Brief Definitive Report

Major Histocompatibility Complex-restricted Recognition of Retroviral Superantigens by Vβ17+ T Cells

By Marcia A. Blackman,* Frances E. Lund,‡ Sherri Surman,* Ronald B. Corley,‡ and David L. Woodland*

*From the *Department of Immunology, St. Jude Children's Research Hospital, Memphis, Tennessee 38105, and the ‡Department of Microbiology and Immunology, Division of Immunology, Duke University Medical Center, Durham, North Carolina 27710*

Summary

It has been established that at least some Vβ17+ T cells interact with an endogenous superantigen encoded by the murine retrovirus, Mtv-9. To analyze the role of major histocompatibility complex (MHC) class II molecules in presenting the Mtv-9 encoded superantigen, vSAG-9 to Vβ17+ hybridomas, a panel of nine hybridomas was tested for their ability to respond to A20/2J (H-2^d) and LBK (H-2^a) cells which had been transfected with the vSAG-9 gene. Whereas some of the hybridomas recognized vSAG-9 exclusively in the context of H-2^a, other hybridomas recognized vSAG-9 exclusively in the context of H-2^d or in the context of both H-2^d and H-2^a. These results suggest that: (*a*) the class II MHC molecule plays a direct role in the recognition of retroviral superantigen by T cells, rather than serving simply as a platform for presentation; and, (*b*) it is likely that components of the TCR other than Vβ are involved in the vSAG-9/TCR/class II interaction.

Superantigens are defined by their ability to stimulate high frequencies of T cells based predominantly on the Vβ component of the TCR. Bacterial superantigens are toxins produced by certain strains of bacteria, whereas endogenous superantigens are encoded by the 3′ LTR of the mouse mammary tumor virus (MMTV) (1–3).

T cell recognition of superantigen differs from recognition of conventional antigen in two fundamental ways. First, in contrast to recognition of conventional antigen, which is dependent upon contributions of both the α and β chains of the TCR to the combining site, T cell recognition of superantigen is mediated primarily through the Vβ element of the receptor. Second, T cell recognition of superantigen is not classically MHC restricted (1–3).

The Mtv-9 encoded superantigen (vSAG-9) interacts with most murine Vβ5.1+, Vβ5.2+, Vβ11+, Vβ12+, and Vβ17+ T cells (4, 5, and D. L. Woodland and M. A. Blackman, unpublished results). Here, we investigate the role of MHC class II molecules in presenting this endogenous superantigen by examining the response of a panel of Vβ17+ T cell hybridomas to Mtv-9 3′LTR transfectants that express vSAG-9 in the context of either H-2^d or H-2^a. It is surprising that hybridomas are shown to distinguish between vSAG-9 presented on different MHC alleles, resulting in a form of MHC restriction. This observation contrasts strongly with the view that T cell responses to retroviral superantigens are independent of the MHC haplotype of the presenting cell, and suggests that non-Vβ (Dβ, Jβ, Vα, Jα) elements of the TCR influence its interaction with the MHC class II/superantigen complex.

Materials and Methods

Cells. The Vβ17+/CD4+ hybridomas were derived from C57/L (H-2^b) T cells as described previously (6). 11-40 (Vβ11+/CD4+) and KE8 (Vβ5.1+/CD4+) are T cell hybridomas that react with the Mtv-9 3′LTR encoded superantigen, vSAG-9, as detailed elsewhere (4, 5). The Mtv-9 3′LTR, under the control of the human β-actin promoter, was transfected into A20 or LBK, as previously described (5, and Lund, et al., manuscript submitted for publication). For this study, we used two A20/2J transfectants, 1H10 and 2C3, and two LBK transfectants, 3G9 and 3H3. A20/2J is derived from BALB/c (I-A^d, I-E^d) mice, and LBK is an in vitro-adapted subclone of CH12 that is derived from B10.H-2^{a}H-4^{b}p-Wts (I-A^k, I-E^k) mice.

Stimulation Assays. 10^5 responding hybridomas were cultured either with 10^5 B cell tumors (A20/2J, LBK, or Mtv-9 3′LTR transfectants), 10^6 LPS/IL-4–treated spleen cells (7), or immobilized anti-TCR antibody in duplicate 250-μl cultures. Supernatants were tested for IL-2, as previously described (7). Responses of the hybridomas to staphylococcal enterotoxin D (SED) (Toxin Technology, Sarasota, FL) was determined in the standard stimulation assay by including varying concentrations (10, 1, 0.1, or 0.01 μg/ml)

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of SED in the presence of A20 or LBK. Antibody inhibition assays were done in the standard stimulation assay by adding purified antibodies (5 μg/ml) to the cultures. The mAbs 10-3.6 (anti-I-$A\beta^k$) and 14.4.4S (anti-I-E) were generously provided by Dr. John Freed (National Jewish Center for Immunology, Denver, CO) and MKD6 (anti-I-A^d) was purchased from Becton Dickinson & Co. (San Jose, CA). All of these antibodies brightly stained the relevant transfectants and parental B cell lines, were capable of inhibiting IL-2 production in appropriate controls, and were not nonspecifically toxic (data not shown).

