

# **Pathomechanism of autoimmune diseases**

**I.**

**Bone Marrow  
Transplants**

**Solid Organ  
Transplants**

**Autoimmune  
Diseases**



# **Immunologic Tolerance**



**Infectious Diseases/  
Vaccine Development**

**Allergic  
Diseases**

# What does it mean „autoimmunity” ?



**5-8 % of the population suffering in autoimmune diseases in the industrialized countries!**

# AUTOIMMUNITY

- **Physiological autoimmunity: part of the normal immunological regulation**
- **Pathological autoimmunity: diseases caused by self reacting immune responses with permanent tissue/organ injury**

# Pathomechanism of autoimmunity

- **Inflammation and tissue necrosis**

- **Cellular components:**

- (T cells CD8 and Th1, Th2, Th9, Th17, Treg, NK, Mf, DC, Ne, Eo, Ba, Mc)

- **Humoral components:**

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

# Pathomechanism of autoimmunity

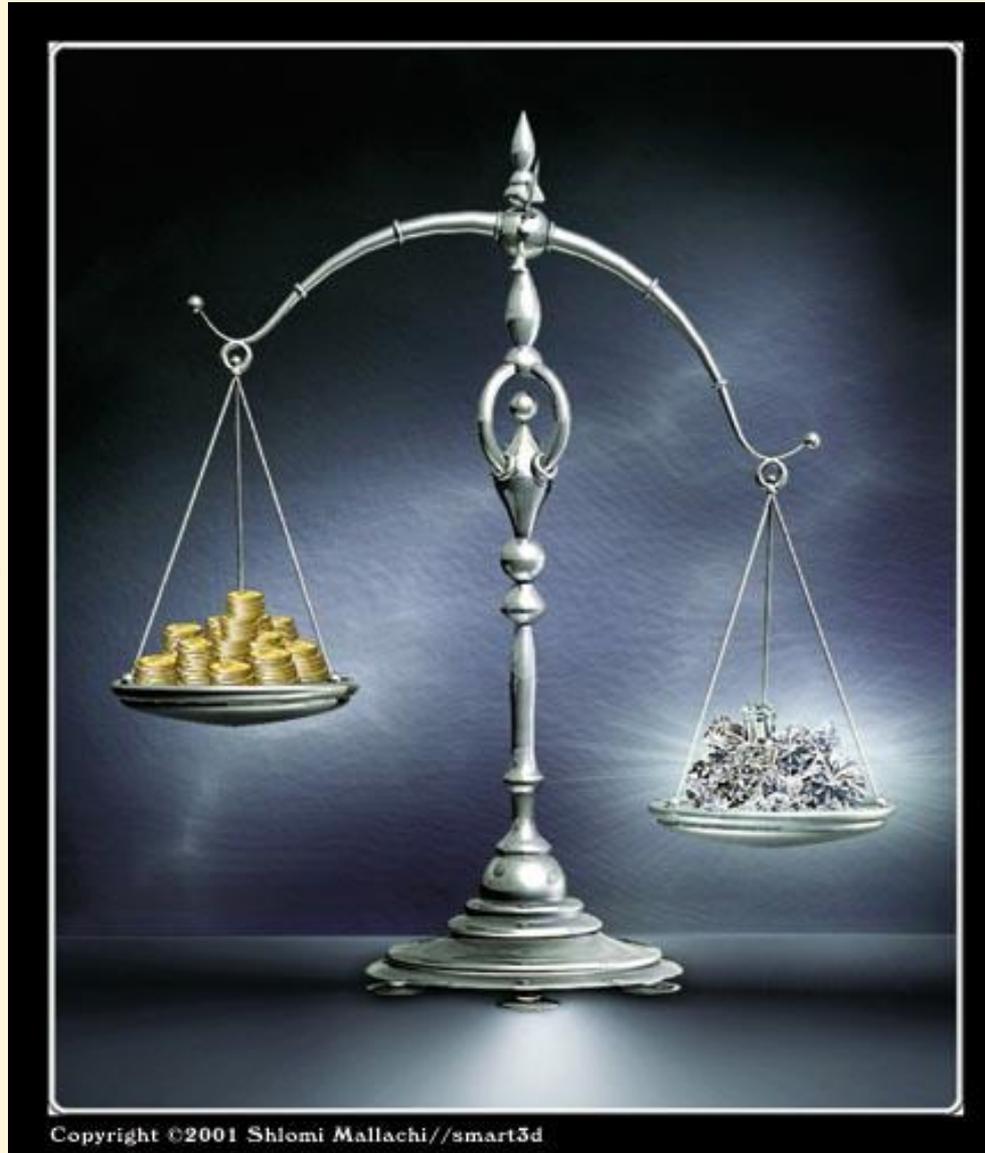
- **Multifactor mechanism**

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

- **Autoimmune “*steady state*”** (failure of the dynamic balance of self tolerance and autoimmunity)
- **Role of infections:** inflammatory environment, molecular mimicry, (similar “molecular shape”)
- **Genetic background:** MHC, gender, microchimerism

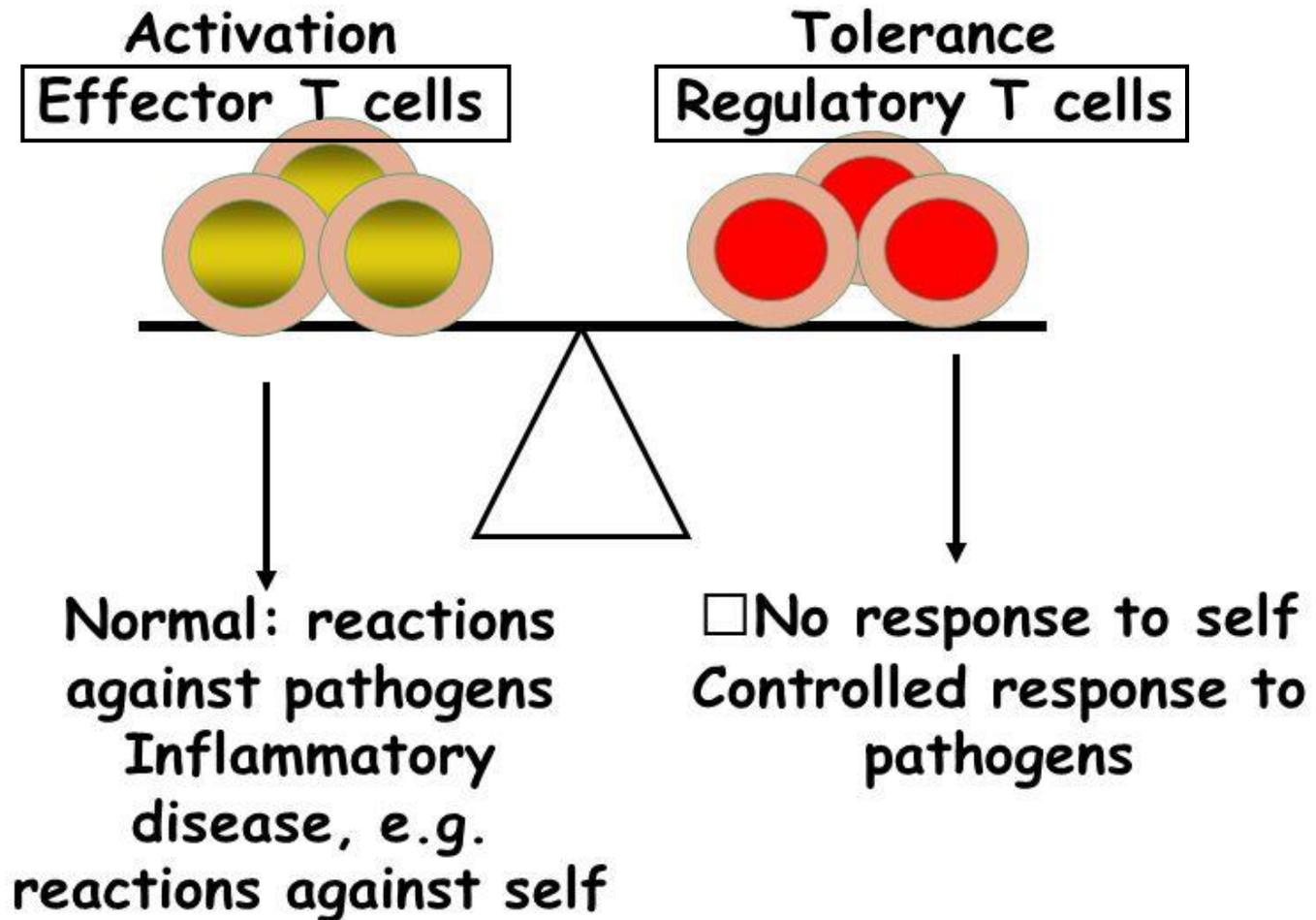
# Autoimmune steady state

**Self  
reacting  
immune  
response  
with  
tissues  
damages**



**Active  
tolerance  
and  
tissue  
repair**

# Balancing lymphocyte activation and control



# **Pathomechanisms of autoimmune diseases**

- Autoimmunity by the antigen**
- Autoimmunity by the failed immune regulation**
- Role of genetic factors**

# **Autoimmunity by the antigen**

- **Release of sequestered self antigens**

(mechanic injuries, inflammatory reactions, malignant tumors)

- **Structural alterations of self antigens**

(viruses, chemicals, drugs, physical influences)

