* Immune system reacts against self Ag. during which our own tissues are destroyed.

Auto immunity

* Immune sys. reacts against self antigens during which self tissues are damaged.

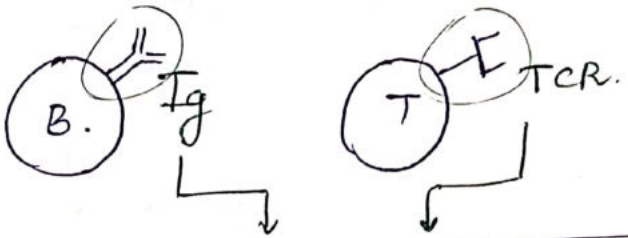
1° immune mediated damage

* Immune system reacts against Foreign Ag. (Virus) during which viral infected cells are destroyed.

Loss of Self tolerance. → Autoimmunity

* Even in Normal persons, self reactive lymphocytes are regularly generated.

* Self reactive B & T-cells → Tolerance → Destroyed.
  ↑⊖
  Autoimmunity.



We produce a BROAD SPECTRUM of TCR & Ig bcoz each Ag is unique

↓

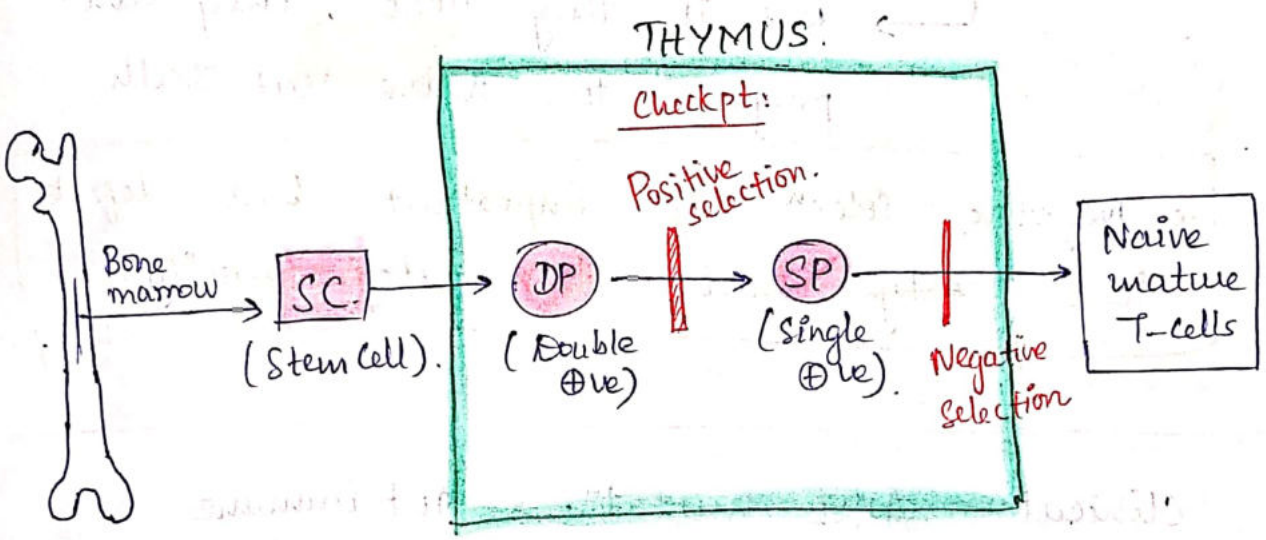
Randomized generation of Ig & TCR to match the Ag. Thats why self reactive lymphocytes are regularly produced

Tolerance: Liver BM Organs in lymphocytes develop

peripheral (Thymus & BM)

Tolerance Happens in peripheral tissues.

Central Tolerance in Thymus: (T-cells)



Double ⊕ve ⇒ T-cell has both CD4+ & CD8+ & also TCR

Single ⊕ve ⇒ ... either CD4 (or) CD8+ & TCR.

Positive selection: (takes place in Cortex)

* DP are checked whether they can bind MHC & Ag.
  - → If they can Recognize MHC then they progress to SP.
  - → But if they fail, they undergo Apoptosis.

Negative selection (takes place in Medulla)

* Here SP are checked whether they can bind with self Ag.

→ If they avidly binds with self Ag they undergo Apoptosis.

