Review Articles

Mechanisms of Disease

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ANTIBODIES TO DNA

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ANTIBODIES to DNA are of interest to a broad spectrum of physicians and other scientists. The presence of large amounts of serum antibodies to double-stranded DNA is specific for systemic lupus erythematosus, and some subgroups of these antibodies are pathogenic. It is likely that people are predisposed to have systemic lupus erythematosus if they can make pathogenic subgroups of antibodies to DNA and if they cannot down-regulate them appropriately. Studies of patients with systemic lupus erythematosus and of murine models of the disease have provided information regarding the different types of antibodies to DNA, their role in pathogenesis, and new methods for suppressing the production or action of pathogenic antibodies to DNA in ways that target these subgroups more specifically than the currently used nonspecific immunosuppressive regimens.

DIFFERENT TYPES OF ANTIBODIES TO DNA

Antibodies to DNA were first described in 1957.[1-3] They constitute a subgroup of antinuclear antibodies that bind single-stranded DNA, double-stranded DNA, or both. They may be IgM antibodies or any of the subclasses of IgG antibodies. In general, tests for IgG complement-fixing antibodies to DNA, especially those that bind double-stranded DNA, have the greatest diagnostic value in patients in whom systemic lupus erythematosus is suspected, and in patients with systemic lupus erythematosus the results often correlate with the clinical activity of the disease and with the risk of glomerulonephritis. However, these are not the only types of anti-DNA antibodies that can cause nephritis: some subgroups of IgM antibodies to DNA and some antibodies to single-stranded DNA can probably cause it as well.[4-6]

Antibodies that bind exclusively to single-stranded DNA can bind its component bases, nucleosides, nucleotides, oligonucleotides, and ribose–phosphate backbone, all of which are exposed in single strands of DNA (Table 1). In contrast, antibodies that bind double-stranded DNA bind to the ribose–phosphate backbone, base pairs (deoxyguanosine–deoxycytidine and deoxyadenosine–deoxythymidine), or particular conformations of the double helix.[7,8] Double-stranded DNA exists primarily in a right-handed helical form called B DNA; there is also a left-handed helical form called Z DNA. Some patients with systemic lupus erythematosus have antibodies against both forms, whereas others have antibodies that react preferentially with Z DNA.[7,9] Studies of monoclonal antibodies have shown that antibodies that bind exclusively to double-stranded DNA are rare; most antibodies to double-stranded DNA bind both double-stranded DNA and single-stranded DNA.

Most normal subjects have IgM antibodies to single-stranded DNA in their serum. These antibodies, which belong to the repertoire of natural autoantibodies, have low affinity for DNA and for several other self-antigens, such as thyroglobulin and myosin.[10-12] In contrast, IgG antibodies to double-stranded DNA are less prevalent in normal subjects and are more likely to include high-affinity subgroups with narrow cross-reactivity.[11,12] DNA may bind to antibodies that also bind antigens other than naked DNA; such cross-reactivity may be important in causing disease.[13-18] Additional characteristics that contribute to the pathogenicity of antibodies to DNA include their complement-fixing capability, their affinity for DNA and cross-reactive antigens, the charge of the antibody molecule or of the immune complex containing it, and the amino acid sequences of associated proteins.[4-6,16,19] Most widely available tests for measuring antibodies to DNA are based on reactivity with B DNA; it is not clear whether the results of tests of other antigenic reactivities might correlate better with the clinical activity of systemic lupus erythematosus or with the involvement of particular organs.

TESTS FOR ANTIBODIES TO DNA

Some laboratories offer tests for serum antibodies to single-stranded DNA, but these tests are not useful for diagnosing systemic lupus erythematosus, because these antibodies are present in patients with many different inflammatory disorders and in normal subjects. Older tests identified antibodies to

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TABLE 1. POTENTIAL REACTIVITY OF ANTIBODIES TO DNA.

