Dr. Muntaha M. Hassan

IMMUNE TOLERANCE

- Immune tolerance or immunological tolerance is the process by which the immune system does not attack an antigen.

-Immunological tolerance is not simply a failure to recognize an antigen; it is an active response to a particular epitope and is just as specific as an immune response.

*Both B cells and T cells can be made tolerant, but it is more important to Tolerize T cells than B cells because B cells cannot make antibodies to most antigens without the help of T cells.

- Immunological tolerance a state of indifference or non-reactivity towards a substance that would normally be expected to excite an immunological response.. It is induced by prior exposure of that antigen.
- The antigen which causes the tolerance is called tolerogen.

- It can be either

- 'natural' or 'self tolerance', in which the body does not mount an immune response to self antigens, or

-induced tolerance', in which tolerance to external antigens can be created by manipulating the immune system.

Types of tolerance

- **Self tolerance includes:**
  - Central tolerance,
  - Peripheral tolerance

- **Acquired tolerance.**

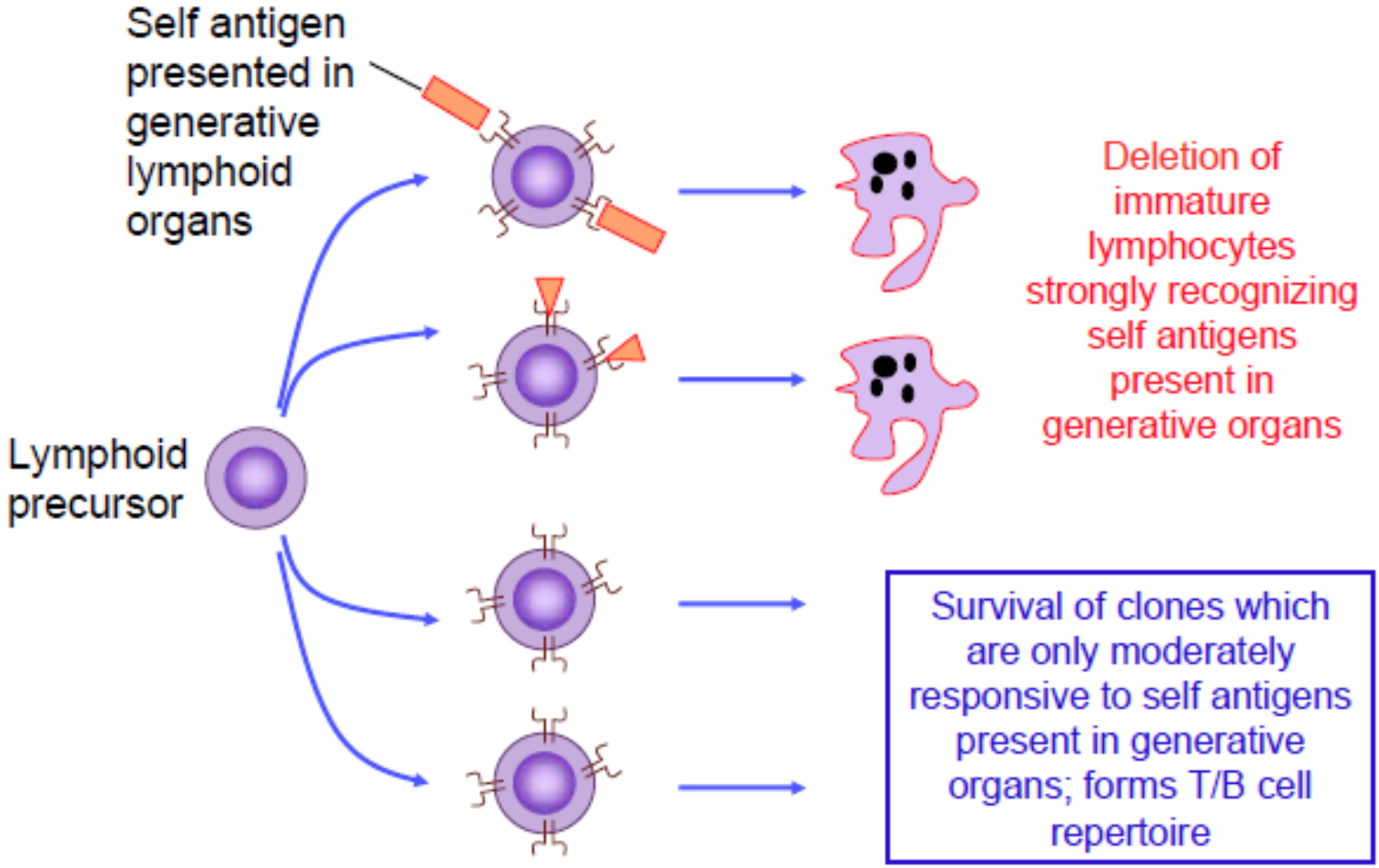
SELF TOLERANCE

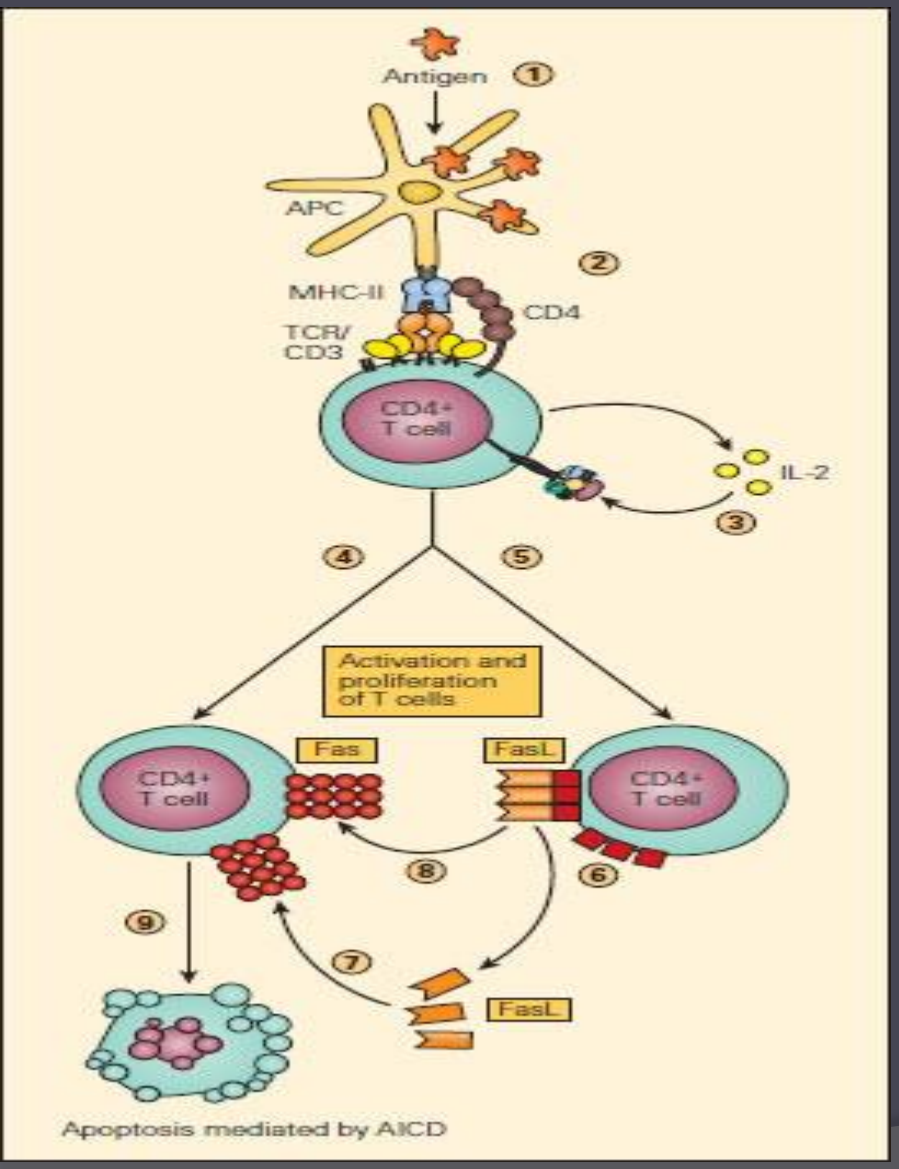
- The normal lack of the ability to produce an immunological response to autologous (self) antigens. A breakdown of self tolerance leads to autoimmune diseases.
- The ability to recognize the difference between self and non-self is the prime function of the immune system.
- Genetic defects in these processes lead to autoimmunity, such as in Autoimmune polyendocrine syndrome type 1 (APS-1) and immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX).

