IMMUNE TOLERANCE AND PATHOPHYSIOLOGY OF AUTOIMMUNE DISEASES

Master 1 D2HP Drug discovery and Healthcare products

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Outline

- Introduction
- Immune tolerance
- Tolerance breakdown and autoimmunity
- Risk factors
- Autoimmune disorders: two examples
  - Systemic lupus erythematosus
  - Multiple sclerosis

Slides or part of slides to be learned for the exam are in orange rectangles

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Introduction

SELF VS NON-SELF

- Paul Ehrlich: *horror autotoxicus* in 1938
  - **Detection of self and non-self**
    - Destruction of foreign antigens → protection
  - If abnormalities in this distinction
    - **destruction of self-antigens**

AUTOIMMUNITY: clinical consequences of the activation of an individual's immune system against one or more of its constituents

Introduction

Self vs Non-Self

"Immunological Self"

Self

- Constitutive antigens of the organism

Environmental components

- Harmless environmental antigens
- Food
- Inhaled antigens
- Microbiota

"Immunological Non-Self"

Cells or molecules to which adaptive immune cells are **not exposed during their maturation** or that they don't encounter in the body at the steady state.

Introduction

- Burnet & Medawar: Nobel prize in 1960
  - Discovery of acquired immunological tolerance

Peter Medawar and colleagues

Sir Frank Macfarlane Burnet

- Cells from the adaptive immune system do react to self
  - **Recognition** of self
  - **Tolerance estabishment**: active process

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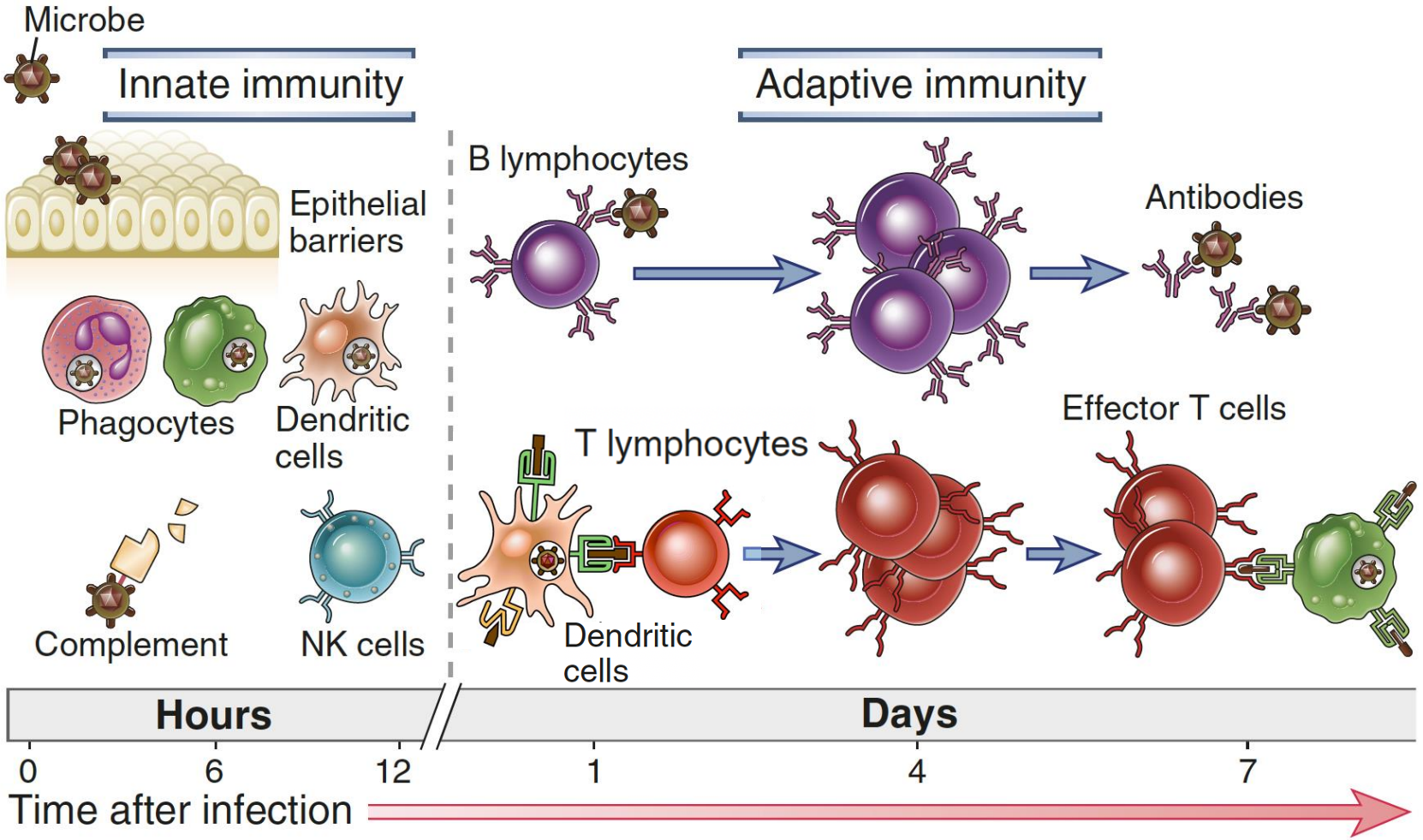
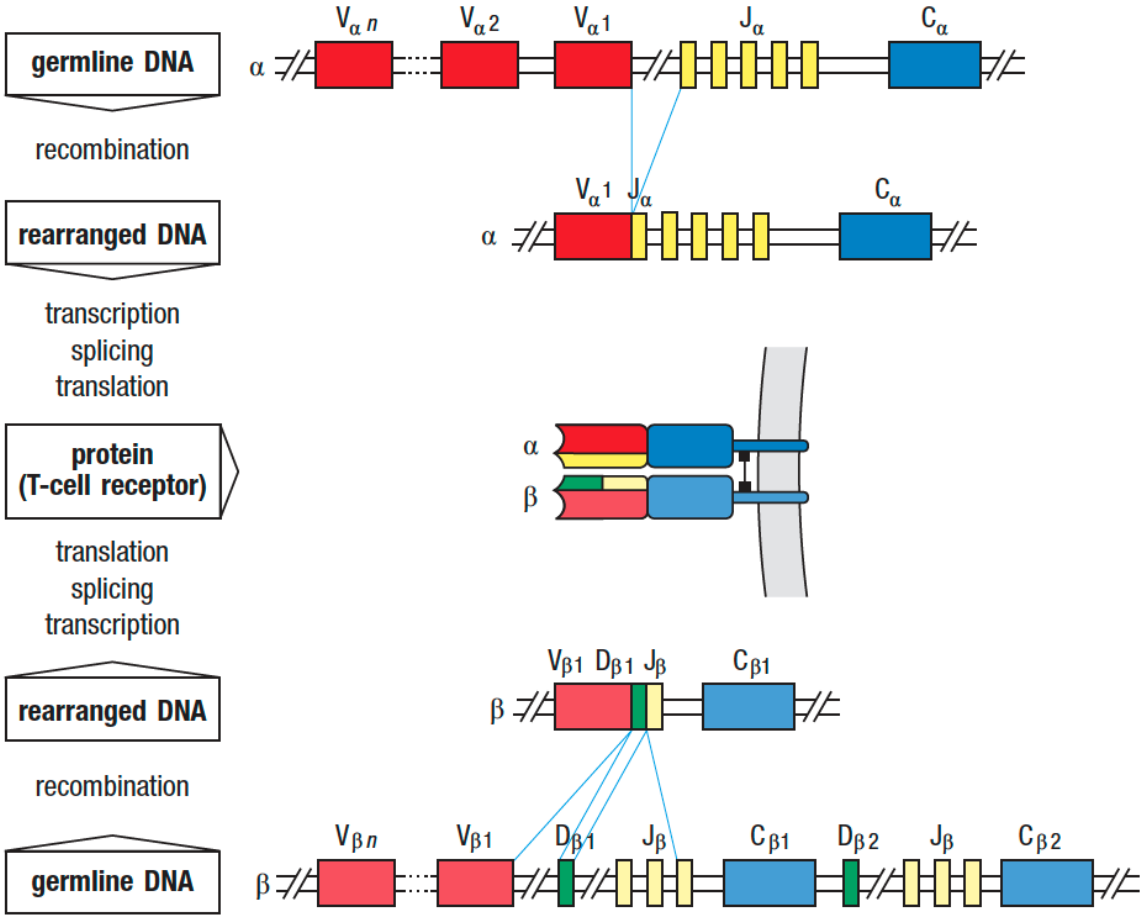
Innate and adaptive immunity



BCR and TCR gene rearrangement occurs randomly in primary lymphoid organs

Example: TCR rearrangement



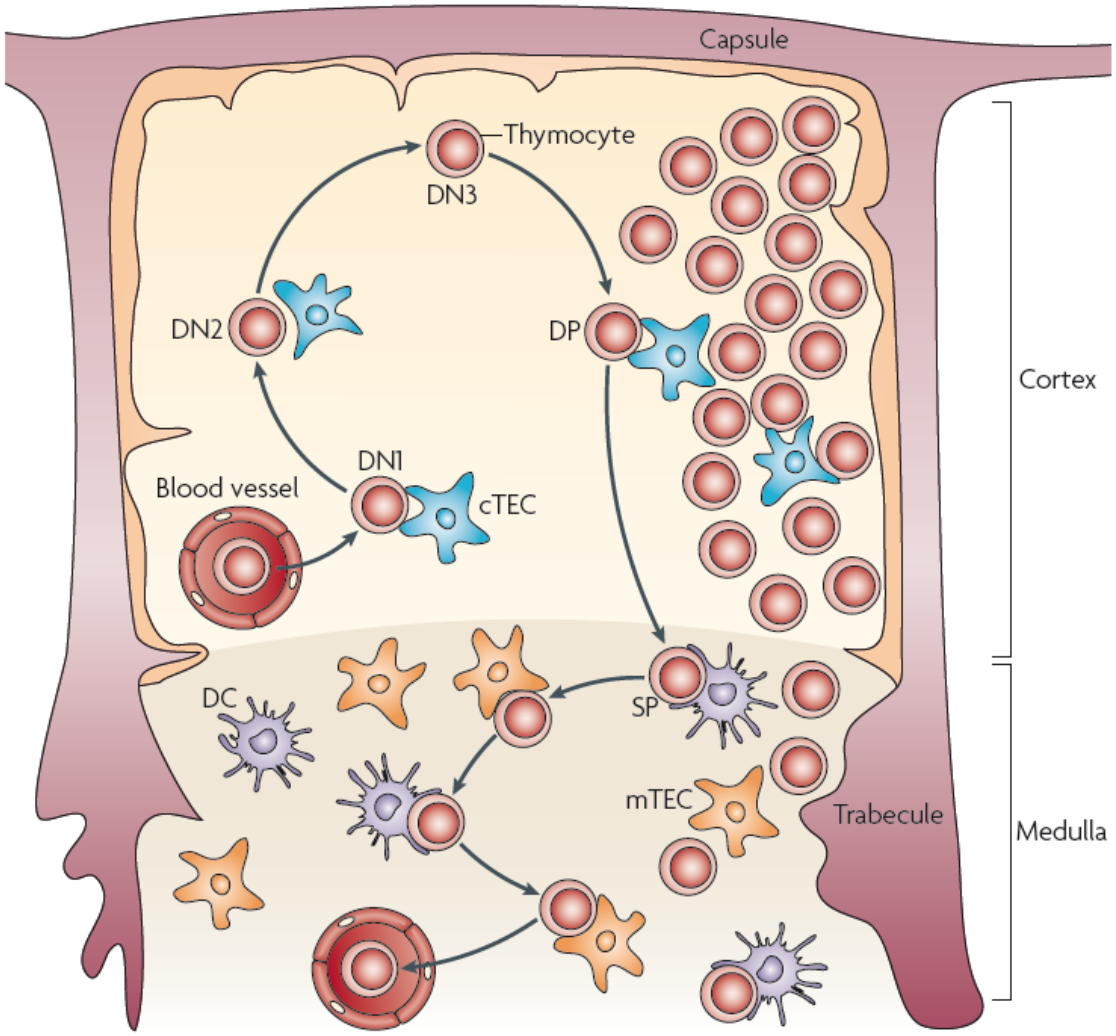
High frequency of autoreactive BCR and TCR

Central tolerance of T Cells

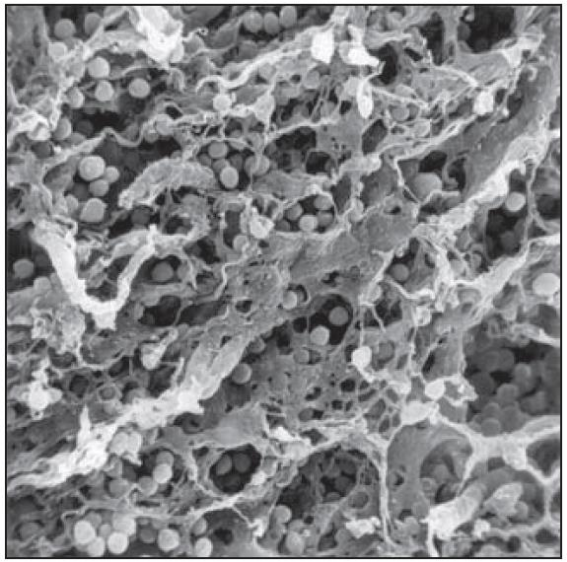
in the thymus

- MECHANISMS
  - Clonal deletion – recessive
  - Regulatory T-cell induction - dominant

T cell development and education in the thymus



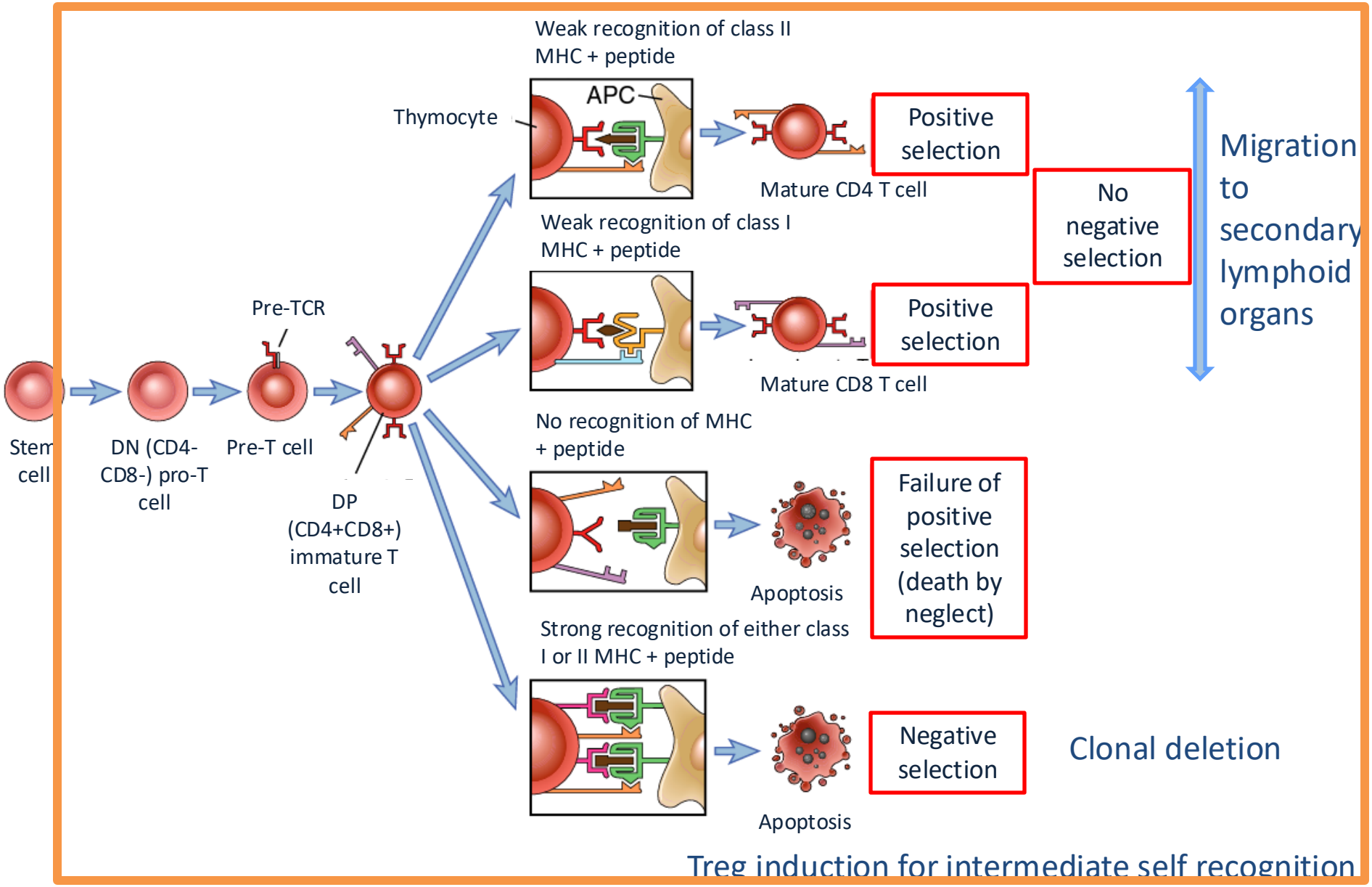
DN: CD4-CD8-
DP: CD4+CD8+
SP: CD4+CD8- or CD4-CD8+



cTEC : cortical thymic epithelial cells
mTEC : medullary thymic epithelial cells

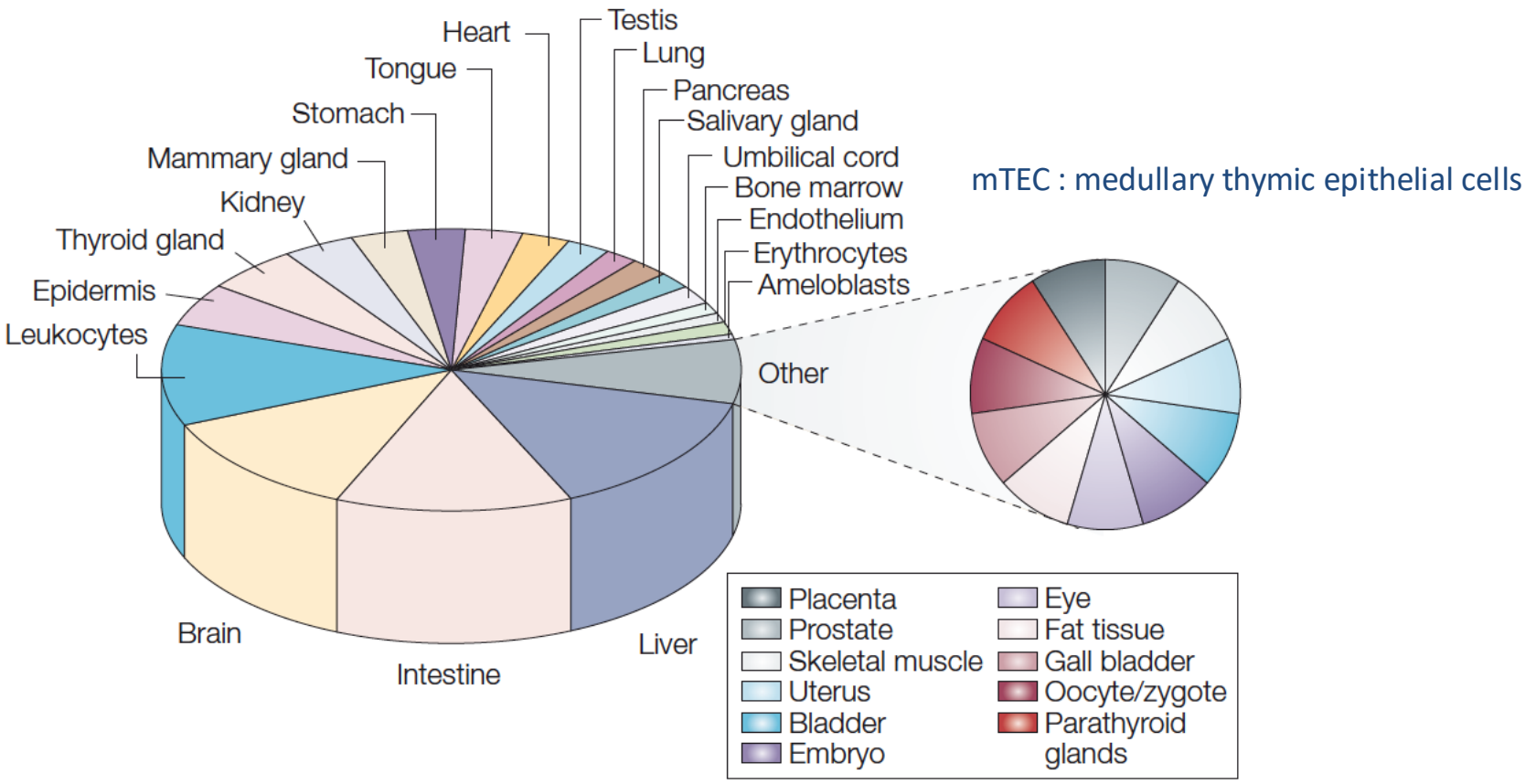
Klein et al, Nat. Rev. Immunol. 2009

Positive and negative selection in the thymus



Tolerance to tissue-specific antigens (TSAs)

