

## IDIOTYPIC ANALYSIS OF LYMPHOCYTES IN VITRO

### II. Genetic Control of T-Helper Cell Responsiveness to Anti-Idiotypic Antibody\*

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We have recently shown that antigen receptors of T-helper cells and B cells with specificity for Group A streptococcal carbohydrate (A-CHO)<sup>1</sup> share idiotypic determinants (1-3). This conclusion was derived from the following set of experiments: Anti-idiotypic antibodies of the IgG1 class were prepared from antisera raised in guinea pigs either against strain A/J anti-A-CHO antibody of the A5A clone (4), or against the BALB/c myeloma protein S117 which as the A5A antibody specifically binds A-CHO (5). The two preparations of anti-idiotypic antibody (anti-Id) are referred to as anti-A5A Id1 and anti-S117 Id1, respectively. Immunization of A/J mice with anti-A5A Id1 and of BALB/c mice with anti-S117 Id1 resulted not only in the stimulation of B cells expressing the appropriate idiotypes in their antibody products, but also in the stimulation of T-helper cells. The activity of the latter was determined in a hapten-carrier system *in vivo* (1) and *in vitro* (2, 3) utilizing hapten-conjugated Group A streptococcal vaccine (Strep.A) particles as immunogen. Helper cell function could be specifically inhibited by anti-Id (2, 3) and must therefore be mediated through idiotype (Id)-bearing receptor molecules.

The A5A and S117 idiotypes are strain-specific markers for variable (V) genes in the heavy-chain linkage group (6). The A5A Id is present in antibodies to A-CHO in A/J, but not BALB/c mice, whereas the reverse is true for the S117 Id. Since, similarly, only anti-A5A Id1 was able to stimulate Id-bearing helper cells in A/J mice, whereas BALB/c responded to anti-S117 Id1 only, it appears likely that the A5A idiotypic determinants on helper cell receptors are coded for by genes in the heavy-chain linkage group.

In the present paper we explore this crucial question in more detail. This appears particularly important, since the numerous cases of histocompatibility linked specific controls of immune responsiveness suggest that the antigen specificity of helper cells is determined by immune response (*Ir*) genes (7) which are located in the *I* region of the *H-2* complex and are thus not linked to the heavy-chain linkage group [*Ig-1* complex (8)]. One might speculate, therefore, that the genome of the mouse carries two similar or identical sets of V genes, one linked to the *Ig-1* complex and expressed in B lymphocytes and the other mapping in the *I* region of the *H-2* complex and expressed in T lymphocytes.

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<sup>1</sup> Abbreviations used in this paper: A-CHO; Group A streptococcal carbohydrate; anti-Id, anti-idiotypic antibody; anti-Id1, anti-idiotypic antibody of the IgG1 class of guinea pig IgG; IBC, Id-binding capacity; Id, idiotype; *Ig-1*; heavy-chain constant region allotype locus; NGPS, normal guinea pig serum; PFC, plaque-forming cell; Strep.A, Group A streptococcal vaccine; TNP, 2,4,6-trinitrophenyl; V, variable.

The present experiments do not support this concept. Responsiveness of T-helper cells to stimulation by anti-Id correlated strictly with the expression of Id in the B-cell line and was not restricted to a particular *H-2* haplotype.

### Materials and Methods

*Mice.* Strains B10.S(7R) (gift from Dr. D. C. Shreffler, University of Michigan Medical School, Ann Arbor, Mich.) and BAB 14 (originally by Dr. L. A. Herzenberg, Stanford University School of Medicine, Stanford, Calif., given to us by Dr. M. Weigert, Institute for Cancer Research, Philadelphia, Pa.) were bred in our own animal facilities. BALB/c mice were obtained from Zentralinstitut für Versuchstierzucht, Hannover, West Germany. All other mice were purchased from The Jackson Laboratory, Bar Harbor, Maine.

*Idiotypes, Anti-Id, and Immunizations.* These are described in detail in the accompanying paper (2). The A5A antibody is a major antibody species in the immune response of A/J mice against Strep.A (4). S117 is a myeloma protein of BALB/c origin (5). Both immunoglobulins bind specifically A-CHO. Anti-idiotypic antisera were prepared in guinea pigs (9) and IgG1 was isolated from these sera by agarose block electrophoresis (10). We thus obtain two kinds of anti-Id, namely anti-A5A Id1 and anti-S117 Id1. Immunization consisted of a single intraperitoneal injection of either 0.1  $\mu$ g Id-binding capacity (IBC) of anti-Id or of  $1 \times 10^9$  particles of Strep.A (1, 2).

*In Vitro Helper Cell Assay.* Again the details of the experimental procedure are fully described in the accompanying paper (2). We used a modified Mishell-Dutton culture system (11) in order to determine helper activity specific for Strep.A. One million spleen cells were challenged with  $1.5 \times 10^8$  2,4,6-trinitrophenyl (TNP)-conjugated Strep.A particles in a vol of 110  $\mu$ l medium. 4 days after initiation of the cultures the number of TNP-specific plaque-forming cells (PFC) was determined on TNP-coated sheep erythrocytes (TNP-SRBC). Only direct plaques were found. Helper cell specificity was examined by admixing anti-idiotypic antiserum to the cultures (0.01–0.03  $\mu$ g IBC/well). Control cultures contained equivalent dilutions of normal guinea pig serum (NGPS) instead. When specific inhibition by anti-Id was obtained, it was concluded that helper cells bearing the corresponding Id were present in the cultures. For each strain of mice, the spleens from several animals were analyzed individually.

### Results

In order to explore the genetic basis of helper cell responsiveness to anti-Id, a panel of 13 inbred strains of mice was selected which were defined for their *H-2* haplotypes and for the expression of the A5A and S117 idiotypes in their immunoglobulins (reference 6, and our own unpublished results). One group of animals of each strain was immunized with Strep.A, another with anti-A5A Id1, and a third with anti-S117 Id1. 3–6 wk later we measured in each group the splenic helper cell activity towards Strep.A by in vitro challenge with TNP-Strep.A and subsequent determination of TNP-specific PFC (2). The idiotypic specificity of helper cell receptors was verified by inhibition experiments in which anti-idiotypic antisera were included in the cultures. In all cases, spleen cells of unimmunized animals were also analyzed. In the present experiments, helper activity was never detected in such animals, and the data are therefore not represented in the tables.

In Table I we present the results of our analysis in A/J, A.SW, B10.A, and B10.S(7R) mice, the genotypes of which are as follows: A/J (*H-2<sup>a</sup>*, *Ig-1<sup>e</sup>*, *A5A<sup>+</sup>*, *S117<sup>-</sup>*), A.SW (*H-2<sup>s</sup>*, *Ig-1<sup>e</sup>*, *A5A<sup>+</sup>*, *S117<sup>-</sup>*), B10.A (*H-2<sup>a</sup>*, *Ig-1<sup>b</sup>*, *A5A<sup>-</sup>*, *S117<sup>-</sup>*), and B10.S(7R) (*H-2<sup>th</sup>*, *Ig-1<sup>b</sup>*, *A5A<sup>-</sup>*, *S117<sup>-</sup>*).