→ But if they don't, they can progress to Naive Mat. T-cells

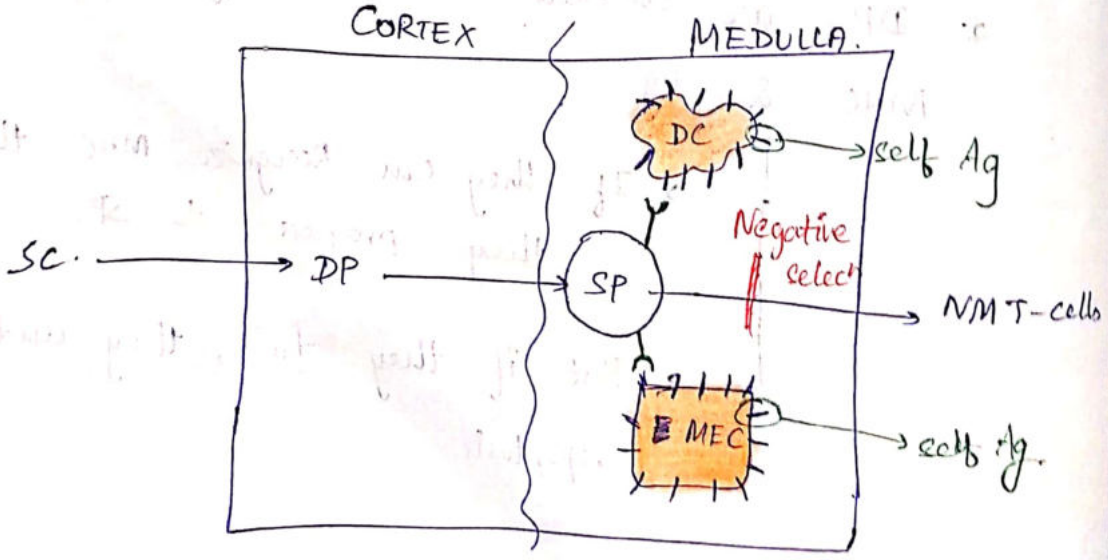
* Negative selecn is important bcoz defects here ~~only~~ lead to Autoimmunity.

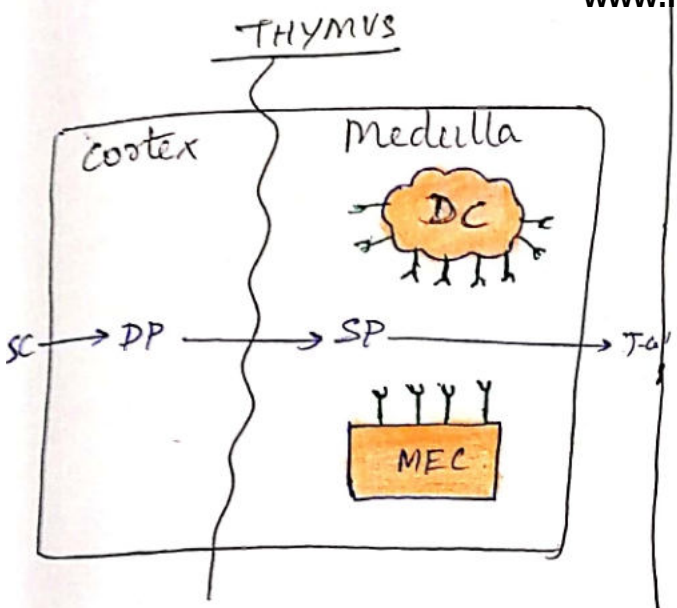
Clinical: AIRE mutatn → Autoimmune Polyendocrine Syndrome.

⇓

* defect in central tolerance in thymus.

* To understand this ds, we need to understand about Negative selection clearly



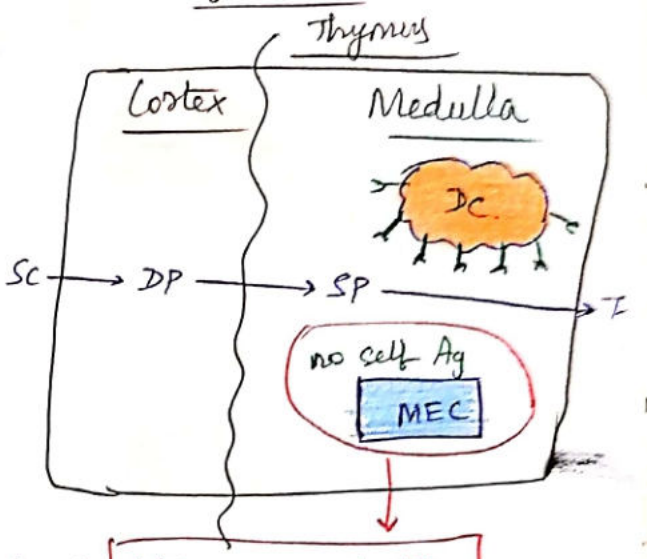


DC - Dendritic cells.

