BHARATHIDASAN UNIVERSITY

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Programme: M.Sc., Biomedical Science

Course Code: BM35C6
Course Title: Immunology

Unit-V
Overview of Autoimmunity and Transplantation

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Unit V:

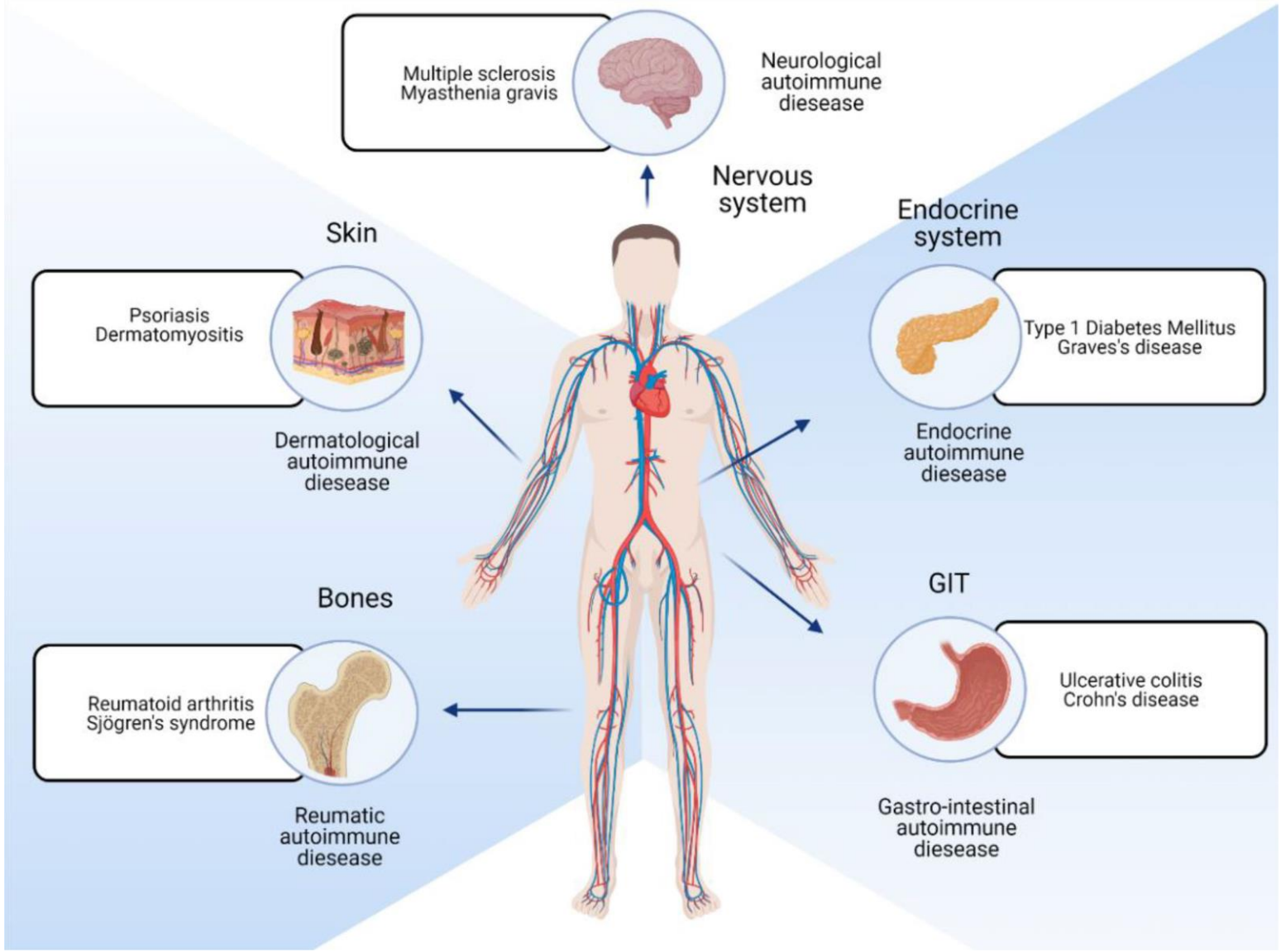
Overview of Autoimmunity and Transplantation - Autoimmune disease – Spectrum – organ specific (thyroid diseases, IDDM, pernicious anemia) and non-organ specific (Systemic sclerosis & SLE). Factors governing autoimmune diseases- genetic, hormonal, microbial and non-microbial. Regulatory mechanisms involved in autoimmune diseases- Tolerance – breakdown of tolerance (Modification of auto antigen, Cross-reactions with B cell epitopes, molecular mimicry of T cell epitopes. Transplants –auto, allo and Xeno- immunological complications of transplantation – graft rejection, GVHD –mechanisms – prevention of graft rejection- Immunosuppressant Drugs (Glucocorticoids, Calcineurin inhibitors, Antiproliferative/Antimetabolic agents) and antibodies as immunosuppressant

