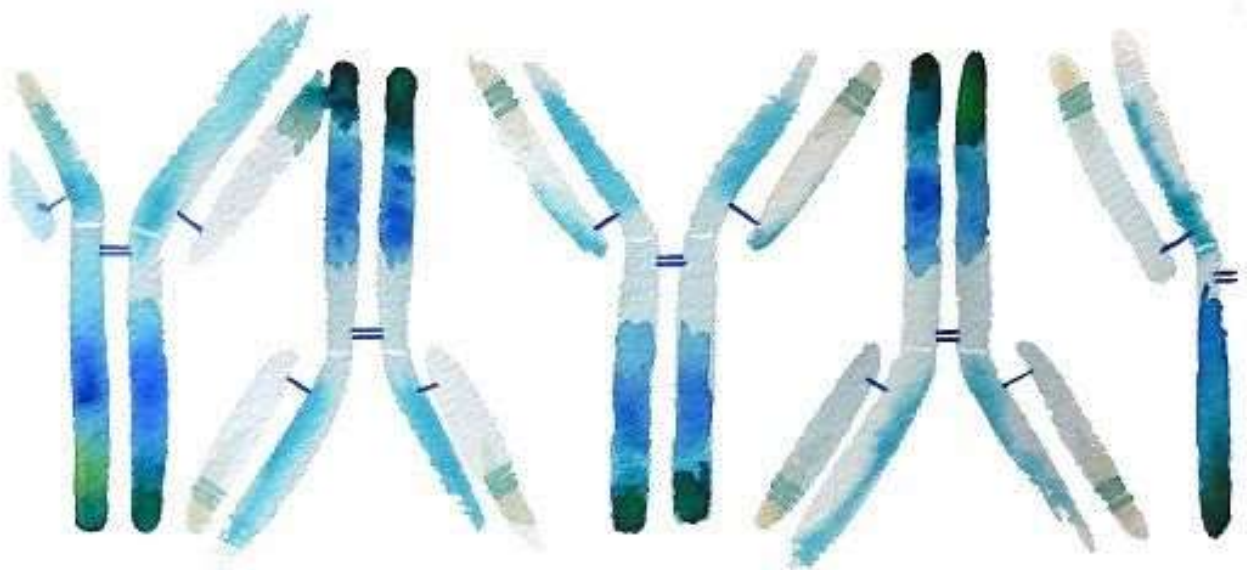
Medical Immunology



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Lecture 18

Autoimmunity

In this lecture we will discuss:

- Autoimmunity examples.

