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Review Article

Anti-DNA Autoantibodies: the Other DNA-binding Proteins

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Introduction

Autoantibodies that bind DNA (anti-DNA) were first reported in 1957 following their detection in the serum of lupus patients.[1] Nearly 40 years later, anti-DNA are still studied extensively since they are believed to play a direct role in mediating the kidney damage associated with this common autoimmune disorder via anti-DNA · DNA immune complex formation. Anti-DNA also provide a model for studying the recognition of single- and double-stranded DNA by proteins in the context of a defined molecular architecture: the β-barrel antibody binding site.

Studies of both the specificity and affinity of anti-DNA for DNA antigens, and of the mode of binding of these two moieties are crucial for a fuller understanding of anti-DNA · DNA complex formation. An understanding of this complexation may, in turn, shed light both on the pathology of lupus and also on the process of nucleic acid molecular recognition. Despite a wide-ranging interest in anti-DNA, and although several hundred anti-DNA have been isolated from both humans and mice,[2] the general features of DNA epitopes, the parameters that distinguish high- and low-affinity anti-DNA, and the molecular mechanisms used in DNA recognition by anti-DNA remain to be well defined. In this article, we review some of the more common approaches that have been used to examine the specificity, affinity and mode of binding of lupus anti-DNA for DNA antigens. In particular we highlight the recent application of biophysical techniques that have been used to study DNA-binding proteins, such as transcription factors,[3] and demonstrate their utility when used in the study of lupus anti-DNA.

Specificity for DNA antigens

Before the advent of hybridoma technology, studies of the specificity and affinity of anti-DNA for DNA antigens were performed using polyclonal lupus sera from both human and murine sources. By examining specificity for DNA antigens immobilized on a solid support, three kinds of anti-DNA were identified: those that bind either single-stranded DNA (ssDNA), double-stranded DNA (dsDNA), or both ss- and dsDNA.[4–6] Competition assays with single-stranded oligonucleotides of varying length and base composition defined an anti-ssDNA binding-site size of approximately five bases long,[7] similar to that found for several other ssDNA-binding proteins. However, using polyclonal sera to identify an anti-dsDNA binding-site size proved to be more difficult. It was only possible to demonstrate that anti-dsDNA sera could be grouped according to the length of dsDNA oligonucleotides that inhibit binding to native DNA in a radioimmunoassay: inhibition requires competition with DNA either 20–25, 40–50 or >180 base-pairs long.[8]

The inherent heterogeneity of polyclonal sera represented a major problem in these early studies of anti-DNA. Hence, the ability to produce monoclonal anti-DNA (mAbs), prepared primarily from murine models of lupus, using hybridoma technology, greatly facilitated the characterization of these proteins.[9–19] Early studies of murine monoclonal anti-DNA found a high degree of variability in specificity towards synthetic oligonucleotides. In many cases, thymine was apparently immunodominant for anti-ssDNA.[12,20,21] Furthermore, many monoclonal anti-ssDNA do not bind polyribonucleotides.[6,21,22] This observation suggests either that anti-ssDNA can discriminate between the two different sugar moieties or that more complicated secondary or tertiary structures exist in these polymers that limit access to the nucleotide bases in RNA relative to DNA. Since anti-DNA bind oligo(dU), it would seem that the latter explanation is more likely.[21,22]

Based on the findings described above, it appears that anti-ssDNA can possess base selectivity, but whether anti-ssDNA are truly sequence-specific has not yet been determined. However, sequence-specific ssDNA-binding proteins, such as the adenovirus major late transcription factor,[23] the major cold-shock protein of *Bacillus subtilis*, CspB,[24] and the HeLa pur factor[25] are

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well documented. We have therefore used in vitro selection (e.g., SELEX) experiments[26] to determine whether sequence-specificity is a feature of anti-ssDNA, in this case anti-ssDNA derived from an MRL MpJ-*lpr*/*lpr* (MRL-*lpr*) mouse model of lupus. By isolating a high affinity consensus sequence from a random oligonucleotide pool, this technology has enabled us to demonstrate the first clear example of sequence-specific single-stranded DNA binding by a lupus anti-DNA mAb. This antibody shows a thermodynamic specificity similar to that typically seen for dsDNA-binding proteins (i.e., the affinity of the specific sequence is >1000-fold greater than the affinity for random DNA).[27] Hence, we have identified the first example of an important new class of sequence-specific DNA-binding proteins. These findings are perhaps clinically relevant since recent evidence suggests that the specificity of anti-DNA may be important in determining the ability of these autoantibodies to induce kidney disease in lupus.[28]

Relatively few monoclonal anti-dsDNA mAbs have been isolated and these mAbs have not been characterized as thoroughly as anti-ssDNA. By measuring the helix-coil transition of poly(dA)·poly(dT) in the presence of different concentrations of a monoclonal anti-dsDNA, Jel241, Braun and Lee find that each binding site on this antibody binds approximately six base pairs.[29] This value is in good agreement with the binding site size of other dsDNA binding proteins which recognize six to 10 base pairs of dsDNA.[30] It has been difficult to determine the specificity of anti-dsDNA on account of the relatively low affinities for the synthetic homopolymers that have been used as ligands. It is possible that the observed affinities obtained in these experiments might only represent nonspecific binding and that tighter binding could be observed if more appropriate ligands were identified using the SELEX methodology. The SELEX approach was used recently by Herrman and colleagues who demonstrated that consensus motifs can be selected by anti-dsDNA from lupus sera and two monoclonal anti-dsDNA.[31] However, equilibrium dissociation constants were not presented to quantify any increased affinity for the selected epitopes over random dsDNA.

Specificity for non-nucleic acid antigens: cross-reactivity

The existence of anti-DNA challenges a basic principle of immunology: DNA is a 'self' molecule and yet appears to be acting as an immunogen in the immune system. Moreover, animals immunized with DNA do not develop lupus. Although lupus anti-DNA have the features of antibodies that arise in an antigen-selected immune response,[32] the nature of the initial antigenic stimulus is controversial. Several investigators have therefore focused on possible cross-reactions of anti-DNA in order to explain their origins as a by-product of stimulation with an antigen other then DNA.[33] However, this hypothesis cannot account for anti-DNA that do not display extensive cross-reactivity,[34–36] such as our panel of MRL-*lpr*-derived anti-DNA.[22] Thus, DNA or DNA-containing complexes, such as nucleosomal particles,[37] remain the most likely of the candidate antigens.

Cross-reactivity has also been implicated in the mechanism of immune complex deposition, which is believed to cause the kidney damage observed in many lupus patients. Many potentially relevant anti-DNA interactions with components of the glomerular basement membrane have been described, including binding to fibronectin, collagen and laminin.[38] However, the extent of cross-reactivity of anti-DNA has typically been measured in solid-phase binding assays and hence these measurements are not necessarily reflections of physiological cross-reactivity. To address this point, Edberg and Taylor[39] defined the cross-reactivity of 19 lupus serum samples to phospholipids, heparan sulfate, condroitin sulfate and polyglutamic acid using two solution-phase assays. They found that only a 1500-fold excess of phospholipids inhibited antibody binding to both ds- and ssDNA. They concluded that even in solution, cross-reactivity might not represent physiologically relevant interactions between serum anti-DNA and non-nucleic acid antigens. Thus, although several studies have addressed the issue of cross-reactivity of serum and monoclonal anti-DNA, there remains conflicting evidence on its nature and extent.

Affinity for DNA antigens

The affinity of anti-DNA for specific polynucleotides is commonly quantified using competition ELISA and the Farr assay. However, the use of both assays has been criticized since they introduce artifacts, such as the enhancement of nonspecific binding, and hence preclude an accurate assessment of affinity at equilibrium. Thus, it is not suprising that changes in DNA specificity are seen between nonequilibrium and equilibrium experiments.[21,22] In order to avoid these problems, a small number of groups has examined the affinity of anti-DNA for polynucleotides using equilibrium measurements. Both Lee and colleagues and Voss's group have obtained binding constants for the monoclonal anti-ssDNA, HEd10 and BV04-01, respectively, using fluorescence quenching measurements with synthetic homopolymers.[21,40] Most recently, Komissarov and colleagues have obtained binding data for a recombinant ssDNA-binding Fab using both fluorescence spectroscopy and equilibrium gel filtration.[41] We have used an electrophoretic mobility assay to obtain binding data for both BV04-01 and our panel of MRL-*lpr*-derived anti-ss- and anti-dsDNA.[22,42,43] In all cases, anti-ssDNA bind poly(dT) with dissociation constants in the micromolar to nanomolar range and reduced affinity is detected for other polynucleotides. This pattern of reactivity is similar to that seen for other ssDNA-binding proteins. However, it is not possible to directly compare these affinity data with those for ssDNA-binding proteins

such as the phage T4 gene 32 protein and the phage M13 gene 5 protein (reviewed by Coleman and colleagues),[44] since these latter two proteins bind cooperatively to DNA, in contrast to the noncooperative binding by anti-DNA.

Equilibrium binding constants have been determined for only a few anti-dsDNA. For example, Braun and Lee[29] have shown that the affinity of the monoclonal antibody, Jel241, for both poly(dA)·poly(dT) and native calf thymus DNA is in the micromolar range. Along similar lines we find that two of our MRL-*lpr*-derived anti-DNA, which have a low relative affinity for oligo(dT) (~0.5 μM) also recognize short DNA duplexes with micromolar affinity. In the absence of a tighter binding dsDNA ligand, several groups have subsequently suggested that the heterocyclic bases of dsDNA are not a major antigenic determinant and that anti-dsDNA might recognize features of the dsDNA backbone.[2,29,45,46] Since sequence has a marked effect on the structure of the sugar-phosphate backbone of DNA, it may be difficult to distinguish the relative importance of sequence and structure in dsDNA antigens.[47]

Mode of binding

The structural basis of anti-DNA·DNA interactions at atomic resolution has been directly obtained for a single Fab derived from anti-ssDNA mAb, BV04-01, liganded to d(pT3).[48] In this complex, the trinucleotide is stabilized by interactions that involve stacking of thymine bases between aromatic residues on the protein side-chains. This mode of binding is thought to be a general feature of sequence-independent ssDNA-binding proteins, such as the phage T4 gene 32 protein and the phage M13 gene 5 protein.[44] In contrast, there are no high-resolution structures of autoimmune anti-dsDNA complexes available and hence a convincing theory to describe recognition of duplex DNA is not available. However, Stollar and colleagues have suggested that the antibody binding site may straddle the backbone of dsDNA and that residues in the binding site project into the major and minor grooves of the dsDNA.[45] An alternative model has been proposed by Marion and colleagues in which anti-dsDNA bind primarily to the backbone of dsDNA and there are few contacts with the major or minor grooves.[46] Both models propose that dsDNA contacts the heavy chain of anti-dsDNA, which is supported by light chain swapping experiments and UV crosslinking of dsDNA.[49,50]

Since crystallographic structures of neither free nor bound lupus anti-DNA have been widely reported, other strategies are required to investigate anti-DNA structure and the key interactions in anti-DNA·DNA complexes. An approach that is commonly used to investigate DNA-binding proteins of known sequence, such as transcription factors,[51] involves techniques such as high-resolution binding measurements and DNA footprinting to establish the protein residues involved in such complexation. Surprisingly, this approach was applied only recently to the study of BV04-01 both by our group and by Voss and colleagues.[40,42,43,48,52] We have subsequently used footprinting data in conjunction with affinity data to construct a computational model of the BV04-01 complex. The salient aspects of this model agree with the published crystal structure of BV04-01·d(pT3) and confirm the relevance of the structure to binding in solution. These results demonstrate the validity of this approach that we have now extended to our panel of anti-DNA.[22] We find that anti-ssDNA show specificity for oligo(dT), display relative insensitivity of K_d with $[Na^+]$, use tryptophan and tyrosine residues on binding DNA and have a binding site of about five nucleotides in length. Within this framework we are currently using molecular models to assist in a site-directed mutagenesis study to identify key interactions in anti-DNA·DNA complexes.

The collective binding, X-ray, and computational data obtained from both the crystallographic and modeling analyses of anti-ssDNA·DNA complexes indicate that (1) the binding site for ssDNA is a long, relatively deep cleft with a maximum width of ~12 Å between the tips of the V_L and V_H domains, (2) ssDNA ligands are stabilized by stacking of thymine bases between aromatic side-chains in this cleft, (3) hydrogen bonding occurs to both the phosphate backbone and to the bases themselves on binding, and (4) ion pair formation in the complexes is limited. The involvement of aromatic residues on complexation finds parallels not only with the mode of binding of sequence-independent ssDNA-binding proteins, such as the phage T4 gene 32 protein and the phage M13 gene 5 protein, but also with other immunoglobulins such as anti-lysozyme antibodies. For example, Padlan has indicated that both aromatic side-chains and arginine residues have structural features especially suited to the binding of ligands.[53] Indeed, tyrosine and tryptophan allow a large surface area for interaction with a wide variety of ligands via stacking interactions.[53] Further, these residues are over-represented in the binding sites of immunoglobulins,[54] DNA-binding proteins and anti-DNA.[53]

Stacking interactions with tyrosine and tryptophan are seen in anti-ssDNA that have a secondary structure comprising anti-parallel β-sheets. Although α-helices are most commonly used in the interaction of proteins with DNA (through motifs such as the helix-turn-helix, the zinc finger and the leucine zipper), proteins that use β-sheets in their interactions with DNA, such as the TATA-binding protein (TBP), have precedents in the literature.[55–57] TBP binds DNA in a sequence-dependent manner and it is thus possible to conjecture that the sequence-specificity observed for anti-ssDNA may be related to their use of β-sheets on complexation with DNA.

