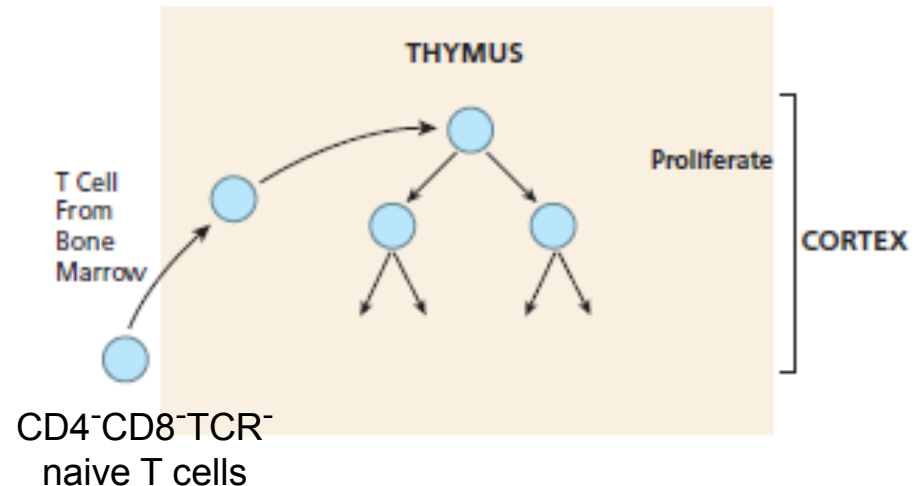
From bone marrow and thymus, selection of immune cells that we believe are good and competent **MOSTLY THYMUS**

Thymus: site of maturation of T cells. (The t cells migrate from the bone marrow via the blood to the thymus to be educated)

Peripheral tolerance: if some autoreactive immune cells left the main primary organs and went to the periphery how do you deal with that

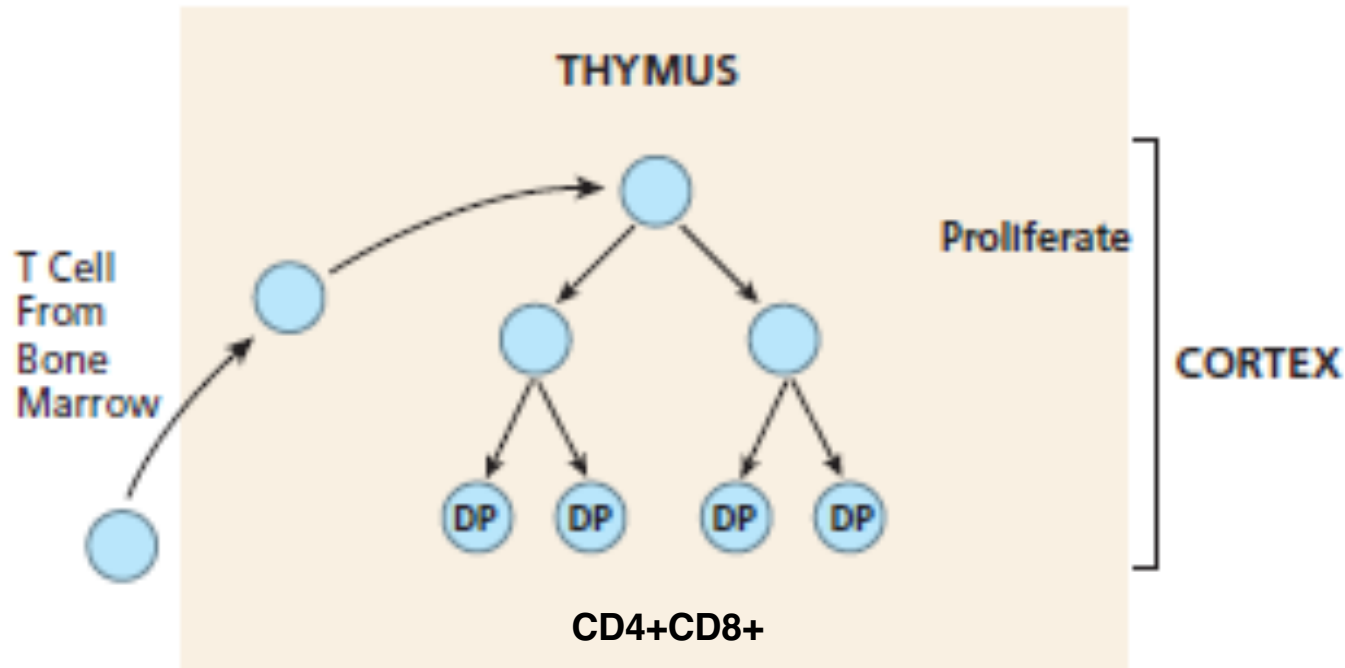
Spleen does not have incoming lymphatics
cells enter through high endothelial cells.

