Autoimmunity

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Autoimmunity

- Basically means immunity to self
- A condition that occurs when the immune system mistakenly attacks and destroys healthy body tissue
- Condition in which structural or functional damage is produced by the action of immunologically competent cells or antibodies against the normal components of the body.
- Protection against self – injury to self

- **Autoimmunity** is called that the organism reacts to its self Ags.
- Antibody, formed in this condition, is called **autoantibody**
- The resulting disease is called **autoimmune disease**

- Causes: Happens when the immune system can't tell the difference between healthy body tissue and antigens. Immune response will destroys normal body tissues. This response is a hypersensitivity reaction similar to the response in allergic conditions.
- In allergies, the immune system reacts to an outside substance.
- Under normal circumstances immune system will not destroy self antigens.
- In numerous autoimmune diseases it is well recognized that products of the immune system cause damage to the self.

- With autoimmune disorders, the immune system reacts to normal body tissues.
- An autoimmune disorder may result in: • The destruction of one or more types of body tissue • Abnormal growth of an organ • Changes in organ function

Mechanism of Autoimmunity

- **Ag released from hidden location.**
- **Antigen generated by molecular changes.**
- **Molecular mimicry.**
- **Alteration in Ag processing.**
- **Infection.**
- **Genetic factors.**
- **Lymphocytes abnormalities.**
- **Failure of central tolerance.**
- **Overcome of peripheral tolerance.**
- **Polyclonal lymphocytes activation.**

Ag related from hidden location

Many self Ag are found in hidden location eg. TESTES ,EYE (CORNEA)

organ damage

↓

Hidden Ag released

↓

Reaches blood stream

↓

Encounter Ag sensitive cells

↓

Stimulate autoimmunity

Release of Sequestered Antigen

Antibodies in blood can attack Myelin Basic Protein if Blood-Brain barrier is breached.

- Antigen generated by molecular changes: **Development of completely new epitopes on normal protein.**

- Cross-reactivity (Molecular and Viral Mimicry)

Viral and nonviral peptides can mimic self-peptides and induce autoimmunity

TABLE 20-3 MOLECULAR MIMICRY BETWEEN PROTEINS OF INFECTIOUS ORGANISMS AND HUMAN HOST PROTEINS

Protein*	Residue†	Sequence‡
Human cytomegalovirus IE2	79	P D P L G R P D E D
HLA-DR molecule	60	V T E L G R P D A E
Poliovirus VP2	70	S T T K E S R G T T
Acetylcholine receptor	176	T V I K E S R G T K
Papilloma virus E2	76	S L H L E S L K D S
Insulin receptor	66	V Y G L E S L K D L
Rabies virus glycoprotein	147	T K E S L V I I S
Insulin receptor	764	N K E S L V I S E
Klebsiella pneumoniae nitrogenase	186	S R Q T D R E D E
HLA-B27 molecule	70	K A Q T D R E D L
Adenovirus 12 E1B	384	L R R G M F R P S Q C N
α-Gliadin	206	L G Q G S F R P S Q Q N
Human immunodeficiency virus p24	160	G V E T T T P S
Human IgG constant region	466	G V E T T T P S
Measles virus P3	13	L E C I R A L K
Corticotropin	18	L E C I R A C K
Measles virus P3	31	E I S D N L G Q E
Myelin basic protein	61	E I S F K L G Q E

*In each pair, the human protein is listed second. The proteins in each pair have been shown to exhibit immunologic cross-reactivity.

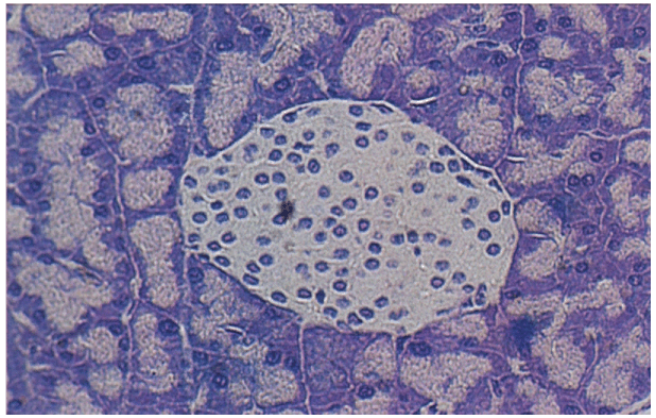
†Each number indicates the position in the intact protein of the amino-terminal amino acid in the listed sequence.