Self-tolerance

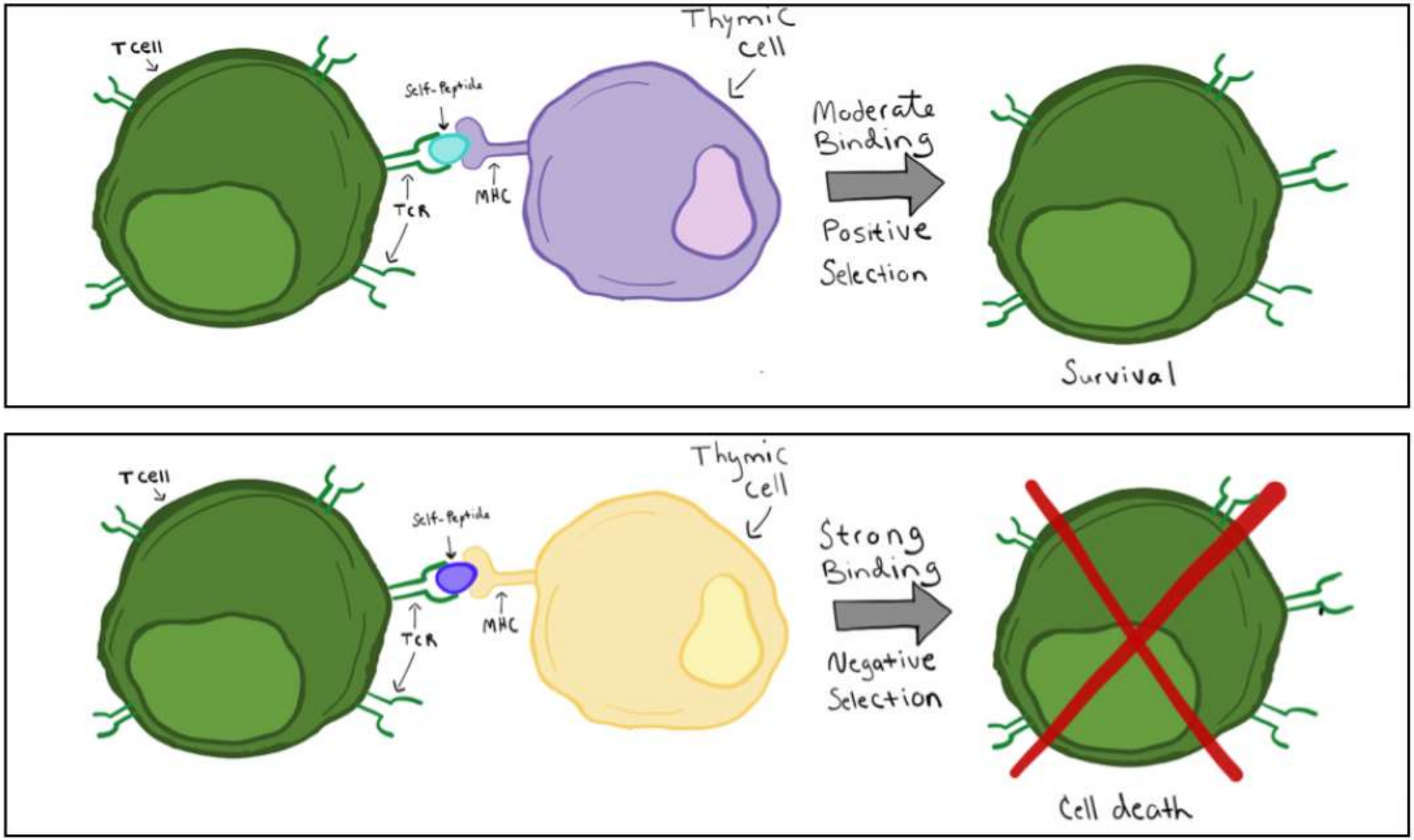
- Self-tolerance may be induced in immature self-reactive lymphocytes in the generative lymphoid organs (**central tolerance**) or in mature lymphocytes in peripheral sites (**peripheral tolerance**)

- **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**.

Self-tolerance



Autoimmune diseases overview

- 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** or **organ-specific.**

- 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**.

- Autoimmunity affects ∼8% of the global population. However, the incidence is increasing because of a number of factors, including awareness and improved clinical diagnoses.

- https://autoimmune.org/disease-information/

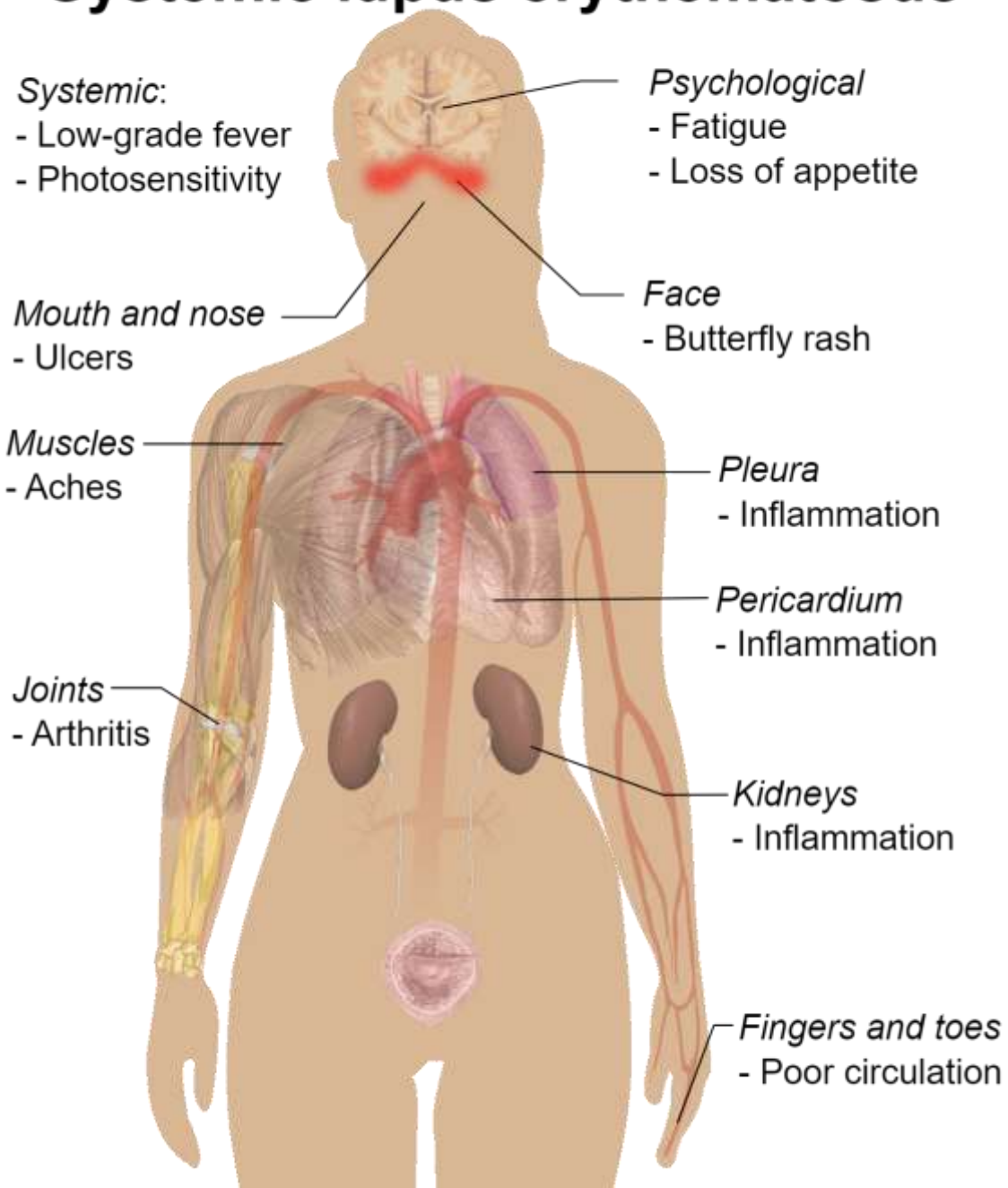
Autoimmunity in systemic lupus erythematosus (SLE الذئبةُ الحمامية المَجموعِيَّة)

