INDUCTION OF ANTIPHOSPHORYLCHOLINE ANTIBODY FORMATION BY ANTI-IDIOTYPIC ANTIBODIES*

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The induction of antibody formation is dependent in part upon the direct interaction of antigen with cellular receptors specific for the antigen. It has been proposed that each antibody-forming cell precursor (P-AFC)[1] carries antibody receptors of only one specificity which is identical to the antibody synthesized after induction (1,2). Mitchison (3) has suggested that antigen interacts with cell surface-associated receptor antibody molecules delivering the induction signal for the differentiation of P-AFC into antibody-forming cells (AFC).

Many efforts have been undertaken to characterize these receptors on B lymphocytes using radioactive antigen binding (reviewed in 4), fluorescent antigen binding and cell sorting (5), and fractionation of cells on antigen-coated columns (6). These studies indicate that receptor antibody molecules have heavy and light chain determinants of all immunoglobulin classes, and that the cells detected by antigen binding appear to be the precursors of AFC.

The finding that anti-idiotype antisera injected into unimmunized mice suppress the formation of antibodies carrying the corresponding idiotype also suggests that antigen-binding cells and P-AFC are the same (7,8). Claflin et al. have demonstrated recently that the receptors on phosphorylcholine-binding cells are IgM immunoglobulins with the hapten specificity and the idiotype specificity of a series of phosphorylcholine-binding myeloma proteins. These authors suggested a strong correlation between receptor antibody molecules and synthesized antibody (9,10), concluding that antigen-binding cells and P-AFC are the same.

In earlier studies we have reported that nonimmunogenic monovalent haptens could be converted into immunogens in the presence of lipopolysaccharide (LPS) or allogeneic T cells (11,12). These results demonstrated that the interaction of receptor antibody molecules with monovalent hapten is sufficient to deliver the antigenic signal.

In this study experiments have been designed to characterize receptor anti-

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[1] *Abbreviations used in this paper:* AFC, antibody-forming cells; FBS, fetal bovine serum; LPS, lipopolysaccharide; P-AFC, antibody-forming cell precursor; PC, phosphorylcholine; PFC, plaque-forming cells.

body molecules on B lymphocytes using anti-idiotype antibodies as antigen. These anti-idiotype antibodies which should be directed against receptor antibody molecules (1–3) were used to induce hapten-specific antibody formation. Phosphorylcholine-binding IgA protein from plasmacytoma S107 grown in BALB/c mice has been shown to carry the genetically controlled idiotype characteristic of normal BALB/c antiphosphorylcholine antibodies (13–15). Antibodies against S107 raised in rabbits and A/HeJ mice have been chosen as antireceptor antibodies. The results presented in this study suggest that: (*a*) receptor antibody molecules on the surface of P-AFC specific for PC carry the S107 idiotype; (*b*) binding of anti-idiotype antibody to receptor antibody molecule delivers the antigenic signal; (*c*) induction of antibody formation with anti-idiotype results in the production of antibodies of the same idiotype indicating that cellular receptors and secreted antibodies are the same; and (*d*) the induction is T-cell dependent.

Materials and Methods

Mice. BAB/14 breeding stock was obtained from Dr. L. Herzenberg, Stanford University; C.AL-9 breeding stock was obtained from Dr. M. Potter, National Institutes of Health; and BALB/c mice were obtained from The Salk Institute colony. C57BL/6J mice were purchased from the Jackson Laboratories, Bar Harbor, Maine.

Antigens. L-glycerophosphorylcholine (PC) was obtained from Sigma Chemical Co., St. Louis, Mo. Pneumococcal C carbohydrate was a gift from Dr. Alan Sher (13).

Preparation of Anti-S107 Antibodies. Phosphorylcholine-binding IgA protein from plasmacytoma S107 was purified as described by Cohn et al. (16). The anti-idiotypic antiserum against S107 was raised in A/HeJ mice following the schedule of Potter and Lieberman (17). The rabbit anti-S107 antiserum was a gift from Dr. Melvin Cohn. Rabbit anti-S107 was purified over immunoabsorbent columns of Sepharose coupled with a different BALB/c IgAκ myeloma protein to eliminate nonidiotype antibodies. The antibodies were also absorbed onto a S107-Sepharose column and eluted by glycine-HCl buffer pH 2.2. These antibodies precipitated only S107 protein. However, much protein of this preparation may be inactive.

