# Self Tolerance and MHC Restriction

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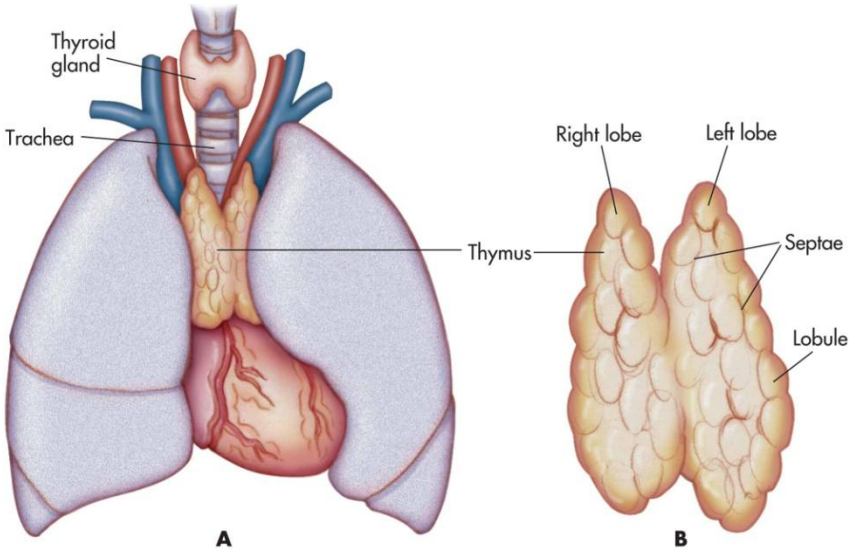
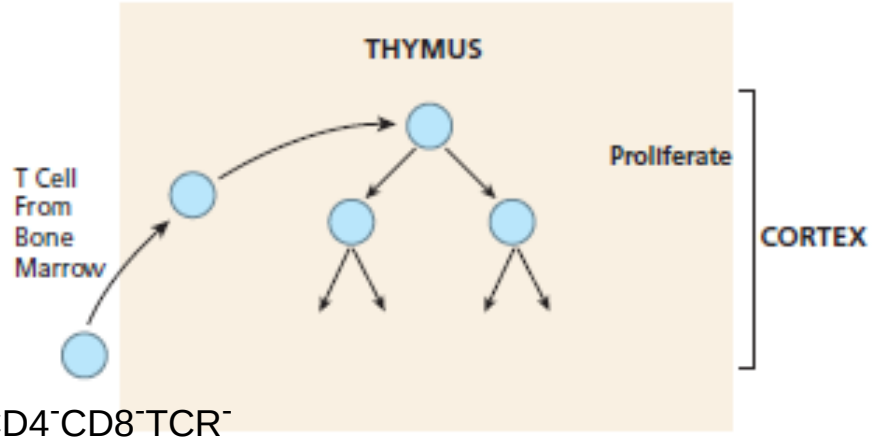
How do we teach B and T cells not to recognise self antigens as dangerous?

