AUTOIMMUNE EXAMPLES

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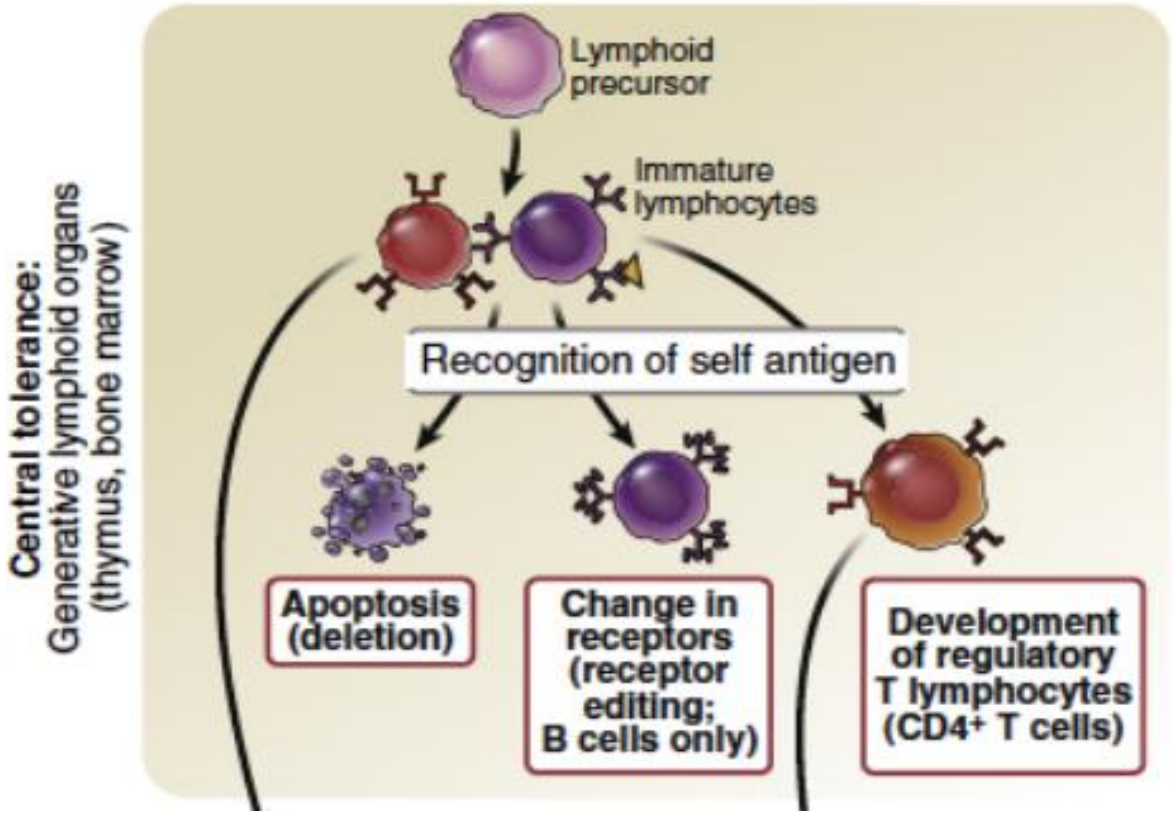
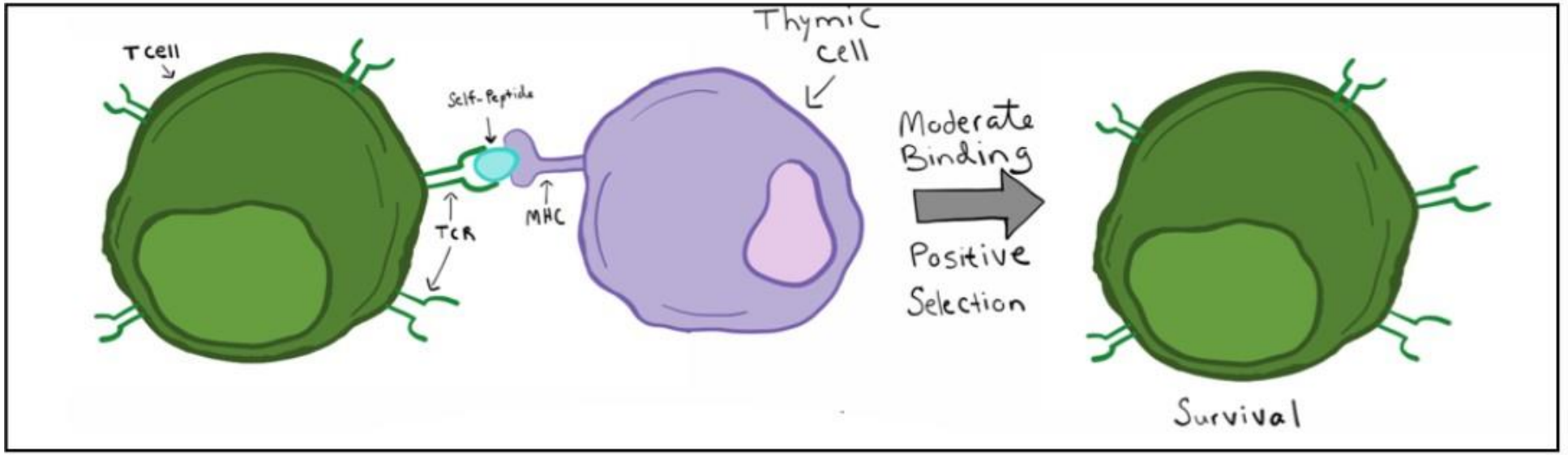
TOPICS OF THIS LECTURE

