

IMMUNOLOGICAL STUDIES OF T-CELL RECEPTORS

II. Limited Polymorphism of Idiotypic

Determinants on T-Cell Receptors Specific for Major Histocompatibility Complex Alloantigens*

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Recently, several groups have produced anti-idiotypic (α Id) antisera which have provided important probes for characterization of antigen specific receptors on thymus-derived (T)¹ lymphocytes (1-9). A combination of serologic, genetic, and immunochemical studies using these anti-idiotypic reagents has established that T-cell receptors specific both for conventional antigens and for alloantigens of the major histocompatibility complex (MHC) share idiotypes with immunoglobulin (Ig) molecules. These findings can be taken as evidence that antigen specific T-cell receptors are encoded, at least partially, by Ig-variable (V) region genes.

Some of these same studies have also demonstrated genetic polymorphism in the expression of MHC receptors on T cells from different inbred strains of rats and mice. Antisera raised by immunization of Lewis/DA F₁ rats with Lewis T cells, bearing α DA MHC receptors, Lewis/DA α (Lewis α DA) antisera, react with Lewis α DA blast cells from mixed lymphocyte cultures (MLC), but not with BN α DA MLC blast cells (10). Further genetic studies showed that expression of the α DA T-cell receptors of the Lewis genome was linked to the IgA allotype locus (11). In mice, similar genetic studies with α Id antisera indicated that expression of α MHC T-cell receptors on MLC blast cells is associated with two different, unlinked loci; the first controls Ig-heavy chain allotypes and the second is the MHC itself (12). Because of the importance of this finding both in considerations of the identity of antigen receptor molecules on T cells and also for understanding of the phenomenon of alloaggression, these studies must be confirmed, ideally with several different systems.

Despite concerted efforts on our part, we have been unable to produce anti-idiotypic antibodies to α MHC T-cell receptors. However, these efforts have generated evidence that α MHC receptors can evoke strong T-cell mediated immune responses in rats (13-15). This evidence comes from the observation that T cells from parental strain (A) rats are unable to cause graft-versus-host (GVH) reactions in irradiated A/B F₁ rats if the recipients have been treated before irradiation with small numbers of strain A T cells. These inoculations with A T cells have no effect on the GVH reactivity of T cells from the other parental strain, B (13, 14). From a variety of approaches we

* Supported by grants from the U. S. Public Health Service AI-1096, CA-15822, and CA-09140.

¹ Abbreviations used in this paper: α Id, anti-idiotypic; GVH, graft-versus-host; Ig, immunoglobulin; MHC, major histocompatibility complex; MLC, mixed lymphocyte cultures; T, thymus-derived; V, Ig-variable.

TABLE I*
Rat Strains Used in this Study and Their Immunogenetic Markers

Strain	Designation	Ag-B	I α	I κ	Source
Fischer 344	F	1	1a	1b	‡
Lewis	L	1	1a	1a	‡§
Wistar/Furth	WF	2	1a	1a	§
Brown Norway	BN	3	1a	1a	‡, §
L.B3	L.B3	3	1a	1a	Dewitt, U. Utah
Aug.B3	Aug.B3	3	1.	1a	
DA	DA	4	1.	1b	§
August 28807	AUG	5	1.	1a	§

* From a review by Gasser, 1977 (16).

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concluded that the specific resistance to GVH disease induced under these circumstances reflects a host-T-cell-mediated immune response to α MHC receptors (A α B) on the donor strain A T cells (15).

In this paper we demonstrate that this immunity is also effective for α B receptors on third party strain (C, D, E, . . .) T cells some of which differ with respect to both Ig and MHC phenotypes. Contrary to the findings with α Id antisera (10–12), we are led to conclude that T-cell α MHC idiotypes recognized by other T cells show little or no polymorphism. This finding could be taken as evidence that α MHC T-cell receptors may be encoded by highly conserved germ line genes.

Materials and Methods

The rat strains together with a list of their relevant immunogenetic markers are shown in Table I (16). The L.B3 strain contains the B3 MHC haplotype derived from the BN strain. It was derived ultimately from the colonies of O. Štark (17). It has been tested here in Philadelphia and shown to carry both the MLC and serological markers of the B3 haplotype.

