Immunological tolerance

DR. AYSER HAMEED

LEC.1

Immunologic tolerance is a state in which the individual is incapable of developing an immune response to a specific antigen. Self-tolerance refers to lack of responsiveness to an individual's own antigen.

Both T- and B-cells bear self-reactive molecules (receptors) that can recognize self-antigens and react with them to produce eventually tissue damage and this is the essence in the production of various autoimmune diseases. To avoid such incidents T- and B-cells bearing such molecules (receptors) must be either eliminated or down-regulated so that the immune system is made specifically non-reactive i.e. tolerant to self antigens. Since T-cells and in particular CD4+ T-cells, have a central role in controlling all immune responses , the process of T-cell tolerance is much more important than B-cell tolerance in the avoidance of autoimmunity. This is because not only T-cells may produce tissue damage directly but also self-reacting B-cells will not be able to produce auto-antibodies unless they receive appropriate T-cell help.

Processes that induce specific self-tolerance are central tolerance and peripheral tolerance.

Central tolerance:

Is achieved through death (deletion) of self-reactive T- and B-lymphocytes during their maturation in the central lymphoid organs (the thymus for T cells and the bone marrow for B cells), by process of apoptosis.

Peripheral tolerance:

Those self-reactive T- and B-lymphocytes that escape central tolerance should be deleted by peripheral tolerance through several mechanisms include the followings:-

1- **Anergy:** CD4 + T-cells require two signals to become activated and initiate an immune response: an antigen - specific signal through the T-cell antigen receptor and a second, nonspecific signal through interaction of CD4 + cells with antigen presenting dendritic cells. Such an interaction is only likely to occur in secondary lymphoid tissues such as lymph nodes i.e. the encounter of both cells is very restricted. If no second signal is available then stimulation through T-cell receptor alone leads to apoptosis or a state of longstanding unresponsiveness called anergy.

2- **Activation-induced cell death:** CD4 + T-lymphocytes will undergo apoptosis after persistent, repeated stimulation by self-antigens.

3- **Suppression by regulatory T cells:** CD4+ T lymphocytes are divided into two subsets TH1 (helper Tl) cells and TH2 (helper T2) lymphocytes. TH2 helper T-lymphocytes secrete cytokines (interlukin 4, IL-5 and IL-10), that antagonize TH1 effect, so by this way it has a regulatory function. Self-reactive T-cells may be actively suppressed by cytokines secreted by the regulatory TH2 T-helper lymphocytes.

4- **Antigen sequestration:** Some antigens are hidden from the immune system because the tissues in which these antigens are located do not communicate with the blood and lymph, as the eye, testis and brain. If the antigens of these tissues are released, for example, after trauma or infection, the immune system will regard them as foreign antigens and will form auto antibodies against them, leading to post traumatic uveitis, or post traumatic orchitis.

5- **B-cell tolerance:** this is less complete than T-cell tolerance. The production of self-reactive antibodies by these B-lymphocytes is limited mainly by the lack of T-cell help for B-cells.

Breakdown of tolerance

For autoimmune diseases to occur, the above mechanisms of immunological tolerance must be broken down.

1. **Overcoming peripheral tolerance;** resulting from excessive access of self- antigens to antigen presenting cells, excessive nonspecific signaling, or alterations in which self-antigens are presented to the immune system. All these are likely to happen when inflammation or tissue damage is present.

The structures of the self-antigen's peptides (self-peptides) may be altered by viruses, free radicals or ionizing radiation. With such structural changes the previously established tolerance is bypassed. Tissue damage may release antigens that are already sequestrated from the immune system e.g. spermatozoa & ocular antigens. Post-traumatic uveitis & orchitis (after vasectomy) probably result from immune responses against antigens normally sequestered in the eye & the testis.

2. Molecular mimicry: structural similarity between self-antigens and microbial antigens may trigger an immune response. In systemic infection, this cross reactivity will cause expansion of the responsive T-cell population recognizing the self-peptide if local conditions allow. The process is known, as molecular mimicry. For example, rheumatic heart disease sometimes follows Streptococcal infection because antibodies to Streptococcal M protein cross-react with cardiac glycoproteins.

Once tolerance has broken down, the resulting immunological mediated inflammation and tissue damage may allow presentation of further peptides. The immune response broadens and local tissue damage accelerates. This domino-like process is known as **epitope spreading.**

(Domino effect: by which one event triggers a succession of other, often similar, events, like a falling domino at the beginning of a line of up-ended dominoes).

Etiology of autoimmune diseases

The interaction between genetic and environmental factors is important in the pathogenesis of autoimmune diseases.

Genetic factors

Family studies have confirmed a genetic contribution in all autoimmune diseases. This is supported by the findings that

1. Different autoimmune diseases may cluster within the same family (such as SLE, autoimmune hemolytic anemia & autoimmune thyroiditis).
2. Subclinical autoimmunity is common among family members.

The genetic contribution to autoimmune disease usually involves multiple genes. The strongest associations between genetic factors and autoimmunity involve alleles of the major histocompatibility complexes (MHC). This is because of central role of the products of many of these genes in the:-

1. T-cell function.
2. Control of immunity and inflammation.

It is likely that the MHC class II alleles influence the presentation of autoantigenic peptides to T-cells.