MEC - Medullary Epithelial cells

In Normal persons, both these cells express self Ag, which are used to select the self reactive T-cells & conseq. destroy them

(Autoimm. polyendocrine syndromes)



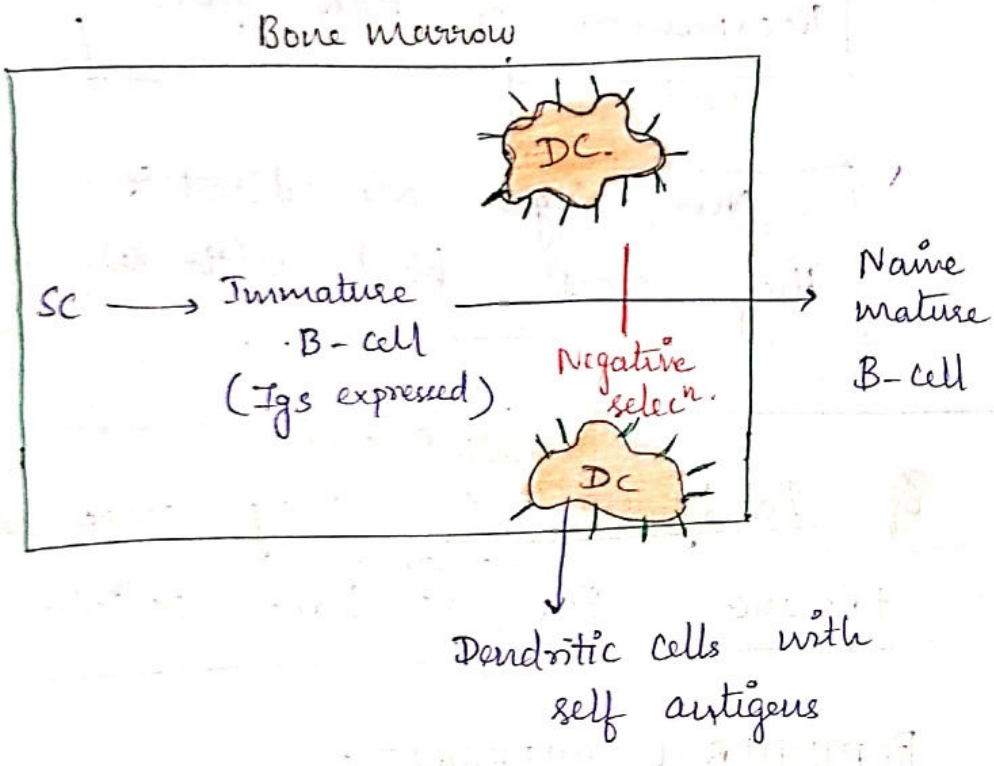
due to AIRE mutatn.

MEC can't express self Ag. bcoz AIRE gene is responsible for it

DC & MEC express diff types of self Ag., so Here the self Ag expressed by DC & the resp. T-cells are selected but that of MEC not selected & Released into blood

Which attacks endocrine organs causing.

(i) Hypo para thyroidism
(ii) Adrenal ~~insufficiency~~ failure
(iii) Candida infec.



Here in Negative selectn, the immature B-cells are checked whether they can bind with self Ag expressed by Dendritic cells

→ If Ig ~~they~~ dont bind with self Ag then immature B-cell → Naive mature B-cell.

→ If the Ig of immat. B-cells binds with self Ag then it will undergo either of the following ② mechanisms to prevent Autoimmunity

(i) Receptor Editing
(ii) Apoptosis (Mitoch. pathway).

