

## 3) Autoimmunity Examples

### Core Mechanisms of Self-Tolerance

- **Self-tolerance** is 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 maturation in the **central (generative) lymphoid organs**, where encounter with antigen leads to **cell death** or **replacement** of a self-reactive antigen receptor.
- **Peripheral tolerance** occurs when **mature lymphocytes** recognize self antigens and become incapable of responding, are induced to die by **apoptosis**, or are actively suppressed by **regulatory T cells**.
- In the thymus, **positive selection** occurs with **moderate binding** to a **self-peptide**, leading to **survival**.
- **Negative selection** occurs with **strong binding** to a **self-peptide**, leading to **cell death**.

### Overview of Autoimmune Diseases

- **Autoimmune diseases** are distinguished into **systemic** or **organ-specific** based on the location of the attack.
- These diseases occur as a result of **genetic predisposition** (commonly involving **HLA genes**) and **environmental influences**.
- The incidence of autoimmunity is increasing globally due to factors like awareness and improved **clinical diagnoses**.

### Systemic Lupus Erythematosus (SLE)

- **SLE** is a chronic autoimmune disease caused by perturbations of the immune system with a **heterogeneous** clinical presentation.
- Several genetic factors are associated with susceptibility, particularly genes related to the **classical complement pathway** such as **C1q, C2, and C4**.
- **B lymphocyte** plays a central role in the production of **autoantibodies**, presentation of **autoantigens**, and activation of **autoreactive T cells**.
- **T lymphocyte** plays a role through **co-stimulator-mediated signaling** pathways and cytokines.
- The **innate immune response** involves **TLR (Toll-like Receptor) signaling** on **pDCs (Plasmacytoid Dendritic Cells)**, which induces **IFN- $\alpha$**  production and the formation of **NETs**.
- Loss of **adaptive immune tolerance** leads to an increase in **autoreactive B cells**.
- **Innate immune defects** lead to increased availability of self-antigens through **increased NETosis**, **impaired clearance of apoptotic debris**, and **reduced phagocytosis**.

## Type 1 Diabetes (T1D)

- **T1D** is characterized by chronic inflammation of the **pancreatic islets of Langerhans** where **T cells attack** the insulin-producing **\beta cells**.
- It is generally viewed as a **T cell-driven** autoimmune disease with a strong genetic association with the **human leukocyte antigen locus (HLA)**.
- Decreased efficiency of **negative selection** in the thymus allows for the increased escape of **\beta cell-specific T cell clones** into the periphery.
- Pathogenic **effector T cells (Teff)** infiltrate the islets and drive inflammation, leading to reduced **\beta cell function and/or survival**.

## Grave's Disease

- **Grave's disease** is the most common cause of **hyperthyroidism** and often results in an **enlarged thyroid**.
- The hallmark of the disease is autoimmunity directed against the **TSH receptor**.
- **Autoantibodies** against this receptor mimic the action of **TSH**, inducing **hyperthyroidism and goiter**.