The following conclusions can be drawn from the data: All four strains respond to immunization with Strep.A and, as we expect on the basis of our previous findings (2), helper cells thus generated can be inhibited only partially,

TABLE I  
Strain Distribution of Helper Cell Responsiveness to Anti-Id

Strain	Priming‡ antigen	Anti-TNP PFC/culture*				
		–	Inhibition by:			
			Anti-A5A	NGPS	Anti-S117	NGPS
A/J	Strep.A	430	356	422	322	312
	Anti-A5A	402	62	378	274	246
	Anti-S117	6	–	–	–	–
B10.A	Strep.A	126	122	140	–	–
	Anti-A5A	6	–	–	–	–
	Anti-S117	22	–	–	–	–
A.SW	Strep.A	168	156	184	–	–
	Anti-A5A	442	58	438	480	–
	Anti-S117	26	–	–	–	–
B10.S(7R)	Strep.A	98	110	92	–	–
B10.S(7R)	Strep.A	98	110	92	–	–
	Anti-A5A	1	–	–	–	–
	Anti-S117	2	–	–	–	–

\* Inhibitions were performed by addition of either 0.033  $\mu$ g IBC anti-A5A serum (final dilution of 1:720) or with 0.01  $\mu$ g IBC anti-S117 serum (final dilution 1:400). The nonspecific inhibitory effect was controlled for by normal guinea pig serum (NGPS) at final dilutions of 1:720 or 1:400, respectively. After a 4 day culture period the number of direct anti-TNP PFC was determined. Data are expressed as the geometric mean of six to eight cultures. Standard deviation coefficients ranged from 1.1 to 1.5.

‡ 3-6 wk after immunization of mice with either anti-A5A Id1, anti-S117 Id1, or Strep.A, spleen cell suspensions were prepared and challenged in vitro with a TNP-Strep.A conjugate.

or not at all, by anti-Id. Responsiveness of helper cells to priming with anti-Id is restricted to those strains which express the corresponding Id in their immunoglobulins. Thus, none of the strains responds to anti-S117 Id1, and only A/J and A.SW respond to anti-A5A Id1. In the latter case, helper activity is largely inhibitable by anti-A5A but not anti-S117. This is again expected on the basis of our previous results (2), which showed that helper cells induced by anti-Id display idiotypic specificity. The results in strains B10.A and B10.S(7R) show that helper cell responsiveness to anti-idiotypic stimulation does not depend on a particular *H-2* haplotype. B10.A carries the *H-2* complex of strain A/J and B10.S(7R) carries the *K*, *I*, and *S* regions of strain A.SW, both on the background of strain C57BL/10, which is negative for the A5A and S117 idiotypic markers. Both strains fail to develop a helper cell response upon stimulation with anti-A5A Id1, in contrast to strains A/J and A.SW.

A similar situation is encountered in the analysis of a second group of strains, namely BALB/c (*H-2<sup>d</sup>*, *Ig-1<sup>a</sup>*, *A5A<sup>-</sup>*, *S117<sup>+</sup>*), DBA/2 (*H-2<sup>d</sup>*, *Ig-1<sup>c</sup>*, *A5A<sup>cr</sup>*, *S117<sup>cr</sup>*), B10.D2 (*H-2<sup>d</sup>*, *Ig-1<sup>b</sup>*, *A5A<sup>-</sup>*, *S117<sup>-</sup>*), 129 (*H-2<sup>b</sup>*, *Ig-1<sup>a</sup>*, *A5A<sup>-</sup>*, *S117<sup>+</sup>*), and C57BL/10Sn (*H-2<sup>r</sup>*, *Ig-1<sup>b</sup>*, *A5A<sup>-</sup>*, *S117<sup>-</sup>*).

Again, all strains are responsive to Strep.A, whereas responsiveness to anti-Id is restricted to strains expressing the corresponding Id in their immunoglobulins. Sensitization by anti-Id also occurs in strain DBA/2 which expressed

idiotypes which are weakly cross-reactive with both the A5A and S117 idiotypes (reference 6, and unpublished results). Accordingly, helper activity in this strain is stimulated by both anti-A5A Id1 and anti-S117 Id1. As in the previous experiments, the inhibition data point to the presence of idiotypic determinants on the receptors of helper cells induced by anti-Id. The results again clearly show that responsiveness of T-helper cells to anti-Id does not depend on a certain *H-2* haplotype. Responsiveness correlates in all cases with the idiotypic  $V_H$  gene marker and in no case with a given *H-2* haplotype. The argument is particularly strong for one pair of strains, namely DBA/2 and B10.D2. Here, the situation is strictly analogous to that in the two strain combinations analyzed in Table I. T cells from DBA/2 mice respond to both anti-A5A and anti-S117 Id1, in accordance with the expression of cross-reacting immunoglobulin idiotypes in this strain. In contrast, T cells from the B10.D2 strain which is negative for the two idiotypic markers but carries the *H-2* complex of DBA/2, are unresponsive to both anti-idiotypes.