- **Historical hypothesis:** tolerance to tissue-specific Ag, not expressed in the thymus, is established in the periphery
- **In reality**: ectopic expression of tissue-specific Ag by mTECs



mTEC : medullary thymic epithelial cells

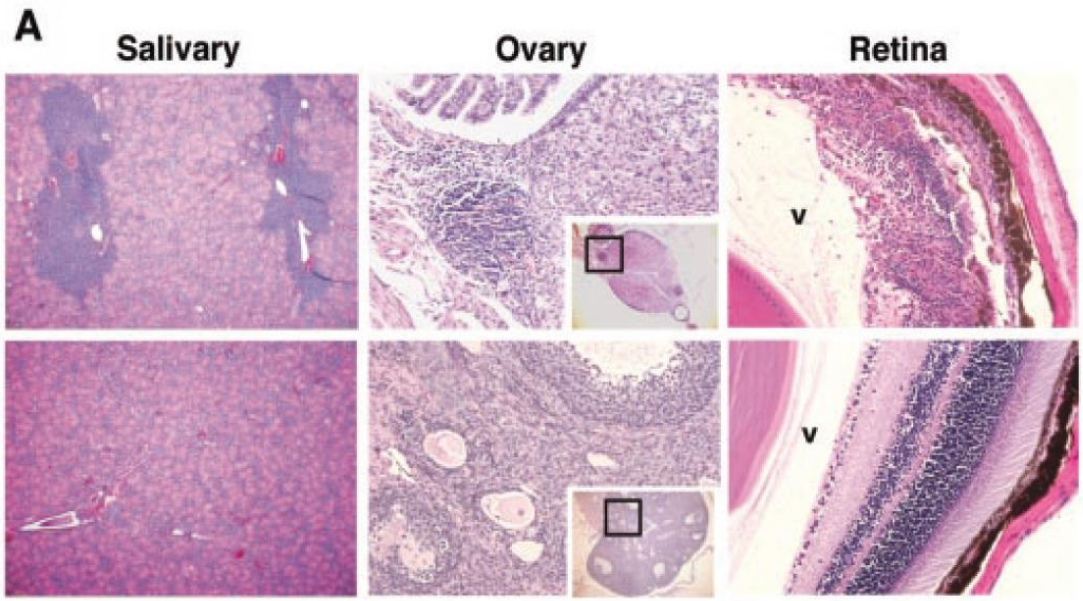
Kyewsky et Derbinsky, Nat. Rev. Immunol. 2004

Tolerance to TSAs

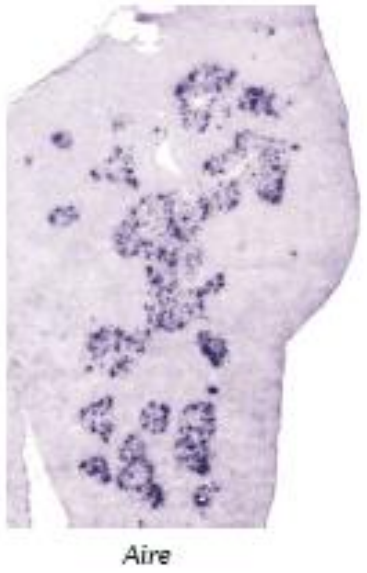
Projection of an Immunological Self Shadow Within the Thymus by the Aire Protein

Mark S. Anderson,[1] Emily S. Venanzi,[1] Ludger Klein,[2] Zhibin Chen,[1] Stuart P. Berzins,[1] Shannon J. Turley,[1] Harald von Boehmer,[2] Roderick Bronson,[3] Andrée Dierich,[4] Christophe Benoist,[1]* Diane Mathis[1]*

APECED/APS-1: autoimmune polyendocrinopathy candidiasis ectodermal dystrophy / autoimmune polyendocrine syndrome

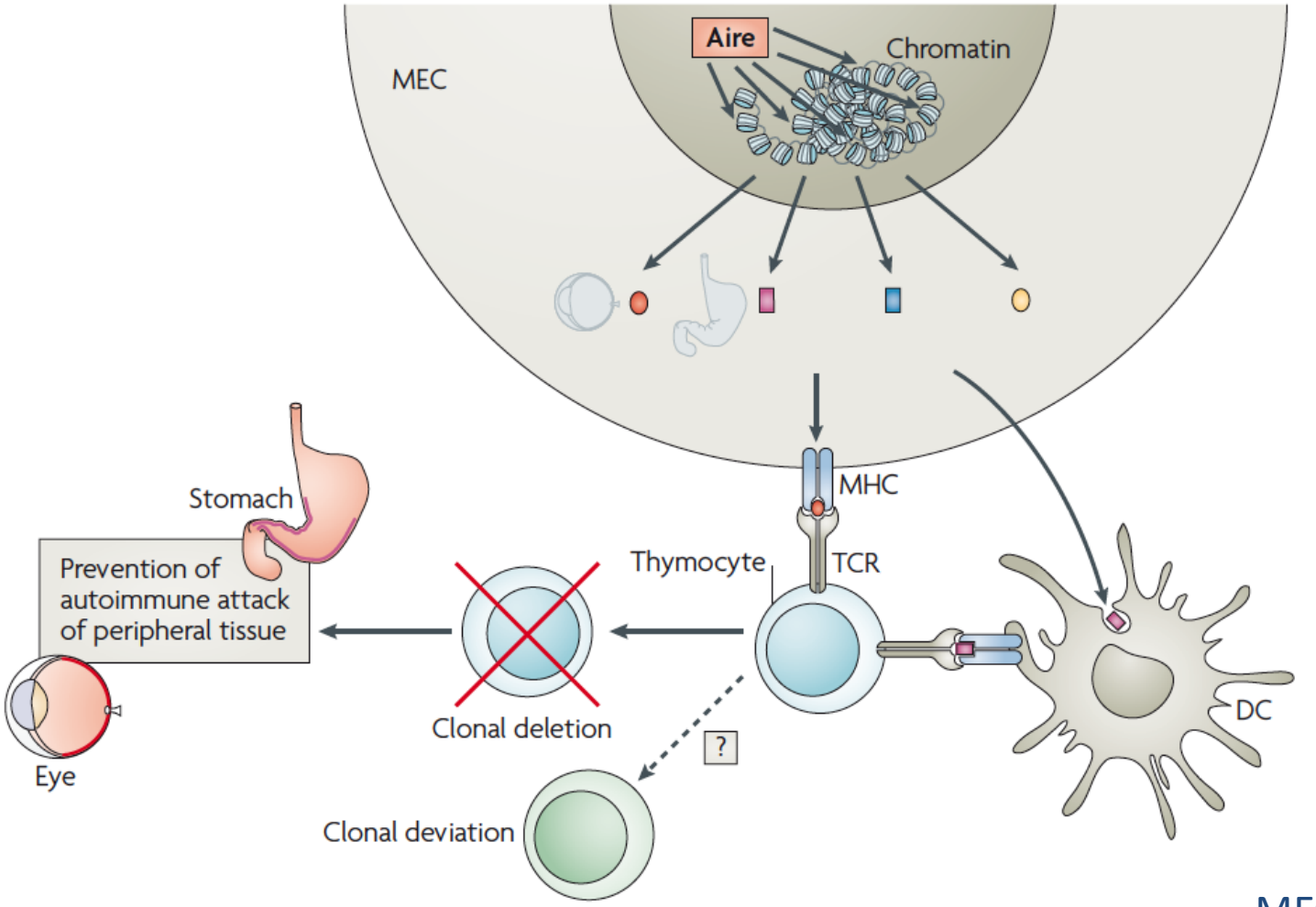


AIRE: autoimmune regulator



Anderson et al, Science 2002
Klein et al, Nat. Rev. Immunol. 2014

AIRE: from transcriptional regulation to tolerance induction



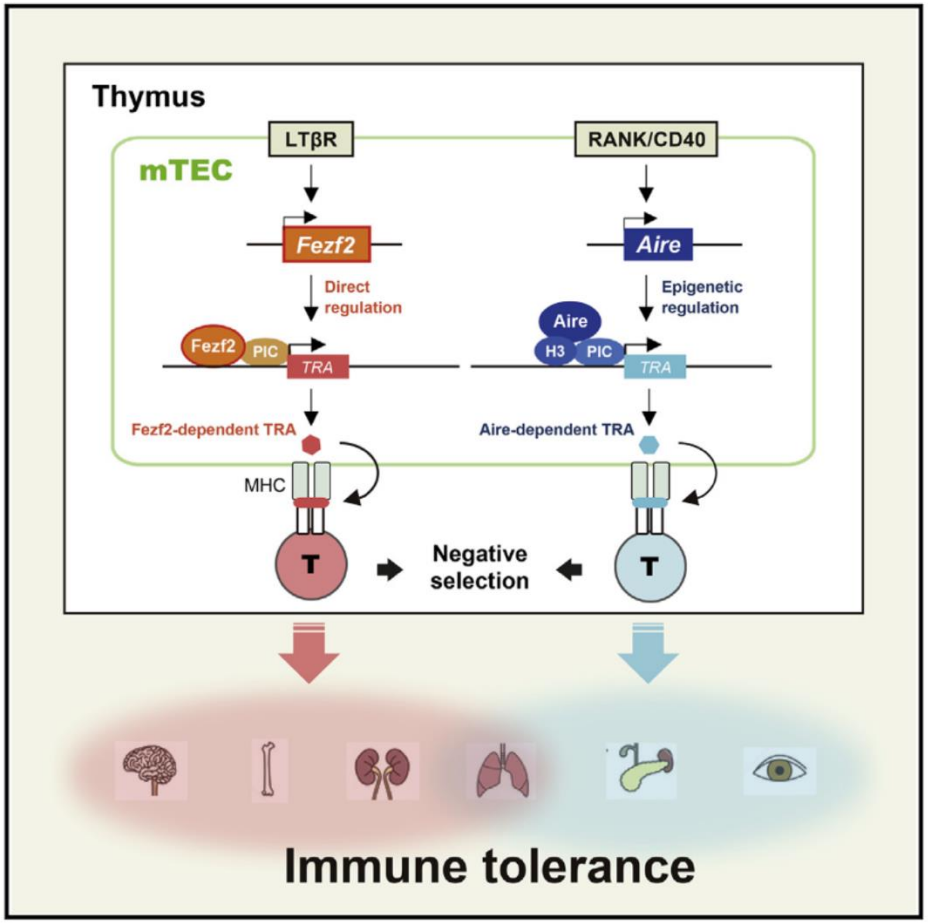
MEC =mTEC

Mathis et Benoist, Nat. Rev. Immunol. 2007

Cell

Fezf2 Orchestrates a Thymic Program of Self-Antigen Expression for Immune Tolerance

Graphical Abstract



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Correspondence

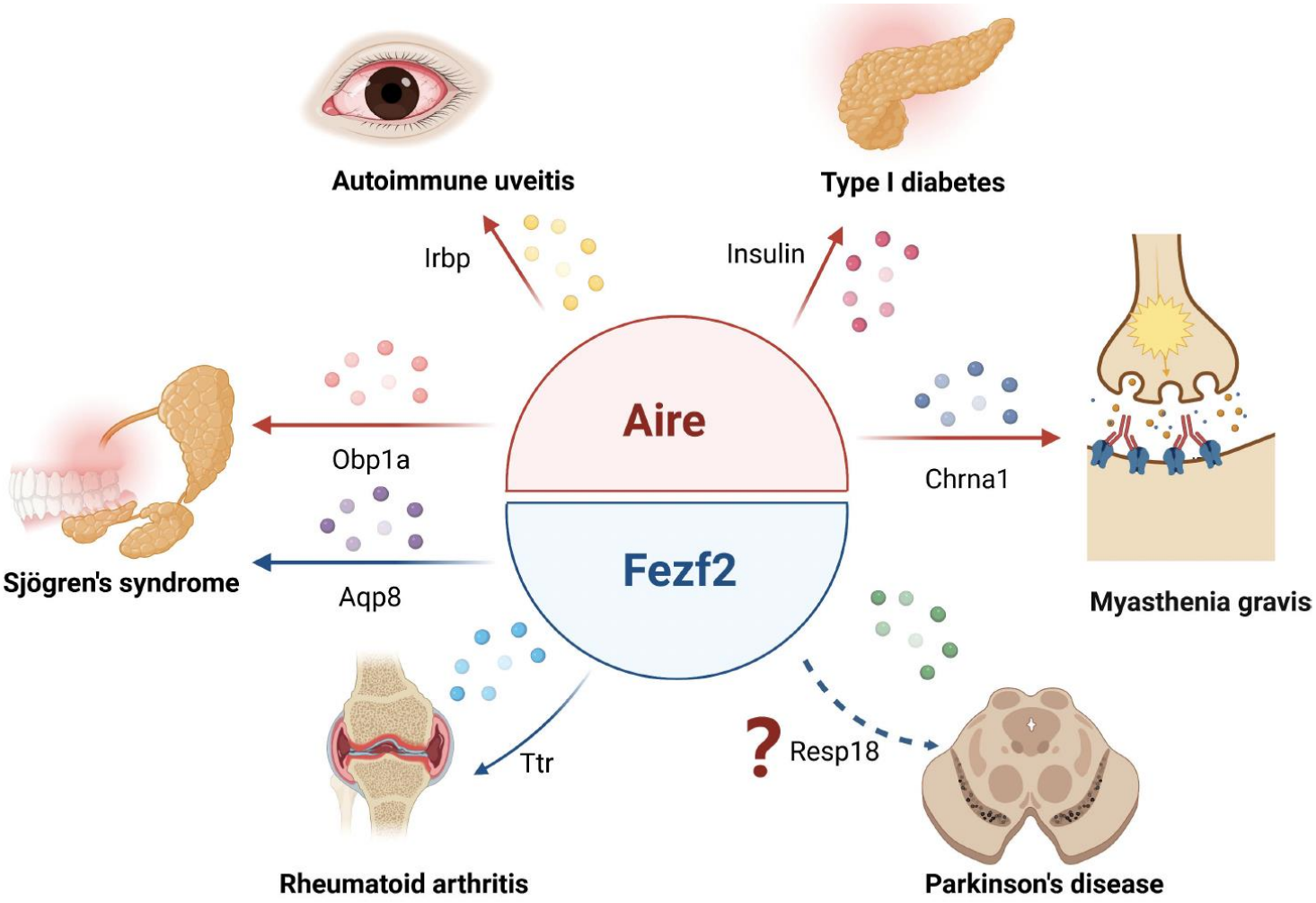
takayana@m.u-tokyo.ac.jp

In Brief

To promote immunological tolerance of one's own proteins, the protein Fezf2 directly regulates transcription of tissue-restricted antigen genes in in the thymus, where it functions independently and via a distinct pathway from Aire, the transcriptional regulator widely thought to be primarily responsible for self-tolerance.

