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

ANTIGEN

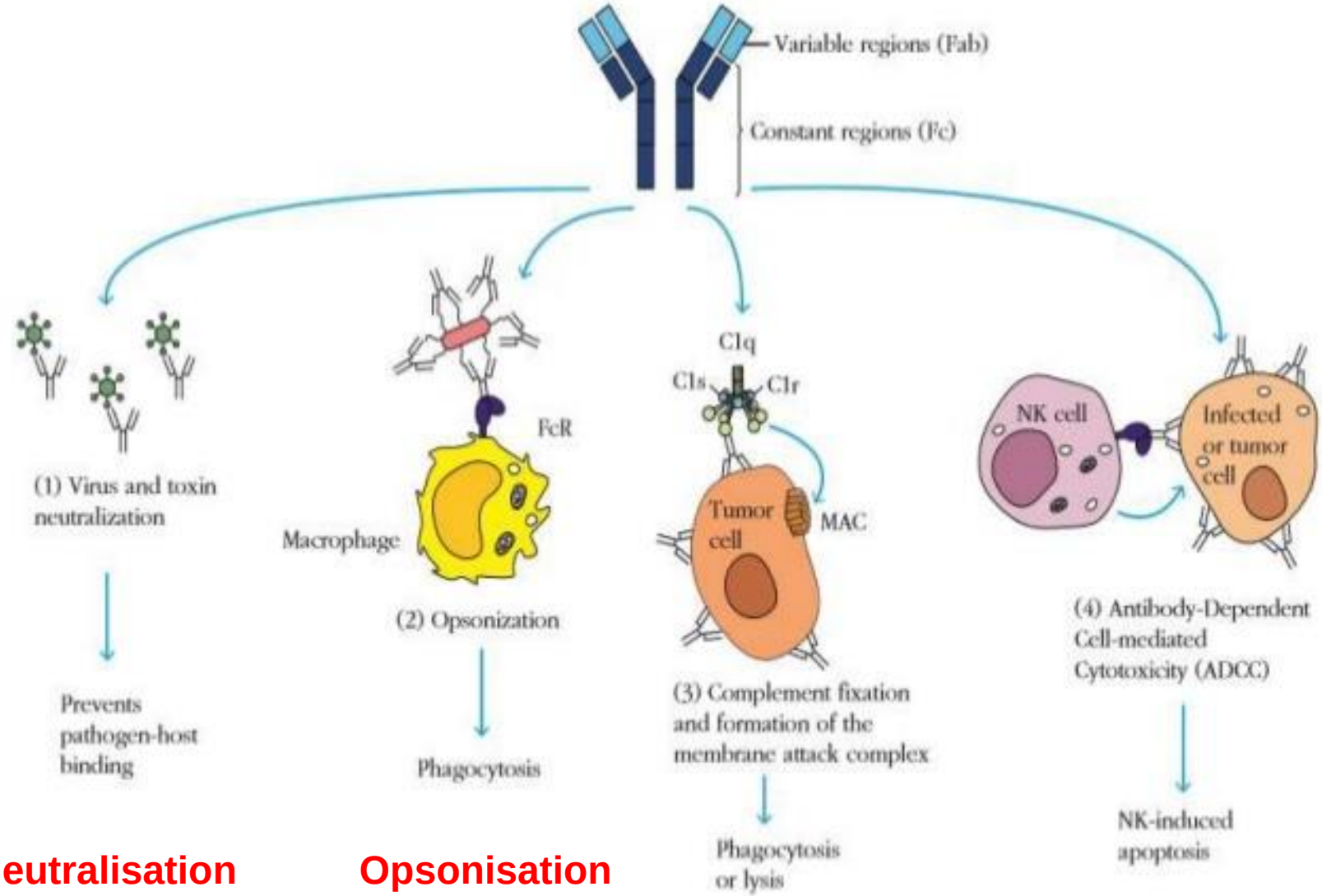
Targeting type immune response

or

Tolerance

Immune system performs permanent decision between targeting type and tolerating type immune response on actual antigen. Both the nature and occurrence of the antigen and the actual status of the immune system influence the type of response in a wide range.

Antibody effector functions



Neutralisation

Opsonisation

Complement fixation

ADCC

Cell-mediated immuneresponse (CMI)

Direct cytotoxicity	***DTH***
Effector cells with direct cytotoxic activity: - CTL (CD8+ Tc), - γδ T cells - NK cells, - Macrphages	**Effector cells** with cytokine production: - T_{DTH} cells = Th1 cells - Macrophages
Target cell (cytosolic antigen): - allogen cells (transplantation, minor histocompatibility antigen) - malignant cells - virally infected cells - chemically modified cells	**Antigen in phagolysosome:** - intracellular bacterium, fungi, parasite, virus - contact antigens (small molecules - haptens - in skin protein complexes)

Tolerated skin grafts on MHC (H2) identical mice

TOLERANCE & AUTOIMMUNITY

- 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 **Immunodefficiencies**

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

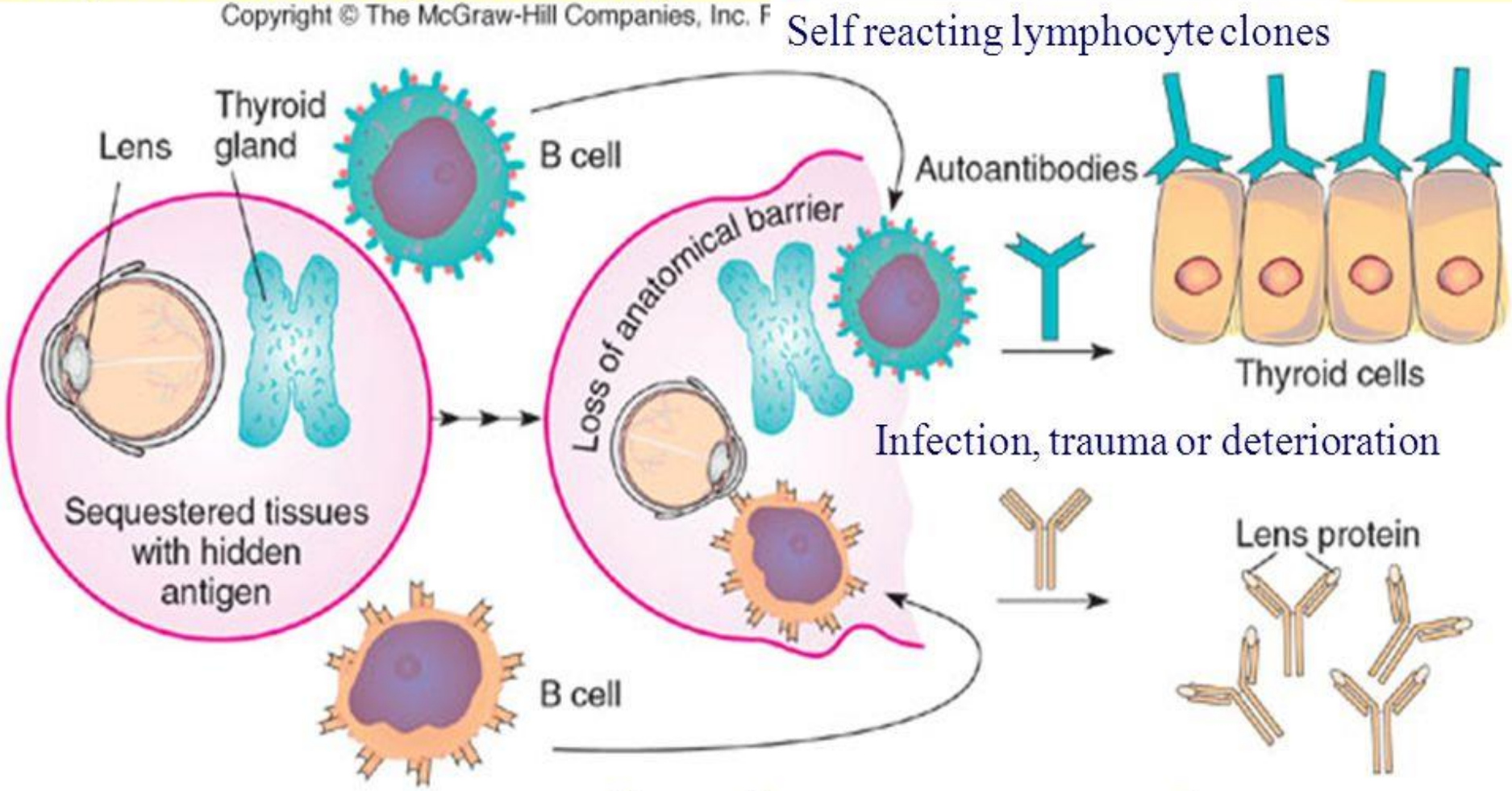
- chemical nature
- dose of the antigen
  - **low dose tolerance** (T cell mediated, long ranging)
  - **high dose tolerance** (B cell mediated, short ranging)
- mode of the administration

