HUMAN RHEUMATOID FACTORS BEAR THE INTERNAL IMAGE OF THE Fc BINDING REGION OF STAPHYLOCOCCAL PROTEIN A

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Rheumatoid factors (RFs)[1] are autoantibodies that bind to antigenic determinants on the Fc portion of autologous IgG found in sera and synovial fluids of most patients with adult rheumatoid arthritis (RA). These antibodies are not specific for RA and are seen in other autoimmune conditions, as well as in patients with certain bacterial, viral, and parasitic infections, and at low titer in many normal individuals. The inciting stimuli and mechanisms for their production in each of these situations are unknown.

Recent studies (1, 2) have shown that the site on IgG Fc regions that binds to IgG and IgM RFs from patients with RA is in the same location and involves some of the same amino acid residues as the site that binds to staphylococcal protein A (SPA). Streptococcal Fc binding proteins also appear to bind to the same location (3, 4), and Fc binding proteins with the same specificity have been demonstrated on cells infected with herpes virus type I (5).

The binding site similarities between RFs and microbial Fc binding proteins suggested conformational similarities between the antigen-combining site of RFs and the Fc binding sites of these microbial structures (1, 4). In this report we demonstrate that antibodies to SPA bind to a shared idiotypic determinant on human IgM and IgG RFs, indicating that RFs carry the internal image of this bacterial Fc binding protein.

Materials and Methods

Preparation of IgM and IgG RFs and Non-RF Igs and Fc Fragments. IgM and IgG RFs from patients with RA were isolated using previously described methods (1, 6). Briefly, sera from patients with RA were passed over IgG affinity columns in borate buffer (0.2 M borate, 0.15 M NaCl, pH 8.8), and the adsorbed RFs were eluted with 0.1 M acetate, pH 3.5. The eluted RFs were then gel filtered on Sephacryl S-300 (Pharmacia Fine Chemicals, Piscataway, NJ) in acetate buffer (0.1 M acetate, 0.15 M NaCl, pH 3.5) to separate IgM RFs and IgG RFs. Serum containing a monoclonal IgM with RF activity from a patient with a lymphoproliferative disorder (Jan) was provided by Dr. Harvinder Luthra, Mayo Clinic, Rochester, MN. Jan IgM RF was prepared by affinity chromatog-

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[1] *Abbreviations used in this paper:* RA, rheumatoid arthritis; RF, rheumatoid factor; SPA, staphylococcal protein A.

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raphy and gel filtration as described for RA sera. Isolated RFs were then dialyzed into borate buffer. Some isolated RFs were stored at −70°C before use.

IgM RFs from patients with cryoglobulinemia were isolated by cryoprecipitation. Cryoprecipitates were washed three times with chilled borate buffer, solubilized, and gel filtered on Sephacryl S-300 in acetate buffer, or applied to an HPLC (Waters Associates, Milford, MA) gel filtration column (Protein Pak 300 SW; Waters Associates) equilibrated in acetate buffer, pH 3.5. RF activity of the isolated proteins was assayed by latex agglutination or by ELISA. Plasma from patients Les and Pal were provided by Dr. Dennis Carson, Scripps Clinic and Research Foundation, La Jolla, CA.

Non-RF IgMs were isolated from patients with monoclonal IgM gammopathy by preparative starch block electrophoresis and S-300 gel filtration. Purified polyclonal IgM (Behring Diagnostics, San Diego, CA) was purchased. Polyclonal IgG was prepared by DEAE ion-exchange chromatography and gel filtration of human Cohn fraction II (Miles Scientific Div., Naperville, IL).

Fc fragments of IgG were prepared and isolated from papain digested human IgG as described previously (6).

