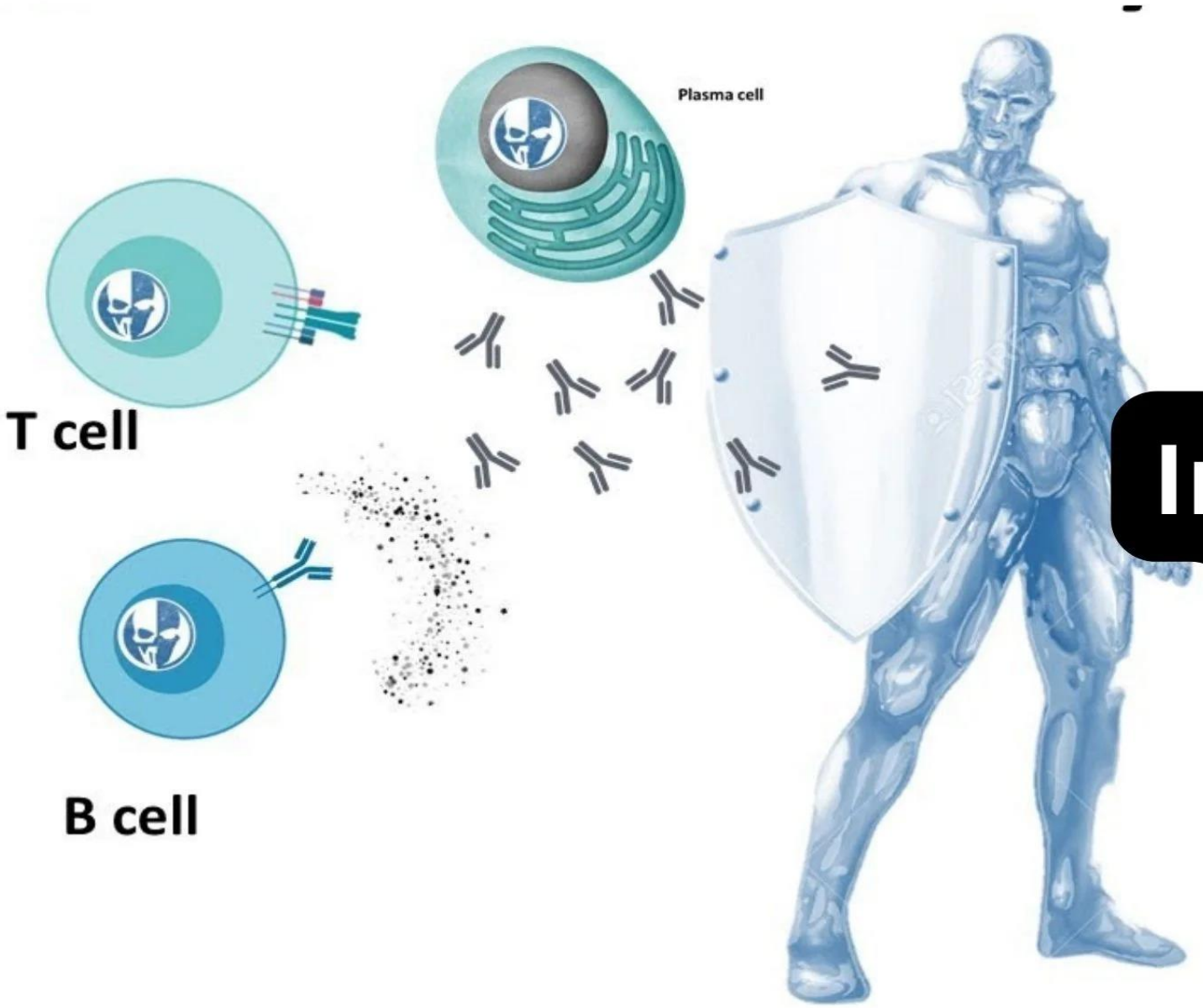


Immunological Tolerance

Presenter: Lilia Tacu

Immune tolerance:

♦ The ability of the immune system to “tolerate" the presence of its own antigens or foreign antigens without manifesting an immune defense reaction.

● Disturbance of tolerance to one's own antigens (autoantigens, self antigen) causes autoimmune diseases.
These antigens that elicit such a response are said to be immunogenic.

● Immune tolerance to non-self antigens (bacteria, viruses, allogeneic cells, etc.) leads to the absence or a very weak immune response against pathogens

Immune tolerance:

The immune tolerance can be congenital and adaptive.

- The congenital immune tolerance – tolerance to Ag (tolerogenic) occurs when the immune system contacts Ag during the embryonic period. After birth this Ag will be recognized as self-Ag without triggering an immune response. Precursor clones of T lymphocytes capable of recognizing this Ag as non-self Ag will be eliminated by apoptosis.
- Ag-self tolerance refers to congenital tolerance.
- A special pattern – the mother's tolerance to fetal antigens during gestation.

Adaptive immune tolerance:

It occurs when Ag enters the body in large or very large doses, which is associated with apoptosis of reactive lymphocytes (immunological paralysis).

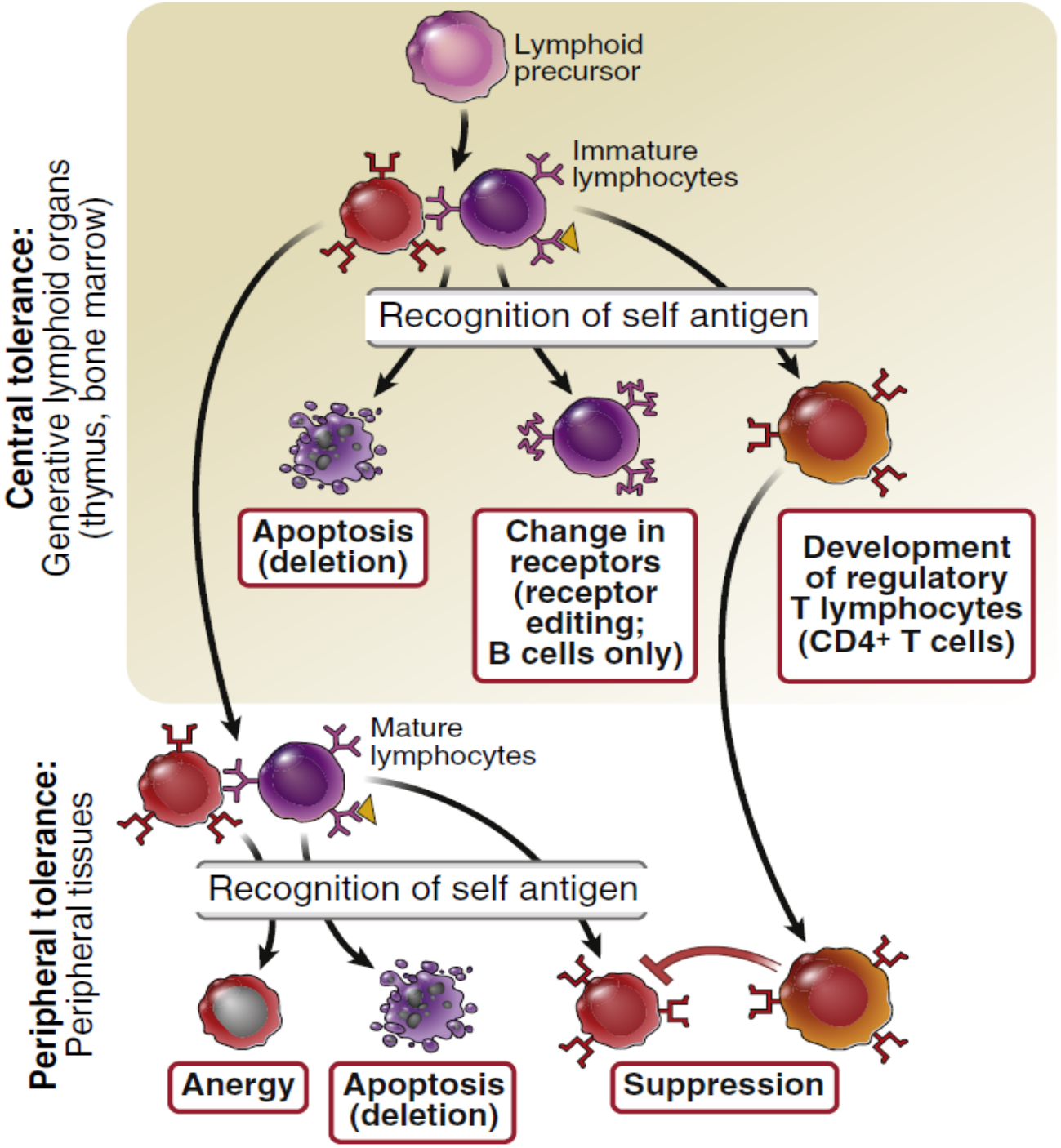
- Clonal deletion – it is elimination of the antigen-reactive cell clone, or
- anergy – blocking the receptors of specific B and T lymphocyte clones.

- Classical Anergy is considered as a variant of tolerance induced by high doses of Ag on the background of inhibition of the immune response.

Adaptive immune tolerance:

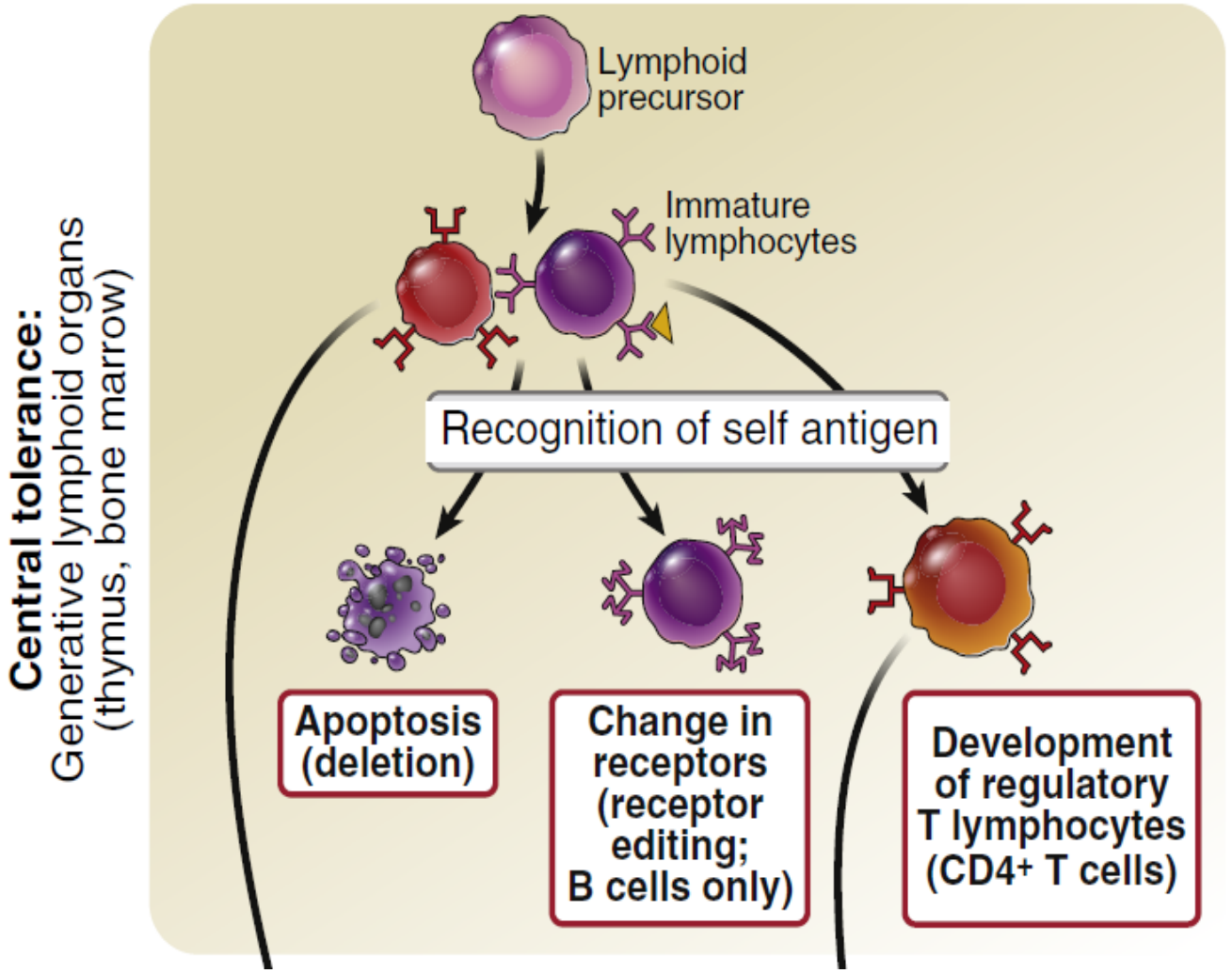
♦ Upon penetration of very small doses of Ag the suppression of the immune system occurs through the activation of suppressor T and B lymphocytes.

