

# Basic Immunology

## *Lecture 20<sup>th</sup>*

### **Immunological tolerance**

Cellular and molecular mechanisms of the immunological tolerance

### **Autoimmunity**

# **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

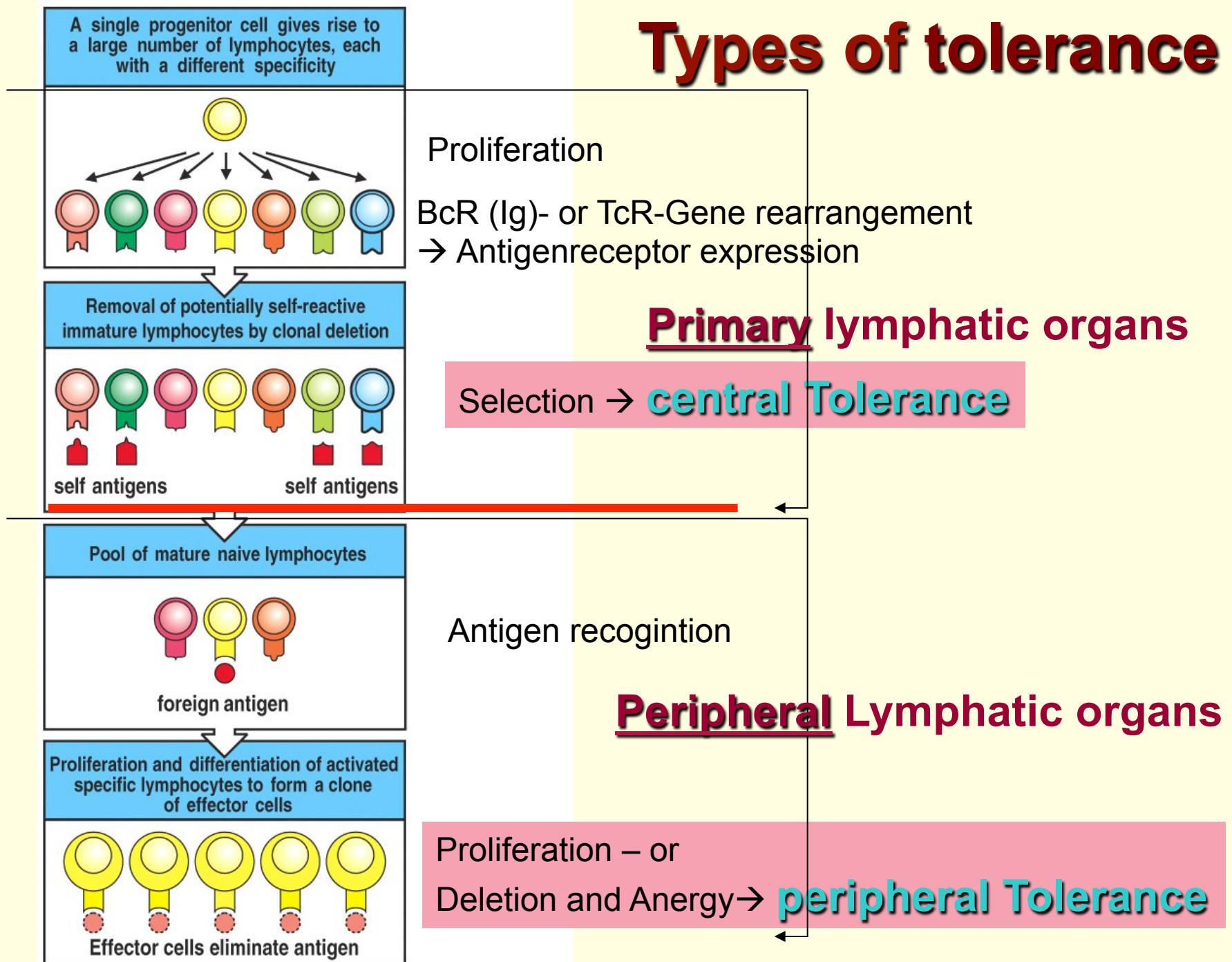


Figure 1-14 Immunobiology, 6/e. (© Garland Science 2005)

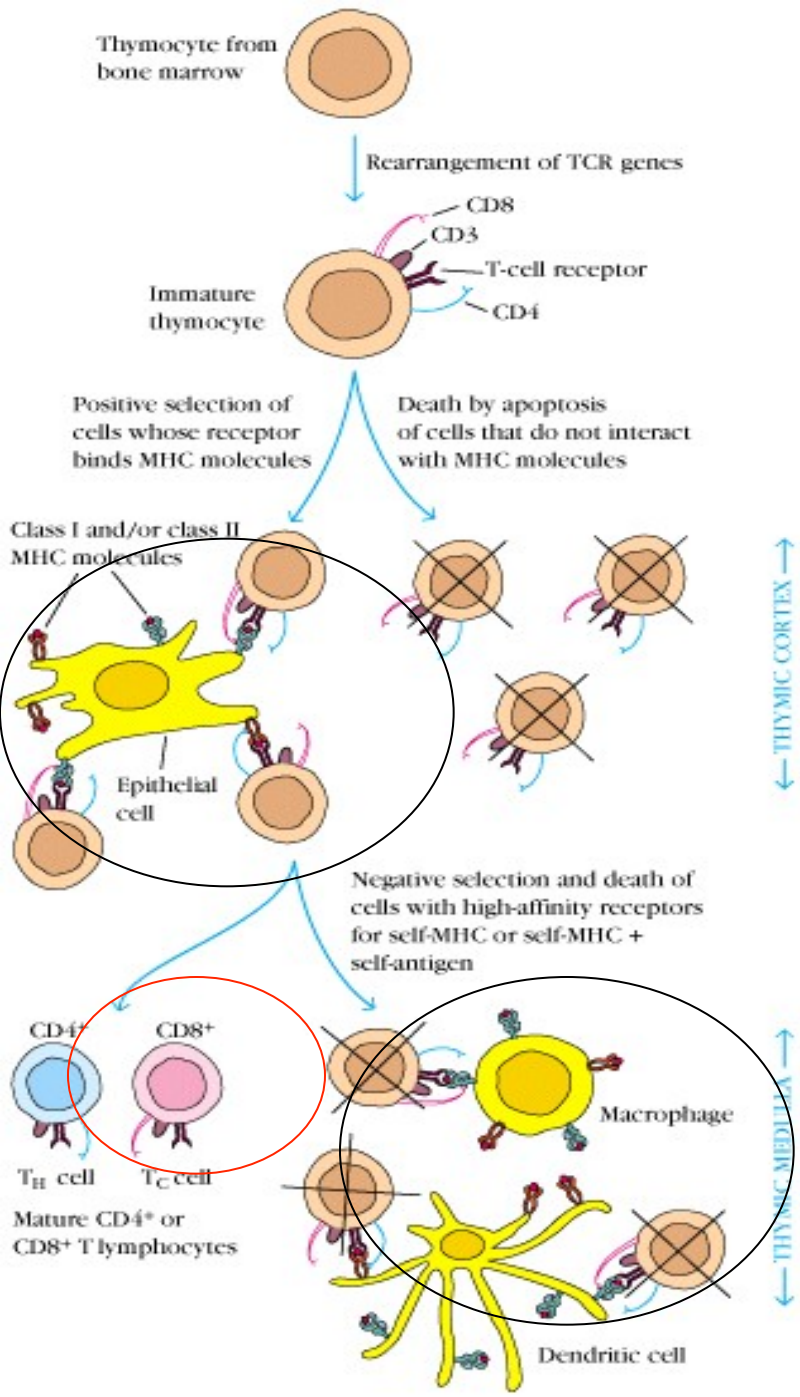
# Central T-cell -Tolerance thymic selection

