Disease of immune system

Lec.3

AUTOIMMUNE DISEASES:

Immune reactions against self-antigens (i.e. autoimmunity) are an important cause of certain diseases in human

Normal persons are unresponsive (tolerant) to their own (self) antigens, and autoimmunity results from a failure of self-tolerance

Immunologic Tolerance: is a state of unresponsiveness to an antigen that is induced by exposure of specific lymphocytes to that antigen.

Self-tolerance refers to lack of immune responsiveness to individual's own tissue antigens and it underlies our ability to live in harmony with our cells and tissue.

The mechanisms of self-tolerance

can be broadly classified into two groups:

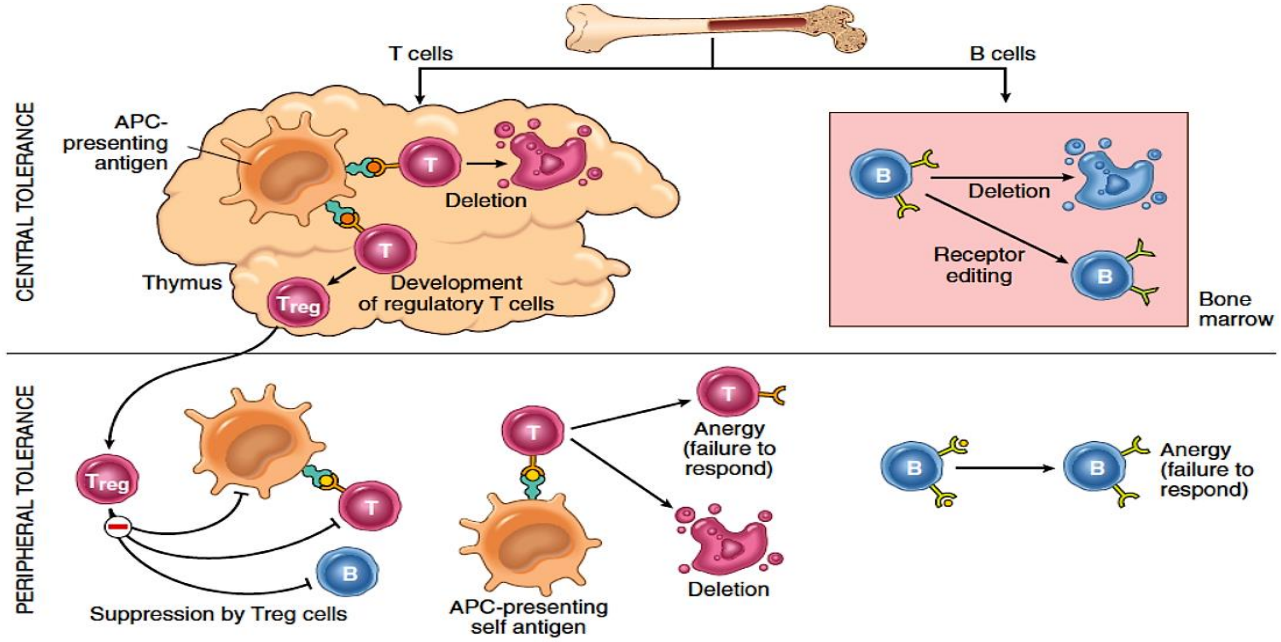
1.Central Tolerance. In this process, immature self-reactive T- and B-lymphocyte clones that recognize self-antigens during their maturation in the central (or generative) lymphoid organs (i.e., in the thymus for T cells and in the bone marrow for B cells). are killed by apoptosis (**process called deletion**)

2-Peripheral Tolerance: Mature lymphocytes that recognize self -antigen in the peripheral tissue become silence by several mechanisms

