Autoimmunity

Learning objectives

By the end of this session student should be able to understand

- Central and peripheral tolerance
- Theories of autoimmunity
- Autoimmune diseases

AUTOIMMUNITY

- Condition in which the body's own immunologically competent cells or antibodies act against its self-antigens resulting in structural or functional damage.
- Paul Ehrlich had first introduced the concept of autoimmunity; he termed this condition as "horror autotoxicus".

AUTOIMMUNITY

- Normally immune system does not react to its own antigens due to a protective mechanism called tolerance.
- Any breach in tolerance mechanisms predispose to several autoimmune diseases.

IMMUNOLOGICAL TOLERANCE

- State in which an individual is incapable of developing an immune response against his own tissue antigens.
- Mediated by two broad mechanisms:
  - Central tolerance
  - Peripheral tolerance.

Central tolerance

- Refers to the deletion of self-reactive T and B lymphocytes during their maturation in central lymphoid organs (i.e., in the thymus for T cells and in the bone marrow for B cells).
- In thymus:
  - During the T cell development in thymus → any self-antigens are encountered → processed and presented by thymic antigen presenting cells (APCs) in association with self-MHC.
  - Any developing T cell that expresses a receptor for such self-antigen is negatively selected (i.e. deleted by apoptosis).

Central tolerance

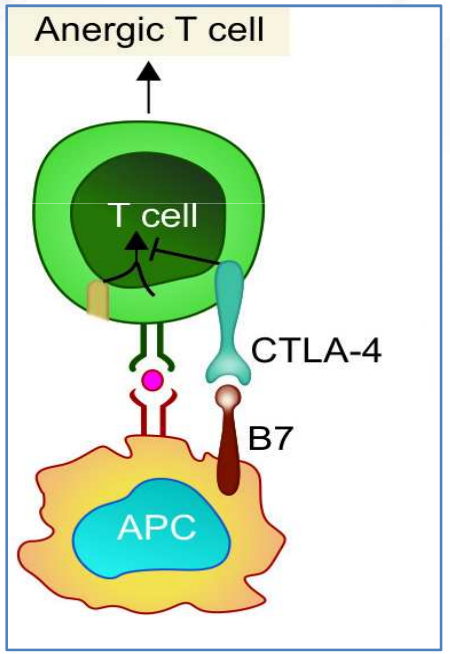
- In bone marrow: Self antigens are eliminated by
  - ***Receptor editing -*** process by which many of the B cells reactivate the machinery of antigen receptor gene rearrangement (mainly genes coding for light chains), so that a different (edited) B cell receptor will be produced which no longer recognizes the self-antigen.
  - ***Negative selection***- If receptor editing fails, they undergo apoptosis.

Peripheral tolerance

- Back-up mechanisms that occur in the *peripheral* tissues to counteract the self-reactive T cells that escape central tolerance.

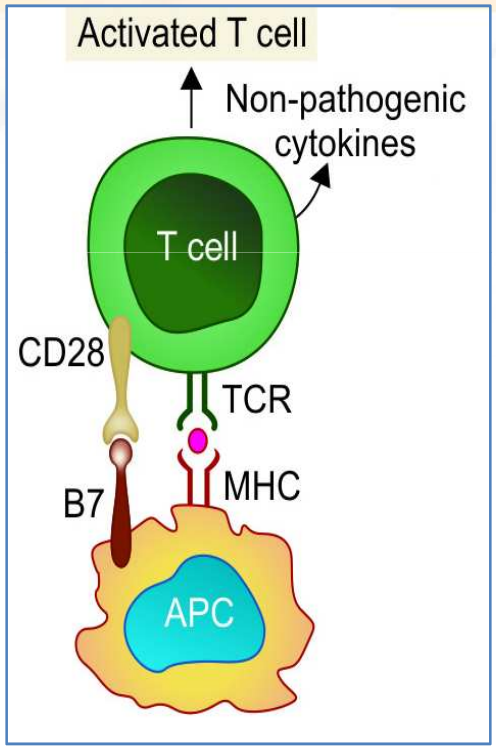
Peripheral tolerance - Mechanisms

- ***Ignorance-*** Self-reactive T cells might never encounter the self-antigen which they recognize.
- ***Anergy:***
  - Defined as unresponsiveness to antigenic stimulus.
  - The self-reactive T cells interact with the APCs presenting the self antigen, but the co-stimulatory signal is blocked.
  - The B7 molecules on APC bind to CTLA-4 molecules on T cells instead of CD28 molecules.