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

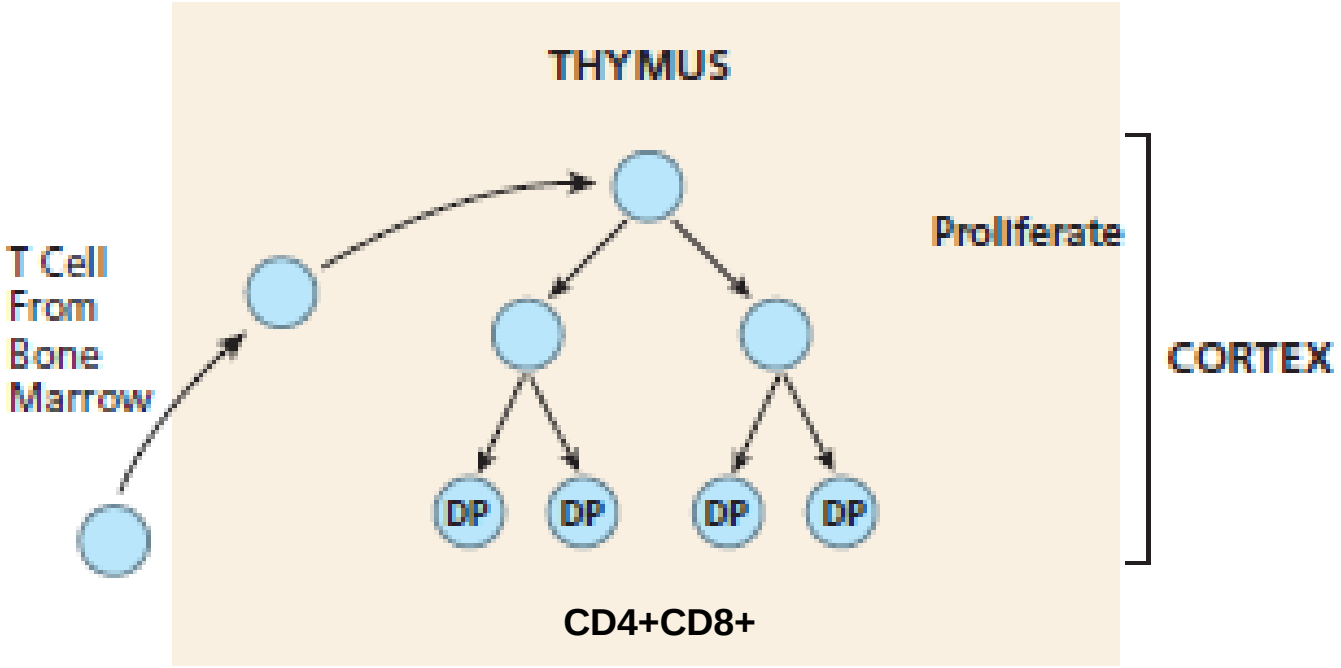
# Central Tolerance Induction




$CD4^-CD8^-TCR^-$
naive T cells

# Generation of Double Positive cells

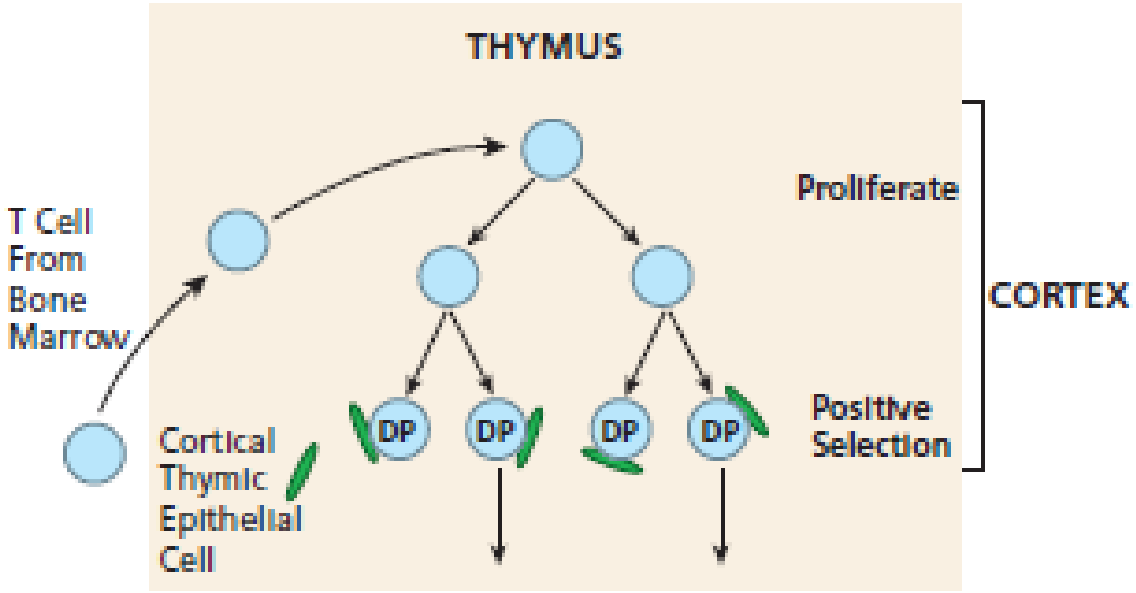



Rearrangement of α and β chains of the TCR. If successful, CD3, CD4, and CD8 become expressed.

