

Principles of autoimmunity: Part II - Modes of autoimmune damage

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This is Part II of the article *Principles of autoimmunity*. Part I (pp. 22-25) and Part II are treated as a single CME/CPD article. Readers who study it, answer the questions related to it on page 29, and send a copy of the Answer Sheet (page 54) to the CME Center of KIMS become eligible for 1 CME/CPD credit in Category 1 in the MPC Program of KIMS. To claim credit, the reader has to be registered in the MPC Program, the answer sheet should be received by the CME Center before 31st May 2007, and all questions should have been attempted. Readers would then receive a certificate from the CME Center indicating the credit data.

Part I of this article discussed mechanisms that maintain immunological tolerance by controlling potentially self-reactive lymphocytes and events that lead to the loss of one or more of these preventive mechanisms which finally results in autoimmunity. In this Part II, we discuss mechanisms of autoimmune damage and basic principles of immunologic treatment of autoimmune diseases.

As discussed in Part I of this article, the bypass of tolerance mechanisms or a breakdown in immunoregulation can result in the activation of self-reactive B and T cells which can then lead to humoral or cell-mediated responses against self antigens. These autoimmune reactions can cause damage to cells, tissues and organs, sometimes with serious consequences. We shall first discuss how immunological damage is mediated in autoimmune disease.

Tissue injury in some autoimmune diseases is caused by autoantibodies, in others by autoreactive T cells, and in yet other diseases by both antibodies and T cells (Fig. 1). Antibodies can bring about tissue damage either directly by binding to cell surface autoantigens or by forming antibody-antigen complexes that get deposited in tissues. For example, autoantibodies to red blood cell antigens destroy these cells and bring about a form of

anemia called autoimmune hemolytic anemia. Similarly, autoantibodies to thyroid antigens mediate substantial thyroid tissue destruction in Hashimoto's thyroiditis. On the other hand, the culprits in autoimmune diseases such as insulin-dependent diabetes mellitus and multiple sclerosis are autoreactive T cells. Armed effector T cells can cause local inflammation by activating macrophages via cytokines or can damage tissue cells directly. Interestingly, rheumatoid arthritis results from tissue destruction brought about by both T cells and by antibody-antigen complexes that induce inflammatory reactions.

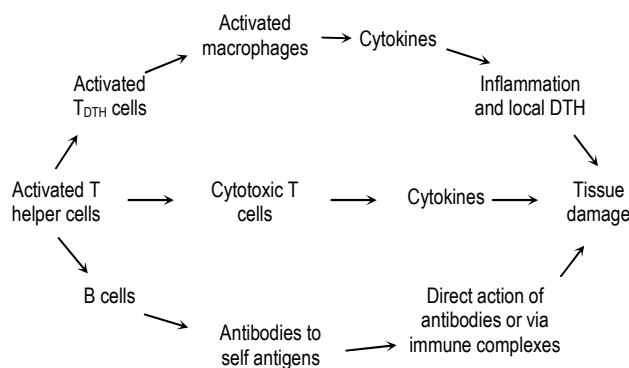


Figure 1. Tissue injury in some autoimmune diseases

Autoimmune diseases can be categorized into organ-specific and non-organ-specific (or systemic) autoimmune diseases. Organ-specific autoimmune diseases are those in which autoimmune reactivity is directed at antigens that are unique to a particular organ; thus manifestations are generally limited to that organ (Fig. 2). Tissue damage in these diseases

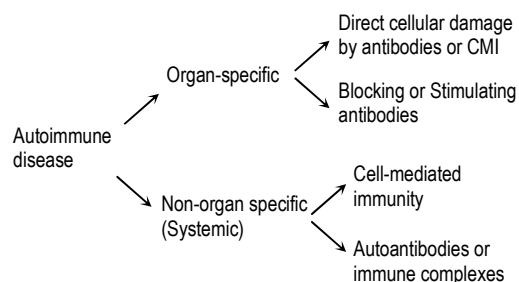


Figure 2. Categorization of autoimmune diseases

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can be mediated by autoantibodies or T cells that attack that organ. Non-organ-specific or systemic autoimmune diseases result from autoimmune responses directed at a wide range of antigens that involve several organs or tissues. Tissue destruction in these diseases is due to autoantibodies or antibody-antigen complexes or by cell-mediated immunity.

Organ-specific Autoimmune Diseases

Cells of target organs or glands may be damaged (1) directly by antibodies or cell-mediated immunity, or (2) by antibodies that may either block normal functioning of the organ or may overstimulate the organ or gland.