PRESENTATION: 1

Overview of Autoimmunity and Transplantation

- **Autoimmunity** occurs when the immune system mistakenly attacks the body's own tissues, leading to various autoimmune diseases.
- This breakdown in self-tolerance can affect specific organs or multiple systems.
- **Transplantation** involves the transfer of cells, tissues, or organs from a donor to a recipient, often triggering immune responses that need to be carefully managed to prevent rejection.

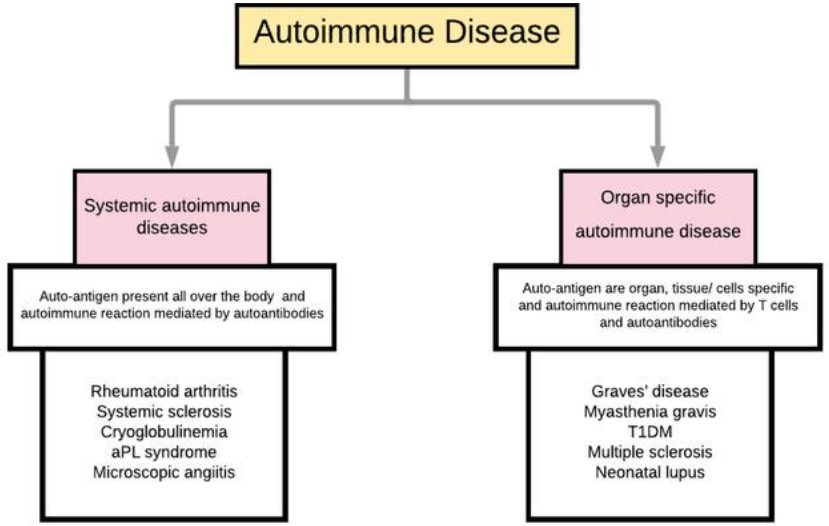
AUTOIMMUNITY



1. Organ-Specific Autoimmune Diseases

In organ-specific autoimmune diseases, the immune response is directed against antigens of a particular organ, leading to localized tissue damage.

(A)

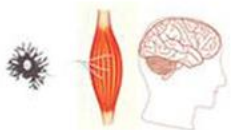


(B)

ORGAN-SPECIFIC AUTOIMMUNE DISEASES

Gastrointestinal tract
- pernicious anemia (Biermer anemia)
- autoimmune liver diseases (autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis)

Muscle, nerves and brain
- myasthenia gravis
- polyneuropathies
- Guillain-Barré syndrome
- multiple sclerosis



Eyes
- autoimmune uveitis
- autoimmune retinopathy
- sympathetic ophthalmia

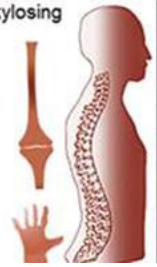
Skin
- vitiligo
- autoimmune bullous diseases
- alopecia areata

Autoimmune cytopenia
- autoimmune haemolytic anaemia
- autoimmune neutropenia
- autoimmune thrombocytopenia

