Recent advances in autoimmunity

Randall S. Krakauer, M.D.
John D. Clough, M.D.

Department of Rheumatic and Immunologic Diseases

David Ilfeld, M.D.*

Although autoimmunity in terms of immune reaction of an organism against itself has been postulated as a significant cause of human disease for many years, only in the past few years have advances in our understanding of immunoregulation brought us to the point where we feel we may speculate intelligently on pathogenesis. The immune system is divided broadly into cell-mediated immunity, which is influenced early in life by the thymus and humoral immunity. T- or thymic-dependent lymphocytes are effector organs of cell-mediated immunity and B- or bursal-equivalent (referring to an avian organ that influences humoral immunity) lymphocytes are responsible for humoral immunity. In order to secrete antibody, B-lymphocytes undergo differentiation into plasma cells that are antibody-secreting cells. B-lymphocytes only differentiate into antibody-secreting plasma cells in the presence of a subpopulation of T-lymphocytes that give a "signal" that antibody to a particular antigen should be secreted. These lymphocytes are referred to as helper T cells and represent one limb of immunoregulation. The other limb of immunoregulation is that of suppressor T cells that can suppress antibody synthesis. In the presence of normal B-lymphocytes, whether antibody will be secreted in response to exposure of the system to a

* *Department of Medicine, Shaare Zedek Medical Center, Jerusalem, Israel.*

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given antigen will therefore be a summation of the helper and suppressor T-cell influences on the B cell. One may therefore presume that in a normal organism foreign or bacterial antigens will result in a net helper effect and antibody synthesis, whereas self-antigens will result in a net suppressor effect and little or no antibody synthesis.

Under this scheme autoimmunity may arise through three theoretic mechanisms. First, is an intrinsic B-cell defect resulting in autoantibodies or antibodies against self, regardless of immunoregulatory influences. A second possibility would be an abnormally active helper T cell driving the system to produce autoantibodies despite the suppressor influence. The third possible mechanism would be deficient or defective suppressor-cell function allowing autoantibodies to be produced in the absence of the normal negative immunoregulatory influence. In any one disease presumed to be of autoimmune etiology, any one, or perhaps a combination of these factors, may play a role, and the effects of abnormal immune regulation may cause not only autoantibodies against target organs, but more distant effects and tissue damage also. We shall discuss recent work in this field on two autoimmune diseases: systemic lupus erythematosus (SLE) and progressive systemic sclerosis (PSS).

Systemic lupus erythematosus

SLE is a disease primarily of autoantibody formation with primary sites of involvement being the joints, skin, kidneys, erythrocytes, leukocytes, platelets, lungs, central nervous system, heart, peripheral nerves, and muscle. It is characterized both by autoantibodies against target organs, which are directly damaged, such as autoantibodies to erythrocytes and platelets, and also by formation of toxic immune complexes, which themselves cause immune damage. The toxic complexes most commonly implicated in this disease are those of native DNA combined with antibodies to native DNA. These circulating immune complexes are passively absorbed to vascular endothelium where they initiate immune damage at such sites as the skin or kidney. Although the target organ that is destroyed is not the organ to which the antibody is directed, these complexes nonetheless represent autoimmunity in as much as they formed with antibodies against self-antigens to which the organism is normally "tolerant", that is, one to which antibodies are normally not produced, in this case native DNA.

There has been extensive investigation recently into the cause of autoimmunity in both human SLE and the mouse model of the disease, the New Zealand Black by New Zealand White F_1 hybrid or NZB/NZW. There is some evidence in the NZB/NZW mouse for all the mechanisms of autoimmunity discussed above: intrinsic B-cell defect,[1] helper T-cell excess,[2] and suppressor T-cell defect.[3] Which abnormality is predominant or whether all three are necessary to produce disease in this model is unknown. It should be noted, however, that therapeutic attempts to restore suppressor activity with a soluble suppressor product of T-lymphocytes, soluble immune response suppressor (SIRS) results in prevention of the development of the autoimmunity when this therapy is initiated before the development of disease manifestations.[4] If therapy is begun after disease has already occurred, the results are considerably less dramatic,[5] perhaps because in these animals there are mature

plasma cells already committed to autoantibody production, which are no longer susceptible to suppression. Nonetheless, this does suggest a possible approach to therapy based on our understanding of the disease mechanism.