Results

MHC-restricted Recognition of vSAG-9 by Vβ17⁺ Hybridomas. We had previously shown that at least some Vβ17⁺ hybridomas respond to a superantigen encoded by the retroviral integrant Mtv-9 (vSAG-9) (5). To further investigate the interaction, we screened a panel of 41 Vβ17⁺CD4⁺ T cell hybridomas derived from C57L (H-2^b) mice for reactivity against spleen cells from B10.D2 (H-2^d, Mtv-9⁺) or B10.BR (H-2^k, Mtv-9⁺) mice (6). Approximately half of the hybridomas (20 of 41) were reactive to B10.D2 and/or B10.BR spleen cells. However, whereas some of the hybridomas responded exclusively to B10.BR spleen cells (13 of 20), other hybridomas responded either exclusively to B10.D2 spleen cells (3 of 20), or to spleen cells from both strains (4 of 20; data not shown). This result was surprising, because T cell interaction with other endogenous superantigens had not revealed an MHC-restricted pattern of reactivity.

To eliminate the possibility that these findings were due to the expression of multiple retroviral superantigens by the spleen cells, we analyzed the responses of a selected panel of nine Vβ17⁺/CD4⁺ hybridomas to two sets of transfectants expressing vSAG-9 in the context of H-2^d or H-2^a. The response of the hybridomas to the transfectants correlated directly with the MHC-restricted reactivity observed on B10.D2 and B10.BR spleen cells (Table 1). Thus, some of the hybridomas (2B23-10, -11, and -12) were H-2^a (A^kE^k)–restricted, in that they responded to vSAG-9 presented on LBK transfectants but not A20/2J transfectants. Conversely, other hybridomas (2B23-40 and -53) were H-2^d–(A^dE^d) restricted, in that they responded to vSAG-9 presented by A20/2J transfectants but not LBK transfectants. The hybridoma, 2B23-18, responded to vSAG-9 presented on both types of transfectants, and this dual reactivity did not segregate in subclones (data not shown). Some of the hybridomas (2B23-8, -26, and -30) failed to respond to any of the transfectants, despite the fact that they secreted IL-2 in response to immobilized anti-Vβ17 antibody, and they responded to IE⁺ spleen cells from mice expressing MHC haplotypes other than H-2^k and H-2^d (see Discussion section). The MHC-restricted pattern of vSAG-9 recognition by Vβ17⁺ hybridomas cannot be explained by a failure of vSAG-9 to bind to class II molecules on either H-2^d or

Table 1. *Response of Vβ5.1⁺, Vβ11⁺ and Vβ17⁺ Hybridomas to vSAG-9 Presented on Spleen Cells, A20/2J Transfectants, and LBK Transfectants**

		Spleen cells‡		A20 transfectants (H-2^d)			LBK transfectants (H-2^a)			Immobilized	
Hybridoma	(Vβ)	B10.D2	B10.BR	A20	1H10	2C3	LBK	3H3	3G9	KJ23 (anti-Vβ17)	Jβ Usage§
None	–	–*	–	–	–	–	–	–	–	–	–
11-40	(11)	112	325	–	129	47	–	126	346	ND	ND
KE8	(5.1)	56	200	–	800	653	–	1,166	1,211	ND	ND
2B23-10	(17)	–	253	–	–	–	–	133	373	340	2.1
2B23-11	(17)	–	65	–	–	–	–	20	427	560	1.2
2B23-12	(17)	–	20	–	–	–	–	320	1,013	1,920	2.6
2B23-40	(17)	267	–	–	87	80	–	–	–	187	2.1
2B23-53	(17)	840	–	–	820	987	–	–	–	1,080	2.2/2.3
2B23-18	(17)	90	445	–	230	507	–	1,333	1,333	1,066	2.3
2B23-8	(17)	–	–	–	–	–	–	–	–	100	2.6
2B23-26	(17)	–	–	–	–	–	–	–	–	400	2.5
2B23-30	(17)	–	–	–	–	–	–	–	–	1,920	1.2

* Hybridoma responses are presented as IL-2 secretion in U/ml as outlined in Materials and Methods. Responses below the level of detection (<10 U/ml) are indicated by a dash (–). Data represent the mean responses of at least three independent experiments.
‡ Spleen cells were pretreated with LPS and IL-4 to enhance vSAG-9 expression as described by Woodland et al. (7).
§ Jβ usage by the Vβ17⁺ hybridomas was previously determined by Blackman et al. (6).

