Origins of Anti-DNA Autoantibodies

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Introduction

One of the main goals of research in immunology is to identify the origins of autoantibodies. A comprehensive solution of the problem will have to recognize that the predominant autoantibodies in most autoimmune diseases are tissue specific (Table I), whereas the autoantibodies in systematic lupus erythematosus (SLE)[1] react with numerous constituents of normal cells, including macromolecules as ubiquitous as DNA, cytoskeletal proteins, and phospholipids (Table II). What accounts for this difference? Does the diversity of autoantibodies in SLE imply a more extensive disruption of immunological mechanisms than in other autoimmune diseases? Is the serology of the disease reliable evidence of its cause? The answers to these questions require detailed knowledge of the autoantibodies themselves, which is the topic that forms the basis of this article.

The autoantibodies that bind to DNA are of central interest. For clinicians they dominate SLE, fluctuating in tempo with its clinical activity (1, 2) and participating in the formation of its lesions (3). For immunologists they are an enigma: how does the immune system permit the formation of antibodies against the very substance of the genetic code? If immunological tolerance developed under an evolutionary pressure to avoid autoimmunization, then the ability to form anti-DNA antibodies should be a lost trait. Yet, as we shall see, the capacity to produce them is an inherent property of the normal immune system. An exact definition of these antibodies is therefore essential to understand not only the etiology and pathogenesis of SLE but the rules that govern their production by lymphocytes from normal persons.

Antigenic properties of DNA

The native double helical form of DNA (B-DNA) is a polymer formed by two polydeoxyribose-phosphate backbones that spiral around centrally oriented purine and pyrimidine bases. The deoxyribose-phosphate atoms of the surface of the molecule are readily accessible to antibodies. By contrast, portions of the bases are exposed only at several ångströms deep within its major or minor grooves. Antibodies directed primarily against the bases cannot reach into the grooves and do not react with native DNA.

When native DNA is irreversibly denatured, the individual strands collapse into compact single chains, in part randomly coiled and in part comprised of short regions of base-paired secondary structure. This single-stranded form of the molecule is accessible to antibodies in regions where individual bases or stacked bases are exposed to solvent or where the backbone is exposed in the form of a single chain or a short helical structure. A variety of potential antigenic determinants is thus available in single-stranded DNA. And by contrast with native DNA, denatured DNA reacts with antibodies to bases, nucleosides, nucleotides, and oligonucleotides (reviewed in 4).

Reactions of serum anti-DNA antibodies. A large portion of the anti-DNA antibodies in lupus serum react with single-stranded DNA, but not with the native helical form. Some lupus antibodies specific for single-stranded DNA recognize short base sequences (5, 6), whereas others react with nuleosides (7), including cytidine and guanosine (8). Munns et al. (9) demonstrated that all of the anti-single-stranded DNA activity of some sera from lupus-prone MRL-*lpr*/*lpr* and New Zealand Black/New Zealand White (NZB/NZW) mice was removed by absorption with a nucleoside-protein-Sepharose conjugate containing nucleosides of all four DNA bases; a guanosine conjugate removed 60% of the anti-single-stranded DNA activity and a thymidine conjugate removed 25%. However, the nucleosides did not absorb anti-double-stranded DNA antibodies.

Studies of the reactions of lupus sera with synthetic polynucleotides have revealed different populations of antibodies. Some react primarily with poly(dT), others with poly(dT) and single-stranded DNA, and still others with poly(dT), poly(dC), and single-stranded DNA (10). Additional antibodies cross react with single-stranded DNA and the left-handed Z-helical DNA, or bind only to the Z-form (11). Lupus sera also contain antibodies that bind to other kinds of polynucleotides, including poly(A) (12), double-stranded RNA (13), single-stranded RNA (14), RNA-DNA hybrid (15), and poly(ADP ribose) (16). An important issue, in view of all of the above findings, is how to explain the apparent diversity of lupus autoantibodies even when only nucleic acid antigens are considered.