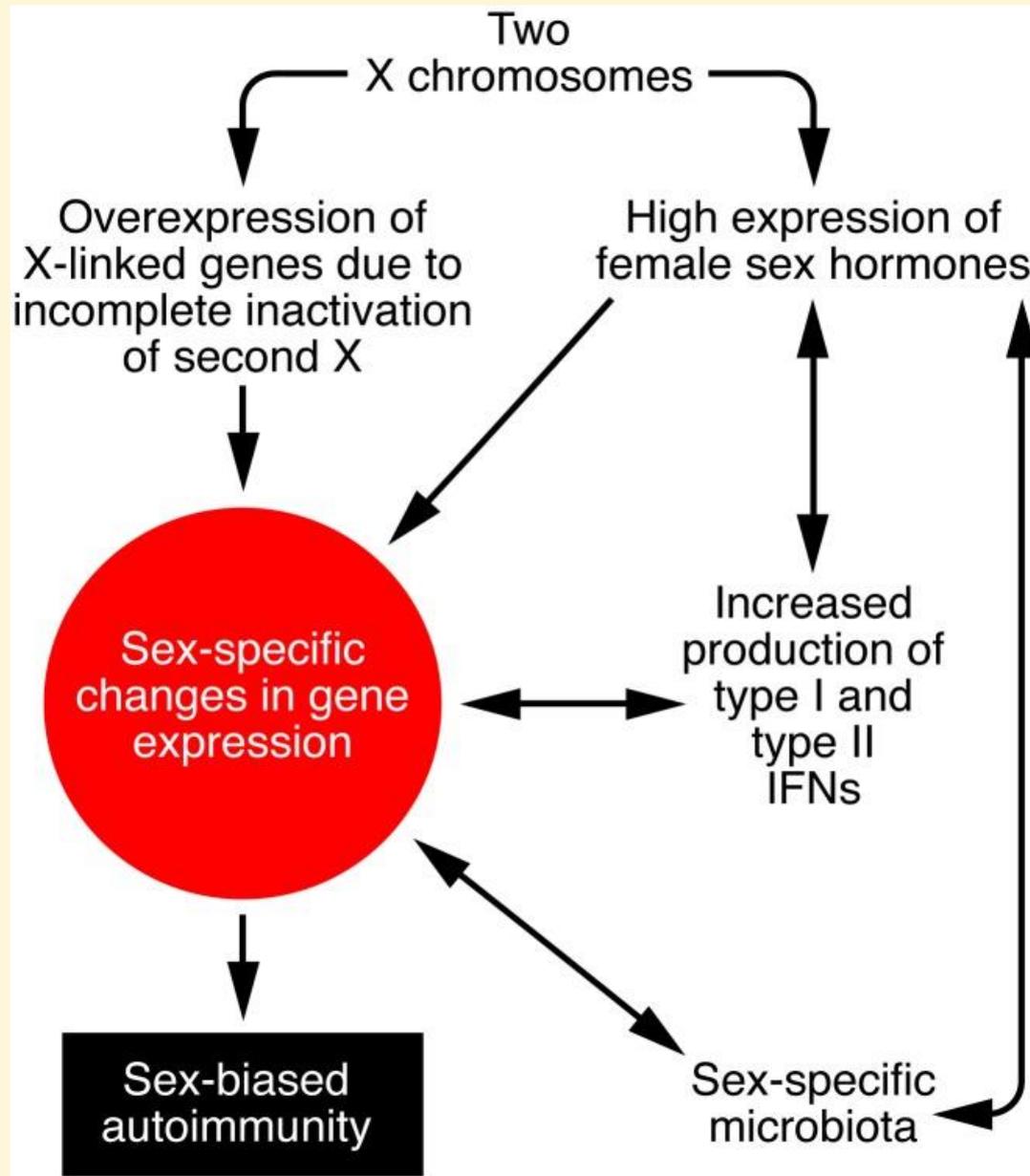
- **Increased co-stimulation on tissue APCs**

(paraneoplastic syndrome, chronic inflammations)

# **Autoimmunity by the failure of self tolerance**

- **Abnormal selection of lymphocytes**
- **Polyclonal activation of anergic self-reactive lymphocytes**
- **Stimulation by foreign antigens that cross-react with self**
- **Gender differences**
- **Immuno-genetic factors**
- **Environmental factors**

# Sex differences in autoimmunity



**Target organ vulnerability**

**Reproductive function**

Puberty  
Pregnancy  
Microchimerism  
Menopause

**The environment**

Infectious agents  
Chemicals  
Drug exposure  
Pesticides  
Organic solvents  
Sunlight/Vit-D

**Hormones**

Estrogen  
Progesterone  
Androgens  
Prolactin

**Gender differences  
in autoimmune  
disease**

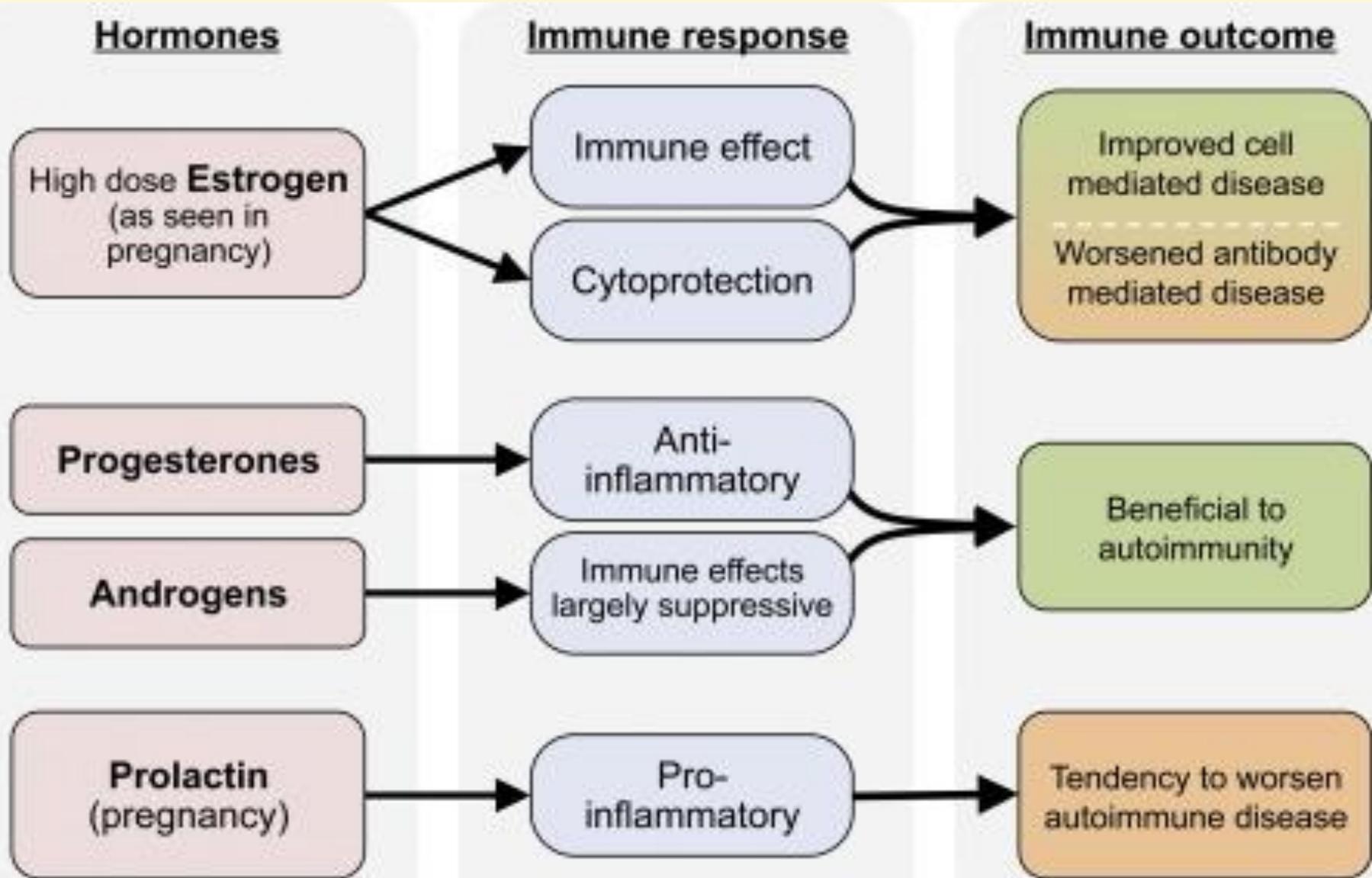


**Genetics**

Chromosomes  
Parental inheritance  
- (X/Y-linked)  
Epigenetics  
Genomic imprinting

**Immune response**

T-lymphocytes  
B-lymphocytes  
NK cells  
Microglia  
Astrocytes  
Mast cells  
Dendritic cells



# HLA association with autoimmune diseases

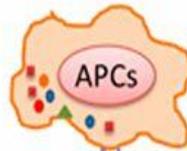
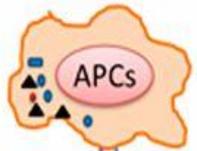
## Susceptibility to Autoimmune Diseases

### Autoimmune-prone HLA class II alleles

HLA-DQ6 (0602)

HLA-DR2/DR3/DR4 (0401)

HLA-DQ8 (0302)



IFN $\gamma$  IL17

IFN $\gamma$  IL17

IFN $\gamma$  IL17

### Autoimmune-prone haplotype

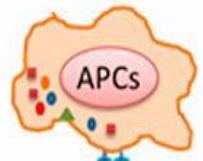
HLA-DR4 (0401).DQ8



IFN $\gamma$  IL17

### Highest autoimmune-prone heterozygous haplotype

HLA-DR3 (0301).DQ2  
HLA-DR4 (0401).DQ8



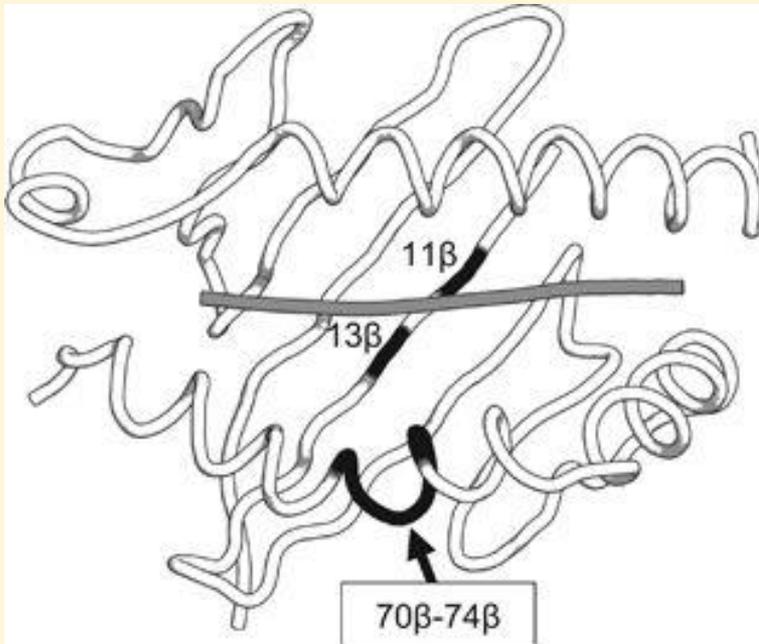
IFN $\gamma$  IL17

HLA class II alleles as HLA-DR2, DR3, DR4, DQ6 (0602), and DQ8 (0302) predispose to autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, type 1 diabetes, and systemic lupus erythematosus through secretion of proinflammatory cytokines.