‡Amino acid residues are indicated by single-letter code. Identical residues are shown in blue.

SOURCE: Adapted from MBA Oldstone, 1987, *Cell* **50:**819.

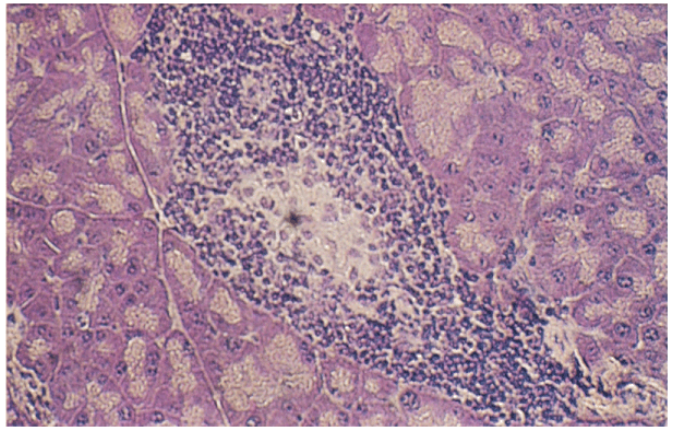
Inappropriate MHC Expression

(a)



Normal Pancreas

(b)



Pancreas with Insulitis

Type I Diabetes: Pancreatic β cells express *abnormally high levels* of MHC I and MHC II (?)

Infection

- Here autoimmunity is not due to infectious agent itself ,but results from dis regulation of host immune response by the microbes.

This may be due to :

- Polyclonal lymphocyte activation.
- Inhanced stimulation of co stimulator.
- Alteration of self Ag(cross reactive neo-Ag)

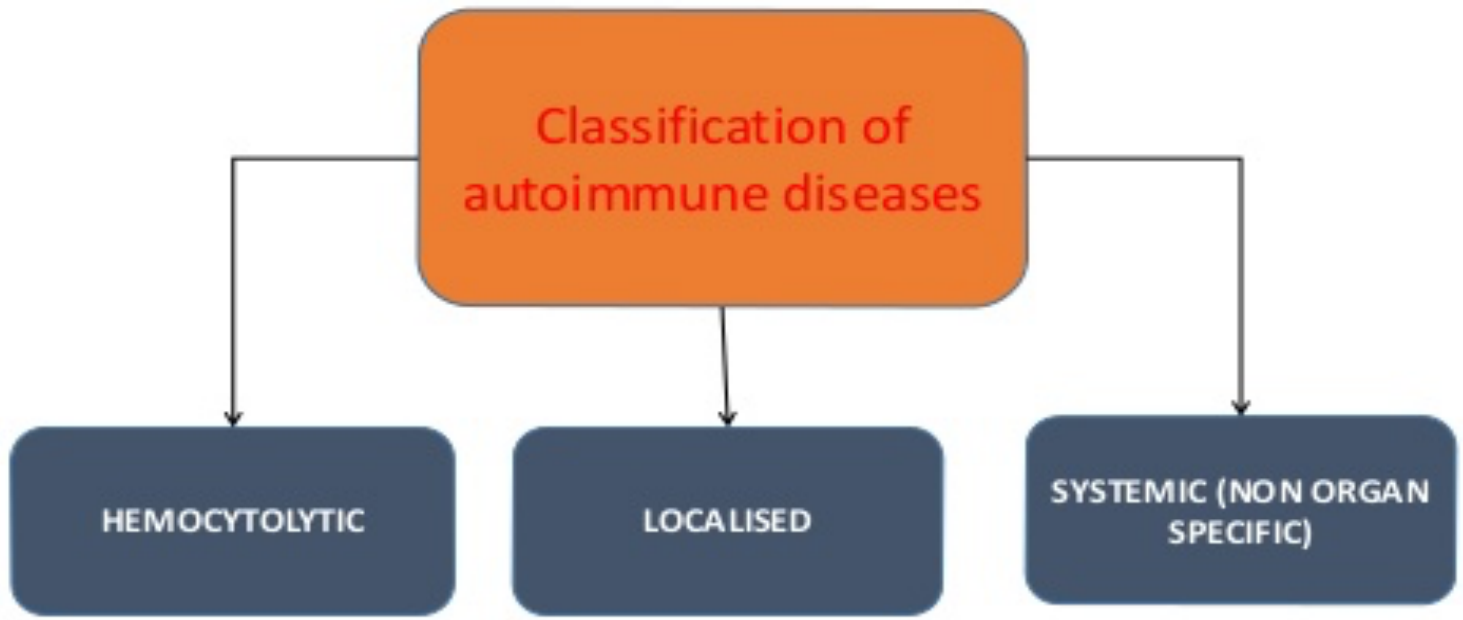
Polyclonal B Cell Activation by Viruses and Bacteria

