Immunopathology
2025’

BALANCE BETWEEN TARGETING TYPE (AUTO)IMMUNE RESPONSE AND IMMUNOLOGICAL TOLERANCE

Nobel prize 2025

for regulatory T cells

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ANTIGEN

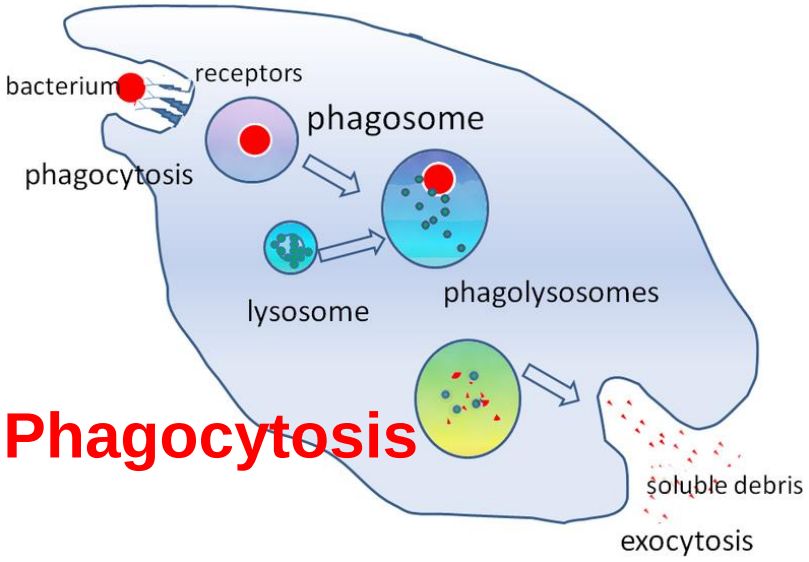
Targeting type immune response

or

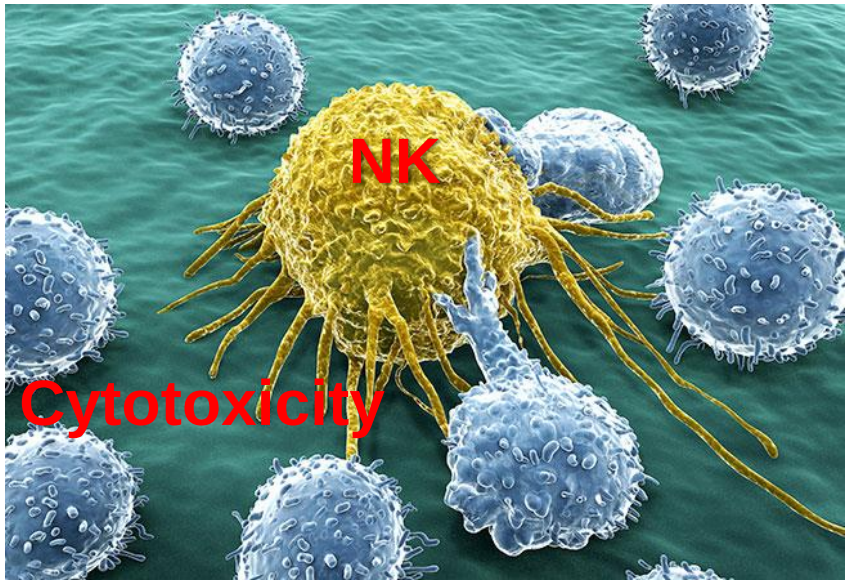
Tolerance

The immune system makes a permanent decision about whether to target or tolerate an antigen. The nature and occurrence of the antigen, as well as the status of the immune system, influence the type of response.

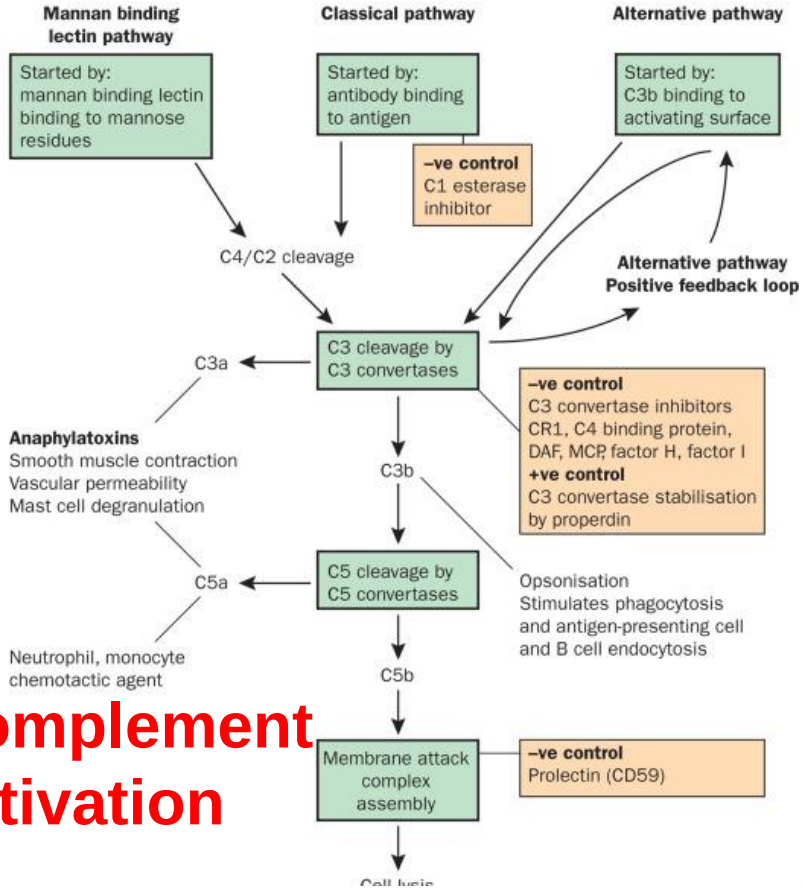
Innate effector mechanisms



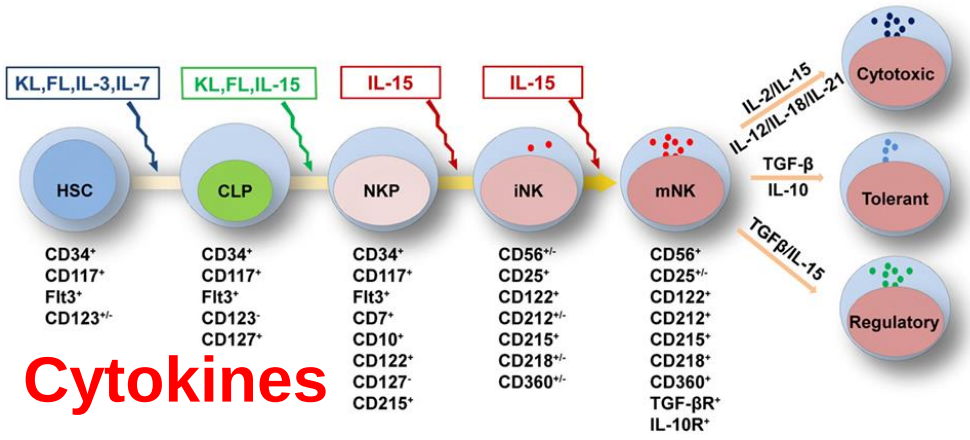
Phagocytosis



Cytotoxicity



Complement activation



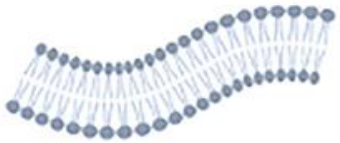
Cytokines

INNATE IMMUNITY

Agents involved:

i) The first line of defense:

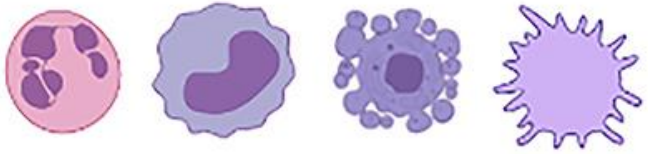
skin



mucus membrane

ii) The second line of defense:

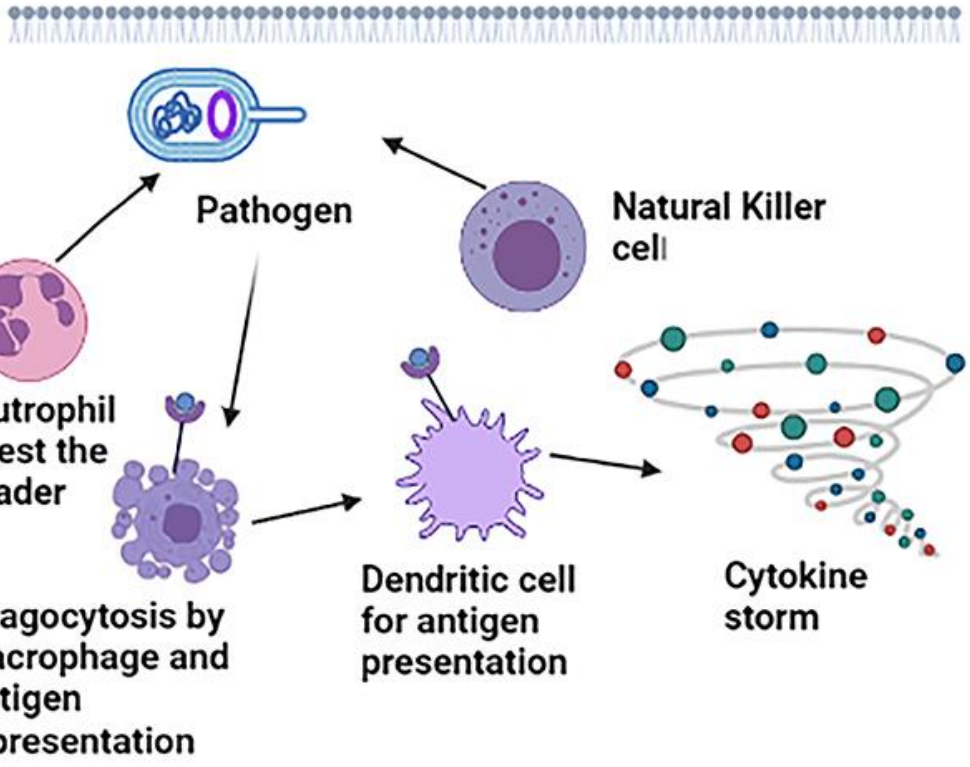
Mast cell eosinophil basophil;



