Autoimmune diseases

Autoimmunity: *an inappropriate response of the immune system against self-components.* They are a heterogenous group of diseases, characterized by tissue damage or disturbed physiological function due to humoral or cell-mediated immune response against one or more of the self-Ag.

It was believed that all self-reactive lymphocytes were eliminated during their development in the bone marrow and thymus and that a failure to eliminate these lymphocytes led to autoimmune consequences.

These reactions can cause serious damage to cells and organs, sometimes with fatal consequences.

AID are characterized by:

1-Frequent in those **with advancing age**, where there is a decline in the number of regulatory T-cells, which allows any survived auto-reactive cells to proliferate, one major exception being the childhood onset form of IDDM.

2-Almost all autoimmune disease **are more common in women**, there are however, notable exceptions such as ankylosing spondylitis.

3-Autoimmune disease show evidence of **clustering within families** with genetic predisposition that is determine by their MHC-genes.

4- Frequent in those who **exposed to an environmental agents that triggers immune response** against self-Ags. these agents are (infections, drugs, hormones, physical agents, psychological stress and dietary factors).

- -The bias towards Th-1 response and the general tendency of the female to mount a vigorous immune response is due to, **Sex hormones**, some of the female sex hormones have ability to stimulate the autoimmune disorders eg. **Estrogen and the Prolactine** have a profound influence on immune system and the presence of hormone receptor on B- and T-cells is further evidence that this hormone play a role in the regulation of the immune system and it may turn cells towards Th-1 dominant immune response.
- Pregnancy and repeated exposure to fetal Ags, presence of fetal cells in maternal circulation could play a role in such diseases.

What is the role of MHC in developing of autoimmune diseases?

MHC play a central role in the development of both humoral and cell-mediated immune response, for this reason, the MHC play important role in determines the type and the potency of immune response of an individual to Ag of infectious agent

therefore, MHC has been implicated in the susceptibility to autoimmune diseases. So individual with certain HLA-allele have a greater chance in acquiring autoimmune diseases than those in the same population who lack that allele.eg. 90% of those with ankylosing spondylitis express the HLA-B27, Psoriasis associate with Cw6, myasthenia graves associated with B8, multiple sclerosis associated with DR2, Hashimoto's thyroditis associate with DR5, SLE associated with DR3 and the rheumatoid arthritis associated with DR4.

Etiology of autoimmune diseases:

- ***idiopathic:*** often develop in subjects with certain genetic propensity, most often linked or associated with HLA on chromosome 6 .
- ***secondary to:***

a-cancer (neo-Ag viewed as foreign Ag).

b- drug induce.

c-Interplay between environmental (glutens in wheat) and genetic factors eg. Celiac disease.

d-Infections, different mechanism for activation of autoreactive cells by infectious agents eg.-molecular mimicry, super-Ags, polyclonal activation, and the induction of inflammation-.

Understanding of the relationship between different etiological factor and autoimmunity may allow the prevention of autoimmune squeale in some of these diseases.

Proposed Mechanisms for Induction of Autoimmunity

A variety of mechanisms have been proposed to account for the T-cell–mediated generation of autoimmune diseases

1-Release of Sequestered Antigens Can Induce Autoimmune Disease: For example, sperm arise late in development and are sequestered from the circulation. However, after a vasectomy, some sperm antigens are released into the circulation and can induce auto-antibody formation in some men. Similarly, the release of lens protein after eye damage or of heart-muscle antigens after myocardial infarction has been shown to lead on occasion to the formation of auto-antibodies.

2-Molecular Mimicry May Contribute to Autoimmune Disease

This, coupled with the fact that a number of viruses and bacteria have been shown to possess antigenic determinants that are identical or similar to

normal host-cell components. Cross-reacting antibodies are also thought to be the cause of heart damage in rheumatic fever, which can sometimes develop after a *Streptococcus* infection. In this case, the antibodies are to streptococcal antigens, but they cross-react with the heart muscle.

