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Recent Trends in Systemic Lupus Erythematosus*

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SYSTEMIC lupus erythematosus (SLE) is an autoimmune disease with an unusual diversity of clinical and immunological manifestations (22). Clinically, the disorder may affect virtually any organ in the body: it is truly a systemic disease (13). One explanation for its clinical manifestations is that many lupus lesions develop as a consequence of the deposition of antigen-antibody complexes on basement membranes in a variety of organs and tissues, including the skin, joints, kidneys, pleura, and pericardium (12). In addition, certain lupus autoantibodies can bind directly to target structures located in the brain (8) or on blood cells (11). Those kinds of antibodies may produce cerebritis (41), hemolytic anemia (39), or thrombocytopenia (26).

The serological manifestations of SLE are also diverse. Antibodies that bind to DNA, RNA, DNA:RNA hybrids, nucleoproteins, cytoplasmic antigens, and even phospholipids are common in this disease (table 1). The impressive list of autoantibodies in SLE suggests the existence of a fundamental disturbance of the immune system (31). The nature of that disturbance has been the subject of intensive investigations for more than 25 years. Many of them have centered around animal models of the disease and they have yielded a wealth of information, as well as conflicting and sometimes confusing data (13, 14). The original animal model, the NZB mouse, develops a form of lupus characterized principally by the development of autoimmune hemolytic anemia. More recently, several other strains of mice that spontaneously develop SLE have also been described (table 2). The manifestations of the disease in the newer animal models include arthritis, nephritis, and dermatitis. In some animals—B/W, for example—the disease has a late onset, whereas in others—MRL/l and BXSB—early death from severe nephritis and vasculitis is the rule (2, 38).

Numerous immunological abnormalities have been uncovered in animal models of SLE (31, 14, 38, 37). Every possible limb of the immune response has been implicated in one or another defect, and a unified theory that explains all of the abnormalities has not gained credence. The diversity of the findings suggests that SLE is not a specific entity, but a *syndrome* that may arise through various immunological aberrations. In a given individual, the syndrome could entail multiple immunological defects, some of which may be primary, whereas others may be secondary. We may consider the latter disturbances as *lesions*; in other words, autoantibodies can damage the immune system itself. As an example, autoantibodies against lymphocytes (lymphocytotoxic antibodies) are a common feature of SLE, both in humans and in mice (15). Such autoantibodies can react with specific subsets of T lymphocytes (e.g., suppressor cells) (35) and secondarily cause an impairment of immunoregulatory circuits. This impairment, however, represents a lesion of the immune system that is caused by the primary disturbance. Selective breeding of mice with SLE has demonstrated that the secondary "lesions" segregate as independent Mendelian traits (33).

Studies of inbred mice that spontaneously develop SLE have revealed one incontestable fact: the disease has a genetic basis. The uniform development of a particular form of SLE in inbred mice is *prima facie* evidence of a genetic disorder. Moreover, the discovery that a single gene, *lpr*, greatly accelerates the disease in experimental mice (29) strongly supports the influence of genetic factors in SLE. There is evidence that the human disease also has a genetic basis. SLE has familial occurrence (36), and its concordance in identical twins is about 70% (6). Moreover, clinically healthy relatives of patients with SLE have a high frequency of serological abnormalities, such as positive antinuclear antibody tests (6, 30, 16). The function of suppressor T cells is often abnormal in patients with SLE (10, 19), and when family studies were carried out a similar abnormality was detected in 13/50 clinically healthy first degree relatives (27). That result implies a genetic basis for the immunological abnormalities in human SLE. It seems, moreover, that defective suppressor cell function cannot, *by itself*, account for the development of the disease. Thus, SLE may be regarded as a multifactorial, complex genetic disorder that culminates in the production of pathogenetic autoantibodies that cause diverse lesions, either by forming immune complexes or by binding directly to antigens exposed on cell surfaces.