Rats of the AUG.B3 strain contain the B3 MHC haplotype of BN on the AUG background. The animals were derived from F₂ matings of 11th backcross parents; it also has been shown to carry the MLC and serological markers of the BN strain Ag-B3 MHC and none of the AUG Ag-B5 MHC haplotype.

All other procedures involved in the preparation of lymphocyte suspensions, the induction of GVH resistance, and in the conduct of GVH mortality assays have been described earlier (15).

Results

Preliminary Considerations: GVH Resistance in F₁ Hybrid Rats Suppresses Immune Reactivity of Parental Strain T Cells Specific for Both Major and Minor Alloantigens of the Host. Earlier studies clearly demonstrated that F₁ rats (A/B α A) previously immunized with parental strain lymphocytes (A) specifically suppress GVH reactions of A strain lymphocytes against host B alloantigens (13–15). Table II shows results of a study with MHC congenic rat strains that confirm and extend our previous conclusion (15) that the suppressed parental T-cell clones include those bearing receptors specific for major (MHC) and minor alloantigens. For example (group A 3), prior inoculation of L/BN rats with BN lymphocytes can be presumed to induce an immune response against subpopulations of BN T cells bearing receptors for B1 MHC alloantigens as

TABLE II
GVH Resistance Reflects an Immune Response Directed to T-Cells Reactive to MHC Alloantigens

Experimental group	Recipients*	Mortality (dead/total) after inoculation with:							
		L		BN		L.B3		BN/L.B3	
		$(\alpha B3 \text{ MHC } \alpha BN \text{ minor})\ddagger$		$(\alpha B1 \text{ MHC } \alpha L \text{ minor})$		$(\alpha B1 \text{ MHC } \alpha BN \text{ minor})$		$(\alpha B1 \text{ MHC})$	
		50§	100	50	100	50	100	50	100
A1	L/BN	7/7		7/7		5/5		3/3	2/2
2	L/BN α L	0/7		7/7		7/7	3/3	4/4	2/2
3	L/BN α BN	7/7		0/9	0/5	1/6	2/3	0/3	0/3
4	L/BN α L.B3	8/8		2/7	0/2	0/4		0/3	0/3
5	L/BN α BN/L.B3	3/3	2/2	0/3	0/2				
		AUG		BN		AUG.B3			
		$(\alpha B3 \text{ MHC } \alpha BN \text{ minor})$		$(\alpha B5 \text{ MHC } \alpha AUG \text{ minor})$		$(\alpha B5 \text{ MHC } \alpha BN \text{ minor})$			
		50		50		50			
B1	AUG/BN	4/4		4/4		4/4			
2	AUG/BN α BN	4/4		0/7		0/4			

* Recipients immunized with 50×10^6 TDL from indicated sources; they were irradiated (450 rads) 7 d after immunization.

‡ Relevant specificities of GVH-inducing T cells.

§ 50×10^6 or 100×10^6 TDL from indicated sources injected on day of irradiation to cause systemic GVH disease.

well as against other BN T-cell populations that are specific for L minor alloantigens. Such an immune response in L/BN α BN rats against α MHC receptors is clearly revealed by the complete suppression of GVH reactivity of cells from both BN and BN/L.B3 donors. For genetic reasons, the only relevant T-cell clones from BN/L.B3 donors capable of causing GVH disease in L/BN rats are those which have specificity for B1 MHC alloantigens of L.

This experiment also suggests that GVH resistance involves suppression of T cells specific for minor alloantigens: L/BN α BN rats are completely resistant to α L GVH reactivity of BN cells even in large numbers, but they are partially vulnerable to large numbers of L.B3 cells. It seems probable that the α B1 receptor bearing clones of BN and L.B3 cells are completely suppressed in L/BN α BN rats and that GVH disease caused by L.B3 cells is a result of clones having specificity for BN minor alloantigens.

An important question is raised by these findings. L/BN α BN animals suppress α B1 GVH reactions by T cells from BN, BN/L.B3, and L.B3 donors; similarly AUG/BN α BN rats suppress GVH reactions of BN and AUG.B3 T cells. Thus, the α B1 receptors of T cells of BN and L.B3 donors are antigenically crossreactive or are identical, as are the α B5 receptors of BN and AUG.B3 donors. This finding suggests two possible models for genetic control of the expression of α MHC receptors on T cells: namely that (a) they are encoded in the MHC itself, or else (b) they are encoded elsewhere in the genome, and are antigenically similar regardless of genetic background. This important question is the subject of the following studies in this paper.