Endocrine glands
- type 1 diabetes
- autoimmune thyroiditis (Hashimoto's thyroiditis and Graves's disease)
- Addison's disease
- autoimmune polyendocrinopathies

SYSTEMIC OR NON ORGAN-SPECIFIC AUTOIMMUNE DISEASES

- systemic lupus erythematosus
- Gougerot-Sjögren syndrome
- systemic autoimmune rheumatic diseases (rheumatoid arthritis, ankylosing spondylitis, rheumatic fever, rheumatic heart disease, etc.)
- scleroderma
- polymyositis
- dermatopolymyositis
- mixed connectivity
- primitive vasculitis
- atrophic polychondritis
- antiphospholipid syndrome
- celiac dise ase
- myocarditis



CLINICAL CONTEXT
- central neurological/ neuropsychiatric involvement
- peripheral neuropathies
- eye involvement
- lung involvment
- cardiac/muscular involvement
- valvulopathy
- cutaneous vascular involvement
- renal involvement
- joint involvement

A. Thyroid Diseases

- **Hashimoto's Thyroiditis:**
  - **Pathogenesis:** Autoantibodies and autoreactive T cells target thyroid antigens (e.g., thyroglobulin, thyroid peroxidase).
  - **Clinical Features:** Hypothyroidism, goiter, fatigue, weight gain, cold intolerance.
- **Graves' Disease:**
  - **Pathogenesis:** Autoantibodies (thyroid-stimulating immunoglobulins) mimic TSH, leading to overproduction of thyroid hormones.
  - **Clinical Features:** Hyperthyroidism, goiter, exophthalmos, heat intolerance, weight loss.

B. Type 1 Diabetes Mellitus (IDDM)

- **Pathogenesis:** Autoimmune destruction of insulin-producing beta cells in the pancreas by autoreactive T cells.
- **Clinical Features:** Hyperglycemia, polyuria, polydipsia, polyphagia, weight loss.

C. Pernicious Anemia

- **Pathogenesis:** Autoimmune destruction of gastric parietal cells or intrinsic factor, leading to vitamin B12 deficiency.
- **Clinical Features:** Megaloblastic anemia, fatigue, neuropathy, glossitis.

2. Non-Organ Specific Autoimmune Diseases

- In non-organ specific autoimmune diseases, the immune response targets multiple organs and tissues, leading to systemic manifestations.

A. Systemic Lupus Erythematosus (SLE)

- **Pathogenesis:** Production of autoantibodies (e.g., anti-dsDNA, anti-Smith) that form immune complexes, causing inflammation and tissue damage.
- **Clinical Features:** Butterfly rash, arthritis, nephritis, serositis, hematologic abnormalities, CNS involvement.

B. Systemic Sclerosis (Scleroderma)

- **Pathogenesis:** Autoimmunity leads to excessive collagen deposition and fibrosis in the skin and internal organs.
- **Clinical Features:** Skin thickening (sclerodactyly), Raynaud's phenomenon, esophageal dysmotility, pulmonary fibrosis.

Spectrum of Autoimmune Diseases

- Autoimmune diseases can vary widely in their manifestations, severity, and progression. Some key points along the spectrum include:
- **Subclinical Autoimmunity:**

  Presence of autoantibodies without symptoms.
- **Chronic Autoimmune Disease:**

  Persistent, progressive disease with flares and remissions.
- **Systemic vs. Organ-Specific:**

  Systemic diseases affect multiple organs, while organ-specific diseases target a single organ.

Mechanisms of Autoimmune Disease Development

1.Genetic Susceptibility:

1. HLA haplotypes (e.g., HLA-DR3/DR4 in Type 1 diabetes) are associated with increased risk.

2.Environmental Triggers:

1. Infections, drugs, or toxins can initiate autoimmunity by molecular mimicry or bystander activation.

3.Breakdown of Tolerance:

1. Central tolerance (in thymus) and peripheral tolerance mechanisms (e.g., Treg cells) fail, allowing autoreactive lymphocytes to persist.

