

Autoimmunity

George Moxley, MD

Please note: for you to derive maximal meaning from this syllabus, you will need to read the text and refer to the figures as you peruse this.

A. The nature of immune responses to self. *Autoimmunity* is defined as tissue damage caused by immune response to self antigens, that is, autoantigens.

13-26. A critical function of the immune system is to discriminate self from nonself.

That immune effector mechanisms can, if directed toward the host, inflict severe damage was termed *horror autotoxicus* by Ehrlich. However, severe autoimmune diseases are uncommon. The reason they are uncommon is that the immune system goes to extreme lengths to tell self from nonself. It uses multiple layers of surrogate markers that are likely to reflect self rather than nonself. These are properties that lymphocytes use to distinguish between self and nonself:

- Self ligands encountered when the lymphocytes are immature are a negative signal. The result is apoptosis or inactivation.
- Self ligands are present in high and constant concentrations. The result is tolerance.
- Self ligands are bound in absence of costimulatory signals that reflect activation of the innate immune system. The outcome is a negative signal and anergy.

13-27. Specific adaptive immune responses to self antigens can cause autoimmune disease. Most autoimmune diseases come from when self antigens activate self-reactive lymphocytes. Sometimes these are induced in experimental animals by immunization with a tissue extract mixed with adjuvant, but most occur spontaneously. Some, like rheumatic fever, stem from infections, but many result from a disordered regulation of the immune system.

13-28. Autoimmune diseases can be classified into clusters that are typically organ-specific or systemic. See the examples in Figure 13.1 like Graves' disease and Hashimoto's thyroiditis for organ-specific, and systemic lupus erythematosus for systemic. Thumbnail sketches of these disorders:

diabetes mellitus: a disorder of insulin deficiency with hyperglycemia and long-term consequences of hyperglycemia. Type I DM refers to the autoimmune kind usually found in thin younger persons; type II DM is entirely a different kind typically found in obese older adults.

Goodpasture's syndrome: an illness with lung and kidney hemorrhage

multiple sclerosis: an illness due to demyelination of the central nervous system with a chief consequence being weakness

Graves' disease: hyperthyroidism, sometimes with swelling of extraocular muscles

Hashimoto's thyroiditis: hypothyroidism

autoimmune pernicious anemia: anemia reflecting vitamin B12 deficiency, in turn due to absence of intrinsic factor necessary for B12 absorption in the terminal ileum.

autoimmune Addison's disease: hypofunction of the adrenal cortex, with resulting deficiency of cortisol

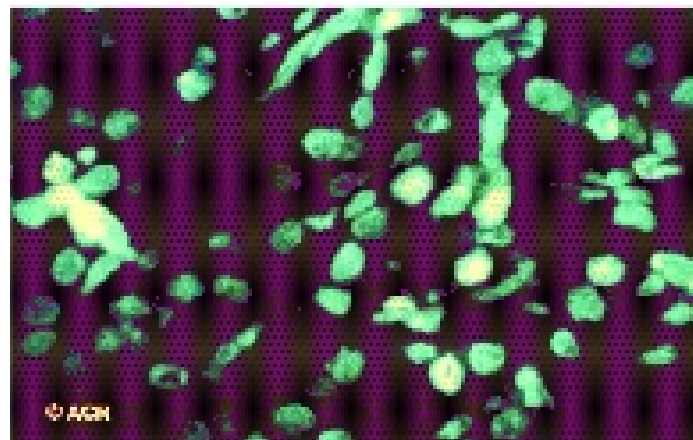
vitiligo: autoimmune destruction of melanin-producing skin cells, resulting in hypopigmented skin patches

myasthenia gravis: autoimmune illness with neuromuscular weakness

rheumatoid arthritis (RA): a chronic inflammatory disease typically characterized by destructive arthritis and often associated with serum autoantibodies directed toward immunoglobulin G (rheumatoid factors).

scleroderma: a chronic illness characterized by skin thickening, Raynaud's phenomenon, usually with esophageal inflammation due to weakness of the lower esophageal sphincter.

systemic lupus erythematosus (SLE): a chronic systemic inflammatory illness typically causing arthritis, skin rash, nephritis, and inflammation of serosal surfaces (pleurisy or pericarditis) and characterized by presence of serum autoantibodies directed toward cell nuclei and associated antigens.



3: Clinical Immunology

3-D-3 Antinuclear antibody: diffuse pattern (photomicrograph)

The diffuse pattern of nuclear fluorescence may be found in sera of patients with systemic lupus erythematosus, whether they are acutely ill or not. It can be demonstrated in sera from other patients such as those with rheumatoid arthritis, chronic discoid lupus, and in a small percentage of normal elderly individuals. High titers are most common in patients with systemic lupus erythematosus. The diffuse pattern is caused by antibody to nucleoprotein (DNA-histone complex) and can mask a speckled or peripheral pattern.

primary Sjogren's syndrome: an illness characterized by dryness of eyes and mouth reflecting autoimmune damage to lacrimal and salivary glands

polymyositis: an illness characterized by muscular weakness due to muscle inflammation and destruction

13-29. Multiple limbs of the immune system are typically recruited in autoimmune disease.

Transfer of disease with either autoantibody or T-cells proves autoimmune nature of disease, but most autoimmune diseases are not simply due to one or another part of the

immune system bearing an autoimmune response. Autoimmune diseases usually require participation of all immune cell types and several effector functions.

- Myasthenia gravis can be transferred with autoantibody directed toward acetylcholine receptor, and experimental allergic encephalomyelitis with T cells.
- Some mothers with an autoimmune illness may deliver a newborn who has a form of the same illness, like Graves' hyperthyroidism with neonatal hyperthyroidism, SLE with neonatal lupus.

13-30. Initial loss of tolerance and autoimmunity may evolve to a chronic disease state because of positive feedback from inflammation as well as the inability to clear most self antigens.

Because self antigens cannot be eliminated, chronic inflammation often results from autoimmune responses, with the result being release of more self antigens. This may result in

- losing sequestration (some organs, like the eye, are normally kept isolated from the immune system)
- attracting nonspecific effector cells, like macrophages and neutrophils, that release chemokines and cytokines.
- some self antigens initially not targeted are attacked later in disease. Epitope spreading refers to the observation that initial immune responses may be directed toward a few self antigenic epitopes, and with autoimmunity, the later immune responses are directed toward other self epitopes.
- in some situations, self antigens are eliminated so completely that too little is available to interact with lymphocytes. Example, DNA in SLE.

A. Multiple tolerance mechanisms normally prevent autoimmunity. Control is mediated by a series of partially effective layers acting together.

13-31. Some degree of autoimmunity is the evolutionary price of being able to make effective responses against pathogens. Evolution cares only about getting you to reproductive age; it does not much care what chronic disease you get after your children are born. In this context, autoimmunity stems from vigorous immunity. The immune system has several checkpoints to control autoreactivity.

13-32. Central deletion or inactivation of newly formed lymphocytes is the first checkpoint of self-tolerance. This means that newbie lymphocytes that bind tightly to self antigens die in the thymus and bone marrow, and newbie lymphocytes that bind too weakly are made unresponsive (anergy). Tissue-specific self antigens are presented by thymic dendritic cells because of the effects of a nuclear factor AIRE (autoimmune regulator). This means, for example, that that ovarian epitopes may be expressed in the thymus.

13-33. Lymphocytes that bind self antigens with relatively low affinity usually ignore them but in some circumstances become activated. Low-affinity cells may become active if: