Lecture five & six **Dr. wurood &Dr. Zaid**

Lec 5 : Immunological Tolerance

Immunological tolerance is a fundamental property of the immune system that prevents immune responses against self-antigens while maintaining the ability to respond to foreign pathogens. **Failure of tolerance mechanisms leads to autoimmune diseases**, **allergies, and chronic inflammatory conditions**. Tolerance is established and maintained through multiple mechanisms that operate at different stages of lymphocyte development and activation. These mechanisms are broadly classified into **central tolerance** and **peripheral tolerance**, with **anergy** being a key functional outcome of peripheral tolerance.

1. Central Tolerance

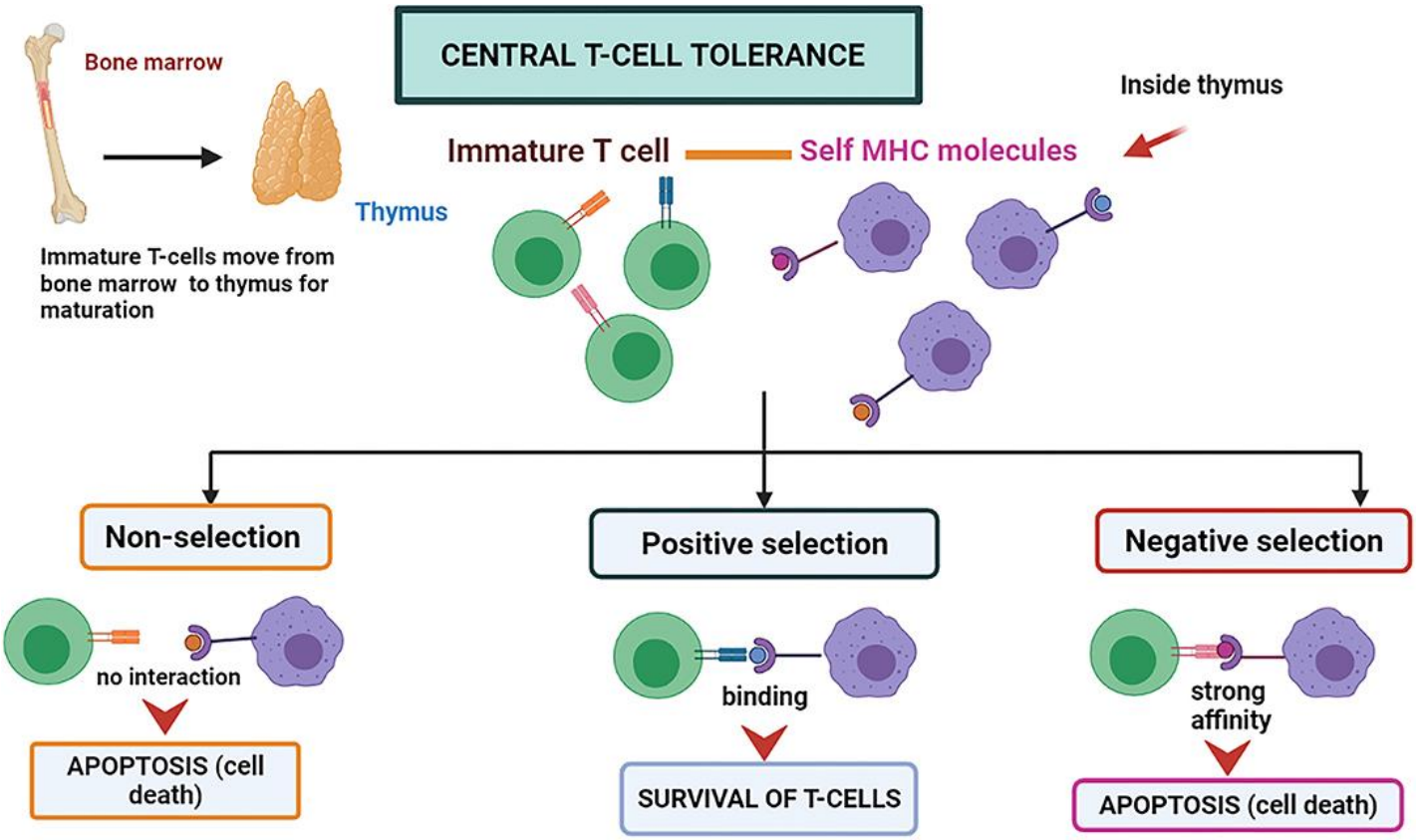
Central tolerance : the elimination or modification of self-reactive lymphocytes during their development in the **primary lymphoid organs**—the thymus for T lymphocytes and the bone marrow for B lymphocytes.

