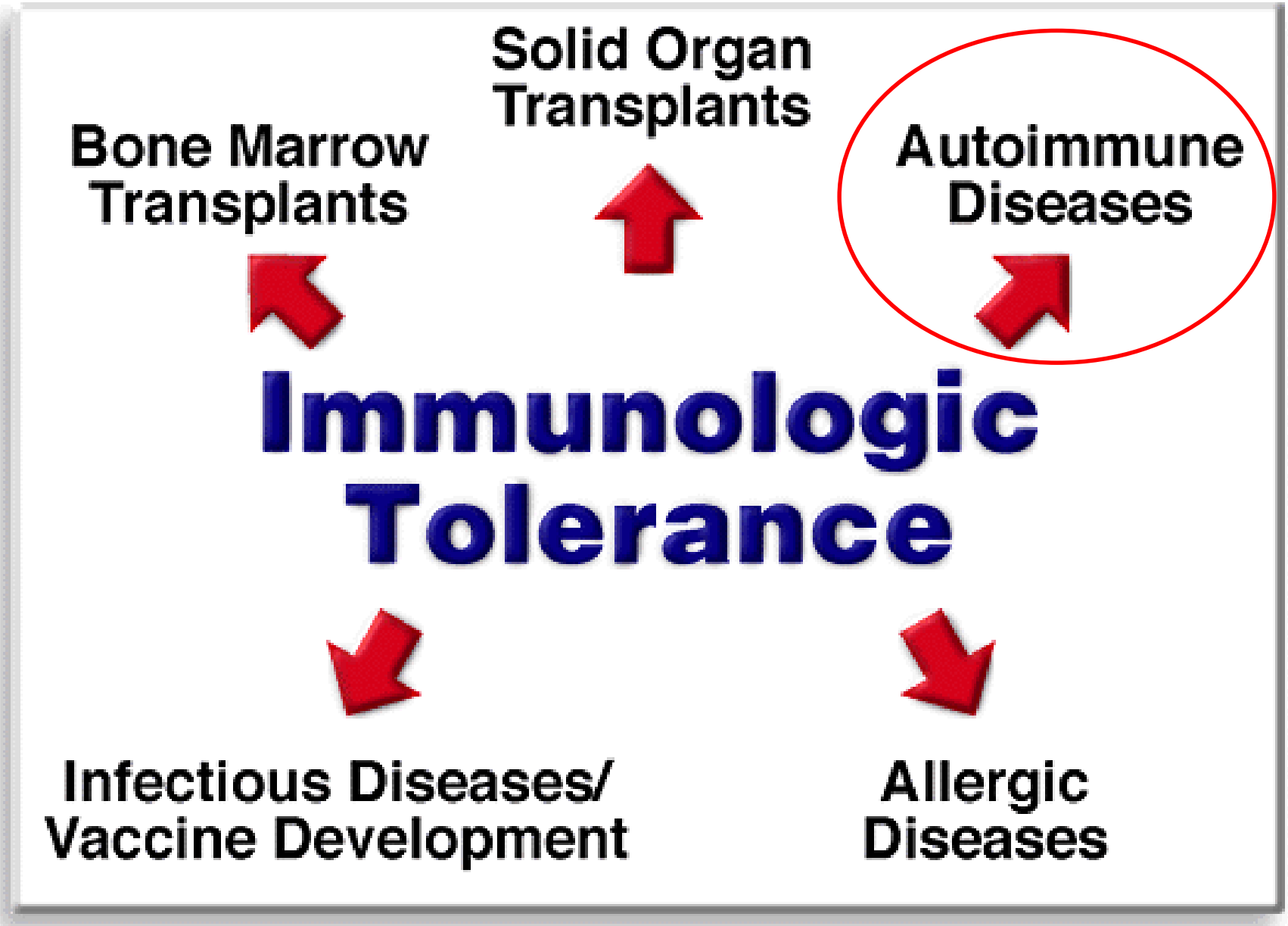
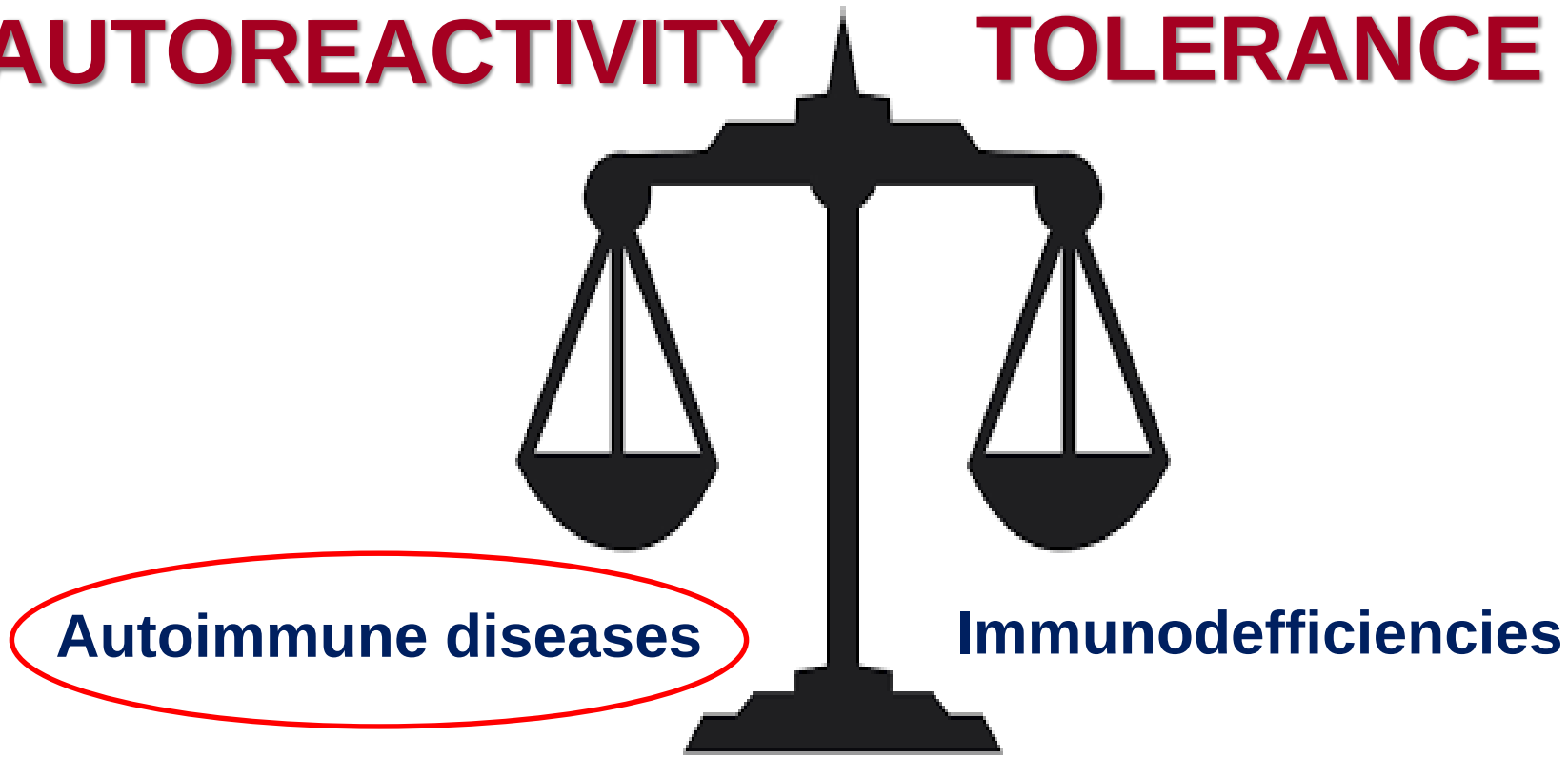
Immunopathology 2025’

Pathomechanism of autoimmune diseases
I.

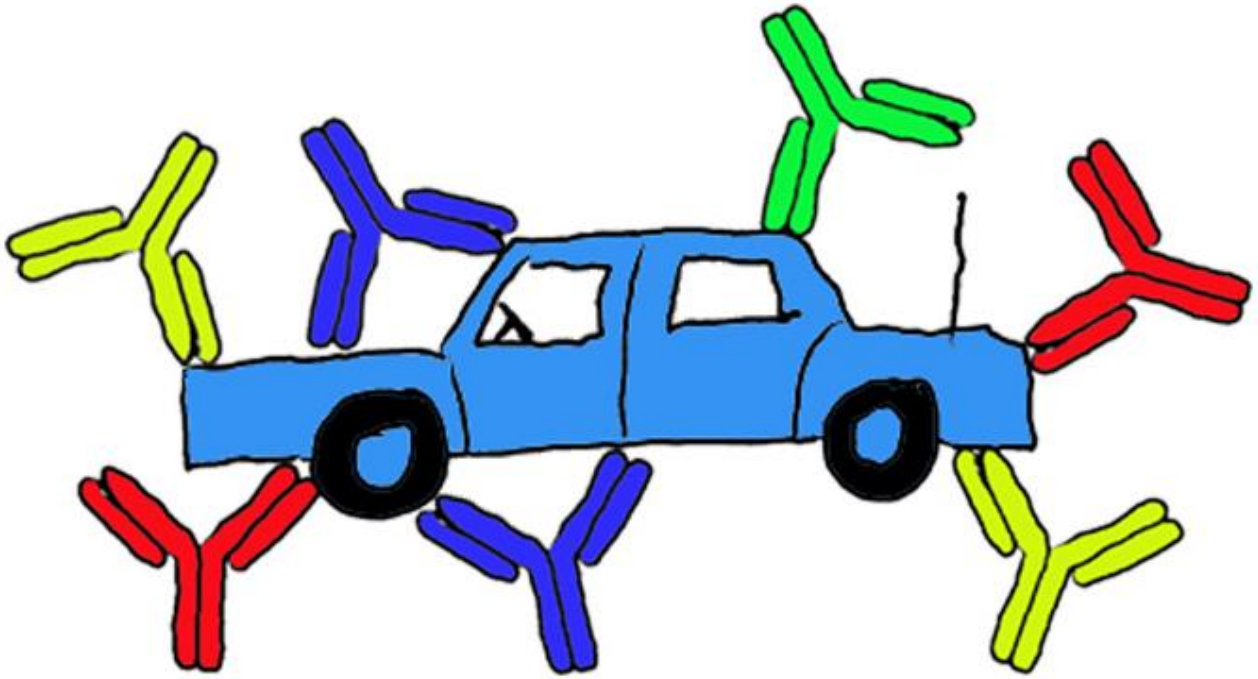

Solid Organ Transplants
Bone Marrow Transplants
Autoimmune Diseases
Immunologic Tolerance
Infectious Diseases/ Vaccine Development
Allergic Diseases

AUTOREACTIVITY TOLERANCE



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.

What does it mean „autoimmunity” ?



7-10 % 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)

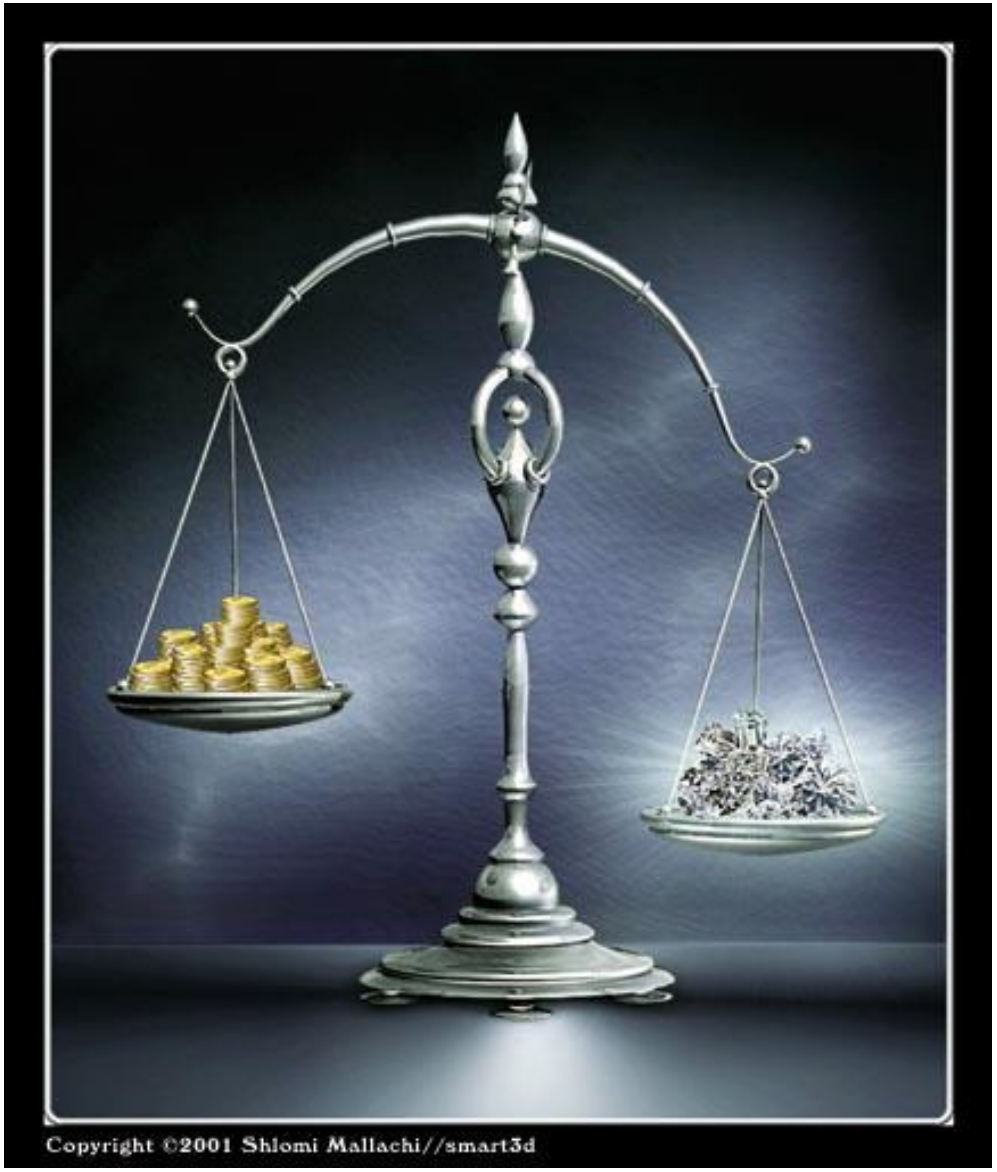
  - Autoimmune *"steady state"* (failure of the dynamic balance of self tolerance and autoimmunity)

