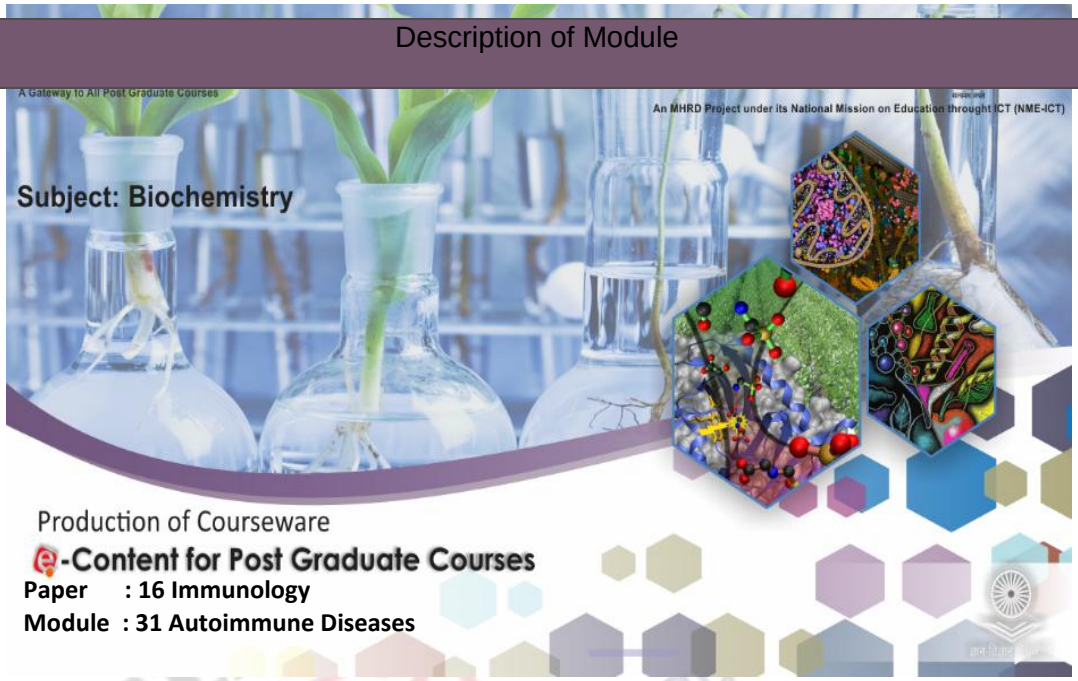
Description of Module



Paper : 16 Immunology

Module : 31 Autoimmune Diseases

Principal Investigator	**Dr. Sunil Kumar Khare,** Professor Dept. of Chemistry, I.I.T. Delhi
Paper Coordinator and Content Writer	**Dr. M.N.Gupta,** Emeritus Professor Dept. of Biochemical Engg. and Biotechnology, I.I.T. Delhi
Content Reviewer:	**Dr. Prashant Mishra,** Professor Dept. of Biochemical Engg. and Biotechnology, I.I.T. Delhi

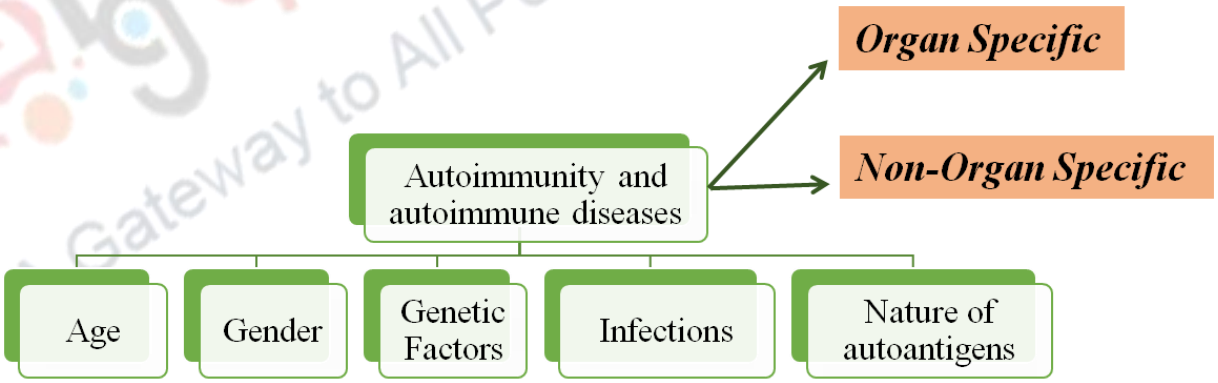
Subject Name	Biochemstry
Paper Name	16 Immunology
Module Name/Title	31 Autoimmune Diseases

A Gateway to All Post Graduate Courses

1. Objectives

- ✓ To look at the spectrum of autoimmune diseases and their prevalence
- ✓ To understand factors which are responsible for autoimmune diseases.
- ✓ To understand various mechanisms of autoimmunity
- ✓ To briefly look at pathogenesis and therapy of autoimmune diseases.

