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AUTOIMMUNITY AND AUTOIMMUNE DISEASES

64.1 INTRODUCTION

Normally the function of immune system in our body is to recognize foreign elements and to destroy these before they could harm us either by humoral immune response (specific antibody formation) or cell mediated immune response by activation and clonal expansion of T cells. Thus the immune system defends the body against infections and certain other diseases by identifying, attacking, and destroying germs and other foreign substances. Sometimes the immune system makes a mistake and starts attacking the body's own tissues or organs. This is called autoimmunity. There are many autoimmune diseases one example being type 1 diabetes in which the Islets cells (produce Insulin) in the pancreas are destroyed by the immune system.

An autoimmune disease is a case of mistaken identity; it is an abnormal condition in which the body reacts against constituents of its own tissues. The result may be simple hypersensitivity reaction and or autoimmune disease when the body begins attacking its own healthy tissues. We can say it is a case of mistaken identity resulting in failure of the immune system to differentiate between self and non self. About 5 % to 7 % of adults suffer from autoimmune diseases and two thirds of these are females. Somehow left handed people are more prone the reason for this is not known.

This failure to differentiate between self and non self may result due to some extraneous environmental factors like some viral infections and exposure to some mutagenic agents; can be due to the breakdown and failure of immune regulation and due to some aberration in the genes. Whatever the reason the result is autoimmune disease which may involve a particular organ when it is called an organ specific disease (e.g. Addison's disease involving Adrenal

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OBJECTIVES

After reading this lesson you will be able to:

- define autoimmunity
- describe the history of autoimmunity
- describe the various disease states caused by autoimmunity
- describe the causes of autoimmunity
- discuss the immunopathology of these diseases
- describe the diagnosis of autoimmune diseases
- describe the treatment of autoimmune diseases

History

A very famous, Nobel laureate Paul Ehrlich (1854-1915) coined the term “Horror autotoxicus” to emphasize that body has innate aversion to immunological self-destruction. “Horror autotoxicus” literally means the horror of self-toxicity. However, as we now know, the immune system can upon occasion attack own body and result is autoimmune disorders.

Scientists started talking about autoimmunity around 1900. By 1904 the antibody nature of the autohemolysin responsible for cold hemoglobinuria was described, and soon confirmed. However, the concept that autoimmunization caused cold hemoglobinuria was not yet clear and was not accepted. It was only during early 1960s that the concept of autoimmunization as cause of some diseases was accepted. The publication of a monograph on autoimmune disease in 1963, and surely by the consensus reached at a large international conference published as proceedings in 1965 lead to acceptance of the state of autoimmunity. The history of autoimmunity is far from over as autoimmunity is being incriminated in aetiopathogenesis of more and more disease conditions.

64.2 DEFINITION

Autoimmunity refers to the body’s development of intolerance of the antigens on its own cells i. e. there is an immune response to one’s own tissue antigens. This type of body response results in a disease state characterized by a specific

antibody or cell-mediated immune response against the body's own tissues (auto antigens). So, we can say that autoimmunity is the breakdown of mechanisms responsible for self tolerance and induction of an immune response against components of self.

The immunological mechanism of the body is dependent on two major factors: (1) the inactivation and rejection of foreign substances and (2) the ability to differentiate between the body's own antigens ('self') and foreign ('non self'). It is not yet known exactly what causes the body to fail to recognize self proteins as its own and to react to them as if they were foreign resulting in autoimmunity and may be autoimmune diseases. Prominent examples include celiac disease, diabetes mellitus type 1 (IDDM), sarcoidosis, systemic lupus erythematosus and many others.



INTEXT QUESTIONS 64.1

1. The function of immune system is to & foreign bodies
2. Immune system attacking the body's own tissue is known as
3. Autoimmune disease when involves a particular organ is called as
4. Auto immune disease when involves the whole body is called as disease

64.3 AUTOIMMUNE DISEASE STATES

The autoimmune diseases can be divided into systemic, localized and haemolytic disorders, depending on tissue/cells affected and the clinico-pathologic features

64.3.1 Systemic autoimmune diseases

These diseases are associated with auto antibodies to antigens which are not tissue specific. One example can be polymyositis, here the tissue involved are muscles, however the auto antibodies are found against the auto antigens which are often ubiquitous "t-RNA synthetases". Another example is rheumatoid arthritis (RA). There is symmetric poly arthritis with muscle wasting and may be associated with myositis, and vasculitis, etc. The specific marker (auto antibody) found in blood in these patients is Rheumatoid Factor (RF) which is usually 19 s IgM. RF is an antibody against Fc fragment of immunoglobulins. Other systemic autoimmune diseases are polyarteritis nodosa, systemic lupus erythematosus and Sjogren's syndrome as shown in the figure.



