Rat T Cell Responses to Superantigens. II. Allelic Differences in Vβ8.2 and Vβ8.5 β Chains Determine Responsiveness to Staphylococcal Enterotoxin B and Mouse Mammary Tumor Virus-encoded Products

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Summary

The previous paper in this series demonstrates that rat T cells developing de novo in the presence of mouse mammary tumor virus (Mtv) antigens in rat → severe combined immunodeficiency (SCID) mouse xenochimeras display a distinct pattern of Vβ-restricted deletion; this deletion pattern is remarkably similar to that occurring during thymic development of mouse T cells in Mtv^+ strains. In addition, T cells developing in the absence of Mtv antigens in these rat → mouse xenochimeras are tolerant of host antigens, but show strong primary proliferative responses in cultures stimulated with $Mtv\text{-}7^+$ (Mls^a) mouse cells; like the mouse, these rat T cell responses are dominated by Vβ6 and Vβ8 T cells. Here, we continue analysis of rat T cell responses to superantigens; we show that T cells from Lewis and Fischer 344 rats expressing Vβ8.2 display an important all-or-nothing difference in their responses to Mtv-7 superantigens. This all-or-none strain difference in the response to Mtv-7 applies also to the response by Vβ8.2 and Vβ8.5 T cells to the soluble superantigen staphylococcal enterotoxin B. Because these two rat strains express different alleles of these two Vβ8 family members, this finding identifies additional, hitherto unreported residues of the T cell receptor β chain important in T cell responses to superantigens.

In the preceding paper (1), evidence is presented that rat T cells closely resemble mouse T cells in possessing strong Vβ-restricted reactivity for mouse mammary tumor virus (Mtv)[1] superantigens. This evidence came from studies on rat-derived T cells developing in immunodeficient C.B-17 SCID mice reconstituted with fetal liver (FL) cells from Lewis (LEW) rat embryos. Provided that rat FL cells are coinjected with mature mouse B cells, the rat T cells arising in the chimeras display an extensive pattern of Vβ-restricted clonal deletion in response to various endogenous Mtv antigens of the host. Interestingly, this pattern of Vβ deletion is remarkably similar to the deletion pattern seen in normal mice. In addition to responding to mouse Mtv antigens in terms of clonal deletion, T cells from rat → mouse chimeras mount strong proliferative responses to non-self Mtv antigens, i.e., to the Mtv-7 (Mls^a) antigens of the BALB.D2 and DBA/2 strains.

In this paper we show that proliferative responses of T cells from LEW FL → SCID mouse chimeras to Mtv-7 antigens involve Vβ6 and Vβ8.2 T cells. Surprisingly, however, this does not apply to chimeras prepared with FL cells from the Fischer 344 (F344) strain. Here the Mtv-7 response involves Vβ6 cells but not Vβ8.2 T cells. The ability of LEW but not F344 Vβ8.2 T cells to respond to mouse Mtv-7 antigens also applies to responses to a soluble superantigen, staphylococcal enterotoxin B (SEB). Genomic sequences of Vβ8.2 (and also Vβ8.5) indicate that LEW and F344 express different alleles of these two Vβ8 family members (Gold, D.P., S. Wiley, and D.B. Wilson, unpublished data). These findings identify residues distant from the defined superantigen combining site (2–5) that have not previously been appreciated to be involved in responses to superantigens.

Materials and Methods

Animals. Female rats of the LEW, F344, and ACI strains were purchased from Harlan Sprague Dawley, Inc. (Indianapolis, IN). Female DA rats were purchased from Bantin and Kingman, Inc. (Fremont, CA). Rats were 3–4 mo of age when used as donors for cell cultures. LEW and F344 → C.B-17 SCID chimeras were prepared as described (1).

[1] *Abbreviations used in this paper:* F344, Fischer 344; FL, fetal liver; LEW, Lewis; Mtv, mammary tumor virus; SEB, staphylococcal enterotoxin B.