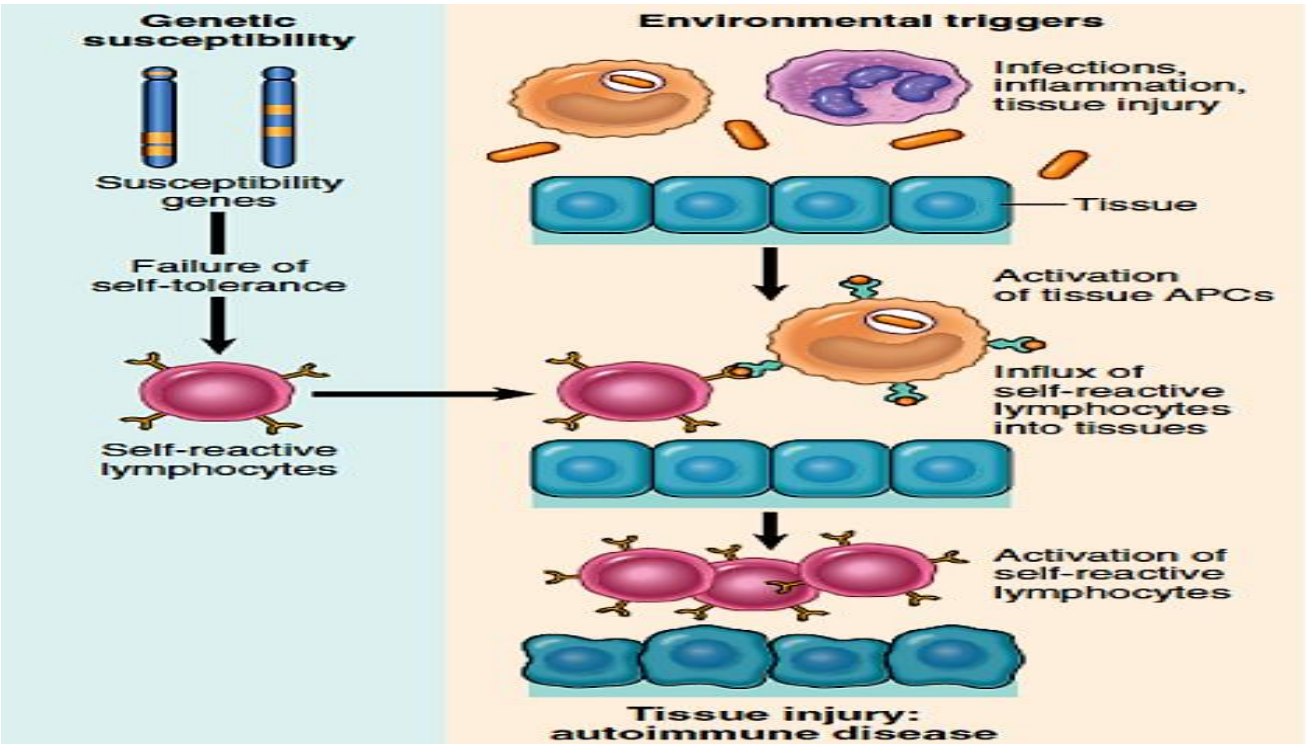
1-functional inactivation (anergy)

2- suppression by regulatory T cells

3- Activation induced cell death (die by apoptosis)



Mechanisms of Autoimmunity: Autoimmunity arises from a combination of the inheritance of susceptibility genes, which may contribute to the breakdown of self-tolerance, and environmental triggers, such as infections and tissue injury which promote lymphocyte entry into tissues, activation of self-reactive lymphocytes, and tissue damage



Rheumatoid Arthritis

is systemic disease in which chronic inflammation affected many tissue & principally attacking joints to produce non-suppurative synovitis that frequently progresses to destroy articular cartilage and underlying bone result in disabling arthritis, also can affect other organs like skin, heart, muscles, blood vessels & lung.

RA presented as systemic arthritis usually affect small joints of hands & feet typically the proximal interphalangeal and metacarpophalangeal joints, axial involvement affects upper cervical spines.

MORPHOLOGY:

The characteristic histologic features include
1-synovial cell hyperplasia
2-dense inflammatory infiltrates
3-increased vascularity
4-osteoclastic activity in underlying bone

all these changes produce **pannus**: a mass of edematous synovium, inflammatory cells, granulation tissue, and fibroblasts that grows over the articular cartilage and causes its erosion. In advanced untreated cases the pannus can bridge the bones to form a **fibrous ankylosis**, which may later ossify as a **bony ankyloses**

Transplant Rejection

It is a complex immunologic phenomenon involving both cell & antibodies mediated hypersensitivity responses of the host directed against histocompatibility molecules on the donor allograft.

Allograft: transplantation of organs from one individual to another of same species.

Immune Recognition of allograft: Rejection of allograft is a response to MHC molecules, which are so polymorphic that no two individuals in a population are likely to express exactly the same set of MHC molecules (except the identical twins).

