T Cell Tolerance

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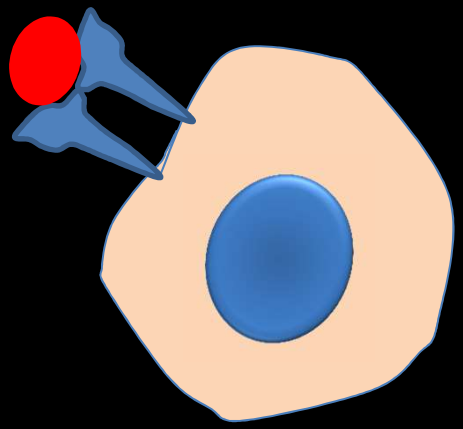
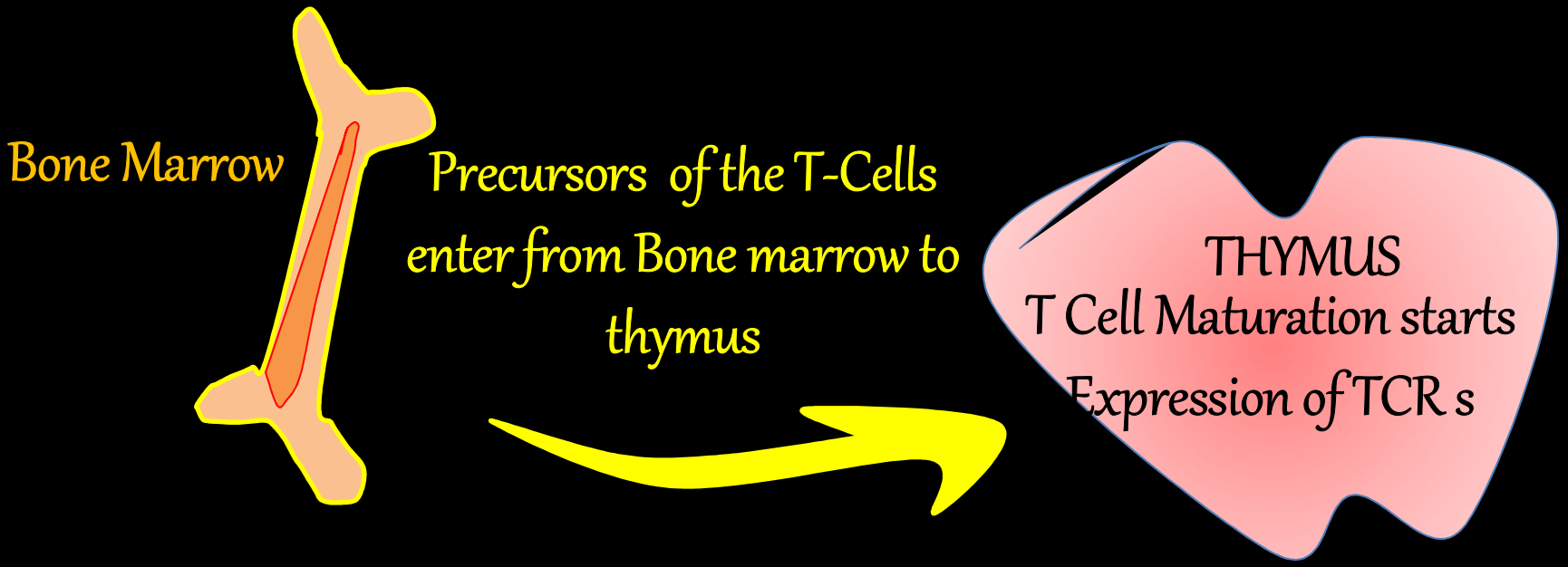


DEVELOPMENT OF T-CELLS

- Immature T-Cells enter in the thymus after differentiating in the bone marrow.
- These T-cells undergo maturation and develop TCRs through Somatic Recombination.