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



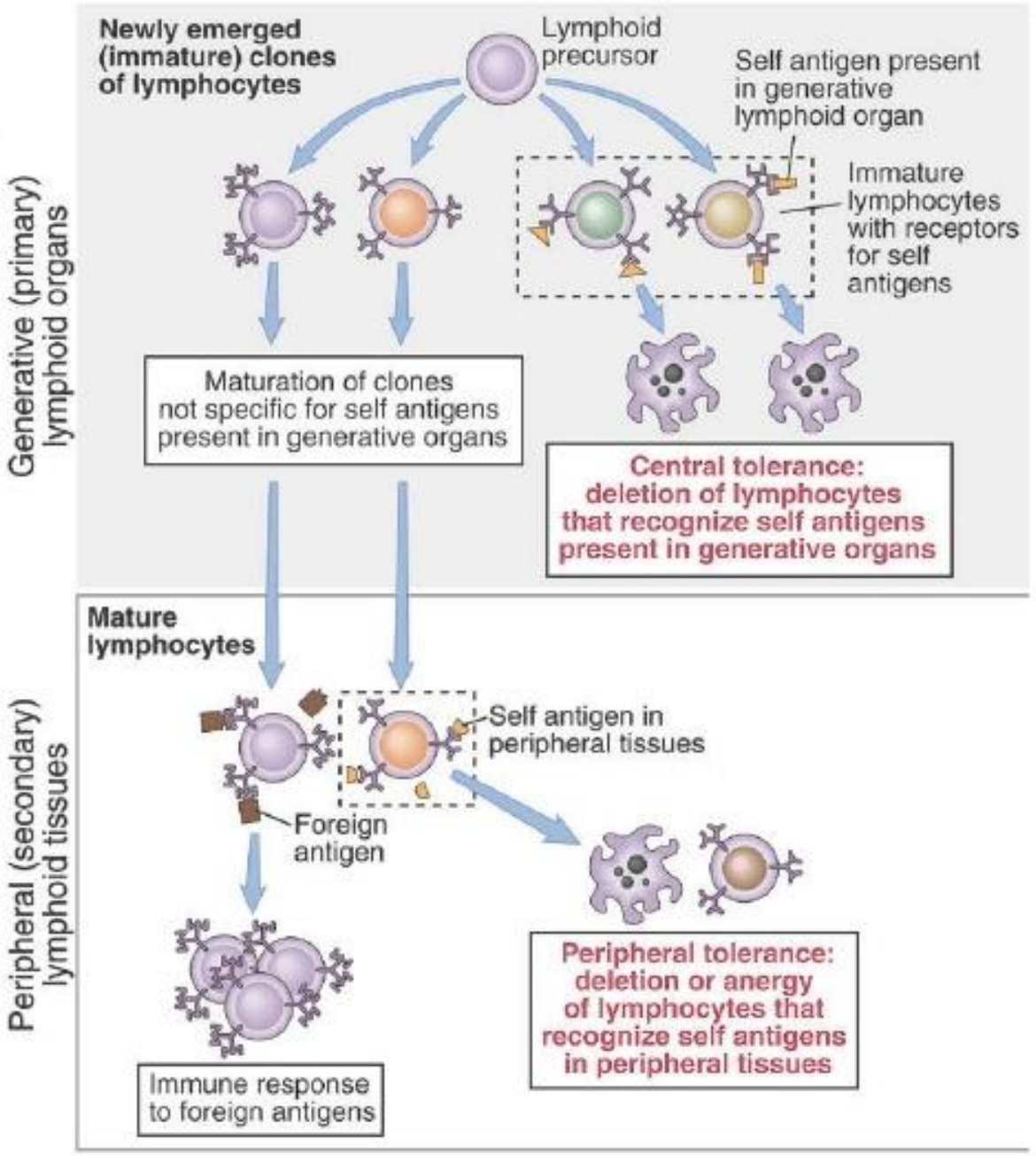
(a) **Sequestered Antigen Theory**

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

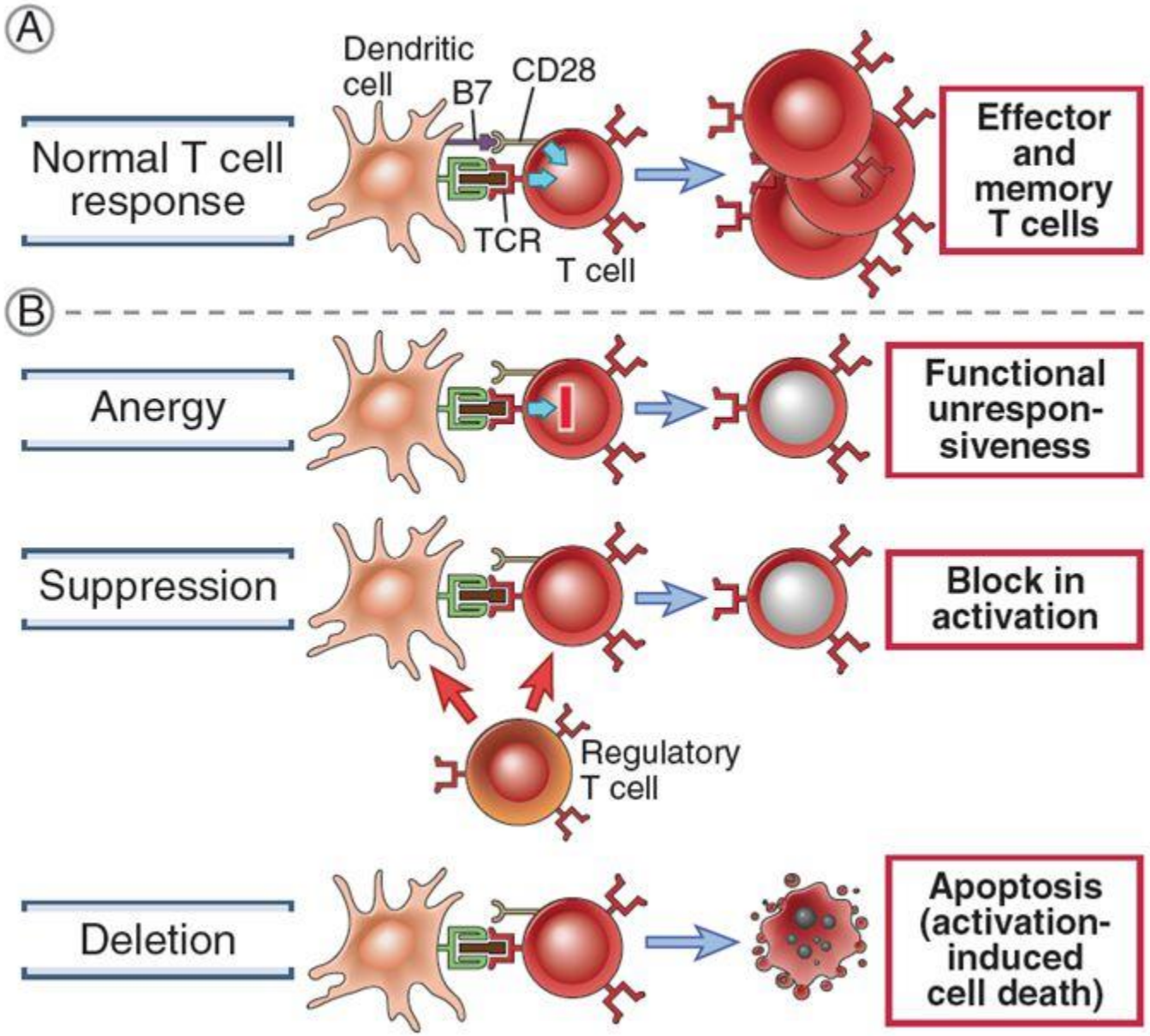
CNS, lens, thyroid & testes

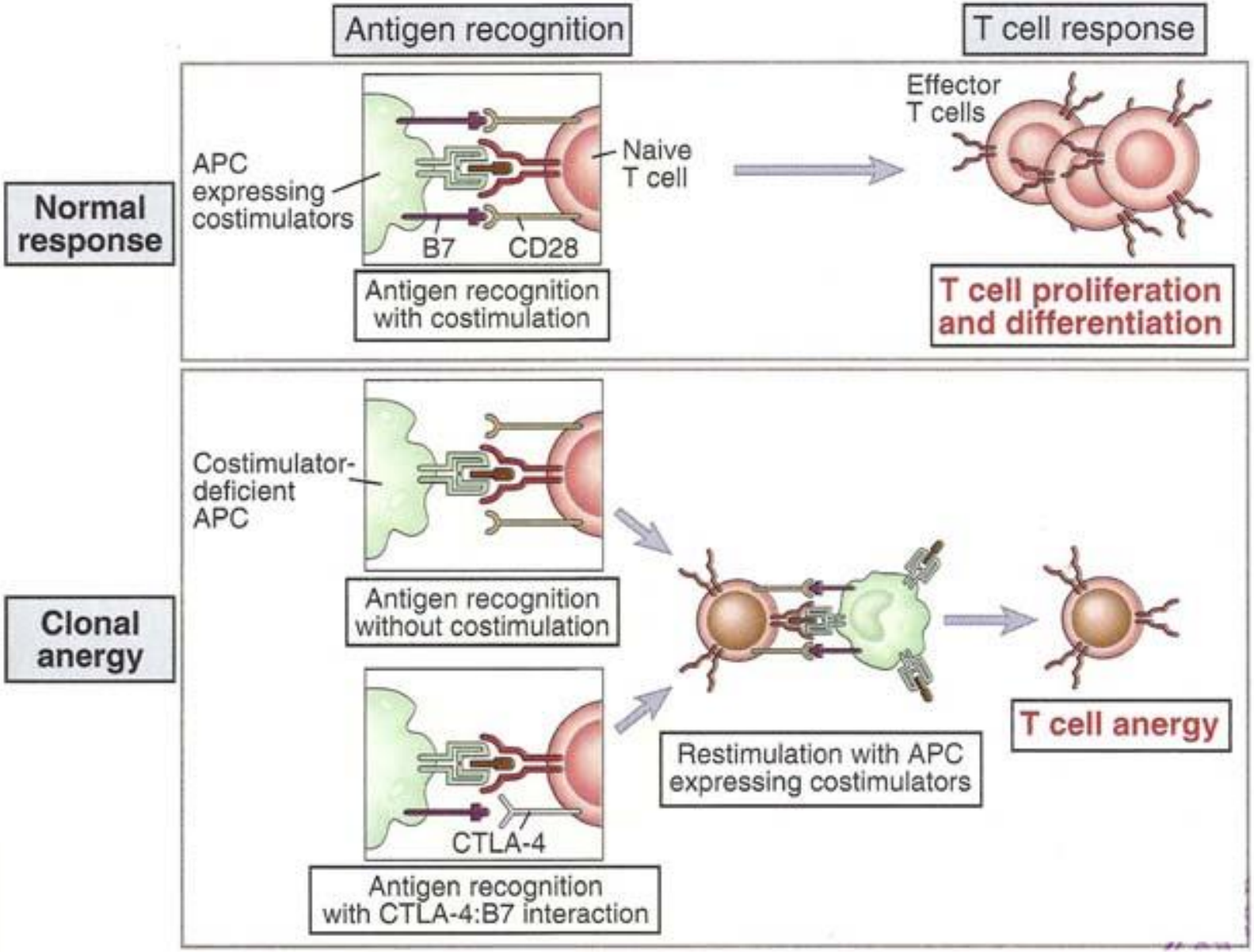
Central & peripheral tolerance to self Ags

- Central tolerance
  - Immature lymphocytes specific for self Ags may encounter these Ags in the generative lymphoid organs (bone marrow & thymus) and are deleted
- Peripheral tolerance
  - Mature self-reactive lymphocytes may be **inactivated** or **deleted** by encounter with self antigens in peripheral lymphoid tissues

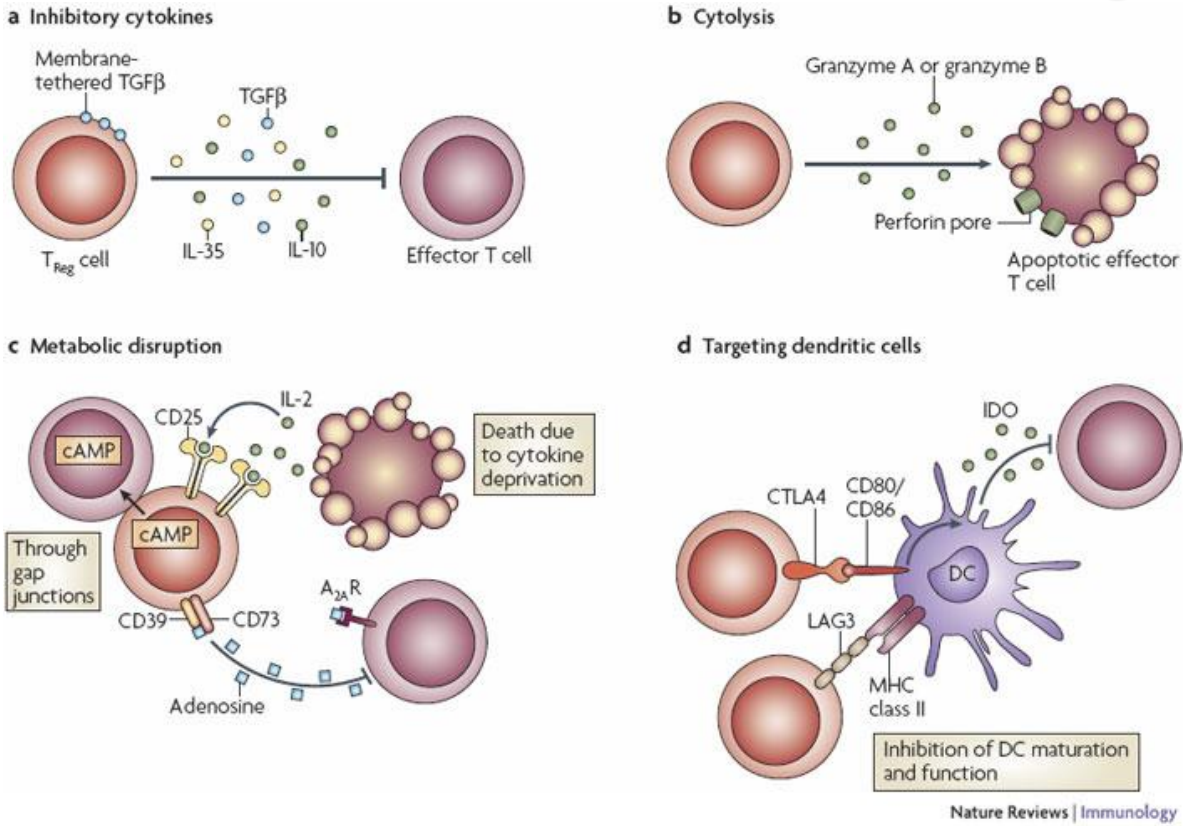


Peripheral tolerance




Antigen recognition
T cell response
Normal response