2. Concept map



Gateway to All Post Graduate Courses

We have seen how overreaction by immune system results in many hypersensitivity reactions. In all cases, this overreaction results in damage to host tissues.

The similar consequences result when immune system starts attacking self antigens. Some aspects of it are already covered when we discussed tolerance. So, it will help to recollect that discussion.

Also, as we saw in type V hypersensitivity, chronic stimulation overlaps autoimmune phenomena.

Autoimmunity is mediated by acquired immunity mechanism which starts operating against self antigens.

In some cases, the disease is due to primarily autoantibody or T-cells or by both. Whatever are the primary causes, T-cells play an important role which is not surprising as these cells are involved in regulation of immunity.

Again, the irony is that no new molecules/cell are involved. It is just the breakdown of the balance among various factors involved in usual immune processes.

Autoimmune diseases are of two types:

Organ Specific Diseases	Thyroiditis
	Diabetes Mellitus
	Multiple sclerosis (MS)
	Celiac disease
	Inflammatory bowel disease

Multiple tissue site	Systemic autoimmunity	Systemic lupus erythematosus (SLE)
		Rheumatoid arthritis (RA)
		Systemic vasculitis
		Scleroderma

The autoimmune diseases in organ specific disease involve attack on specific self antigens. Different organs/multiple tissue sites in many cases share these self antigens. That is apparently responsible for systemic autoimmunity. Systemic lupus erythematosus is an example where widely distributed antigen is involved. Anti DNA antibody is produced in this disease.

A given individual can develop autoimmune disease of more than one type.

Autoimmune disease	Associated autoimmune disease
Thyroid autoimmunity	Gastric autoimunity
Celiac disease	Sjogren syndrome
	Type I diabetes
	Thyroiditis

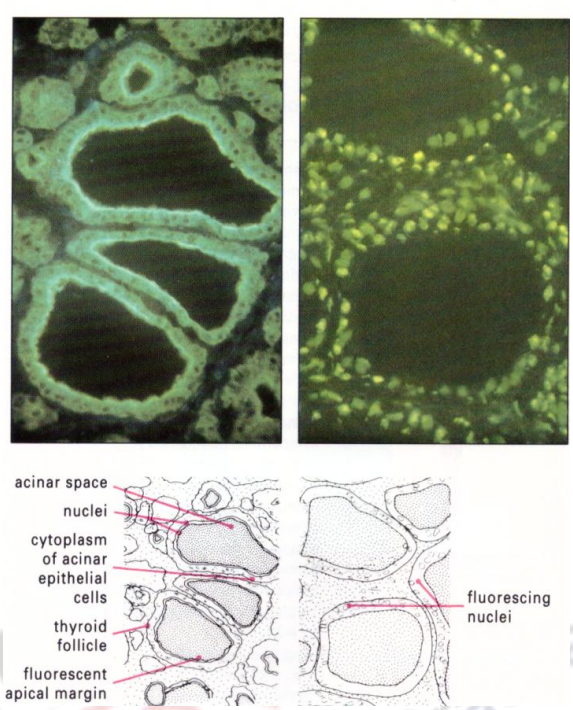


Figure 1: Autoantibodies to thyroid

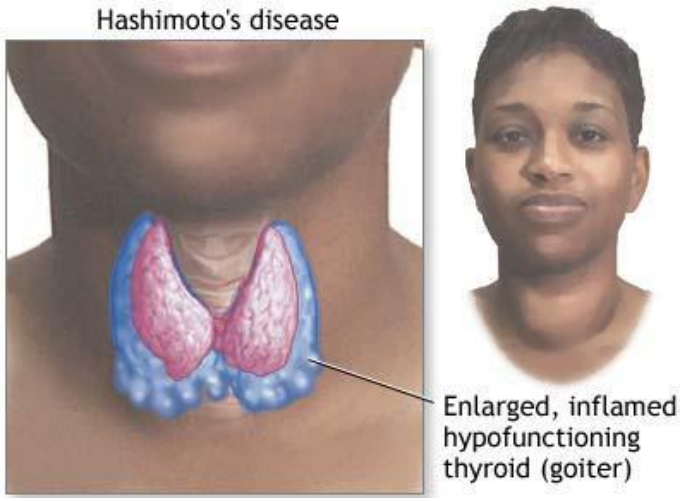


Figure 2: Hasimoto's thyroiditis

We had referred to Hashimoto's thyroiditis while discussing Graves' disease as an example of type V hypersensitivity. Hashimoto's disease is in fact one of the early examples where an organ specific autoimmunity was identified.