Thymus also does not have incoming lymph .
Not understood how the cells enter yet



Generation of Double Positive cells

T cell from bone marrow is double negative, it goes from bone marrow to thymus and it starts to proliferate



Start of education:

Rearrangement of α and β chains of the TCR. If successful, CD3, CD4, and CD8 become expressed.

CD3 is the maker for all the T cells.

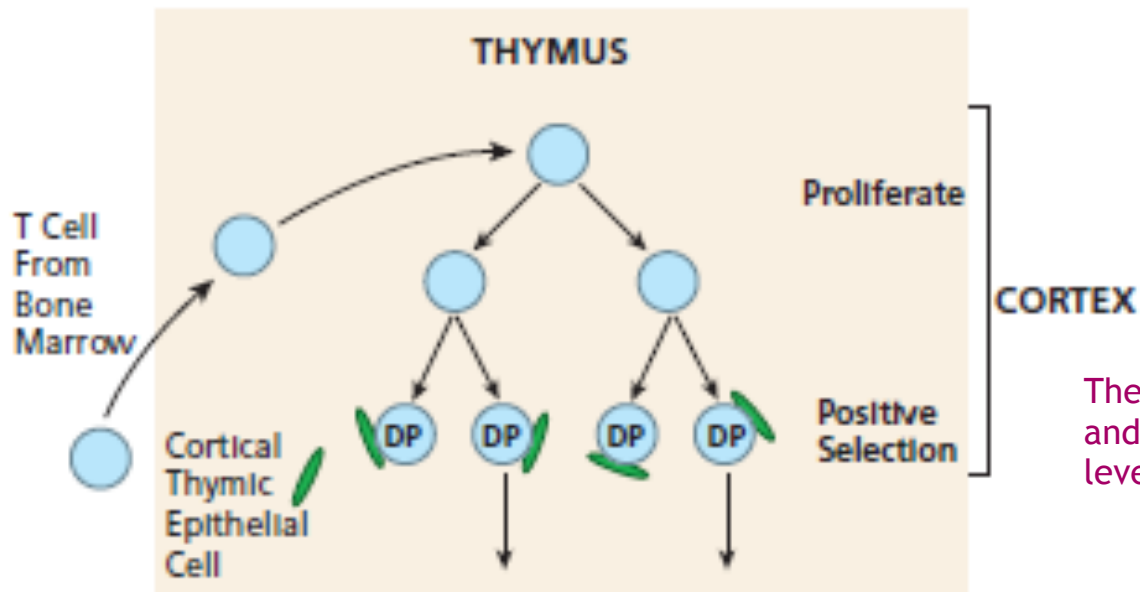
When they express CD4 and CD8 we call them double positive

DP express high Fas and low Bcl-2, failing any self tolerance or MHC restriction test will induce death by apoptosis.

Are very sensitive to death and apoptosis. The Fas is highly expressed because it is involved in apoptosis. So high fas and low BCL2. Any failure will induce death by apoptosis

MHC Restriction

Positive selection:



The interaction continues and goes to the next level.

Midterm is the positive selection test

We ask by the cortical thymic epithelial cells that have MHC on their surface:

Q: Do you have receptors that recognise one of my surface MHC molecules?

A: Yes → Live!

No → Die! By apoptosis

The logic of MHC restriction?

Most of us live and die without seeing foreign MHC (ex: transplant), so why do we need to test T cells for self MHC recognition?

It is about Focus!

MHC molecules are only presenting if there is invasion and processing and other cells that agree that there should be presentation MHC stabilizes the complexes

Selecting T cells that will only recognise antigens presented by an MHC molecule

Otherwise, the whole system of antigen presentation will not work!

The main idea behind MHC is focusing T cells. So show them to the cells, and the foreign exogenous antigen, so the concept is very imp to have the T cells identify the frigid H antigens at the right time.