APC expressing costimulators
B7
CD28
Naive T cell
Effector T cells
Antigen recognition with costimulation
T cell proliferation and differentiation
Clonal anergy
Costimulator-deficient APC
Antigen recognition without costimulation
CTLA-4
Antigen recognition with CTLA-4:B7 interaction
Restimulation with APC expressing costimulators
T cell anergy

Basic mechanisms used by T_{Reg}



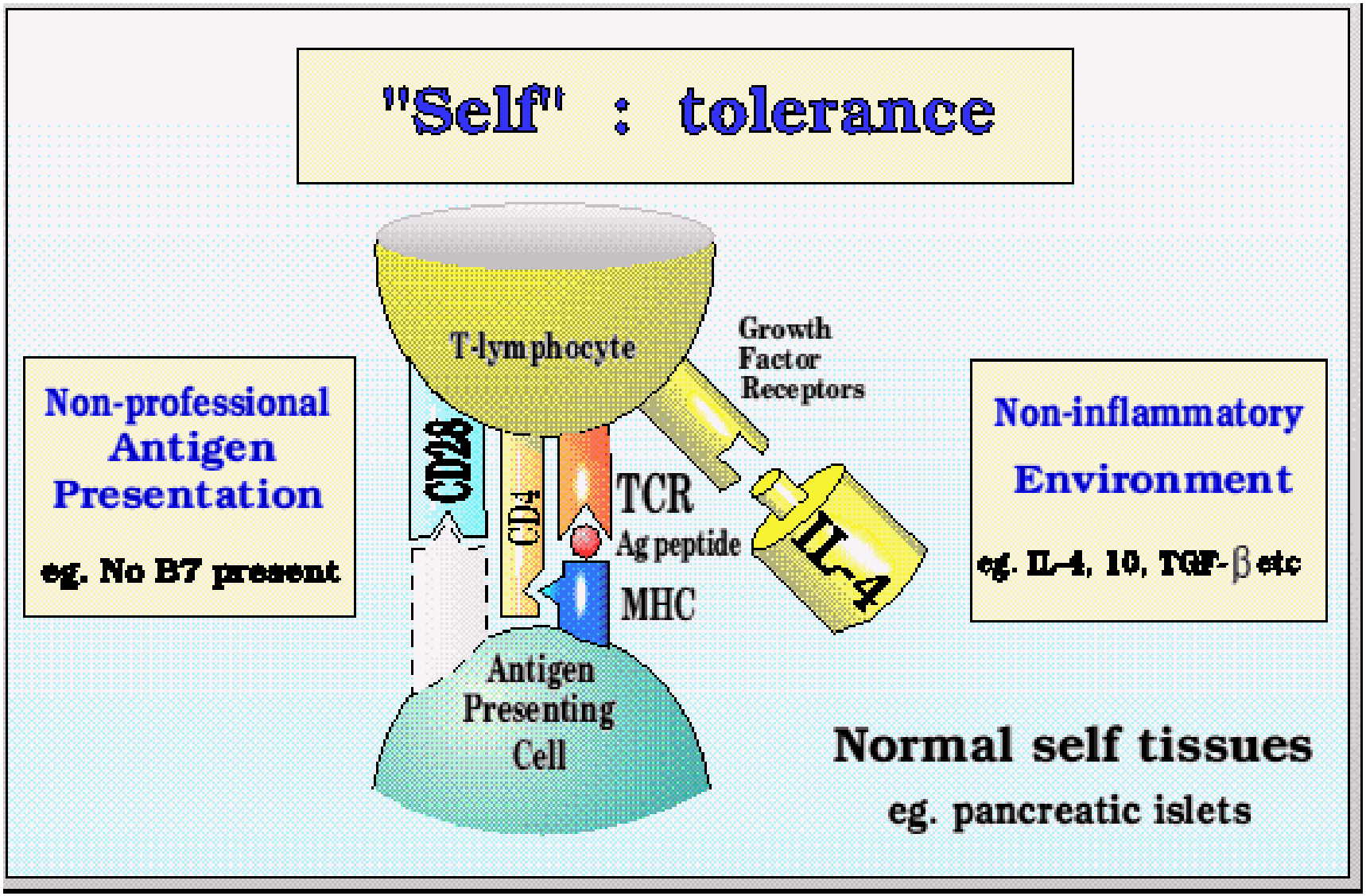
a.) Inhibitory cytokines include IL-10, IL-35 and TGFβ. **b.)** Cytolysis includes granzyme-A- and granzyme-B-dependent and perforin-dependent killing mechanisms. **c.)** Metabolic disruption includes high-affinity CD25 (IL-2 receptor)-dependent cytokine-deprivation-mediated apoptosis, cAMP-mediated 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.