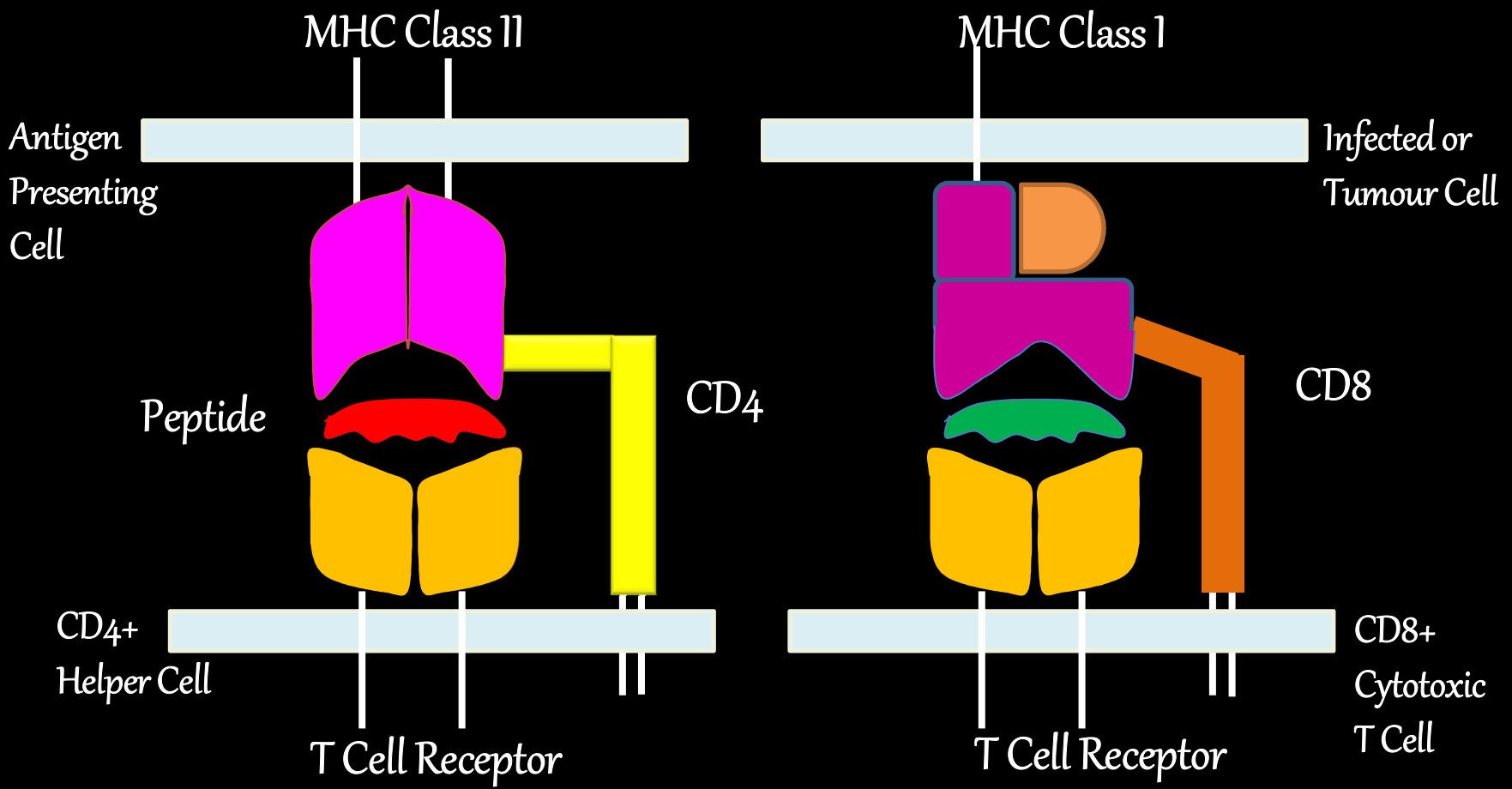
DEVELOPMENT OF T-CELL RECEPTORS (TCRs)

- Some of T-Cells in the thymus develop receptors which are useless with no antigen specificity and while others develop TCRs with specificity for self antigens and non-self antigens.
- Thymocytes having TCRs with low affinity for auto antigens, displayed in the MHC class I and II, undergo positive selection and further differentiate to become part of adaptive immunity, whereas the one with non-functional receptors die off because of negligence.
- Clonal deletion of T-cells with useless TCRs and high affinity receptors along with clonal diversion for development of "Treg", are the major processes operative in the thymus towards elimination or regulation of self-reactive T cells.

