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J Clin Invest. 1991;87(3):842-846. https://doi.org/10.1172/JCI115088.

Research Article

There is evidence in both murine and human lupus that the production of anti-DNA antibodies may be triggered by environmental antigens. To explore this further, we studied the serum of 10 nonautoimmune individuals immunized with a polyvalent pneumococcal polysaccharide vaccine. All 10 patients showed a rise in the titer of antipneumococcal antibodies bearing an anti-DNA-associated idiotype. The antipneumococcal response was specific as no idiotypic antitetanus antibodies were detected. Furthermore, no anti-DNA antibodies were present in postvaccination sera. The molecular analysis of antipneumococcal and anti-DNA antibodies bearing a common idiotype will help elucidate how foreign antigen might lead to the production of anti-DNA antibodies in susceptible individuals.

Antibodies Elicited by Pneumococcal Antigens Bear an Anti-DNA-Associated Idiotype

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Abstract

There is evidence in both murine and human lupus that the production of anti-DNA antibodies may be triggered by environmental antigens. To explore this further, we studied the serum of 10 nonautoimmune individuals immunized with a polyvalent pneumococcal polysaccharide vaccine. All 10 patients showed a rise in the titer of antipneumococcal antibodies bearing an anti-DNA-associated idiotype. The antipneumococcal response was specific as no idiotypic antitetanus antibodies were detected. Furthermore, no anti-DNA antibodies were present in postvaccination sera. The molecular analysis of antipneumococcal and anti-DNA antibodies bearing a common idiotype will help elucidate how foreign antigen might lead to the production of anti-DNA antibodies in susceptible individuals. (*J. Clin. Invest.* 1991. 87:842–846.) Key words: antibody • idiotype • antipneumococcal • anti-DNA

Introduction

Over the past several years much has been learned about the serologic and molecular characterization of autoantibodies. Idiotypic studies have demonstrated a relationship between autoantibodies and antibodies against foreign antigen (1–4). These studies have led to the hypothesis that there is a genetic relationship between autoantibodies and antibodies to foreign antigens, with the same immunoglobulin variable region genes encoding both pathogenic and protective antibodies. It has been shown that the same monoclonal antibody may bind to both an autoantigen, DNA, and to microbial antigens (5–8). Furthermore we have previously demonstrated that a protective antibody may somatically mutate to acquire autoreactivity (4). The S107 mouse myeloma cell line produces an antiphosphorylcholine antibody protective against a lethal pneumococcal infection; a single amino acid substitution in the S107 antibody leads to a marked reduction in binding to phosphorylcholine and an acquisition of DNA binding activity. These observations have raised questions about the role of microbial antigens in the pathogenesis of certain autoimmune diseases. Microbial antigens might elicit an antibody response in which the antibodies to the foreign antigens also bind autoantigen. Antimicrobial antibodies might mutate to bind autoantigen. Finally, it is possible that a microbial antigen could initiate an idiotypic network leading to the production of autoantibodies idiotypically and genetically related to the antimicrobial antibodies.

We have been studying the anti-DNA antibodies present in patients with systemic lupus. Using a murine monoclonal antiidiotype, 3I, we have identified a cross-reactive idiotype present on kappa light chains of anti-DNA antibodies in a large number of unrelated patients with lupus (9, 10). Not all 3I-positive antibodies in the serum, however, bind DNA (11). 3I-positive antibodies in normal individuals are not DNA binding and in lupus patients only 50% of 3I-positive antibodies bind DNA. Because of data in the murine system showing that antiphosphorylcholine antibodies can be encoded by the same germ line immunoglobulin genes as antibodies to double-stranded DNA, we studied expression of the 3I idiotype in the serum of individuals before and after immunization with a polyvalent pneumococcal vaccine (Pneumovax; Merck, Sharpe, and Dohme, Rahway, NJ). We report here the production of 3I-positive antibodies against pneumococcal antigens after immunization.

Methods

Sera. Serum was obtained from 10 patients seen in the rheumatology clinic at Montefiore Hospital, Bronx, NY. Six patients had degenerative joint diseases, two patients had gout, one patient had polymyalgia rheumatica, and one patient had sero-negative polyarthritis. All patients were immunized for clinical indications following guidelines issued by the outpatient department clinic director and gave informed consent for serial blood samples to be drawn. Samples were obtained just before immunization with Pneumovax and 3 wk after immunization.

Control sera were obtained from 20 medical students without regard to medical history.