1.1 Central Tolerance in T Cells

T cells develop in the thymus and undergo two critical selection processes:

1. **Positive Selection**
    - Occurs in the thymic cortex
    - Ensures T cells can recognize self-MHC molecules
    - T cells that fail to recognize self-MHC undergo apoptosis
2. **Negative Selection**
    - Occurs mainly in the thymic medulla
    - Eliminates T cells that bind strongly to self-peptide–MHC complexes
    - Prevents the survival of potentially autoreactive T cells

The transcription factor **AIRE (Autoimmune Regulator)** plays a crucial role by promoting the expression of tissue-specific antigens in thymic epithelial cells, allowing deletion of T cells reactive to peripheral self-antigens.



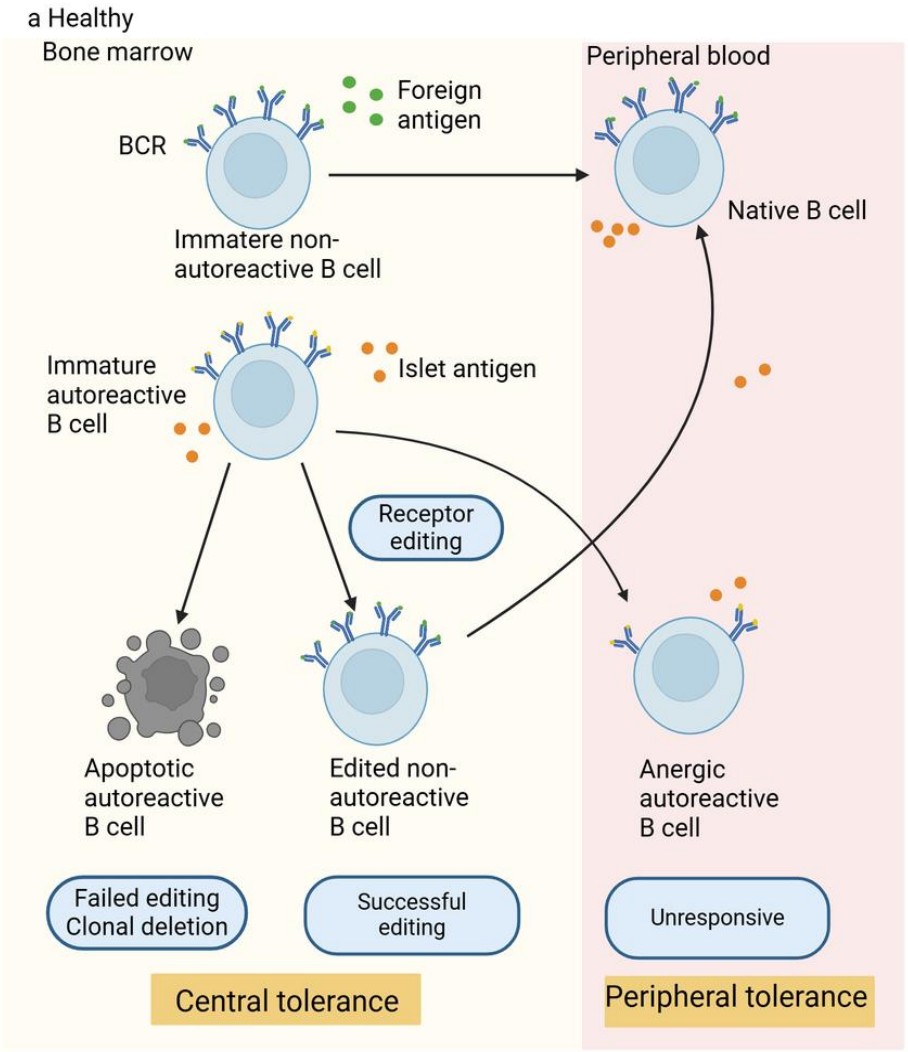
1.2 Central Tolerance in B Cells

B cells develop in the bone marrow, where self-reactive B cells are controlled by:

- **Clonal deletion**: elimination of strongly self-reactive B cells
- **Receptor editing**: rearrangement of light-chain genes to change antigen specificity
- **Anergy**: functional inactivation of self-reactive B cells

2. Peripheral Tolerance

The mechanisms that control self-reactive lymphocytes that escape central tolerance and reach peripheral tissues.



2.1 Mechanisms of Peripheral Tolerance

1. Anergy

- Occurs when lymphocytes recognize antigen without appropriate costimulatory signals
- Common in T cells when antigen presentation lacks **CD28–B7** interaction
- Results in functional unresponsiveness

2.2 Suppression by Regulatory T Cells (Tregs)

- $CD4^+CD25^+FoxP3^+$ T cells
- Suppress immune responses through:
  - IL-10 and TGF-β secretion
  - Inhibition of antigen-presenting cells
  - Direct cell–cell contact

3. Deletion (Activation-Induced Cell Death)

- Repeated stimulation of self-reactive lymphocytes
- Mediated by apoptotic pathways such as **Fas–FasL interaction**

3. Anergy

Anergy is a state of **functional inactivation** in which lymphocytes remain alive but are unable to respond to antigenic stimulation.

3.1 Mechanism of T Cell Anergy

- Antigen recognition in the absence of costimulatory signals
- Leads to:
  - Reduced IL-2 production
  - Impaired proliferation
  - Altered intracellular signaling pathways

Key molecular events include increased expression of inhibitory receptors such as **CTLA-4** and **PD-1**.

3.2 Anergy in B Cells

- Occurs when B cells bind soluble self-antigens
- Results in:
  - Reduced surface IgM expression
  - Shortened lifespan
  - Failure to respond to activation signals
  -

Autoimmunity: mechanisms and types.

The immune system is designed to protect the body against foreign antigens such as bacteria, viruses, and parasites. One of its most important features is **self-tolerance**, which allows the immune system to distinguish between self and non-self antigens. **Autoimmunity** occurs when this tolerance is lost, leading the immune system to attack the body's own cells and tissues, resulting in **autoimmune diseases**.

Autoimmune diseases can affect almost any organ system and may be localized to a single tissue or involve multiple organs.

1. Definition

Autoimmunity is defined as an **immune response directed against self-antigens**, caused by a breakdown in immune tolerance mechanisms. These responses may involve **autoantibodies**, **autoreactive T lymphocytes**, or both.

Self-Tolerance and Its Importance

Self-tolerance refers to the immune system's ability to avoid reacting against the body's own components. It is established through two main mechanisms:

- **Central tolerance**
- **Peripheral tolerance**

Failure of these mechanisms is the fundamental cause of autoimmunity.

