

Basic Immunology

Lecture 23rd

Immunological tolerance

Cellular and molecular mechanisms of the immunological tolerance

Autoimmunity

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 cells 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

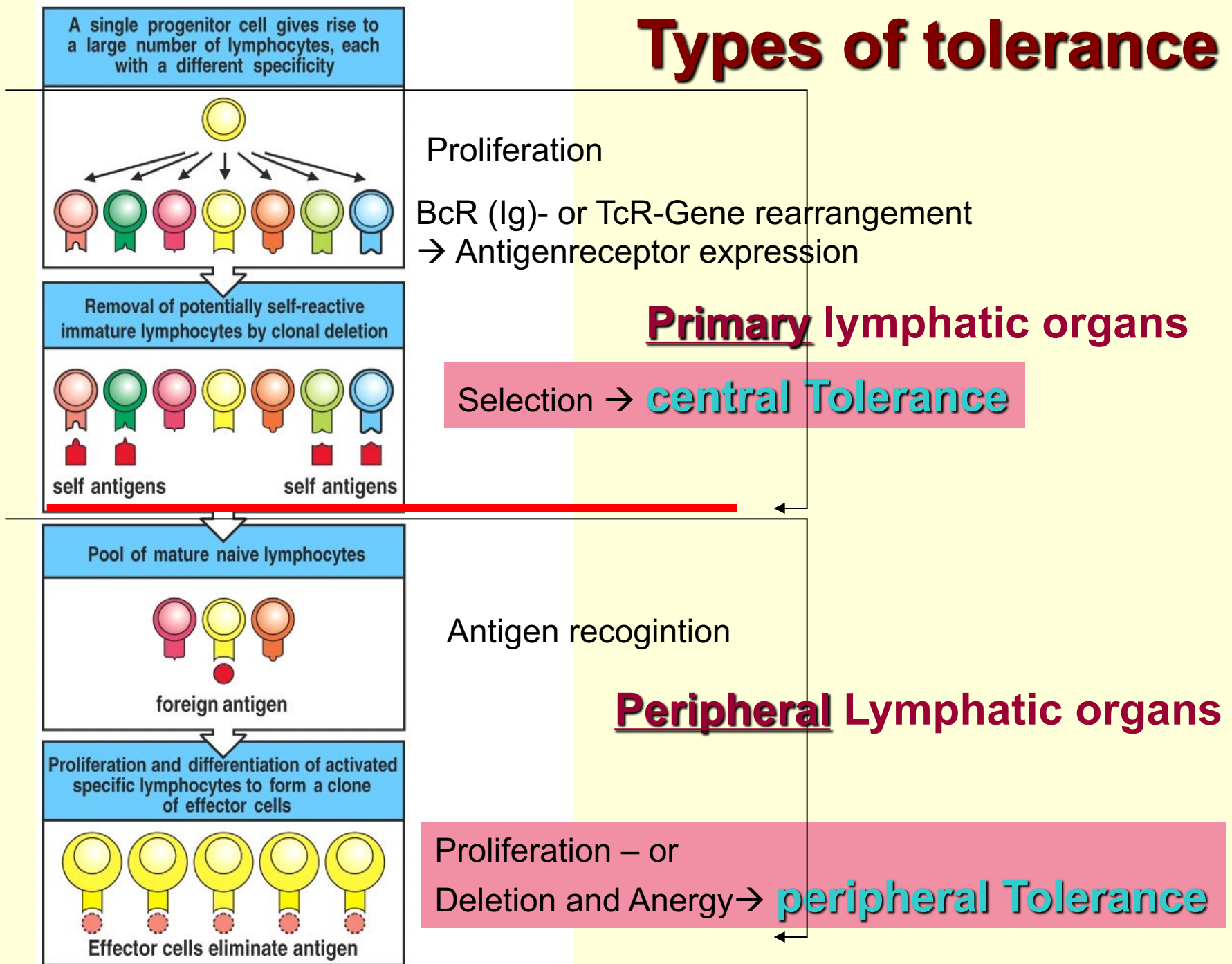


Figure 1-14 Immunobiology, 6/e. (© Garland Science 2005)

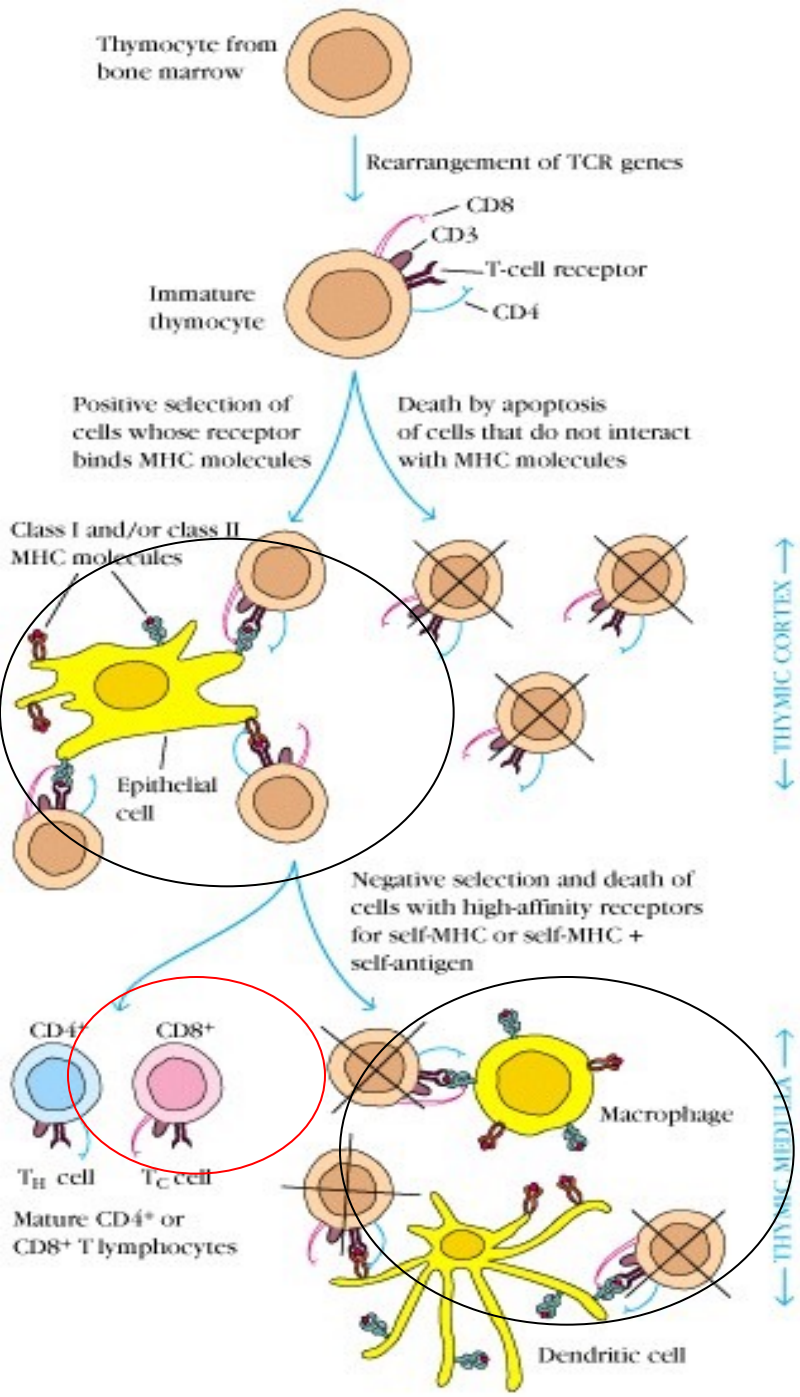
Central T-cell -Tolerance thymic selection

Positive Selection:

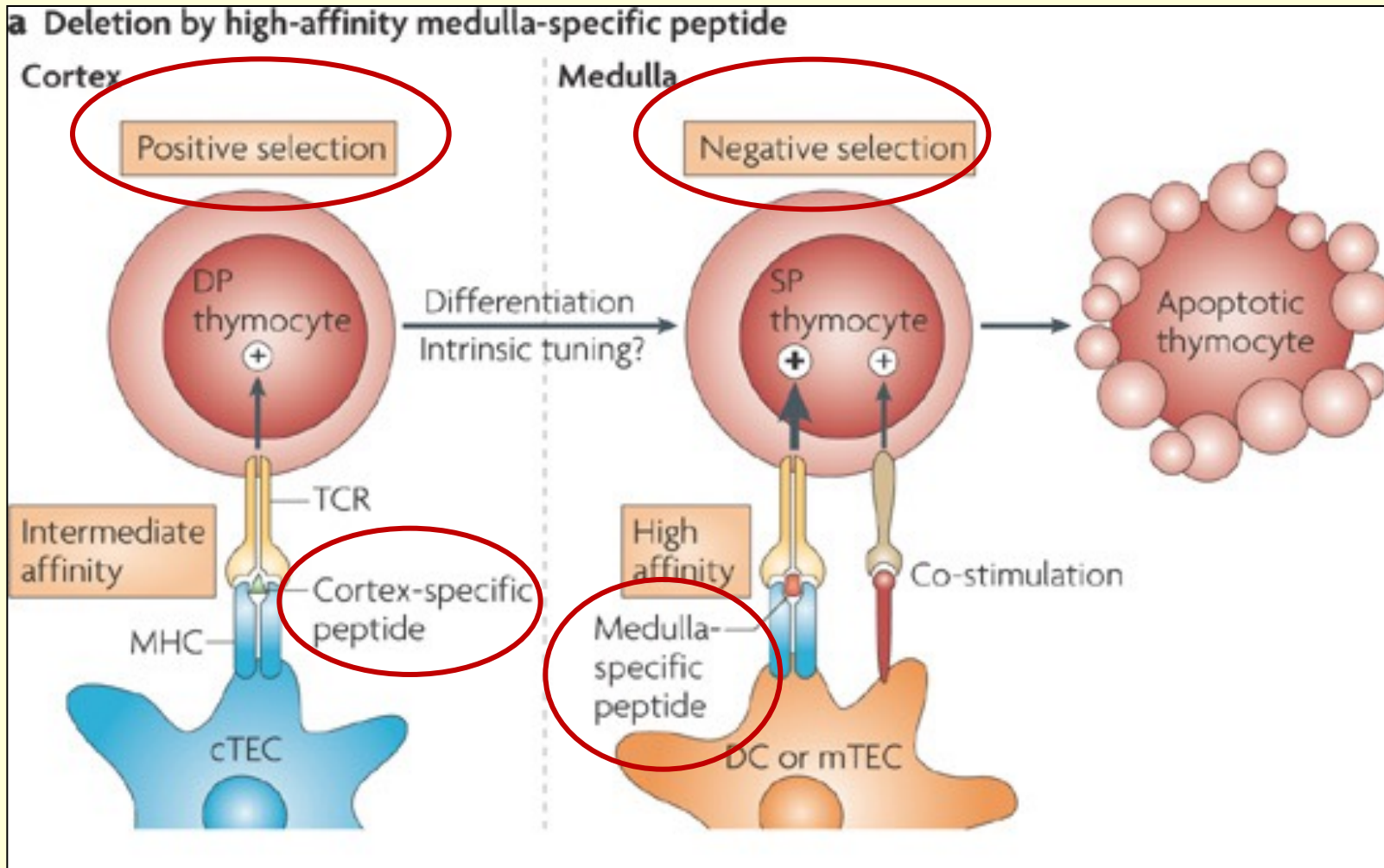
→ MHC RESTRICTION

Negative Selection:

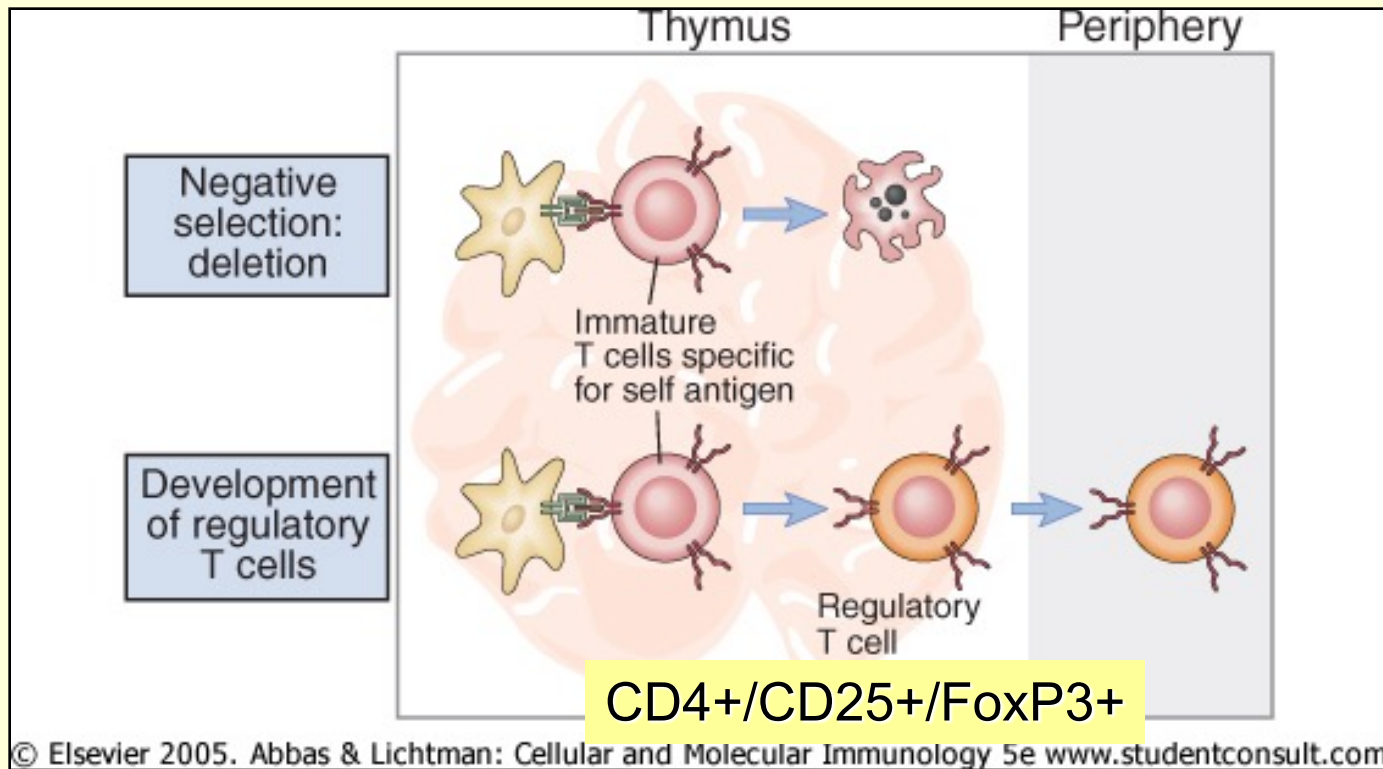
→ TOLERANCE



Affinity model of thymocyte selection



Natural regulatory T-cell (Treg)