Spleen Cell Cultures. In vitro immune responses were studied in cell cultures prepared from BALB/c, C.AL-9, and BAB/14 as detailed elsewhere (11,18). These cultures contained 1×10^7 spleen cells in Eagle's minimum essential medium supplemented with 5% fetal bovine serum (FBS) and antigen as specified in the text. Cultures were fed daily with a nutritional mixture supplemented with FBS (18). Approximately 3×10^6 viable cells were recovered from each culture on day 4. Each result presented is the mean of at least four experiments.

Specificity of Antibody-Forming Cells. The number of direct hemolytic plaque-forming cells (PFC) in spleen cultures was determined in a microscope slide assay (12,18). Palmitylated C-carbohydrate was coupled to horse red blood cells (HRBC) (13) and used as the target cell in the plaque assay. The specificity of each response was determined by inhibiting replicate slides with 10^{-4} M PC. Only 10–15% of the plaques were not inhibitable, and this number agreed well with the number of plaques measured on unsensitized HRBC. The noninhibitable plaques were subtracted from the data presented here.

Tolerization of BAB/14 Mice. BAB/14 mice tolerized against deaggregated rabbit IgG were prepared by Dr. Jacques Chiller by injection of 5 μg of deaggregated rabbit IgG i.p. The mice were used 10–20 days after injection.

Activation of T Cells to Rabbit IgG. Thymus-derived cells from BALB/c were activated to rabbit IgG (T_{rIgG}). BALB/c mice (6 wk old) were irradiated following exactly the procedure described previously (12). 0.1 ml of cell suspension containing $5–10 \times 10^7$ thymus cells was prepared from 15- to 20-day old BALB/c mice and injected intravenously into the irradiated hosts. Spleen cell suspensions were prepared from these mice and used as a source of T cells activated to rabbit IgG. Thymus-derived cells from C57BL/6 were activated against *H-2d* ($T_{BALB/c}$) as described earlier (12).

TABLE I

Inhibition of Anti-PC Plaque Formation in Mouse Strains with Different Idiotypes Using Mouse and Rabbit Anti-S107 Antisera

Strain	No inhibitor	A/HeJ anti-S107	Rabbit anti-S107	10^{-4} M PC
BALB/c	1,140*	50	170	85
BAB/14	1,420	130	580	60
C.AL-9	820	850	785	75
C57BL/6	910	895	900	85
BALB/c anti-HRBC	3,250	3,080	3,100	3,280

Two mice of each strain were immunized with pneumococcus vaccine. Their spleens were pooled and assayed for PFC at day 5.

* PFC/10^7 spleen cells.

Priming of Spleen Cells. To increase the number of antibody-forming cells to PC, BALB/c, C.AL-9, and BAB/14 mice were primed where indicated in the text by injecting i.p. 10^8 heat- and formalin-inactivated R36A pneumococci per mouse. The mice were used 10–15 days after priming as outlined in the text.

Results

Characterization of Rabbit Anti-S107 Antiserum. To characterize the idiotypic specificity of the antibodies used for induction of hapten-specific antibodies, mouse and rabbit anti-S107 sera were used to inhibit plaque formation in mouse strains which carry different idiotypes against PC. The results are shown in Table I. BALB/c, BAB/14, C.AL-9, and C57BL/6 were injected with 10^8 cells per animal of heat- and formalin-inactivated pneumococcus strain R36A. After 5 days, spleens were assayed in the Jerne plaque assay as described elsewhere (12). The number of plaques presented represents the average of two samples inhibitable by 10^4 M PC, and dilutions 10^{-2} of isolated rabbit anti-S107 and 10^{-6} of A/HeJ anti-S107 serum. Both sera did not inhibit anti-HRBC plaque formation.