Antibodies to single-stranded DNA
Antigens in DNA
Nucleic acid bases
Nucleosides
Nucleotides
Oligonucleotides
Ribose–phosphate backbone
Antibodies to double-stranded DNA
Antigens in DNA
Base pairs (deoxyguanosine–deoxycytidine, deoxyadenosine–deoxythymidine)
Deoxyribose–phosphate backbone
Antigens with which antibodies to double-stranded DNA cross-react
Chromatin
Nucleosomes
Components of glomerular basement membrane
Laminin
Heparan sulfate
Type IV collagen
Antigens trapped in membranes
DNA
Nucleosomes

double-stranded DNA that fixed complement or precipitated with DNA (very-high-affinity antibodies). The results of these tests, which are rarely available now, correlated better with the presence of active lupus glomerulonephritis than do the results of current tests. Nevertheless, the currently available methods of detecting antibodies to double-stranded DNA (Table 2) are clinically useful.[20-22]

In the Farr assay, radiolabeled DNA is incubated with serum, and the DNA–anti-DNA complexes are precipitated with ammonium sulfate or polyethylene glycol. This assay may be the most specific test for systemic lupus erythematosus, and it is the assay most likely to predict the occurrence of disease flares, particularly flares of glomerulonephritis.[21,22] In the crithidia assay, antibodies to double-stranded DNA are detected by their ability to bind the kinetoplast of *Crithidia luciliae,* a protozoan organism with a double-stranded circular DNA structure at one pole. This assay detects antibodies to double-stranded DNA almost exclusively.

The enzyme-linked immunosorbent assay (ELISA) for antibodies to DNA is widely available and relatively easy to perform. In this assay, plastic wells in a microtiter plate are coated with double-stranded DNA and test serum is added. IgG antibodies bound to the double-stranded DNA are detected by adding enzyme-labeled antihuman IgG and then substrate, which changes color when acted on by the enzyme. Single-stranded breaks in the double-stranded DNA can occur during incubation. This assay detects both high- and low-affinity IgG antibodies to double-stranded DNA and can give a weakly positive result when antibodies to single-stranded DNA are present.

A strongly positive result with any of these assays for antibodies to double-stranded DNA supports the diagnosis of systemic lupus erythematosus, and in some patients it predicts exacerbations of the disease. Since antibodies other than anti-DNA antibodies can be found in the glomeruli of patients with systemic lupus erythematosus,[18] future tests for these non–DNA-binding antibodies may be useful. To date, assays measuring serum antibodies that bind to extracts of glomeruli, chromatin, nucleosomes, or other antigens are no more useful clinically than standard assays for antibodies to double-stranded DNA.

CLINICAL APPLICATIONS OF TESTS FOR ANTIBODIES TO DOUBLE-STRANDED DNA

Tests for antibodies to double-stranded DNA are useful in establishing the diagnosis of systemic lupus

TABLE 2. CLINICAL ASSAYS FOR SERUM ANTIBODIES TO DNA.

ASSAY	ANTIGEN	COMMENTS
Farr	Radiolabeled double-stranded DNA	Assay does not discriminate between IgM and IgG antibodies to DNA. High titers are diagnostic of systemic lupus erythematosus if other disease features are present. Changes in titer may be the best predictor of impending disease exacerbation, particularly glomerulonephritis or vasculitis.
Crithidia	Double-stranded DNA polar body of *Crithidia luciliae*	Antibodies to single-stranded DNA are not detected, an advantage. High titers are diagnostic of systemic lupus erythematosus if other disease features are present. In some patients, titers correlate with disease activity.
ELISA	Double-stranded DNA, mammalian or bacterial	Assay is widely used because it is easy to perform. High titers are diagnostic of systemic lupus erythematosus if other disease features are present. In some patients, titers correlate with disease activity.

erythematosus. Between 60 percent and 83 percent of patients with systemic lupus erythematosus are found to have antibodies to double-stranded DNA when they are tested by the Farr assay, the crithidia assay, or ELISA at some time during their illness.[20-22] Patients with positive tests for antibodies to double-stranded DNA are considered to have one of three immunologic disorders according to the widely used American College of Rheumatology criteria for the classification of systemic lupus erythematosus, which were revised in 1997.[23,24] (The other immunologic disorders are antibodies to Sm and antibodies to phospholipids.) The presence of immunologic disorders constitutes 1 of the 11 criteria for systemic lupus erythematosus, with a positive test for antinuclear antibodies being a separate criterion. A patient who meets 4 of the 11 criteria can be classified as having systemic lupus erythematosus with approximately 95 percent specificity and 85 percent sensitivity.[25,26]

The ability of tests for antibodies to double-stranded DNA to predict exacerbations of systemic lupus erythematosus is controversial. Some studies suggest strong correlations between increasing levels of these antibodies and subsequent activation of disease,[21,22,27] but others suggest that such correlations are weak.[28,29] A small minority of patients with systemic lupus erythematosus have high titers of IgG antibodies to double-stranded DNA for prolonged periods without having exacerbations of disease or glomerulonephritis.[30] In general, when tests for serum antibodies to double-stranded DNA are performed at regular intervals, regardless of symptoms, rising titers suggest that the risk of exacerbation of disease is increased by a factor of approximately two to three in the subsequent three to four months; an abrupt, marked increase is usually followed by exacerbation within weeks.[22] Exacerbations of glomerulonephritis, vasculitis, or both are the disease manifestations most likely to be heralded by rising titers of antibodies to double-stranded DNA.[28,29] Falling plasma concentrations of total hemolytic complement (C3 and C4) can also precede an exacerbation.[6,20,25]