- 1- introduction
- 2- Overview of autoimmune diseases
- **3- systemic lupus erythematosus (SLE الذئبةُ الحمامية المَجموعِيَّة)**
- **4- Type 1 diabetes**
- 5- Graves disease
- 6- Examples of autoantigens

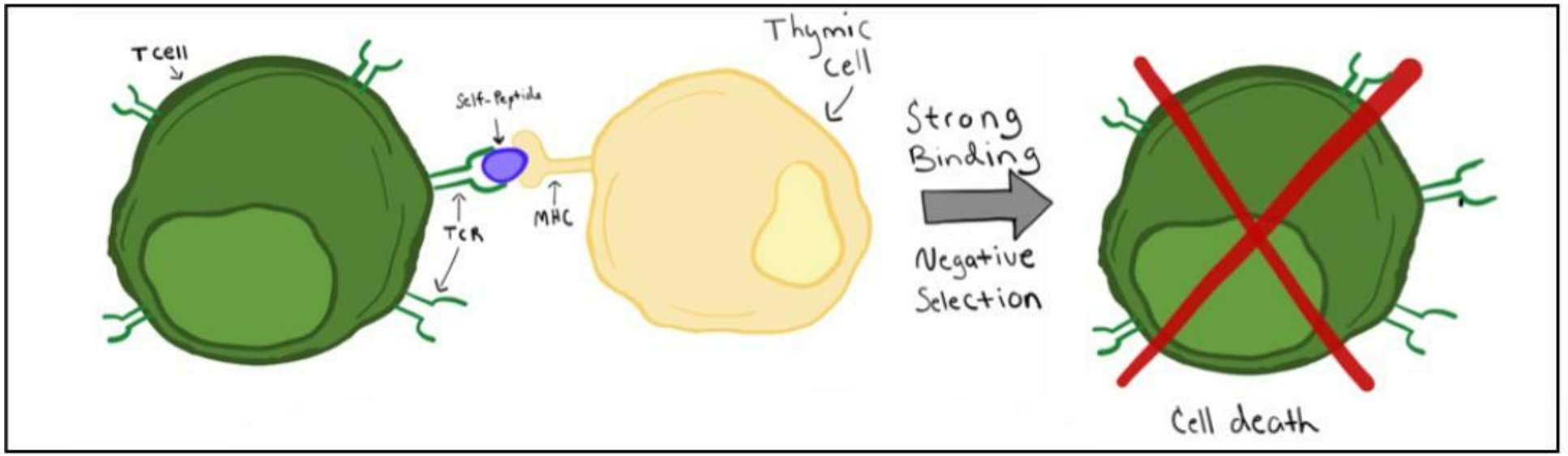


In the thymus, how are T cells exposed to all self-antigens in the body? **(epithelial cells within the thymus are the cells presenting these antigens to the T cells)**

- Epithelial cells of the thymus have a gene that encodes for a transcription factor called **AIRE** (autoimmune regulator) that induces the transcription of proteins and antigens from all over the body. This transcription factor is active primarily in these thymocytes, so that T cells would encounter all self-antigens.



Positive selection: Cells that bind to MHC molecules will receive survival signals