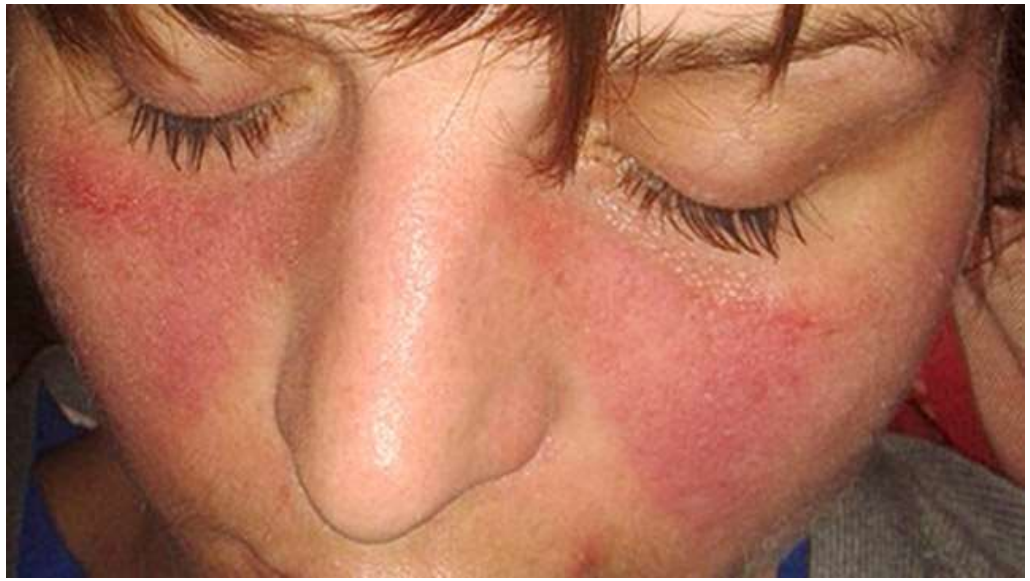
- **SLE** is a **chronic autoimmune disease** caused by perturbations of the immune system. The clinical presentation is heterogeneous, largely because of the **multiple genetic and environmental factors** that contribute to disease initiation and progression.

- 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.