- If B cells reactive to self-peptides are activated, autoimmunity can occur.

Example: Epstein-Barr Virus, which is the cause of infectious mononucleosis.

Briefly

- Autoimmunity can be caused by immunological, genetic, viral, drug-induced, and hormonal factors.
- There are 4 immunological mechanisms of autoimmunity.
- All mechanisms cause abnormal B or T cell activation.
- Most instances of autoimmune diseases occur with multiple mechanisms, which makes treatment difficult.


Classification of autoimmune diseases
HEMOCYTOLYTIC
LOCALISED
SYSTEMIC (NON ORGAN SPECIFIC)

1-Hemolytic autoimmune diseases

- Clinical disorder due to destructions of blood components. Auto Ab are formed against one’s own RBCs, Platelets or Leucocytes. - E.g. Haemolytic anaemia, Leucopenia, Thrombocytopenia, etc.

2-Localised autoimmune diseases (Organ specific autoimmune diseases)

A particular organ is affected due to auto Abs. - For example:

- Thyroiditis (attacks the thyroid)
- Multiple sclerosis (attacks myelin coating of nerve axons)
- Myasthenia gravis (attacks nerve-muscle junction)
- Juvenile diabetes or Type I DM (attacks insulin-producing cells)

- **Hashimoto thyroiditis** is an autoimmune disease in which the immune system reacts against a variety of thyroid antigens. There is progressive depletion of thyroid epithelial cells (thyrocytes), which are gradually replaced by mononuclear cell infiltration and fibrosis.

THE SYMPTOMS:

- many of the symptoms associated with thyroid hormone deficiency.
- Fatigue
- Drowsiness
- Difficulty with learning
- Dry, brittle hair and nails
- Dry, itchy skin
- Puffy face
- Constipation.
- Weight gain
- Heavy menstrual flow
- Increased frequency of miscarriages
- Increased sensitivity to many medications.

Juvenile diabetes or Type I DM

- Beta cells that produce insulin slowly are destroyed by the body's immune system in the blood vessels of the pancreas which prevents glucose from getting into cells because of the low insulin levels. Genetics have been linked to the development of Type 1Diabetes.

Multiple sclerosis (MS)

- It is a condition of the central nervous system. In MS, the coating around nerve fibres (called myelin) is damaged, causing a range of symptoms.
- It's normally diagnosed in people between the ages of 20 and 40, and affects almost three times as many women as men.
- Once diagnosed, MS stays with you for life, but treatments and specialists can help you to manage the symptoms.
- We don't know the reason as to why certain people are more susceptible in developing MS then others, and we haven't yet found a cure, but research is progressing fast.
- MS is complex and can cause many different symptoms.

Myasthenia gravis

- It is an autoimmune disorder affecting the myoneural junction, is characterized by varying degrees of weakness of the voluntary muscles.
- CAUSES:• In MG, the receptors at the muscle surface are destroyed or deformed by antibodies that prevent a normal muscular reaction from occurring.• The causative factor is unknown, but the disorder may have a genetic link.

Risk factors for myasthenia gravis include:

- Female gender and age under 40 years
- Male gender and age over 60 years
- Other autoimmune disorders

Factors that can worsen myasthenia gravis

- Fatigue
- Illness
- Stress
- Extreme heat
- Some medications — such as beta blockers, calcium channel blockers, quinine and some antibiotics

3-Systemic autoimmune diseases (Non-organ specific autoimmune diseases)

- Immune complexes accumulate in many tissues and cause inflammation and damage.
- Affects many organs or the whole body

Systemic Lupus Erythematosus (SLE)

