Basic Immunology

Lecture 25-26

Immunological tolerance

Cellular and molecular mechanisms of the immunological tolerance

Autoimmunity

Main tasks of the immune system

The immune system is a structural and functional network.

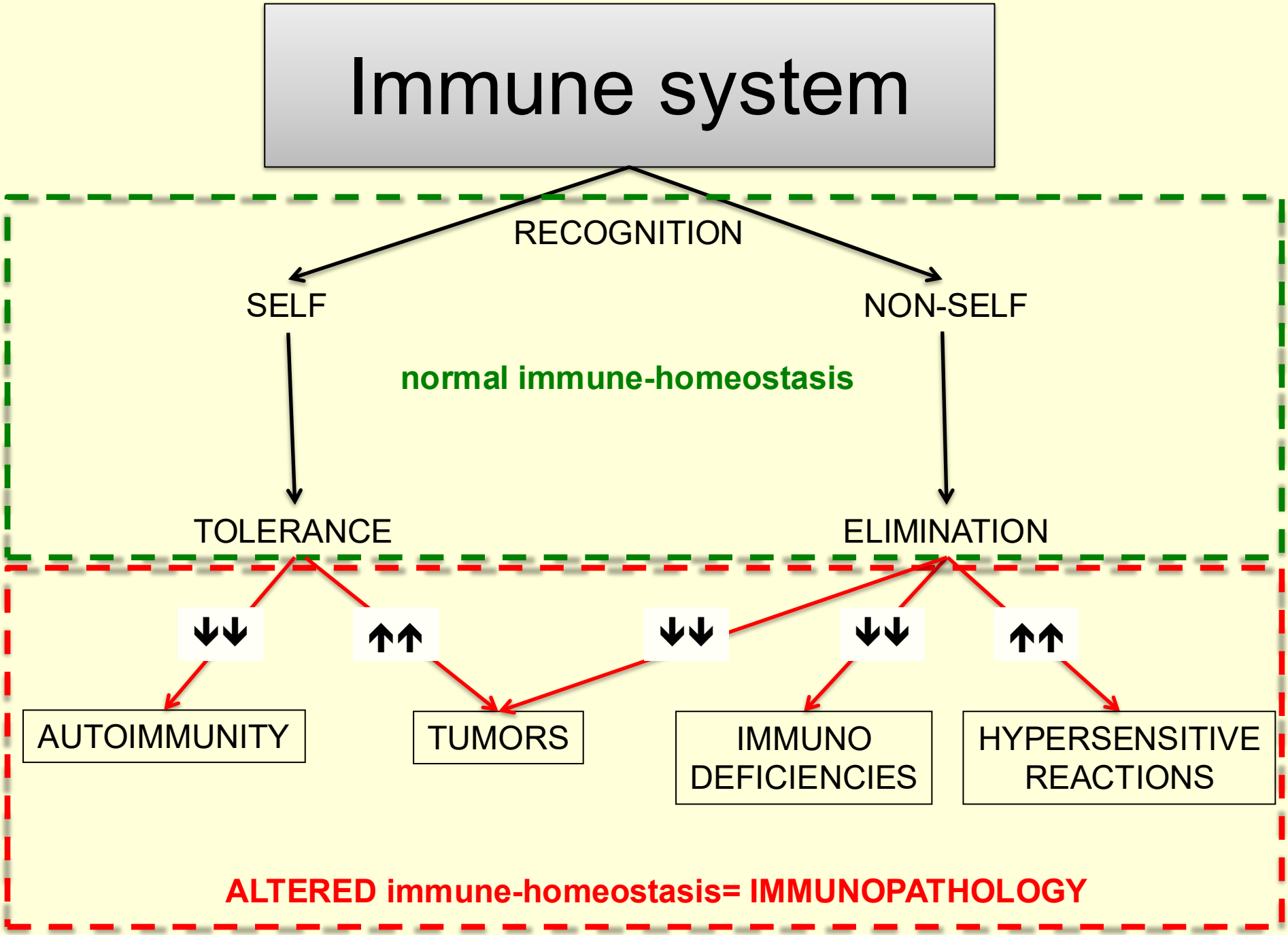
Preserving the integrity of an organism

Defense against **external pathogens** (e.g. viruses, bacteria, parasites)

Elimination of one's **pathologically altered cells** (e.g. virally infected cells, cancer cells)

Altered self- and foreign structures must be **recognized** and **distinguished** from the organism's own healthy cells.

IMMUNE RESPONSE (either an aggressive response or immunological tolerance)


Immune system
RECOGNITION
SELF
NON-SELF
normal immune-homeostasis
TOLERANCE
ELIMINATION
AUTOIMMUNITY
TUMORS
IMMUNO DEFICIENCIES
HYPERSENSITIVE REACTIONS
ALTERED immune-homeostasis= IMMUNOPATHOLOGY

TOLERANCE

- CENTRAL
- PERIPHERAL: PASSIVE and ACTIVE

AUTOIMMUNITY

- PHYSIOLOGIC REGULATION
- AUTOIMMUNE DISEASES

Types of tolerance

- Central tolerance (selection of autoreactive T and B celle in the Thymus and Bone marrow)

- Peripheral tolerance
  - Lack of co-stimulation
  - Failure to encounter self antigens
  - Receipt of death signal
  - Control by regulatory T cells

Types of tolerance

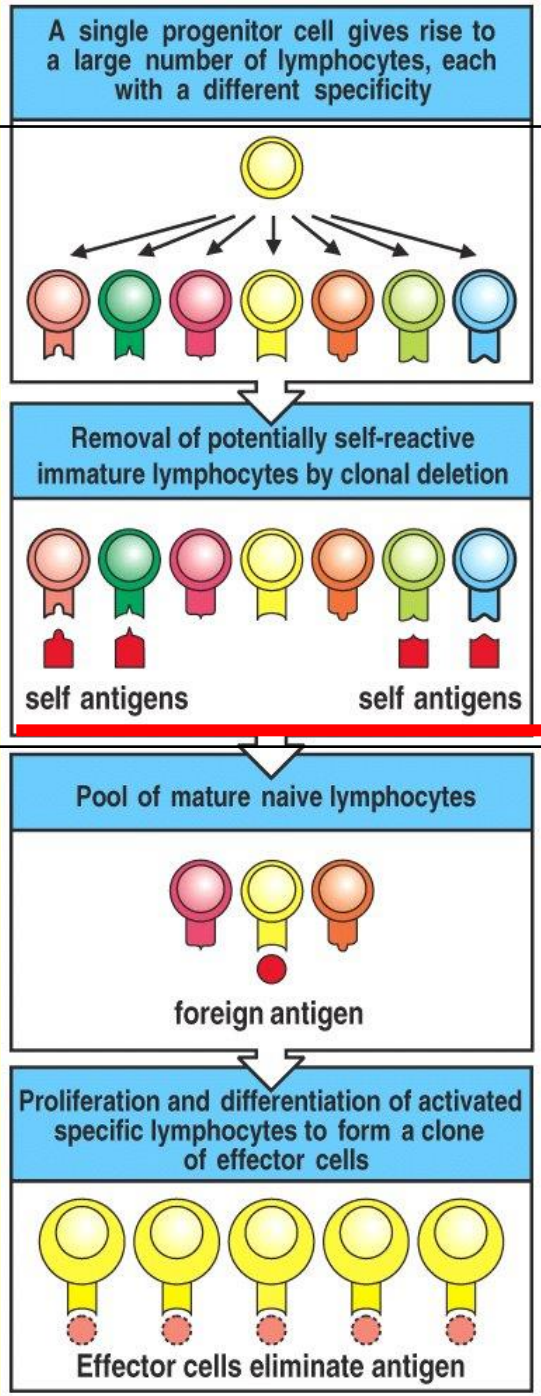


Figure 1-14 Immunobiology, 6/e. (© Garland Science 2005)

Proliferation

BcR (Ig)- or TcR-Gene rearrangement
→ Antigenreceptor expression

Primary lymphatic organs

Selection → central Tolerance

Antigen recogintion

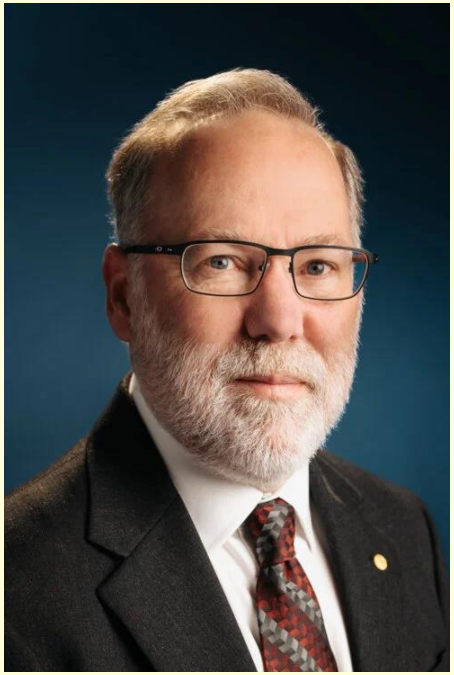
Peripheral Lymphatic organs

Proliferation – or
Deletion and Anergy→ peripheral Tolerance

Nobel Prize in Physiology or Medicine 2025



Mary E. Brunkow
Born: 1961, Portland, OR, USA
Institute for Systems Biology, Seattle, WA, USA



Frederick J. Ramsdell
Born: 4 December 1960, Elmhurst, IL, USA
Sonoma Biotherapeutics, San Francisco, CA, USA

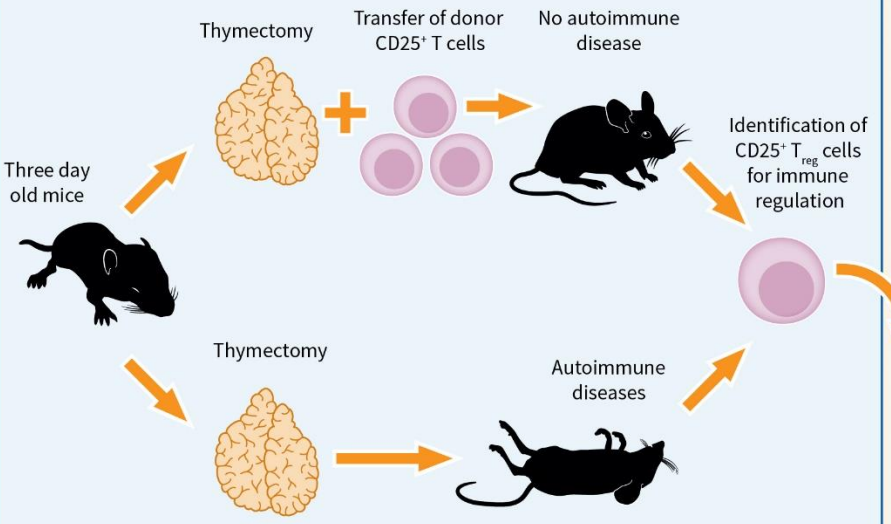


Shimon Sakaguchi
Born: 19 January 1951, Nagahama, Shiga, Japan
The University of Osaka, Osaka, Japan

Nobel Prize in Physiology or Medicine 2025:

FoxP3⁺ regulatory T cells play a pivotal role in the induction of peripheral immune tolerance.

Shimon Sakaguchi:
CD25⁺ T cells can prevent experimental autoimmune diseases



Mary E. Brunkow and Frederick J. Ramsdell:
Identification of FOXP3 gene

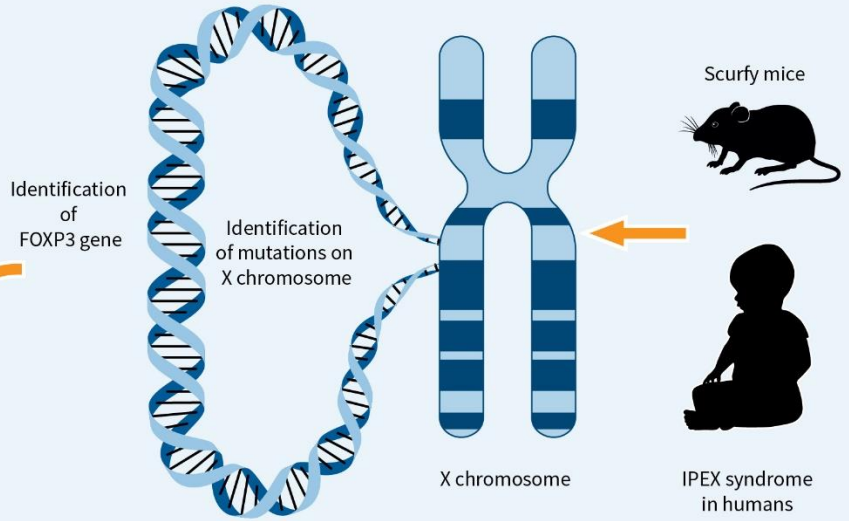
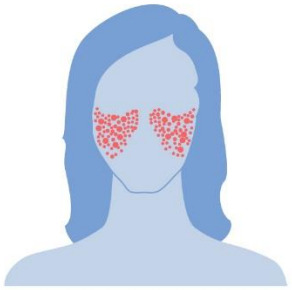
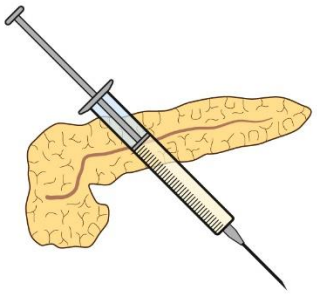