Polyspecificity of monoclonal anti-DNA autoantibodies. Immunochemical studies of numerous monoclonal anti-DNA autoantibodies obtained from both murine and human hybridomas have revealed parallels with the reactions of serum antibodies. Some show specificity for individual bases or nucleotides, with guanine and oligo(dT) sequences as prominent determinants (9, 17–19), whereas others react preferentially or even specifically with double-stranded DNA (20–22). Most of them bind single-stranded DNA better than the native form. More striking, however, is that the majority react with several nucleic acids, including varying combinations of double-

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1. *Abbreviations used in this paper:* NP, (4-hydroxy-3-nitrophenyl)acetyl; NZB/NZW, New Zealand black/New Zealand white; SLE, systematic lupus erythematosus.

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Table I. Representative Autoimmune Diseases and Their Corresponding Autoantigens

Disease	Principal autoantigen
Hashimoto's thyroiditis	Thyroglobulin
Graves' disease	Thyrotropin receptor
Insulin-resistant diabetes	Insulin receptor
Myasthenia gravis	Acetylcholine receptor
Pemphigus vulgaris	Intercellular cement
Bullous pemphigoid	Basement membrane (skin)
Goodpasture's disease	Basement membrane (glomeruls)

stranded DNA, single-stranded DNA, and synthetic polynucleotides. The reactions of a single antibody with multiple polynucleotides can be explained by its ability to combine with variations of an antigenic determinant (epitope) in the sugar phosphate backbone that is common to all polynucleotides. Presumably, each antibody prefers a particular geometry of the epitope, thus accounting for the range of specificities of large groups of monoclonal anti-DNA autoantibodies; a given autoantibody may bind avidly to poly(dT), but only weakly to poly(I), whereas another may react strongly with Z-DNA but not at all with B-DNA. These results reflect the dependence of the binding reaction on conformations of the nucleic acid surfaces (backbones), which vary according to the base composition of the polynucleotide.

Other cross-reactions of anti-DNA autoantibodies. An important characteristic of monoclonal anti-DNA autoantibodies is their remarkable cross reactivity with molecules other than polynucleotides. Table III contains a summary of the principal

Table II. Principal Autoantigens in SLE

- Nucleus
  - DNA
  - DNA-histone complex
  - Histones
  - Nonhistone proteins
  - Sm ribonucleoprotein antigen
  - RNP antigen
- Cytoplasm
  - Ribosomal ribonucleoproteins
  - Ro ribonucleoprotein antigen
  - La ribonucleoprotein antigen
  - Cytoskeletal proteins
- Membranes
  - Erythrocytes
  - Platelets
  - Granulocytes
  - Lymphocytes
- Other
  - RNA
  - Coagulant proteins
  - Cardiolipin
  - IgG (Fc)

Table III. Cross-reactions of 24 Monoclonal Human Lupus Autoantibodies

Hybridoma	sDNA	nDNA	Cardiolipin	Cytoskeleton	Platelets
2/113b	+++	0	+	+++	+++
2/19b	+++	0	—	++	+++
2/1-17	+		0	0	++
2/1-43	+	0	—	+++	+
2/12-6	+++	+	0	+	++
2/12-33	++	0	+	+++	0
2/12-11a	+	0	+	+	+
2/18-2	++	++	0	+++	+
2/18-7	++	±	0	+	+
2/18-9	+	±	0	+++	+
6/21-28	++	+	0	++	+
6/21-29	+++	+	0	+	+
6/21-37	++	+	—	+	0
6/32-9	+	+	0	+++	+
6/32-15	++	+	0	0	+
6/3-1	++	+	+	0	+
3/3-47	+	+	+++	+	+
3/13-3	+++	±	—	—	—
3/15-2	++	+	—	—	—
3/15-6	++	+	—	—	—
3/15-13	++	0	++	—	—
3/15-17	+++	++	—	—	+
3/16-6	+++	±	0	++	+
14/134	++	+++	—	++	++