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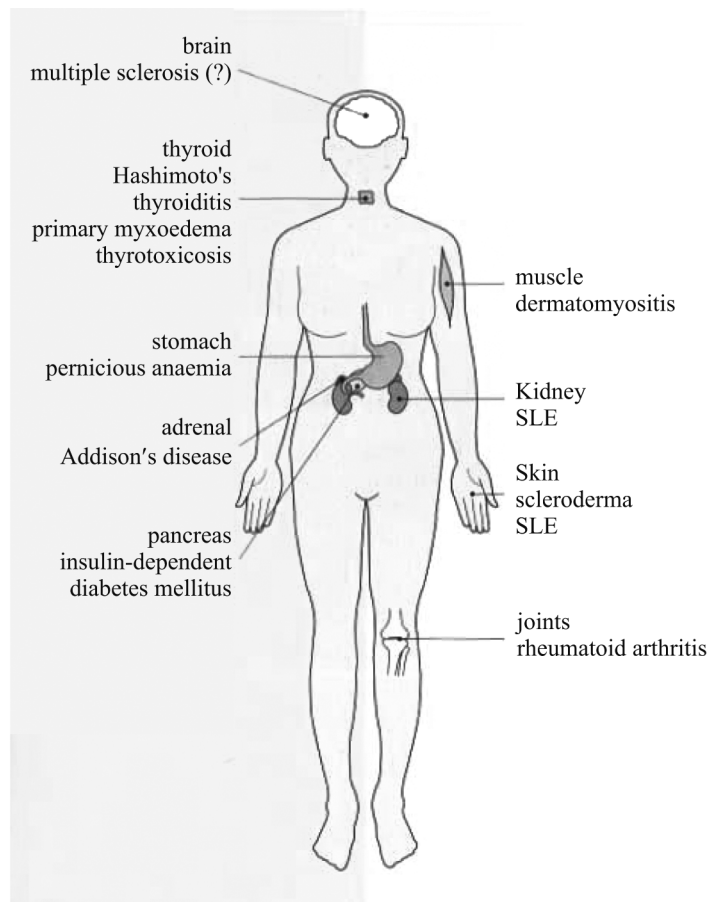


Fig. 64.1 Two types of autoimmune disease

So, let us recap, in case of systemic autoimmune diseases the incriminating antigens and the autoimmunity are distributed in many tissues. The systemic diseases are:

- Rheumatoid arthritis
- Systemic lupus erythematosus (SLE)
- Scleroderma
- Primary Sjogrens's syndrome
- polymyositis

64.3.2 Organ specific or localized autoimmune diseases

As the name indicates in these cases the autoimmunity involves a particular organ. One best studied organ is thyroid and examples are Hashimoto's disease which affects thyroid gland causing lymphadenoid goitre and the other is Graves disease causing thyrotoxicosis. Anti thyroglobulin antibodies are produced in

both these cases and these can be shown in sera of the patients by various tests. However, the pathology in the two is different and so are the resulting symptoms. In Hashimoto's goitre there is hypothyroidism and in Graves disease there is hyperthyroidism. Another example is Addison's disease in which the adrenal glands are affected. There is lymphocytic infiltration of the adrenal glands and production of antibodies directed against zona glomerulosa. Other diseases include autoimmune disease of eyes, brain, skin and many others.

In organ specific autoimmune diseases the implicated antigens and the autoimmunity are restricted to specific organs in the body

- Type I diabetes
- Goodpasture's syndrome
- Multiple sclerosis
- Grave's disease
- Hashimoto's thyroiditis
- Myasthenia gravis

64.3.3 Haemolytic autoimmune diseases:

Auto antibodies are formed against RBCs leading to autoimmune haemolytic anaemia; auto antibodies may form against platelets resulting in autoimmune thrombocytopenia; and formation of anti leucocyte antibodies resulting in autoimmune leucopenia and so on.