Overview of Transplantation

Transplantation involves replacing damaged or dysfunctional tissues or organs with healthy ones from a donor. However, the recipient's immune system may recognize the transplanted tissue as foreign and mount an immune response, leading to rejection.

Types of Transplants:

1. **Autograft:** Tissue transplanted from one part of the body to another in the same individual.
2. **Allograft:** Transplantation between genetically different individuals of the same species.
3. **Xenograft:** Transplantation between different species.

Immune Response in Transplantation

1. Hyperacute Rejection:

- Occurs within minutes to hours due to preformed antibodies against donor antigens (e.g., ABO incompatibility).
- **Mechanism:** Antibody-mediated complement activation leads to vascular thrombosis and graft necrosis.

2. Acute Rejection:

- Occurs within days to weeks post-transplant, mediated by recipient T cells recognizing donor antigens.
- **Mechanism:** Direct cytotoxicity by CD8+ T cells and helper T cell-mediated inflammation.

3. Chronic Rejection:

- Occurs months to years after transplantation, characterized by progressive graft fibrosis and vessel occlusion.
- **Mechanism:** Chronic immune-mediated damage and repair processes lead to graft dysfunction.

Immunosuppressive Therapy in Transplantation

- To prevent rejection, recipients are placed on immunosuppressive therapy, including:
- **Calcineurin Inhibitors:** Tacrolimus, cyclosporine.
- **Antimetabolites:** Azathioprine, mycophenolate mofetil.
- **Corticosteroids:** Prednisone.
- **Monoclonal Antibodies:** Basiliximab, alemtuzumab.

Challenges in Transplantation

- **Graft-Versus-Host Disease (GVHD):**

  Occurs in bone marrow transplants where donor immune cells attack the recipient’s tissues.

- **Infections:**

  Immunosuppressive therapy increases the risk of opportunistic infections.

- **Rejection:**

  Despite advances, chronic rejection remains a significant challenge.

FACTORS GOVERNING AUTOIMMUNE SYSTEM

INTRODUCTION

- Autoimmune diseases are conditions where the immune system mistakenly attacks the body’s own tissues, mistaking them for harmful pathogens.
- These diseases encompass a wide range of disorders, including rheumatoid arthritis, lupus, multiple sclerosis, and type 1 diabetes, among others.
- Autoimmune diseases affect millions of people worldwide and pose significant challenges for public health due to their chronic nature and the complexity of their underlying causes.
- Studying autoimmune diseases is crucial for developing effective treatments and improving the quality of life for those affected.

- Autoimmune diseases are prevalent globally, affecting an estimated 5-8% of the population.
- They can lead to significant morbidity and mortality, necessitating lifelong medical care.
- Factors governing these autoimmune diseases are