Negative selection: cells that react strongly to self antigens undergo apoptosis

1- INTRODUCTION

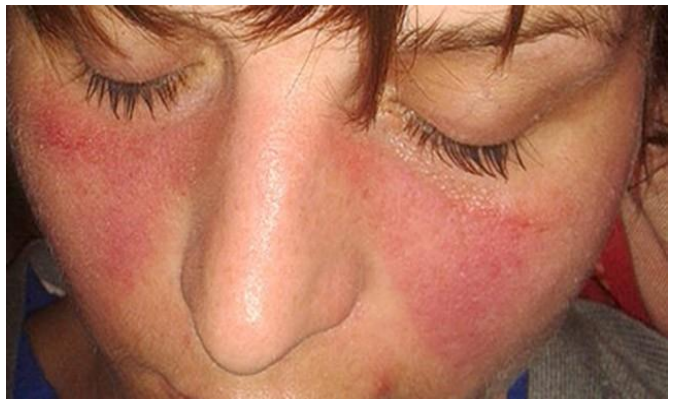
- Self-tolerance may be induced in immature self-reactive lymphocytes in the generative lymphoid organs (**central tolerance**) or in mature lymphocytes in peripheral sites (**peripheral tolerance**)
- **Central tolerance** occurs during the maturation of lymphocytes in the central (generative) lymphoid organs, where all developing lymphocytes pass through a stage at which encounter with antigen may lead to **cell death** or **replacement of a self-reactive antigen receptor** with a new one.
- The antigens normally present in the thymus and bone marrow include ubiquitous, or widely disseminated, self antigens including those bought in by the blood.
- **Peripheral tolerance** occurs when, as a consequence of **recognizing self antigens**, mature lymphocytes become **incapable of responding** to that antigen, or are induced to die by **apoptosis**, or mature T cells are actively **suppressed by regulatory T cells**.