## Positive Selection:

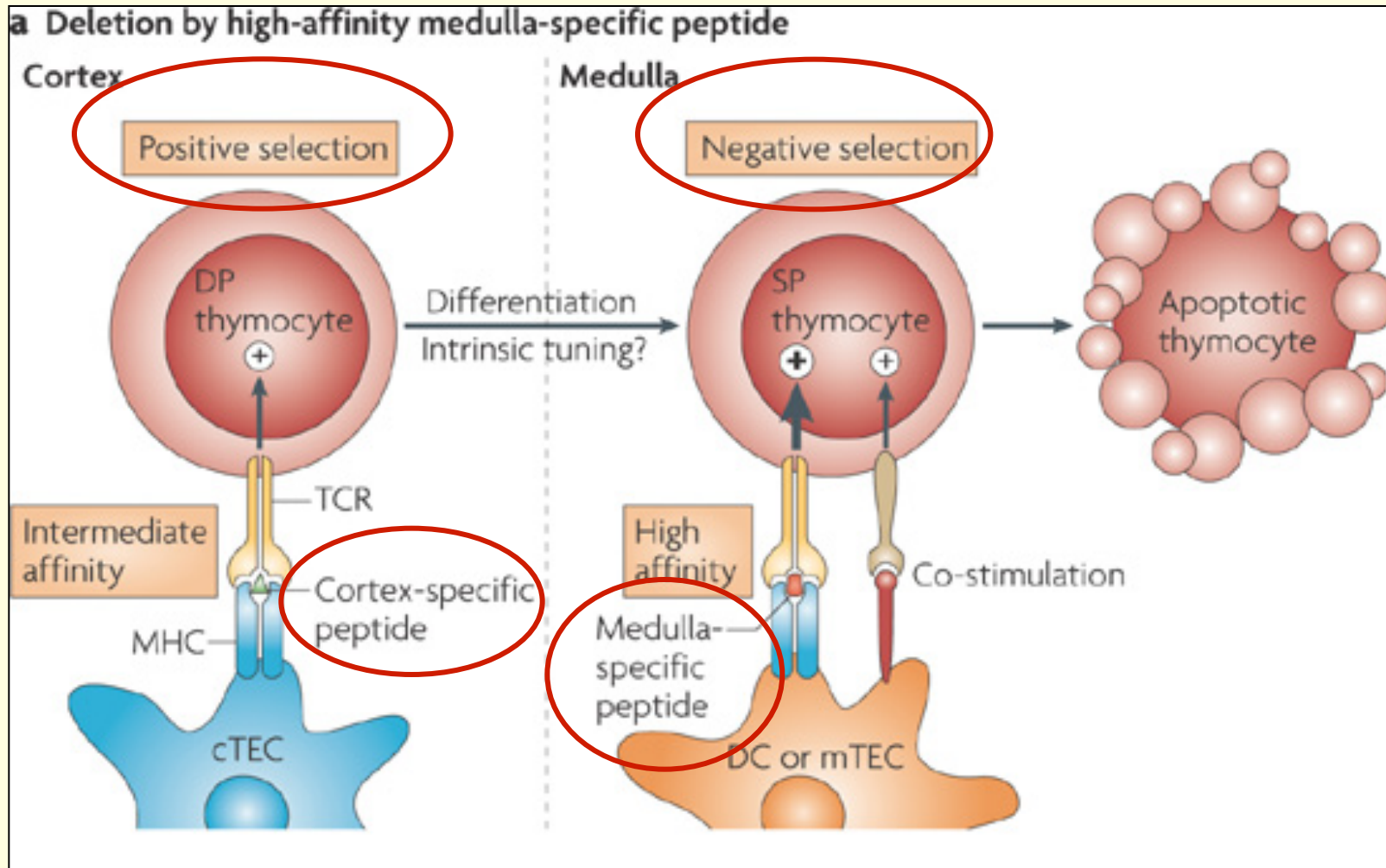
→ **MHC RESTRICTION**

## Negative Selection:

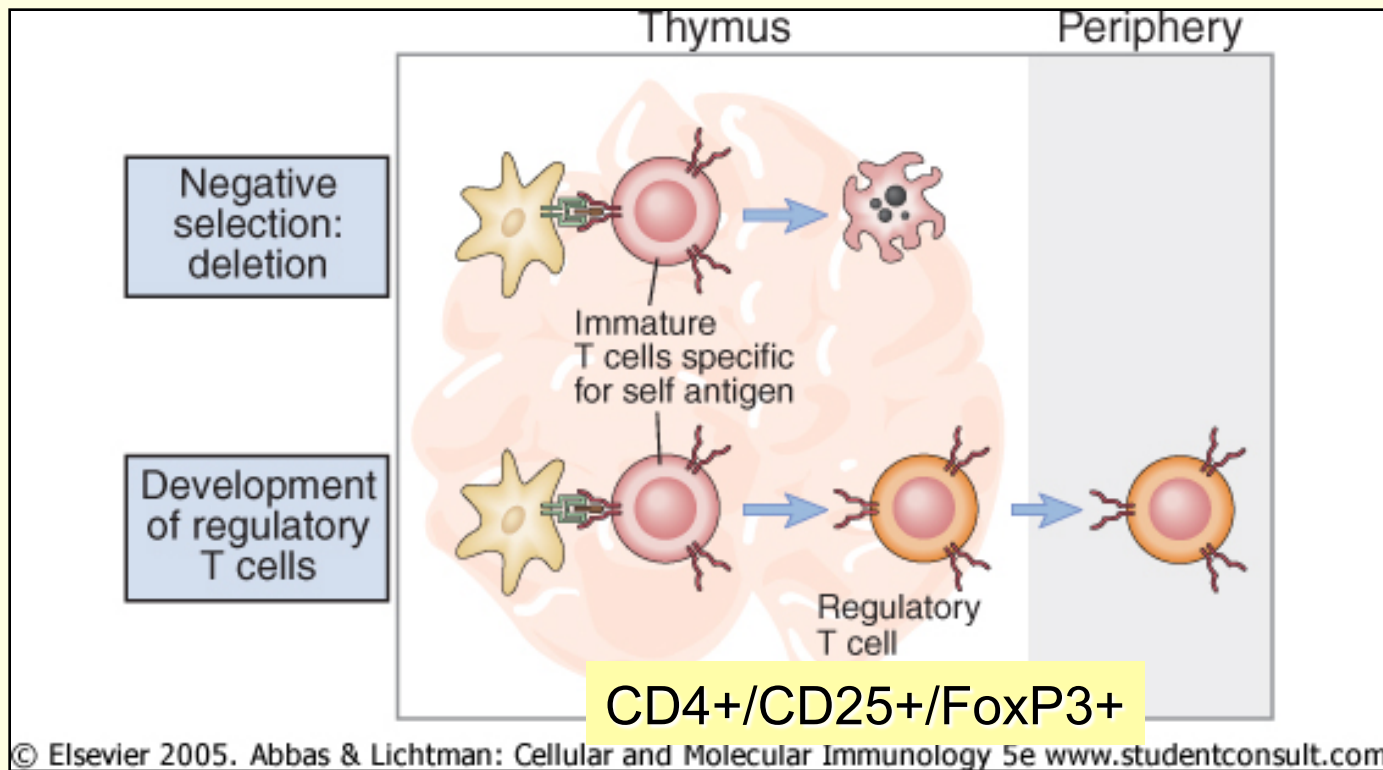
→ **TOLERANCE**



# Affinity model of thymocyte selection



# Natural regulatory T-cell (Treg)



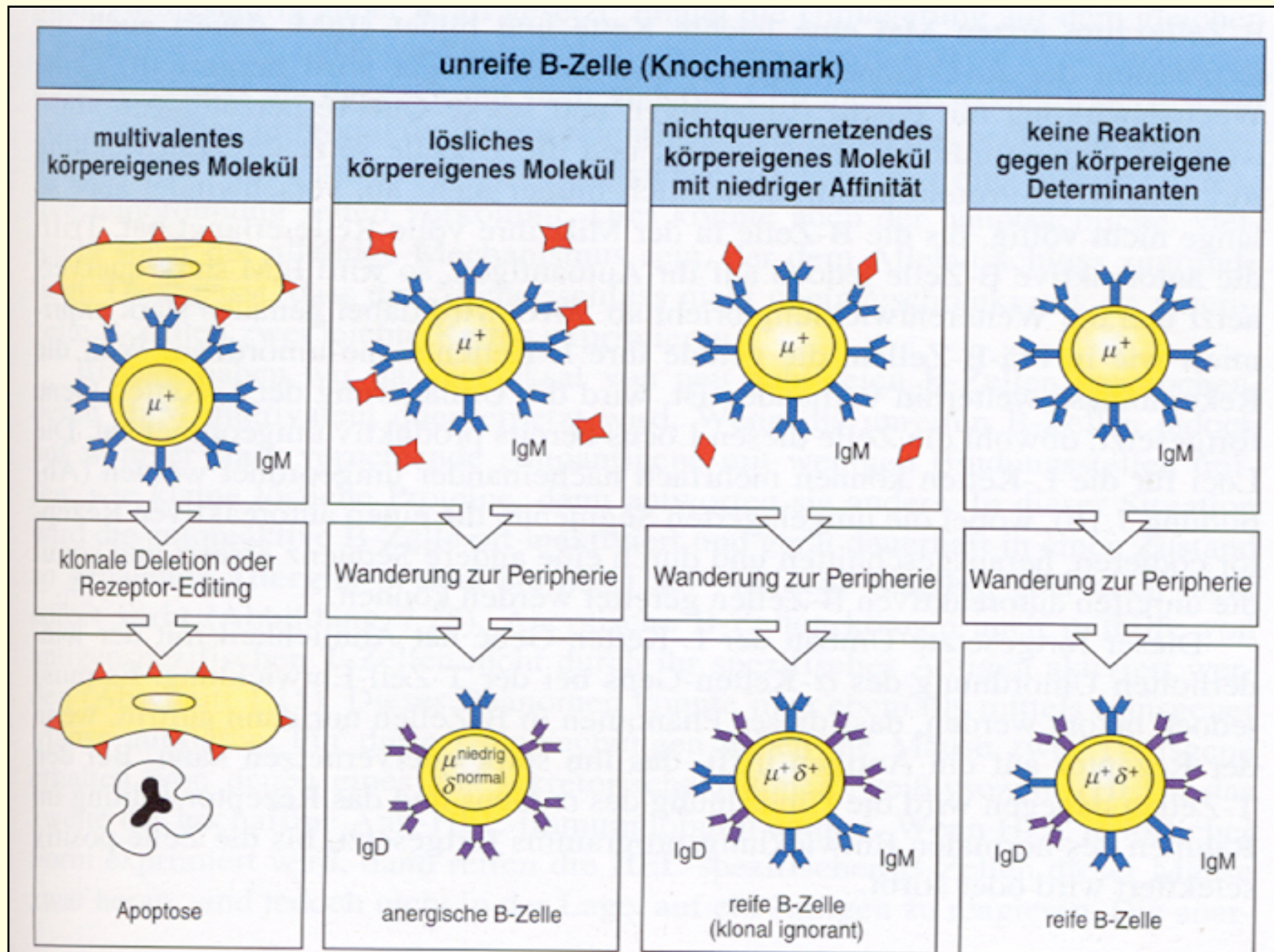
# In Thymus presented antigens

- 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

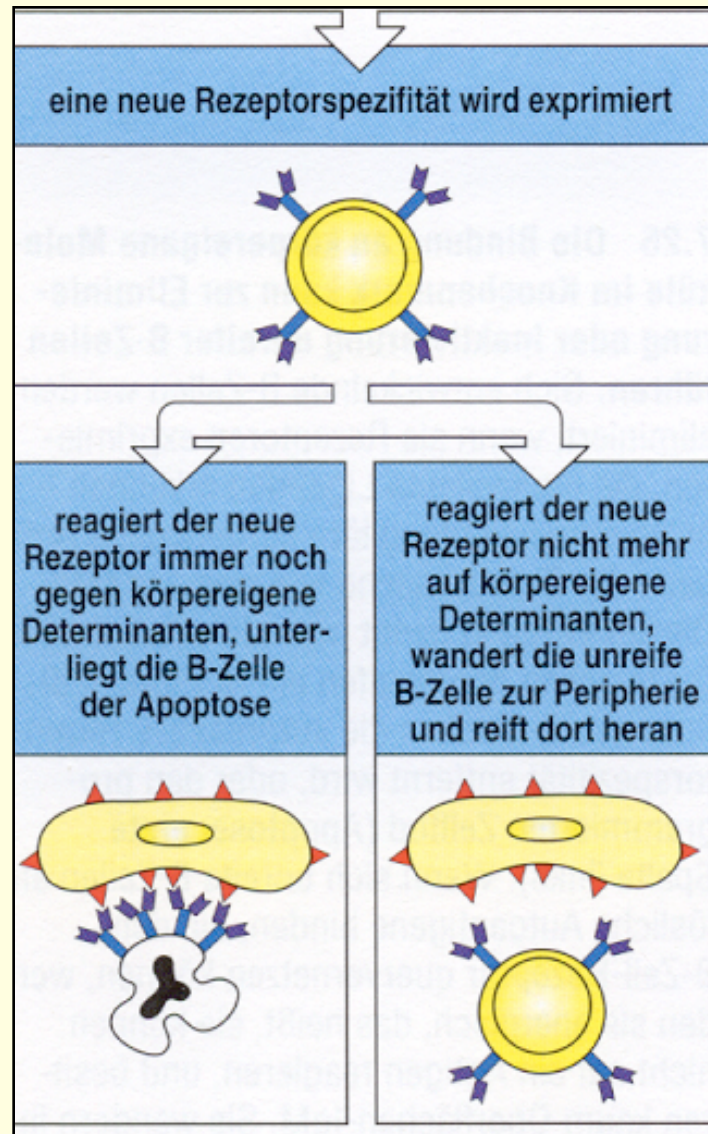
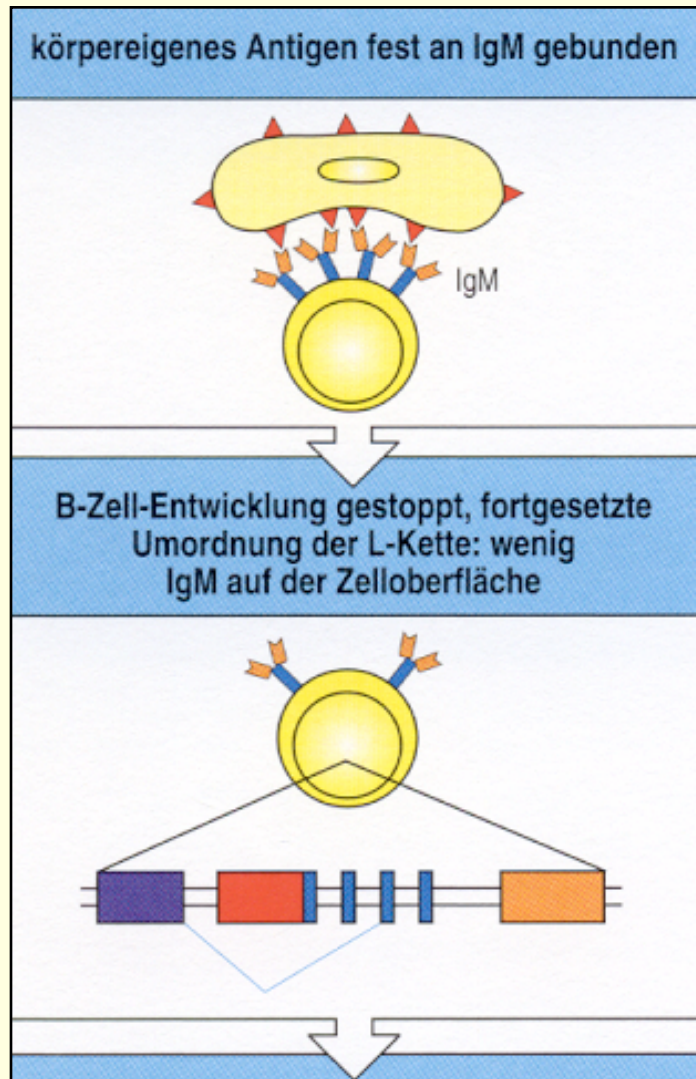
# Central B-cell tolerance in BM