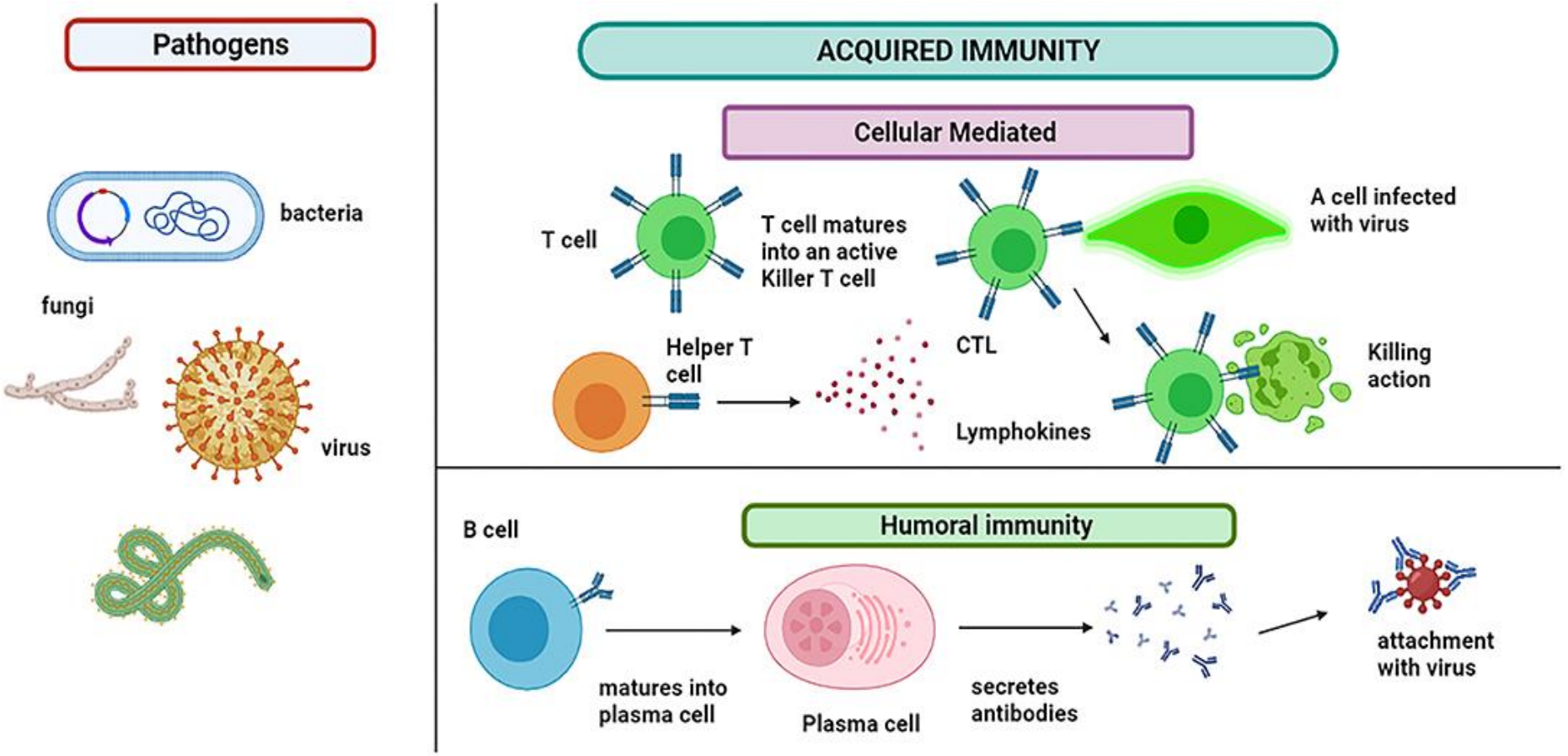
neutrophil monocyte macrophage DC cell

Mechanism

PAMP's/PRR



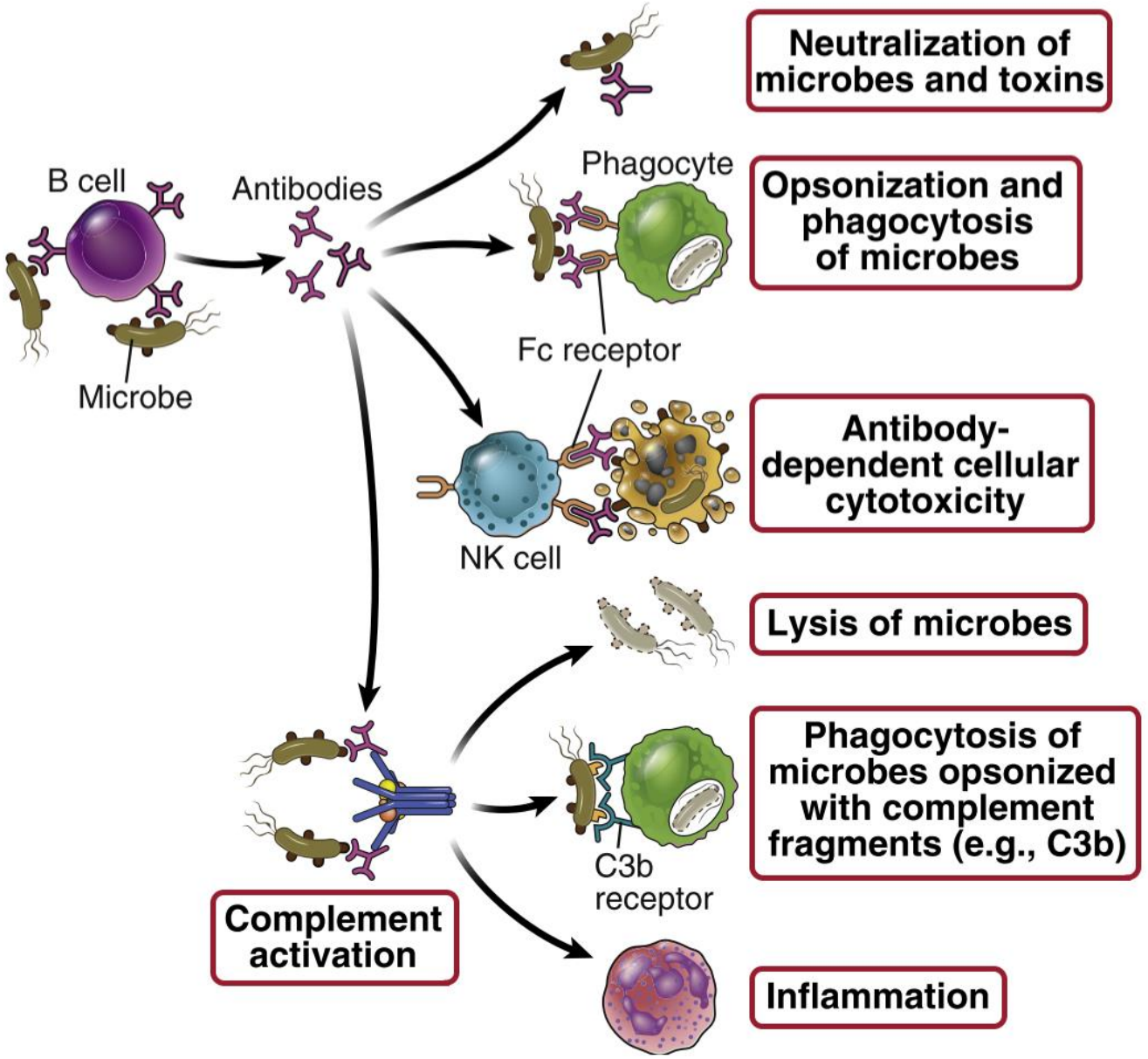
Adaptive immune reactivity



Adaptive effector functions

- Immunoglobulin mediated
  - Neutralisation
  - Opsonisation
  - Complement fixation
  - ADCC
- Cell mediated
  - Direct cytotoxicity
  - Cytokine mediated cytotoxicity

Antibody mediated effector functions



Cell mediated immune response

Direct cytototxicity	DTH
Effector cells with direct cytotoxic activity: • CTL (CD8+ Tc) • γ/δ T cell • NK cell • Macrophages	**Effector cells** with cytokine production: • Th1 cells (T_{DTH} cells) • Activated macrophages
Target cell (cytosolic antigen):	**Antigen in phagolysosoma**
• Allogenic cells (tissue/cell transplantation, minor histocompatibility antigens) • Virally infected cells • Mutated cells • Malignant tumor cells • Chemically modified cells	• Intracellular bacterium, virus, fungi, parasite • Contact antigen (small molecules – hapten – in skin protein complexes)

Tolerated skin grafts on MHC (H2) identical mice

Rupert E. Billingham

- The phenomenon of **immune tolerance** was first described by **Ray D. Owen in 1945**, who noted that dizygotic twin cattle sharing a common placenta also shared a stable mixture of each other's red blood cells, and retained that mixture throughout life. This observation was experimentally validated by Leslie Brent, Rupert E. Billingham and Peter Medawar in 1953, who showed by injecting foreign cells into fetal or neonatal mice, they could become accepting of future grafts from the same foreign donor.
- The theories of immune tolerance formulated by Sir Frank McFarlane Burnet and Frank Fenner, who were the first to propose the deletion of self-reactive lymphocytes to establish tolerance, now termed clonal deletion.
- **Burnet and Medawar** were ultimately credited for "the discovery of acquired immune tolerance" and shared the Nobel Prize in Physiology or Medicine in 1960**.**

Autoreactivity/Autoimmunity

- **Paul Ehrlich**'s dictum (1900) of *horror autotoxicus* inhibited acceptance of the reality of autoimmune disease.
- The first autoantibodies were discovered in the 1940s, when antinuclear antibodies and rheumatoid factors were described as serum factors that could bind nuclear antigens and immunoglobulins, respectively.
- The discoveries of allergy and anaphylaxis were the first signs that the immune system was capable of self-damage. The studies on chronic thyroiditis and clinical laboratory breakthroughs led to the acceptance of autoimmune disease in the 1950s.
- Autoimmunity was accepted as a pathologic phenomena, however, existence of self-reactive autoantibodies were find in healthy individuals

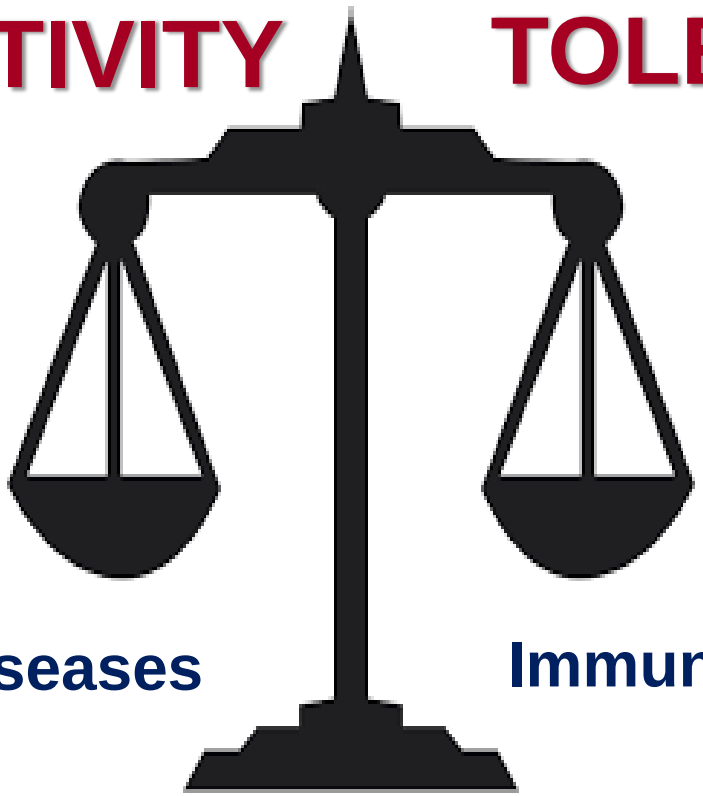
However, the natural immune system…

- **Irun Cohen** (1992) proposed revising the clonal selection theory and replacing it with the **cognitive paradigm**, there were already a lot of data on natural autoimmunity. The presence of autoantibodies (nAAb) in the blood serum of healthy individuals without clinical symptoms of autoimmune diseases has long been known about.
- Subsets of cellular immunity as some T cell subpopulations with invariant T cell receptor chains, the gamma–delta (γδ) T, invariant natural killer T cells (iNKT), and mucosa associated invariant T cells (MAIT) together with the nAAb network and nAAb-producing B1 cells and their role in immune have been described.
- Today is accepted that cellular and humoral components of natural immune system play basic role in regulation of both tolerating and targeting type immune response.

TOLERANCE & AUTOREACTIVITY

- Upon encountering an antigen, the immune system **can either develop a targeting type immune response or a tolerance**.
- Immunological tolerance is thus the lack of ability to develop a targeting type immune response to epitopes to which an individual has the potential to respond.
- Targeting type and tolerating type immune responses composed by the same cellular and molecular components, the differences are in the effector phase only.

AUTOREACTIVITY **TOLERANCE**



Autoimmune diseases **Immunodeficiency**

Targeting type immune response or tolerance needs to be carefully regulated since an inappropriate response – whether it be autoimmune reaction to self-antigens or tolerance to a potential pathogen – can have serious and possibly life-threatening consequences.

Immune tolerance can result from a number of causes including:

- No direct contact with the antigen;
- Prior contact with the same antigen in fetal life or in the newborn period when the immune system is not yet mature;
- Prior contact with the antigen in extremely high or low doses;
- Exposure to radiation, chemotherapy drugs, or other agents that impair the immune system;
- Heritable diseases of the immune system;
- Acquired diseases of the immune system such as HIV/AIDS.