In some patients, the titer of antibodies to double-stranded DNA is an excellent measure of disease activity; in others, increasing disease activity is better measured by falling plasma complement concentrations, rising erythrocyte sedimentation rates, falling leukocyte counts, increasing urinary protein levels, or the occurrence of microscopic hematuria. For each patient, it is useful to establish the pattern of changes, if any, in laboratory test results that are associated with exacerbation, improvement, or remission of systemic lupus erythematosus. If a pattern associated with exacerbation appears in a patient, it is advisable to change therapy in order to prevent the exacerbation.[27]

ORIGIN OF ANTIBODIES TO DNA

Several mechanisms can lead to the production of antibodies to DNA (Table 3 and Fig. 1). Antibodies to single-stranded and double-stranded DNA are part of the normal repertoire of natural autoantibodies; most of these are low-affinity IgM antibodies that react weakly with several self-antigens.[31] However, these natural antibodies can undergo an isotype switch (from IgM to IgG) that increases their potential to be pathogenic. In addition, somatic mutations in the encoding immunoglobulin genes may result in the production of high-affinity IgG antibodies to DNA, the type of antibody most frequently linked to glomerulonephritis in patients with systemic lupus erythematosus.[11,12,31,32]

Antibodies to DNA can be induced in mice by the injection of irritating chemicals, such as pristane; by stimulation with antigens, such as bacterial DNA, bacterial cell-wall phospholipids, and viruses; and by stimulation by complexes of DNA and proteins.[13-16,33-36] These induced antibodies can then be deposited in the glomeruli, where damage may or may not result. Antibodies to DNA, particularly those that cause damage, are more readily induced by immunization of animals with DNA–protein complexes than by immunization with protein-free DNA.[35] The antigens that initiate the formation of potentially pathogenic antibodies to DNA may be chromatin (packages of nucleosomes connected by DNA linkers) or nucleosomes (166 to 240 base pairs of DNA wound around an octameric complex of several different types of histone).[14-16,18] Evidence of the central role of chromatin and nucleosomes includes the presence of antibodies to these substances in the serum of patients with systemic lupus erythematosus[14] and the ability of these macromolecular complexes to block the binding of serum immunoglobulins from patients with systemic lupus erythematosus to extracts of glomeruli.[18] In addition, nucleosome-activated T lymphocytes from patients with systemic lupus

TABLE 3. ORIGINS OF ANTIBODIES TO DNA.

Natural autoantibodies (normal repertoires of broadly self-reactive low-affinity antibodies)
Polyclonal B-cell activation
Specific antigenic stimulation
Bacteria (phospholipids, DNA, DNA–protein complexes)
Viruses
Chemical irritants (e.g., pristane)
DNA–protein complexes (e.g., nucleosomes, chromatin)
RNA–protein complexes
T-cell help
Activation by nucleosomal peptides
Activation by immunoglobulin peptides
Broadening cross-reactivity of vigorous immune responses
Determinant spreading in T and B lymphocytes
Degeneracy in the T-cell repertoire
Idiotypic network expansion