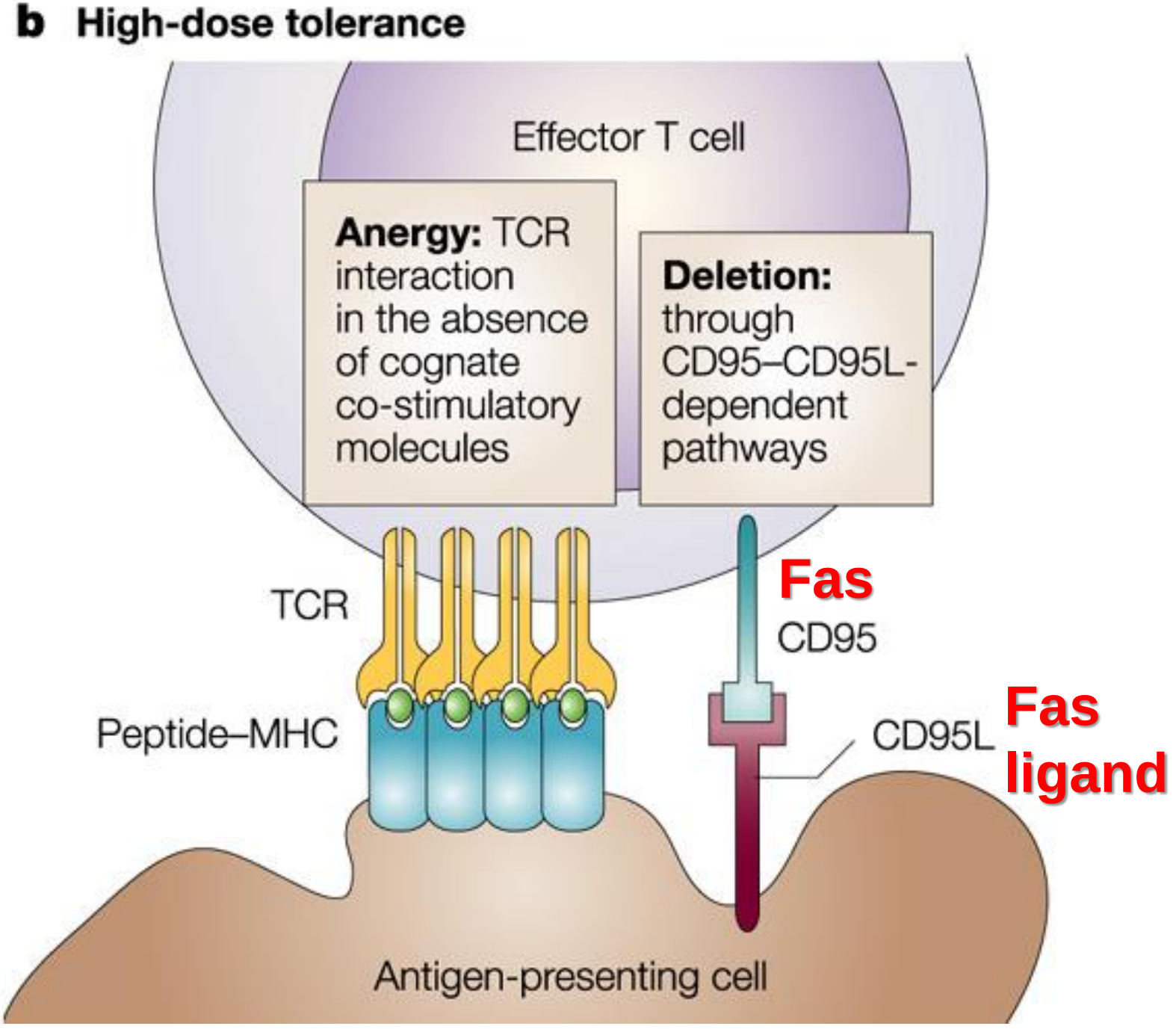
T-cell tolerance

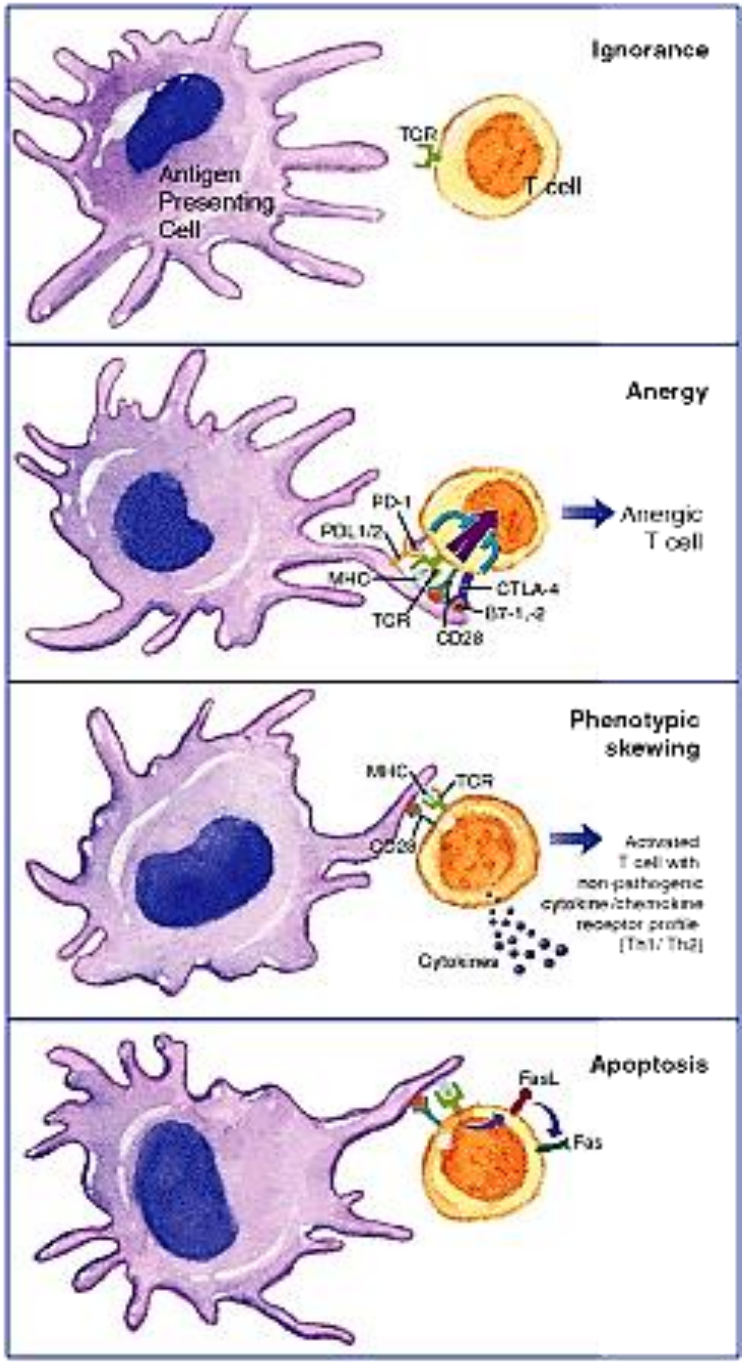
- Central Tolerance (selection in the Thymus)