Antibodies. mAbs specific for rat T cell markers TCR-α/β (R73 [6]), Vβ8.2 (R78) (7), Vβ8.5 (B73) (7), CD4 (OX-38) (8), and activated CD4$^+$ T cells (OX-40) (9) were obtained from PharMingen (San Diego, CA). Biotin-modified rat F(ab')$_2$ anti-mouse IgG (H+L) was purchased from Accurate Chemical & Scientific Corp. (Westbury, NY).

Con A and rSEB Cultures. Lymph node cells (1.5×10^6/ml) were cultured in RPMI 1640 (6 ml) supplemented with FCS (8% [vol/vol]), 2-ME (5×10^{-5} M), glutamine (2 mM), penicillin/streptomycin (100 μg/ml), indomethacin (1 μM; Sigma Chemical Co., St. Louis, MO), and either Con A (3 μg/ml; Calbiochem, San Diego, CA) or recombinant SEB (rSEB; 2 μg/ml). The rSEB was generously provided by Dr. John Kappler (National Jewish Hospital, Denver, CO) (10). After 3 d in culture, cells were expanded further in complete medium supplemented with supernatant (10%) from rat spleen cells activated with Con A for 48 h, as a source of IL-2, and methyl α-D-mannopyranoside (50 mM; Sigma Chemical Co.). T cell blasts were harvested 48 h later.

MLR Cultures. MLR cultures were established as described (1). Activated T cell blasts from the MLR cultures were purified by centrifugation through a stepwise Percoll gradient for 30 min at 1,400 *g*. Blast cells were harvested from the top of the 1.07-density Percoll layer.

Flow Cytometric Analysis. T cell blasts from Con A- and rSEB-stimulated cultures were labeled with the indicated anti-rat TCR mAbs on ice for 30 min, washed to remove unbound antibody, incubated for 20 min on ice with biotin-modified rat F(ab')$_2$ anti-mouse IgG (H+L), washed again, and then incubated for 20 min with PE-streptavidin (Biomeda, Foster City, CA). Labeled cells were analyzed on a FACScan® flow cytometer (Becton Dickinson & Co., Sunnyvale, CA). T cell blasts recovered from MLR cultures were doubly stained with the indicated anti-TCR mAbs and anti-CD4, or with OX-38 and OX-40 mAbs as described earlier (1).

Determination of TCR Vβ Usage. Relative Vβ utilization among populations of T cells recovered from cultures was determined by a semiquantitative PCR assay (1).

Results

Strain Differences in the Vβ8.2 T Cell Response to Mtv-7. In the accompanying paper (1), we report that T cells arising in LEW FL → C.B-17 SCID mouse chimeras are tolerant of host-type BALB/c (and C.B-17) stimulators in vitro but give strong proliferative responses to DBA/2 and BALB.D2. Since BALB/c and BALB.D2 are congenic strains that differ

Table 1. *PCR Analysis of TCR Vβ Usage by T Cells from LEW and F344 Rat → SCID Mouse Xenochimeras in Response to Mtv-7*

	LEW → SCID			F344 → SCID		
Vβ	None	BALB.D2	DBA/2	None	BALB.D2	DBA/2
1	1	1	1	2	6	1
2	2	4	7	6	10	2
3	1	0	1	3	1	0
4	7	1	2	3	1	0
5	0	2	1	1	1	0
6	27	51	45	16	61	85
7	0	1	1	5	2	2
8.2	2	10	11	14	3	4
8.5	3	2	3	4	2	2
8.6	3	8	3	4	2	0
9	5	2	2	5	1	1
10	12	3	3	6	2	0
11	1	0	0	4	1	0
12	0	0	0	0	0	0
13	0	1	0	0	0	0
14	13	3	3	3	2	1
15	10	4	4	4	1	0
16	0	0	1	2	0	0
17	2	0	2	3	0	0
18	1	1	3	2	0	0
19	5	1	2	8	1	0
20	3	1	2	4	2	0

