Autoimmune Diseases

It was once believed that normal/healthy animals were unable to mount any response against their own body components. This is partially true. Generally self-reactive T cells are largely eliminated by negative selection while they are in the thymus by apoptosis when they react to self-antigens in the thymus. Some self-reactive T cells may escape the negative selection and colonize in secondary lymphoid organs. These self-reactive T cells are always present in lymphoid organs, but regulatory mechanisms usually keep them under control. On occasion, this control may break down. When this happens, these lymphocytes generate autoantibodies or self-reactive T cells may cause tissue damage and autoimmune disease.

Criteria to decide autoimmune etiology or disease:

1. An autoimmune response, humoral, cellular, or both, must be regularly associated with the disease.
2. The antigen responsible for the immune response must be identified, isolated, and characterized.
3. The same antigen must be induced in experimental animals' immunopathological changes as in the disease.
4. Passive transfer of the disease must be possible by the transfer of antibodies or sensitized lymphocytes.

Features of disease of autoimmune origin:

The disease of immune origin usually exhibits the following features:

1. An elevated level of immunoglobulins.
2. Demonstrable autoantibodies.
3. Deposition of autoantibodies at the site of election, such as renal glomeruli.
4. Accumulation of lymphocytes and plasma cells at the sites of lesions.
5. Temporary or lasting benefit from corticosteroid or other immunosuppressive therapy.
6. The occurrence of more than one type of autoimmune lesion in an individual.
7. A genetic predisposition towards autoimmunity.

Mechanisms of auto-immunization (conditions responsible for auto-immunization)

Autoimmunization can result under the following conditions:

1. **Hidden antigens:** Many cell antigens are found in locations where they do not encounter circulating lymphocytes. e.g., Antigens may be hidden in the CNS or the testes, a location not normally visible by the lymphocytes. When these hidden (or cryptic) antigens are revealed, they may trigger an autoimmune attack. If the brain or testes are injured, this permits proteins released by damaged tissues to reach the blood circulation, encounter antigen-sensitive cells, and stimulate an immune response.

2. Cells or tissue undergoing antigenic alteration:

The production of some autoantibodies may be triggered by the development of completely new epitopes on normal proteins.

e.g., Rheumatoid factors are antibodies directed against epitopes on other immunoglobulins. When the antibody binds to an antigen, the molecule is stabilized in such a way that new epitopes are exposed on its Fc region. These new epitopes may stimulate RF formation. RFs are produced in diseases in which large amounts of immune complexes are generated. These include Rheumatoid arthritis and SLE (Systemic lupus erythematosus, where B cells respond to many antigens.

e.g., **Immunoconglutinins**: Are autoantibodies directed against the complement components C2,C4 and especially C3.The epitopes that stimulate the IK formation are sites on complement components that are exposed when complement is activated.

3. Immunological damage resulting by cross-reaction of antigens

4. Breakdown of immunological homeostasis may lead to cessation of tolerance and the emergence of forbidden clone of immuno-competent cells capable of mounting immune response against self-antigens.

5. T & B cell defect

Classification of autoimmune diseases (In brief)

1.Hemolytic,

a. Haemolytic anaemias: Antibodies to antigens on the red blood cells will provoke their destruction (leads to type II hypersensitivity reaction) and thus cause autoimmune haemolytic anaemia. (AIHA). Such AIHA are well recognized in human beings, dogs, cattle, horses, cats, mice, rabbits and raccoons.

e.g., Genetic predisposition is seen in some animals. German shepherds, Old English sheep dogs, Irish setters, Scottish terriers, Miniature dachshunds and American cocker spaniels appear to have relatively high susceptibility to the condition.

b. Leucopoenia: Non agglutinating anti-leukocyte antibodies were demonstrated in systemic lupus erythematosus and rheumatoid arthritis.

c. Thrombocytopenia: In this antiplatelet antibody are developed. These antibodies interfere the normal functioning of platelet. The antibodies against platelet leads to shortened lifespan as a result of extravascular destruction of opsonized platelets in the spleen. The clinical signs reflect the inability of the animal to repair minor capillary damage. The affected animals usually show multiple petechiae in the skin, gingival, other mucus membranes and conjunctiva. Epistaxis may occur and dog may show melena and hematuria. The predominant cause of death in these dogs is severe gastrointestinal hemorrhage. Has been reported in horses, dogs, and cats.