H-2^a presenting cells, since both of these haplotypes are good presenters of vSAG-9 to 11-40 (Vβ11$^+$) and KE8 (Vβ5.1$^+$), hybridomas previously shown to recognize vSAG-9. Thus, the reactivity of Vβ17$^+$ T cells to endogenous superantigens showed a strong and unexpected influence of the MHC haplotype of the presenting cells.

Class II Presentation of vSAG-9. To clarify exactly which class II molecules are involved in the presentation of the Mtv-9 superantigen, we tested the ability of various MHC class II specific antibodies to inhibit the response of Vβ17$^+$ hybridomas to vSAG-9 presented by H-2^d (1H10) or H-2^a (3G9) transfectants (Table 2). Those hybridomas that responded to vSAG-9 in the context of H-2^d (11-40, KE8, 2B23-18, -40, and -53) were strongly inhibited by antibodies specific for I-E^d (14-4-4), but not I-A^d (MKD6), indicating that this response is specific for the I-E^d molecule. Those hybridomas that responded to vSAG-9 in the context of H-2^a (11-40, KE8, 2B23-10, -11, -12, and -18) showed a surprising restriction pattern. The response of these hybridomas to the H-2^a transfectant (3G9) was partially blocked by antibodies specific for either I-A^k (10-3.6) or I-E^k (14-4-4S), and was completely blocked by combinations of these two antibodies. This pattern was observed consistently in several experiments, and suggests that these hybridomas recognize vSAG-9 presented in association with both I-A^k and I-E^k. This observation was unexpected since Vβ17$^+$ T cell responses have been genetically mapped to the I-E molecule.

Jβ Does Not Correlate with the MHC Restriction Pattern of vSAG-9 Reactivity of Vβ17$^+$ Hybridomas. Although the Vβ element of the TCR dominates vSAG-9 reactivity of Vβ17$^+$ T cells, some other elements of the receptor may be responsible for conferring the property of MHC restriction. However, comparison of TCR Jβ usage (previously determined by Blackman, et al., reference 6) with the MHC-restricted pattern of vSAG-9 recognition revealed no obvious correlation (Table 1). For example, two hybridomas, 2B23-40 and 2B23-10, both use the same Jβ2.1 element in the construction of their receptors, despite the fact that they have very different restriction patterns (2B23-40 is I-E^d restricted whereas 2B23-10 is I-A^k and I-E^k restricted). Similarly, hybridomas with identical restriction patterns (2B23-11 and 2B23-12) use very different Jβ elements (Jβ1.2 and Jβ2.6, respectively).

MHC-restricted Recognition of Bacterial Superantigens. Because there are functional similarities between superantigens from retroviruses and bacteria, we tested the ability of Vβ17$^+$ hybridomas to recognize the bacterial superantigen SED presented on either H-2^d (A20/2J) or H-2^a (LBK) (Table 3). All of the Vβ17$^+$ hybridomas and 11-40 (Vβ11$^+$) responded to SED presented by either A20/2J or LBK, irrespective of their MHC restriction for vSAG-9. The inability of KE8 to recognize SED presented on any MHC haplotype is consistent with the fact that murine Vβ5.1$^+$ T cells do not recognize this superantigen (1).

Table 2. *Inhibition of Hybridoma Responses to vSAG-9 by mAbs Specific for MHC Class II Molecules**

		Inhibitory antibodies‡					
Hybridoma	Stimulator	None	MKD6 (A^d)	10-3.6 (A^k)	14-4-4s (E^d/E^k)	MKD6$^+$ 14-4-4s (A^d,E^d/E^k)	10-3.6$^+$ 14-4-4s (A^k,E^d/E^k)
11-40	1H10	160	320	80	–*	–	–
KE8	1H10	1,280	1,280	1,280	–	–	–
2B23-40	1H10	640	640	640	–	–	–
2B23-53	1H10	2,560	2,560	2,560	–	–	–
2B23-18	1H10	640	640	640	–	–	–
11-40	3G9	5,120	5,120	160	80	160	–
KE8	3G9	5,120	5,120	320	320	640	–
2B23-10	3G9	5,120	5,120	640	640	1,280	–
2B23-11	3G9	320	320	–	–	–	–
2B23-12	3G9	>5,120	>5,120	2,560	320	320	–
2B23-18	3G9	5,120	2,560	1,280	640	640	20