Similarity of α B1 Receptors. Table III is a summary of several experiments, including

TABLE III
Similarity of $\alpha B1$ Receptors of L.B3, BN, and BN/DA Rats

Recipients	Mortality (dead/total) after inoculation with:															
	L($\alpha B3$)*				BN($\alpha B1$)				BN/DA($\alpha B1$)				L.B3($\alpha B1$)			
	25	50	100	200	25	50	100	200	25	50	100	200	25	50	100	200
L/BN	14/14	5/5	2/2	19/19	5/5	7/7	4/4	4/4	2/2	1/1			4/4	5/5		
L/BN αL	0/5	1/9	3/10	3/26		3/3	4/4	8/8	3/3	6/6				7/7	3/3	
L/BN αBN	3/3	2/2	4/4	2/2	0/2	0/2	0/1	0/2	1/3	1/6			1/6	2/3		
L/BN $\alpha L.B3$		8/8			2/7	0/2							0/4			

See Table II footnotes.

* Specificity of relevant alloreactive clones causing GVH disease.

TABLE IV
Similarity of $\alpha B3$ Receptors of L and DA Rat Strains

Recipients	Mortality (dead/total) after inoculation with:																			
	L($\alpha B3$)*				BN($\alpha B1$)				DA($\alpha B3, \alpha B1$)				DA-L($\alpha B3$)				L/DA($\alpha B3$)			
	25	50	100	200	25	50	100	200	25	50	100	200	25	50	100	200	25	50	100	200
L/BN	14/14	5/5	2/2	19/19	5/5	7/7	4/4	4/4	2/2	3/3	2/2	1/1	1/1	1/1	1/2		2/2	2/2	1/1	
L/BN αL	0/5	1/9	3/10	3/26		3/3	4/4	8/8	0/2	3/5	5/6	4/4	0/3	0/2	2/3		0/5	0/7	0/1	
L/BN αBN	3/3	2/2	4/4	2/2	0/2	0/2	0/1	0/2				3/3					3/3	2/2		

See Table II footnotes.

* Specificity of relevant alloreactive clones causing GVH disease; mortality caused by L and BN lymphocytes is the same control data presented in Table III.

data from Table II, which demonstrates that immunization of L/BN rats with BN cells causes the suppression of $\alpha B1$ GVH reactivity of T cells from both BN and BN/DA donors, and that similar immunization with L.B3 cells suppresses $\alpha B1$ GVH reactions of both L.B3 and BN lymphocytes. These results demonstrate the antigenic similarity of $\alpha B1$ receptors encoded in the L, BN, and DA genomes.

Similarity of $\alpha B3$ Receptors of L and DA Rat Strains. Data in Table IV shows that GVH immunity demonstrable in L/BN rats for $\alpha B3$ receptors of the L genome extends to $\alpha B3$ receptors on TDL from a third party strain, DA, differing from L with respect to both background and MHC genes. For this study, L/BN αL rats, presumed to have an immunity to $\alpha B3$ receptors of the Lewis strain, were injected with TDL from the following sources: L, reactive to B3 MHC ($\alpha B3$); BN ($\alpha B1$); DA ($\alpha B1$ and $\alpha B3$); DA-L ($\alpha B3$) from DA donors negatively selected for reactivity to B1 by acute filtration through DA/L rats; and L/DA TDL ($\alpha B3$).

The results show that L/BN αL rats were marginally resistant to DA TDL, significantly resistant to DA-L TDL and fully resistant to L and L/DA TDL populations. Thus, it appears that $\alpha B3$ receptors of the L and DA genomes are similar.