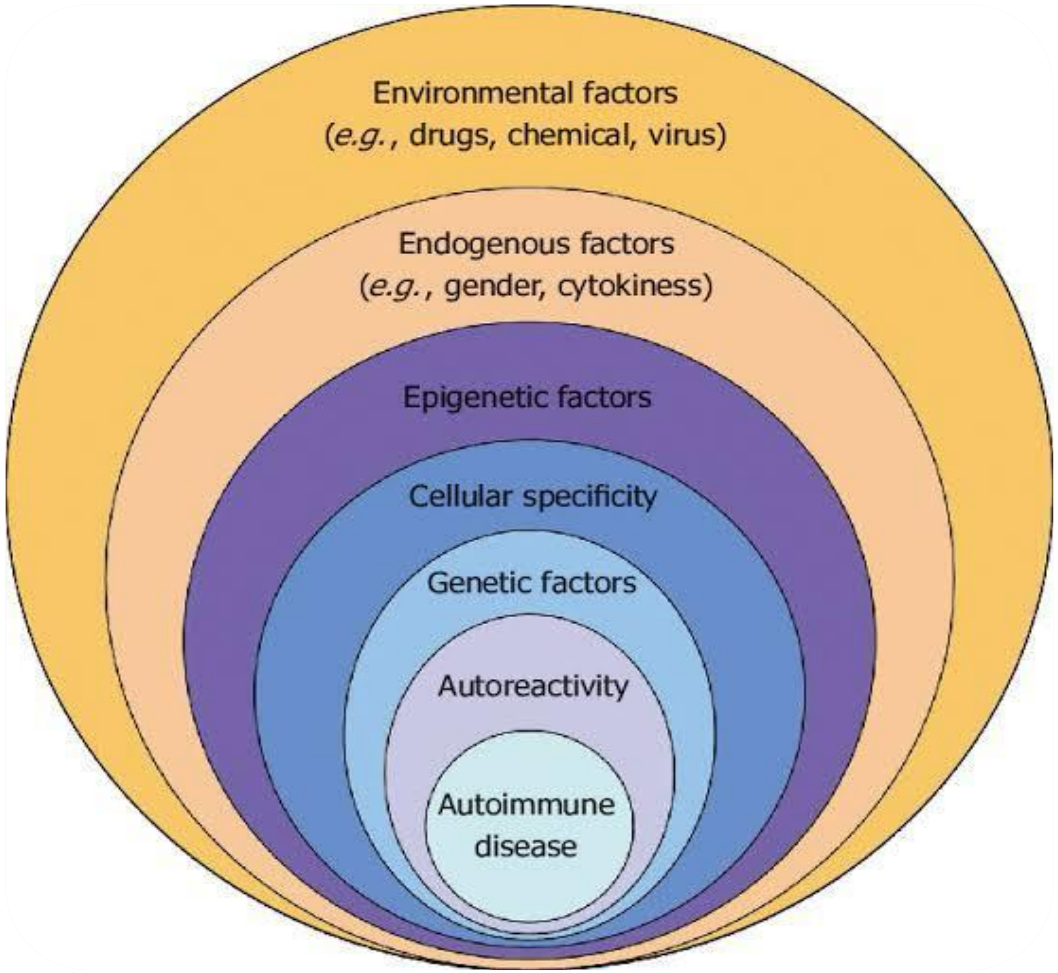
- Genetic

- Environmental

- Immunological

- Hormonal

Factors governing autoimmune system



The Immune system

- **Role:**

  Protects the body from infections and diseases.

- **Components:**

  White blood cells, antibodies, and other elements.

Normal function involves recognizing and eliminating pathogens like bacteria and viruses.

What are immune disease?