TOLERNACE

- PASSIVE
- ACTIVE

AUTOIMMUNITY

- PHYSIOLOGIC REGULATION
- AUTOIMMUNE DISEASES

Types of immune tolerance

- **Tolerance induced by the nature of the antigen**
- **Tolerance induced by the body**
- **Passive** (unresponsive) **tolerance**: no MHC recognition or inhibited cellular differentiation

Tolerance induced by the nature of the antigen

- chemical nature
- dose of the antigen
  - **low dose tolerance** (mainly T cell mediated, long ranging)
  - **high dose tolerance** (mainly B cell mediated, short ranging)
- mode of the administration

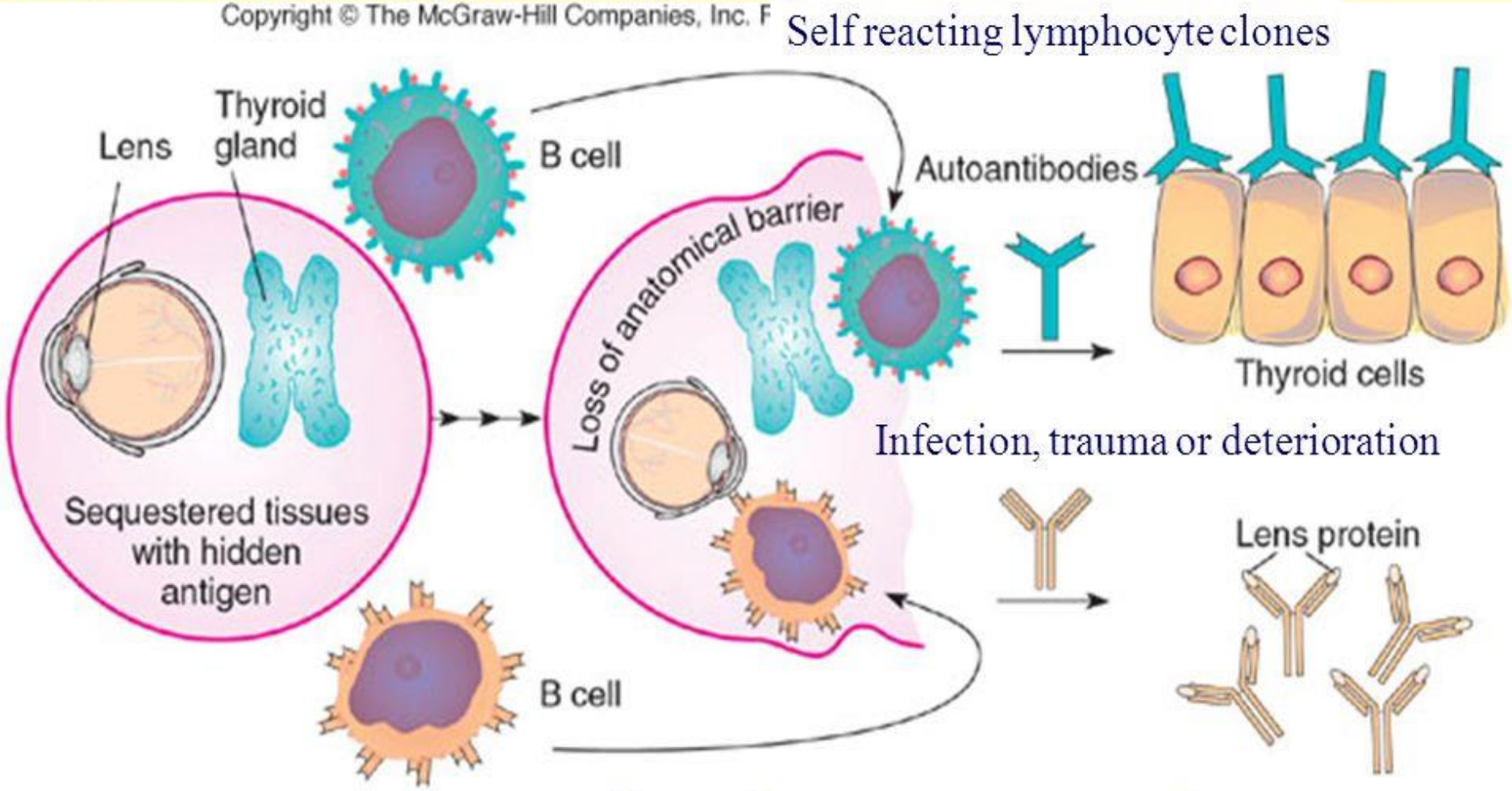
Passive tolerance induced by the body

- **sequestered antigens**
  - no MHC recognition
  - no antigen presentation
  - no systemic response

- **heredited or acquired immunodeficiencies**

Sequestered Antigen Theory

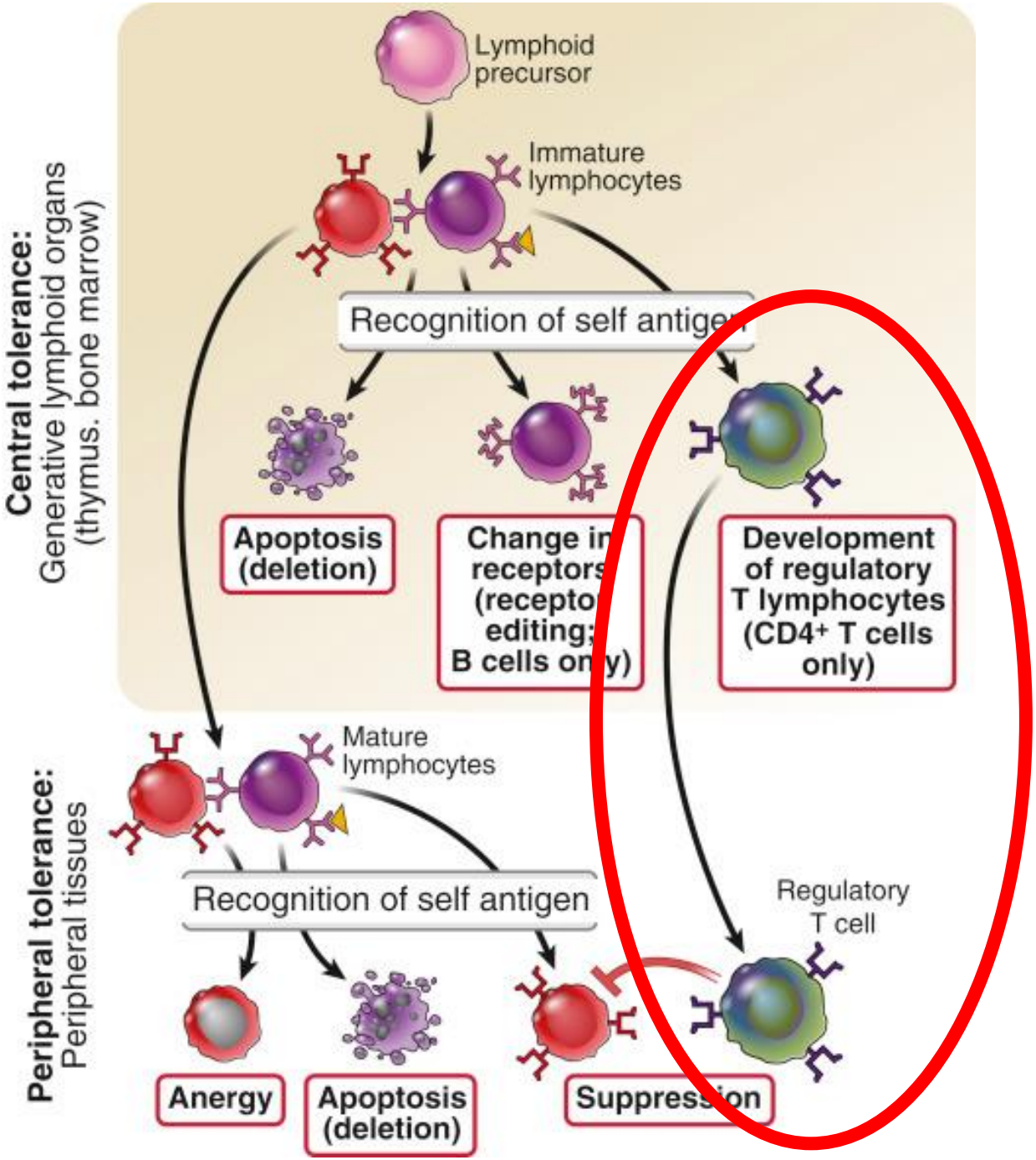
Sequestered behind anatomical barriers

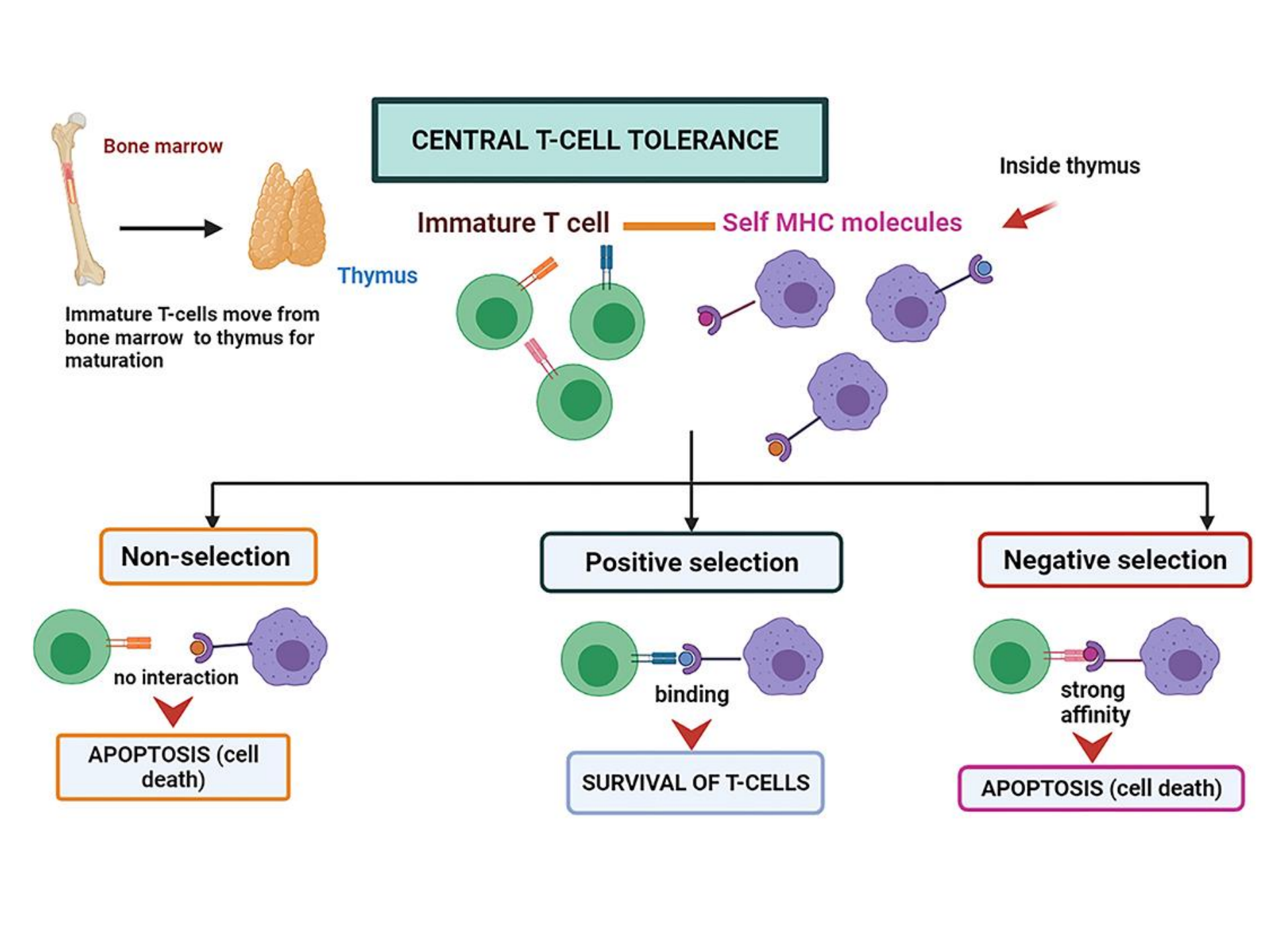


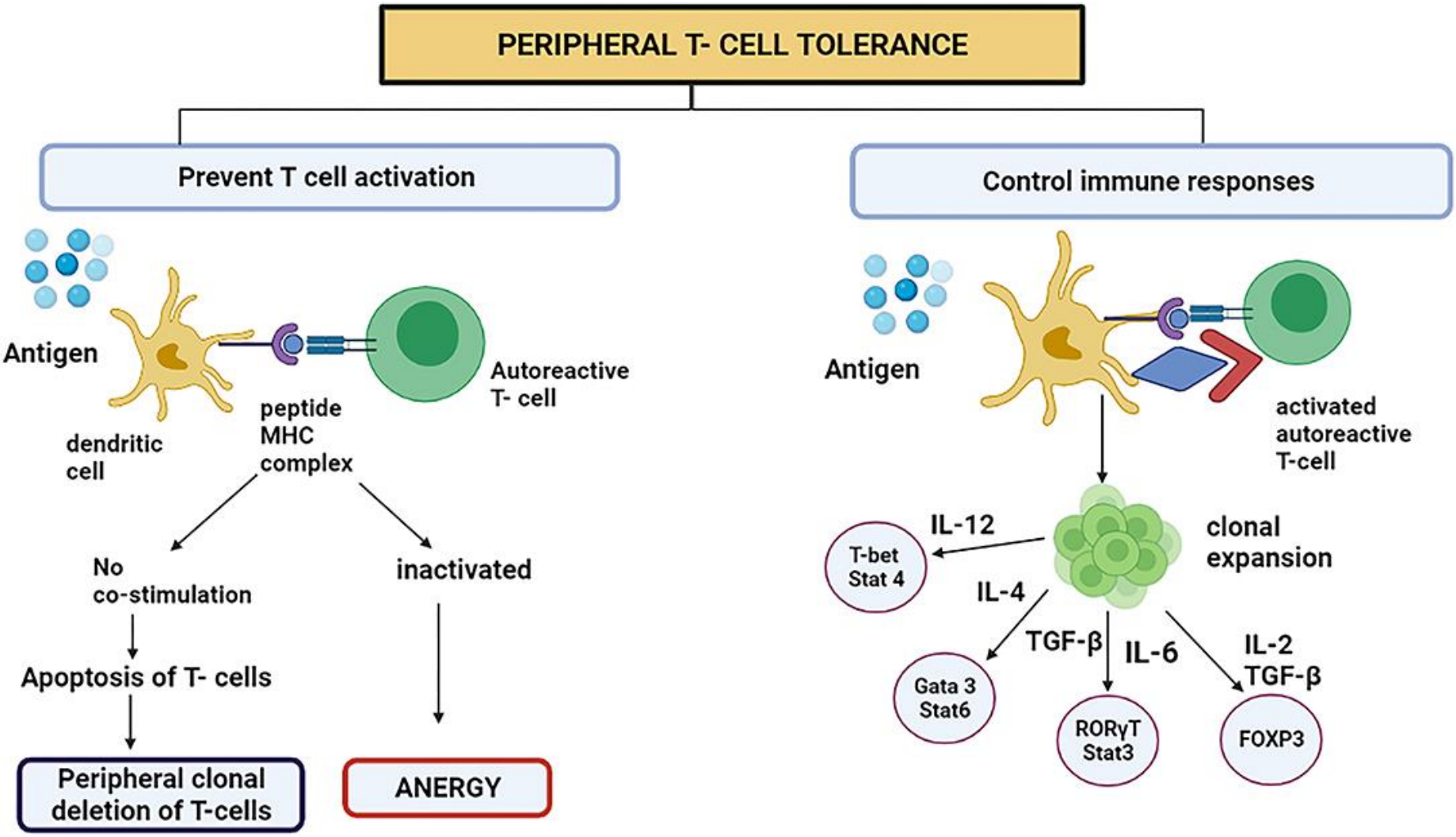
(a) **Sequestered Antigen Theory**

Some tissues are not scanned by the immune system during embryonic growth.