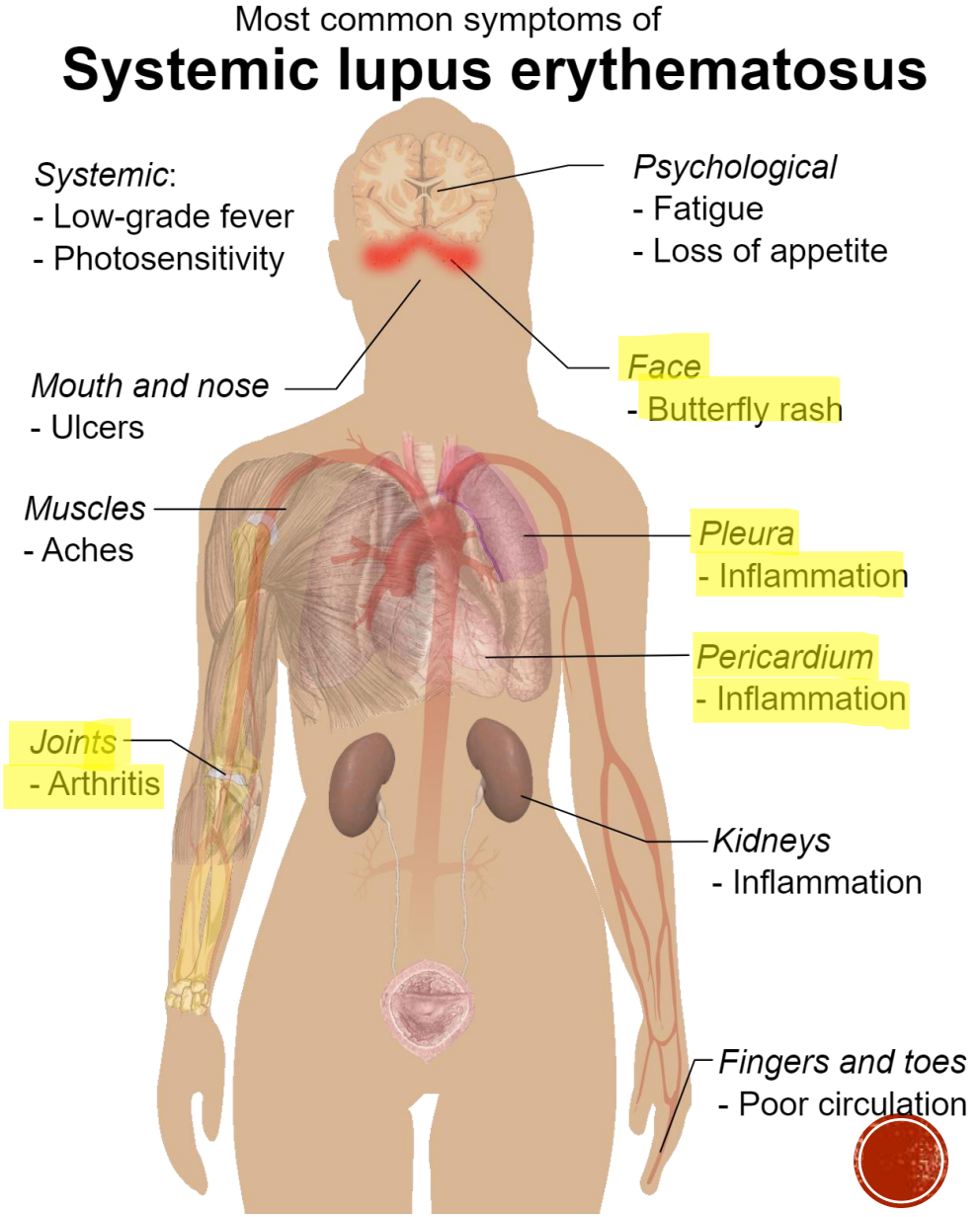
2- OVERVIEW OF AUTOIMMUNE DISEASES

- Autoimmune diseases can be classified according to several criteria. One of them is the location of the autoimmune attack. Based on this criterion, autoimmune diseases are distinguished into **systemic** (When autoantigen is found all around the body) or **organ-specific** (when autoantigen is specific to an organ).
- Scholars may disagree on the criteria that need to be fulfilled to consider a disease "autoimmune“. There are over “too many” autoimmune diseases that are clinically heterogenous, with numerous **subtypes** and **variants**.
- Autoimmune diseases occur as a result of **genetic predisposition (commonly involving HLA genes)** and **environmental influences** (such as molecular mimicry/ UV radiation and Microbiota/ tissue damage).
- Autoimmunity affects ~8% of the global population. However, the incidence is increasing because of a number of factors, including awareness and improved clinical diagnoses.

3- systemic lupus erythematosus (SLE الذئبةُ الحمامية المَجموعِيَّة)