* The responses of a panel of Vβ5.1$^+$, Vβ11$^+$, and Vβ17$^+$ hybridomas to either a LBK transfectant (3G9) (H-2^a) or an A20/2J transfectant (1H10) (H-2^d) were measured in the presence of purified mAbs specific for various MHC class II molecules as described in Materials and Methods. Hybridoma responses are presented as U/ml IL-2 and responses below the level of detection (<10 U/ml) are indicated by a dash (–). The data are representative examples of three or more independent experiments.

‡ The relevent specificities of each antibody are shown under each antibody's name.

Table 3. *Response of Vβ11⁺, Vβ5.1⁺, and Vβ17⁺ Hybridomas to the Bacterial Superantigen, SED, Presented by either A20/2J or LBK**

Hybridoma	A20/2J + SED‡				LBK + SED‡				Immobilized H57-597 (anti-TCR)
	10	1	0.1	0	1	0.1	0.01	0	
None	–*	–	–	–	–	–	–	–	–
11-40	>1,280	>1,280	>1,280	–	>1,280	>1,280	>1,280	–	>1,280
KE8	–	–	–	–	–	–	–	–	>1,280
2B23-10	640	–	–	–	1,280	160	–	–	640
2B23-11	1,280	640	–	–	1,280	640	40	–	640
2B23-12	>1,280	>1,280	20	–	>1,280	>1,280	160	–	>1,280
2B23-40	>1,280	320	–	–	>1,280	1,280	–	–	1,280
2B23-53	1,280	160	–	–	>1,280	640	–	–	>1,280
2B23-18	1,280	40	–	–	>1,280	640	–	–	640
2B23-8	1,280	–	–	–	1,280	160	–	–	640
2B23-26	>1,280	1,280	–	–	>1,280	1,280	20	–	1,280
2B23-30	>1,280	–	–	–	>1,280	40	–	–	>1,280

* Hybridoma responses are presented as U/ml IL-2 secreted as described in Materials and Methods. Responses below the level of detection (<10 U/ml) are indicated by a dash (–). The data are a representative example of three independent experiments. No hybridomas responded to SED (10 μg/ml) in the absence of presenting cells.
‡ SED concentrations are in μg/ml.

Discussion

Whereas the requirement for class II in the presentation of superantigens has been established, the molecular details of the interaction are unclear. It has been suggested that both retroviral and bacterial superantigens function by simultaneously binding to the class II molecule of the presenting cell and the Vβ element of the responding T cell (2). In this model, the MHC class II molecule acts simply as a generic support for the superantigen, which is consistent with the observations that superantigen stimulation of individual T cells is essentially independent of the class II haplotype of the presenting cells. The general hierarchy of presentation of bacterial and retroviral superantigens to T cells can largely be explained by differences in the affinity of the superantigen for a particular MHC class II allele. However, in several examples, the responses of individual hybridomas and clones to bacterial superantigens have exhibited MHC allelic and isotypic preference that cannot be attributed simply to differences in superantigen binding to MHC (8–10). The data presented in this paper extend these observations to show that T cell responses to endogenous superantigens can be MHC restricted.

We have studied the response of Vβ17⁺ hybridomas to a series of transfectants which express the MMTV superantigen, vSAG-9, and found, unexpectedly, that there was an MHC haplotype–restricted pattern of recognition. Whereas some hybridomas responded to vSAG-9 presented exclusively by H-2^d transfectants, others responded exclusively to H-2^a transfectants. The MHC-restricted response patterns cannot be simply attributed to (*a*) differences in levels of class II or vSAG-9 expression on the transfectants; (*b*) preferential binding of vSAG-9 to class II molecules of one or the other haplotype; or (*c*), influence of adhesion molecule interactions such as LFA-1/intercellular adhesion molecule-1, since both the H-2^d and H-2^a transfectants and spleen cells are good presenters of vSAG-9 to appropriate hybridomas.