The results demonstrate that anti-PC plaque formation was inhibitable by both mouse and rabbit anti-S107 sera in BALB/c and BAB/14 mice which carry similar idiotypes. The inhibition of BAB/14 plaque formation with either serum was less than that seen in BALB/c but was significant. In other experiments up to 75% inhibition of BAB/14 plaque formation was obtained with the rabbit antiserum. The lower degree of inhibition found with BAB/14 might have been due to the use of concentrations of anti-idiotype sera which were correct for BALB/c but may have been suboptimal for BAB/14. In contrast, no inhibition could be observed in C.AL-9 and C57BL/6 mice which have different idiotypes. Plaque formation could be inhibited by 10^{-4} M PC in all cases. The results indicate that the rabbit anti-S107 antiserum used in the following experiments is recognizing the same or a similar idiotype as A/HeJ anti-S107 sera.

Induction of PC-Specific Antibody Synthesis Using Anti-Idiotype Antibodies. To demonstrate that receptor antibody molecules on B and T lymphocyte cell surfaces not only bind antigens but also are responsible for the induction of hapten-specific antibody synthesis, rabbit anti-S107 idiotype antibodies have

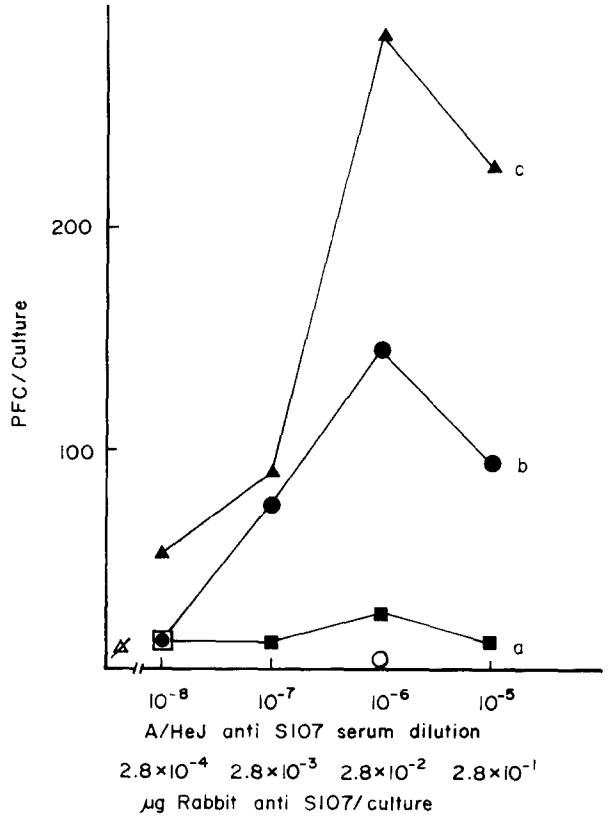

FIG. 1. The stimulation of immune responses to PC induced by A/HeJ anti-S107 antisera (■—■) and purified rabbit anti-S107 antibodies in primed (▲—▲) and unprimed (●—●) BALB/c spleen cell cultures. Each culture contained 10^7 cells and various concentrations of anti-S107 antisera. Cultures were assayed on day 4 using C-carbohydrate coupled HRBC as the target cells in the plaque assay. The data expressed are the number of PFC observed after the background response to uncoated HRBC was subtracted. This background was generally 10% of the total PFC observed. When 10^{-4} M PC was added to the plaque assay more than 95% of non-HRBC PFC were inhibited (○). BALB/c spleen cells primed with 10^8 R36A and not stimulated in vitro with anti-S107 showed no response to C-carbohydrate-coated HRBC (△).

been used as antigen in spleen cultures in vitro. The results plotted in Fig. 1 show that the antihapten response is dependent upon (*a*) the concentration of purified anti-idiotype antibody (Fig. 1 b and c). Maximum stimulation was obtained in a range of 3×10^{-2}–3×10^{-3} μg protein/10^7 cells which is equivalent to about 10^{14} or 10^{13} antibody molecules, assuming that the IgG fraction used contains only anti-idiotypic antibodies; (*b*) priming the mice with 10^8 R36A/mouse increases the number of AFC (Fig. 1 c); (*c*) whole anti-S107 antisera raised in A/HeJ mice do not induce antibody formation (Fig. 1 a). As will be shown this is due to inefficient induction of cooperating T cells; (*d*) in primed cultures without anti-S107 antibodies no plaque formation has been observed (±△); (*e*) more than 95% of the anti-PC PFC were inhibited from developing by the addition of 10^{-4} M PC to the assay mixture (○). Therefore, PFC obtained by