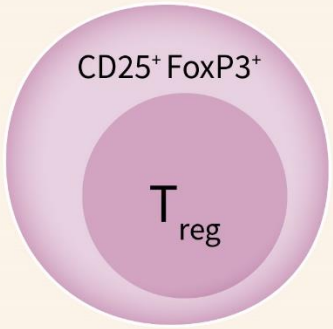
illustration: hegasy.de



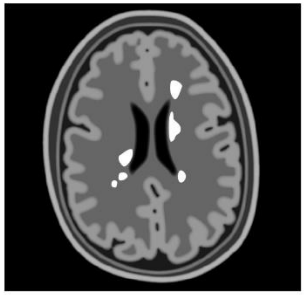
Systemic Lupus Erythematosus



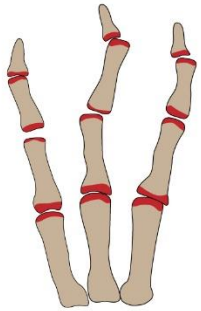
Type I Diabetes



Regulatory T cell



Multiple Sclerosis



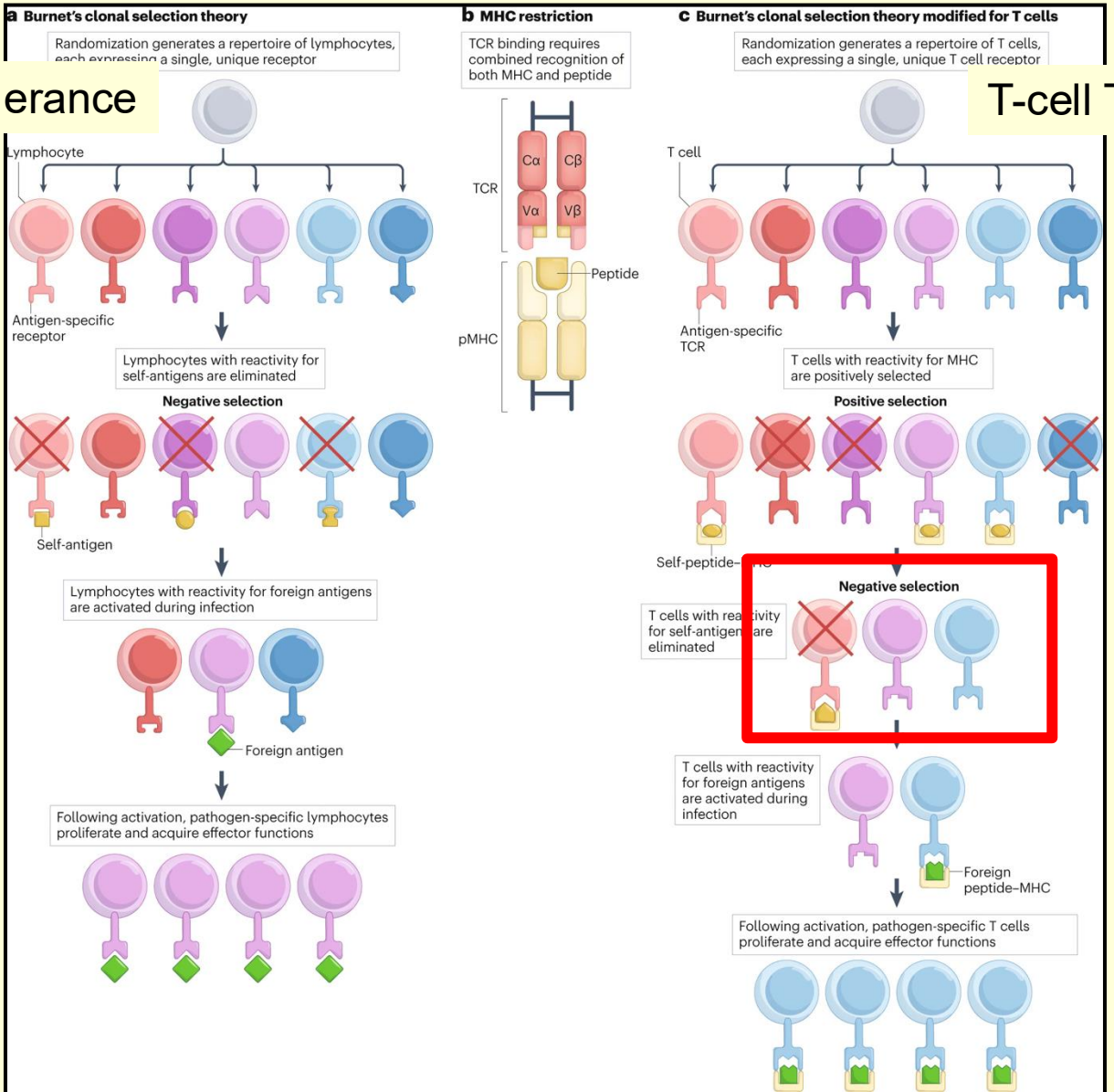
Rheumatoid Arthritis

Clonalselection Theorie Frank Macfarlane Burnet 1956

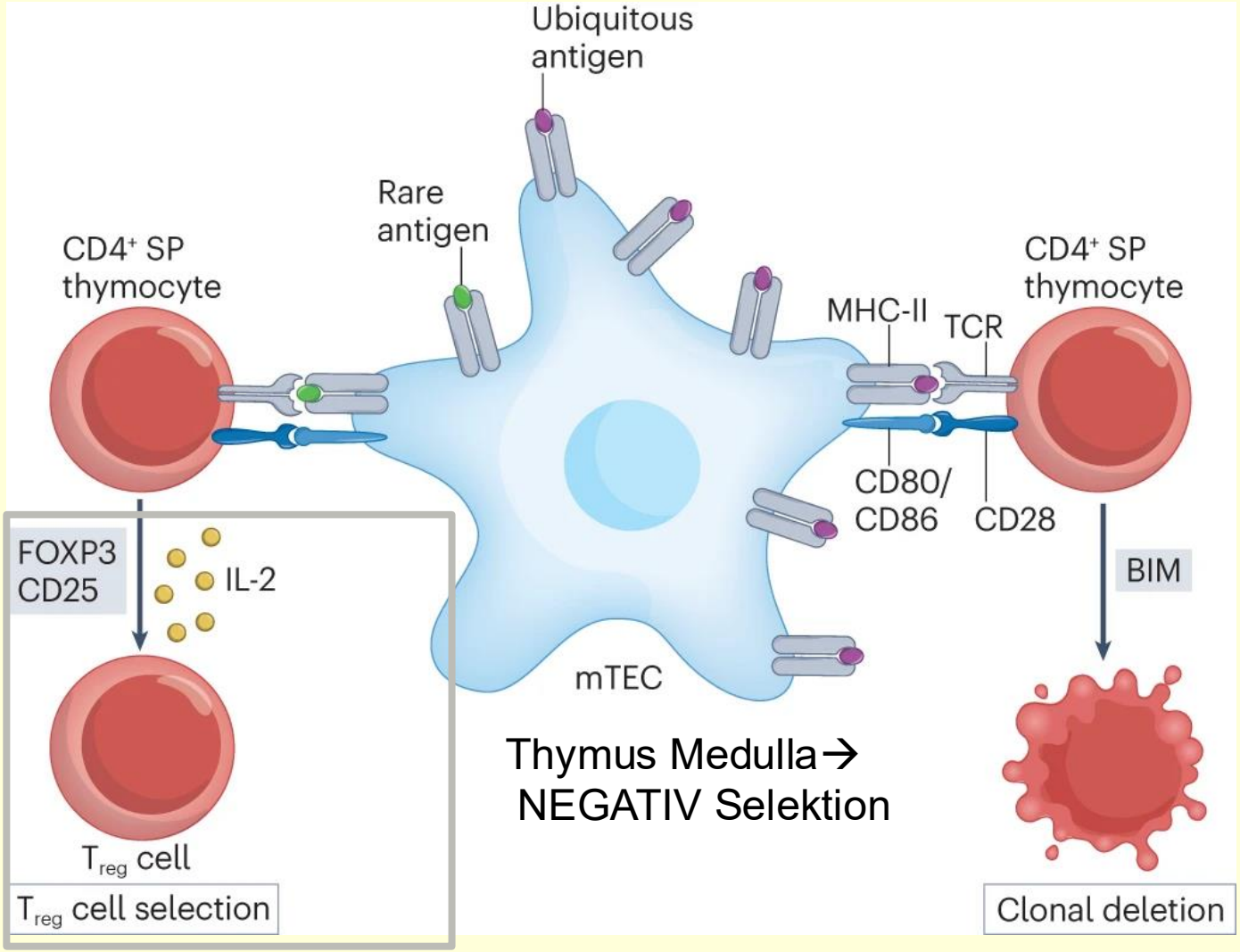
Central TOLERANCE

B-cell Tolerance

T-cell Tolerance



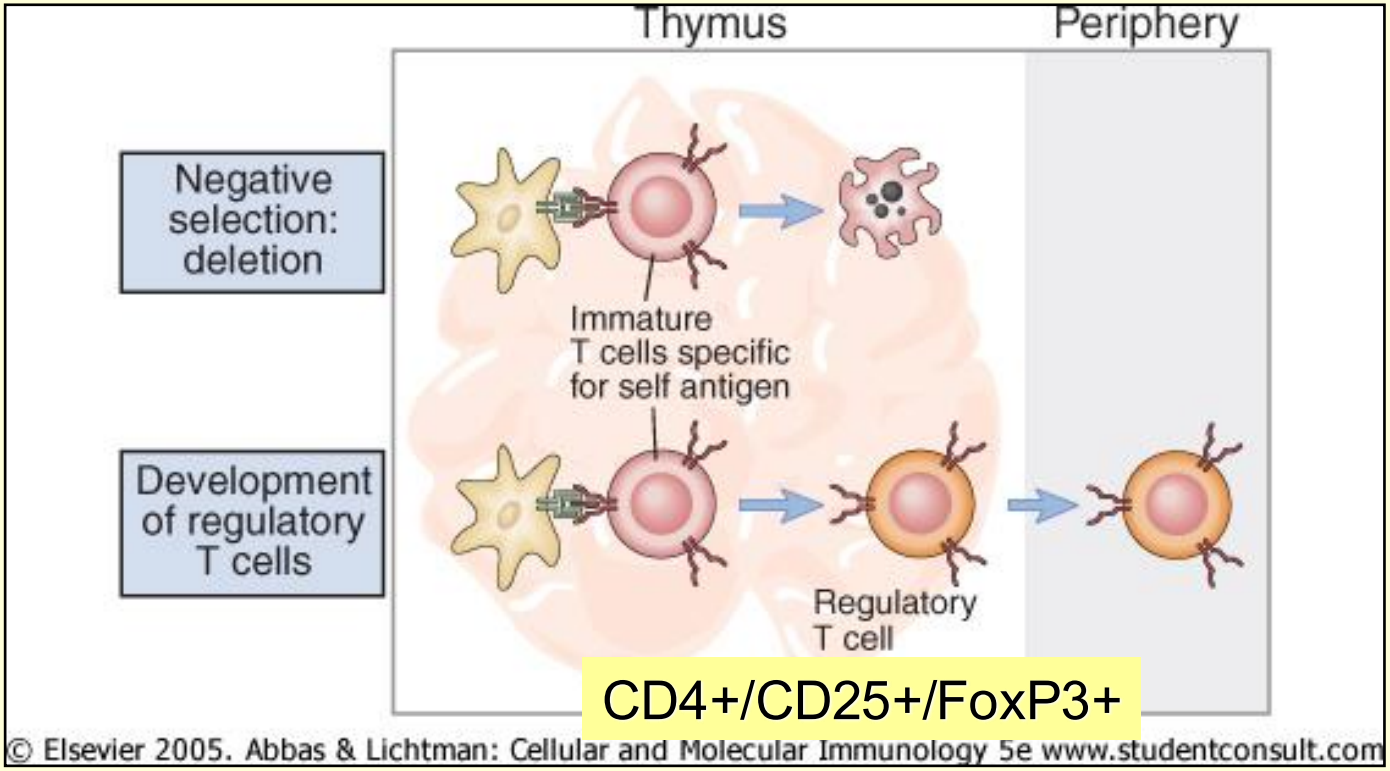
Clonal Deletion and Selection of regulatory T-cells are the main mechanisms of central (Thymus-)Tolerance



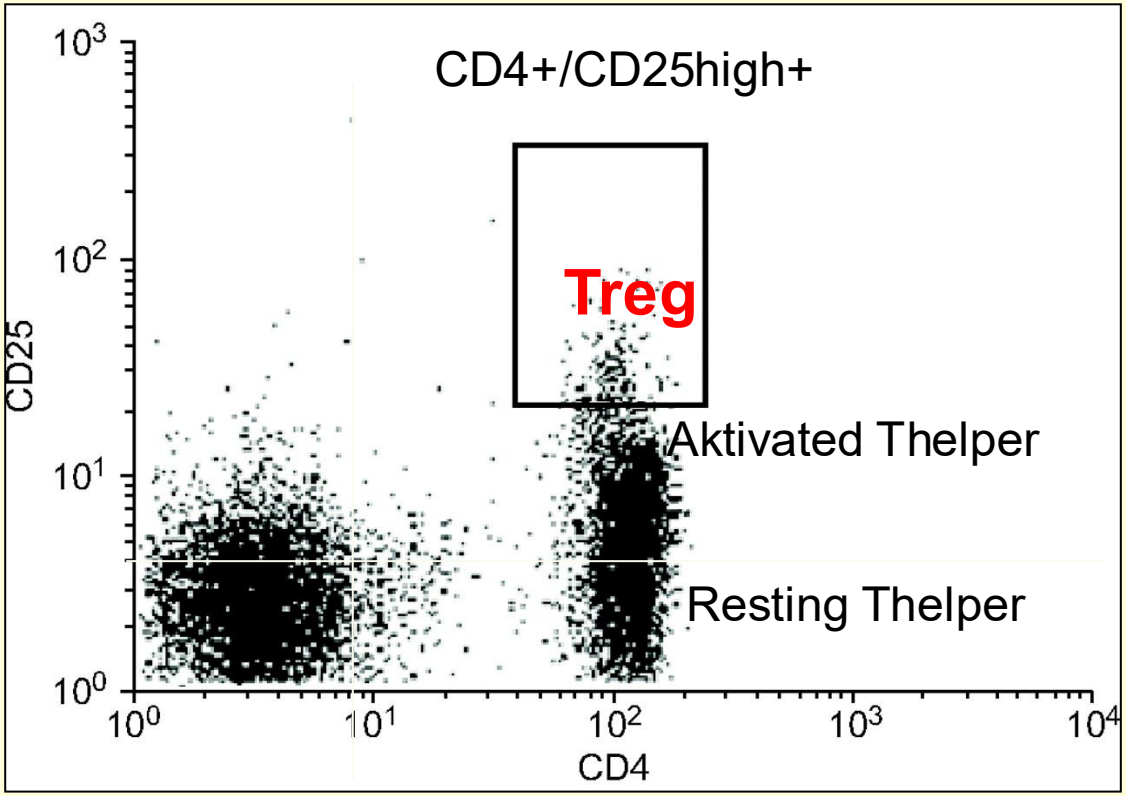
In Thymus presented antigens

- Own thymus antigens of epithelial cells, DC, Macrophages
- General cell antigens
- Extracellular antigens
- Medullar epithelial cells express other organ specific antigens (gens) → „promiscuous Gene expression through AIRE (Autoimmune regulator transcription factor)
- Infection related antigens