  - Role of infections: inflammatory environment, molecular mimicry, (similar "molecular shape")

  - Genetic background: MHC, gender, microchimerism

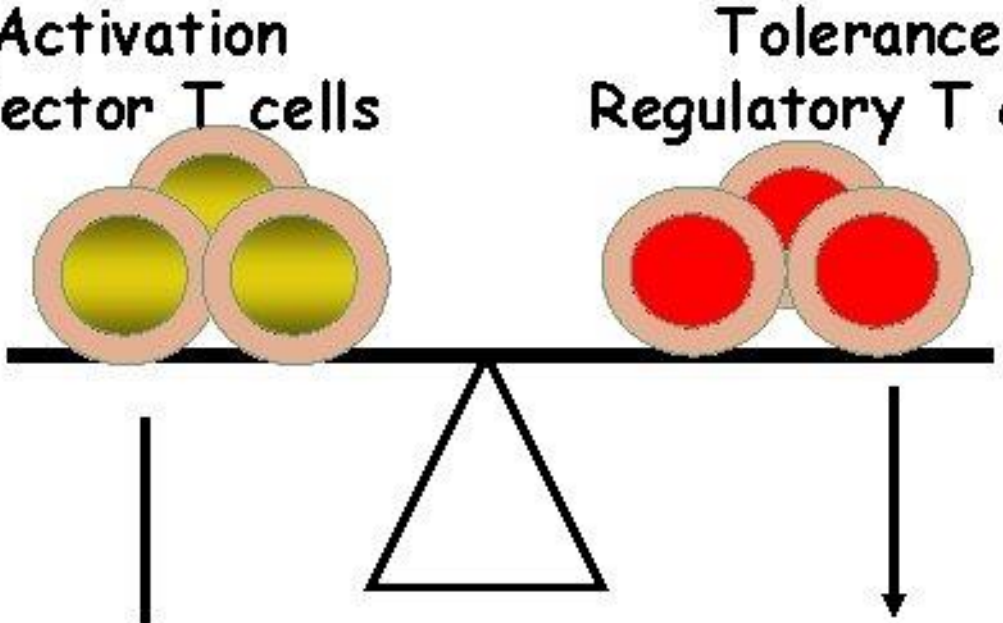
Autoimmune steady state

Self reacting immune response with tissues damages



Active tolerance and tissue repair

The immunological equilibrium: balancing lymphocyte activation and control



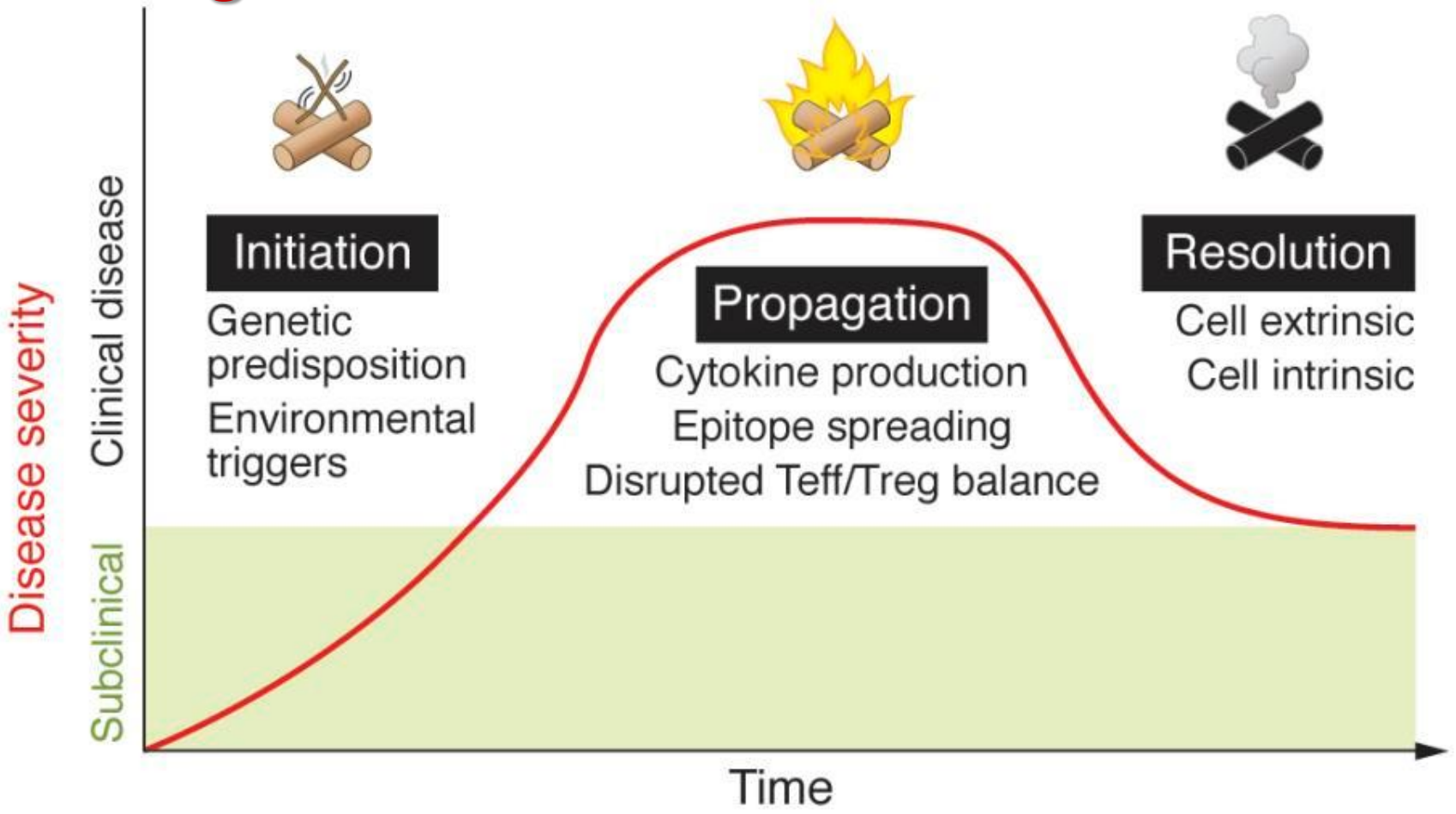
Normal: reactions against pathogens

Inflammatory disease, e.g. reactions against self

Controlled response to pathogens

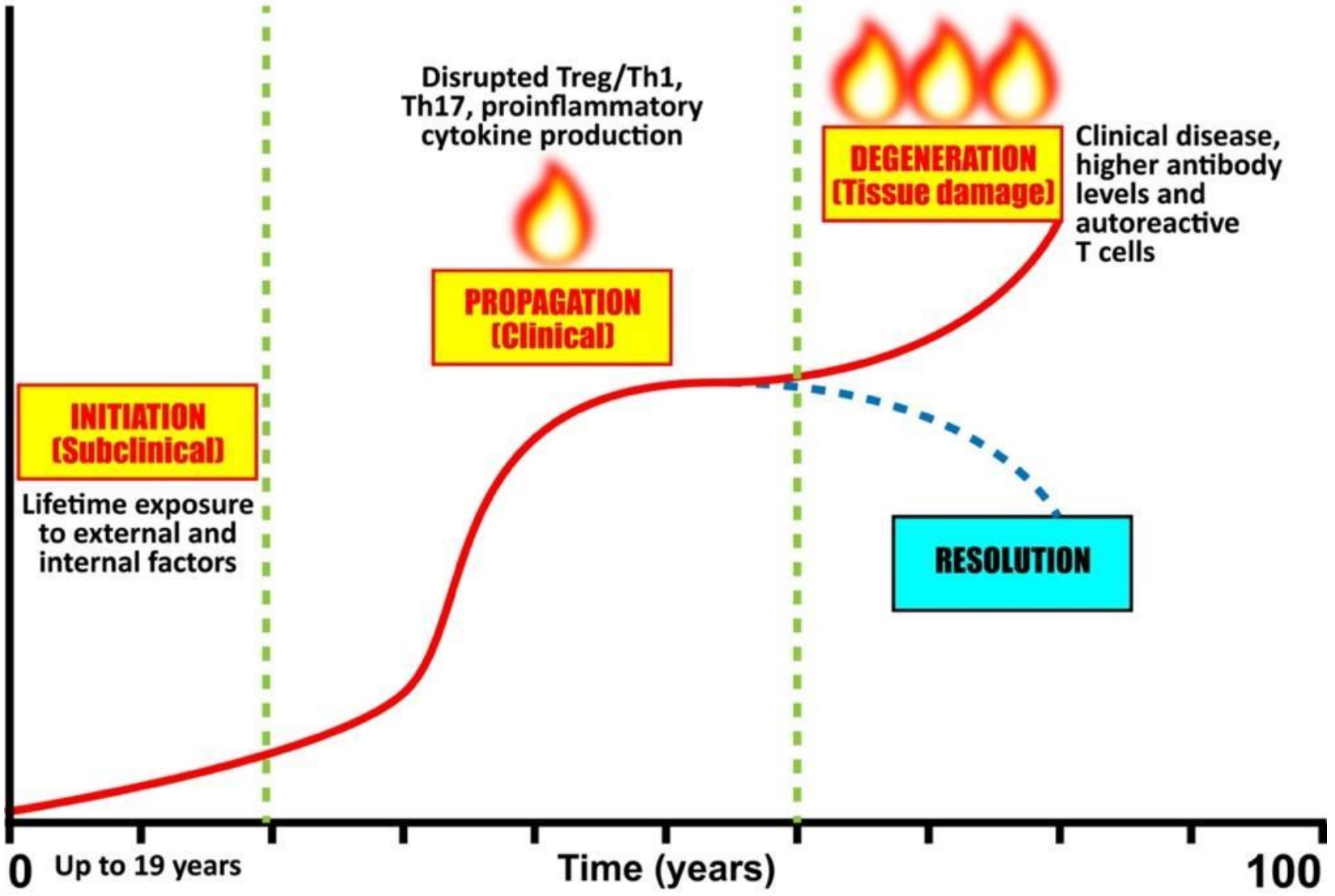
No response to self

Progression of autoimmune reactions



Patients in the initiation phase of disease are typically unaware of clinical symptoms (subclinical). Patients present with clinical disease during the propagation phase, which is characterized by self-perpetuating inflammation and tissue damage. Autoimmune reactions resolve with the activation of cell-intrinsic (inhibitory pathways) and cell-extrinsic (Tregs) mechanisms to limit effector responses and restore the Teff/Treg balance.

Time kinetics of autoimmune reactions



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)

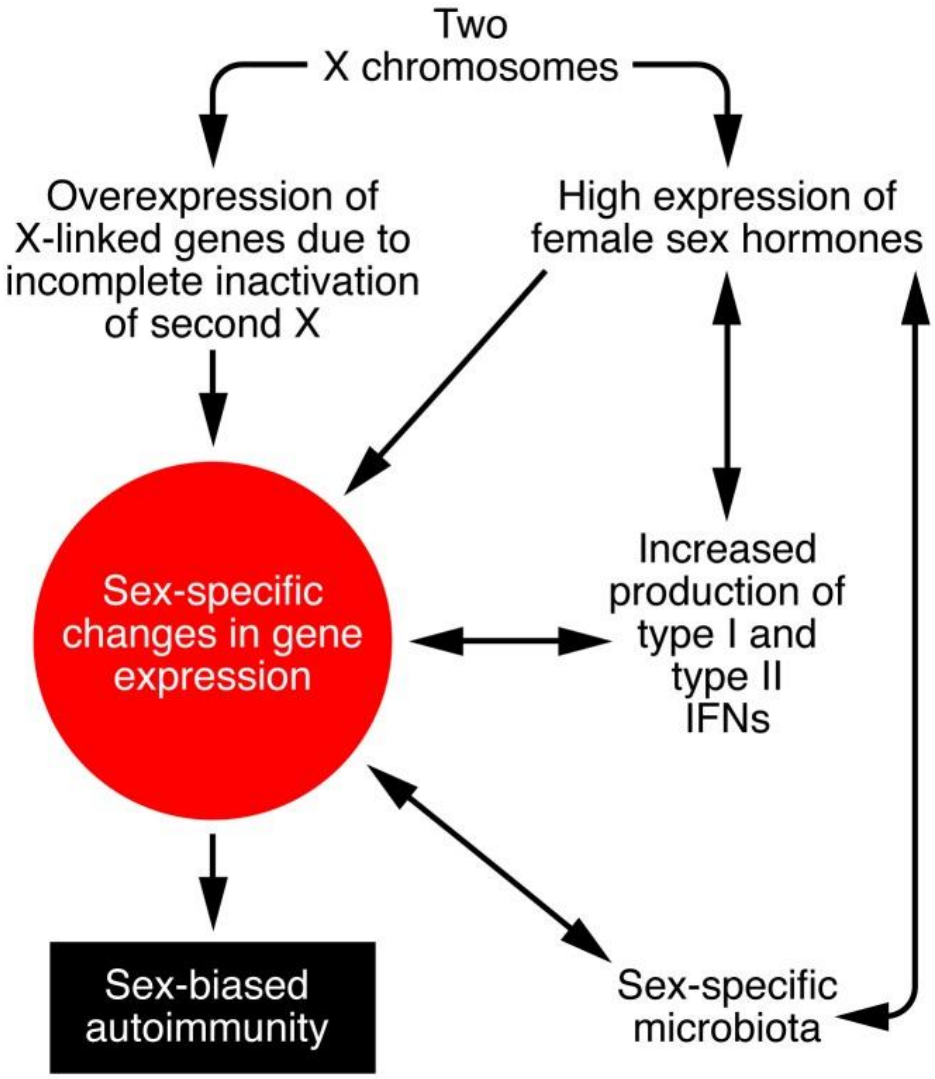
- Increased co-stimulation on tissue APCs