Positive effects of immune tolerance	Negative effects of immune tolerance
1. Avoid the destruction of own structures. 2. Avoid the development of autoimmune disorders. 3. Avoid transplant rejection.	1. Not assure the elimination of pathogenic antigen. 2. It is the risk of septicemia.

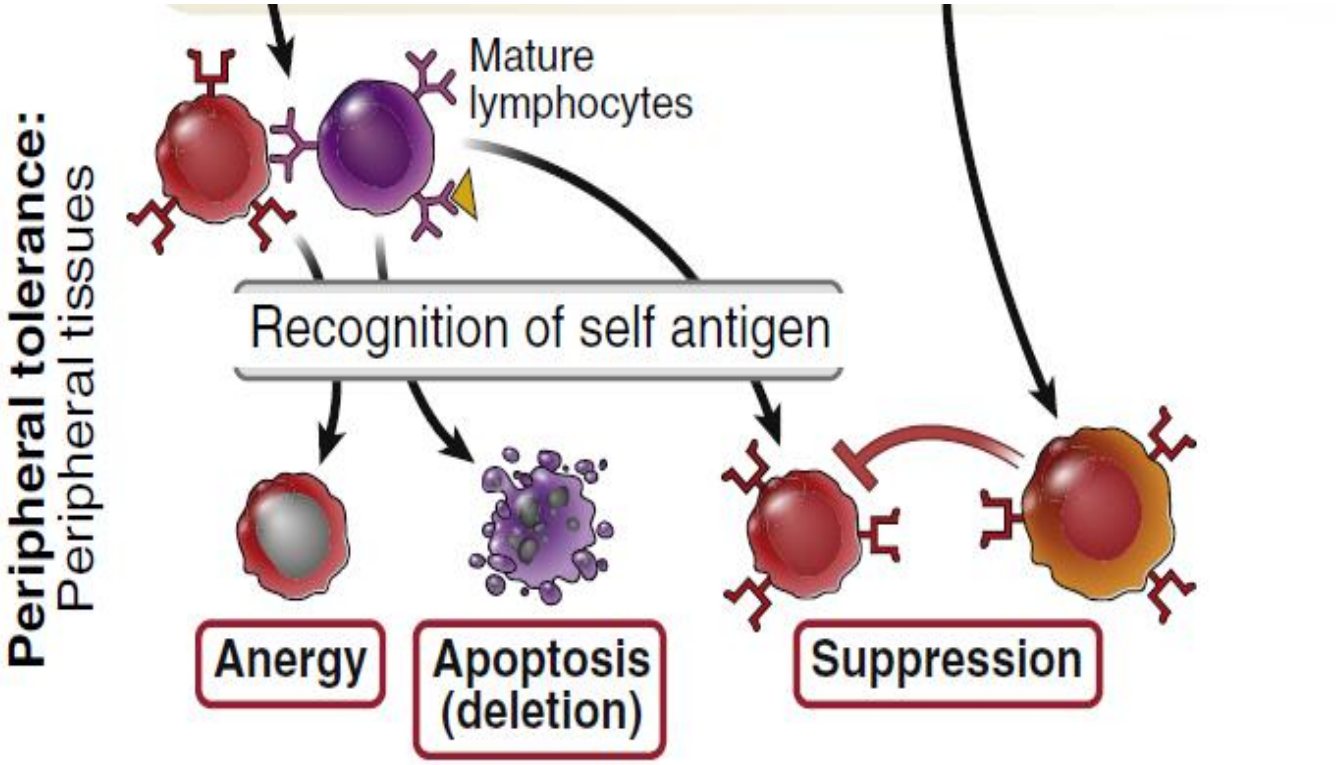


Mechanisms of central immune tolerance (thymus and marrow) Peripheral tolerance – down

Immunological tolerance to different self antigens may be induced when developing lymphocytes encounter these antigens in the generative (central) lymphoid organs, a process called central tolerance, or when mature lymphocytes encounter self antigens in peripheral (secondary) lymphoid organs or peripheral tissues,



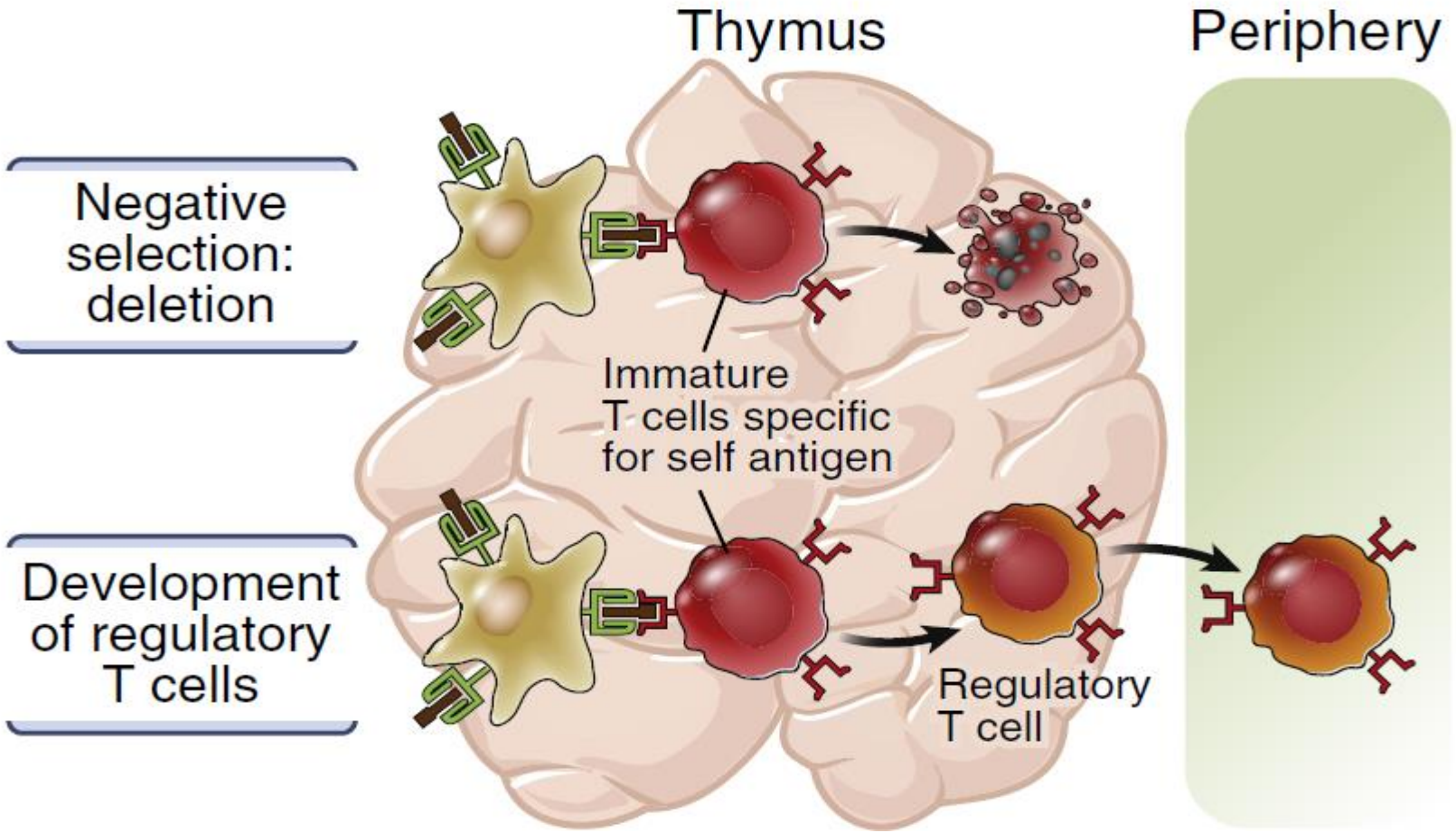
Central Tolerance – It develops during the maturation of naïve T and B cells in the thymus and respectively in the bone marrow, so that upon contact with Ag → the self reactive T and B lymphocytes will die by apoptosis or take over a receptor that does not react with self-Ag.



- Peripheral Tolerance – T and B lymphocytes that undergo maturation in the periphery will lose the ability to interact with self Ag – through 3 maneuvers: anergy, apoptosis, and influences by suppressor or regulatory lymphocytes, CD3.
- CD3 (cluster of differentiation 3) is a protein complex and T cell co-receptor that is involved in activating both the cytotoxic T cell (CD8+ naive T cells) and T helper cells

Tolerance of T lymphocytes:

Central tolerance
Peripheral tolerance



There are 2 important mechanisms of central T lymphocyte tolerance:

1. TLs with high affinity for Ag will die by apoptosis (negative selection).

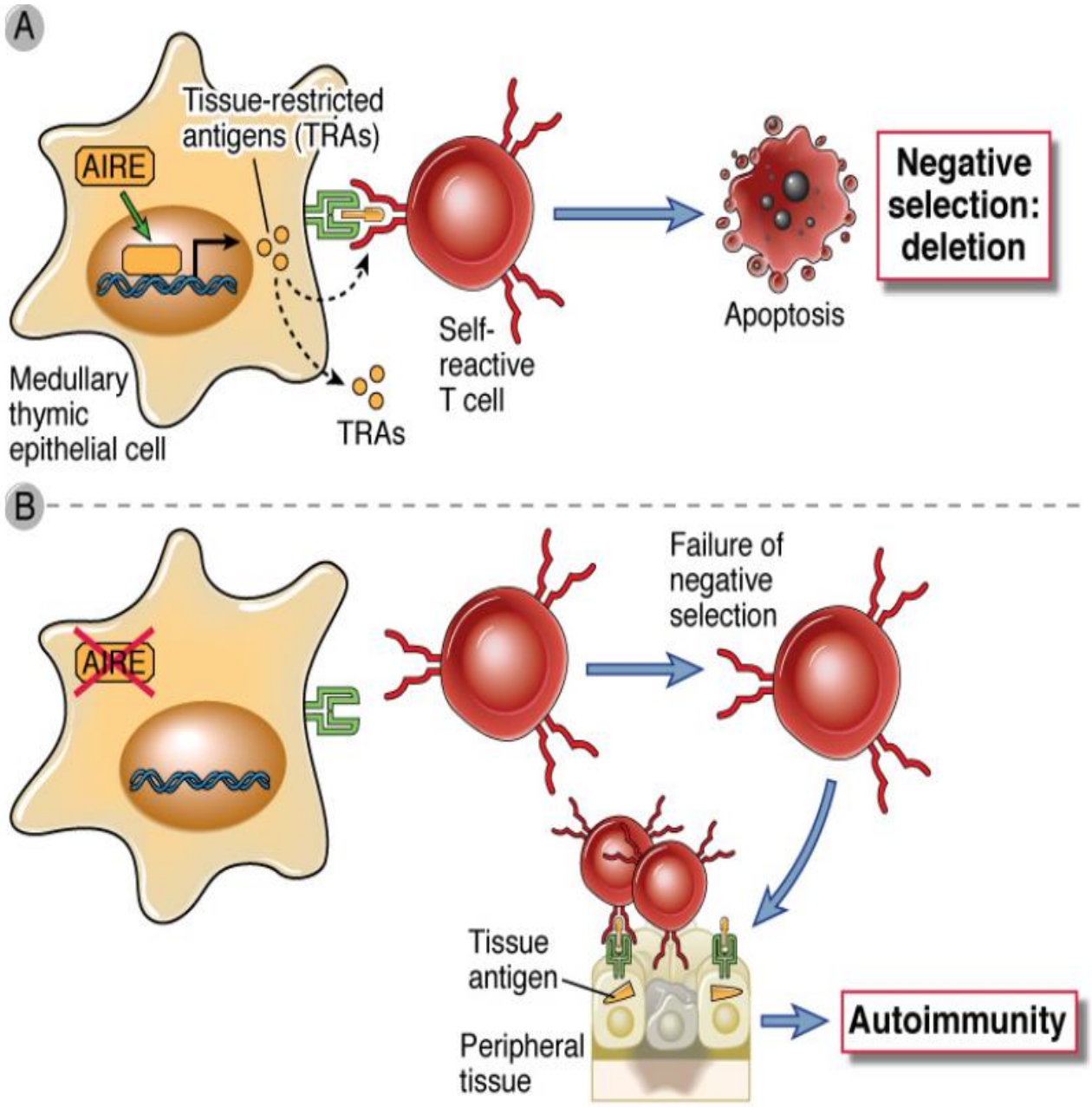
NEGATIVE SELECTION OF T LYMPHOCYTES

- The process of negative selection affects self-reactive CD4+ T cells and CD8+ T cells, which recognize self peptides displayed by class II MHC and class I MHC molecules, respectively.
- Immature T lymphocytes that recognize the expressed antigens will die by apoptosis.
- It is not known why immature lymphocytes die upon receiving strong T cell receptor (TCR) signals in the thymus, whereas mature lymphocytes that get strong TCR signals in the periphery are activated.
- Some immature CD4+ T cells that recognize self antigens in the thymus with high affinity do not die but develop into regulatory T cells and enter peripheral tissues.
- What determines whether a thymic CD4+ T cell that

AIRE (autoimmune regulatory protein)

- Epithelial cells in the medulla of the thymus are capable of expressing the entire range of antigens, which are characteristic for all peripheral organs. This expression is controlled by a special protein, defined as the autoimmune regulatory protein (AIRE), it is a transcription factor expressed in the medulla (inner part) of the thymus.

- Mutations in the AIRE gene will lead to various autoimmune diseases, especially to the polyendocrine autoimmune syndrome, characterized by TL affecting the adrenals, parathyroids, pancreas.



Central tolerance of T-lymphocytes

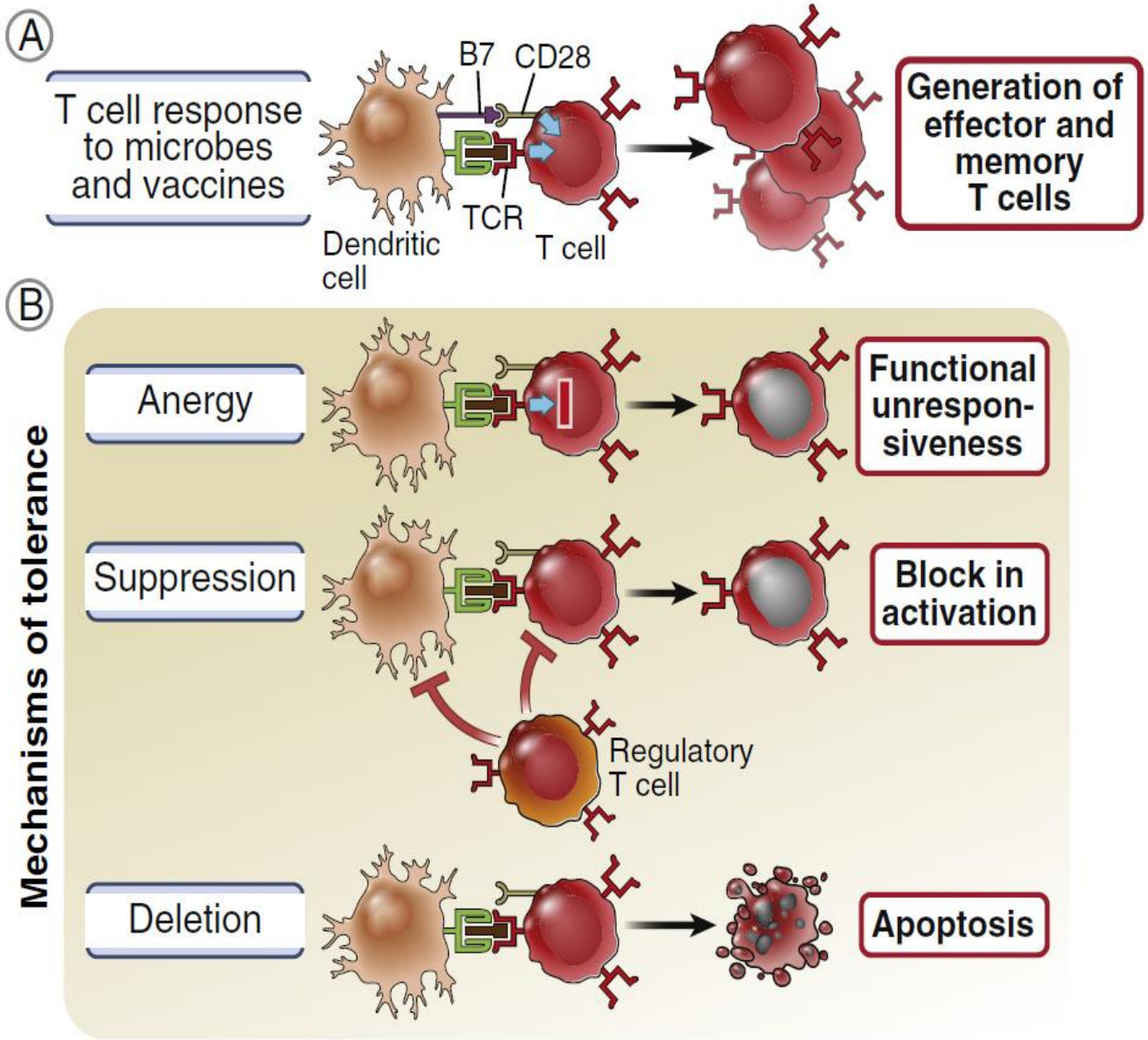
A- normal evolution

B- defective evolution:

Mutations in the AIRE gene do not ensure apoptosis of T lymphocytes, which recognize self-Ag and do not support negative selection.

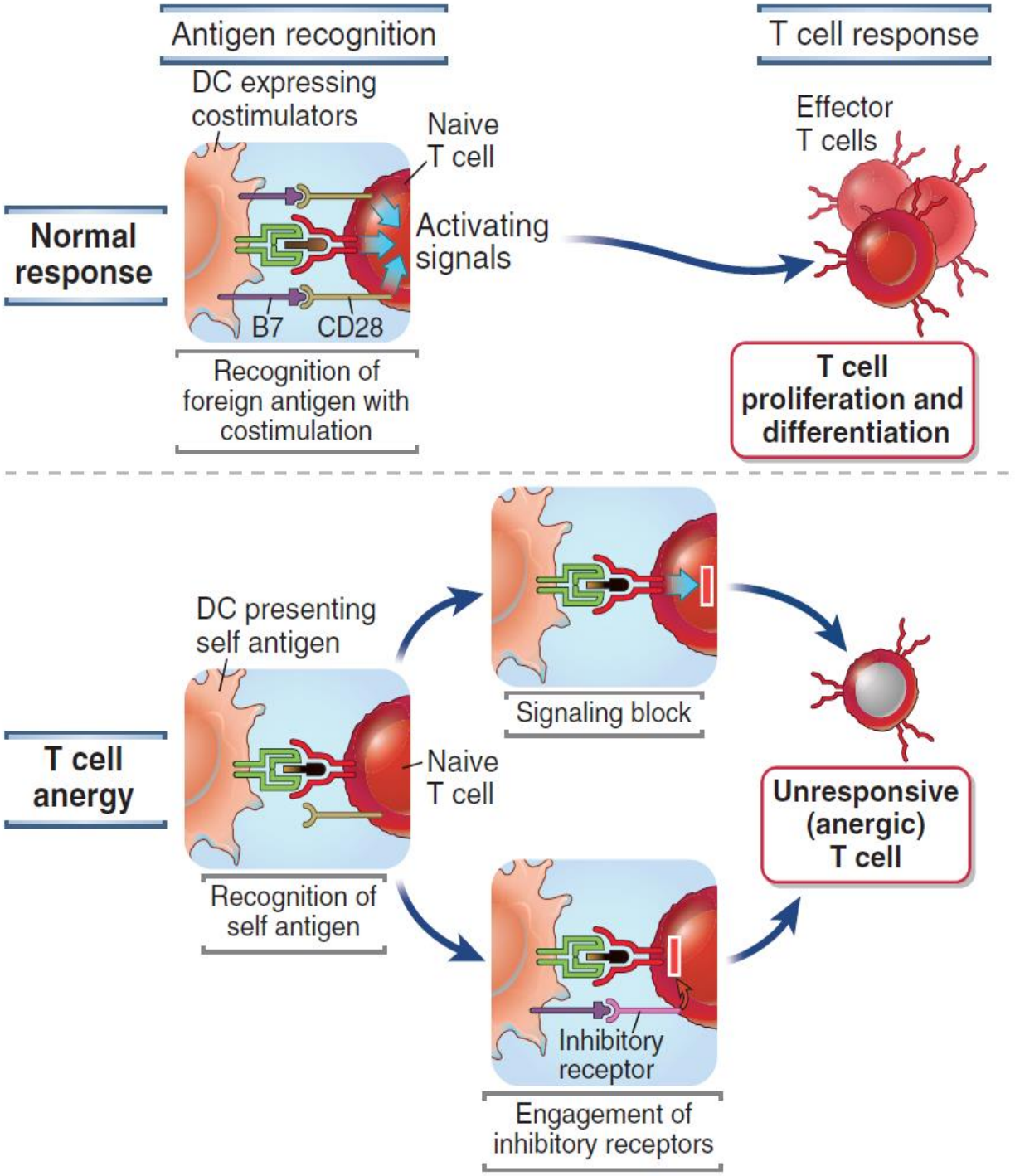
In the periphery, TL that escape negative selection will induce peripheral

Peripheral immune tolerance of T lymphocytes



When mature T cells recognize self antigens in peripheral tissue.

- Anergy;
- T-regulators lymphocytes
- Apoptosis.