TABLE II
Stimulation of C.AL-9 Cells with Anti-S107 Idiotype

Exp.	Strain	PFC/culture immunogen	
		R36A	Rabbit anti-S107*
1	BALB/c	380	212
	C.AL-9	352	<10
2	BALB/c	489	215
	C.AL-9	516	<10
3	BALB/c	396	192
	C.AL-9	428	12

* 0.03 μg anti-S107 antibodies were used for induction.

stimulation with anti-idiotype antibody appear to be specific for the PC hapten.

Idiotype Specific Inductions. As described in Table I anti-S107 idiotype antisera inhibit anti-PC plaque formation in BALB/c and BAB/14 but not in C.AL-9 or C57BL/6 mice. This indicates that anti-S107 antisera recognize idiotypic determinants on the antibodies synthesized in BALB/c and BAB/14 but not in C.AL-9 or C57BL/6.

To determine whether the induction of antibodies by anti-idiotype antibodies is dependent upon the recognition of the idiotype determinants on receptors, cultures of 10^7 R36A primed BALB/c and C.AL-9 spleen cells have been used for induction in vitro. As described in Table II, no antibody formation was elicited when C.AL-9 cells were stimulated with anti-S107 idiotype although their in vitro response to R36A was comparable to BALB/c. On the other hand BALB/c cultures gave a high response to anti-idiotype stimulation. Therefore the induction of antihapten antibodies caused by interaction of anti-idiotype antibodies and receptor antibody molecules appears to be idiotype specific.

T-Cell Dependency of the Induction of Anti-PC Antibody Formation. The results described in Fig. 1 a suggested that the induction of anti-PC antibodies may be dependent upon the recognition of the Fc fragment of the anti-idiotype antibody by cooperating T cells. To examine this possibility the following experiments were carried out.

(*a*) BAB/14 mice can be tolerized more efficiently against deaggregated gamma globulin than BALB/c (footnote 2) and carry the same idiotype for PC as BALB/c mice (Table I). This strain was used to demonstrate that induction was not obtained when T cells were tolerized against rabbit IgG, whereas the response to pneumococcal vaccine was unaffected.

The results are shown in Table III. No response was observed when cooperating T cells were made tolerant against rabbit IgG. However, the response was restored when T cells educated against rabbit IgG were added to tolerized cultures. The tolerance of BAB/14 to rabbit IgG in this case does not appear to be

[2] Chiller, J. M. Personal communication.

TABLE III
In Vitro Induction of Anti-PC Antibodies by Rabbit Anti-S107 Antibodies in Mice Tolerized Against Rabbit IgG

Exp.	PFC/culture immunogen		
	Rabbit anti-S107*	Rabbit anti-S107* + T_{rIgG}‡	R 36A
1 BAB/14	180	586	890
BAB/14 tolerized	<10	253	775
2 BAB/14	142	426	728
BAB/14 tolerized	<10	200	758
3 BAB/14	208	518	898
BAB/14 tolerized	15	286	790

* 0.03 μg anti-S107 antibodies were used for induction.
‡ T_{rIgG}: BALB/c T cells educated to rabbit immunoglobulin as described in Materials and Methods. BALB/c and BAB/14 are congenic, differing only at heavy chain allotype loci and are completely histocompatible.

TABLE IV
In Vitro Induction of BALB/c Anti-PC Antibody Synthesis Using Rabbit Anti-S107 or A/HeJ Anti-S107 and LPS or Allogeneic T Lymphocytes

	PC-specific PFC/culture		
Antigen	—	+5 μg LPS*	+3 × 10^6 $T_{BALB/c}$
Rabbit anti-S107 Fab_2	<10	180	95
A/HeJ anti-S107	<10	245	100
No antibody	<10	32	<10

* The LPS-induced polyclonal response to HRBC was 80–120 per culture. This was subtracted from the data shown here.

caused by suppressor cells, since it can be reversed by the addition of primed cooperating T cells. The response to R36A vaccine was the same in normal and tolerized cultures.