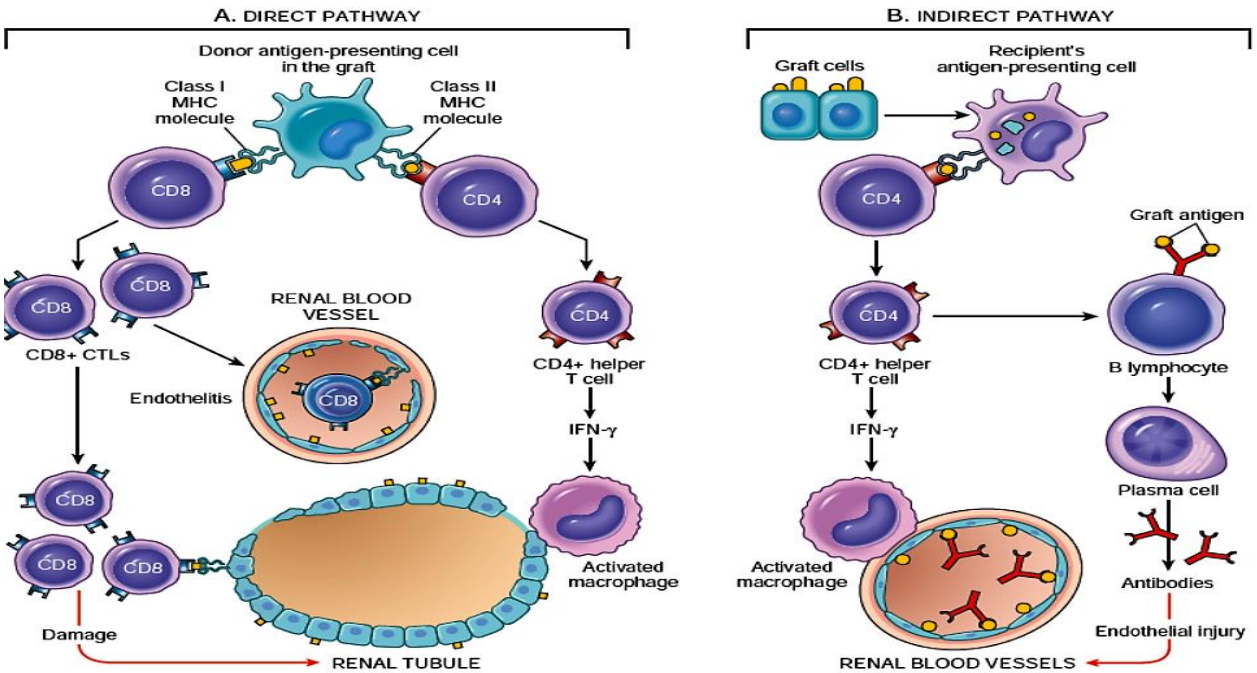
There two main mechanisms by which immune system recognizes & responds to the MHC molecule on the graft:

1–Direct recognition: the host T cell directly recognize the allogeneic (foreign) MHC molecules that are expressed on graft cells.

Host CD4+ helper T cells are trigger into proliferation and cytokine production by recognition of donor class II MHC molecule and derive the delayed hypersensitivity reaction (DTH) response.

While the CD8+ T cells recognize class I MHC and differentiated to cytotoxic T lymphocytes (CTLs) which kill the cells on the graft

2–Indirect recognition: in which host CD4+ T cells recognize donor MHC molecules after these molecules are picked up, processed and presented by the host own antigen presenting cells (APCs), this form of recognition activate DTH pathway.



On the basis of time course & morphology of graft rejection reaction; rejections are classified to:

1-Hyperacute rejection: occurs within minutes to a few hours after transplantation just after the vascular anastomosis is completed.

kidney rapidly becomes cyanotic and flaccid. Histologically: arteritis, thrombosis & ischemic necrosis, hyper acute rejection is not a common problem, because every donor and recipient are matched for blood type and potential recipients are tested for antibodies against the cells of the prospective donor, a test called a cross-match.

2-Acute Rejection: Acute rejection may occur within days to weeks of transplantation in a non-immunosuppressed host.