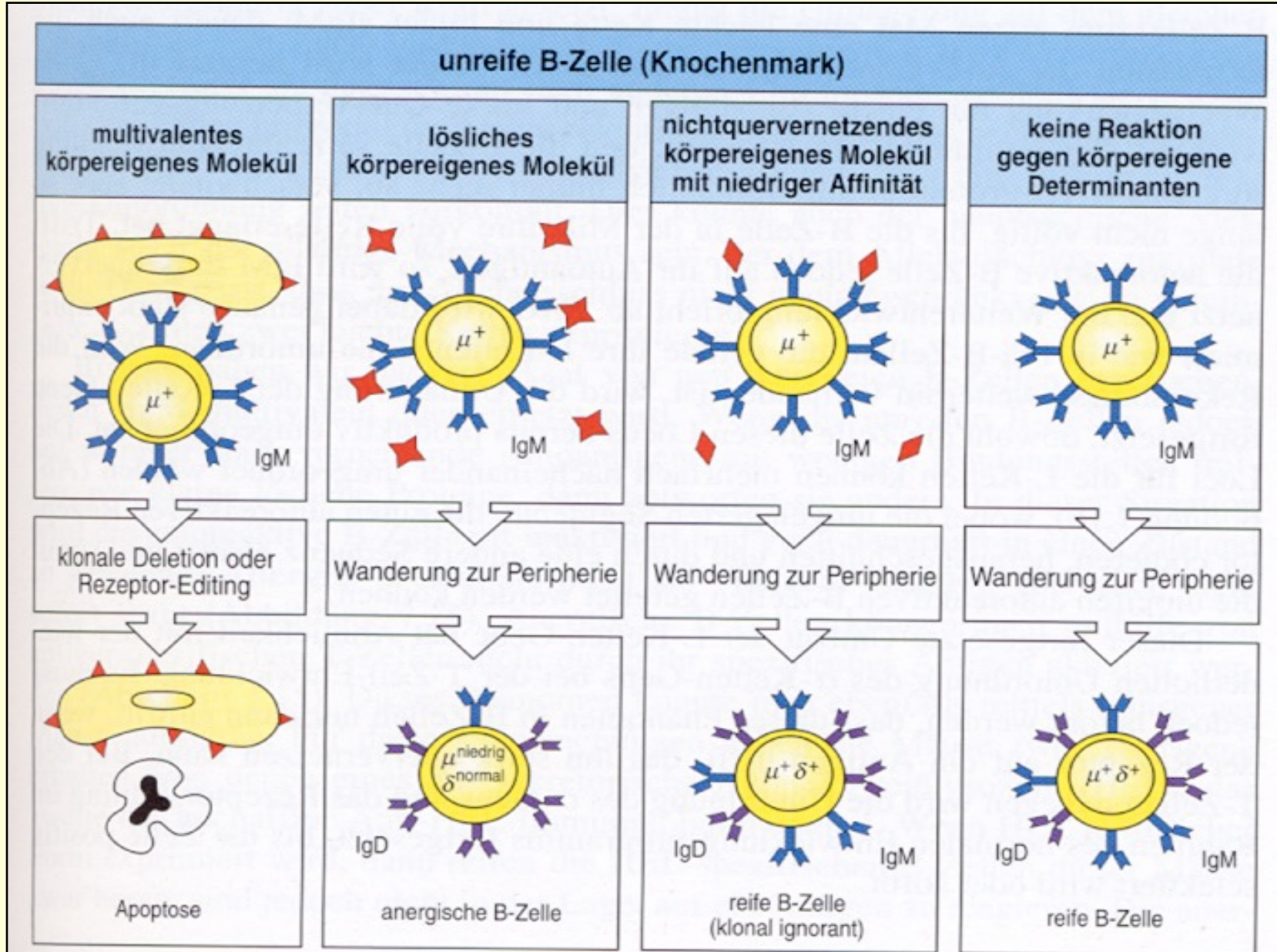
In Thymus presented antigens

- 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

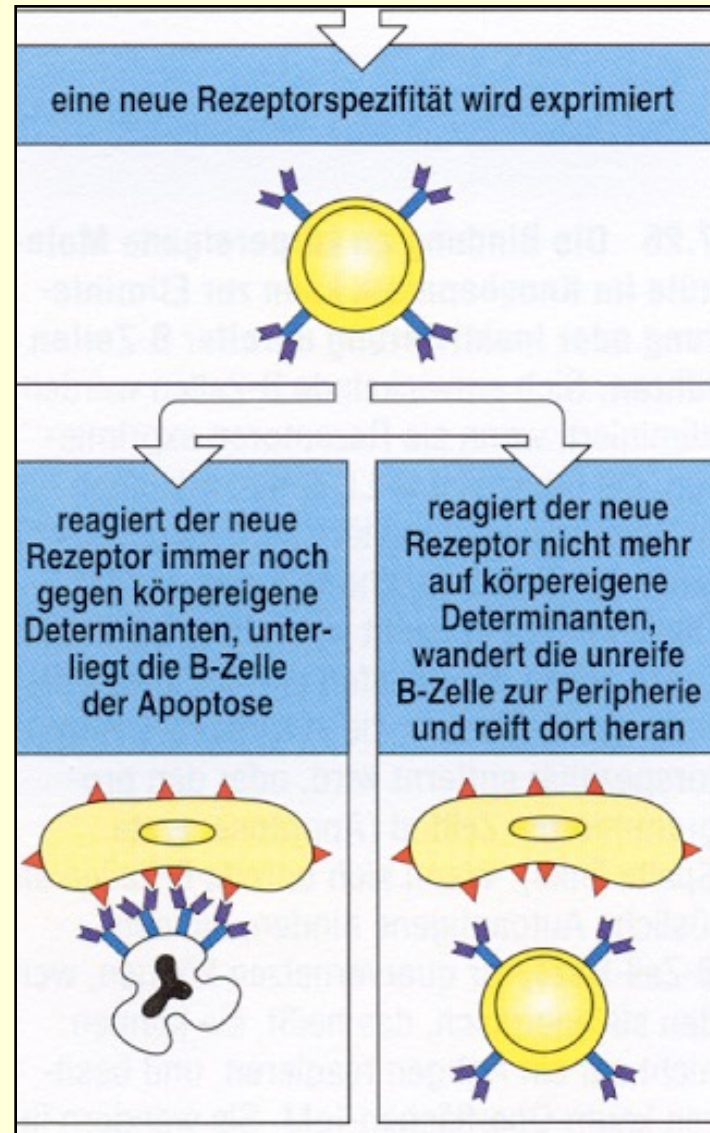
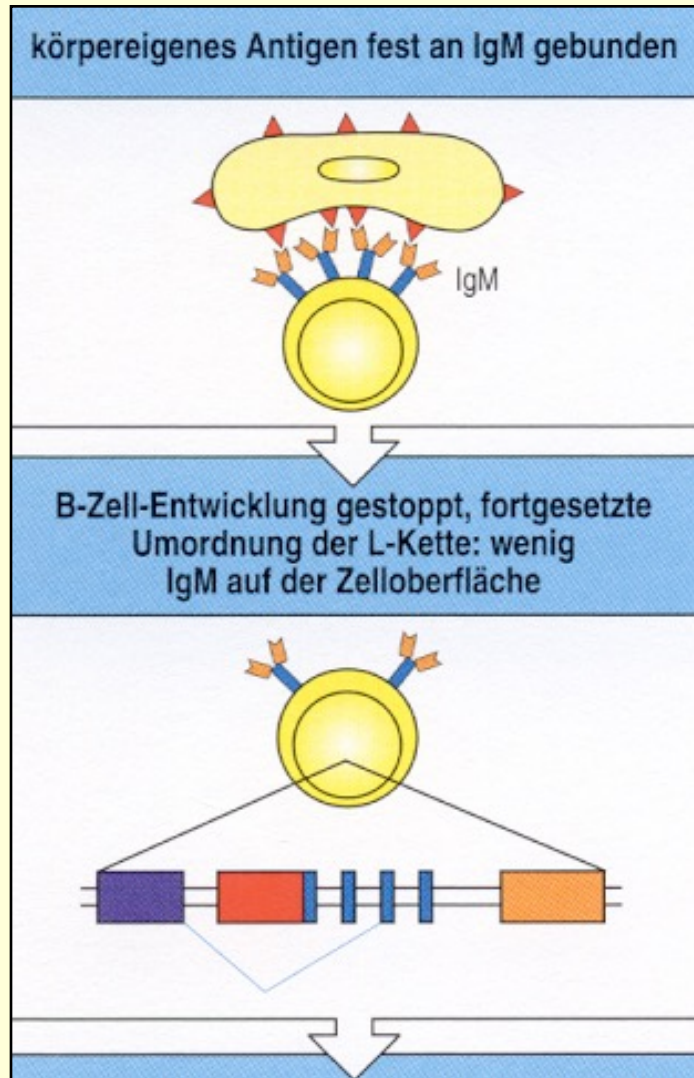
Central B-cell tolerance in BM

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

B cell selection in BM



Rezeptor-Editing



Passive tolerance

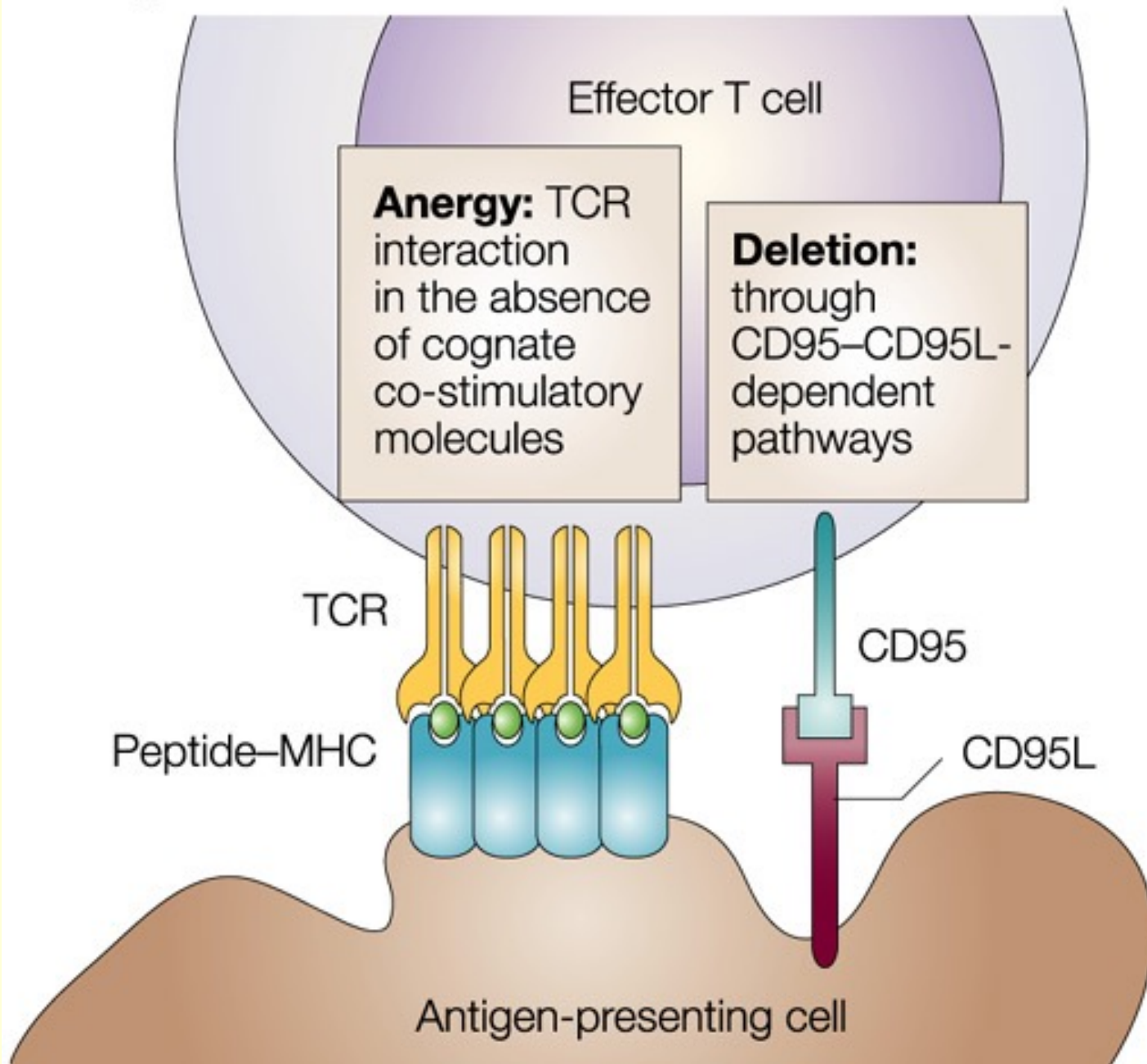
Unresponsiveness: no MHC recognition or inhibited cellular differentiation.

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

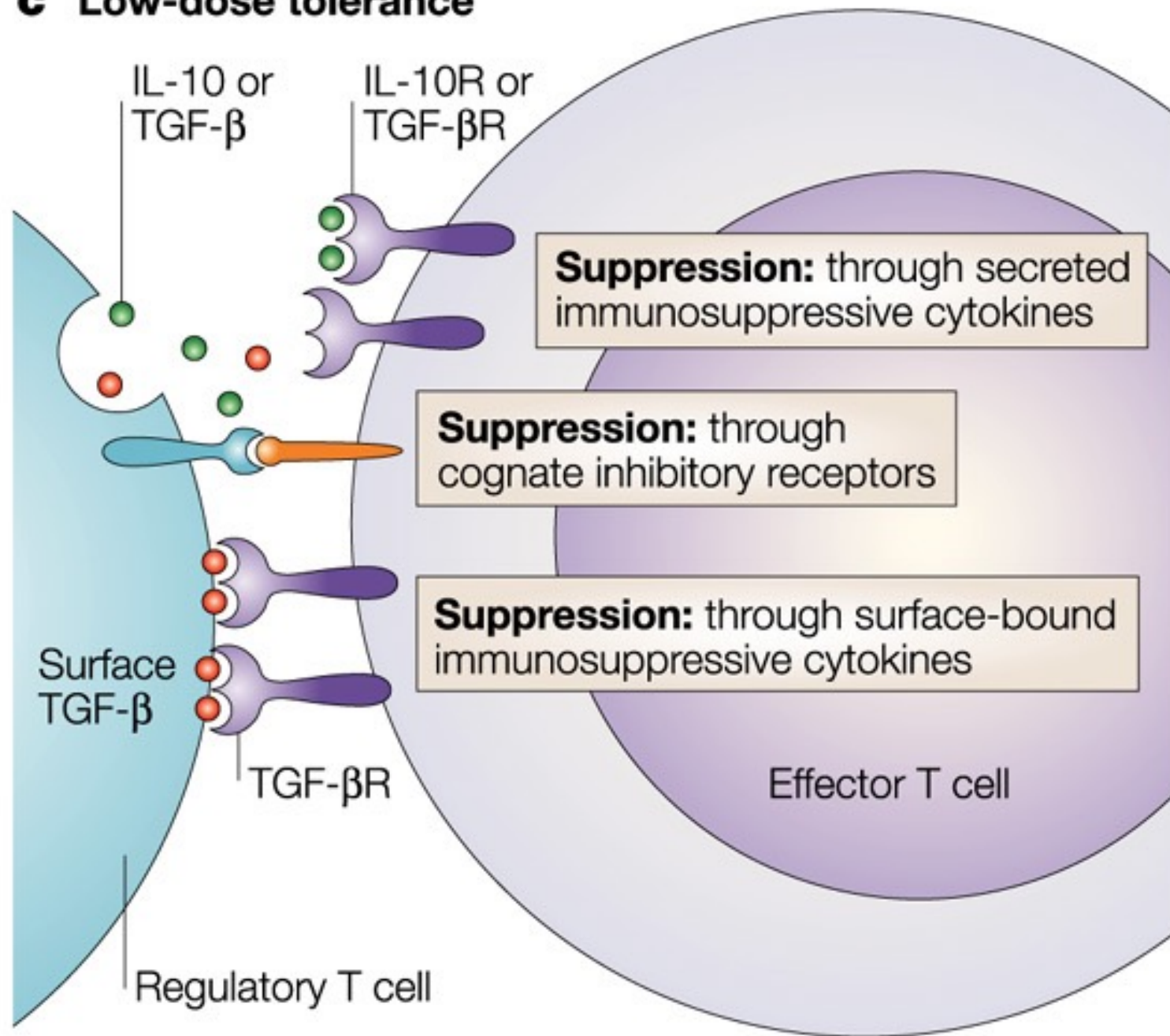
Passive tolerance induced by the nature of the antigen