Receptor editing

Reexpression of RAG genes

↓

Now Igs are edited & they don't bind with self Ag

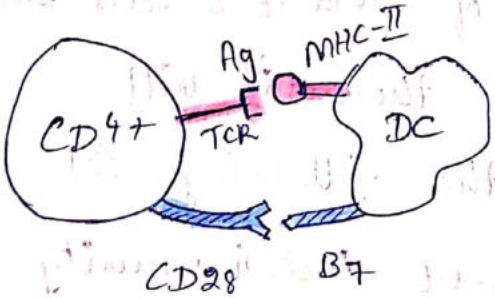
Rarely some self Reactive cells may escape central tolerance. But No worries we have peripheral tolerance

PERIPHERAL TOLERANCE :

If a lymphocyte recognizes an Ag without COSTIMULATN then it will undergo...

Anergy

(lymphocytes shut down (or) goes to sleep).



Co-stimulatn

↓

if it doesn't happen then CD4+ will undergo Anergy

Apoptosis

(Death Receptor - FAS).

No costimulatn

↓

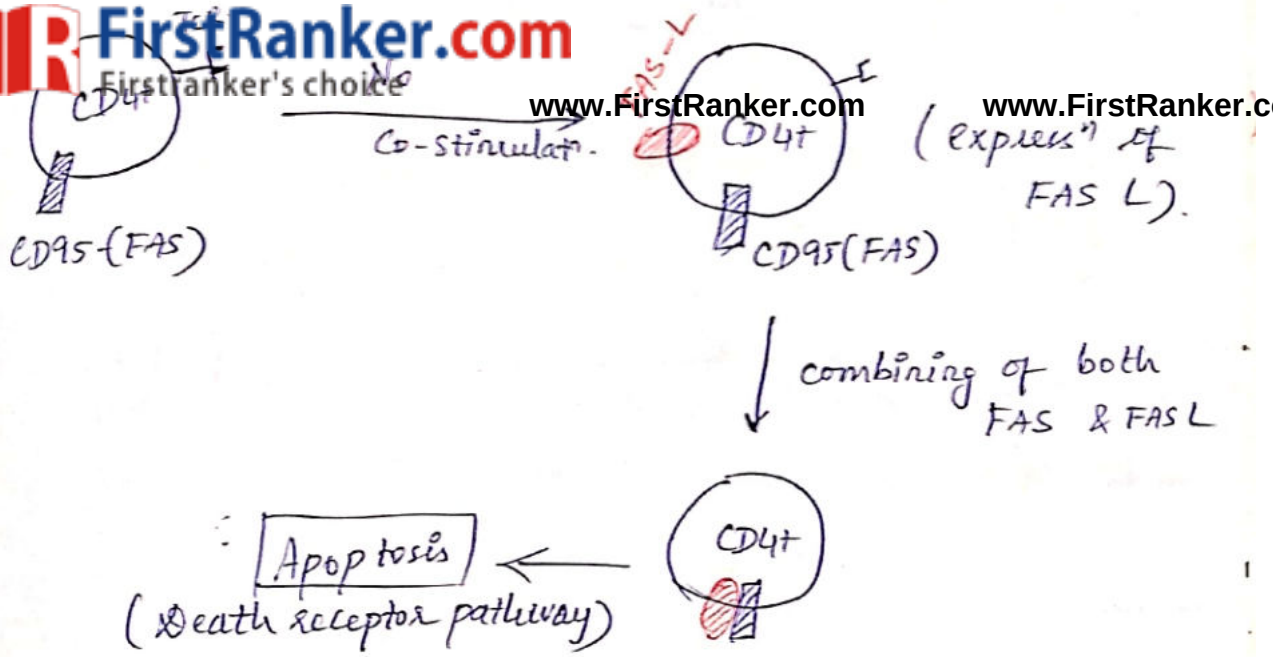
expressn of FAS ~~(CD95)~~ ligand

↓

FAS-L ⊕ FAS (CD-95)

↓

Apoptosis



Note:

* FAS-L can also bind with other cells' FAS (CD95) which don't undergo co-stimulatn & destroy them

Clinical: "ALPS" - Auto immune Lympho Proliferative Syndrome. (extremely Rare)

* Mutatn in FAS apoptosis pathway (CD95) either in CD95 (FAS) (or) FAS-L.

↓

Self reactive B/T-cells don't die → Auto immunity

↓

IgG are secreted against blood cells causing "CYTOPENIA" (Anemia, Thrombocytopenia)

(Next pg.. contd.)

IgG against blood cells.