CNS, lens, thyroid & testes


Central tolerance:
Generative lymphoid organs
(thymus. bone marrow)
Lymphoid precursor
Immature lymphocytes
Recognition of self antigen
Apoptosis (deletion)
Change in receptors (recepto editing; B cells on y)
Development of regulatory T lymphocytes (CD4+ T cells only)
Peripheral tolerance:
Peripheral tissues
Mature lymphocytes
Recognition of self antigen
Regulatory T cell
Anergy
Apoptosis (deletion)
Suppression

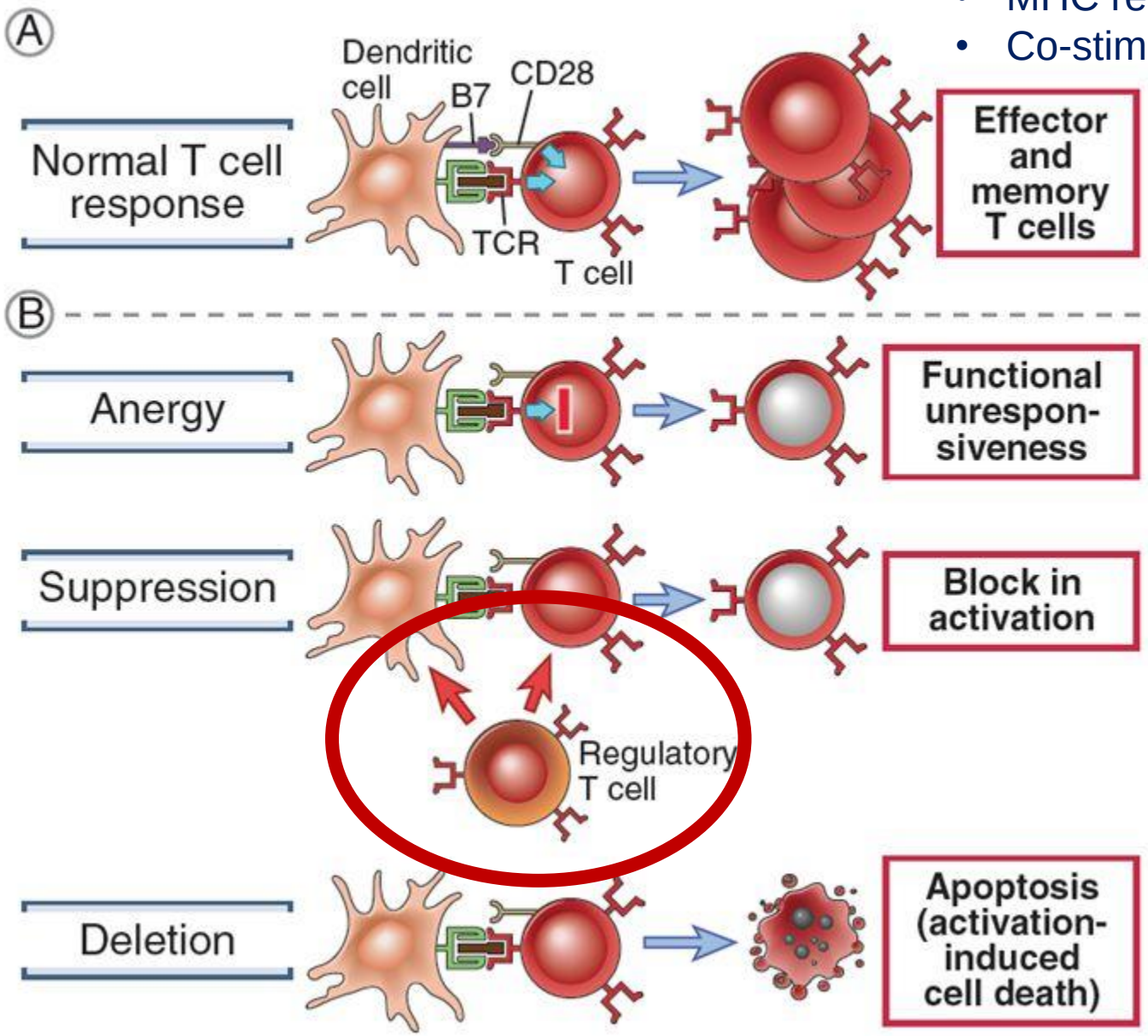

CENTRAL T-CELL TOLERANCE
Bone marrow
Thymus
Immature T-cells move from bone marrow to thymus for maturation
Inside thymus
Immature T cell
Self MHC molecules
Non-selection
no interaction
APOPTOSIS (cell death)
Positive selection
binding
SURVIVAL OF T-CELLS
Negative selection
strong affinity
APOPTOSIS (cell death)



Peripheral T cell tolerance prevents T cell activation or controls the immune responses by switching on certain signaling pathways. However, to present T cell activation, the DC representing antigen either attaches to autoreactive T cell or starts apoptosis because the stimulatory component was absent on DC. This is called peripheral clonal deletion of T cells. If the T cell is inactivated, the process is called anergy.

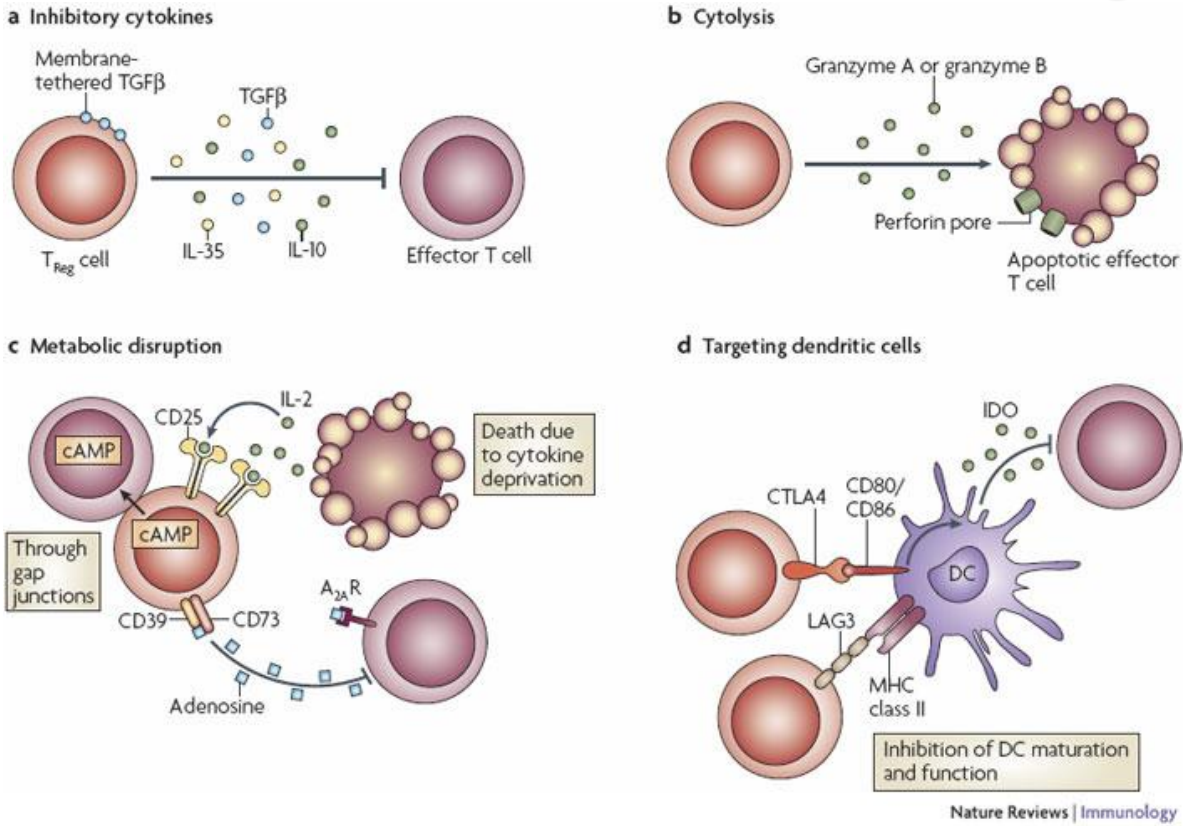
Peripheral tolerance

- Antigen recognition
- MHC restriction
- Co-stimulation



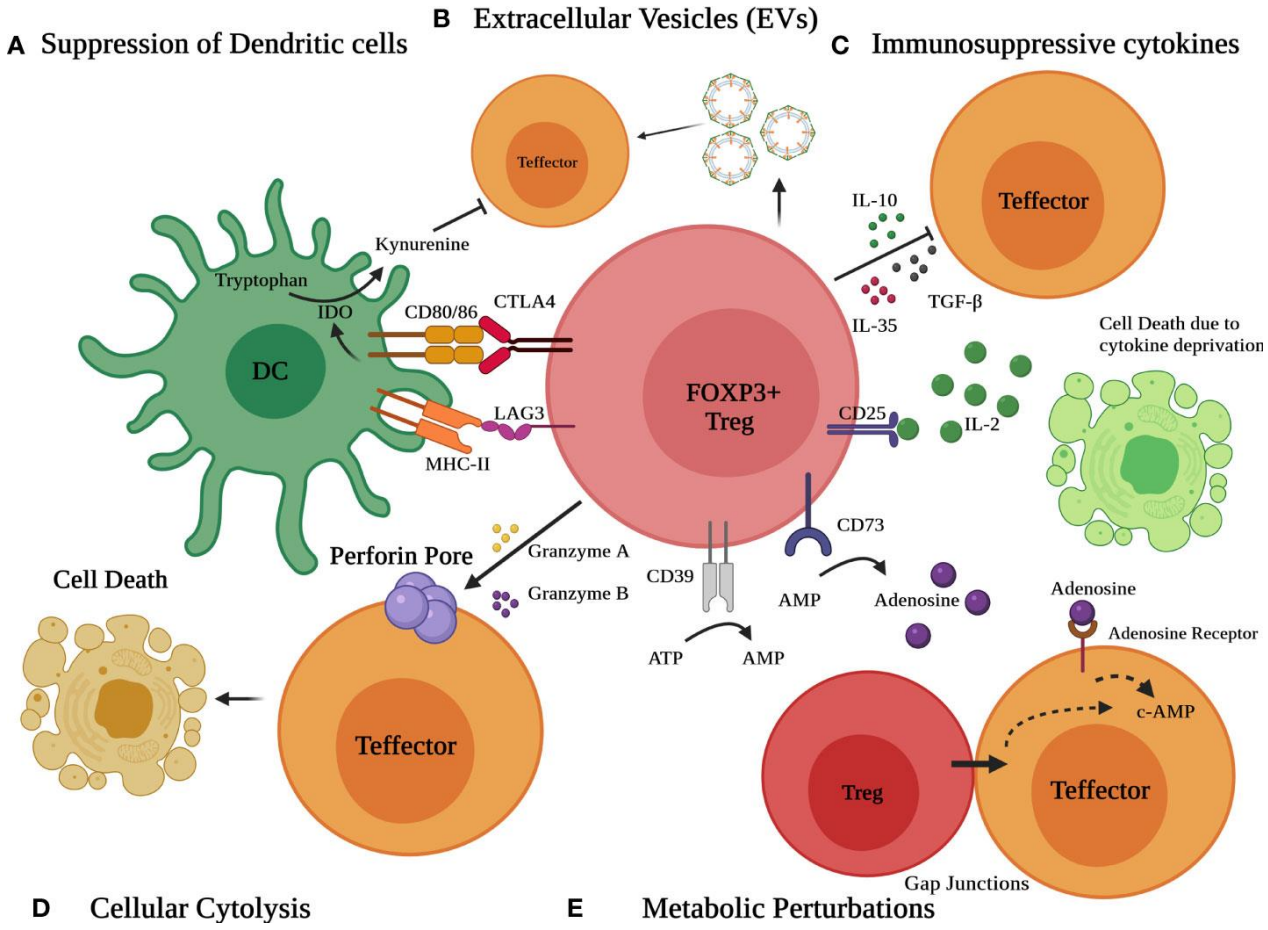
No co-stimulation

Basic mechanisms used by T_{Reg}



a.) Inhibitory cytokines include IL-10, IL-35 and TGFβ. **b.)** Cytolysis includes granzyme-A- and granzyme-B-dependent and perforin-dependent killing mechanisms. **c.)** Metabolic disruption includes high-affinity CD25 (IL-2 receptor)-dependent cytokine-deprivation-mediated apoptosis, cAMP-mediated inhibition, and CD39- and/or CD73-generated adenosine receptor 2A-mediated immunosuppression. **d.)** Targeting dendritic cells (DCs) includes mechanisms that modulate DC maturation and/or function such as lymphocyte-activation gene 3 (LAG3; also known as CD223)–MHC-class-II-mediated suppression of DC maturation, and cytotoxic T-lymphocyte antigen-4 (CTLA4)–CD80/CD86-mediated induction of indoleamine 2,3-dioxygenase (IDO), which is an immunosuppressive molecule made by DCs.