- The exact genesis of immunological tolerance is still vague, but several theories have been proposed since the mid-twentieth century to explain its origin.
- Many hypotheses have gained widespread attention among immunologists:
- **CLONAL DELETION THEORY**, proposed by Burnet, according to which self-reactive lymphoid cells are destroyed during the development of the immune system in an individual. For their work Frank M. Burnet and Peter B. Medawar were awarded the 1960 Nobel Prize in Physiology or Medicine "for discovery of acquired immunological tolerance".

Mechanisms of unresponsiveness:

Central tolerance in B and T cells (I): Clonal Deletion

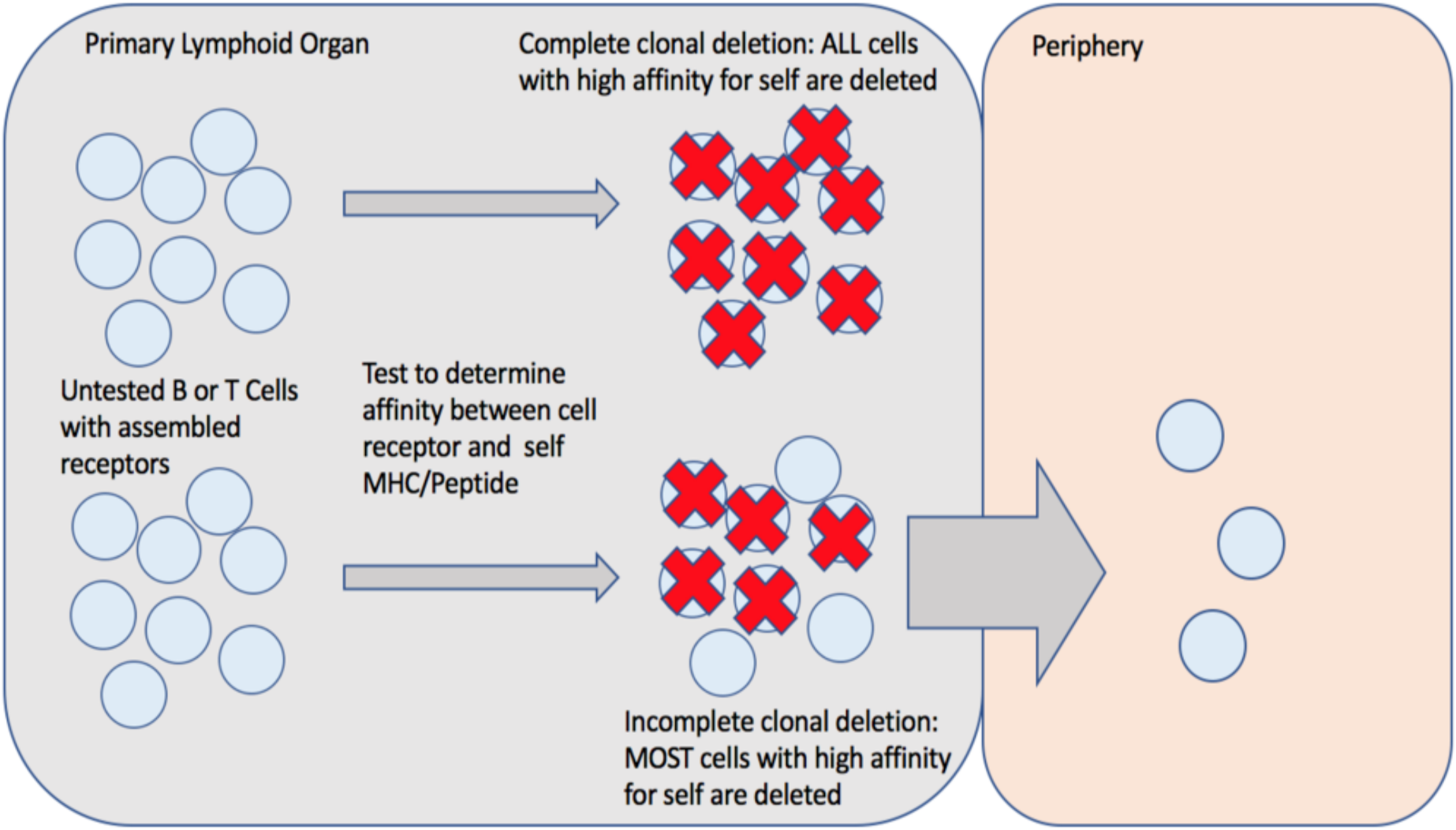




- . Upon uptake and processing of antigen by APCs (1) and subsequent presentation of the processed peptide to a CD4+ T cell (2), IL-2 production and expression of the IL-2R occurs followed by their autocrine binding (3), leading to T cell activation. Activated T cells express Fas (4) and FasL (5) on their surfaces or as soluble s-FasL after cleavage of the membrane-associated FasL (6). The interaction of Fas either with s-FasL (7) or with membrane-associated FasL (8) leads to apoptosis (9) by activation-induced cell death (AICD), thus ending the immune response

Complete vs. Incomplete Clonal Deletion

- A visual representation of incomplete and complete clonal deletion
- Complete clonal deletion results in apoptosis of all B and T lymphocytes expressing high affinity for self antigen.
- Incomplete clonal deletion results in apoptosis of most autoreactive B and T lymphocytes.
- Complete clonal deletion can lead to opportunities for molecular mimicry, which has adverse effects for the host. Therefore, incomplete clonal deletion allows for a balance between the host's ability to recognize foreign antigens and self antigens.