64.4 CAUSES OF AUTOIMMUNE DISEASES

Let us understand why normally immune response does not occur against our own tissue antigens. This is due to "Tolerance to self antigens" which is acquired by various mechanisms. Failure in immune recognition of self and injury of self tissues (autoimmunity) results from a loss of self tolerance. Let us discuss the mechanisms of self tolerance and how it is broken down to result in autoimmunity.

64.4.1 Mechanisms of self tolerance

One mechanism is that the clones of lymphocytes which act against self antigens are deleted. This is the "clonal deletion" theory. Clonal deletion is mediated by ubiquitous self antigens. The second is inactivation of developing lymphocytes so our immune system becomes self tolerant, no activation of immunity against self antigens as specific lymphocytes are either deleted or inactivated. Clonal inactivation can be mediated by tissue-specific antigens.





Notes

Peripheral T cell tolerance mechanisms:

These are explained below:

- Immunological Ignorance: Very few self proteins contain peptides that are presented by a given MHC molecule at a level sufficient for T cell activation, Autoreactive T cells are present but not normally activated.
- Suppressor or regulatory T cells: mediate active suppression of autoreactive cells
- Immunologically privileged sites: no lymphatic drainage or non-vascularized areas; presence of immunosuppressive factors.

Peripheral B cell tolerance mechanisms

- Contact with soluble antigens: this leads to downregulation of surface IgM, and so there is inhibition of signaling resulting in anergic (non reactive) cells and so no immune response occurs against these soluble antigens, there is tolerance to these antigens.
- Another mechanism of self tolerance is the Fas-mediated apoptosis (programmed cell death) of anergic B cell following secondary encounter with CD4 T cell



INTEXT QUESTIONS 64.2

1. Systemic autoimmune diseases are associated with auto antibodies to antigens are
2. Examples of systemic autoimmune diseases are, &
3. Example of organ specific diseases are,..... &
4. theory is associated with self tolerance

64.4.2 Mechanisms of breakdown of self tolerance resulting in autoimmunity:

There may be loss of “Self Tolerance” germinal centers due to some genetic aberration or some environmental factors.

64.4.2.1 MHC (Major Histocompatibility complex) molecules normally should present the peptide (antigen) at optimal level to T cells for immune response to occur. The level of autoantigenic peptide presented is determined by polymorphic residues in MHC molecules that govern the affinity of peptide binding.

If the peptide is presented at levels too low to engage effector T cells, there will be tolerance to such self antigens and if peptide is presented at very high levels then there is clonal deletion or anergy (tolerance).

Only a few peptides can act as autoantigens so there are a relatively few autoimmune syndromes.

Individuals with a particular autoimmune disease tend to recognize the same antigens with the same MHC.

Autoimmunity (breakdown of tolerance) arises most frequently to tissue-specific antigens with only certain MHC molecules that present the peptide at an intermediate level recognized by T cells without inducing tolerance.

64.4.2.2 Gene mutation/s leads to one or more autoimmune diseases. Autoimmune diseases are associated with particular MHC genotypes. Sometimes there may be more than one gene involved and the result is complex autoimmune diseases.

64.4.2.3 Environmental factors which can cause breakdown of self tolerance include pathogens (bacterial, viral and others), drugs, hormones, and toxins. These are just a few ways that can trigger autoimmunity.

- Drugs
 - Drug induced lupus
- Toxins
 - Example: Toxic Oil Syndrome
- Hormones
 - Example: Endometriosis and preeclampsia are both thought to be autoimmune in nature

64.4.2.4 Complement deficiency: deficiencies in the classical complement pathway renders patients more likely to develop immune complex diseases like:

- SLE
- RA

64.4.2.5 Molecular mimicry

Rheumatic fever is a classic example of molecular mimicry as shown in picture below.