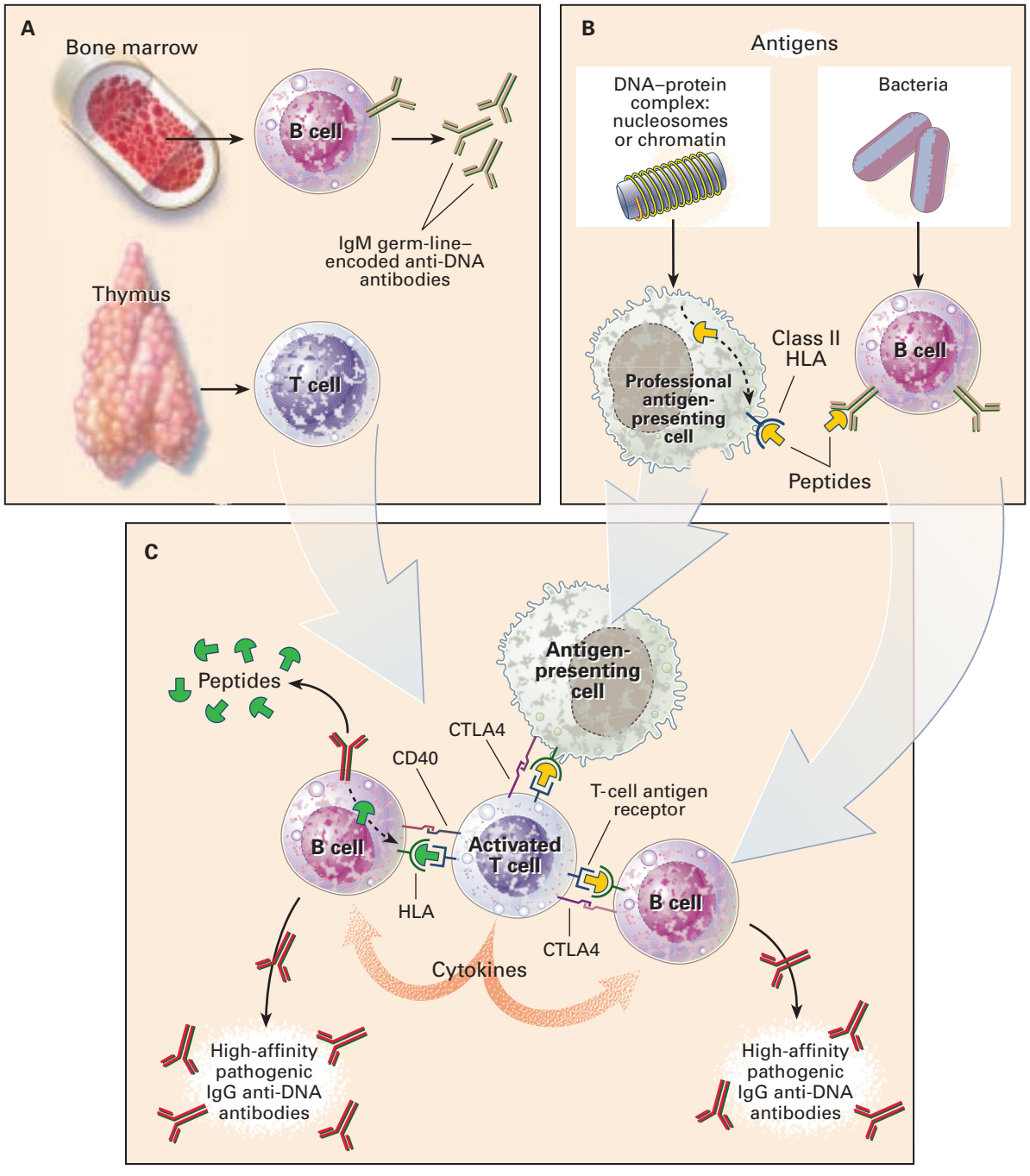


Figure 1. Origin of Pathogenic Antibodies to DNA.

Panel A shows a normal immune system, with B cells secreting low-affinity IgM antibodies to DNA, with little or no T-cell help. Panel B shows activation of the normal immune system by a self-antigen (DNA–protein complexes, shown as chromatin or nucleosomes) and an environmental antigen (shown as bacteria). These antigens are taken up by professional antigen-presenting cells or bind to antibodies (induced by the antigens) on the surface of the B cells. Both antigen-presenting cells and B cells process the antigens into peptides and present them to T cells as complexes with surface HLA molecules of the cells (Panel C). In addition, peptides from the immunoglobulin molecules themselves are presented (by the B cell on the left of Panel C). If second-signal molecules on the T cells are also linked with their ligands on B cells or antigen-presenting cells (the CD40 and CTLA4 systems are shown), the T cells become activated. By release of cytokines and by contact with B cells, those helper T cells cause the B cells to secrete high-affinity IgG antibodies to DNA, and disease may result.

erythematosus can help B lymphocytes produce IgG antibodies to DNA.[16,37]

The ability to make antibodies to chromatin, nucleosomes, and DNA depends in part on genetic susceptibility. For example, in one strain of lupus-prone mice, four regions on four different chromosomes are linked to the production of antibodies to chromatin.[38] In humans a region on chromosome 1 (1q41–42) may contain a gene or genes predisposing carriers to the production of antibodies to chromatin and predisposing them to systemic lupus erythematosus.[39]