Most common symptoms of

Systemic lupus erythematosus

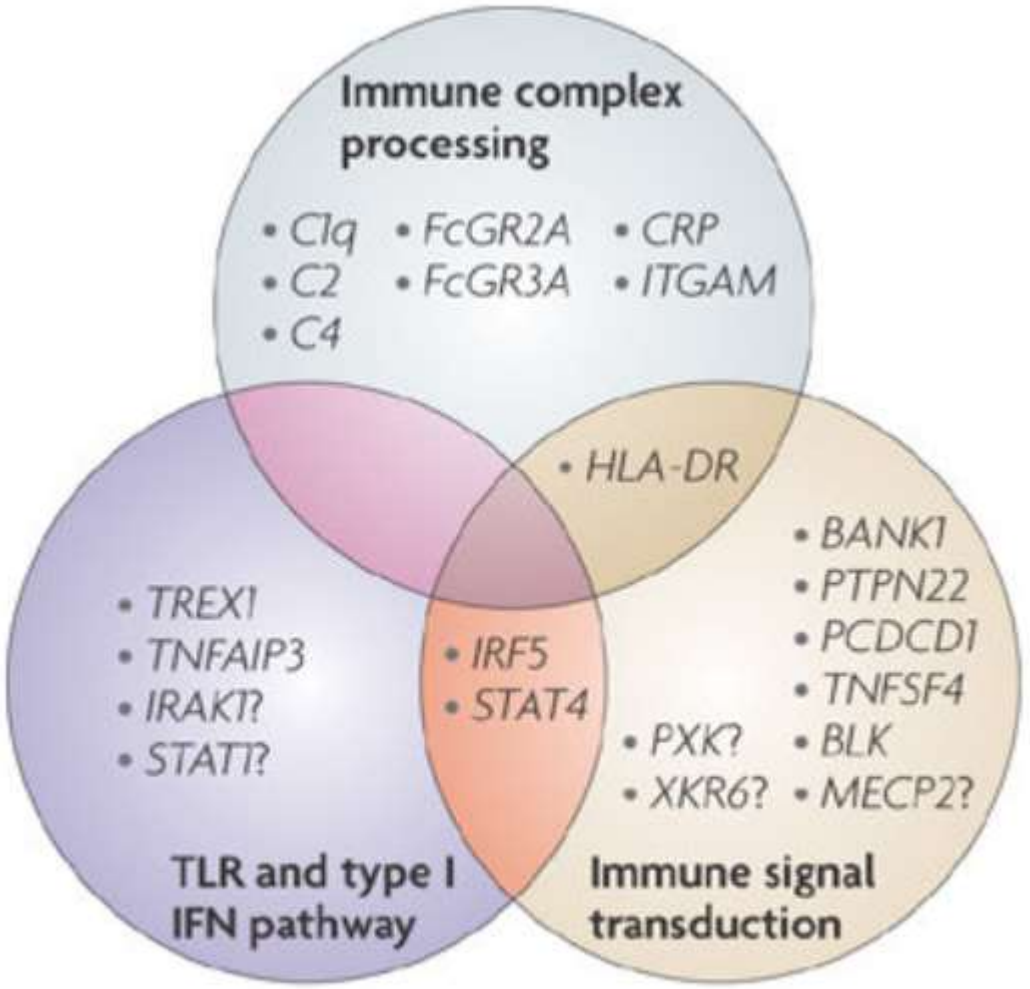




Autoimmunity in systemic lupus erythematosus (SLE الذئبةُ الحمامية المَجموعِيَّة)

- 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**.



Nature Reviews | Genetics

Breaking immune tolerance and the development of SLE

- **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

- The role of **innate immune response** in SLE pathogenesis has also been noticed, especially the discovery of TLR on pDC that can be activated by immune complex, inducing the **production of IFN-α** and **the formation of NETs**.