Serologic assays. 3I is a murine monoclonal antibody that recognizes anti-DNA antibodies in ~ 70–80% of patients with systemic lupus and anti-DNA activity. The antiidiotype binds to a determinant on kappa light chains. In lupus sera only about half of the 3I-reactive antibodies bind DNA.

Total 3I reactivity was determined by adsorbing serum, diluted 1:300 in 0.02 M PBS pH 7.4, to microtiter wells. At this dilution saturating amounts of immunoglobulin are present and differences in total serum IgG are not relevant (9). Wells were blocked with 3% FCS PBS. Culture supernatant containing the murine monoclonal 3I antibody was added to the plates for 60 min at room temperature. Following three washes, a radiolabeled antibody to mouse kappa chain was added for 60 min at room temperature. The wells were washed and radioactivity was quantified in a scintillation counter.

Antibody reactivity to pneumococcal antigen was determined in an ELISA. Pneumovax, 15 μg in 0.1 ml PBS, was adsorbed to microtiter wells overnight at 4°C. Patient serum at 1:10 or 1:20 dilutions was added to the wells for 60 min at room temperature. Following three washes with PBS 0.05% Tween, peroxidase conjugated goat anti-hu-

This work was presented in part as a poster at the American College of Rheumatologists' Northeast Regional Meeting, New York, May 1990.

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Received for publication 11 May 1989 and in revised form 4 September 1990.

J. Clin. Invest.

0021-9738/91/03/0842/05 $2.00
Volume 87, March 1991, 842–846

man IgG plus IgM (Kirkegaard & Perry Laboratories, Inc., Gaithersburg, MD) was added for 60 min. The wells were washed and 2,2' azino-di-(3 ethyl benzthiazoline sulfonate) (ABTS) substrate was added. Wells were read in an automated ELISA reader (Flow Laboratories Inc., McLean, VA).

3I-positive antibodies to Pneumovax were assayed in a similar manner except that after the incubation with human serum, 3I culture fluid was added for 60 min. The wells were washed three times. A peroxidase-linked antibody to mouse IgG, non–cross-reactive to human IgG, (Kirkegaard & Perry) was then added for 60 min, followed by ABTS substrate.

Antibody to individual polysaccharide antigens was also determined by ELISA. Each of the 23 component antigens at a concentration of 15 μg/well was adsorbed to microtiter plates. Varying dilutions of serum were added followed by a peroxidase conjugated goat antiserum to human IgG and IgM (Kirkegaard and Perry Laboratories). ABTS substrate was added and the assay read in an ELISA reader.

3I-positive antibodies to individual pneumococcal antigens were also determined by ELISA. Each of the 23 component antigens, at a concentration of 15 μg in 0.1 ml PBS, was adsorbed to microtiter plates overnight at 4°C. Wells were blocked with 5% FCS-PBS. Sera diluted at 1:30 were then added, followed by 3I ascites diluted 1:50 in PBS. A peroxidase-conjugated sheep antiserum to mouse IgG that has no cross-reactivity to human IgG (Cappel Laboratories, Cochranville, PA) was next added. The assay was read in an ELISA reader at 405 nm after the addition of ABTS substrate.

Antitetanus reactivity was determined in an analogous manner. Tetanus toxoid, 100 μg/well in PBS, was adsorbed to microtiter plates. Dilutions 1:10 of human sera were then added to the wells. After washing with PBS-Tween, wells were incubated with either peroxidase-linked goat antibody to human IgG plus IgM (Kirkegaard & Perry) followed by substrate, or with 3I supernatant, followed by peroxidase-linked antibody to mouse IgG followed by substrate.

DNA binding assay. Anti-DNA activity was determined by an ELISA as previously described (12). Sera at varying dilutions were incubated on disks coated with double-stranded DNA. An enzyme-linked antibody to human immunoglobulin was added, followed by substrate. Reactivity was recorded in international units obtained with a standardized control serum.

Antibody to single-stranded DNA was also determined by ELISA. Microtiter wells were coated with ssDNA at a concentration of 5 μg/ml. Sera were diluted 1 to 20 and incubated in the wells. Peroxidase-conjugated anti–human Ig was added, followed by substrate.