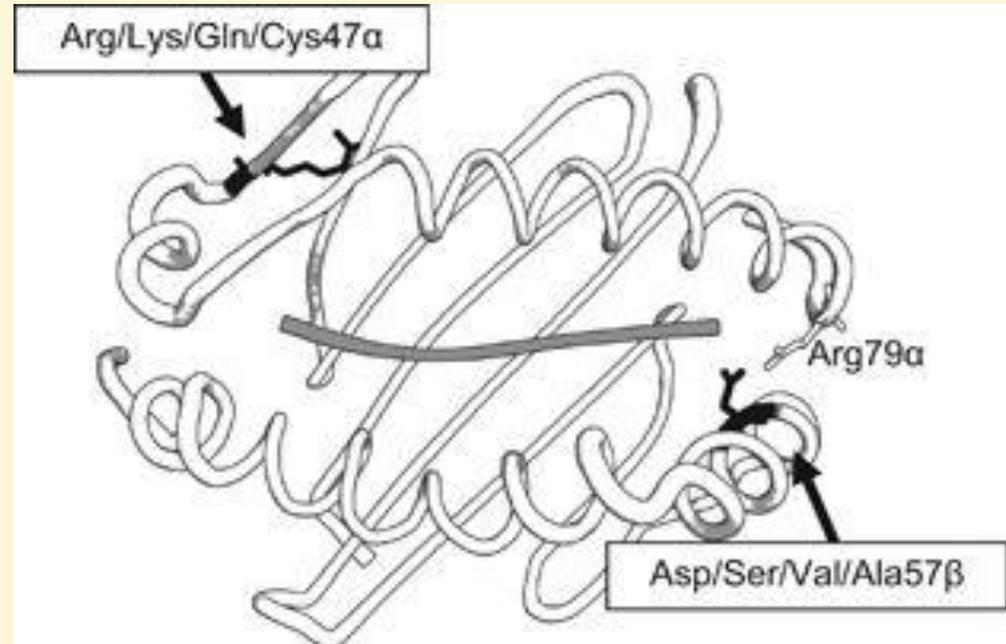
## Associations of HLA serotype with susceptibility to autoimmune disease

Disease	HLA allele	Relative risk	Sex ratio (♀:♂)
Ankylosing spondylitis	B27	87.4	0.3
Acute anterior uveitis	B27	10	<0.5
Goodpasture's syndrome	DR2	15.9	~1
Multiple sclerosis	DR2	4.8	10
Graves' disease	DR3	3.7	4–5
Myasthenia gravis	DR3	2.5	~1
Systemic lupus erythematosus	DR3	5.8	10–20
Type I insulin-dependent diabetes mellitus	DR3/DR4 heterozygote	~25	~1
Rheumatoid arthritis	DR4	4.2	3
Pemphigus vulgaris	DR4	14.4	~1
Hashimoto's thyroiditis	DR5	3.2	4–5

# HLA association in RA and T1DM

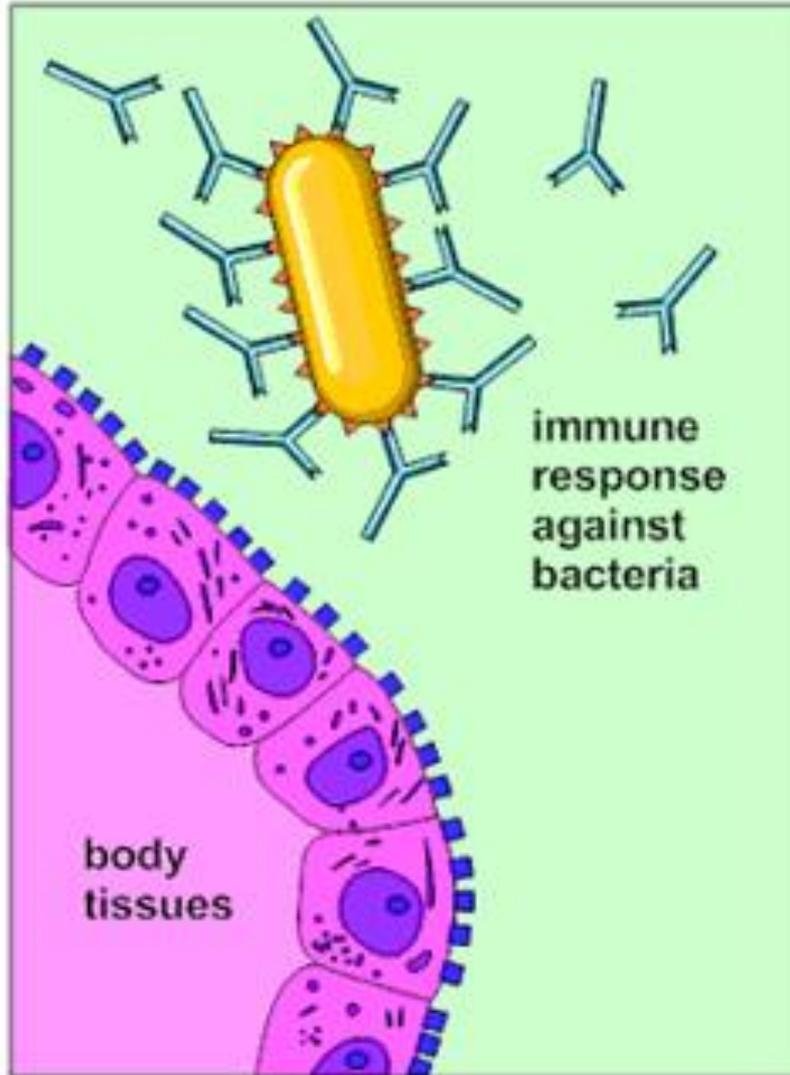


Locations of amino acid residues in DRB1 product that are associated with **rheumatoid arthritis (RA)**. Locations of 11 $\beta$ , 13 $\beta$  and shared epitope (SE) residues in the structure of DR protein (PDB: 2seb)<sup>75</sup> are shown.

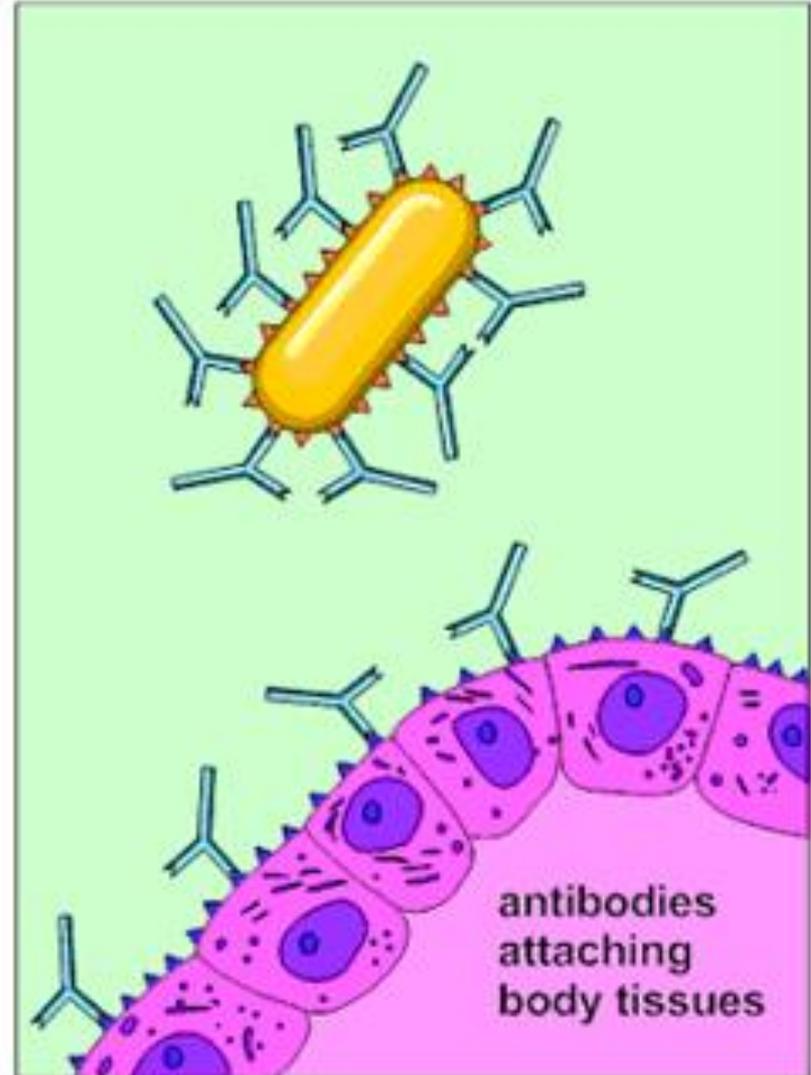


Locations of amino acid residues in DQA1 and DQB1 products that are associated with **type 1 diabetes (T1D)**. Locations of 47 $\alpha$  and 57 $\beta$  in the structure of DQ protein (PDB: 1uvq)<sup>77</sup> are shown.