Actions of Treg cells



(A) suppression of dendritic cells (DCs) to modulate their maturation and function *via* CTLA4 and LAG3 **(B)** release of extracellular vesicles (EVs) **(C)** secretion of suppressive immuno-regulatory cytokines such as TGF-β, IL-10, and IL-35 **(D)** Granzyme/perforin mediated cellular cytolysis and **(E)** metabolic perturbations involving CD25 dependent cytokine deprivation, generation of adenosine by ectoenzymes CD39 and CD73 and c-AMP mediated inhibition.

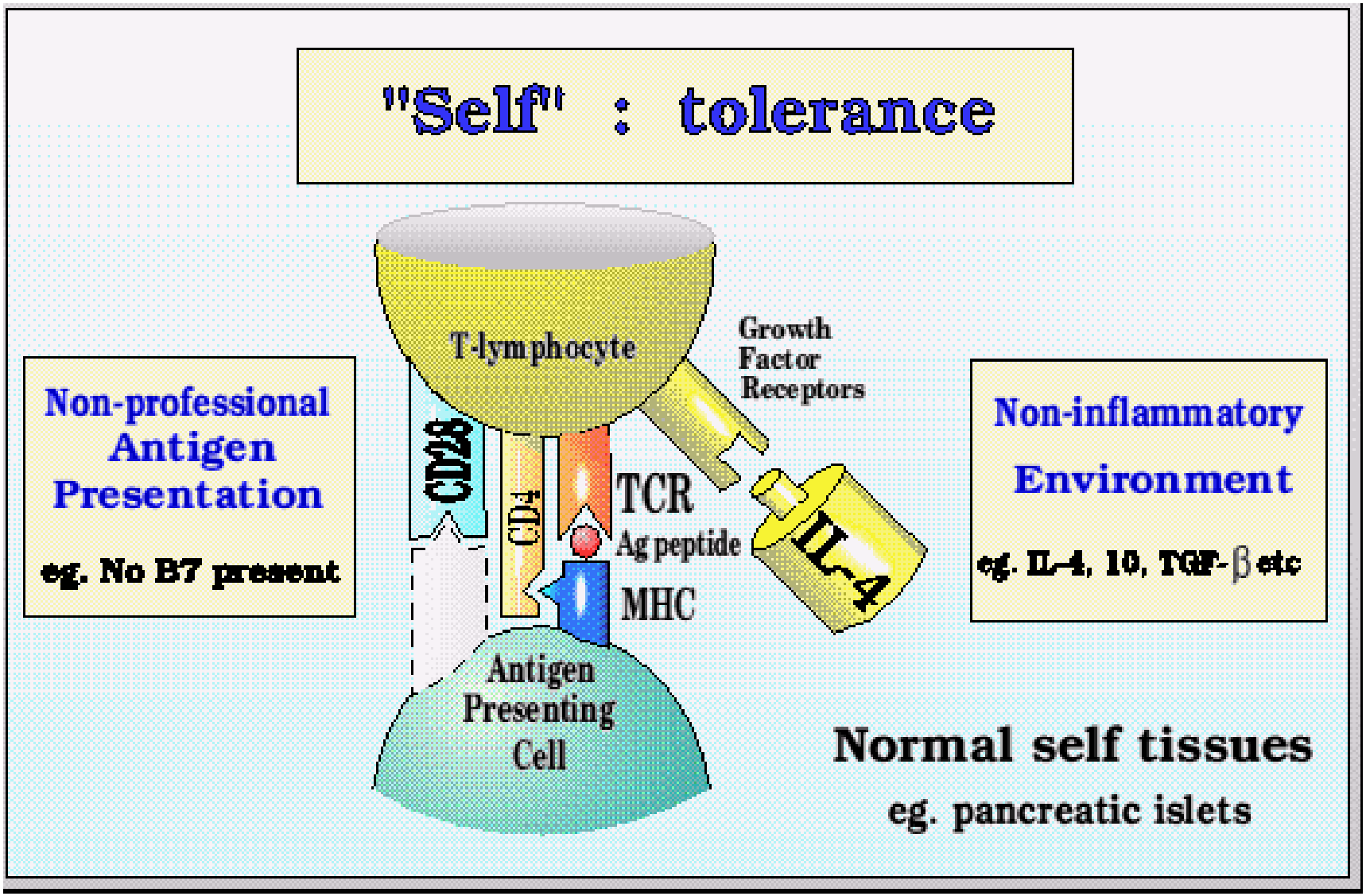
- **FOXP3** (forkhead box P3), also known as **scurfin**, is involved in the development and function of regulatory T cells.
- FOXP3 transcription factor occupies the promoters for genes involved in Treg cell function, and may inhibit transcription of key genes following stimulation of T cell receptors
- Treg cells generally turn the immune response down. In cancer can prevent the immune system from destroying cancer cells.
- In autoimmune disease, a deficiency of Treg cell activity can allow other autoimmune cells to attack the body's own tissues.
- The use of Treg cells in therapy may be risky, as the T regulatory cell transferred to proinflammatory Th17 cells.

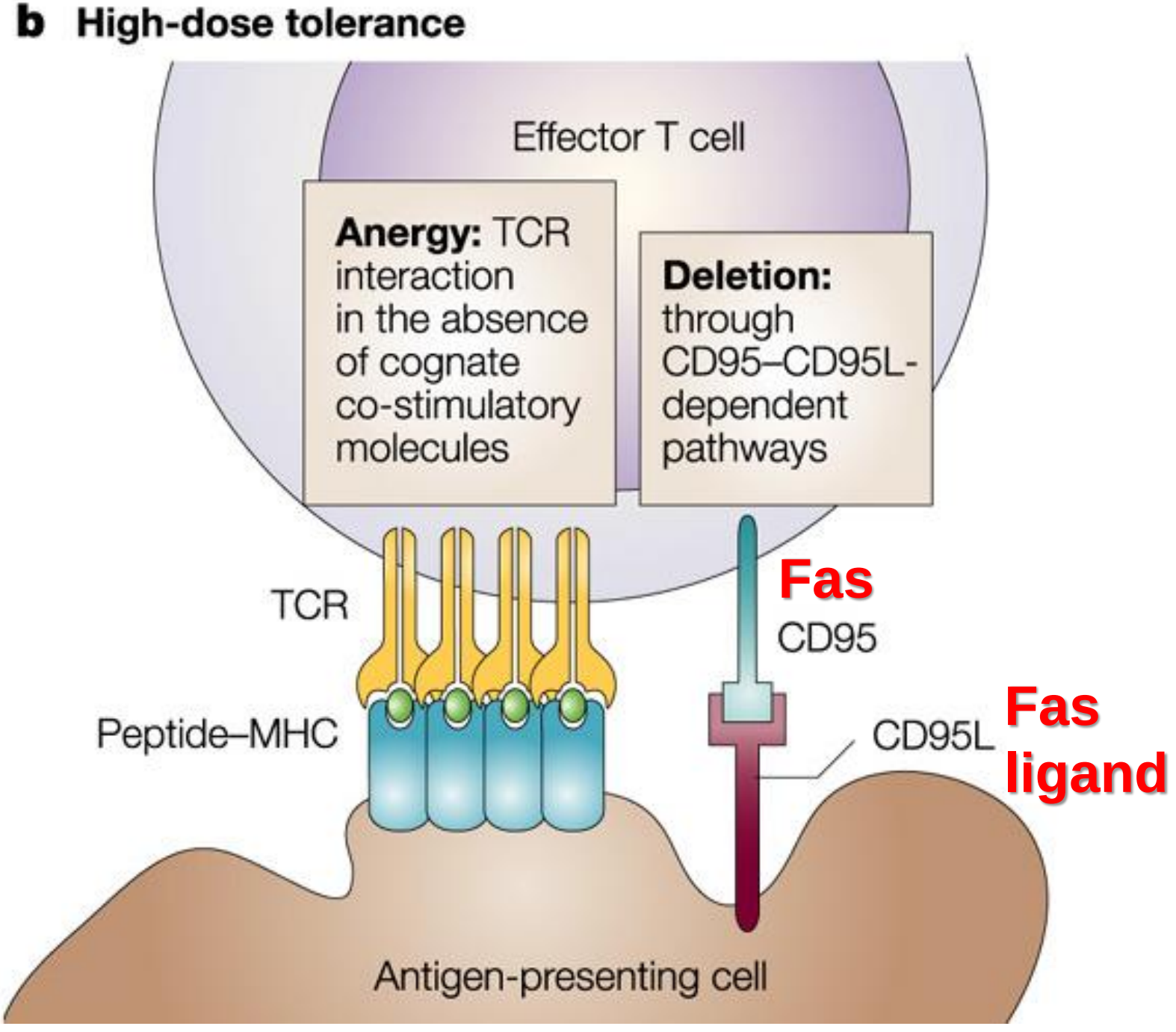
T-cell tolerance

- Central Tolerance (selection in the Thymus)

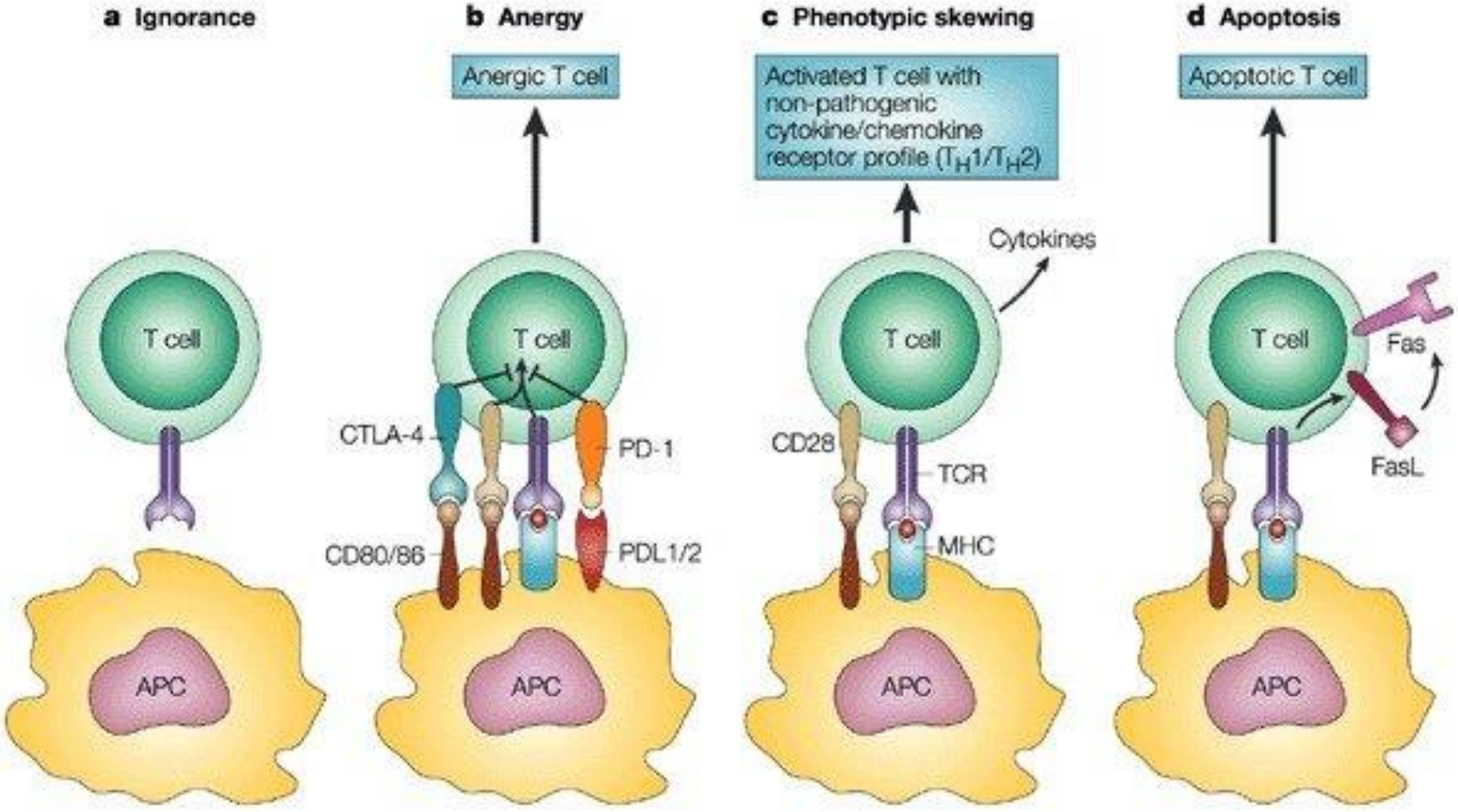
- Peripheral Tolerance
  - Lack of Co-stimulation
  - Failure to Encounter Self Antigens
  - Control by Regulatory T cells
  - Receipt of Death Signal