- 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



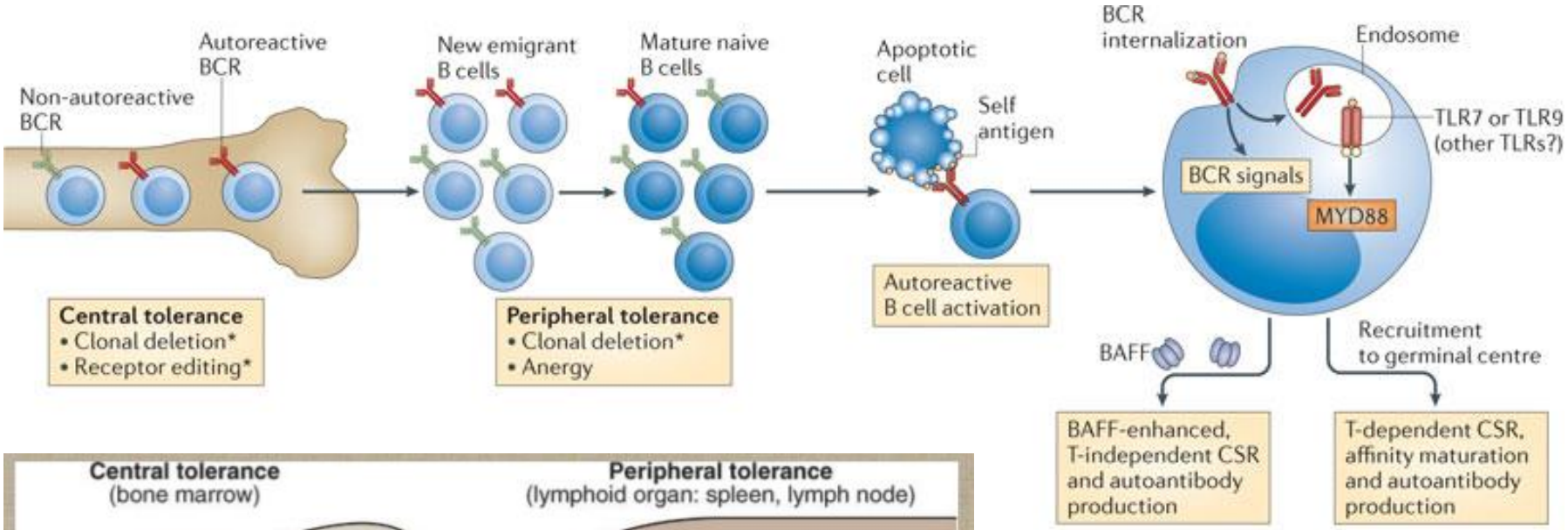
No response

Anergy

Anergy

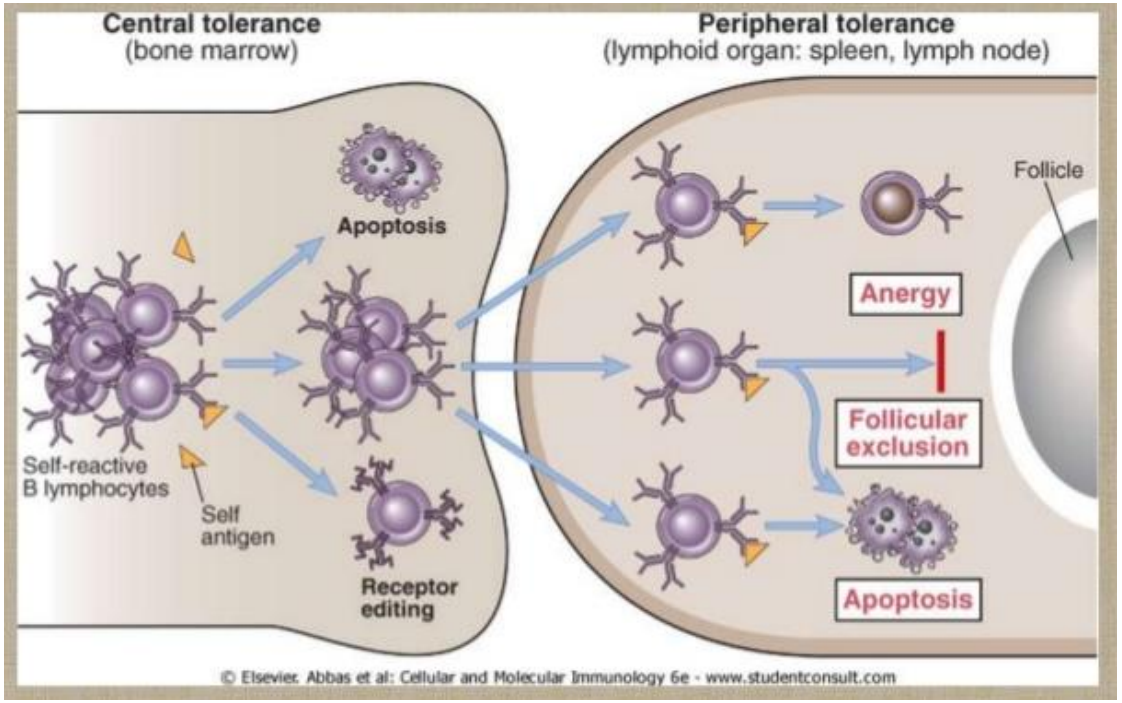
Deletion

B cell toerance

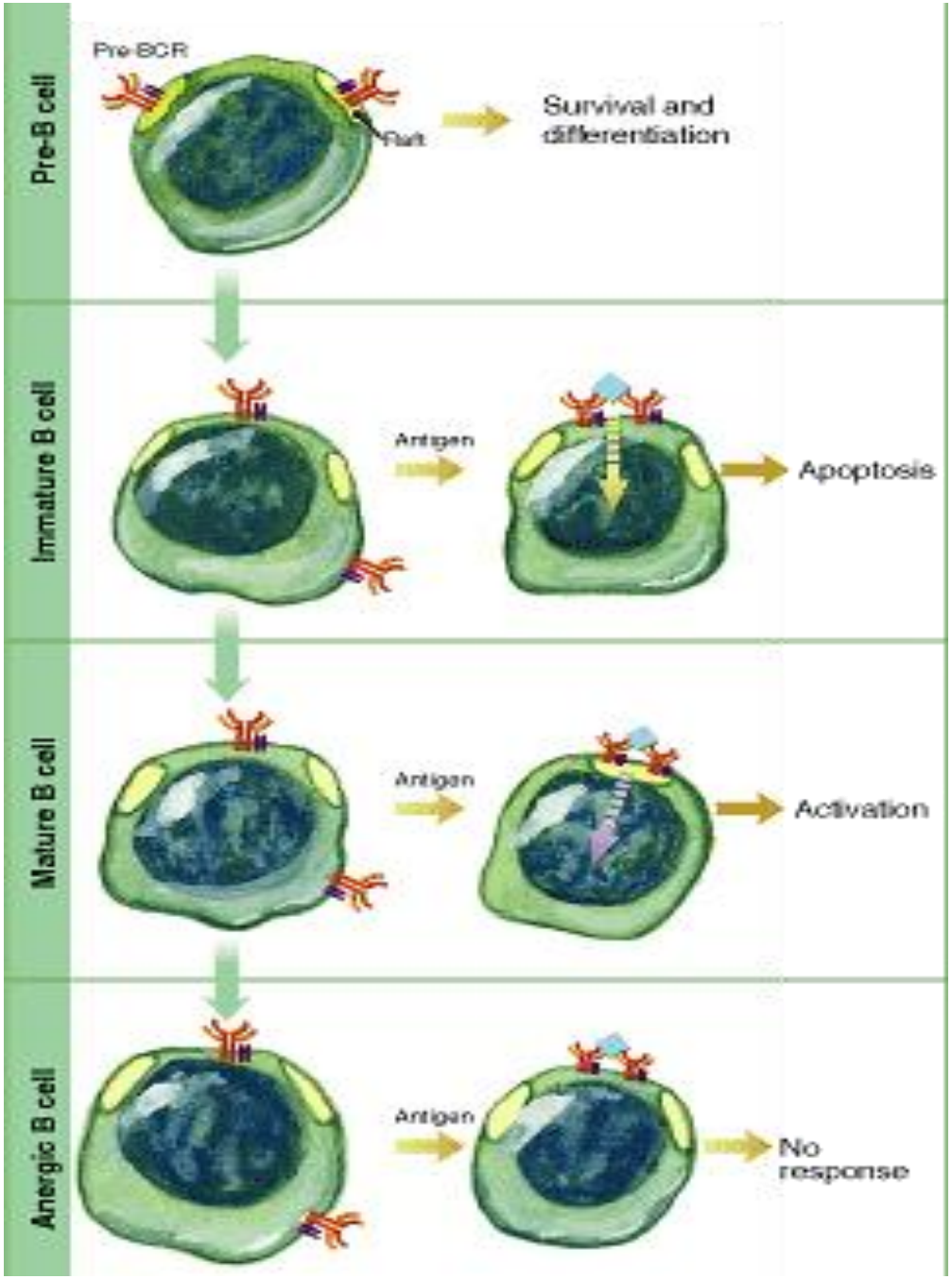


AUTOIMMUNITY

Nature Reviews | Immunology



TOLERANCE

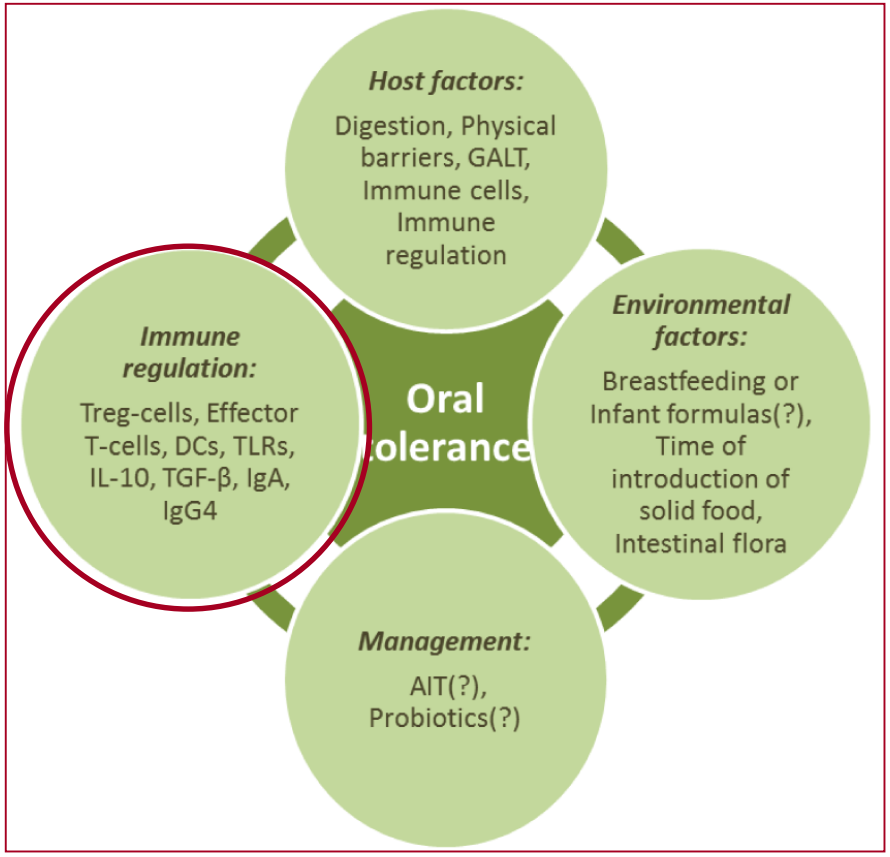


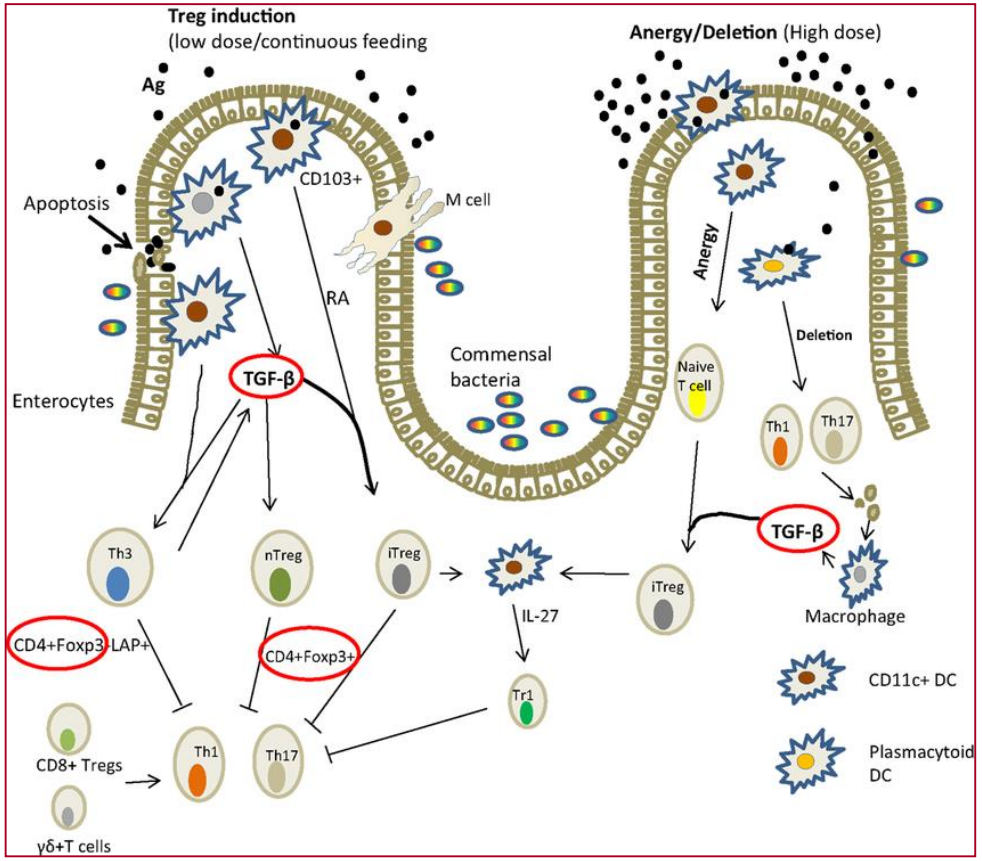
B-cell Tolerance