Preparation of Chicken Ig. Affinity-purified chicken anti-SPA (Accurate Chemical & Scientific Corp., Westbury, NY) and chicken gamma globulin (Sigma Chemical Co., St. Louis, MO) were assayed for SPA binding by double immunodiffusion before use. A single precipitin line formed between SPA and chicken anti-SPA, but not with chicken gamma globulin. To exclude the possibility of contaminating SPA in the affinity isolated preparation, both chicken anti-SPA and chicken gamma globulin were passed over a human IgG affinity column in borate buffer, pH 8.0, and the fall-through fraction was used in ELISA. No contaminating human IgG was detected in either preparation by a sensitive ELISA using peroxidase-conjugated rabbit antibodies to human Fcγ (Cooper-Biomedical, Inc., Malvern, PA) as the detecting reagent.

Pepsin-digested chicken gamma globulin and chicken anti-SPA were prepared by incubating chicken proteins in 0.1 M acetate buffer, pH 4.5, with pepsin (Worthington Biochemical Corp., Freehold, NJ) at a 1:25 pepsin/protein weight ratio for 16 h at 37°C. Previous studies (7) have shown that pepsin digestion of chicken Igs at pH 4.5 yields predominantly Fab′ fragments rather than $F(ab')_2$ fragments. The digestion mixtures were applied to an HPLC gel-filtration column (Superose 12; Pharmacia Fine Chemicals). Pepsin-digested chicken gamma globulin and chicken anti-SPA each yielded major peaks of ~50 kD. These isolated peaks were used to coat microtiter wells in an ELISA assay.

Enzyme Linked Immunosorbent Assays (ELISA). Chicken anti-SPA and nonimmune chicken gamma globulin were shown to coat flat-bottomed microtiter plates (Nunc Immunoplate II; Scientific Resource Associates, Bellevue, WA) equivalently, as detected with biotinylated rabbit anti–chicken IgG in a preliminary ELISA. Assays for binding of human Igs to chicken anti-SPA and chicken gamma globulin were performed as follows. Microtiter plate wells were coated by overnight incubation with chicken Igs using 50 μl/well at 25 μg/ml in 0.1 M bicarbonate buffer, pH 9.6. After washing three times with 0.5% Tween 20 (J. T. Baker Chemical Co., Phillipsburg, NJ) in borate buffer, human non-RF IgM, IgG, or RF preparations were added at 50 μg/ml in 0.05% Tween-borate buffer pH 8.0 and incubated overnight at 4°C. After washing, horseradish peroxidase–conjugated $F(ab')_2$ of goat antibodies to human $F(ab')_2$ of IgG (CooperBiomedical, Inc.), diluted 1:3,000 in 0.05% Tween, 0.3% BSA in borate buffer were added and incubated 3 h at room temperature. These detecting antibodies bound both human IgG and IgM. After a final wash, the peroxidase substrate 2,2′-azino-di-[3-ethyl-benzthiazoline sulfonate] and H_2O_2 were added and absorbance at 405 nm was detected on a plate reading spectrophotometer (Bio-Tek Instruments, Inc., Burlington, VT). All samples were run in duplicate and control wells were included in each assay to exclude nonspecific adsorption. Background binding of peroxidase-conjugated goat anti–human $F(ab')_2$ to chicken anti-SPA and to chicken gamma globulin were identical and were subtracted from experimental values. SPA and fragment D inhibition assays were performed by adding dilutions of SPA (Sigma Chemical Co.) and fragment D (generously provided by Dr. John Sjöquist, University of Uppsala, Sweden) in 0.05% Tween-borate buffer to coated wells 1 h before

the addition of IgM RF. The preparations of SPA and fragment D were shown to be free of human IgG by RIA.