The disease is most common in middle aged women and leads to promotion of a goitre due to hypothyroidism.

The thyroid gland gets infiltrated with mononuclear phagocytes and lymphocytes. The gland in this disease often shows regeneration of thyroid follicles which distinguishes it from primary myxoedema in which thyroid shrinks and is nearly destroyed.

Hashimoto's thyroiditic and SLE mentioned above are the extreme ends of the list of organ specific and systemic autoimmunity.

There are remarkable overlaps at each end of this spectrum. Thyroid antibodies occur quite often in pernicious anemia patients who also generally have stomach autoimmunity. Similarly, stomach autoantibodies are often found in patients with thyroid autoimmunity.

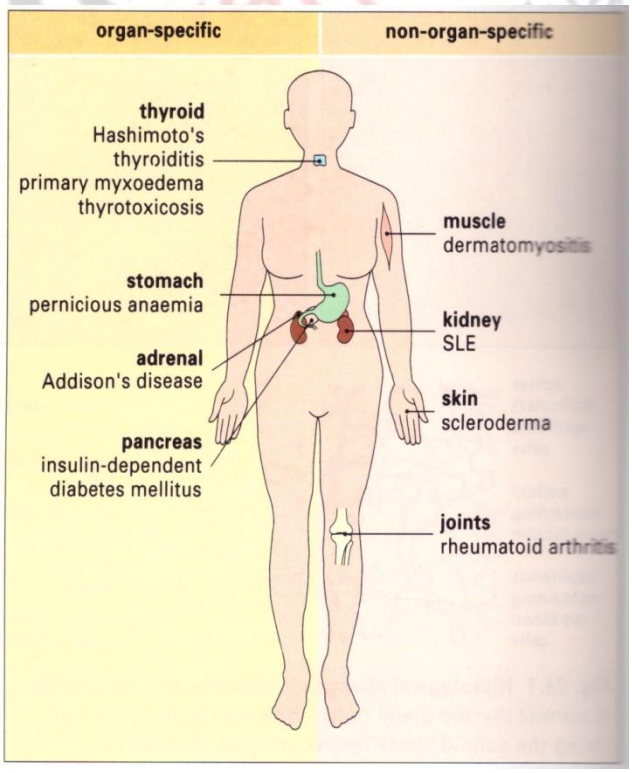


Figure 4: Two types of autoimmune diseases

Among systemic autoimmunity, clinical picture of SLE is often associated with features of Rheumatoid arthritis.

However, overlap of diseases at either end is very rare. Although in non-organ specific diseases, symptoms appear in skin, joints, kidney and muscle, specific organs are more markedly affected.

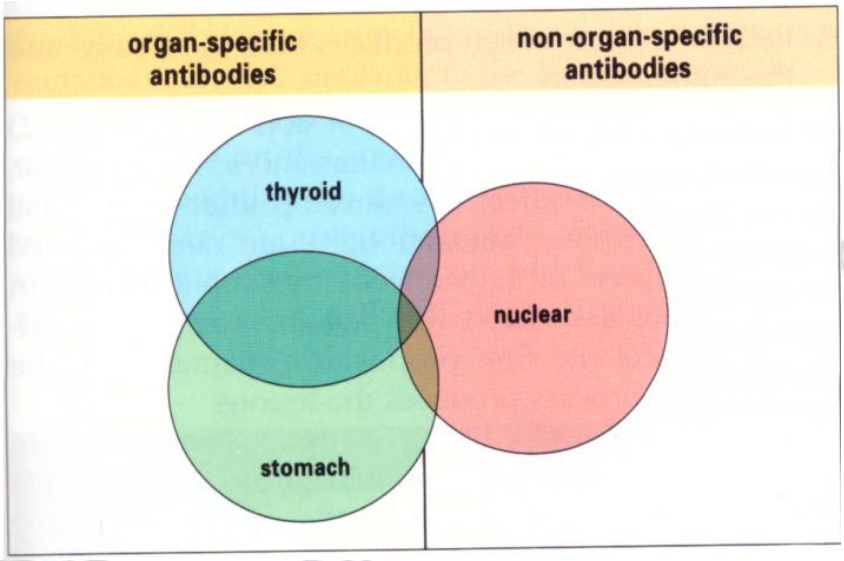


Figure 5: Overlap of autoantibodies

It may seem that the classification into organ specific and systemic may not be strictly valid. Its validity originates in the fact that within an individual or family either organ specific or systemic autoimmunity diseases cluster together.