In addition to DNA–protein complexes, RNA–protein complexes may induce antibodies to DNA. Immunization of rabbits with peptides from the RNA–protein complexes contained in small nuclear RNA particles can induce antibodies to DNA as well as antibodies to small nuclear RNA particles.[40] The processes by which the responses of T and B lymphocytes to one antigen expand to include reactivity to additional antigens depend on the degeneration of T-cell antigen receptors so that a single receptor binds more than one peptide–HLA complex (either more than one peptide is bound to one HLA molecule, or one peptide is bound to more than one HLA molecule). Expanded reactivity also depends on determinant spreading, in which expanding populations of T and B cells with different receptors recognize additional regions in the initiating antigen as the immune response matures. Both of these processes occur in human T cells in vitro.[41] Therefore, single T or B cells, initially activated by a single antigen, eventually respond to multiple self- and non–self-antigens.

Through these mechanisms, multiple exposures to bacterial, viral, or chemical antigens and to self-antigens (particularly nucleic acid–protein complexes) can lead to the formation of antibodies to DNA. In people genetically predisposed to systemic lupus erythematosus, some of the antibodies to DNA are pathogenic and the ability to down-regulate the production of those antibodies is defective; therefore, disease results. How do DNA–protein and RNA–protein complexes that should be tolerated by the immune system become immunogenic? In human cells stressed in certain ways, such as by exposure of keratinocytes to ultraviolet light, apoptosis occurs, and during apoptosis particles from the nucleus and cytoplasm are packaged in blebs of the cell membrane.[42] Some of these blebs contain RNA–protein complexes, such as the Ro(SSA) antigen, antibodies to which are associated with rash in patients with subacute cutaneous lupus and in neonates with lupus. Other blebs contain nucleosomes plus small nuclear RNA particles and Ro(SSA). Perhaps the immune system can react to these antigens when they are presented in this manner. In addition, nucleosomes released from dying cells could stimulate the production of antibodies to DNA. A relevant finding is that lymphocytes from patients with systemic lupus erythematosus release increased quantities of nucleosomes.[43]

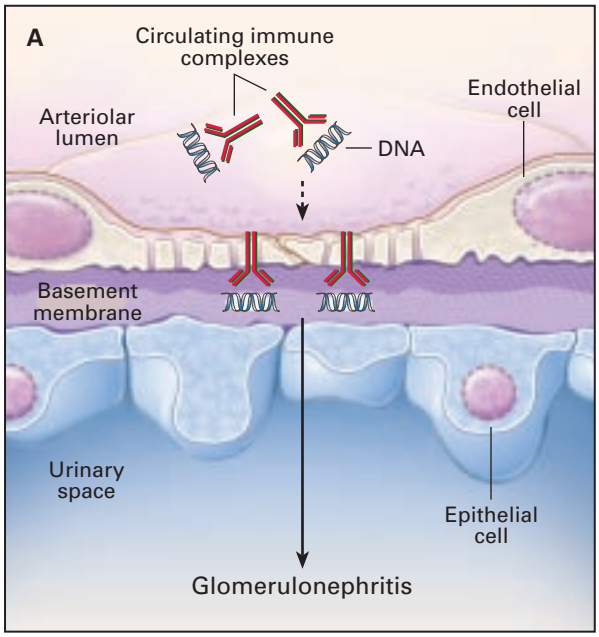
STRUCTURE OF ANTIBODIES TO DNA

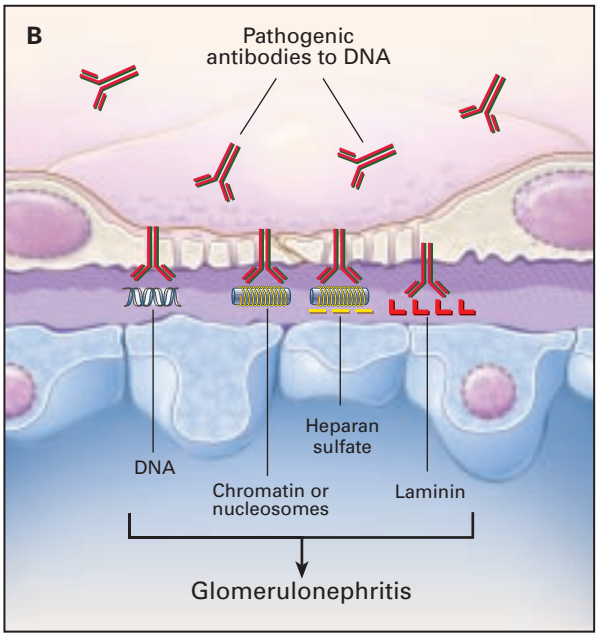
Segments of DNA that encode different portions of the immunoglobulin molecule join to form coding regions for the heavy and light chains of an antibody. The constant regions of the heavy chains determine the immunoglobulin isotype; the constant regions of the light chains determine whether they are of the kappa or the lambda type. The V regions determine antigenic specificity.[31] They are assembled from germ-line V_H, D_H, and J_H genes encoding heavy chains and V_L and J_L genes encoding light chains. The V regions of several human antibodies to DNA have been sequenced.[11,44-46] There is little evidence that unique germ-line genes encode these antibodies.[12,31,32,45,46] Instead, antibodies to DNA are the products of many different combinations of normal genes of the V, D, and J regions that encode the heavy and light chains. The clonality of B cells that produce antibodies to DNA is somewhat limited, but probably no more so than that of normal B cells stimulated by external antigens.[31,32,46,47]