All cells display the antigen on MHC1, MHC2 the antigen is coming through external pathway

Testing for Self Tolerance

During and a little after they start to become single positive so they are either CD4 or CD8, they go from the cortex to the medulla, now they are ready for the negative selection.

Positive selection: are you seeing the MHC, you show them both MH1 and MHCII. Cells w strong or medium interaction with MHC live

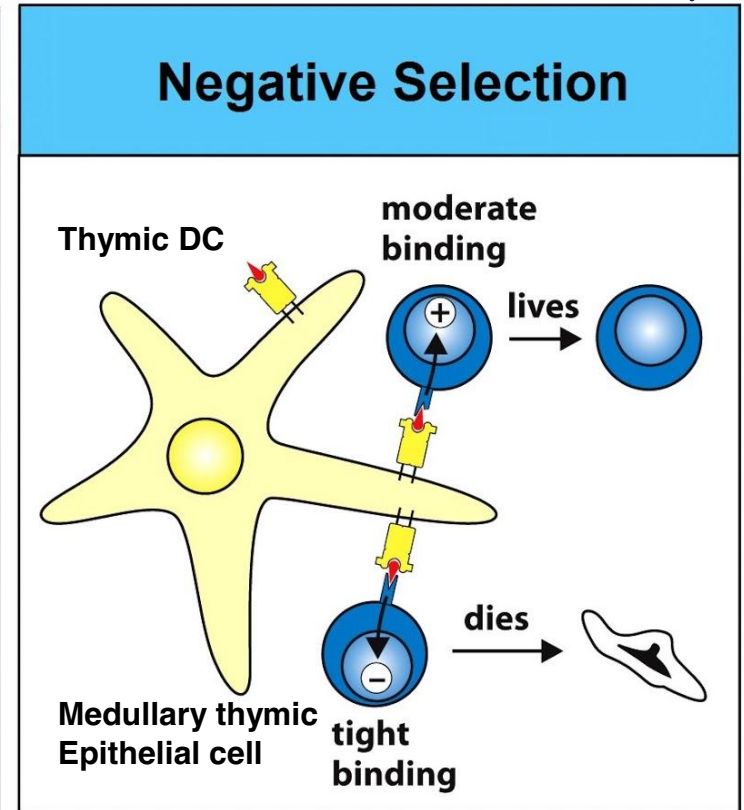
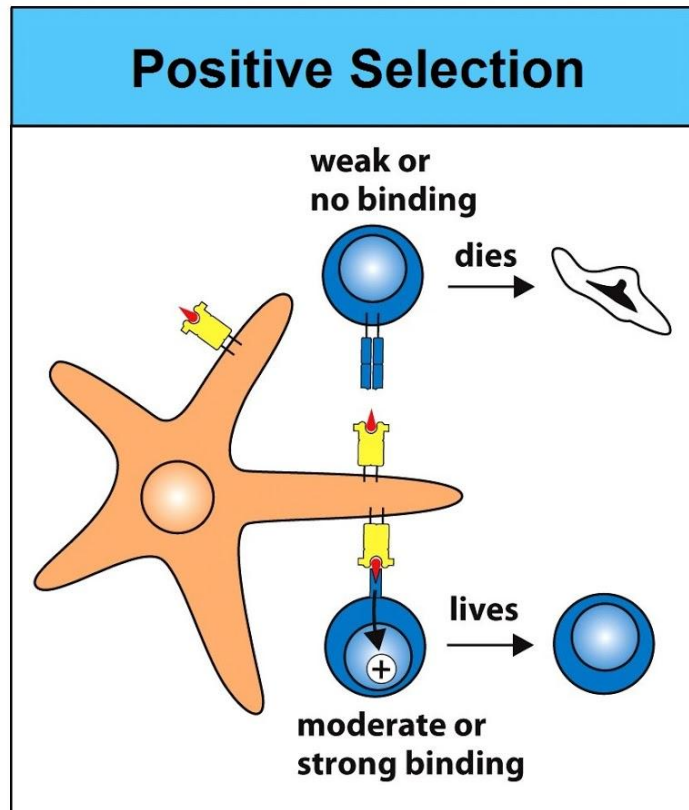
During or slightly after positive selection, cells become “single positive”; expressing either CD4+ or CD8+. Autophagy, brings the old organisms to the lysosome to be Lysenko, so these cells can use autophagy to bring the antigens into the lysozyme and you get MCHII. Seen in aging cells for example. We show them class 1 and 2

The selected cells travel to thymic medulla to undergo **Negative selection**.