Looked at from another point of view, the organ specific antibodies, say in thyroid and stomach, may occur together in an individual, but then that individual is highly unlikely to have non-organ specific antibodies.

It is estimated that nearly 3.5% of the population have autoimmune diseases.

The most common are:

Graves disease, type I diabetes, pernicious anaemia, rheumatoid arthritis, thyroiditis, CD, vitiligo, MS and SLE. These together account for 94% of all cases. Other autoimmune diseases together represent only 6% of the incidences.

Women are estimated to be affected 2-7 times more but this number can vary and is as high as 10 timesfor SLE.

Factors predisposing the development of immunity

Table 1: Factors contributing to development of autoimmune diseases

Genetics	Some diseases are HLA associated
Gender	Females generally more prone than males
Infections	Some common infections e.g. EBV, streptococcus, malaria, etc.
Nature of autoantigen	Often conserved antigens e.g. heat shock proteins and enzymes
Drugs	Some drugs e.g. procainamide, hydralazine induce SLE-like symptoms
Age	Higher incidence in aged population

The role of gender has already been mentioned. Genetics is definitely important. Within a family there is high predisposition to development of antiantibodies against the same organ specific diseases. So genetics control which organ is likely to be affected.

Table 2: Some autoimmune diseases showing HLA association.

Disease	HLA	Risk*
Ankylosing spondylitis	B27	90
Reiter's disease	B27	36.0
Systemic lupus erythematosus	DR3	15
Myasthenia gravis	DR3	2.5
Juvenile diabetes mellitus (insulin dependent)	DR3/DR4	25
Psoriasis vulgaris	DR4	14
Multiple sclerosis	DR2	5
Rheumatoid arthritis	DR4	4

*Based on a comparison of the incidence of the autoimmune disease in patients with a given HLA type with the incidence of the autoimmune disease in patients without this HLA type.

Figure 6: Associations of HLA serotype and sex with susceptibility to autoimmune disease.

MHC which presents antigen or autoantigens has an important role in this. There is a well established correlation between HLA type and relative risk of various autoimmune diseases. While the % risk is more strongly correlated with MHC class II alleles but in some cases strong correlation also exists with particular MHC class I alleles.

The strongest correlation between HLA allele and % risk has been observed with Ankylosing spondylitis with an individual with HLA-B27 is about 90 times more likely to develop the disease as compared to one who lacks HLA-B27.

Insulin-development diabetes mellitus patients invariably express HLA-DR3 and/or HLA-DR4. These alleles are highly linked to HLA-DQ alleles which shows high association with IDDM but is not detectable by serotyping.

HLA-DR2 infact seems to protect development of IDDM. It is rarely detected in IDDM patients. (X represents any other alleles)

Serotyping and tracking family histories have been two approaches in looking at the genetic factors.

Now, HLA genotyping has led to establishing more precise associations.

The usefulness of HLA genotyping and the insights it can provide is best illustrated in case of IDDM. DR3 and DR4 alleles are tightly linked genetically to DQβ alleles.

Polymorphism at specific position in DQβ amino acid sequence has been found to be closely associated with the incidence.

In the DQβ sequence, Asp 57 forms a self bridge with Arg at the end of the peptide binding cleft. The diabetic patients instead have Val, Ser, or Ala at 57 position. This abolishes the salt bridge and changes the stability of DQ molecule.

This is a critical feature as similar molecular picture exists in case of nonobese diabetic (NOD) mice which have Ser at 57 position in the homologous chain. The correlation has been confirmed with transgenic NOD mice which have Asp 57 and show drastic reduction in incidence of IDDM.

As in all autoimmune diseases, MHC genotype alone does not completely decide risk factors for the development of disease.

Witebsky's Postulates

We have referred to serology as one tool in study of autoimmunity. Before going any further, it is necessary to clarify that presence of autoantibodies is not a sure clinical diagnosis of a particular disease.

Many decades back, Ernest Witebsky postulated:

- ✓ The autoantibodies being used to correlate with a disease should be ones which are present in all cases of the disease.
- ✓ It should be verified experimentally that the corresponding antigen if used as an immunogen cause the manifestation of the disease.

- ✓ The disease thus experimentally induced must show immunopathological lesions which are characteristics of the disease in confirmed patents.
- ✓ The disease should be transferable from an affected animal to a normal one by serum or lymphoid cells.

These postulates were very helpful in that early era in bringing clarity to the studies on autoimmunity.

Thus the finding of autoantibodies does not confirm the corresponding disease. In any case, it should be clear from the earlier discussion, that even in organ specific diseases, one may find several autoantibodies in the sera.

There are three possibilities when autoantibodies are detected. The obivious one to suspect is that autoantibodies are responsible for observed lesions.