Similarity of $\alpha B3$ Receptors of Lewis and Fischer 344 Rat Strains. Rats of the L and F strains are phenotypically identical at the MHC, with one known exception (18), and they display numerous differences involving minor alloantigen loci in the rest of their genomes. In the experiments shown in Table V, L/BN αL rats are resistant to GVH disease caused by TDL from L and from F donors, demonstrating the similarity of L $\alpha B3$ and F $\alpha B3$ receptors. The reverse combination L/BN αF was not resistant to

TABLE V
Similarity of α B3 Receptors of L and F

Recipients	Mortality (dead/total) after inoculation with:					
	L		BN		F	
	50	100	50	100	50	100
L/BN	7/7		7/7		2/2	3/3
L/BN α L	0/5		7/7		2/6	2/4
L/BN α BN	7/7		0/7		3/3	2/2
L/BN α F	5/5				0/4	0/3

See Table II footnotes.

GVH disease caused by L TDL; this may indicate some difficulty in generating immunity to α MHC receptors when other antigenic differences prevail.

Discussion

The principal finding of this study is that A/B F₁ hybrid rats derived from matings of MHC-incompatible parent strains (A, B) injected with immunocompetent T lymphocytes of one parental strain (e.g., A), (a) specifically suppress α B-GVH reactivity of lymphocytes from strain A donors, (b) resist α B-GVH reactivity of lymphocytes from MHC incompatible third-party donor strains (C, D, E, ...), and yet (c) remain fully vulnerable to α A-GVH reactions caused by lymphocytes from any donor strain, parental (B) or otherwise.

This finding has direct relevance for several questions dealing with functional T-cell specificity and the nature of antigen-specific receptors on T cells. Before considering these however, it is important to establish whether the GVH resistance assay used in these studies does indeed represent a host immune response to α MHC receptors on parental T cells. Several sources have been tested for their ability to induce GVH resistance, and the only ones found to be effective are T-cell populations containing demonstrable alloreactivity for host alloantigens (13-15), and alloantisera specific for host alloantigens (6, 9). T-cell populations negatively selected for alloreactivity to host MHC antigens (A-B) are unable to induce GVH resistance to A T cells in A/B hosts, but are fully effective in A/C hosts (13-15). Purified populations of B lymphocytes depleted of T cells, and suspensions of nonlymphoid cells are routinely ineffective (13). These findings indicate that the immunogenic molecule in GVH resistance is clonally distributed and is associated with immunocompetence to host alloantigens.

The general alternative explanation, namely that target immunogens in GVH resistance are surface molecules peculiar to parental cells other than antigen-specific receptors cannot be formally dismissed in the absence of direct biochemical evidence; however there are several observations in this and in previous studies that raise objections to this explanation.

(a) The immunogen does not seem to be unique to homozygous donors, for example, a recessively expressed alloantigen(s). Data in Tables II, III, and IV show that A/B rats immunized with T cells from strain A donors suppress α B GVH responses of lymphocyte populations from homozygous A donors; they suppress α B-GVH reactivity of heterozygous third party A/C F₁ donors as well.

(b) The results with MHC congenic combinations (Table II) would suggest that if the target immunogen is a surface molecule of T cells other than a receptor, it must be encoded by the MHC. Furthermore, because F_1 's suppress GVH reactivity by T cells from the immunizing parent, but not T cells from the other parent, it could be concluded that the target immunogen is uniquely different for each MHC haplotype. This conclusion conflicts with the data of Table IV, showing that the target immunogen can be shared by MHC incompatible strains. Thus, for example, L/BN α L animals suppress GVH reactions by T cells from both L and DA donors, especially if the latter have been negatively selected for reactivity to L alloantigens, leaving alloreactivity for BN antigens intact.

Finally, (c) experiments currently in progress deal with the possibility that the immunogen in GVH resistance is a nonclonally distributed MHC-gene product requiring ongoing allogeneic effects occurring during a GVH reaction to be immunogenic. According to this possibility, the determinants should be present on parental, e.g. L, T cells regardless of their MHC reactivity, and therefore it should be possible to transfer GVH resistance against L T cells adoptively from L/BN α L donors to both L/BN and L/DA irradiated recipients. Thus far, attempts to suppress L α DA GVH reactions in L/DA hosts after adoptive transfer of spleen cells from L/BN α L donors, made tolerant of DA alloantigens at birth, have failed.