The negative selection, I want to show you autoantigens, if it binds to them tightly it dies, *by apoptosis*
weaker binding
It lives.

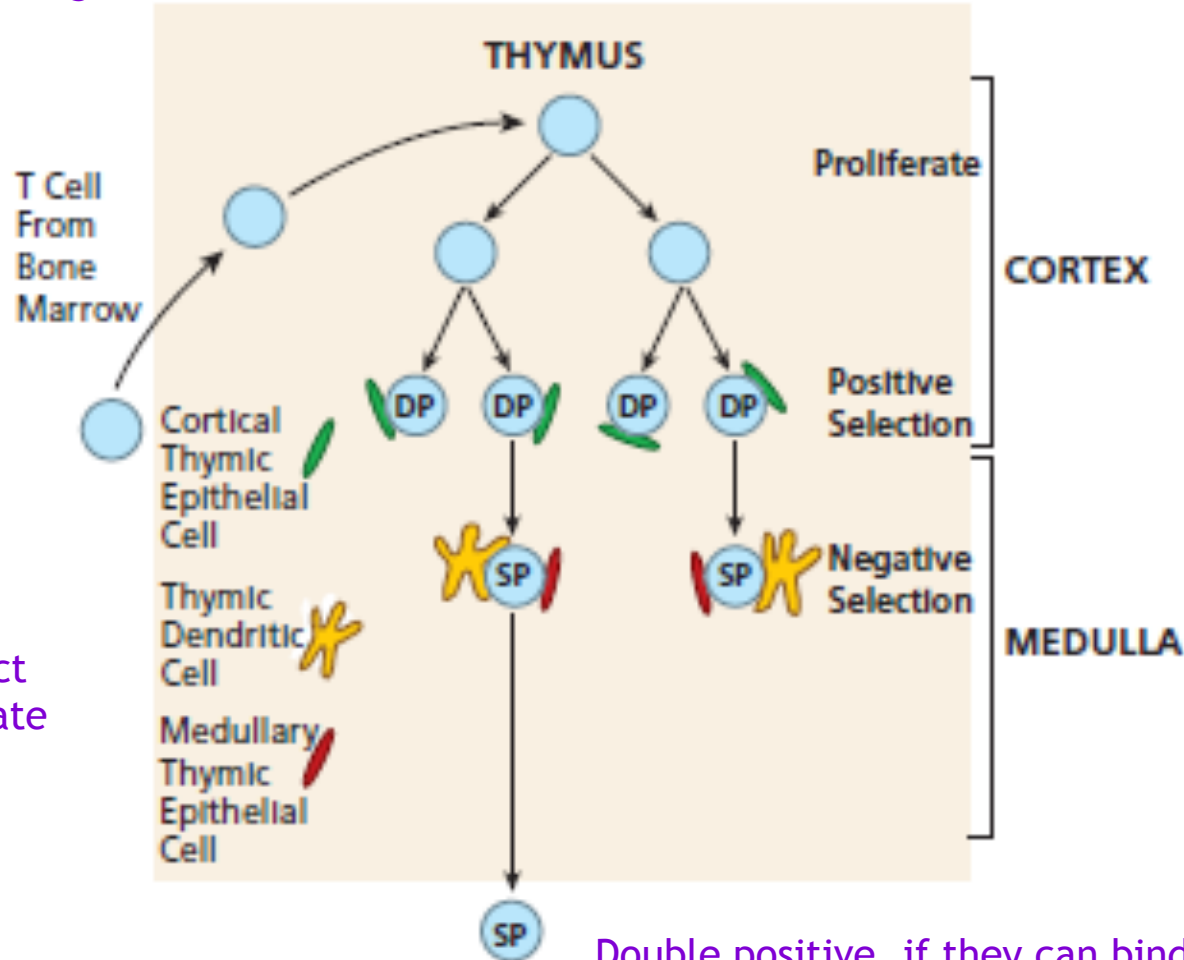
Class I screening happens through direct peptide display on DC and Thymic epithelial cells.

Class II screening happens through autophagy in Thymic epithelial cells.