The simplest explanation for the MHC-restricted interaction between Vβ17⁺ hybridomas and vSAG-9⁺ transfectants is that there is a direct interaction either between the TCR and the class II molecule itself, or between the TCR and an MHC haplotype–specific dominant peptide presented on class II. This is consistent with the idea that superantigen binding may force the intimate contact of the TCR with class II, as originally proposed by Janeway et al. (2). It is possible that superantigen recognition is generally not MHC restricted because the interactions between superantigen and class II, or between superantigen and TCR are strong, rendering the forced intimacy between TCR and class II irrelevant. However, if either of the interactions is weak, the contact between non-Vβ elements of the TCR with polymorphic determinants on the class II molecule may either stabilize, or interfere with, the TCR/class II/superantigen complex, resulting in MHC-biased patterns of recognition. Thus, the finding that recognition of vSAG-9, but not SED, by Vβ17⁺ hybridomas was MHC restricted, could be explained either by the differences

in binding affinity of vSAG-9 and SED with class II, or by the differences in strength of interaction of Vβ17 elements with vSAG-9/class II and with SED/class II.

The finding that the recognition of vSAG-9 by Vβ17$^+$ hybridomas is MHC restricted contrasts starkly with data on the recognition of other endogenous retroviral superantigens by T cells. For example, Mls-1 is presented by several different MHC haplotypes, and most Mls-1 reactive hybridomas and clones respond strongly to Mls-1/H-2^k and Mls-1/H-2^d (3, 11–13). In terms of the model described above, a likely possibility is that Mls-1 has a higher affinity for the class II molecule and/or Vβ element than vSAG-9, such that an interaction between class II and TCR does not influence the specificity.

The data presented here suggest that the TCR directly interacts with the MHC class II molecule during the recognition of vSAG-9. This interaction likely involves non-Vβ elements of the TCR since the Vβ17 element is encoded by a single member gene family. Although analysis of Jβ usage did not reveal an obvious role for Jβ in the MHC restriction of these cells, it is possible that the Dβ element DβJβ junction, or α chain elements control the MHC specificity. Alternatively, the MHC specificity may be determined by combinatorial determinants contributed by both the α and β chains, obscuring a simple correlation with individual elements of the TCR. We have independent data that shows a role for the TCR-α chain in recognition of Mls-1 by a panel of hybridomas bearing an identical (transgenic) Vβ8.1$^+$ beta chain (14).

One intriguing result of our studies is that 3 of 3 of the k-restricted hybridomas recognized vSAG-9 in the context of both I-E^k and I-A^k. This contrasts with genetic analyses that have suggested that only I-E molecules are able to mediate the clonal elimination of Vβ17$^+$ cells (15). However, it is possible that the original genetic analyses were misleading because only the few strains that express Vβ17 could be examined, and because the stronger deletion on I-E masked the weaker contribution of I-A. Recently, the Vβ17-expressing TCR locus has been backcrossed onto a number of MHC-congenic strains of mice (16). Analysis of these mice support a role for I-A^k–mediated deletion of Vβ17$^+$ T cells. Thus, in Vβ17-expressing B10.A(4R)$_{\beta L}$ mice (I-A^k, I-E$^-$), the percentage of Vβ17$^+$ T cells was reduced, compared with C57/L mice (I-A^b, I-E$^-$), and the low frequency of Vβ17$^+$ T cells was dominant in I-A^b/I-A^k heterozygous mice, consistent with clonal deletion. These data are in agreement with our finding that at least some Vβ17$^+$ T cells recognize vSAG-9 in the context of I-A^k. In support of this, recent data has shown that Vβ17$^+$ T cells interact with additional MMTV encoded superantigens presented in association with I-A molecules (17).

It is not clear why only some (20 of 41) of the Vβ17$^+$ T cell hybridomas responded to the vSAG-9$^+$ spleen cells. The lack of response was not due to either low levels of CD4 or TCR, nor to an inability to produce IL-2. Moreover, the hybridomas all responded strongly to SED illustrating that they are able to respond to at least some superantigens. One possible explanation, predicted by our model, is that these hybridomas recognize vSAG-9 in the context of MHC molecules other than either H-2^d or H-2^a. In support of this, the original typing of these hybridomas revealed reactivity to spleen cells of haplotypes not tested here, such as I-E$\alpha^d\beta^s$ (6).

Taken together, these studies illustrate a central role of class II molecules in presenting retroviral superantigens to T cells. It is likely that each component of the class II/TCR/superantigen trimolecular complex interacts with the other two components, and that each of these interactions contributes to the overall avidity of the complex. The interactions between TCR and class II may play a major role in T cell recognition of superantigen if the association between class II and superantigen and/or superantigen and TCR is weak.

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Address correspondence to David L. Woodland, Department of Immunology, St. Jude Children's Research Hospital, 332 North Lauderdale, Memphis, TN 38105.

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