Central and Peripheral Tolerance and Autoimmunity

- Overview of immune tolerance mechanisms, selection processes, and autoimmune disease pathogenesis.

1. Introduction to Immune Tolerance

- Tolerance prevents the immune system from attacking self-antigens.
- Mechanisms:

  - Central tolerance: in thymus and bone marrow.

  - Peripheral tolerance: in secondary lymphoid organs and tissues.
- Loss of tolerance → autoimmunity.

2. Central Tolerance – Overview

- Site: Thymus (T cells), Bone marrow (B cells).
- Function: Eliminate or inactivate strongly self-reactive lymphocytes.
- Key outcome: prevention of autoreactive clones from entering circulation.

3. Positive and Negative Selection in T Cells

- Positive selection (thymic cortex):
  - Ensures T cells recognize self-MHC molecules.
  - Cells that cannot bind MHC die by apoptosis.
- Negative selection (thymic medulla):
  - Eliminates T cells that bind too strongly to self-peptides.
  - Mediated by AIRE (autoimmune regulator) protein.

4. B Cell Central Tolerance

- Occurs in bone marrow.
- Strongly self-reactive B cells undergo:
  - Receptor editing (light chain rearrangement)
  - Apoptosis (clonal deletion)
  - Anergy (functional unresponsiveness).
- Prevents autoreactive B cells from maturing.

5. Peripheral Tolerance Mechanisms

- Controls self-reactive lymphocytes that escape central tolerance.
- Mechanisms:
  - Anergy: no co-stimulation → inactivation.
  - Regulatory T cells (Tregs): secrete IL-10, TGF-β to suppress activation.
  - Deletion: apoptosis of activated autoreactive cells.
  - Immune privilege: tissues like brain and eye protected from immune attack.

6. Breakdown of Tolerance and Autoimmunity

- Autoimmunity results from defects in central or peripheral tolerance.
- Causes:
  - Genetic (HLA types, AIRE, FOXP3 mutations)
  - Environmental (infections, UV exposure, smoking)
  - Molecular mimicry, bystander activation, or epitope spreading.

7. Immunopathology of Autoimmune Diseases

- Mechanisms of tissue injury:
  - Type II: antibody-mediated cytotoxicity.
  - Type III: immune complex-mediated inflammation.
  - Type IV: T-cell mediated destruction.
- Chronic inflammation → fibrosis and organ failure.

8. Epidemiology of Autoimmune Diseases

- Affect 5–10% of global population.
- Female predominance (3–9:1 ratio).
- Common triggers: infections, hormones, drugs, UV exposure.
- Genetic predisposition (HLA-DR3, DR4, B27) increases risk.

9. Organ-Specific Autoimmune Diseases

- Type 1 Diabetes Mellitus – CD8+ T cell destruction of β-cells.
- Graves' Disease – stimulating antibodies against TSH receptor.
- Myasthenia Gravis – blocking antibodies to acetylcholine receptor.
- Multiple Sclerosis – T cell-mediated demyelination.

10. Systemic Autoimmune Diseases

- Systemic Lupus Erythematosus (SLE): immune complexes and autoantibodies to nuclear antigens.
- Rheumatoid Arthritis: synovial inflammation by T cells and RF/anti-CCP antibodies.
- Sjögren's Syndrome: lymphocytic infiltration of salivary and lacrimal glands.
- Systemic Sclerosis: fibrosis and autoantibodies to centromere or topoisomerase I.

11. Key Takeaways

- Immune tolerance ensures self-recognition without self-destruction.
- Central and peripheral tolerance act at different stages.
- Autoimmunity arises from loss of tolerance.
- Both genetic and environmental factors contribute.
- Understanding these pathways aids in therapy development.