Results are summarized from references 20, 27, and 32, and from unpublished experiments. All values are approximated, for comparative purposes, ranging from +++ (strong) to 0 (negative); —, not done.

cross-reactions of a representative group of human monoclonal anti-DNA autoantibodies from seven patients with SLE. The ability of anti-DNA autoantibodies to bind to the phospholipid cardiolipin (23, 24) is noteworthy because its backbone, like that of polynucleotides, also contains phosphate esters (but no bases or sugars). In phospholipid micelles the repeating arrays of phosphodiester groups that face the solvent may mimic the geometry of phosphate esters on the polynucleotide backbone. Monoclonal anti-DNA autoantibodies that react with cardiolipin are not rare; 10 of 21 human antibodies had that property (19). Most patients with active SLE have serum antibodies that react with cardiolipin (25); moreover, cardiolipin-binding activity in lupus serum is present in the DNA-binding fraction (26).

Monoclonal anti-DNA autoantibodies can also bind to cytoskeletal proteins, notably the intermediate filament vimentin (27). This cross-reaction is observed by immunofluorescence with a substrate of fibroblasts or epithelial cells that contain a well-developed system of intermediate filaments (Fig. 1). Immunoprecipitation of fibroblast extracts by monoclonal anti-DNA autoantibodies followed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis demonstrated that the cellular antigen is a protein with the same molecular weight of vimentin, 54,000. Vimentin may be a target of autoantibodies. Studies of two patients with Waldenstrom's macroglobulinemia and peripheral neuropathy revealed that their IgM monoclonal

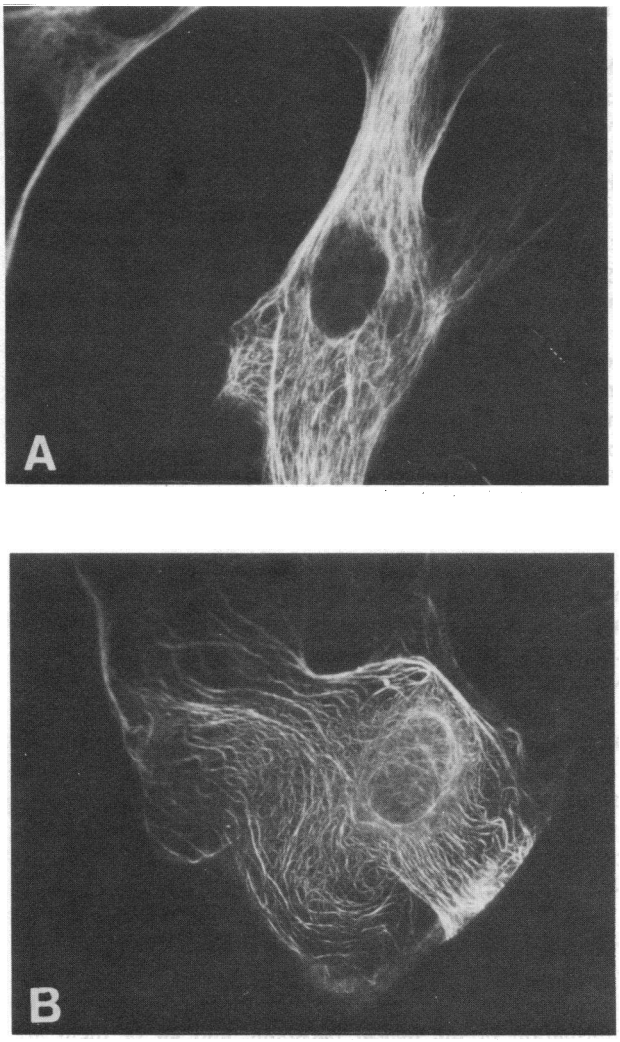

Figure 1. Cytoskeletal staining by a monoclonal anti-DNA antibody (H18/2). (*A*) Human fibroblast; the staining pattern is consistent with that of the intermediate filament vimentin. (*B*) PTK-2 cell reacted with the same antibody. This epithelial cell contains both keratin and vimentin, but the staining pattern shown is that of vimentin. Photographs courtesy of Dr. Janine Andre-Schwartz.

immunoglobulins bound to intermediate filaments of the Schwann cells of peripheral nerve (28). Vimentin filaments also occur in vascular endothelial cells of the kidney, skin, and brain (29–31), any of which can be affected in SLE.