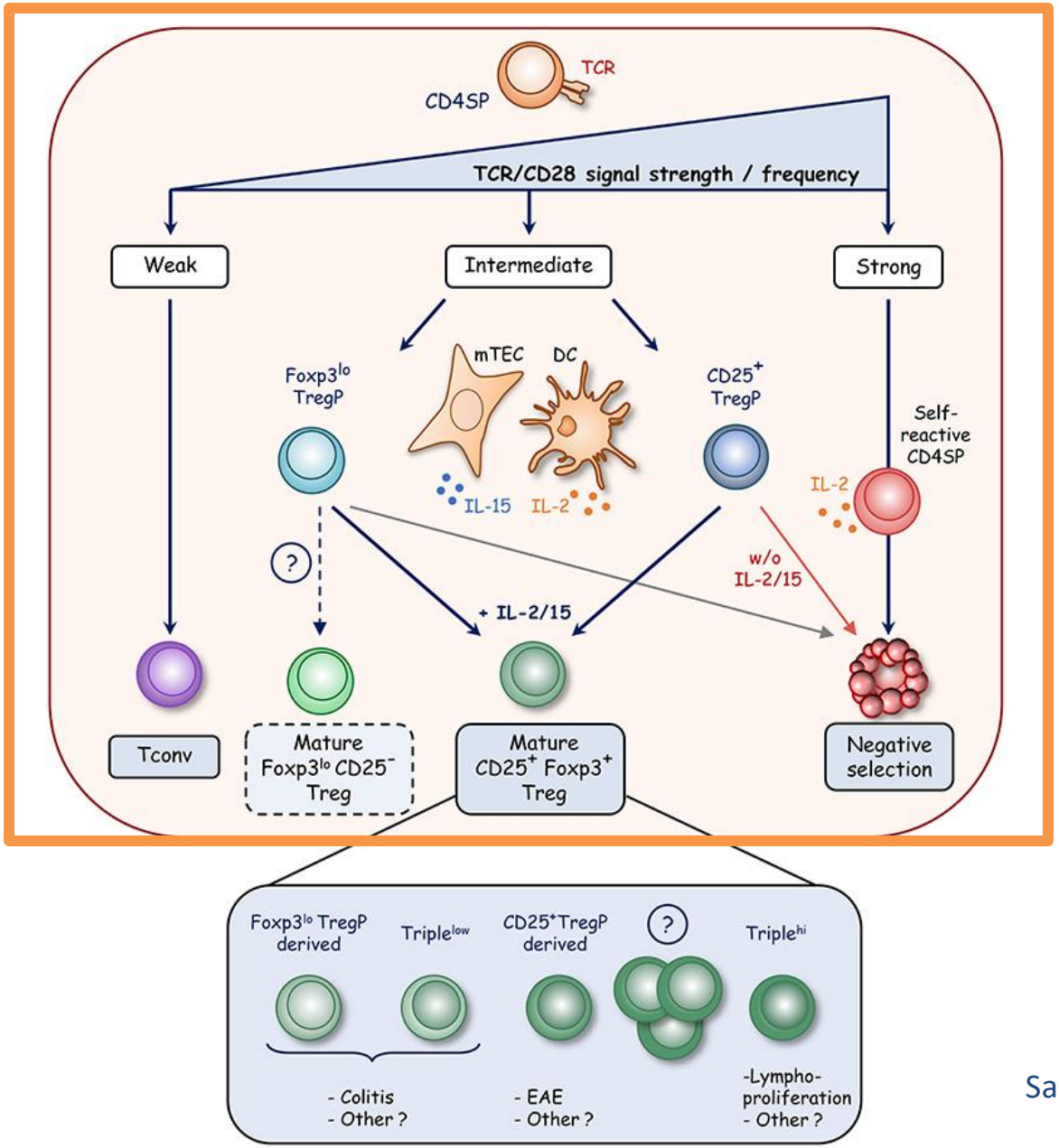
FEZ family zinc finger 2 (Fezf2)

Complementary actions of Aire and Fezf2 in central tolerance induction



Qiet al, Front. Immunol. 2022

Treg induction in the thymus



Santamaria et al, Front. Immunol. 2021

Central tolerance of B cells

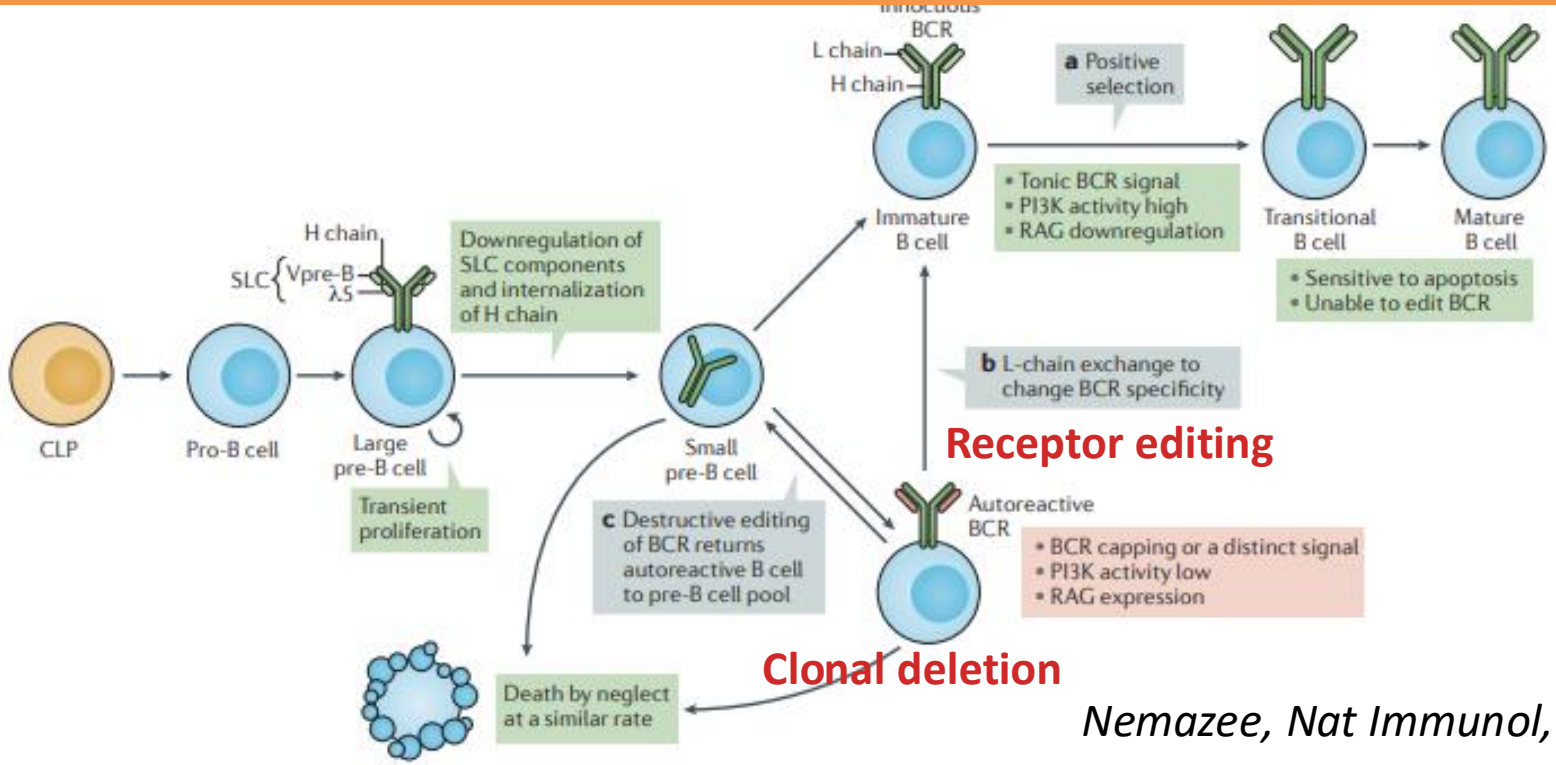
in the bone marrow

Early in ontogeny :

- **Receptor editing**: if the BCR is specific to a self antigen, L-chain recombination in pre-B cells ➔ change in the specificity of the BCR
- **Clonal deletion**: for B cells that cannot correct the BCR by exchanging L-chain, apoptosis

Before leaving the bone marrow:

- **Anergy**: inactivation of autoreactive B cells

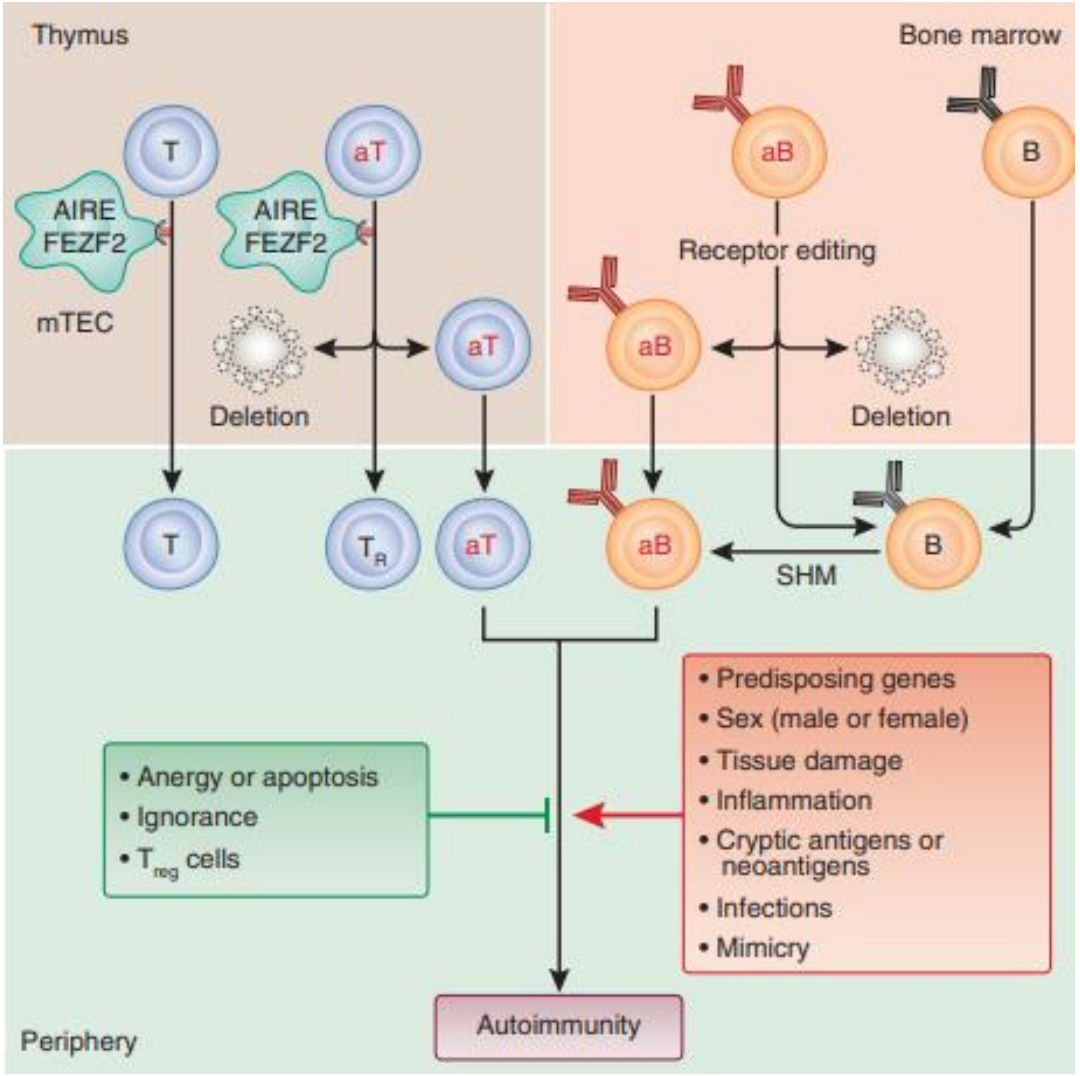


Nemazee, Nat Immunol, 2017

Central tolerance

- Central tolerance is **incomplete**
- Autoreactive B and T cells can egress to the periphery

➔ **Peripheric tolerance needed**



Theofilopoulos, Nat Immunol, 2017

Peripheral tolerance of T cells

- MECHANISMS
  - Anergy
  - Peripheral clonal deletion

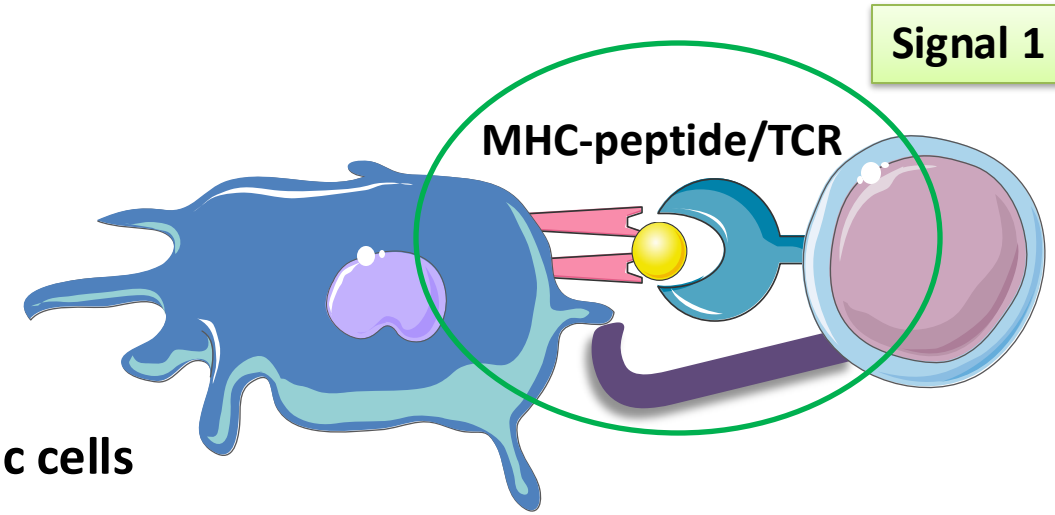
  } **PREVENTION OF T CELL ACTIVATION**

  - Immune privilege
  - Regulatory T cells
  - Immune deviation

  } **CONTROL IMMUNE RESPONSES**

Peripheral tolerance of T cells

ANERGY



Low expression of MHC and costimulatory molecules by DC

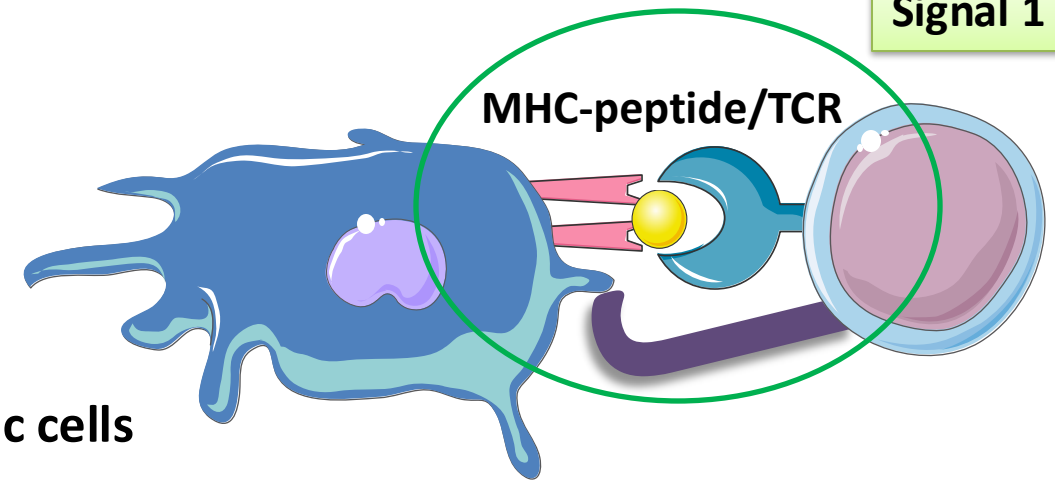
∅ Signal 2

INACTIVATION OF T CELLS = ANERGY

No production of IL-2

Peripheral tolerance of T cells

DELETION/APOPTOSIS



Fas/FasL

Low expression of MHC and costimulatory molecules by DC

∅ Signal 2

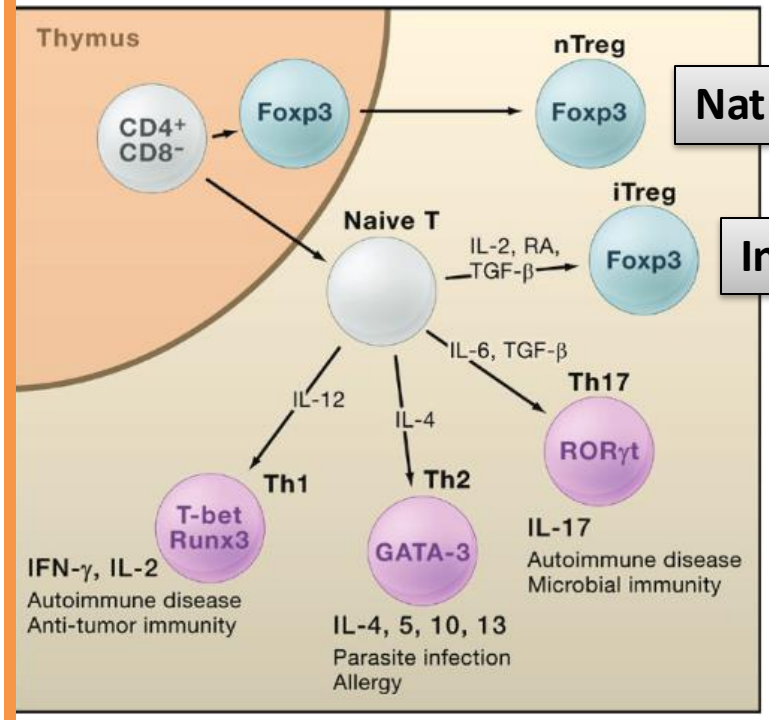
APOPTOSIS OF T CELLS = PERIPHERAL CLONAL DELETION OF T CELLS

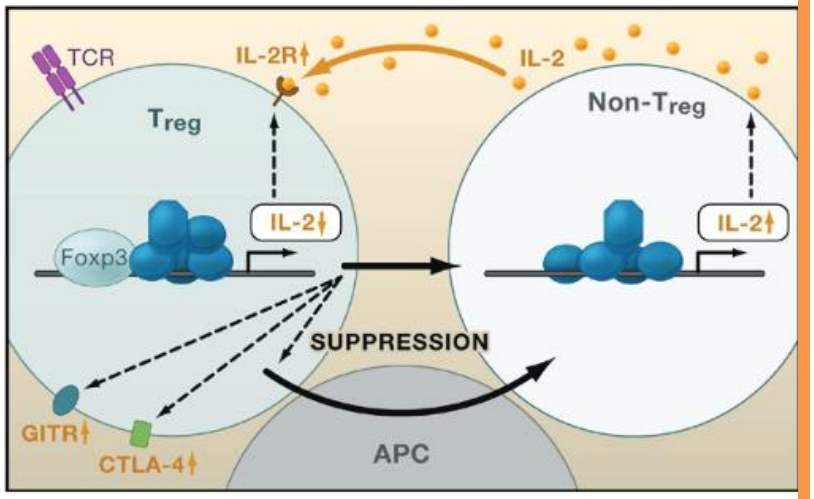
Peripheral tolerance of T cells

- **IMMUNE PRIVILEGE = IGNORANCE**
  - TSAs poorly presented in the thymus
  - Anatomical regions that are less subject to immune responses

Peripheral tolerance of T cells

- **IMMUNE REGULATION = REGULATORY T CELLS**





LT reg : CD4+CD25+ Foxp3+

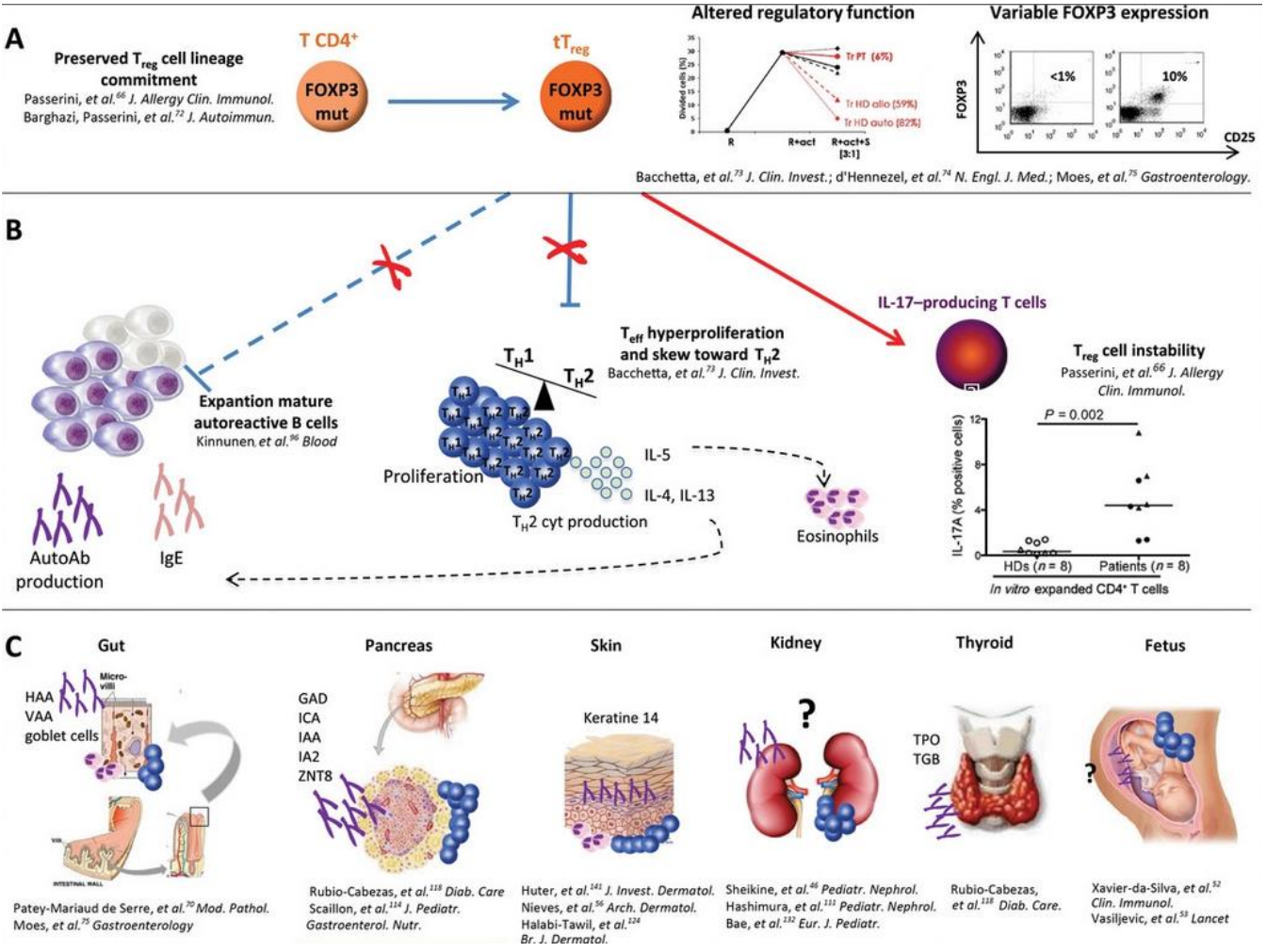
Suppression activity conferred through

- **Inhibitory cytokines (IL-10, TGF-β, IL-35)**
- **Negative costimulatory molecules (CTLA-4..)**
- **Metabolic disruption**
- **Cytolysis of effector T cells (perforine, granzyme)**
- **Competition on DC**