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

# MHC Restriction

**Positive selection:**




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

**A**: Yes → Live!
No → Die!

# 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!

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

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

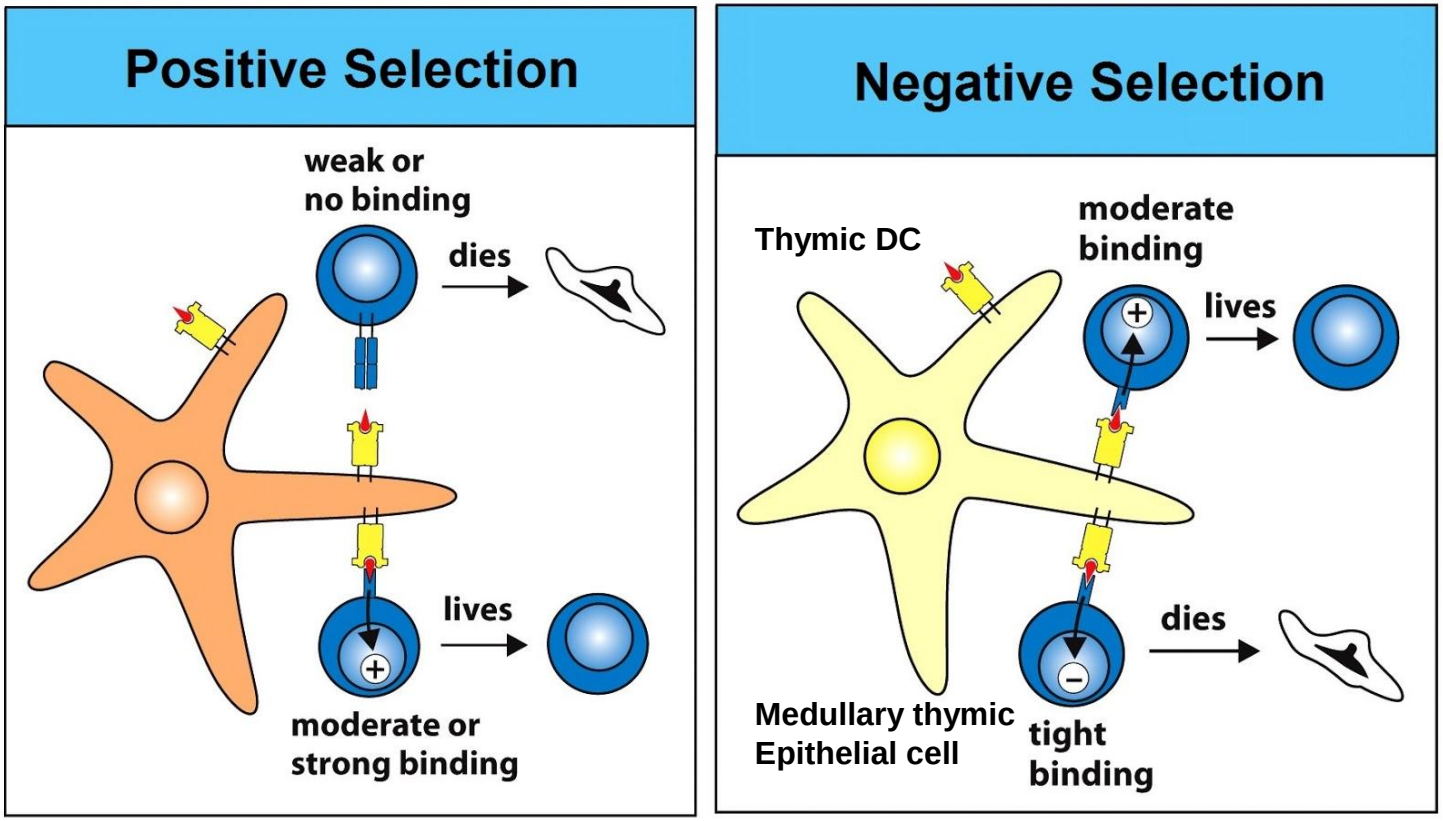
# Testing for Self Tolerance

During or slightly after positive selection, cells become “single positive”; expressing either CD4+ or CD8+.