# Molecular mimicry



Normal



Autoimmune Disorder

## Pathogens and human antigens

## Peptid residues

## Overlapping sequences

Human cytomegalovirus  
IE2  
HLA-DR molecule

79  
60

PDPLGRPDED  
VTELGRPDAE

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

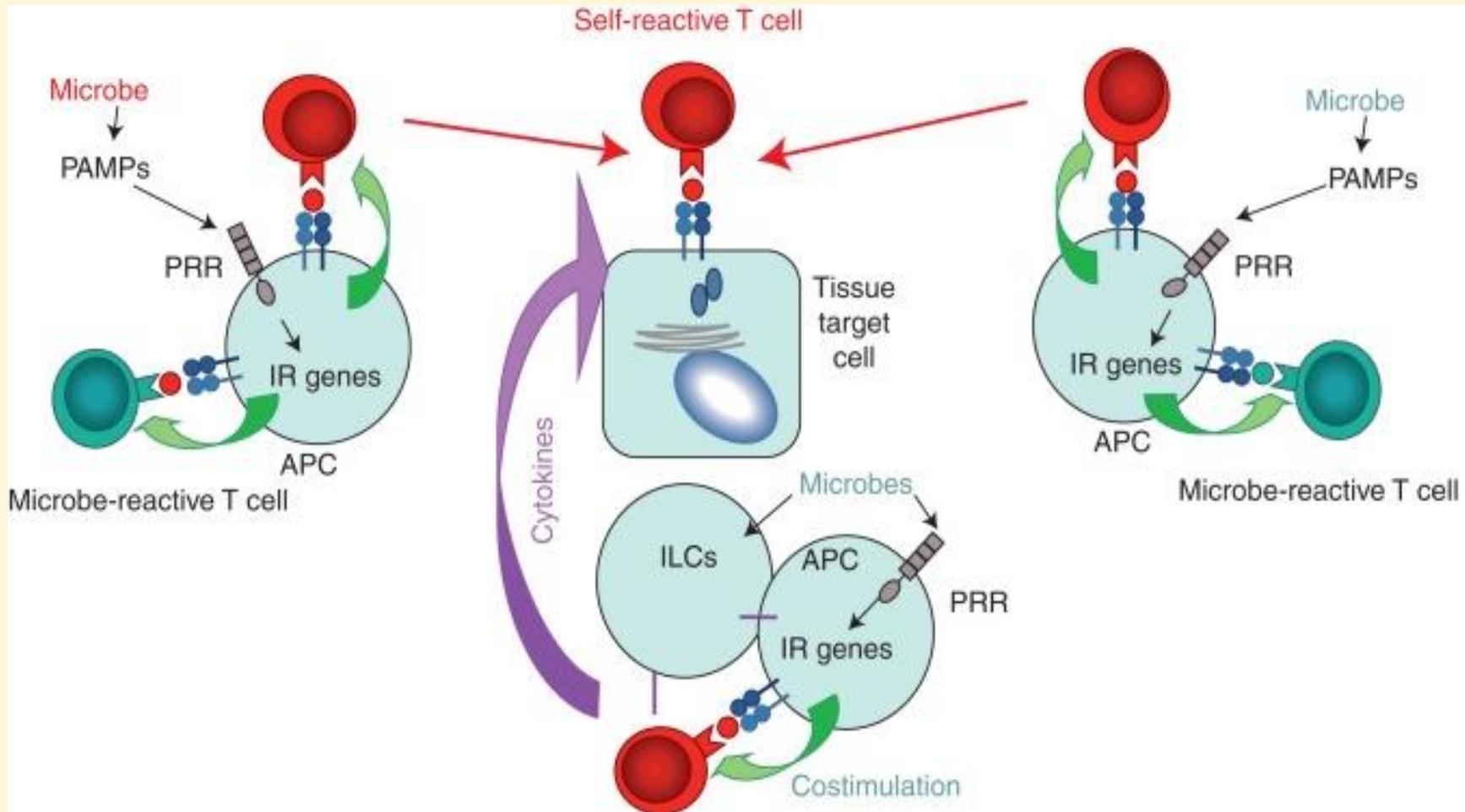
GVETTTPS  
GVETTTPS

Measles virus P3  
Myelin basic protein

31  
61

EISDNLGQE  
EISFKLGQE

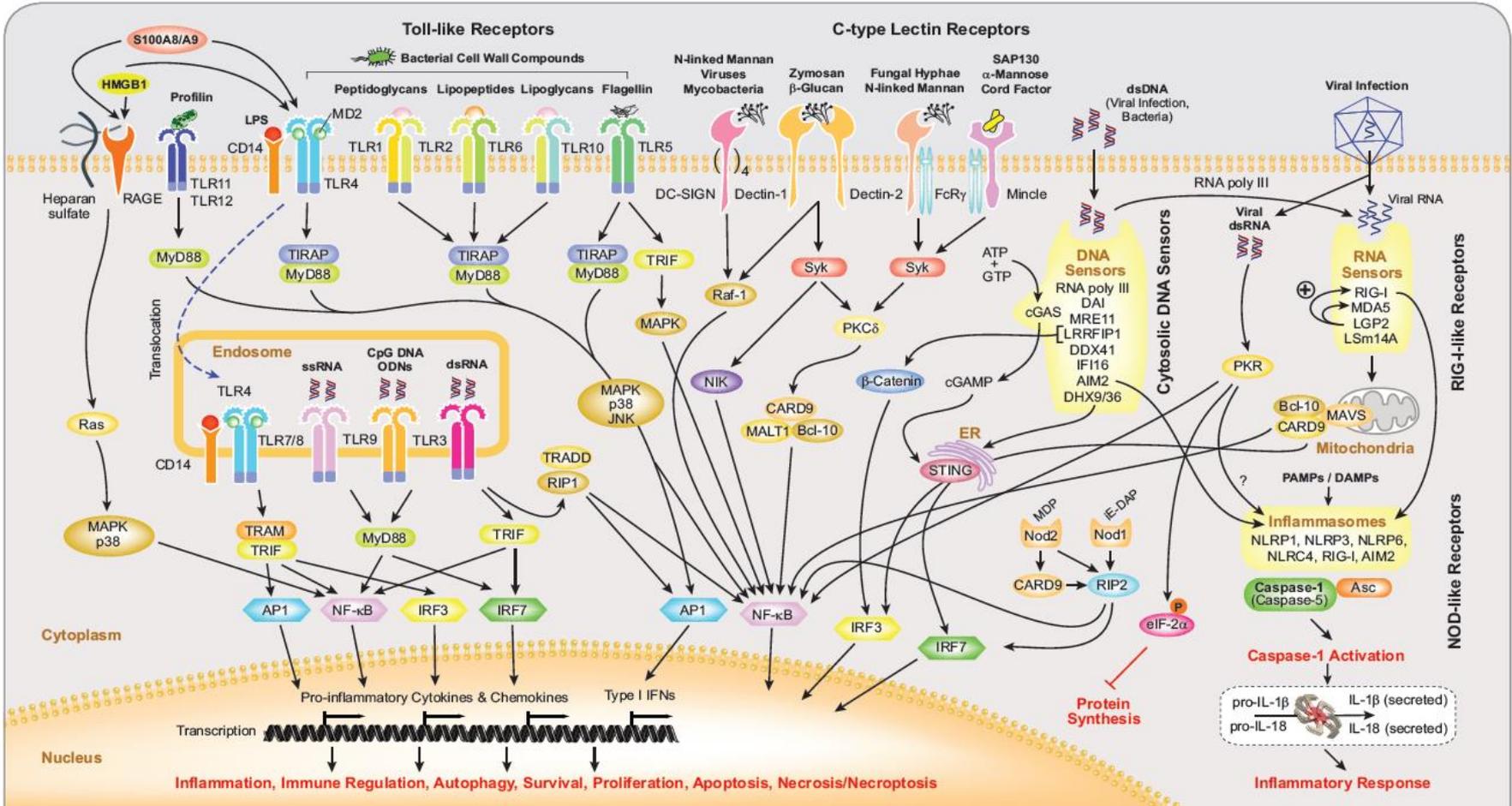
# Microbes contribute to initiation or severity of autoimmunity



# Pattern Recognition Receptors (PRRs) Signaling Pathways

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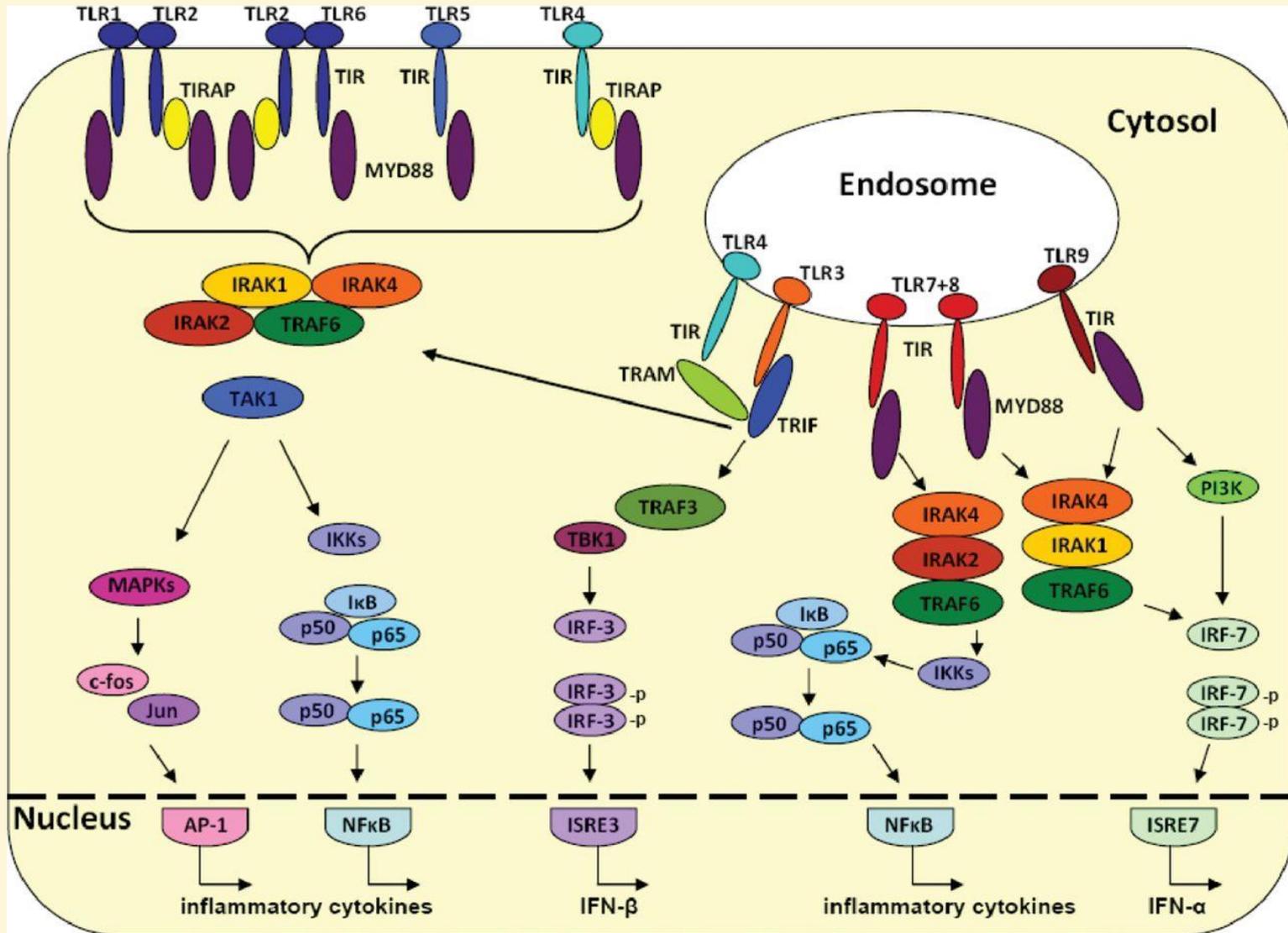