Inhibition of chicken anti-SPA binding to IgM RF by human IgG and human Fc was tested in an assay in which $F(ab')_2$ of rabbit antibodies to chicken IgG (CooperBiomedical, Inc.) were used to detect binding. In this assay, IgM RFs were used to coat microtiter wells at a concentration of 30 μg/ml in bicarbonate buffer. After washing, dilutions of human IgG, Fc fragment of IgG, or BSA in 0.05% Tween-borate buffer were added to wells and incubated overnight at 4°C. Chicken anti-SPA or chicken gamma globulin was then added at a concentration of 50 μg/ml in Tween-borate buffer and plates were again incubated overnight. After washing, biotinylated $F(ab')_2$ of rabbit antibodies to chicken IgG were added at a dilution of 1:1,000 in 0.05% Tween-borate buffer and incubated 3 h at room temperature. Plates were again washed, and peroxidase-conjugated avidin (Sigma Chemical Co.) was added at a 1:1,000 dilution in 0.05% Tween-borate buffer containing 0.3% BSA. For each dilution of inhibitor, absorbance of chicken gamma globulin–containing wells was subtracted from the absorbance of chicken anti-SPA–containing wells to eliminate background binding.

Inhibition curves were generated by fitting the observed data to the binding equation: $P = [(K_{d_{50}} \times P_{min}) + (I \times P_{max})]/(K_{d_{50}} + I)$, where P is the absorbance at 405 nm; P_{min} is the asymptote at low I; P_{max} is the asymptote at high I; $K_{d_{50}}$ represents the dissociation constant, and is equal to I when P is 50% of control binding; I is the concentration of inhibitor. The fitting was accomplished with a computer program using a weighted nonlinear least-squares function (1).

Results

Binding of Human IgM and IgG RFs to Chicken Anti-SPA. Nineteen isolated IgM RFs, two IgG RFs, three monoclonal IgM preparations without RF activity, polyclonal non-RF IgM, and a polyclonal non-RF IgG preparation were tested for binding to chicken anti-SPA and chicken gamma globulin. 18 of the 19 RF preparations showed significant binding to chicken anti-SPA. Five of these (Moe, Hou, Van, Sch, EG) were IgM RFs isolated from sera of patients with RA. 13 IgM RFs were isolated from cryoglobulins of patients with mixed cryoglobulinemia. The monoclonal cryoglobulins Les and Pal bear the major crossreactive idiotypes Po and Wa, respectively (Carson, D., personal communication). These RFs differ from one another in their expression of primary sequence dependent light chain idiotypes (8), yet both bind to chicken anti-SPA. One preparation (Jan), a monoclonal noncryoglobulin IgM with RF activity from a patient with a lymphoproliferative disorder, did not bind significantly to chicken anti-SPA. Two IgM preparations without RF activity from patients with Waldenstrom's macroglobulinemia (Gil, Dok) and a non-RF IgM cryoglobulin isolated from a patient with Type I cryoglobulinemia (Eri), as well as polyclonal non RF human IgG and IgM, also did not bind significantly to chicken anti-SPA (Fig. 1). Two polyclonal IgG RFs were also tested for binding to chicken anti-SPA. These IgG RFs were derived from sera of patients with RA whose IgM RFs bound chicken anti-SPA (Moe, Hou). Both IgG RFs bound chicken anti-SPA but not chicken gamma globulin. Polyclonal human non RF IgG showed insignificant binding to anti-SPA (Fig. 2).

Chicken antibodies were used in these assays because Igs from that species do not bind to SPA (9). Most of the RFs also did not bind significantly to chicken Ig, although five IgM RFs showed low-level binding (Eva, Buc, Les, Moe, Sch). This may suggest heterogeneity in the binding site specificity of these RF preparations.