3-Inappropriate Expression of Class II MHC

Molecules Can Sensitize Auto-reactive T Cells. The pancreatic beta cells of individuals with insulin-dependent diabetes mellitus (IDDM) express high levels of both class I and class II MHC molecules, whereas healthy beta cells express lower levels of class I and do not express class II at all

4-Polyclonal B-Cell Activation Can Lead to Autoimmune Disease

A number of viruses and bacteria can induce nonspecific polyclonal B-cell activation. Gram-negative bacteria, cytomegalovirus, and Epstein-Barr virus (EBV) are all known to be such polyclonal activators, inducing the proliferation of numerous clones of B cells that express IgM in the absence of TH cells. If B cells reactive to self-antigens are activated by this mechanism, auto-antibodies can appear.

5-Alteration of normal proteins. Drugs can bind to normal proteins and make them immunogenic eg. In procainamide induce SLE.

6-**Inappropriate access of self-Ags to APCs and Inappropriate local expression of costimulatory molecules**. Local inflammation (virus infection, free radicals, or ionizing radiation) can increase traffic of self-Ag to regional lymph node (APC), induce expression of MHC-II molecules and costimulatory molecules, increase proteolytic enzyme activity cause both intracellular and extracellular breakdown of protein.

Autoimmune diseases can be divided into two broad categories:

1-Organ-Specific Autoimmune Diseases

In an organ-specific autoimmune disease, the immune response is directed **to a target antigen unique to a single organ or gland,** so that the manifestations are largely limited to that organ. The cells of the target organs may be damaged directly by humoral or cell-mediated effector mechanisms.

Alternatively, the antibodies may over-stimulate or block the normal function of the target organ.

HASHIMOTO'S THYROIDITIS

In Hashimoto's thyroiditis, which is most frequently seen in middle-aged women, an individual produces auto-antibodies and sensitized TH1 cells

specific for thyroid antigens.. Antibodies are formed to a number of thyroid proteins, including thyroglobulin and thyroid peroxidase, both of which are involved in the uptake of iodine. Binding of the auto-antibodies to these proteins interferes with iodine uptake and leads to decreased production of thyroid hormones (hypothyroidism).

INSULIN-DEPENDENT DIABETES MELLITUS

A disease afflicting 0.2% of the population, **insulin-dependent diabetes mellitus (IDDM)** is caused by an autoimmune attack on the pancreas. The attack is directed against specialized insulin-producing cells (beta cells) that are located in spherical clusters, called the islets of Langerhans, scattered throughout the pancreas. resulting in decreased production of insulin and consequently increased levels of blood glucose. Several factors are important in the destruction of beta cells.

1-First, activated CTLs migrate into an islet and begin to attack the insulin producing cells. Local cytokine production during this response includes IFN-_, TNF-_, and IL-1.

2-Auto-antibody production can also be a contributing factor in IDDM. Auto-antibodies to beta cells may contribute to cell destruction .

AUTOIMMUNE ANEMIAS

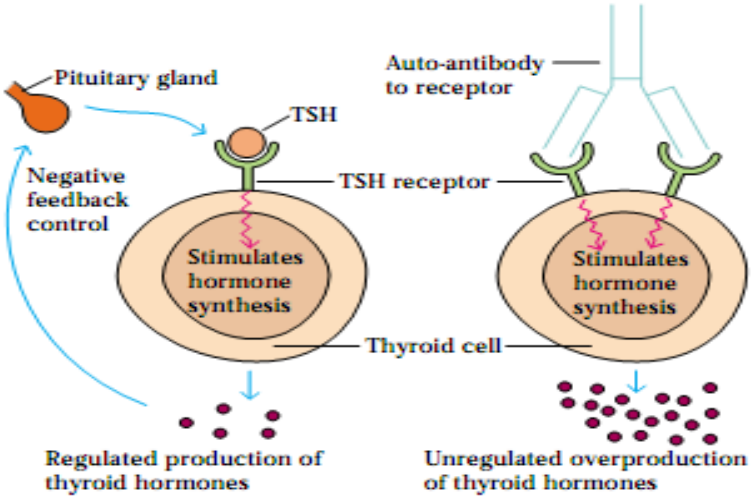
Autoimmune anemias include **pernicious anemia, autoimmune hemolytic anemia, and drug-induced hemolytic anemia.**