Sakaguchi, Cell, 2008

Peripheral tolerance of T cells

- **IMMUNE REGULATION = REGULATORY T CELLS**



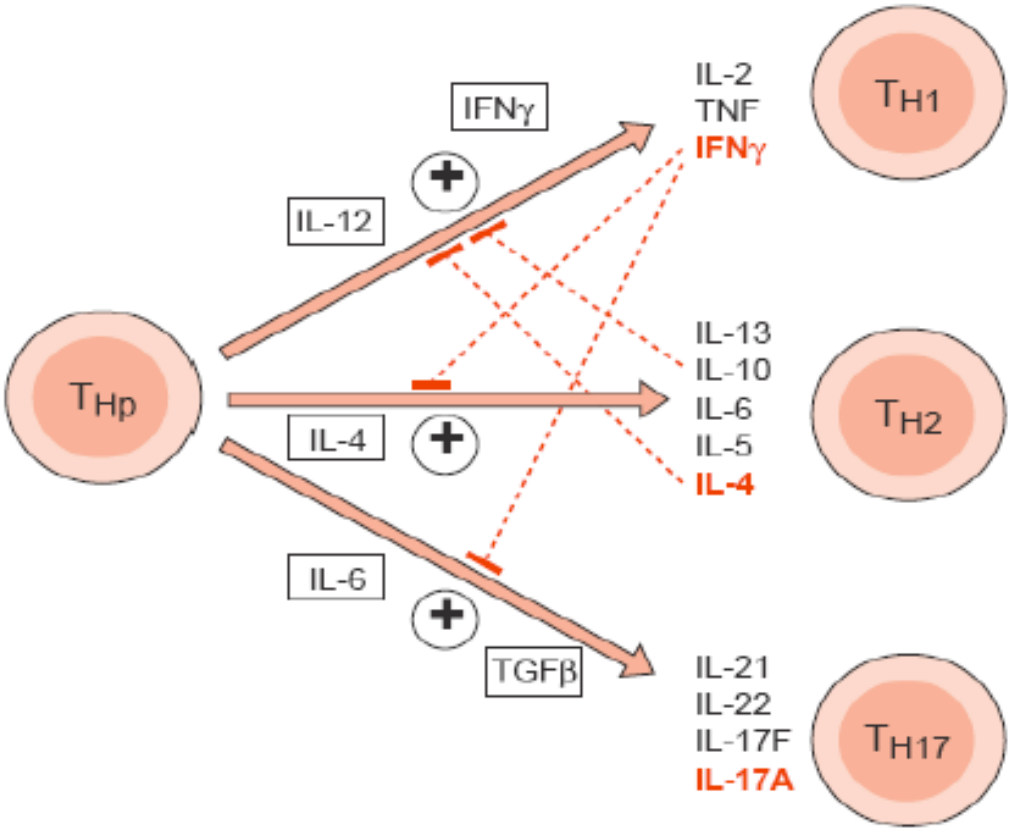
IPEX SYNDROME

- IMMUNE DYSREGULATION, POLYENDOCRINOPATHY, ENTEROPATHY, X-LINKED SYNDROM
- Mutation in FoxP3 gene on X chromosome
- Treg depletion ➔ Effectory T cell hyperproliferation and expansion of mature autoreactive B cells

Peripheral tolerance of T cells

- **IMMUNE DEVIATION**

Modification of cytokine environment
=> Switch in T helper polarization



Peripheral tolerance of B cells

- B cells do not encounter all the self-antigens in the bone marrow
- For self tissue-specific cell surface proteins or secreted self-proteins

- **CLONAL DELETION**
  - If autoreactive B-cells have high affinity for the antigen

  ➔ APOPTOSIS

- **ANERGY**
  - Absence of signal 2 provided by T cells ➔ INACTIVATION

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- Introduction
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- Tolerance breakdown and autoimmunity
- Risk factors
- Autoimmune disorders: two examples
  - Systemic lupus erythematosus
  - Multiple sclerosis

Tolerance breakdown

- Activation of **ignorant** **autoreactive lymphocytes**
- Activation of **anergic** **autoreactive lymphocytes**
- **Apoptosis default** in **autoreactive lymphocytes**
- **Upregulation** of **costimulatory** molecules on APCs
- **Default in regulatory T cells**
- **Dysregulation in cytokine balance**

Sources of auto-Ags?

- Healthy tissues and organs shed low levels of self-components
  - Cells undergo apoptosis (normal turnover process)
- Cross-reactivity: **molecular mimicry** with pathogens
- **Modification** of auto-antigens (mutation, chemical)
- **Tissue damage**
- **Default in clearance** systems

AUTOIMMUNITY RESULTS FROM THE CONJUNCTION OF SEVERAL FACTORS

Tolerance breakdown

- Activation of **ignorant autoreactive lymphocytes**
  - sequestration of peripheral TSAs can be broken by **infectious agents** or other causes of **tissue damage**
  - depends on:
    - The nature and dose of the antigen, the number of exposures
    - The frequency of activated T cells
    - The upregulation of MHC and costimulatory molecules expression in the affected tissues

- Activation of **anergic autoreactive lymphocytes**
  - Reversion under **inflammatory conditions**: infections…
    - Upregulation of **costimulatory molecules** in the presence of **danger signals**
    - **Signal 2** for costimulation **: CD40L/CD40 ; CD28/CD80-CD86**
  - Stimulation by specific antigens

Tolerance breakdown

- **Apoptosis default** in **autoreactive lymphocytes**
  - **Extrinsic apoptosis**
    - **Fas/FasL** and recruitment and activation of caspases
  - **Intrinsic apoptosis**
    - Proapoptotic Bcl-2 family member : **Bim**
  - Both pathways of apoptosis have been linked to **SLE pathophysiology**

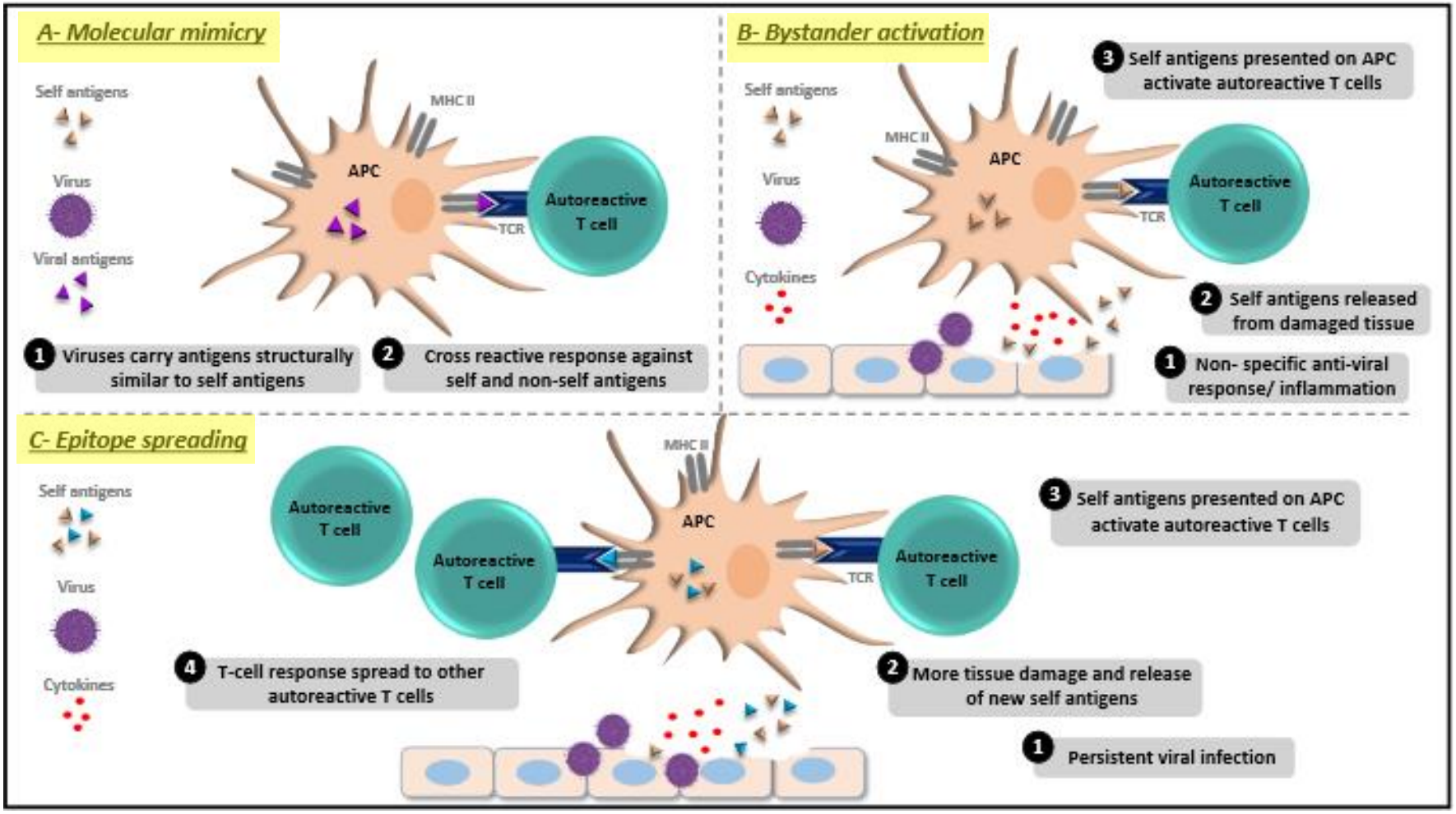
- **Fas mutant mice** develop systemic vasculitis, arthritis, splenomegaly, lymphoproliferation, autoantibodies in the kidney

- **Mice lacking Bim** develop lymphadenopathy, splenomegaly, high amounts of autoantibodies and hypergammaglobulinemia
  - Bim : maintenance of anergic B cells and survival of autoreactive B cells

Hutcheson, Cell, 2008

Tolerance breakdown

CROSS REACTION = MOLECULAR MIMICRY



Smati, Viruses, 2019

Tolerance breakdown

CROSS REACTION = MOLECULAR MIMICRY

TABLE 1. PROPOSED MOLECULAR MIMICRY IN AUTOIMMUNE DISEASES.*

AUTOIMMUNE DISEASE	PROPOSED AUTOANTIGEN	PROPOSED PATHOGEN OR EPITOPE	IMMUNOLOGIC CROSS-REACTIVITY	ANIMAL MODEL†
Type 1 diabetes mellitus[1-8]	GAD65	Coxsackievirus P2-C	T cell (concept controversial in humans)	LCMV–RIP transgenic mouse
Rheumatoid arthritis[9]	HLA-DRB1	40-kd heat-shock protein (dnaJ)	T and B cells	—
Rheumatoid arthritis[10]	Heat-shock protein 60	*Mycobacterium tuberculosis* heat shock protein 65	T and B cells	Adjuvant arthritis (rat)
Multiple sclerosis[11,12]	Myelin basic protein	Multiple viruses	T cell	LCMV–oligodendrocyte transgenic mouse
Spondyloarthropathies[13-17]	HLA-B27	Multiple gram-negative bacterial proteins	B cell	—
Graves' disease[18,19]	Thyrotropin receptor	*Yersinia enterocolitica*	B cell	—

Epstein, NEJM, 1999

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Risk factors

Endogenous risk factors: genetics/epigenetics

Exogenous risk factors: environment

induction *protection*

MULTIFACTORIAL

GENETICS

- >30 genes associated with AI disorders ➔ **polygenic**
- Evidence for **genetic implication**

Concordance rates	Monozygous twins	Dizygous twins
Rheumatoid arthritis	12-32	4-9
Insulin dependent diabetes	30-54	0-13
Multiple sclerosis	9-26	0-4
Crohn's disease	44	4

Deapen, Arthritis Rheum, 1992

Risk factors

GENETICS

- **Association with HLA genes**
  - Capacity of specific HLA alleles to recognize auto-antigens

Spondylarthropathy

HLA-B27: 8% healthy / 90 à 95% ankylosing spondylitis

Rheumatoid arthritis

HLA-DRB1: 28% healthy / 70% RA

Insulino-dependent diabetes

HLA-DR3 or 4: 40% healthy / 95% diabetes

Celiac disease

HLA-DR3-DQ2: 30% healthy / 90% celiac

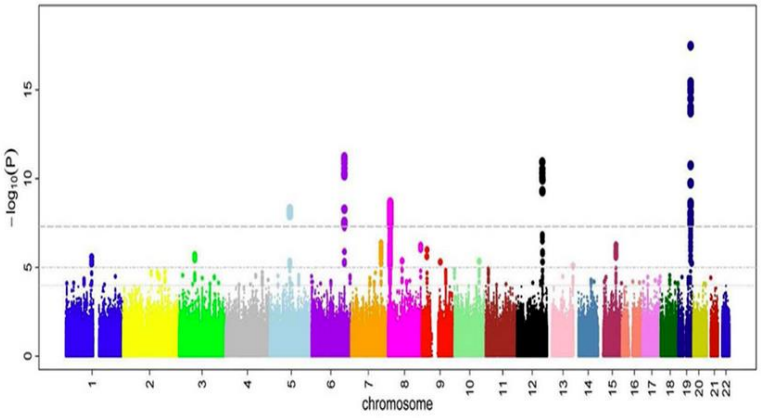
Multiple sclerosis

HLA-DR2-Dw2: North Europe, American black people

HLA-DR6: Japan and Mexico

Risk factors

GENETICS



GWAS studies

Complement genes

C1q, C2, C4 deficiency are associated with **SLE**

Co-stimulatory pathways

CTLA-4, CD28, ICOS, CD80

Association with **T1D, Graves' disease, RA, SLE**

T-cell signalling and activation

Ex PTPN22

*A*ssociated with **T1D, SLE, Graves' disease, and RA**

TNF-receptor pathways

Upregulation of TNFα-receptor signaling ➔ **inflammatory diseases**

CD, RA, SLE, T1DM…

FcR receptors genes

Decrease in opsonisation of immune complexes

Cytokines genes

IL1RL1 (CD, IBD), **IL2** (T1DM, CD), **IL6** (RA)…

Marson, JCI, 2015

Zhernakova, Nature Review 2013

Risk factors

INFLUENCE OF SEXUAL HORMONES

- **Prevalence of autoimmune disorders in women**
- **Implication of steroids regulatory genes**
- **SLE**
  - High prevalence during reproductive life
  - Triggering of contraceptive pills or pregnancy
  - Disease activity decreases after menopause
- **Multiple sclerosis**
  - First clinical signs after puberty
  - Disease activity decreases during pregnancy
  - Exacerbations after pregnancy

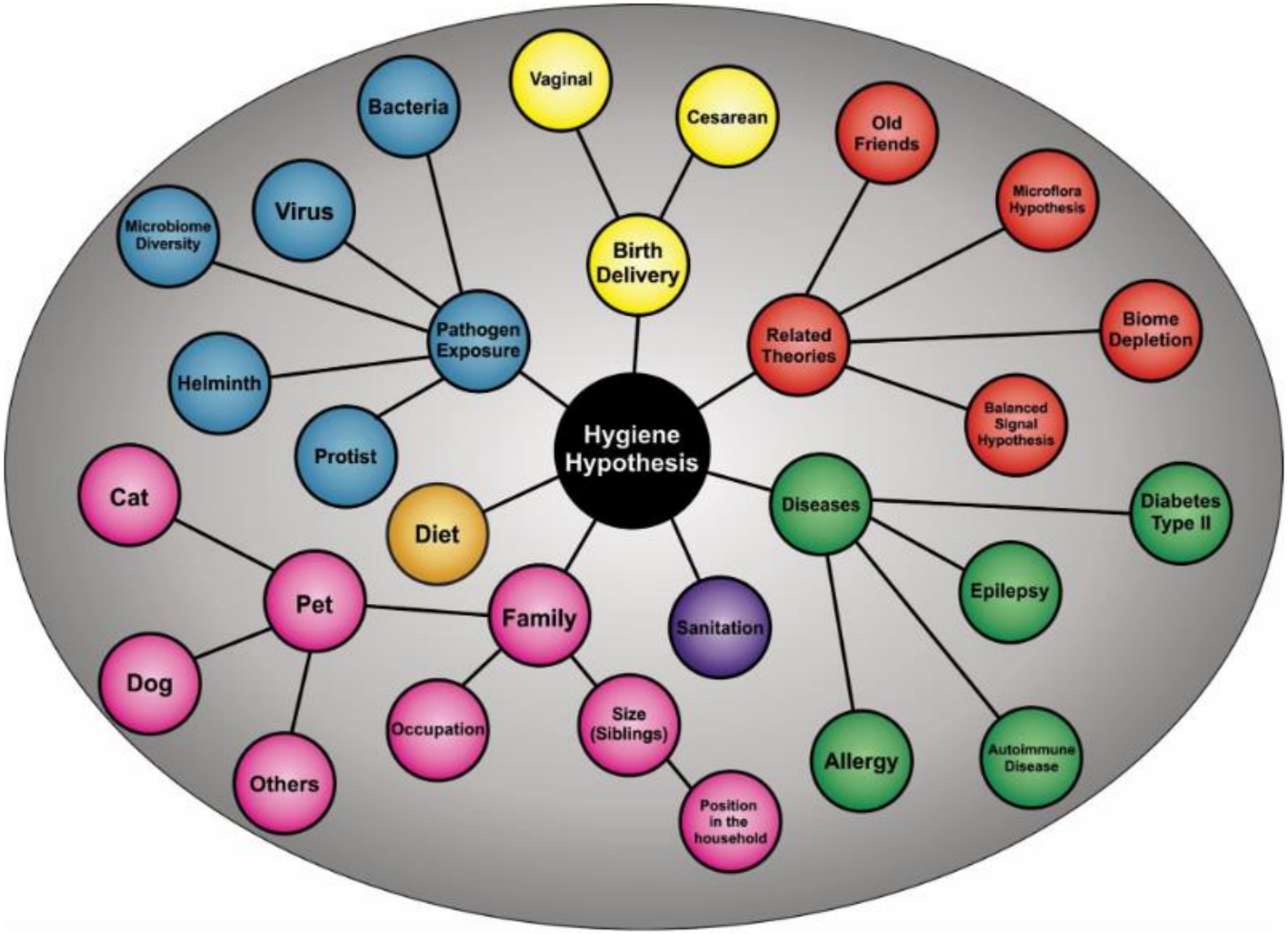
Female to male ratio reported for autoimmune diseases. Diseases in which a male predominance is observed are italicized.