A syndrome that resembles SLE may develop in connection with certain drugs (40). There is no apparent similarity among these drugs, which range in type from anti-convulsants to laxatives (34). Moreover, the production of autoantibodies (especially antinuclear antibodies) *in the absence of clinical manifestations* is common with certain drugs (e.g., procainamide) (7). Drug-induced SLE differs from spontaneous SLE in several ways, the most important of which is that nephritis and antibodies to native (double-strand) DNA are rare complications of drug-induced SLE (40).

The association between certain HLA haplotypes and

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TABLE 1
Autoantibodies in SLE

Nucleus
DNA (double-strand and single strand)
DNA-histone complex
Histones
Nonhistone proteins
Sm (DNA-binding protein)
RNA-protein complex
SS-B antigen
Blast cell nuclear antigen
Nucleolar antigens
Cytoplasm
Ribosomal ribonucleoprotein
Ro antigen
La antigen
Membranes
Red cells
Platelets
Granulocytes
Lymphocytes
Other
RNA (double-strand and single-strand)
Coagulant proteins
Cardiolipin
IgG (Fc)

TABLE 2
Characteristics of SLE mice

Strain	Anti-DNA	Anti-SM	Nephritis	Arthritis	Anemia
NZB	+	0	±	0	++
B/W	++	0	+++	0	0
MRL/1	+++	+	+++	+	0
BXSB	++	0	+++	0	0

hydralazine-induced autoantibodies (5) suggests a genetic predisposition that is linked to immune-response genes, a linkage that implies a hapten-like mechanism for the drug. Immunization of rabbits with hydralazine-protein conjugates has led to the formation of both anti-hydralazine and anti-DNA antibodies (43), a result that supports the concept that certain lupus-inciting drugs might act as haptens. Recent investigations demonstrated that hydralazine can interact directly with thymidine (17), and perhaps with other structures in DNA (42). These effects could account for both the lupogenicity and carcinogenicity of hydralazine, but the explanation remains incomplete because lupus-inciting drugs cause the production of autoantibodies other than anti-DNA antibodies. Indeed, antibodies against histones are characteristic of drug-induced lupus (20), and patients with procainamide-induced lupus commonly form autoantibodies against lymphocytes (9). Moreover, the persistence of drug-induced autoantibodies long after cessation of procainamide (1) suggests that the drug need not be physically present for the maintenance of the immunopathological events. Those kinds of observations support the possibility that drug-induced autoimmunity might come about by interference with normal immunoregulatory mechanisms (28).

Recent studies with monoclonal anti-DNA autoantibodies, produced by hybridoma technology (3), indicate that the diversity of lupus autoantibodies is not as great as previously envisioned. The numerous serological abnormalities of the disease seem instead to be associated with a restricted number of antigenic determinants (epitopes) that are present in a variety of different biological molecules.

Hybridomas that produce monoclonal autoantibodies have been prepared by the fusion of spleen cells from MRL/l mice with the SP/2 myeloma line (3). MRL/l mice, as mentioned, spontaneously develop a severe form of SLE and they produce large amounts of lupus autoantibodies. Hybridomas that produce monoclonal DNA-binding antibodies have been subjected to extensive analyses with regard to their ligand-binding properties. A finding of considerable importance is that all of the monoclonal autoantibodies bind not only DNA, but also several other polynucleotide ligands (fig. 1) (4). This property suggests that epitopes shared by nucleic acid antigens can account for some of the serological diversity in lupus serum.

The sugar-phosphate backbone of nucleic acids is a structural feature of all polynucleotides, and therefore a likely source of the shared epitopes to which monoclonal anti-DNA antibodies bind. The backbone consists of phosphate groups, in phosphodiester linkage, separated by three carbon atoms of adjacent sugar molecules. Such groups also occur in the phospholipid cardiolipin. It is therefore of interest that certain monoclonal anti-DNA autoantibodies bind equally well to cardiolipin (fig. 2) (25). These "polyspecific" autoantibodies have other features. For instance, one of them has the property of a lupus anticoagulant because it causes prolongation of the partial thromboplastin time, an effect that reflects the ability of the antibody to bind to the phospholipid that is required for clot formation in the assay. This particular autoantibody also produces a strongly positive fluorescent antinuclear antibody test that is inhibited by prior incubation of the antibody with cardiolipin. A single molecular species of autoantibody can therefore manifest itself as an anti-DNA antibody, an antinuclear antibody, or a lupus anticoagulant.