Unstimulated rat T cells or T cell blasts stimulated in culture with mouse spleen cells for 5 d were assessed for TCR Vβ utilization by PCR. Blasts were purified by Percoll gradient. Values expressed are percent of total Vβs.

only at the *Mtv*-7 locus, the proliferative MLC response of chimera rat T cells to BALB.D2 (and DBA/2) is presumed to be directed to Mtv-7 antigens. As shown in Table 1, culturing T cells from LEW FL → SCID chimeras with Mtv-7$^+$ BALB.D2 or DBA/2 stimulators generates T cell blasts that, measured by PCR, are selectively enriched for two Vβs, i.e., Vβ6 and Vβ8.2; the enrichment for these cells correlates with the selective elimination of Vβ6 and Vβ8.2 cells in Mtv-7$^+$ chimeras, i.e., in LEW FL → SCID chimeras coinjected with DBA/2 B cell blasts that express Mtv-7 antigens (1). Other Vβ members, for example, Vβ2, sometimes showed modest increases, but this was variable from animal to animal.

Different results apply to F344 FL → SCID chimeras. T cells from these animals give strong MLR responses to DBA/2 and BALB.D2. In this situation, however, the blast response does not involve Vβ8.2 T cells and is largely restricted to Vβ6 cells.

These data apply to detection of Vβ by PCR. Vβ analysis by flow cytometry (limited to Vβ8.2, with Vβ10 as a control) is shown in Fig. 1 *a*. In this experiment, T cells from LEW → SCID chimeras and LEW FL → SCID chimeras injected at birth with BALB/c B cell blasts (1) were cultured in vitro with BALB.D2 or DBA/2 stimulators. With these two Mtv-7$^+$ stimulators, a high proportion of the OX-40$^+$ CD4$^+$ blasts in the cultures were Vβ8.2$^+$ (25–35%). With Mtv-7$^-$ H-2-different B10.BR stimulators, by contrast, there was no enrichment for Vβ8.2$^+$ T cells. Control Vβ10$^+$ T cells were rare with BALB.D2 and DBA/2 stimulators, but were somewhat increased with B10.BR stimulators. These data refer to LEW chimeras. With F344 chimeras (F344 → SCID), stimulation with BALB.D2 and DBA/2 cells also generated large numbers of OX-40$^+$ blast cells, but here very few of these blasts were Vβ8.2$^+$.

The above data indicate, both by PCR and flow cytometry, that the response of Vβ8.2$^+$ T cells to Mtv-7 applies only to LEW and not to F344 T cells. As shown in Fig. 1 *b*, this strain difference in the response of rat Vβ8.2$^+$ cells to Mtv-7 also applies to primary MLR by normal (nonchimeric) T cells. Thus, in marked contrast to LEW T cells, culturing normal F344 T cells with BALB.D2 stimulators fails to cause a selective enrichment in Vβ8.2 T cells (relative to BALB/c stimulators).

The data presented below indicate that the inability of F344 Vβ8-bearing T cells to respond to Mtv-7 also applies to responses to SEB.

Strain Differences in the Vβ8.2 and Vβ8.5 T Cell Response to rSEB. In a previous study we demonstrated by PCR analysis that T cells from LEW rats preferentially use Vβ7, 8.2, 8.5, and 14 in the proliferative response to rSEB in culture (11). During the course of those studies, we noted that whole T cell populations from the DA strain responded well to rSEB, but T cells of the Vβ8.2 subset did not. With the recent description of two mAbs specific for Vβ8.2 and Vβ8.5 T cells of the rat (7), we were able to confirm and extend these findings.