→ Activation  
 - - - Translocation  
 —| Inhibition

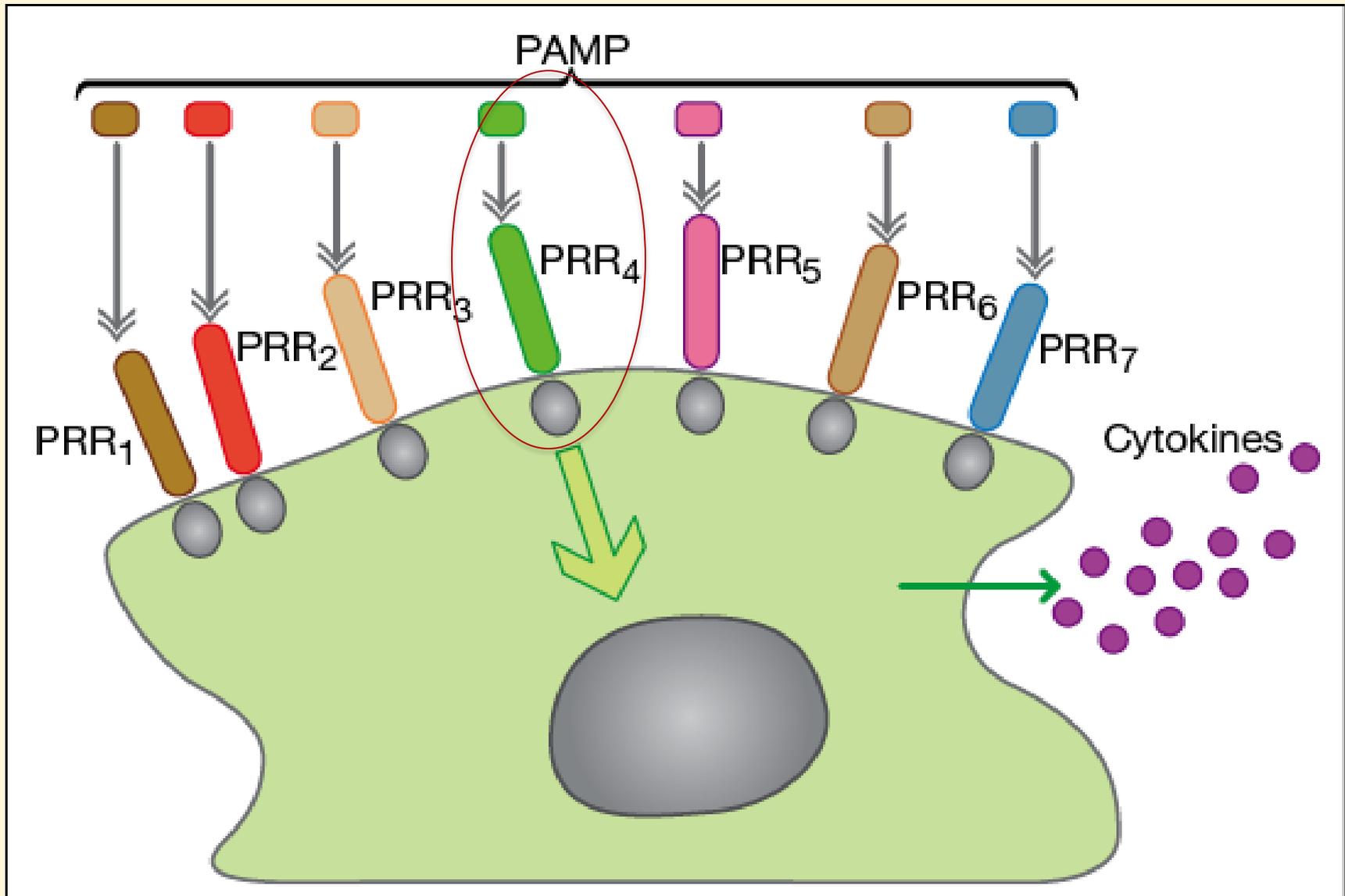
TLRs — Horseshoe-shaped solenoid N-terminal extracellular leucine-rich repeat (LRR) motifs  
 — Compact and globular C-terminal intracellular Toll/interleukin-1 receptor (TIR) domain

TLR11/TLR12: Expressed in mice only

# Role of the Toll like receptors in production of inflammatory cytokines



# Pattern recognition receptors on macrophage



# Macrophages express receptors for many microbial constituents

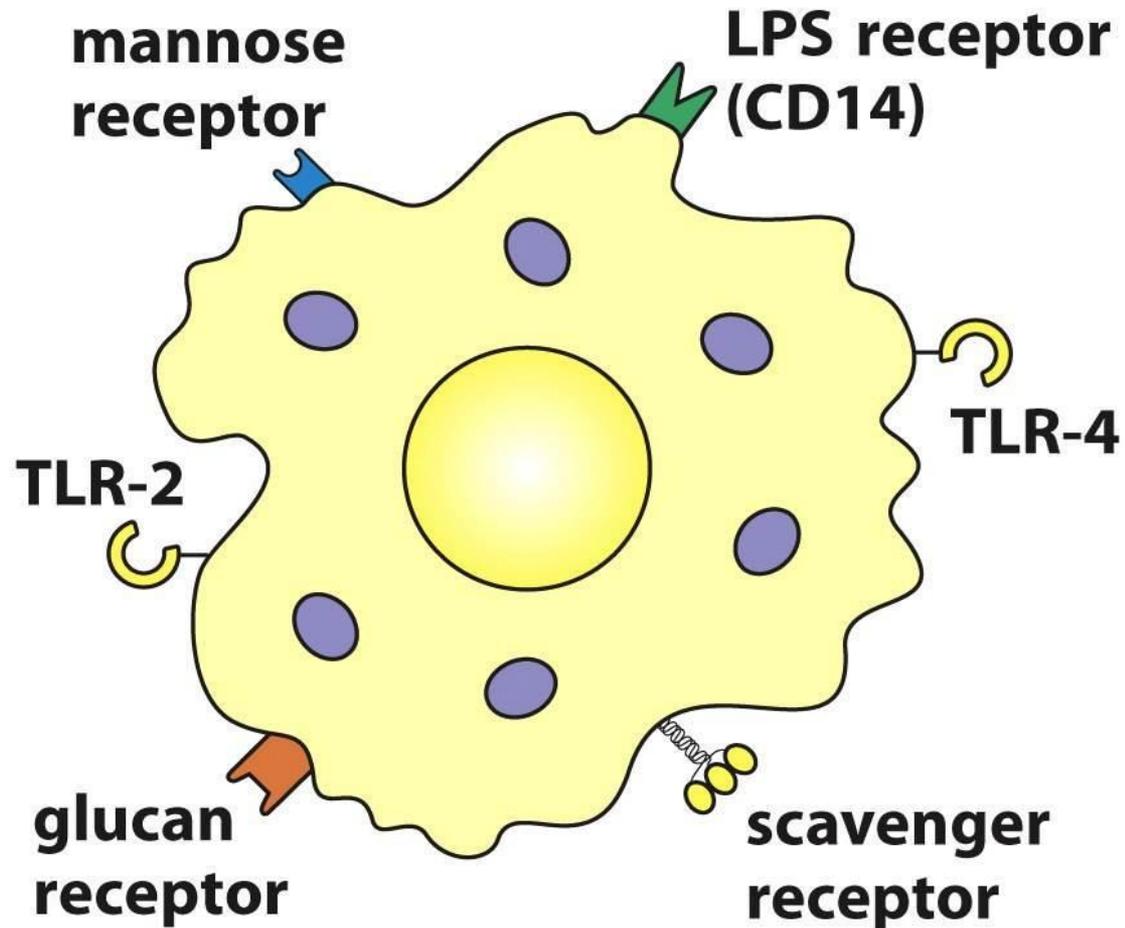
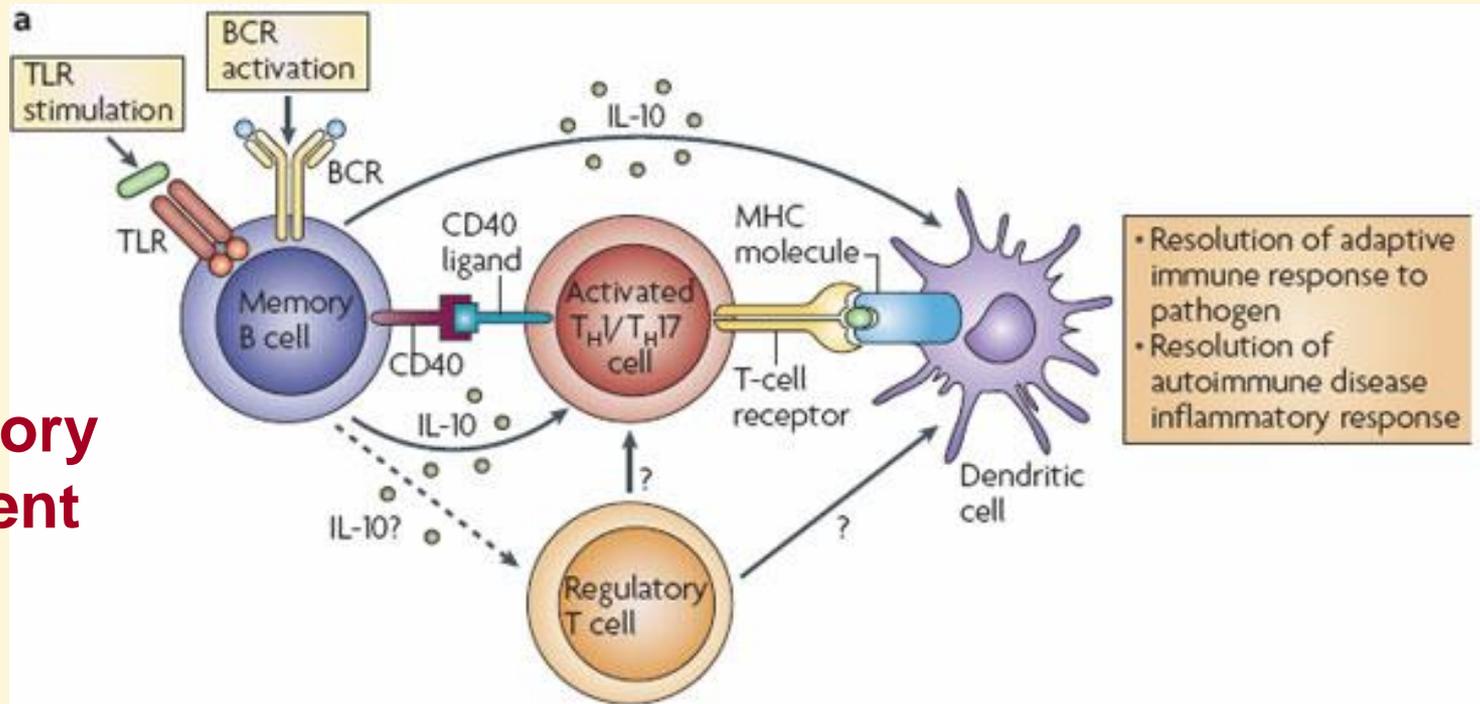
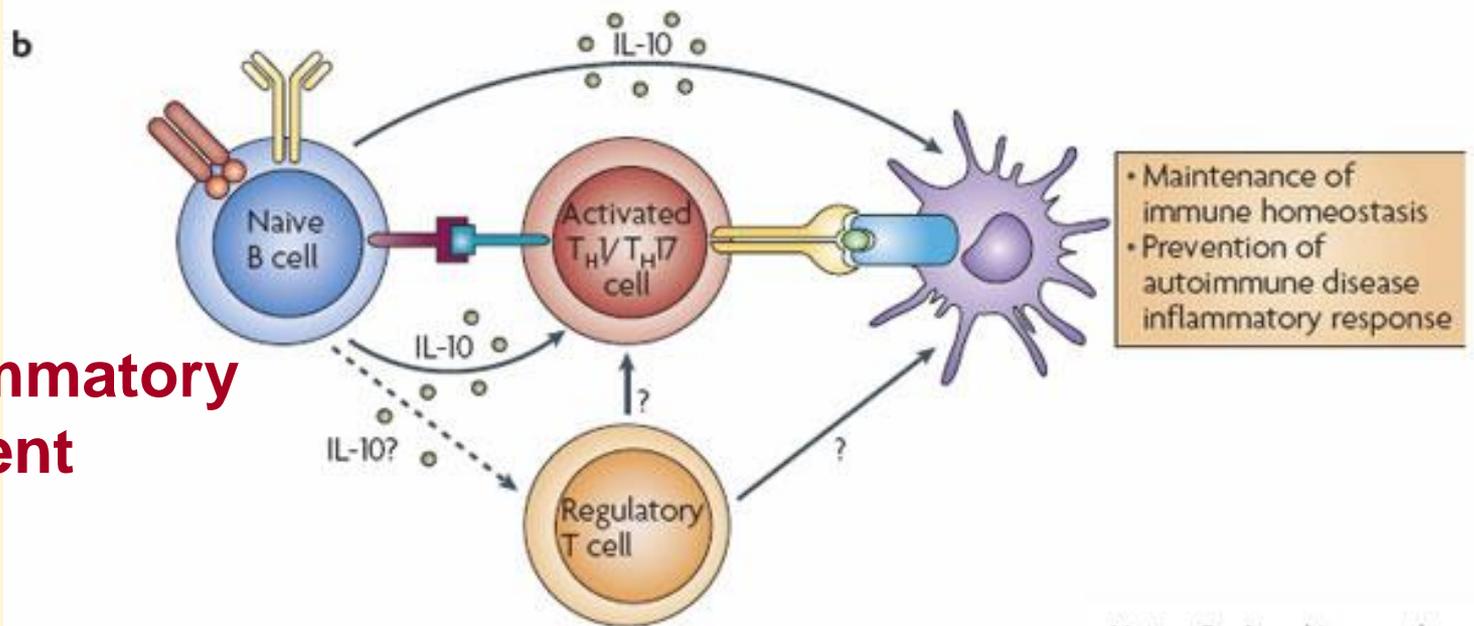