Thus, lupus autoantibodies can be serologically polymorphic. Their capacity to react with a diversity of molecules may seem surprising until it is realized that the true specificity of an antibody reflects its interaction with submolecular structures on antigens, so-called epitopes. Therefore, the presence of identical or similar epitopes in a diversity of molecules can cause the diverse reactions of monoclonal lupus autoantibodies. In the example given, the epitope is a particular arrangement of phosphate groups, and the diversity of molecules includes nucleic acids, synthetic polynucleotides, and phospholipids.

Another approach toward the definition of diversity among autoantibodies exploits the serological analysis of

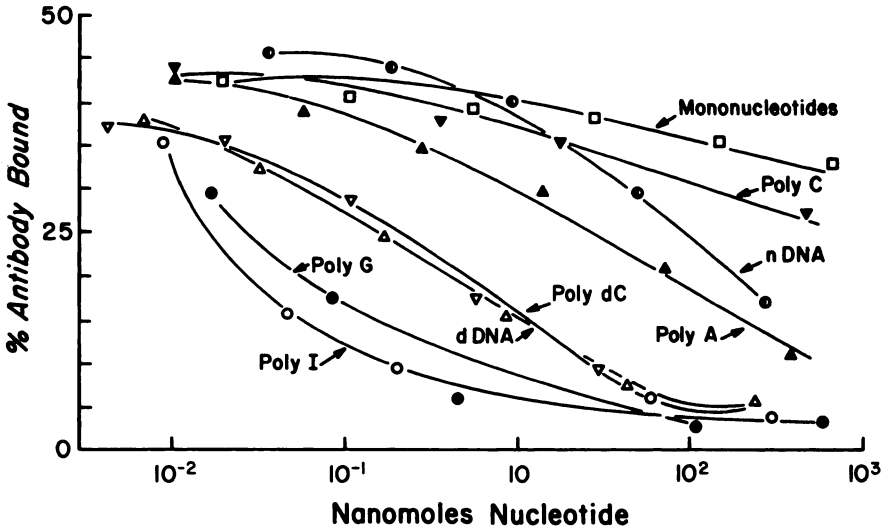

FIG. 1. Analysis of a monoclonal lupus autoantibody (H104). S_1 nuclease-treated *Escherichia coli* DNA was adsorbed to wells of polyvinyl microtiter plates (solid phase) and the monoclonal antibody was added in the presence of the stated amounts of inhibitors. After washing, bound antibody was detected with ^{125}I-rabbit anti-mouse IgG serum. See Andrzejewski et al. (4) for further details of assay.

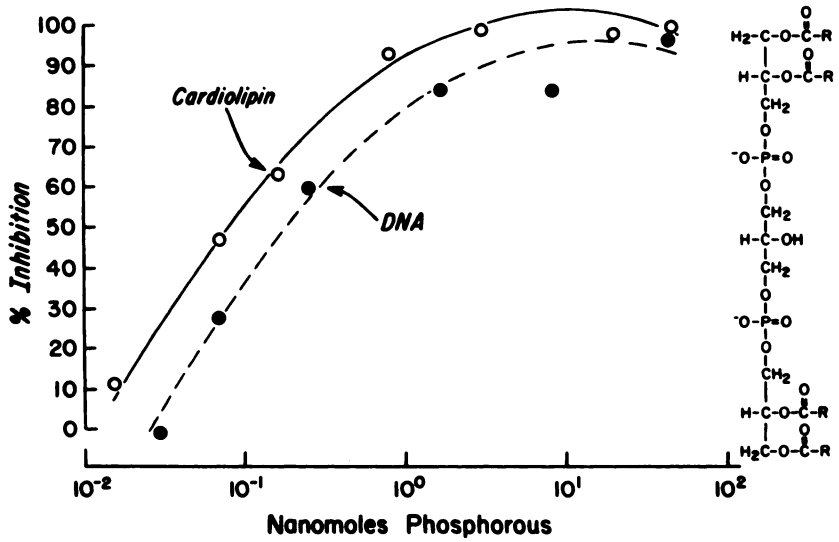

FIG. 2. Competitive inhibition of a monoclonal lupus autoantibody (130) by both DNA and cardiolipin. The chemical formula of cardiolipin is shown at the right. The assay was carried out as mentioned in figure 1; binding in the absence of inhibitor was 50%.