(paraneoplastic syndrome, chronic inflammations)

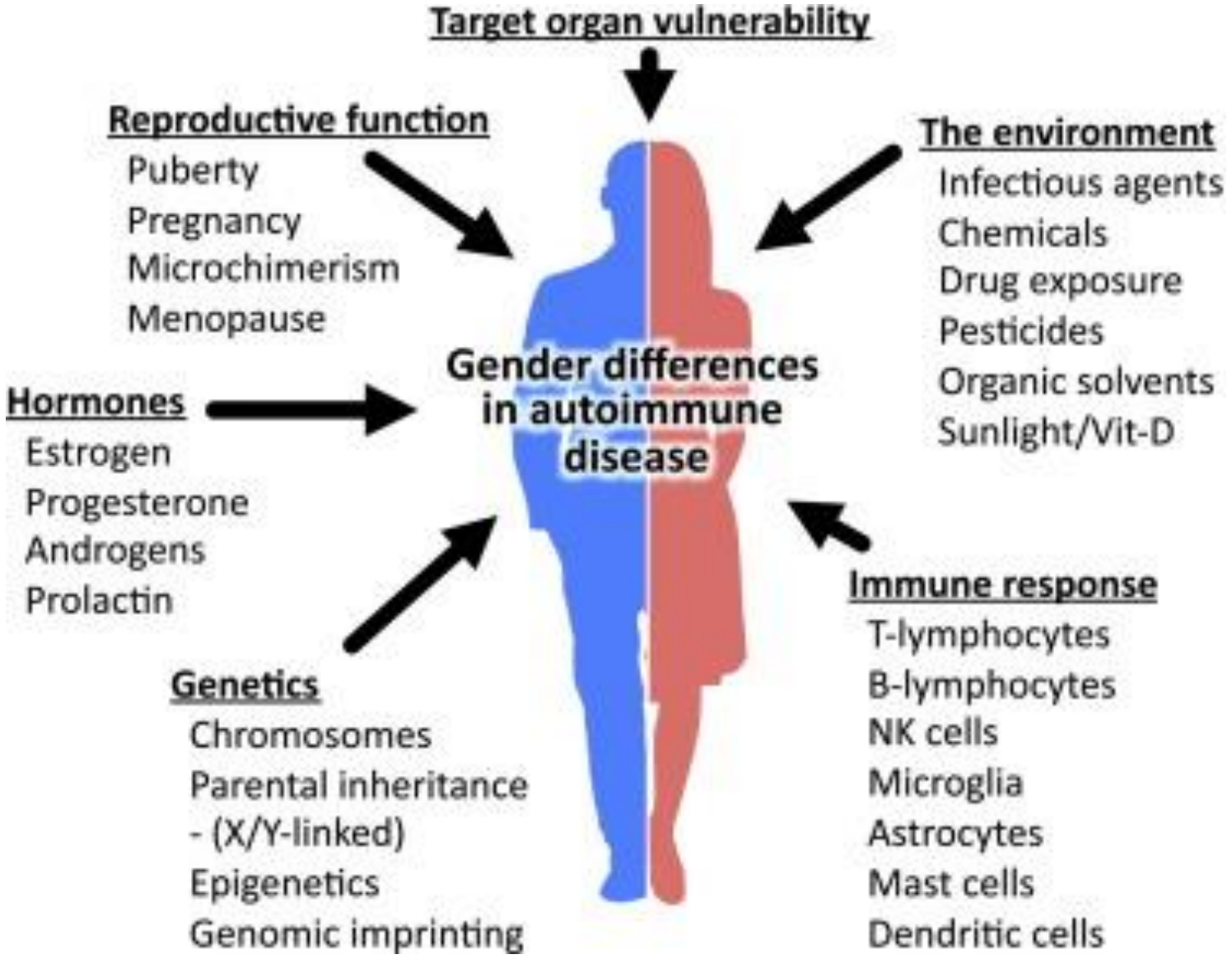
Autoimmunity by the failure of self tolerance

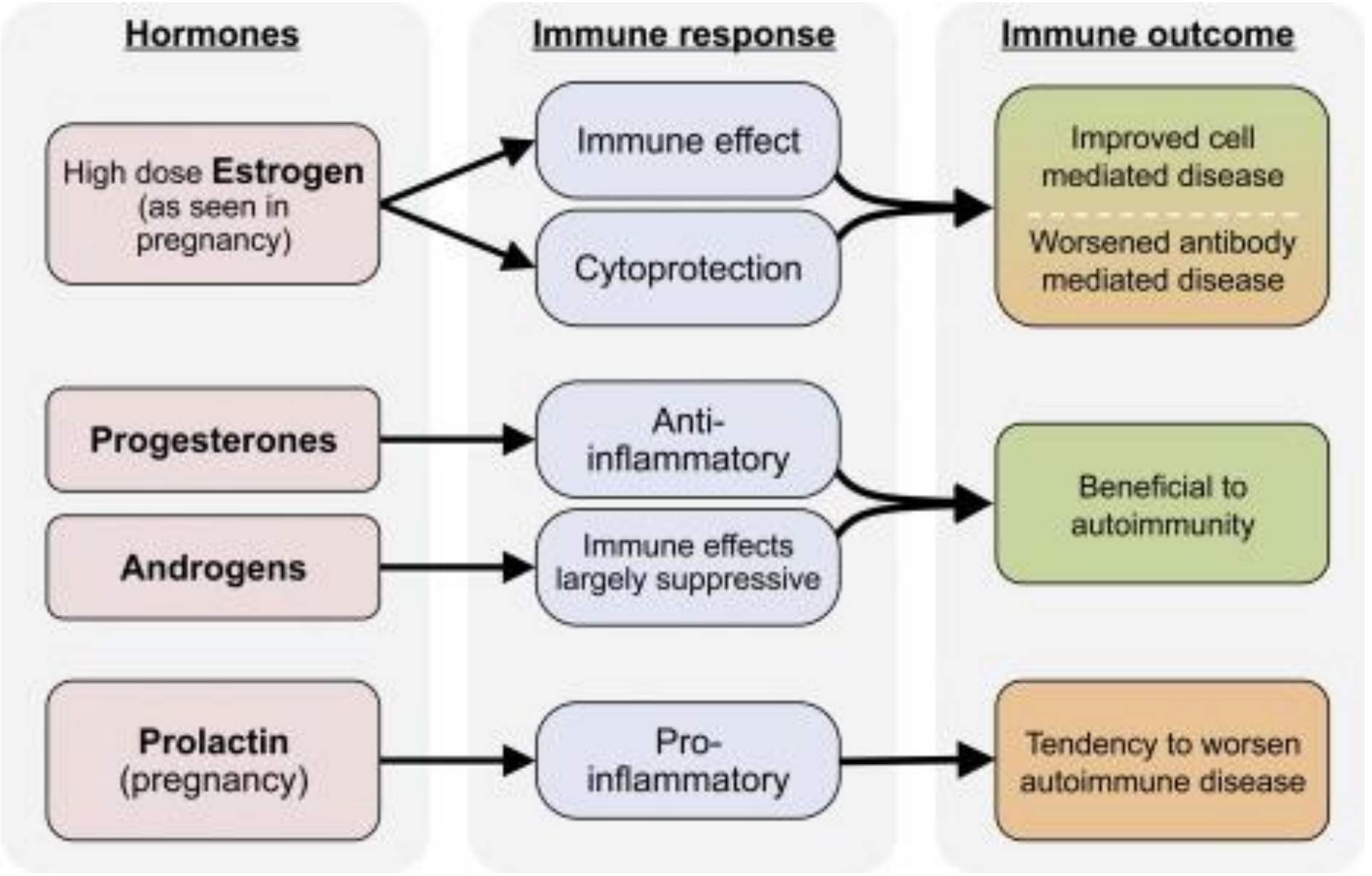
- Abnormal selection of lymphocytes
- Polyclonal activation of anergic self-reactive lymphocytes
- Stimulation by foreign antigens that cross-react with self (molecular mimicry)
- Gender differences
- Immuno-genetic factors (HLA association)
- Environmental factors

Sex differences in autoimmunity

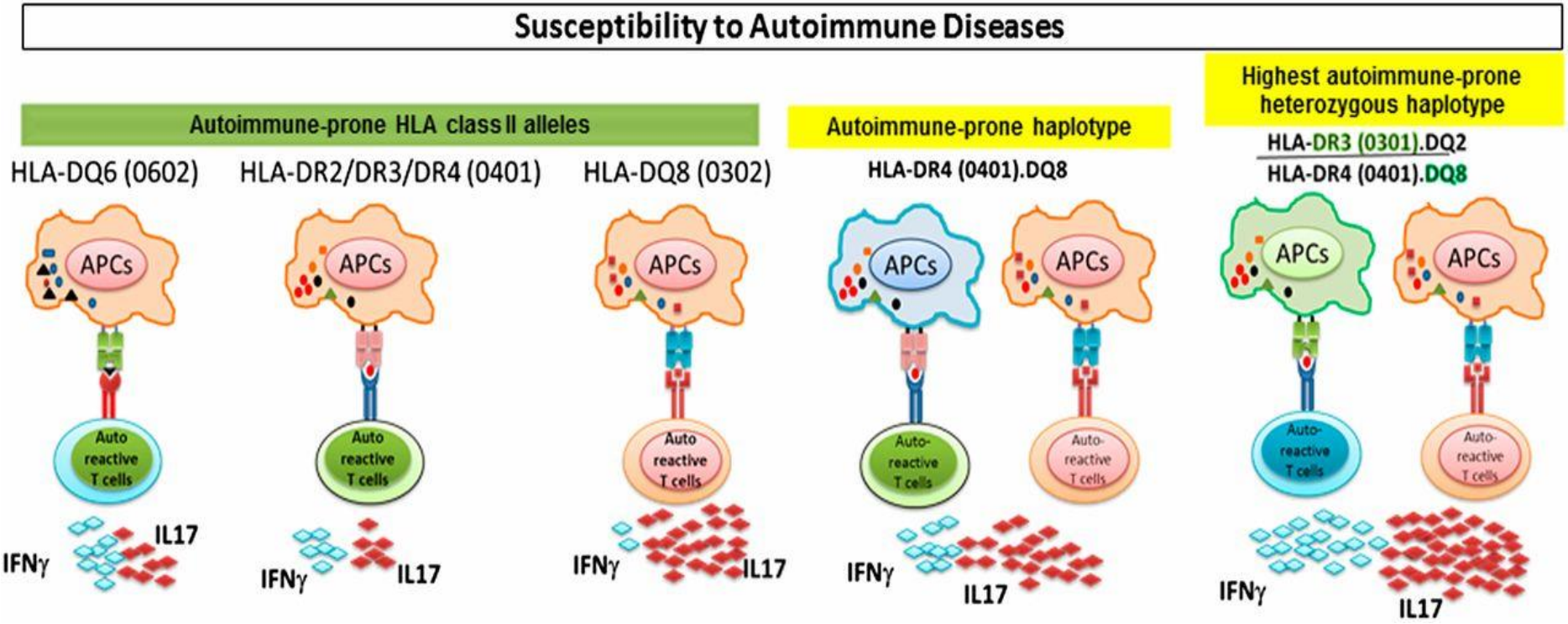


Autoimmune disease	Female/male ratio
Ankylosing spondylitis	1:2
Antiphospholipid antibody syndrome	5:1
Autoimmune chronic hepatitis	7:1
Celiac disease	1:1
Grave's disease	7:1
Hashimoto's disease	5-18:1
Multiple sclerosis	2:1
Myasthenia gravis	3:1
Primary biliary cirrhosis	10:1
Psoriasis	1:1
Rheumatoid arthritis	3:1
Sjogren's syndrome	9:1
Systemic lupus erythematosus	9:1
Systemic sclerosis	5:1


Target organ vulnerability
Reproductive function
Puberty
Pregnancy
Microchimerism
Menopause
The environment
Infectious agents
Chemicals
Drug exposure
Pesticides
Organic solvents
Sunlight/Vit-D
Gender differences in autoimmune disease
Hormones
Estrogen
Progesterone
Androgens
Prolactin
Immune response
T-lymphocytes
B-lymphocytes
NK cells
Microglia
Astrocytes
Mast cells
Dendritic cells
Genetics
Chromosomes
Parental inheritance
- (X/Y-linked)
Epigenetics
Genomic imprinting


Hormones
Immune response
Immune outcome
High dose Estrogen (as seen in pregnancy)
Immune effect
Cytoprotection
Improved cell mediated disease
Worsened antibody mediated disease
Progesterones
Androgens
Anti-inflammatory
Immune effects largely suppressive
Beneficial to autoimmunity
Prolactin (pregnancy)
Pro-inflammatory
Tendency to worsen autoimmune disease