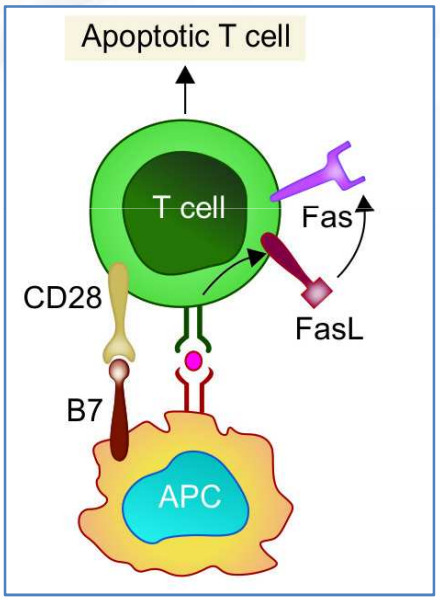
Peripheral tolerance

- ***Phenotypic skewing:***
  - Self-reactive T cells interacting with APCs presented with self-antigens, undergo full activation.
  - Secrete non-pathogenic cytokines and chemokine receptors profile.



Peripheral tolerance

- ***Apoptosis by AICD***:
  - Activation-induced cell death
  - Activation of T cells induces upregulation of Fas ligand which subsequently interacts with the death receptor Fas leading to apoptosis.



Peripheral tolerance

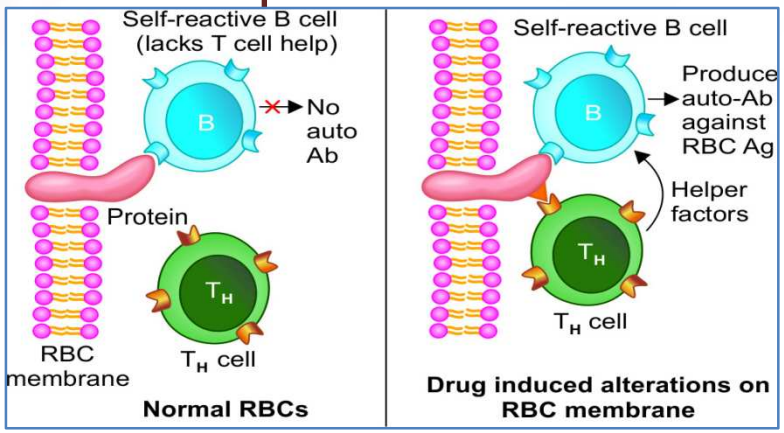
- ***Regulatory T cells (T_{reg} cells):***
  - T_{reg} cells can down regulate the self-reactive T cells through secreting certain cytokines (e.g., IL-10 and transforming growth factor β [TGF-β]) or killing by direct cell to cell contact.
- ***Dendritic cells (DCs):***
  - Immature DCs and tolerogenic DCs capture the self-antigen for processing.
  - Down regulate the expression of molecules of co-stimulatory ligands such as CD40 and B7 molecules or act indirectly by induction of regulatory T cells.
- ***Sequestration of self-antigen:*** Certain self-antigens can evade immune recognition by sequestration in immunologically privileged sites, e.g. corneal proteins, testicular antigens and antigens from brain.

MECHANISMS OF AUTOIMMUNITY

- **Breakdown of T-Cell Anergy:** In the presence of tissue necrosis and local inflammation express co-stimulatory molecules (B7) .
  - Multiple sclerosis, rheumatoid arthritis and psoriasis
- **Failure of AICD**- Failure of the auto reactive activated T cells to undergo activation induced cell death (AICD)
  - SLE (systemic lupus erythematosus)

MECHANISMS OF AUTOIMMUNITY

- **Loss of T_{reg} cells.**
- **Providing T cell help to stimulate self-reacting B cells**:
  - Antibody response to self-antigens occurs only when potentially self-reactive B cells receive help from T cells.



MECHANISMS OF AUTOIMMUNITY

- **Release of Sequestered Antigens:**
  - Sequestered antigens -never been exposed to the tolerance mechanisms during development of immune system.
  - Injury to the organs leads to release of such sequestered antigens which are very well capable of mounting an immune response.
  - Spermatozoa and ocular antigens release can cause post vasectomy orchitis and post-traumatic uveitis.

MECHANISMS OF AUTOIMMUNITY

- **Molecular Mimicry:**
  - Some microorganisms share antigenic determinants (epitopes) with self-antigens.
  - Immune response against such microbes would produce antibodies that can cross-react with self-antigen.
  - Example: Acute rheumatic fever and multiple sclerosis (molecular mimicry involving T-cell epitopes).