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

# B cell selection in BM



# Rezeptor-Editing



# Passive tolerance

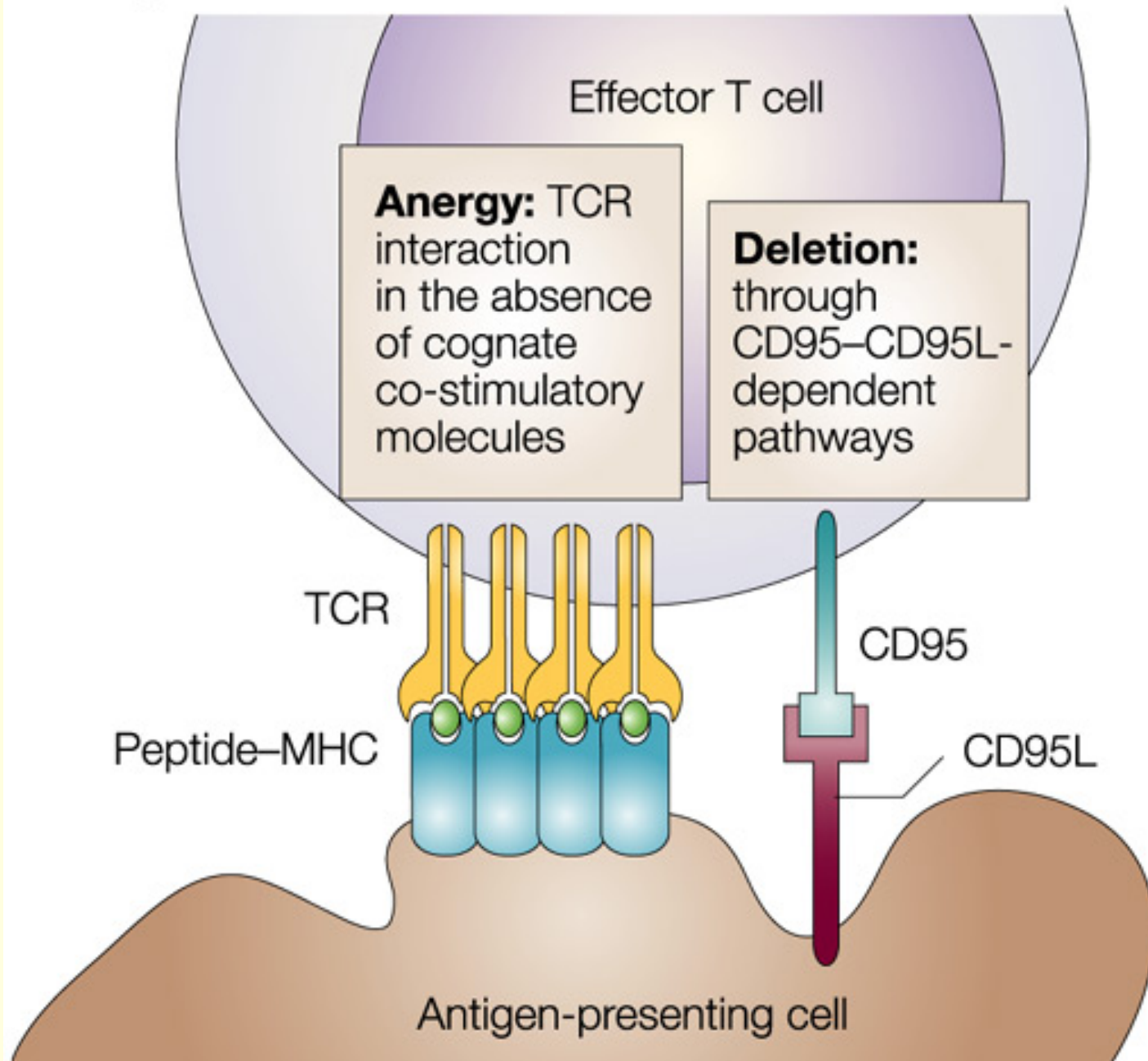
**Unresponsiveness:** no MHC recognition or inhibited cellular differentiation.

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

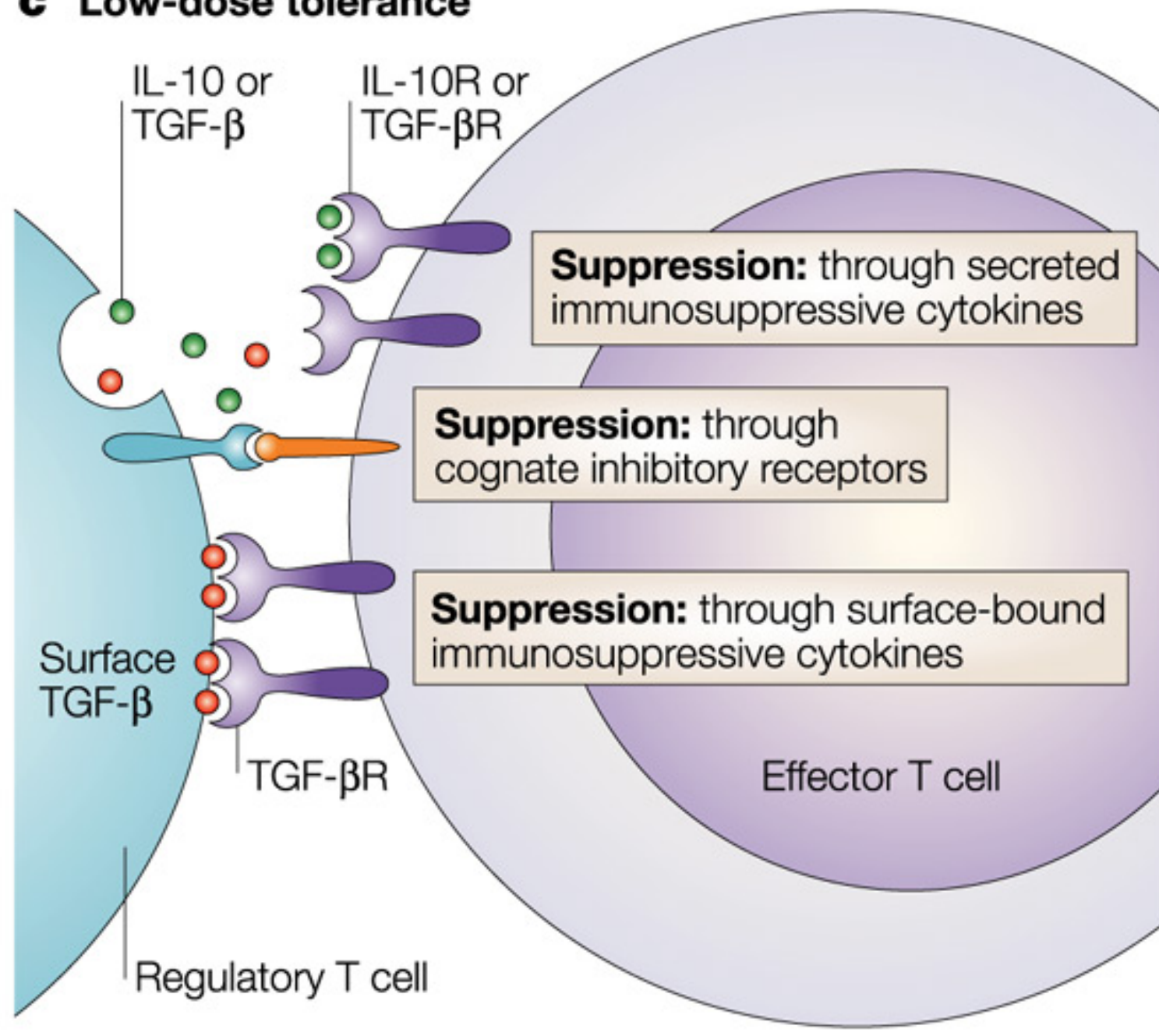
# **Passive tolerance induced by the nature of the antigen**