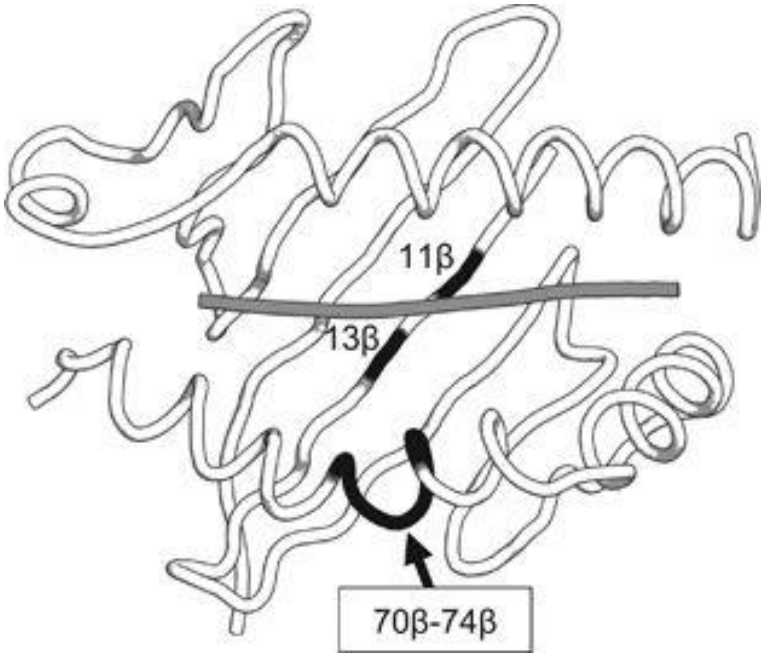
HLA assotiation with autoimmune diseases



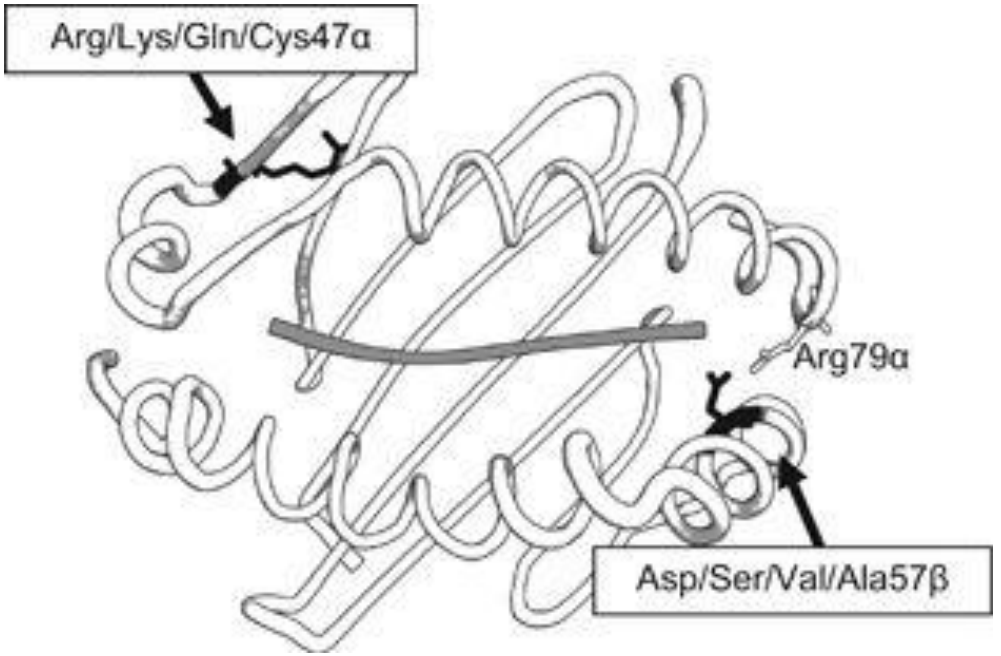
HLA class II alleles as HLA-DR2, DR3, DR4, DQ6 (0602), and DQ8 (0302) predispose to autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, type 1 diabetes, and systemic lupus erythematosus through secretion of proinflammatory cytokines.

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 11β, 13β and shared epitope (SE) residues in the structure of DR protein (PDB: 2seb)75 are shown.

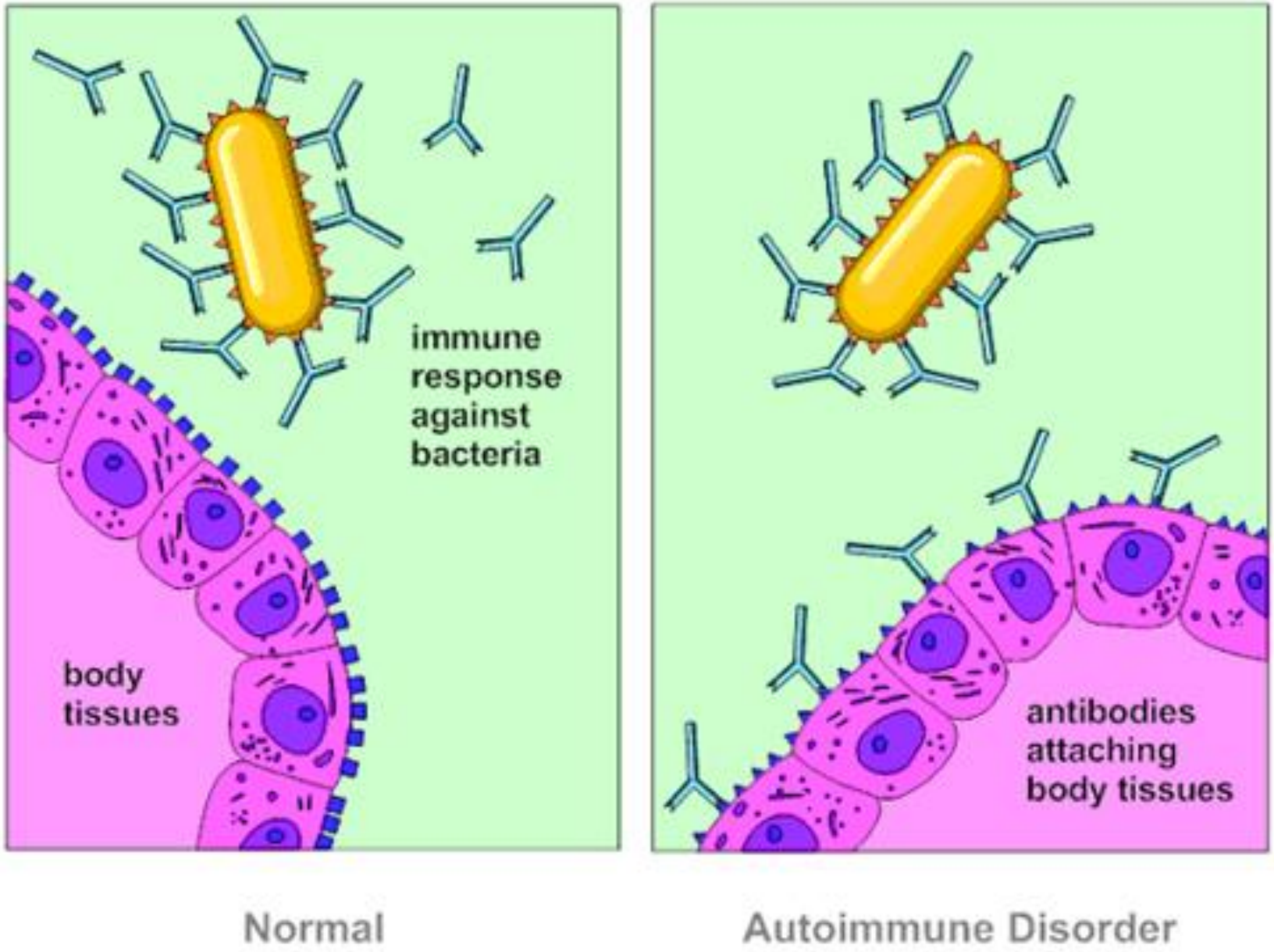


Locations of amino acid residues in DQA1 and DQB1 products that are associated with **type 1 diabetes (T1D)**. Locations of 47α and 57β in the structure of DQ protein (PDB: 1uvq)77 are shown.

HLA-class I and -class II-associated diseases and key polymorphic positions

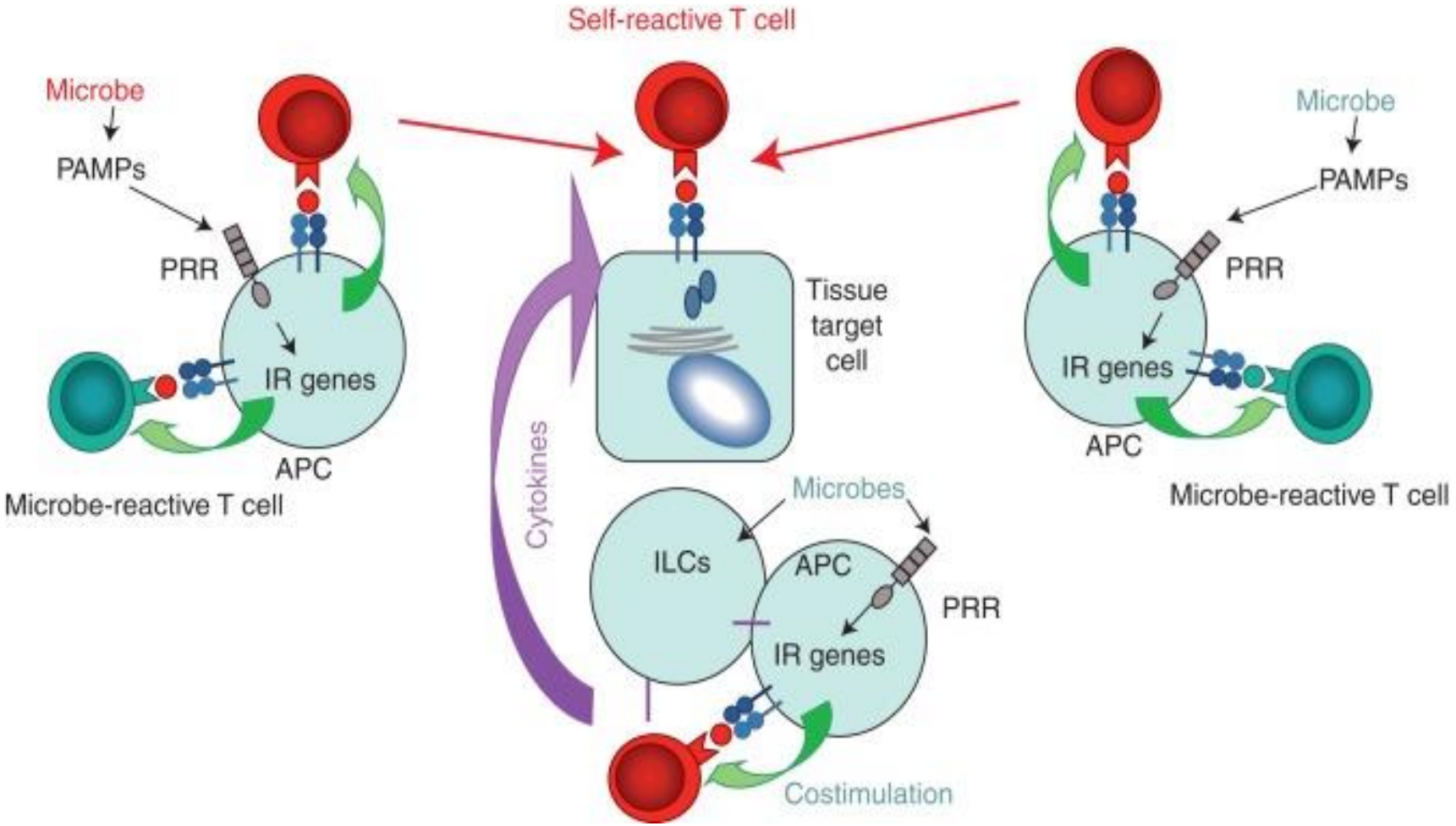
Disease	HLA-associated allele	Position	Amino acid
Ankylosing spondylitis	HLA-B*27	116	Asp
Psoriasis	HLA-C*06	156	Trp
Chronic beryllium disease	HLA-DPB1	69	Glu
Rheumatoid arthritis	HLA-DRB1	11, 13, 71, 74	Val, His, Lys, Ala
Celiac disease	HLA-DQB1	71	Lys
Type 1 diabetes	HLA-DQB1	57	Non-Asp
Multiple sclerosis	HLA-DRB1*1501	71, 74, 57	Ala, Ala, Asp