immunoglobulin variable region structures. These structures constitute the antigen-binding portion of the immunoglobulin molecule and are themselves immunogenic. The serologically defined variable region structures of immunoglobulins are called *idiotypes* (24). As an example, immunization of a rabbit with a monoclonal lupus autoantibody can produce antibodies against the antigen-binding portion of the autoantibody. After removal of irrelevant antibodies (e.g., those against Fc structures) by absorption, the rabbit immune serum defines serologically epitopes associated with the variable (antigen-binding) region and serves as an anti-idiotypic antibody. Reactions between the idiotype and the anti-idiotype are completely inhibitable by antigen (4, 25).

Idiotypic analyses have revealed two noteworthy aspects of monoclonal lupus autoantibodies in MRL/l mice. The first is that cross-reactive idiotypes exist among different hybridoma anti-DNA antibodies (25). Antibodies with related idiotypes may be produced by clones derived not only from the same MRL/l mouse, but also from different MRL/l mice. The second aspect is that a common idiotypic marker has been found in the serum of all MRL/l mice (32). Such findings imply that germline genes specify at least some autoantigen-binding immunoglobulins. They add further support to the genetic concept of SLE because they indicate that a serologically defined structure in the antigen-binding region of autoantibodies is genetically determined. This kind of autoantibody may therefore not arise by somatic mutation, but seems to be represented in DNA as a mendelian trait. It is now within the capabilities of molecular biological techniques to determine whether nor-

mal individuals possess such "autoantibody genes." If they do, then the mechanisms that regulate the expression of these genes in autoimmune diseases are susceptible to analysis, and perhaps ultimately to control. The definition of idiotypic markers possessed by autoantibodies may therefore provide important information about the genetic mechanisms of autoimmunization.

Is there any practical value to these results? Here we must speculate, but not without a solid basis of experimental support. From one point of view, antibodies are footprints of antigens. Therefore, a precise definition of the antigen-binding properties of autoantibodies could, in principle, reveal information about immunogenic structures that may instigate autoimmune reactions. Knowledge of those epitopes could lead to the development of therapeutically effective desensitizing or tolerizing agents. Manipulation of the immune respone by means of anti-idiotypic sera has already proven feasible (23). Such reagents can either provoke or suppress antibody synthesis, depending on dosage and certain qualitative aspects of the anti-idiotypic antibody (18). Steps toward the control of immune responses with anti-idiotypic antibodies have begun (21), but they are still in their infancy. Finally, genetic markers on autoantibody molecules may prove useful for the analysis of drug-induced lupus. By such means, the question as to whether drug-induced autoantibodies derive from the same pool of genetically inscribed molecules as spontaneously produced autoantibodies can be solved.

Lupus research seems to have reached an important crossroad. What began as clinical, immunopathological, and serological descriptions has evolved into a fusion of genetics, immunochemistry, and membrane biology. In the foreseeable future this new trend will link up with molecular biology. There is every reason to expect that these new trends will lead to an improved understanding of the cause, control, and prevention of this fascinating, multifaceted disorder.

REFERENCES

1. Alarcon-Segovia, D.: Drug-induced systemic lupus erythematosus and related syndromes. Clin. Rheum. Dis. **1:** 573–582, 1975.
2. Andrews, B. S., Eisenberg, R. A., Theofilopoulos, A. N., et al.: Spontaneous murine lupus-like syndromes. Clinical and immunopathologic manifestations in several strains. J. Exp. Med. **148:** 1198–1215, 1978.
3. Andrzejewski, D. A., Jr., Stollar, D. B., Lalor, T. M., et al.: Hybridoma autoantibodies to DNA. J. Immunol. **124:** 1499–1501, 1980.
4. Andrzejewski, D. A., Jr., Rauch, J., Lafer, E., et al.: Antigen binding diversity and idiotypic cross reactions among hybridoma autoantibodies to DNA. J. Immunol. **126:** 226–231, 1981.
5. Batchelor, J. R., Welsh, K. I., Tinoco, R. M., et al.: Hydralazine-induced systemic lupus erythematosus: Influence of HLA-DR and sex on susceptibility. Lancet **1:** 1107–1109, 1980.
6. Block, S. R., Winfield, J. B., Lockshin, M. D., et al.: Studies of twins with systemic lupus erythematosus. Am. J. Med. **59:** 533–552, 1975.
7. Blomgren, S. E., Condemi, J. J., Bignall, M. C., et al.: Antinuclear antibody induced by procainamide. N. Engl. J. Med. **281:** 64–66, 1969.
8. Bluestein, H. G., and Zvaifler, J. Brain reactive lymphocytotoxic antibodies in the serum of patients with sytemic lupus erythematosus. J. Clin. Invest. **57:** 509–516, 1976.
9. Bluestein, H. G., Zvaifler, N. J., Weisman, M. H., et al.: Lymphocyte alteration by procainamide: Relation to drug-induced lupus erythematosus syndrome. Lancet **2:** 816–818, 1979.
10. Bresnihan,B., and Jasen, H. E.: Suppressor function of peripheral blood mononuclear cells in normal individuals and in patients with systemic lupus erythematosus. J. Clin. Invest. **59:** 106–116, 1977.
11. Budman, D. R., and Steinberg, A. D.: Hematologic aspects of systemic lupus erythematosus. Ann. Intern. Med. **86:** 220–229, 1977.
12. Cochrane, G. D., and Koffler, D.: Immune complex disease in experimental animals and man. Adv. Immunol. **16:** 185–264, 1973.
13. Decker, J. L., Steinberg, A. D., Gershwin, M. E., et al.: Systemic lupus erythematosus. Contrasts and comparisons. Ann. Intern. Med. **82:** 391–404, 1975.
14. Decker, J. L., Steinberg, A. D., Reinersten, J. L., et al.: Systemic lupus erythematosus: Evolving concepts. Ann. Intern. Med. **91:** 587–604, 1979.
15. DeHoratius, R. J.: Lymphocytotoxic antibodies. Prog. Clin. Immunol. **4:** 151–174, 1980.
16. DeHoratius, R. J., Pillarisetty, R., Messner, R. P., et al.: Anti-nucleic acid antibodies in systemic lupus erythematosus patients and their families. J. Clin. Invest. **56:** 1154, 1975.
17. Dubroff, L. M., and Reid, R. J., Jr.: Hydralazine-pyrimidine interactions may explain hydralazine-induced lupus erythematosus. Science **208:** 404–406, 1980.
18. Eichmann, K.: Idiotype suppression I. Influence of the dose and of the effector functions of anti-idiotypic antibody on the production of an idiotype. Eur. J. Immunol. **4:** 296–302, 1974.
19. Fauci, A. S., Steinberg, A. D., Haynes, B. F., et al.: Immunoregulatory aberrations in systemic lupus erythematosus. J. Immunol. **121:** 1473–1479, 1978.
20. Fritzler, M. J., and Tan, E. M.: Antibodies to histones in drug-induced and idiopathic lupus erythematosus. J. Clin. Invest. **60:** 560–567, 1979.
21. Geha, R. S.: Regulation of the immune response by idiotypic-antiidiotypic interactions. N. Engl. J. Med. **305:** 25–28, 1981.
22. Hahn, B. H.: Systemic lupus erythematosus. *In* Clinical Immunology, ed. by Charles W. Parker, p. 583–631, W. B. Saunders Co., Philadelphia, 1980.