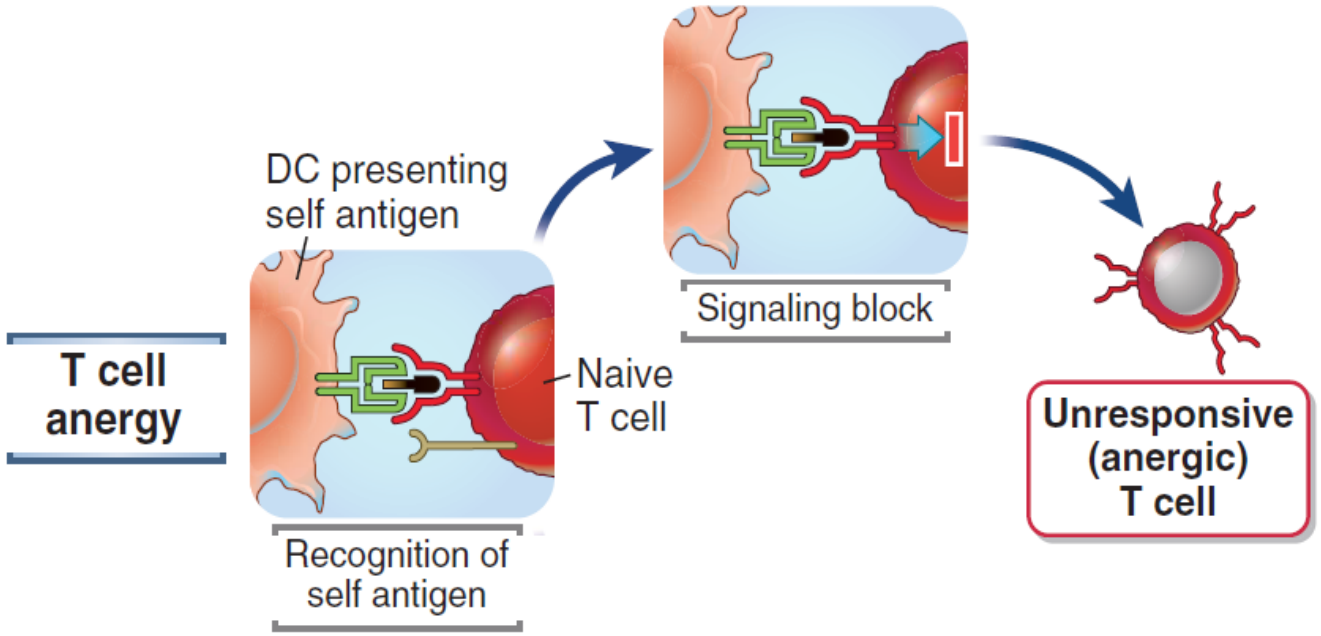


Anergy: functional non-responsiveness

- T cell responses are induced when the cells recognize an Ag presented by a APC and activating receptors on the T cells (such as CD28) recognize costimulators on the APCs (such as B7).

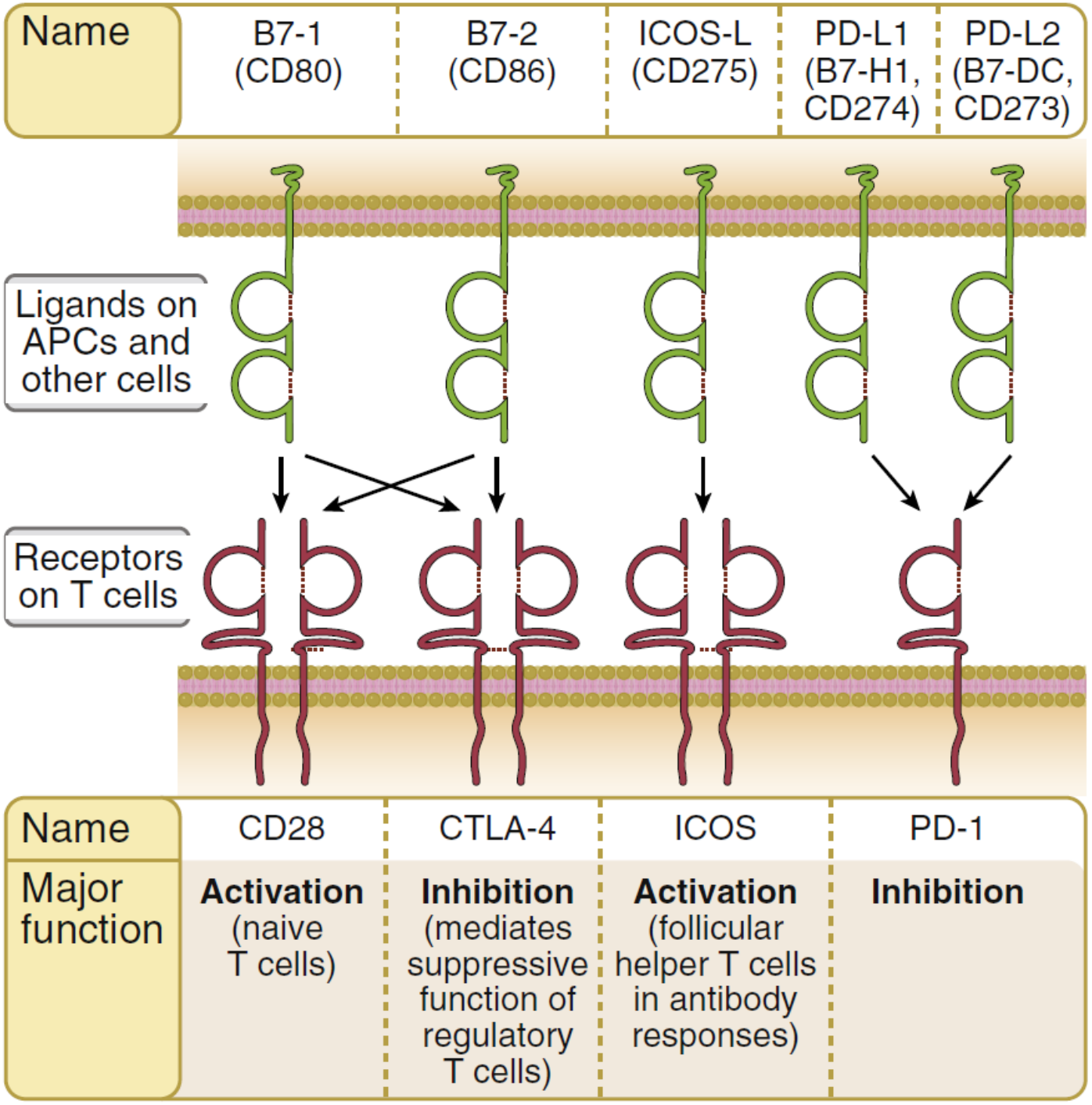
- If the T cell recognizes a self antigen without costimulation, the T cell becomes unresponsive to the antigen due to:

- signaling block from the TCR complex or



Anergy: functional non-responsiveness:

The signaling block may be the result of recruitment of phosphatases to the TCR complex or the activation of ubiquitin ligases that degrade signaling proteins. The T cell remains viable but is unable to respond to the self antigen.

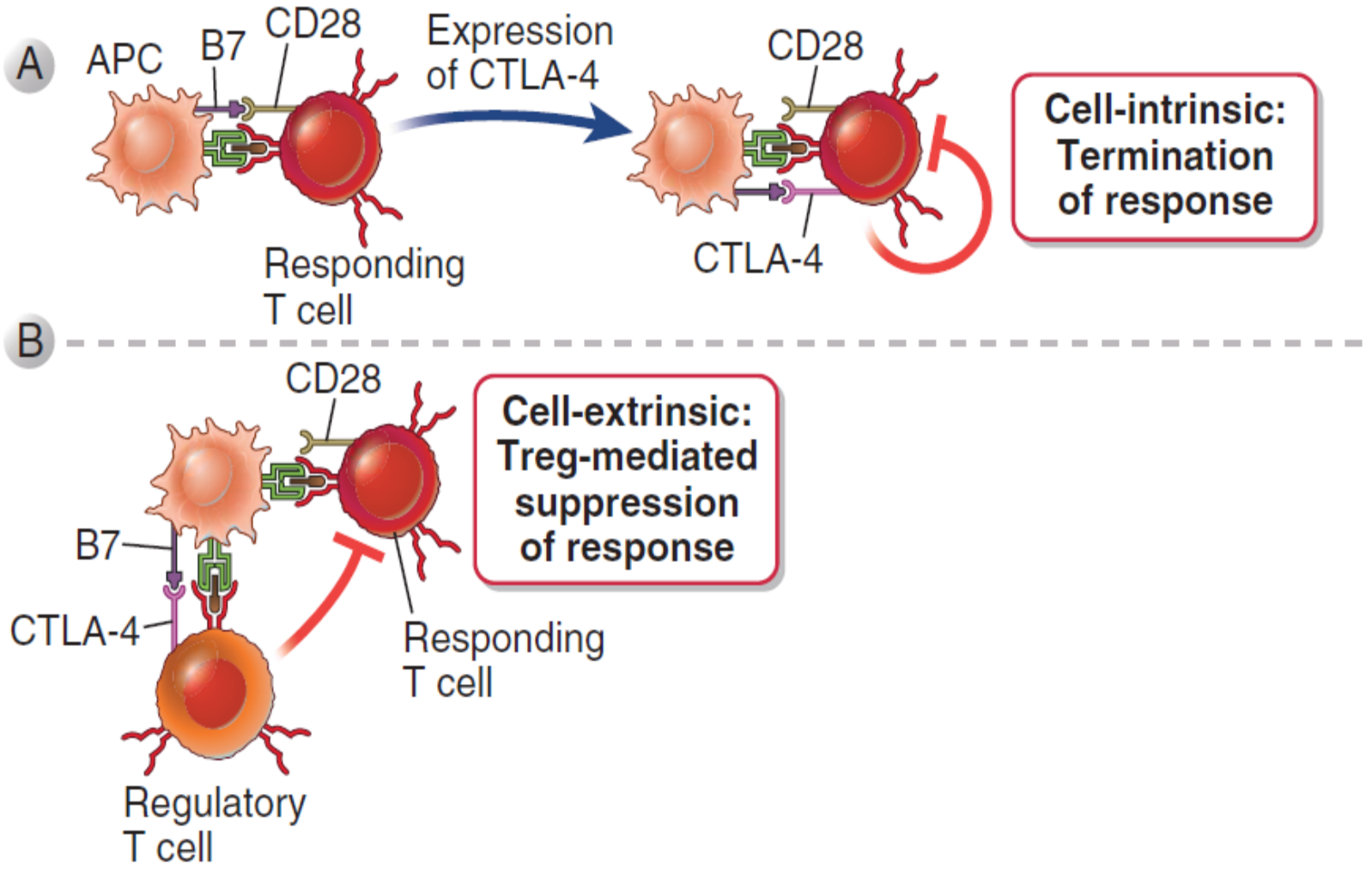


Anergy: functional non-responsiveness:

may be the result of inhibitory receptor expression:

- CTLA-4 (Cytotoxic T-Lymphocyte Antigen -4) - a receptor from the CD28 family, but which inhibits the B7 receptor expressed on the antigen-presenting cell. Genetic polymorphism and genetic mutations of CTLA-4 can lead to autoimmune conditions such as type 1 diabetes and Graves' disease.[17]