Molecular mimicry



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

Microbes contribute to initiation or severity of autoimmunity



Pattern Recognition Receptors (PRRs) Signaling Pathways

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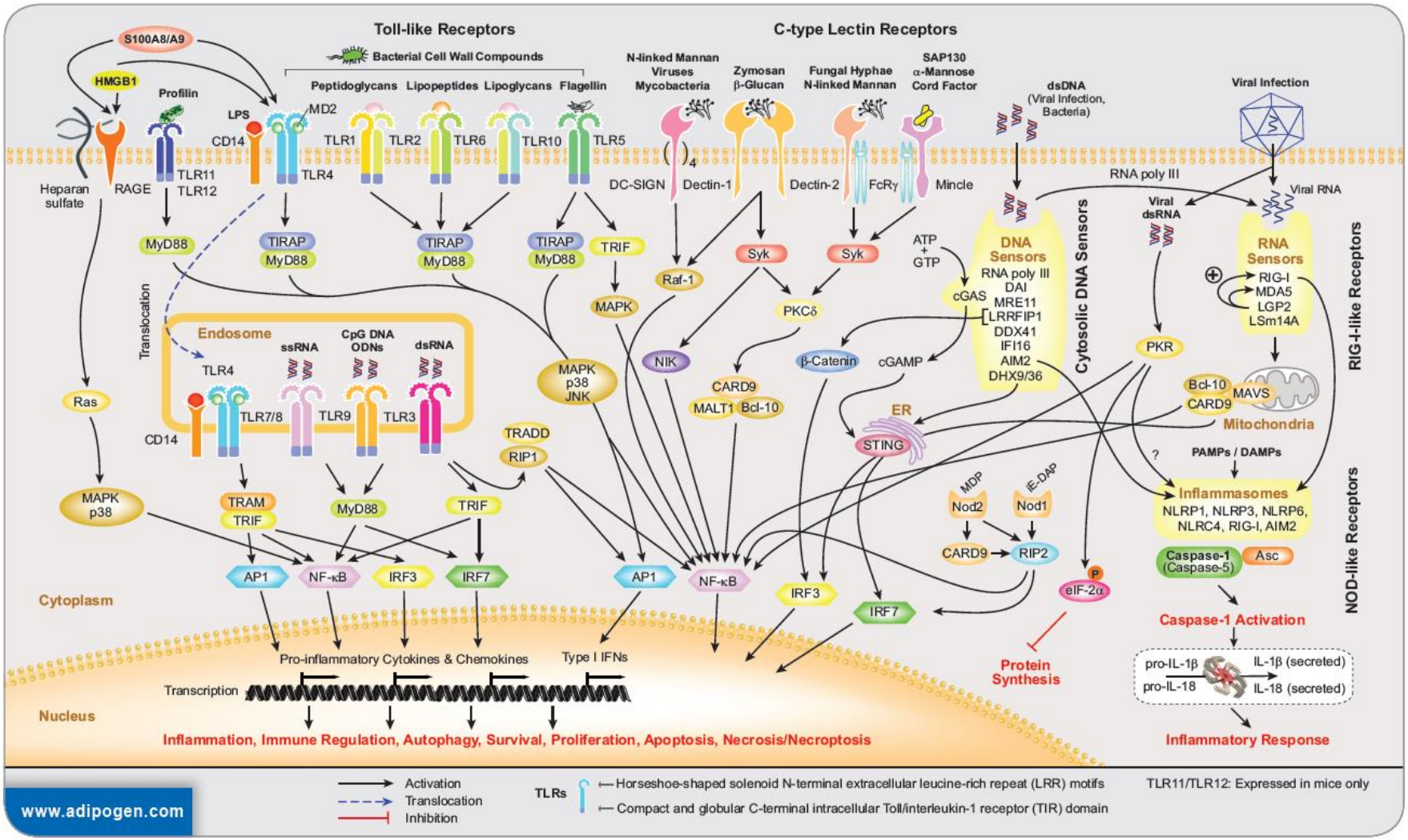

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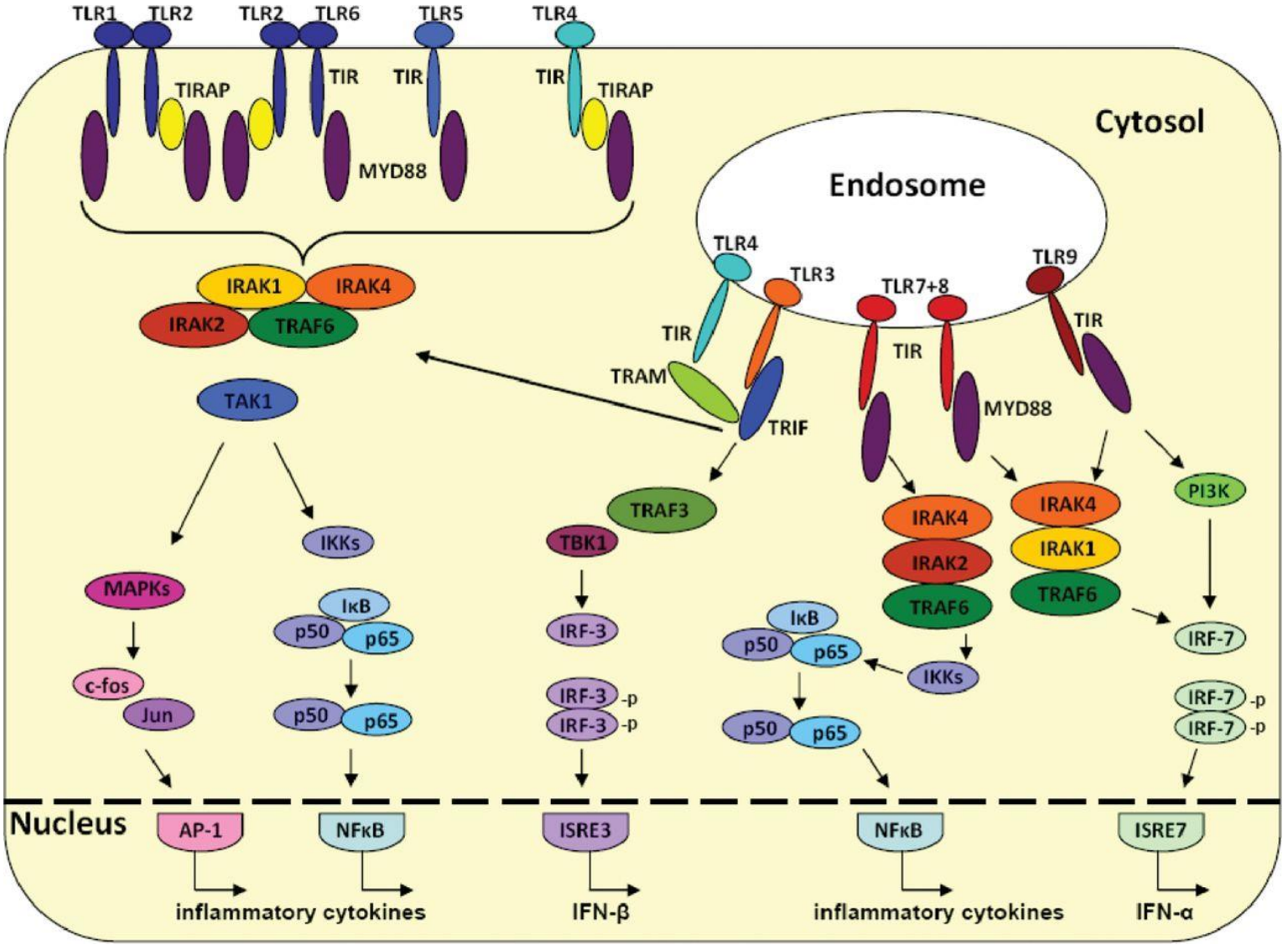
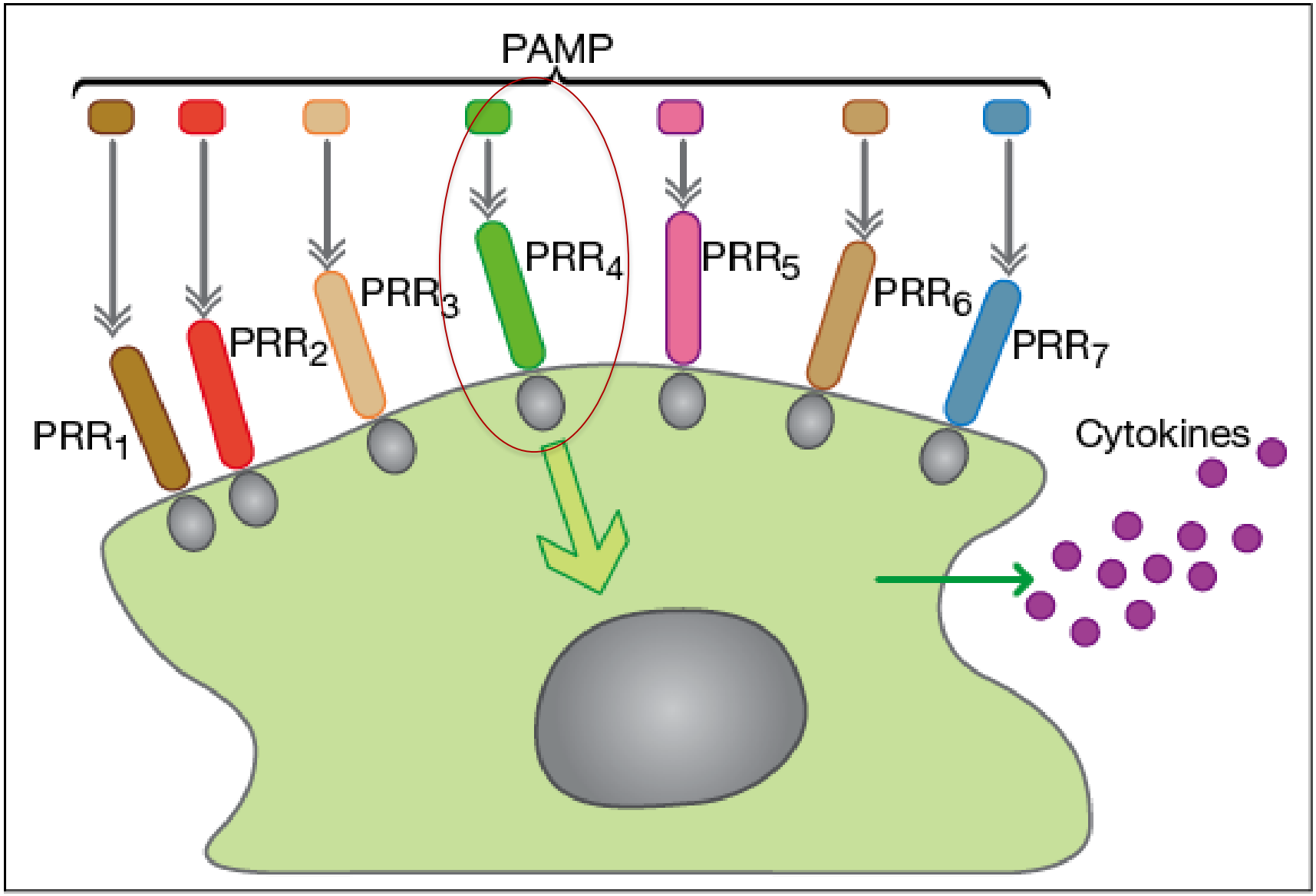
Role of the Toll like receptors in production of inflammatory cytokines



Pattern recognition receptors on macrophage

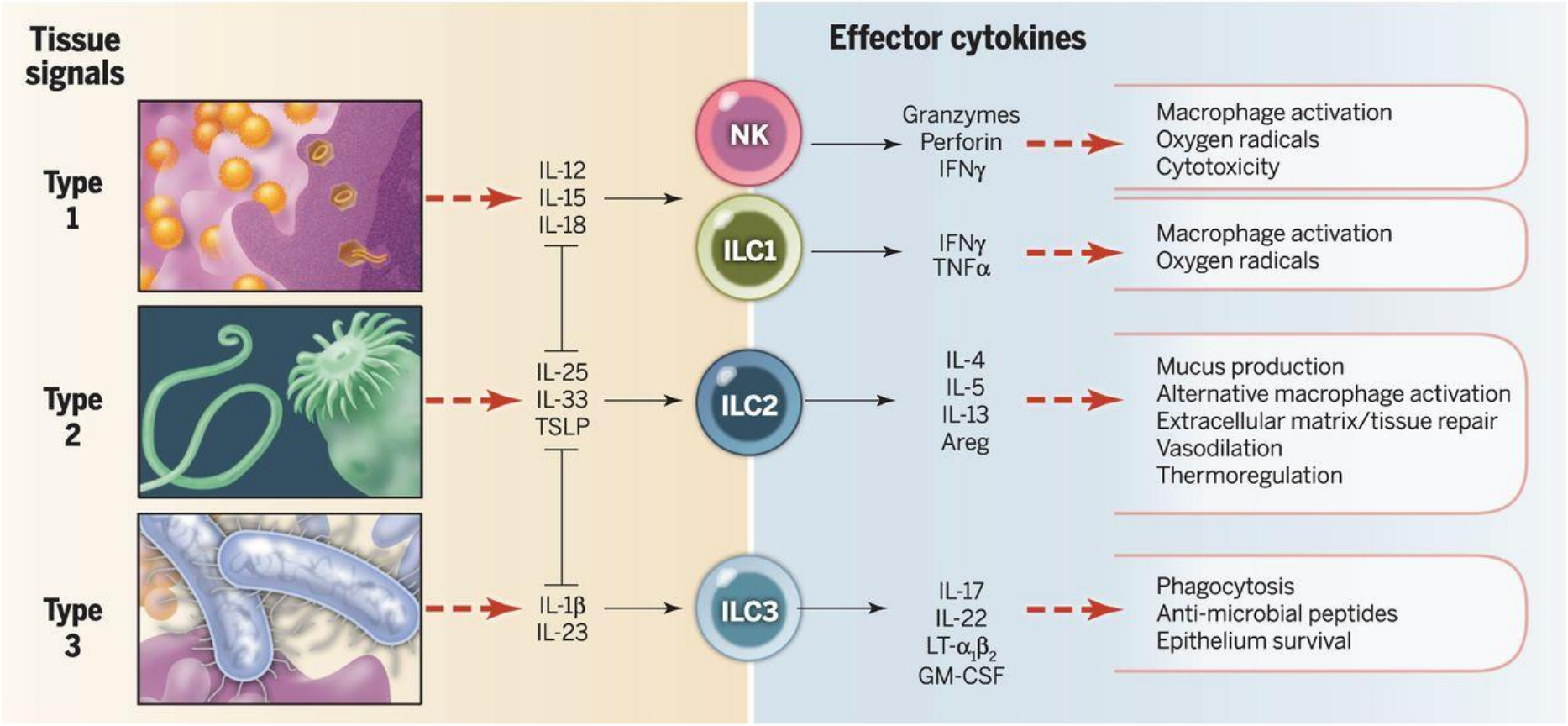


Innate lymphoid cells

- Innate lymphoid cells (**ILCs**) belong to the lymphoid lineage without expression of antigen-specific receptors, but contribute to immune responses by secreting effector cytokines and regulating the functions of other innate and adaptive immune cells.
- These cells have important functions in innate immune responses to infectious microorganisms and in the regulation of homeostasis and inflammation.
- ILCs are present in lymphoid and non-lymphoid organs and are particularly abundant at the mucosal barriers, where they are exposed to allergens, commensal microbes, and pathogens.