DISEASES MEDIATED BY DIRECT CELLULAR DAMAGE

Autoantibodies or autoreactive lymphocytes can bring about direct cellular damage by cell lysis and/or by initiating an inflammatory reaction in the target organ or gland. As the damage to the organ's cellular structure progresses, connective tissue replaces the destroyed cells and normal functioning of the organ is adversely affected. Hashimoto's thyroiditis, for instance, is characterized by antibodies and sensitized T cells specific for thyroid antigens; these T cells instigate a delayed-type hypersensitivity reaction consisting of infiltrating T cells, macrophages, and plasma cells, which together form lymphocytic follicles leading to an inflammatory reaction which causes goiter. In Hashimoto's thyroiditis, antibodies are formed against thyroglobulin and thyroid peroxidase, both of which play important roles in the uptake of iodine. Antibodies against these proteins interfere with iodine uptake leading to hypothyroidism.

Another good example is insulin-dependent diabetes mellitus (IDDM), which is caused by autoimmune attack on the insulin-producing islets of Langerhans within the pancreas. This destruction of the islet cells by cytotoxic T cells results in decreased production of insulin and thus increased levels of blood glucose. Cytotoxic T lymphocytes first infiltrate into the pancreas, and in addition to destroying β cells, also activate macrophages which produce cytokines leading to a cell-mediated delayed-type hypersensitivity reaction.

DISEASES MEDIATED BY AUTOANTIBODIES

Antibodies are the culprits in several autoimmune diseases; in some diseases, antibodies are of the *blocking* type, while in others antibodies are of the *stimulating* type. An antibody to a hormone receptor can either block the binding of the hormone to its receptor or can stimulate the cell bearing that receptor. Blocking antibodies bind to hormone receptors and thus block receptor function, leading to poor secretion of mediators and eventual atrophy of the organ or gland. Stimulating antibodies, on the other hand, bind to hormone receptors and stimulate exaggerated activity leading to an overproduction of mediators or increased cell growth.

Patients with Graves' disease, for instance, make autoantibodies to the thyroid-stimulating hormone (TSH), which mimic TSH and elicit excessive production of thyroid hormones. Binding of normal levels of TSH results in 'normal' production of thyroxine and triiodothyronine; however, anti-TSH receptor antibodies stimulate the unregulated production of these hormones due to overstimulation of the receptor.

A good example of blocking antibody-mediated organ-specific autoimmune disease is myasthenia gravis, which is characterized by autoantibodies to the acetylcholine receptors on motor end-plates of muscles. These antibodies bind to the receptors and then block the normal binding of acetylcholine to acetylcholine receptors, leading eventually to weakening of the muscles.

Non-organ Specific or Systemic Autoimmune Diseases

Autoimmune responses in this form of autoimmune disease target a range of target antigens involving several organs and tissues. Consequently tissue damage is extensive, and is caused by cell-mediated immune responses as well as from autoantibodies and/or antibody-antigen complexes.

An illustration of systemic autoimmune disease mediated by cellular immunity is multiple sclerosis, a disease that may be characterized by numbness in the limbs, paralysis or loss of vision. The offender in this condition is the T cell; autoreactive T cells directed at antigens in the myelin sheath of nerve fibers form inflammatory lesions along the myelin

sheath. Inflammatory destruction of the myelin sheath in multiple sclerosis results in several neurologic dysfunctions.

Another example of non-organ specific or systemic autoimmune disease is SLE or systemic lupus erythematosus, a disease characterized by symptoms such as fever, weakness, arthritis, skin rashes, pleurisy and kidney dysfunction. Patients with SLE generally produce autoantibodies to a range of antigens present in all nucleated cells such as DNA; these patients often also have autoantibodies to RBC, platelets, and leukocytes. When these antibodies interact with their corresponding antigens a variety of deleterious consequences occur. Anti-DNA antibodies form complexes with DNA (i.e. the antigen) and when these immune complexes get deposited in different tissues of the body, several problems can arise. When deposited on the walls of blood vessels, immune complexes activate the complement cascade, which results in damage to the blood vessels and thus in vasculitis. When deposited in the small blood vessels in the renal glomerulus and in the glomerular basement membranes, a similar complement activation cascade leads to damage to the basement membrane and thus to glomerulonephritis. The excessive complement activation that occurs in SLE can also lead to neutrophil activation and subsequent binding of neutrophils to blood vessels and the formation of occlusions, i.e. vasculitis.

Autoantibodies to surface antigens on RBC and platelets can cause rapid destruction of RBC and platelets respectively, thus causing hemolytic anemia and thrombocytopenia respectively. As one can see from these examples, the tissue damage is widespread, i.e. it is systemic and not specific to any organ or gland.