Natural regulatory T-cell (Treg)

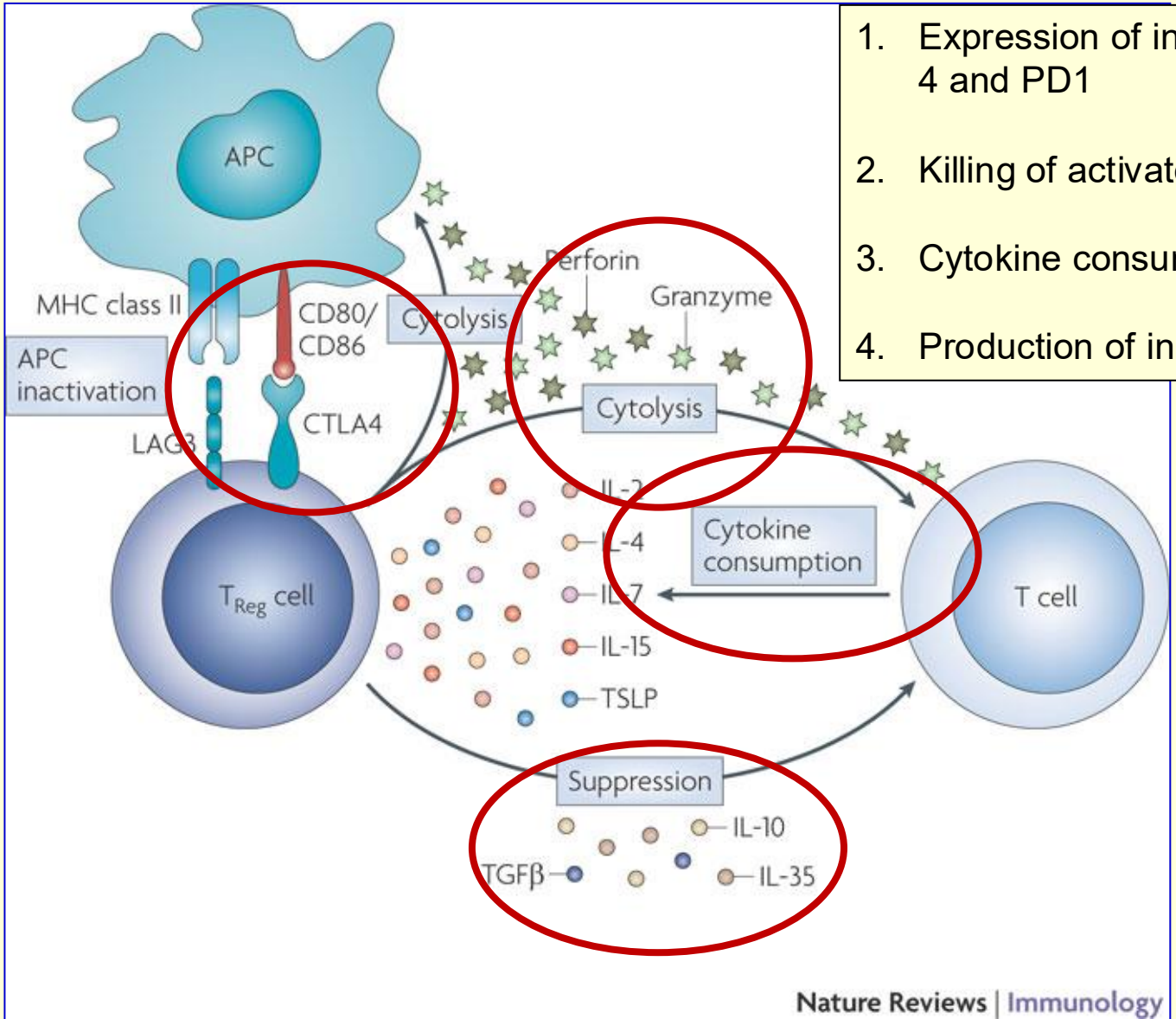


Phenotype of Treg cells



CD4+ CD25high+, CD45RBlow+, FoxP3+
MHC-II-Restriction similar to CD4+-Th-cells
Active Recirculation
IL-2-dependent Differentiation and Function

The inhibitory functions of Treg

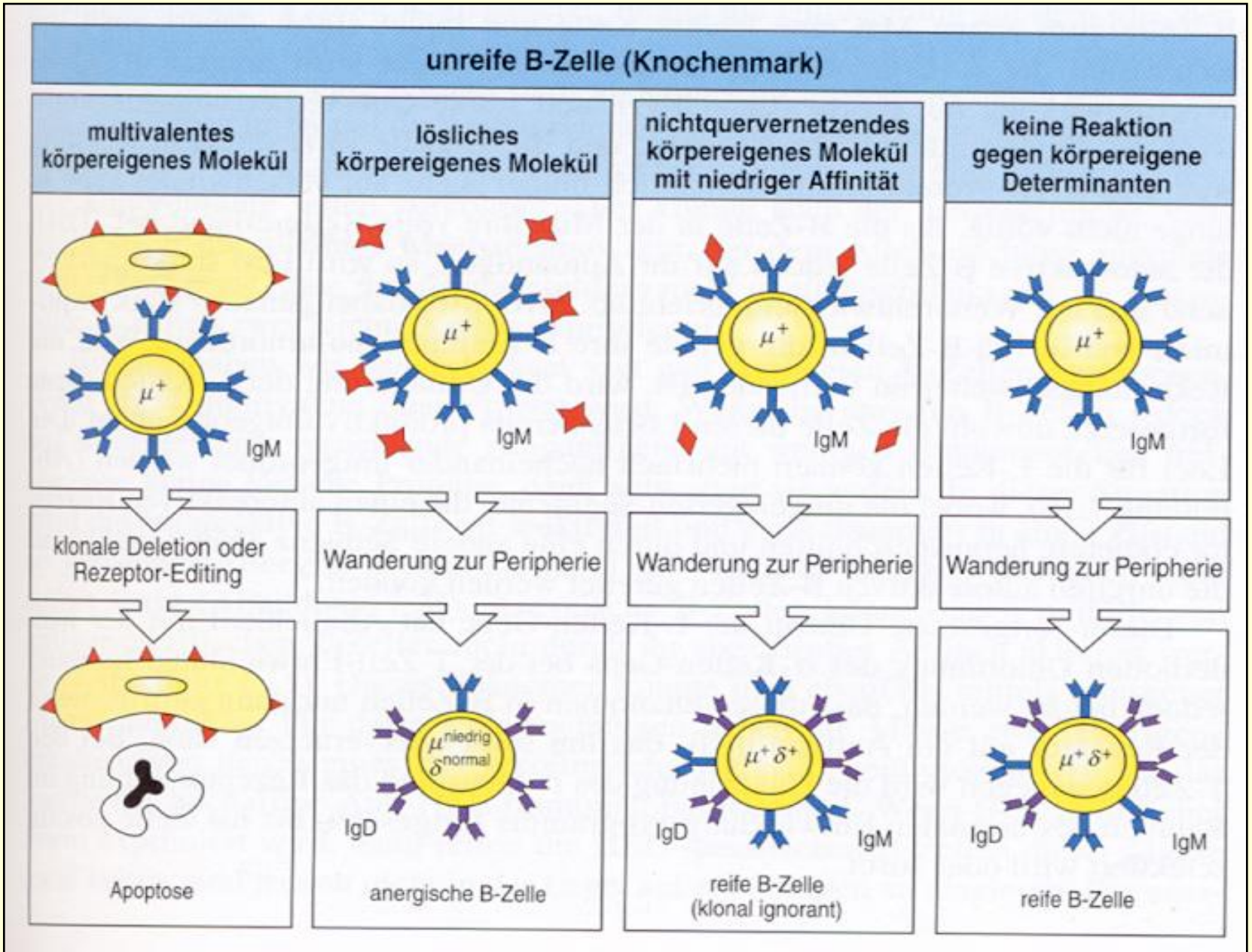


1. Expression of inhibitory Receptors: CTLA-4 and PD1
2. Killing of activated T-cells
3. Cytokine consumption
4. Production of inhibitory cytokines

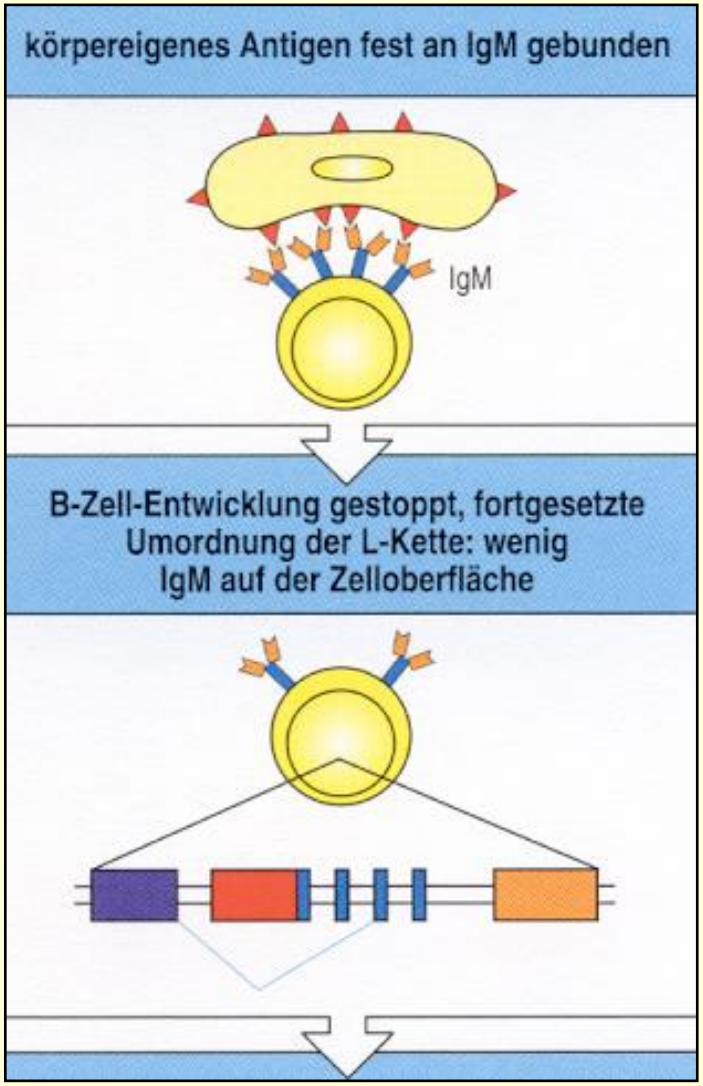
Central B-cell tolerance in BM

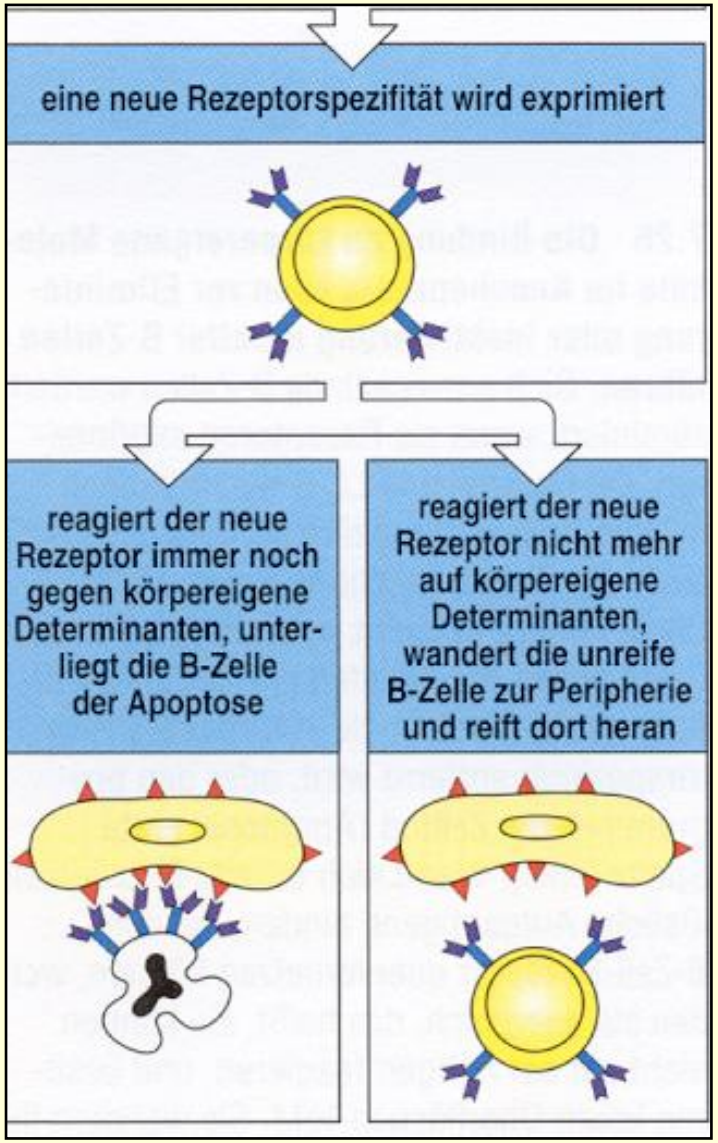
1. Receptor-Editing
2. Deletion with Apoptosis
3. Rezeptormodulation: BcR-downregulation→ Anergy