Pernicious anemia is caused by auto-antibodies to intrinsic factor, a membrane-bound intestinal protein on gastric parietal cells. Intrinsic factor facilitates uptake of vitamin B1from the small intestine. Binding of the auto-antibody to intrinsic factor blocks the intrinsic factor–mediated absorption of vitamin B12. In the absence of sufficient vitamin B12, which is necessary for proper hematopoiesis, the number of functional mature red blood cells decreases below normal. Pernicious anemia is treated with injections of vitamin B12,

GRAVES' DISEASE

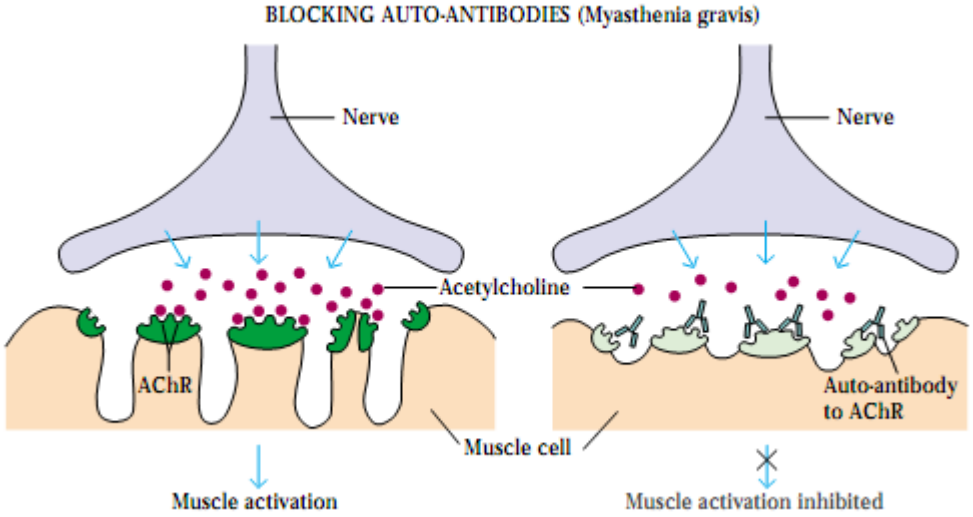
The production of thyroid hormones is carefully regulated by thyroid-stimulating hormone (TSH), which is produced by the pituitary gland. Binding of TSH to a receptor on thyroid cells activates adenylate cyclase and stimulates the synthesis of two thyroid hormones, thyroxine and triiodothyronine. A patient with **Graves' disease** produces auto-antibodies that bind the receptor for TSH and mimic the normal action of TSH,

activating adenylate cyclase and resulting in production of the thyroid hormones.



MYASTHENIA GRAVIS

Myasthenia gravis is the prototype autoimmune disease mediated by blocking antibodies. A patient with this disease produces auto-antibodies that bind the acetylcholine receptors on the motor end-plates of muscles, blocking the normal binding of acetylcholine and also inducing complement mediated lysis of the cells. The result is a progressive weakening of the skeletal muscles .Ultimately, the antibodies destroy the cells bearing the receptors. The early signs of this disease include drooping eyelids and inability to retract the corners of the mouth, which gives the appearance of snarling. Without treatment, progressive weakening of the Autoimmunity muscles can lead to severe impairment of eating as well as problems with movement.



Systemic Autoimmune Diseases

In systemic autoimmune diseases, the response is directed toward a broad range of target antigens and involves a number of organs and tissues. These diseases reflect a general defect in immune regulation that results in hyperactive T cells and B cells. Tissue damage is widespread, both from cell-mediated immune responses and from direct cellular damage caused by auto-antibodies or by accumulation of immune complexes.