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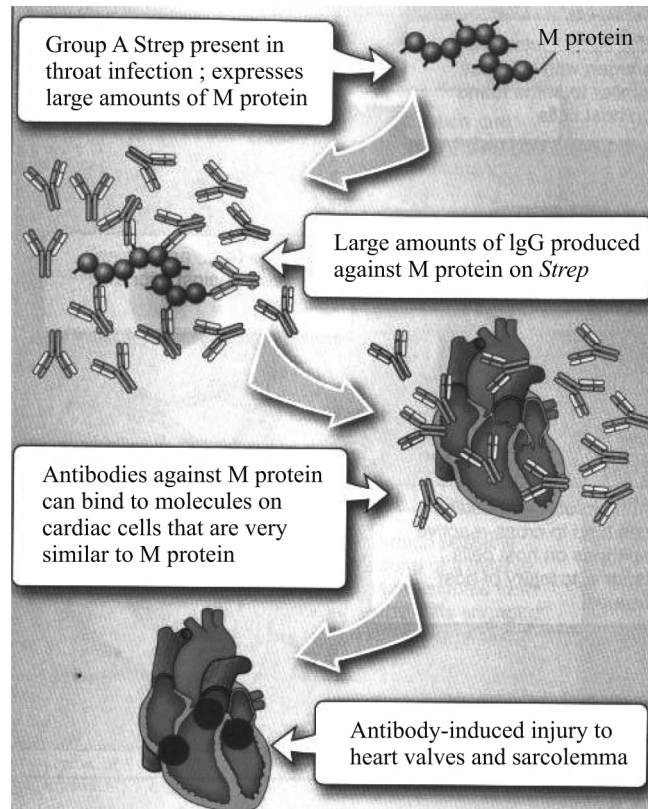


Fig. 64.2

Let us enumerate causes of autoimmunity

- Lymphocytes abnormalities and polyclonal lymphocytes activation
- Cytokine dysregulation due to changes in lymphocytes
- Failure of central tolerance and peripheral tolerance
- Overcome of Ag released from hidden location
- Antigen modified/ generated by molecular changes in the body
- Molecular mimicry
- Alteration in Ag processing
- Infection
- Genetic factors.

64.5 IMMUNOPATHOLOGY OF AUTOIMMUNE DISEASES

These are autoimmune diseases, so the pathology is immune response to self antigens as explained above. Antibody mediated immune response by formation of antibody to antigens on cell surface or in tissue matrix. Examples are

glomerulonephritis (Ab to basement membrane); rheumatic myocarditis (molecular mimicry as described above), etc. Another mechanism is immune complex mediated, Type III immune response to self antigen. Examples are Rheumatoid arthritis. The third mechanism is cell mediated (Type IV immune response) immune response against brain components, example is experimental auto immune encephalomyelitis.

So you see type II, III and Type IV immune responses are involved in immunopathology of autoimmune diseases.

64.6 LE CELL

The LE cell was so termed because of its exclusive presence in the bone marrow of 25 patients with confirmed or suspected SLE at the Mayo Clinic. LE cells are polymorphonuclear cells which have phagocytosed the nuclear material of other cells. LE cells are not usually found in peripheral blood. However, sometimes LE cell phenomenon could form in the buffy coat of peripheral blood after a period of]. LE cells are common in bone marrow but have also been found in synovial fluid, cerebrospinal fluid and pericardial and pleural effusions from patients with SLE.

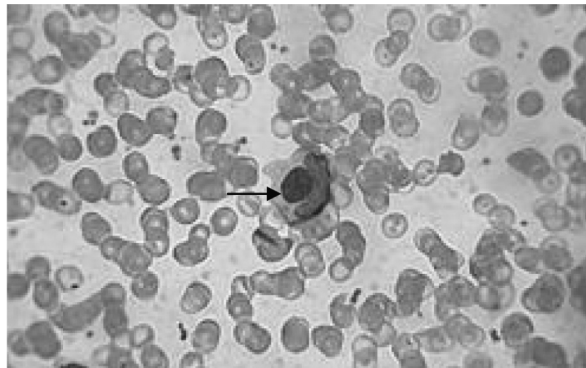


Fig. 64.3: LE cells are formed in response to an auto immune factor present in plasma in cases of SLE.

64.7 DIAGNOSIS OF AUTOIMMUNE DISEASES

It is very difficult to exactly diagnose autoimmune diseases. Clinical presentation and physical examination are done to make a probable diagnosis. Laboratory tests performed are of general nature and in case of organ specific disease specific tests can be performed.

General tests:

- C Reactive Protein
- Autoantibody titers (anti DNA, anti phospholipids, etc)



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- Presence of Rheumatoid Factor
- Erythrocyte sedimentation rate

Disease specific tests:

- Neurological exam – MS
- Fasting glucose – Diabetes

64.8 TREATMENT OF AUTOIMMUNITY

The general principle is to somehow stop the immune response to self antigens. This can be achieved by the following methods:

- Immunosuppression (e.g., prednisone, cyclosporin A);
- Removal of thymus (some Myasthenia Gravis patients);
- Plasmapheresis (to remove Antigen+Antibody complexes);
- T-cell vaccination (to activate suppressing T cells so that immune response to self antigens is suppressed??);
- Block MHC with similar peptide, so antigen processing is stopped;
- anti-CD4 monoclonal Antibody to inhibit immune response;
- anti-IL 2R monoclonal Antibody to inhibit immune response.



