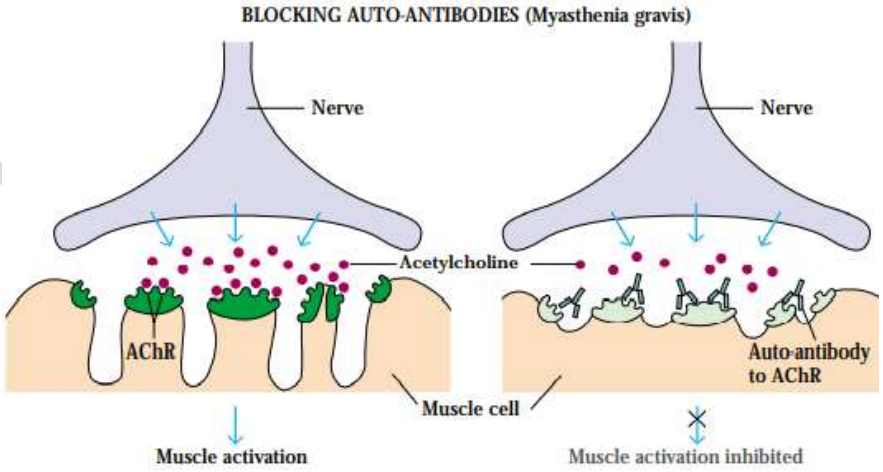
Autoimmunity

- All self-reactive lymphocytes are not deleted during T-cell and B-cell maturation.
- Their activity must be regulated in normal individuals through clonal anergy or clonal suppression.
- A breakdown in this regulation can lead to activation of self-reactive clones of T or B cells, generating organ-specific or systemic autoimmune disease.

Organ-Specific Autoimmune Diseases

- Immune response is directed to a target antigen unique to a single organ or gland.
- Some autoimmune diseases are mediated by direct cellular damage.
- In Hashimoto's thyroiditis, mostly seen in middle-aged women, an individual produces auto-antibodies and sensitized T_H1 cells specific for thyroid antigens. The response includes an intense infiltration of the thyroid gland by lymphocytes, macrophages, and plasma cells, and development of goiter, or visible enlargement of the thyroid gland, reduced uptake of iodine, decreased production of thyroid hormones (hypothyroidism).
- Autoimmune anemias include pernicious anemia (auto-antibodies to a proteinaceous intrinsic factor on gastric cells, facilitating uptake of vitamin B_{12}, necessary for proper hematopoiesis), autoimmune hemolytic anemia (auto-antibody to RBC antigens, triggering complementmediated lysis or antibody-mediated opsonization and phagocytosis), and drug-induced hemolytic anemia (drugs such as penicillin or the anti-hypertensive agent methyldopa interact with red blood cells, the cells become antigenic).
- 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, hence progressive kidney damage and pulmonary hemorrhage.

- Insulin-dependent diabetes mellitus (IDDM) is caused by an autoimmune attack on the insulin-producing cells (beta cells) in the islets of Langerhans, scattered throughout the pancreas. Activated CTLs migration, activation of macrophage, cytokine release and the presence of auto-antibodies lead to a cell-mediated DTH response and destruction of beta cells, decreased production of insulin and consequently increased levels of blood glucose.
- Some autoimmune diseases are mediated by stimulating or blocking auto-antibodies.
- 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 (hormones, thyroxine and triiodothyronine). Unlike TSH, the autoantibodies are not regulated, and consequently overstimulate the thyroid, hence called long-acting thyroid-stimulating (LATS) antibodies.
- Myasthenia gravis is the prototype autoimmune disease mediated by blocking 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, destruction of the cells bearing the receptors, severe impairment of eating as well as problems with movement.



Systemic Autoimmune Diseases

- The response is directed toward a broad range of target antigens and involves a number of organs and tissues.
- Systemic lupus erythematosus (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.
- 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, resulting in vasculitis and glomerulonephritis.
- Excessive complement activation produces elevated serum levels of the complement split products C3a and C5a. C5a induces increased expression of the complement receptor (CR3) on neutrophils, facilitating neutrophil aggregation and attachment to the vascular endothelium. Thus, the number of circulating neutrophils declines (neutropenia) and various occlusions of the small blood vessels develop (vasculitis), which can lead to widespread tissue damage.

- Multiple sclerosis (MS) is the most common cause of neurologic disability associated with disease in Western countries (diagnosed between the ages of 20 and 40; affects women two to three times more frequently than men). The symptoms range from numbness in the limbs to paralysis or loss of vision.
- Autoreactive T lymphocytes in the cerebrospinal fluid infiltrate the brain tissue and cause characteristic inflammatory lesions, destroying the myelin, which insulate the nerve fibers.
- Epidemiological studies indicate that MS is most common in the Northern hemisphere indicating influence of environmental component and genetic factors.
- Certainly some viruses can cause demyelinating diseases, and it is tempting to speculate that virus infection plays a significant role in MS.
- 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.
- Group of auto-antibodies called rheumatoid factors 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.

Treatment options of Autoimmune Diseases

- Palliatives, aimed at reducing symptoms to provide the patient with an acceptable quality of life.
- Nonspecific suppression of the immune system, no distinction between a pathologic autoimmune response and a protective immune response. Immunosuppressive drugs (e.g., corticosteroids, azathioprine, and cyclophosphamide) often puts the patient at greater risk for infection or the development of cancer.
- A somewhat more selective approach employs cyclosporin A or FK506, which block signal transduction mediated by the T-cell receptor.
- Plasmapheresis has been beneficial to patients with autoimmune diseases involving antigen-antibody complexes, which are removed with the plasma.
- Low doses of autoimmune T-cell clones, which apparently elicit regulatory T cells specific for TCR variable-region determinants of the autoimmune clones, as a vaccine showed promising result in animal model.
- Monoclonal antibodies (e.g. anti-CD4, anti-IL-2Rα subunit) have been used successfully to treat autoimmune disease in several animal models.
- Increased or inappropriate MHC expression in some autoimmune disease, offers the possibility that monoclonal antibodies against MHC molecules might retard development of autoimmunity.

Reference and further readings

- Kuby Immunology. W.H. Freeman.
- Roitt's EssentialImmunology. John Wiley and Sons, Ltd
- Basic Immunology by Abbas & Lichtman. Elsevier Inc.