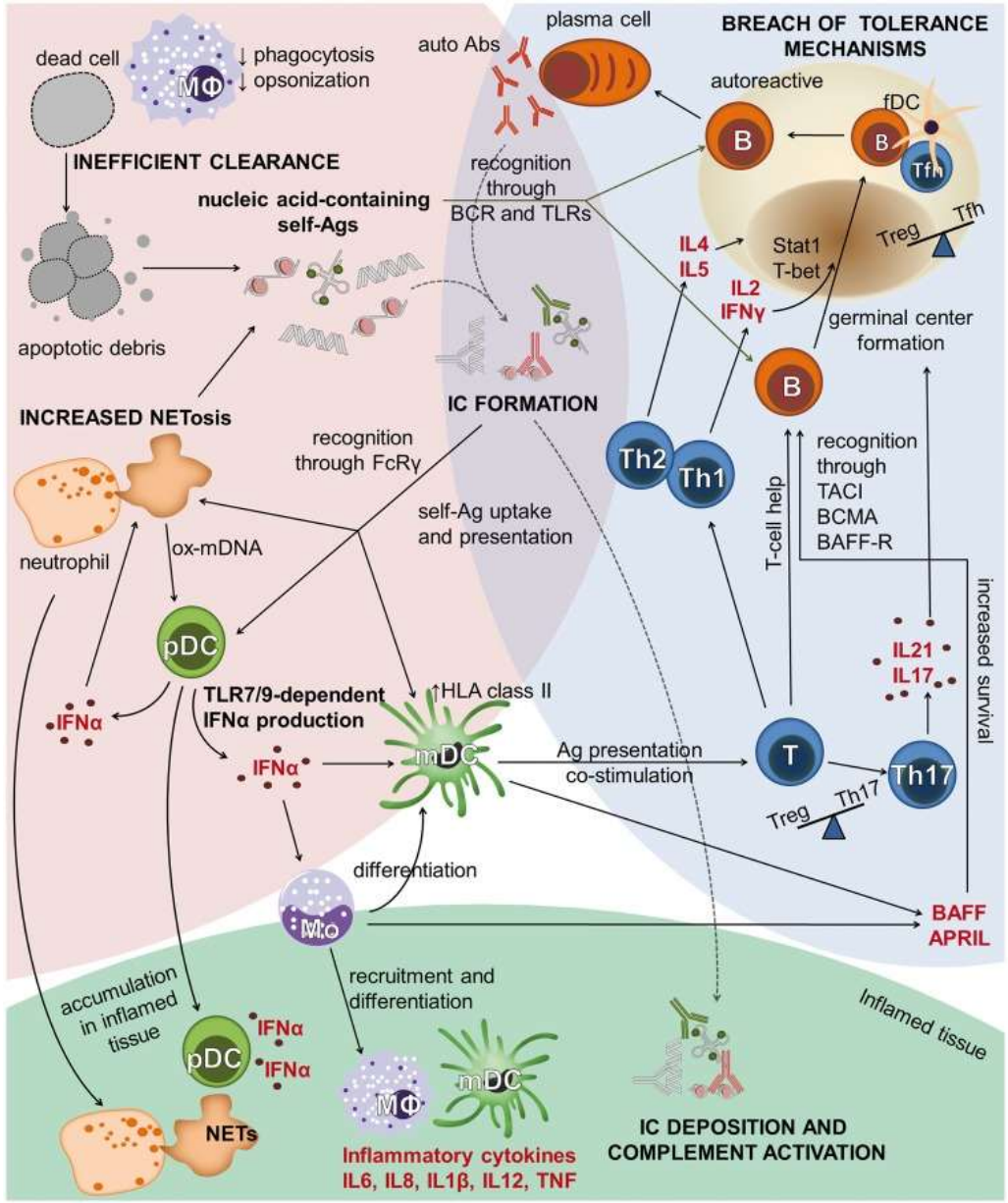
Breaking immune tolerance and the development of SLE

- The development of SLE occurs in three interconnected phases.

- **Loss of adaptive immune tolerance** 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 include increased **NETosis**, **impaired clearance of apoptotic debris** and **reduced phagocytosis**

Breaking immune tolerance and the development of SLE



Autoimmunity in 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.