- **Definition:**

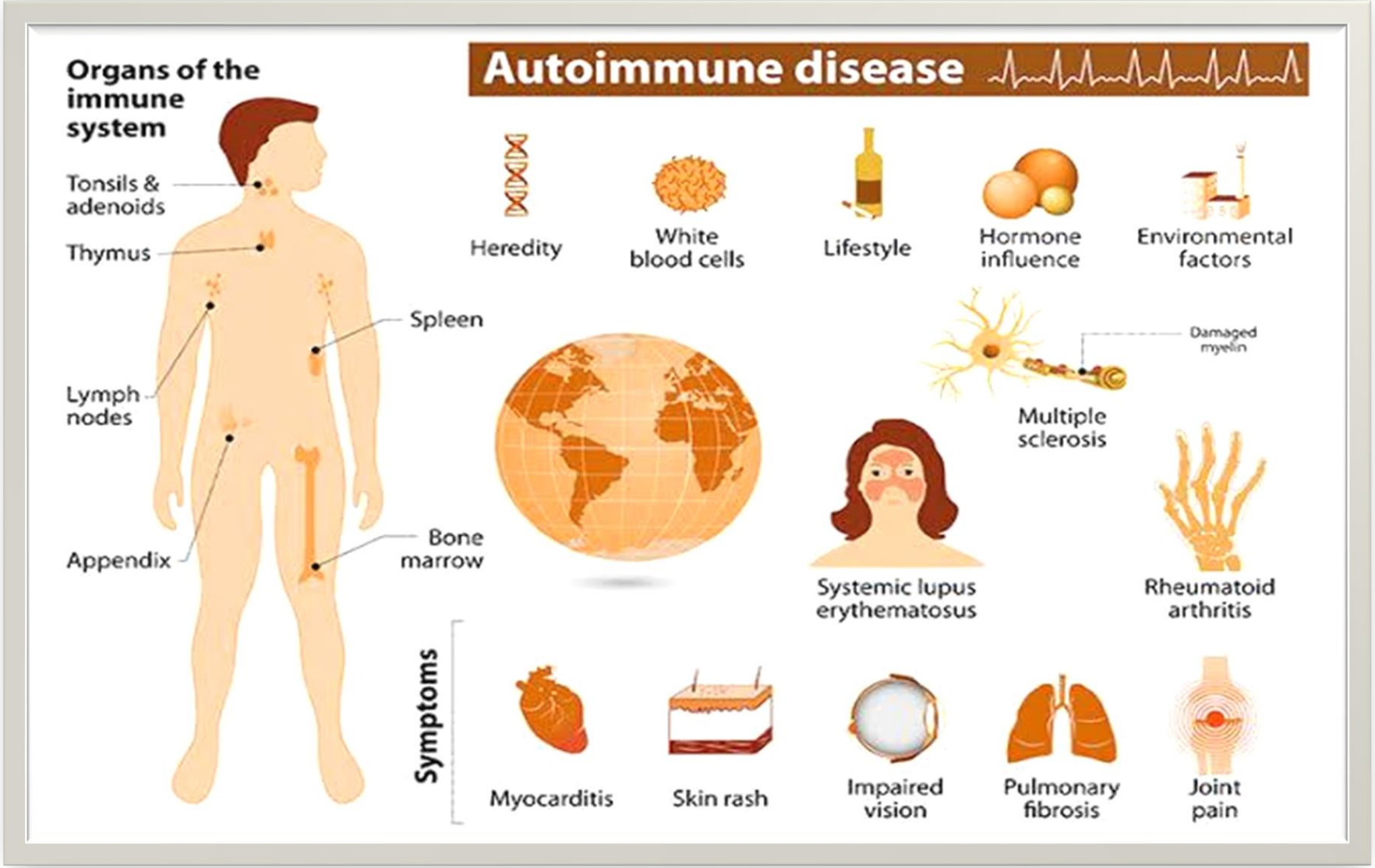
Autoimmune diseases occur when the immune system attacks the body’s own cells.

- **Examples:** Rheumatoid arthritis, lupus, multiple sclerosis.
- Symptoms vary widely, including chronic pain, fatigue, and organ damage.

Autoimmunity

- Occurs when the immune system mistakenly attacks the body’s own tissues.
- Leads to chronic inflammation and tissue damage.
- The exact cause is often unknown, but involves multiple factors.

Outline of auto immune disease



Genetic factors

- Genetics play a significant role in autoimmune diseases.
- Certain genes, such as HLA genes, increase susceptibility.
- Family history is a strong indicator of risk.

Role of Genetics

- Genetics play a pivotal role in the development of autoimmune diseases.
- Specific genes can increase an individual's susceptibility to these disorders. For instance, the Human Leukocyte Antigen (HLA) gene complex, located on chromosome 6, is strongly associated with several autoimmune diseases.
- Variants of HLA genes can influence the immune system's ability to distinguish between self and non-self, leading to autoimmunity

Key genes involved

- **HLA Genes**: Variations in HLA class I and II genes are linked to diseases such as type 1 diabetes, rheumatoid arthritis, and multiple sclerosis. For example, HLA-DRB1 is associated with rheumatoid arthritis, while HLA-DQB1 is linked to type 1 diabetes.
- **PTPN22**: This gene encodes a protein tyrosine phosphatase, which regulates T-cell receptor signalling. Variants in PTPN22 are associated with an increased risk of rheumatoid arthritis, lupus, and other autoimmune diseases.
- **CTLA4**: This gene encodes a protein that functions as an immune checkpoint, regulating T cell activation. Polymorphisms in CTLA4 are linked to diseases such as type 1 diabetes and Graves' disease

Environmental trigger

- Environmental factors can trigger autoimmune diseases.
- Common triggers include infections, toxins, and pollutants.
- The "hygiene hypothesis" suggests that a lack of early exposure to pathogens may increase risk.