Graduation

Bone marrow -> thymus -> positive selection -> strong binding live -> go to medulla -> negative selection weak binding lives -> the % of cells that live is 3% and it takes two weeks



You don't want to produce 20% for example that react to inappropriate antigens

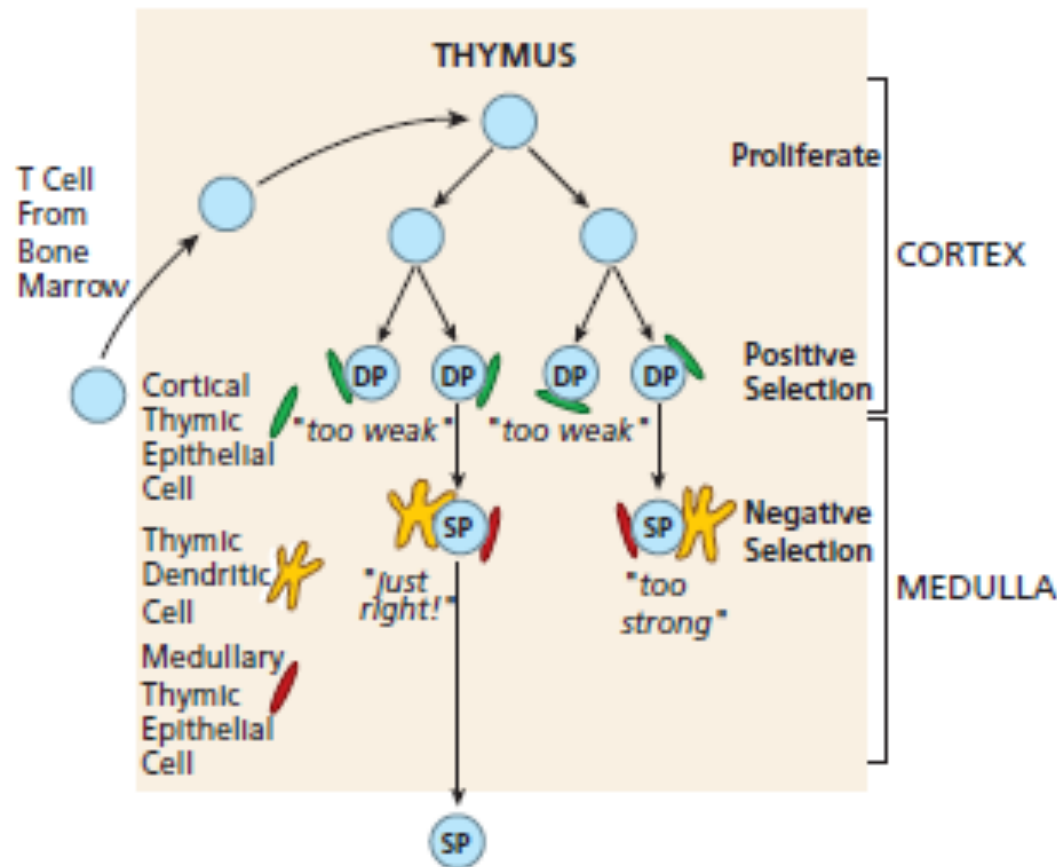
Pass rate= **3%**
Duration of exam= **2 weeks!**

Double positive, if they can bind strongly they go to the medulla, where they get their final exam where you get negative selection and the cells that can't identify them strongly ...

The riddle?

Don't positive and negative selection tests contradict each other??

It is looking for the exact right amount of binding, if the selection is positive is too weak we get rid of them. In the negative selection if it is too wrong we get rid of them. So the autoantigen is being presented on the MHC. There is increased affinity to the autoantigen. You will negatively select the cells.



End of
cellular
tolerance
cells go to
periphery

Tolerance by ignorance

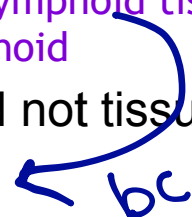
What about some self-reactive T cells that escape negative selection?

Some cells that leave to the periphery but are autoreactive

(Rare Ag, had a lower binding affinity in -ve selection?)

Lymphoid trafficking, the naive B and T cells do not exit to tissue, but go from one lymphoid tissue to another. This happens here too. Virgin T cells are only allowed to secondary lymphoid

Traffic pattern (Virgin T cells allowed to secondary lymphoid organs and not tissue!)



Ag profile in secondary lymphoid organs is similar to that in the thymus!

So if there is a rare antigen the t cell did not see in the thymus it won't be seen in the secondary lymphoid organ. So they see a similar pattern of the thymus.

