**Autoimmunity**

Simply stated, autoimmune disease is caused by failure of the tolerance processes to protect the host from the action of self-reactive lymphocytes. These diseases result from the destruction of self proteins, cells, and organs by auto-antibodies or self-reactive T cells.

**Definition:**

Autoimmunity can be defined as breakdown of mechanisms responsible for self-tolerance and induction of an immune response against components of the self. Such an immune response may not always be harmful (e.g., anti-idiotype antibodies or recognition of self-MHC molecules). However, in numerous (autoimmune) diseases it is well recognized that products of the immune system cause severe damage to the self.

The factors that contribute to the development of autoimmunity are genetic susceptibility and environmental triggers, such as infections and local tissue injury.

**Immunologic Abnormalities Leading to Autoimmunity**

Autoimmunity results from some combination of three main immunologic aberrations.

1. **Defective tolerance or regulation**. Failure of the mechanisms of self-tolerance in T or B cells, leading to an imbalance between lymphocyte activation and control, is the underlying cause of all autoimmune diseases. The potential for autoimmunity exists in all individuals because some of the randomly generated specificities of clones of developing lymphocytes may be for self antigens, and many self antigens are readily accessible to lymphocytes. Loss of self-tolerance may result if self-reactive lymphocytes are not deleted or inactivated during or after their maturation and if APCs are activated so that self antigens are presented to the immune system in an immunogenic manner. Experimental models and limited studies in humans have shown that any of the following mechanisms may contribute to the failure of self-tolerance:

* Defects in deletion (negative selection) of T or B cells or receptor editing in B cells during the maturation of these cells in the generative lymphoid organs
* Defective numbers and functions of regulatory T lymphocytes
* Defective apoptosis of mature self-reactive lymphocytes
* Inadequate function of inhibitory receptors

1. **Abnormal display of self antigens**. Abnormalities may include increased expression and persistence of self antigens that are normally cleared, or structural changes in these antigens resulting from enzymatic modifications or from cellular stress or injury. If these changes lead to the display of antigenic epitopes that are not present normally, the immune system may not be tolerant to these epitopes, thus allowing anti-self responses to develop.
2. **Inflammation or an initial innate immune response**. The innate immune response is a strong stimulus for the subsequent activation of lymphocytes and the generation of adaptive immune responses. Infections or cell injury may elicit local innate immune reactions with inflammation. These may contribute to the development of autoimmune disease, perhaps by activating APCs, which overcomes regulatory mechanisms and results in excessive T cell activation. Much recent attention has focused on the role of T cells in autoimmunity for two main reasons. **First**, helper T cells are the key regulators of all immune responses to proteins, and most self antigens implicated in autoimmune diseases are proteins. **Second,** several autoimmune diseases are genetically linked to the MHC (the HLA complex in humans), and the function of MHC molecules is to present peptide antigens to T cells. Failure of self- tolerance in T lymphocytes may result in autoimmune diseases in which tissue damage is caused by cell mediated immune reactions. Helper T cell abnormalities may also lead to autoantibody production because helper T cells are necessary for the production of high-affinity antibodies against protein antigens.

**Both Intrinsic and Extrinsic Factors Can Favor Susceptibility to Autoimmune Disease**

what tips the balance toward a break in tolerance and the development of autoimmunity?

1. Experiments with germ-free mouse models,
2. discordance data in identical twins,
3. and epidemiologic studies of geographic associations all suggest roles for both the{ environment and genes} in susceptibility to the development of autoimmunity.

**Environmental Factors Favoring the Development of Autoimmune Disease**

lifestyle factors, such as diet, suggest a link in the development of autoimmune disease. For instance, we now know that cross-talk between gut **microflora** and the systemic immune system may help regulate peripheral tolerance, which could impact the development of autoimmune disease.

**Infections** may also influence the induction of autoimmunity. The molecular structures of certain microbes may share chemical features with self components, resulting in the activation of immune cells with cross-reactive potential.

**The Role of Genes in Susceptibility to Autoimmunity:**

**Most autoimmune diseases are complex polygenic traits in which affected individuals inherit multiple genetic polymorphisms that contribute to disease susceptibility, and these genes act with environmental factors to cause the diseases**.