Infections

- Infections are significant environmental triggers for autoimmune diseases.
- Pathogens, such as viruses and bacteria, can trigger autoimmune responses through mechanisms like molecular mimicry, where the immune system mistakes self-antigens for foreign antigens.
- For example, the Epstein-Barr virus has been implicated in multiple sclerosis, and Streptococcus infections are linked to rheumatic fever.

Diet and toxins

- Dietary factors and exposure to toxins can influence the risk of autoimmune diseases.
- High salt intake, for instance, has been associated with an increased risk of autoimmune diseases by promoting inflammation.
- Exposure to certain chemicals, such as mercury and pesticides, can also trigger autoimmune responses by causing tissue damage and altering immune function.

Life style factors

- Lifestyle factors, including stress and smoking, can exacerbate the risk of autoimmune diseases. Chronic stress can lead to immune dysregulation, increasing susceptibility to autoimmunity.
- Smoking is a well-established risk factor for diseases such as rheumatoid arthritis and lupus, as it can induce inflammation and alter immune responses.

IMMUNOLOGICAL FACTORS

Immune System Dysregulation

- The immune system plays a central role in the development of autoimmune diseases.
- Normally, the immune system can distinguish between self and non-self-antigens, but in autoimmune diseases, this self-tolerance is lost.
- This loss of self-tolerance can result from genetic predisposition, infections, or other environmental factors

Cytokines and Immune Mediators

- Cytokines are signalling molecules that regulate immune responses.
- Dysregulation of cytokine production and signalling can contribute to autoimmune diseases.
- For example, elevated levels of pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), are observed in rheumatoid arthritis and other autoimmune diseases.