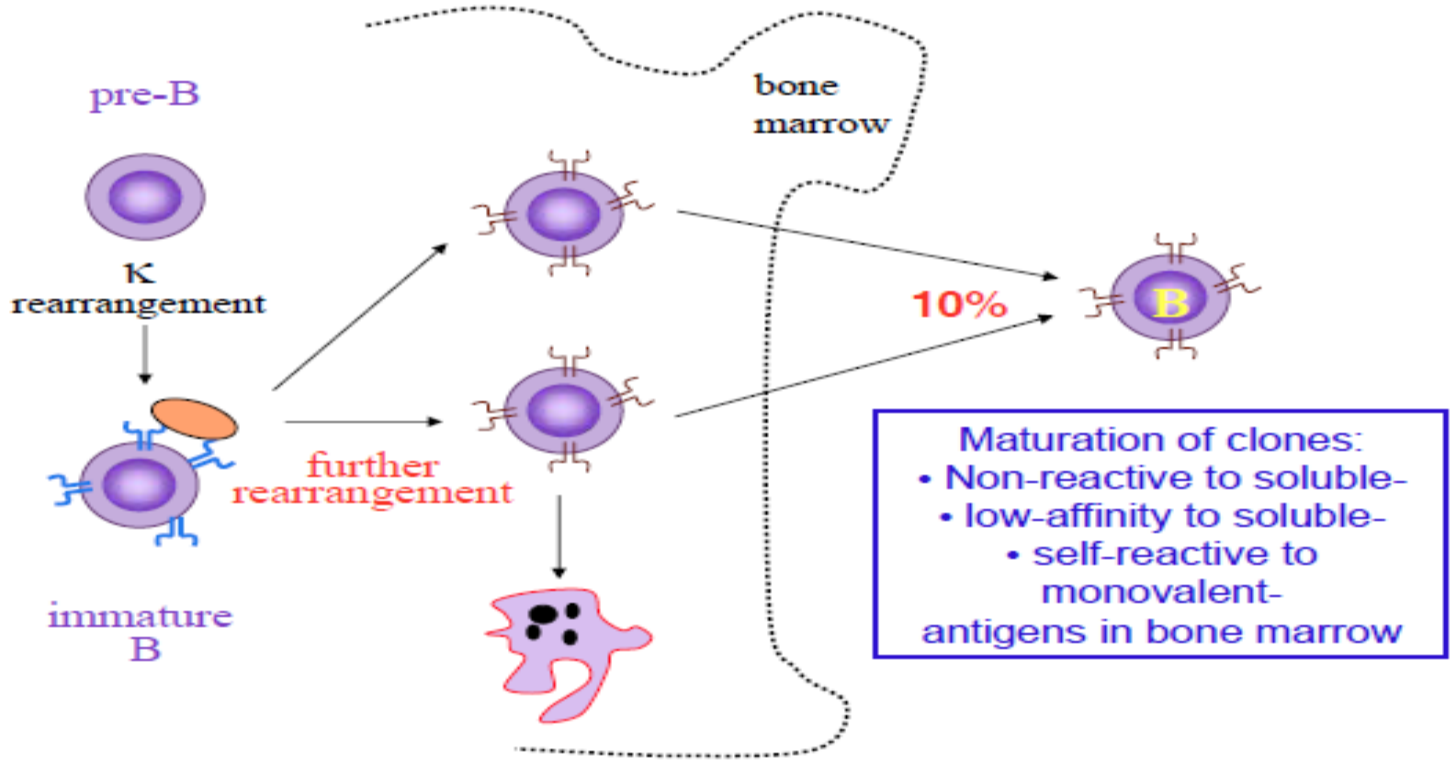

Primary Lymphoid Organ
Complete clonal deletion: ALL cells with high affinity for self are deleted
Periphery
Untested B or T Cells with assembled receptors
Test to determine affinity between cell receptor and self MHC/Peptide
Incomplete clonal deletion: MOST cells with high affinity for self are deleted

RECEPTOR EDITING

- During maturation in the bone marrow, B cells are tested for interaction with self antigens, which is called negative selection.
- If the maturing B cells strongly interact with these self antigens, they undergo death by apoptosis.
- Negative selection is important to avoid the production of B cells that could cause autoimmune diseases. They can avoid apoptosis by modifying the sequence of light chain V and J genes (components of the antigen receptor) so that it has a different specificity and may not recognize self antigens anymore. This process of changing the specificity of the immature B cell receptor is called **receptor editing**

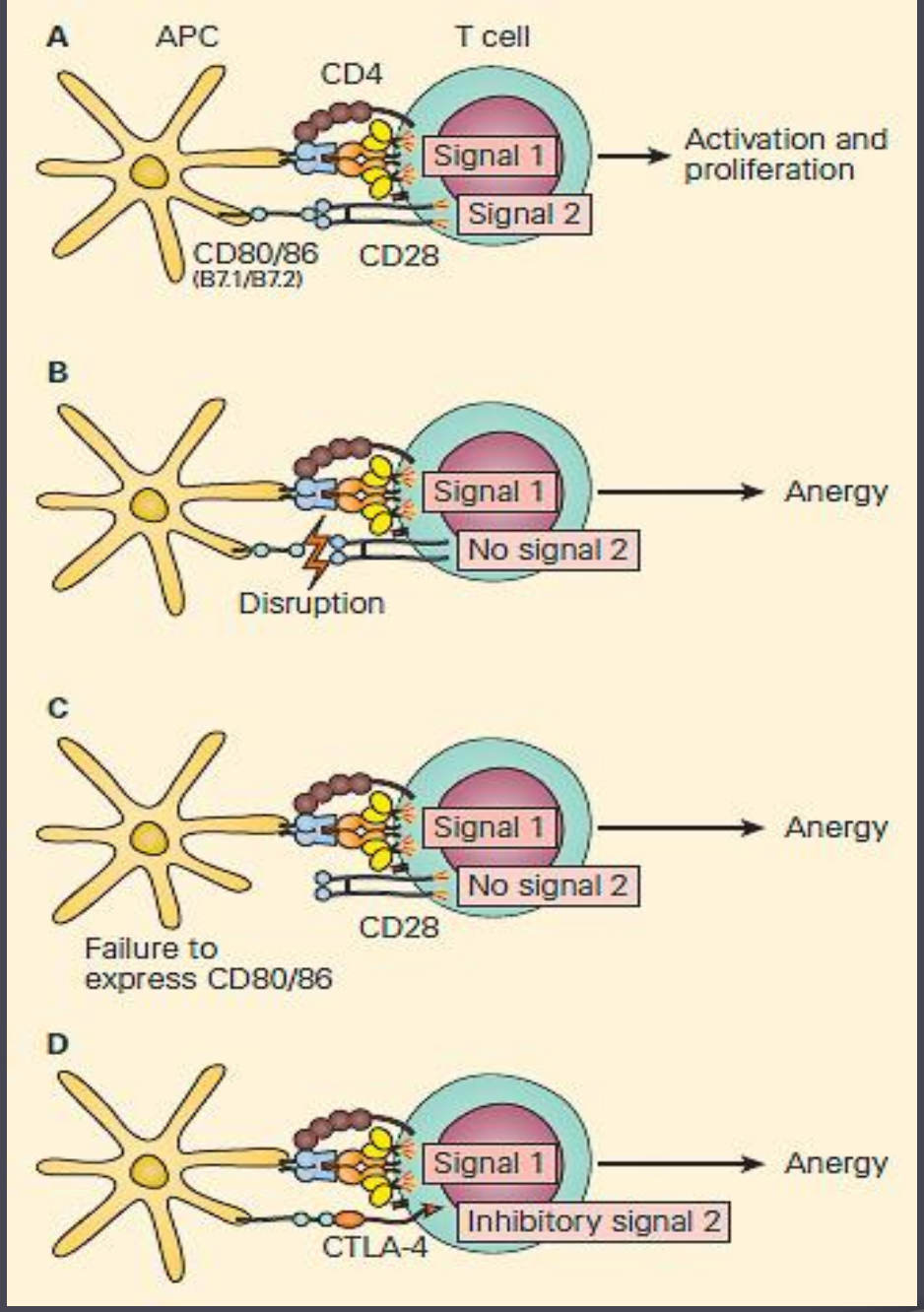
- Receptor editing is a process that occurs during the maturation of B cells, which are part of the adaptive immune system. This process forms part of central tolerance to attempt to change the specificity of the antigen receptor of self reactive immature B-cells, in order to saving them from programmed cell death, called apoptosis. It is thought that 20-50% of all peripheral naive B cells have undergone receptor editing making it the most common method of removing self reactive B cells.

Mechanisms of unresponsiveness:
Central tolerance in B cells (II): Receptor editing



- **CLONAL ANERGY THEORY**, proposed by Nossal, in which self-reactive T- or B-cells become inactivated in the normal individual and cannot amplify the immune response.

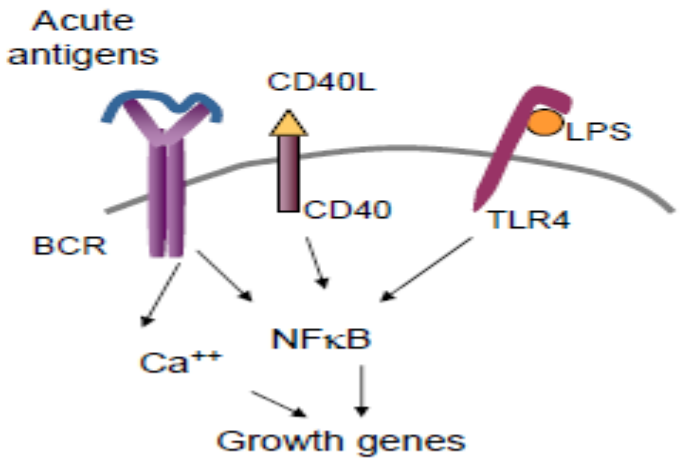
- **IDIOTYPE NETWORK THEORY**, proposed by Jerne, wherein a network of antibodies capable of neutralizing self-reactive antibodies exists naturally within the body.