Another clinically relevant immunochemical property of monoclonal anti-DNA autoantibodies is their cross reaction with platelets (32) (Table III). The nature of the cross-reacting antigen on the platelet surface is unknown. Nevertheless, the finding is remarkable because thrombocytopenia of varying severity is common in SLE. An additional cross-reaction has been found between monoclonal anti-double-stranded DNA autoantibodies and a group of five membrane proteins of Raji cells (33). This result suggests that if anti-DNA autoantibodies in serum bind directly to Raji cells they may produce an overestimate of its content of immune complexes.

Some autoantibodies can also bind both to the Fc portion of IgG and to denatured DNA (34) or nucleosome subunits of chromatin (35, 36), a phenomenon first observed with serum antibodies and later confirmed with monoclonal autoantibodies derived from MRL-*lpr/lpr* mice (37). The cross-reactive determinants have not been identified. The reaction has technical importance because the binding of such monoclonal antibodies to rabbit immunoglobulins, which are commonly employed as second-step reagents, may interfere with immunoassays.

Serological implications of the cross-reactions of monoclonal lupus autoantibodies. These studies of the ligand-binding properties of monoclonal anti-DNA autoantibodies provide a new view of the diversity of serological abnormalities in SLE. We can now appreciate that the same antibody (or group of related antibodies) can account for several different serological phenomena, depending on the test system that registers their presence. It is highly likely, for example, that the same kind of antibody causes reactions with both DNA and cardiolipin. This can explain the frequent occurrence of false positive tests for syphilis in SLE. Such phospholipid-binding antibodies can also behave like lupus anticoagulants by combining with the phospholipids that are employed in determining the partial thromboplastin time. The same antibodies, moreover, can produce the fluorescent antinuclear reaction (23). The occurrence of immune thrombocytopenia in patients with anti-DNA autoantibodies, even in those with no other evidence of SLE, may be due to binding of the antibodies with the platelet membrane. It remains to be seen, however, whether other important autoantibodies in SLE, such as those directed against ribonucleoprotein antigens and histones, are subject to such a unifying interpretation of the serology of SLE.

How can a single antibody react with several apparently unrelated molecules? The results we have cited are not without precedent. For example, monoclonal antibodies against a measles virus protein have been found to react with vimentin (38) and immunoglobulins with multiple reactivities have been isolated from normal human sera (39). One interpretation of the data is that the antibody-combining site has more than one contact region for unrelated epitopes. An alternative explanation is that certain epitopes, phosphodiester groups are a relevant example, recur in a variety of molecules. This kind of antigenic mimicry is exemplified by rheumatic carditis (40) and Chaga's disease (41), both of which entail an immunological attack by anti-microbial antibodies that cross react with normal tissue antigens.

The hypothesis of recurring epitopes has been tested by immunizing normal mice with a cardiolipin-protein conjugate (42). The animals responded by producing both anti-cardiolipin and anti-DNA antibodies, and hybridomas prepared from their spleens yielded monoclonal antibodies that were indistinguishable from monoclonal lupus anti-DNA autoantibodies in their reactions with cardiolipin and several different polynucleotides. This result demonstrates that cardiolipin shares immunogenic epitopes with DNA, but whether other molecules that cross-react with anti-DNA autoantibodies have similar epitopes is an open question. The cross-reactions with proteins are perplexing. Vimentin is a phosphorylated helical structure (43), but we do not know if those features can explain its cross-reaction with monoclonal anti-DNA antibodies. Nothing is known about the chemistry of the cross-reactions of DNA with IgG or the Raji cell membrane proteins.