- **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



c Low-dose tolerance

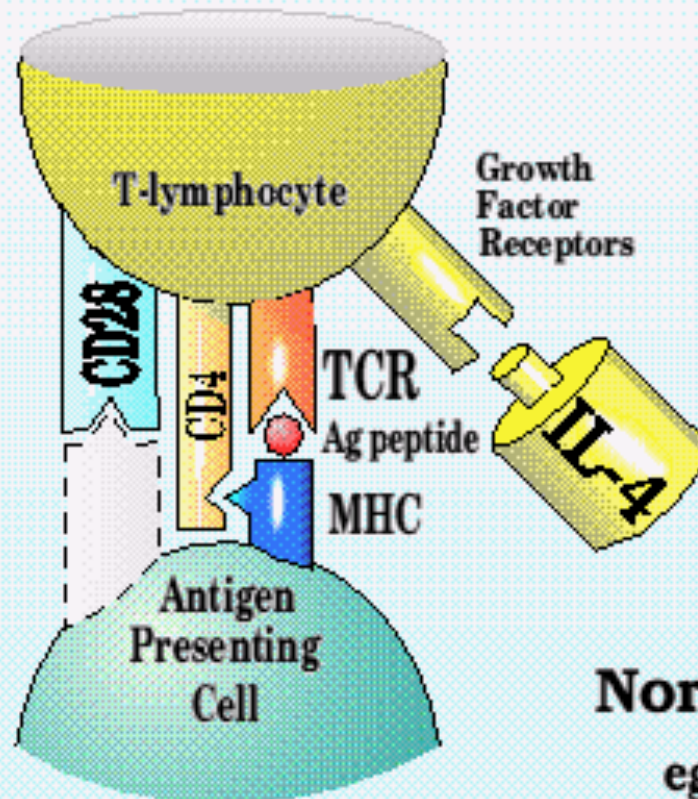


Failed co-stimulation results low dose tolerance

"Self" : tolerance

**Non-professional
Antigen
Presentation**

eg. No B7 present



Growth
Factor
Receptors

**Non-inflammatory
Environment**

eg. IL-4, 10, TGF- β etc

Normal self tissues

eg. pancreatic islets

Tolerance induced by the body

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

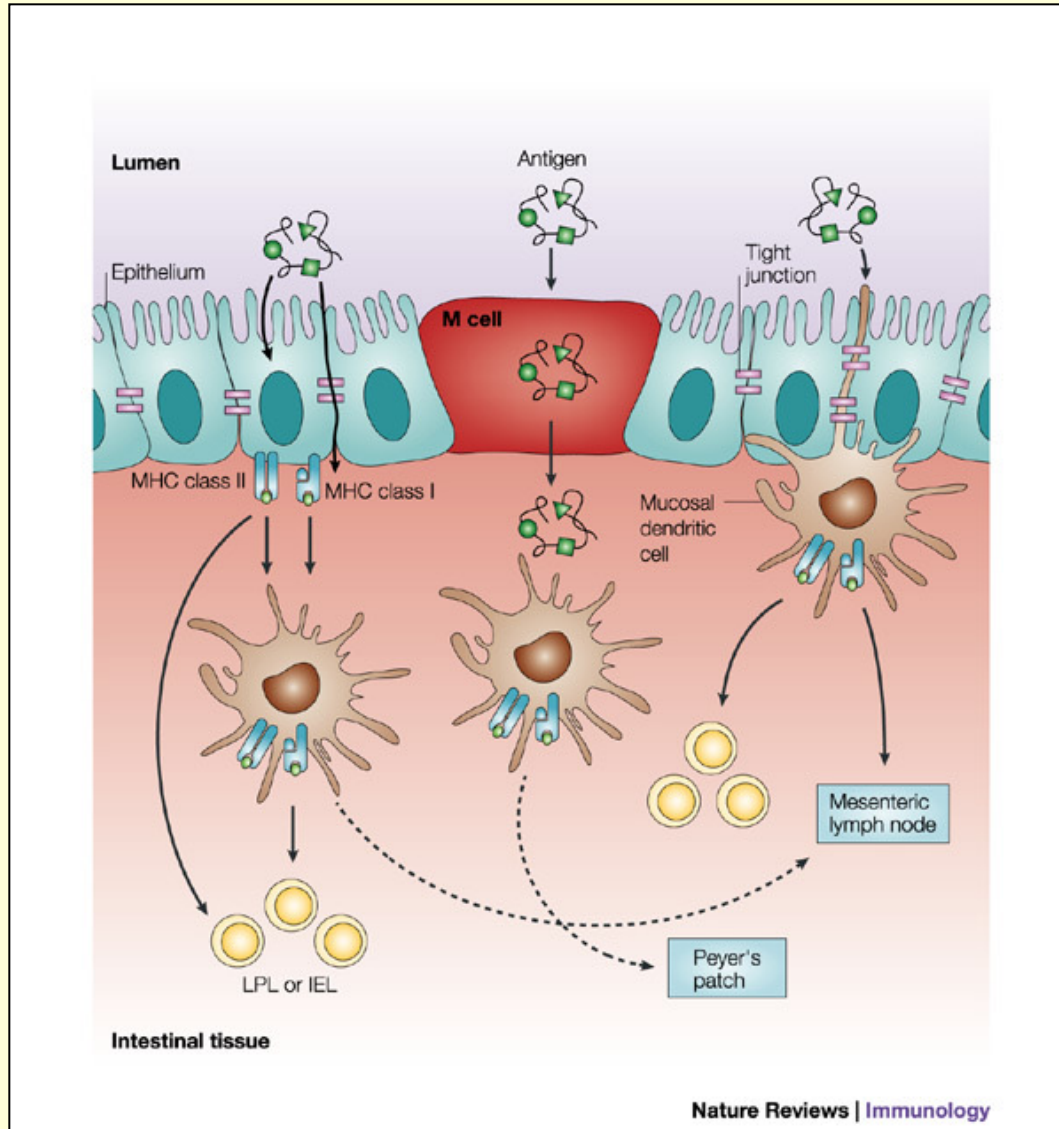
ACTIVE TOLERANCE

“Immunological homunculus”

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

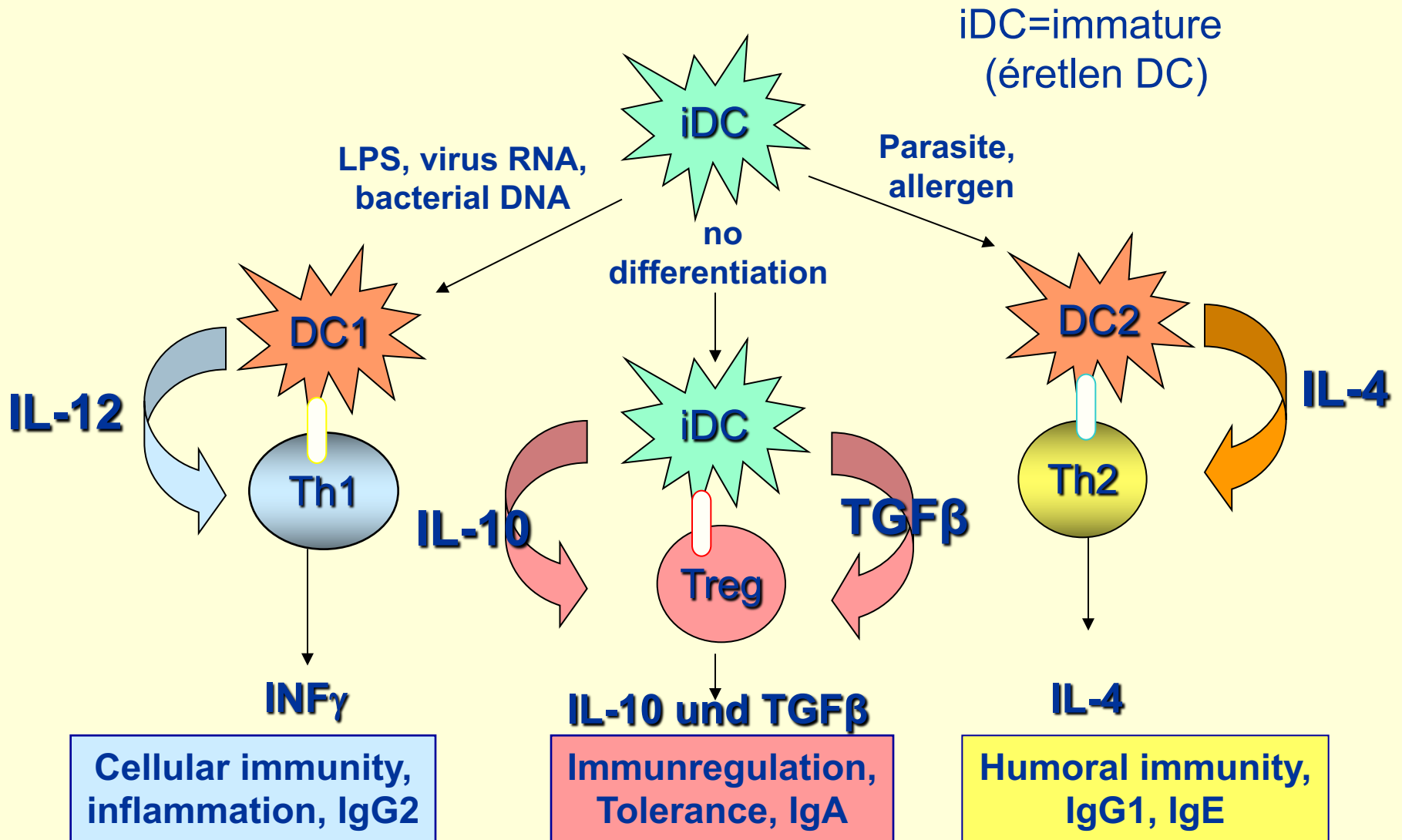
INDUCED Treg Cells

Oral tolerance



M-Cells - Endocytosis
Epithelial cells – Transcytosis
DC
Through Tight Junctions

Development of induced Treg



Genetically well conserved antigens recognized by natural (auto)antibodies

Heatshock proteins	hsp65, hsp70, hsp90, ubiquitin
Enzymes	aldolase, citockrom c, SOD, NADPH, citrate synthase, topoisomerase 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