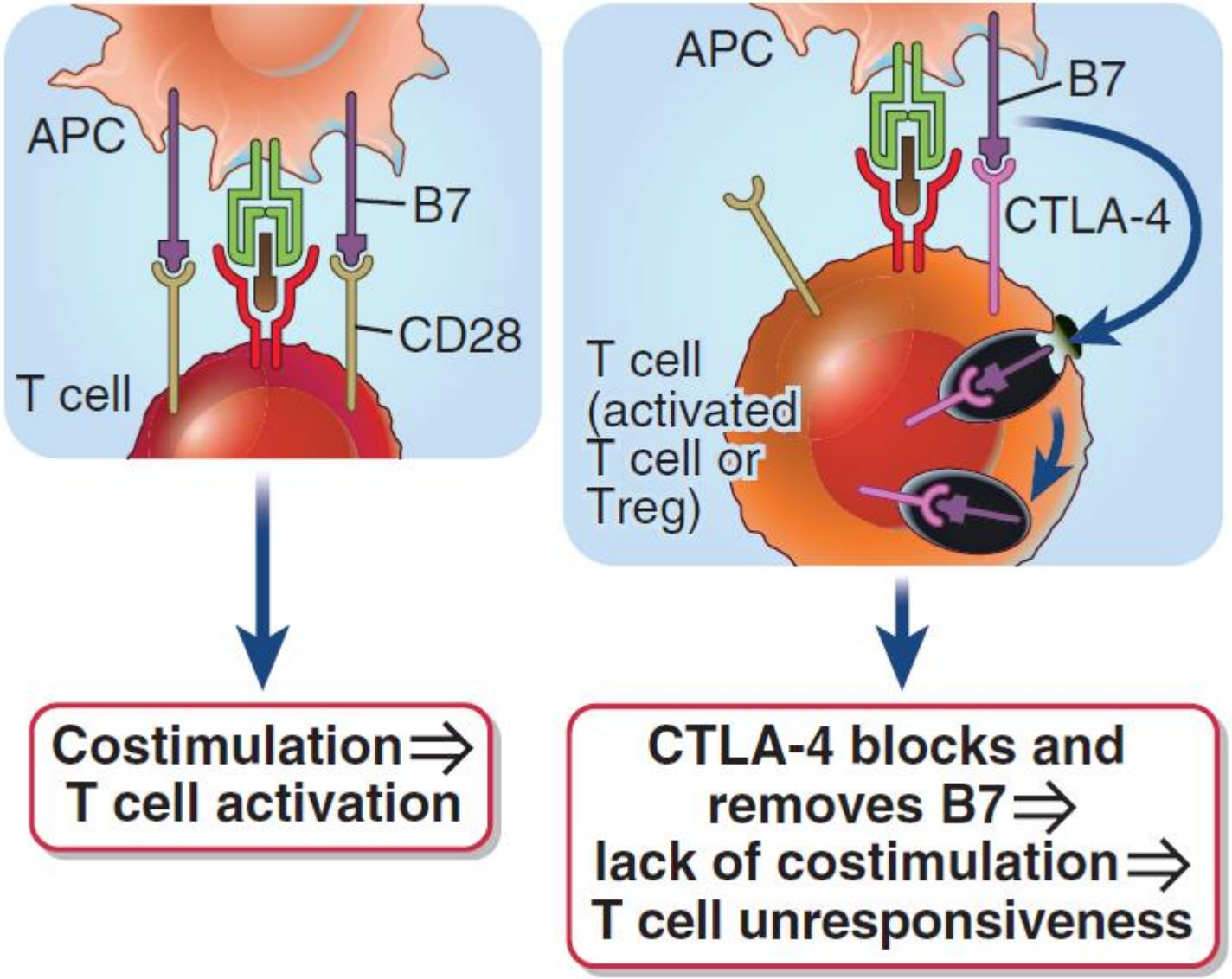
Peripheral tolerance of T lymphocytes



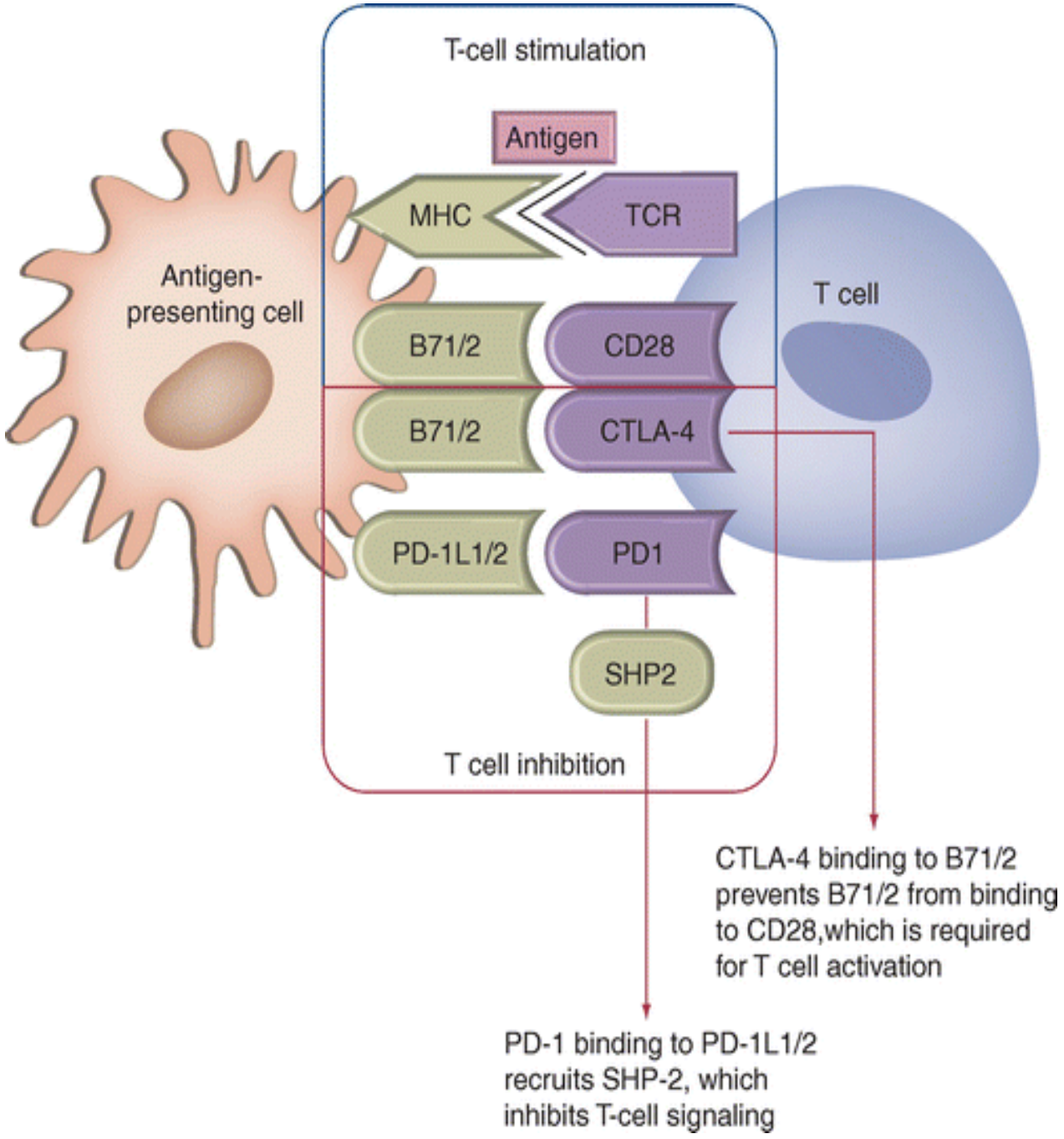
The CTLA-4 inhibits TL via 2 mechanisms:

- Intrinsec, by the expression of proper inhibitory receptor of CTLA-4.
- Extrinsec, by engagement of CLTA- 4 expressed on Treg lymphocytes

Peripheral tolerance of T lymphocytes



- CTLA-4 also can inhibits the activation of T lymphocytes by its competitive action with B7 to the CD28.
- Compering the affinity of CD28 to CTLAA-4 is 10-20 times more than to B7, so the costimulatory effect of B7-CD28 is easy



Inhibitory receptor PD-1

recognised 2 types of ligands:

- PD-L1 expressed on APC and on others.
- PD-L2 expressed exclusively on APC.

The receptor PD-1 is expressed on antigen-activated T cells. Engagement of PD-1 by either of its ligands leads to the recruitment of protein-tyrosine phosphatase (SHP-2) to the cytoplasmic tail of PD-1. These enzymes counteract kinase-induced signaling and inhibit signals from the TCR-coreceptor

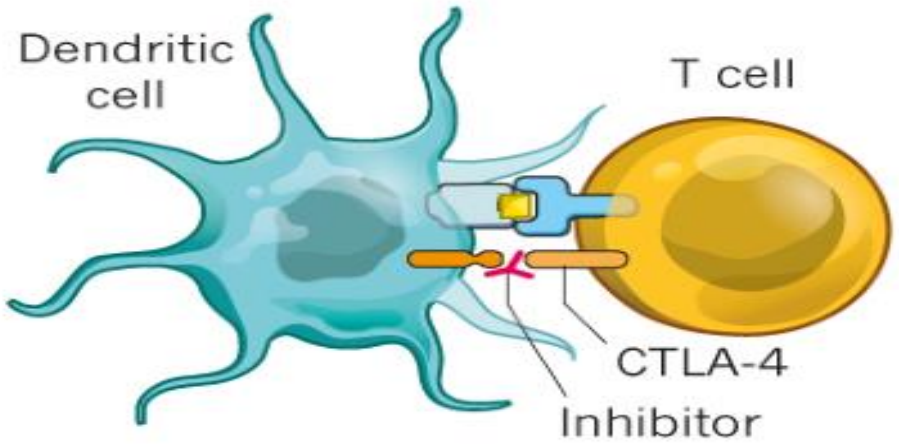
CTLA-4 acts in lymphoid tissue.
CTLA-4 assure the inhibition in equal manner of CD4 and CD8.
CTLA-4 can be expressed also on regulatory TL.

PD-1 acts in peripheral tissue.
PD-1 assure more inhibition of CD8.
PD-1 is expressed on the activated T lymphocytes.

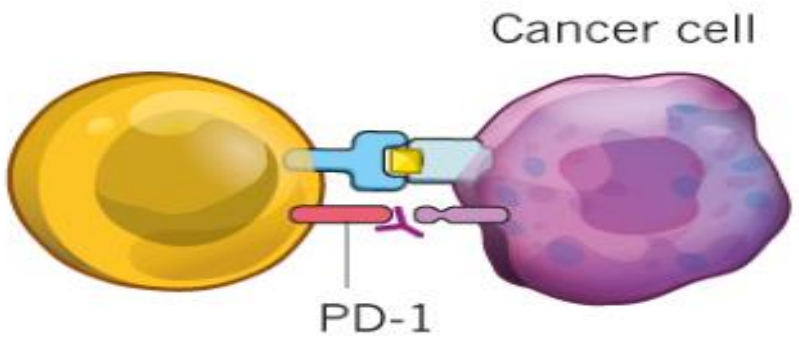
The Nobel Assembly at Karolinska Institute has decided to award the 2018 Nobel Prize in Physiology or Medicine jointly to James P. Allison and Tasuku Honjo

CHECKPOINT INHIBITOR DRUGS

'Checkpoint' proteins block T-cell activity. Inhibitor drugs can release the brakes on T cells at different stages.



The CTLA-4 checkpoint protein prevents dendritic cells from priming T cells to recognize tumours. Inhibitor drugs block the checkpoint.



The PD-1 checkpoint protein prevents T cells from attacking cancer cells. The inhibitor drug allows T cells to act.