Fig. 2 presents the results of a flow cytometric analysis

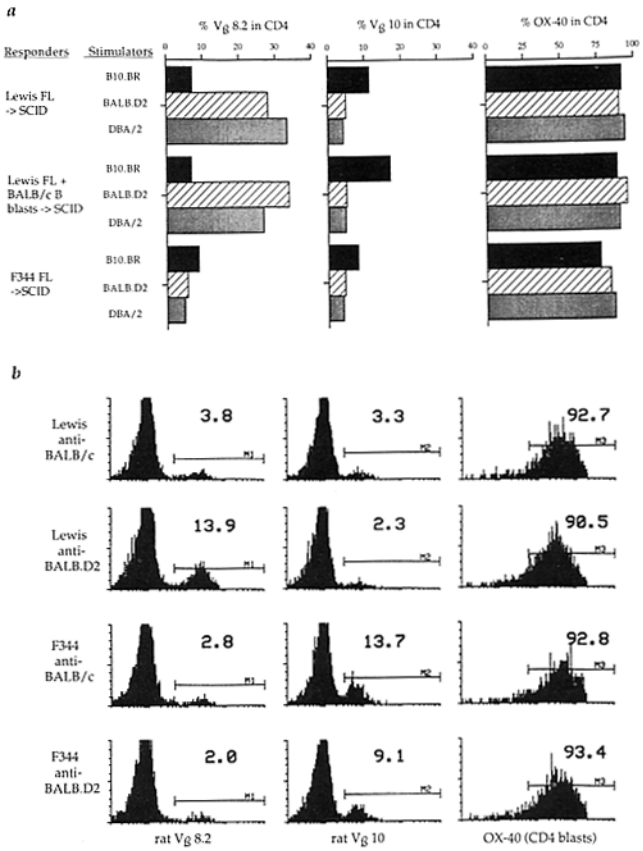

Figure 1. Percent rat Vβ8.2$^+$ and Vβ10$^+$ cells among activated (*OX-40*$^+$) CD4 T blasts derived by FACS® analysis of MLC stimulated with third-party (*B10.BR*) or Mtv-7$^+$ (*BALB.D2* and *DBA/2*) spleen cells. Responders are LN cells from (*a*) LEW FL → SCID (with or without BALB/c B cell blasts) and F344 FL → SCID xenochimeras, or (*b*) normal LEW and F344 donors. Vβ8.2 T cells from LEW and LEW → SCID chimera donors respond to Mtv-7, but Vβ8.2 T cells from F344 and F344 → SCID donors do not.

showing the percent TCR-α/β^+, Vβ8.2$^+$, and Vβ8.5$^+$ T cell blasts present after stimulation in culture with Con A or with rSEB. Blasts were gated on the basis of forward and orthogonal light scatter criteria. These results indicate that Vβ8.2 and Vβ8.5 T cells from LEW donors, normally present at the level of 5–7% of the peripheral T cell pool, make a substantial contribution to the blast population stimulated with rSEB, but T cells of these two subsets from F344 donors do not.

Table 2 presents a summary of comparisons of Vβ8.2 and Vβ8.5 T cell responses to SEB involved several different rat strains. The results show that the frequency of LEW Vβ8.2 and Vβ8.5 T cells responsive to rSEB is two- to threefold higher than the response to Con A, while for the other strains, it is about the same or less. The Vβ8.2 and Vβ8.5 T cell responses to Con A were similar among the three strains and approximated the level found among normal, nonstimulated T cells.

Predicted Amino Acid Sequences of the TCR Vβ8.2 and Vβ8.5 Chains. Genomic clones encoding for both the Vβ8.2 and