INSIDE THE THYMUS THE T-CELLS UNDERGO AN ELABORATE SCREENING PROCEDURE THROUGH FOLLOWING **3** MECHANISMS

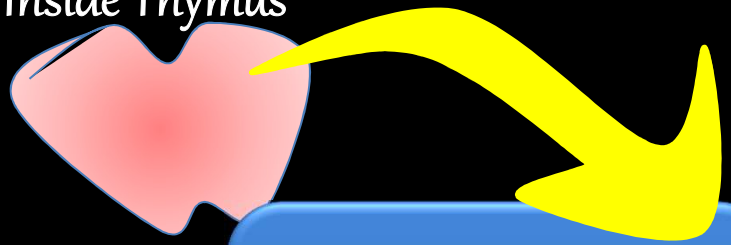
- Non-selection
- Positive Selection
- Negative Selection

T CELLS RECOGNIZE ANTIGEN DERIVED PEPTIDES PRESENTED BY MHC MOLECULES



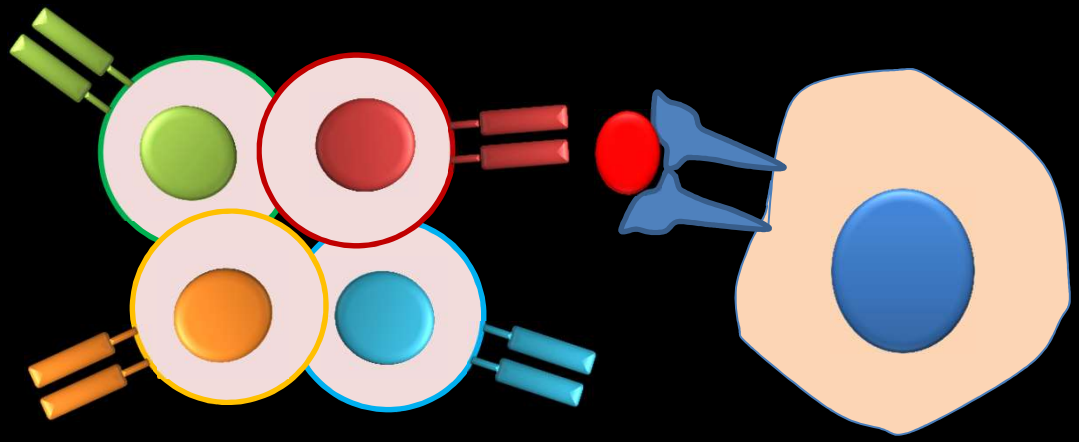
T CELLS RECOGNIZE ANTIGEN DERIVED PEPTIDES PRESENTED BY MHC MOLECULES

Inside Thymus

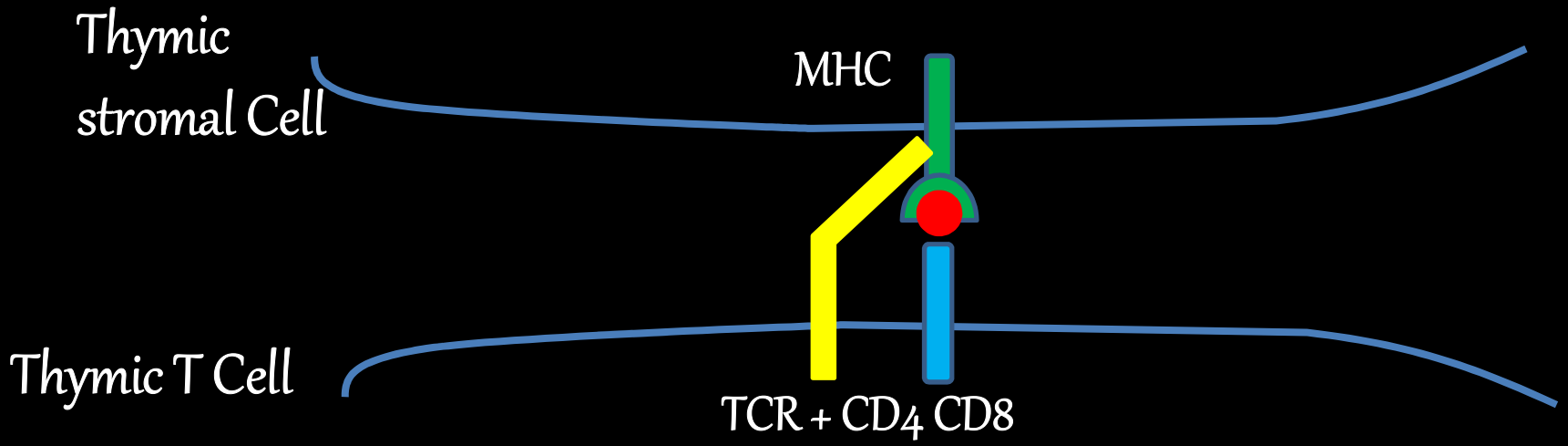


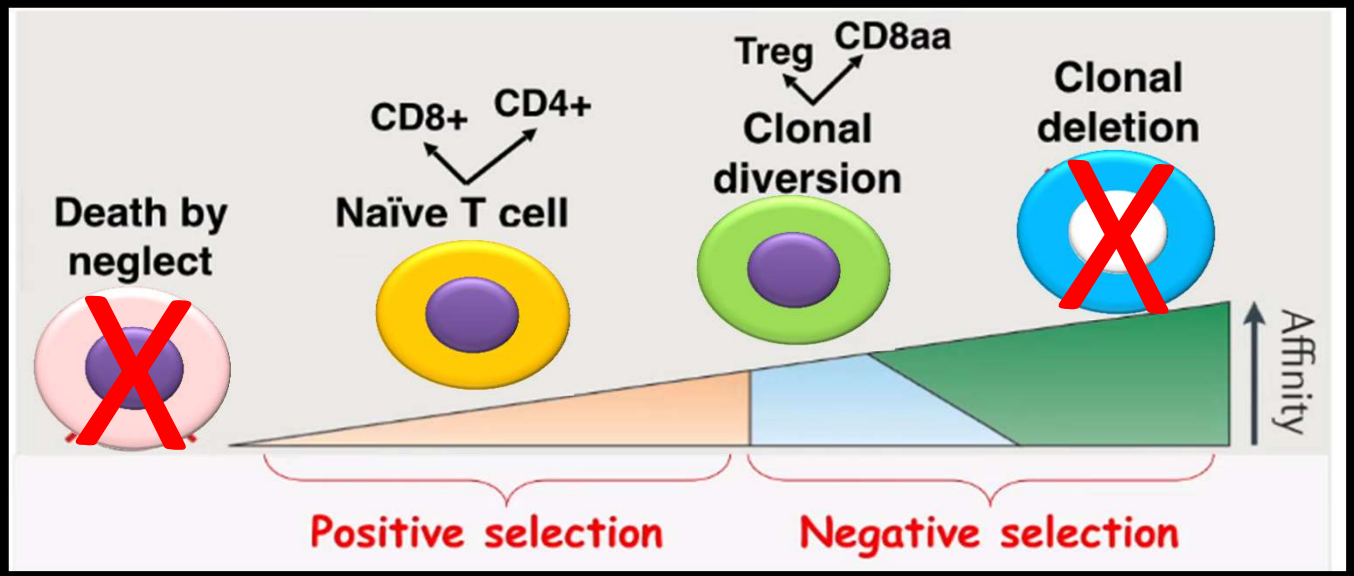
Immature T cell

Self Peptide: Self MHC complex



THYMIC T-CELL FATE IS DETERMINED BY STRENGTH OF TCR-MHC/PEPTIDE INTERACTION



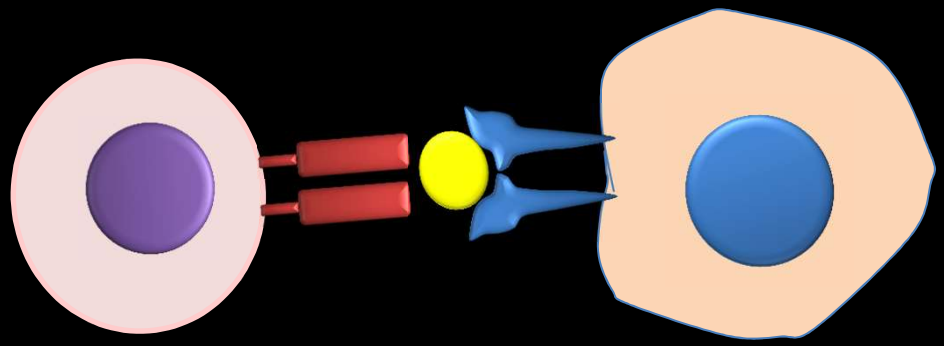


CENTRAL T-CELL SELECTION

NEGATIVE SELECTION