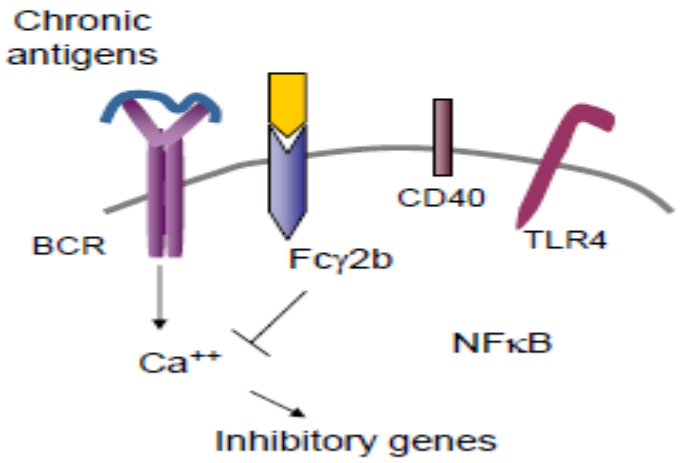
- Co-stimulation is important for the activation of T cells.
- Panel A: Following the activation of the 80/86 on the antigen-presenting cell provides the second signal, leading to T cell activation and proliferation.
- Panel B: Disruption of the CD28/CD80/86 signal or
- Panel C: Failure to express CD 80/86 can lead to anergy.
- Panel D: At the same time, the activated T cells upregulate the expression of CTLA-4, a molecule that also interacts with greater affinity to CD80/86, leading to disruption of the costimulatory signal and anergy

Mechanisms of unresponsiveness:
Peripheral tolerance in B cells (I): Anergy

Immunogenic signaling

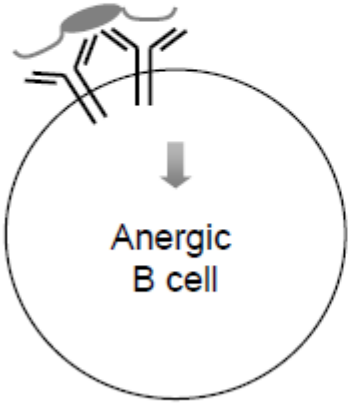


Tolerogenic signaling



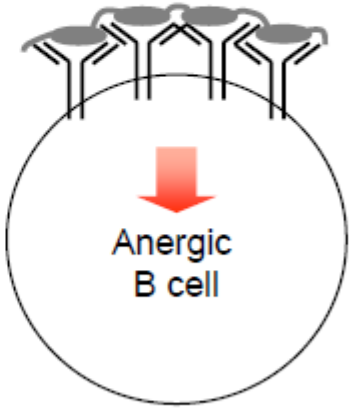
Anergic B cells can respond to "Stronger" antigens