Rare antigens in the thymus are also rare in 2° lymphoid organs, and usually insufficient to trigger an immune response.

Some T cells will escape the tolerance, there could be a rare antigen, it leaves and gets out of the circulation. There are multiple cases we can use to get an autoimmune. In the lymphoid organs and trafficking, the naive T cells and B cells can only circulate in the secondary lymphoid organs. You look for HLA cognate antigens, you are not allowing them to leave the tissues, therefore tolerance by ignorance. There are in the thymus similar to the secondary lymphoid organs.

Tolerance Induction in 2° lymphoid organs

What if a rare antigen is suddenly increased in blood and lymphatics (injury)???

T regulatory cells, inducible, responsible in restraining the immune response. There is also the naturally occurring with the transcription factor Foxp3⁺ and its function is to go and roam around the secondary lymphatic organs. So if autoreactive the T cell sees it, T reg will stop it and compete with the costimulation.

Naturally occurring Tregs (Foxp3⁺)

From the thymus, they tour 2° lymphoid organs and can suppress autoimmune reactions of T cells that have a similar TCR specificity.

Mechanisms: decrease co-stimulation of APC, cell-cell contact needed.

Also it secretes the antiinflammatory cytokines such as interleukin 10

nTreg vs. Induced Tregs?? (Autoimmunity vs. Restraining the immune system)

T regulatory cells. If you have a response that you want to end, you do a T reg, in the case of immune tolerance we are not talking about the inducible, we are talking about natural occurring, one of the main ones is Foxp3⁺ cells. For the bone marrow they are destined to be secondary, they are roaming around, if they found an inappropriately active it will suppress that immune response from a cell mediated response.

Peripheral Tolerance

What about those autoreactive T cells that break the law and go to tissues??

T cell entered the tissue, there is a requirement for costimulation. The APC that are present in the tissue for example goes to the kidney tissue the cells in the tissue are not good costimulants, don't express MHC and don't express B7

Two key requirement!

So it doesn't get its second signal.

Lack of co-stimulatory signal in tissue: Anergy and death!

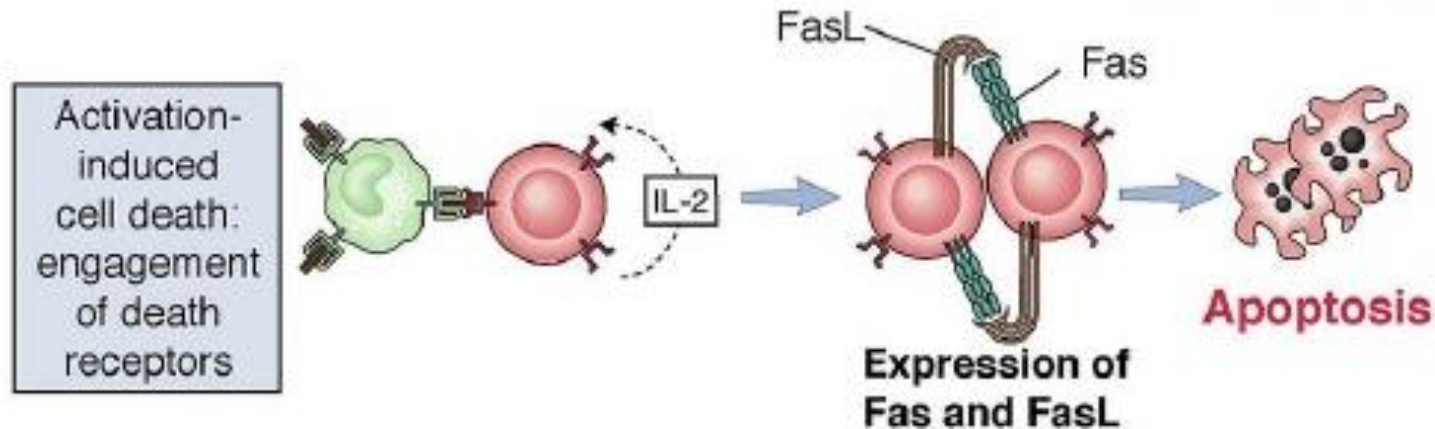
We need two signals to activate the immune system. This T cell that was able to leave to the tissue to get activated there has to be costimulation. Normal tissue it is not high and does not express costimulatory molecules, so the second signal it is difficult to find, so you protect the cells from the autoimmune process.