©nature

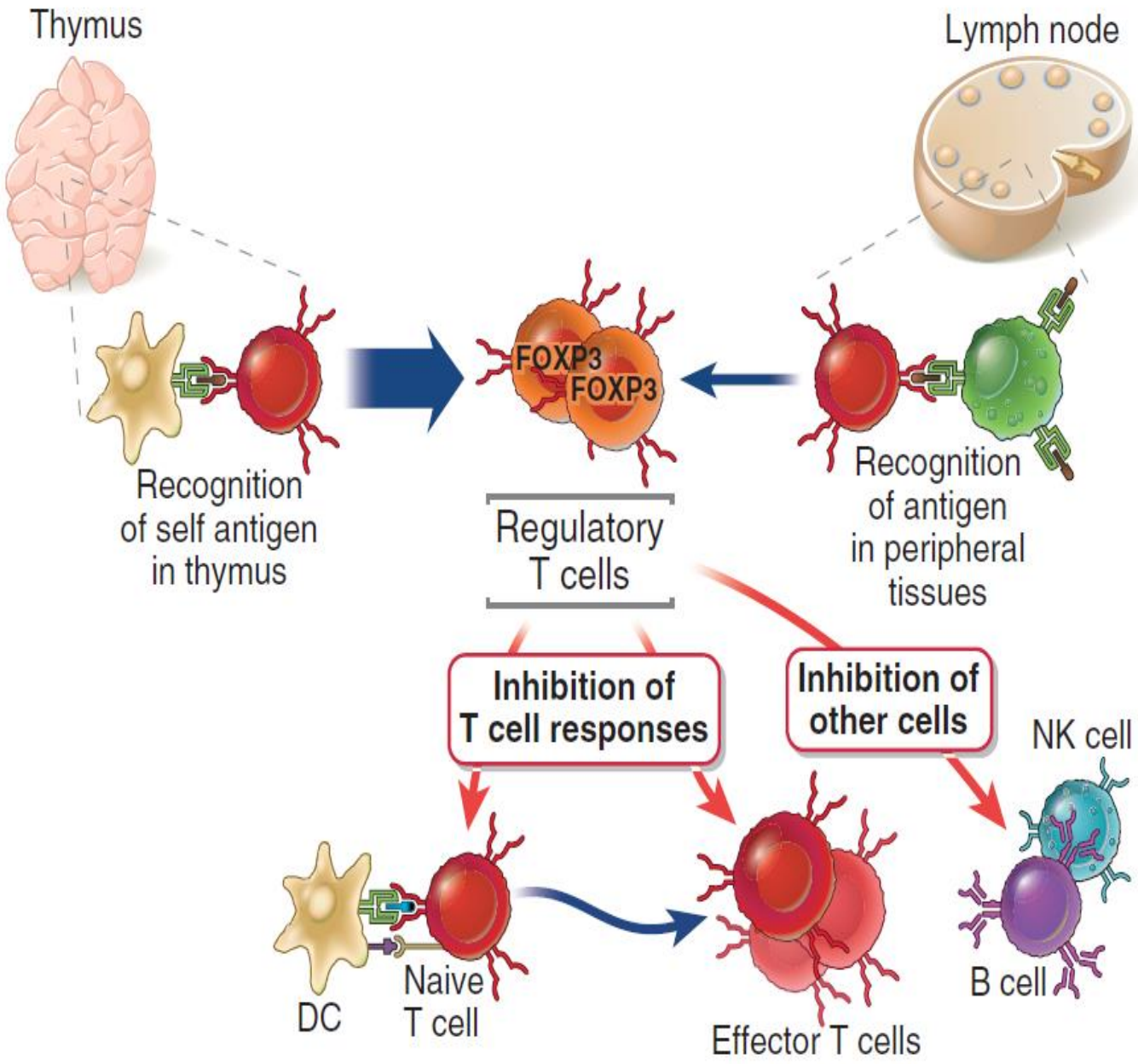
T regulatory T cell (T reg)

are a subpopulation which derived from CD4 T lymphocytes.

They maintain immune autointolerance by 2 mechanisms:

1. They express receptors for IL-2 (CD25), which is an interleukin that stimulates activation and proliferation of B and T lymphocytes.

2. They express FoxP3, FoxP3 is a member of the forkhead family of transcription factors and is

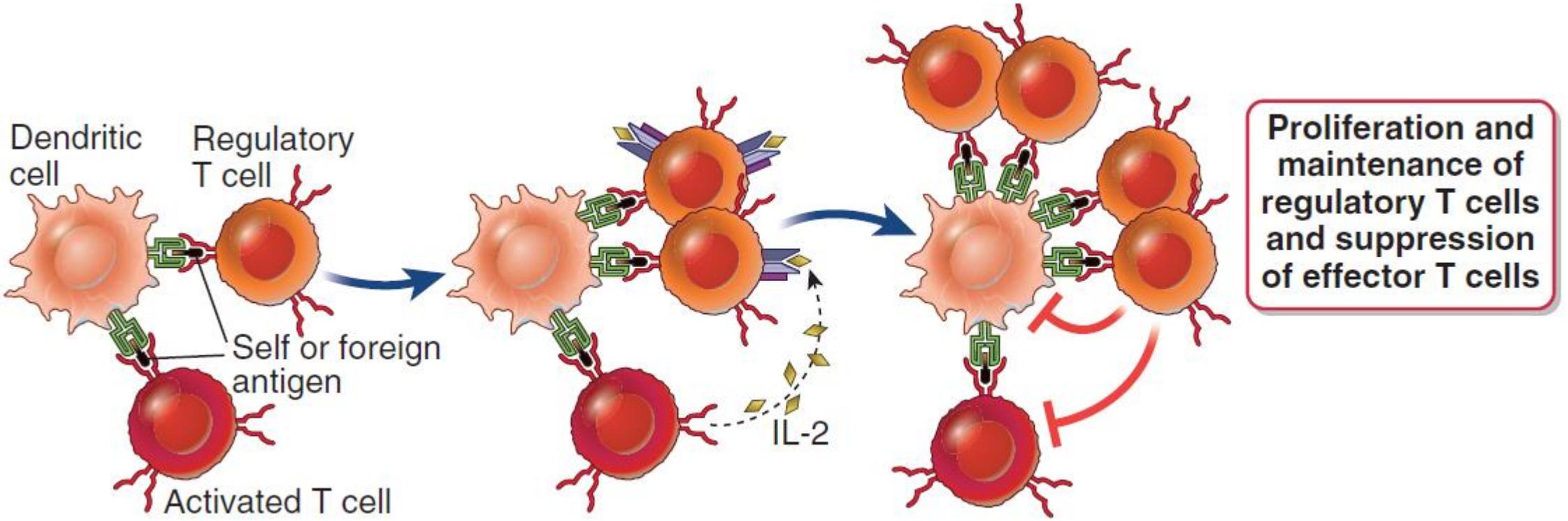


The lymphocytes T regulatory are the result of:

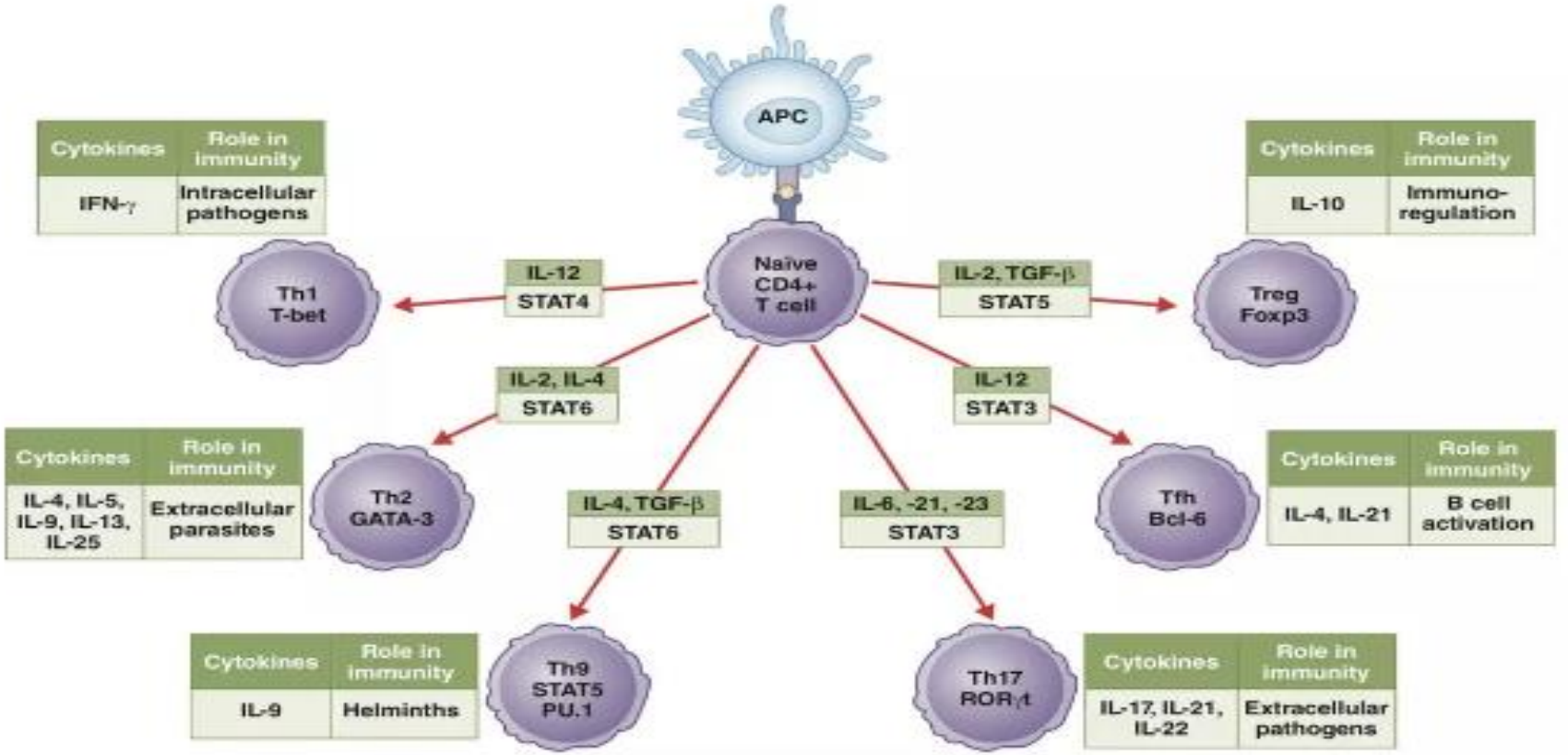
- The recognition process of self – Ag in the thymus (T reg from thymus);
- The recognition process of self – Ag and of non-self-Ag from peripheric lymphoid tissue (natural T reg cells);
- The TGF-beta action, which is important for normal expression process of transcription factor FoxP3.