↓

cytopenia

proliferatn of self reactive lymphocytes

↓

so areas where lymphocytes resides such as L.N, Spleen gets enlarged

↓

Lymph - Adeno - pathy i.e

HSM - Hepatosplenomegaly

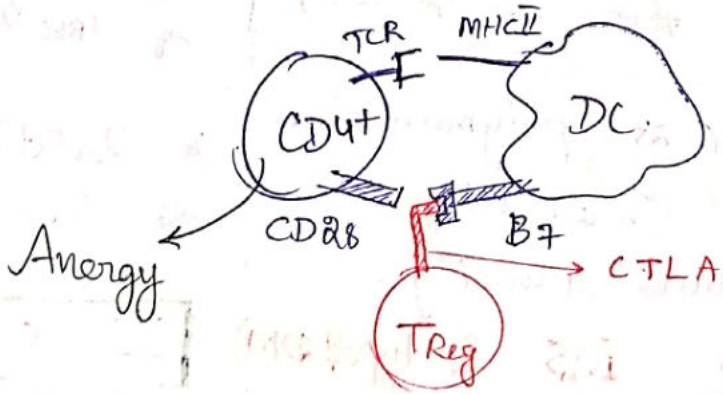
↓

∵ so much lymphocytes divide again & again, mutatn happen & leads to CANCER

ie) LYMPHOMA.

3rd way of preventing Autoimmunity

Regulatory T-cells ⇒ (1) Compete with CD28 to bind with B7. thro' the ® - CTLA4



... of cytokines

- **IL-10**
  - ⊖ macrophages & Dendritic cells.
  - ⊖ (or) limits the expression of MHC-II (self reactive).
    - ↓ Thus T-cell can't be stimulated.
  - limits the express^n of co-stimulatory molecule (ie) B7
- **TGF-β**
  - Also ⊖ macrophages.

Phenotype of TREG cell:

- **CD 4+**
  - TREG are also CD4+ cells.
- **CD 25+**
  - Component of
  - * IL-2 (R).
    (IL-2 is a growth factor for Treg cells)
  - * C-25 polymorphism are linked with Autoimmunity.
    (eg: MS (multiple sclerosis) & type 1 DM)
- **FOX P3 +**
  - Transcrip^n factor
    - ⇓ * required for growth & maintenance of TREG cell
  - * Mutations of FOXP3
    - ⇓ **IPEX** syndrome.

(contd...)

Immune dysfunc^{n} — Enteropathy — X-linked syndrome.

Poly Endocrino-pathy → * Thyroiditis, * Type I DM

Enteropathy → Diarrhea

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ii) Why Autoimm. ds. are more common in women? (classically affects women of child bearing age).

↓

* Estrogen inhibits Apoptosis of "self reactive - B - cells"

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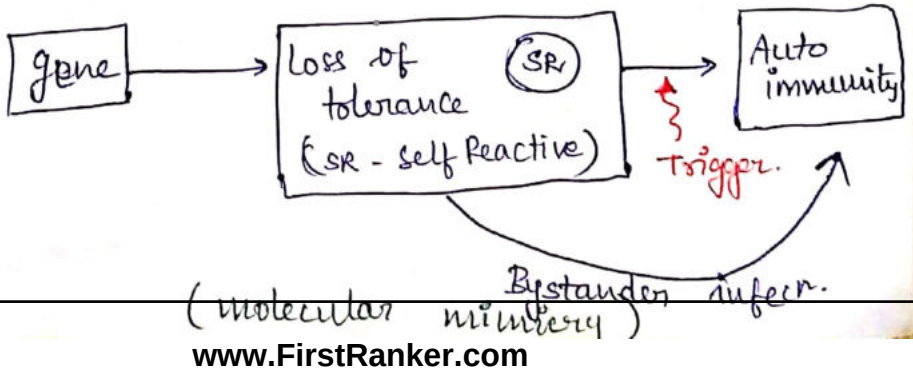
iii) Autoimm. ds. occurs when ~~when~~ environmental factor triggers genetically suspectible individuals.

eg) ↳ i) increased incidence in Twins.

ii) assoc^{n} ē HLA subtypes (especially HLAB27) & PTPN 22 polymorphism (Tyrosine Phosphatase) ↓ signalling via cytokines

iii)



Role of Trigger in Autoimmunity

* If a person is having a genetic susceptibility then he will not Autoimmunity (HLA B 27).

* A trigger is needed for the PROLIFERATN of self Reactive cells.

Characteristics of Autoimmune ds.

- clinically progressive
- Relapses & Remissions
- Overlapping features