Given these considerations, it seems most likely that the immunogenic targets in GVH resistance are the receptor molecules on T lymphocytes specific for MHC alloantigens, and therefore, that the underlying basis of GVH resistance is an immune response against antigenic determinants of antigen specific T-cell receptors. Results of previous studies of the conditions under which this immunity can be transferred adoptively to irradiated syngeneic secondary F_1 recipients indicated that it is mediated by F_1 T cells (15). Thus, these conclusions carry the direct implication that T cells can recognize and respond to antigenic determinants present on antigen specific receptors of other T cells and it seems valid, therefore, to employ this model of GVH resistance as an alternative approach to questions of the genetic control of the expression of MHC receptors on T cells.

Thus far we have refrained from referring to the determinants on MHC specific receptors described in these studies as idiotypes (Id). This term has been reserved in the past to indicate the set of antigenic determinants unique to a particular variable domain of antibody or receptor molecules recognized by anti-idiotypic antibody (α Id). Because they may not be totally shared, Eichmann (19) has distinguished between idiotypic determinants detected by antisera raised against antibody molecules (BId) and idiotypic determinants detected by antisera raised against T cells (TId). Formally, at least, there is a possibility that some of the antigenic determinants of the variable domains of receptor molecules may not be immunogenic for B cells although they may induce T-cell responses, and vice versa. It seems justified, therefore, to extend the Eichmann idio type classification to distinguish between idiotypic determinants detected by B-cell immune responses and those detected by T-cell responses.

The studies described in this paper were designed to explore genetic factors controlling expression of T-cell idiotypes of α MHC receptors as detected by T cells. The approach using the model of GVH resistance is based on the same principals used by others for idiotypic analysis of antibody molecules and antigen specific receptors on T lymphocytes with anti-idiotypic sera (6, 7, 19, 20). Those studies

demonstrated the specific binding by parental T cells of anti-idiotypic antibodies raised against alloantibodies, an important observation which indicates the sharing of variable region domains by T cell receptors and antibody molecules. In turn, this is considered as partial evidence that α MHC T-cell receptors are encoded, at least in part, by immunoglobulin variable region genes. Several studies with α Id reagents have demonstrated polymorphism in the expression of α MHC receptors (6, 8, 10–12) and that inheritance in both mice and rats of a particular idio type is linked to heavy chain allotype genes (6, 11, 12). In addition, one study (12), but not others (6, 10) has shown that expression of a particular α MHC idio type detected with α Id reagents made against MLC blasts is also linked to the MHC locus itself. This important observation was interpreted as an indication that α MHC T-cell receptors may also be encoded by MHC genes.

In the present studies, rather than anti-idiotypic antibodies, an immune response mediated by T cells was used to probe the extent of idio typic similarity of α MHC T-cell receptors expressed in different strains of rats. The results can be generalized as follows:

(a) A/B F₁ rats immunized with α MHC receptors on strain A T cells specific for host B MHC alloantigens suppress function of A α B T Cells, but not B α A T cells. This clearly indicates that idiotypes of A α B and B α A T cell receptors detected by T cells are not antigenically cross-reactive gene products in this assay.

(b) A/B α A recipients can also suppress T cells of third party strains (C, D, E, . . .) reactive to the same B host alloantigens. This suppression of α B-GVH reactivity is somewhat difficult to detect with T cells from homozygous third party donors because they carry the potential for GVH reactivity for both of the parental MHC haplotypes of the recipient (e.g., C α A, C α B). However, it is particularly marked with third-party T cells from genetically tolerant heterozygous (A/C) donors reactive only to the B MHC haplotype and also with homozygous third-party cells if they have been negatively selected for the appropriate MHC haplotype (C-_A).

The simplest and most direct interpretation that can be placed on these findings is that T cells can detect antigenic determinants associated with α MHC receptors on other T cells, that these idio typic determinants are unique for each of the different α MHC specificities, and that T-cell receptors of a particular MHC specificity encoded in different genetic backgrounds carry similar, if not identical idiotypes. The apparent idio typic identity in different strains of α MHC receptors for a particular MHC haplotype seems to be a general finding; the present studies show the similarity of 3 different α MHC specificities in 5 different rat strains, α B1 receptors from BN, DA, and L (Tables II, and III), α B3 receptors of L, F, and DA (Tables IV, and V), and α B5 from BN and AUG (Table II). It should be noted that some of these combinations which show idio typic identity, for example α B1 receptors of BN and DA strains and α B3 receptors of DA and L strains, also differ with respect to Ig genes controlling κ -light chain and α -heavy chain allotypes in addition to MHC (Table I). Therefore, an important conclusion to be drawn from these data is that idiotypes of α MHC receptors of a particular specificity detectable by T cells are shared, at least by several strains in the species, showing little, if any, polymorphic diversity associated with MHC or Ig loci.