Remember:

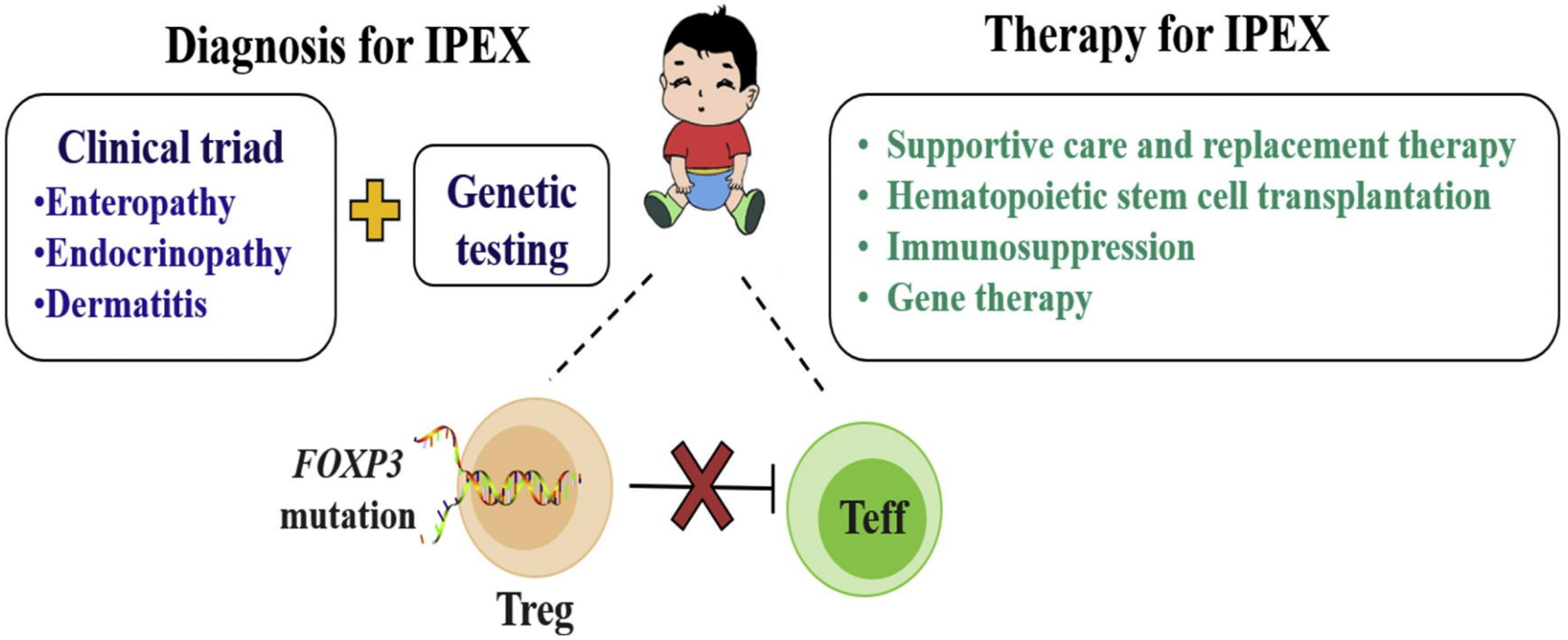
The surviving and functionality of regulatory T lymphocytes



IL-2 it is important for the differentiation of lymphocytes T into T reg and assure their functioning capacity.
IL-2 is expressed on T lymph which contacts with the self-Ag and non-self-Ag and is not realised by T regulatory cells.



- IL-2 activates the transcription factor STAT-5 for following activation of FoxP3 genes.
- The activation of this gene lead to realising of IL-10.
- The activation of this gene is stimulated by the gene that is activated by retinoic acid , (analog of vitamin A).

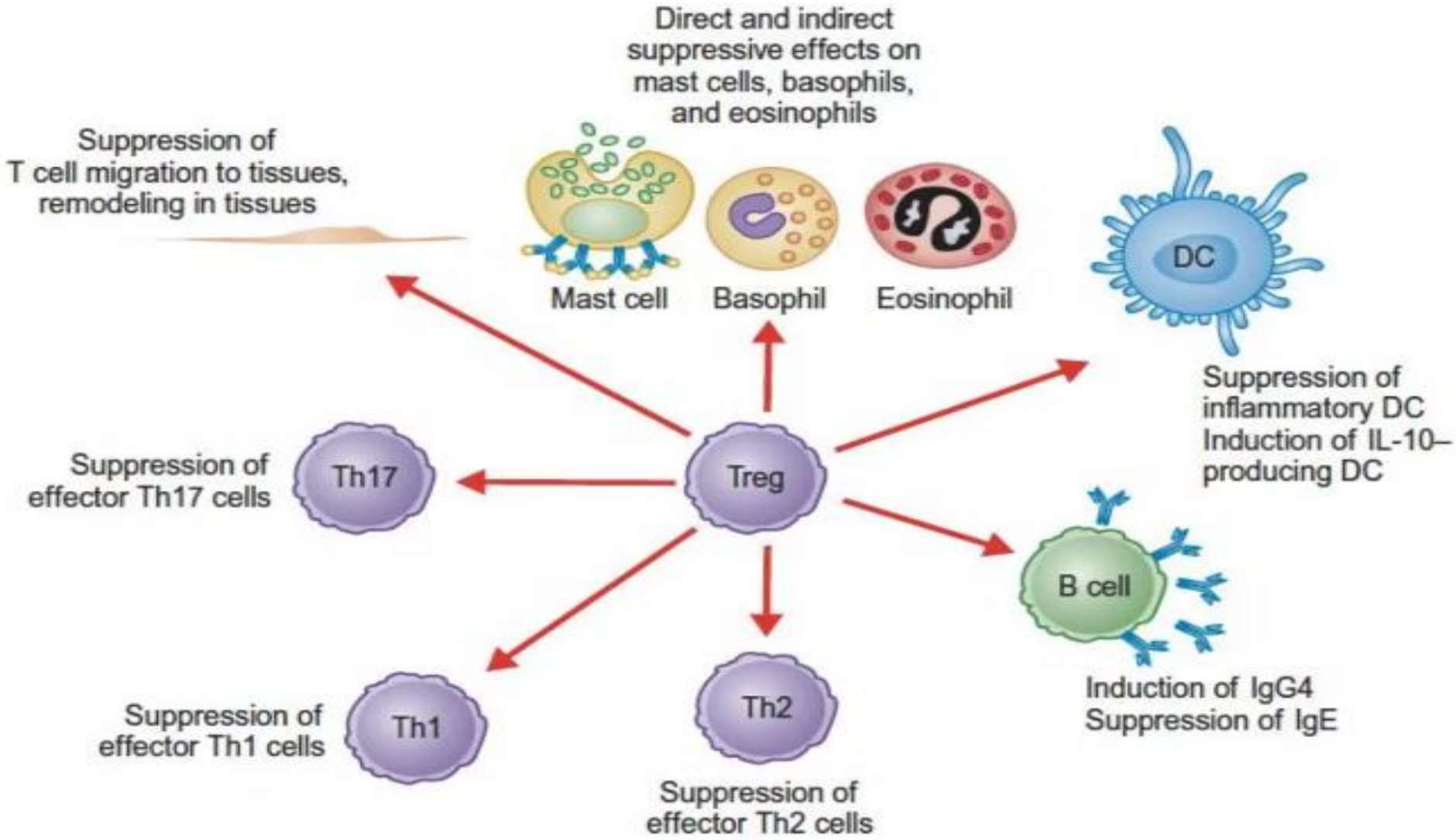


The mutation of FoxP3 gene which is associated with a deficiency of Tregs, can induce a rare autoimmune disease in humans called IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked).

Regulatory T cells may suppress immune responses by several mechanisms

- Some regulatory cells produce cytokines (e.g., IL-10, TGF-β) that inhibit the activation of lymphocytes, dendritic cells, and macrophages.
- Regulatory cells express CTLA-4, which, as discussed earlier, may block or remove B7 molecules made by APCs and make these APCs incapable of providing costimulation via CD28 and activating T cells.
- Regulatory T cells, by virtue of the high level of expression of the IL-2 receptor, may bind and consume this essential T cell growth factor, thus reducing its availability for responding T cells.

General effects of T regulatory lymphocytes



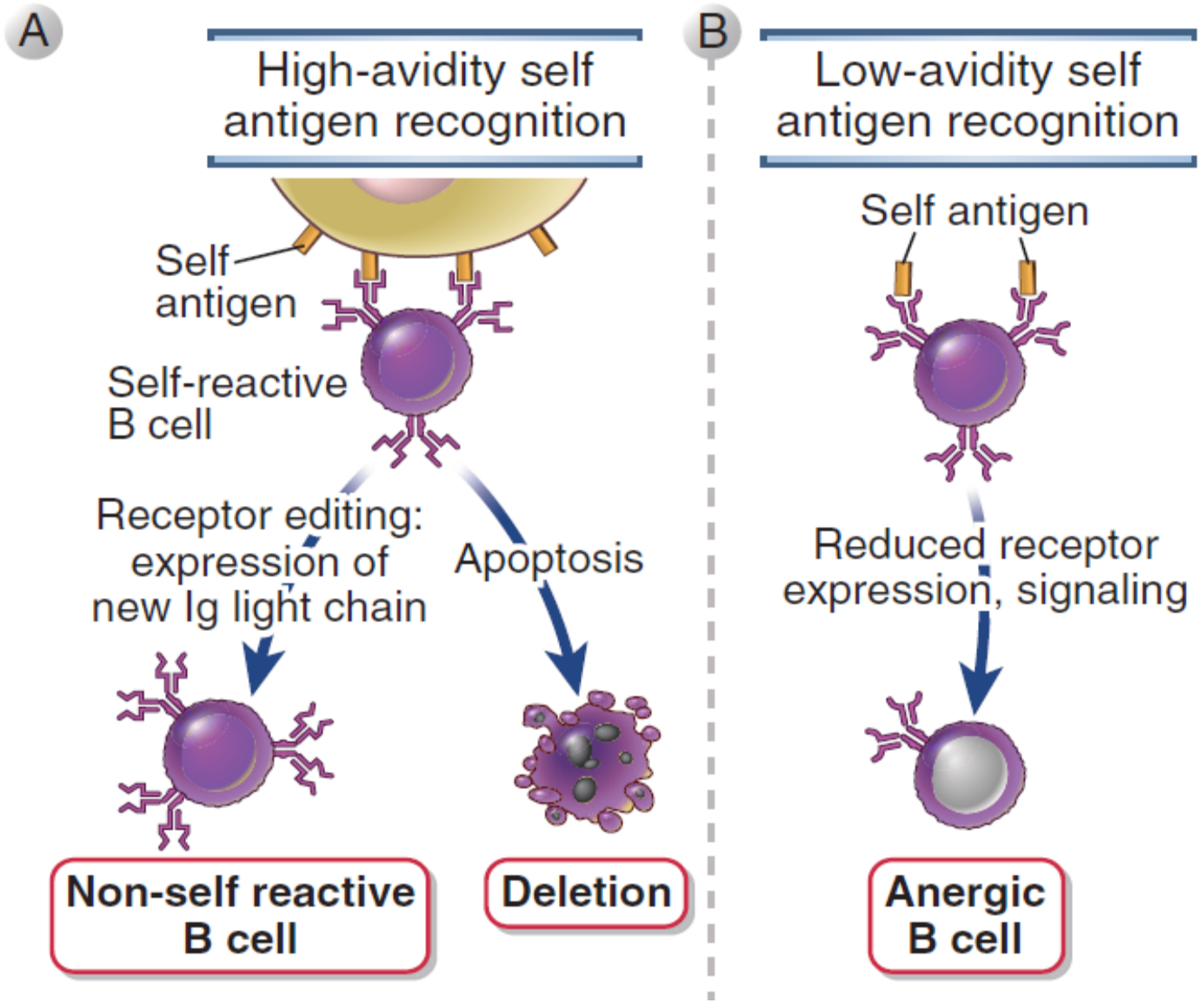
The factors which determine the decreasing of immune- suppressive capacity of T reg lymphocytes and compromise the immune auto-intolerance:

1. Excess of IL-6;
2. Excess of TNF- alpha;
3. Excess of IL-7 și IL-15;
4. The hyperergic inflammatory response;
5. Activation of dendritic cells in area of inflammatory focus