- **SLE** is a systemic **chronic autoimmune disease** caused by perturbations of the immune system. The clinical presentation is heterogeneous, largely because of the **multiple genetic and environmental factors** that contribute to disease initiation and progression.
- Immunity is formed against nuclear antigens that are found all around our body
- Symptoms of these diseases can affect many different body systems, including joints, skin, kidneys, blood cells, heart, and lungs. The most common and most severe form is systemic lupus erythematosus (when several systems are affected).
- Young females have higher risk of developing disease

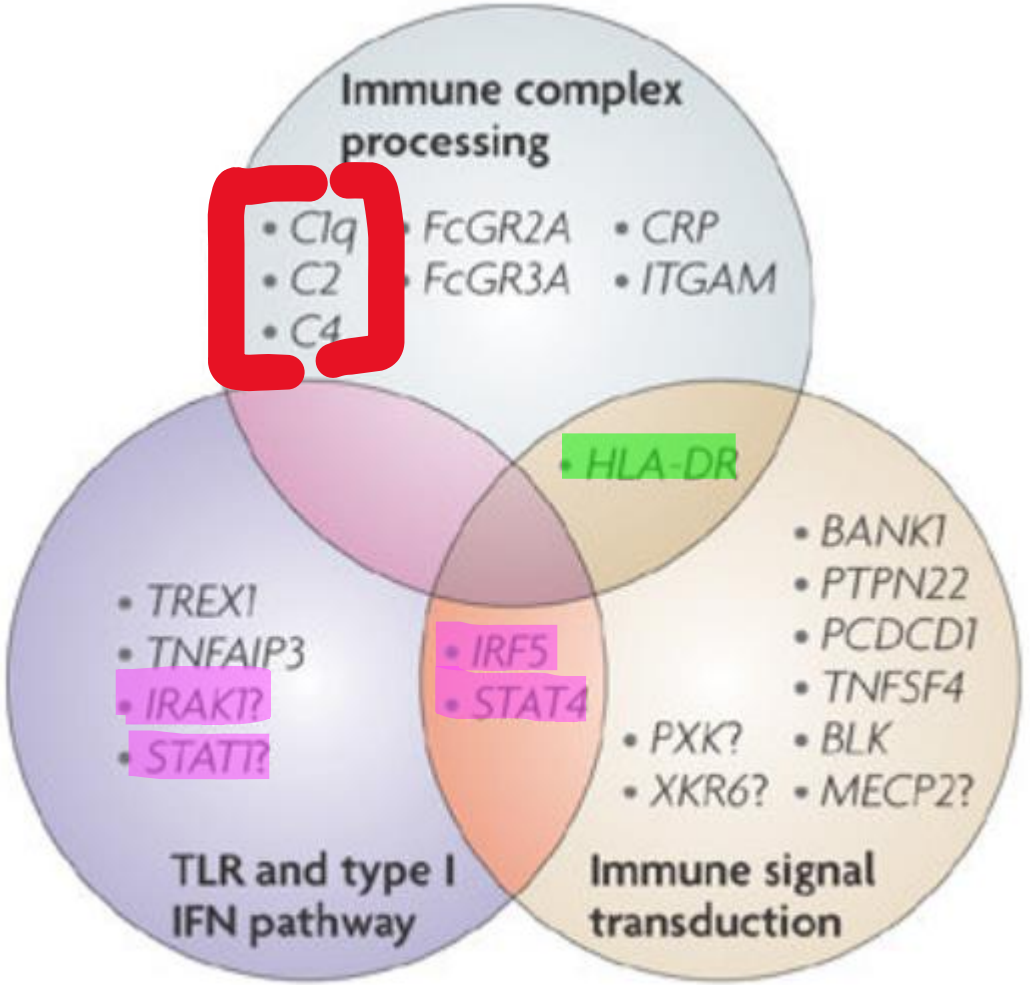




3- systemic lupus erythematosus (SLE الذئبةُ الحمامية المَجموعِيَّة)

- Several genetic factors are associated with increased susceptibility to SLE as revealed by genetic studies such as **genome wide association studies.**

- Of importance are genes related to the classical complement pathway such as **C1q, C2, and C4**.



