Autoimmunity and autoimmune disease

Autoimmunity is an acquired immune reactivity to self and autoimmune antigens. Autoimmune diseases occur when autoimmune responses lead to tissue damage. Auto immune diseases may be organ-specific, for example autoimmune diabetes mellitus, where the pancreas is the target organ, conditions or systemic (non-organ-specific), for example systemic lupus erythematosus (SLE), where multiple organs may be involved. Pathogenesis associated with these diseases may be mediated primarily by antibody, by T cells, or a combination of both.

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 Many Tissues

One of the best examples of a systemic autoimmune disease is **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 (Figure 1).

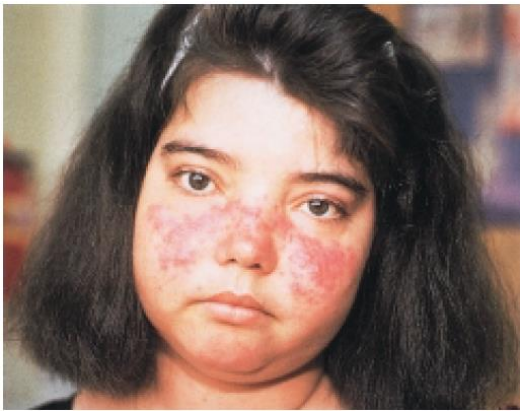

Figure 1: Characteristic “butterfly” rash over the cheeks of a young girl with systemic lupus erythematosus

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. C5a induces increased expression of the type 3 complement receptor (CR3) on neutrophils, facilitating neutrophil aggregation and attachment to the vascular endothelium. As neutrophils attach to small blood vessels, the number of circulating neutrophils declines (neutropenia) and various occlusions of the small blood vessels develop (vasculitis). These occlusions can lead to widespread tissue damage.

Multiple Sclerosis Attacks the Central Nervous System

Multiple sclerosis (MS) is the most common cause of neurologic disability associated with disease in Western countries. The symptoms may be mild, such as numbness in the limbs, or severe, such as paralysis or loss of vision. Most people with MS are diagnosed between the ages of 20 and 40. Individuals with this disease produce autoreactive T cells that participate in the formation of inflammatory lesions along the myelin sheath of nerve fibers. The cerebrospinal fluid of patients with active MS contains activated T lymphocytes, which infiltrate the brain tissue and cause characteristic inflammatory lesions, destroying the myelin. Since myelin functions to insulate the nerve fibers, a breakdown in the myelin sheath leads to numerous neurologic dysfunctions. Epidemiological studies indicate that MS is most common in the Northern hemisphere. There is an environmental component of the risk of contracting MS. This is not the entire story, however, since genetic influences also are important.While the average person in the United States has about one chance in 1000 of developing MS, close relatives of people with MS, such as children or siblings, have 1 chance in 50 to 100 of developing MS. The identical twin of a person with MS has a 1 in 3 chance of developing the disease. These data point strongly to the genetic component of the disease. And, as is described in the Clinical Focus of this chapter, MS affects women two to three times more frequently than men. The cause of

MS, like most autoimmune diseases, is not well understood. However, there are some suggestions that infection by certain viruses may predispose a person to MS. Certainly some viruses can cause demyelinating diseases, and it is tempting to speculate that virus infection plays a significant role in MS, but at present there is no definitive data implicating a particular virus.

Rheumatoid Arthritis Attacks Joints

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 an activate the complement cascade, resulting in a type III hypersensitive reaction, which leads to chronic inflammation of the joints.

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 overstimulate or block the normal function of the target organ.

Some Autoimmune Diseases Are Mediated by Direct Cellular Damage

Autoimmune diseases involving direct cellular damage occur when lymphocytes or antibodies bind to cell-membrane antigens, causing cellular lysis and/or an inflammatory response in the affected organ. Gradually, the damaged cellular structure is replaced by connective tissue (scar tissue), and the function of the organ declines. This section briefly describes a few examples of this type of autoimmune disease.

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. The DTH

response is characterized by an intense infiltration of the thyroid gland by lymphocytes, macrophages, and plasma cells, which form lymphocytic follicles and germinal centers. The ensuing inflammatory response causes a goiter, or visible enlargement of the thyroid gland, a physiological response to hypothyroidism. 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).