(*b*) As described earlier, nonimmunogenic haptens can be rendered immunogenic when allogeneic T cells can interact with receptors on P-AFC or when LPS was used as a proliferating signal (11,12). This system has been used in this study to demonstrate that anti-idiotypic antibodies without Fc fragments would only induce antibody formation in the presence of a cooperating signal, proving that T-cell recognition of the Fc fragment is required for induction. As shown in Table IV, induction has been observed only when proliferating signals were present in addition to Fab_2. Furthermore, A/HeJ anti-S107 antibodies which did

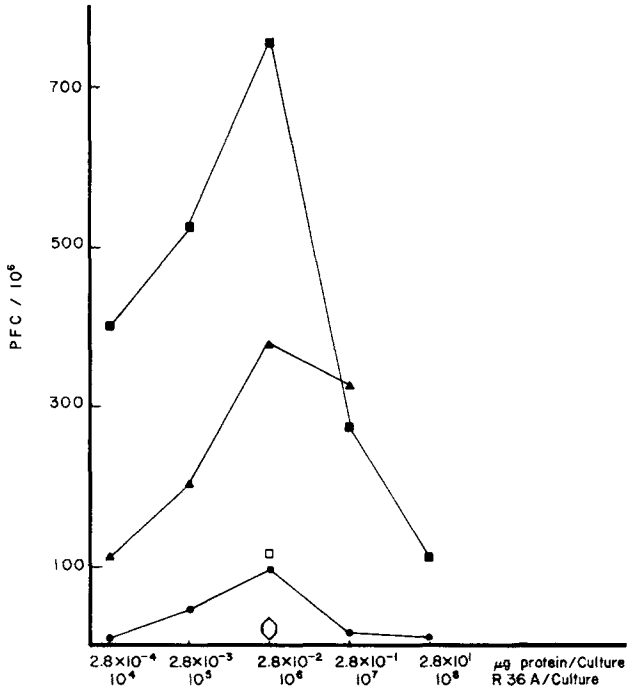

FIG. 2. Cooperation between R36A and rabbit anti-S107 antibodies during the immune response in BALB/c spleen cultures. 10^7 BALB/c spleen cells were incubated for 4 days together with various concentrations of anti-S107 antibodies (●—●) R36A (▲—▲) and 10^6 R36A plus various concentrations of rabbit anti-S107 antibodies (■—■). The plaque formation was inhibited by adding 10^{-5} dilution of A/HeJ anti-S107 sera (□) or 10^{-4} M PC (○) to the plaque assay. The data plotted represent the mean of two cultures. Anti-HRBC response had been subtracted.

not induce antibody formation by themselves (Fig. 1) were converted into an immunogen in the presence of LPS or allogeneic T cells. Therefore, the recognition of Fc fragments by cooperating T cells is necessary for the induction of antihapten antibodies.

Cooperation between Pneumococcus and Anti-Idiotype During Anti-PC Induction In Vitro and In Vivo. A synergistic effect was observed when both rabbit anti-idiotype antibodies and R36A were used together to induce spleen cell cultures. Fig. 2 shows the dose response curves for the induction of anti-PC plaques by rabbit anti-idiotype and R36A separately and the response obtained by the addition of varying amounts of anti-idiotype to the optimal amount of R36A. A 1.5- to 2.5-fold enhancement was observed with amounts of anti-idiotype between 2.8×10^{-4} and 2.8×10^{-2} μg protein per culture. Higher concentrations of anti-idiotype resulted in an inhibition of the response. (The actual amount of anti-idiotypic antibody is unknown.) The additional plaques obtained by the synergistic stimulation had normal anti-PC specificity since they were inhibited by either 10^{-4} M PC or A/HeJ anti-S107.