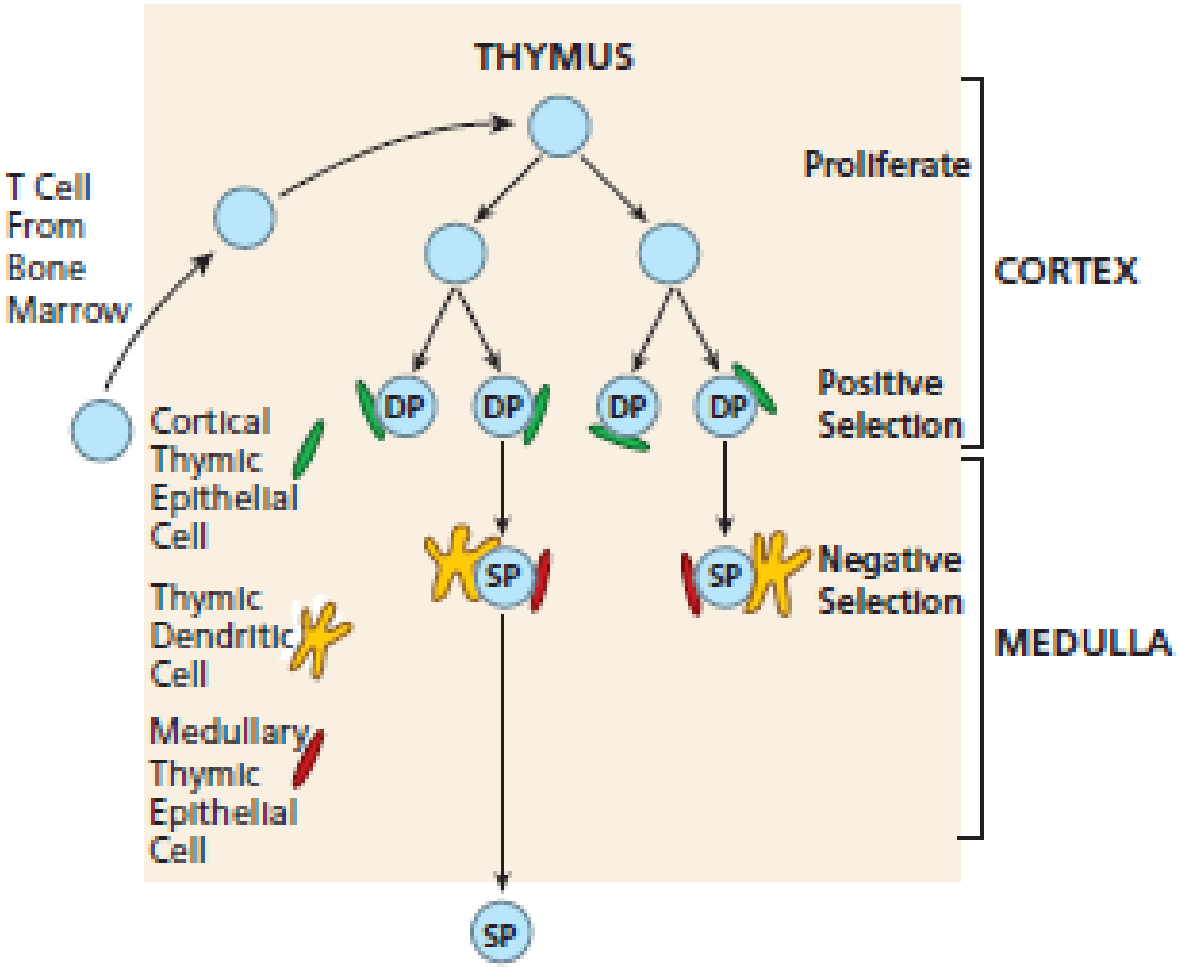
The selected cells travel to thymic medulla to undergo **Negative selection**.