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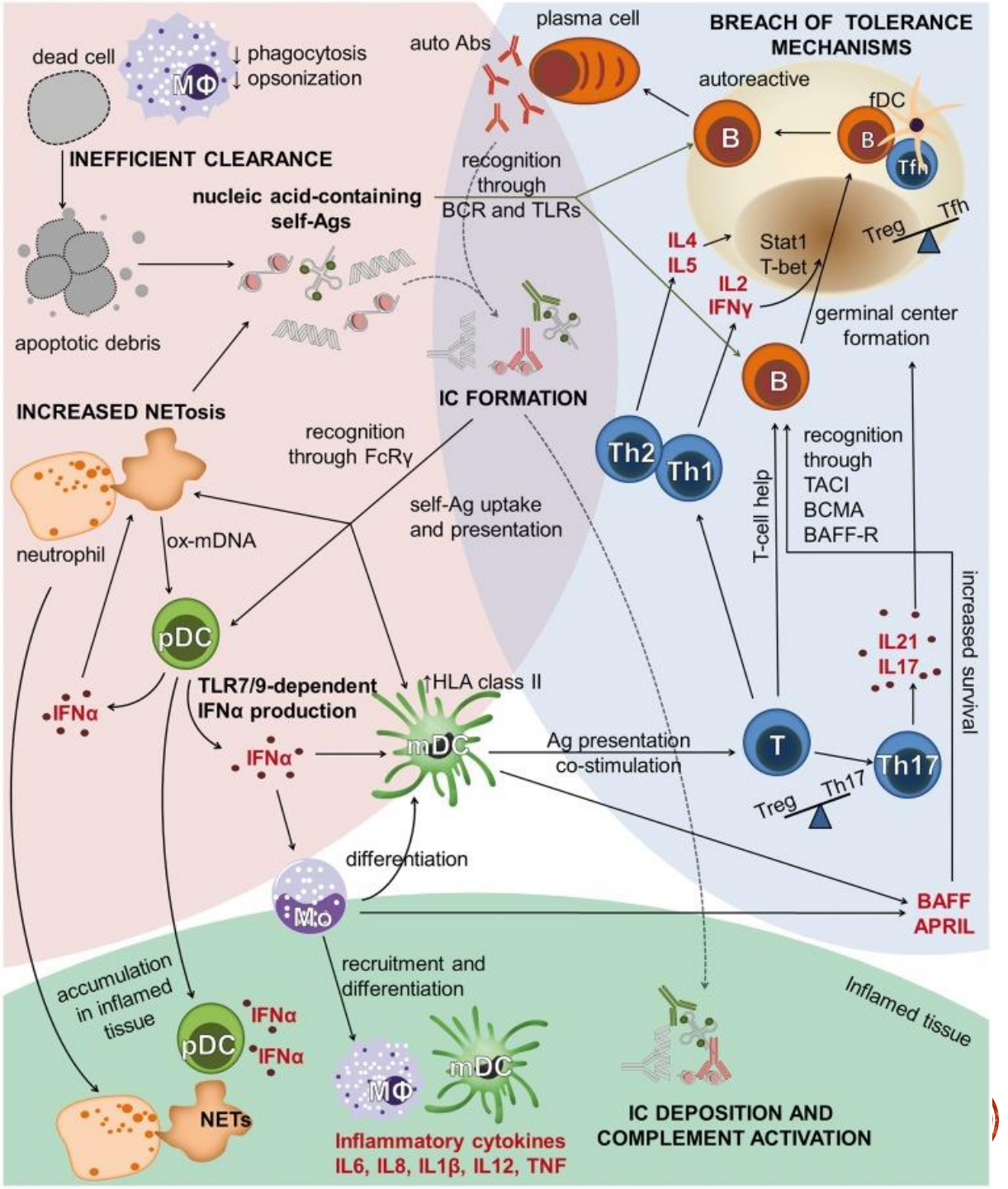
→ Loss of adaptive immune tolerance (blue) leads to an increase in autoreactive B cells. Signals from self-antigens, TLR ligands, BAFF/APRIL and T-cell-derived cytokines promote the formation of germinal centres and the production of autoantibodies. Innate immune defects leading to increased availability of self-antigens (pink) include increased NETosis, impaired clearance of apoptotic debris and reduced phagocytosis. Self-antigens form ICs with autoantibodies, enabling FcRγ-mediated uptake and activation of several downstream pathways. Inflammation and tissue damage (green) is caused by mediators released by recruited inflammatory cells and IC-induced complement activation.