- Auto-antibodies formed against variety of self antigens
- Anti-double stranded DNA,RNA and histones
- Antibodies against cell surface antigens on RBC's and/or platelets
- Tissue damage caused by Type III hypersensitivity reactions
- Immune circulating complexes formed against self deposit on tissues
- Vasculitis, synovitis, glomerulonephritis

Rheumatoid Arthritis

- Rheumatoid arthritis (RA) affects peripheral joints and may cause destruction of both cartilage and bone.
- Systemic autoimmune disease
- Genetic factors (HLA-DR1, HLA-DR4)
- Autoreactive B-cells synthesize auto antibody against Fc portion of IgG
- Rheumatoid factor (RF)
- Chronic inflammation of synovial joints
- Proliferation of synovial lining cells
- Erosion of articular cartilage and adjacent bone

Rheumatic fever

- Rheumatic fever (RF) is an inflammatory disease that can involve the heart, joints, skin, and brain. The disease typically develops two to four weeks after a streptococcal throat infection
- Cross-reaction between antibodies to streptococcus and auto-antibodies.

http://ktthebest4u.blogspot.com.tr/2014/11/rheumatic-fever.html

- Major involvement of systemic connective tissue, it often violate connective tissue of heart, joint, skin, and subcutaneous and vascular connective tissue. Key pathologic features is Rheumatic Granuloma.
- The clinical course of rheumatic fever involves a childhood infection with complications in adulthood (cardiac defect).

Sclerosis (Scleroderma)

- Limited form: Skin changes limited to hands, face, feet and forearms Skin calcification
- Systemic sclerosis: In addition to skin changes in systemic form, it can lead to damage to blood vessels, internal organs such as the lungs, heart and kidneys.

Sjögren's Syndrome

- It is a systemic autoimmune disease in which exocrine glands (saliva, tears, vaginal secretions, lower and upper respiratory tract glands) are affected. Persistent dryness of mouth and eye due to functional and structural deterioration of the salivary and lacrimal glands is the most important sign of the disease.

Reiter syndrome

- Reactive arthritis, also known as Reiter's syndrome, is a form of inflammatory arthritis[1] that develops in response to an infection in another part of the body (cross-reactivity). Coming into contact with bacteria and developing an infection can trigger the disease.
- Reactive arthritis can affect especially knee and ankle joints and heels, fingers and waist.

The general symptoms of autoimmune disease

- In general all autoimmune diseases
- Weakness,
- Fatigue,
- Quick fatigue,
- Fever,
- The general disease state is seen.

Diagnosis of Autoimmune disease

- Diagnosed by clinical symptoms.
- Confirmed by detecting the auto Ab in the serum of the patients.
- Autoantibodies are demonstrated by immunoflurescent Ab test, haemagglutination, Complement fixation, immunodiffusion, Radio immuno assay, etc.
- Blood test
- CRP
- Sedimentation

Treatment

- Some autoimmune diseases are treated with medications that alleviate specific symptoms.
- Haemolytic anaemia: Treated with Vit B 12
- Throtoxicosis: Treated with antithyroid drugs.
- Myasthenia Gravis: Treated with Choline estrase inhibitors
- Rhemotoid Arthritis: Anti-inflammatory drugs
- Lupes Erythematosus: Treated with immono suppresive or antimitiotic drugs such as Corticosteoid, Cyclophosphamide and azothioprine.

IMMUN COMPLEX DISEASE

- Type III Allergic reaction
- Allergen (Drug).....antibody
- Ag+Ab+ complement
- This triple complex goes to tissues like vascular endothelium, kidney glomeruli, and collapses. (immune complex formation)
- The mast cells in that area are active and chemotactic substances are secreted. Polymorphonuclear leukocytes come to that region and break down cells with secreted lysosomal enzymes. Tissue damage and inflammation occur.
- Exp: Serum disease

IMMUNODEFICIENCIES

- The absence or dysfunction of any of the components of our immune system is called immunodeficiency diseases. These are classified as primary and secondary.
- Immunodeficiency disorders are associated with or predispose affected patients to various complications, including infections, autoimmune disorders, and lymphomas and other cancers. Primary immunodeficiencies are hereditary; secondary immunodeficiencies are acquired. Secondary immunodeficiencies are much more common.