Some antibodies to DNA are encoded from germline DNA and are unchanged, but the majority (particularly IgG) contain somatic mutations. This finding strongly suggests that many antibodies to DNA are produced in response to stimulation by specific antigens, although some arise from nonspecific stimulation of polyclonal B cells.[12,31,32,44-47] In many antibodies to DNA, the ability to bind DNA resides predominantly in the heavy chain, but the light chains can enhance or prevent binding.[31,44,48] How particular V-region sequences permit DNA binding is not fully understood: enrichment in certain amino acids, such as arginine, is critical to the binding of DNA in some, but not all, molecules.[31,47] Binding of antibodies to tissue antigens is probably increased if the antibodies contain positively or negatively charged amino acids and the antigens contain oppositely charged regions. Therefore, the enrichment of antibodies to DNA in charged amino acids may contribute to antigen specificity and to pathogenicity. In addition, several noncharged amino acids form hydrogen bonds with DNA.

THE ROLE OF ANTIBODIES TO DNA IN THE PATHOGENESIS OF DISEASE

Some antibodies to double-stranded DNA cause glomerulonephritis by forming complexes with DNA that are passively trapped in the glomeruli, whereas others cause glomerulonephritis by direct attachment to glomerular structures (Fig. 2). Antibodies to DNA can be eluted from diseased glomeruli and





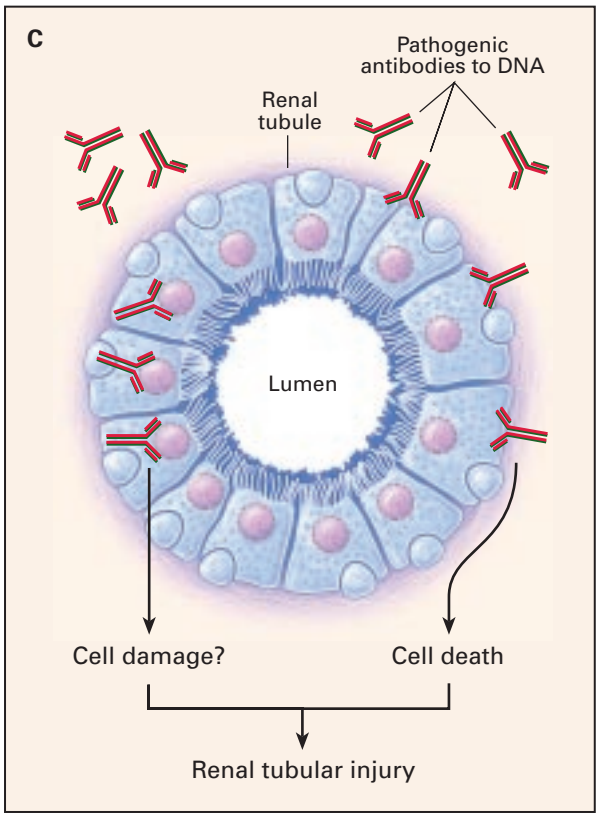


Figure 2. Three Mechanisms by Which Antibodies to DNA Cause Tissue Damage.