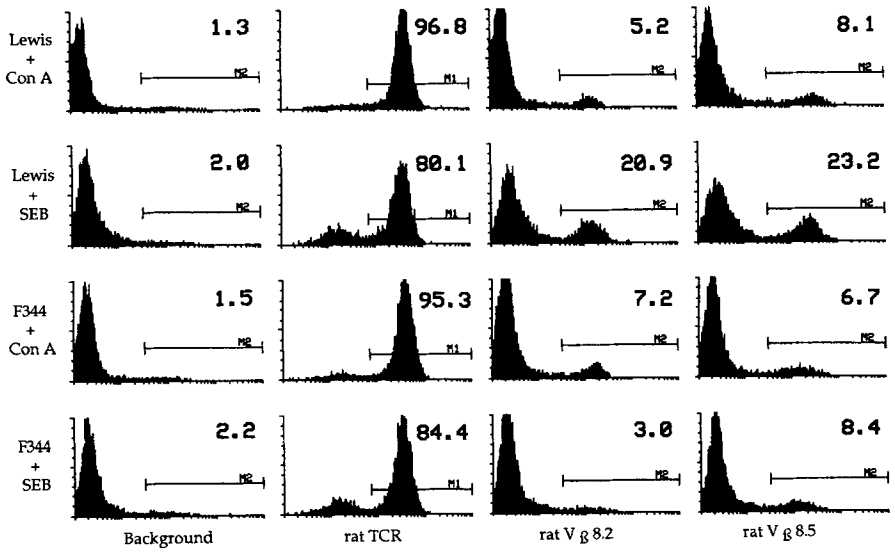

Figure 2. Flow cytometric analysis of rat TCR-α/β, Vβ8.2, and Vβ8.5 expression among T cell blasts from cultures stimulated with Con A or rSEB. Vβ8.2 and Vβ8.5 T cells from LEW donors respond to rSEB, but F344 T cells bearing these Vβ8 family members do not.

Vβ8.5 gene segments were sequenced from liver DNA of F344, DA, and ACI rats (Gold, D. P., S. Wiley, and D. B. Wilson, manuscript in preparation); the predicted amino acid sequences are shown in Table 3. Sequences for the Vβ8.2 gene segments from F344, DA, and ACI animals are identical for these three rat strains, as are the sequences for the Vβ8.5 chain. Both gene segments encode functional genes, but of particular interest, both display allelic differences from the published predicted sequences for these β chain segments in LEW animals (12, 13).

Discussion

This study explores responses by Vβ8.2$^+$ and Vβ8.5$^+$ T cells from different rat strains to two different superantigens. The general finding here is that T cells from some rat strains bearing these TCR β chain members respond to these superantigens while T cells from other strains do not. This all-or-nothing difference in response to these two superantigens correlates with polymorphic sequence differences in the Vβ8.2 and Vβ8.5 TCR β chains known to exist in these strains.

When stimulated with the Mtv-7 superantigen, Mls^a, Vβ8.2 T cells from normal LEW donors respond in xenogeneic rat–mouse MLC cultures to Mtv-7$^+$ BALB.D2 stimulator cells, but contribute almost no cells to the population responding to H-2-identical Mtv-7$^-$ stimulators. Vβ8.2 T cells from F344 donors give no response to Mtv-7 (Fig. 1 *b*). Similarly, LEW and F344 T cells made tolerant of mouse H-2^d MHC antigens as a consequence of thymic development in rat → SCID mouse chimeras show a major differ-

Table 2. *Flow Cytometric Analysis of Strain-specific Differences in Responses to rSEB by Vβ8.2 and V8.5 T Cells*

		Percent of blast cells			
Strain	Stimulus	Control	R73 TCR-α/β	R78 Vβ8.2	B73 Vβ8.5
LEW	Con A	2.6	99	6.3	9.1
	rSEB	1.2	83	21	24
F344	Con A	1.6	98	7.7	7.5
	rSEB	2.4	86	3.0	8.2
DA	Con A	2.9	99	9.0	7.3
	rSEB	0.9	83	3.3	3.8
ACI	Con A	1.1	98	7.7	6.2
	rSEB	4.9	70	3.4	5.3

Lymph node cells from the indicated strains were incubated with either Con A or rSEB for 3 d. Surviving cells were isolated and further expanded for 2 d in medium supplemented with Con A supernatant. Results are given as percent of blast cells expressing TCR-α/β, Vβ8.2, or Vβ8.5. Blasts were gated on the basis of forward and orthogonal light scatter critera.