- **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

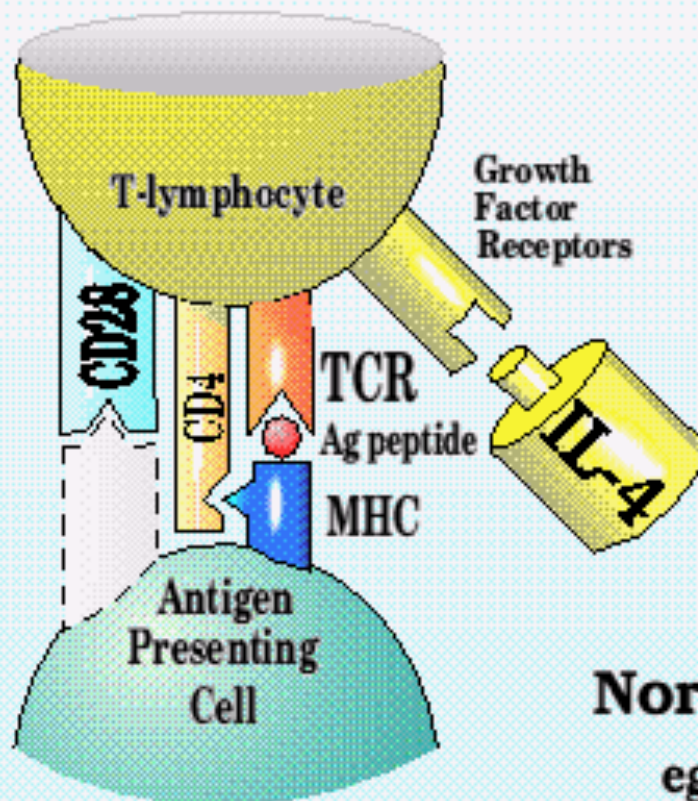


# Failed co-stimulation results low dose tolerance

**"Self" : tolerance**

**Non-professional  
Antigen  
Presentation**

**eg. No B7 present**



**Non-inflammatory  
Environment**

**eg. IL-4, 10, TGF- $\beta$  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**

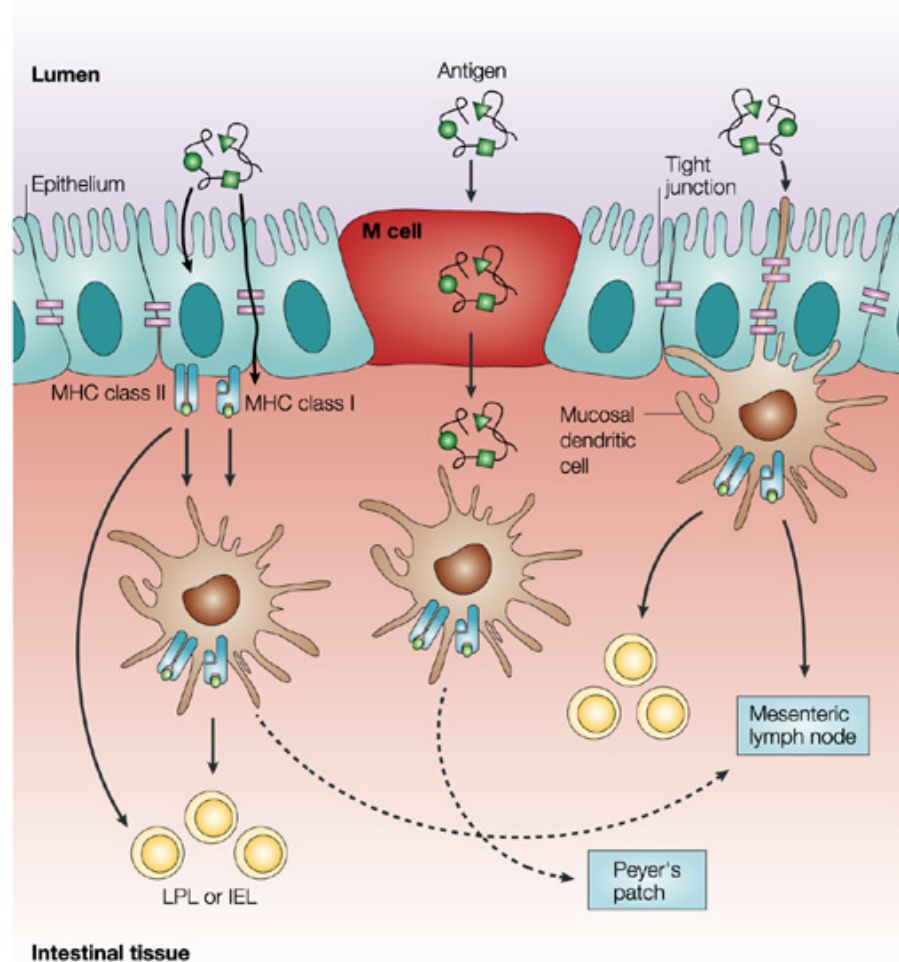
# ACTIVE TOLERANCE

## **“Immunological homunculus”**

- Low affinity IgM natural autoantibodies produced by CD5+ B cells
- $\gamma/\delta$  T cells
- **Innate-like** function