A schematic representation of the overall results is given in Table III. Represented in this table are the various strains of mice in which we have so far analyzed helper cell responsiveness to anti-A5A Id1 and anti-S117 Id1. The list of these strains includes data on four mouse strains in addition to those contained in Tables I and II; namely strains AKR, RF, B10.Br, and BAB 14. The latter carries a recombinant *Ig-1* complex, namely C57BL/6 allotypes and BALB/c idiotypes on the BALB/c background (6, 12). The detailed experimental data for these additional strains are not given, but were strictly analogous to those

TABLE II  
*Strain Distribution of Helper Cell Responsiveness to Anti-Idiotype*

Strain	Priming antigen	Anti-TNP PFC/culture				
		-	Inhibition by:			
			Anti-A5A	NGPS	A-S117	NGPS
BALB/c	Strep.A	294	284	262	144	162
	Anti-A5A	12	-	-	-	-
	Anti-S117	218	182	196	10	128
DBA/2	Strep.A	276	264	252	-	-
	Anti-A5A	386	62	400	282	280
	Anti-S117	304	300	-	132	256
B10.D2	Strep.A	98	96	98	-	-
	Anti-A5A	5	-	-	-	-
	Anti-S117	6	-	-	-	-
129	Strep.A	356	334	320	104	240
	Anti-A5A	8	-	-	-	-
	Anti-S117	182	124	116	72	194
C57BL/10	Strep.A	134	112	92	-	-
	Anti-A5A	10	-	-	-	-
	Anti-S117	8	-	-	-	-

For explanations see Table I.

TABLE III  
Strain Distribution of Helper Cell Responsiveness to Anti-Idiotypic (Summary)

Strain	<i>H-2</i> complex	Ig-1 complex			Helper cell stimulation with:		
		<i>Ig-1</i>	A5A	S117	Anti-A5A	Anti-S117	Strep.A
DBA/2	<i>d</i>	<i>c</i>	<i>cr*</i>	<i>cr</i>	+	+	+
RF	<i>k</i>	<i>c</i>	<i>cr</i>	<i>cr</i>	+	+	+
A/J	<i>a</i>	<i>e</i>	+	-	+	-	+
A.SW	<i>s</i>	<i>e</i>	+	-	+	-	+
BALB/ <i>c</i>	<i>d</i>	<i>a</i>	-	+	-	+	+
129	<i>b</i>	<i>a</i>	-	+	-	+	+
BAB 14	<i>d</i>	<i>b</i>	-	+	-	+	+
C57BL/10Sn	<i>b</i>	<i>b</i>	-	-	-	-	+
B10.A	<i>a</i>	<i>b</i>	-	-	-	-	+
B10.S(7R)	<i>th</i>	<i>b</i>	-	-	-	-	+
B10.D2	<i>d</i>	<i>b</i>	-	-	-	-	+
B10.BR	<i>k</i>	<i>b</i>	-	-	-	-	+
AKR	<i>k</i>	<i>d</i>	-	-	-	-	+

\* Strain expresses idiotypes which are cross-reactive but clearly distinct from A5A and S117.

represented in Tables I and II. Inspection of Table III reveals a perfect correlation between helper cell responsiveness to anti-idiotypic stimulation and presence of the corresponding idiotypic  $V_H$  gene marker at the immunoglobulin level. No such correlation is found between responsiveness and any of the various *H-2* haplotypes. In addition, the *H-2* complexes of three responding strains (A/J, A.SW, and DBA/2) do not establish responsiveness when inserted into the genome of a nonresponder (C57BL/10Sn).