Failed co-stimulation results low dose tolerance

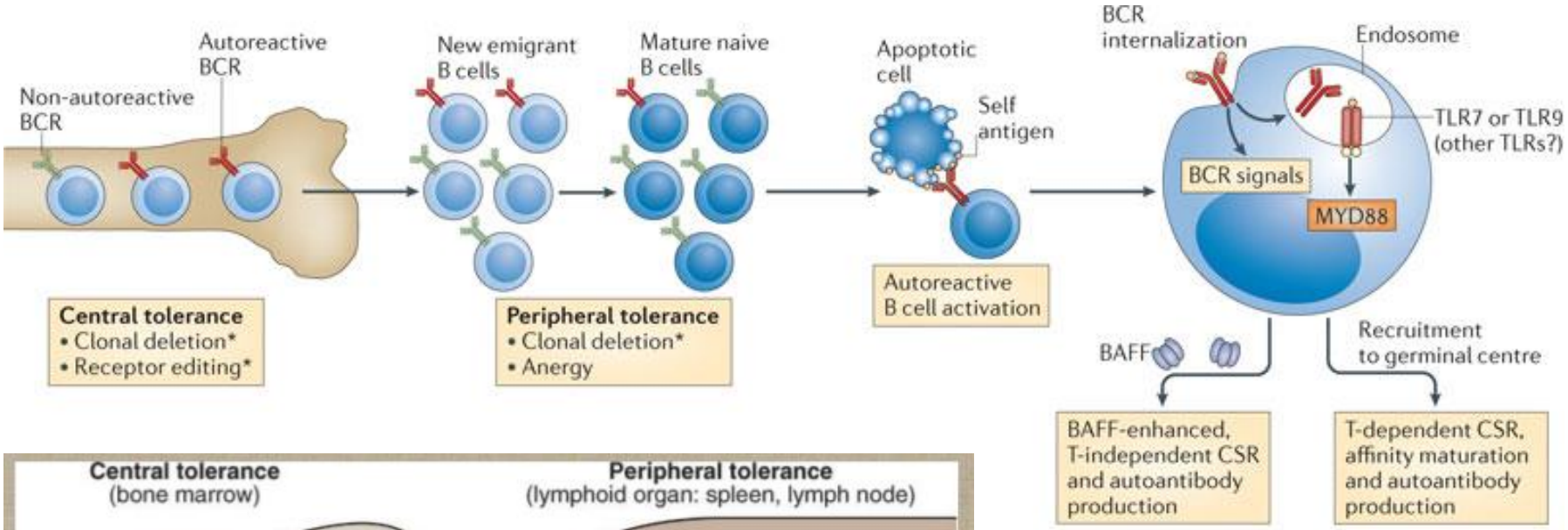



b High-dose tolerance
Effector T cell
Anergy: TCR interaction in the absence of cognate co-stimulatory molecules
Deletion: through CD95–CD95L-dependent pathways
TCR
Peptide–MHC
Fas
CD95
CD95L
Fas ligand
Antigen-presenting cell