B cell selection in BM



Rezeptor-Editing





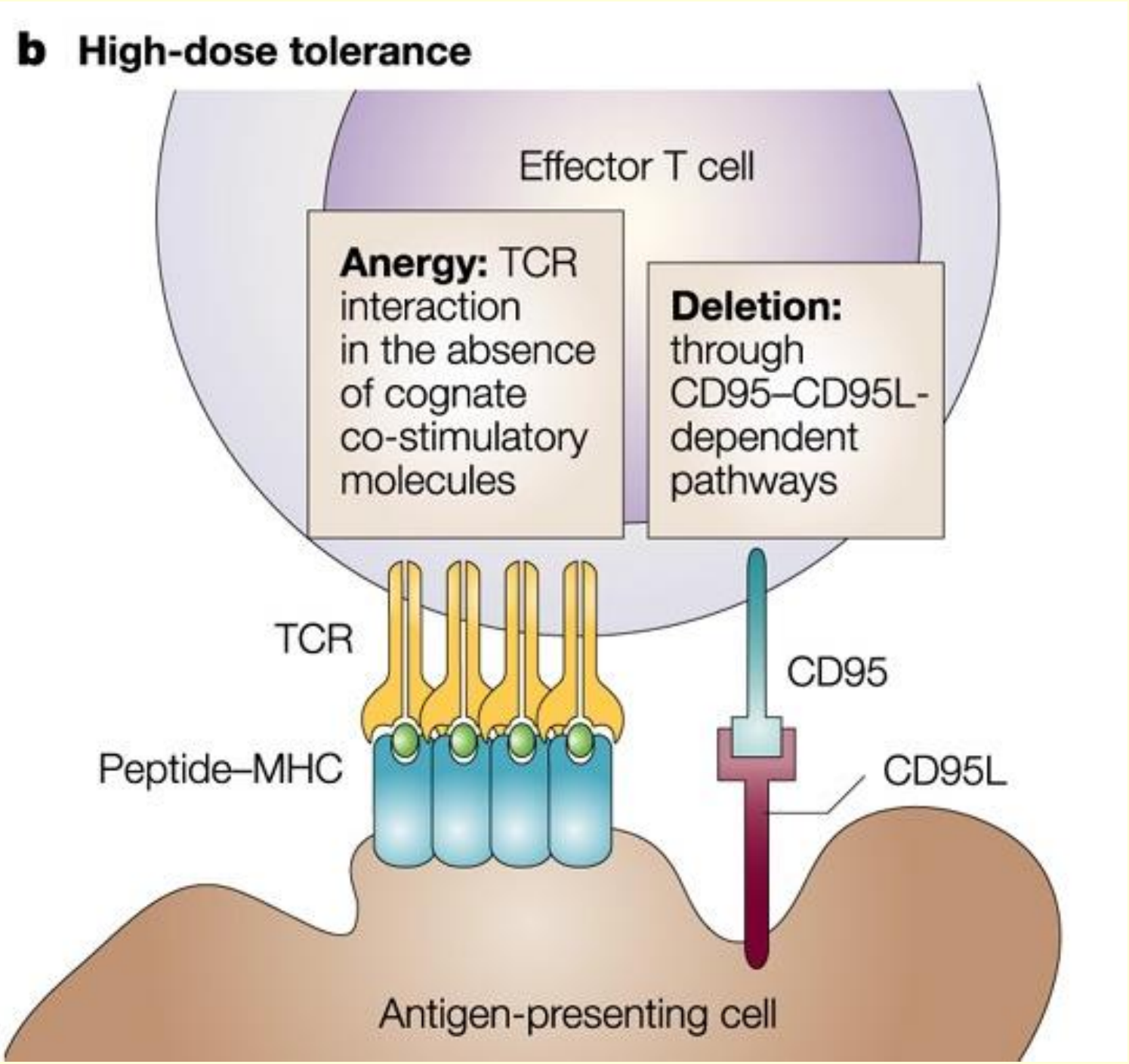
Passive tolerance

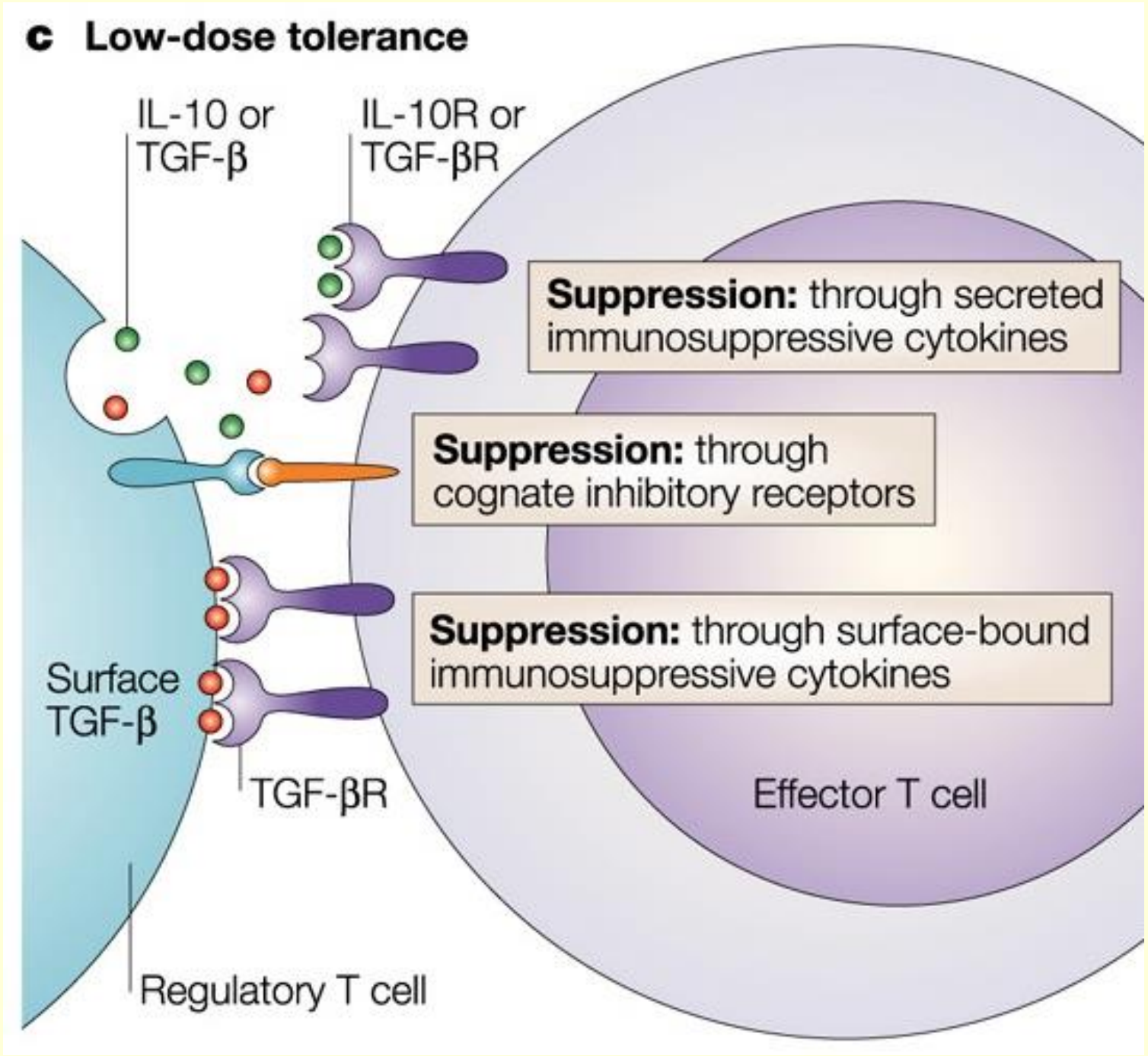
Unresponsiveness: no MHC recognition or inhibited cellular differentiation.

- **Tolerance induced by the nature of the antigen**
- **Tolerance induced by the body**

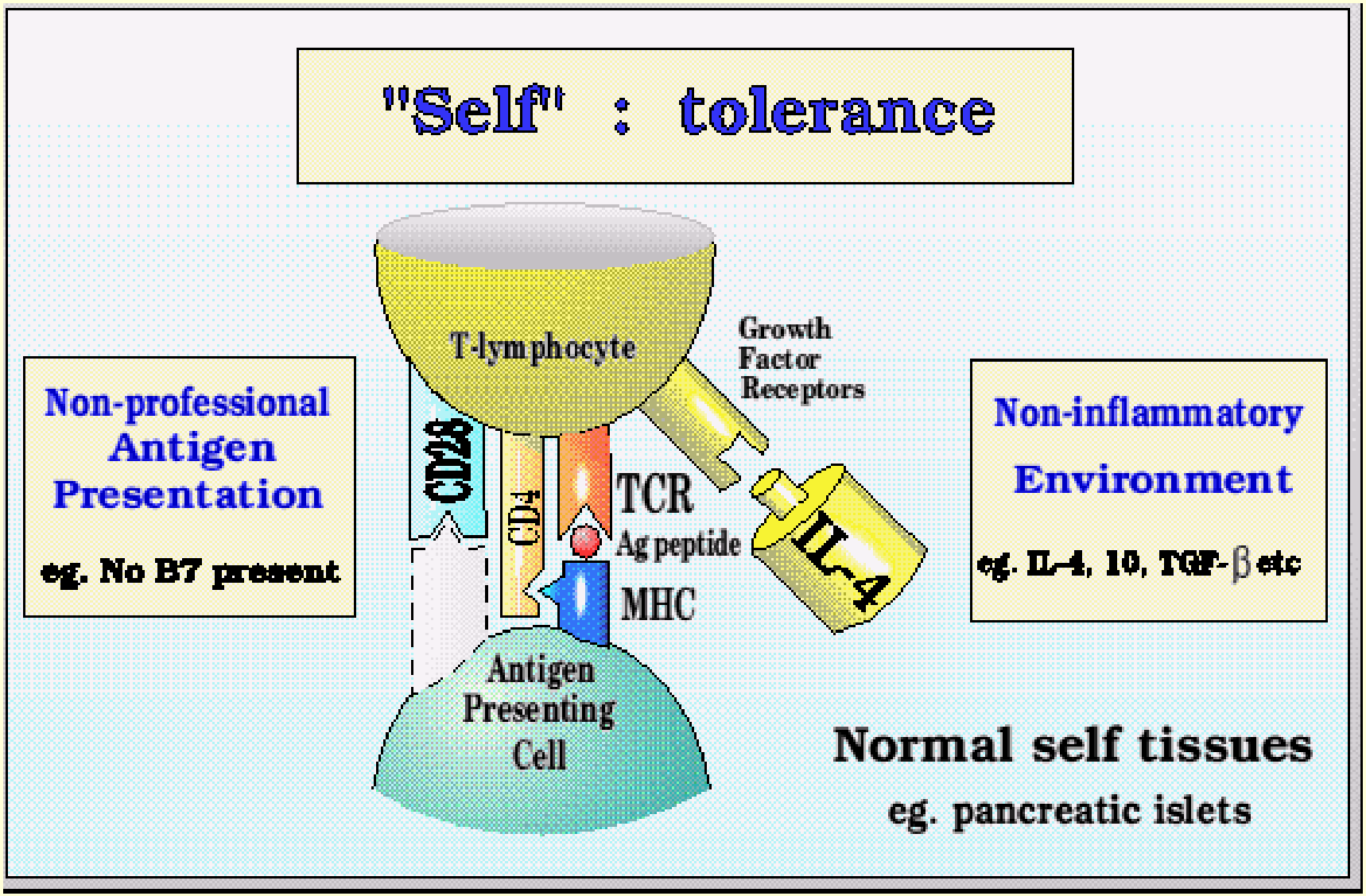
Passive tolerance induced by the nature of the antigen

- 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


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
CD95
Peptide–MHC
CD95L
Antigen-presenting cell


c Low-dose tolerance
IL-10 or TGF-β
IL-10R or TGF-βR
Suppression: through secreted immunosuppressive cytokines
Suppression: through cognate inhibitory receptors
Suppression: through surface-bound immunosuppressive cytokines
Surface TGF-β
TGF-βR
Effector T cell
Regulatory T cell

Failed co-stimulation results low dose tolerance



Tolerance induced by the body

- sequestered antigens
  - no MHC recognition
  - no antigen presentation
  - no systemic response
- heredited or acquired immunodeficiency
- clonal anergies
- induced tolerance

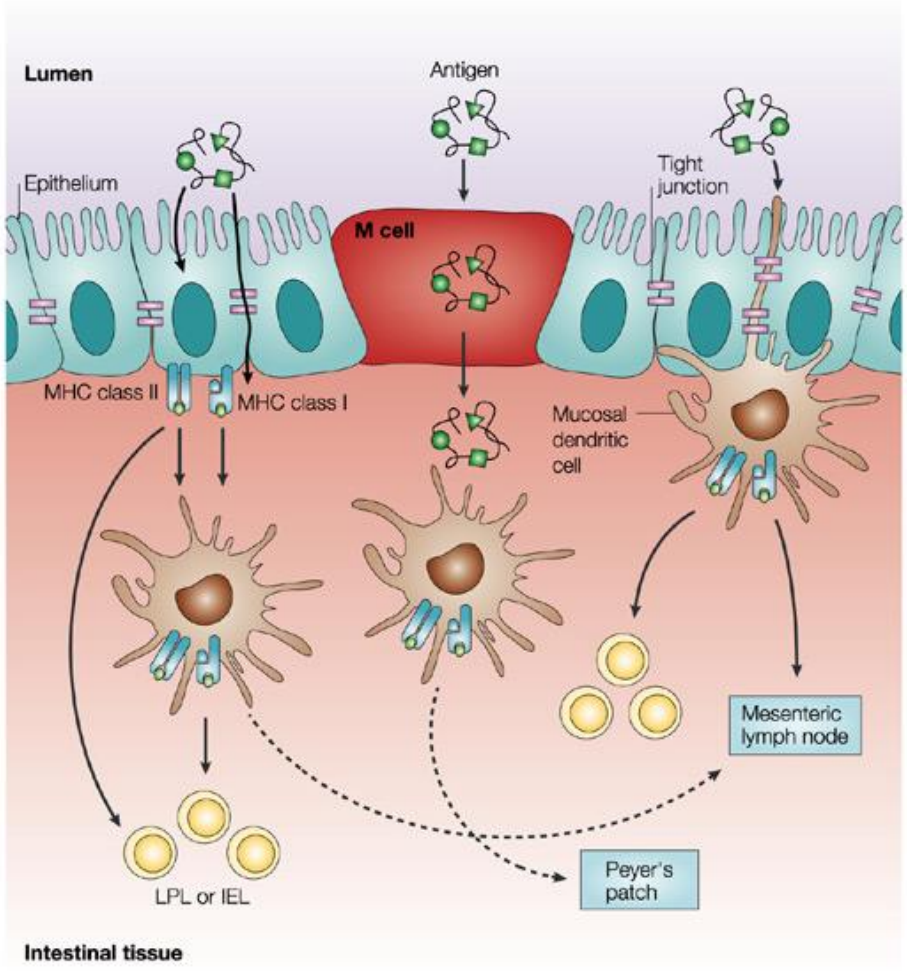
ACTIVE TOLERANCE

"Immunological homunculus"