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

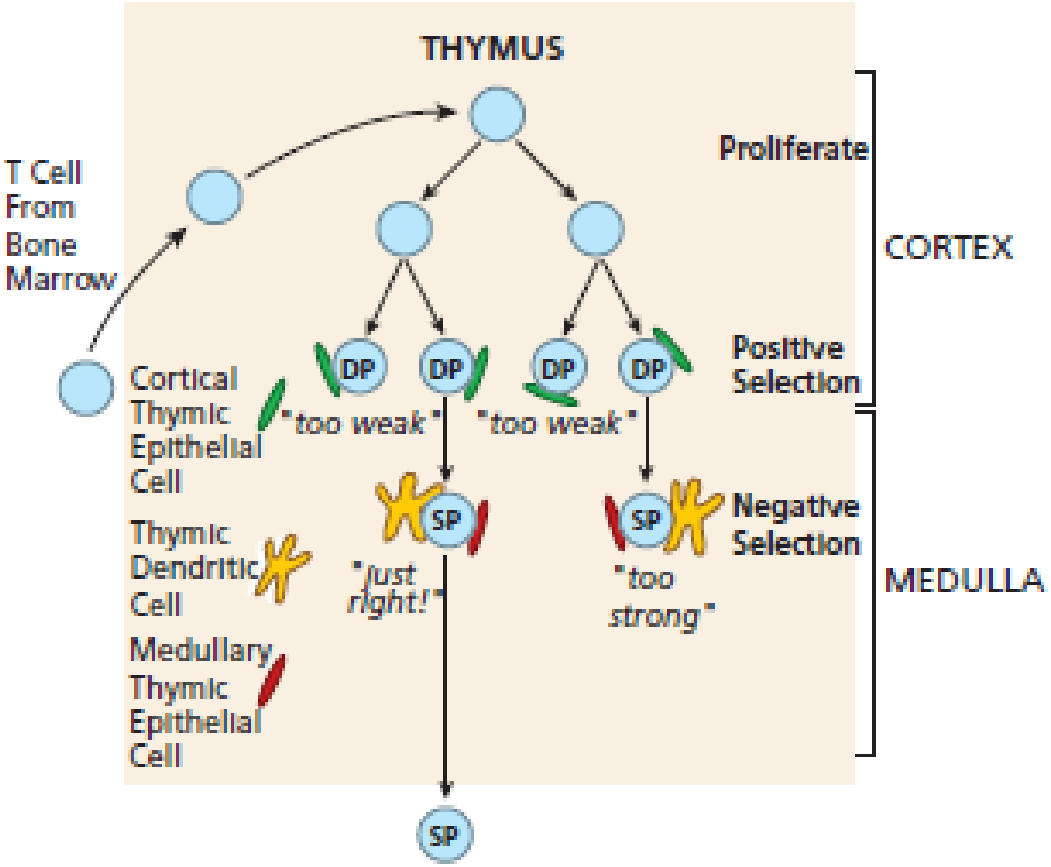



Pass rate= **3%**

Duration of exam= **2 weeks!**

# The riddle?

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



# Tolerance by ignorance

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

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

**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!

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

# Tolerance Induction in 2° lymphoid organs

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