3- systemic lupus erythematosus (SLE الذئبةُ الحمامية المَجموعِيَّة)

- Pathogenesis of this disease include: activation against self antigens, and releasing of these self antigens from destroyed tissues, It's not well understood which one starts first.
- people with SLE are found to have problems with clearing apoptotic cells by phagocytosis, so autoantigens will accumulate and at a certain point, tolerance will break, that will lead to more tissue damage, and more tissue damage will lead to more activation and so on (so disease get worse with time & you will find more autoantibodies)
- **B lymphocyte** plays a **central role** in adaptive immune response of SLE, which involved in the production of **autoantibodies**, **presentation of autoantigens** and activation of autoreactive T cells.
- **T lymphocyte** plays a role through **co-stimulator-mediated signaling pathway** and **cytokines** secreted by subsets of T cells
- Also innate immunity plays role as deficiency in clearing apoptotic cells = problem in macrophages /nuclear antigens are found in Neutrophil extracellular traps (NETs)/ complement system is activated when antibodies are bound to apoptotic cells/ TLR on pDC can be activated by immune complex, inducing the **production of IFN-α** and **the formation of NETs**.
- Treatment: We use immunosuppressant drugs, but there should be a balance in the dose as we don't want the patient to become susceptible to develop infections

3- systemic lupus erythematosus (SLE الذئبةُ الحمامية المَجموعِيَّة)

- In SLE, we look for these autoantibodies (increase as severity increases) in addition to clinical symptoms and complement protein levels. Usually, C3 and C4 levels are decreased due to complement consumption; high activation of complement system by immune complexes containing autoantibodies causes more consumption (cleavage) of C3 and C4, thus lowering their levels. On the other hand, if you looked at C3a levels for example you'll find it higher than usual.

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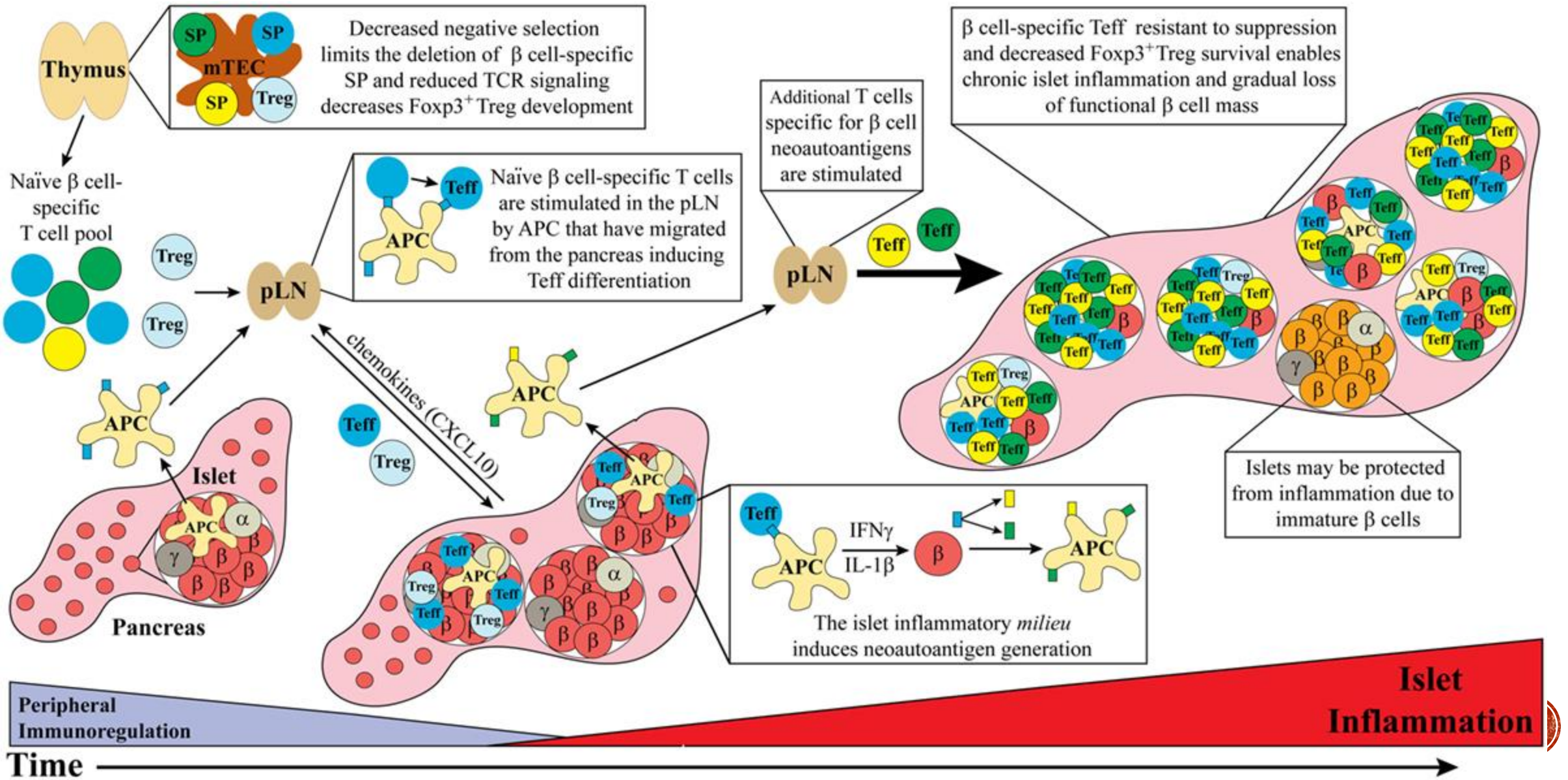
4- Type 1 diabetes