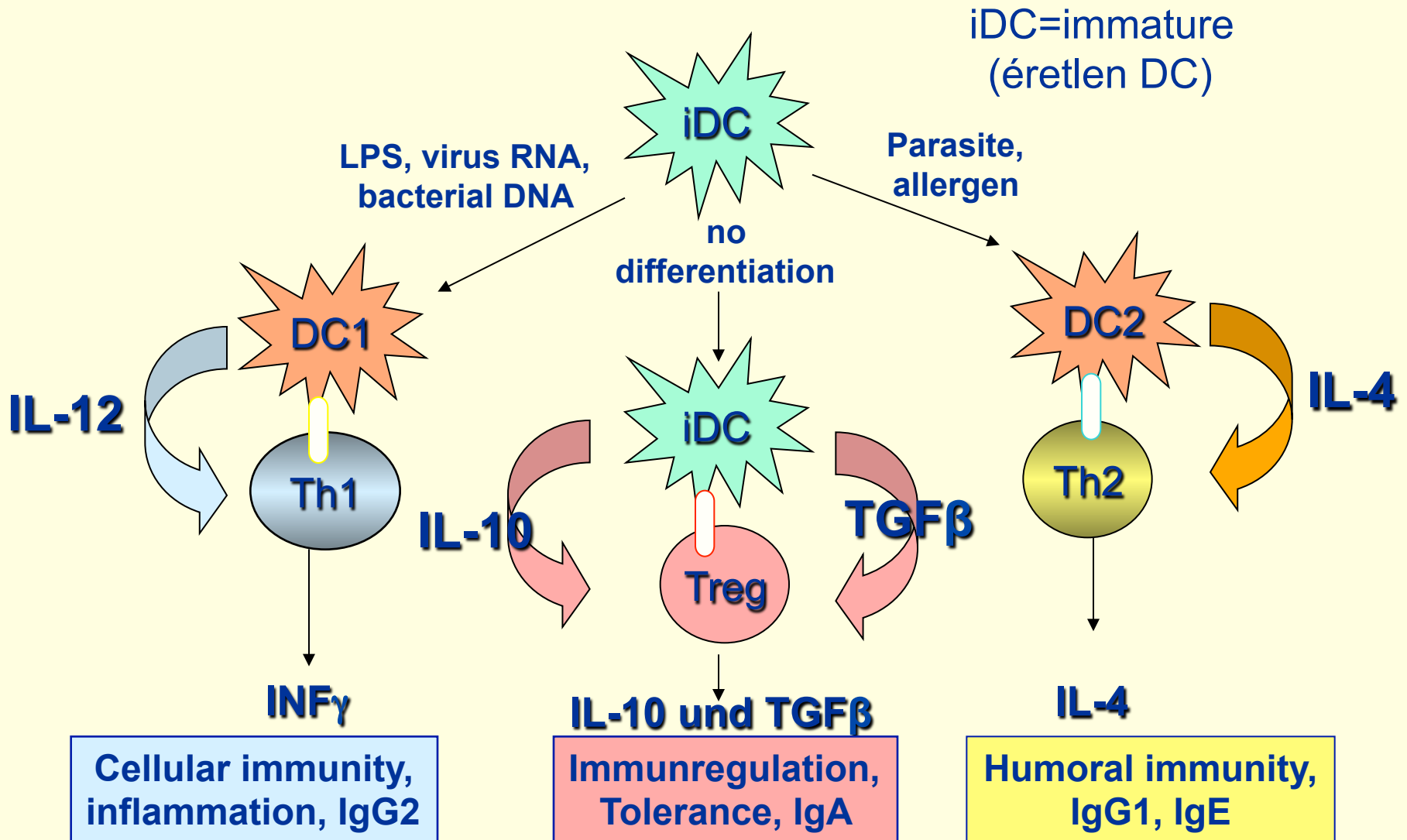
## **INDUCED Treg Cells**

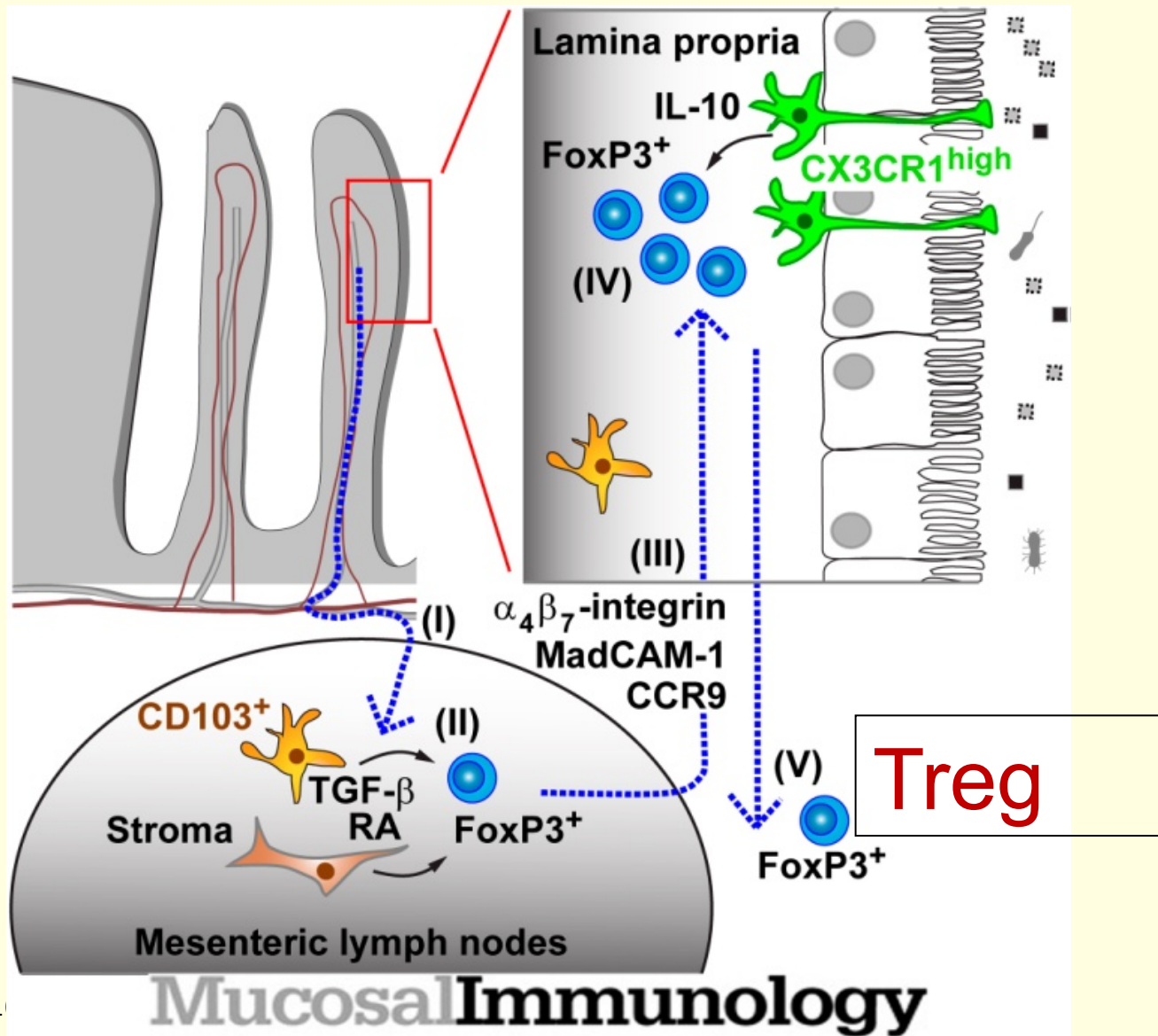
# Oral tolerance



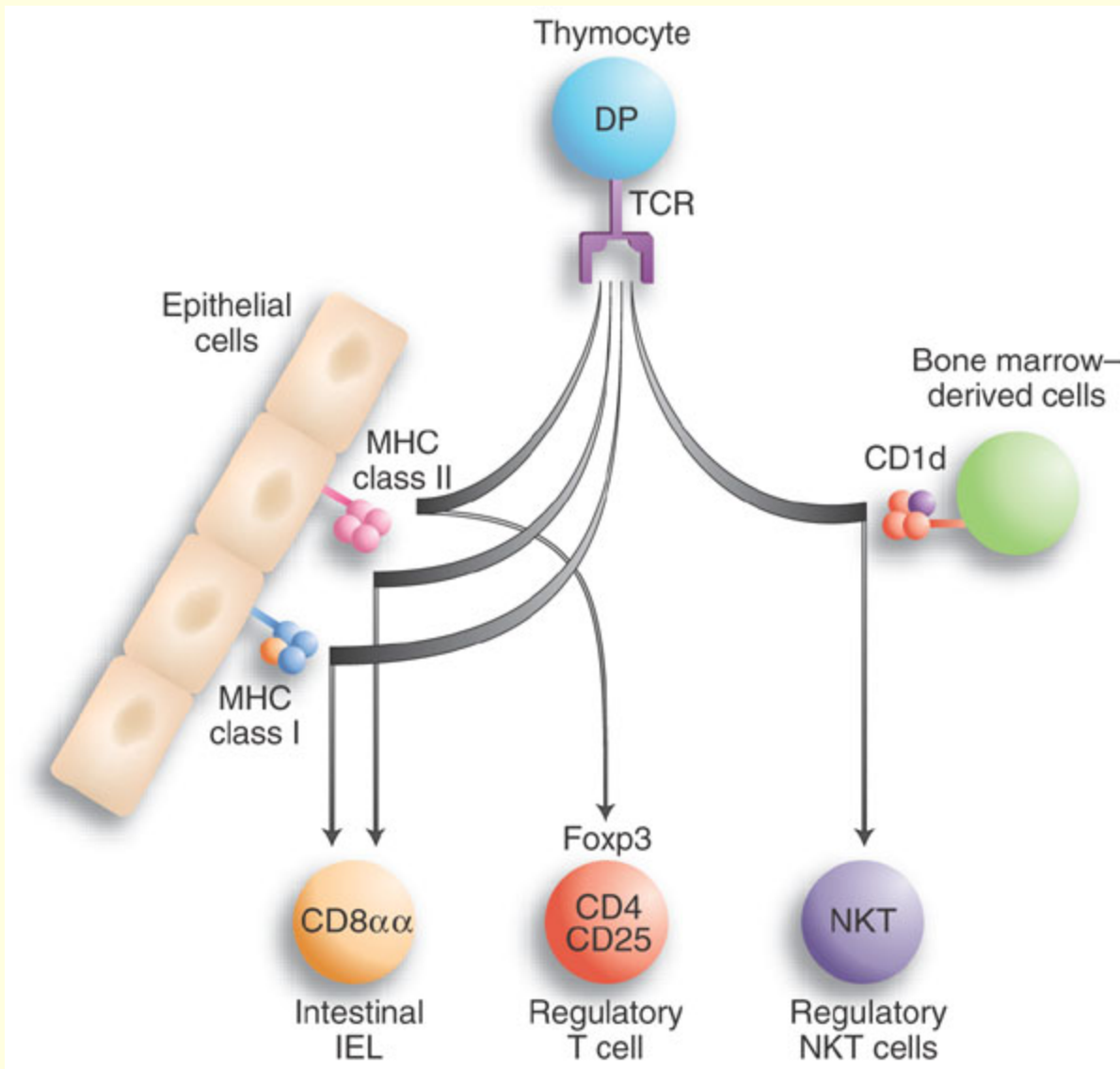
M-Cells - Endocytosis  
Epithelial cells – Transcytosis  
DC  
Through Tight Junctions

# Development of induced Treg





# Role of intestinal Tregs in the maintenance of tolerance



# **Genetically well conserved antigens recognized by natural (auto)antibodies**

<b>Heatshock proteins</b>	<b>hsp65, hsp70, hsp90, ubiquitin</b>
<b>Enzymes</b>	<b>aldolase, citockrom c, SOD, NADPH, citrate synthase, topoisomerase I.</b>
<b>Cell membrane components</b>	<b><math>\beta</math>2-microglobulin, spectrin, acetylcholin receptor</b>
<b>Cytoplasmic components</b>	<b>actin, myosin, tubulin, myoglobin, myelin basic protein</b>
<b>Nuclear components</b>	<b>DNS, histones</b>
<b>Plasma proteins</b>	<b>albumin, IgG, transferrin</b>
<b>Cytokines, hormones</b>	<b>IL-1, TNF, IFN, insulin, thyreoglobulin</b>