Peripheral T cell tolerance

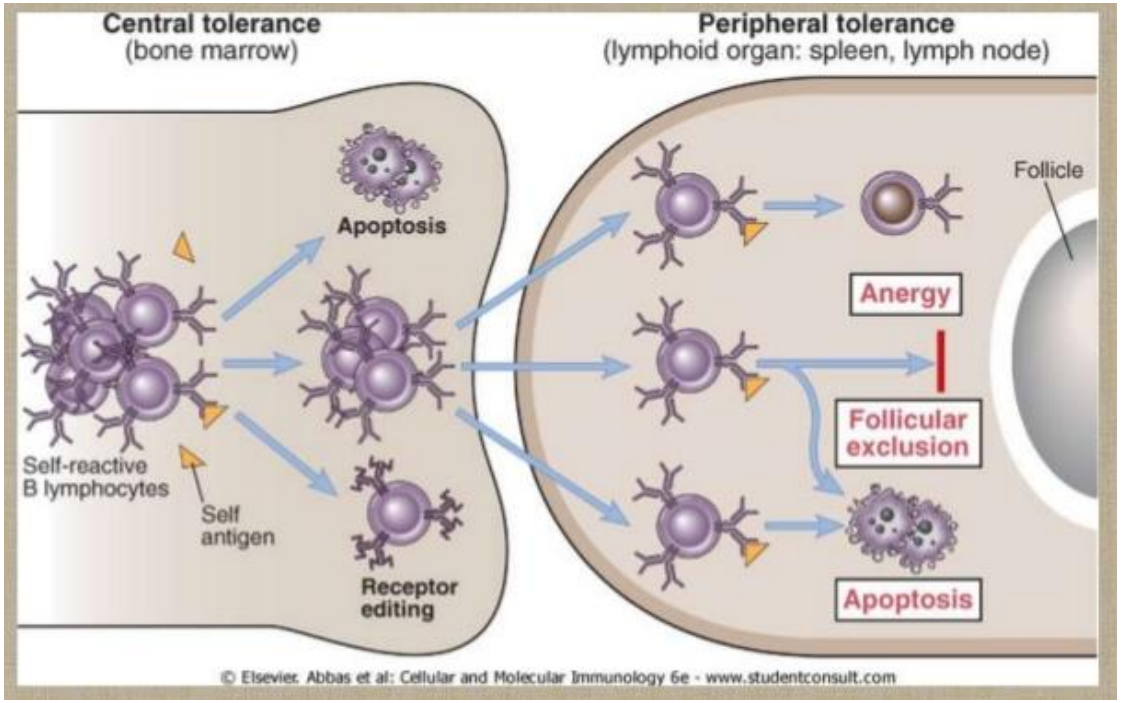


B cell toerance

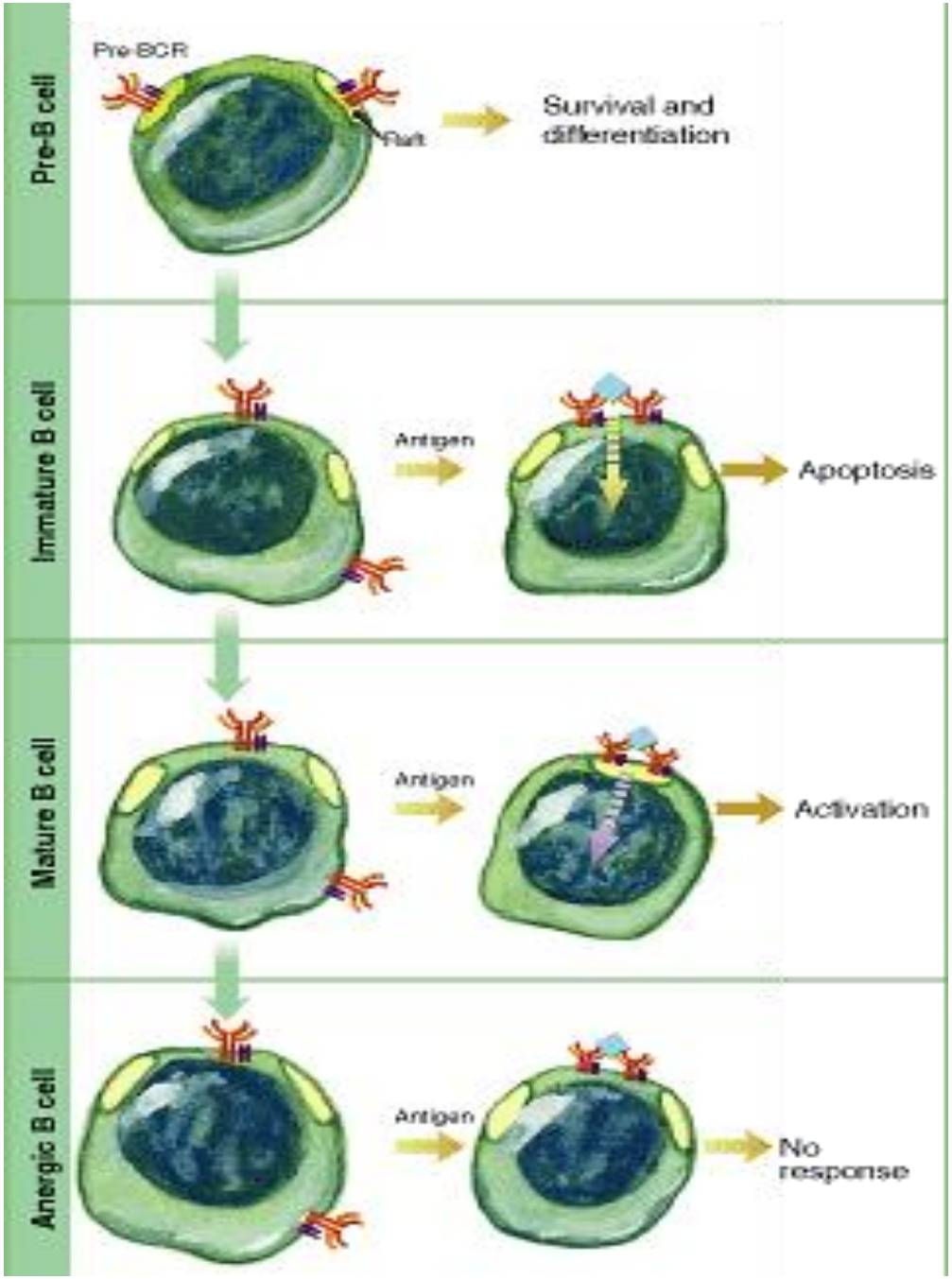


AUTOIMMUNITY

Nature Reviews | Immunology



TOLERANCE

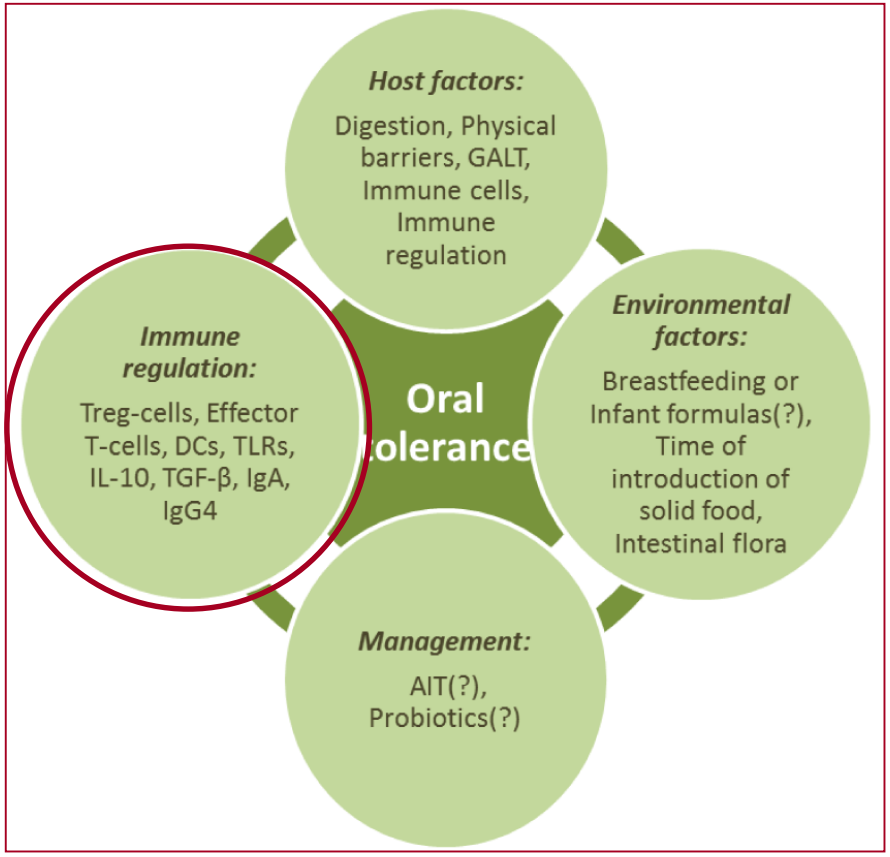


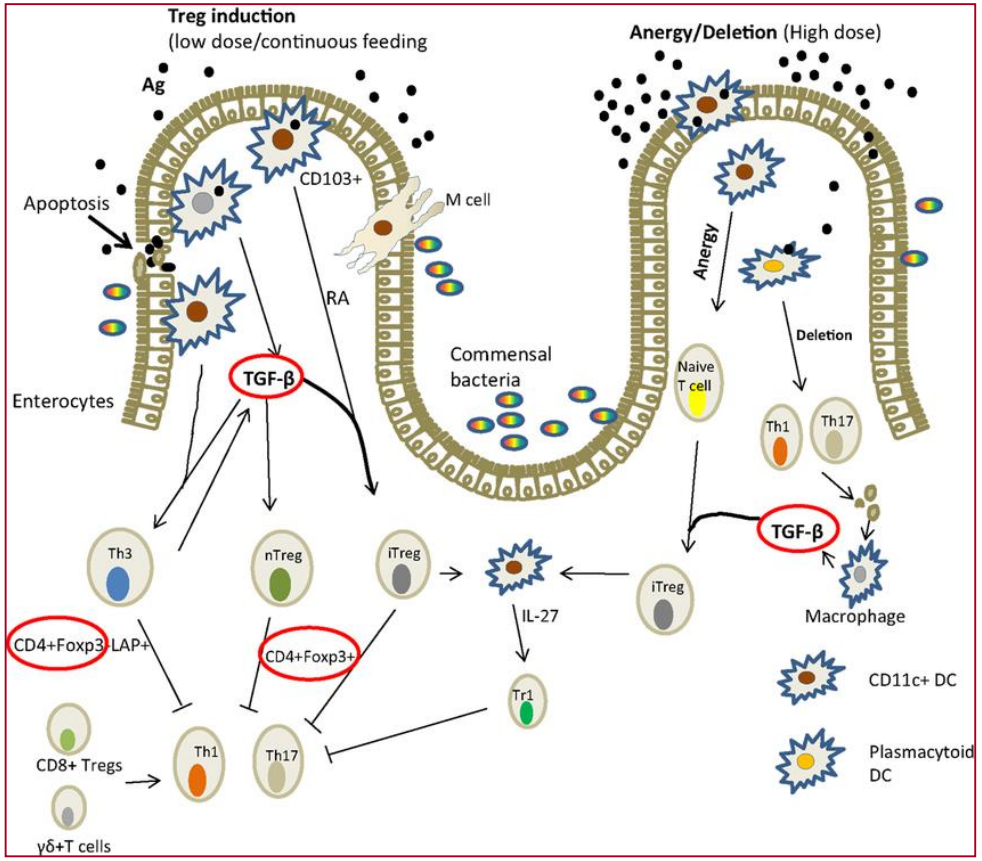
B-cell Tolerance

Central tolerance

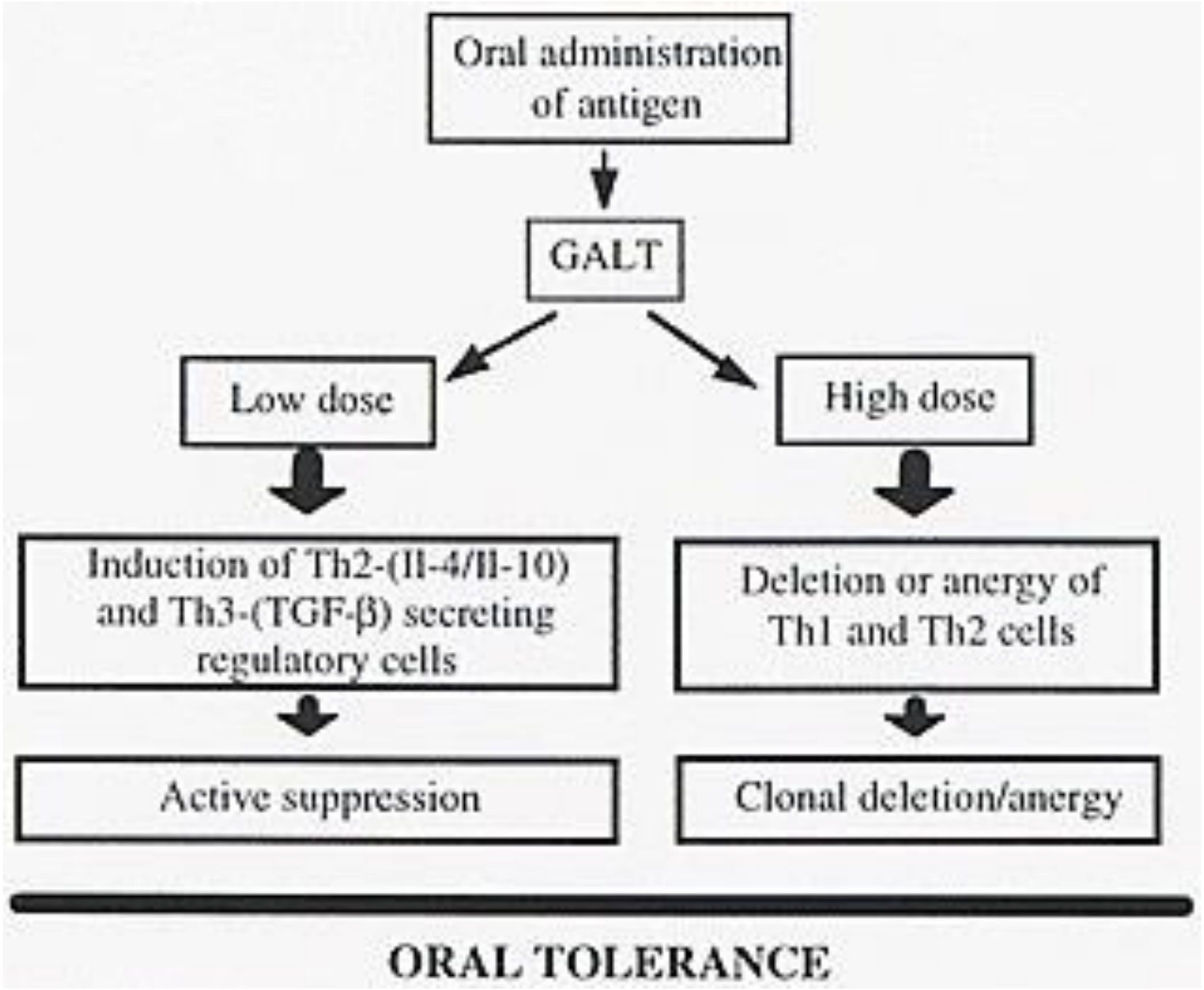
- Peripheral tolerance

Oral tolerance

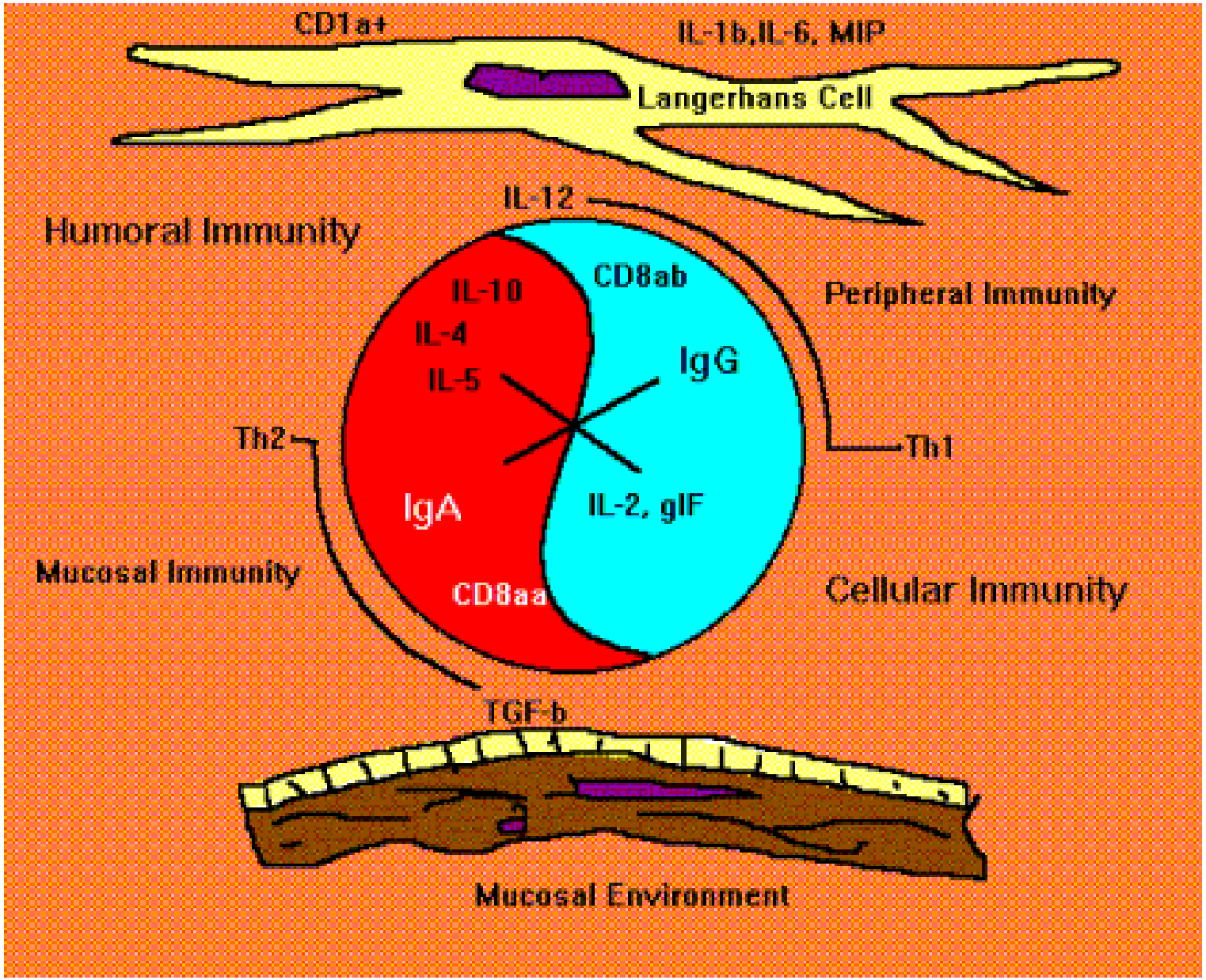




Oral tolerance is an active process of local and systemic immune response to orally ingested antigens such as food. The gut immune system must balance responses to commensal bacteria (microbiome) and pathogens. Specialized populations immune cells and lymph nodes create a unique environment in the gut, and the systemic effector sites are also critical to establishing and maintaining oral tolerance.