* Certain alleles within the MHC have been linked to several different autoimmune disorders. The strongest association between an HLA allele and autoimmunity is seen in **ankylosing spondylitis**, an inflammatory disease of vertebral joints. Individuals who express HLA-B27 are 90 times more likely to develop ankylosing spondylitis than individuals with a different HLA allele at this locus.
* Some non-MHC inherited genetic mutations can have causative effects on the development of autoimmunity. mutations in immune-related gene, FoxP3, result in forms of autoimmunity that impact peripheral tolerance, respectively . The product of this gene is required for the formation of many, but not all, regulatory T cells, suggesting that disease is caused by an inability to generate the TREG cells needed to maintain peripheral tolerance.
* Genes for cytokines and their receptors, antigen processing and presentation, signaling pathways, adhesion molecules, and costimulatory or inhibitory receptors have all been linked to specific autoimmune diseases

**The Role of Certain T Helper Cell Types in Autoimmunity**

In both organ-specific and systemic autoimmunity, CD4+ rather than CD8+T cells have been linked to disease pathogenesis. However, the T helper (TH) cell type or set of cytokines most closely associated with autoimmunity depends somewhat on the model system or human disease in question.

**Several Possible Mechanisms Have Been Proposed for the Induction of Autoimmunity**

In addition to genetic and environmental predisposing factors, autoimmunity likely develops from a number of different events. Disease may be induced by:

1. certain genetic mutations,
2. the release of sequestered antigens,
3. over stimulation of antigen-specific receptors,
4. In most cases, a combination of these is the cause.
5. Another issue is the sex difference in autoimmune susceptibility, with diseases such as Hashimoto’s thyroiditis, SLE, MS, and RA preferentially affecting women. Factors that may account for this, such as:

* hormonal differences between the sexes and
* the potential effects of fetal cells in the maternal circulation following pregnancy,

1. As a result over half of all antigen-specific receptors recognize self proteins. Not all of these are deleted during negative selection. Potentially self-reactive T and B cells found in the periphery are normally held in check by: 1) anergic or 2) regulatory mechanisms, such as TREG cells.
2. However, *exposure to carcinogens or infectious agents that favor DNA damage can potentially interfere with this regulation and/or lead to the expansion and survival of rare T- or B-cell clones with autoimmune potential*.
3. Gram-negative bacteria, cytomegalovirus, and EBV are all known polyclonal activators, inducing the proliferation of numerous clones of B cells that express IgM in the absence of T-cell help. If B cells reactive to self antigens are activated by this mechanism what will happen ??, **autoantibodies can appear.**
4. A role for particular microbial agents in autoimmunity is that a number of viruses and bacteria possess antigenic determinants that are similar or even identical to normal host-cell components, led to a hypothesis known as **molecular mimicry**. This proposes that some pathogens express protein epitopes resembling self components. **example**, rheumatic fever, a disease caused by autoimmune destruction of heart muscle cells, can develop after a Group A Streptococcus infection. In this case, antibodies to streptococcal antigens have been shown to cross-react with the heart muscle proteins, resulting in immune complex deposition and complement activation, a type II hypersensitivity reaction.

**Some Autoimmune Diseases Target Specific Organs**

Autoimmune diseases are caused by immune stimulatory lymphocytes or antibodies that recognize self-components, resulting in [ cellular lysis and/or an inflammatory response in the affected organ]. Gradually, the damaged cellular structure is replaced by connective tissue (fibrosis), and the function of the organ declines.

**In an organ-specific autoimmune disease,** the immune response is usually 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, anti-self antibodies may over stimulate or block the normal function of the target organ.

**Hashimoto’s Thyroiditis**

* In Hashimoto’s thyroiditis, an individual produces autoantibodies and sensitized TH1 cells specific for thyroid antigens. This disease is much more common in women, often striking in middle-age.
* 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, leading to decreased thyroid function and hypothyroidism (decreased production of thyroid hormones).
* The resulting delayed-type hypersensitivity (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.

**Type 1 Diabetes Mellitus**

* Type 1 diabetes mellitus (T1DM) or insulin-dependent diabetes seen mostly in youth under the age of 14 and is less common than Type 2, or non-insulin dependent diabetes mellitus.
* T1DM is caused by an autoimmune attack against insulin-producing cells (beta cells) scattered throughout the pancreas, which results in decreased production of insulin and consequently increased levels of blood glucose.
* The attack begins with cytotoxic T lymphocyte (CTL) infiltration and activation of macrophages, frequently referred to as insulitis ,
* followed by cytokine release and the production of autoantibodies, 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.
* Autoantibodies specific for beta cells may contribute to cell destruction by facilitating either antibody-mediated complement lysis or antibody-dependent cell-mediated cytotoxicity (ADCC). This disorder also involves lymphocytic infiltration of the pancreas and destruction of beta cells, and carries a strong association with certain MHC alleles.
* In genome-wide scans, over 20 insulin-dependent diabetes (Idd) loci associated with disease susceptibility have been identified, including at least one member of the TNF receptor family.