The situation in human SLE may or may not be analogous to its murine model. We and several others have in fact demonstrated a deficiency in suppressor T-cell function in this disease;[6-8] however, both the cause of the suppressor-cell defect and the question of whether it is in fact involved in the pathogenesis of the disease itself remain unclear. We have studied the degree of suppressor function as it relates to disease activity and find that with progressing disease activity as measured by the affinity of serum antibodies for native DNA, suppressor T-cell function as measured in vitro progressively decreases with nearly normal suppressor function in patients in disease remission.[9] This relationship would at least suggest that the suppressor-cell defect is related to the disease itself. In addition, we have shown that serum from SLE patients induces a suppressor-cell defect when incubated with normal peripheral blood lymphocytes, and others have in fact shown antibodies active against suppressor cells in this disease.[9] This appears analogous to the murine lupus situation wherein an antibody (natural thymocytotoxic antibody) occurs in the late stages of disease, which is selectively active against suppressor T cells.[10]

We would therefore propose a scheme for lupus disease activity whereby a defect in suppressor T cells results in autoantibody synthesis including antibodies to suppressor cells, which results in further suppressor-cell defect in a destructive loop. This scheme would explain disease propagation or flare, but not the underlying defect, which remains present in the intercritical period between disease flares. In addition, the homeostatic mechanisms capable of breaking this destructive cycle remain unknown. It does suggest, however, some possible therapeutic modalities. One would be soluble factors secreted by human suppressor cells, which we and others have demonstrated exist and are capable of suppressing immunoglobulin synthesis by SLE lymphocytes in vitro.[11] Further work remains to be done in the mice (noted above) to validate this concept. Another approach may be soluble products of thymic epithelium, termed thymic hormones, which are capable of increasing suppressor-cell function in certain situations.[12] Unfortunately, they are also capable of increasing helper cell function, and it would, therefore, be unclear whether the net effect would be helpful. Indeed, use of thymic factors therapeutically in the NZB/NZW mice have been disappointing in that it corrects certain in vitro immunologic abnormalities without improving the clinical manifestations of autoimmunity.[13] Nonetheless, in one patient we studied SLE developed subsequent to thymectomy for myasthenia gravis; not only were suppressor cells deficient, but the abnormality could be substantially corrected by a thymic hormone, factor thymique serique (supplied by Jean Francois Bach, Paris, France).[14] This would suggest that there may be at least a subpopulation of SLE patients who could be identified by in vitro testing who may respond to thymic hormones. Indeed, there is also a possibility of separating thymic hormones into those selectively active on suppressor T cells.

Considerable work has been done both here and elsewhere on plasma-

pheresis in SLE with the object of improving disease manifestations through removal of circulating immune complexes. This approach may also be useful in breaking the destructive loop by removing antibodies to suppressor T cells, though we have no evidence at this time that it would be effective.

A final possibility would be other medication designed to stimulate T cells including suppressor T-cell function, somewhat the opposite end of the spectrum of cytotoxic drugs, which have been used for some time in this disease. Among therapeutic possibilities along these lines being investigated here and elsewhere are levamisol and frentizole.

Progressive systemic sclerosis

If we perceive SLE to be autoimmunity based on suppressor-cell defect, PSS may represent another mechanism through which autoimmunity may develop. Though we find suppressor T-cell function in this disease to be substantially normal, T cells from patients with PSS, when co-cultured with normal B cells induce appreciably greater IgM synthesis in vitro than do allogeneic normal T cells at certain critical T- to B-cell ratios.[15] This suggests increased helper T-cell function in the presence of at least normal suppressor function. Through this mechanism one may also apparently arrive at certain manifestations of autoimmunity including, but not limited to, autoantibodies. In addition, it appears that a soluble product of lymphocytes from PSS patients is capable of stimulating human embryonic lung fibroblasts to increase collagen synthesis in vitro.[16] Evidence for this occurring in vivo is suggested by a serum factor present in patients with PSS, which stimulates collagen synthesis in vitro.[17] It is, therefore, possible that excessive helper T-cell function may, in part, be responsible for autoantibodies in PSS as well as for collagen accumulation associated with scleroderma skin. In addition, the in vitro model of immune function and collagen accumulation appears to represent an in vitro model of the disease, which may be useful in terms of learning more about abnormal immune mechanisms and testing various potential therapeutic approaches.

Summary

Of the three theoretic mechanisms by which autoantibody production can arise (intrinsic B-cell defect, helper T-cell excess, and suppressor T-cell defect) we have evidence suggesting that a helper T-cell excess is involved in scleroderma and a suppressor T-cell defect in SLE. These may represent two ends of defects in the immunoregulatory spectrum that may result in autoimmunity. Further understanding of abnormal immunoregulation that may occur in or be responsible for autoimmunity will hopefully result in new and better therapeutic approaches to these diseases. Other situations in which defective immunoregulation has been implicated recently include sarcoidosis,[18] juvenile rheumatoid arthritis,[19] chronic active hepatitis,[20] inflammatory bowel disease,[21] psoriasis,[22] and thyroiditis.[23] The list of diseases of presumed autoimmune etiology in which evidence for specific immunoregulatory defects is present is still increasing and this may indeed prove to be a sizable area of medical science.

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