It is also possible that a disease caused tissue damage which in turn led to the development of the autoantibodies.

For example, cardiac antibodies may develop after myocardial infection. However, autoantigens released by simple trauma rarely leads to corresponding autoantibodies.

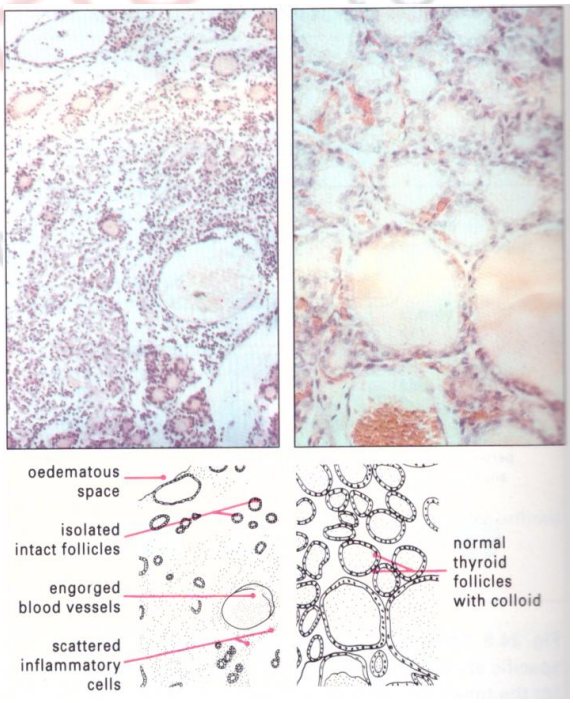


Figure 10: The histological appearance of experimental autoallergic thyroiditis

Thyroglobulin injected animals produce thyroid autoantibodies and show thyroiditis which is very similar to Hashimoto's disease in humans.

We have been discussing genetic factors. This is also shown by the fact that not all strains of an animal do not respond similarly when used for inducing autoimmunity.

Let us return to the other factors which we mentioned which are part of multifactorial dependence of autoimmunity. What is more complicated is that those factors do not influence the % risk factors independently. Genetics and gender, for example interact as factors.

Age and gender

Older humans and other animals are more prone. This is understandable since aging immune system is known to display laxity in immunoregulation.

While in general, females are more prone, ankylosing spondylitis is almost exclusive to males.

Neuroendocrine system is implicated. In a strain of female mice, removal of estrogen secreting gland ovaries or treatment with male hormone testosterone prevented SLE development. On the other hand, castrated males become prone to SLE.

Infections

Correlation between infectious agents and autoimmune diseases have been known. Chronic infections with *Borrelia burgdorferi* is responsible for Lyme arthritis. This is transmitted by len ticks to deer and rodents to people.

Crossreactivity with microbial antigens is known to also induce autoimmunity through infection.

Trypanosome cruzi causes Chagas disease in humans as its antigens crossreacts with antigens on neurons and cardiac muscles.

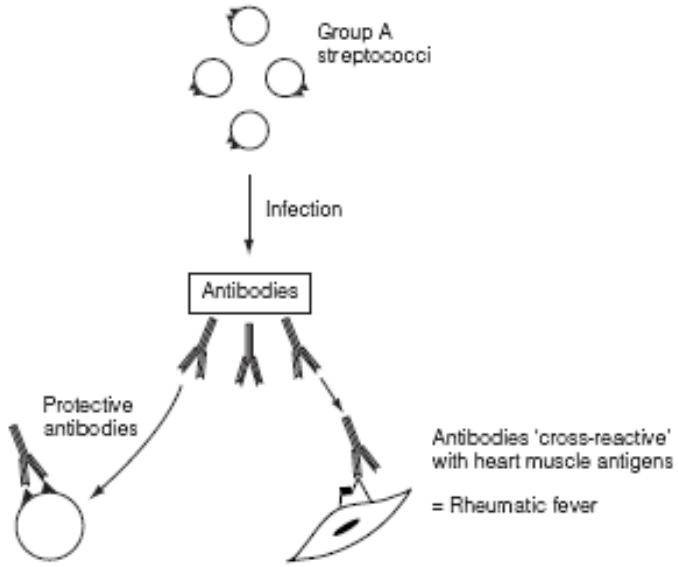


Figure 11: Group A streptococci and rheumatic fever

An epitope common to heart muscle and group A streptococci is responsible for rheumatic heart disease. In fact, once infection is controlled, the disease also goes away.

Viruses are also known to induce autoimmunity. Viruses infecting lymphoid tissues are especially important in this regard as immunological control mechanism are affected. SLE is possibly associated with a virus. It is also believed that juvenile type I diabetes may be due to viral infection.