Immune Checkpoints

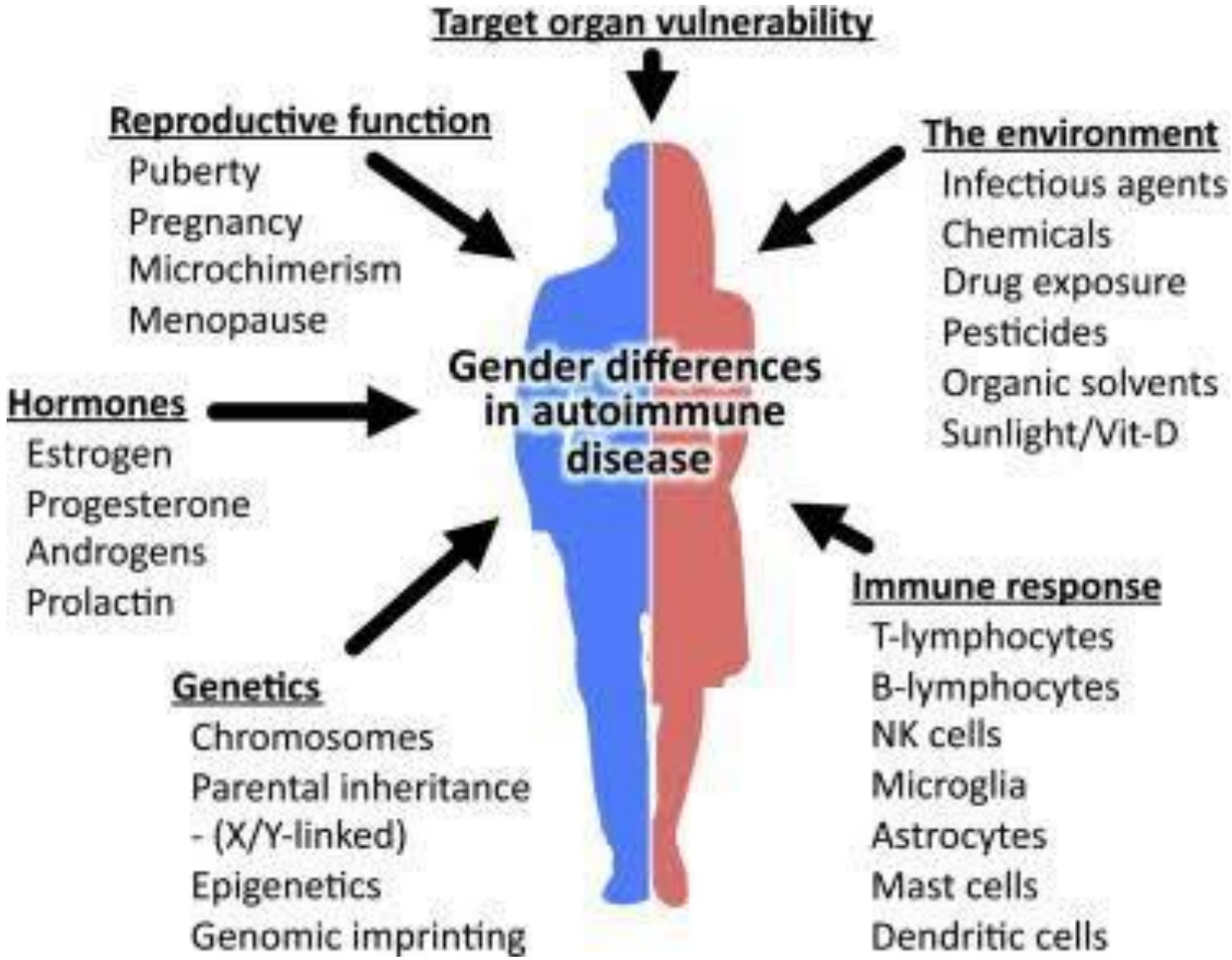
- Immune checkpoints, such as CTLA-4 and PD-1, play a crucial role in maintaining self-tolerance by regulating T-cell activation.
- Dysregulation of these checkpoints can lead to uncontrolled T-cell activity and autoimmunity.

Hormonal factors

- Hormones, particularly sex hormones, influence autoimmune disease prevalence.
- Women are more prone to autoimmune diseases, possibly due to hormonal differences.
- Hormonal changes during pregnancy and menopause can affect disease activity.

Gender Differences

- Autoimmune diseases exhibit a gender bias, with women being more frequently affected than men.
- This disparity suggests that hormonal factors play a significant role in autoimmunity. For instance, diseases like lupus and multiple sclerosis are more common in women, particularly during their reproductive years.


Target organ vulnerability
Reproductive function
Puberty
Pregnancy
Microchimerism
Menopause
The environment
Infectious agents
Chemicals
Drug exposure
Pesticides
Organic solvents
Sunlight/Vit-D
Hormones
Estrogen
Progesterone
Androgens
Prolactin
Gender differences in autoimmune disease
Genetics
Chromosomes
Parental inheritance
- (X/Y-linked)
Epigenetics
Genomic imprinting
Immune response
T-lymphocytes
B-lymphocytes
NK cells
Microglia
Astrocytes
Mast cells
Dendritic cells

Role of Sex Hormones

- **Estrogen**: Estrogen has been shown to enhance immune responses, potentially increasing the risk of autoimmunity in women. It can promote the activation and survival of autoreactive B cells and T-cells.
- **Progesterone**: Progesterone has immunomodulatory effects and can suppress inflammatory responses. Its role in autoimmune diseases is complex and may vary depending on the disease and stage of the immune response.

Other Hormones

- Other hormones, such as thyroid hormones, also influence autoimmune diseases. For example, hyperthyroidism and hypothyroidism can result from autoimmune conditions like Graves' disease and Hashimoto's thyroiditis, respectively.

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