### Discussion

Our previous experiments have established that humoral antibodies and T-helper cell receptors with the same binding specificity share idiotypic determinants (1-3). Similar results have been obtained by other workers who have compared the idiotypic specificity of antibody molecules and antigen-binding receptors on other T-cell subpopulations, namely those mediating cellular immune reactions like cytotoxicity, graft-vs.-host reaction and graft rejection (13-15).

Since in general, anti-Id are highly specific for the variable portion(s) of a single or a few species of antibody molecules, these results point to a striking structural similarity of the binding sites of T-cell receptors and humoral antibodies. However, the exact range of cross-reactivity of an anti-Id is difficult to establish so that the mere demonstration of serological cross-reaction does not permit conclusions as to the molecular identity of T- and B-cell antigen receptors. Therefore, with structural information missing, it is clear that a detailed genetic analysis is required in order to establish this important point beyond doubt. The present study represents a first step in this direction.

Our analysis of T-helper cell receptors is based on the finding that anti-Id of

the IgG1 class can induce helper cells, the receptors of which display idiotypic specificity. Since the two idiotypes employed in our experiments (A5A and S117) are strain-specific markers for antibody  $V_H$  genes in the heavy-chain linkage group (6), we are in the position to investigate whether responsiveness of T-helper cells to stimulation by anti-Id is genetically linked to these genes, or to other known linkage groups in the mouse, particularly the *H-2* complex.

We have analyzed helper cell responsiveness to anti-idiotypic stimulation in a panel of 13 strains. At the immunoglobulin level, two of these strains express the A5A and three the S117 marker. Two strains produce antibodies which cross-react with the A5A and the S117 Id. In six strains, neither of the two idiotypes is expressed. The mouse strains employed in our study were also selected such that we would be able to detect a possible control of T-cell responsiveness to anti-idiotypic stimulation by the *H-2* complex. Three of the strains are congenic resistants in which the *H-2* complex of a responder strain has been introduced into the genetic background of the nonresponder C57BL/10.

Our data argue against the possibility that T-cell responsiveness to anti-idiotypic stimulation is determined by genes in the *H-2* complex for two reasons. The first is the evidence discussed below which is in favor of linkage of this phenomenon to the heavy-chain linkage group. The second is the apparent irrelevance of the *H-2* haplotype for helper cell sensitization by anti-Id (c.f. Table III). When the *I* regions of three different strains which are responsive to anti-idiotypic stimulation (DBA/2, A/J, and A.SW) are crossed into the genome of a nonresponder strain (C57BL/10), responsiveness is not established. The argument hinges on the assumptions that (a) the A5A and S117 idiotypes can be expressed on the C57BL/10 genetic background and (b) the C57BL/10 strain is not a low responder to anti-idiotypic stimulation in general. Both assumptions appear reasonable, although we cannot so far prove them to be correct. We have shown, however, that the unresponsiveness of the various *H-2* congenic strains with the B10 background cannot be explained on the basis of a possible general control of nonresponsiveness to anti-idiotypic stimulation by *Ir* genes in the *H-2* complex, because the responding strains A/J, A.SW and DBA/2 carry the same *I* regions of *H-2* in their genome as do the nonresponding strains B10.A, B.10S(7R), and B10.D2, respectively.

Our results are fully compatible with the notion that the expression of strain-specific immunoglobulin idiotypes on T-helper cells is controlled solely by genes in the heavy-chain linkage group. We found that in all cases, without exception, helper cell responsiveness to anti-idiotypic stimulation correlated with the presence of the corresponding Id or a cross-reacting one in the antibody population. Whenever helper cells could be induced by anti-Id, their function could be specifically inhibited by the same and only the same anti-idiotypic. This is, as far as we can see, proof of the idiotypic nature of the functional receptors for antigen of those cells.