- Negative selection occurs at the Double positive stage in the thymic cortex, or at the Single Positive stage in the thymic medulla.
- T-cell receptors (TCRs) having high avidity to self-antigens (expressed on thymic epithelia) undergo apoptosis.
- Most of the T-cells udergo elimation to the extent that about 10^9 receptor specificities are screened in the thymus and only a fraction of the total reach the peripheral tissues.

NO INTERACTION



APOPTOSIS

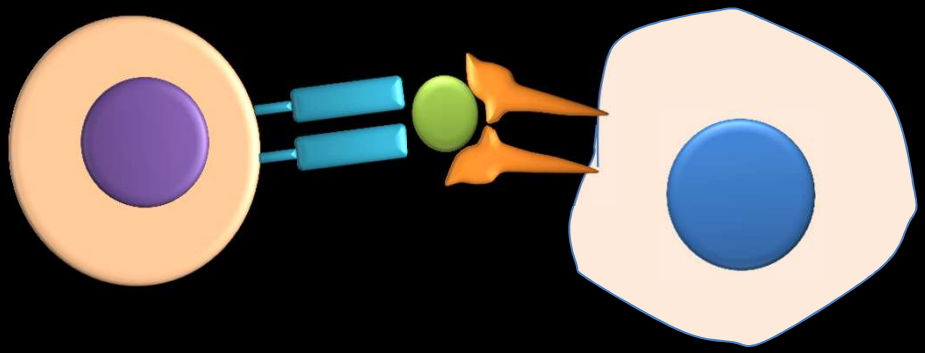
NON SELECTION

Immature T-Cells in the thymus fail to recognize and bind MHC Peptide: Self MHC Complex

Non functional TCRs

Lack of receptors recognizing MHC Molecules

STRONG INTERACTION



APOPTOSIS

NEGATIVE SELECTION

Immature T-Cells in the thymus recognize and bind MHC Peptide: Self MHC Complex with too strong affinity