Results

The 3I antiidiotype recognizes a determinant on kappa light chains of anti-DNA antibodies in a high percentage of individuals with systemic lupus erythematosus (SLE) and anti-DNA activity. The titer of 3I-reactive antibodies is high not only in patients with SLE but also in unaffected family members of patients with SLE. In most of these individuals, the 3I-reactive antibodies do not bind DNA. Even in SLE patients approximately half of the 3I-reactive antibodies are not DNA binding. To determine the antigenic specificity of 3I-reactive antibodies that do not bind DNA and to determine if the 3I idiotype system might participate in an antibacterial response, we assayed individuals for changes in 3I reactivity after immunization with Pneumovax. All sera were assayed for 3I reactivity before and 3 wk after Pneumovax immunization. As shown in Table I, all sera showed normal titers of 3I reactivity before immunization. There was no increase in 3I reactivity after immunization.

When antipneumococcal antibodies were assayed, we found that all patients showed increases in antipneumococcal activity after immunization (Table II). Finally, we assayed the antipneumococcal antibodies for 3I reactivity. 3I-reactive antipneumococcal antibodies were present in all individuals after immunization (Table III). In Fig. 1, the rise in total anti-Pneumovax activity is compared with the rise in 3I reactive anti-Pneumovax antibodies in all immunized individuals. While only a small percentage of total immunoglobulin bears the 3I idiotype and no major increase in idiotype titer is seen postimmunization, it is apparent that a substantial portion of the anti-Pneumovax antibodies bear the 3I idiotype and that the titer of 3I-positive anti-Pneumovax antibodies does increase with immunization.

To identify those antigens in the vaccine against which 3I-positive antibodies were produced, we assayed sera from 7 patients for 3I-reactive antibodies against each of 23 pneumococcal polysaccharide antigens. While each patient developed titers of 3I-reactive antibodies to some of the antigens, there was no consistent pattern of reactivity. For example, for patient IC, the titer of 3I-reactive antibodies to polysaccharide 2 rose

Table I. 3I Reactivity by Radioimmunoassay of Sera Before and 3 Wk after Pneumovax

Patient	Pre	Post
	cpm	
LB	2738	1834
IC	2464	2456
LG	2718	2147
LH	2699	1313
TJ	1861	1810
RL	2135	1984
LM	2463	2321
PR	2833	2933
CS	2514	2249
JS	2283	2024

Mean reactivity of control sera was 1946±510. All serum samples had 31 reactivity within the normal range (i.e., < 2 SD above the mean of control sera).

Table II. IgG and IgM Binding to Pneumovax

Patient	Pre	Post
	OD 405	
LB	0.105	0.268
IC	0.032	0.070
LG	0.022	0.118
LH	0.039	0.191
TJ	0.021	0.042
RL	0.009	0.066
LM	0.026	0.068
PR	0.067	0.142
CS	0.044	0.097
JS	0.016	0.044

Serum at a 1:20 dilution was incubated on Pneumovax adsorbed wells. An enzyme-linked antibody to human IgG and IgM was added followed by substrate. Net absorbance is shown after subtracting blank (no human serum) of 0.026.

Table III. 3I Reactivity of Pneumovax-binding Antibodies

Patient	Pre	Post
	OD 405	
LB	0.170	0.780
IC	0.072	0.350
LG	0.035	0.318
LH	0.096	0.578
TJ	0.072	0.158
RL	0.024	0.219
LM	0.0	0.078
PR	0.041	0.358
CS	0.064	0.225
JS	0.021	0.083

Patients' sera were incubated at a 1:20 dilution on Pneumovax adsorbed wells. 3I culture supernatant was added followed by an enzyme-linked antibody to mouse IgG. The binding of an irrelevant isotype matched murine antibody (MOPC 21) was never greater than OD 0.028 implying that the serum samples contained no rheumatoid factor activity. Net absorbance after subtraction of blank (0.028) is shown.

from OD.264 to OD.483, but patient TJ showed a slight decline in titer from OD.432 to OD.384. Similarly for polysaccharide 9V, LH showed a rise in titer of 3I reactive antibodies from OD.512 to OD.905, while TJ showed a drop from OD.626 to OD.452.

To determine if the 3I-positive antipneumococcal antibodies represented an antigen-specific rise in 3I-positive antibodies, we tested these sera for antibodies to tetanus toxoid. As shown in Table IV, there was no rise in antibody binding to tetanus toxoid after Pneumovax immunization and similarly, except in patient TJ, there was no increase in the binding of 3I-positive antibodies to tetanus toxoid. Only patient LH showed substantial titers of anti-tetanus toxoid antibodies; however, neither before nor after immunization was there evidence of 3I-positive antitetanus antibodies in this individual. While there was an increase in 3I-reactive antipneumococcal antibodies, there was no increase in 3I-reactive antibodies to an irrelevant antigen.