**Bone Marrow  
Transplants**

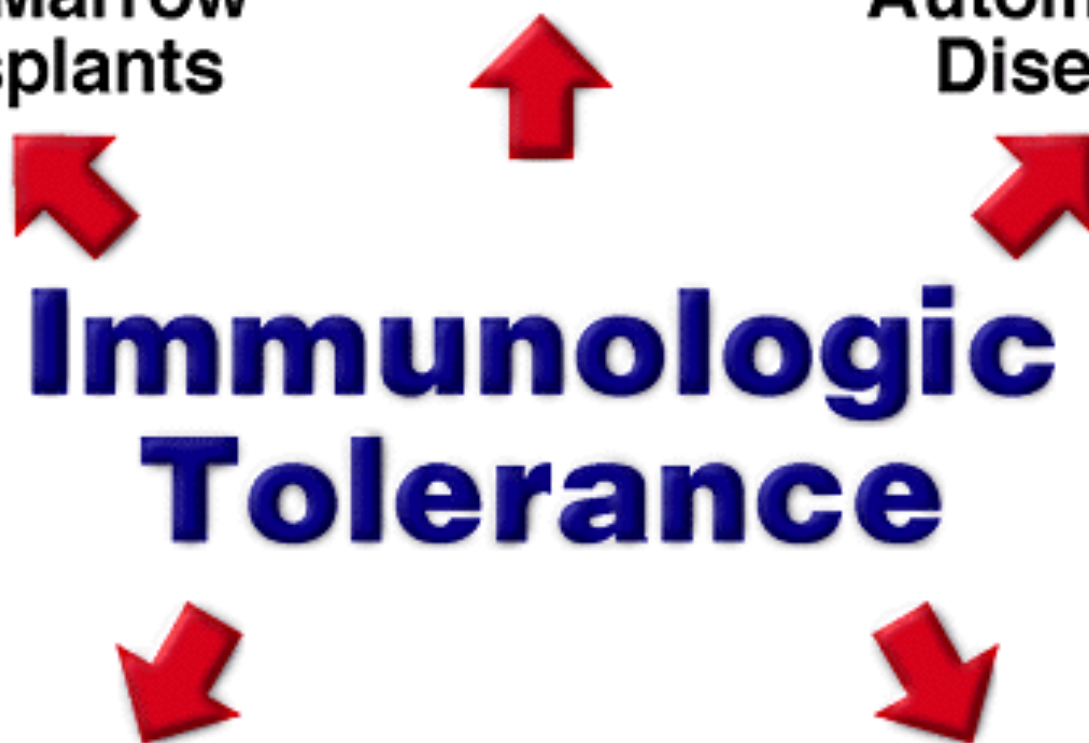
**Solid Organ  
Transplants**

**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

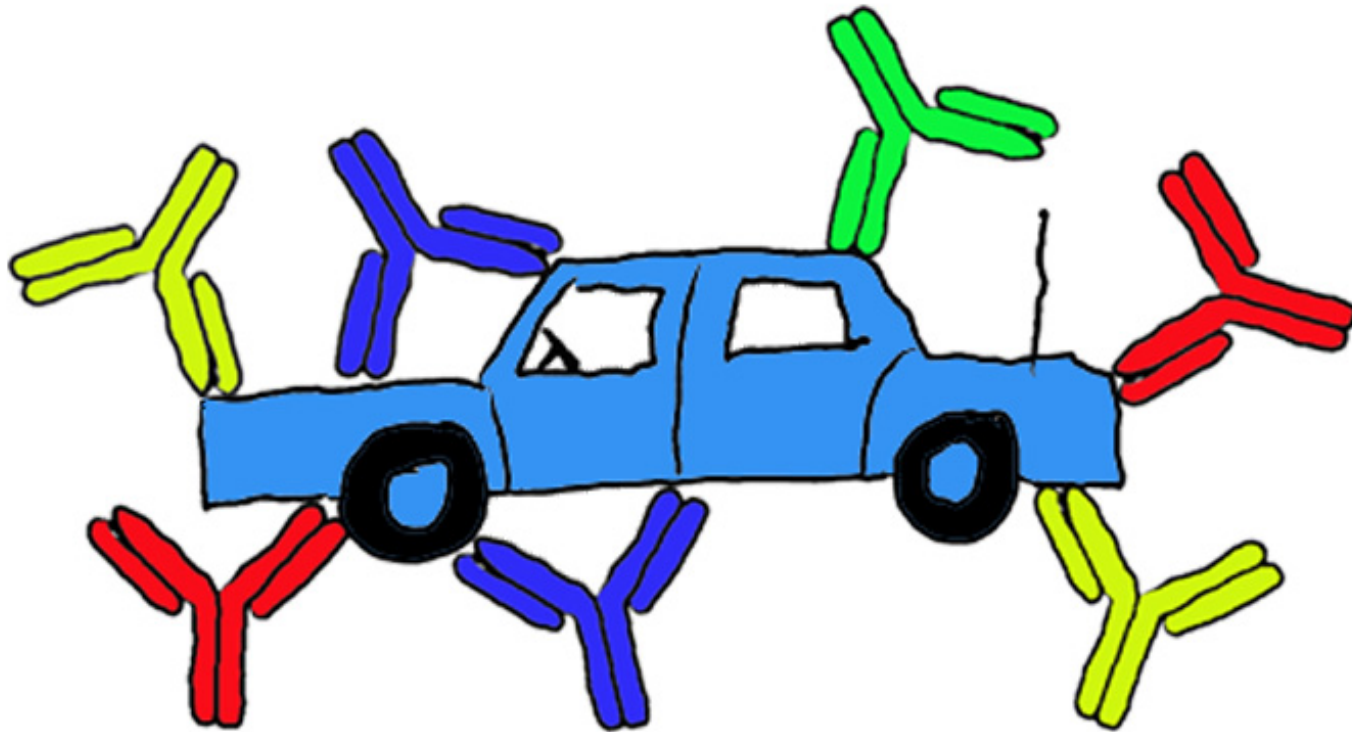
# Natural and pathologic autoimmunity

## 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:**

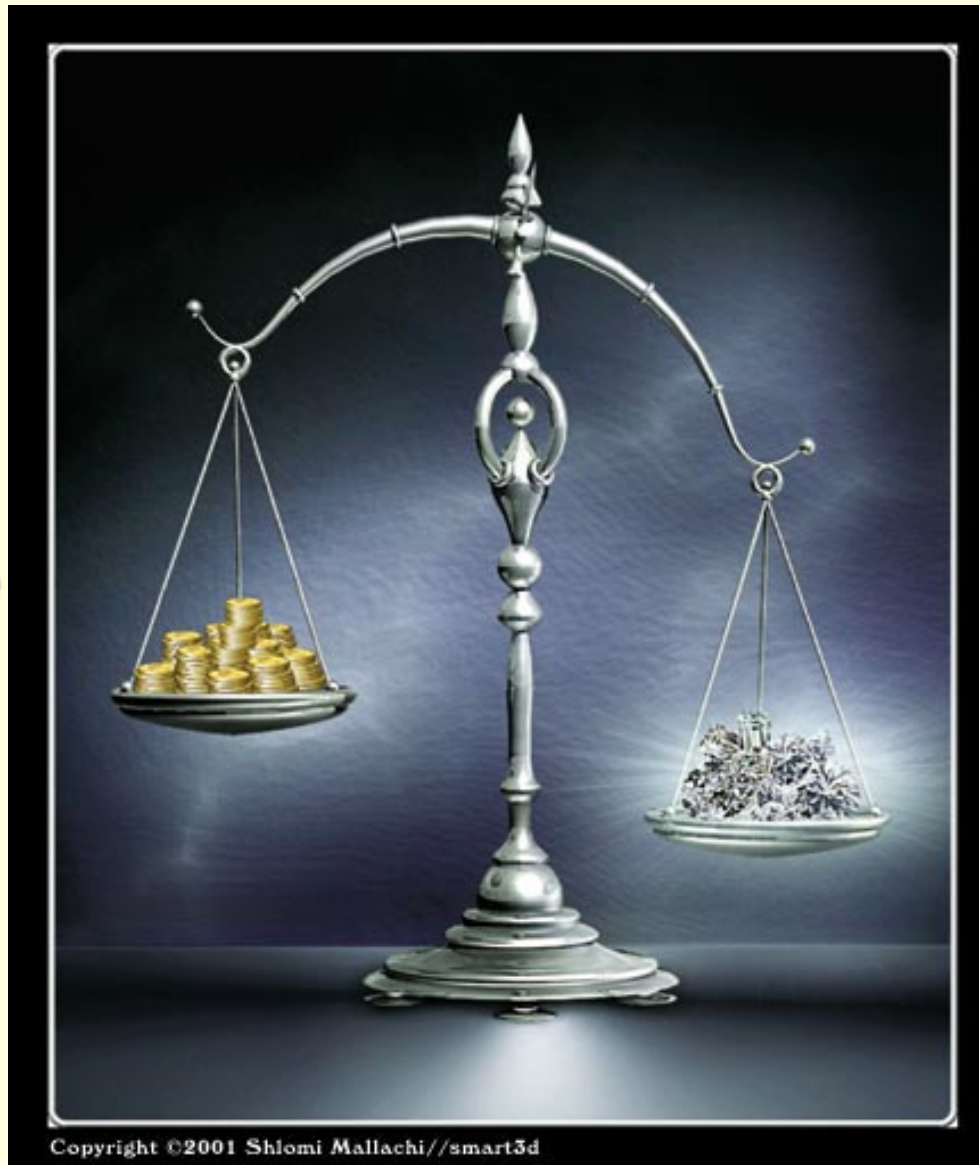
- (T cells CD8 and Th1, NK, Mf, DC, Ne, Eo, Ba, Mc)

- **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

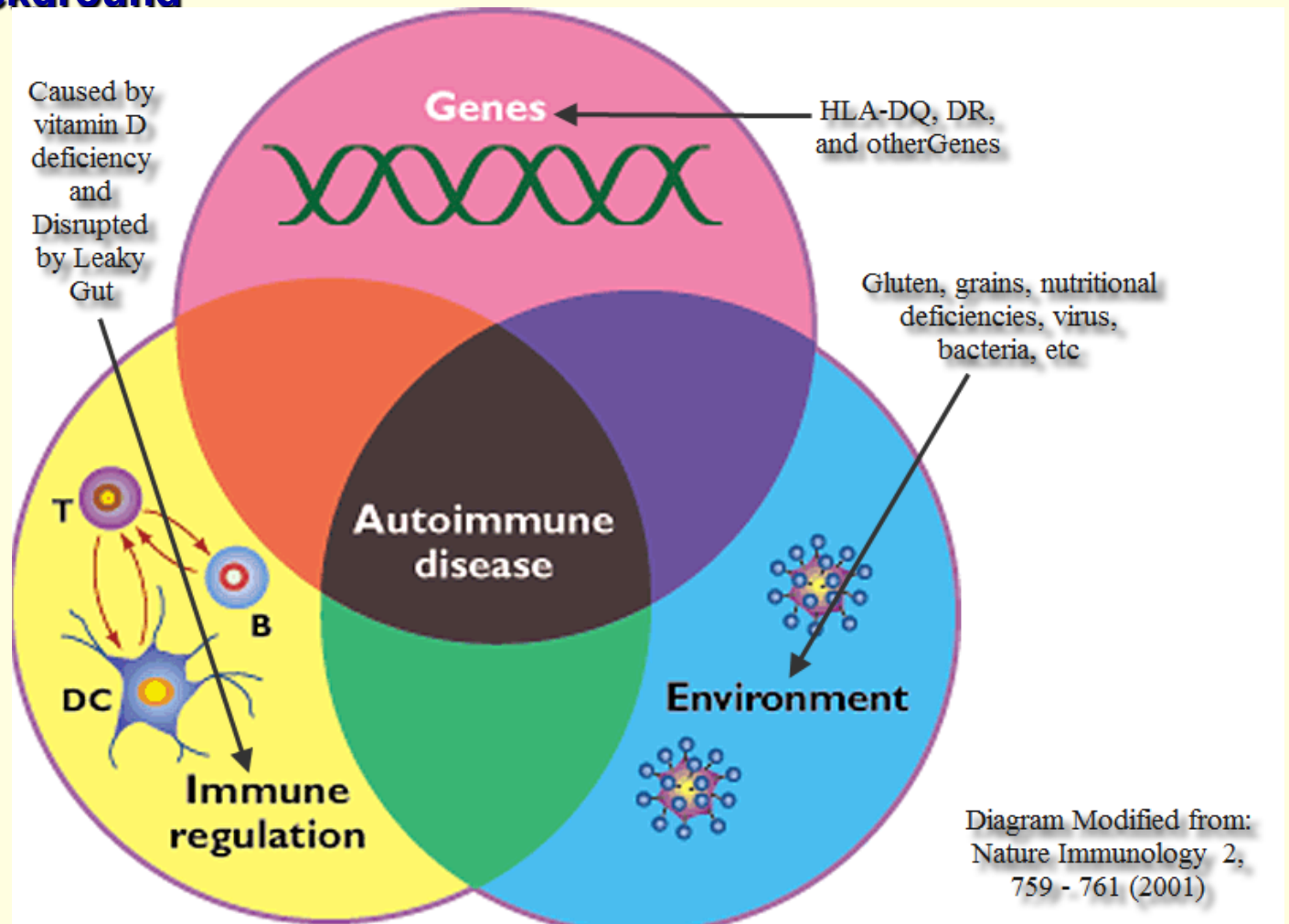
- Multifactor mechanism

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

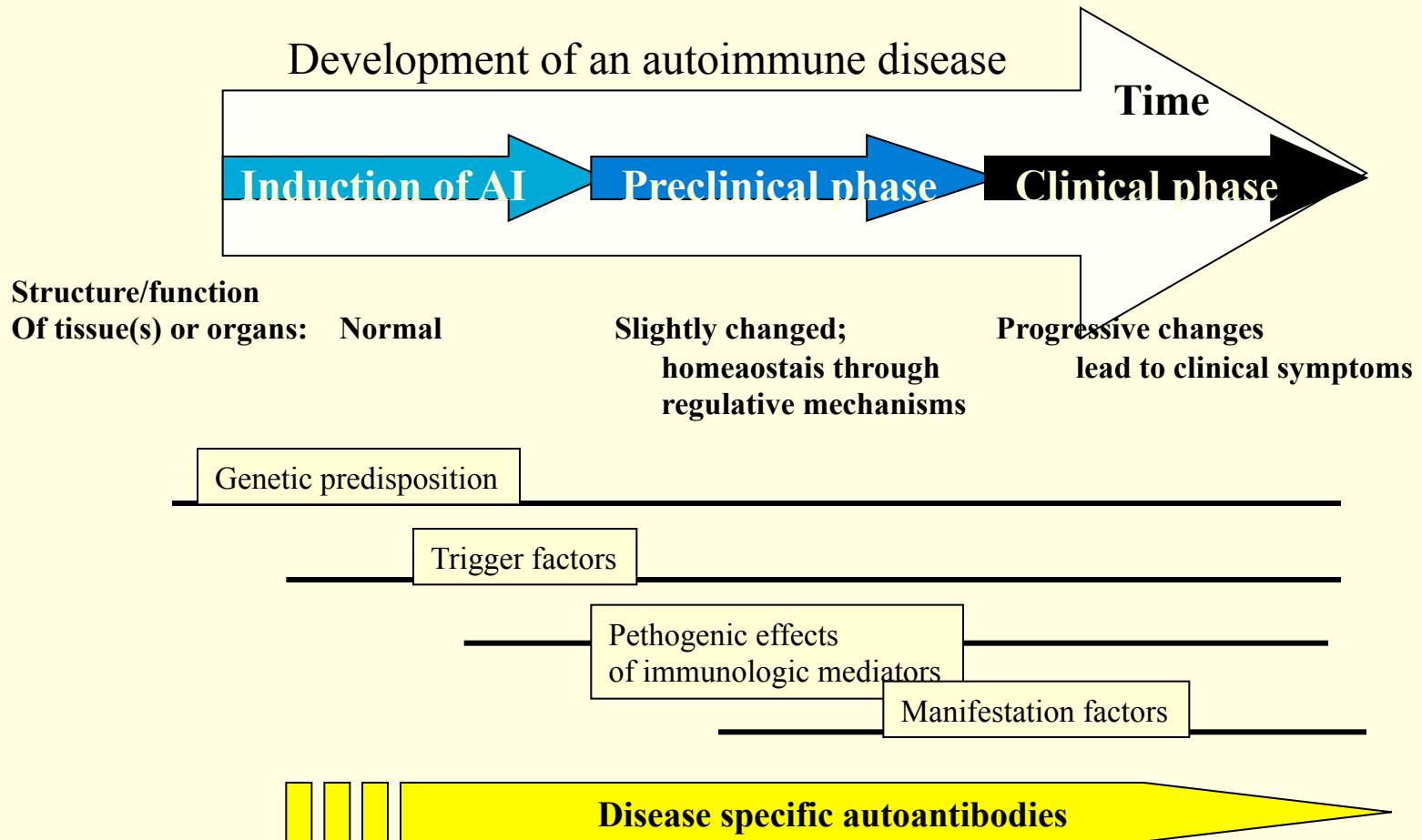
- **Autoimmune “steady state”** (failure of dynamic balance on self tolerance and autoimmunity)
- **Role of infections** (molecular mimicry or inefficient natural antibody network)