Idiotypes of anti-DNA autoantibodies

Idiotypes are serologically defined structures of the variable (V) region of the antibody and therefore, they mark an important functional site of the molecule. An idiotype may be confined to only one antibody, in which case it is termed a private idiotype, or it may be a public idiotype that several or even many antibodies share. The anti-DNA autoantibodies of MRL/*lpr-lpr* and NZB/NZW mice bear a high frequency public idiotypic marker (44, 45); in the former strain up to 50% of the serum anti-DNA antibodies share an idiotype termed H130. In humans, a public idiotypic marker termed 16/6 was found in the serum of more than one-half of 74 patients with active SLE (46). Solomon et al. (47) immunized mice with affinity-purified serum anti-DNA antibodies and produced a monoclonal anti-idiotype that reacted with the serum of seven patients with the disease. The anti-DNA antibodies of (NZB/SWR) F_1 mice, which develop a severe form of lupus nephritis (48), do not have the H130 idiotype of MRL-*lpr/lpr* mice (49). By contrast, the sharing of idiotypes by anti-DNA antibodies from unrelated humans seems to be the rule. A public idiotype in antibodies from different patients implies that the corresponding V region structure is encoded in the germ line, but that is only a surmise until the genes themselves have been characterized by molecular probes.

Clinical relevance. Serum levels of the H130 idiotype rise progressively during the course of SLE in MRL-*lpr/lpr* mice (44), and in some patients, serum levels of the 16/6 idiotype fluctuate with disease activity (46). Moreover, immunoglobulins with the 16/6 marker have been found in the renal lesions of SLE (50). This idiotype, therefore, identifies a group of pathogenic antibodies. Nevertheless, not all serum antibodies with the idiotype are necessarily anti-DNA antibodies. In MRL-*lpr/lpr* mice, for example, only about 25% of the serum immunoglobulins that bear the H130 idiotype have anti-DNA activity (44); the binding specificities of the remainder are unknown. Such "idiotype-positive, antigen-negative" antibodies can exert immunoregulatory effects (51). Therefore, an excess of them in the face of persistent autoantibody production suggests a defect in a particular immunoregulatory network. Indeed, injection of biologically active anti-idiotype serum into MRL-*lpr/lpr* mice was without discernible effect on their serum levels of anti-DNA antibodies (52). Attempts to treat NZB/NZW mice by immunization with idiotype (to raise endogenous anti-idiotype) produced only marginal effects on the outcome of the disease, but this may have been due to the ascendency of new idiotypes in the animals (53).

Origins of anti-DNA autoantibodies

Immunochemical clues. The ligand-binding properties of monoclonal anti-DNA autoantibodies indicate that for many of them DNA is not the preferred antigen. Results of the experiments we discussed above demonstrated a high frequency of monoclonal DNA-binding antibodies with marked quantitative preferences for polynucleotides other than single-stranded or double-stranded DNA. In those cases, therefore, the immunizing antigen may not be DNA. We must draw that inference cautiously, however, because the ligand-binding properties of an antibody do not necessarily reveal the immunizing antigen. For example, immunization of mice with the hapten (4-hydroxy-3-nitrophenyl)acetyl (NP) elicits antibodies with a higher affinity for 5-iodo-NP than for NP (54). The immunochemical properties of anti-DNA autoantibodies, however, do differ qualitatively from antibodies that arise after immunization with exogenous polynucleotides. By contrast with the extensive cross-reactivity of anti-DNA autoantibodies, the induced antibodies are highly specific for the immunizing nucleic acid. Induced antibodies to Z-DNA, for example, react only with the zig-zag leftward-turning helix and not at all with right-handed B-DNA or denatured DNA (55).