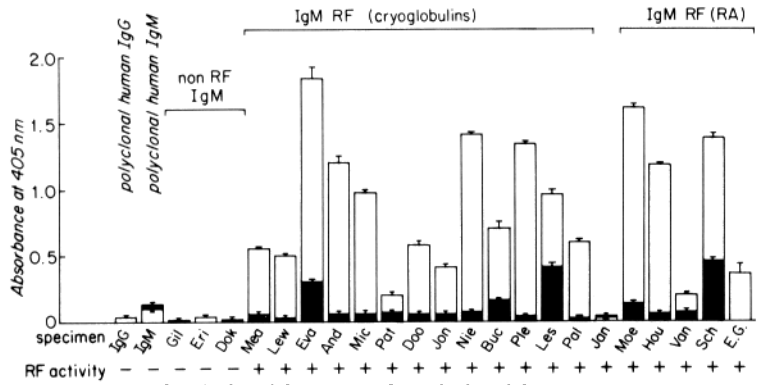

FIGURE 1. Binding of polyclonal human IgG, polyclonal human IgM, non-RF IgM from three individuals (Gil, Eri, Dok), and isolated IgM RF from 19 individuals to affinity-purified chicken anti-SPA (*open bars*) and nonimmune chicken gamma globulin (*solid bars*) in ELISA. Presence (+) or absence (−) of RF activity is indicated below the letter codes of the specimens. Error bars indicate absorbance at 405 nm of duplicate wells. Les and Pal represent members of Po and Wa crossreactive idiotypic groups, respectively.

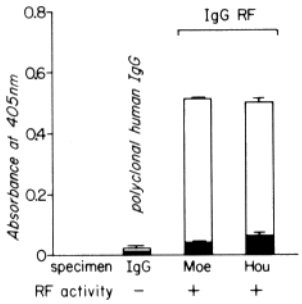

FIGURE 2. Binding of polyclonal human IgG and IgG RFs from two individuals with RA (Moe, Hou) to affinity-purified chicken anti-SPA (*open bars*) and nonimmune chicken gamma globulin (*solid bars*) in ELISA. For these patients, substantial binding of both IgM RFs (Fig. 1) and IgG RFs to chicken anti-SPA was observed.

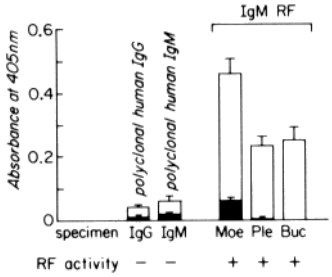

FIGURE 3. Binding of polyclonal human IgG, polyclonal human IgM, and isolated IgM RFs from three individuals (Moe, Ple, Buc) to Fab′ fragments of chicken anti-SPA (*open bars*) and nonimmune chicken gamma globulin (*solid bars*) in ELISA.

To exclude nonspecific binding of the RFs to chicken IgG via the Fc region, binding of three RFs was tested to Fab′ fragments of chicken anti-SPA and chicken gamma globulin. These experiments showed that the tested RFs bound to pepsin-digested chicken anti-SPA and not to pepsin-digested chicken gamma globulin. Polyclonal human non-RF IgM and IgG did not bind significantly to the Fab′ fragments of anti-SPA (Fig. 3). When SPA was added to wells coated with Fab′ fragments of anti-SPA, polyclonal IgG binding could then be detected, indicating that these fragments retained antigen-binding activity when used to coat microtiter wells (data not shown). Fab′ fragments of normal chicken gamma globulin bound neither RFs nor SPA.

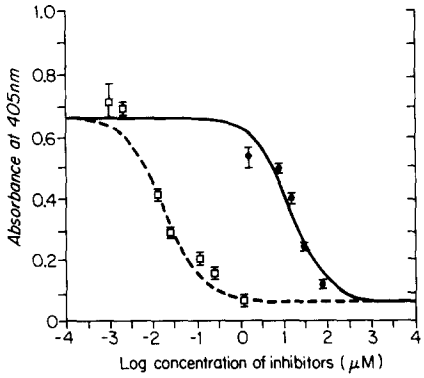

FIGURE 4. Inhibition of binding of Moe IgM RF to solid-phase chicken anti-SPA by SPA (*squares*) and fragment D of SPA (*circles*). Error bars indicate standard deviations of duplicate wells.