# 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  
60

PDPLLGRPDED  
VTELLGRPDAE

Poliovirus VP2  
Acetylcholine receptor

70  
176

STTKESRGTT  
TVIKESRGTK

Papilloma virus E2  
Insulin receptor

76  
66

SLHLESLKDS  
VYGLESLKDL

*Klebsiella pneumoniae*  
nitrogenase enzym  
HLA-B27 molecule

186  
70

SRQTDREDE  
KAQTDREDL

Adenovirus 12 E1B  
Alfa-gliadin

384  
206

LRRGMFRPSQCN  
LGQGSFRPSQQN

HIV p24  
Human IgG

160  
466

GVETTTPS  
GVETTTPS

Measles virus P3  
Myelin basic protein

31  
61

EISDNLGQE  
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

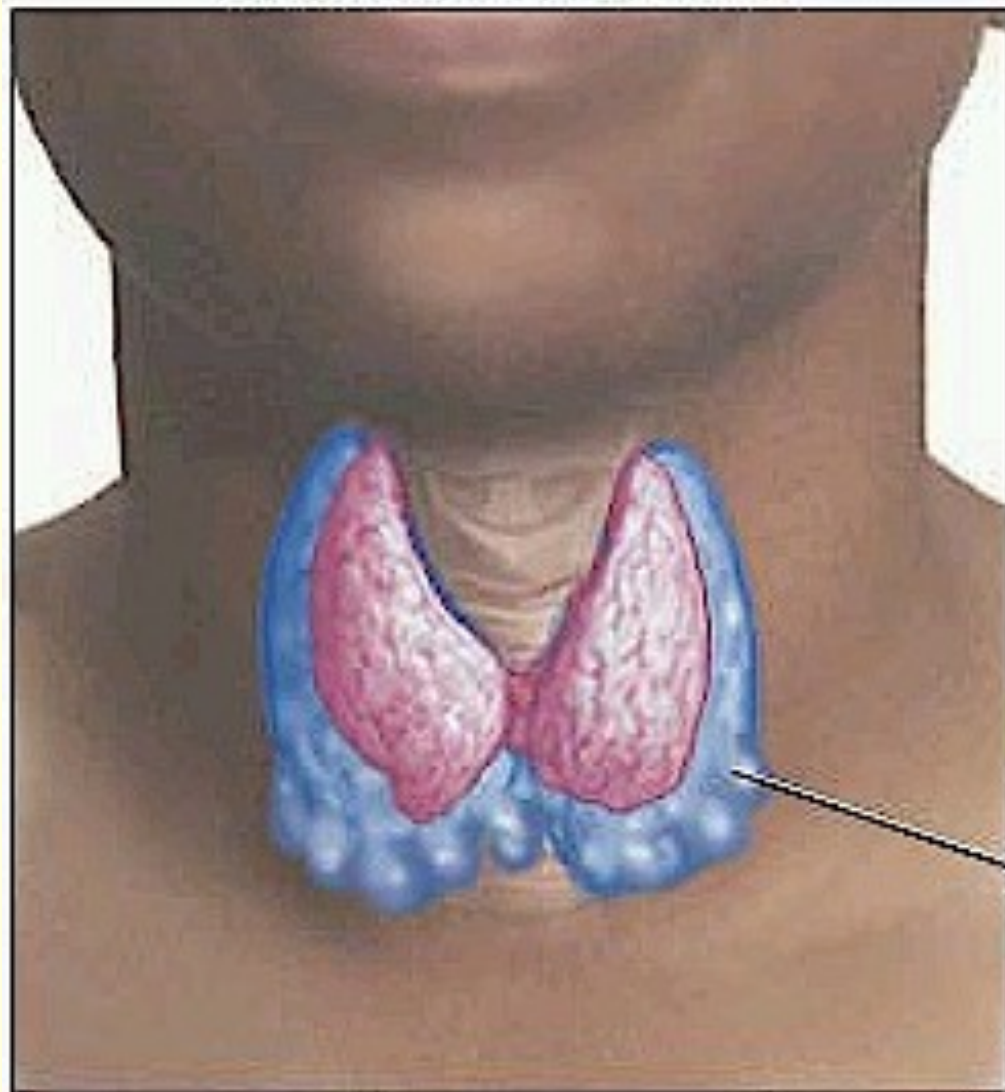
Chlamydia, Yersinia

Salmonella/Shigella arthritis

**B27**

20.7

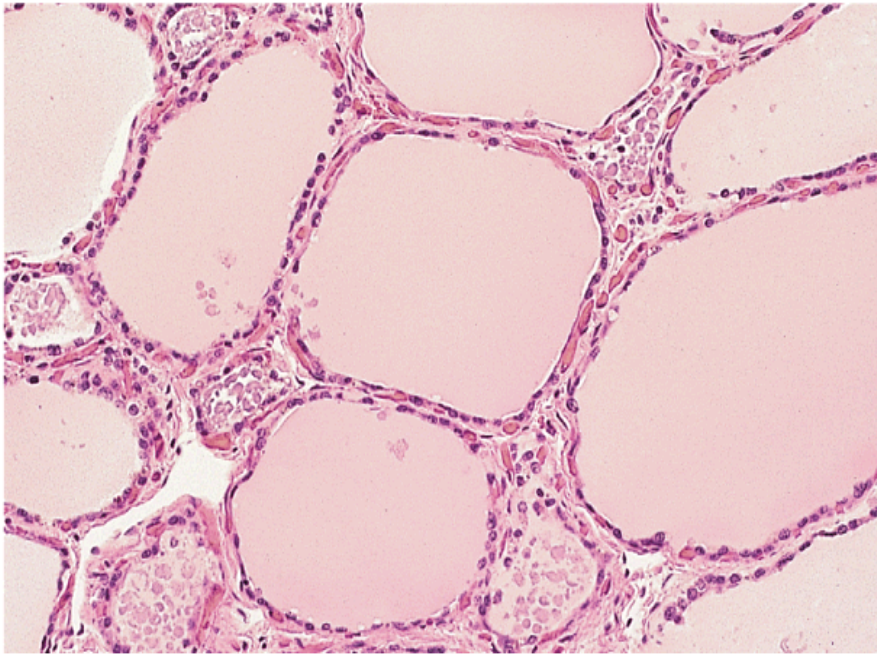
## Hashimoto's disease



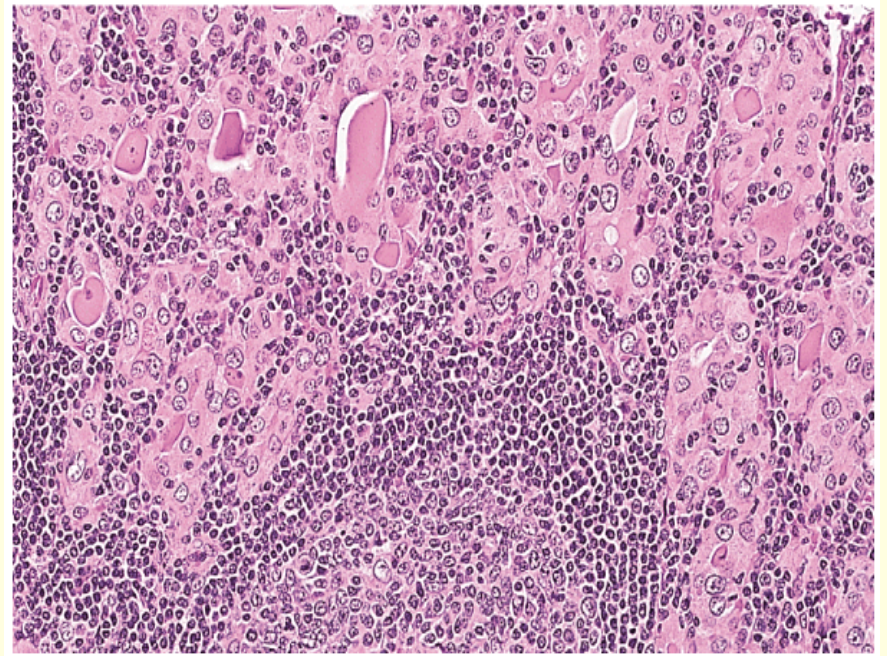
Enlarged, inflamed  
hypofunctioning  
thyroid (goiter)

# Hashimoto's thyroiditis

(a)



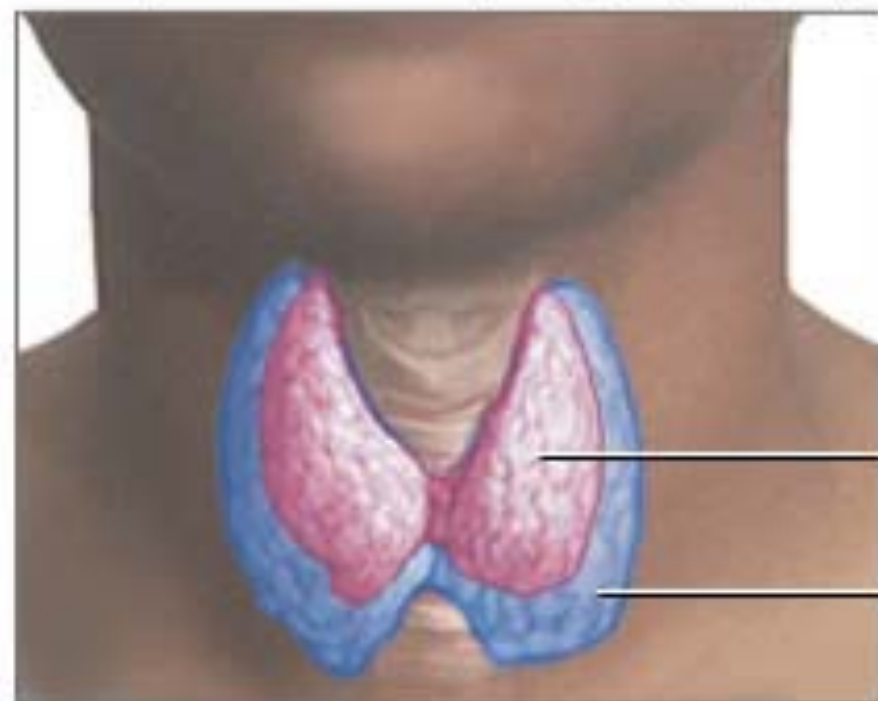
(b)





Exophthalmos (bulging eyes)