Immunogenicity of DNA. It has not been possible to produce experimental models of SLE by immunizing normal animals with DNA because double-stranded DNA is not immunogenic, or only barely so. Even lupus-prone MRL/++ mice fail to respond to immunization with double-stranded DNA, and their responses to single-stranded DNA, an immunogenic polynucleotide in normal mice, are surprisingly feeble (56). The defect is selective because Z-DNA elicits high titers of specific antibodies in these animals. The curious lack of immunogenicity of DNA stands in contrast to the immunogenicity of many other autoantigens, such as thyroglobulin and the acetylcholine receptor, and raises the possibility that DNA is not the instigating antigen in SLE.

Could some unusual form or fragment of DNA be the immunogen? Helical nucleic acid polymers other than B-DNA are immunogenic, but they induce antibodies specific for conformational features that differ from those of native DNA (with which they do not react) (57). Up to 2 mg/ml of serum antibody has been induced by double-stranded RNA, RNA-DNA hybrid, triple-helical polynucleotides (reviewed in 57), or by Z-DNA (55). Weaker responses have been induced by right-handed polydeoxyribonucleotides that differ from B-DNA, such as poly(dG)·poly(dC) (58, 59) or poly(dC-dA)·poly(dT-dG) (56). In these cases, the antibodies probably recognize the conformation of the helical backbone and all of them are specific for the immunizing polynucleotide.

Low molecular weight DNA harvested from supernatants of cultured splenocytes can elicit anti-DNA antibodies in mice, but its immunogenicity is weak (60). Low molecular weight DNA is also present in circulating immune complexes from lupus patients (61), perhaps because some anti-DNA antibodies can protect a 35–45 base-pair DNA fragment from DNase, thereby contributing to the formation of stable immune complexes (62). Sano and Morimoto (63) proposed that DNA fragments with a high content of guanosine and cytosine, which they had identified in immune complexes, could be immunogenic. That is unlikely, however, because even pure poly(dG-dC) or poly(dG)·poly(dC) fail to induce antibodies to native DNA (55, 58, 59). An altered form of DNA also develops following exposure of the molecule to UV light. Its antigenic determinant is the conformational distortion produced by the formation of thymine dimers (64). It is plausible that UV-DNA could be immunogenic in SLE (65), but antibodies to UV-DNA do not cross-react with native DNA because it does not contain thymine dimers. In summary, it is unlikely that an altered form of DNA can stimulate the production of the anti-DNA autoantibodies that are characteristic of SLE. Nucleic acid molecules or fragments with conformations that

diverge from the helical structure of native DNA are indeed immunogenic, but in no case have they been found to elicit antibodies of the type that is characteristic of SLE. It seems, therefore, that anti-DNA autoantibodies and antibodies to exogenous polynucleotides are products of different lymphocytes; perhaps the stimulus for their activation is also different.

Effects of polyclonal activation of B cells. The ability to produce anti-DNA antibodies is not confined to patients with SLE. On the contrary, it is an inherent property of the normal immune system. Cultured B cells of normal mice and humans produce anti-DNA antibodies in the presence of polyclonal activators (66, 67). Moreover, the production of anti-DNA antibodies also occurs in vivo following polyclonal B cell activation by lipopolysaccharide (68), peptidoglycan (69), or the graft-versus-host reaction (70). In the latter case, the antibodies react with both single-stranded and double-stranded DNA and the animals develop typical lesions of SLE.

The *lpr* gene has the same effect. It was originally identified in the MRL-*lpr*/*lpr* mouse and in that strain it causes massive lymphadenopathy, polyclonal activation of B cells, and an accelerated form of SLE (71). The gene was subsequently transferred to several normal strains, in which it also induces the production of antibodies to double-stranded DNA (72).

A striking example of the ability of B cells from normal persons to make anti-DNA antibodies has been reported by Cairns et al. (73). They prepared hybridomas from the tonsillar lymphocytes of a normal 7-yr-old child. Growth occurred in 110 wells, of which 13 (11.8%) produced anti-DNA antibodies. Subclones of those hybridomas produced monoclonal antibodies with polyspecific ligand-binding properties that were indistinguishable from those of monoclonal lupus autoantibodies. In this case, it is important to note that the tonsillar lymphocytes had been activated in vivo by bacterial infection, an event we shall discuss below.