Systemic Lupus Erythematosus Attacks

systemic lupus erythematosus (SLE), which typically appears in women between 20 and 40 years of age; the ratio of female to male patients is 10:1. SLE is characterized by fever, weakness, arthritis, skin rashes, pleurisy, and kidney dysfunction.

Affected individuals may produce autoantibodies to a vast array of tissue antigens, such as DNA, histones, RBCs, platelets, leukocytes, and clotting factors; interaction of these auto antibodies with their specific antigens produces various symptoms. Auto-antibody specific for RBCs and platelets, for example, can lead to complement-mediated lysis, resulting in hemolytic anemia and thrombocytopenia, respectively. When immune complexes of auto-antibodies with various nuclear antigens are deposited along the walls of small blood vessels, a type III hypersensitive reaction develops.

The complexes activate the complement system and generate membrane-attack complexes and complement split products that damage the wall of the blood vessel, resulting in vasculitis and glomerulonephritis. Excessive complement activation in patients with severe SLE produces elevated serum levels of the complement split products C3a and C5a, which may be three to four times higher than normal.

Rheumatoid arthritis: is a common autoimmune disorder, most often affecting women from 40 to 60 years old. The major symptom is chronic inflammation of the joints, although the hematologic, cardiovascular, and respiratory systems are also frequently affected. Many individuals with rheumatoid arthritis produce a group of auto-antibodies called **rheumatoid factors** that are reactive with determinants in the Fc region of IgG. The classic rheumatoid factor is an IgM antibody with that reactivity. Such auto-antibodies bind to normal circulating IgG, forming IgM-IgG complexes that are deposited in the joints. These immune complexes can activate the complement cascade, resulting in a type III hypersensitive reaction, which leads to chronic inflammation of the joints.

Transplantation

Transplantation: refers to the act of transferring cells, tissues, or organs from one site to another. The desire to accomplish transplants stems from the realization that many diseases can be cured by implantation of a healthy organ, tissue, or cells (a **graft)** from one individual (**the donor**) to another in need of the transplant (**the recipient or host**).

The immune system has evolved complex and effective mechanisms to protect the organism from attack by foreign agents, and these same mechanisms cause rejection of grafts from anyone who is not genetically identical to the recipient.

The first human kidney transplant, attempted in 1935 by a Russian surgeon, failed because there was a mismatch of blood types between donor and recipient. This incompatibility caused almost immediate rejection of the kidney, and the patient died without establishing renal function.

The rapid immune response experienced here, termed hyperacute rejection, is mediated by antibodies. The first successful human kidney transplant, which was between identical twins, was accomplished in Boston in 1954. Today, kidney, pancreas, heart, lung, liver, bone-marrow, and cornea transplantations are performed among non identical individuals with ever increasing frequency and success. A variety of immunosuppressive agents can aid in the survival of the transplants, including drugs and specific antibodies developed to diminish the immunologic attack on grafts, but the majority of these agents have an overall immunosuppressive effect, and their long-term use is toxic.

The following terms are used to indicate different types of transplants:

Autograft is self-tissue transferred from one body site to another in the same individual. Transferring healthy skin to a burned area in burn patients and use of healthy blood vessels to replace blocked coronary arteries are examples of frequently used **autografts.**

Isograft is tissue transferred between genetically identical individuals. In inbred strains of mice, an isograft can be performed from one mouse to another **syngeneic** mouse. In humans, an **isograft** can be performed between genetically identical (monozygotic) twins.

Allograft is tissue transferred between genetically different members of the same species. In mice, an allograft is performed by transferring tissue or an organ from one strain to another. In humans, organ grafts from one

individual to another are allografts unless the donor and recipient are identical twins.

Xenograft is tissue transferred between different species (e.g., the graft of a baboon heart into a human). Because of significant shortages in donated organs, raising animals for the specific purpose of serving as organ donors for humans is under serious consideration.