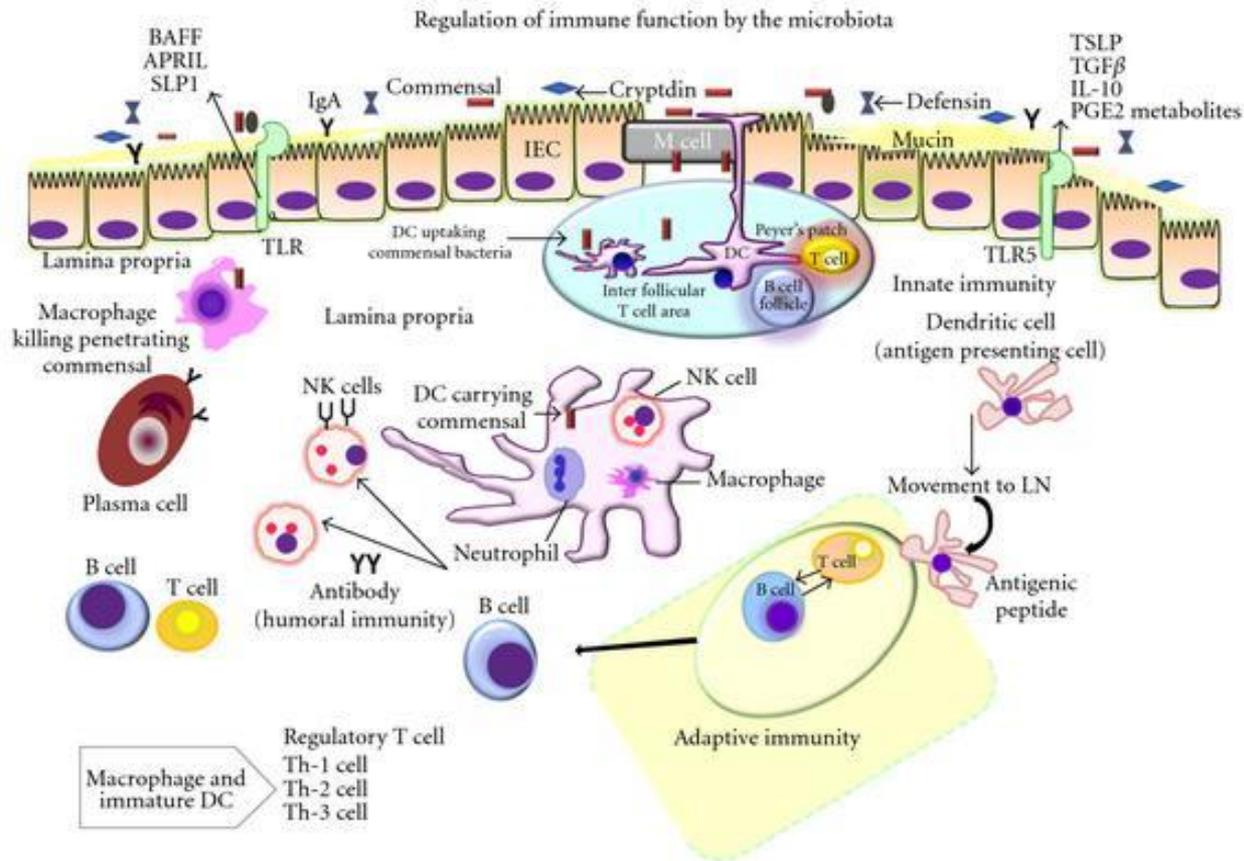
Figure 1.10 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