**Bone Marrow
Transplants**

**Solid Organ
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

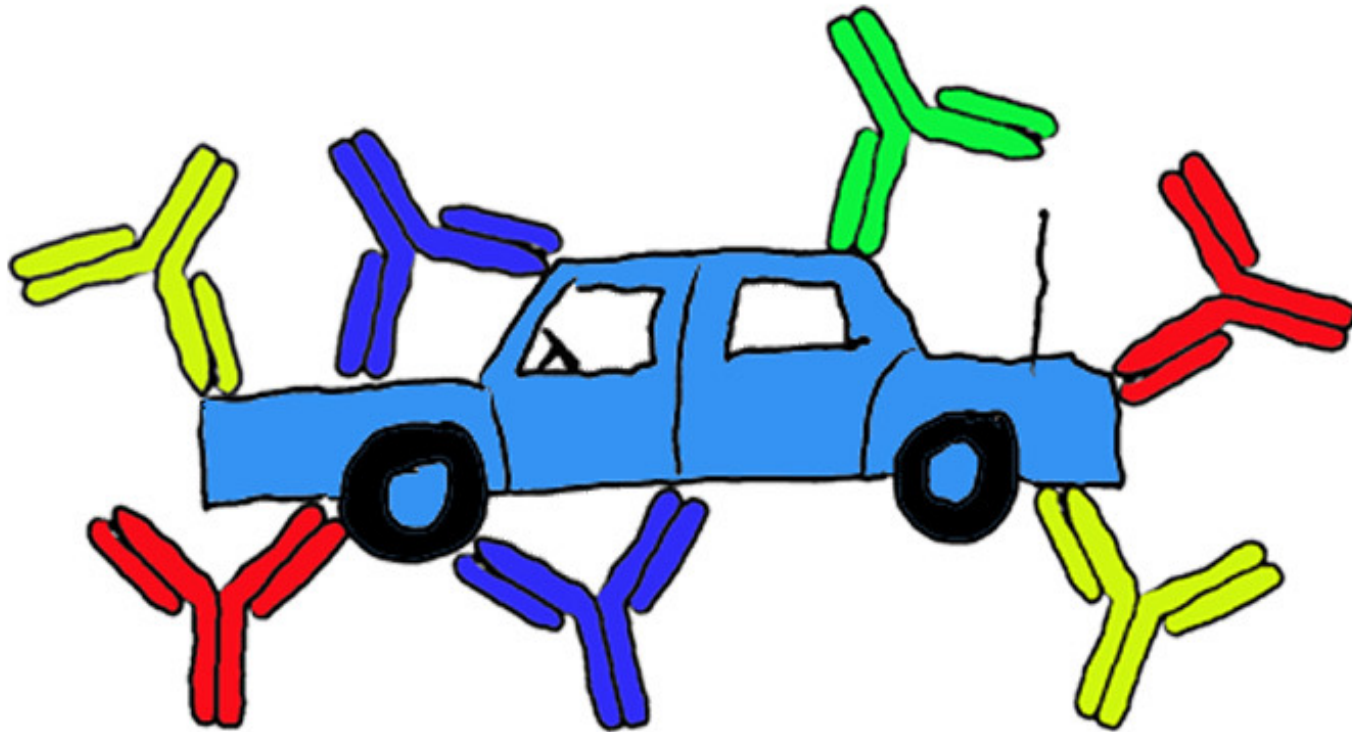
Natural and pathologic autoimmunity

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



Autoimmunity

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Autoimmune diseases affect 5-7% of the population !

Autoimmunity by the failure of self tolerance

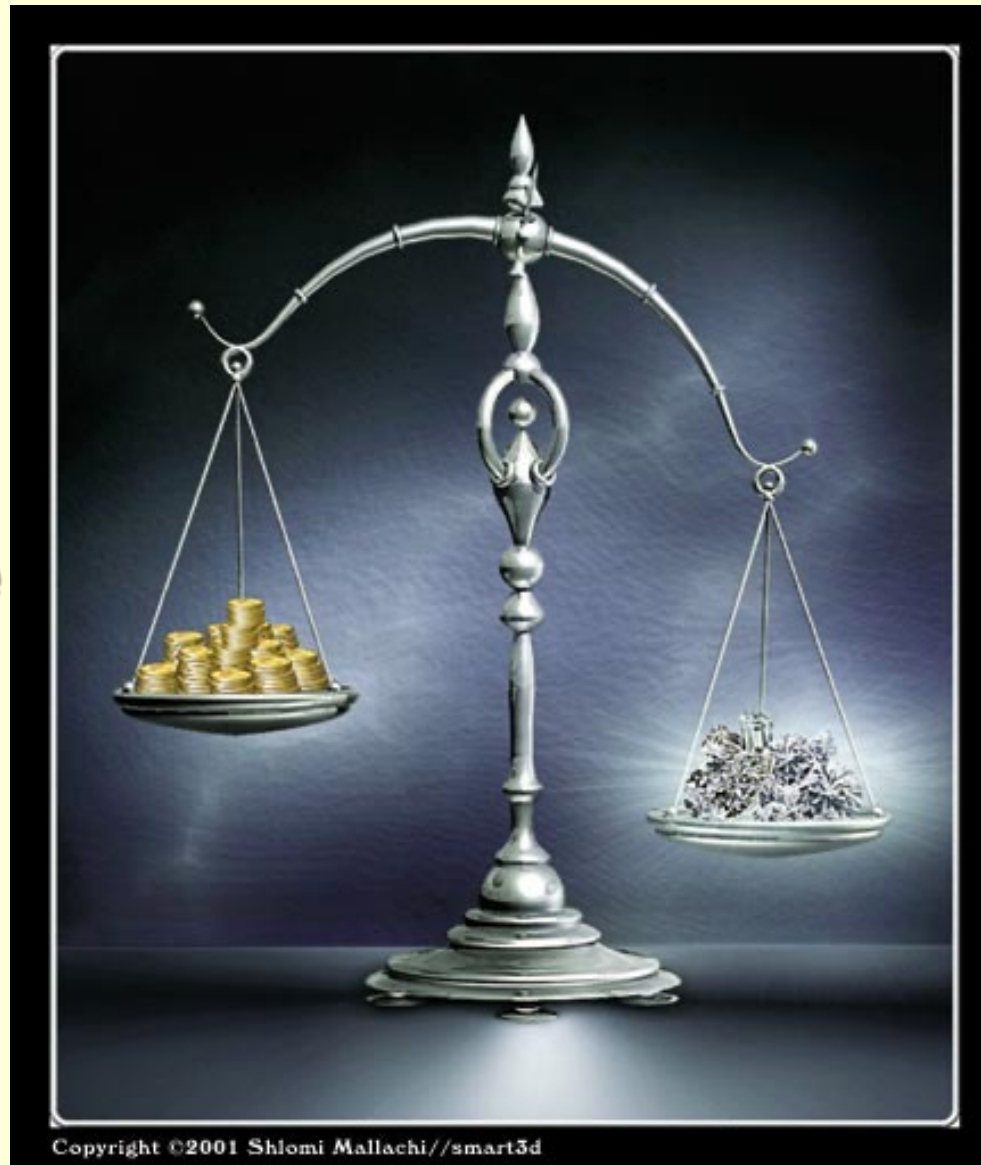
- **Abnormal selection of lymphocyte repertoire**
- **Polyclonal activation of anergic self-reactive lymphocytes**
- **Stimulation by foreign antigens that cross-react with self**