Oligovalent self antigens
Constitutively exposed



Remains anergic

Multivalent foreign antigens
Acutely exposed

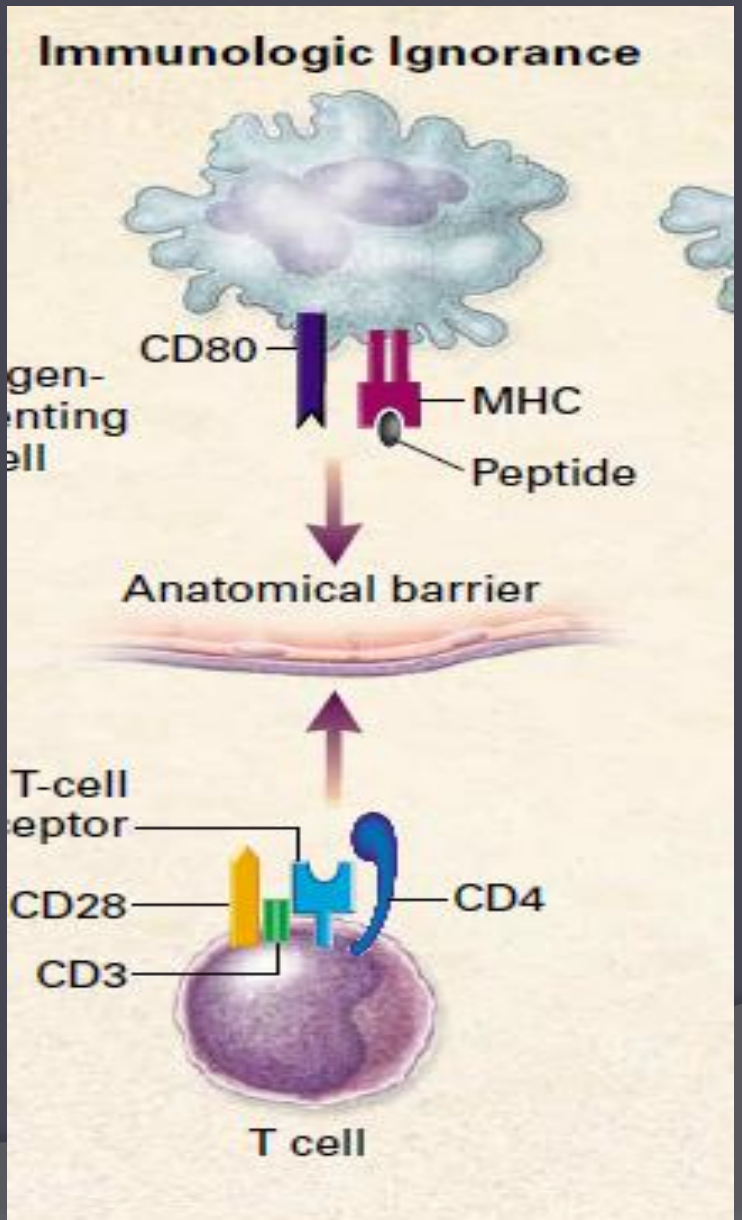


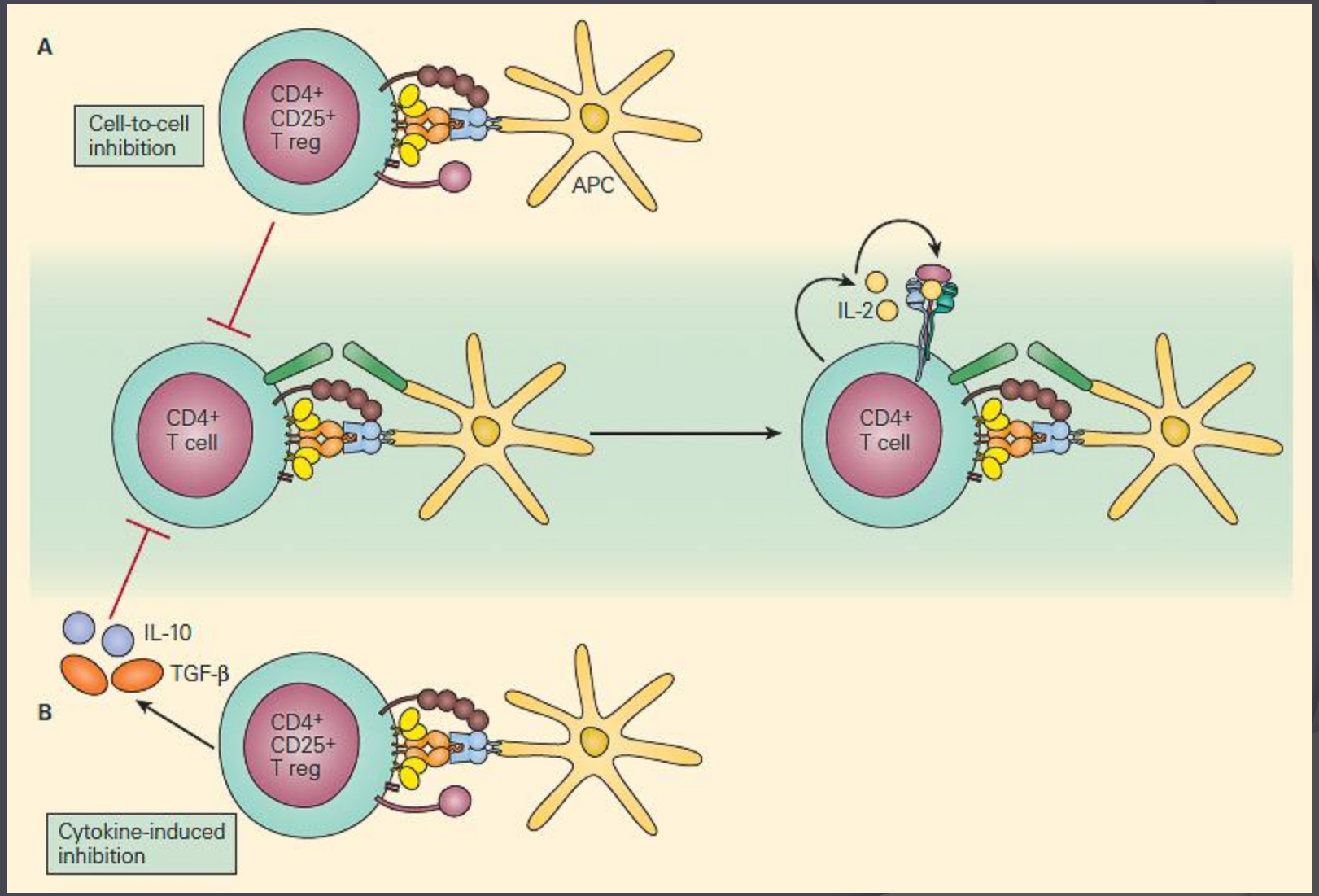
Activated

In addition, two other theories are under intense investigation:

- **CLONAL IGNORANCE THEORY**, according to which autoreactive T cells that are not represented in the thymus will mature and migrate to the periphery, where they will not encounter the appropriate antigen because it is inaccessible tissues. Consequently, auto-reactive B cells, that escape deletion, cannot find the antigen or the specific helper T-cell.

- **SUPPRESSOR POPULATION OR REGULATORY T CELL THEORY**,
- wherein regulatory T-lymphocytes (commonly $CD4^+FoxP3^+$ cells, among others) function to prevent, downregulate, or limit autoaggressive immune responses in the immune system.


Immunologic Ignorance
CD80
MHC
Peptide
Anatomical barrier
CD28
CD4
CD3
T cell


A
Cell-to-cell inhibition
CD4+ CD25+ T reg
APC
CD4+ T cell
IL-2
CD4+ T cell
IL-10
TGF-β
B
CD4+ CD25+ T reg
Cytokine-induced inhibition

Mechanisms of immune tolerance:

Peripheral T cell tolerance (IV): Suppression by T_{reg}

Neonate thymectomy --> Autoimmune diseases

1. The disease is transferable by T cells.

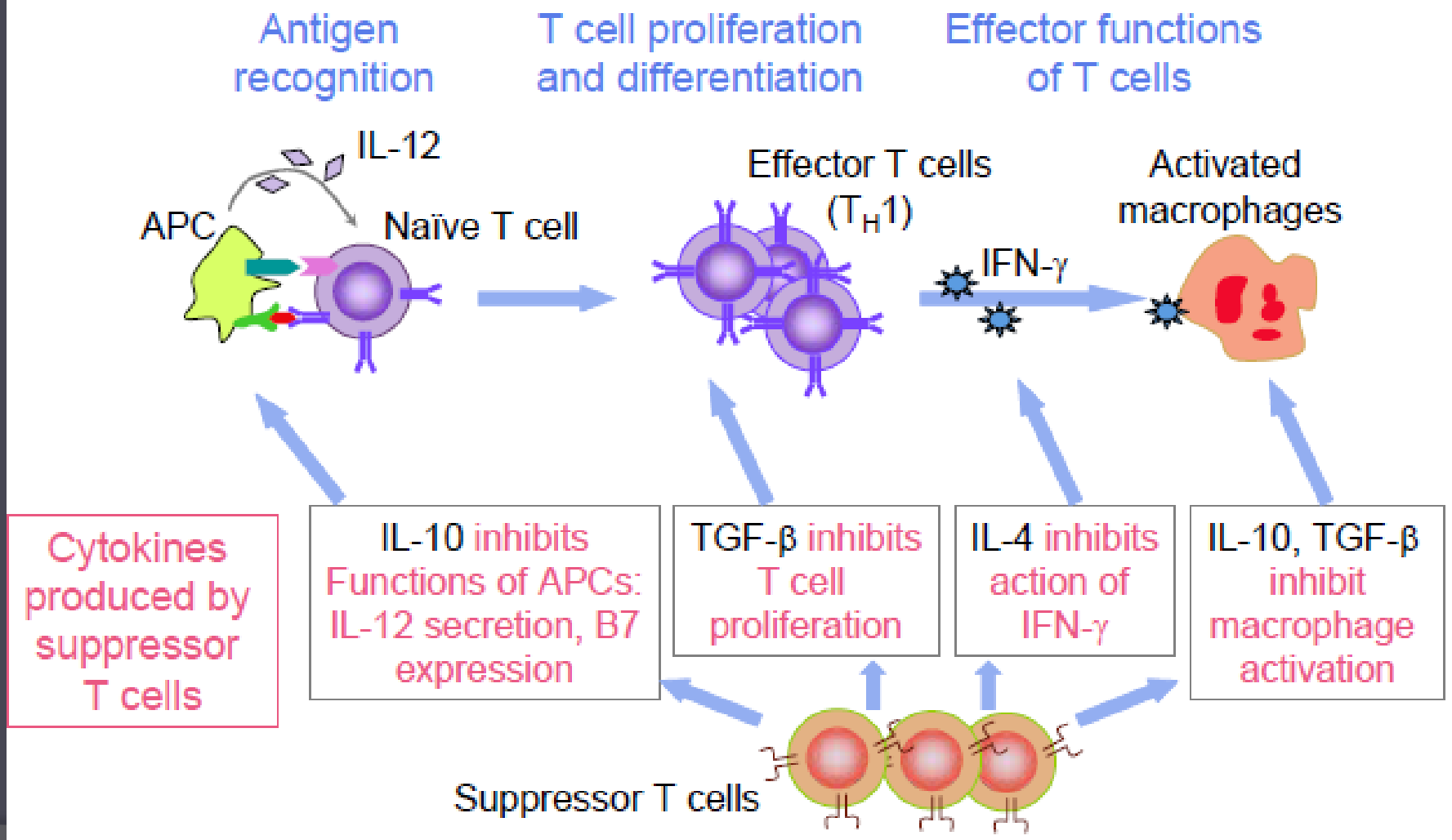
2. The disease can be prevented by delayed thymectomy or by transplantation of normal $CD4^+$ T cells.

Regulatory T cells (T_{reg}) in self tolerance

- **Phenotype and functions:**

- $CD4^+CD25^+$ cells, develop in the thymus.
- Recognize self-antigens.
- Express Foxp3. Foxp3 mutation causes the early onset of fatal autoimmune disorder observed in scurfy mutant mice and human IPEX patients (immune dysregulation, polyendocrinopath, enteropathy, X-linked syndrome).
- Prevent T-cell activation; supress cell proliferation and IL-2 production.

Role of cytokines in suppression of cell-mediated immune responses



1. Central Tolerance

T cells develop in the thymus. As they mature, recombination of gene segments creates the two chains that make up the T-cell receptor for antigen (TCR). Although the receptors on a single T cell are all alike, there is a virtually unlimited repertoire of receptor specificities