Panel A shows the entrapment of circulating immune complexes in glomerular-capillary basement membrane. Panel B shows the direct binding of pathogenic subgroups of anti-DNA to components of glomerular-capillary basement membrane. Panel C shows damage to living cells resulting from binding of anti-DNA to their surfaces or entry into the cells to bind to their nuclei. In Panel A, circulating complexes of DNA and anti-DNA in blood are trapped in the basement membrane of glomerular capillaries, where they fix complement (not shown) and damage tissue. In Panel B, pathogenic subgroups of antibodies to DNA (or those antibodies bound first to DNA and then to nucleosomes) bind to components of glomerular-capillary basement membrane or to antigens trapped in the membrane. These antigens may include DNA, nucleosomes, heparan sulfate, and laminin. Complement is fixed and activated, causing tissue damage. In Panel C, pathogenic subgroups of antibodies to DNA bind to renal tubular epithelial cells. If they remain attached to cell membranes, they induce complement-mediated cell death. If they gain access and bind to the nuclei of living cells, they probably alter cell function, but the exact effects are not known. This process probably results in tissue damage.

other tissues in some patients with systemic lupus erythematosus,[19] suggesting that these antibodies cause tissue damage. High titers of serum antibodies to double-stranded DNA were correlated with the presence of active systemic lupus erythematosus and especially with glomerulonephritis in many studies.[4,6,20-22,25,27] Serum samples from some patients with lupus glomerulonephritis (and also from some without nephritis) contain immunoglobulins that bind to extracts of human glomerular basement membrane[18]; pretreatment of the extracts with DNase abolishes much of the reactivity. This suggests that antibodies to DNA cause nephritis by binding to DNA planted in components of glomerular basement membrane. In normal mice, lupus-like glomerulonephritis can be induced by the transfer of monoclonal mouse antibodies to DNA[49] or by the introduction into the germ line of genes encoding the heavy and light chains of a murine IgG antibody to double-stranded DNA.[50] Some human monoclonal antibodies to DNA produced by B-cell hybridomas transplanted into mice with severe combined immunodeficiency cause glomerulonephritis.[51]

It is not clear what features distinguish pathogenic from nonpathogenic antibodies to DNA. Complement fixation may be essential for tissue damage; thus IgG1 and IgG3, which fix complement, are enriched in pathogenic antibodies.[4-6] However, IgG2 antibodies as well as IgG1, IgG3, and IgM antibodies to DNA are found in glomerular lesions of patients with lupus glomerulonephritis.[52] Among blacks in the United States and whites in the Netherlands, subjects with lupus glomerulonephritis are more likely than normal subjects to have alleles for FcRIIa that bind the Fc portions of IgG2 more weakly than do the Fc receptors in normal subjects.[53,54] In blacks and whites in the United States, inheritance of an allele encoding FcRIIIa receptors predisposes them to systemic lupus erythematosus and its nephritis.[55] Taken together these data suggest that a decrease in the ability of mesangial cells and cells of monocyte–macrophage lineage to bind or phagocytize immune complexes containing IgG1, IgG2, or IgG3 predisposes such people to lupus nephritis. Cationic charge gives an antibody to DNA a pathogenic advantage,[56] probably because the antibody binds to negatively charged molecules in glomerular basement membrane. High affinity for DNA also probably gives a pathogenic advantage to an antibody,[19] at least in terms of inducing glomerulonephritis. Immunoglobulins deposited in lupus lesions are enriched in idiotypes that are commonly present in antibodies to DNA; these idiotypes may serve as markers of pathogenic antibodies.[57-60]

Some antibodies to DNA from patients with systemic lupus erythematosus bind to membranes of living cells in vitro, penetrate the cells (probably through the myosin in cell membranes), and bind to cytoplasmic or nuclear structures (Fig. 2).[61-63] The consequences of this cell penetration are not known, but it could influence cell proliferation, protein synthesis, and apoptosis. The ability of antibodies to DNA to bind additional antigens in glomerular basement membrane (such as C1q or nucleosomes bound to type IV collagen, for example) or tissue components of glomeruli or vessel walls (such as laminin or heparan sulfate) may be a major determinant of pathogenicity.[17,18,64] Antibodies to DNA that bind nucleosomes seem to be particularly pathogenic, because they can bind heparan sulfate (probably because of the positive charges on nucleosomes), and they can bind nucleosomes trapped in type IV collagen in glomerular basement membrane.[14-16,18,49,64] Binding of serum immunoglobulin from patients with systemic lupus erythematosus to extracts of glomerular basement membrane is inhibited more effectively by nucleosomes than by protein-free DNA.[18] Thus, there are several mechanisms by which antibodies to DNA can damage glomeruli and probably other tissues as well.