- Type 1 diabetes (T1D) is an autoimmune disease characterized by the **chronic inflammation of the pancreatic islets of Langerhans**

- In type 1 diabetes (T1D), T cells attack the insulin producing β cells in the pancreatic islets. **Genetic** and **environmental** factors increase T1D risk by in part altering central and peripheral tolerance inducing events. The strongest genetic association is with the **human leukocyte antigen locus (HLA),** consistent with a **key role for T cells** in T1D

- When a sufficient amount of β cell mass has been rendered nonfunctional and/or destroyed, **hyperglycemic blood levels** are achieved, and clinical diabetes established.
- T1D is generally viewed as a T cell-driven autoimmune disease.

4- Type 1 diabetes

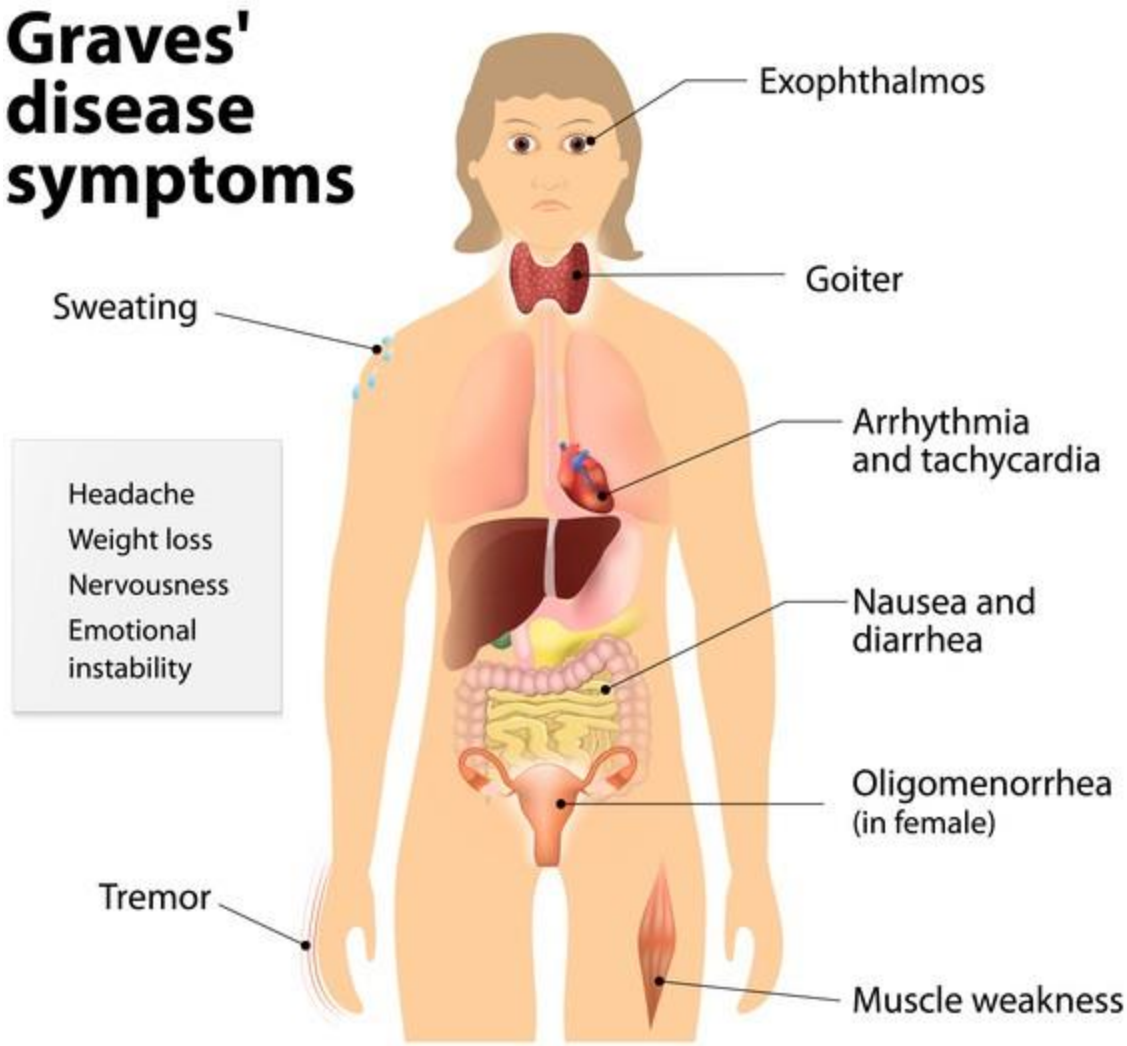


4- Type 1 diabetes

- **Decreased efficiency of negative selection** in the thymus, either due to altered tissue-specific antigen expression or due to T cell receptor (TCR) signaling, allows for the increased escape of β cell-specific T cell clones into the periphery.
- β cell-specific **Foxp3+Treg development** may also be **suboptimal** due to dysregulation of TCR signaling
- β cell-specific T cells are stimulated in the pancreatic lymph nodes (pLN) by APC derived from the islets, leading to effector **T cell (Teff) differentiation**. These pathogenic **Teff then infiltrate the islets and drive inflammation** leading to **reduced β cell function and/or survival**.
- Ongoing islet inflammation also leads to the **generation of neoautoantigens** either directly in β cells or during antigen processing by APC.

5- GRAVES DISEASE

- **Grave's disease** is an autoimmune disease that affects the **thyroid**. It frequently results in and is the most common cause of hyperthyroidism. It also often results in an enlarged **thyroid**.
- Although the cause of Graves' disease is unknown, autoimmunity directed against the **TSH receptor** is the hallmark of Graves' thyroid disease. **Autoantibodies** against this receptor mimic the action of its natural ligand, **TSH**, inducing **hyperthyroidism (increase metabolism)** and **goiter (enlargement of thyroid gland)**.
- Treatment: Thyroidectomy + Thyroxine supplement



6- EXAMPLES OF AUTOANTIGENS

Autoantigen	Function/Complex	Occurrence (% in SLE)	Reference
Nucleolin	Nucleolar structural integrity	>50	[26]
U1RNP	Spliceosome component	40	[26]
U1RNA	Spliceosome component	<5	[26]
Sm epitopes	Spliceosome proteins	25	[26]
SSA/Ro	RNA pol III chaperone	40–50	[26]
SSB/La	RNA pol III chaperone and termination	15	[26]
Ribosomal P proteins	Phospho proteins, bind 28S RNA	12–16	[27]
Ku	dsDNA break repair	20–40	[26]
Cardiolipin	Similar epitopes to nucleophosmin	20–40	[26]
Centromere components	CENP-B and others	~6	[26]
Lamins	Complexed with nucleolin	unknown	[28]

6- EXAMPLES OF AUTOANTIGENS

Disease	Target Organ	Known Autoantigens
Thyroiditis (autoimmune)	Thyroid	Thyroglobulin Thyroperoxidase
Graves' disease	Thyroid	Thyroid-stimulating hormone receptor
Type 1 diabetes	Pancreatic Beta cells	Insulin, GAD, IA-2
Addison's disease	Adrenal	21OH hydroxylase 17OH hydroxylase
Gastritis	Stomach	H+/K+ ATPase Intrinsic Factor
Celiac disease	Small bowel	Transglutaminase
Vitiligo	Melanocytes	Tyrosinase Tyrosinase-related protein-2
Multiple sclerosis	Brain, spinal cord	Myelin basic protein Proteolipid protein
Pemphigus	Skin	Desmogleins
Hepatitis (autoimmune)	Liver	Hepatocyte antigens Cytochrome; P450-1A2
Myasthenia gravis	Muscle	Acethylcholine receptor
Primary biliary cirrhosis	Liver bile ducts	2-Oxoacid dehydrogenase complexes

→Myasthenia gravis is a disease where autoantigens are on muscles.
→ Recently we use a bacterial enzyme against autoantibodies in some autoimmune diseases (e.g. Myasthenia gravis)