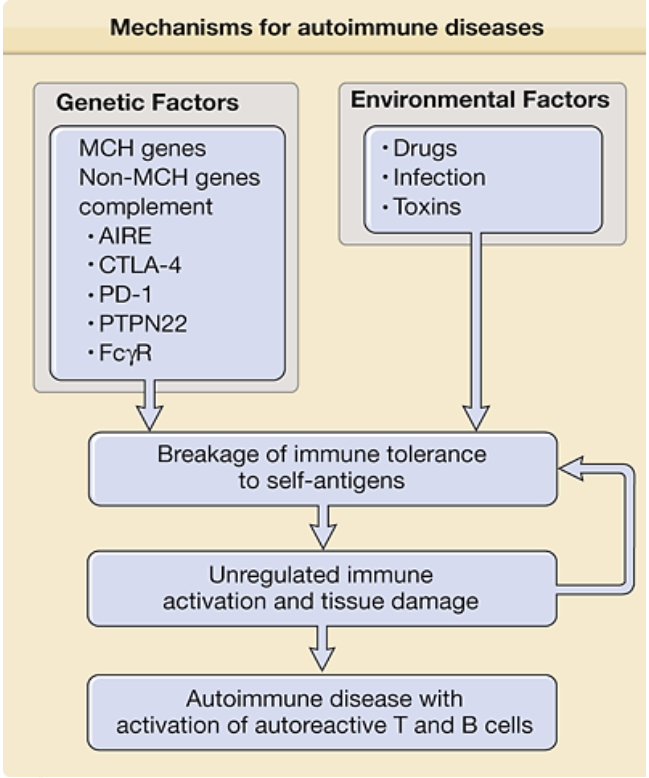
2. Mechanisms of Autoimmunity

2.1. Breakdown of Central Tolerance

Central tolerance occurs in the **thymus (T cells)** and **bone marrow (B cells)**, where self-reactive lymphocytes are eliminated through negative selection.

Defects in this process allow autoreactive lymphocytes to escape into the peripheral circulation. Example: Mutations affecting thymic selection can predispose individuals to autoimmune diseases.

2.2. Failure of Peripheral Tolerance



Peripheral tolerance controls self-reactive lymphocytes that escape central tolerance. Its main mechanisms include:

- **Anergy** (functional inactivation of lymphocytes)
- **Suppression by regulatory T cells (Tregs)**
- **Activation-induced cell death**

Failure of these mechanisms leads to sustained activation of autoreactive immune cells.

2.3. Molecular Mimicry

Molecular mimicry occurs when **microbial antigens resemble self-antigens**. Immune responses directed against the pathogen may cross-react with host tissues. Example: Rheumatic fever following Streptococcus infection, where antibodies cross-react with heart tissue.

2.4. Release of Sequestered (Hidden) Antigens

Some self-antigens are normally hidden from the immune system (e.g., eye, brain, testis). Tissue injury may expose these antigens, triggering an autoimmune response. Example:Autoimmune uveitis after eye trauma.

2.5. Polyclonal Lymphocyte Activation

Certain infections or drugs can cause **non-specific activation of lymphocytes**, including autoreactive ones, leading to autoimmunity.

2.6. Genetic Predisposition

Genetic factors play a major role in autoimmunity. Many autoimmune diseases are associated with specific **HLA alleles**, such as:

- HLA-DR3 and HLA-DR4 (Type 1 diabetes mellitus)

3. Types of Autoimmune Diseases

Autoimmune diseases are classified into two main types:

3.1. Organ-Specific Autoimmune Diseases

In these diseases, the immune response is directed against a **single organ or tissue**.

Examples:

- **Type 1 Diabetes Mellitus** – destruction of pancreatic β-cells
- **Hashimoto's thyroiditis** – autoimmune destruction of the thyroid gland
- **Graves' disease** – autoantibodies stimulate thyroid hormone production
- **Myasthenia gravis** – antibodies against acetylcholine receptors at the neuromuscular junction

3.2. Systemic (Non-specific) Autoimmune Diseases

These diseases involve **multiple organs and tissues**, often with circulating immune complexes.