An example of such a connection is the well-known strong association of HLA-B_{27} with ankylosing spondylitis.

Environmental factors

These may trigger autoimmune diseases and include:-

1. Hormones.
2. Infections.
3. Drugs.
4. UV radiation.

1. Hormones

The contribution of hormones in the pathogenesis of autoimmune diseases is supported by the following:-

1. Most autoimmune diseases affect females much more commonly than males; hormonal factors, besides genetics, must play a major role in this gender difference.
2. The peak age of onset of most autoimmune diseases is within the

reproductive years. Evidences implicate estrogens as triggering factors.

3. In animal models removal of the ovaries inhibits the occurrence of autoimmune diseases (e.g. SLE), while estrogen administration accelerates the onset of the disease.

2.Infections

Infections may cause autoimmune diseases by two mechanisms:-

a. It may alter the structure of self-Ag peptides leading to breakdown of clonal anergy and activation of T-cells specific for self-Ags.

b. By molecular mimicry.

3.Drugs

Drug-induced autoimmunity may involve mechanisms comparable to molecular mimicry, whereby the drug or drug-self molecule complex has a structural similarity to self that allows bypassing tolerance. Drug-mediated autoimmunity affects only a small proportion of those treated and is probably genetically determined. For example, HLA-DR2 is associated with penicillamine-induced myasthenia gravis, whereas DR3 is associated with penicillamine-induced nephritis. Genetic variation in drug metabolism is also important. Individuals who are slow metabolizers of the offending drug are more prone to develop the disease (for e.g. drug-induced SLE) than rapid metabolizers. Slow metabolism of the offending drug may give more time for the formation of immunogenic conjugates between the drug and self-molecule.

4. Ultraviolet radiation

Exposure to UV radiation, usually in the form of sunlight is a known trigger for skin eruptions (photosensitivity skin eruption) and sometimes systemic involvement in patients with SLE. UV radiation acts in this context through two possible mechanisms:-

a. Modifying self-antigens to become immunogenic.

b. Enhancing apoptosis (cell death) of the cells, which lead to cell surface expression of auto-antigens that are usually hidden within the cell. Such exposure of the antigens leads to Ag-Ab reaction that triggers tissue damage.

Autoimmune diseases may be either organ specific (response directed against a single component of a single tissue) or more often, a non-organ-specific autoimmune disease (response directed against a component that present in many tissues & organs throughout the body).

The organ specific autoimmune diseases are listed in following table

Organ	**Disease**	**Associated autoantibody**	**Comment**
Skin	Vitiligo	Antityrosine Ab	Hypopigmentation
Thyroid	Grave's disease	Anti-TSH receptor autoantibody	Hyperthyroidism
Thyroid	Hashimoto's disease	1.Thyroglobulin autoantibodies 2. follicular epithelial cells autoantibody	Hypothyroidism
Adrenal cortex	Addison's disease	Anti-adrenal Ab	Hypoadrenocorticalism
Stomach	Autoimmune (type A) gastritis	Anti-intrinsic factor & parietal cell Ab	Pernicious anemia
Pancreatic islet cells (insulin-producing)	Type I diabetes mellitus	Anti-islet B-cell (insulin) Ab	Diabetes mellitus

Skeletal muscle	Myasthenia gravis	Acetylcholine receptors Ab	Muscle fatigue

Multi-organ involvement is frequently caused by secondary damage due to circulating immune complex. This group of disorders is often collectively called the "connective tissue diseases" or "collagen vascular diseases".

Disease	**Main organ involved**
Systemic lupus erythematosus	Skin , kidney, joints , heart, lung
progressive systemic sclerosis	Skin , gut, lung
Polymyositis- dermatomyositis	Skeletal muscle, skin
Rheumatoid disease	Joints , lungs , systemic vessels

Systemic lupus erythematosus (SLE)

SLE is an autoimmune disease and one of the "connective tissue disorders". It is a fairly common disease, with a prevalence of 1:2500 persons. Like most autoimmune diseases, there is a strong female predominance (9:1) and is particularly common in young & middle-aged individuals. Clinically, the disease is characterized by remissions & relapses, with an acute or insidious onset that may involve any organ in the body. Acute flare-ups are usually controlled by steroids or other immunosuppressive drugs. Renal failure, intercurrent infections & diffuse central nervous system involvement are the major causes of death.

Etiology & pathogenesis

SLE is a complex disease of multifactorial origin including genetic, hormonal, & environmental factors, resulting in a T-cell & B-cell activation that leads to the production of several autoantibodies. The main defect in SLE is a failure to maintain self-tolerance.

Many types of autoantibodies can be identified in SLE patient particularly antinuclear antibodies (ANAs), which are directed

against several nuclear antigens. ANAs can be identified using the indirect immunofluorescence test, which is positive in virtually every patient with SLE, so that the test is quite sensitive. However, it is not specific.

However, the presence of autoantibodies against double stranded DNA is diagnostic to SLE.

Antibodies against blood cells, including red cells, platelets & lymphocytes, are found in many patients.

Antiphospholipid antibodies are found in 40% to 50% of SLE patients.

Because phospholipids are required for blood clotting, SLE patients with antiphospholipid antibody tend to have venous and arterial thrombosis, thrombocytopenia & recurrent spontaneous miscarriages (antiphospholipid syndrome).