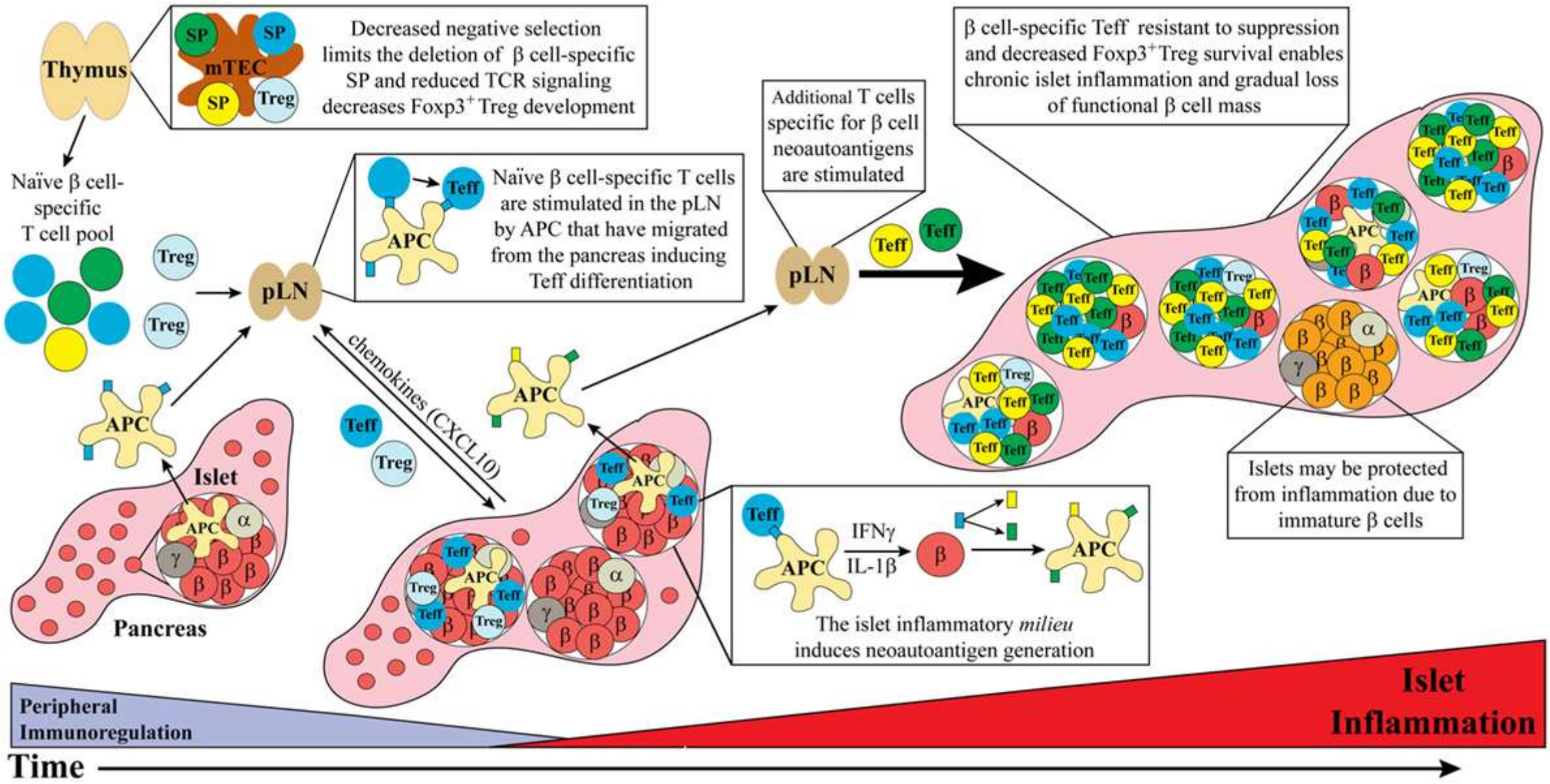
Autoimmunity in Type 1 Diabetes

- **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.

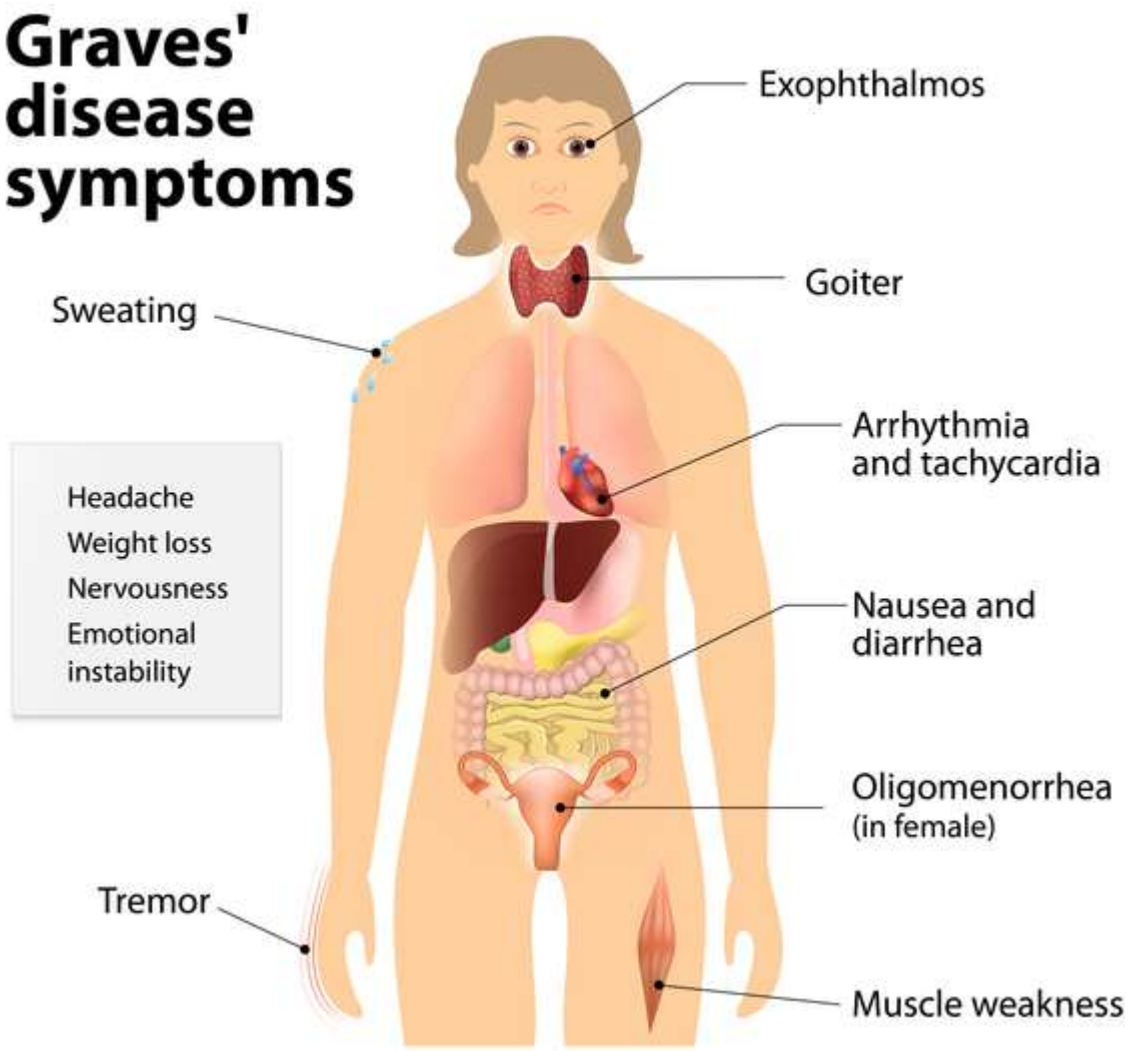

Thymus
SP
SP
mTEC
SP
Treg
Decreased negative selection limits the deletion of β cell-specific SP and reduced TCR signaling decreases Foxp3+ Treg development
Naïve β cell-specific T cell pool
Treg
Treg
pLN
Teff
APC
Naïve β cell-specific T cells are stimulated in the pLN by APC that have migrated from the pancreas inducing Teff differentiation
APC
Islet
Pancreas
chemokines (CXCL10)
Teff
Treg
APC
Additional T cells specific for β cell neoautoantigens are stimulated
pLN
Teff
Teff
β cell-specific Teff resistant to suppression and decreased Foxp3+ Treg survival enables chronic islet inflammation and gradual loss of functional β cell mass
Islets may be protected from inflammation due to immature β cells
Teff
APC
IFNγ
IL-1β
β
APC
The islet inflammatory milieu induces neoautoantigen generation
Peripheral Immunoregulation
Islet Inflammation
Time

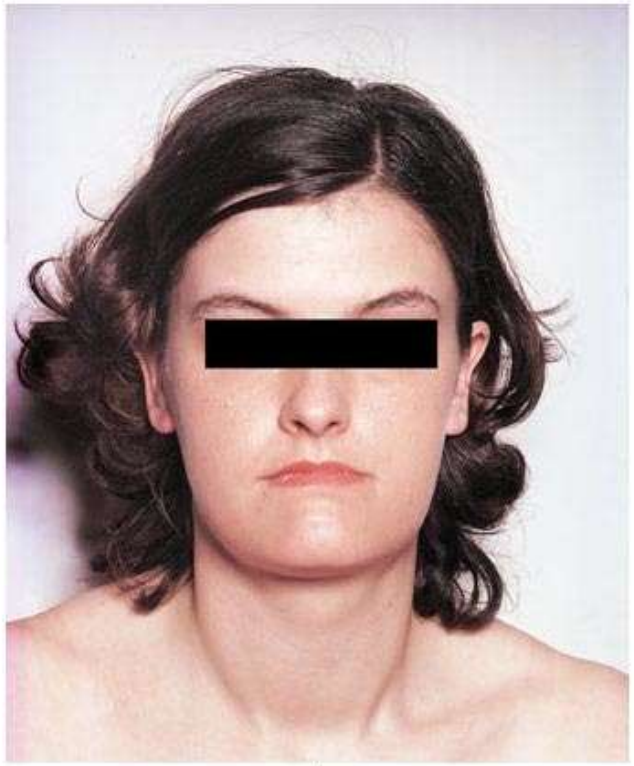
Autoimmunity in Grave’s disease

- **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** and **goiter**.