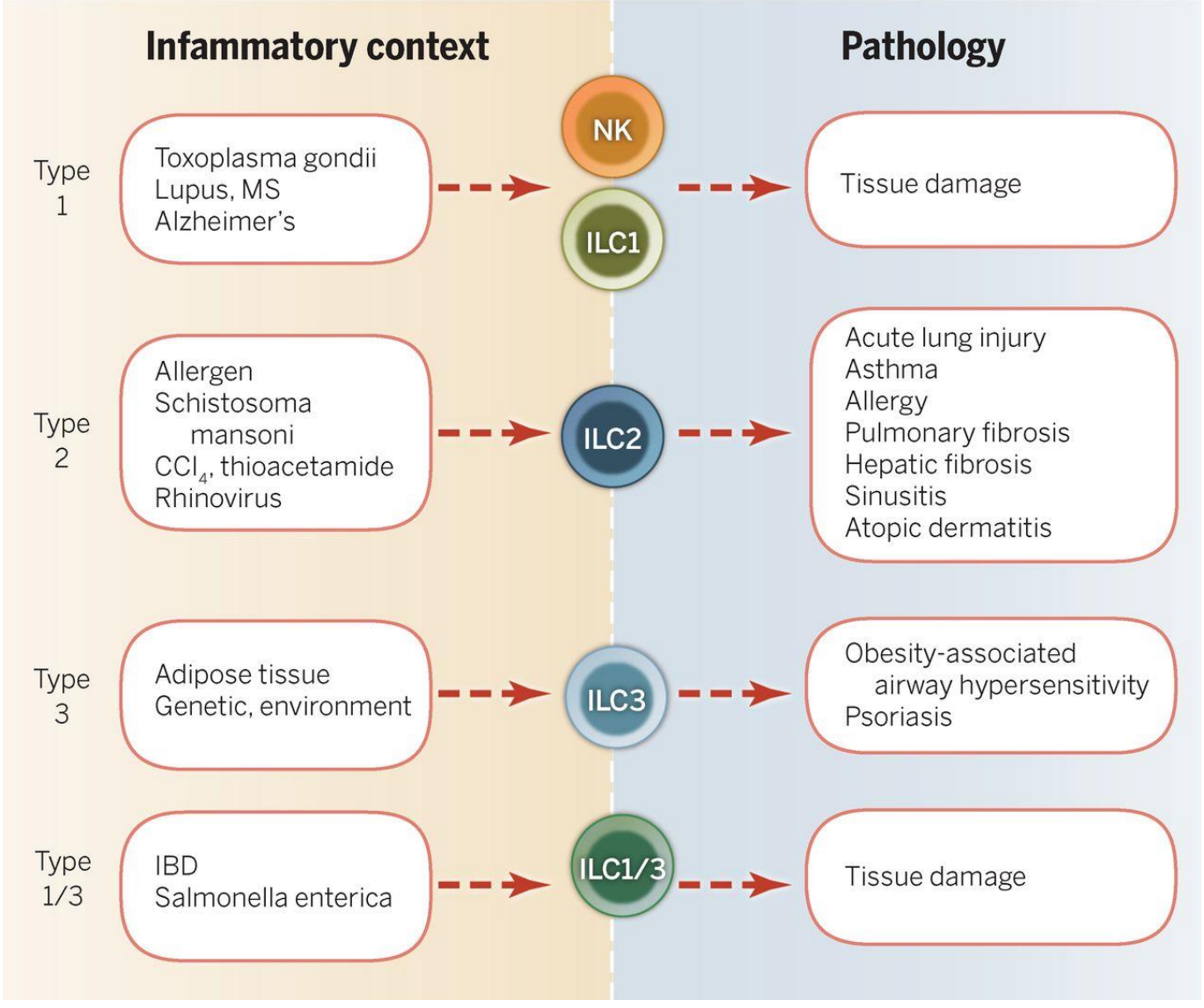
Innate lymphoid cells

- Innate lymphoid cells (ILCs) are immune cells that provide a rapid, non-antigen-specific response to pathogens and contribute to tissue homeostasis.
- They do not have diverse antigen receptors like T and B cells but instead mirror the effector functions of T helper cells.
- ILCs are classified into three main groups based on their signature cytokines and transcription factors: ILC1s (IFN-γ-producing), ILC2s (IL-5, IL-13-producing), and ILC3s (IL-22, IL-17-producing). These cells are abundant at mucosal barriers and are involved in immunity, tissue repair, and can contribute to inflammatory and autoimmune diseases when dysregulated.

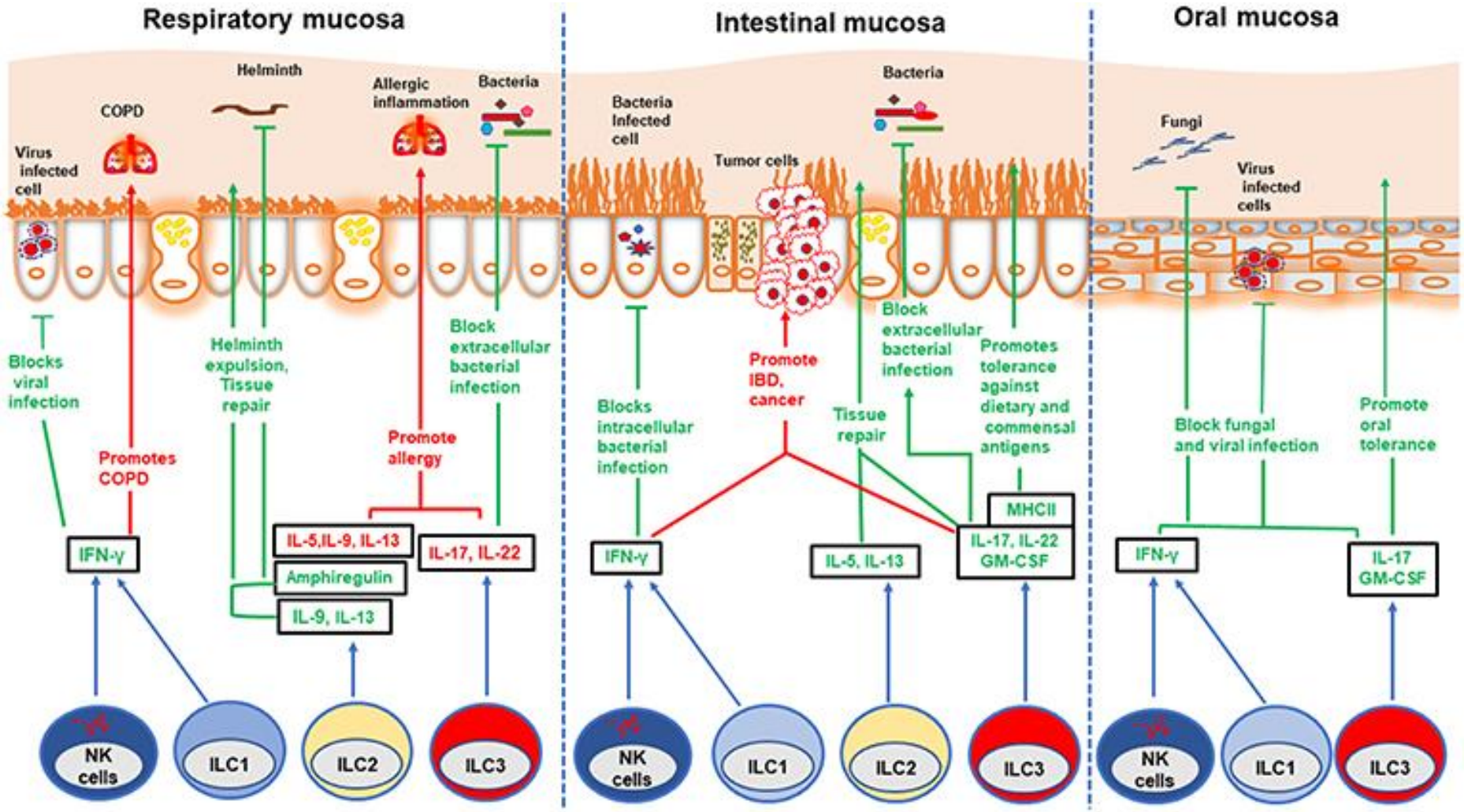


The effector functions of ILCs mirror the functions of CD8+ and CD4+ T cells, with the major difference being the prompt activation of ILCs and their lack of (relatively slow) antigen-dependent clonal selection and expansion.

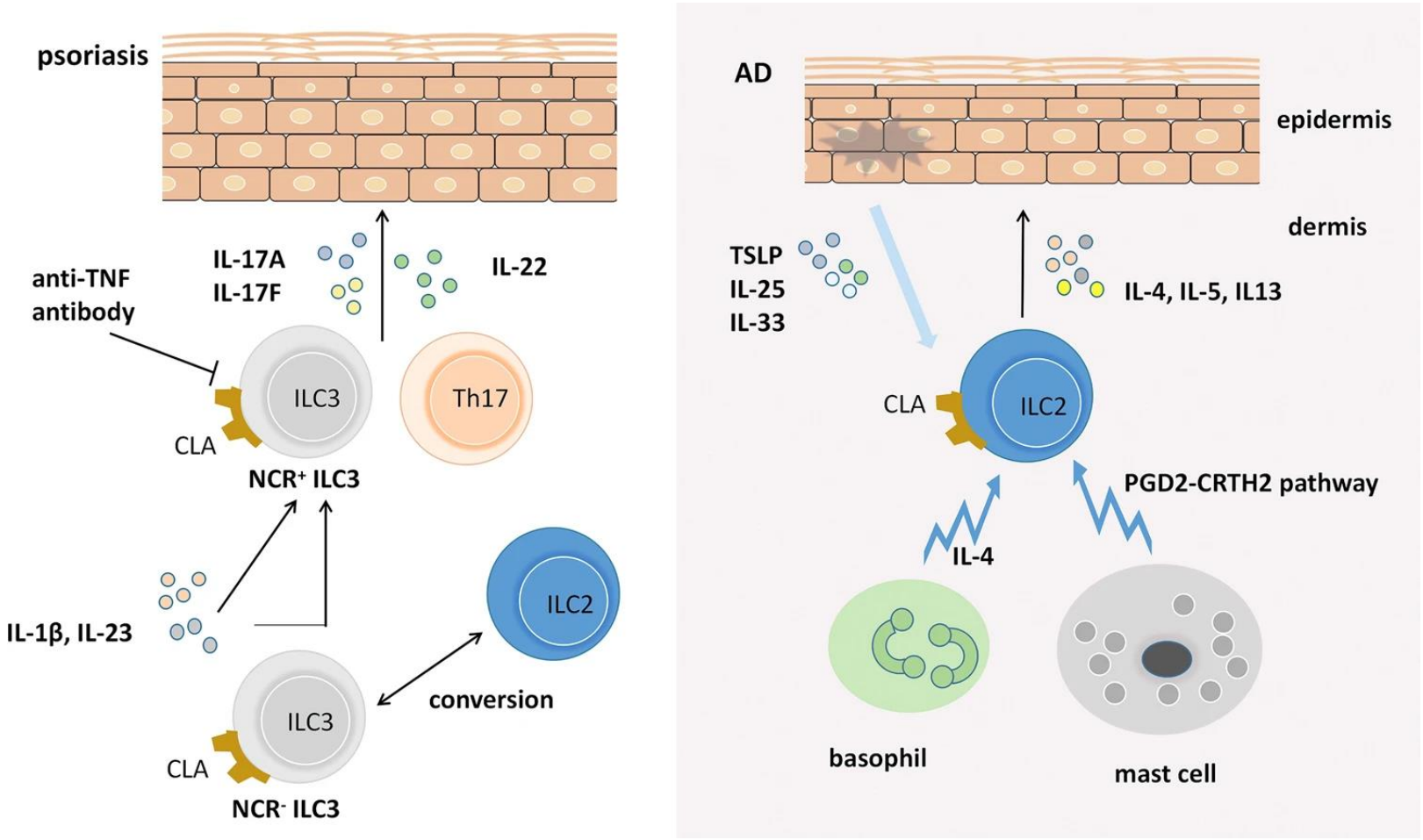
Role of Innate Lymphoid Cells in inflammatory diseases