Autoimmune disease	Female:male ratio
Addison's disease [1–5]	0.8–2.4
Antiphospholipid antibody syndrome [1–4]	5
Autoimmune chronic hepatitis [4–19]	7
Giant cell arteritis [1–5]	2.5
Graves' disease [33]	7
Hashimoto's disease [33]	5–18
Idiopathic thrombocytopenic purpura [1–5]	3
Multiple sclerosis [73]	2
Myasthenia gravis [1–4]	3
Myositis [1–5]	2
Pernicious anemia [1–5]	2
Primary biliary cirrhosis [90]	10
Primary sclerosing cholangitis [1–19]	*0.6*
Rheumatoid arthritis [30]	2
Sjogren's syndrome [1–5]	9
Systemic lupus erythematosus [73]	9
Systemic sclerosis [3–26]	5
Type 1 diabetes [4–31]	*0.8–1.2*

Selmi, Autoimmunity reviews, 2012

Risk factors

ENVIRONMENT : HYGIENE HYPOTHESIS



Risk factors

ENVIRONMENT : HYGIENE HYPOTHESIS

- **Role of the gut microbiome**
  - western lifestyle
    - **limits the exposure** to microbial organisms
    - modifies the colonization of children's gastrointestinal tract
    - increases the probability of allergic and autoimmune diseases development due to an **immature immune system "Missing immune deviation"**
  - Colonizing germ-free mice with various intestinal bacteria can reduce type I diabetes in NOD-MyD88-negative mice *(Burrows, 2015).* Mechanisms?

- **Role of helminth infections**
  - **Inverse relation** between **prevalence of helminth infections** and **autoimmune diseases**
  - **Th2 polarization of T cells** : **modulating role on Th1 and Th17** responses that are exacerbated in autoimmune and autoinflammatory disorders

- **Hypothesis still debated**

Alexandre-Silva, Acta Trop, 2018

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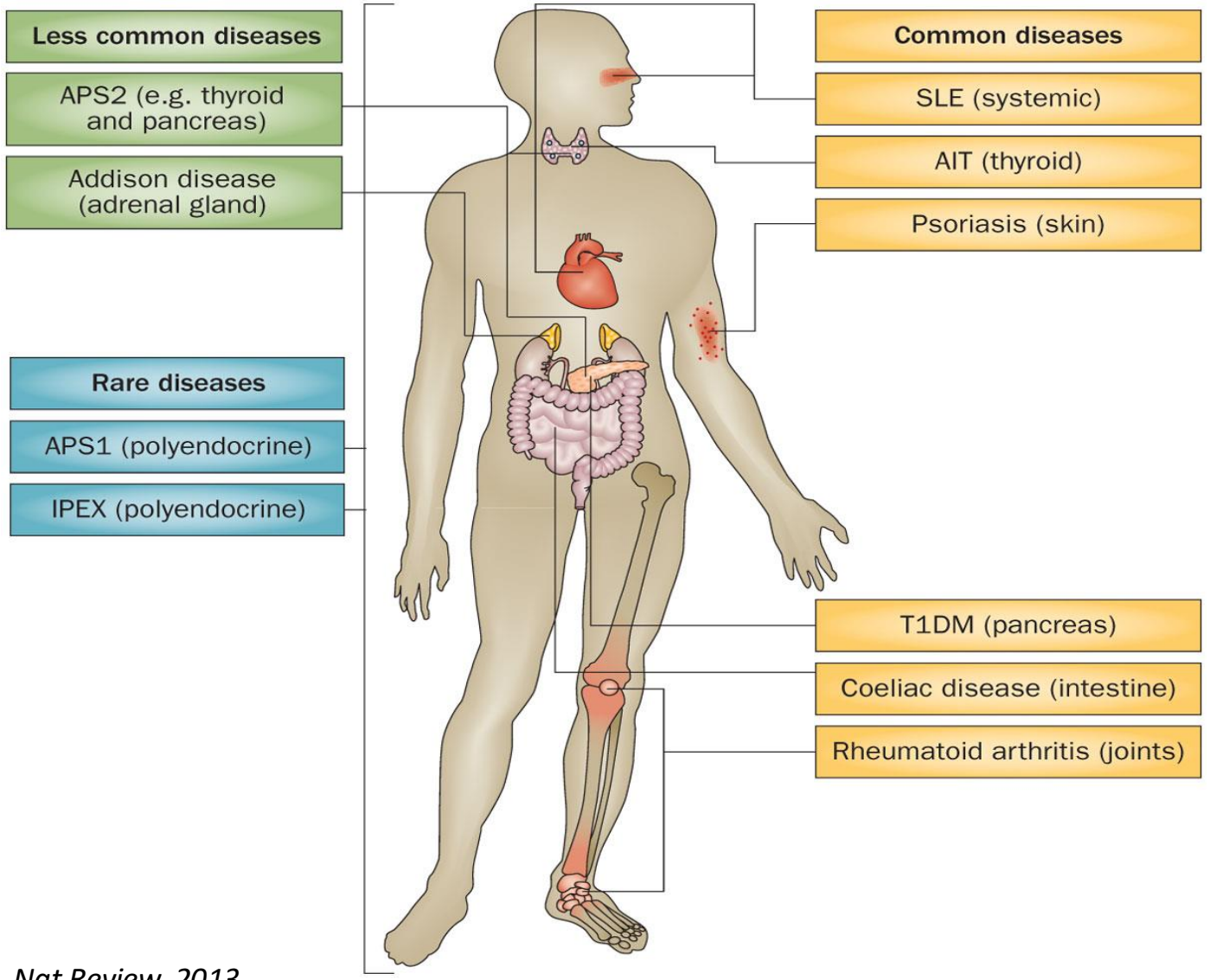
Autoimmune diseases

CLASSIFICATION ON THE FREQUENCY AND THE AFFECTED ORGANS



Zhernakova, Nat Review, 2013

Autoimmune diseases

NON-ORGAN SPECIFIC DISORDERS

Auto-antigen present in multiple organs

CONNECTIVE TISSUE DISEASES

Common clinical symptoms : arthralgy, fever, cutaneous symptoms

- **Systemic lupus erythematosus**
- **Rheumatoid arthritis**
- **Antiphospholipids syndrome**
- **Systemic sclerosis**
- **Sjögren's syndrome**
- **Myositis**

VASCULITIS

Blood vessels damage

- **ANCA-associated vasculitis**
  - Microscopic polyangeitis
  - Granulomatosis with polyangeitis (ex Wegener)

ORGAN SPECIFIC DISORDERS

Target of auto-antibodies localized in one organ

Target	Disease	Autoantigenes
Thyroid	Hashimoto's disease Grave's disease	TG, TPO, TSH receptor
Intestin	Celiac disease Crohn's disease	Gliadin, transglutaminase, endomysium Microbiota
Liver	Autoimmune hepatitis Primary biliary cholangitis	LKM1, actin, type 2 mitochondria
Pancreas	T1 diabetes	GAD, IA2, β islets of Langerhans
Skin	Bullous pemphigoid Pemphigus vulgaris	BP180, BP230 Desmoglein
Stomach	Autoimmune gastritis	Parietal cells, IF
PNS	Autoimmune neuropathy	MAG, ganglioside
CNS	Multiple sclerosis	Myelin
Muscles	Myasthenia	Acetylcholin receptor
Red blood cells	Heamolytic anemia	Red blood cells

Autoimmune diseases

DIFFERENT MECHANISMS OF PATHOGENY

- **Autoantibodies**
  - Activating/blocking
    - TSH receptor: Graves' disease
    - Acetylcholine receptor: myasthenia
  - Haemolytic: autoimmune anemia
- **Immune complexes**: SLE
- **CD4 T cells**
  - Infiltration of thyroid: Hashimoto's disease
  - Myelin auto-reactive CD4 T cells in multiple sclerosis
- **Cytokines**
  - TNFα in Crohn's disease and rheumatoid arthritis

Autoimmune diseases

DIFFERENT MECHANISMS OF PATHOGENY

- **Autoantibodies**
  - Activating/blocking
    - TSH receptor: Graves' disease
    - Acetylcholine receptor: myasthenia
  - Haemolytic: autoimmune anemia

- **Immune complexes**: SLE

- **CD4 T cells**
  - Infiltration of thyroid : Hashimoto's disease
  - Myelin auto-reactive CD4 T cells in multiple sclerosis

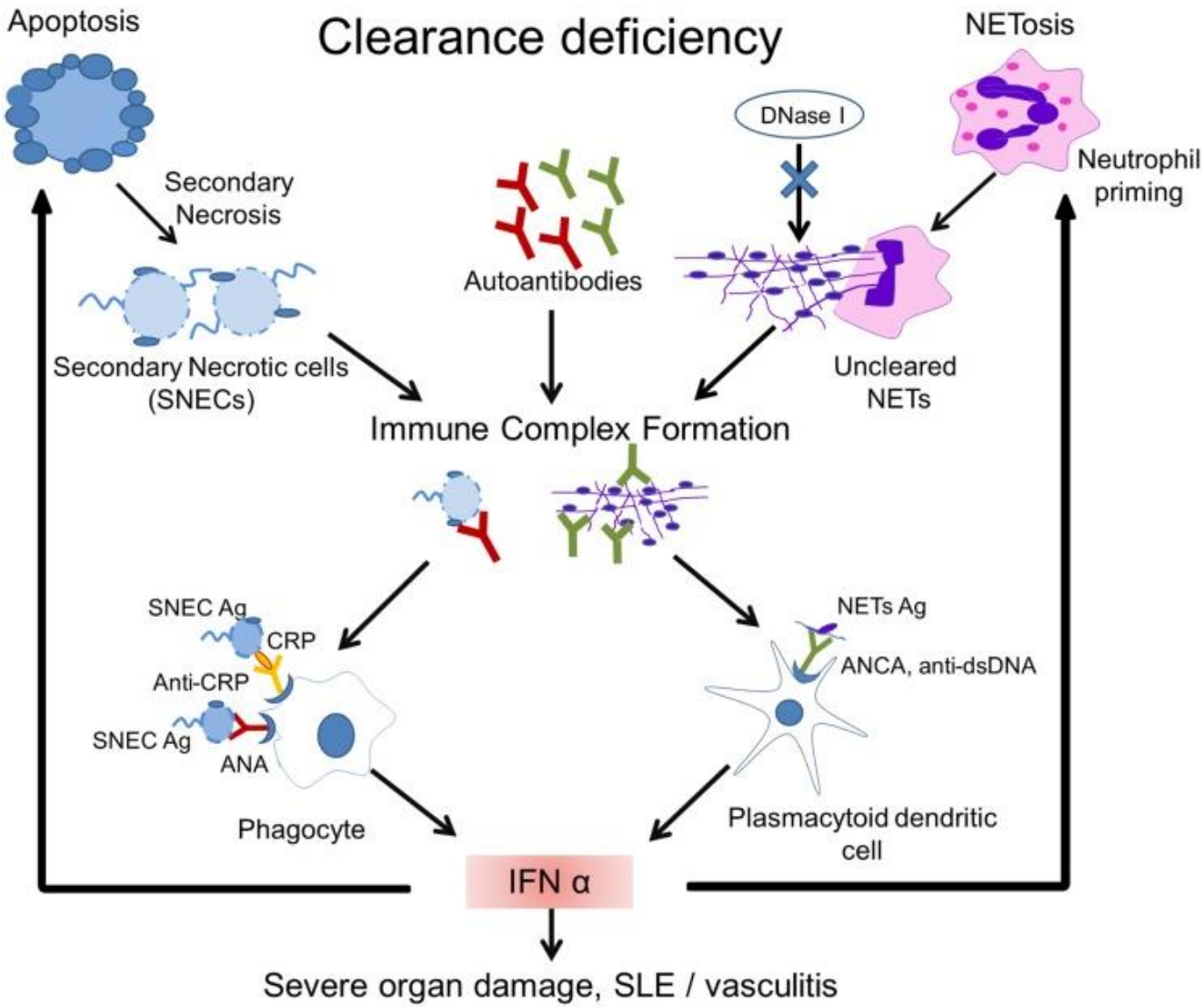
- **Cytokines**
  - TNFα in Crohn's disease and rheumatoid arthritis

Systemic lupus erythematosus

- **Non-organ specific connective** tissue disease
- Fever, weakness, arthritis, skin rashes, pleurisy, and kidney dysfunction
- **Polymorphic**
- Sex ratio **9W**/1M
- Incidence: **20-30** year old

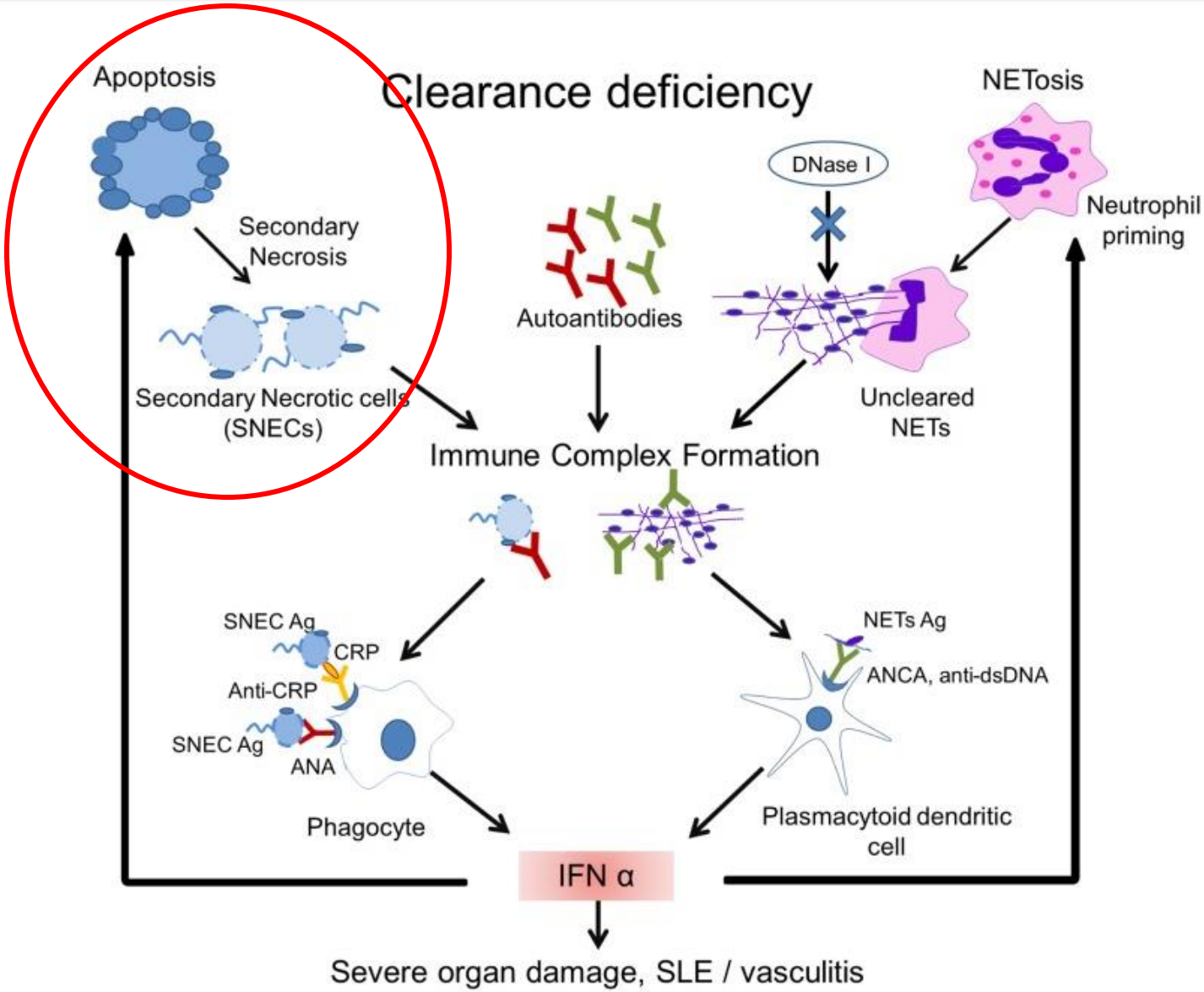
CLINICAL SYMPTOMS AND DIAGNOSIS

Systemic lupus erythematosus



Mahajan, Front Immunol, 2016

Systemic lupus erythematosus



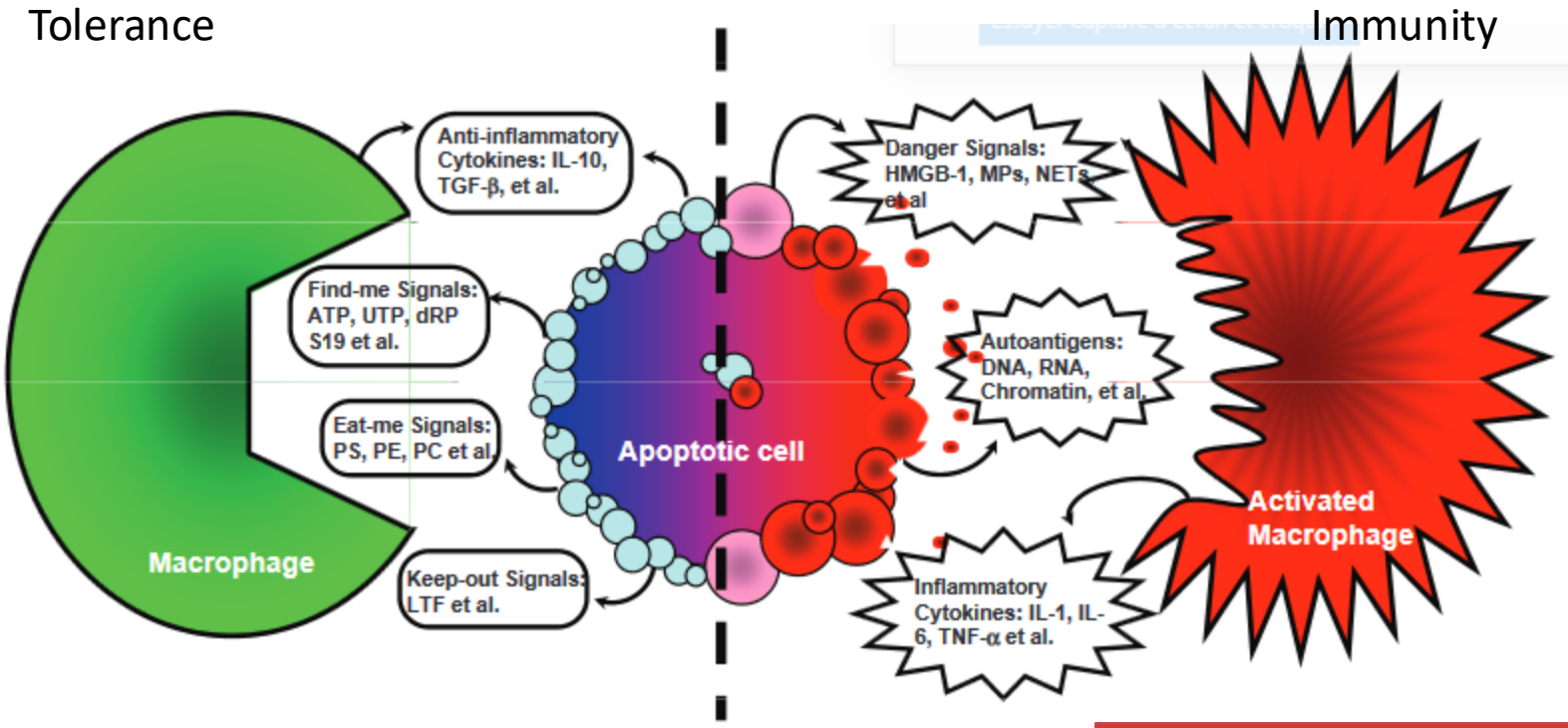
Mahajan, Front Immunol, 2016

Systemic lupus erythematosus

APOPTOTIC CELLS ARE THE MAIN SOURCE OF AUTO-AG

- **Excessive apoptosis**
- **Default** in cellular components **clearance**
  - Mutations in **C1q, C2, C4** associated with SLE
  - Mice KO for **c-Mer, MFG-E8, SAP, TIM-4** develop SLE
- **Activation of TLR and FcγR** on macrophages and DC ➔ TNF-α, IL-8 secretion
- **Presentation of auto-Ag** by DC to **autoreactive B and T cells**
- Reaction against self-antigens is promoted by
  - the **inflammatory environment: IFNα, TNFα, IL-17**
  - the formation of **neoepitopes** (post-translational modifications)