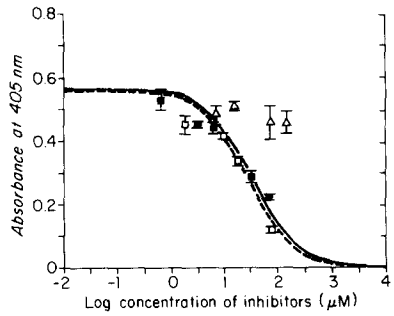

FIGURE 5. Inhibition of binding of chicken anti-SPA to solid-phase Hou IgM RF by IgG (*filled squares*) and Fc fragment of IgG (*open squares*). The effect of addition of BSA, an unrelated protein, at comparable molar concentrations is shown for comparison (*triangles*). Error bars indicate standard deviations of duplicate wells.

Inhibition with SPA, Fragment D of SPA, and Human IgG. To demonstrate that the antigen-combining sites on chicken anti-SPA as well as on IgM RFs were involved in the interaction of chicken anti-SPA and IgM RFs, inhibition assays using SPA, the 7-kD fragment D of SPA, and IgG Fc were performed.

Binding of Moe IgM RF to chicken anti-SPA was inhibited by the addition of SPA and by the monovalent fragment D of SPA (Fig. 4). 50% inhibition ($K_{d_{50}}$ ± SEM) of IgM RF binding occurred at an SPA concentration of 0.017 ± 0.002 μM and at a fragment D concentration of 13.72 ± 2.21 μM. Using a sensitive RIA, we have found that several commercially available preparations of SPA contain trace amounts of IgG, resulting possibly from use of IgG affinity columns for their isolation (data not shown). The SPA preparation used in these assays was free of IgG contamination by RIA.

The interaction of chicken anti-SPA and IgM RF was also inhibitable by human Fc and human IgG. As compared with inhibition using SPA, much higher concentrations of IgG were required for inhibition. This probably reflects the relatively low binding affinity of RFs for monomeric IgG in solution. Inhibition of chicken anti-SPA binding to Hou IgM RF is shown in Fig. 5. 50% inhibition ($K_{d_{50}}$ ± SEM) of Hou IgM RF binding occurred at an IgG concentration of 32.58 ± 8.27 μM and at an Fc concentration of 27.71 ± 2.67 μM. Chicken anti-SPA binding to Moe IgM RF was also inhibitable by Fc of IgG, with a $K_{d_{50}}$ ± SEM of 80.71 ± 12.08 μM. An unrelated protein, BSA, added at comparable molar concentrations, did not significantly inhibit the interaction.

Discussion

The obtained results indicate that human RFs from different individuals share a determinant that is recognized by antibodies to SPA, suggesting a conformational resemblance of these human autoantibodies to an Fc binding protein of microbial origin. The presence of this determinant on 18 of 19 IgM RFs, including members of the Po (Les) and Wa (Pal) crossreactive idiotype groups, as well as on two IgG RFs, and its absence on non-RF Igs suggest that the site recognized by anti-SPA is an idiotypic determinant related to the combining site of these antibodies. This is further supported by inhibition of the interaction of anti-SPA and IgM RF by Fc. Despite differences in the primary structures of RFs, broadly crossreactive "internal image" antiidiotypic antibodies against a conformational binding site determinant on human RFs have been elicited in rabbits by immunization with polyclonal or monoclonal RFs (10). Idiotypic network theory suggests that idiotypic determinants on antibodies can mimic exogenous antigens (11). The data presented here, combined with the observation that SPA and many human RFs show similar IgG binding properties and bind to a site at the $C\gamma2$-$C\gamma3$ junction of human Fc (1, 2), suggest that RFs carry the conformational internal image of the site on SPA that binds to the Fc region of human IgG.