This conclusion carries several important implications for questions of the genetic control of α MHC receptors and of the relationship between alloreactivity and self-MHC restricted T-cell responses to conventional antigens. First, it indicates that

MHC receptors are encoded by shared genes of a highly conserved locus (loci) and are therefore quite likely to be constructed, at least partially, from germ line gene products, a possibility that has been suggested before (21).

Secondly, it provides strong evidence against the view that the alloreactive T-cell repertoire evolves from clones of T cells reactive to conventional antigens in the context of self-MHC gene products. It is difficult to understand, for example, how α A-allo-specific receptors in strain B animals evolving from α self B receptors, and α A-allo-receptors deriving in strain C animals from α self C receptors develop identical idiotypes.

Third, the suggestion that the specificity repertoire associated with T-cell responses to MHC alloantigens is not generated from the heterogeneous groups of α self reactive clones in turn adds further weight to the question of what the normal function in the individual of alloreactive T cell clones might be. Despite their vast majority in the recirculating T cell pool, the collection of alloreactive T-cell clones may have no function in self-MHC restricted T-cell responses to conventional antigens unless the gene products which function as α MHC receptors are not allelically excluded on T cells. Alternatively, T-cell responses to conventional antigens in vivo may not show the degree of restriction to self-MHC gene products that they display in various culture systems. Then, according to a two receptor model, one specific for MHC antigens and the other specific for conventional antigens, the alloreactive T-cell pool may function in vivo via its repertoire of receptors specific for conventional antigens.

Thus far neither iso- nor allo-anti-idiotypic antibodies has been described which are specific for the nonpolymorphic idiotypes of T cell receptors detectable by T cells. Why these determinants do not stimulate the production of anti-idiotypic antibodies is not clear, however two interesting possibilities seem worth consideration: (a) idiotypes detected by T cells may be linear peptide fragments of T-cell receptors which are more highly conserved, whereas B-cell responses to T-cell idiotypes may be preferentially directed to conformational, three dimensional determinants of the receptor molecule; (b) T-cell responses to T-receptor idiotypes may be more easily and rapidly generated than B-cell responses, and they may exert a significant suppression of B-cell responses. At present, there is no information which favors either of these two possibilities, however the second possibility would provide a rational explanation for the difficulty that several laboratories have experienced in their attempts to produce anti-idiotypic antibodies to α MHC T-cell receptors.

Summary

These studies explore the extent of genetic polymorphism in the expression of anti-MHC receptors by T cells in different strains of rats. This question was approached with the use of the model of specifically induced GVH resistance in F₁ rats which has been shown to reflect a specific T-cell mediated immune response against parental strain T cell anti-MHC receptors specific for host alloantigens. When A/B F₁ rats derived from MHC incompatible matings are immunized with lymphocytes from one parental strain (A) they display a specific resistance to anti-B GVH reactivity caused by T cells from that parental strain, but not anti-A GVH reactions from the other. In addition, they resist anti-B GVH reactivity by T cells from third-party donors (C, D, E, ...), a finding taken to indicate that the idiotypes of anti-MHC receptors on T cells, recognized by other T cells, show little or no polymorphism. This conclusion

suggests that anti-MHC receptors are shared in the species and may be encoded, at least partially, by germ-line genes.

The authors are particularly grateful to Dianne Wilson, Karen Nowell King, and Joan Taylor for help in the conduct of these studies, to Doctors Jonathan Sprent, William Elkins, Baruj Benacerraf, and Martin Raff for very helpful discussions concerning the interpretations placed on the experimental results, and finally to Doctors Sprent and Thomas McKearn for critical comments of the manuscript.

Received for publication 25 September 1978.

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