- Low affinity IgM natural autoantibodies produced by CD5+ B cells
- γ/δ T cells
- **Innate-like** function

INDUCED Treg Cells

Oral tolerance



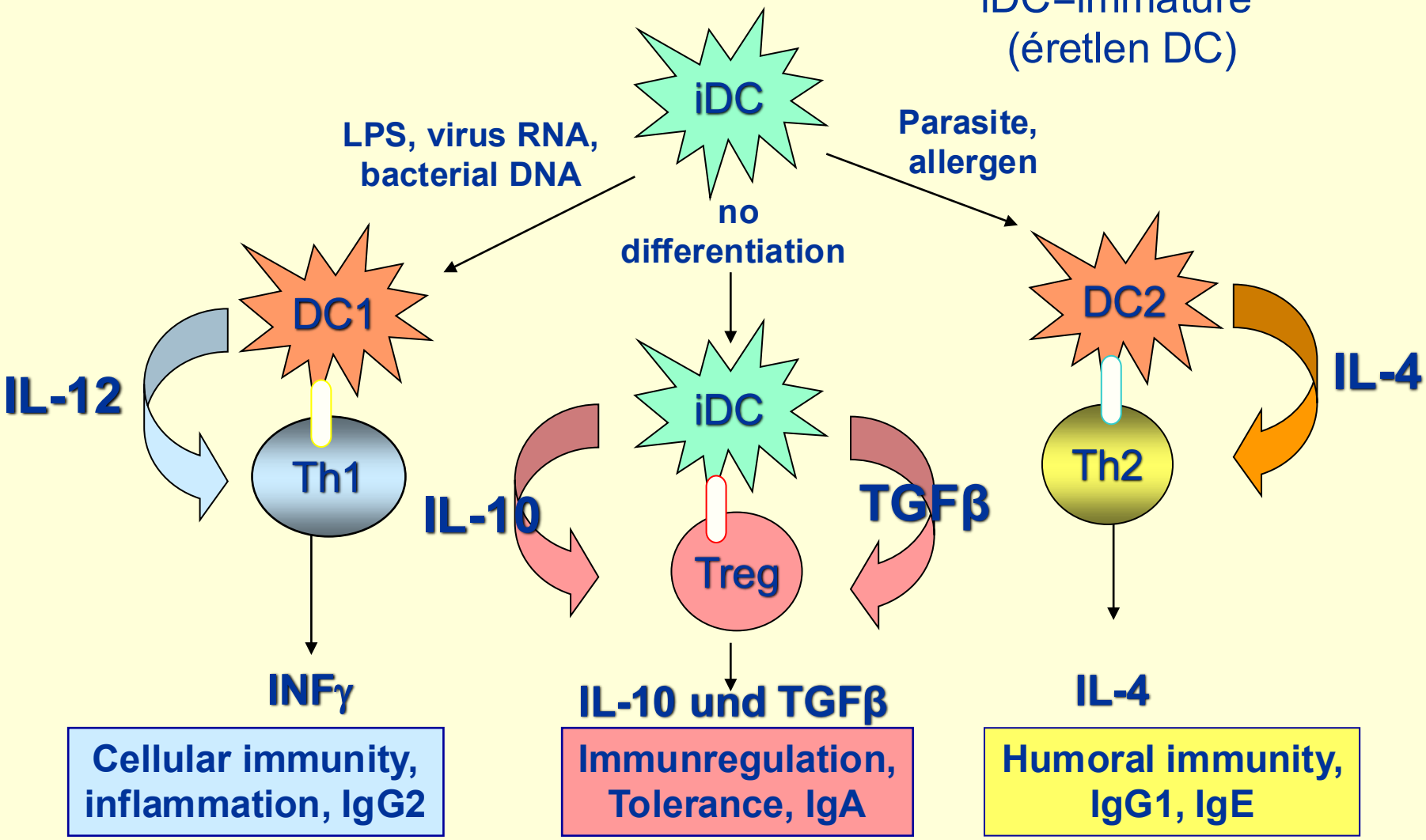
M-Cells - Endocytosis

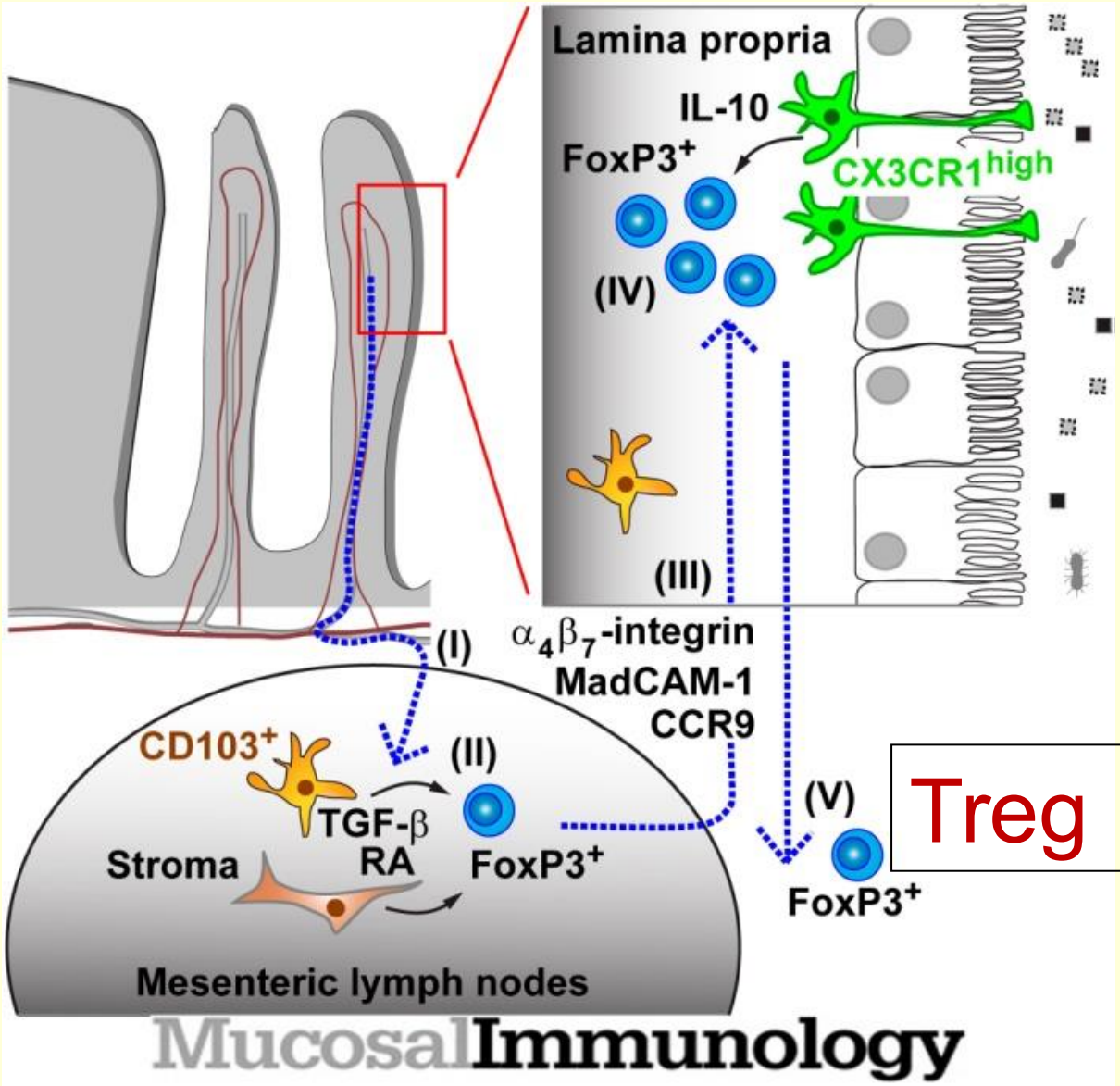
Epithelial cells – Transcytosis

DC

Through Tight Junctions

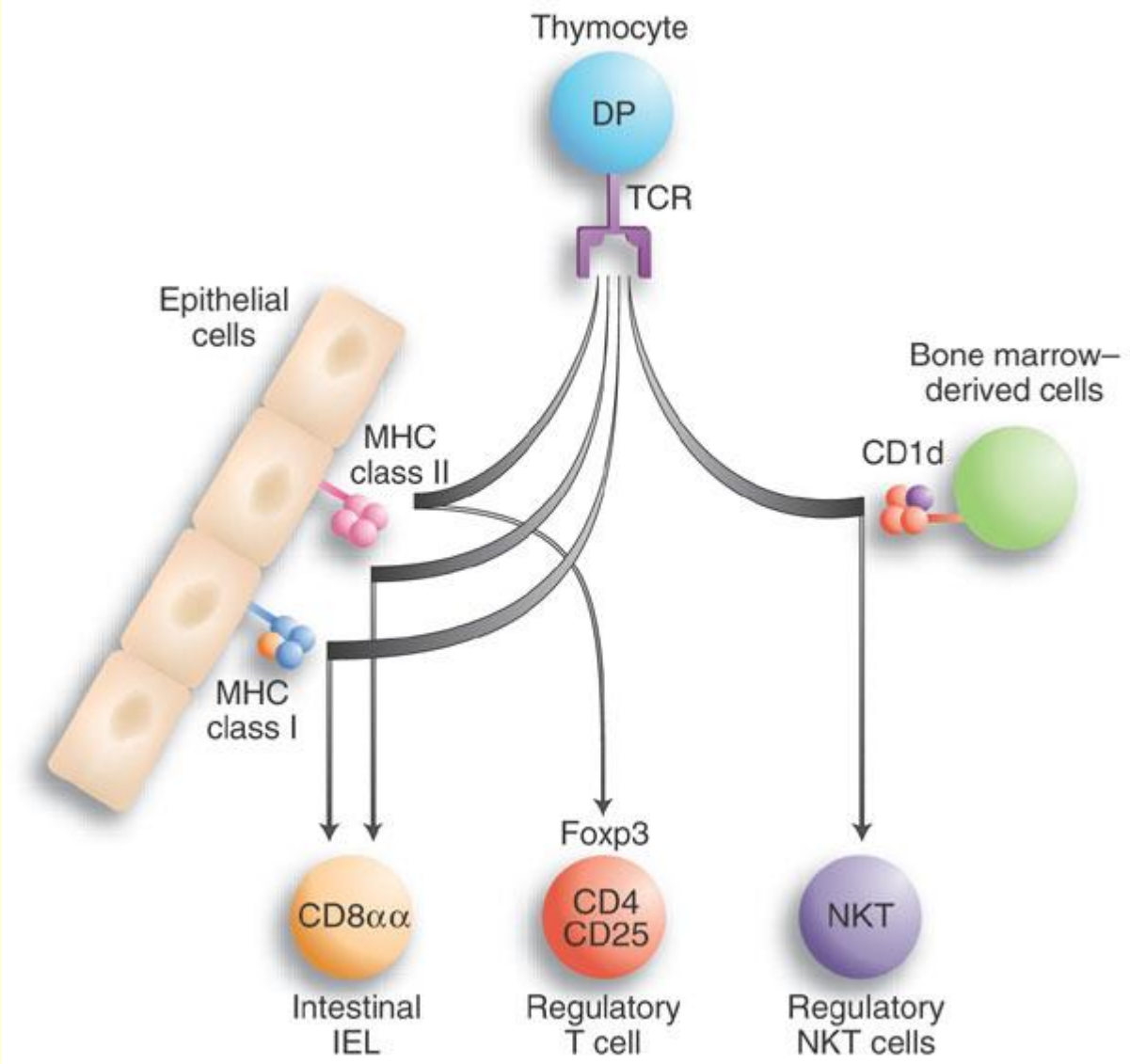
Development of induced Treg





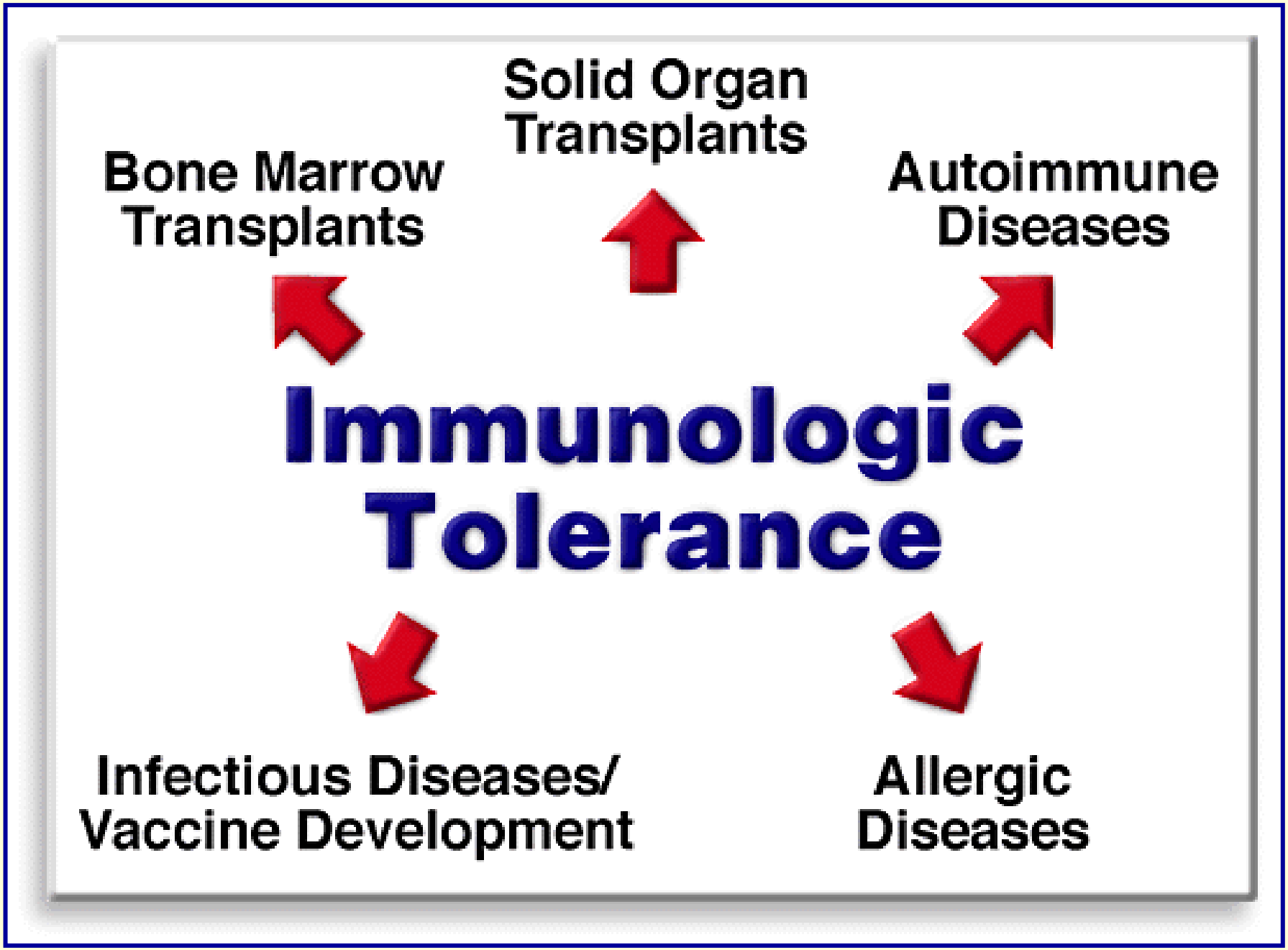
Mucosal
doi:10.1

Role of intestinal Tregs in the maintenance of tolerance



Genetically well conserved antigens recognized by natural (auto)antibodies

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


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

AUTOIMMUNITY

- **Physiological autoimmunity: part of the normal immunological regulation**

Natural autoantibodies: low affinity IgM produced by B1 cells

- **Pathological autoimmunity: diseases caused by self reacting immune responses with permanent tissue/organ injury**

High affinity IgG autoantibodies produced by T dependent B2 cells

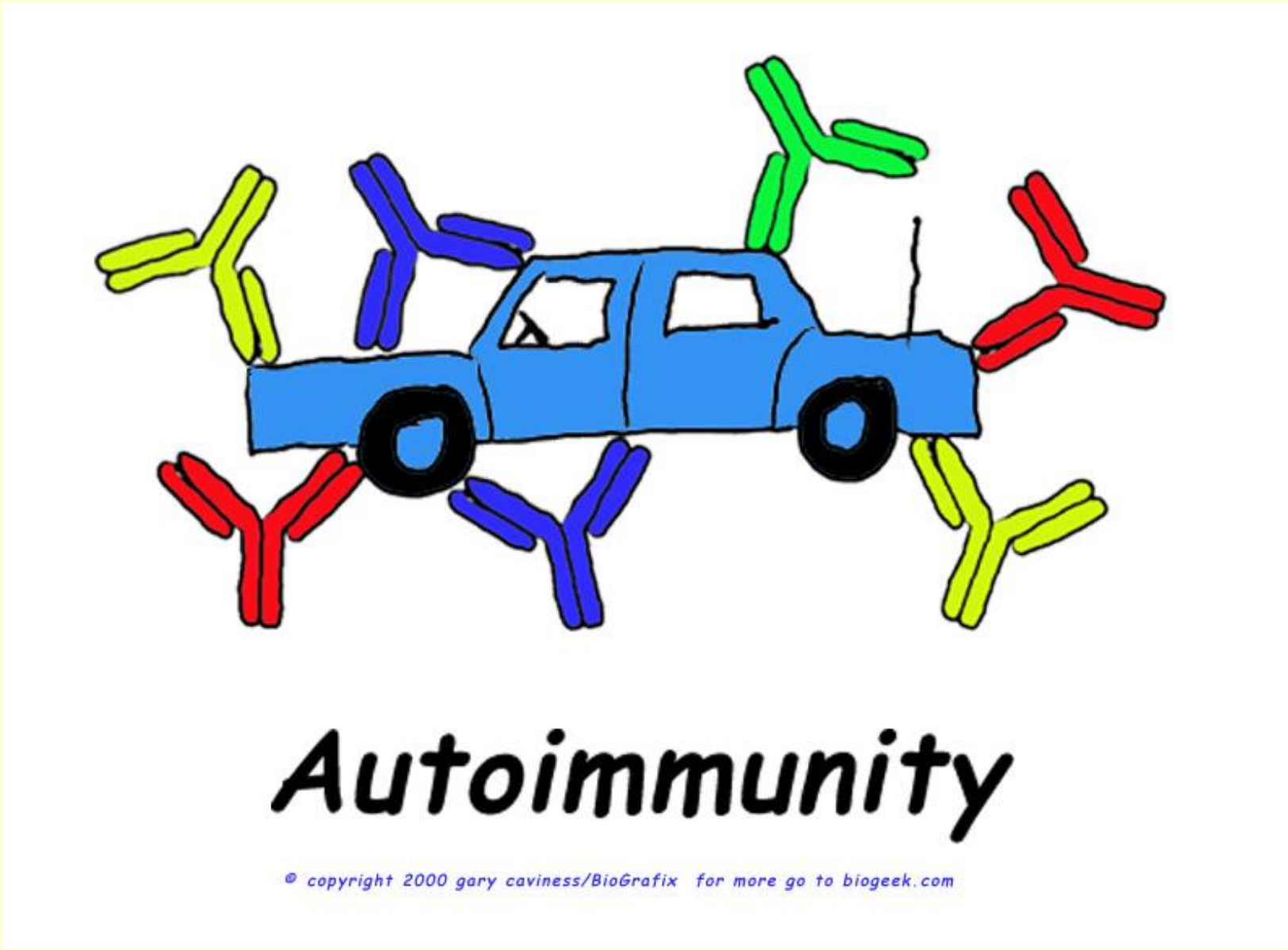
Natural and pathologic autoimmunity

Natural autoantibodies

- Polyreactivity
- Low affinity
- Usually IgM
- ng/ml conc.