Rheumatoid arthritis provides an excellent illustration of a systemic autoimmune disease in which the immunopathogenesis involves both B cells (antibodies) and T cells. Patients with rheumatoid arthritis (R.A.) suffer chronic inflammation of the joints; often other systems such as the hematologic, respiratory and cardiovascular systems are also affected. Many, not all, individuals with R.A. have antibodies to the immunoglobulin IgG, i.e. rheumatoid factors. These autoantibodies bind to normal, circulating IgG, and form complexes which get deposited in the joints; locally deposited immune complexes activate the comple-

ment cascade which results in the release of inflammatory cytokines, generation of a respiratory burst, and the production of prostaglandins and leukotrienes, resulting in local, chronic and powerful inflammation of the joints. Interestingly, in R.A. the immunopathogenesis can also involve autoreactive T cells, specific to as yet uncharacterized antigens in the synovial tissue of joints. These autoreactive T cells secrete pro-inflammatory cytokines which provoke local inflammatory reactions in the joints.

Having discussed the mechanisms of immunological tissue damage in autoimmunity, let us proceed to a brief discussion on treatment modalities in autoimmune diseases.

Treatment of Autoimmune Diseases

For therapeutic intervention in autoimmune diseases, ideally one would like to target the autoimmune response itself without affecting normal immune defense reactions. However, this remains an ideal situation, because current therapies are generally directed at suppressing immune reactions and are, therefore, not curative.

CURRENT TREATMENT MODALITIES

Immunosuppressive drugs such as corticosteroids, azathioprine and cyclophosphamide are usually given with the objective of suppressing immune reactivities by suppressing the proliferation of lymphocytes. Methotrexate is also a standard, conventional drug in conditions such as rheumatoid arthritis. These drugs tend to decrease the severity of the disease. Cyclosporin A, an immunosuppressive drug that targets antigen-activated lymphocytes, offers a rather more selective approach to treatment.

EMERGING THERAPEUTIC APPROACHES

An exciting approach initiated recently is the use of antibodies to cytokines and cytokine receptors. As mentioned earlier in this article (Fig. 1), cytokines play critical roles in initiating inflammatory reactions seen in autoimmune diseases and in bringing about tissue damage. A classic example of this is rheumatoid arthritis in which autoreactive T cells as well as antibody-antigen complexes initiate local production of pro-inflammatory cytokines such as $\text{TNF}\alpha$, IL-1 and IL-6.

Promising results were obtained when patients were administered antibodies to TNF α or antibodies to the IL-1 receptor or IL-6 receptor. Anti-TNF antibodies are now routinely used in rheumatology clinics to treat rheumatoid arthritis.

Considering the major health risks posed by autoimmune diseases as well as the heavy financial implications, intense research on developing safe, effective and optimal therapies for these diseases continues to be important.

References

1. Chapel M, Haeney M, Misbah S, Snowden N. *Essentials of Clinical Immunology*. Oxford: Blackwell Science; 1999.
2. Gabriel Virella. *Medical Immunology*. Newbury, Berks: Marcell Dekker; 2001.
3. L W. Moreland, editor. *Rheumatology & Immunology Therapy*. Berlin Heidelberg: Springer-Verlag; 2004.
4. Wicker L, Wekerle H. Autoimmunity. *Curr Opin Immunol* 1995;6:783-812.
5. Flavell RA, Hafler DA. Autoimmunity. *Curr Opin Immunol* 1999;11:635-70.
6. Autoimmunity. Available from URL: http://en.wikipedia.org/wiki/Autoimmune_diseases
7. Autoimmune Diseases Online. Available from URL: <http://www.autoimmune-disease.com/>

CME/CPD Questions

After you have completed reading the article *Principles of autoimmunity: Part I - Induction of autoimmunity* and *Part II - Modes of autoimmune damage*, take the test given below. Circle T (True) or F (False) in the answer sheet (page 54) to show the correct answer to each question. Questions 1 to 10 are related to the content in this article.

1. Immunological tolerance is developed by a process that educates immune cells to distinguish between self and non-self.
2. 'Negative selection' is a process in thymic education during which T cells with receptors for 'foreign' antigens are selected for proliferation.
3. *Clonal anergy* is a state of induced non-responsiveness to self antigens.
4. *Molecular mimicry* is a method for the bypass of tolerance in which hidden molecules are exposed to the immune system.
5. The abnormal expression of HLA molecules in the pancreatic islet cells of insulin-dependent diabetes mellitus can be attributed in part to abnormal cytokine regulation.
6. In organ-specific autoimmune diseases target cells can be directly damaged by antibodies or cell-mediated immunity.
7. Blocking antibodies bind to hormone receptors and stimulate exaggerated activity leading to an overproduction of mediators or increased cell growth.
8. The immunopathogenesis of the systemic autoimmune disease rheumatoid arthritis can involve both antibodies and T cells.
9. Immunosuppressive drugs such as corticosteroids are not found to be therapeutic in autoimmune diseases.
10. The targeting of cytokines and cytokine receptors using antibodies has been found to be an effective therapeutic approach to treat autoimmune diseases.