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

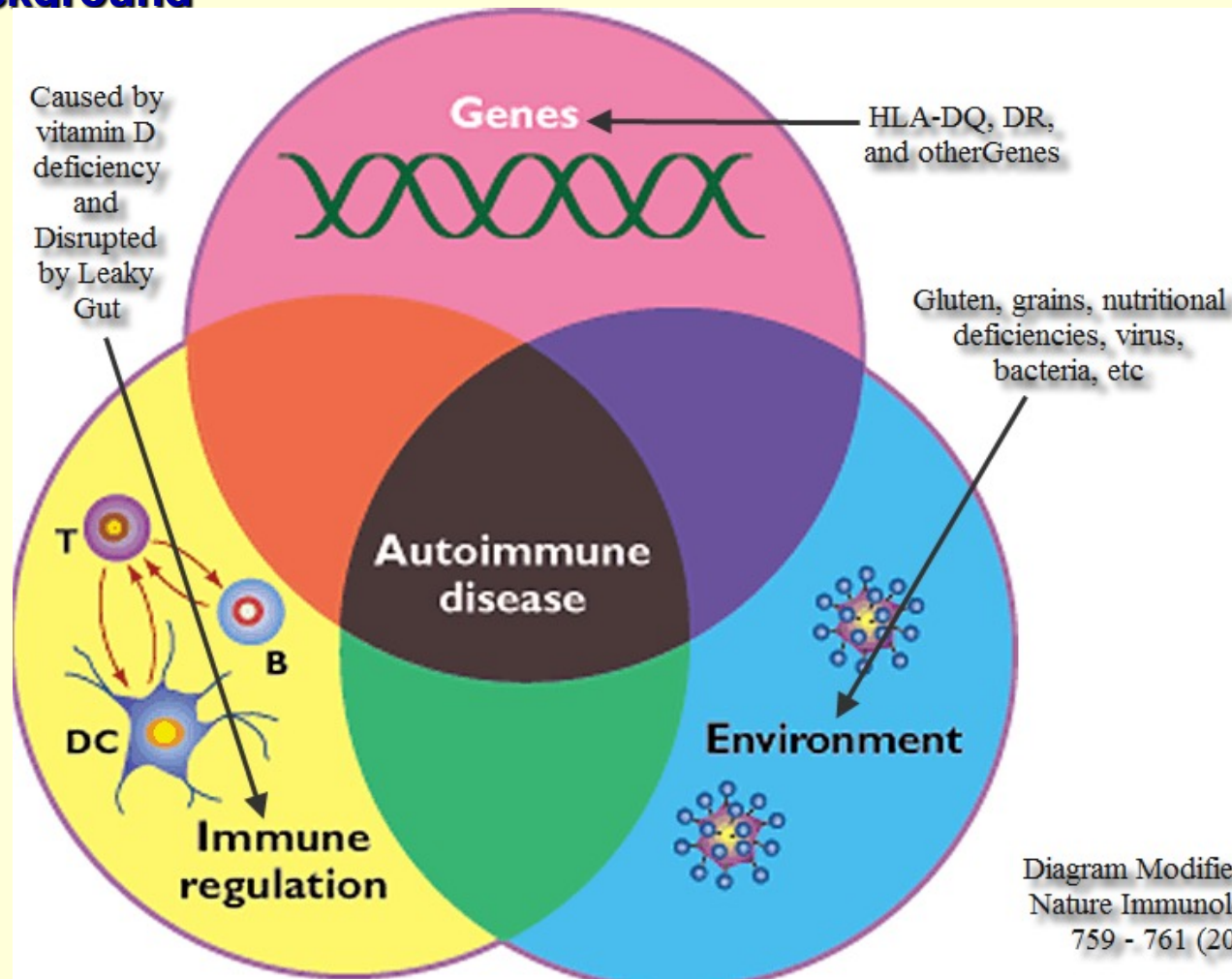
- Multifactor mechanism

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

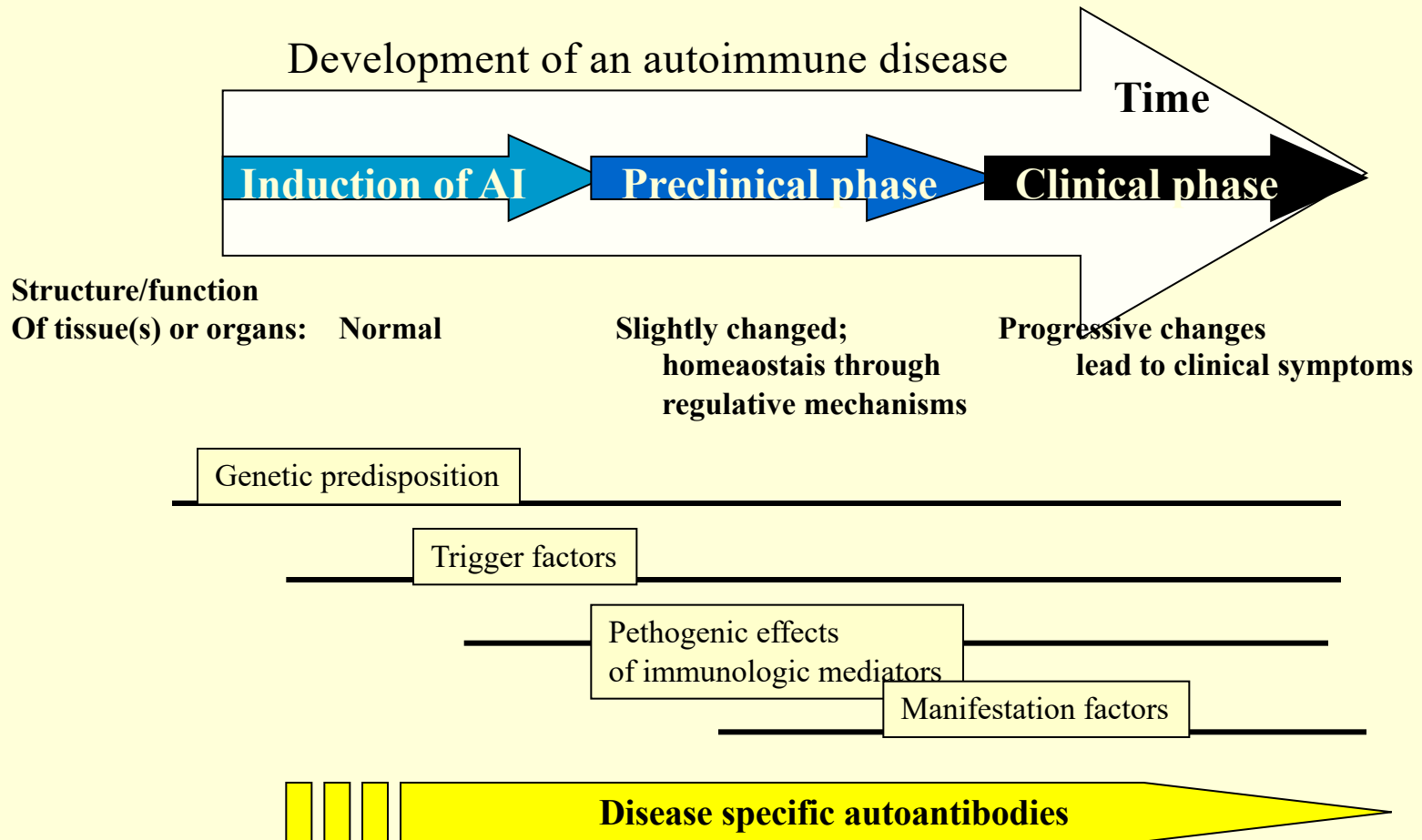
- **Autoimmune “*steady state*”** (failure of dynamic balance on self tolerance and autoimmunity)
- **Role of infections** (molecular mimicry or inefficient natural antibody network)

Pathomechanisms of autoimmune diseases

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



The predictive relevance of autoantibodies



Pathogens and human antigens

Peptid residues

Overlapping sequences

Human cytomegalovirus
IE2
HLA-DR molecule

79

PDPLLGRPDED

60

VTELLGRPDAE

Poliovirus VP2
Acetylcholine receptor

70

STTKESRGTT

176

TVIKESRGTK

Papilloma virus E2
Insulin receptor

76

SLHLESKDS

66

VYGLESLKDL

Klebsiella pneumoniae
nitrogenase enzym
HLA-B27 molecule

186

SRQTDREDE

70

KAQTDREDL

Adenovirus 12 E1B
Alfa-gliadin

384

LRRGMFRPSQCN

206

LGQGSFRPSQQN

HIV p24
Human IgG

160

GVETTTPS

466

GVETTTPS

Measles virus P3
Myelin basic protein

31

EISDNLGQE

61

EISFKLGQE

Thyroid

Graves disease

DR3 3.7

TSH receptor ↑

Hashimoto thyroiditis

DR5

Thyroid microsoma
peroxidase, thyroglobin ↓

Pancreas

IDDM

DR4/

20

DR3

Beta island cells ↓

DQB

100

0302

GAD, HSP60, junB, insulin,
pre/pro insulin

Neural system

Sclerosis multiplex

DR2 4.8

Brain medulla, MBP, PLP,
MOG, MAG

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, heart, 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