Anergic cells usually die by apoptosis.

Activation-Induced Cell Death (AICD)

What if an autoreactive T cell makes it to the tissue, and somehow manages to receive a co-stimulatory signal?

The cell comes in, the amount of MHC causes stimulation, so then you get activation induced cell death. Nothing to push it further, hyperactivation causes expression of Fas and FASL so makes it very susceptible to apoptosis. Very fast response.



B cell tolerance

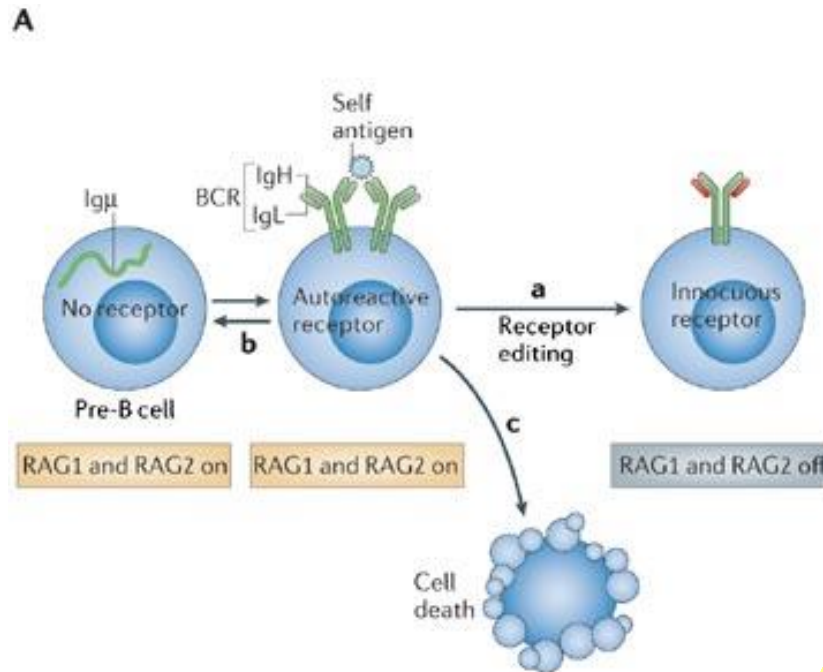
Needs activation by T helper cell, but still they need to be regulated if they are acting without T cells, especially when the antigen is not a peptide,

Initially thought to be unnecessary.....(Covered by T cell selection)

Process takes place in the BM. (Receptor editing)

Bone marrow -> secondary lymphatic organs -> same as T cell.

These mechanisms that are mostly in the bone marrow, the RAG1 and RAG2 cause VDJ recombination to form immune receptors of IgM and IgD, so you get exposure of bone marrow if you find an autoantigen you give it a second chance to recombine the light chain and you try it again, if it is still self reacting then it dies by apoptosis.



So 90% of B cells are dying by apoptosis .

Pass rate= 10% !

Traffic pattern and other mechanisms similar to T cell tolerance apply.

Maintenance of B cell Tolerance in Germinal Centres

When activated in germinal centers they become plasma cells, but they undergo class switch and somatic hypermutation (hoping we produce ab that bind better to antigens)

Can Somatic hypermutation cause autoimmunity??

The b cell was initially activated by the T cell when there was foreign antigen but after the somatic hypermutation when it becomes self the T cell no longer restimulates it Lack of costimulation from the T cells.

Very unlikely! (Lack of the two required signals)

1- B cells in germinal centres are very fragile. An autoreactive B cell will look for the self antigen presented on a FDC to remain alive.

2- It will require a germinal centre Th cell to provide help. (Once BCR is directed towards an autoantigen, the Th cell previously involved in the activation will not cooperate).

Since this T helper cell is not seeing the same antigen it won't give the costimulation.

The tolerance mechanisms are multilayered, if it gets loose for the first one it goes to the second, so we have central tolerance, the T cells that are autoreactive. If it goes to the lymphoid organs, because of the trafficking pattern they won't see that about the antigens, if this rare antigen was abundant and there could be activation. The T reg dwells will come and cause inhibition of the immune response, if the T cells were able to leave and enter the tissue, and for a reason, if there is a missing signal you will get overactivation by the AICD mechanism in the Fas and FasL.