Autografts and isografts are usually accepted, owing to the genetic identity between graft and host .Because an allograft is genetically dissimilar to the host, it is often recognized as foreign by the immune system and is rejected. Obviously, xenografts exhibit the greatest genetic disparity and therefore engender a vigorous graft rejection.

Allograft Rejection Displays Specificity and Memory

the immune response culminating in graft rejection always displays the attributes of specificity and memory

T Cells Play a Key Role in Allograft Rejection

both CD4+ and CD8+ T-cells participated in rejection and that the collaboration of both subpopulations resulted in more pronounced graft rejection.

Similar Antigenic Profiles Foster Allograft Acceptance

Tissues that are antigenically similar are said to be **histocompatible;** such tissues do not induce an immunologic response that leads to tissue rejection. Tissues that display significant antigenic differences are *histoincompatible* and induce an immune response that leads to tissue rejection. The various antigens that determine histocompatibility are encoded by more than 40 different loci, but the loci responsible for the most vigorous allograft-rejection reactions are located within the **major histocompatibility complex (MHC).** Because the MHC loci are closely linked, they are usually inherited as a complete set, called a **haplotype,**from each parent.

Graft Donors and Recipients Are Typed for RBC and MHC Antigens

Since differences in blood group and major histocompatibility antigens are responsible for the most intense graft-rejection reactions, various tissue-typing procedures to identify these antigens have been developed to screen potential donor and recipient cells. Initially, donor and recipient are screened for

ABO blood-group compatibility. The blood-group antigens are expressed on RBCs, epithelial cells, and endothelial cells. Antibodies produced in the recipient to any of these antigens that are present on transplanted tissue will induce antibody mediated complement lysis of the incompatible donor cells.

HLA typing of potential donors and a recipient can be accomplished with a microcytotoxicity test. HLA typing based on antibody-mediated microcytotoxicity can indicate the presence or absence of various MHC alleles.

Clinical Manifestations of Graft Rejection

Graft-rejection reactions have various time courses depending upon the type of tissue or organ grafted and the immune response involved.

Hyper-acute Rejection

In rare instances, a transplant is rejected so quickly that the grafted tissue never becomes vascularized. These hyperacute reactions are caused by preexisting host serum antibodies specific for antigens of the graft. The antigen-antibody complexes that form activate the complement system, resulting in an intense infiltration of neutrophils into the grafted tissue.

The ensuing inflammatory reaction causes massive blood clots within the capillaries, preventing vascularization of the graft.