Systemic lupus erythematosus



Later apoptotic cells

- **loss of membrane integrity**
- **release of danger signals**
- **Modified auto-antigens**

Inflammatory clearance of apoptotic cells

- **Inflammatory stimuli**
- **Breakdown of tolerance**

Systemic lupus erythematosus

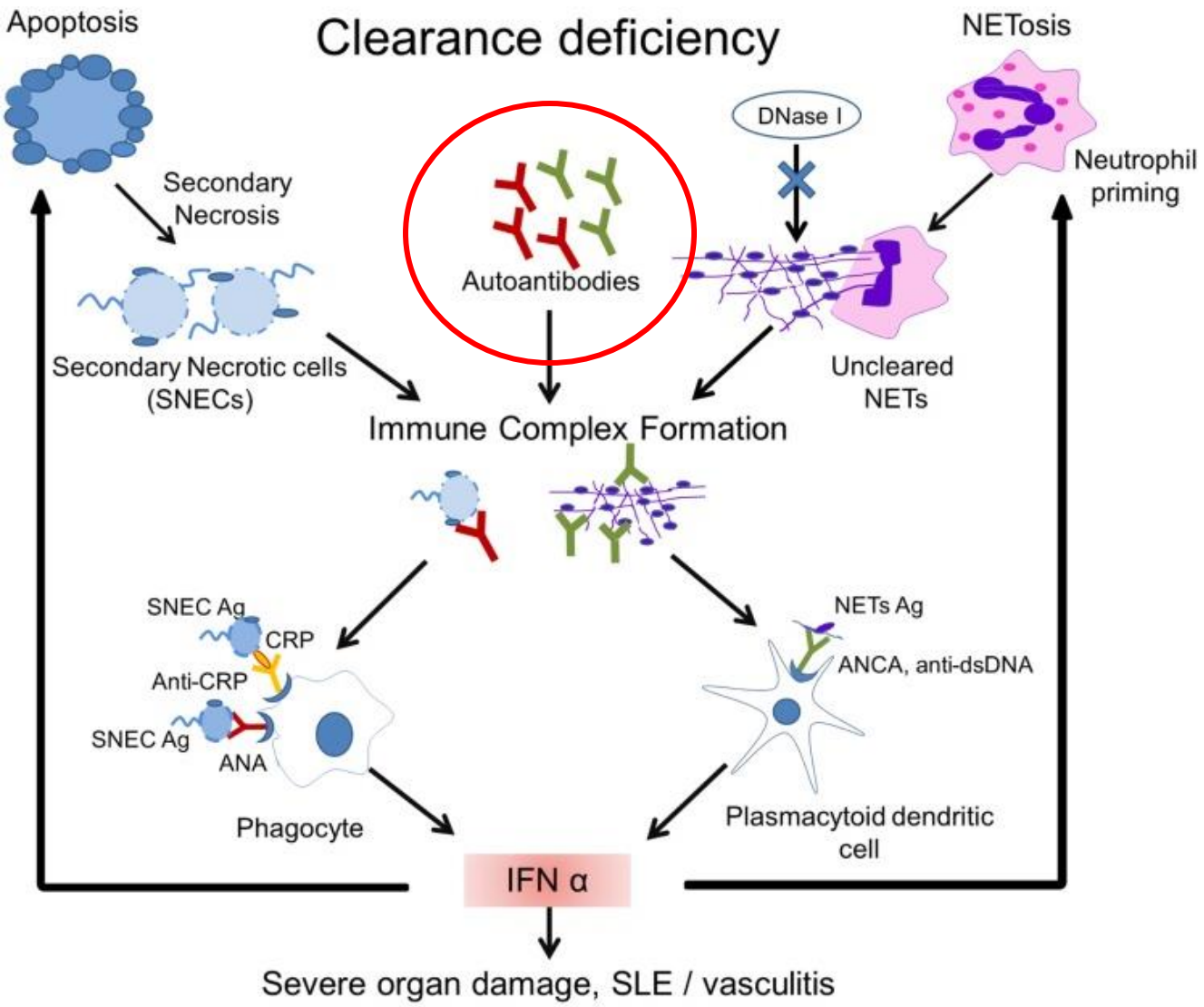
Sources of auto-Ag

- **UV light**: keratinocytes destruction → increase of apoptotic cells
- **Viruses** (EBV): molecular mimicry between SSA/Sm and EBNA-1

Other factors influencing lupus

- **Estrogens**: stimulation of B and T lymphocytes through ERα
- **Silicium**: polyclonal activation of immune system
- **Drugs**: hydralazine and procainamide inhibitof DNA methylation → favor lupus

Systemic lupus erythematosus

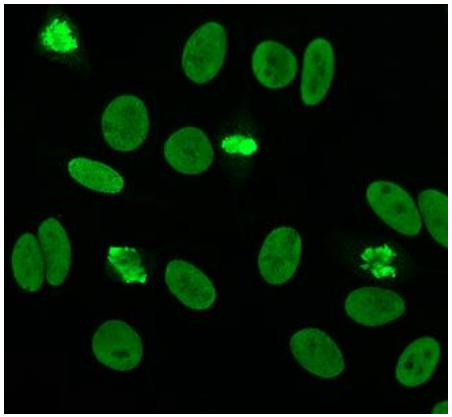


Mahajan, Front Immunol, 2016

Systemic lupus erythematosus

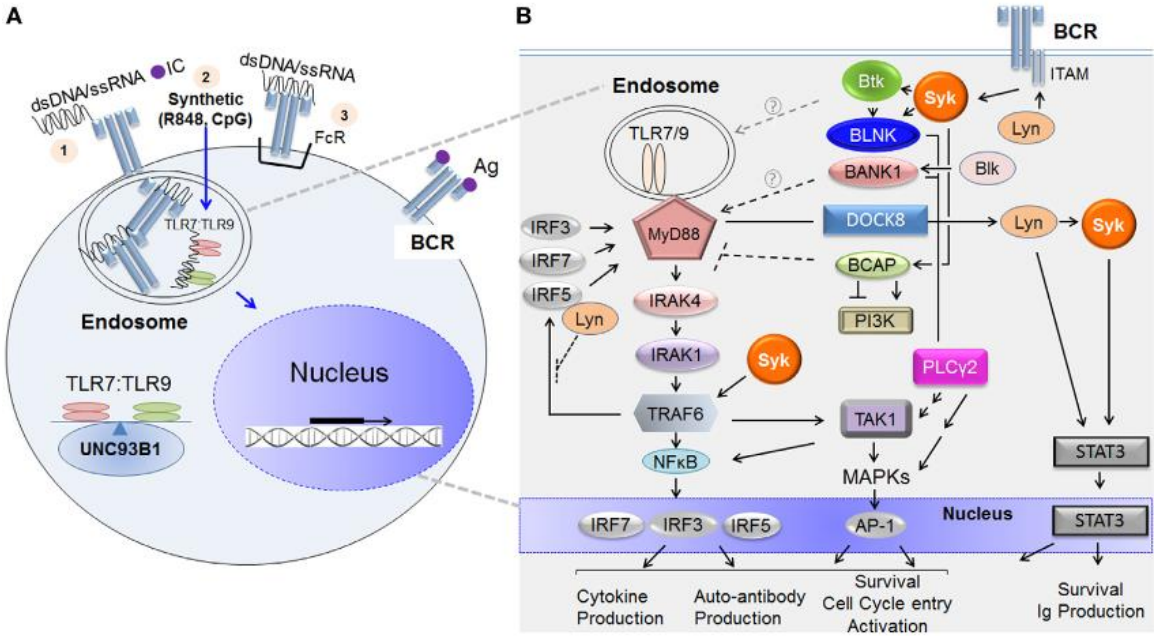
Antinuclear antibodies

- Present in **all SLE patients**
- Antibodies **against chromatin** and its **constituants**
  - **dbDNA, sbDNA, RNA, histone, nucleosome**
- Antibodies against **soluble nuclear antigens**
  - **SSA, SSB, Sm, RNP**



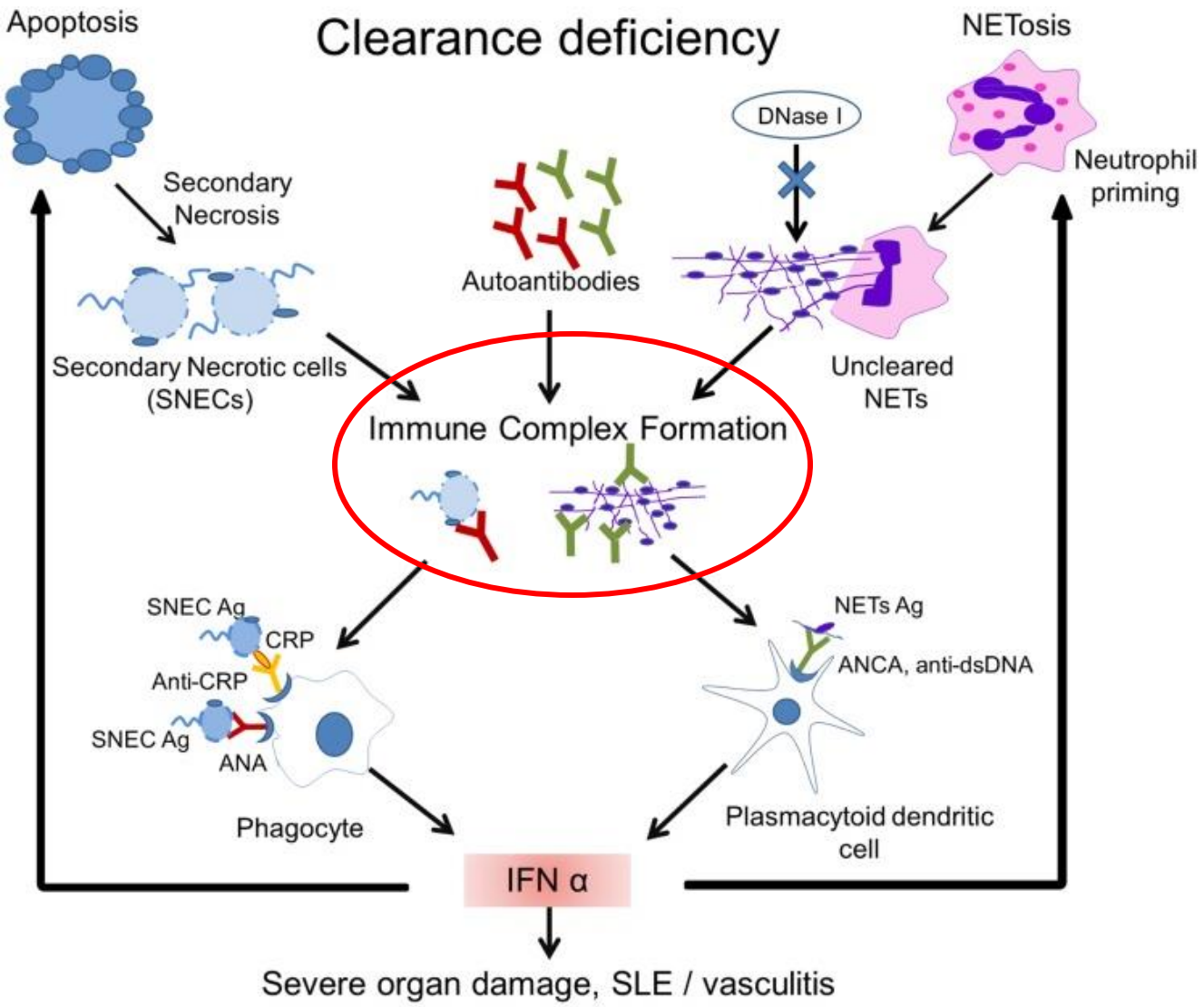
Central role for B cells

- **Hyperactivation of B cells**
  - Activation by **excess of auto-Ag**
  - Increased **BLyS** production
  - → increased B cell survival
- Co-engagement of **TLR and BCR**
  - **T cell-independent activation**
- Production of **cytokines**
  - **IL-4, IL-6, IL-10, TNF-α**



Suthers, Front Immunol, 2017

Systemic lupus erythematosus

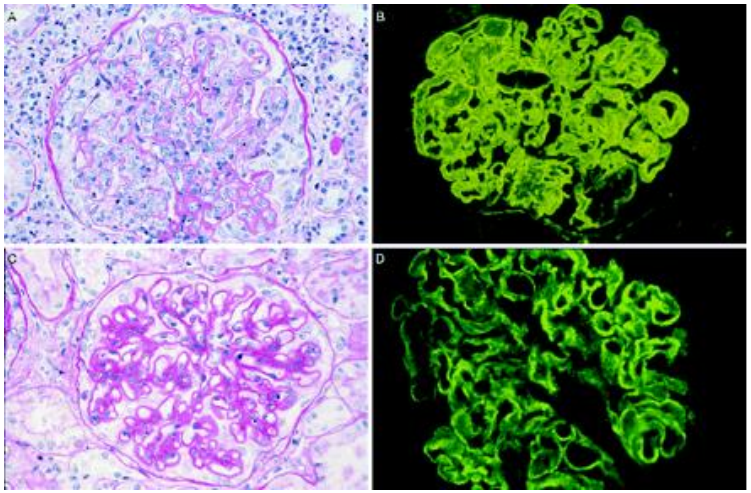


Mahajan, Front Immunol, 2016

Systemic lupus erythematosus

TISSULAR LESIONS

- **Immune complexe formation**
  - Complement activation and inflammation
  - Deposition of IC in tissues (glomerulonephritis++, vasculitis)
  - Accumulation of C3a and C5a: inflammation and leucocyte recruitment

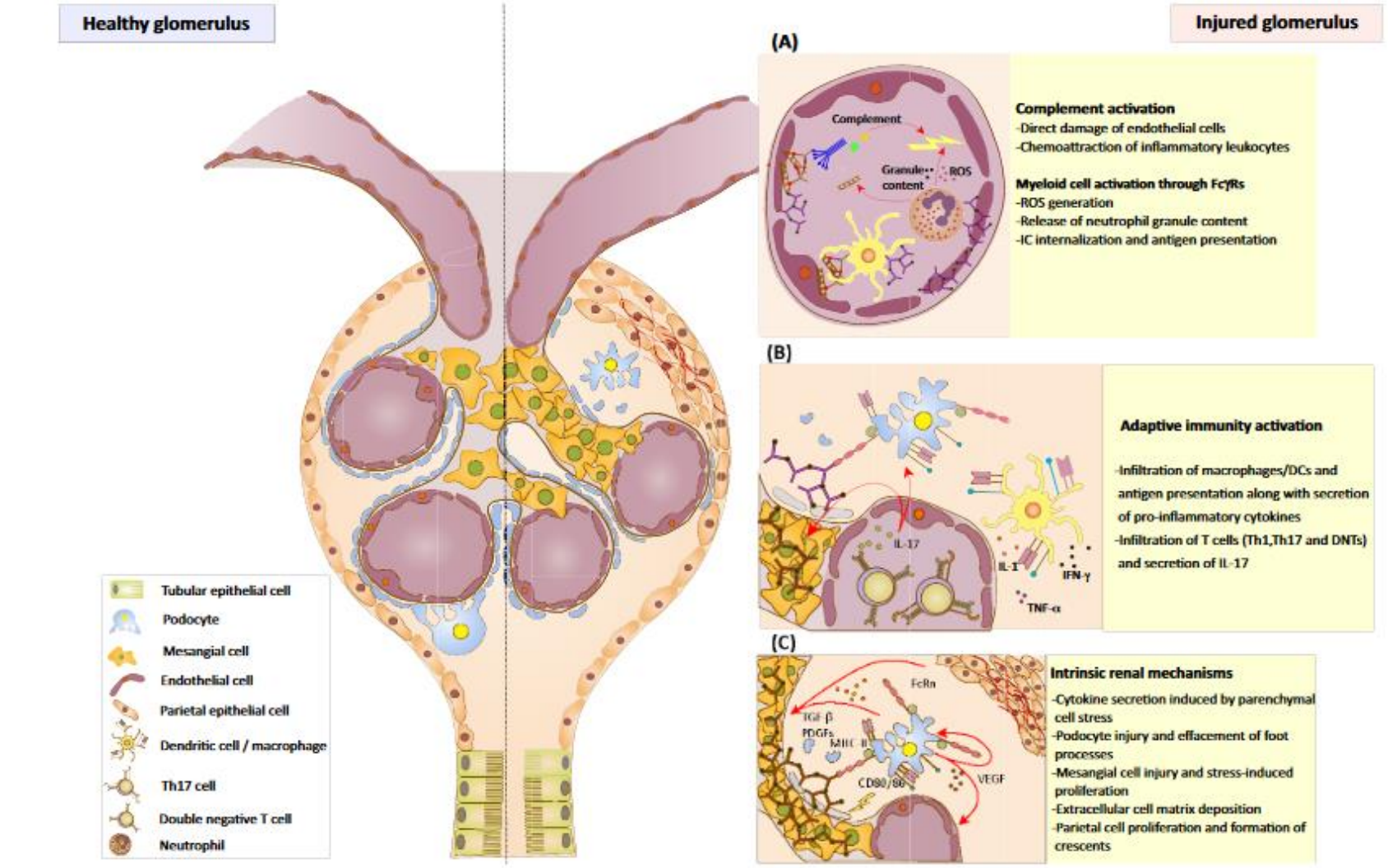


Stewart Cameron, JASN, 1999

- **Direct action of auto-Abs**
  - Anti-NMDA receptor: neuropsychiatric manifestations
  - Anti-RBC, anti-platelets… : anemia, thrombocytemia…