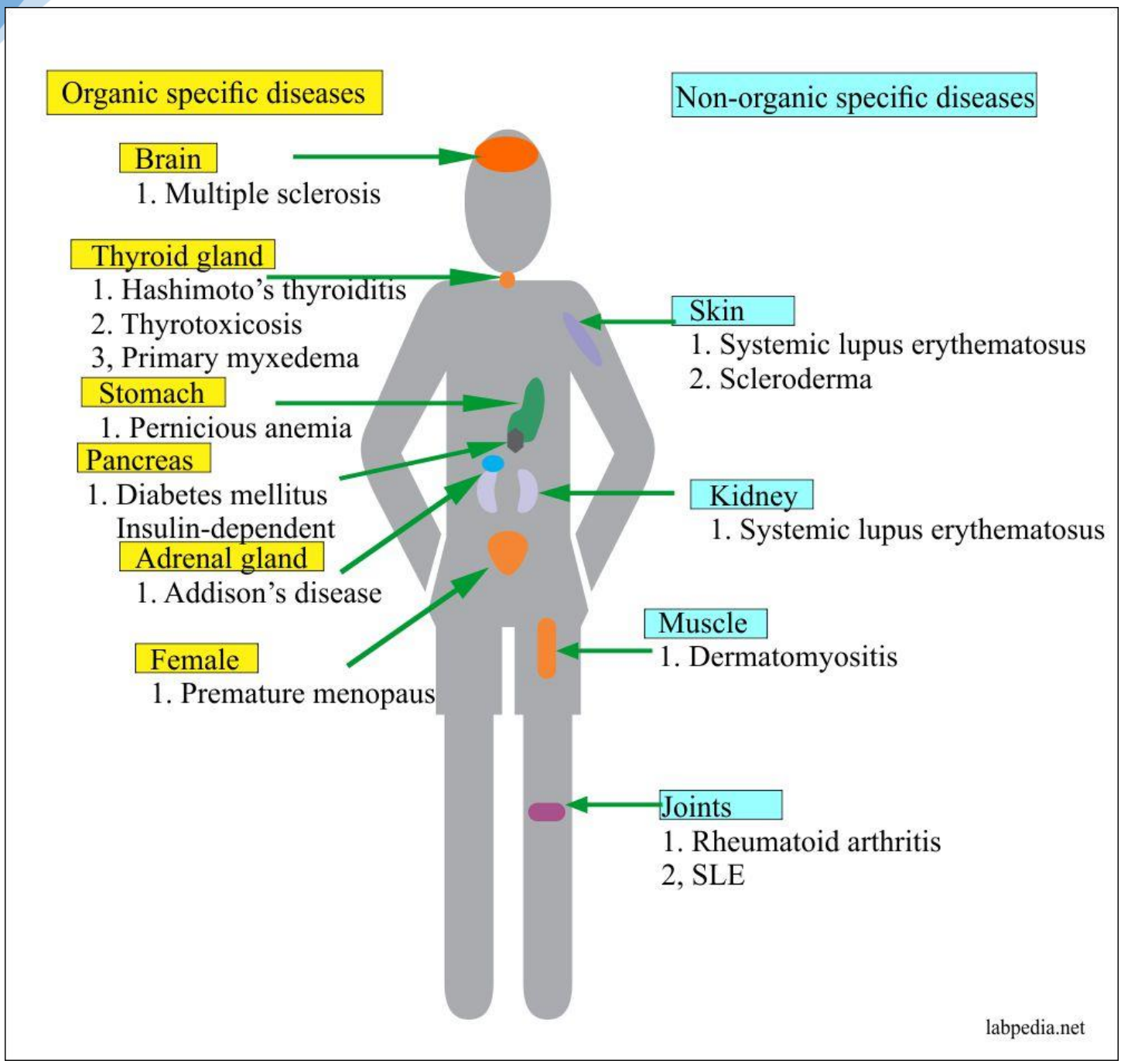
Examples:

- **Systemic lupus erythematosus (SLE)** – affects skin, joints, kidneys, and CNS
- **Rheumatoid arthritis (RA)** – chronic inflammation of synovial joints
- **Systemic sclerosis (scleroderma)** – fibrosis of skin and internal organs
- **Sjogren's syndrome** – affects salivary and lacrimal glands

4. Immunological Mechanisms Involved

Autoimmune diseases may be mediated by:

- **Autoantibodies** (Type II or III hypersensitivity)
- **T cell–mediated immune responses** (Type IV hypersensitivity)
- **Immune complex deposition**


Organic specific diseases
Non-organic specific diseases
Brain
1. Multiple sclerosis
Thyroid gland
1. Hashimoto's thyroiditis
2. Thyrotoxicosis
3, Primary myxedema
Stomach
1. Pernicious anemia
Pancreas
1. Diabetes mellitus
Insulin-dependent
Adrenal gland
1. Addison's disease
Female
1. Premature menopaus
Skin
1. Systemic lupus erythematosus
2. Scleroderma
Kidney
1. Systemic lupus erythematosus
Muscle
1. Dermatomyositis
Joints
1. Rheumatoid arthritis
2, SLE
labpedia.net