- products of CD5+ B1 cells
- Target antigens:
  HSP, DNS, ACh R, (conservative structures)

Pathological autoantibodies

- High affinity
- IgG, IgA, IgM type antibodies
- mg/ml serum conc.
- products of Mature B2 type lymphocytes
- target antigens:
  Cell surface structures, receptors, proteins from the cytoplasm, nucleoproteins



Autoimmune diseases affect 5-7% of the population !

Autoimmunity by the failure of self tolerance

- Abnormal selection of lymphocyte repertoire
- Polyclonal activation of anergic self-reactive lymphocytes
- Stimulation by foreign antigens that cross-react with self

Pathomechanism of autoimmunity

- **Inflammation and tissue necrosis**

  - **Cellular components:**

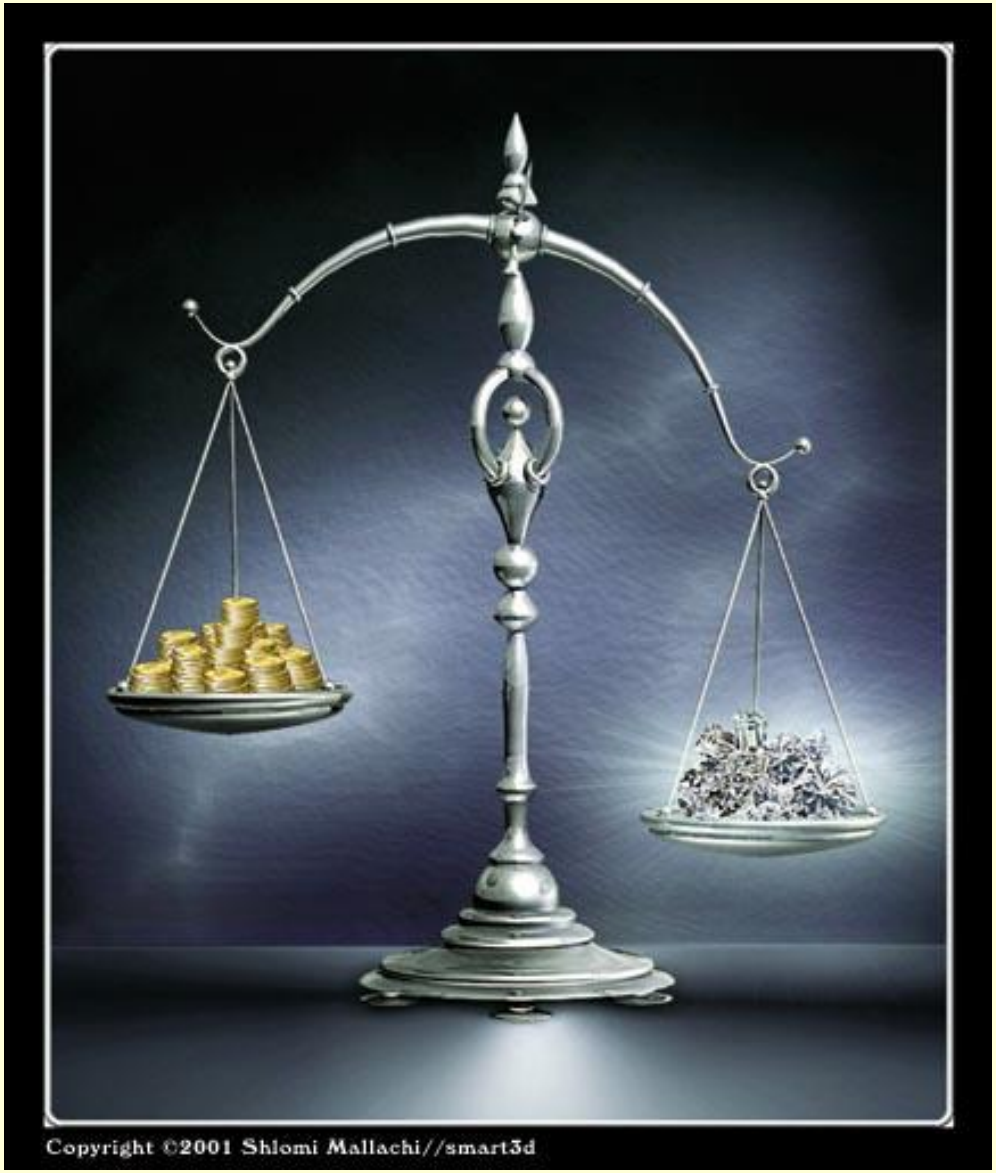
(T cells CD8 and Th1, NK, Mf, DC, Ne, Eo, Ba, Mc)

  - **Humoral components:**

(Ig+complement, ADCC, cytokines, chemokines, tissue hormones and mediators)

Autoimmune steady state

Self reacting immune response with tissues damages



Active tolerance and tissue repair

Pathomechanism of autoimmunity

- **Multifactor mechanism**

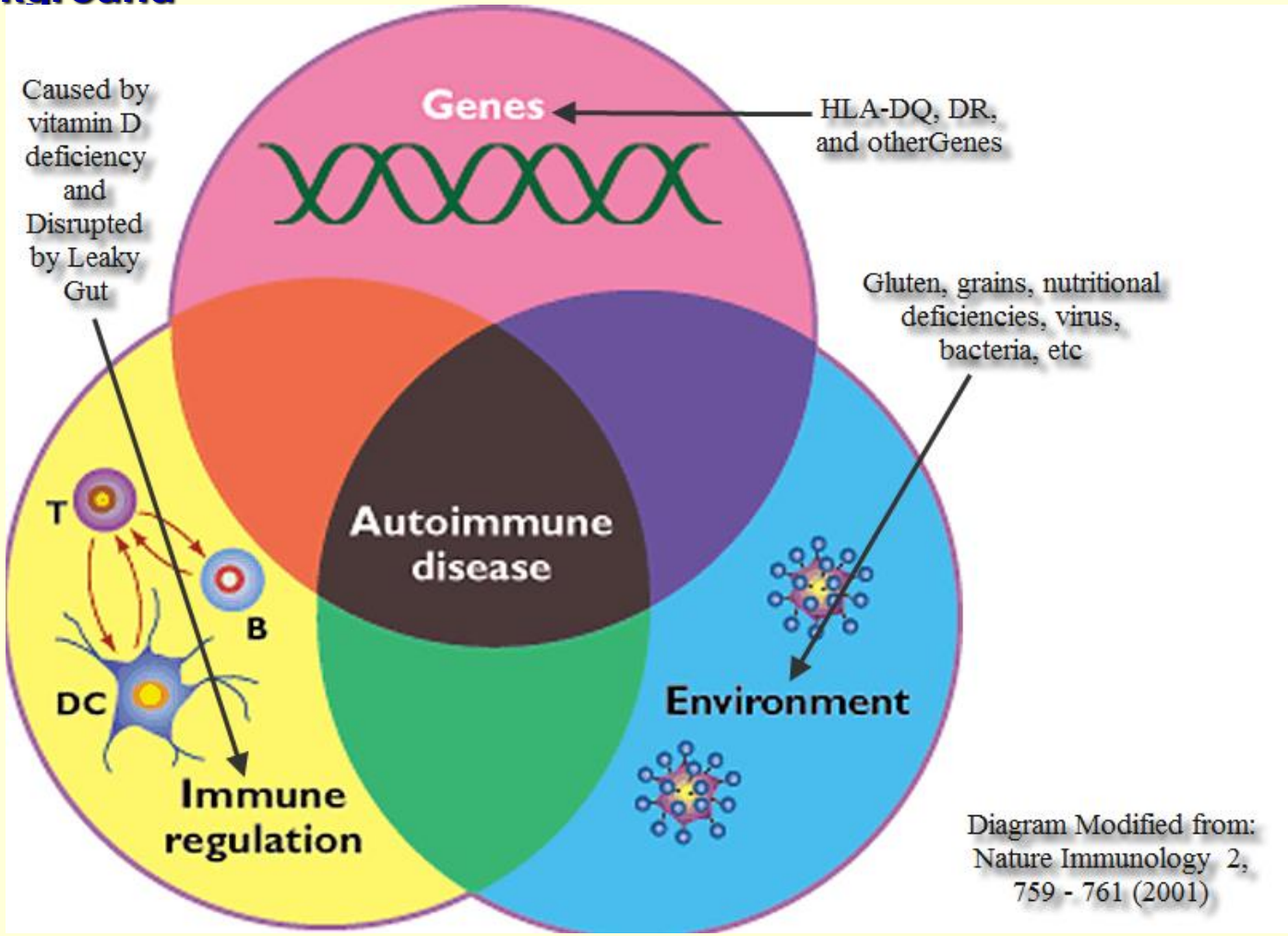
  (general catastrophe of bio-regulation caused by external and internal factors)