Because these findings are based on antigen-antibody interactions in a sensitive ELISA, care was taken to exclude detection of trace contaminants or nonspecific interactions. We considered the possibility that small amounts of SPA present in the affinity-isolated anti-SPA preparation could bind to any IgG contaminating the IgM RF isolates. Possible contaminating SPA was eliminated by passing both the chicken anti-SPA and chicken gamma globulin over a human IgG affinity column before use. The affinity-purified chicken anti-SPA did not bind to human IgG in the ELISA. The presence of contaminating human IgG in the chicken anti-SPA was also carefully excluded, as we have found that a 1% contamination with IgG can result in detectable RF binding in our ELISA assay. No human IgG was detected in the anti-SPA preparation in a sensitive ELISA using peroxidase-conjugated goat or rabbit antibodies to human IgG Fc or $F(ab')_2$ as detecting reagents, with nonimmune chicken gamma globulin as a negative control.

RFs are associated with a variety of conditions both in humans and experimental animals. They have been observed in the course of chronic infections in humans (12, 13) and after repeated immunization with bacterial cell walls in animals (14). The appearance of IgM RF during anamnestic immune responses to protein antigens in mice (15, 16) and after immunization in humans (17) suggests that they may participate in normal immunoregulatory or inflammatory responses. The precise mechanisms for RF production in humans are unknown. RFs produced in normal individuals and RFs associated with autoimmune diseases, such as rheumatoid arthritis, appear to differ in their idiotype expression, as defined by mAbs to structural determinants (8). In RA, RFs are produced in inflamed synovium and are of IgG, IgA, and IgM isotypes (18). These observations raise the possibility that different mechanisms of RF production exist in various conditions. In mice, several mechanisms of RF production have been demonstrated or proposed. Polyclonal B cell activators induce RF production in

a T cell–independent manner in both normal and nude mice (15, 19). RF produced in mice after immunization with immune complexes requires T cell participation and is specific for the subclass of immunizing Ig (14, 15). RF production in 129/Sv mice appears to involve a filterable intestinal infectious agent and is also of restricted IgG subclass specificity (20). Finally, reactivity of certain mouse antibodies with both Fc fragments (RF activity) and Fab fragments of antibodies suggests that RFs might arise as part of an idiotypic network (21, 22).

It has been suggested (23, 24) that autoantibodies may arise as antiidiotypic antibodies to exogenous antigens. If the RF binding site conformationally resembles Fc binding structures on microbial agents, then, given the appropriate immunogenetic background, RFs could arise as internal image antiidiotypic antibodies in the course of an immune response to certain infections. The hypothesis that RFs may be produced as antiidiotypic antibodies against antibodies to microbial Fc receptors has been proposed by us (1, 4) and by others (25, 26). A similar mechanism has been demonstrated to result in production of antibodies to hormone receptors. Immunization of mice with insulin resulted in the production of antiidiotypic antibodies that mimicked insulin in binding to cellular insulin receptors (27). Alternatively, the immune response to microbial Fc-binding proteins could induce or modulate rheumatoid factor production through other mechanisms.

There is some evidence to suggest that modulation of autoantibody production through perturbation of the idiotype-antiidiotype network occurs after bacterial infections. The transient appearance of antiidiotypic antibodies to a human RF, accompanied by a marked reduction in rheumatoid factor activity of the serum of a patient with mixed cryoglobulinemia, has been reported in association with pneumococcal bacteremia (28). An idiotypic connection between antibodies to the α-1,3-dextran determinant on certain bacteria and autoantibodies to the acetylcholine receptor has been proposed as a mechanism for the initiation of autoimmunity in myasthenia gravis (29). Antiidiotypic serum from mice and rabbits immunized with human RFs has been shown to react with a cell wall peptidoglycan preparation from group A *Streptococcus pyogenes* (30). This may indicate the presence of more than one crossreactive idiotypic determinant on RFs that is also present on some bacteria. Alternatively, it is possible that small amounts of the group A streptococcal Fc-binding protein contaminating the peptidoglycan preparation could crossreact with RFs in a manner resembling SPA (4).

The data presented herein show that a subset of chicken antibodies to SPA bind to human RFs. It will be important to determine whether similar RF binding antibodies arise in humans in the course of the immune response to SPA or other microbial Fc-binding proteins and whether such antibodies can induce or modulate RF production.