Nature of the Autoantigens

Table 2: Antigens targeted in autoimmune diseases

The antigens involved may be a cell surface, cytoplasmic, nuclear or an extranuclear one. Generally these are highly conserved proteins like heat shock proteins (HSPs).

A microbial infection elicits an anti HSP response followed by response to the microbial components. Given the strong homology between microbial HSP and human HSP, human HSP crossreact.

The autoantigens covers a wide range. Proteins, lipids, nucleic acids and their conjugates all could act as autoantigens. Receptors, structural proteins and enzymes all can act as autoantigens.

Table 3: Enzymes as autoantigens

Enzyme	Disease
Pyruvate dehydrogenase	Primary biliary cirrhosis
Glutamic acid decarboxylase	Insulin dependent diabetes
Myeloperoxidase	Glomerulonephritis
Thyroid peroxidase	Autoimmune thyroiditis
17α and 21 hydroxylase	Addison's disease
Proteinase 3	Wegener's granulomatosis
Tyrosinase	Vitiligo
Transglutaminase	Coeliac disease

Many enzymes have been identified as auto antigens in specific diseases. In celiac disease, auto antibodies of IgA type have been detected against tissue transglutaminase.

IgG ab to glutamic decarboxylase in diabetes and thyroid peroxidase in thyroiditis are other well known examples.

Drugs and autoimmunity

There are reports that antinuclear antibody appear in the blood during treatment of ventricular arrhythmias with procainamide and some small percentage (-100%) develop SLE like symptoms. Discontinuation of the drug at an early stage leads to disappearance of these symptoms. So, in principle drugs can initiate autoimmunity by unknown mechanism.

Thrombocytopenia (low platelet count) and anaemia (low RBC) are often drug induced.

Immunodeficiency

Immune deficiency is associated with autoimmunity. This may seem like a paradox but in some cases immune deficiency leads to persistence of infection or inflammation.

Deficiency of complement compounds C2, C4, C5 or C8 correlates with autoimmune disease, particularly SLE. In such cases, immune complexes which are no longer efficiently cleared by the complement system accumulate.

IgA deficiency also increases the risk of common variable immunodeficiency (CVID).

Environmental factors

In Goodpasture's disease (in which autoantibodies against type IV collagen are produced), only patients who smoked had pulmonary haemorrhage. Injury to endothelial lining is necessary to expose basement membranes.

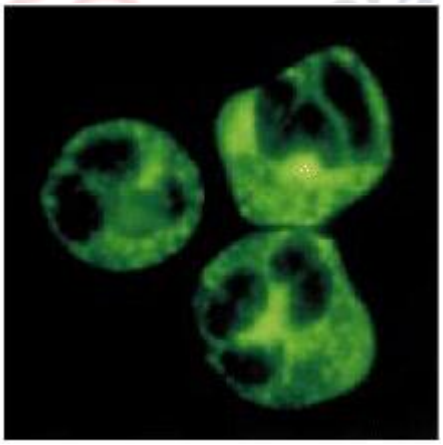


Figure 12: Serum from patients with Wegener's granulomatosis contains autoantibodies reactive with neutrophil cytoplasmic granules

Wegener's granulamotosis has necrotising vasculitis due to antibodies against a neutrophil protease (proteinase-3). An infection results in cytokine activated neutrophils translocating the antigen to the cell surface. This results in severe vasculitis.

Mechanisms of autoimmunity

In normal individual, tolerance is an inherent texture of immune system which avoids autoimmunity. Hence self reactive lymphocytes are either eliminated or fail to produce enough antibodies/are unable to present it in enough concentration.

Release of a sequestrated antigen is followed by its uptake by an APC which now present it to T_h

In another route, a cell expresses MHC class II which it should not and thus becomes an APC for an autoantigen.

In third mechanism, Ts and other cells are unable to send adequate suppression signals to T_h which becomes active.

Lastly, polyclonal antigens bypass T_h control.