2.Localized (organ specific)

Autoimmune Orchitis: On injury or experimental induction, the sperm when comes in contact with the lymphocytes, and the antibodies are developed resulting into progressive damage to germinal epithelium and aspermatogenesis.

Myasthenia gravis: Is a disease of skeletal muscle characterized by abnormal fatigue and weakness after relatively mild exercise. It is seen in human, dogs & cats.

e.g., A dog with myasthenia gravis will collapse after trotting for only a few yards. Myasthenia is a result of failure of transmission of nerve impulses across the motor end plate of striated muscles as a result of a deficiency of acetylcholine receptors.

Autoimmune disease of thyroid gland
Autoimmune diseases of the eye
Autoimmune disease of the nervous system
Autoimmune diseases of the skin.

Pernicious anemia:
Autoantibodies are directed against the parietal cells of the gastric mucosa and against the intrinsic factor and prevent the absorption of vitamin B_{12} .

3. Systemic

Rheumatoid arthritis:
Is a symmetric polyarthritis with muscle wasting and subcutaneous nodules, The synovial membranes of the affected joints are swollen and oedematous, with dense filtration of lymphocytes and plasma cells.

A striking feature is presence of circulating autoantibody 'Rheumatoid Factor'. Rheumatoid factors are antibodies directed against epitopes on other immunoglobulins. When antibody binds to an antigen, the molecule is stabilized in such a way that new epitopes are exposed on its Fc region. These new epitopes may stimulate RF formation. RFs are produced in diseases in which large amounts of immune complexes are generated.

Systemic lupus erythematosus:
Is a chronic multisystem disease. Patients having variety of autoantibodies directed against cell nuclei, intra-cytoplasmic cell constituents, Immunoglobulins, thyroid. The variety of autoantibodies suggests breakdown ion the central control of immunological methods.

Polyarteritis nodosa & Sjogren's syndrome.

4. Transitory diseases

Include conditions such as anemia, thrombocytopenia, or nephritis that follow certain infections or drug therapy. The infecting agents or drug induces antigenic alterations in some self-antigens. The immune response setup causes tissue damage. The disease is transient and undergoes spontaneous cure when the infection is controlled or the drug is withdrawn.

Pathogenesis of autoimmune disease:

The relative importance of the humoral and cellular immune processes in the etiology of autoimmune diseases is not known. Autoantibodies may cause damage by either of the hypersensitivity reactions.

Type I Hypersensitivity:

Milk allergy in cattle is an autoimmune disease in which milk *alpha* casein, normally found only in the udder, gains access to the general circulation and so stimulates an immune response. This happens when milking is delayed and intramammary pressure forces milk proteins into the circulation. The affected cows show clinical signs of acute systemic anaphylaxis.

Type II Hypersensitivity:

Autoantibodies directed against cell surface antigens may cause target cell lysis with the assistance of either complement or cytotoxic cells.

If the autoantibodies are directed against:

RBCs results into autoimmune hemolytic anemia
Platelets results into autoimmune thrombocytopenia
Thyroid cells results into autoimmune thyroiditis.

Type III Hypersensitivity:

Autoantibodies will form immune complexes when bound to antigens and these complexes may participate in type III hypersensitivity reactions.

e.g., In SLE, a disease in which a wide variety of antibodies are produced, most significant of which are those directed against nucleic acids and proteins associated with them. Immune complexes are formed in affected animals and are deposited in the glomeruli to provoke the development of membranoproliferative glomerulonephritis.

e.g., In Rheumatoid arthritis, immune complexes are formed between rheumatoid factor and IgG are deposited into the joints and by activating complement, contribute to the local inflammatory response.

Type IV Hypersensitivity:

Many lesions in autoimmune diseases are heavily infiltrated with mononuclear cells. T cells contribute to the pathogenesis of this type of disease.

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