Central tolerance

- Peripheral tolerance

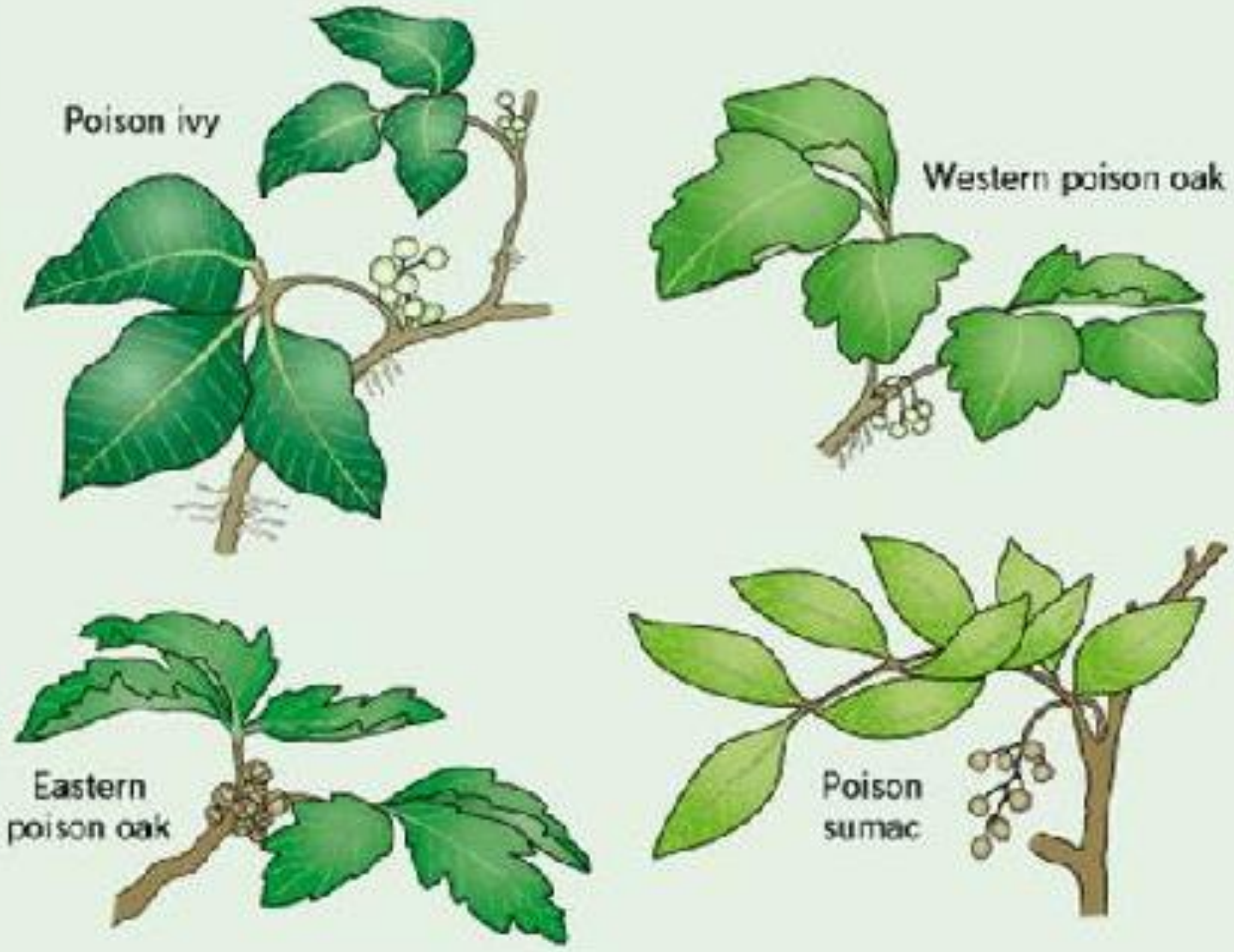
Oral tolerance

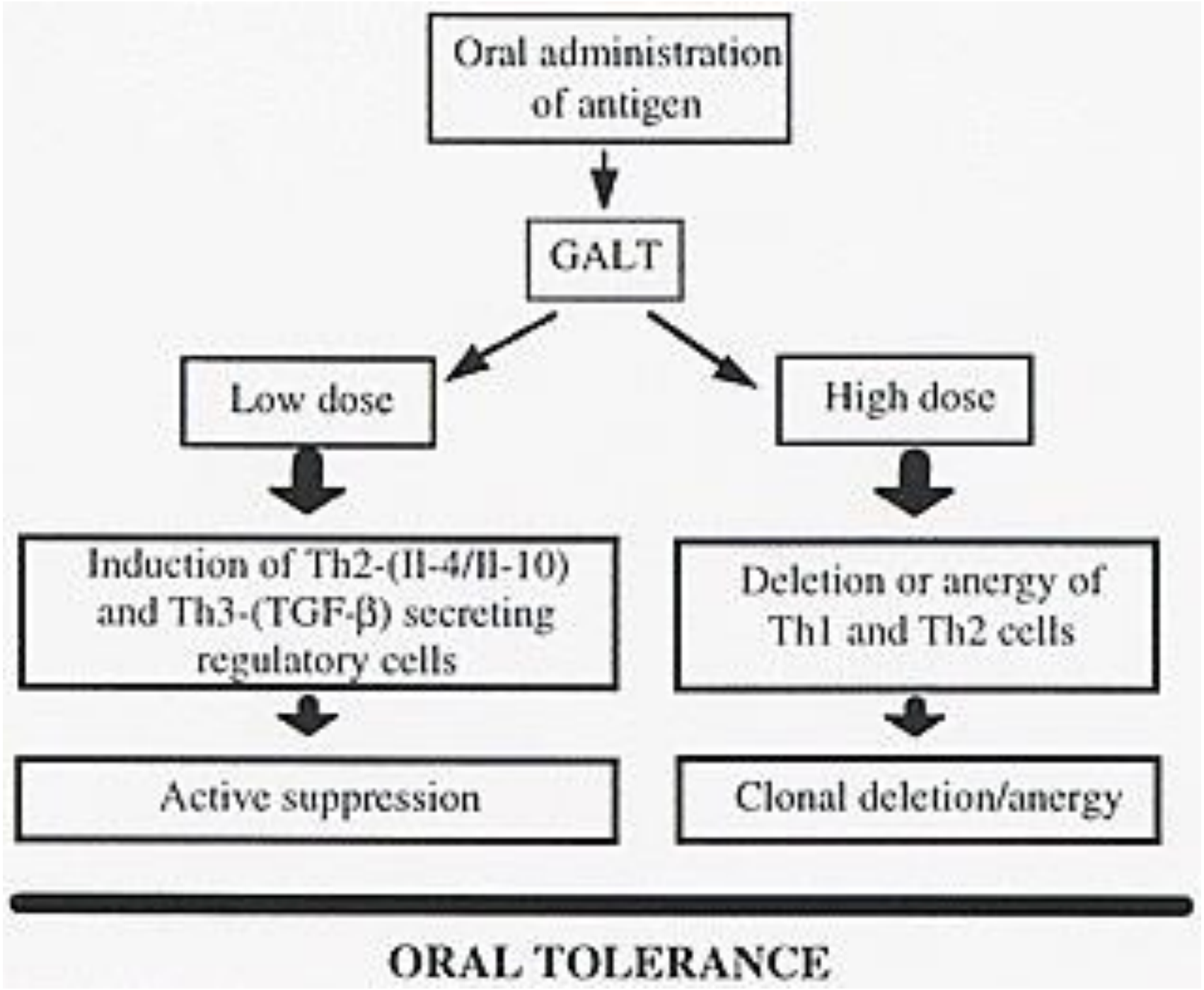




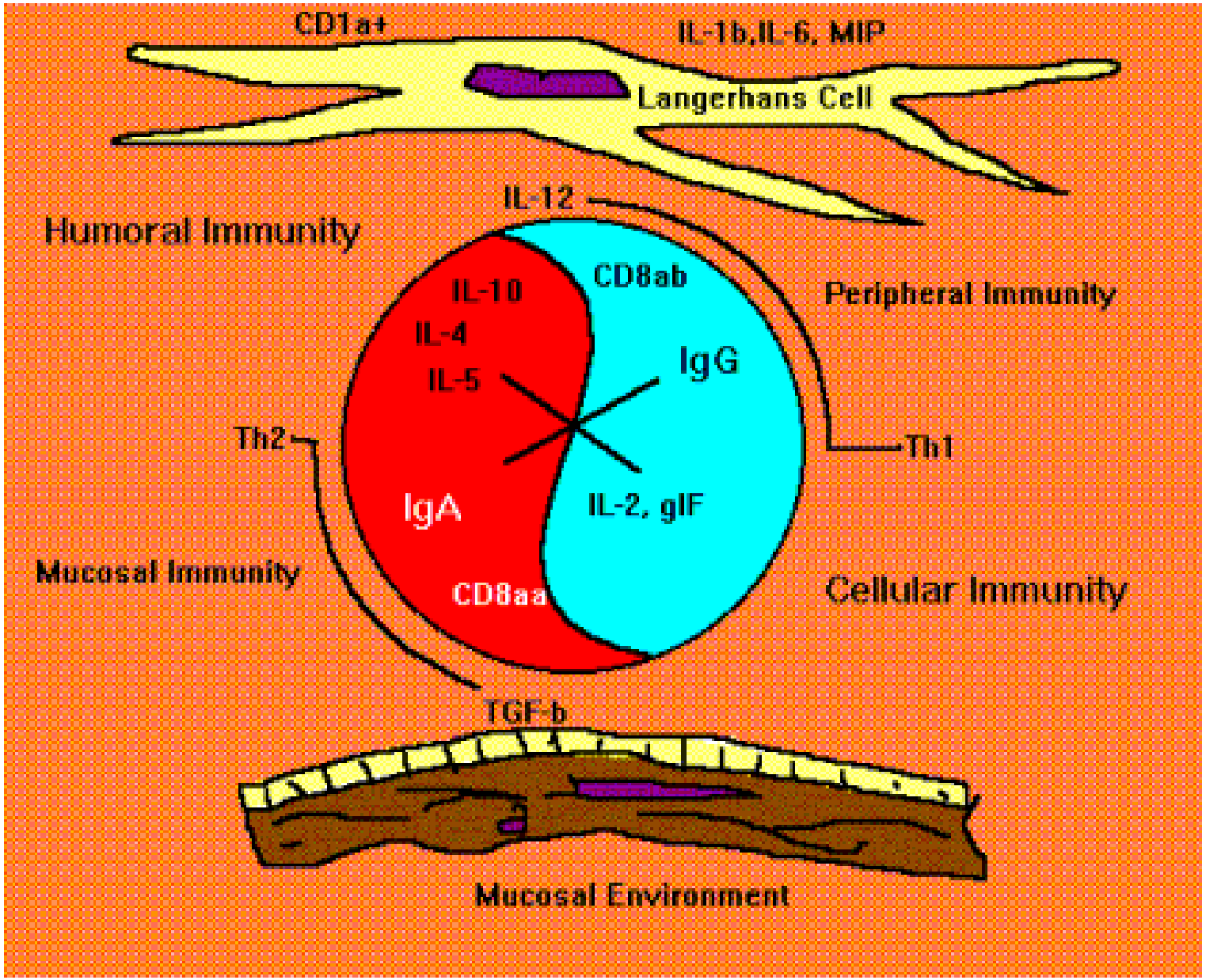
Oral tolerance is an active process of local and systemic immune response to orally ingested antigens such as food. The gut immune system must balance responses to commensal bacteria (microbiome) and pathogens. Specialized