Summary

The binding specificity of rheumatoid factors (RFs) to human Fc resembles that of some microbial Fc-binding proteins, suggesting conformational similarities in their Fc-binding regions. Using polyclonal chicken antibodies against SPA, we

have detected a crossreactive determinant shared by human RFs from different individuals, but not by non-RF IgM and IgG. Chicken anti-SPA was shown to bind to 18 of 19 IgM RFs and 2 of 2 IgG RFs isolated from different individuals. This binding was inhibitable with SPA, fragment D of SPA, human IgG, and Fc fragment of IgG. The binding site for RF was located on the Fab′ fragment of chicken anti-SPA. The antigenic mimicry of RFs by a protein of microbial origin suggests that the immune response to infectious agents could induce or modulate RF production through an internal image autoantiidiotype mechanism.

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References

1. Nardella, F. A., D. C. Teller, C. V. Barber, and M. Mannik. 1985. IgG rheumatoid factors and staphylococcal protein A bind to a common molecular site of IgG. *J. Exp. Med.* 162:1811.
2. Sasso, E., F. A. Nardella, and M. Mannik. 1986. High prevalence of rheumatoid factors inhibitable by a fragment of staphylococcal protein A. *Arthritis Rheum.* 29:13.
3. Schröder, A. K., F. A. Nardella, M. Mannik, M. L. Svensson, and P. Christensen. 1986. Interaction between streptococcal IgG Fc receptors and human and rabbit IgG domains. *Immunology.* 57:305.
4. Nardella, F. A., A. K. Schröder, M. Svensson, J. Sjöquist, C. Barber, and P. Christensen. 1987. T15 group A streptococcal Fc receptor binds to the same location on IgG as Staphylococcal protein A and IgG rheumatoid factors. *J. Immunol.* 138:922.
5. Johansson, P. J. H., A. K. Schröder, F. A. Nardella, M. Mannik, and P. Christensen. 1986. Interaction between herpes simplex type 1 induced Fc receptor and human and rabbit immunoglobulin G (IgG) domains. *Immunology.* 58:251.
6. Nardella, F. A., D. C. Teller, and M. Mannik. 1981. Studies on the antigenic determinants in the self-association of IgG rheumatoid factors. *J. Exp. Med.* 154:112.
7. Benedict, A. A., and K. Yamaga. 1976. Immunoglobulins and antibody production in avian species. *In* Comparative Immunology. J. Marchalonis, editor. Halsted Press, 335–375.
8. Fong, S., P. P. Chen, T. A. Gilbertson, J. R. Weber, R. I. Fox, and D. A. Carson. 1986. Expression of three cross-reactive idiotypes on rheumatoid factor autoantibodies from patients with autoimmune diseases and seropositive adults. *J. Immunol.* 137:122.
9. Kronvall, G., U. S. Seal, J. Finstad, and R. C. Williams. 1970. Phylogenetic insight into evolution of mammalian Fc fragments of γG globulin using staphylococcal protein A. *J. Immunol.* 104:140.
10. Fong, S., T. A. Gilbertson, P. P. Chen, J. F. Karras, J. H. Vaughan, and D. A. Carson. 1986. The common occurrence of internal image type anti-idiotypic antibodies in rabbits immunized with monoclonal and polyclonal human IgM rheumatoid factors. *Clin. Exp. Immunol.* 64:570.
11. Urbain, J., M. Slaoui, and O. Leo. 1982. Idiotypes, recurrent idiotypes and internal images. *Ann. Immunol. (Paris).* 133D:179.