  - Autoimmune *"steady state"* (failure of dynamic balance on self tolerance and autoimmunity)

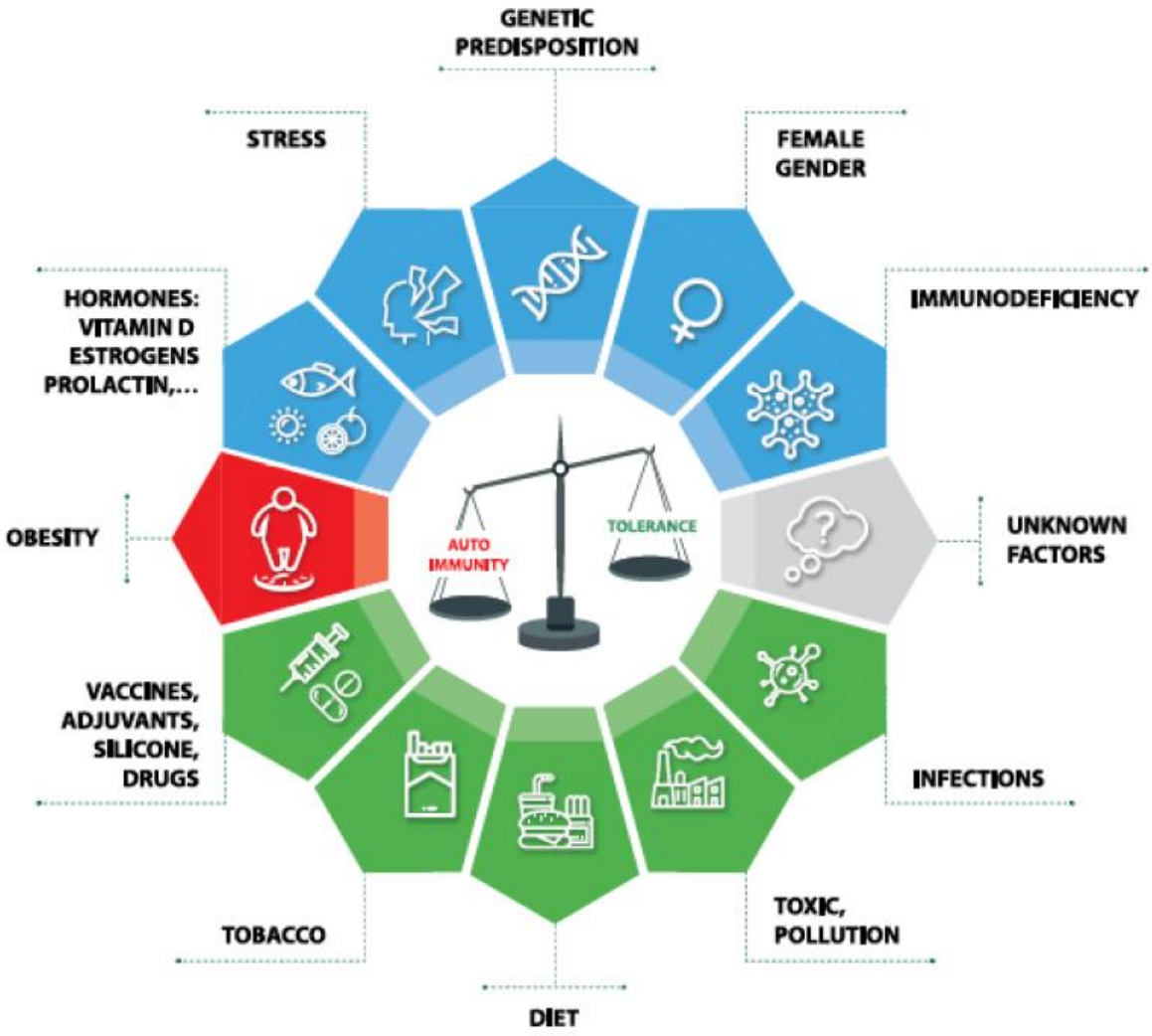
  - Role of infections (molecular mimicry or inefficient natural antibody network)

Pathomechanisms of autoimmune diseases

- Autoimmunity by the antigen
- Failed differentiation and selection of lymphocytes
- Genetic background

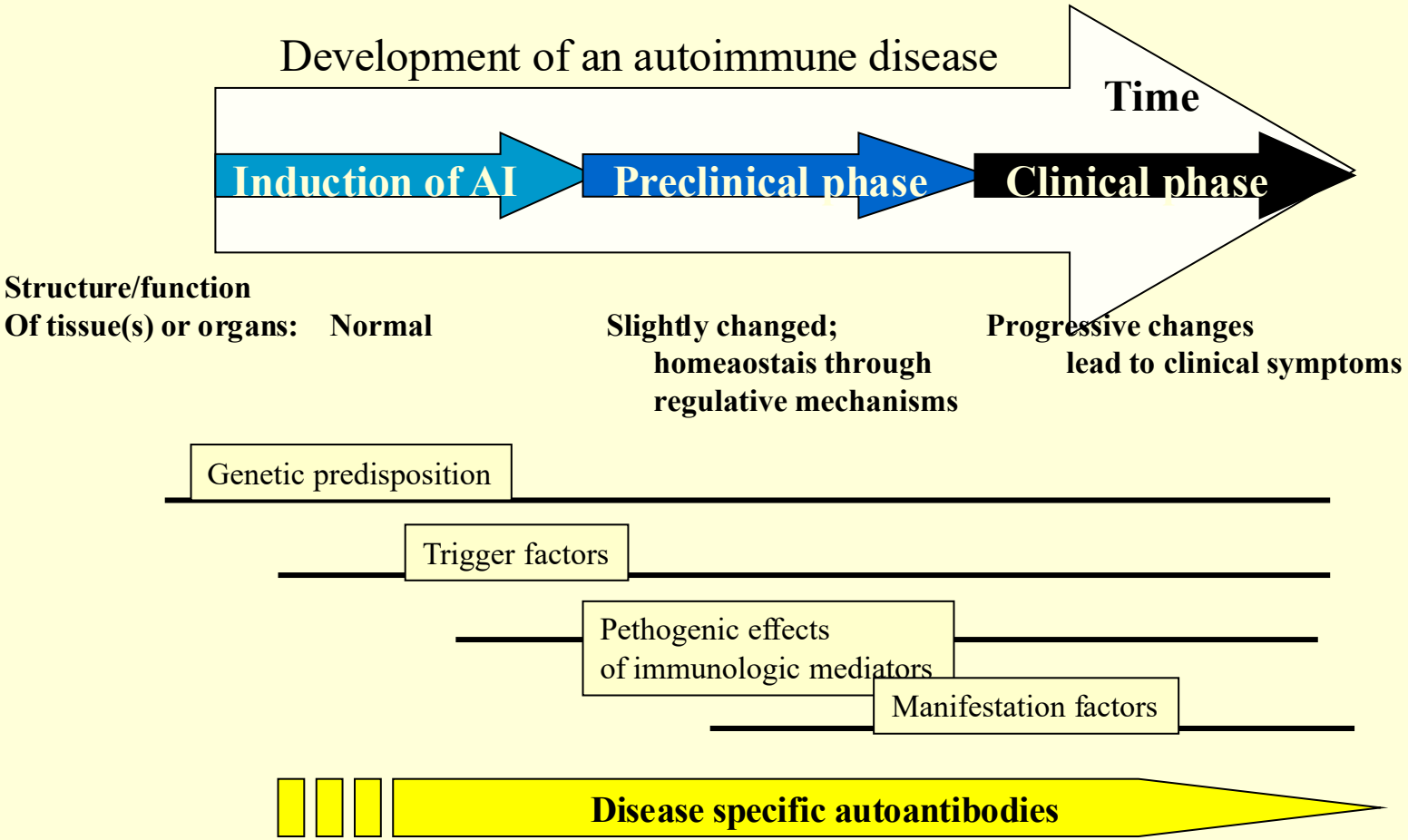


ENDOGENOUS FACTORS



EXTERNAL FACTORS

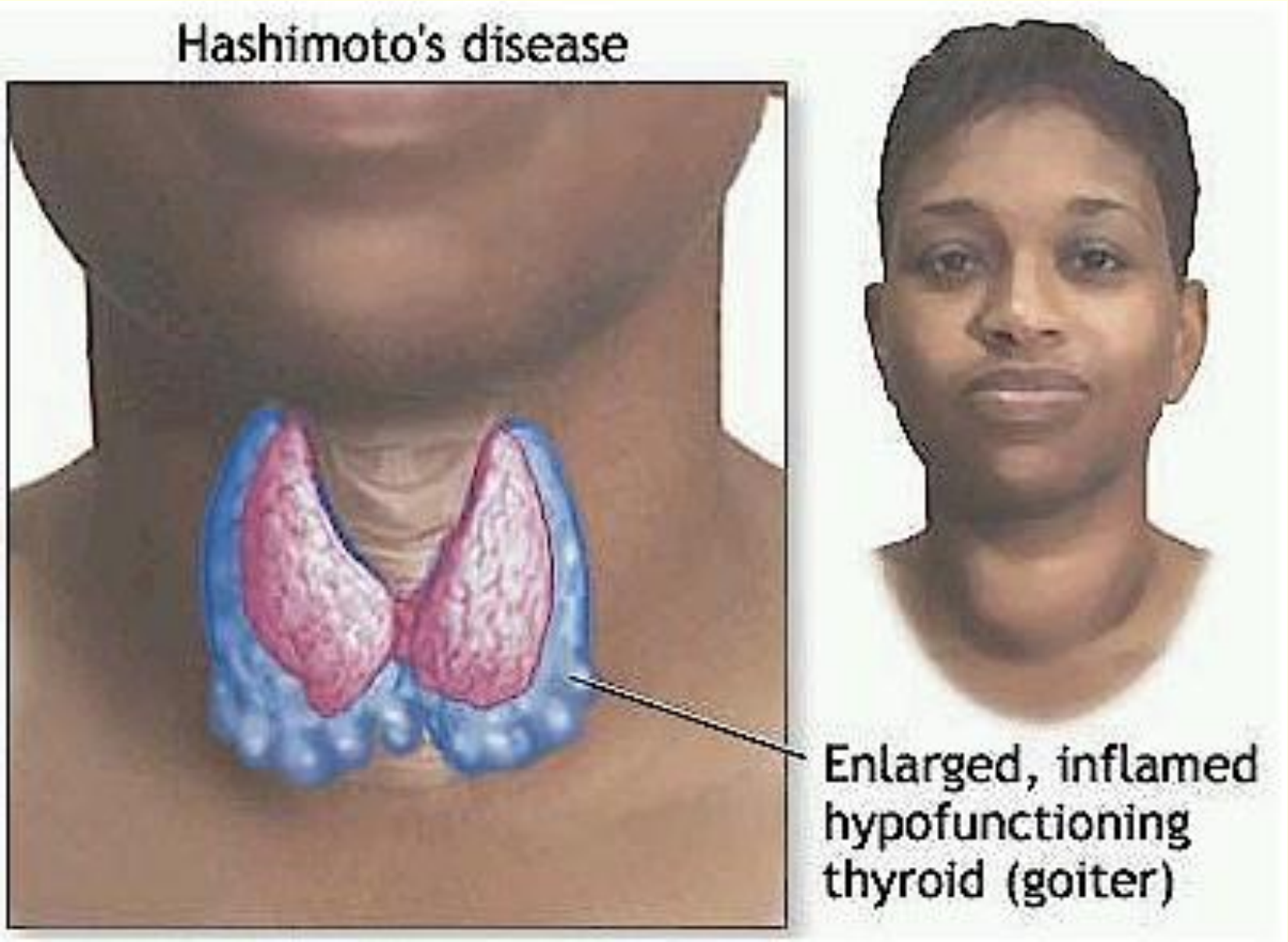
The predictive relevance of autoantibodies