**Inflammatory environment**



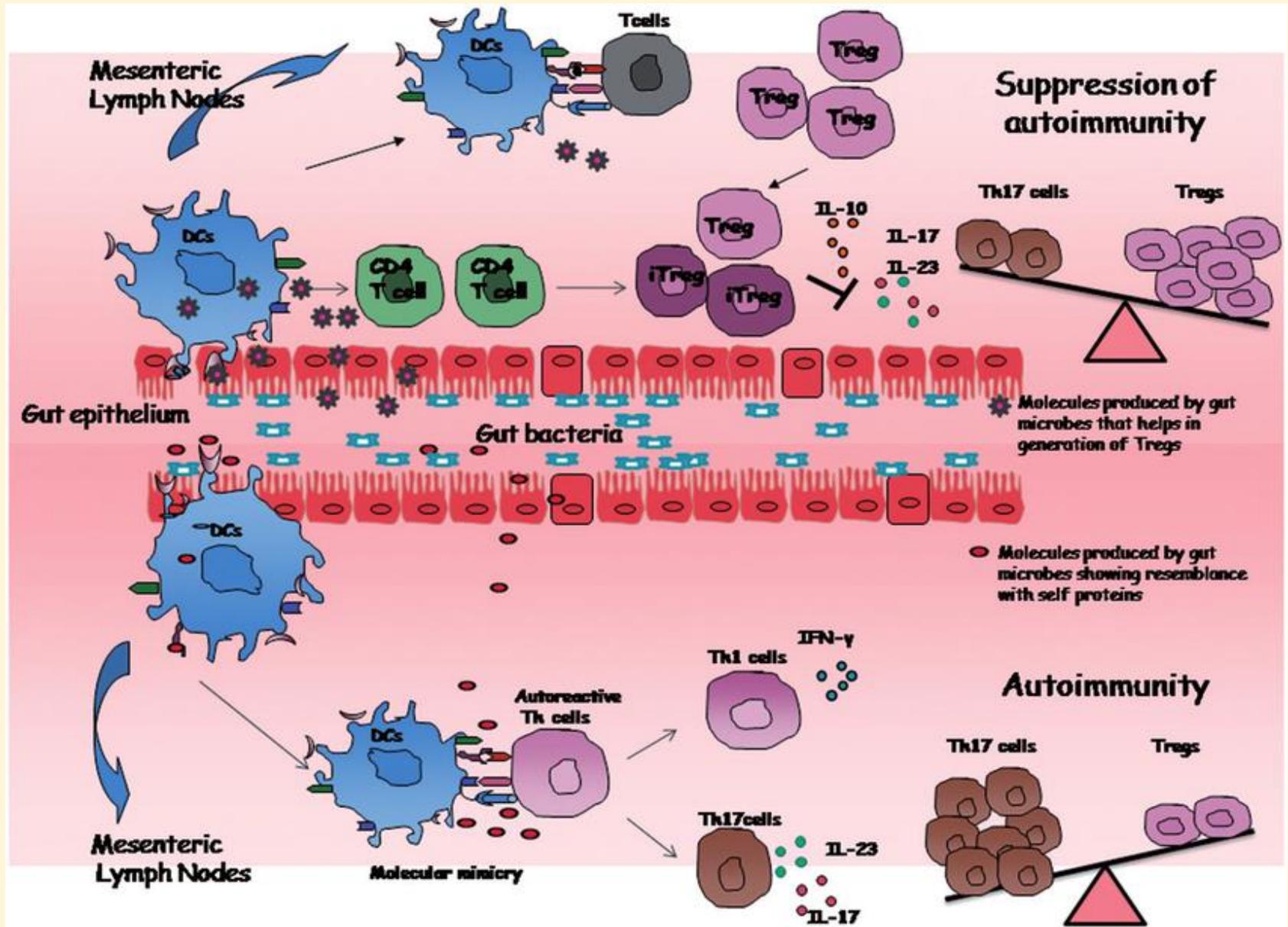
**Non-inflammatory environment**



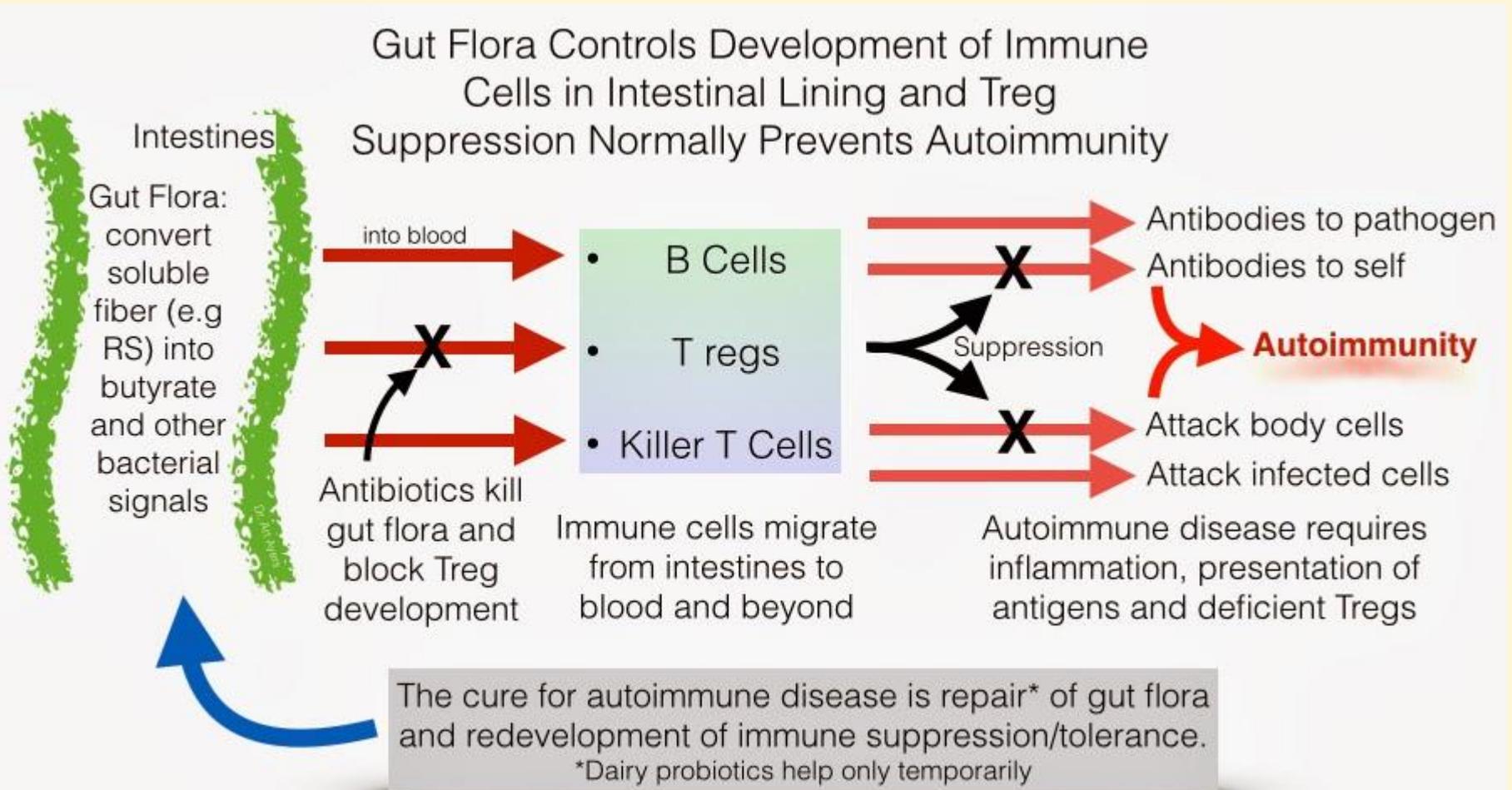


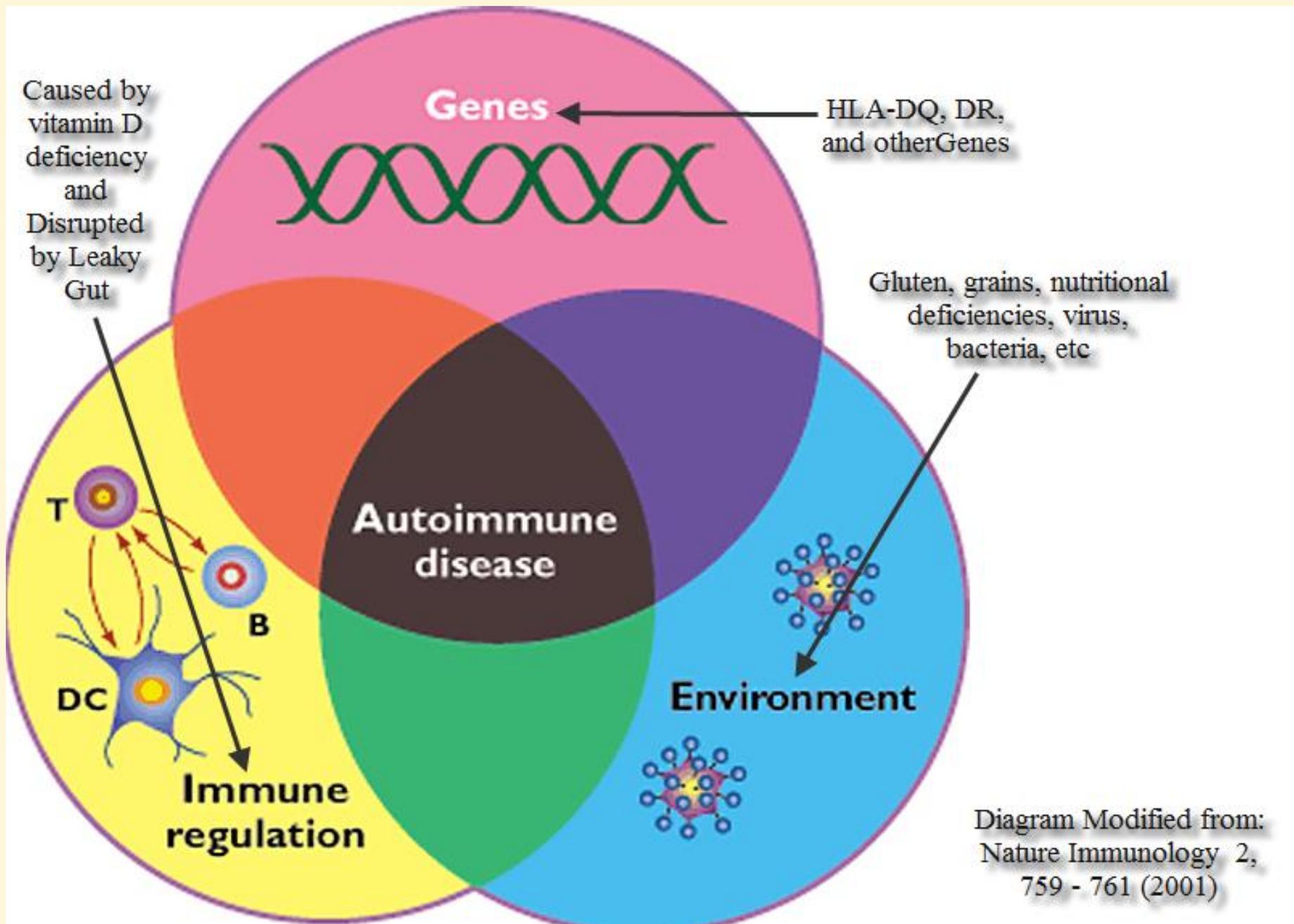
Influenced by the **microbiota**, intestinal epithelial cells (IECs) elaborate cytokines, including thymic stromal lymphoprotein (TSLP), transforming growth factor (TGF), and interleukin-10 (IL-10), that can influence pro-inflammatory cytokine production by dendritic cells (DC) and macrophages present in the lamina propria (GALT) and Peyer's patches. Signals from commensal organisms may influence tissue-specific functions, resulting in T-cell expansion and regulation of the numbers of Th-1, Th-2, and Th-3 cells. Also modulated by the microbiota, other IEC derived factors, including APRIL (a proliferation-inducing ligand), B-cell activating factor (BAFF), secretory leucocyte peptidase inhibitor (SLPI), prostaglandin E2 (PGE2), and other metabolites, directly regulate functions of both antigen presenting cells and lymphocytes in the intestinal ecosystem.