To determine if 3I-positive anti-DNA antibodies were present after Pneumovax immunization, we tested sera for anti-DNA activity (Table V). Only normal titers of anti-DNA activity were present and there were no increases following immunization. When sera were tested for 3I-positive anti-DNA antibodies, there was similarly no increase detected after immunization (data not shown). Sera were tested for reactivity with single-stranded DNA. No change in anti-ssDNA activity was detectable as a consequence of Pneumovax immunization (Table VI).

Discussion

In an in vitro system we had previously shown that an antibody to pneumococcal polysaccharide can undergo somatic mutation to acquire specificity for DNA. This paradigm suggested that microbial antigens could trigger production of autoantibodies. This study was therefore undertaken to see if immunization with pneumococcal antigen could lead to production of anti-DNA antibodies or of antibodies bearing an anti-DNA–associated idiotype. The results demonstrate that while anti-DNA activity did not develop postimmunization, in most individuals there was an increase in expression of 3I-reactive antipneumococcal antibodies. These data suggest that some 3I-reactive antibodies are indeed directed to microbial antigens.

It was not possible to identify one or even a few polysaccharide antigens that dominate the response. Each serum tested displayed an individual pattern of antigenic reactivity, suggesting a spectrum of related antigenic specificities within the 3I idiotype system.

It is clear that microbial antigens can elicit 3I-reactive antibodies. Therefore it is possible, as we have hypothesized, that in susceptible individuals these antibodies can mutate to become DNA binding. It is now possible to test this hypothesis by com-

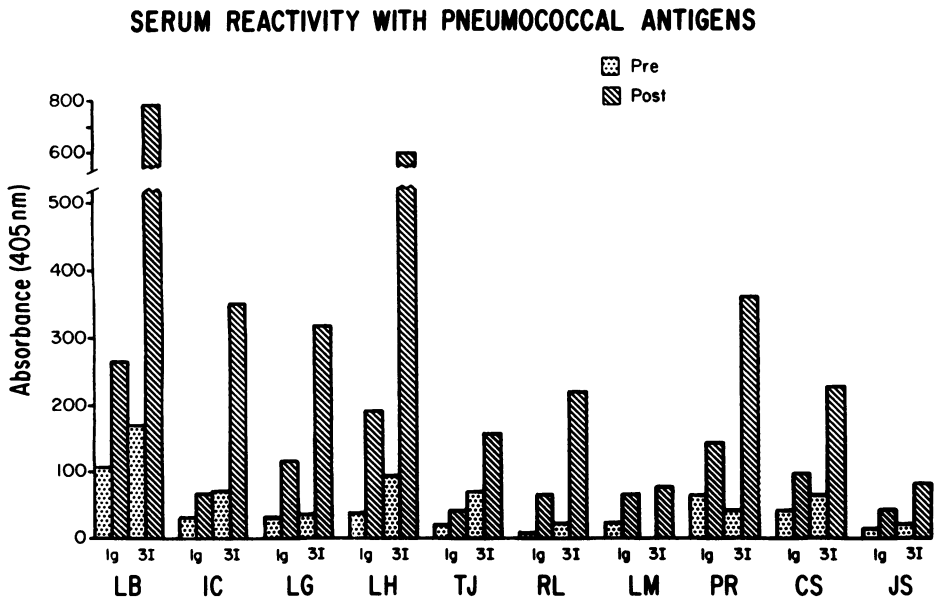

Figure 1. Serum samples before and after immunization with Pneumovax were assayed for antipneumococcal activity (*Ig*) and for 3I-reactive antipneumococcal activity (*3I*).

Table IV. Anti-Tetanus Toxoid Activity Pre and Post Immunization with Pneumovax

Patient	IgG and IgM		3I	
	Pre	Post	Pre	Post
	OD 405			
LB	0.208	0.168	0.057	0.059
LC	0.242	0.242	0.048	0.058
LG	0.227	0.177	0.058	0.076
LH	1.360	1.280	0.071	0.057
TJ	0.570	0.461	0.053	0.104
RL	0.174	0.145	0.060	0.062
LM	0.388	0.334	0.113	0.100
PR	0.240	0.166	0.068	0.084
CS	0.463	0.284	0.055	0.113
JS	0.233	0.225	0.067	0.060

Patients' sera diluted 1:20 were incubated on tetanus toxoid adsorbed wells. Either an enzyme-linked antiserum to human IgG and IgM was added followed by substrate or 3I culture supernatant was added, followed by an enzyme-linked antibody to mouse IgG and substrate. While some patients had high titers of antitetanus antibodies, there was no increase in 3I-reactive antibodies binding tetanus toxoid after Pneumovax immunization. Net absorbance after subtraction of blank (0.076 for IgG and IgM and 0.045 for 3I) is shown.

paring the nucleic acid sequences encoding 3I-reactive anti-DNA antibodies to those encoding 3I-reactive antibodies that bind to pneumococcal antigens and to germ line sequences that encode 3I reactivity.