populations immune cells and lymph nodes create a unique environment in the gut,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

IDENTIFICATION OF POISON IVY, OAK AND SUMAC




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

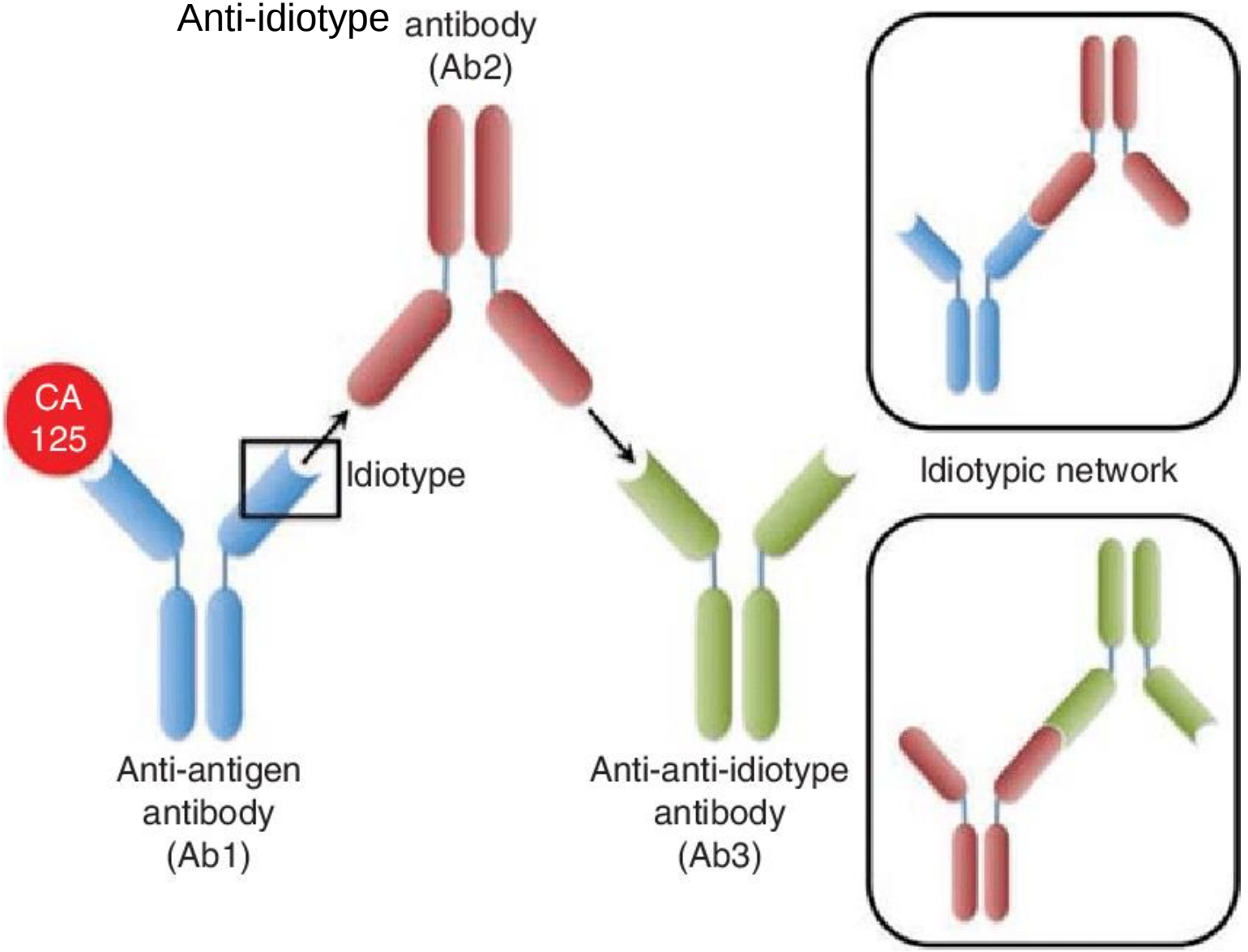
Anti-idiotype network

- 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

"Immunological homunculus"