Binding too strong

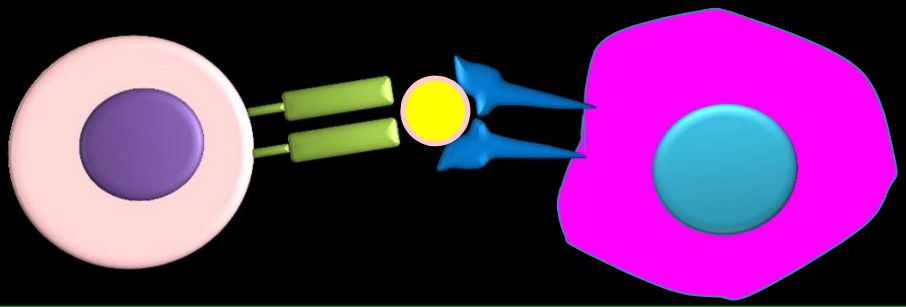
Dead Cells are phagocytised by macrophages in the thymus

CENTRAL T-CELL SELECTION

Positive Selection

- CD4-CD8- (Double negative) progenitors of T-cell make entry in the thymic cortex and their receptors get rearranged to become CD4+CD8+ (double positive) thymocytes.
- Both positive selection and negative selection are operative in the thymus.
- TCRs with moderate affinity to self-peptide-MHC complexes on the epithelium of the thymus survive (positive selection) while with very strong affinity undergo apoptosis (negative selection)
- If MHC II is recognised, the T-cell will display CD4 and if MHC class I is recognized the T-Cell will display CD8 (single positive).