Acute rejection is caused by both cellular (destroyed graft parenchyma) and humoral immune mechanisms (damaged graft vasculature)

3-Chronic rejection: Occur later after transplantation (months or years). It is dominated by arteriosclerosis, interstitial fibrosis & loss of renal parenchyma, this type is probably caused by T-cell reaction and secretion of cytokines that induce proliferation of vascular smooth muscle cells with parenchymal fibrosis.

Immune Deficiency Diseases: It can be divided in to:

A-Primary(inherited) Immune Deficiency Diseases: caused by gene mutations in lymphocytes maturation or function or in innate immunity. E.g.

1-X- linked Agammaglobulinemia : there is failure in B- cell maturation & absence of antibodies.

2-Selective IgA deficiency: failure of IgA production.

3-X- linked (severe combined immunodeficiency) (X-SCID): failure of both T- cell & B- cells maturation.

4-Autosomal SCID: Failure in T- cell development, and secondary defect in antibody response

5-X- linked hyper IgM syndrome: Failure to produced high- affinity antibodies (IgG, IgA, IgE)

B-Secondary (Acquired)Immune deficiency: These states arising as a complication of:

-infection, renal diseases, aging, malnutrition

-Side effects of immune suppression, irradiation , chemotherapy for cancer.

Acquired Immune Deficiency Syndrome (AIDS):

AIDS: is a disease caused by the retrovirus human immune deficiency virus (HIV) and characterized by profound immunosuppression that leads to opportunistic infections, secondary neoplasms and neurologic manifestations.

EPIDEMIOLOGY:

The Human at risk for HIV virus infection are:

- Homosexual or bisexual male (50%).
- Intravenous drug abusers (20%).
- Hemophiliacs (0.5%) & recipients of blood & blood components (1%).
- Heterosexual contacts (20%).
- Mother to Infant: either trans placental, during delivery or ingested of contaminated milk (2%)

Pathogenesis: There are two major targets of HIV infection: the immune system and the central nervous System.

Profound immune deficiency, primarily affecting cell-mediated immunity, is the hall mark of AIDS. This results chiefly from infection of and a severe loss of CD4+ T cells as well as impairment in the function of surviving helper T cells, macrophages and dendritic cells are also targets of HIV infection.

Mechanism of T- Cell Immune deficiency In HIV infection

In addition to direct killing of cells by the virus, other mechanisms may contribute to the loss of T cells:

1. HIV colonizes the lymphoid organs (spleen, lymph nodes, tonsils) and may cause progressive destruction of the architecture and cellular composition of lymphoid tissues.

2. Chronic activation of uninfected cells by HIV itself or other infections, leads to apoptosis of these cells.

3. Loss of immature precursors of CD4+ T cells, either by direct infection of thymic progenitor cells or by infection of accessory cells that secrete cytokines essential for CD4+ T-celles maturation

4. Fusion of infected and uninfected cells with formation of (giant cells) can occur.

5. Apoptosis of uninfected CD4+ T cells by binding of virus molecules to the CD4 molecule.

6. Infected CD4+ T cells may have killed by HIV- specific CD8+ CTLs (cytotoxic T lymphocytes)

Natural history of HIV infection:

A. **An early acute phase**:in 50-70% of adult infected by HIV develop viraemia

B. **Middle chronic phase (clinical latency)**: continuous HIV replication especially in lymphoid tissue.

C. **Final crises phase**: break down of host defense.

Clinical Features:

A-OPPORTUNITIC INFECTIONS:

1-Protozoal & Helminthic infections: Cryptosporidiosis (enteritis),

pneumocystosis (pneumonia), toxoplasmosis (pneumonia or CNS).

2-Fungal infections: Candidiasis (esophageal, tracheal or pulmonary).

3-Bacterial infections: Mycobacteriosis (atypical e.g. M. avium-intracellulare), M. tuberculosis(pulmonary or exrapulmonary), Nocardiosis (pneumonia , meningitis), Salmonella infections.

4-Viral infections: CMV (pulmonary ,intestinal or CNS infections), Herpes simplex virus, Varicella zoster virus.

B-CNS INVOLVEMENT:

40-60% have clinically evident neurological dysfunction:

- opportunistic infections & neoplasms.
- Aseptic meningitis.
- Peripheral neuropathies.
- AIDS-dementia complex-

C-NEOPLASMS:

Kaposi sarcoma 40%.

Non- Hodgkin lymphoma (NHL (Burkett, immunoblastic)

Primary lymphoma of the brain 20%.

Invasive cancer of the uterine cervix