**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.

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

# Peripheral Tolerance

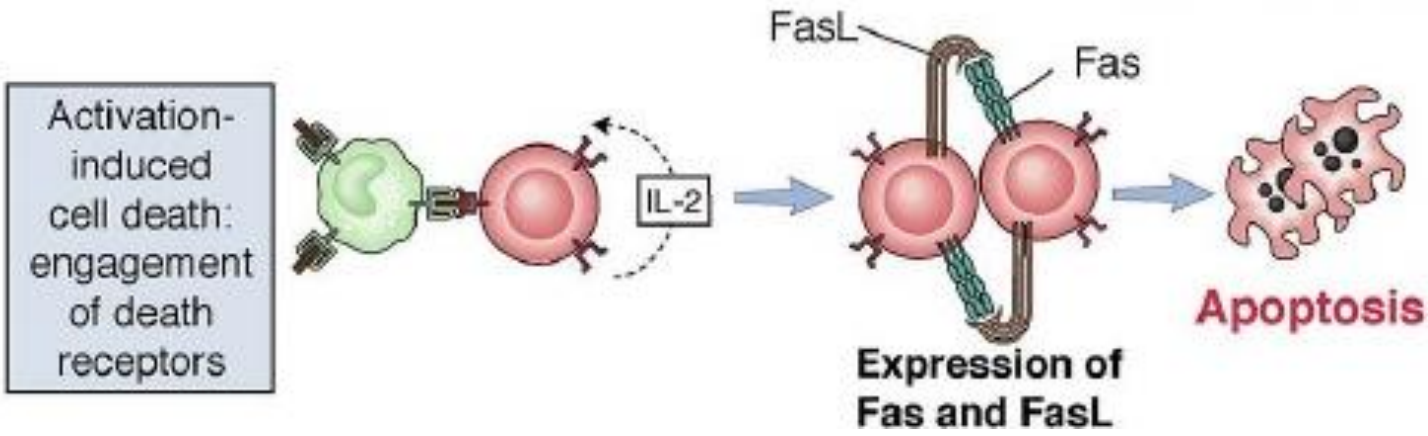
What about those autoreactive T cells that break the law and go to tissues??

**Two key requirement!**

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

# Activation-Induced Cell Death (AICD)

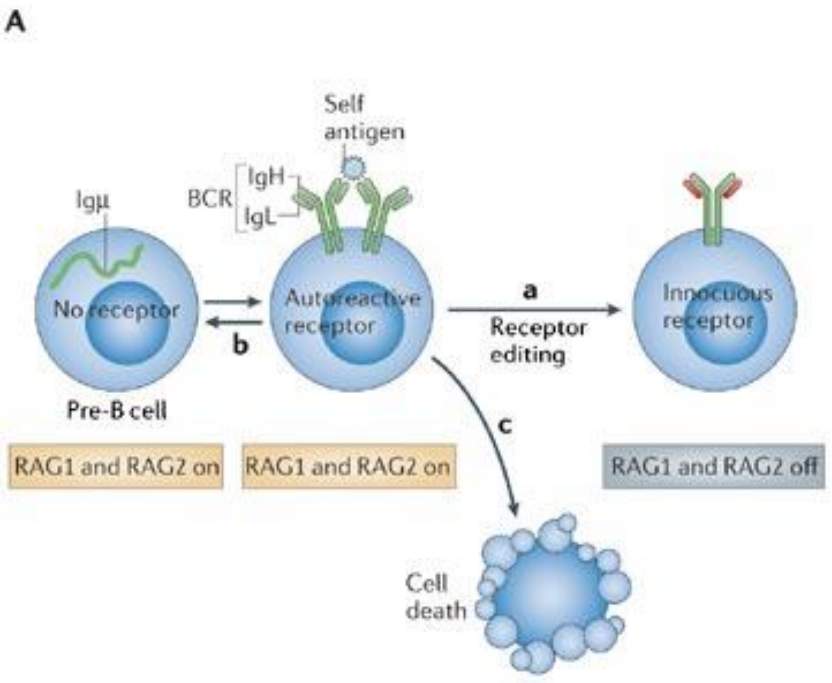
What if an autoreactive T cell makes it to the tissue, and somehow manages to receive a co-stimulatory signal?



