



- What are the mechanisms of autoimmunity:

- **Induction of an autoimmune response by virally induced T-cell activation:** a virus (antigen) will be presented to T-cells by antigen presenting cells (APCs) leading to activation of a wide variety of T-cells –those which are specific for the antigen and others which are not specific- which will result in cytotoxicity.
- **Induction of autoantibodies by T-cell help after autoantibody-mediated antigen presentation.**
- **Induction of an autoimmune reaction by molecular mimicry:** which means that a virus –for example- might resemble a self antigen of the body. Therefore, T-cells cannot differentiate between self and non-self and will start attacking tissues of the body.
- **Induction of an autoimmune response after viral infection by aberrant (شاذّ- منحرف) MHC class-II antigens.**

- Mention five examples on autoimmune diseases.

- SLE
- Grave’s disease
- Diabetes mellitus type-I
- Multiple Sclerosis (MS)
- Rheumatoid arthritis.

**Notes:**

- ✓ In autoimmune diseases, there is loss in the function of regulatory T-cells.
- ✓ Autoimmune diseases can be:
  - ❖ *Organ-specific:* such as in diabetes mellitus type-I (pancreas).
  - ❖ *Organ non-specific:* such as in SLE (systemic).

- There are four types of hypersensitivity:

<u>Type of hypersensitivity</u>	<u>Immune mechanisms</u>	<u>Mechanisms of tissue injury</u>
<b>Immediate (type-I)</b>	IgE	Mast cells and their mediators
<b>Antibody-mediated (type-II)</b>	IgM and IgG antibodies against cell or tissue antigens	Opsonization and phagocytosis of cells; complement and Fc receptor-mediated recruitment and activation of neutrophils and macrophages; abnormalities in cellular functions (hormone/receptor signaling)
<b>Immune complex-mediated (type-III): being most important because it is responsible for SLE</b>	Immune complexes of circulating antigens and IgM or IgG antibodies	Complement and Fc receptor-mediated recruitment and activation of leukocytes
<b>Delayed-type hypersensitivity (type-IV)</b>	CD4+ TH1 and TH17 cells, their cytokines and the cells of CMI that they stimulate	Macrophage activation, cytokine-mediated inflammation (granuloma formation)

- In type-III hypersensitivity, there is formation of immune complexes which will get deposited in different tissues and this is what is seen in SLE. Notice that an immune complex is composed of:

- **Antigen + Antibody: leading to activation of complement.**

- How are immune complexes normally transported and removed?

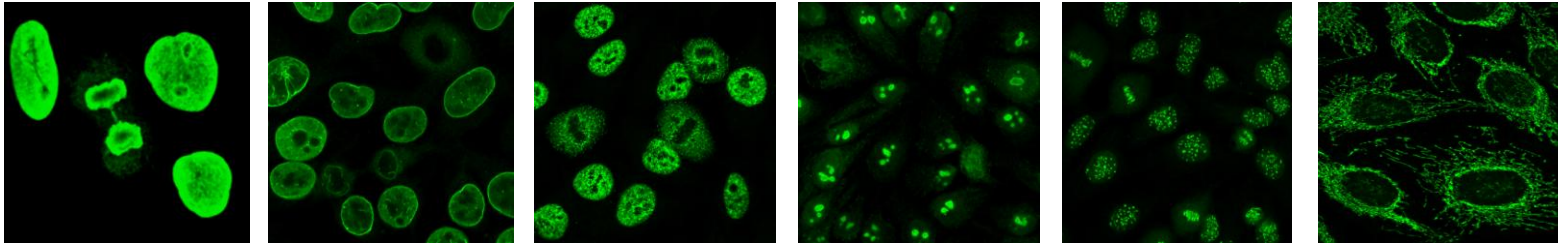
- Erythrocytes are the ones which will carry and transport immune complexes away from the walls of blood vessels (so they do not get deposited there). Notice that large immune complexes are cleared most quickly because they present an IgG-Fc lattice to reticuloendothelial cells with Fc-receptors, permitting higher avidity binding to these cells. They also fix complement better than small complexes.