MECHANISMS OF AUTOIMMUNITY

- **Polyclonal Lymphocyte Activation**
  - *Polyclonal T cell activation* **-** Superantigens released from microbes (e.g. *Staphylococcus aureus*), polyclonally activate the T cells directly by binding to antigen non-specific Vβ region of T cell receptors.
  - *Polyclonal B cell activation* can be induced by products of various microbes such as Epstein Barr virus, HIV, etc.

MECHANISMS OF AUTOIMMUNITY

- **Bystander activation:**
  - Nonspecific activation of bystander self-reactive T_H1 cells.
  - Leads to cytokine influx which causes an increased infiltration of various non-specific T cells at the site of infection.

AUTOIMMUNE DISEASES

Single Organ or Cell Type Autoimmune Diseases		
Disease	Self-antigen present on	Type of immune response & Important features
Autoimmune anemias		
Autoimmune hemolytic anemia	RBC membrane proteins	Auto-antibodies to RBC antigens triggers complement mediated lysis or antibody-mediated opsonization of the RBCs
Drug induced hemolytic anemia	Drugs alter the red cell membrane antigens	Drugs such as penicillin or methyldopa interact with RBCs so that the cells become antigenic
Pernicious anemia	Intrinsic factor (a membrane-bound protein on gastric parietal cells)	Auto-antibodies to intrinsic factor block the uptake of vitamin B 12; leads to megaloblastic anemia
Idiopathic Thrombocytopenic Purpura	Platelet membrane proteins (glycoproteins IIb-IIIa or Ib-IX)	Auto-antibodies against platelet membrane antigens leads to ↓platelet count

AUTOIMMUNE DISEASES

Single Organ or Cell Type Autoimmune Diseases		
Disease	Self-antigen present on	Type of immune response & Important features
Goodpasture syndrome	Renal and lung basement membranes	Auto-antibodies bind to basement-membrane antigens on kidney glomeruli and the alveoli of the lungs followed by complement mediated injury leads to progressive kidney damage and pulmonary haemorrhage
Myasthenia gravis	Acetylcholine receptors	Blocking type of auto-antibody directed against Ach receptors present on motor nerve endings, leads to progressive weakening of the skeletal muscles
Graves' disease	Thyroid-stimulating hormone (TSH) receptor	Anti TSH- auto-antibody (stimulates thyroid follicles, leads to hyperthyroid state)

AUTOIMMUNE DISEASES

Disease	Self-antigen present on	Type of immune response & Important features
Hashimoto's thyroiditis	Thyroid proteins and cells	Auto-antibodies and T_{DTH} cells targeted against thyroid antigen leads to suppression of thyroid gland. • Seen in middle aged females • Hypothyroid state is produced (↓ production of thyroid hormones)
Post-streptococcal glomerulonephritis	Kidney	Streptococcal antigen- antibody complexes are deposited on glomerular basement membrane
Insulin-dependent diabetes mellitus	Beta cells present in islets of Langerhans of pancreas	T_{DTH} cells and auto-antibodies directed against pancreatic beta cells cause ↓ production of insulin

AUTOIMMUNE DISEASES

Single Organ or Cell Type Autoimmune Diseases		
Systemic Autoimmune Diseases		
Disease	Self-antigen present on	Type of immune response & Important features
Systemic lupus erythematosus	Auto-antibodies are produced against various tissue antigens such as DNA, nuclear protein, RBC and platelet membranes.	• Age & sex- Women (20-40 years of age) are commonly affected; female to male ratio is-10:1. • Immune complexes (self Ag- auto Ab) are formed; which are deposited in various organs • Major symptoms- Fever, butterfly rash over the cheeks, arthritis, pleurisy, and kidney dysfunction

AUTOIMMUNE DISEASES

Single Organ or Cell Type Autoimmune Diseases		
Systemic Autoimmune Diseases		
Disease	Self-antigen present on	Type of immune response & Important features
Rheumatoid arthritis	Here, a group of auto-antibodies against the host IgG antibodies are produced called RA factor. It is an IgM antibody directed against the Fc region of IgG. ACPA (Anti citrullinated peptide antibodies) are also produced	• Age & sex- Women (40-60 years of age) affected • Auto-antibodies bind to circulating IgG, forming IgM-IgG complexes that are deposited in the joints and can activate the complement cascade. • Major symptoms- Main feature-Arthritis (chronic inflammation of the joints, begins at synovium; most common joints involved are-small joints of the hands, feet and cervical spine) Other features-hematologic, cardiovascular, and respiratory systems are also frequently affected