To confirm the results and to rule out any artifact caused by in vitro culture conditions, the induction was repeated in vivo (Table V). The optimal challenge

TABLE V
In Vivo Induction of Anti-PC Antibodies by Rabbit Anti-S107 Antibodies and by R36A

	Anti-S107			R36A	
Antigen	0.028 μg	Anti-idiotype 0.28 μg	0.5 μg	10^8 R36A	0.28 μg anti-idiotype 10^8 R36A
PFC/spleen	195	1,750	1,620	8,200	20,100

Two BALB/c mice were immunized with each dose of antigen and their spleens pooled for plaque assay at day 5.

doses were found to be 10^8 R36A and 0.28 μg of anti-idiotype antibody. When these were administered together the yield of PFC was about twice the expected sum.

Discussion

It has been postulated that the induction of antibody formation is based on the direct interaction of antigen and receptor antibody molecules on the surface of immunocompetent cells and that the receptor antibody molecules are identical to the antibodies synthesized after induction (1–3).

Evidence has been recently obtained which supports the latter proposal. Certain lineages of AFC can be identified by the idiotypes of their antibody products. The induction of these cells by antigen can be blocked by anti-idiotype serum (7,8,19), indicating that the receptors of P-AFC have the same idiotype and thus are probably the same molecules as serum antibodies. Claflin et al. (9,10) have directly shown that the receptors on P-AFC have the same idiotype and fine specificity of hapten binding as the secreted antibodies. In addition Eichmann (19) has shown that while IgG2a anti-idiotype suppresses, IgG1 anti-idiotype enhances the synthesis of the A5a idiotype. However, no direct evidence has been reported demonstrating the identity of antigen-binding receptor antibody molecules and the receptor mediating the induction of humoral antibody response in AFC, that is, the receptor which delivers the antigenic signal to P-AFC.

The experiments reported here demonstrate that anti-idiotype antibodies can interact with receptor antibody molecules and deliver the antigenic signal to P-AFC in vivo and in vitro. The antibodies induced by rabbit anti-idiotype, mouse anti-idiotype plus LPS or allogeneic T cells are hapten-specific and carry the corresponding idiotype as determined by inhibition of plaque formation with A/HeJ anti-S107. The antigen-binding receptor antibody molecules on P-AFC, which Claflin et al. (9,10) have shown to be identical to the induced serum antibody, have been shown here to be the receptors delivering the antigenic signal and inducing the differentiation to AFC.

As previously reported (11,12), monovalent haptens considered to be too small to participate in cooperative interactions between AFC and T lymphocytes can induce an immune response in the presence of allogeneic T cells or LPS, indicating that the interaction of monovalent haptens and receptor antibody

molecules can deliver the antigenic signal. But it is not understood how the antigenic signal transmits the information to P-AFC via conformational change of the receptor or via aggregation of receptors on the surface of P-AFC by antigen. Our attempts to distinguish between these possibilities failed so far. The system used in this study offers the opportunity to compare the inductive capacities of Fab_1 and Fab_2 in presence of cooperative signals. Preliminary results have shown that a fourfold concentration of Fab_1 compared to Fab_2 does not induce anti-PC antibodies in the presence of LPS or allogeneic T cells, although the Fab_1 preparation can inhibit plaque formation by 70% when added during the plaque assay.[3] Since Fab_1 may bind poorly to the receptor antibody molecule, it is not yet justifiable to conclude that aggregation of receptors is necessary for induction.

As proposed by Bretscher and Cohn (20, 21) and investigated in earlier studies, at least two independent signals are required to induce antibody formation: first, the antigenic signal via interaction between antigen and receptor antibody molecule on P-AFC; and second, a proliferation signal synthesized by cooperating T lymphocytes after interaction with antigen (11,12,22,23).

As shown here, the antigenic signal can be delivered by interaction of anti-idiotype with the receptor. As described in Tables III and IV, the recognition of Fc fragments of the rabbit anti-idiotypic antibody by T cells was required in order to induce the cooperating signal. The inability to obtain induction of AFC with mouse anti-idiotype (A/HeJ anti-S107) was presumably due to a lack of strong carrier determinants on A/HeJ antibodies. This lack was overcome by replacement of specific cooperation with the nonspecific stimulation of LPS and allogeneic T cells. The finding that rabbit anti-idiotype antibodies resulted in induction rather than suppression is presumably due to the strong carrier determinants on rabbit Fc and to the relatively low concentration of anti-idiotype used.