MODERATE INTERACTION



POSITIVE SELECTION

Immature T-Cells in the thymus successfully recognize and bind

MHC Peptide: Self MHC Complex

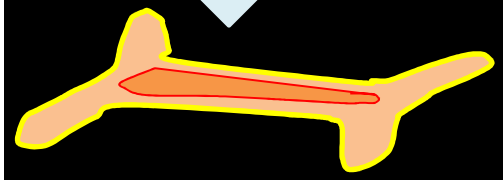
Binding is not too strong or too weak

T -cells learn to focus on Self MHC molecules (MHC Restriction)

SUMMARY CENTRAL TOLERANCE

Fetal Liver

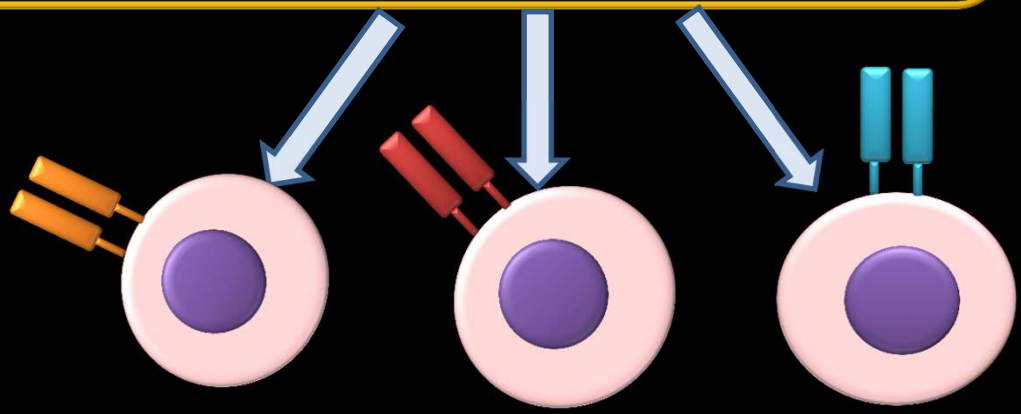
T cell precursor



Adult Bone Marrow

TCR gene arrangements Positive and negative selection

PHENOTYPIC SPECIALIZATION



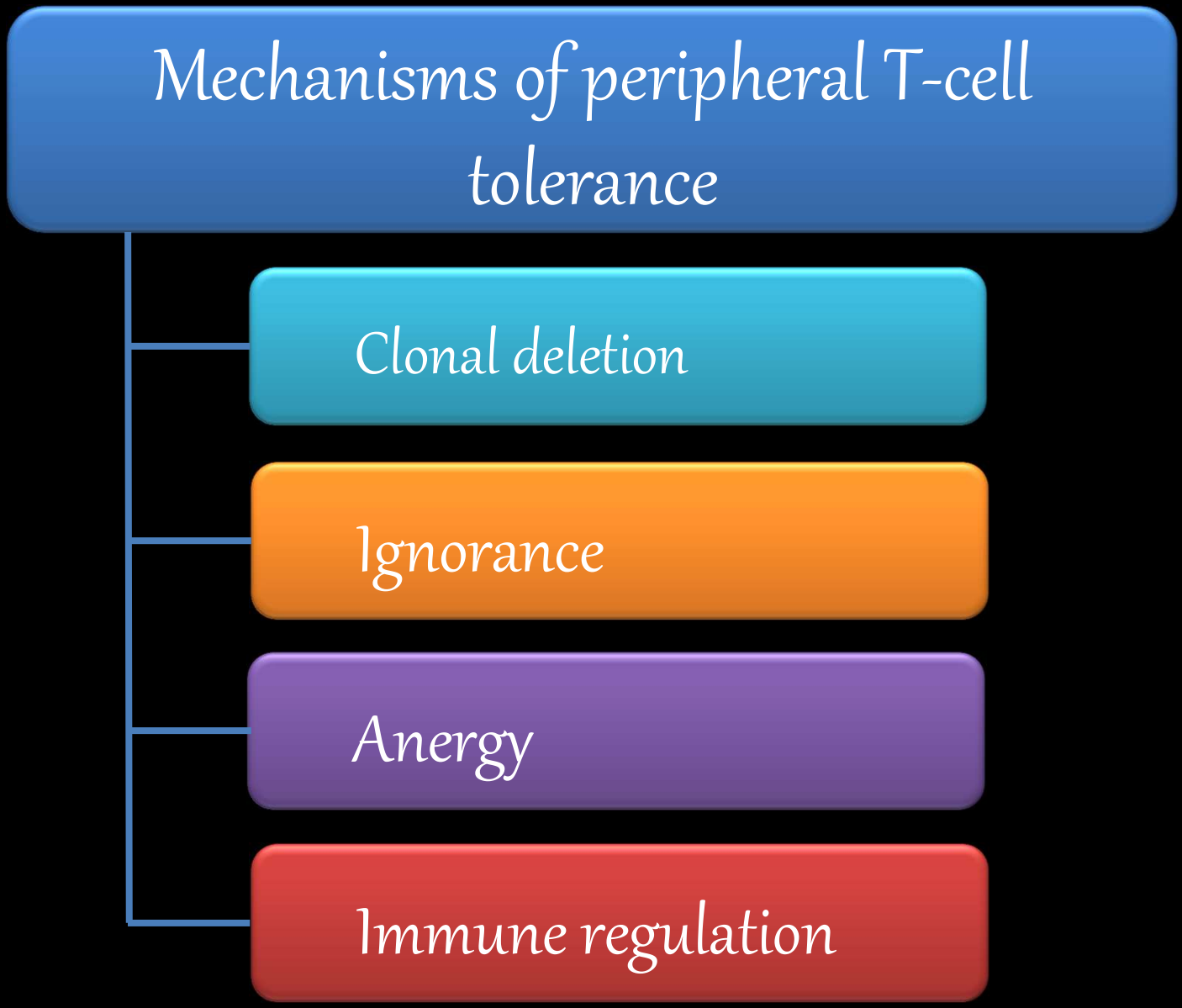
CD 8+ Cytotoxic T-Cell

CD 4+ Helper T-Cell

Foxp3+CD4+ Regulatory cell

CENTRAL TOLERANCE MECHANISMS ARE NOT FOOLPROOF

- The central Tolerance mechanisms are efficient but they fail to screen out all the self-reactive lymphocytes from the ones exiting out of the thymus to peripheral lymphoid tissues.
- Thus in the peripheral tissues exist tolerance mechanisms which finally remove or prevent self-reactive T cells from activation by inducing functional unresponsive (ANERGY) or by deleting such cells after encounter with self-antigens outside the thymus.


Mechanisms of peripheral T-cell tolerance
Clonal deletion
Ignorance
Anergy
Immune regulation

PERIPHERAL TOLERANCE

CLONAL DELETION

- The T-cell clones activated by antigen-presenting cells (APC) are eliminated by activation-induced cell death.
- Such cells express IL-2 and IL-2R for autocrine facilitation of proliferation and have elevated expression of death receptors (e.g. Fas) and their ligands.
- Ligation of Fas induces T-cell deat through apoptosis by activation of caspase pathway, thereby putting an end to the immune response.

PERIPHERAL TOLERANCE

IGNORANCE

- Although some of the T-cell from the peripheral circulation of healthy individuals show reactivity with self-antigens in vitro, this does not normally occur in vivo.
- It is believed that such T-cells showing immuno-reactivity in vitro do not recognise self antigens by ignoring certain self-antigens (Ignorance).
- The T-cells *in vivo* can't react with these Self antigens as they are located in immune-privileged sites or because they have low immunogenicity.