AUTOIMMUNE DISEASES

Single Organ or Cell Type Autoimmune Diseases		
Systemic Autoimmune Diseases		
Disease	Self-antigen present on	Type of immune response & Important features
Sjögren syndrome	Ribonucleoprotein (RNP) antigens SS-A (Ro) and SS-B (La) present on salivary gland, lacrimal gland, liver, kidney, thyroid	Auto-antibodies to the RNP antigens SS-A (Ro) and SS-B (La); leads to immune-mediated destruction of the lacrimal and salivary glands resulting in dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia)

AUTOIMMUNE DISEASES

Single Organ or Cell Type Autoimmune Diseases		
Systemic Autoimmune Diseases		
Disease	Self-antigen present on	Type of immune response & Important features
Scleroderma (Systemic Sclerosis)	Nuclear antigens such as DNA topoisomerase and centromere present in heart, lungs, GIT, kidney, etc	Helper T cell (mainly) and auto-antibody mediated. Excessive fibrosis of the skin, throughout the body Two types- 1.Diffuse scleroderma- Auto-antibodies against DNA topoisomerase I (anti-Scl 70) is elevated 2.Limited scleroderma- ↑Anticentromere antibody, characterized by CREST syndrome-calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia

AUTOIMMUNE DISEASES

Single Organ or Cell Type Autoimmune Diseases		
Systemic Autoimmune Diseases		
Disease	Self-antigen present on	Type of immune response & Important features
Seronegative Spondyloarthropathies	Sacroiliac joints & other vertebrae Several types- • Ankylosing spondylitis • Reiter Syndrome • Psoriatic Arthritis • Spondylitis With Inflammatory Bowel Disease • Reactive arthritis	Common characteristics- They present as rheumatoid arthritis like features, but differ from it by- • Association with HLA-B27 • Pathologic changes begin in the ligamentous attachments to the bone rather than in the synovium • Involvement of the sacroiliac joints, and/or arthritis in other peripheral joints • Absence of RFs (hence the name "seronegative") • Auto-Ab and immune complex mediated

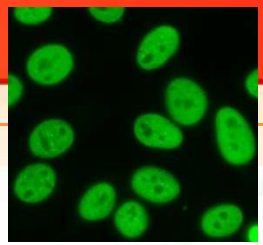
AUTOIMMUNE DISEASES

Single Organ or Cell Type Autoimmune Diseases		
Systemic Autoimmune Diseases		
Disease	Self-antigen present on	Type of immune response & Important features
Multiple sclerosis	Brain (white matter)	Self-reactive T cells produce characteristic inflammatory lesions in brain that destroys the myelin sheath of nerve fibers; leads to numerous neurologic dysfunctions

LABORATORY DIAGNOSIS OF AUTOIMMUNE DISEASES

Autoimmune diseases	Laboratory diagnosis
Autoimmune hemolytic anemias	oCoombs test - red cells are incubated with an anti–human IgG antiserum → IgG auto-antibodies are present on the red cells, the cells are agglutinated by the antiserum
Goodpasture syndrome	Biopsies from patients are stained with fluorescent-labeled anti-IgG and anti-C3b reveal linear deposits of IgG and C3b along the basement membranes.

LABORATORY DIAGNOSIS OF AUTOIMMUNE DISEASES



Autoimmune diseases	Laboratory diagnosis
SLE (Systemic lupus erythematosus)	Detection of autoantibodies by indirect immunofluorescence assay (most widely used) and ELISA based techniques. • ANA (antinuclear antibody)- Positive in >90% cases (screening test). • Anti-double stranded DNA (dsDNA)-Highly specific (Confirmation). • Anti-Sm antibodies **Lupus band test**- Direct immunofluorescence test - detect deposits of immunoglobulins and complement proteins in the patient's skin. **LE cell test**- No longer used because the LE cells are only found in 50–75% of SLE cases.

LABORATORY DIAGNOSIS OF AUTOIMMUNE DISEASES

Autoimmune diseases	Laboratory diagnosis
Scleroderma	Anti-Scl 70 antibody is raised, detected by indirect immunofluorescence assay
Sjögren's syndrome	Detection of SS-A (or anti-Ro) and SS-B (or anti-La) antibodies by indirect immunofluorescence assay.

LABORATORY DIAGNOSIS OF AUTOIMMUNE DISEASES

Autoimmune diseases	Laboratory diagnosis
Rheumatoid arthritis	***RA factor*** (by latex agglutination test)- RA factor is an IgM autoantibody directed against Fc portion of IgG, good sensitivity. False positive - seen in other autoimmune diseases. ***ACPA*** (Anti-citrullinated peptide antibodies) is an auto-antibody to citrullin protein. It is positive only in 67% of cases; but is *highly specific*. ***Rose-Waaler test*** to detect RA factor is of historical importance, no longer used now.