Table 3. *Predicted Amino Acid Sequences for the LEW and F344 TCR Vβ8.2 and Vβ8.5 Chains*

Rat	Vβ	1	10	20	30	40	50	60	70	80	90
LEW	8.2*	EAAVTQSPRNKVTLKGGKVTLSCKQNNNHNMYWYRQDMGHGLRLIHYSYDVNSTEKGDVPNGYKVSRPSQGDFFLTLESASPSQTSVYFCASS
F344	8.2‡	.....S.....V.....D.....
LEW	8.5§	EAAVTQSPRNKVTVTGKNVTFNCHQTDNHNYMYWYRQDMGHGLRLIHYSYGSGSFENGDIPEGYKVSRPNQENFFLTLESASPSQTSVYFCASS
F344	8.5‡	.....K.....S.....

* Smith et al. (12).
‡ Gold, D.P., S. Wiley, and D.B. Wilson (manuscript in preparation).
§ Hashim et al. (13). This sequence corresponds to Vβ8.3 published by Smith et al. (12).

ence in the response of Vβ8.2 T cells to Mtv-7 antigens; LEW T cells contribute ~30% of blasts to the responding population, while F344 T cells contribute <5% (Fig. 1 *a*).

For the SEB superantigen, T cells from LEW, F344, DA, and ACI rats all show strong proliferative responses; exposure to this superantigen for a few days stimulates the T cell population to the extent that it consists mainly (70–100%) of blast cells, the magnitude of the response being similar to that occurring in cultures stimulated with Con A. But, unlike the response to Con A, there appears to be a highly selective, all-or-none difference with respect to whether T cells expressing the Vβ8.2 and Vβ8.5 gene segments contribute to the SEB-responsive population. LEW T cells expressing these two β chain members selectively contribute 20–25% to the SEB-stimulated blast populations, a proportion three- to four-fold greater than that contributed to Con A–stimulated blasts, whereas T cells bearing these two TCR β chain members from F344, DA, and ACI rats show no response to SEB (Fig. 2 and Table 2).

What element(s) might account for the all-or-none response of Vβ8.2 and Vβ8.5 T cells to these superantigens? The simplest and most direct interpretation is that these response differences stem from differences in the primary amino acid sequence of the Vβ8.2 and Vβ8.5 alleles (Table 3). Three amino acids distinguish SEB and Mtv-7 responder LEW Vβ8.2 chains from nonresponder F344 Vβ8.2 chains: these occur at positions 9 (R vs. S), 14 (L vs. V), and 62 (N vs. D). To our knowledge this is the first reported example of allelism being associated with responsiveness, or lack of it, to these two very different kinds of superantigens. Similarly, two amino acids at positions 15 (T vs. K) and 83 (P vs. S) are associated with responsiveness or nonresponsiveness of Vβ8.5$^+$ T cells to SEB.

Other explanations for the difference in responsiveness of Vβ8.2 and Vβ8.5 T cells from LEW and F344 donors to superantigens can be considered. For example, might some gene(s) other than those encoding TCR β chain alleles be involved? This seems unlikely since whole populations of T cells from F344 donors are fully responsive to both SEB and Mtv-7; whether or not a given T cell responds depends on a particular allele of a given TCR β chain.

Several structure–function studies have helped to define the precise residues of the TCR β chain thought to be responsible for recognition in responses to superantigens (2–5). These involve sequence comparison of allelic TCR β chain gene products where one allows for T cell responses to a given superantigen and another does not (2, 4). Sequence comparisons have also been conducted on closely related members of a given β chain family (5), and the functional consequences of sequence differences have been confirmed by direct mutagenesis studies (3). Results of these studies focus on the importance of residues surrounding positions 19–26 on the B β-strand and 68–76 on the loop between the D and E β-strands, using the Chothia alignment where position 23 is cys (14), in the response of murine Vβ8.2$^+$ T cells to Mtv-7. Certain residues in these two regions of the β chain are also associated with Vβ17 responses to some unknown

Table 4. *Summary of TCR Vβ Polymorphisms in Rats and Mice Associated with Responsiveness to SEB and Mtv-7*