Oral administration of antigen
GALT
Low dose
High dose
Induction of Th2-(Il-4/Il-10) and Th3-(TGF-β) secreting regulatory cells
Deletion or anergy of Th1 and Th2 cells
Active suppression
Clonal deletion/anergy
ORAL TOLERANCE

Dichotomy of immune systems



ACTIVE TOLERANCE

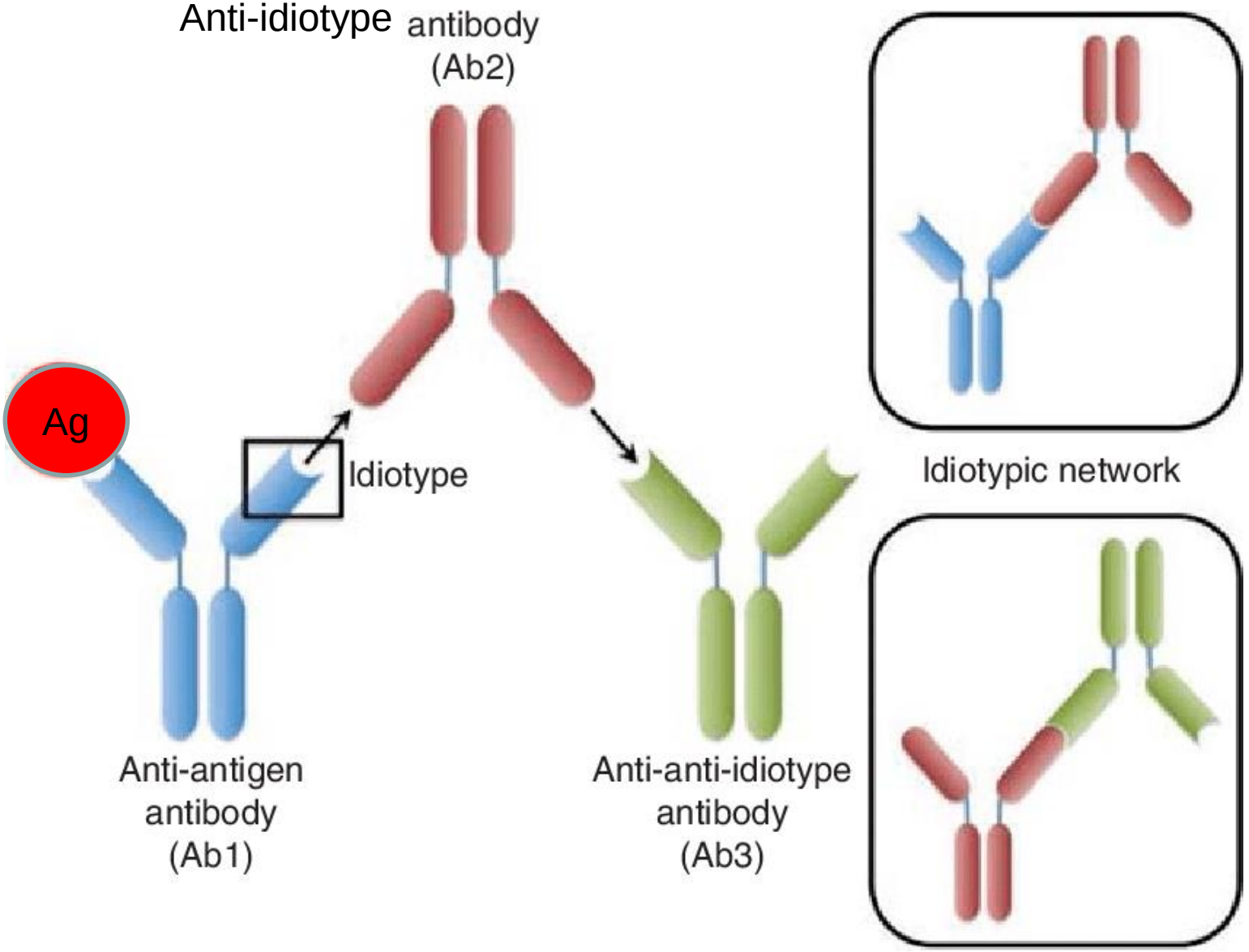
Anti-idiotype network

- Anti-idiotype antibodies against T cell and B cell receptors and immunoglobulins
- Antigen-specific inhibition and induction of memory
- Part of the adaptive immune response

Natural immune system: "Immunological homunculus"

- Natural (auto)antibodies: low affinity (dominantly IgM) autoantibodies produced by CD5+ B cells
- MAIT, iNKT, iγ/δ T cells
- Innate-like adaptive responses

ANTI-IDIOTYPE NETWORK



Naturally occurring (auto)antibodies

Autoantibodies of the **IgM (mostly)**, or IgG and IgA classes, **reactive with a variety of** serum proteins, cell surface structures and intracellular **structures, are 'naturally' found in all normal individuals.** Present in human cord blood and in 'antigen-free' mice, their variable-region repertoire is selected by antigenic structures in the body and **remains conserved throughout life**. Encoded by germline genes with no, or few, mutations, natural autoantibodies are characteristically **'multireactive'** and do **not undergo affinity maturation** in normal individuals. Natural autoantibodies may participate in a variety of physiological activities, from immune regulation, homeostasis and repertoire selection, to resistance to infections, transport and functional modulation of biologically active molecules.

Antigens recognized by natural autoantibodies

Heatshock proteins	hsp65, hsp70, hsp90, ubiquitin
Enzymes	aldolase, citockrom c, SOD, NAPDH, citrate synthase, DNA topoisomarase type I.
Cell membrane components	β2-microglobulin, spectrin, acetylcholin receptor
Cytoplasmic components	actin, myosin, tubulin, myoglobin, myelin basic protein
Nuclear components	DNS, histones
Plasma proteins	albumin, IgG, transferrin
Cytokines, hormones	IL-1, TNF, IFN, insulin, thyreoglobin

Janus faced B lymphocytes in tolerance and autoimmunity

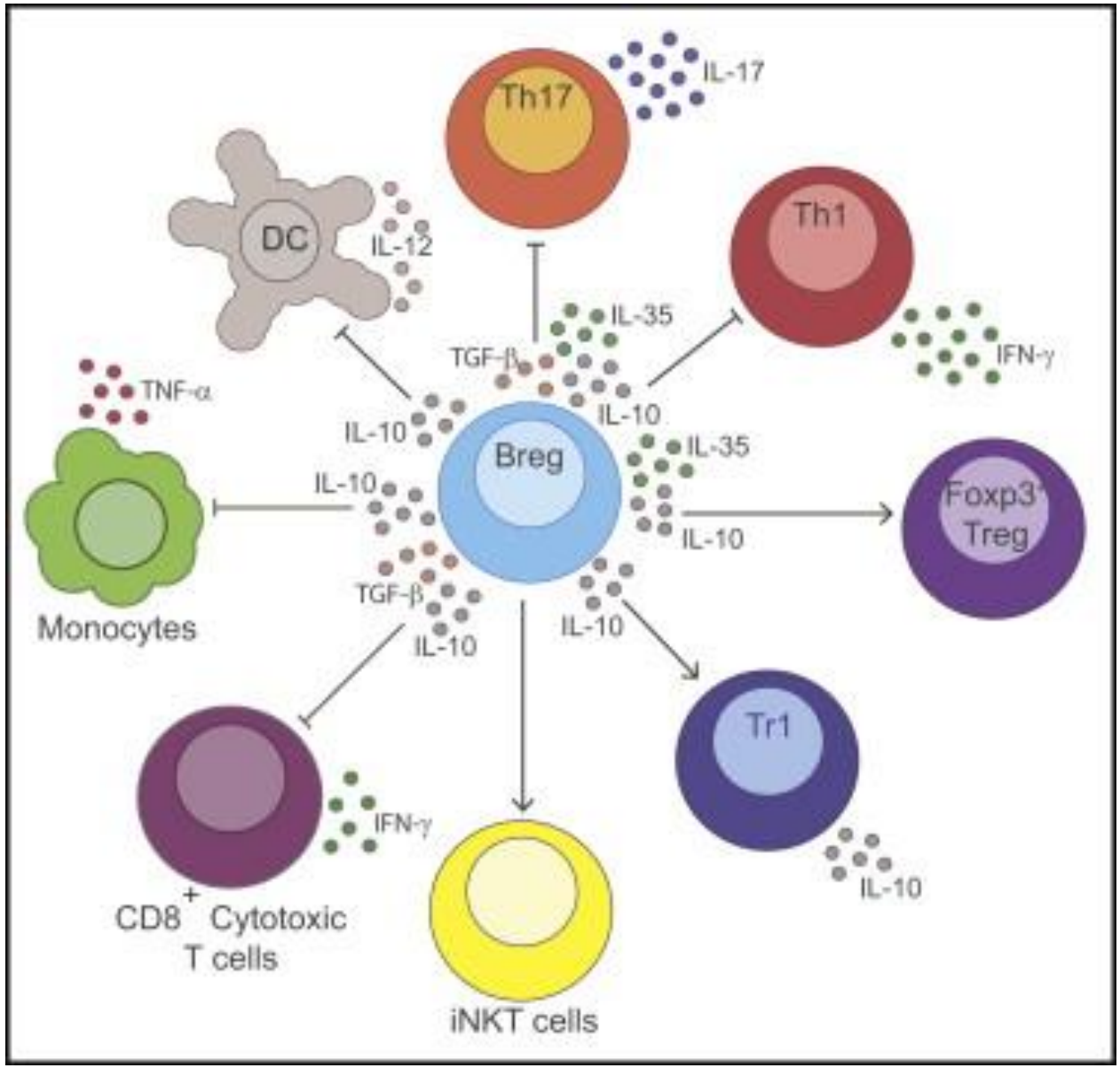
Functions of B cells that suppress autoimmunity

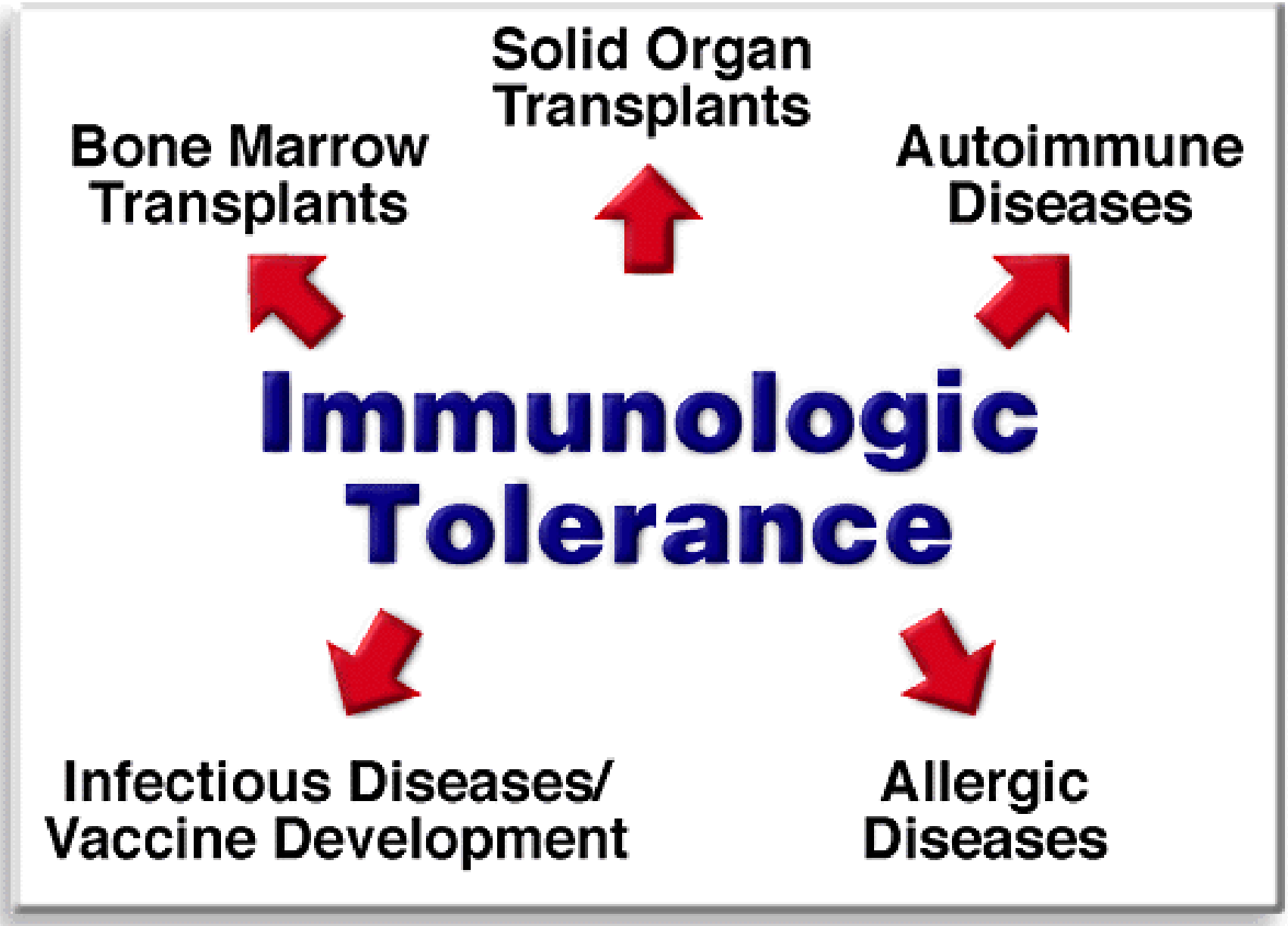
- Natural IgM autoantibodies
- T-cell anergy
- Suppress T_H1/T_H17 cells
- T_{REG} cell priming/expansion
- DC inhibition (IL-10)
- Regulatory cytokines: IL-10, TGF-β…

Functions of B cells that promote autoimmunity

- Pathogenic IgG antibodies
- $CD4^+/CD8^+$ T-cell activation, $CD4^+$ T-cell memory, T_{FH}-cell activation
- T_H1, T_H2, T_H17 cell development
- T_{REG} cell inhibition
- DC recruitment
- Proinflammatory cytokines: TNF, IFN-γ, IL-6, others
- Lymphotoxin-dependent ectopic lymphoid tissue formation

REGULATORY B CELL ACTIONS




Solid Organ Transplants
Bone Marrow Transplants
Autoimmune Diseases
Immunologic Tolerance
Infectious Diseases/ Vaccine Development
Allergic Diseases