# B cell Tolerance

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

Process takes place in the BM. (Receptor editing)




Pass rate= **10% !**

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

# Maintenance of B cell Tolerance in Germinal Centres

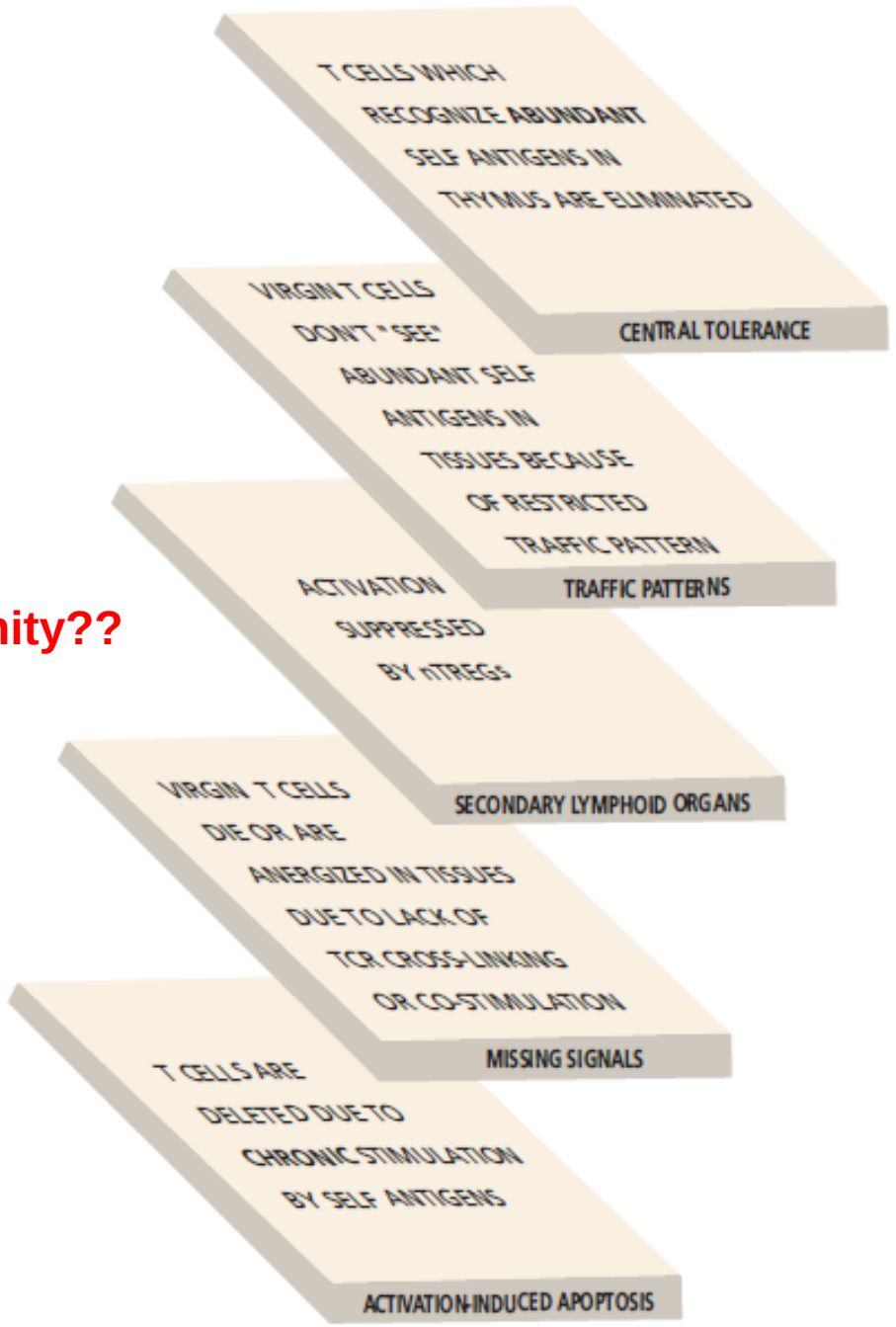
Can Somatic hypermutation cause autoimmunity??

Very unlikely!

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). (Lack of the two required signals)

**How are we protected from autoimmunity??**



?Any question