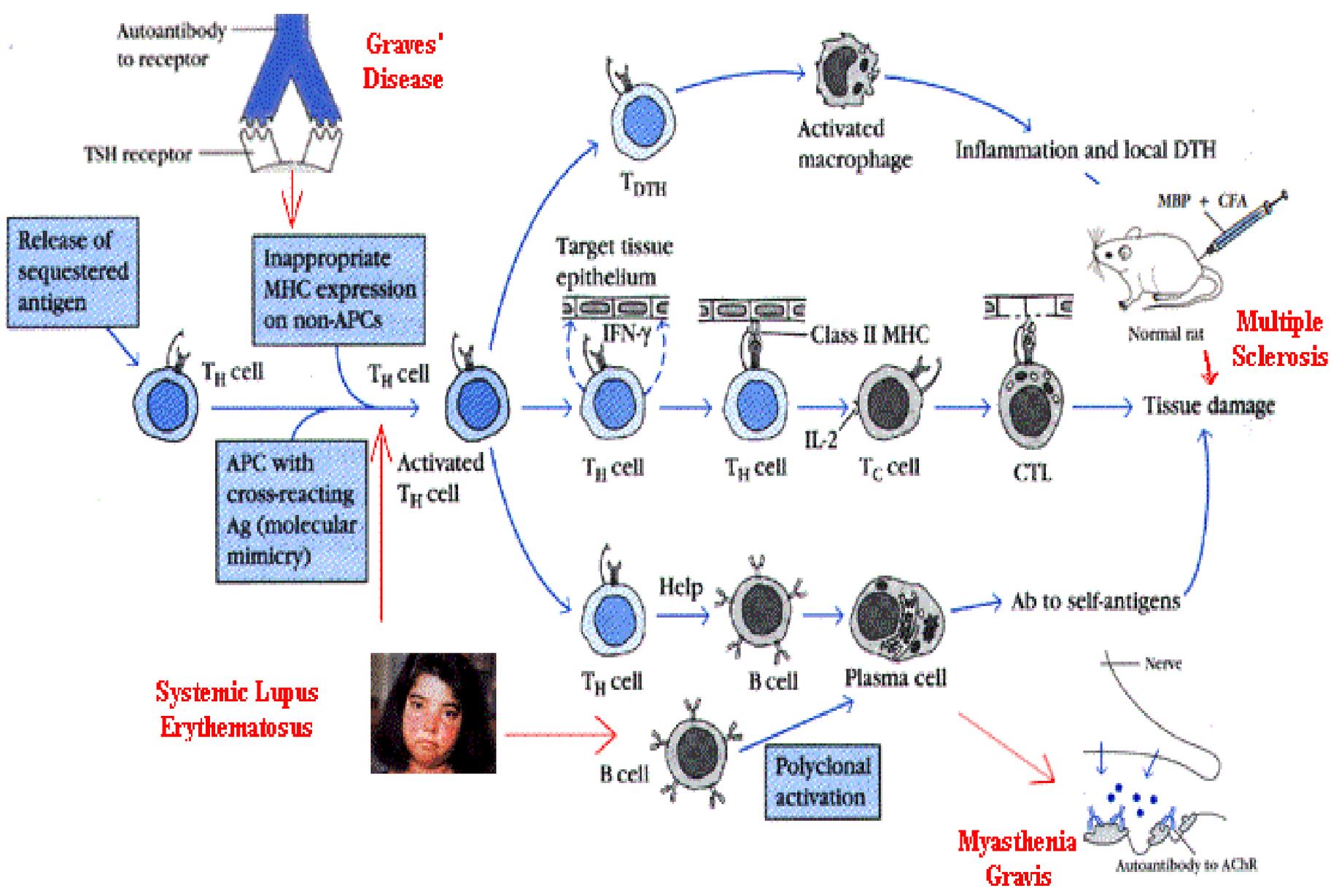
# Gut microbiota and autoimmunity



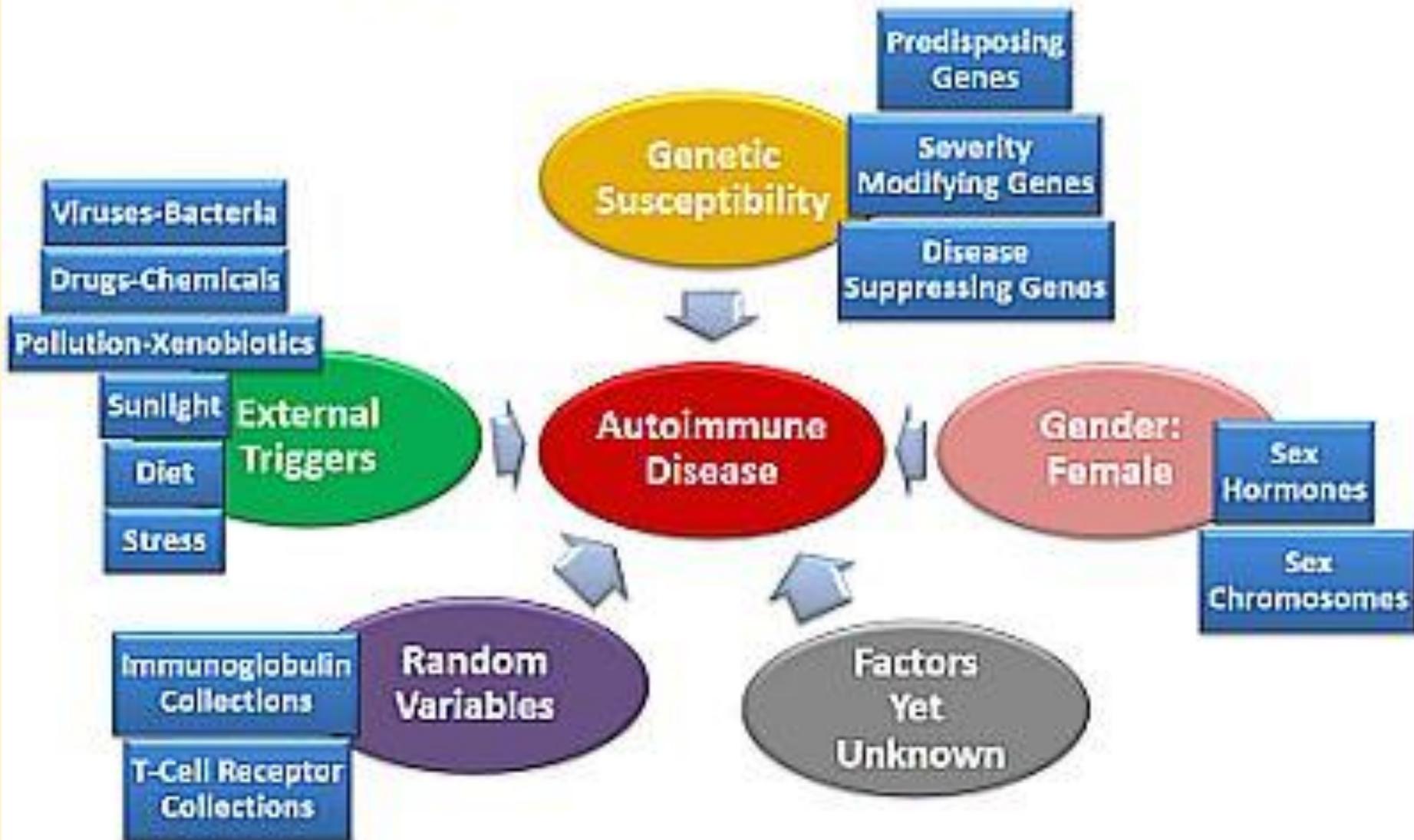
# Possible function of gut microbiota for Treg cells



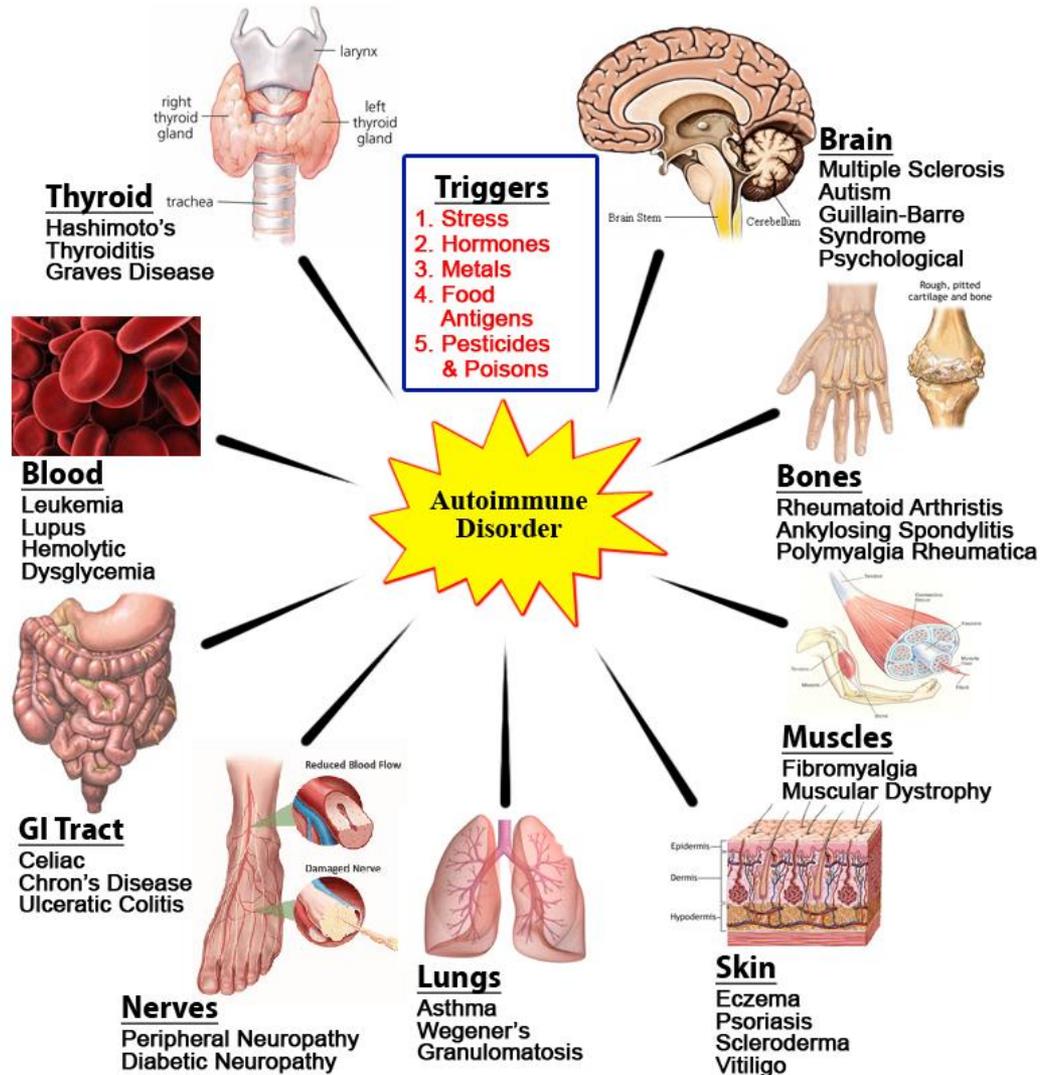




# Etiology of Autoimmune Disease

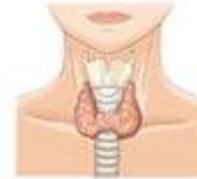


# Tissues of The Body Affected By Autoimmune Attack



# Autoimmune Diseases

**Brain**  
Multiple Sclerosis  
Guillaun-Barre Syndrome  
Autism



**Thyroid**  
Thyroiditis  
Hashimoto's Disease  
Graves' Disease

**Blood**  
Leukemia  
Lupus Erythematosus  
Hemolytic Dysglycemia



**Bones**  
Rheumatoid Arthritis  
Ankylosing Spondylitis  
Polymyalgia Rheumatica



**GI Tract**  
Celiac's Disease  
Crohn's Disease  
Ulceratic Colitis  
Diabetes Type I

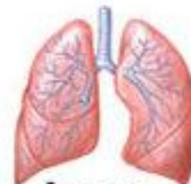


**Muscles**  
Muscular Dystrophy  
Fibromyalgia

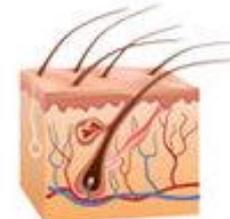


**>100 Autoimmune Diseases**

**Nerves**  
Peripheral Neuropathy  
Diabetic Neuropathy



**Lung**  
Fibromyalgia  
Wegener's Granulomatosis



**Skin**  
Psoriasis  
Vitiligo  
Eczema  
Scleroderma