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

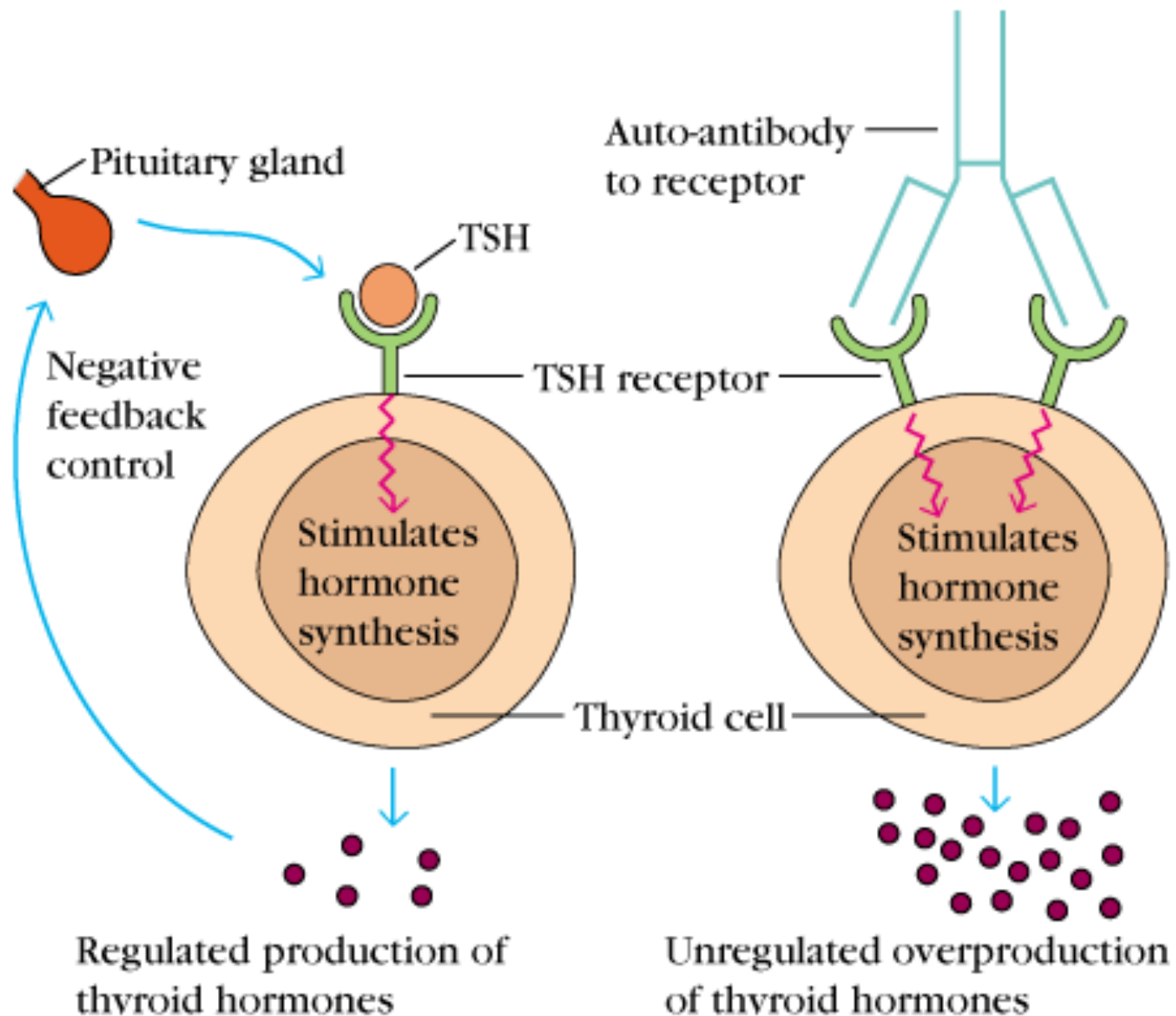


Normal thyroid

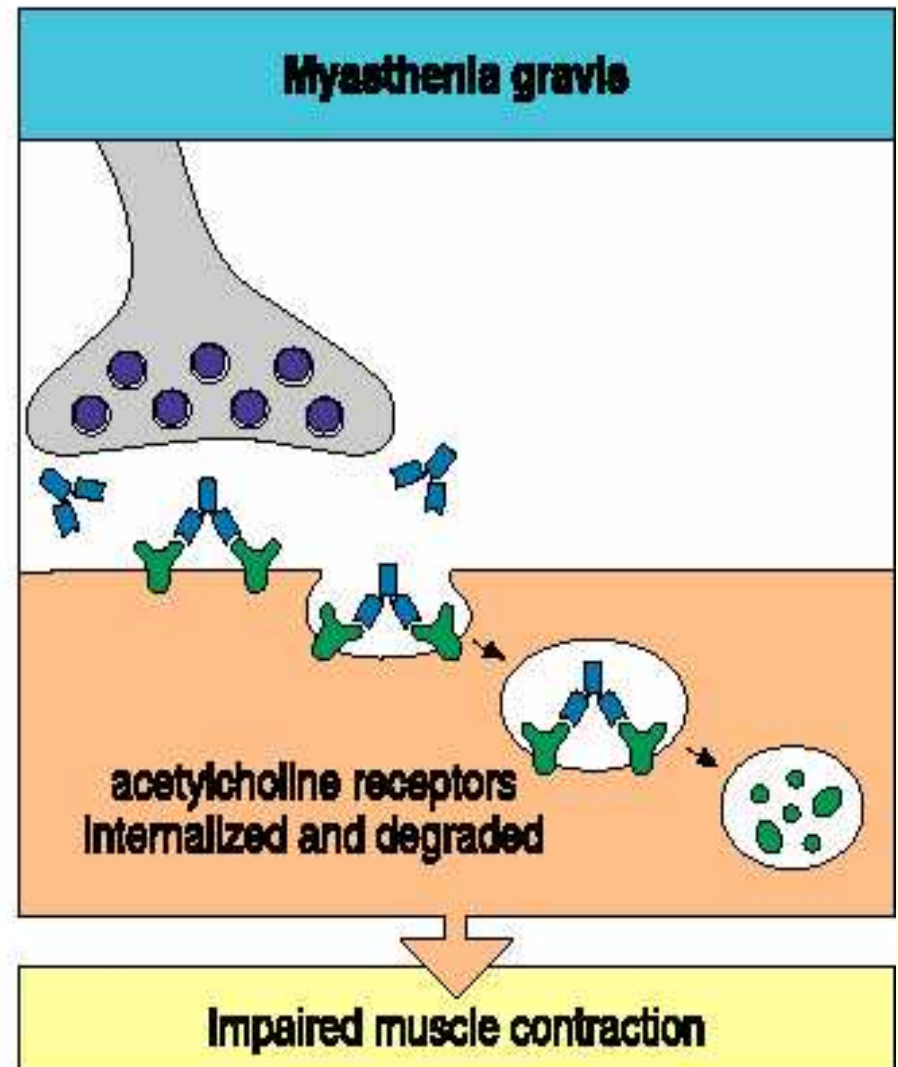
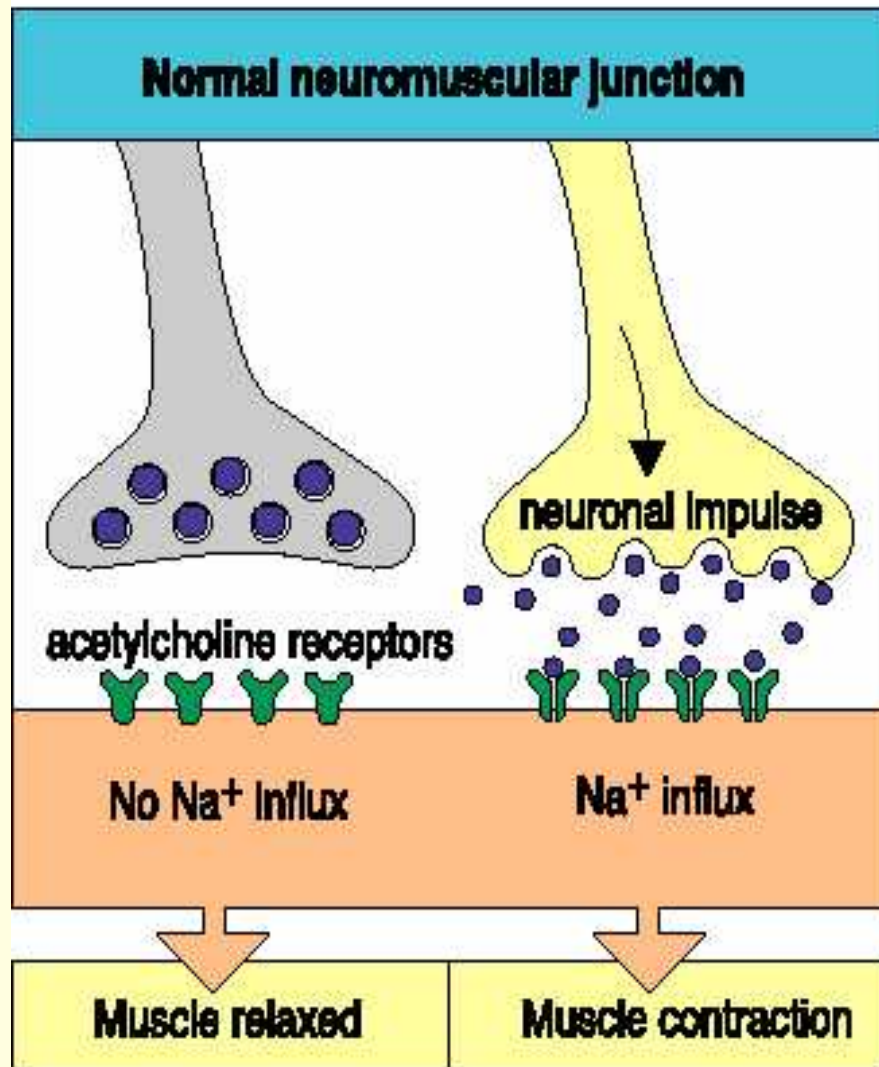
Enlarged thyroid

Diffuse goiter

## STIMULATING AUTO-ANTIBODIES (Graves' disease)



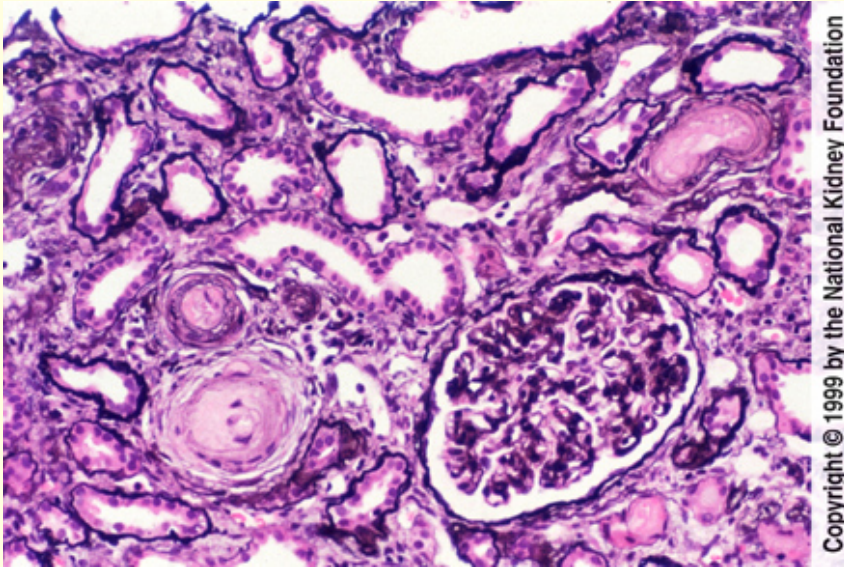
# Myasthenia gravis



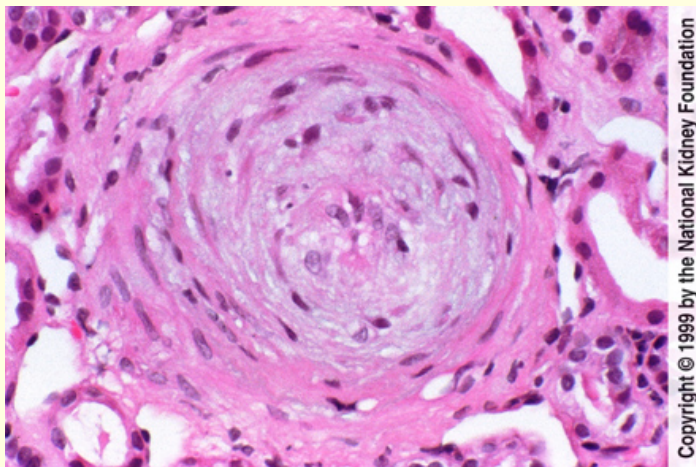
# Raynaud's Syndrome



# 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