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 B12 from 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, thus circumventing the defect in its absorption.

An individual with autoimmune hemolytic anemia makes auto-antibody to RBC antigens, triggering complement mediated lysis or antibody-mediated opsonization and phagocytosis of the red blood cells.

One form of autoimmune anemia is drug-induced: when certain drugs such as penicillin or the anti-hypertensive agent methyldopa interact with red blood cells, the cells become antigenic.

GOODPASTURE'S SYNDROME

In **Goodpasture's syndrome,** auto-antibodies specific for certain basement-membrane antigens bind to the basement membranes of the kidney glomeruli and the alveoli of the lungs. Subsequent complement activation leads to direct cellular damage and an ensuing inflammatory response mediated by a buildup of complement split products. Damage to the glomerular and alveolar basement membranes leads to progressive kidney damage and pulmonary hemorrhage.

Death may ensue within several months of the onset of symptoms. Biopsies from patients with Goodpasture's syndrome stained with fluorescent-labeled anti-IgG and anti- C3b reveal linear deposits of IgG and C3b along the basement membranes.

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. The autoimmune attack destroys beta cells, resulting in decreased production of insulin and consequently increased levels of blood glucose. Several factors are important in the destruction of beta cells. First, activated CTLs migrate into an islet and begin to attack the insulin producing cells. Local cytokine production during this response includes IFN-γ, TNF-α, and IL-1. Auto-antibody production can also be a contributing factor in IDDM. The first CTL infiltration and activation of macrophages, frequently referred to as insulitis, is followed by cytokine release and the presence of auto-antibodies, which leads to a cell-mediated DTH response. The subsequent beta-cell destruction is thought to be mediated by cytokines released during the DTH response and by lytic enzymes released from the activated macrophages. Auto-antibodies to beta cells may contribute to cell destruction by facilitating either antibody-plus-complement lysis or antibody-dependent cell-mediated cytotoxicity (ADCC).

The abnormalities in glucose metabolism that are caused by the destruction of islet beta cells result in serious metabolic problems that include ketoacidosis and increased urine production. The late stages of the disease are often characterized by atherosclerotic vascular lesions—which in turn cause gangrene of the extremities due to impeded vascular flow— renal failure, and blindness. If untreated, death can result. The most common therapy for diabetes is daily administration of insulin.

Some Autoimmune Diseases Are Mediated by Stimulating or Blocking Auto-Antibodies

In some autoimmune diseases, antibodies act as agonists, binding to hormone receptors in lieu of the normal ligand and stimulating inappropriate activity. This usually leads to an overproduction of mediators or an increase in cell growth. Conversely, auto-antibodies may act as antagonists, binding hormone receptors but blocking receptor function. This generally causes impaired secretion of mediators and gradual atrophy of the affected organ.

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.Unlike TSH, however, the autoantibodies are not regulated, and consequently they overstimulate the thyroid. For this reason these auto-antibodies are called long-acting thyroid-stimulating (LATS) antibodies.