REGULATION OF PRODUCTION OF ANTIBODIES TO DNA

Why does the immune system in a patient with systemic lupus erythematosus permit dangerous self-reactive antibodies to persist? The production of IgG antibodies to DNA requires interactions between B cells, which produce the antibodies, and helper T cells, which activate the synthesis and secretion of antibodies by B cells.[10,37,65] In patients with systemic lupus erythematosus, both CD4 T cells (which normally act as helpers) and CD8 and double-negative (CD4−CD8−) T cells activate the synthesis and secretion of antibodies.[37,65] Therefore, cells that normally suppress the activation of B cells, the CD8 T cells and natural killer cells, are defective in their suppressive activity.

The hyperactivity of T-cell help is well illustrated in mice and humans with lupus, in which peptides processed from autoantibodies to DNA activate helper T cells, a process that in turn causes increased synthesis of pathogenic antibodies to DNA.[66,67] In normal mice, in contrast, T cells are not spontaneously activated by immunoglobulin-derived peptides, and the mice have regulatory cells that suppress the synthesis of antibodies to DNA.[67]

Clearing of immune complexes by phagocytic cells is also defective in patients with systemic lupus erythematosus.[53,68] This is due in part to reduced numbers of CR1 receptors for complement on cell surfaces.[69] Defective clearance also may be due to inadequate phagocytosis of IgG2- and IgG3-containing complexes, as discussed above.[53-55] The idiotypic networks that prevent overproduction of antibodies in normal subjects are probably defective in patients with systemic lupus erythematosus.[70,71]

EXPERIMENTAL THERAPIES FOR SYSTEMIC LUPUS ERYTHEMATOSUS THAT REGULATE THE PRODUCTION OF ANTIBODIES TO DNA

Most current immunosuppressive treatments for systemic lupus erythematosus, including glucocorticoids and cytotoxic drugs, suppress the production of antibodies to DNA while suppressing the activity of the clinical disease. Administration of antibodies that nonspecifically deplete or inactivate helper CD4 T cells suppresses the production of antibodies to DNA and prevents or reverses glomerulonephritis in mice with systemic lupus erythematosus[72]; however, these antibodies to T cells have been less effective in humans with autoimmune diseases. Since these therapies are nonspecific and have undesirable side effects, particularly infections, investigators are testing strategies designed to suppress the production or increase the clearance of selected autoantibodies in patients with systemic lupus erythematosus. These strategies include immunoabsorption of antibodies to DNA by plasmapheresis over columns containing immobilized DNA,[73] intravenous administration of immune globulin enriched for antiidiotypes that bind many of the idiotypes present on human antibodies to DNA,[74] and induction of immune tolerance to DNA by injections of nucleosides displayed on a tetrameric scaffold. Injections of an antigen presented in this physical conformation induced tolerance rather than immunity. This preparation lowers serum titers of antibodies to DNA in patients with systemic lupus erythematosus.[75]

Whether or not the production of many of the antibodies characteristic of systemic lupus erythematosus, such as anti-DNA, anti–RNA particles, anti-Sm, and anticardiolipin, is linked, as suggested by experiments in animals, to inhibition of activated T cells (while leaving resting memory T cells intact to deal with infections) might reduce the production of all pathogenic autoantibodies and suppress disease activity. There is substantial interest in interrupting the second signals required for T-cell activation as a way to achieve this suppression. Thus, interruption of interactions between CD40 on B cells and CD40 ligand (CD40L) on activated T cells, or between CD80 and CD86 on activated B cells and their ligand CTLA4 on activated T cells, suppresses the production of antibodies to DNA and prevents glomerulonephritis in murine systemic lupus erythematosus.[76,77] Finally, treatments that alter cytokine release and thus reduce inflammatory and immune responses, which are currently under investigation in patients with rheumatoid arthritis, might also be applied to patients with systemic lupus erythematosus and could prove to be more effective than therapy that targets antibodies to DNA.

CONCLUSIONS

Antibodies to double-stranded DNA are characteristic of human and murine systemic lupus erythematosus. They are good markers of the disease, and some subgroups of the antibodies cause renal and vascular injury. Most of these subgroups are IgG antibodies to double-stranded DNA, and sustained production of these antibodies is dependent on T-cell help and occurs in persons with multiple susceptibility genes. Single measurements of serum titers of antibodies to double-stranded DNA are useful in the diagnosis of systemic lupus erythematosus; serial measurements are often useful in identifying patients at risk for exacerbations of glomerulonephritis or vasculitis. Current research is targeted to specific suppression of the production of antibodies to DNA as a means to suppress the clinical activity of the disease. Such therapy should have fewer adverse effects than the broadly immunosuppressive therapies used now.

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