Tolerance of lymphocytes B

1. The absence of response to the action of Ag-T-independent (lipopolysaccharides, lipids, etc.).

2. The prevention of Ab response to protein Ag action.



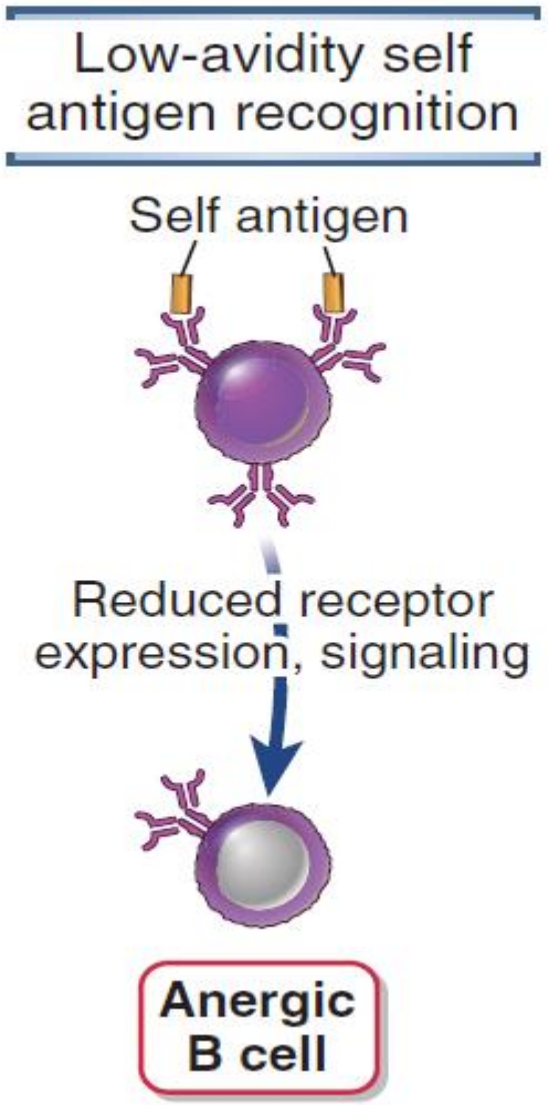
Central immune tolerance of B lymphocytes :

1. Apoptosis
2. Receptor editing
3. Anergy

Central immune tolerance of B lymphocytes :

- Immature B lymphocytes, which in the hematogenous bone marrow have an exaggerated affinity for self-Ag, are removed by apoptosis.

- If immature B cells recognize self antigens that are present at high concentration in the bone marrow, and especially if the antigen is displayed in multivalent form (e.g., on cell surfaces), many antigen receptors on each B cell are cross-linked, thus delivering strong signals to the B cells, which reactivate specific genes. As a result, the previously rearranged segment of Ig of self-reactive immature B cell is deleted, and a new Ig light chain is expressed, thus creating a B cell receptor (BCR) with a new specificity. This process is

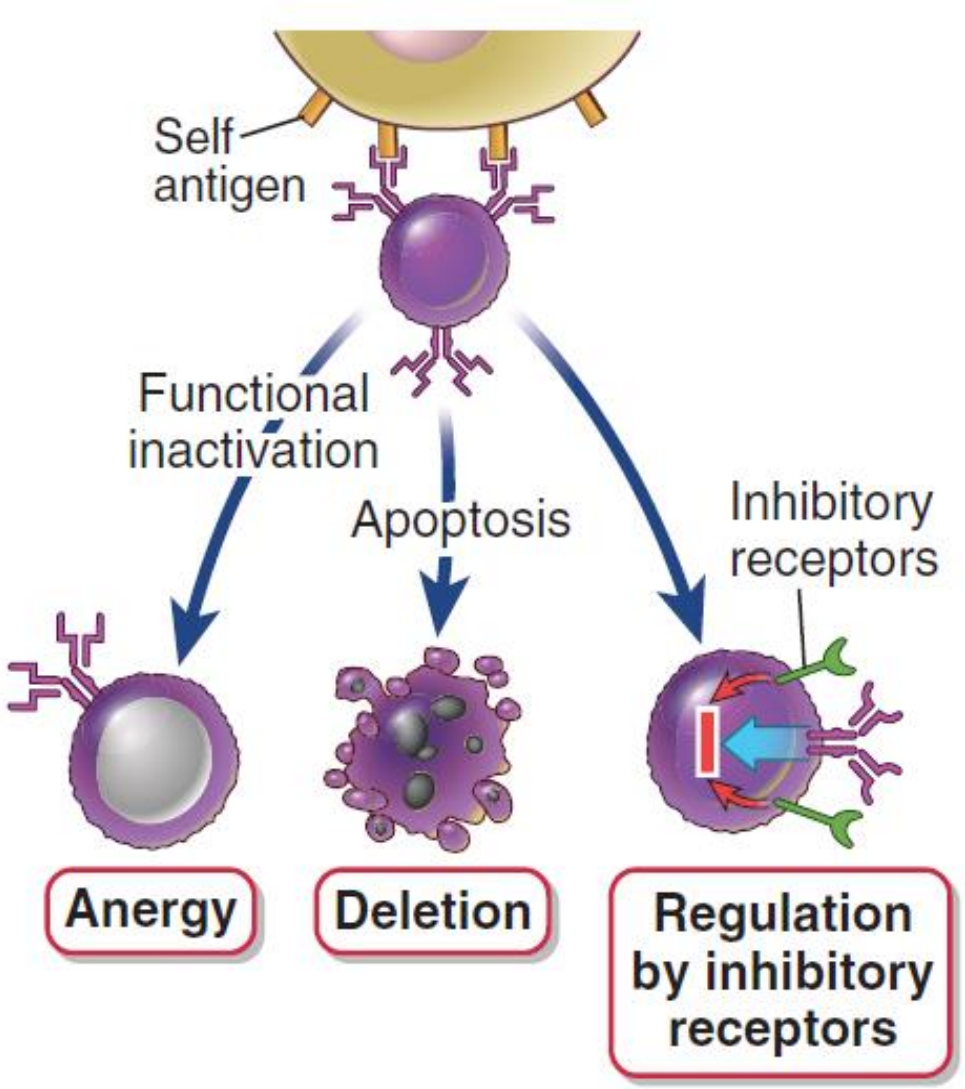


Central immune tolerance of B lymphocytes :

- If BLs weakly recognize Ag-self, anergy develops and they leave the marrow in a very weak functional response status.

- Anergy is determined by decreased expression of receptors and blocking of Ag signaling.

Peripheral immune tolerance of B lymphocytes



If the mature B lymphocyte has recognized the Ag in the peripheral tissue without cooperation with T-CD4 lymphocytes, then the BL may lose the functional response capacity:

1. through the expression of the inhibitory receptor or
2. It is exposed to apoptosis or
3. enters in the anergy

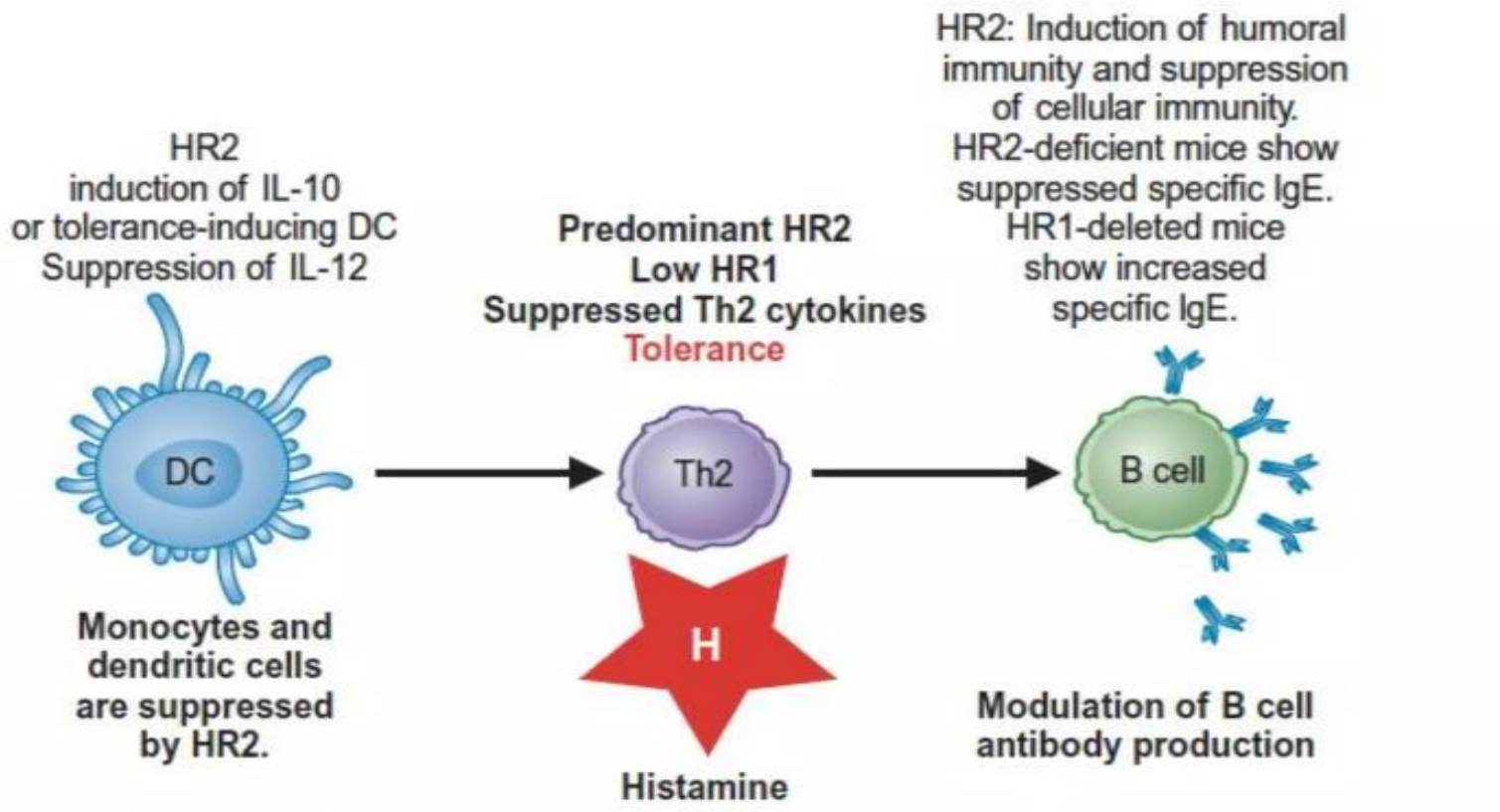
Peripheral immune tolerance of B lymphocytes

- In case of self-Ags are non-protein (T-independent) antigens the CD4 T-lymphocyte signals are weak for BLs activation.
- Mature B lymphocytes that have excessively high affinity for self-Ag can die by apoptosis triggered by the mitochondrial (intrinsic) pathway.
- B lymphocytes that are frequently stimulated by self-Ag assume an inactive functional status (they will no longer respond).
- If BL activation does not occur in association with co-stimulatory actions they will demonstrate immune tolerance

Peripheral immune tolerance of B lymphocytes

- Commensal microorganisms (microorganisms that live and benefit from the human body, without causing damage – skin, intestine) do not induce costimulatory signals or activate regulatory T lymphocytes.
- Repeated administration of protein Ag without an adjuvant will block costimulatory signals.
- Oral administration of protein Ag leads to suppression of the humoral (even cellular) immune response – oral tolerance.

Histamine via H2 receptors has a suppressive action on the immune response



Administration of antihistaminic drugs. used in allergic reaction, increases the expression of H2 receptors!!!

Mechanisms:

- Expression of IL-10 by monocytes and DCs.
- Decreases the Th1 response.
- Augments the suppressive activity of TGF-beta.
- Decreases the proliferation of TLs under the action of IL-4 and IL-13.
- Increases the production of


Thank You!
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