Vβ	Animal	SAg response		Amino acid position										Reference
				9	10	14	15	24	30–31	51–53	62	72–73	83	
8.2	LEW	SEB/Mls	+	**R**	**N**	**L**	**K**	**K**		**GSG**	**N**	**GD**	**P**	12
	F344		–	**S**	**N**	**V**	**K**	**K**		**GSG**	**D**	**GD**	**P**	This paper
	ER34	Mls	+		**S**	**V**		**D**	**DY**	**GAD**	**D**	**KE**	**P**	2
	C57Bl/6		–		**N**	**V**		**N**	**NN**	**GAG**	**D**	**EN**	**P**	2
8.5	LEW	SEB	+	**R**		**V**	**T**	**H**			**E**	**EN**	**P**	13
	F344		–	**R**		**V**	**K**	**H**			**E**	**EN**	**S**	This paper
8.1	C57Bl/6	Mls	+			**V**		**H**		**VAD**	**D**	**EN**	**L**	2

ligand associated with I-E molecules in the mouse (4), and with the response of human Vβ13.1 and 13.2 T cells to the *Staphylococcus aureus* toxin SEC2 (5). These residues, although situated at opposite ends of the primary sequence, have been predicted from computer modeling studies, based on the crystal structure of Ig, to lie juxtaposed on the surface of the TCR molecule in the β-pleated sheets that contribute to the framework of the β chain; this site is accessible to the aqueous interface of the molecule and is located well away from the CDR surface believed to interact with conventional peptide antigen/MHC complexes (14, 15). The region around residues 68–76 has been suggested to be a fourth hypervariable region in Ig molecules (HV4), but it is not known to be involved in antigen binding (14).

The present studies suggest two conclusions. First, it seems clear that other regions of the TCR β variable chain segment are also involved in superantigen responses. The sequence differences associated with responsiveness by rat Vβ8.2 T cells to SEB and Mtv-7 reside at positions 9, 14, and 62, and differences associated with Vβ8.5 responsiveness to SEB reside at positions 15 and 83. These two regions are thought to lie well away from the site responsible for recognition of MHC/peptide antigen (14, 15), but also they appear to be quite removed from the HV4 region reported to be important in responses to Mls superantigens (3).

Second, it is tempting to consider the possibility that a particular amino acid or combination of them, in a given TCR β chain, may be directly involved in the TCR binding interaction to a superantigen that leads to activation. Evidence for such a notion would be provided by the finding that a particular amino acid residue at a given position is always associated with responsiveness (or the lack of it) to a superantigen. But, such predictions based on residues at a given position appear not to be possible. Table 4 is a summary that compares the amino acid residues present at various positions of allelic TCR β chains in mice and rats where one allelic product is responsive to a superantigen and the other is not. For example, in the rat changes from R to S, L to V, and N to D at positions 9, 14, and 62 of the Vβ8.2 chain are associated with an all-or-none difference in the response to rSEB and Mtv-7. Yet these residues of the responder Vβ8.2β chain are present in the nonresponder Vβ8.5 chain; likewise V^{14} and D^{62} present in the nonresponder Vβ8.2 chain are also present in the responder Vβ8.5 chain. This occurs also in mice. Others have focused on the KE to EN substitution at position 72–73 that distinguishes Mls responder and nonresponder Vβ8.2 alleles (2), yet EN is expressed on the mouse Vβ8.1 chain that is responsive to Mtv-7. This situation suggests that the role of a given amino acid residue in the response to a superantigen might be an indirect one, for example, causing a conformational difference at a distant site, and that predictions of superantigen responsiveness based on amino acid residues at a given position on the TCR β chain can be considered only in the context of the total sequence.

We appreciate the technical help of Deanna Mueller and Sandra Wiley.

This study was supported by United States Public Health grants AI-21487, AI-22519, AI-31451, AI-33011, CA-25803, and CA-38355. C.D. Surh is a Special Fellow of the Leukemia Society of America.

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Received for publication 2 July 1993.

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