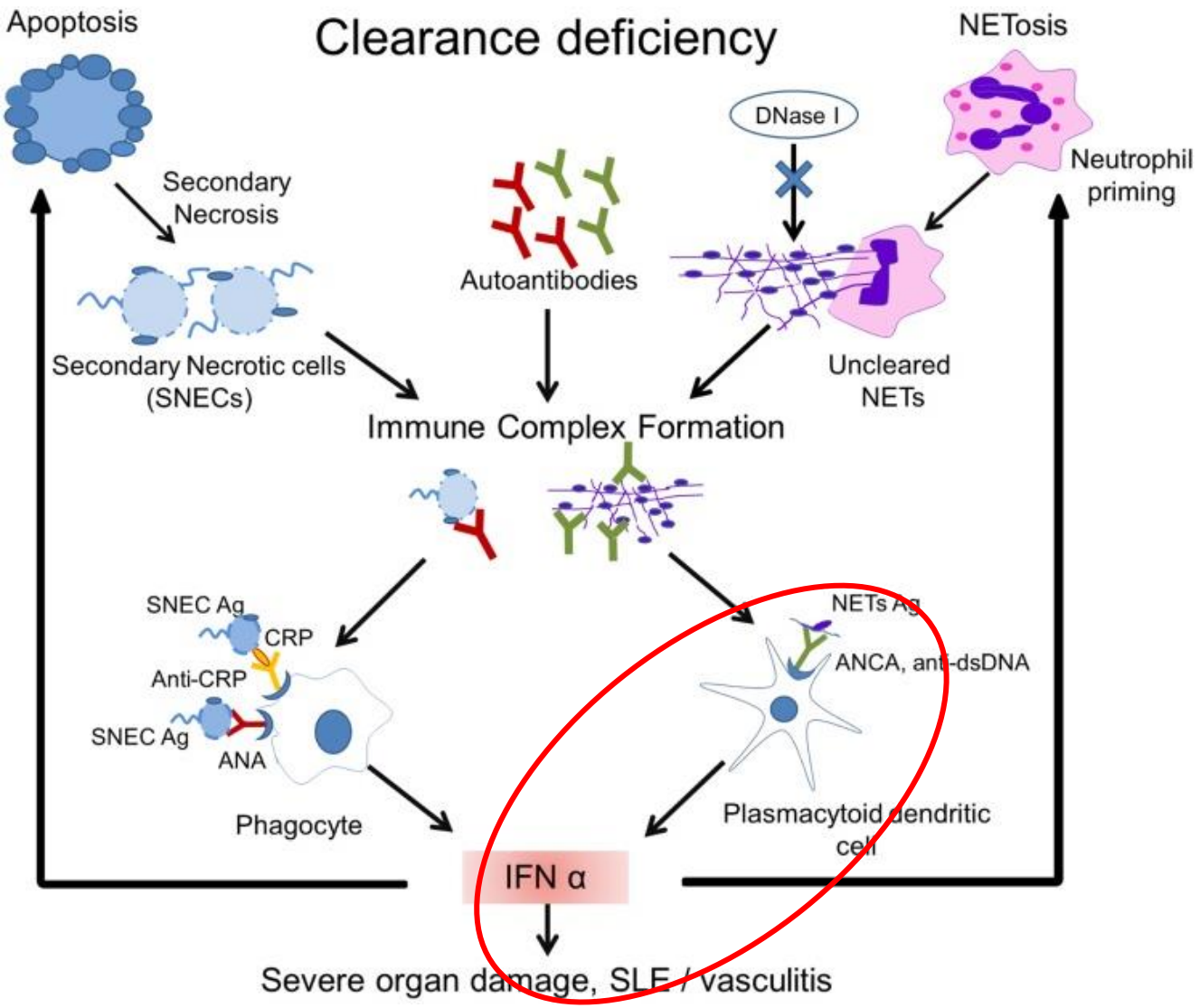
Systemic lupus erythematosus

TISSU LESIONS



Flores Mendoza, Trends in Mol Med, 2018

Systemic lupus erythematosus



Mahajan, Front Immunol, 2016

Systemic lupus erythematosus

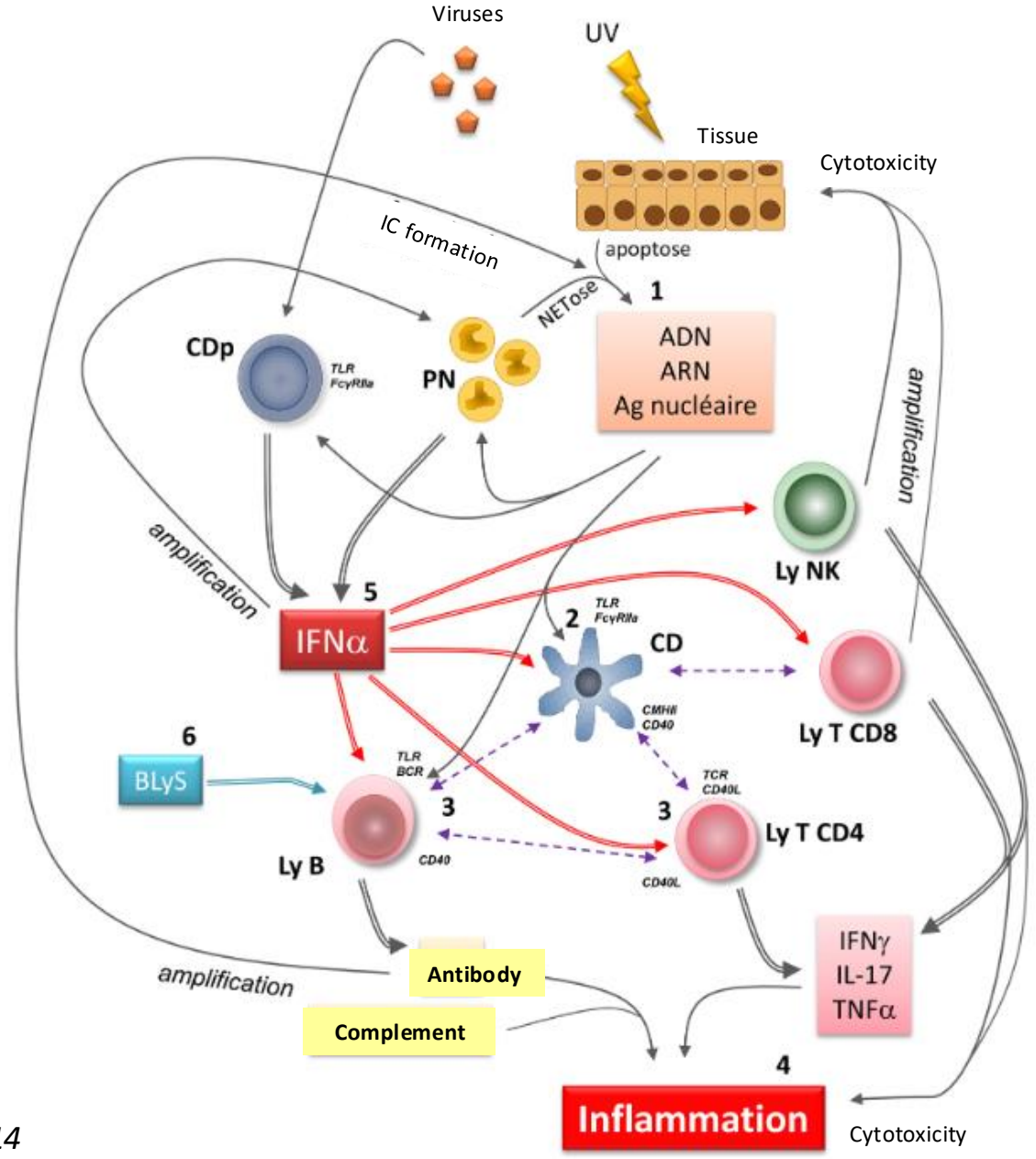
Dendritic cells and IFNα

- **pDC: major source of IFNα**
  - Stimulation by TLR7/9 and FcγR by IC or viruses (EBV)
  - Under the dependence of estrogens
- **Excessive production of IFNα in SLE**
  - Genetics
  - Viral infections
  - Immune complexes and nucleic acids
- **Activation of DC, B, T and NK cells**
  - Major role in activation, proliferation, differentiation and production of auto-Ab by B cells

Amplification loop!

Systemic lupus erythematosus

TO SUM UP

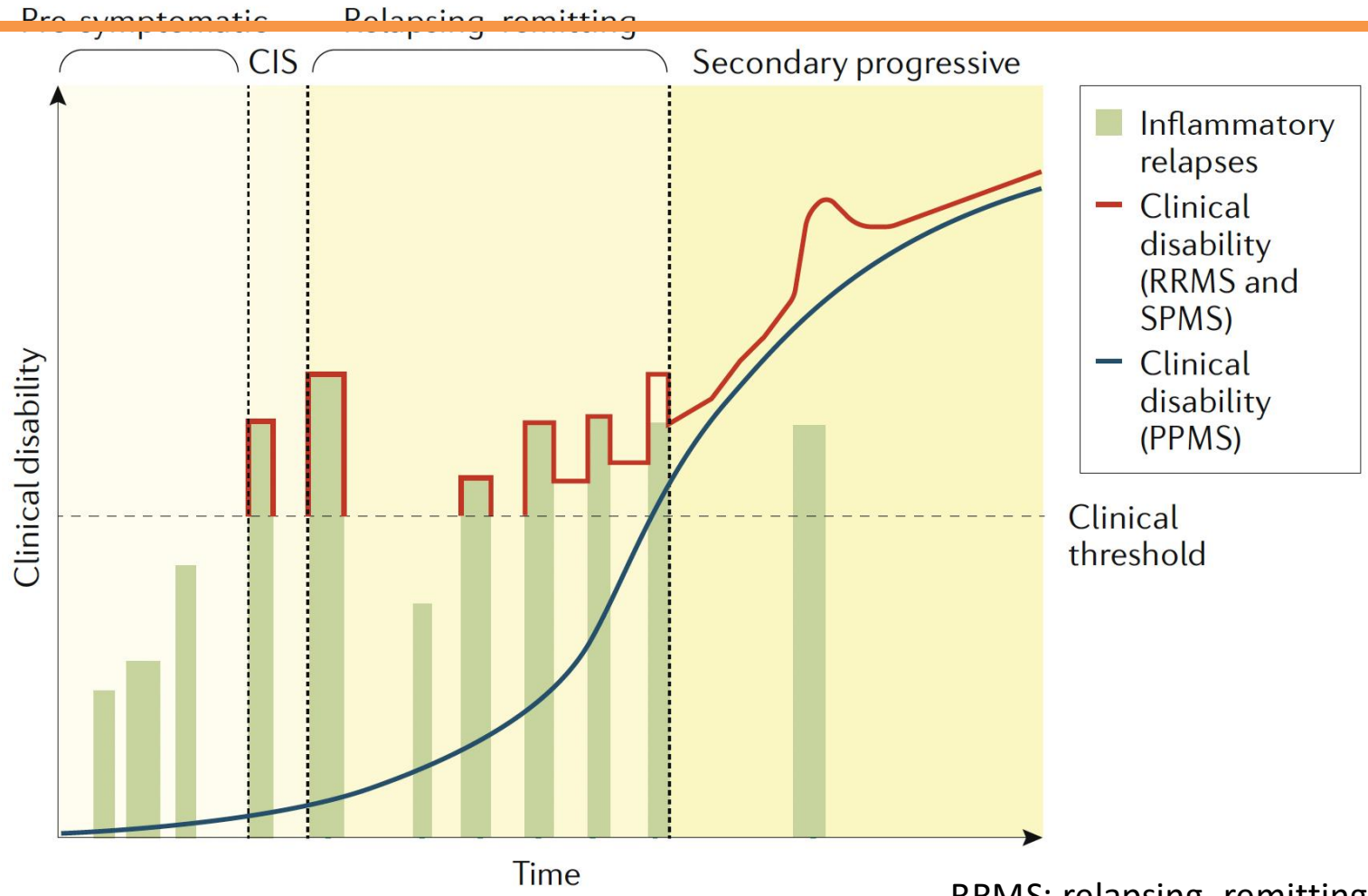


Mathian, Rev Med Int, 2014

Multiple sclerosis (MS)

- **Organ-specific** disease
- Chronic **inflammatory, demyelinating** and **neurodegenerative disease of the central nervous system** – primary cause of non-traumatic disability in young adults
- **Heterogeneous** and **multifactorial**
- **2.8 million people have MS worldwide in 2020**
- Sex ratio **2W**/1M
- Incidence: **20-35** year-old

Multiple sclerosis

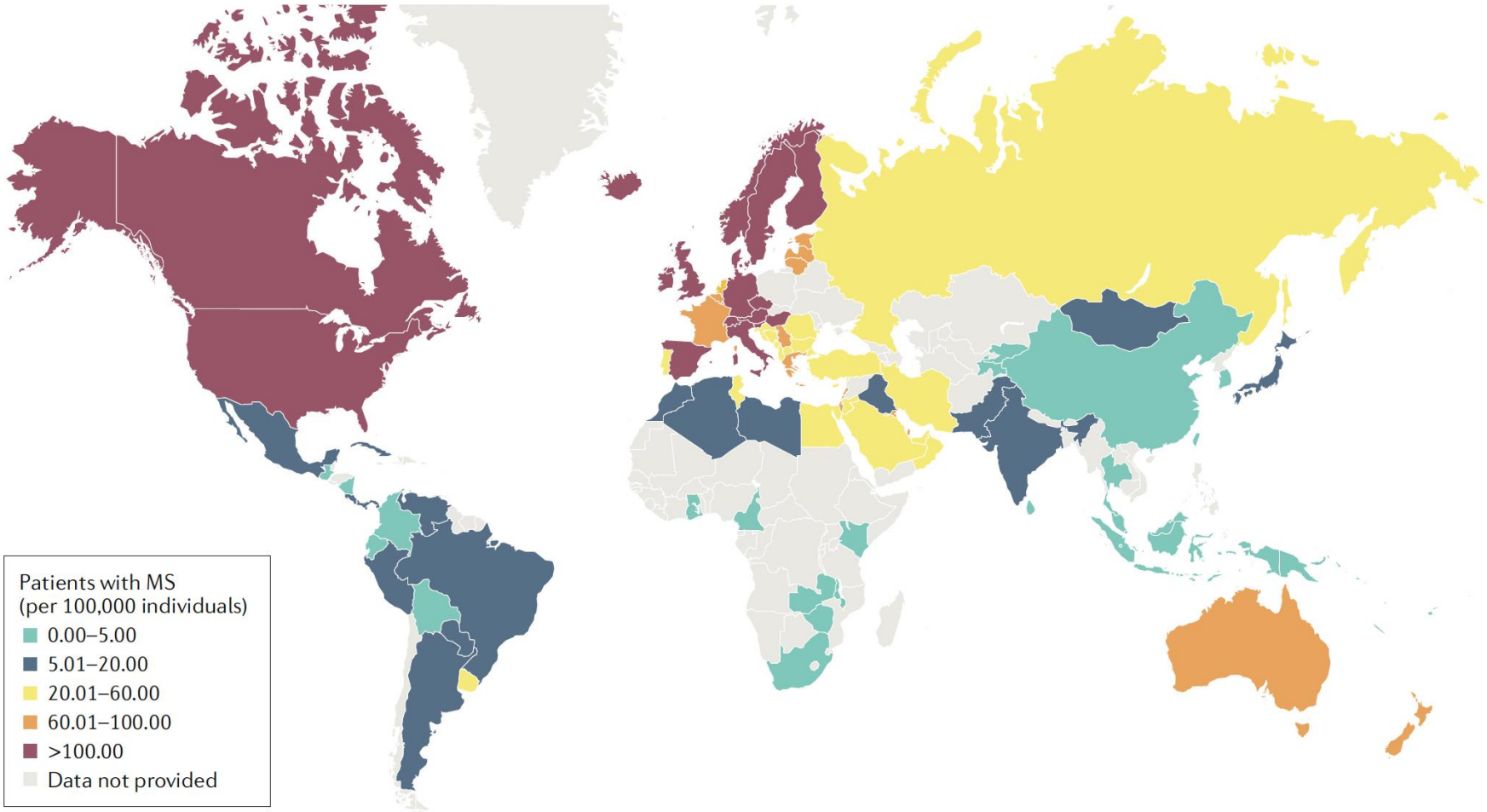


Most common disease type RRMS (~85%)

RRMS: relapsing–remitting MS
SPMS: secondary progressive MS
PPMS : primary progressive MS
CIS: clinically isolated syndrome

Filippi et al, Nat Rev Disease Primers, 2018

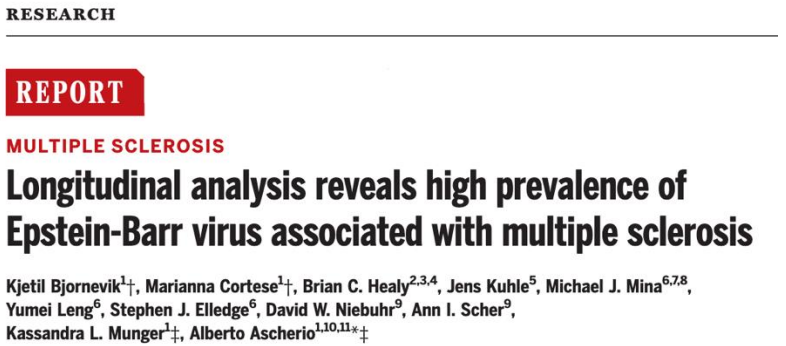
Worldwide prevalence of MS (2013)



Filippi et al, Nat Rev Disease Primers, 2018

Risk factors of MS

- **Lifestyle and environmental risk factors:**
  - Smoking, vitamin D level <50 mM, adolescent obesity, night work
  - **EBV infection,** CMV infection



RESEARCH

REPORT

MULTIPLE SCLEROSIS

Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

Kjetil Bjornevik[1]†, Marianna Cortese[1]†, Brian C. Healy[2,3,4], Jens Kuhle[5], Michael J. Mina[6,7,8], Yumei Leng[6], Stephen J. Elledge[6], David W. Niebuhr[9], Ann I. Scher[9], Kassandra L. Munger[1]‡, Alberto Ascherio[1,10,11]*‡