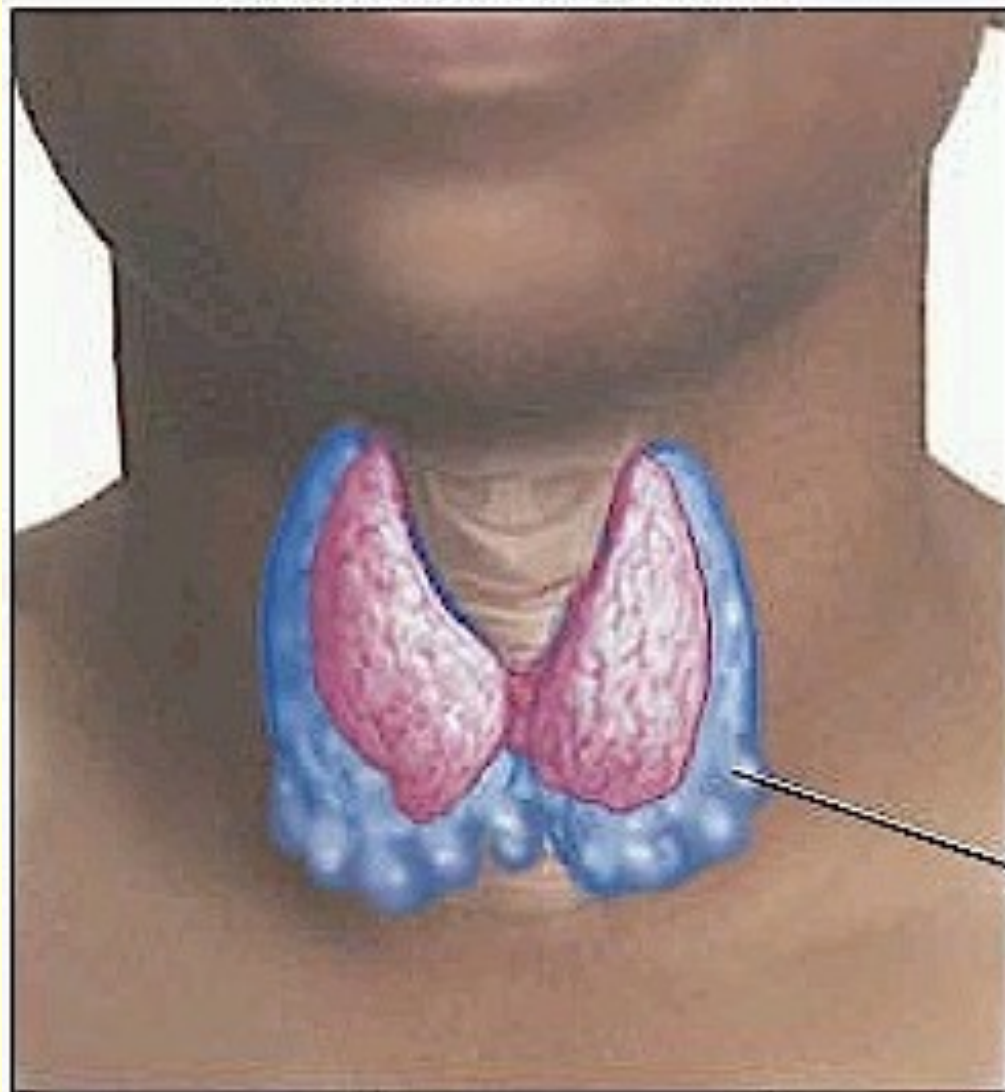
Clamydia, Yersinia

Salmonella/Shigella arthritis

B27

20.7

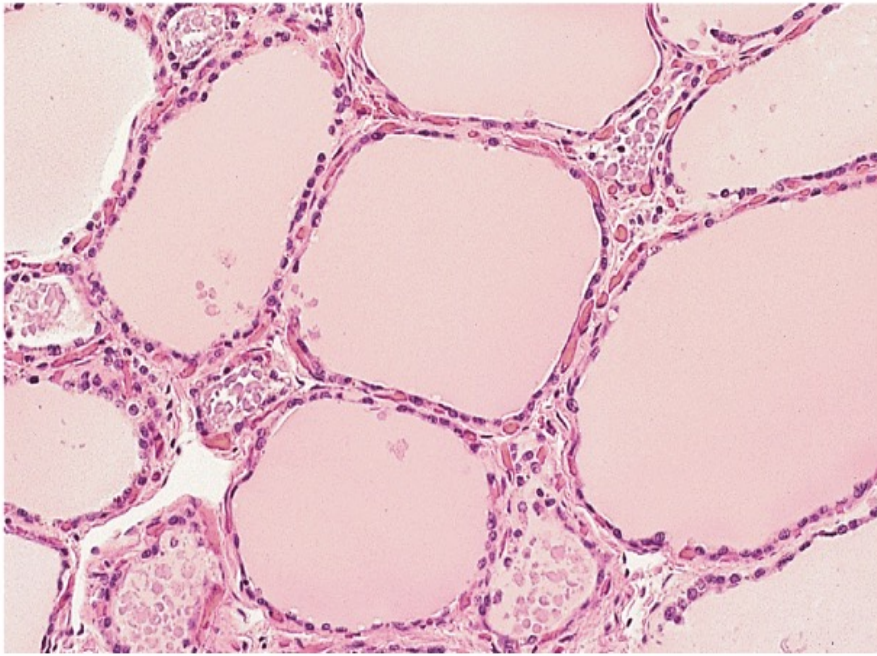
Hashimoto's disease



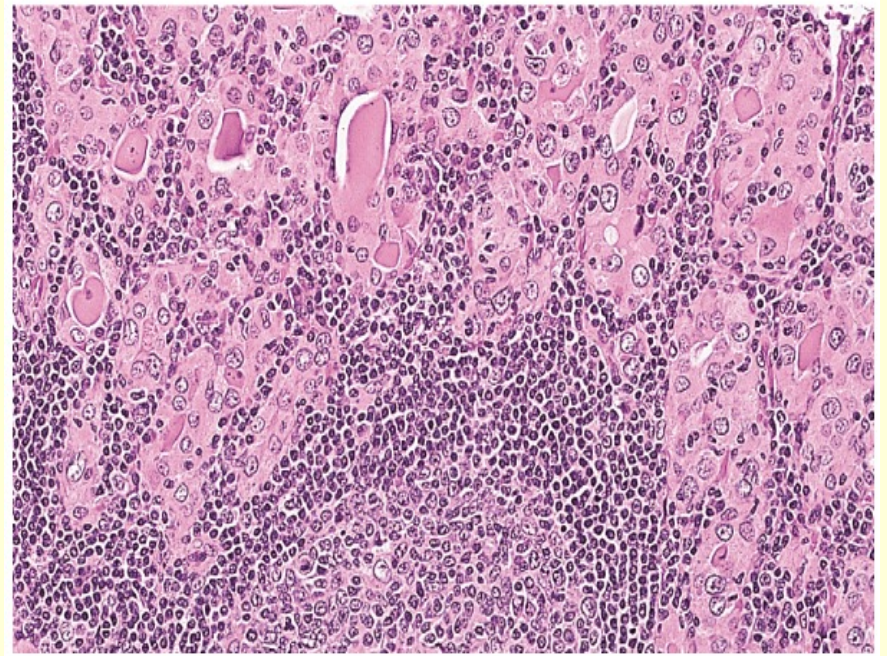
Enlarged, inflamed
hypofunctioning
thyroid (goiter)

Hashimoto's thyroiditis

(a)

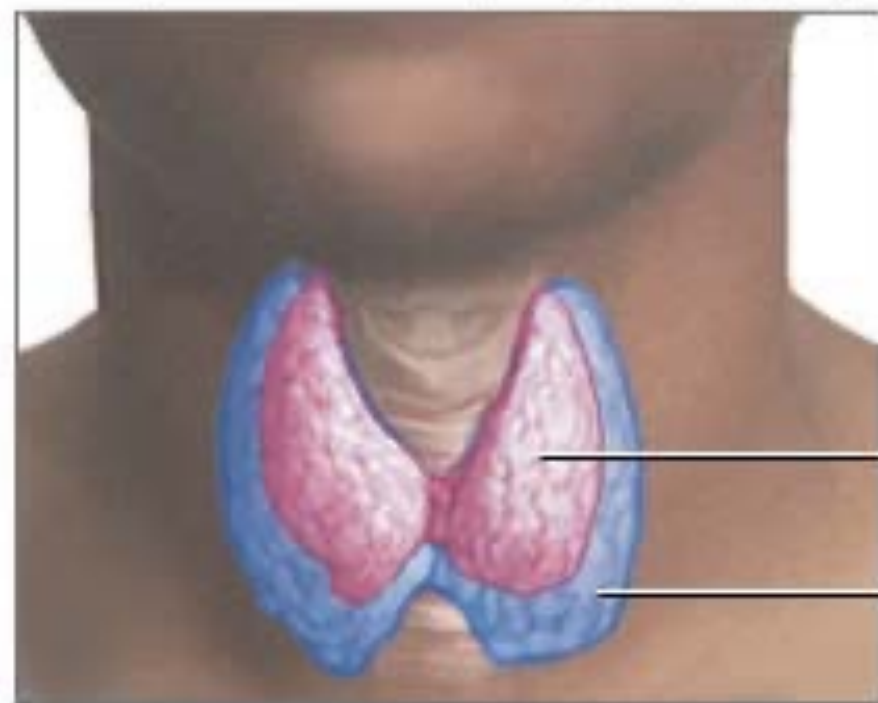


(b)





Exophthalmos (bulging eyes)