Functions of innate lymphoid cells on mucosal surfaces



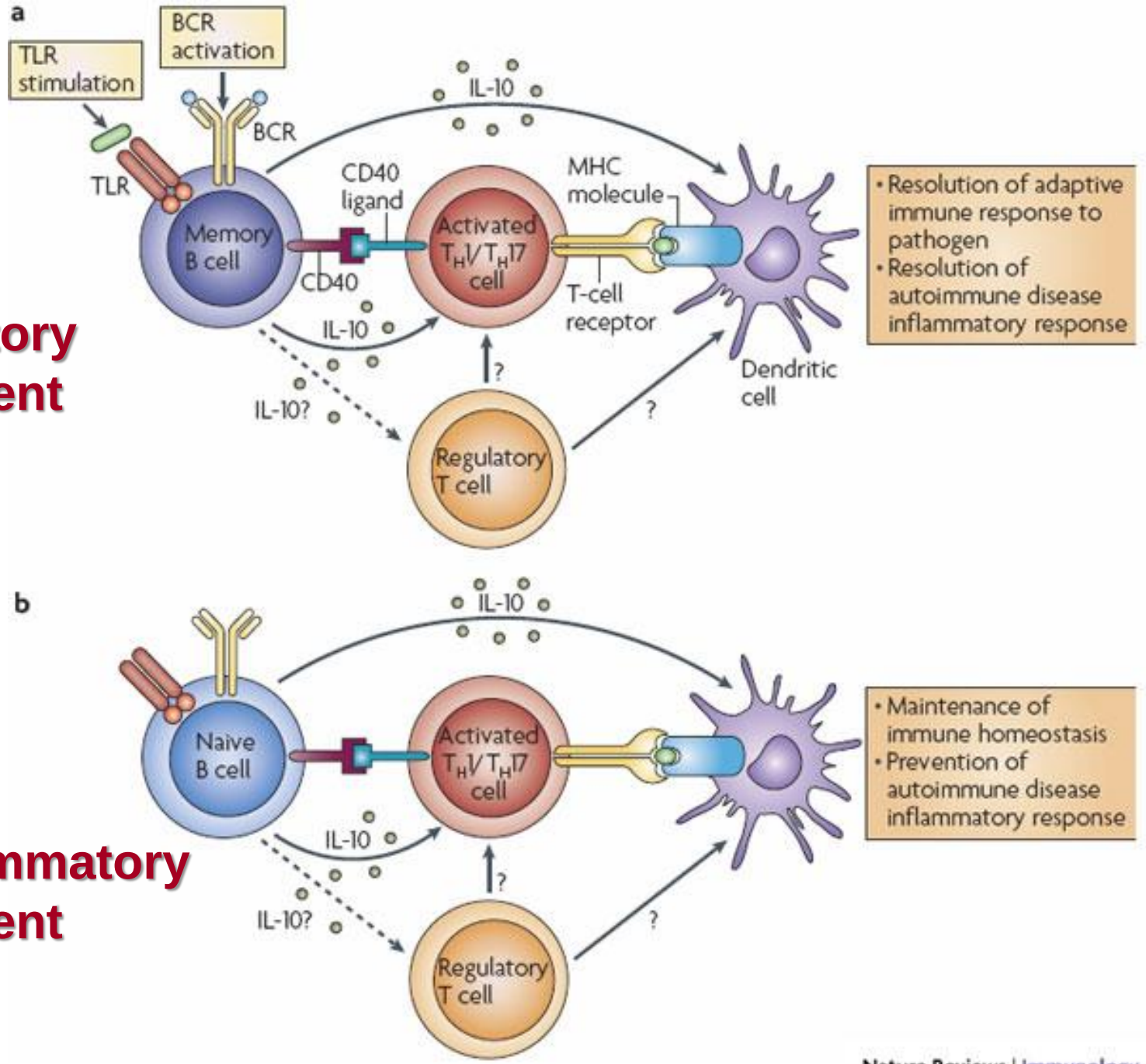
Pathogenic role of ILCs in psoriasis and AD.

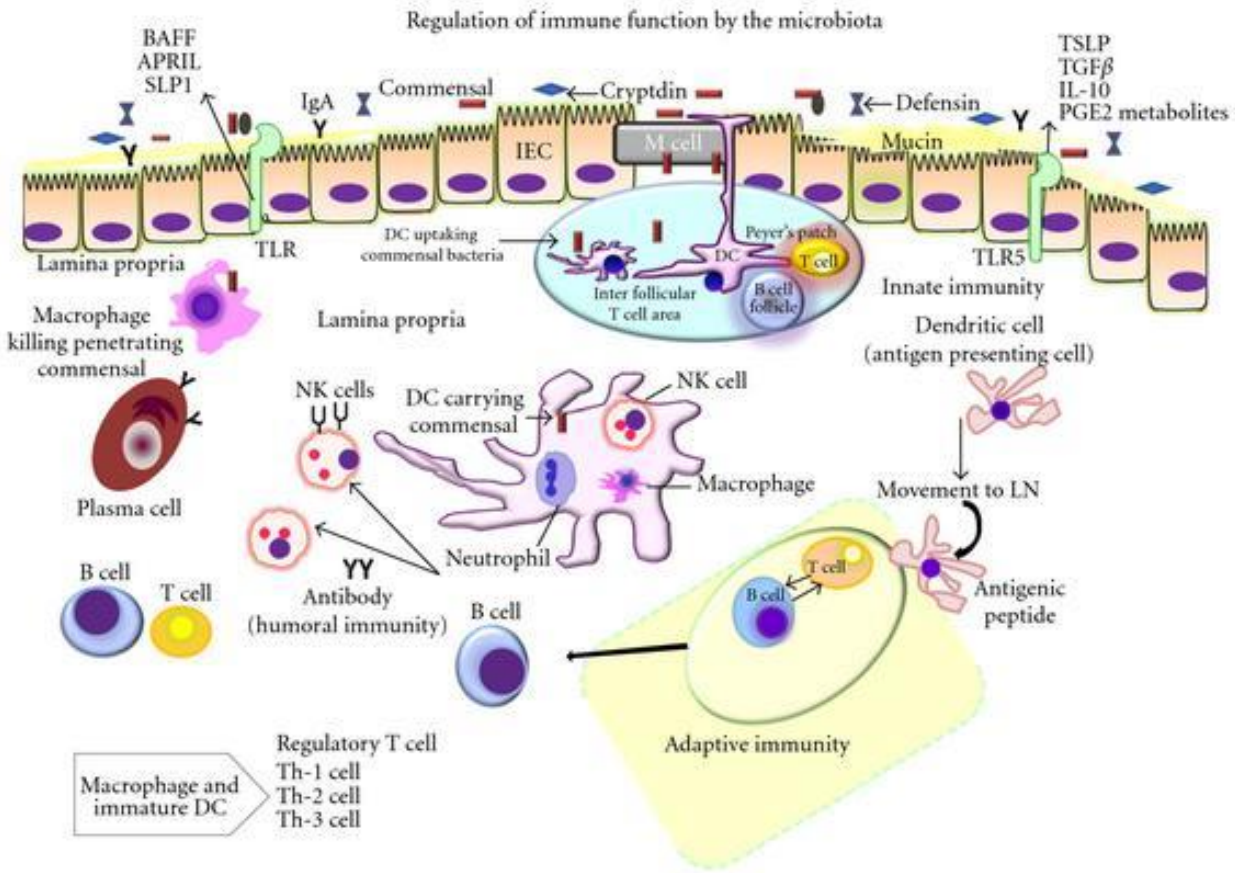


ILC3s are elevated in the skin of psoriasis patients and play a central role in the skin in atopic dermatitis (AD) through the secretion of IL-4, IL-5, and IL-13. In addition, ILC2s interact with mast cells and basophils and participate in driving pathology in atopic dermatitis through cell interactions

Inflammatory environment

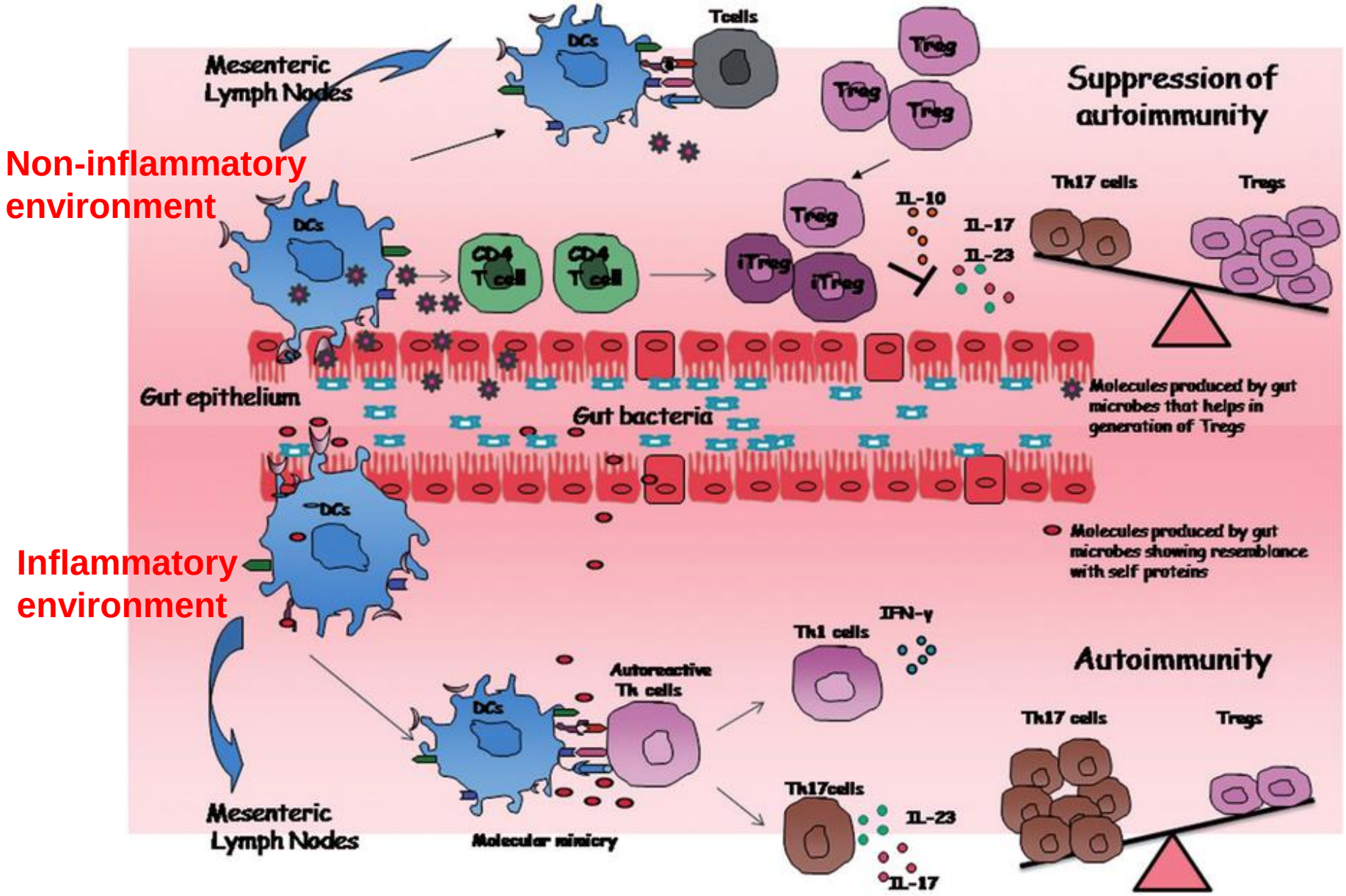
Non-inflammatory environment



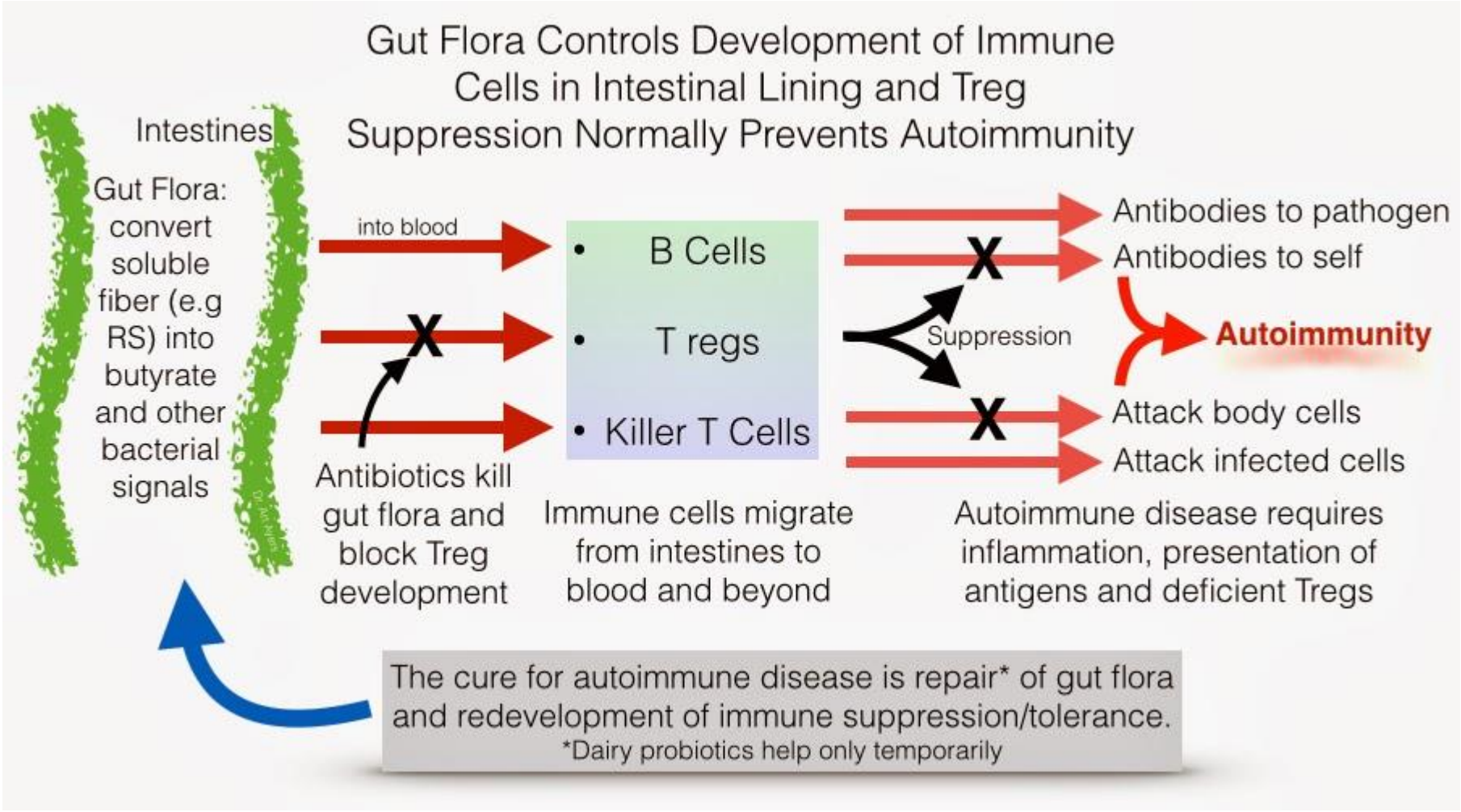


Influenced by the **microbiota**, intestinal epithelial cells (**IECs**) elaborate cytokines, including thymic stromal lymphoprotein (TSLP), transforming growth factor (TGF), and interleukin-10 (IL-10), that can influence pro-inflammatory cytokine production by dendritic cells (DC) and macrophages present 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