A Gateway to All Post Graduate Courses

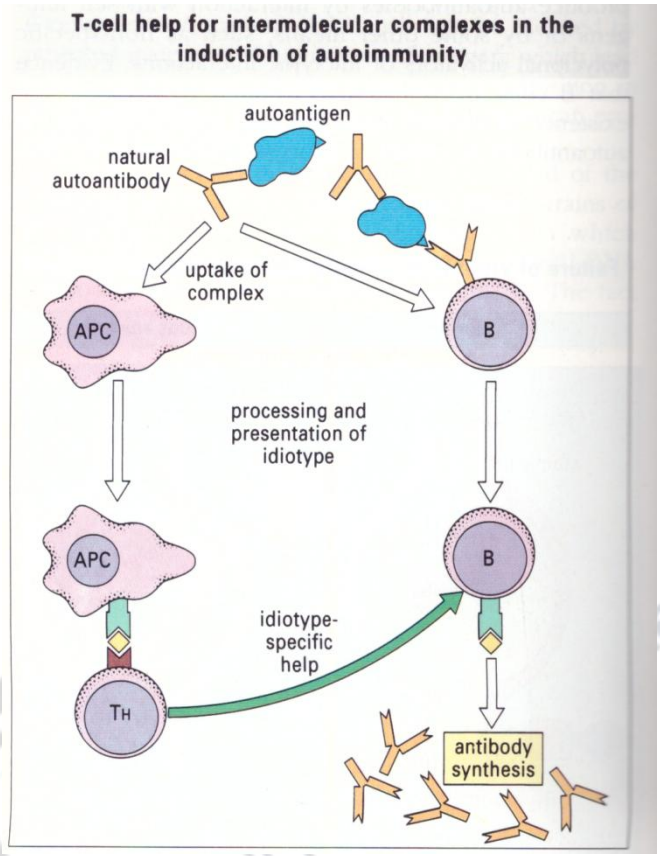


Figure 13

T-cell involvement is critical to development of autoimmunity. Patients with thyrotoxicosis have thyroid specific T-cell clones. Anti-CD4 helps in RA. The role of MHC in autoimmunity is due to their role in inappropriate presentation to T-cells.

In systemic autoimmunity, often anti-antigens involved are not identified. It is possible that T-cells recognise idiotypes. Autoantibodies produced at the low level from immune complexes with autoantigens. These complexes are taken up by APC (which include B-cells) these APC process the complexes and prevent antibody idiotype to T_h cells. The idiotype specific T-cells help corresponding B-cells.

T-cell bypass mechanism

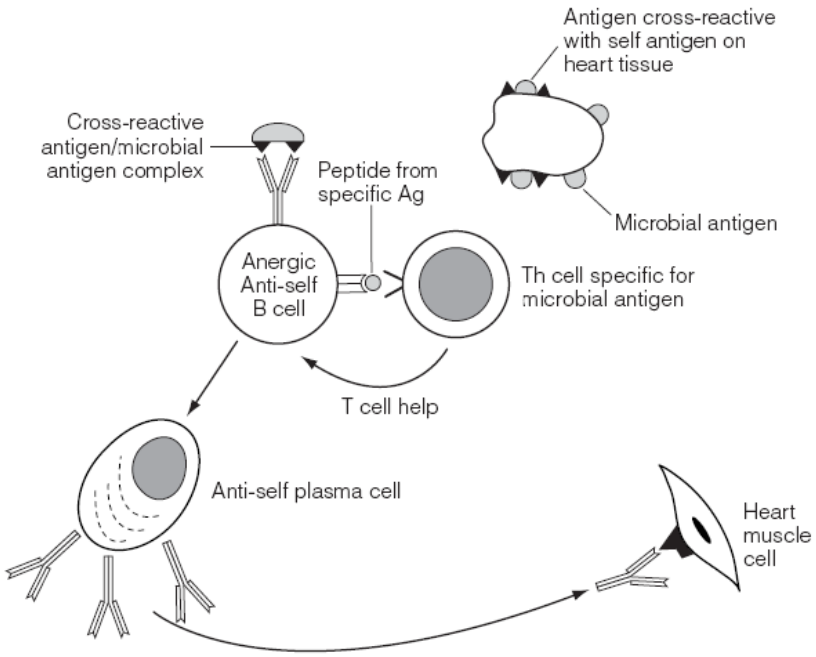


Figure 14: Activation of anergic anti-self B-cells

We have earlier referred to an example of molecular mimicry where rheumatic heart disease is due to identity of epitopes between group A streptococci and heart muscle. Here these specific B cells receive stimulatory signal from streptococci epitope specific T_h cells. The plasma cells secrets antibodies which crossreact with heart muscle cells.