Summary

Using the methods developed to study protein · DNA complexes, a small number of workers has begun to characterize the interactions of lupus anti-DNA antibodies with their DNA antigens. These studies indicate that anti-ssDNA generally possess a high affinity for poly(dT) and use aromatic side-chains on complex formation, in common with many previously reported anti-ssDNA, and several DNA-binding proteins. We find that our anti-ssDNA differ from these latter two species in that they are not cross-reactive with non-nucleic acid antigens, unlike many other anti-ssDNA, and their complexation does not appear to be accompanied by significant cation release, as for some DNA-binding proteins. Moreover, in some cases our anti-ssDNA are apparently sequence-specific. Due to the small number of anti-dsDNA mAbs studied, our current understanding of these proteins is limited. However, we have recently obtained a high-resolution crystal structure of 4B2, that reacts with both ss- and dsDNA. This structure should enable us to facilitate mutagenesis experiments to identify the molecular features of dsDNA recognition.

One can envisage several practical benefits of applying a systematic biophysical approach to studying lupus anti-DNA · DNA. For example, once the molecular basis of anti-DNA · DNA interactions has been defined, it may be possible to use anti-DNA as biochemical reagents such as repressors of protein-DNA binding or as catalysts that manipulate DNA. Indeed, the enormous diversity of the immune repertoire and the ease with which anti-DNA can be customized by site-directed and random mutagenesis provides the potential to generate anti-DNA with a wide range of properties. Alternatively, by understanding the molecular basis of anti-DNA · DNA interactions it may be possible to identify molecules that disrupt the specific interaction between anti-DNA and their DNA antigens. Such molecules could eventually form the basis of new agents to treat immune-complex mediated kidney damage and have fewer complications than the nonspecific agents currently used to treat lupus. In fact, by screening combinatorial small molecule libraries, we have already identified several promising anti-DNA antagonists.[58] Thus, we believe that the next few years will be an exciting period in anti-DNA research.

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Biographical Sketch

Roslyn M. Bill was born in Pontypridd, U.K. on 2 November 1967. She received a first-class M.A. in chemistry from the University of Oxford, U.K. in 1990. In 1991, she was awarded a Wellcome Trust Prize Studentship to work in the laboratory of Sabine Flitsch at Oxford, receiving her D.Phil. in bioorganic chemistry in 1994. After graduating from Oxford, she spent a year in the laboratory of Martin Bobrow at the University of Cambridge, U.K. R.M.B. is currently a Fulbright Junior Fellow in the laboratory of Gary Glick at the University of Michigan. Throughout her postgraduate career, the common theme of her research interests has been the structure–function analysis of biologically important proteins.

Neal B. Blatt was born in Detroit, Michigan on 6 March 1970. He received his undergraduate education at the University of Michigan where he was awarded an A.B. with honors in linguistics. He is currently a fellow in the Medical Scientist Training Program at the University of Michigan where he is pursuing a Ph.D. in chemistry under the mentorship of Gary Glick. In addition to studying anti-DNA autoantibodies, N.B.B. has investigated the thermodynamics of DNA hairpin formation.

Gary D. Glick was born in Queens, New York on 18 June 1961. While an undergraduate at Rutgers University, he conducted research on metal–carbene complexes under the direction of Robert A. Moss. After completing a B.A. with high honors in chemistry, he moved to Columbia University where he obtained his Ph.D. in 1988, studying under the direction of W. Clark Still. After finishing postdoctoral work with Jeremy R. Knowles at Harvard University, he joined the chemistry faculty at the University of Michigan in Ann Arbor. His research interests are in the areas of nucleic acid structure and folding and molecular recognition of DNA and antibodies. His scientific contributions have been recognized with several awards including, a National Arthritis Foundation Arthritis Investigator Award, an American Cancer Society Junior Faculty Research Award, a National Science Foundation Young Investigator Award, a Camille Dreyfus Teacher–Scholar Award, and a Research Fellowship from the Alfred P. Sloan Foundation.