Primary immunodeficiencies

- These disorders are genetically determined; they may occur alone or as part of a syndrome. More than 100 of these disorders have been described.
- Primary immunodeficiencies typically manifest during infancy and childhood as abnormally frequent (recurrent) or unusual infections.
- Primary immunodeficiencies are classified by the main component of the immune system that is deficient, absent, or defective:
    - Humoral immunity
    - Cellular immunity
    - Combined humoral and cellular immunity
    - Phagocytic cells
    - Complement proteins

Secondary immunodeficiencies

- Causes include
  - Systemic disorders (eg, diabetes, undernutrition, HIV infection)
  - Immunosuppressive treatments (eg, cytotoxic chemotherapy, bone marrow ablation before transplantation, radiation therapy)
  - Prolonged serious illness.
- Secondary immunodeficiency also occurs among critically ill, older, or hospitalized patients. Prolonged serious illness may impair immune responses; impairment is often reversible if the underlying illness resolves.

TRANSPLANTATION IMMUNOLOGY

- **Transplantation** is a act of transferring cells, tissue, or organ from one site to another
- **Graft** : Implanted cell, tissue or organ
- **Donor** : Individual who provides the graft
- **Recipient or host** : Individual who receives the graft

Autograft

- Self tissue is transferred from one body site to another
- Antigen present in autograft is same as that present in body
- So immune system recognizes the autograft antigen as a self antigen No immune response is elicited
- Autograft survive through out the life

Eg., - Transferring healthy skin to burned area,

- Use of healthy blood vessels to replace blocked coronary arteries,

- Plastic surgery of skin.

Isograft

- It is also called syngraft
- Tissue is transferred between genetically identical individuals of same species
- In isograft the histo compatibility antigens are identical hence the graft survives and not rejected.

Eg in human isograft can be performed between two twins.

Allograft

- Tissue is transferred between two genetically different members of same species
- In allograft histocompatibility antigens are dissimilar hence immune response is elicited and graft is rejected

Eg., In humans graft is transferred from one individual to another

Xenograft

- Tissue is transferred between two different species
- Eg., Graft of human transferred to animal
- In xenografts histocompatibility complex antigens are so different that the graft is more vigorously rejected

- Alloantigens elicit both cell-mediated and humoral immune responses.
- Recognition of transplanted cells that are self or foreign is determined by polymorphic genes that are inherited from both parents and are expressed co-dominantly.

REJECTION

- Often a transplanted organ is not identified by the immune system as the tissue of the organism
- It can be attacked and destroyed.
- Against this effect, the patient has to swallow Immunesuppressive
- In 15-20 minutes the organ dies, unable to withstand the immune system attack.

- In immune recognition, the task of distinguishing foreign antigens from self antigens is through tissue compatible antigens. Superficial antigens must be compatible between transported tissues. These antigens are called Human Leukocyte antigens. Transplantation success depends on HLA.

Histocompatibility antigens

- Genes that are responsible for rejection
- There are more than 30 gene loci
- Reject at different rate

- In human known as human leucocyte antigens **(HLA)**
- Cellular constituents are called minor histocompatibility antigens
- These induce rejection at a slower rate
- Combination of several minor antigens induce strong rejection

The types of rejection

- Hyperacute rejection
- Acute rejection
- Chronic rejection

- **Hyperacute rejection**

  antibodies to HLA and ABO blood group system (hours or first days)

- **Acute rejection**

  T cells (days or weeks)

- **Chronic rejection**

  various mechanisms: cell-mediated, deposition of antibodies or antigen antibody complexes with subsequent obliteration of blood vessels and interstitial fibrosis (months or years)

GRAFT VERSUS HOST DISEASE (GVH)

- Is common complication in recipients of bone marrow transplants
- Is due to the presence of alloreactive T cells in the graft
- It results in severe tissue damage, particularly to the skin and intestine
- It may be avoided by careful typing, removal of mature T cells from the graft and by immunosuppressive drugs
- It is manifested by marked rise of several cytokines in patient's serum (IFN- γ, TNF, IL-1, IL-2, IL-4)

Before transplantation;

1- Obtaining ABO blood group compliance

2- Investigation of HLA compatibility between recipient and donor

3. Investigating whether the receptor is sensitive to its donor antigens (Cross-match test)

PREVINTION OF REJECTION

- Non specific immunosupression can reduce rejection reaction;
    - Steroid : have anti-inflammatory activity and suppress macrophages
    - Cyclosporin: suppress lymphokines production
    - Azatioprine :blocks Tc proliferation

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