**Myasthenia Gravis**

* Myasthenia gravis is the classic example of an autoimmune disease mediated **by blocking antibodies**.
* A patient with this disease produces auto-antibodies that bind the acetylcholine receptors (AchRs) on the motor end plates of muscles, blocking the normal binding of acetylcholine and inducing complement-mediated lysis of the cells.
* The result is a progressive weakening of the skeletal muscles.
* Ultimately, the antibodies cause the destruction of the cells bearing the receptors.
* **The early signs** of this disease include drooping eyelids and inability to retract the corners of the mouth. Without treatment, progressive weakening of the muscles can lead to severe impairment of eating as well as problems with movement.
* **Treatments** are aimed at increasing acetylcholine levels, decreasing antibody production (using corticosteroids or other immunosuppressants), and/or removing antibodies (using plasmapheresis).

**Some Autoimmune Diseases Are Systemic**

In systemic autoimmune diseases, the immune 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/or B cells.

Tissue damage is typically widespread, both from (1) cell-mediated immune responses and from direct cellular damage caused by auto-antibodies **or** by (2) accumulation of immune complexes.

**Systemic Lupus Erythematosus**

* One of the best examples of a systemic autoimmune disease is **systemic lupus erythematosus (SLE)**.
* Like several of the other autoimmune syndromes, this disease is more common in women.
* In identical twins where one suffers from SLE, the other has up to a 60% chance of developing SLE, suggesting a genetic component.
* Affected individuals may produce auto-antibodies to a vast array of tissue antigens, such as DNA, histones, RBCs, platelets, leukocytes, and clotting factors.
* **Signs and symptoms** include fever, weakness, arthritis, skin rashes , and kidney dysfunction.
* Auto-antibodies specific for RBCs and platelets 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 hypersensitivity reaction develops**. The complexes activate the complement system and generate membrane-attack complexes and complement fragments (C3a and C5a) that damage the wall of the blood vessel, resulting in vasculitis and glomerulonephritis. In severe cases, excessive complement activation produces elevated serum levels of certain complement fragments, leading to neutrophil aggregation and attachment to the vascular endothelium. Over time, the number of circulating neutrophils declines (neutropenia) and occlusions of various small blood vessels develop (vasculitis), which can lead to widespread tissue damage.
* **Laboratory diagnosis** of SLE involves detection of antinuclear antibodies directed against double-stranded or singlestranded DNA, nucleoprotein, histones, and nucleolar RNA HOW ?? 1)Indirect immunofluorescent staining with serum from SLE patients produces characteristic nuclear-staining patterns.

**Multiple Sclerosis**

* Multiple sclerosis (MS) is the most common cause of neurologic disability associated with disease in Western countries. MS occurs in women two to three times more frequently than men and, like SLE, frequently develops during childbearing years (approximately 20–40 years of age).
* Individuals with this disease produce autoreactive T cells that participate in the formation of inflammatory lesions along the myelin sheath of nerve fibers in the brain and spinal cord. Since myelin functions to insulate the nerve fibers, a breakdown in the myelin sheath leads to numerous neurologic dysfunctions, **ranging from** numbness in the limbs to paralysis or loss of vision.
* The cause of MS is not well understood. Infection by certain viruses, such as Epstein-Barr virus (EBV), may predispose a person to MS. Some viruses can cause demyelinating diseases, but the data linking viruses to MS are not definitive.

**Rheumatoid Arthritis**

* Rheumatoid arthritis (RA) is a fairly common autoimmune disorder, most often diagnosed between the ages of 40 to 60 and more frequently seen in women.
* The major symptom is chronic inflammation of the joints, although the hematologic, cardiovascular, and respiratory systems are also frequently affected.
* Many individuals with RA produce a group of auto-antibodies called rheumatoid factors that are reactive with determinants in the Fc region of IgG—in other words, antibodies specific for antibodies! The classic rheumatoid factor is an IgM antibody that binds 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 hypersensitivity reaction, which leads to chronic inflammation of the joints.
* Treatments for RA include nonspecific drugs aimed at reducing inflammation, such as non steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids.

**Autoimmune Diseases Can Be Treated by General or Pathway-Specific Immunosuppression**

Ideally, treatment for autoimmune diseases should reduce only the autoimmune response, leaving the rest of the immune system intact. However this strategy has proven difficult. The current therapies to treat autoimmune disease fall into two categories: **broad spectrum immunosuppressive treatments** and more recent mechanism- or **cell-type-specific strategies.** For example, a monoclonal antibody against the B-cell-specific antigen CD20 depletes a subset of B cells and provides short-term benefit for RA. However, most cell-type specific agents used to treat autoimmune disorders target T cells or their products because these cells are either directly pathogenic or provide help to autoreactive B cells.as well as **Therapies That Block Steps in the Inflammatory Process and Strategies That Interfere with Costimulation because w**ithout costimulation, T cells undergo apoptosis, become anergic, or are induced as immune inhibitors. Therefore, one way to control T-cell activation would be to regulate costimulation.