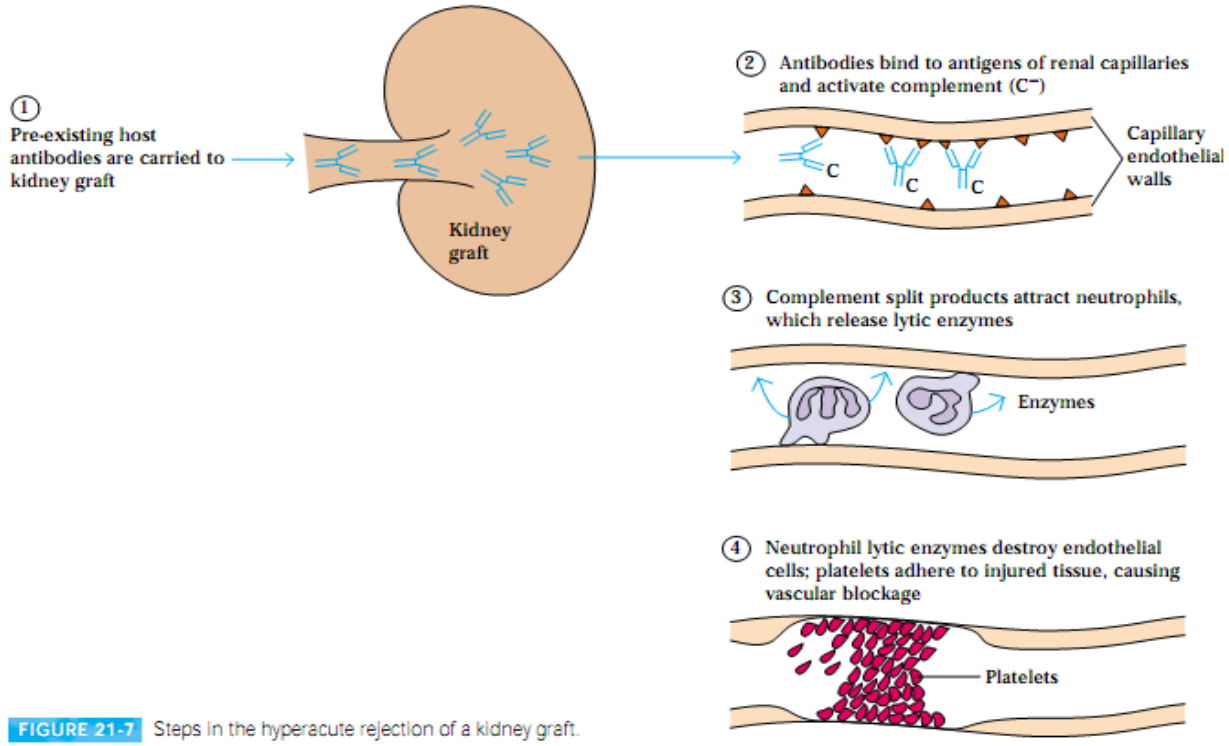


FIGURE 21-7 Steps in the hyperacute rejection of a kidney graft.

Acute Rejection Is Mediated by T-Cell Responses

Cell-mediated allograft rejection manifests as an acute rejection of the graft beginning about 10 days after transplantation. Histopathologic examination reveals a massive infiltration of macrophages and lymphocytes at the site of tissue destruction

The process of graft rejection can be divided into two stages: (1) a sensitization phase, in which antigen-reactive lymphocytes of the recipient proliferate in response to allo-antigens on the graft, and (2) an effector stage, in which immune destruction of the graft takes place.

Chronic Rejection

Chronic rejection reactions develop **months or years after acute rejection** reactions have subsided. The mechanisms of chronic rejection include **both humoral and cell-mediated responses by the recipient**. While the use of immunosuppressive drugs and the application of tissue-typing methods to obtain optimum match of donor and recipient have dramatically increased survival of allografts during the first years after engraftment, little progress has been made in long-term survival.

Chronic rejection reactions are difficult to manage with immunosuppressive drugs and may necessitate another transplantation.

General Immunosuppressive Therapy

Allogeneic transplantation requires some degree of immunosuppression. If the transplant is to survive. Most of the immunosuppressive treatments that have been developed have the disadvantage of being nonspecific; that is, they result in generalized immunosuppression of responses to all antigens, not just those of the allograft, which places the recipient at increased risk of infection.

1-Azathioprine (Imuran), a potent mitotic inhibitor, is often given just before and after transplantation to diminish T-cell proliferation in response to the alloantigens of the graft.Immune Tolerance to Allografts

2-corticosteroids, such as prednisone and dexamethasone, are potent anti-inflammatory agents that exert their effects at many levels of the immune response. These drugs are often given to transplant recipients together with a mitotic inhibitor to prevent acute episodes of graft rejection.

3-Cyclosporin A , (tacrolimus), are fungal metabolites with immunosuppressive properties.

4-x-ray radiation : Because lymphocytes are extremely sensitive to radiation, it can be used to eliminate them in the transplant recipient just before grafting.

- There are instances in which an allograft may be accepted without the use of immunosuppressive measures:
- **1-privileged site :**in the case of tissues that lack alloantigens, such as cartilage or heart valves, there is no immunologic barrier to transplantation. However, there are also instances in which the strong predicted response to an allograft does not occur.
- **2-Tolerance induction**: is when a state of tolerance has been induced biologically, usually by previous exposure to the antigens of the donor in a manner that causes immune tolerance rather than sensitization in the recipient.