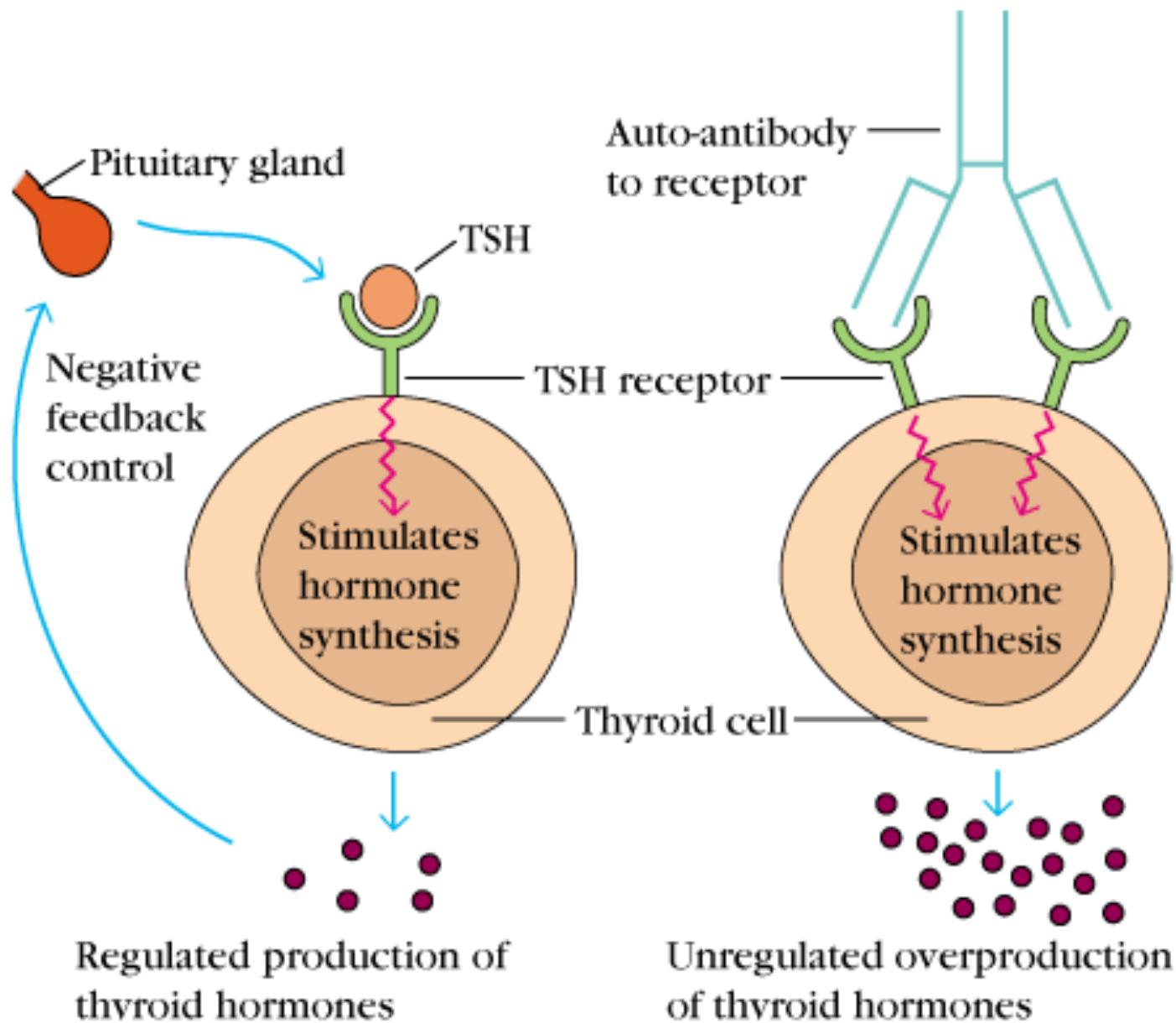
Diffuse goiter

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

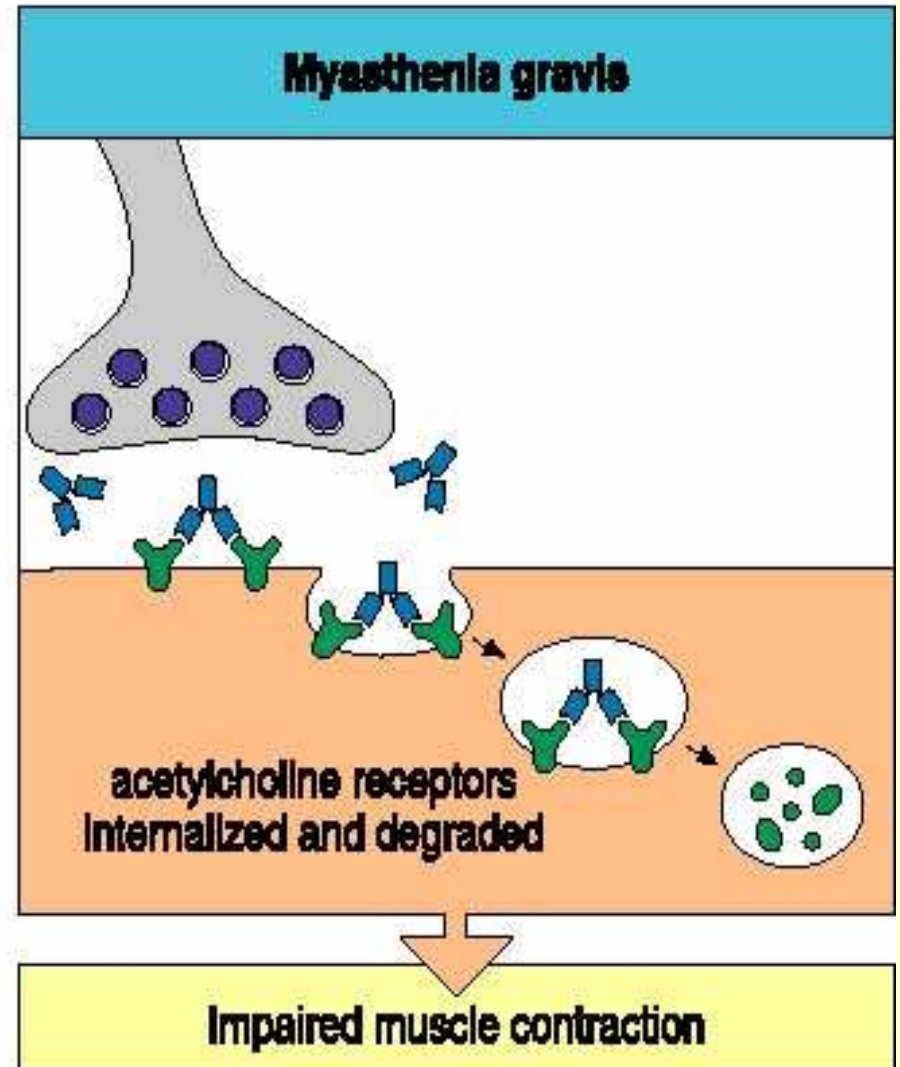
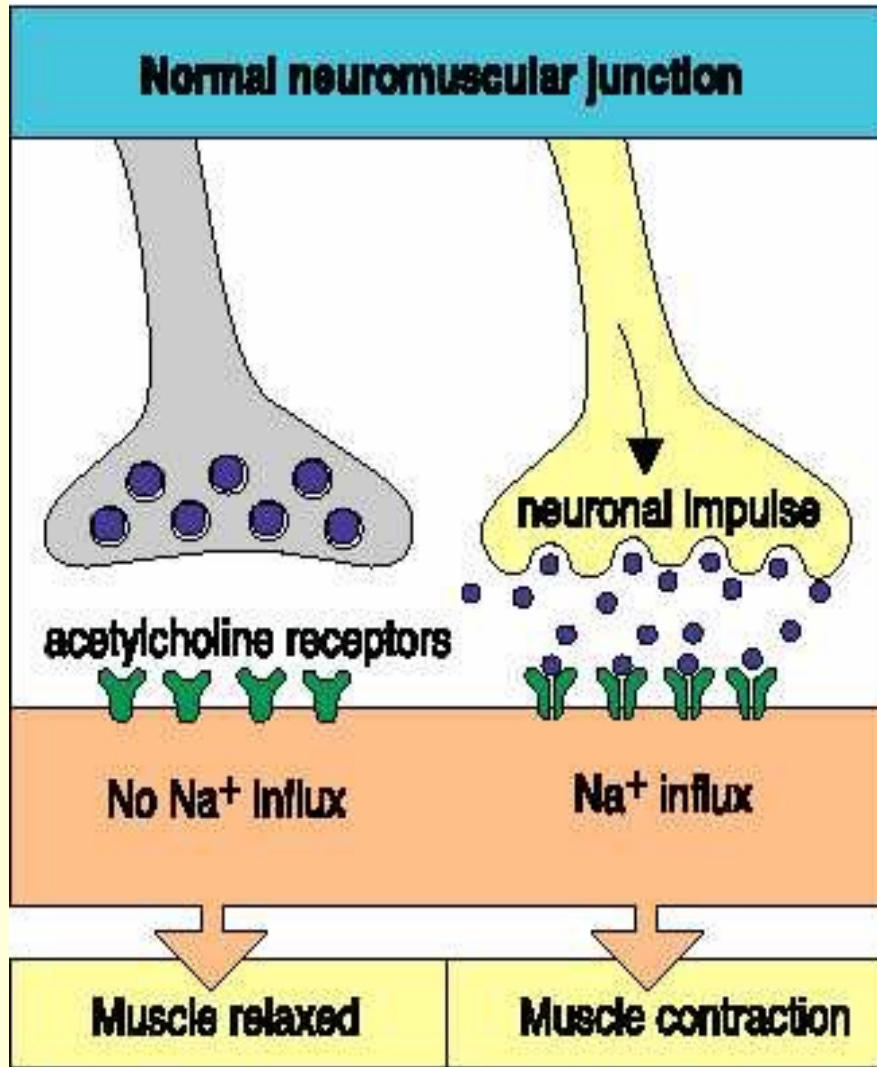
Normal thyroid

Enlarged thyroid

STIMULATING AUTO-ANTIBODIES (Graves' disease)



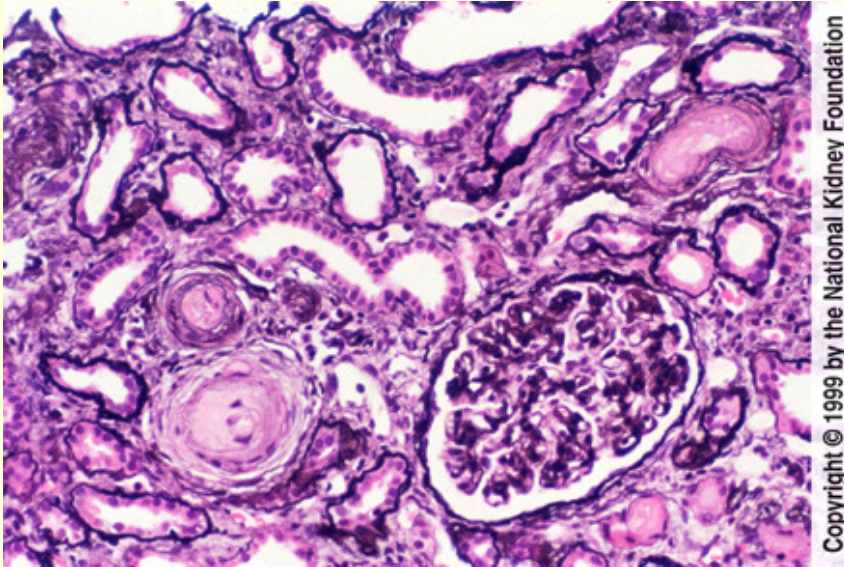
Myasthenia gravis



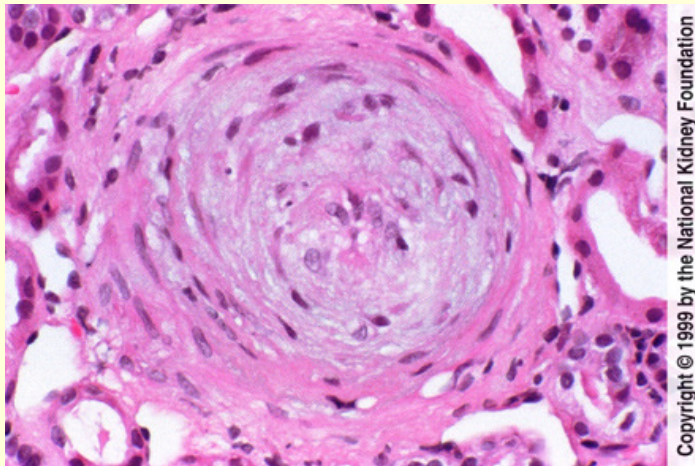
Raynaud's Syndrome



Progressive Systemic Sclerosis



The artery shows early organization with "onion skin" change caused by lamellation and mucoid change with swelling of the intimal layer, with corrugation of the glomerular basement membrane. (Jones' silver stain, magnification X200).



Fibrous organization of the intimal injury of arteries in a more chronic stage of progressive systemic sclerosis . (Periodic acid Schiff reaction, magnification X400).

Rheumatoid arthritis