Polyclonal activation

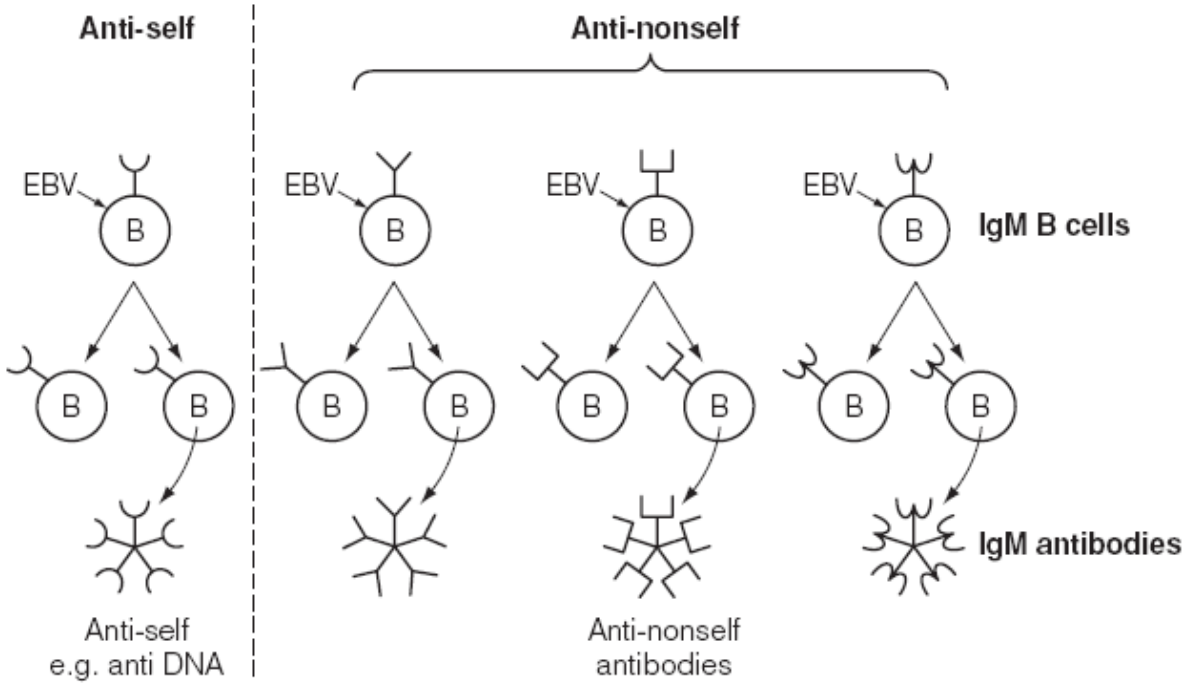


Figure 15: Autoantibodies produced through polyclonal activation of B cells

Infection by Epstein-Barr virus (EBR) in humans leads to polyclonal activation of B-cells of all specificities (not completely eliminated by central tolerance mechanisms) including those against self antigens. Patients with mononucleosis (caused by the EBV) produce IgM against several self antigens including DNA. Class switching does not occur indicating that T_h cells are not involved. Control of infection leads to disappearance of these IgM antibodies.

Defective Tregs

Regulating T-cells (Tregs) maintain self-tolerance. Decrease in Tregs or impairments of their function has been identified as contributory causes in several autoimmune disease in humans.

Tregs keeps autoreactive T_h under control through several ways which include antigen specific suppression. Cytokines like IL-10 and T4Fβ play a role in suppression. Either over responsive T_h cells or impairment of T_s cell functions tilt the balance towards autoimmunity.

Pathogenesis in autoimmunity

- We have earlier pointed out close relationship between hypersensitivity and autoimmunity. In autoimmunity, the tissue damage ultimately operates via one of the hypersensitivity reaction.
- Haemolytic anemia results from antibodies directed against RBC. Thrombocytopenia results from antibodies directed against platelets. These are type II hypersensitivity mediated autoimmune reactions.
- SLE produces a wide variety of auto antibodies, anti-DNA are the most significant among these. The immune complexes deposit in glomeruli. Similarly RA has immune complexes deposited in joints. The tissue damage follows hypersentivity type IV mechanisms.
- Finally, grave's disease and myasthenia gravis involve chronic stimulation of TSH. Tissue damage follow type V hypersensitivity reactions.

A Gateway to All Post Graduate Courses

The treatment approaches can be:

- Replacement therapy
- Suppression of autoimmune process: NSAIDs and glucocorticoids can reduce inflammation

Increasingly, monoclonal ab are emerging as the most important therapy in case of many autoimmune diseases.

Tolerance, hypersensitivity reactions and autoimmune diseases are all interlinked. Autoimmunity is a failure of tolerance mechanism. The tissue damage is due to the mechanism which we discussed while looking at various hypersensitivity reactions.

The diagnosis of autoimmunity is not always straightforward. Here detection of an autoantibody does not mean that the corresponding disease will manifest itself.

There is lot which we do not yet understand about the interplay of various factors which predispose one towards autoimmuntity.

Summary

- Autoimmune diseases can be organ specific or non organ specific.
- Age, gender, genetic factors, infection also influence autoimmunity
- Many mechanisms of autoimmunity are known. T-cells play a crucial role.
- Tissue damage follow hypersensitivity mechanism.
- Replacement therapy and suppression of autoimmunity can be tried to minimize damage.