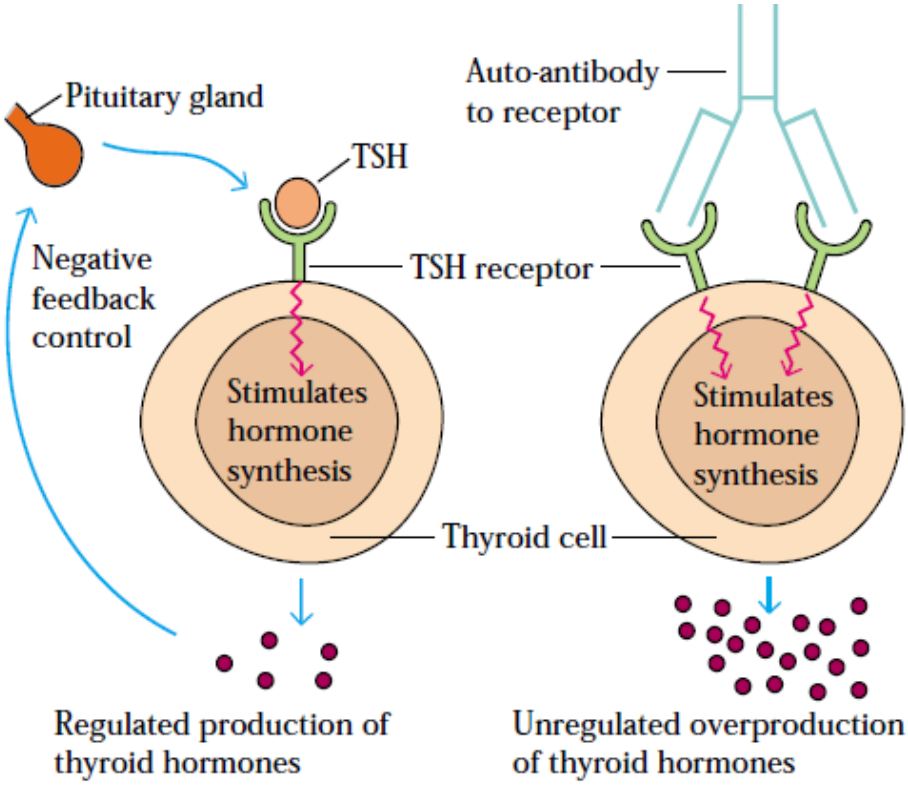

Figure2: In Graves' disease, binding of auto-antibodies to the receptor for thyroid-stimulating hormone (TSH) induces unregulated activation of the thyroid, leading to overproduction of the thyroid hormones (purple dots).

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 (Figure 3).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 muscles can lead to severe impairment of eating as well as problems with movement. However, with appropriate treatment, this disease can be managed quite well and afflicted individuals can lead a normal life

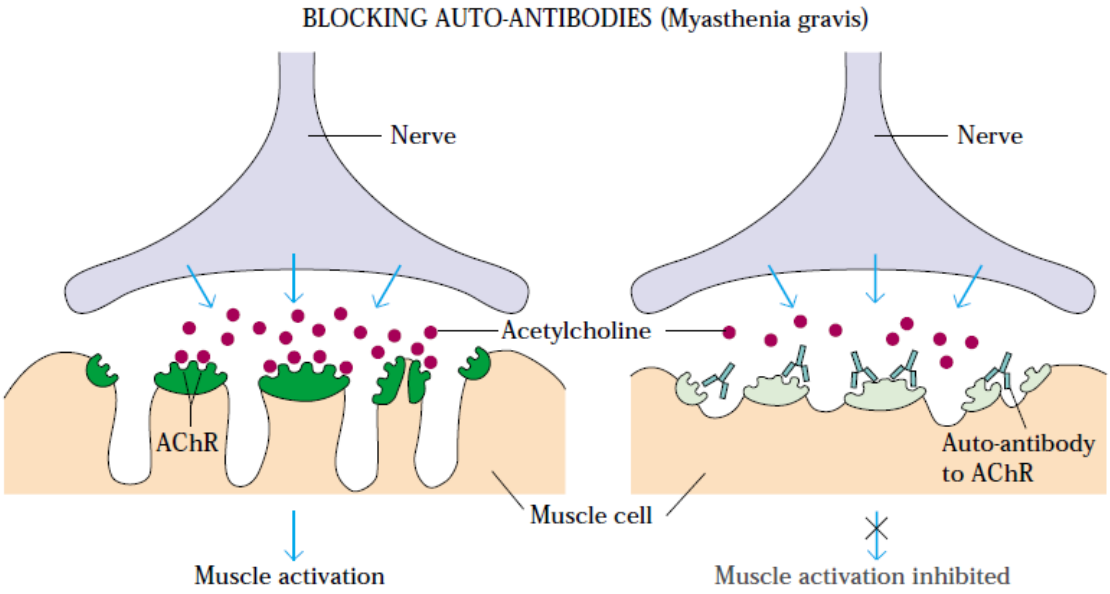

Figure3. In myasthenia gravis, binding of auto-antibodies to the acetylcholine receptor (*right*) blocks the normal binding of acetylcholine (burgandy dots) and subsequent muscle activation (*left*). In addition, the anti-AChR auto-antibody activates complement, which damages the muscle end-plate; the number of acetylcholine receptors declines as the disease progresses. AChR acetylcholine receptor.