- **What is the role of C3 (complement) in processing immune complexes?**
  - It reduces the lattice size of the complex.
  - It promotes the binding of immune complexes in the circulation to CR1 on erythrocytes which transport immune complexes through the circulation.
  - It promotes the uptake of immune complexes by fixed mononuclear phagocytic cells leading to the degradation of antigen.
  - Promotes the localization of antigen in the form of immune complexes to B-lymphocyte and to antigen presenting cells (APCs), including the specialized follicular dendritic cells of lymph nodes.
- **Mention some of the clinical features of SLE.**
  - Butterfly erythema (malar rash).
  - Discoid skin lesions.
  - pleuritis/ pericarditis.
  - Arthralgia and arthritis.
  - Renal involvement (lupus nephritis which can be: focal, membranous or diffuse proliferative).
  - Common symptoms such as fever and fatigue.
  - Vasculitis.
- **Pathogenesis of SLE:**
  1. **There is genetic susceptibility:** by the presence of genes which make the patient more prone to develop the disease. These genes include:
    - Immunoregulatory genes.
    - HLA-DR2 and HLA-DR3
    - Complement deficiency (C1q, C2 and C4). Notice that these fragments are part of the classic complement pathway.
    - FC $\gamma$ RIIb polymorphism.
  2. When a patient develops an autoimmune disease, there will be relapses and remissions of the condition which are mediated by **external triggers:**
    - UV-radiation (from excessive exposure to sunlight).
    - Infections.
    - Gender (female).
    - Smoking.
  3. Notice that both genetic and external factors will lead to **increased apoptosis (programmed cell death) and deficiency in clearance of apoptotic bodies.**
  4. All of the above will result in **failure of self-tolerance, self reactive B and T-cells and generation of autoantibodies leading to the formation of immune complexes.**
  5. These immune complexes will stimulate dendritic cells to produce type-I interferons leading to stimulation of B and T cells → **high levels of autoantibodies (IgG).**
  6. Vasculitis and nephritis are commonly seen in type-III hypersensitivity which is responsible of SLE (there are circulating **immune complexes which will be deposited in many different areas in the body.**
- **Other important autoimmune disease which you must differentiate from SLE include:**
  - **Scleroderma.**
  - **Mixed connective tissue disease.**
  - **Sjogren's syndrome:** an autoimmune disease characterized by many clinical features (one of them is enlarged parotid glands).
- **Antinuclear antibodies (ANA) in autoimmune diseases:**
  - **These can be detected by the following methods:**
    - ✓ ELISA (Enzyme-Linked Immunosorbent Assay).



- ✓ Indirect immunofluorescence: an antibody solution is applied to the section and visualized using fluoresceinated anti-immunoglobulin. This test is more frequently utilized for antibody assays and the following cells are used: (Human Epithelial Cell Line: type 2).
- **Patterns of immunofluorescent staining:**
  - ✓ Homogenous pattern: the antigen is double-stranded DNA histone complex. Further test is anti-dsDNA.
  - ✓ Peripheral pattern: the antigen is double-stranded DNA. Further test is anti-dsDNA.
  - ✓ Speckled pattern: further test for it is anti-ENA (ENA = Extractable Nuclear Antigen).
  - ✓ Nucleolar homogenous pattern.
  - ✓ Centromere pattern.
  - ✓ Mitochondrial (cytoplasmic) pattern: further test is anti-mitochondrial.



- **Anti-ENA:**

- ✓ SSA/Ro: SLE
  - ✓ SSB/La: Sjogren's syndrome
  - ✓ Sm
  - ✓ Centromere: CREST syndrome
  - ✓ RNP: mostly for mixed connective tissue disease.
  - ✓ Scl-70: scleroderma.
  - ✓ Jo-1: polydermatomyositis.
- **Rheumatoid factor:**
    - It is an antibody (IgM) which is commonly present in the sera of patients with rheumatoid arthritis; it combines with slightly denatured human IgG and with sensitized sheep erythrocytes.
    - **Method of detection:** latex agglutination slide test.
    - **Notice that rheumatoid factor is not unique for rheumatoid arthritis. It can be seen in:**
      - ✓ 30% of SLE patients.
      - ✓ 90% of Sjogren's syndrome.
      - ✓ Some patient with scleroderma or polymyositis.