23. Hart, D. A., Wang, A. L., Pawlak, L. L., et al.: Suppression of idiotypic specificities in adult mice by administration of antiidiotypic antibodies. J. Exp. Med. **135:** 1293–1300, 1972.
24. Kunkel, H. G., Mannick, M., and Williams, R. C.: Individual antigenic specificity of isolated antibodies. Science **140:** 1218–1219, 1963.
25. Lafer, E., Rauch, J., Andrzejewski, C. A., Jr., et al.: Polyspecific monoclonal lupus autoantibodies reactive with both polynucleotides and phospholipids. J. Exp. Med. **153:** 897–909, 1981.
26. McMillan, R.: Chronic idiopathic thrombocytopenic purpura. N. Engl. J. Med. **304:** 1135–1147, 1981.
27. Miller, K. B., and Schwartz, R. S.: Familial abnormalities of suppressor-cell function in systemic lupus erythematosus. N. Engl. J. Med. **301:** 803–809, 1979.
28. Miller, K. B., and Schwartz, R. S.: Suppressor cells in autoimmune diseases. Adv. Intern. Med. **27:** 281–314, 1982.
29. Murphy, E. D., and Roths, J. B.: Autoimmunity and lymphoproliferation: Induction by mutant gene 1pr and acceleration by a male-associated factor in strain BXSB mice. *In* Genetic Control of Autoimmune Disease, ed. by N. Rose, P. Bigazzi, and N. Warner, pp. 207–210, Elsevier North Holland, New York, 1978.
30. Pollock, V. E.: Antinuclear antibodies in families of patients with systemic lupus erythematosus. N. Engl. J. Med. **271:** 165–169, 1964.
31. Quimby, F. W., and Schwartz, R. S.: The etiopathogenesis of systemic lupus erythematosus. Pathobiol. Annu. **8:** 35–59, 1978.
32. Rauch, J., Lafer, E., Stollar, B. D., et al.: Submitted for publication.
33. Raveche, E. S., Novotny, E. A., Hansen, C. T., et al.: Genetic studies in NZB mice. V. Recombinant inbred lines demonstrate that separate genes control autoimmune phenotype. J. Exp. Med. **153:** 1187–1197, 1981.
34. Reynolds, T. B., Peters, R. L., and Yamada, S.: Chronic active and lupoid hepatitis caused by a laxative oxyphenisatin. N. Engl. J. Med. **285:** 813–820, 1971.
35. Shirai, T. K., Hayakawa, K., Okumura, K., et al.: Differential cytotoxic effect of natural thymocytotoxic autoantibody of NZB mice on functional subsets of T cells. J. Immunol. **126:** 1924–1929, 1978.
36. Siegel, M., Lee, S. L., and Widelock, D. N.: Comparative family study of rheumatoid arthritis and systemic lupus erythematosus. N. Engl. J. Med. **273:** 893–897, 1965.
37. Steinberg, A. D., Huston, D. P., Taurog, J. D., et al.: The cellular and genetic basis of murine lupus. Immunol. Rev. **55:** 121–154, 1981.
38. Theofilopoulos, A. N., and Dixon, F. J.: Etiopathogenesis of murine SLE. Immunol. Rev. **55:** 179–216, 1981.
39. Videbaek, A.: Autoimmune hemolytic anemia in systemic lupus erythematosus. Am. J. Med. **12:** 197–204, 1952.
40. Weinstein, A.: Drug-induced systemic lupus erythematosus. Prog. Clin. Immunol. **4:** 1–22, 1980.
41. Williams, G. W., Bluestein, H. G., and Steinberg, A. D.: Brain-reactive lymphocytotoxic antibody in the cerebrospinal fluid of patients with systemic lupus erythematosus: Correlation with central nervous system involvement. Clin. Immunol. Immunopathol. **18:** 126–132, 1981.
42. Williams, G. M., Mazue, G., and McQueen, C.A.: Genotoxicity of the antihypertensive drugs hydralizine and dihydralazene. Science **210:** 329–330, 1980.
43. Yamauchi, Y., Litwin, A., Adams, L., et al.: Induction of antibodies to nuclear antigens in rabbits by immunization with hydralazine-human serum conjugates. J. Clin. Invest. **56:** 958–969, 1975.