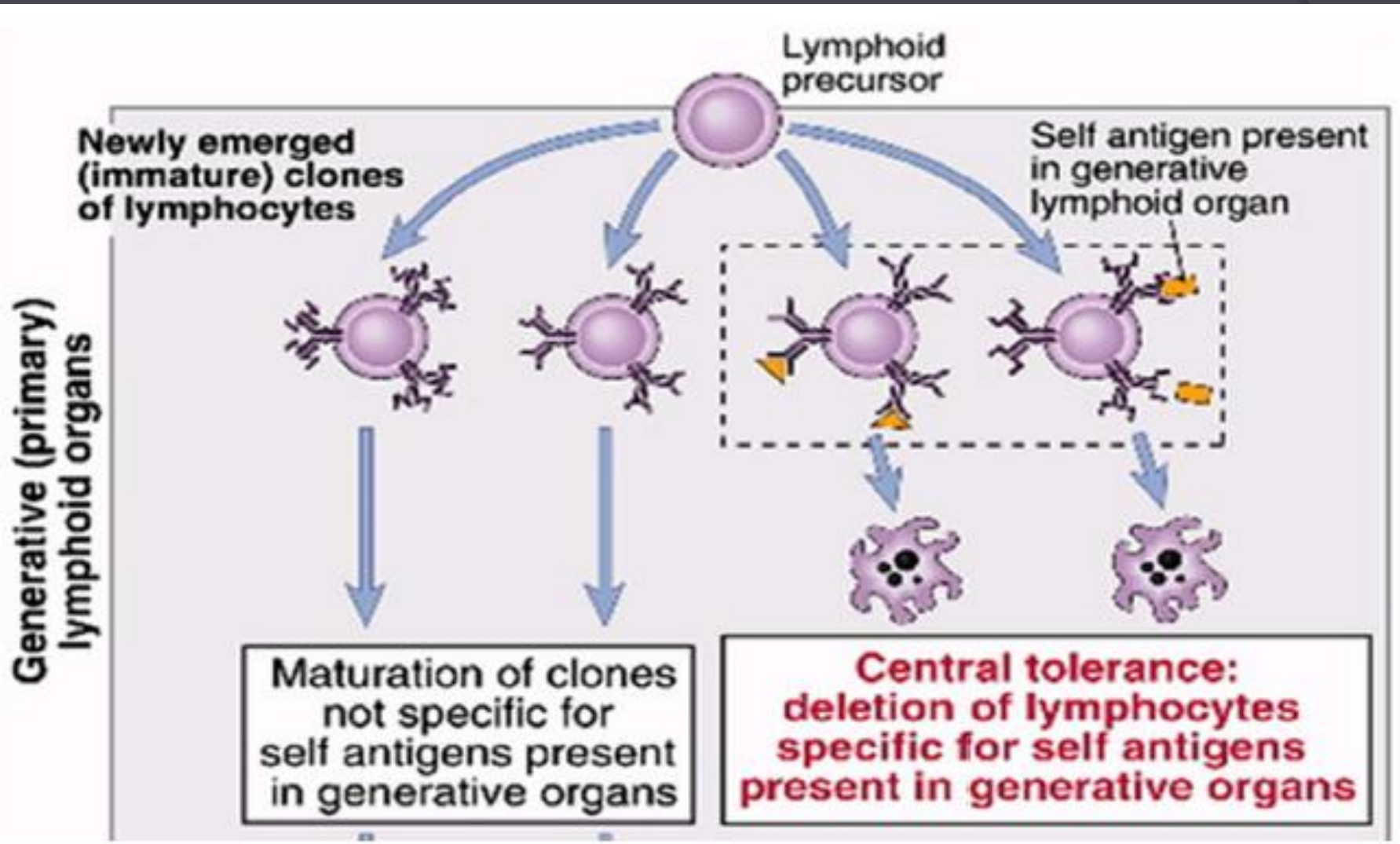
created in the population of T cells within the thymus.

In the thymus, the epitopes recognized by these receptors consist of:

- A small molecule, usually a peptide of 6–8 amino acids derived from body proteins;

that is, "self" proteins nestled in

- A histocompatibility molecule (encoded by the MHC)
  - Class II for $CD4^+$ T cells
  - Class I for $CD8^+$ T cells


Lymphoid precursor
Newly emerged (immature) clones of lymphocytes
Self antigen present in generative lymphoid organ
Generative (primary) lymphoid organs
Maturation of clones not specific for self antigens present in generative organs
Central tolerance: deletion of lymphocytes specific for self antigens present in generative organs

2. Peripheral Tolerance

The T cells that leave the thymus are relatively — but not completely — safe. Some will have receptors (TCRs) that can respond to self antigens

- That are present in such high concentration that they can bind to "weak" receptors;
- That they may not have encountered in the thymus.

Nonetheless, it is clear that there are mechanisms for maintaining T-cell tolerance throughout the body.

Five possibilities for which there is significant evidence

a) Negative Selection in the Peripheral Immune System

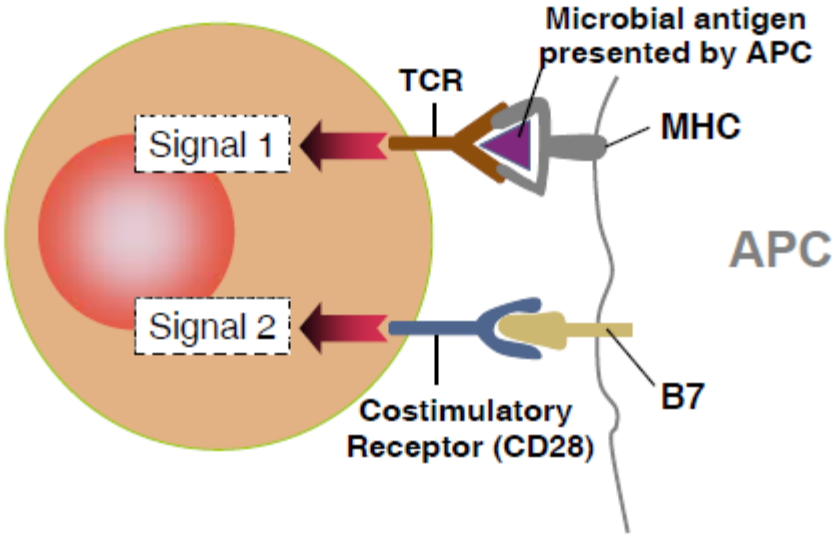
AIRE is also active in some antigen-presenting cells in the organs of the peripheral immune system, e.g., lymph nodes and spleen. So any potentially autoreactive T cells that failed to be eliminated in the thymus can be selected against in these tissues.

b) Lack of Costimulation

- The binding of a T cell to an antigen-presenting cell (APC) is by itself not enough to activate the T cell and turn it into an effector cell.

In order to become activated, the T cell must not only bind to the epitope (MHC-peptide) with its TCR but also receive a second signal from the APC. The receipt of this second signal is called costimulation. Among the most important of these costimulators are molecules on the APC designated B7 and their ligand on the T cell designated CD28. The binding of CD28 to B7 provides the second signal needed to activate the T cell

The two-signal requirement for T cell activation



c) Failure to Encounter Self Antigens

Some tissues are hidden behind anatomical barriers that keep T cells from reaching them.

Examples of such "privileged sites"-

- Interior of the eye
- Testes
- The brain

Mechanical damage can rupture the barrier and an autoimmune attack follow

d) Receipt of Death Signals

Some cells of the body express the Fas ligand, FasL. Activated T cells always express Fas.

When they encounter these cells, binding of Fas to FasL triggers their death by apoptosis.