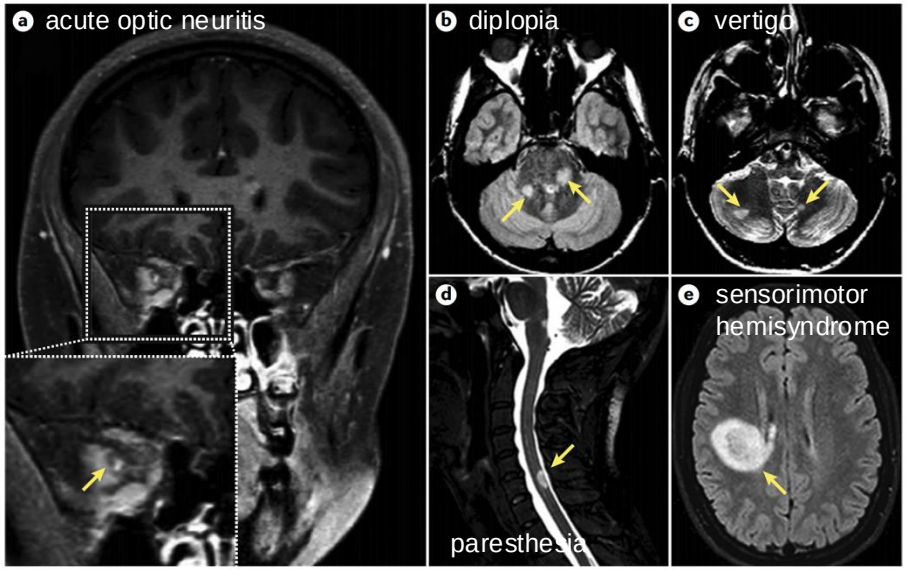
- **Genetic factors:**
  - HLA (increased risk with HLA-DRB1*15:01; HLA-A*02 allele protective), TNF, IL2 and IL7R polymorphisms
  - genes with functions in the nervous system (MANBA and GALC)
  - genes involved in vitamin D metabolism (GC and CYP24A1)

Filippi et al, Nat Rev Disease Primers, 2018

MS pathophysiology

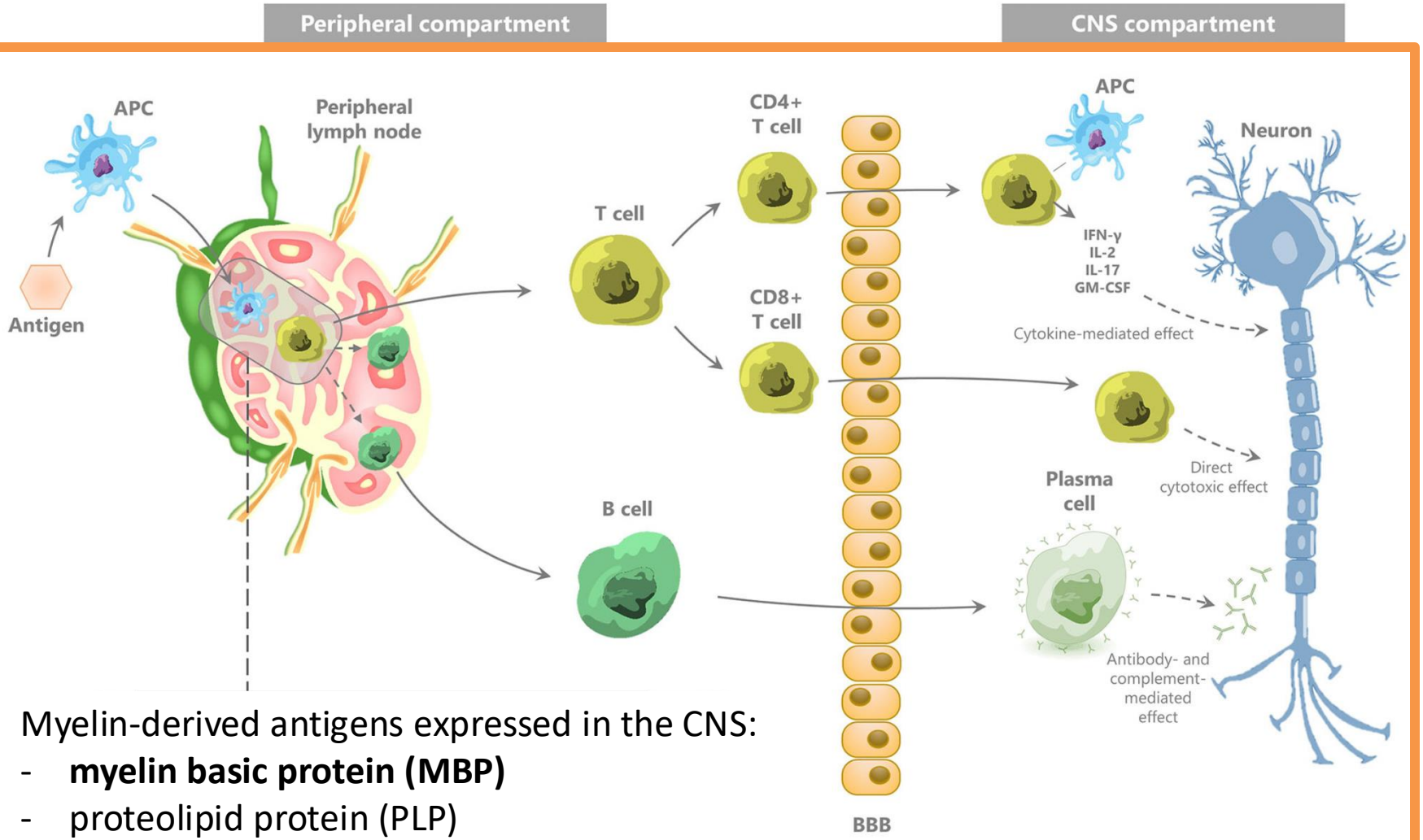
INFLAMMATORY AND NEURODEGENERATIVE PROCESSES

- **White matter lesions – focal lesions**
  - Active demyelinating lesions
- **Normal-appearing white matter**
  - Diffuse inflammation and neuro-axonal damage
- **Grey matter lesions**
  - cortical demyelination in the forebrain and cerebellum
- **Remyelination and degeneration**



Filippi et al, Nat Rev Disease Primers, 2018

MS pathophysiology

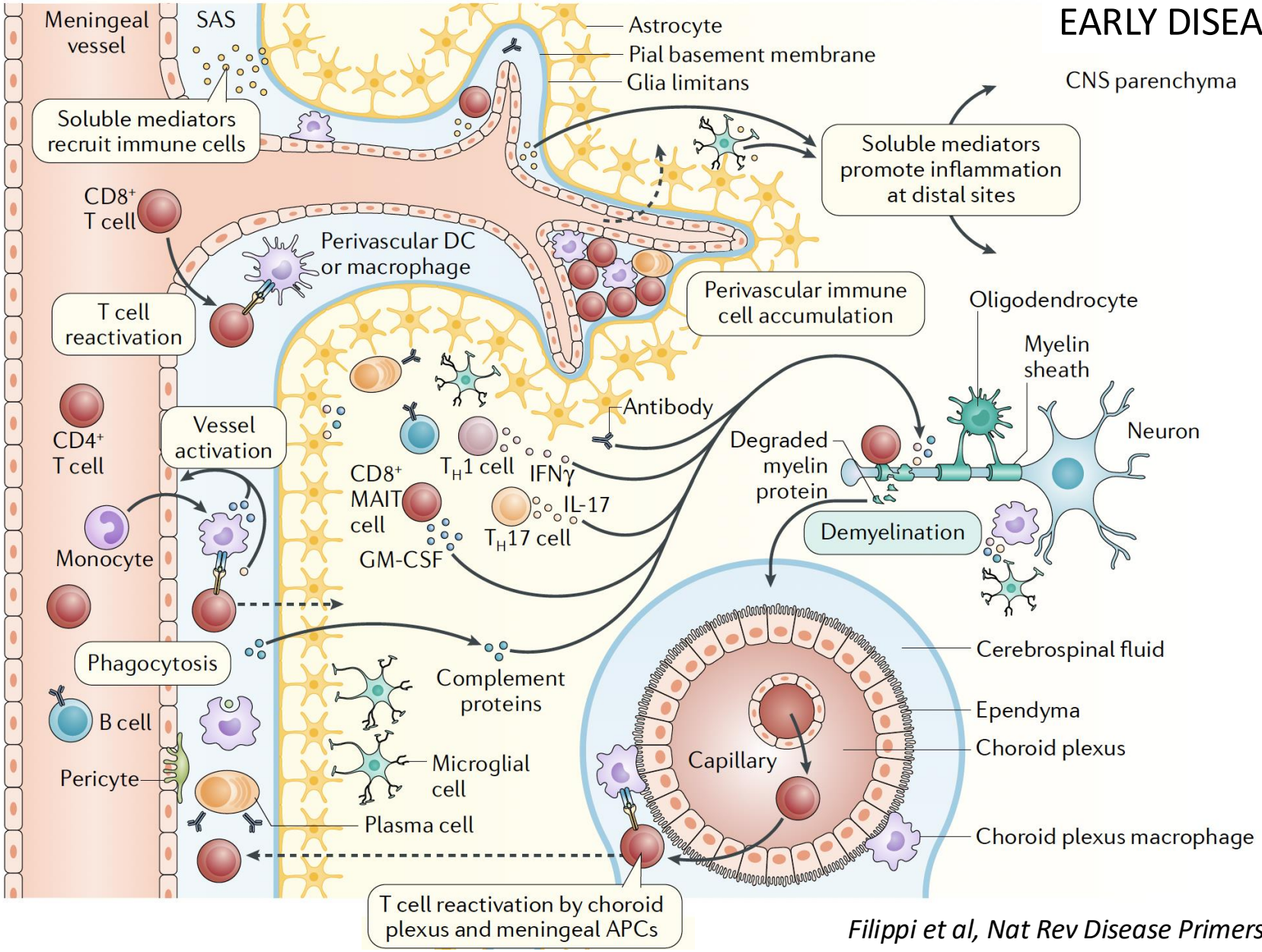


Myelin-derived antigens expressed in the CNS:

- **myelin basic protein (MBP)**
- proteolipid protein (PLP)
- myelin oligodendrocyte glycoprotein (MOG)
- αB-crystallin

Derdelinckx *et al, Front Immunol 2021*

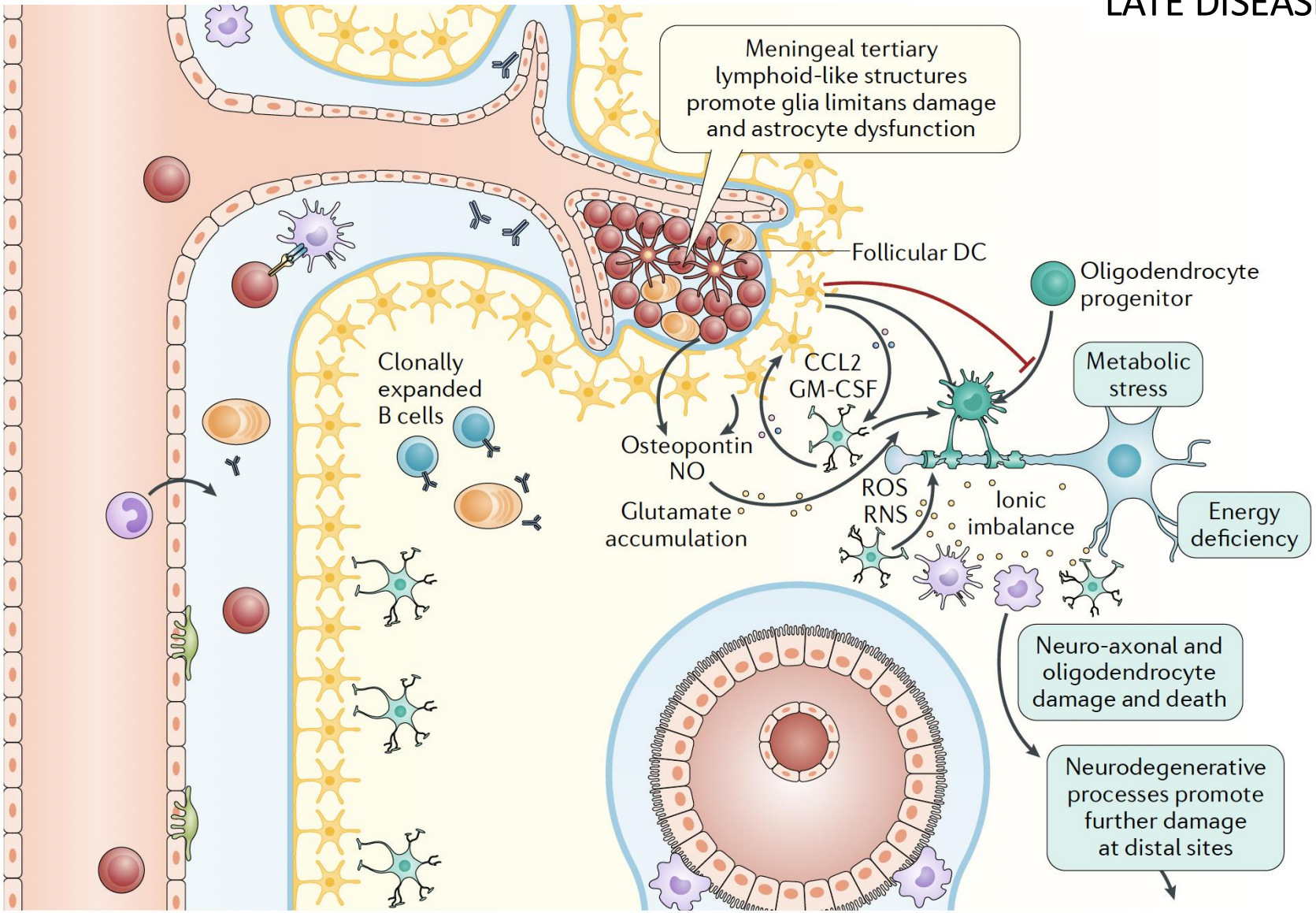
Immune pathophysiology of MS



Filippi et al, Nat Rev Disease Primers, 2018

Immune pathophysiology of MS

LATE DISEASE



Filippi et al, Nat Rev Disease Primers, 2018

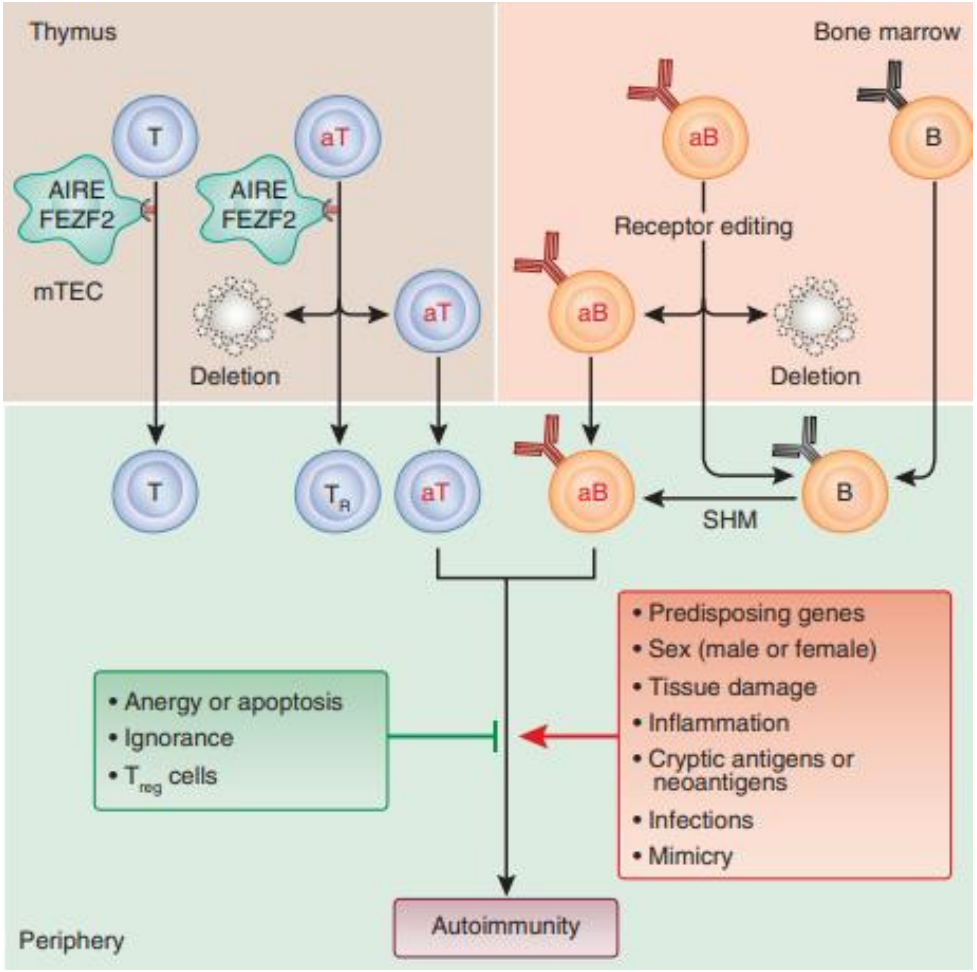
Take-home message

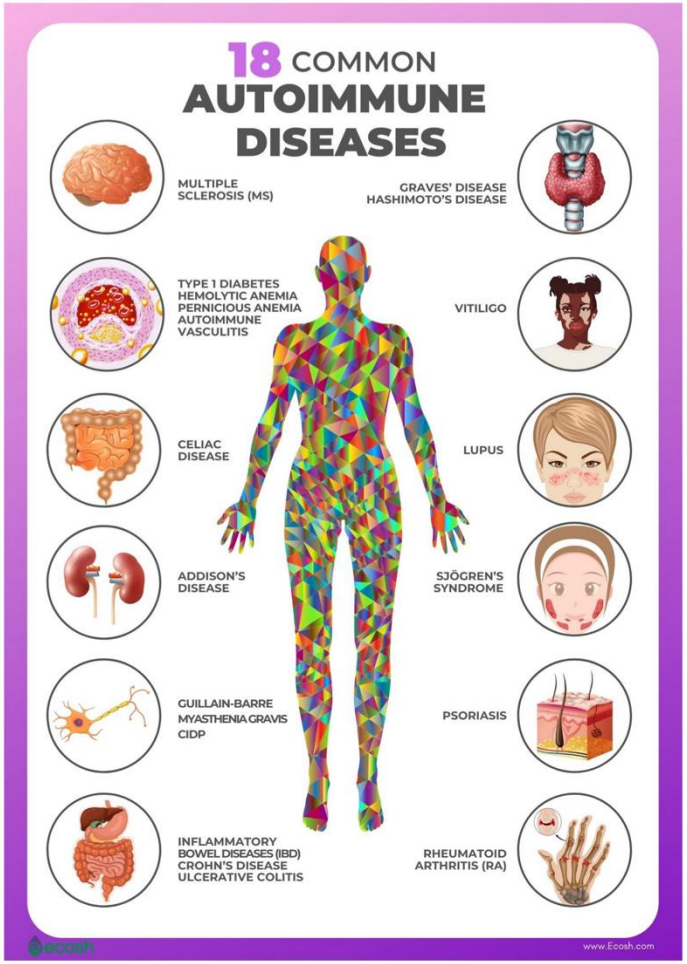
- Tolerance
  - Central
  - Peripheral
- Multiple mechanisms
  - Clonal deletion
  - Functional inactivation (anergy)
  - Regulatory cells
- Trade-off between defense efficacy and preservation of the immunological self

'The highest result of education is tolerance'
Helen Keller

Take-home message

- Autoimmunity is multifactorial





Theofilopoulos, Nat Immunol, 2017