Structural clues. Amino acid sequence analyses of monoclonal anti-DNA antibodies have begun only recently, but important clues have already emerged. Eilat et al. (74) found that the amino terminal sequences of the heavy chain of a monoclonal anti-DNA antibody derived from an NZB/NZW mouse differed at only a single position from the corresponding sequences of an antibody to phosphocholine, an important bacterial antigen. Even more remarkable is the finding that a point mutation in the V_H gene of a mouse myeloma changed the antigenic specificity of its immunoglobulin from antiphosphocholine to anti-DNA (75).

Further evidence of a relationship between anti-DNA autoantibodies and anti-bacterial antibodies comes from structural studies of human antibodies. Four idiotypically related monoclonal anti-DNA autoantibodies from different patients were found to have identical amino terminal light chain sequences and similar amino terminal heavy chain sequences. The light chain sequence was also identical, except for one position, to the sequence of the light chain of a Waldenstrom IgM paraprotein, WEA (76). The WEA protein has combining specificity for a capsular polysaccharide (K30) of *Klebsiella pneumoniae* (77). This monoclonal anti-bacterial antibody also binds to DNA and poly(G) and bears the same idiotypic marker as the monoclonal lupus autoantibodies to which it is structurally related (76).

Idiotypic footprints. The high frequency idiotypic marker H130 (see above) is not confined to the anti-DNA antibodies of MRL-*lpr*/*lpr* mice. It also marks a proportion of the anti-DNA antibodies produced by the lymphocytes of normal mice after polyclonal activation (78). This idiotype, like its human counterpart (16/6), thus seems to be encoded by a widespread germline gene. However, only molecular probes can establish this point definitively. Even so, it is remarkable, as Bottomly (79) has observed, that virtually all dominant idiotypic systems in the mouse, regardless of the immunizing antigen, are related to anti-bacterial antibodies. We suggest that anti-DNA autoantibodies are no exception to this principle.

Conclusion

Lupus research has taken many curious twists and turns during the past three decades. Some of the unexpected detours have brought us close to identifying the specific network of lymphocytes that dominate a major immunological aberration of the disease. Characterization of this network and the defect that perturbs it is now a feasible goal.

We have stressed the antigenic and immunogenic features of the polynucleotide backbone, but the importance of bases and base sequences should not be underestimated. As we have seen, a substantial fraction of antibodies that react with single-stranded DNA bind to these components, among which guanine and thymine seem to be immunodominant. And single-stranded DNA, nucleosides, and oligonucleotides, unlike native DNA, are immunogenic. Nothing, however, is known about the origins of the autoantibodies against them. Are their primary specificities directed against some other antigen? What are the particular features of guanine and thymine that account for their prominence in these autoantigens?

Studies of monoclonal autoantibodies have provided new clues to the origins of an important group of anti-DNA autoantibodies. The apparent diversity of serological reactions with different forms of nucleic acid, and even with macromolecules that are not nucleic acids, can now be accounted for by a restricted number of antibodies that react with recurrent epitopes on diverse structures. Many of these antibodies, even those from different patients, may arise from related V genes. These genes seem to be widely dispersed in the population and they apparently have not diverged greatly from germline genes. They may be closely related to V genes whose products are involved in antibacterial responses. This could account for their conservation in the genome and for the observation that their corresponding antibodies differ from those elicited by immunogenic polynucleotides. With the availability of hybridomas that possess the appropriate genes, these hypotheses can be tested with molecular probes.

A major question concerns the stimulus for activation of these genes in SLE and the mechanism of their suppression in normal persons. Even if they represent only the fringes of an antibacterial response, are they stimulated by released nucleic acids, or by bacterial antigens, or by less specific polyclonal activators? Answers to these questions, along with definition of the target cell populations, could provide a more specific approach to control of this disease than is now available.

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