12. Dresner, E., and P. Trombly. 1959. The latex-fixation reaction in nonrheumatic diseases. *N. Engl. J. Med.* 261:981.
13. Williams, R. C., and H. G. Kunkel. 1962. Rheumatoid factor, complement, and conglutinin aberrations in patients with subacute bacterial endocarditis. *J. Clin. Invest.* 41:666.
14. Bokisch, V. A., D. Bernstein, and R. M. Krause. 1972. Occurrence of 19S and 7S anti-IgGs during hyperimmunization of rabbits with streptococci. *J. Exp. Med.* 136:799.
15. Coulie, P. G., and J. van Snick. 1985. Rheumatoid factor (RF) production during anamnestic immune responses in the mouse. *J. Exp. Med.* 161:88.
16. Nemazee, D. A. 1985. Immune complexes can trigger specific, T cell-dependent, autoanti-IgG antibody production in mice. *J. Exp. Med.* 161:247.
17. Aho, K., A. Konttinen, M. Rajasalmi, and O. Wager. 1962. Transient appearance of the rheumatoid factor in connection with prophylactic vaccination. *Acta Pathol. Microbiol. Immunol. Scand. Sect. A Pathol.* 56:478.
18. Munthe, E., and J. B. Natvig. 1972. Immunoglobulin classes, subclasses and complexes of IgG rheumatoid factor in rheumatoid plasma cells. *Clin. Exp. Immunol.* 12:53.
19. Izui, S., R. A. Eisenberg, and F. J. Dixon. 1979. IgM rheumatoid factors in mice injected with bacterial lipopolysaccharide. *J. Immunol.* 122:2096.
20. Coutelier, J.-P., J. T. M. vander Logt, F. W. A. Heessen, G. Warnier, and J. van Snick. 1986. Rheumatoid factor production in 129/SV mice: involvement of an intestinal infectious agent. *J. Immunol.* 137:337.
21. Bona, C. A., S. Finley, S. Waters, and H. G. Kunkel. 1982. Anti-immunoglobulin antibodies. III. Properties of sequential anti-idiotypic antibodies to heterologous anti-γ globulins. Detection of reactivity of anti-idiotype antibodies with epitopes of Fc fragments (homobodies) and with epitopes and idiotopes (epibodies). *J. Exp. Med.* 156:986.
22. Holmdahl, R., C. Nardling, K. Rubin, A. Tarkowski, and L. Klareskog. 1986. Generation of monoclonal rheumatoid factors after immunization with collagen II-anti collagen II immune complexes. *Scand. J. Immunol.* 24:197.
23. Plotz, P. H. 1983. Autoantibodies are anti-idiotype antibodies to antiviral antibodies. *Lancet.* ii:824.
24. Cooke, A., A. M. Lydyard, and I. M. Roitt. 1984. Autoimmunity and idiotypes. *Lancet.* ii:723.
25. Mouritsen, S. 1986. Rheumatoid factors are anti-idiotypic antibodies against virus-induced anti-Fc receptor antibodies. *Scand. J. Immunol.* 24:485.
26. Carson, C. A., P. P. Chen, R. I. Fox, T. J. Kipps, F. Jirik, R. D. Goldfien, G. Silverman, V. Radoux, and S. Fong. 1987. Rheumatoid factor and immune networks. *Annu. Rev. Immunol.* 5:109.
27. Schechter, Y., R. Maron, D. Elias, and I. R. Cohen. 1982. Autoantibodies to insulin receptor spontaneously develop as anti-idiotypes in mice immunized with insulin. *Science (Wash. DC).* 216:542.
28. Abe, T., T. Takeuchi, M. Kiyotaki, J. Koide, O. Hosono, M. Homma, T. Otake, and S. Kano. 1984. Anti-idiotypic antibodies in a patient with monoclonal rheumatoid factor after pneumococcal bacteremia. *J. Immunol.* 132:2381.
29. Dwyer, D. S., M. Vakil, and J. F. Kearney. 1986. Idiotypic connectivity and a possible cause of myasthenia gravis. *J. Exp. Med.* 164:1310.
30. Johnson, P. M., K. K. Phua, and H. B. Evans. 1985. An idiotypic complementarity between rheumatoid factor and anti-peptidoglycan antibodies? *Clin. Exp. Immunol.* 61:373.