PERIPHERAL TOLERANCE

ANERGY

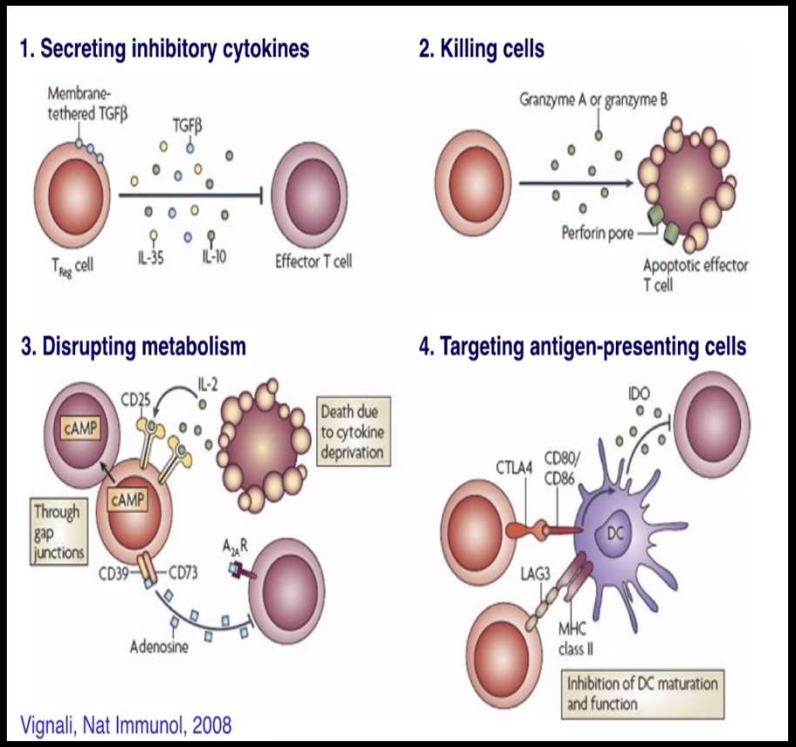
- Anergy is a mechanism used to inactivate peripheral autoreactive T-cells by inducing non-reponsiveness to cognate antigenic stimuli through non-production of IL-2 or IL-2R.
- This ANERGY can occur through many proposed mechanisms:
  1. By disrupting the interaction between the T-cell co-receptor CD28 and APC co-stimualtory molecules CD80/86
  2. Through negative regulation of T-Cell activation by the interaction of CTLA-4 with CD80/86.
  3. T-cells bearing CD28 get activated by APC, while T-cells having CTLA-4 tend to become ANERGIC.

IMMUNE REGULATION IS ACHIEVED BY THE ACTION OF "TREG'S".

- Treg (T-regulatory) cells are important in fine balancingthe peripheral immune cell reaction by allowing certain immune reactions to pproceed and inhibiting others..
- These cell are very important in maintaining peripheral tolerance and their in mice results in development of autoimmunity.
- In humans its dysfunction results in lymphadenopathy and inflammatory infiltrates having auto reactive T-cells reach in multiple organs.

"TREGS" ALSO REGULATE MANY EFFECTOR RESPONSES OF T-CELLS

- Treg display anergic properties *in vitro*, but suppress CD4+CD25- T-cells *in vivo*, via direct cell-cell contact, or through secretion of cytokines.
- During active inflammation (e.g. infection), Treg do not prevent protective immune function.
- Induced CD4+CD25+ Treg can also be activated in peripheral lymphoid organs (e.g. by TGFβ) and suppress immune responses via anti-inflammatory cytokines (e.g. TGFβ) rather than direct contact.



Vignali, Nat Immunol, 2008

"TREGS" IMPOSE CONTROL OVER

AUTOIMMUNE DISEASES

IBD, type-1 diabetes, MS

INFLAMMATORY DISEASES

Rheumatoid arthritis, atherosclerosis

ALLERGIC DISEASES

Asthma, food sensitivities

GRAFT REJECTION

TUMOR ESCAPE

RESPONSES TO INFECTION

Leishmania, Helicobacter, HIV

Thank you

TO BE CONTINUED.....