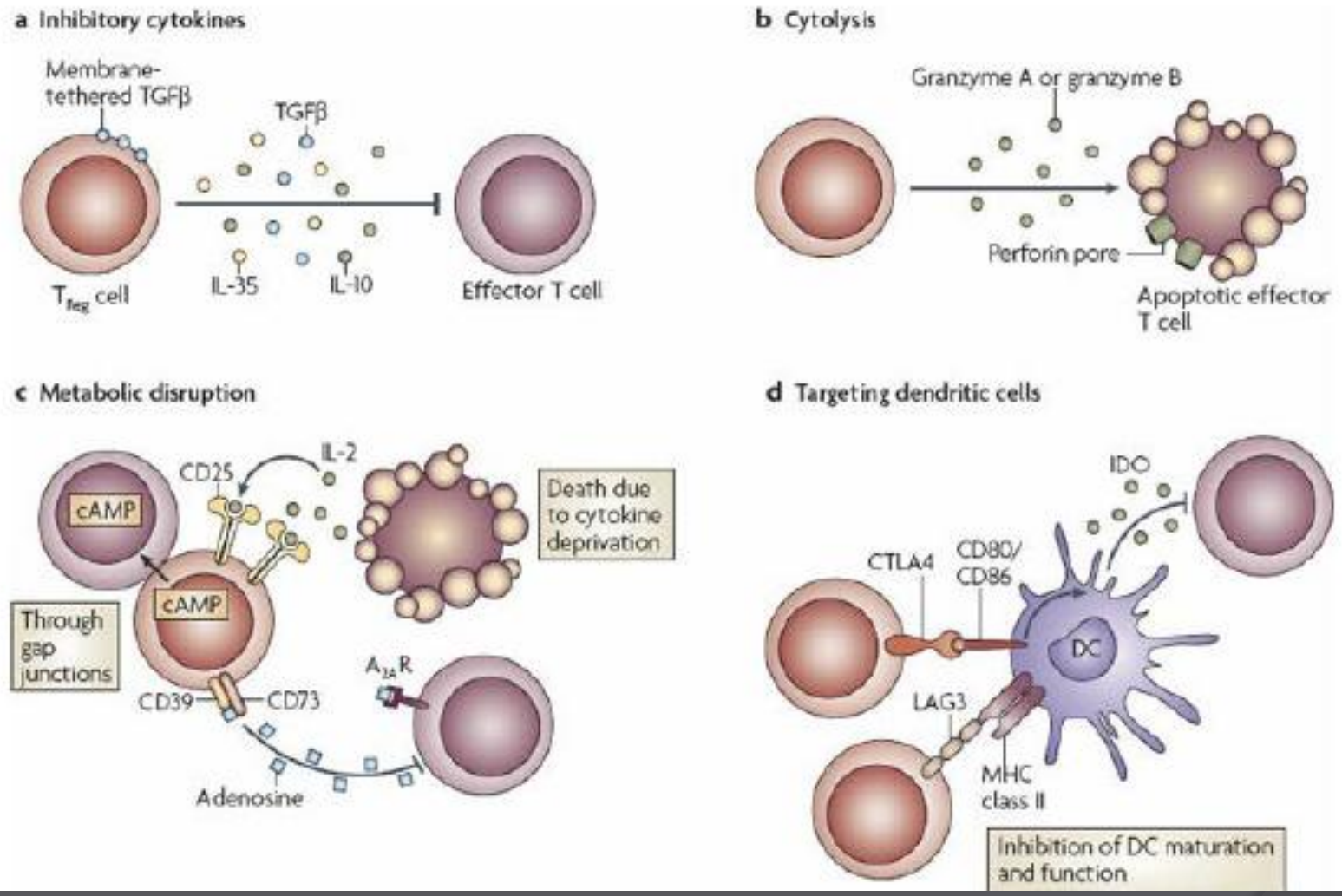
Examples:

- Cells within the eye always express FasL and are thus ready to kill off any rogue T cells that might gain entry.
- Macrophages infected with HIV express FasL and thus kill any anti-HIV T cells that try to kill them. This may account for the disastrous decline in $CD4^+$ T cells late in the development of AIDS.

e) Control by Regulatory T Cells

- A minor population of $CD4^+$ T cells, called regulatory T cells, suppresses the activity of other T cells. They may be important players in protecting the body from attack by its other T cells.

Mechanisms by which Tregs Suppress Immune Responses



B. B-CELL TOLERANCE

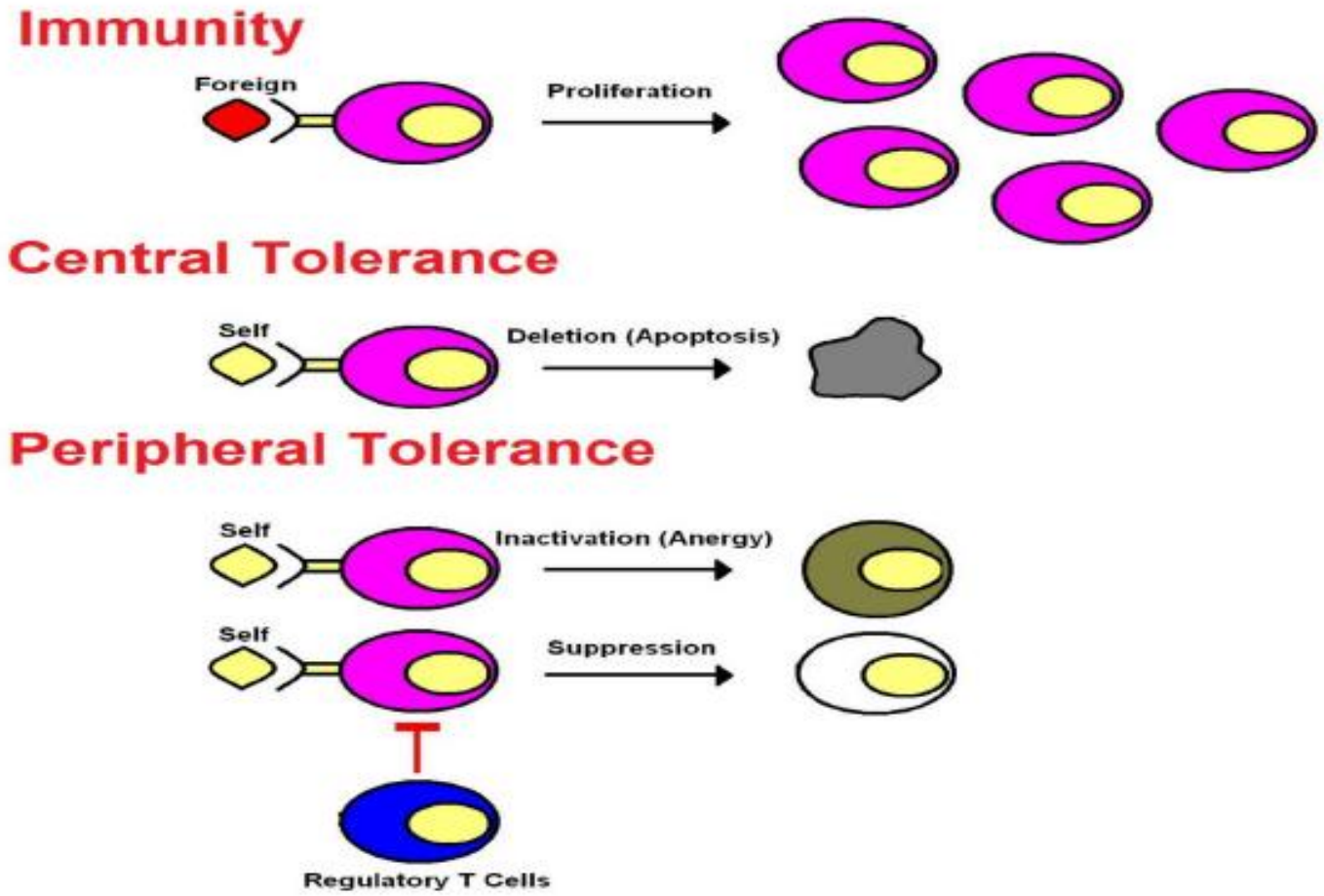
- The problem of B-cell tolerance is not so acute because B cells cannot respond to most antigens unless they receive help from T helper cells.
- Nevertheless, B cells become tolerized to self components and, like T cells, this occurs both

in the bone marrow (central tolerance) and elsewhere in the body (peripheral tolerance)

B cells are formed and mature in the bone marrow. In humans, over half of the developing B cells produce a BCR able to bind self components.

Any cells that produce a receptor for antigen (BCR) that would bind self components too tightly undergo a process of receptor editing. They dip again into their pool of gene segments that encode the light and heavy chains of their BCR and try to make a new BCR that is not a threat. If they fail, they commit suicide (apoptosis).

Despite these mechanisms, some of the B cells that migrate out of the bone marrow continue to express self-reactive BCRs and may still be able to produce anti-self antibodies. So a mechanism is needed to tolerize them out in the tissues ("peripheral tolerance


Immunity
Foreign
Proliferation
Central Tolerance
Self
Deletion (Apoptosis)
Peripheral Tolerance
Self
Inactivation (Anergy)
Self
Suppression
Regulatory T Cells

2. Peripheral Tolerance

- B cells with a potential for attacking self can be kept in check by the absence of the T-helper

cells they need; that is, T-cell tolerance is probably the most important (but not the only) mechanism for maintaining B-cell tolerance

C. INDUCED TOLERANCE

It is an immune tolerance that generating by manipulation of immune system

1. Allergies

Examples:

- The active ingredient in poison ivy that triggers this cell-mediated immune response;
- Allergens that trigger IgE-mediated allergic responses, such as
  - Ragweed, grass, and tree pollens;
  - Insect stings;
  - Food allergens, e.g., peanuts and other nuts

2. Transplant Tolerance

If ways could be found to induce genuine tolerance to allografts (organs transplanted from another person), this would enable the organ to resist rejection without the need for continuous use of immunosuppressive drugs.