The role of microbial antigens in triggering autoantibody production is a very important question. There is a sizeable body of data suggesting that environmental antigens may play a role in triggering anti-DNA responses. The search for a microbial trigger stemmed in large part from experiments showing that DNA itself is poorly immunogenic (13). Subsequent

Table V. Anti-DNA Antibodies Before and After Pneumovax Immunization

Patient	Pre	Post
	OD 405	
LB	0.164	0.100
IC	0.170	0.117
LG	0.251	0.305
LH	0.172	0.107
TJ	0.180	0.160
RL	0.242	0.226
LM	0.267	0.140
PR	0.320	0.286
CS	0.164	0.161
JS	0.136	0.153

Sera was incubated with disks coated with double-stranded DNA. Antibody to human Ig was added followed by substrate. In this assay the binding of normal serum to dsDNA demonstrated an OD < 0.450. There was no increase in anti-DNA activity after Pneumovax immunization.

Table VI. Anti-ssDNA Activity Before and After Immunization with Pneumovax

Patient	Pre	Post
	OD 405	
LB	0.501±0.037	0.586±0.071
IC	0.513±0.098	0.597±0.120
LG	0.638±0.093	0.532±0.032
LH	0.621±0.042	0.643±0.091
TJ	0.393±0.023	0.403±0.105
RL	0.477±0.068	0.500±0.074
LM	0.533±0.127	0.483±0.094
PR	0.350±0.050	0.413±0.047
CS	0.469±0.040	0.473±0.033
JS	0.535±0.016	0.637±0.093

Serum was diluted 1:20. Mean reactivity of normal sera was 0.379±0.170. No increase in anti-ssDNA activity was detectable following immunization. The slightly higher anti-ssDNA activity of the test group probably reflects their increased age compared with the normal controls.

studies showed that NZB/W mice raised in a germ-free environment develop markedly lower titers of anti-DNA antibodies and less severe glomerulonephritis (14). This observation suggests that without appropriate microbial antigens anti-DNA production is diminished. Furthermore, NZB/W mice given the xid mutation, a mutation that makes mice unable to respond to carbohydrate antigens, show a marked reduction in serum anti-DNA antibodies (15).

In human studies it has been demonstrated that individuals with Klebsiella infections produce increased titers of antibodies to single-stranded DNA (16). This study is similar to ours in showing that a microbial antigen can trigger production of autoantibody-associated idiotypes but differs from ours in that anti-DNA antibodies developed in these normal individuals. This difference may reflect differences in the assays for anti-DNA activity, differences in antigen, or differences in the nature of the antibody responses.

The identification of an eliciting antigen for anti-DNA antibodies is consistent with recent studies in mice from several laboratories and recent human studies from our own laboratory suggesting that human anti-DNA antibodies appear to have characteristics of antibodies in a secondary immune response reflecting antigen selection (17–19). The lack of DNA binding by the induced 3I-reactive antibodies can be interpreted in three ways. It is possible that 3I-reactive DNA-binding antibodies do arise in response to Pneumovax vaccination but are downregulated in normal nonautoimmune individuals. Alternatively, there may be polymorphisms of the genes encoding 3I-reactive antibodies such that in most individuals 3I-reactive antibodies do not have anti-DNA activity and do not easily mutate to acquire DNA binding. Finally, it is possible that as there is selection for higher affinity 3I-reactive antimicrobial antibodies, there is a concomitant selection away from DNA binding. Such a model has been proposed in studies of murine antibodies that in a germ line configuration bind DNA but in the somatically mutated clonal progeny of the germ line encoded antibodies, selected for increased affinity to the hapten azophenylarsonate, show reduced DNA binding (20). A study

of the appropriate genes in autoimmune and nonautoimmune individuals can help resolve this problem.

Acknowledgments

We would like to thank Victoria Pascente for technical assistance and Rosalia Cawley for preparation of the manuscript.

This work was supported by National Institutes of Health grant AR-32371, and National Cancer Institute grant CA13330. Dr. Solomon is a fellow of the SLE Foundation. Dr. Aranow is the recipient of an American Cancer Society Physician Researcher Training Fellowship.

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