How are we protected from autoimmunity??

The regulation occurs in layers

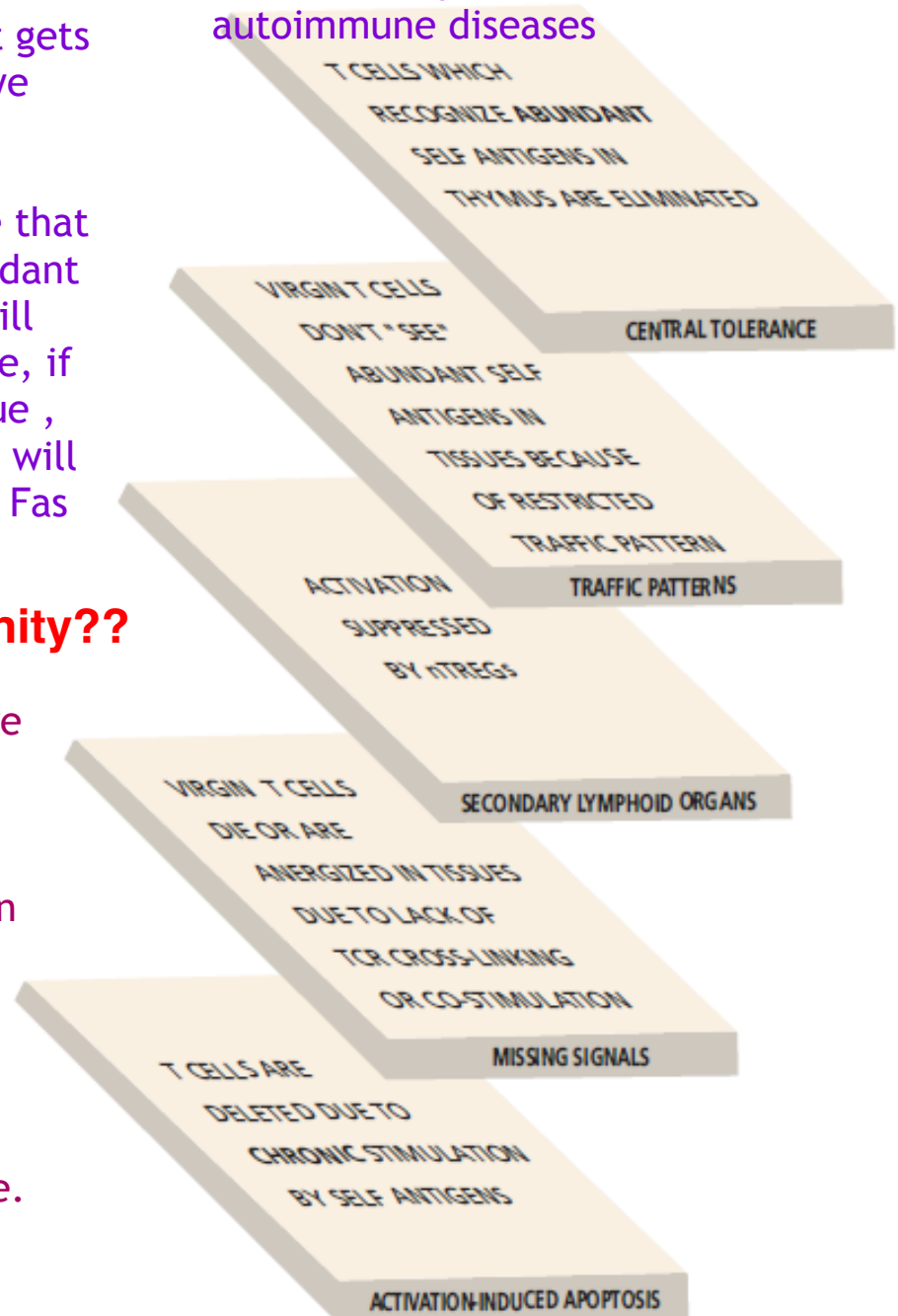
Central tolerance: T cells that recognize self are eliminated

Traffic patterns; they are restricted to secondary lymphoid so they see same antigen in secondary lymph organs.

Missing signal: even if they go to the tissue there is no costimulation

Virgin T cells undergo anergy (not active) or die. Activation induced apoptosis: even if hypersimulated they die via AICD via Fas and FasL.

This is what protects us from autoimmune diseases





?Any question