The increase of PFC during cooperation between R36A and rabbit anti-S107 antibody in vivo and in vitro as demonstrated in Fig. 2 and Table V can be interpreted in different ways: perhaps R36A is not stimulating the same cell clone which is induced by anti-idiotype sera. This interpretation is unlikely because induction of anti-R36A antibody formation can be inhibited by anti-S107 antibodies (Fig. 2). Another explanation is that the anti-idiotypic antibody stimulates helper T cells which also carry receptor antibody molecules on their surface. This induction results in a larger population of cooperating T cells. Experiments are in progress to analyze this phenomenon.[4]

Several aspects of these findings are inconsistent with previous reports. Sher and Cohn (13) found S107 idiotype in the antiphosphorylcholine antibodies of both BALB/c and C57BL/10 using a CE/J anti-S107 anti-idiotype serum. On the other hand, we have shown that an A/HeJ anti-S107 serum detects S107 idiotype specificities in BALB/c but not in C57BL/6. Similarly, Lieberman et al. (14) found T15 antiphosphorylcholine idiotype in BALB/c but not in C57BL strains using an A/HeJ anti-idiotype serum. Apparently anti-idiotype sera produced in

[3] Trenkner, E. Unpublished results.

[4] Trenkner, E., and M. Hoffmann. Manuscript in preparation.

different strains of mice can detect very different determinants on the same purified myeloma protein and show very different patterns of reactivity with various mouse strains.

Another inconsistency is that Lieberman et al. (14) reported that normal BAB/14 and C.B-20 sera were like C57BL sera in that they did not contain the idiotype of TEPC-15, a PC binding protein idiotypically identical to S107 (15). On the other hand, we have shown that BAB/14 anti-PC plaques are inhibitable by both mouse and rabbit strain specific anti-S107 anti-idiotypic sera. BAB/14 and C.B-20 are branches of a family of strains congenic with BALB/c but possessing heavy chain allotype genes derived from C57BL/Ka. The absence of T15 idiotype in their sera was interpreted as reflecting the absence of the V_{H-T15} gene of BALB/c and the presence of the alternative C57BL V_H genes. BAB/14, however, has been shown to be unique among the C.B strains in that it is recombinant with respect to its heavy chain C region and V region genes. It does have the C region allotype genes of C57BL/Ka but the dextran response gene, V_{H-DEX}, is derived from BALB/c (24, footnote 5). The plaque inhibition data shown here indicate that BAB/14 also has anti-PC antibodies of the BALB/c rather than C57BL/Ka type. This implies that BAB/14 does have a V_H gene coding for an S107-type heavy chain variable region. Since S107 and T15 heavy chains have apparently identical structure (25) this must be the V_{H-15} gene. We presume that the original negative findings of Lieberman et al. (14) are due to differences in the amount of environmental PC containing antigens in the different mouse colonies, resulting in undetectably low levels of natural antiphosphorylcholine antibodies. When BAB/14 antipneumococcus vaccine antisera are tested, T15 idiotype should be found.

The induction of hapten specific antibodies by xenogeneic anti-idiotype antibodies in the experiments reported here fulfills the predictions of the two-signal model (20,21) that induction will take place in presence of cooperating signals, whereas under syngeneic conditions the antireceptor antibodies are expected to suppress or paralyze P-AFC. Whether interaction of anti-idiotype antibodies with cellular antibody receptors plays a role in the normal maturation of the immune system in ways suggested by Jerne (26) and Eichmann (19) is the subject of further studies.

Summary

Anti-idiotypic antibodies have been used to mimic antigen in the mouse antiphosphorylcholine response in order to investigate the induction of precursors of antibody-forming cells. We have shown that interaction of anti-idiotype antibody with receptor antibody molecules induces the formation of antibodies that are specific for phosphorylcholine and carry the idiotypic determinants. This induction is dependent on the recognition of carrier determinants on the anti-idiotype antibody by helper T cells. We conclude that receptor antibody molecules on the surface of the precursors of antibody-forming cells deliver the antigenic signal for the induction of these cells.

[5] Riblet, R., B. Blomberg, M. Weigert, R. Lieberman, B. Taylor, and M. Potter. Manuscript in preparation.

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