- Natural (auto)antibodies: low affinity 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, topoisomarase 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

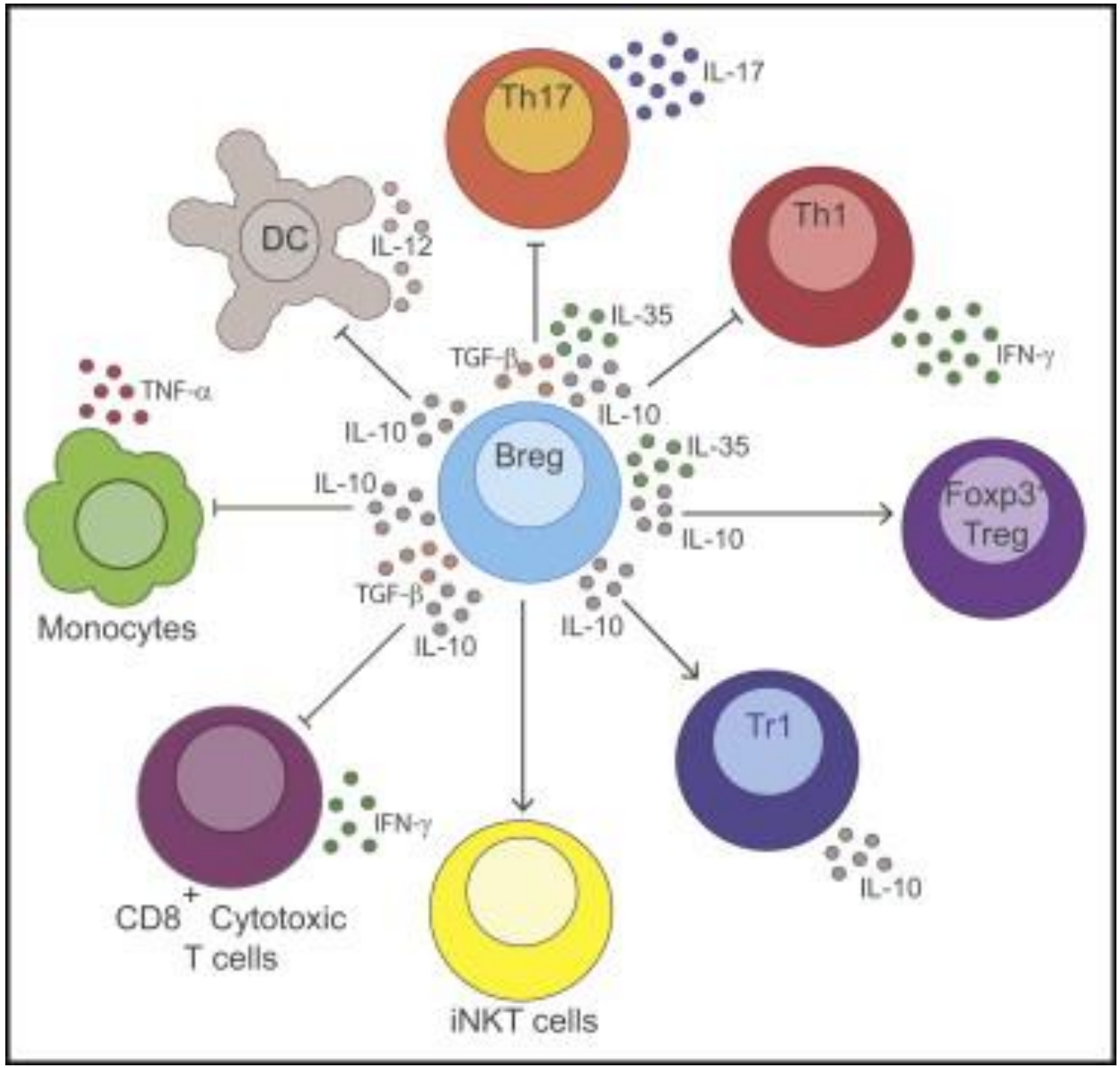
Functions of B cells that suppress autoimmunity

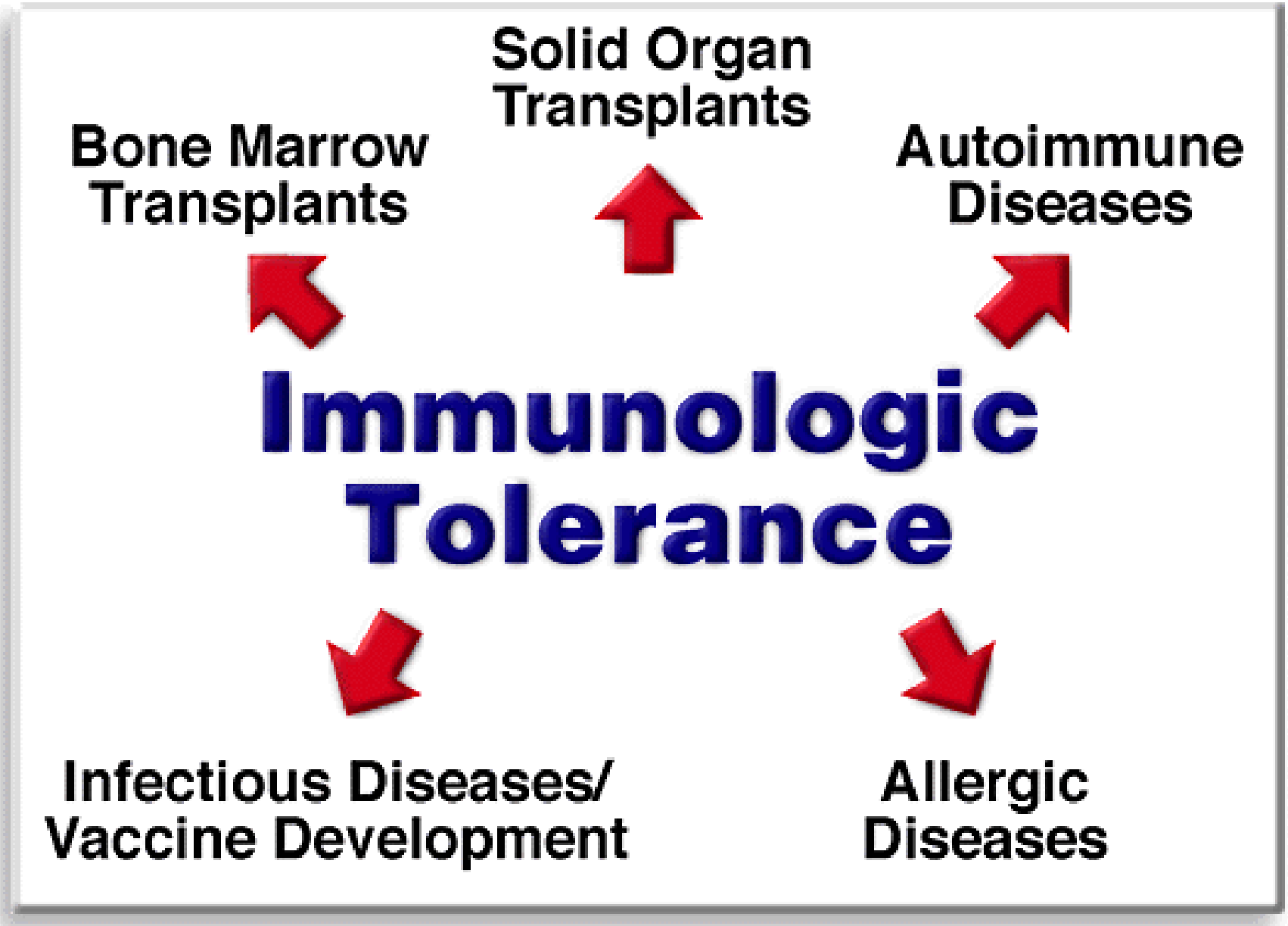
- Natural IgM autoantibodies
- T-cell anergy
- Suppress T_H1/T_H17 cells
- T_{REG} cell priming/expansion
- DC inhibition (IL-10)
- Regulatory cytokines: IL-10, TGF-β…

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