Thus, since (a) the A5A and S117 immunoglobulin idiotypes are markers for *V* genes in the heavy-chain linkage group, (b) helper cell responsiveness to anti-A5A and anti-S117 correlates strictly with the presence of these markers, and (c) the function of helper cells induced by anti-idiotypic can invariably be inhibited specifically by the same anti-idiotypic, it is tempting to conclude that T-helper

cells carry on their receptor molecules idiotypic determinants which are coded for by  $V_H$  genes in the *Ig-1* complex. It should be stressed that this is compatible with the view that helper cells pick up immunoglobulin receptors from B cells rather than synthesizing them themselves (16, 17). However, we do not favor this possibility for a variety of reasons and in particular in the light of recent observations by Binz and Wigzell (personal communication) suggesting that in rats, idiotypic T-cell receptors for alloantigens are synthesized by purified T-cell populations.

In summary, the data presented here support the notion that variable portions of T-helper cell receptors and humoral antibody are coded for by the same genes in the heavy-chain linkage group. However, we are aware that the data do not formally prove this point. As an alternative interpretation one could envisage that helper cells (*a*) bear receptors which cross-react with immunoglobulin idiotypes and (*b*) require for their anti-idiotypic activation the presence of idiotypic immunoglobulin, e.g. idiotypic B-cell receptors, in the environment. In this picture, helper cell receptors could be encoded by V genes in the *I* region of *H-2*, yet T-cell activation by anti-Id would appear to be controlled by the *Ig-1* complex. Our main argument for considering this a rather remote possibility is the exquisite specificity of the idiotypic system. The A5A and S117 idiotypic markers are strictly strain specific despite the extreme diversity of the immunoglobulin system. It is hard to believe in a set of *I*-region V genes the diversity of which would be such that it would allow the expression of products which cross-react with the A5A and/or the S117 idiotypes in a variety of *H-2* haplotypes. Clearly, however, experimental work is required in order to decide the matter definitively.

The notion that the same genes code for variable portions of T- and B-cell receptors has to be reconciled with the *Ir*-gene phenomenon. *Ir* genes in the major histocompatibility complex appear to control antigen recognition by T cells, and recent experiments of Munro et al. (18) and Tada et al. (19) in mice indeed indicate the presence of *H-2*-controlled Ia determinants on antigen-specific T-cell factors. One might speculate, therefore, that either T lymphocytes express two entirely unrelated recognition systems or that the T-cell receptor molecule is composed of products of both V genes in the *Ig-1* complex and genes in the major histocompatibility complex.

### Summary

When the IgG1 fraction of anti-idiotypic antibodies raised in guinea pigs is injected into mice, sensitization of idiotypic T and B lymphocytes occurs (1-3). In the present study we analyze the genetic requirements for T-helper cell sensitization by anti-idiotypic antibody. This was done by measuring, in a suitable panel of mouse strains, helper cell responsiveness to two anti-idiotypic reagents which recognize distinct, strain-specific idiotypes, namely the A5A and the S117 marker.

Whenever helper cell sensitization by anti-idiotypic antibody was successful, helper function could be specifically inhibited by the same and only the same anti-idiotypic. This indicates that helper cells induced by anti-idiotypic antibody express idiotypic determinants on their receptors for antigen.

Helper cell sensitization by anti-idiotypic antibody was found in all strains expressing the corresponding or a cross-reactive idio type at the immunoglobulin level. Idiotypic-negative strains were always unresponsive to anti-idiotypic stimulation. In addition, responsiveness did not depend on the *H-2* haplotype. Since the A5A and the S117 idio type are markers for V genes in the heavy-chain linkage group, the present results support the view that the same genes in the *Ig-1* complex code for variable portions of immunoglobulins and T-helper cell receptors.

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