Autoimmunity in Grave's disease

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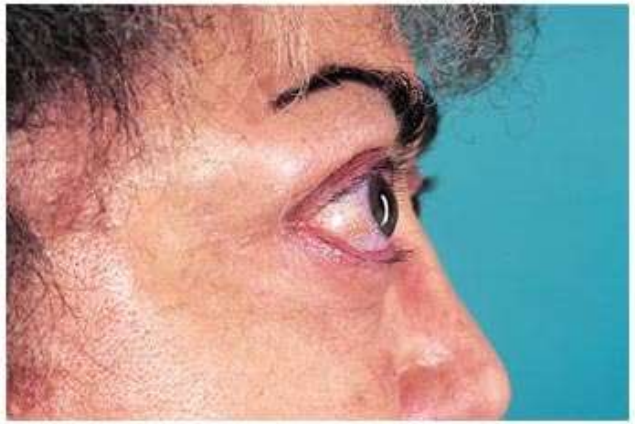
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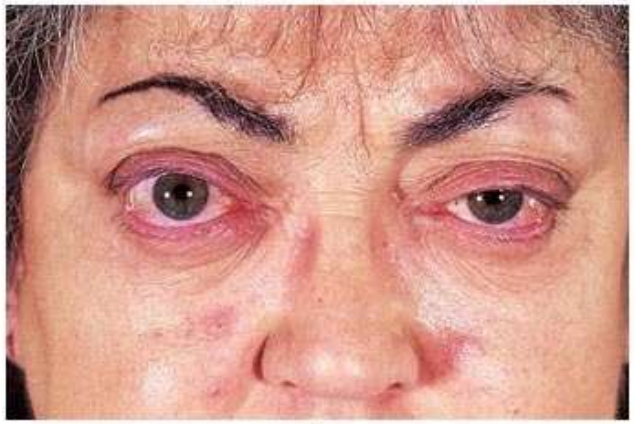
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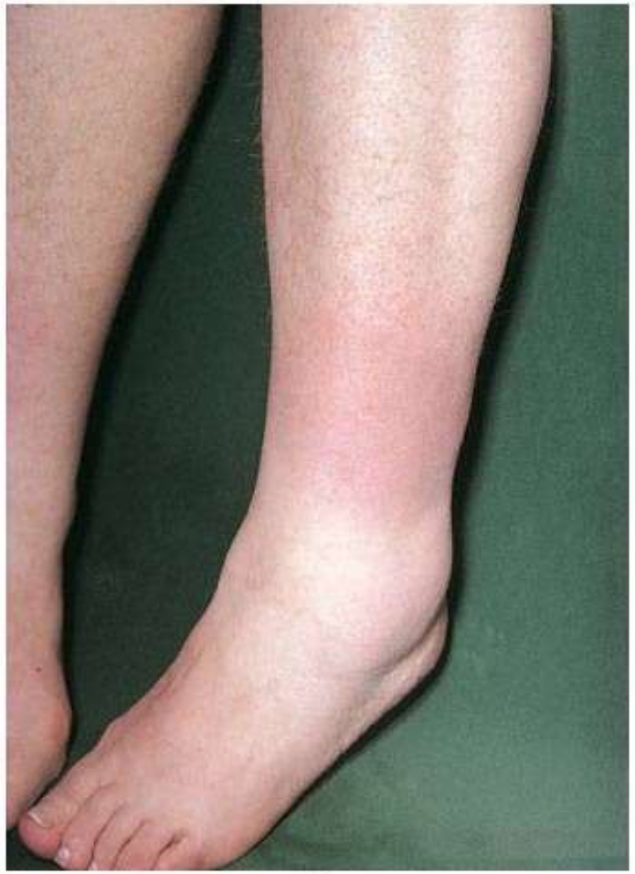
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Examples of autoantigens

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]

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

Further reading:

- Cellular and Molecular Immunology. 7th Edition..

Chapter 14. Immunologic Tolerance and Autoimmunity