INTEXT QUESTIONS 64.3

1. Common environmental factors causing autoimmunity diseases are,, &
2. Disease like systemic lupus Erythromatosis are caused because of deficiency
3. Rheumatic fever occurs because of
4. Common laboratory tests for diagnosis of Autoimmune diseases are



WHAT YOU HAVE LEARNT

- An autoimmune disease is a case of mistaken identity; it is an abnormal condition in which the body reacts against constituents of its own tissues.
- Autoimmunity is defined as the breakdown of mechanisms responsible for self tolerance and induction of an immune response against components of self.

- The autoimmune diseases can be divided into systemic, localized and haemolytic disorders, depending on tissue/cells affected and the clinico-pathologic features.
- Systemic autoimmune diseases are associated with auto antibodies to antigens which are not tissue specific.
- Organ specific or localized autoimmune diseases are diseases in which autoimmunity involves a particular organ.
- In organ specific autoimmune diseases the implicated antigens and the autoimmunity are restricted to specific organs in the body
 - Type I diabetes
 - Goodpasture's syndrome
 - Multiple sclerosis
 - Grave's disease
 - Hashimoto' thyroiditis
 - Myasthenia gravis
- Haemolytic autoimmune diseases involve formation of auto antibodies against RBCs leading to autoimmune haemolytic anaemia; auto antibodies may form against platelets resulting in autoimmune thrombocytopenia; and formation of anti leucocyte antibodies resulting in autoimmune leucopenia and so on.
- Mechanisms of self tolerance are one mechanism is that the clones of lymphocytes which act against self antigens are deleted. This is the "clonal deletion" theory. Clonal deletion is mediated by ubiquitous self antigens. The second is inactivation of developing lymphocytes so our immune system becomes self tolerant, no activation of immunity against self antigens as specific lymphocytes are either deleted or inactivated. Clonal inactivation can be mediated by tissue-specific antigens.
- The causes of autoimmunity are:
 - Lymphocytes abnormalities and polyclonal lymphocytes activation;
 - Cytokine dysregulation due to changes in lymphocytes;
 - Failure of central tolerance and peripheral tolerance;
 - Overcome of Ag released from hidden location;
 - Antigen modified/ generated by molecular changes in the body;
 - Molecular mimicry;
 - Alteration in Ag processing;
 - Infection;



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- The autoimmune diseases can be detected by general tests for autoimmunity and organ specific tests for autoimmunity. The general tests include estimation of C Reactive Protein, Autoantibody titers (anti DNA, anti phospholipids, etc), Rheumatoid Factor, and erythrocyte sedimentation rate. Example of organ specific test is fasting glucose in Type 1 Diabetes.
- General principle for treatment of autoimmunity is to somehow stop the immune response to self antigens. This can be achieved by: immunosuppression, removal of thymus gland, plasmapheresis, T-cell vaccination, block MHC with similar peptide, etc.



TERMINAL QUESTIONS

1. Define autoimmunity. What are autoimmune diseases?
2. Describe the various types of auto immune diseases.
3. Describe the causes of auto immunity.
4. Question: Enumerate the causes of autoimmune diseases.
5. Describe various immunopathology mechanisms of autoimmune diseases.
6. Write short note on LE cell.
7. Name the types of tests used to diagnose autoimmune diseases.
8. Briefly describe the principles and methods of treatment of autoimmune diseases.



ANSWERS TO INTEXT QUESTIONS

64.1

1. Recognize & destroy
2. Auto immunity
3. Organ specific disease
4. Non-organ specific

64.2

1. not tissue specific
2. Rheumatoid Arthritis, Systemic Lupus Erythematosus & Sjogren's syndrome

3. Hashimotos' disease, Graves Disease & Type I diabetes
4. Clonal deletion

64.3

1. Pathogens, drugs, hormones & toxins
2. Complement
3. Molecular mimicry
4. C-Reactive Protein, antibody Titres, Erthrocyte Sedimentation rate & Rheumatoid factor