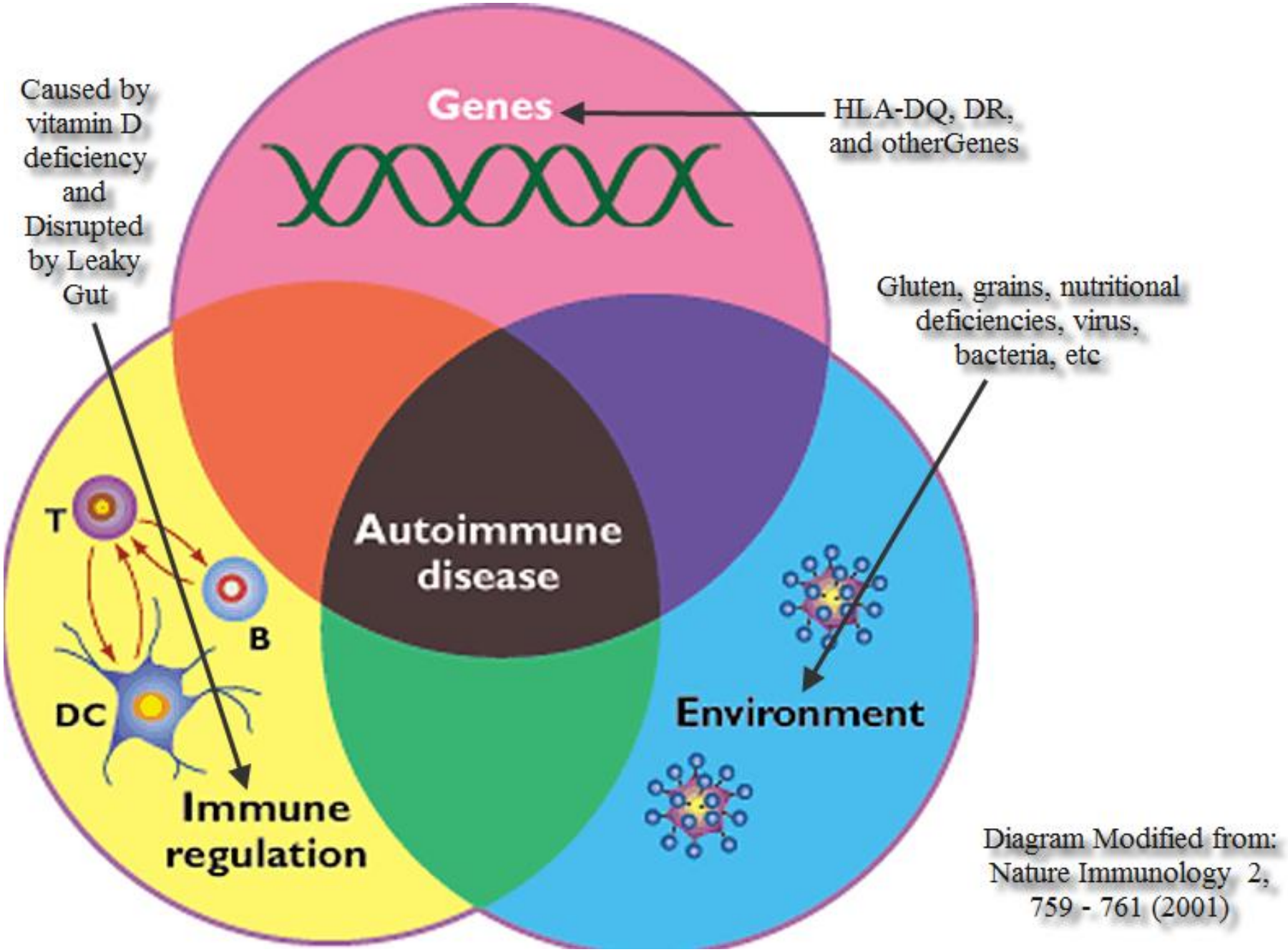
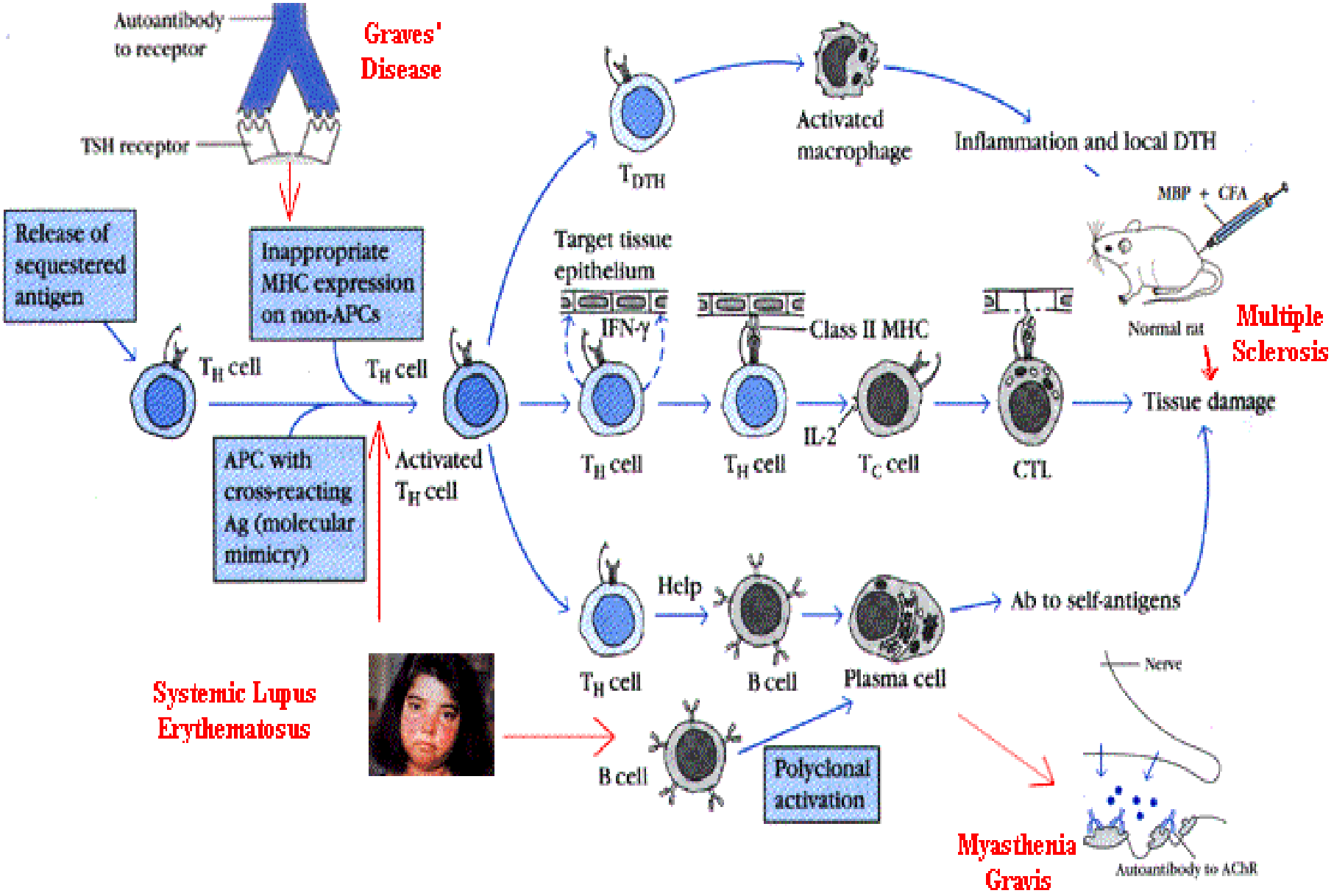
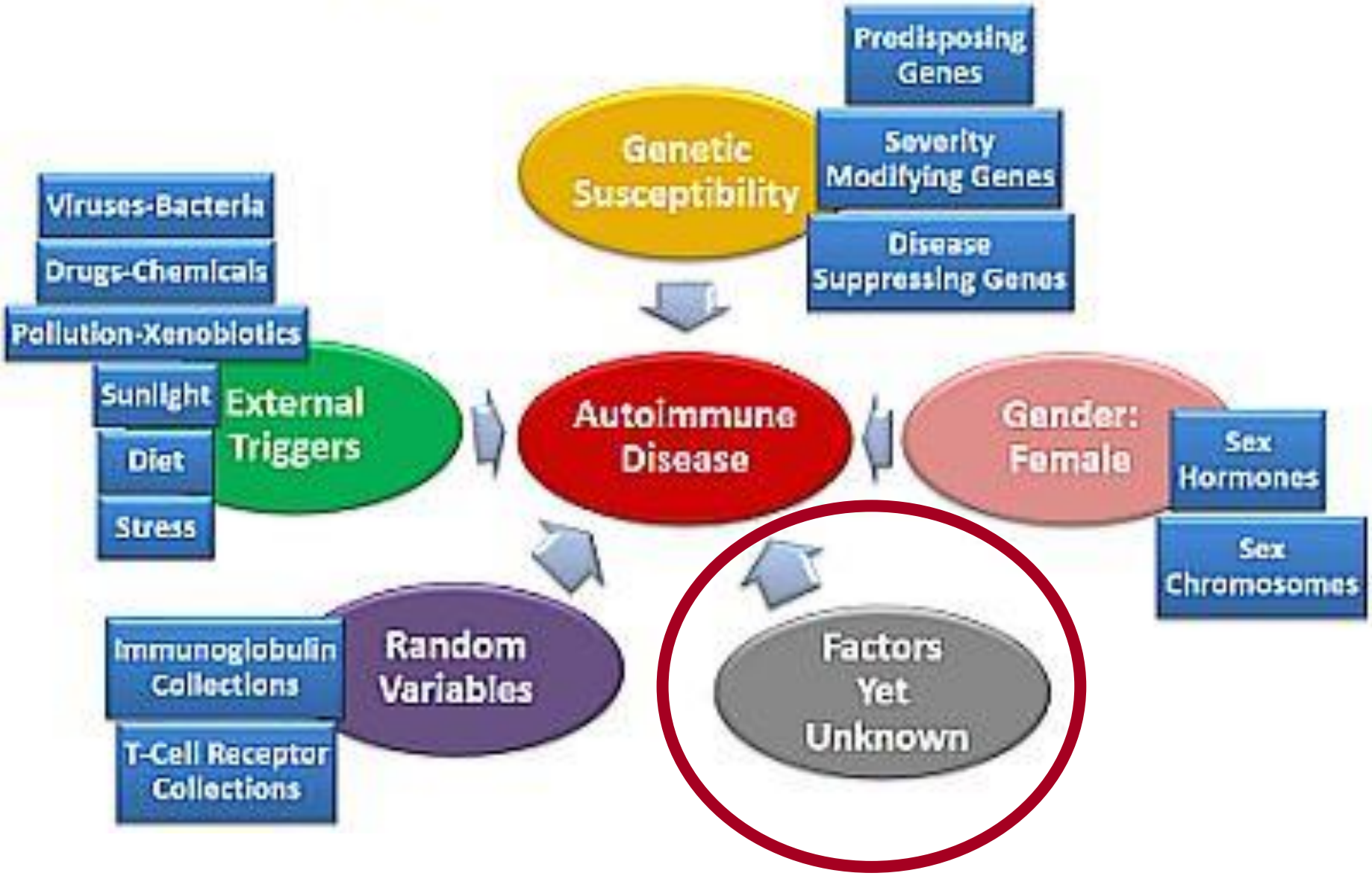


Diagram Modified from:
Nature Immunology 2, 759 - 761 (2001)


Autoantibody to receptor
TSH receptor
Graves' Disease
Release of sequestered antigen
Inappropriate MHC expression on non-APCs
T_H cell
T_H cell
APC with cross-reacting Ag (molecular mimicry)
Activated T_H cell
T_{DTH}
Activated macrophage
Inflammation and local DTH
Target tissue epithelium
IFN-γ
Class II MHC
IL-2
T_H cell
T_H cell
T_C cell
CTL
MBP + CFA
Normal rat
Multiple Sclerosis
Tissue damage
Help
T_H cell
B cell
Plasma cell
Ab to self-antigens
Systemic Lupus Erythematosus
B cell
Polyclonal activation
Nerve
Myasthenia Gravis
Autoantibody to AChR

Etiology of Autoimmune Disease



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

>100 Autoimmune Diseases

Muscles
Muscular Dystrophy
Fibromyalgia

Nerves
Peripheral Neuropathy
Diabetic Neuropathy

Lung
Fibromyalgia
Wegener's Granulomatosis

Skin
Psoriasis
Vitiligo
Eczema
Scleroderma