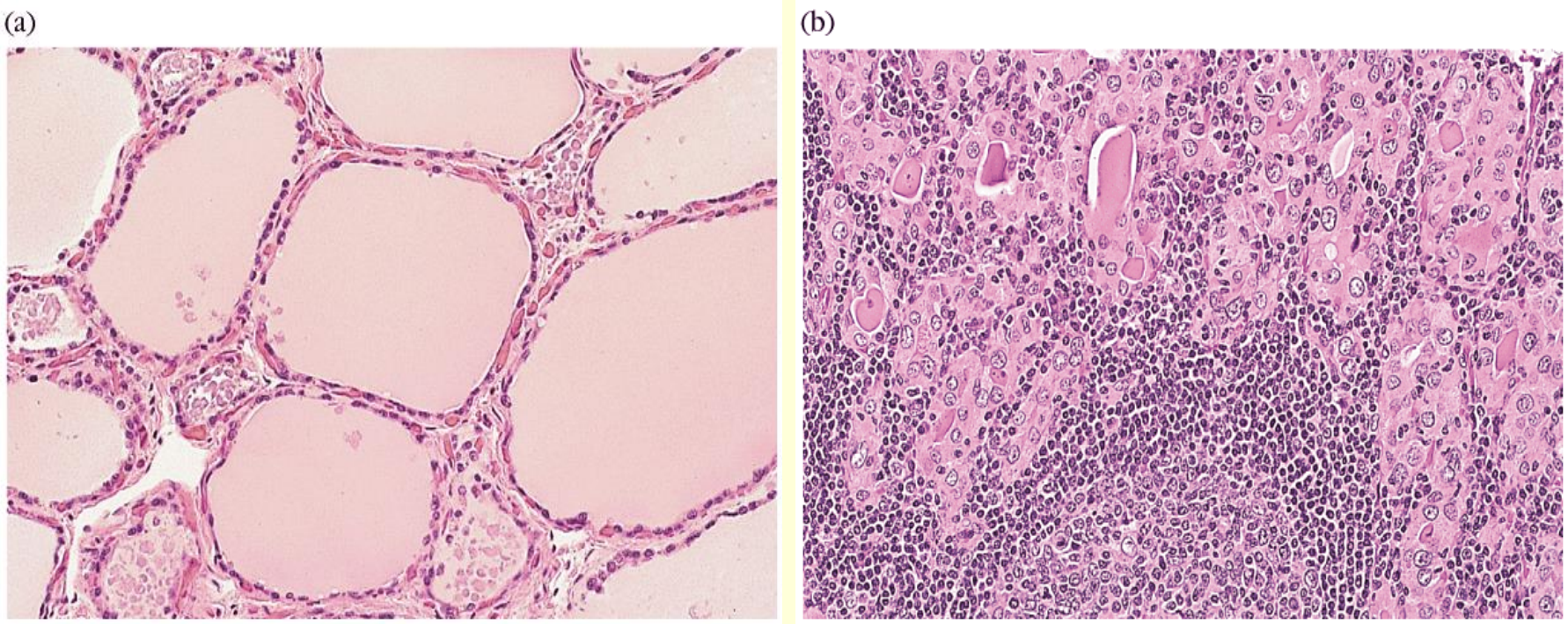
Pathogens and human antigens	Peptid residues	Overlaping sequences
Human cytomegalovirus IE2	79	PDPLGRPDED
HLA-DR molecule	60	VTELGRPDAE
Poliovirus VP2	70	STTKESRGTT
Acetylcholine receptor	176	TVIKESRGTK
Papilloma virus E2	76	SLHLESLKDS
Insulin receptor	66	VYGLESLKDL
Klebsiella pneumoniae nitrogenase enzym	186	SRQTDREDE
HLA-B27 molecule	70	KAQTDREDL
Adenovirus 12 E1B	384	LRRGMFRPSQCN
Alfa-gliadin	206	LGQGSFRPSQQN
HIV p24	160	GVETTTPS
Human IgG	466	GVETTTPS
Measles virus P3	31	EISDNLGQE
Myelin basic protein	61	EISFKLGQE

Thyroid			
Graves disease	**DR3**	3.7	TSH receptor ↑
Hashimoto thyroiditis	**DR5**		Thyroid microsoma peroxidase, thyroglobin ↓
Pancreas			
IDDM	**DR4/ DR3**	20	Beta island cells ↓
	DQB 0302	**100**	GAD, HSP60, junB, insulin, pre/pro insulin
Neural system			**Brain medulla,** MBP, PLP, MOG, MAG
Sclerosis multiplex	**DR2**	4.8	
Myasthenia gravis	**DR3**	2.5	**Peripheral neurons-striated musceles**
			Acetylcholine receptor
Hearth: rheumatic fever	**DR3, DR4**		S. B-haemolythicus M/myosin
Blood: AHA, thrombocytopenia			Vvs gP
			Thrombocyte gP

SLE	DR3/ DR2	5.8	Kidney, serous layers ds/ssDNS, Sm-IC, SSA
Sjögren syndrome			Exocrine glands, salivary glands, liver, kidney, brain, thyroid gland, hearth, lung, gut
Rheumatoid arthritis (RA)	DR4 DR1	4.2	Joint connective tissue, collagen Type II, IgG RF
Spondyloarthritis (SPA)	B27	**90**	Vertebrate
Reiter disease	B27	**33**	Clamydia, Yersinia
Salmonella/Shigella arthritis	B27	**20.7**	

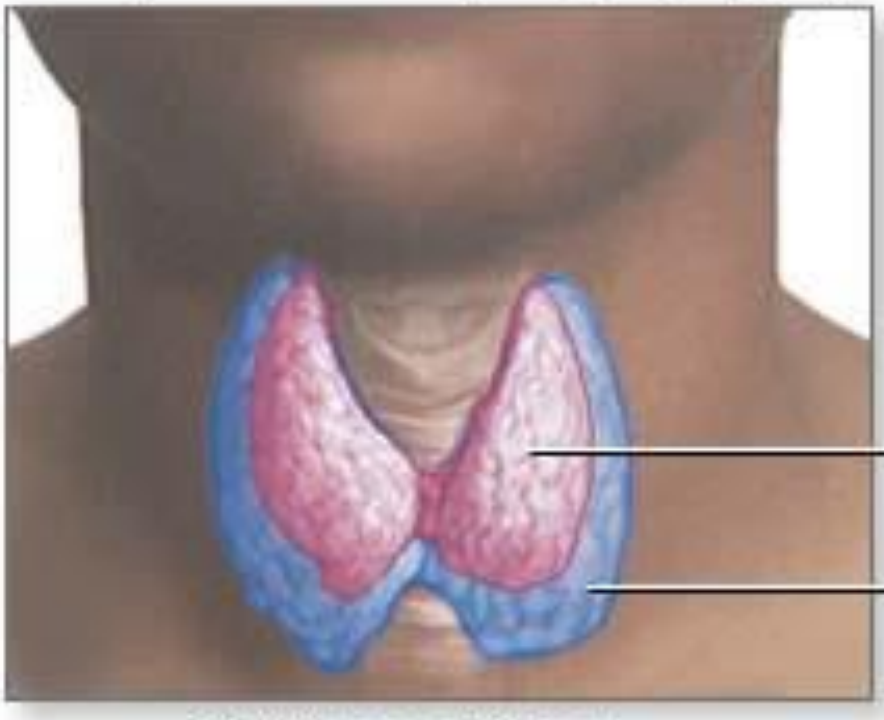

Hashimoto's disease
Enlarged, inflamed hypofunctioning thyroid (goiter)

Hashimoto's thyroiditis





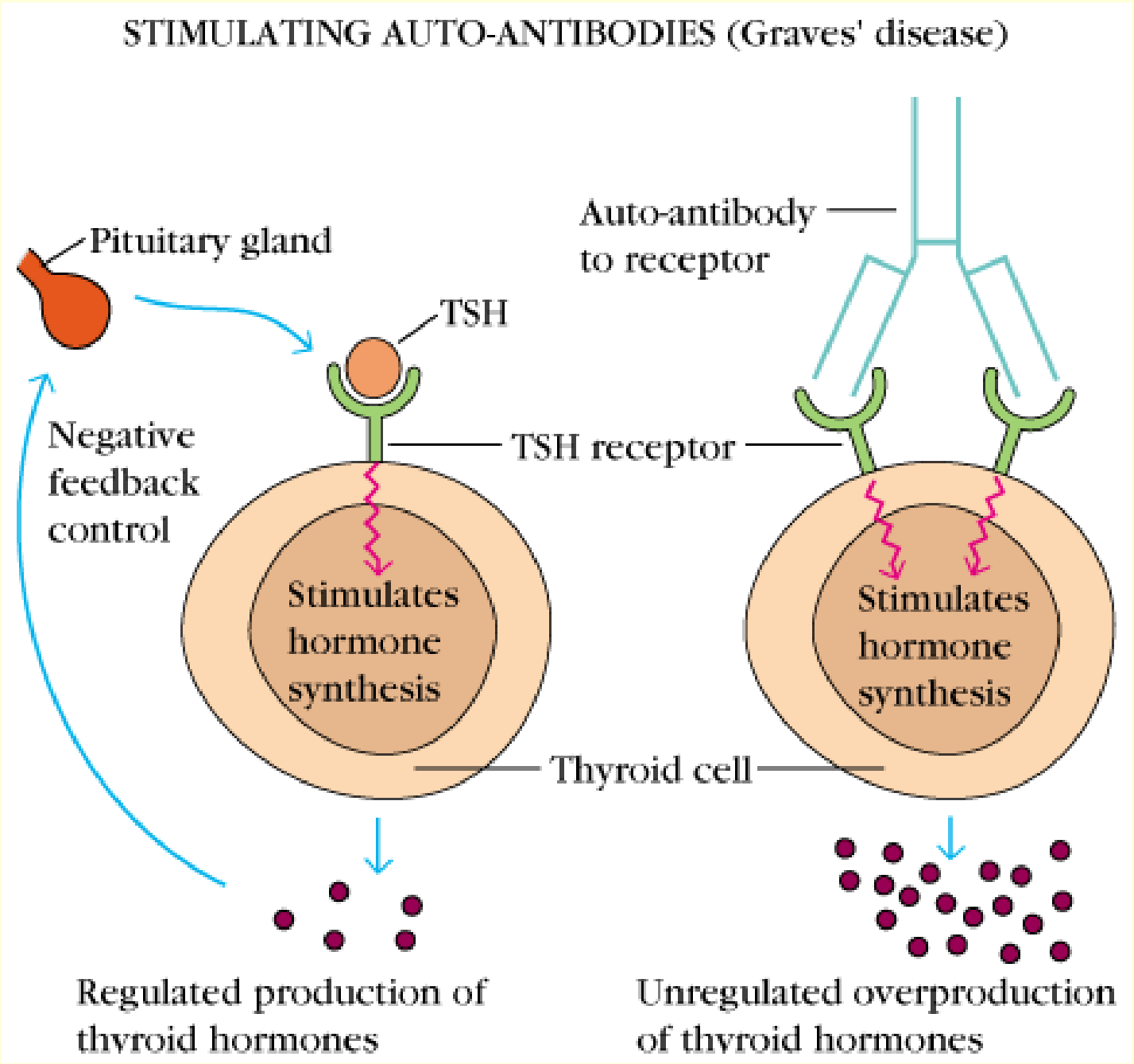
Exophthalmos (bulging eyes)



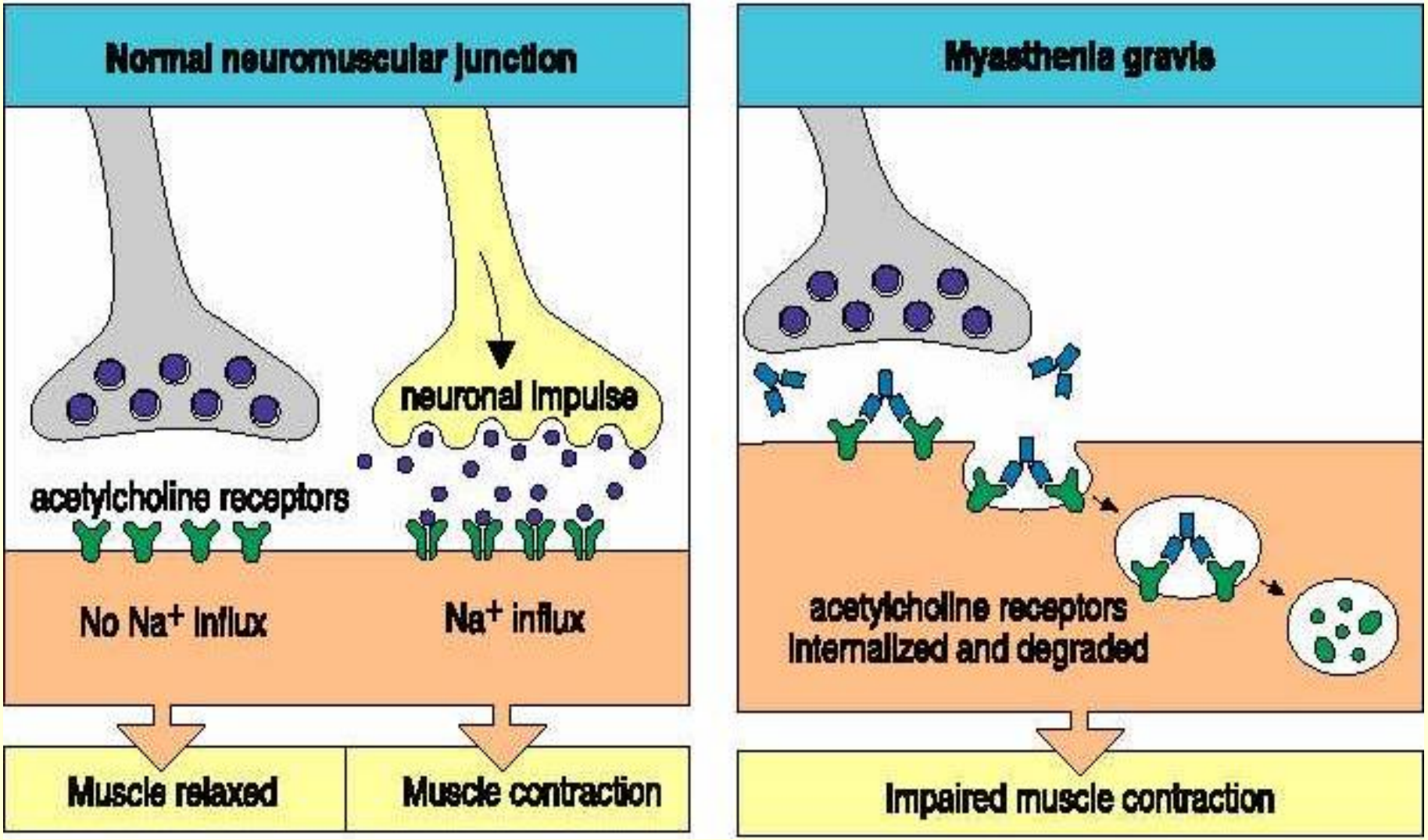
Diffuse goiter

Graves' disease is a common cause of hyperthyroidism, an over-production of thyroid hormone, which causes enlargement of the thyroid and other symptoms such as exophthalmos, heat intolerance and anxiety

A.D.A.M.


STIMULATING AUTO-ANTIBODIES (Graves' disease)
Pituitary gland
TSH
Auto-antibody
to receptor
Negative
feedback
control
TSH receptor
Stimulates
hormone
synthesis
Stimulates
hormone
synthesis
Thyroid cell
Regulated production of
thyroid hormones
Unregulated overproduction
of thyroid hormones

Myasthenia gravis



Rheumatoid arthritis