In such cases (as well as Billingham's), it may be that tolerance of the graft is

- Created because the priming cells are unable to give a second signal to host T cells and
- Maintained by the continued survival in the recipient of these donor cells.

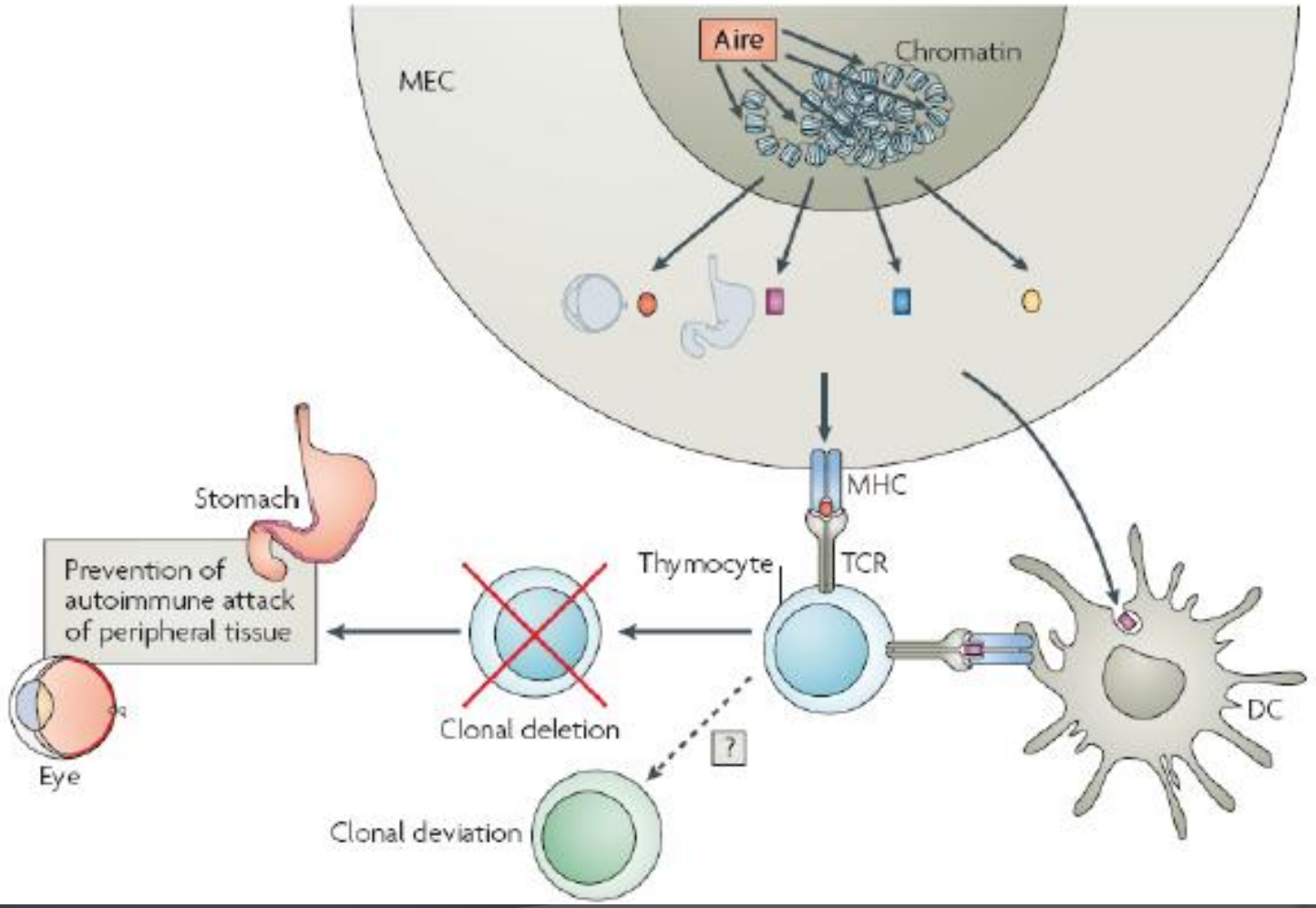
- **3. Tolerance of the Fetus**
- The human fetus is also an allograft, but the mother makes no attempt to reject it (at least for 9 months).

The autoimmune regulator (AIRE)

- is a protein that in humans is encoded by the AIRE gene. AIRE is a transcription factor expressed in the medulla (inner part) of the thymus. It is part of the mechanism which eliminates self-reactive T cells that would cause autoimmune disease. It exposes T cells to normal, healthy proteins from all parts of the body, and T cells that react to those proteins are destroyed.

AIRE Promotes Expression of Peripheral Tissue Antigens in the Thymus, Deleting/Deviating High Affinity Autoreactive T cells

(Mathis and Benoist 2007)



- In the thymus, the AIRE causes transcription of a wide selection of organ-specific genes that create proteins that are usually only expressed in peripheral tissues, creating an "immunological self-shadow" in the thymus It is important that self-reactive T cells that bind strongly to self-antigen are eliminated in the thymus (via the process of negative selection), otherwise they may later encounter and bind to their corresponding self-antigens and initiate an autoimmune reaction.
- So the expression of non-local proteins by AIRE in the thymus reduces the threat of autoimmunity by promoting the elimination of auto-reactive T cells that bind antigens not normally found in the thymus. Furthermore, it has been found that AIRE is expressed in a population of stromal cells located in secondary lymphoid tissues, however these cells appear to express a distinct set of TRAs compared to mTECs

AIRE Mutations are Associated with Autoimmune Polyendocrine Syndrome Type 1

(Kampe et al 2008)

Table 1. Associations between Clinical Manifestations of Autoimmune Polyendocrine Syndrome Type 1 (APS-1) and the Presence of NACHT Leucine-Rich-Repeat Protein 5 (NALP5) Autoantibodies.*

Manifestation	APS-1	APS-1 and NALP5 Autoantibodies		P Value
		With Manifestation	Without Manifestation	
		number/total number (percent)		
Hypoparathyroidism	73/87 (84)	36/73 (49)	0/14	<0.001
Hypogonadism	28/87 (32)	19/28 (68)	17/59 (29)	<0.001
Adrenal insufficiency	69/87 (79)	29/69 (42)	7/18 (39)	0.81
Type 1 diabetes mellitus	11/87 (13)	2/11 (18)	34/76 (45)	0.10
Vitiligo	17/87 (20)	7/17 (41)	29/70 (41)	0.99
Alopecia	30/87 (34)	11/30 (37)	25/57 (44)	0.52
Hepatitis	15/87 (17)	8/15 (53)	28/72 (39)	0.31
Malabsorption	22/87 (25)	10/22 (45)	26/65 (40)	0.66
Pernicious anemia	14/87 (16)	5/14 (36)	31/73 (42)	0.64
Candidiasis	83/87 (95)	34/83 (41)	2/4 (50)	0.72

Factors Determining the Induction, Duration and Extent of Tolerance:

- Competence of the immune system: Tolerance induction is easier in animals with an immature immune system or with a mature immune system that has been compromised by irradiation, drugs or thoracic drug drainage
- Molecular characteristics of the antigen: The size of the antigen is particularly important for molecules that form aggregates and for antigens that exist in monomeric and polymeric forms.

- Route of antigen administration: The introduction route is a key variable in tolerance induction, particularly in adult animals, presumably by determining the accessibility of the antigen to professional cells

- Genetic susceptibility: Induction of tolerance is sometimes difficult in some inbred strains of mice. For example, unlike most strains, BALB/c mice are relatively

resistant to tolerance induction by xenogeneic g-globulin and this resistance segregates among the offspring. It is thus genetically controlled.

- 6. Completeness of tolerance: Immune recognition of a given molecule involves several clones specific for different epitopes and exhibiting different affinities.

As the affinity of the interaction plays a critical role in determining tolerance induction, only some of the clones may be tolerized