Immunological Tolerance and autoimmune diseases

**Tolerance** is a state of specific unresponsiveness to a particular antigen in a fully immune-competent person.

**Types of tolerance:**

1- Naturally acquired (auto-tolerance)
2- Specifically induced (Therapeutic-- to prevent graft rejection, Treat autoimmune & allergic diseases).

**Auto-tolerance (neonatal, natural, self-tolerance):**

All individuals are tolerant of their own antigens (self-tolerance). This is acquired early in life, probably in utero; break down of self-tolerance results in autoimmunity.

Auto-tolerance is established primarily in T- & B- lymphocytes and achieved by different mechanisms.

**T-cell tolerance:** It is established at TWO levels

1- **Central tolerance:** It refers to the selection processes which T-cell precursors undergo in the thymus before they are released as mature naïve T-cells.

Thymic epithelial cells & dendritic cells present self-antigen to immature T-cell precursors. Those T-cell precursors that respond strongly to the self-antigens undergo apoptosis. This is called
negative selection or clonal deletion. (i.e. The major process by which T-cells acquire the ability to distinguish self from non-self-occur in fetal thymus).

2- **Peripheral tolerance**: It refers to the diverse mechanisms that enforce & maintain T-cell tolerance outside thymus. These include:

(a)- **Immunological ignorance**: Prevention of contact between auto-reactive T-cells & their target antigens.

This mechanism is maintained as long as auto-reactive lymphocytes do not enter the tissues in which the auto-antigen that they recognized is expressed.

Ex. Anatomical Barriers (blood-brain barrier; eye lens; testes)

(b)- **T-cell anergy**: Inability of auto-reactive T-cells to mount effector responses upon recognizing their target antigen because proper co-stimulation does not occur.

The mechanism of clonal anergy involves:

1- Signal Block:
   B7 molecule on the APC is not produced; therefore CD28 on Th-cell does not give a co-stimulation signal.

2- Engagement of inhibitory receptors (CTLA-4):
   The inhibitory protein CTLA-4 on the surface of T-cell may display CD28 & interact with B7 molecule.

(c)- **Deletion (activation-induced cell death)**: Stimulation of T-cells by self-antigen triggers apoptosis by engagement of death receptors. The death of T-cells is mediated by the Fas (CD95) & its ligand (FasL-CD95L).
(d) Suppression of immune by T-reg cells (CD4+ CD25+): T-reg cells control peripheral tolerance by secretion of immune-suppressive cytokines IL-10 & TGF-B.

**B- Cell tolerance:** B-cells become tolerant to self-antigen by TWO mechanisms:

1. **Central:** by clonal deletion of auto-reactive B-cells in the bone marrow.

2. **Peripheral:** by clonal anergy of B-cells in the periphery which is mainly due to lack of help from T-cells.

**Note:** T-cells become tolerant more readily and remain tolerant longer than B-cells.

- However, under certain circumstances tolerance may be lost and immune reaction to self-antigens may develop result in autoimmunity.
Peripheral tolerance

Pathways to Peripheral Tolerance

- Normal Response
  - CD28-B7 interaction
  - Proliferation & differentiation
  - Activated T cells

- Anergy
  - Antigen Recognition without co-stimulation
  - CTLA4-B7 interaction
  - Functionally Unresponsive

- Activation induced cell death
  - Fas-FasL interaction
  - Apoptosis

- Cytokine regulation
  - Cytokine-mediated suppression
  - Inhibition of proliferation & effector action
**Autoimmune Diseases:**

They are heterogeneous group of diseases, characterized by tissue damage or disturbed physiological function due to humoral or cell-mediated immune response against one or more of the self-antigens.

These disorders are characterized by chronicity & usually are non-reversible. They tend to occur at high frequencies in women than in men, and the frequency increases with age, most of them first appear in the 20-40 year age group.

**Who gets autoimmune diseases?**

**What are the predisposing factors for autoimmune diseases?**

1. Those with advancing age, where there is a decline in the number of regulatory T- cells, which allow any survived auto-reactive cells to proliferate.

2. Almost all autoimmune disease is more common in women, this is probably due to the influence of sex hormones (ex. Estrogen & prolactin) on immune system, and this may tend to turn cells towards Th1-dominated immune response.

3. Autoimmune disease shows evidence of clustering within families of genetic predisposition that is determined by their MHC-genes.

4. Those who exposed to an environmental agent that triggers immune response against self-Ag., these agents are (infections, drugs, hormones, physical agents -ex. Exposure to UV light-, psychological stress, & dietary factors).
Possible Mechanism for induction of autoimmune disease:

1. **Release of sequestered Ag**: certain tissues ex. Sperm, lens of eye, CNS are sequestered & their Ag are not exposed to the immune system (these are known as immunologically privileged sites). When such antigens enter the circulation accidently ex. after accident, they elicited immune response.

2. **Molecular Mimicry**: in which self-Ag & foreign materials such as viruses or bacteria share identical epitopes. Ex. Rheumatic fever, when carbohydrate Ag of streptococcus pyogenes Cross-react with an antigen on heart valves, so the infection may **bypass T-cell self-tolerance** to heart valve Ag.

3. **Polyclonal B-cell activation**: this is another mechanism to **bypass the tolerant auto-reactive Th-cell**. This is can be induced by bacterial lipopolysaccharide or Epstein- Barr virus that causes direct B-cells activation to produce auto-antibodies.

4. **Alteration of normal proteins**: Drugs can bind to normal proteins and make them immunogenic. Ex. Procainamide induces SLE.

5. **Inappropriate expression of MHC-II molecule**:
   MHC-II molecules are expressed normally on APCs, but under certain conditions they may be expressed in certain tissues & serve to sensitize Th-cells to peptides derived from these tissues. Ex. Trauma or viral infection to pancreatic B-cells induces a localized inflammatory response with the release of IFN-g, inducing an increase of MHC-II expression on these cells resulting in IDDM.

6. **Genetic predisposition** that is determined by their MHC genes.
   Ex. Ankylosing spondylitis and HLA-B27
   Rheumatoid arthritis and HLA-DR4
7. **Cytokine dysregulations & failure of suppressor mechanisms** may induce autoimmunity.

8. **Thymus defect (increasing with age)**

**Clinical types of autoimmune diseases:**

Autoimmune diseases have been divided into TWO clinical types depending on the distribution of lesions:

1. **Organ specific.**
   - Ex. Graves’ disease, Myasthenia gravis (see lecture 4)
2. **Systemic autoimmune disease**
   - Ex. systemic lupus erythematosus (SLE), rheumatoid arthritis

- Multiple autoimmune diseases can be occurred in the same patient

**Types of Tissue injury:**

- Type II hypersensitivity (auto-Ab)
- Type III Hypersensitivity (immune complex)
- Type IV Hypersensitivity (Cellular) as in Multiple sclerosis (MS)
- Mixed as IDDM

**-systemic lupus erythematosus (SLE)** is a chronic, inflammatory, and systemic (multiorgan) disorder that affects young women of childbearing age. Affected individuals may produce auto-antibodies to vast array of tissue antigens, such as DNA, histones, ribosomes, RNA, RBC, platelets, leukocytes, & clotting factors; interaction of these auto-antibodies with their specific antigens produces various symptoms.