

SELF H-2 ANTIGENS INFLUENCE THE SPECIFICITY OF ALLOREACTIVE CELLS*

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The products of the major histocompatibility complex (MHC)¹ play an important role in antigen recognition by T lymphocytes. Experimentally, this becomes apparent through (a) the high frequency of T lymphocytes specific for foreign MHC antigens as compared to conventional antigens (1–4), a phenomenon generally referred to as alloreactivity, and (b) the more recent observation that conventional antigens are recognized by T lymphocytes only in the context of the responding animal's own MHC antigens (5–8), a phenomenon commonly called MHC restriction.

Jerne's theory (9)—formulated well before the discovery of MHC restriction—assigns a central role to self MHC antigens in the generation of the T cell-receptor repertoire: It proposes that pre-T cells express clonally distributed receptors for the MHC antigens of the species. Precursors that express receptors for non-self MHC antigens give rise to the peripheral alloreactive T cell pool without changing their receptor specificity. On the other hand, those precursors possessing receptors for self MHC antigens are stimulated to proliferate and undergo a change in receptor specificity upon recognition of self antigens. Only those descendants of these clones that no longer react with self antigens are permitted to leave the thymus. They form the pool of mature peripheral T-cells specific for conventional antigens.

Experimental evidence confirming the importance of self MHC antigens in the generation of the T cell-receptor repertoire was provided not only by the discovery of H-2 restriction itself, but also, and more directly, by the studies of Bevan (10) and of Zinkernagel et al. (11) that show that H-2 restriction of murine T lymphocytes is not determined by the lymphocytes' own H-2 type, but rather by that of the environment in which they mature. In these experiments, bone marrow stem cells from mice heterozygous at the H-2 complex were transferred to lethally irradiated animals of the H-2 homozygous parental strains. The T cells that had differentiated in the thymus of these chimeric animals, although they were themselves of F₁ type, were predominantly restricted to recognizing antigens in the context of the recipient's H-2 type. This learning of H-2 restriction during differentiation in the thymus (11, 12) is well explained by Jerne's theory: T cells specific for conventional antigens are derived from precursors recognizing the MHC antigens of their thymic environment. There

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¹ *Abbreviations used in this paper:* AKD2, (AKR/J × DBA/2J)F₁; B10. C57BL/10Sn; Con A, concanavalin A; CTL, cytotoxic T lymphocyte(s); H, histocompatibility; MHC, major histocompatibility complex; MLC, mixed lymphocyte culture(s); self-plus-X, conventional antigens ("X") in the context of self MHC antigens; TNP, trinitrophenyl.

is, on the other hand, little evidence to support or disprove the theory's prediction that alloreactive T cells constitute a population separate from the one specific for conventional antigens. Experiments demonstrating that alloreactive cytotoxic T lymphocytes (CTL) can cross-react on hapten-modified, syngeneic target cells (13), and that CTL specific for minor histocompatibility (H) antigens (14) or viral antigens (15) can also react with allogeneic targets support the view that alloreactive T cells are in fact part of the T cell pool specific for conventional antigens ("X") in the context of self MHC antigens (self-plus-X). Jerne's proposal for the development of alloreactive cells can, however, be put to a more direct test by asking the question: Are alloreactive T cells, like those specific for self-plus-X, influenced in their specificity by the MHC products of the environment in which they mature?

In the present experiments, we have stimulated T lymphocytes from radiation chimeras of the types $[A \times B \rightarrow A]$ and $[A \times B \rightarrow B]$ with H-2-different cells and compared the cross-reactivity of the resulting alloreactive CTL on hapten-modified targets of the two parental strains. The results show that a significant proportion of these chimeric alloreactive CTL have a self preference, i.e., a greater fraction of them cross-react on haptenated target cells of host type than on haptenated targets of the other H-2 type. It is concluded that, contrary to the theory's prediction, alloreactive T-cells can be influenced in their specificity by the H-2 type of the environment in which they mature.

Materials and Methods

Mice. AKR/J (H-2^k), C57BL/10Sn (B10) (H-2^b), B10.D2/nSn (H-2^d) and (AKR/J \times DBA/2J)F₁ (AKD2) mice were purchased from The Jackson Laboratory (Bar Harbor, Maine). (B10 \times B10.D2)F₁, DBA/2J (H-2^d), B10.BR/SgSn (H-2^k), and (B10.BR \times B10.D2)F₁ mice were bred at the Center for Cancer Research, Massachusetts Institute of Technology, Cambridge, Mass.

[F₁ \rightarrow Parent] Radiation Chimeras. These were kindly provided by P. Fink, Center for Cancer Research, Massachusetts Institute of Technology. [B10 \times B10.D2 \rightarrow B10] and [B10 \times B10.D2 \rightarrow B10.D2] chimeras were prepared by injecting $\sim 10^7$ liver cells from 17-d-old fetuses into lethally irradiated (950 rad from a ¹³⁷Cs source) mice of the parental strains. They were used 12–18 mo later. Lymph node cells from randomly chosen animals were typed for H-2 and found to contain no detectable parental cells. [AKD2 \rightarrow AKR/J] and [AKD2 \rightarrow DBA/2J] chimeras were prepared by injecting $\sim 10^7$ F₁ bone marrow cells treated with monoclonal anti-Thy-1.2 (16) and rabbit complement into lethally irradiated (950 rad) mice of the parental strains. They were used 9 mo later. CTL generated from spleen cells of these chimeras were typed with monoclonal antibodies against Thy-1.1 and Thy-1.2 (16) and found to be fully sensitive to both treatments.

Priming to Minor H Antigens. AKD2 mice and the related [F₁ \rightarrow Parent] chimeras were primed to minor H antigens of the B10 series by injecting 1.5×10^7 viable spleen cells from (B10.D2 \times B10.BR)F₁ mice intraperitoneally 3 mo before setting up mixed lymphocyte cultures (MLC).

MLC. MLC were set up with 2.5×10^7 spleen cells from primed or unprimed animals as responders and an equal number of irradiated (1,000 rad from a ¹³⁷Cs source) stimulator cells as described previously (17). The CTL response was assayed on day 5 of MLC. For secondary MLC, cultures were fed by replacing one-half of the medium on day 6, harvested on day 10, and restimulated with the original number of stimulator cells but only 5×10^6 responders. The secondary MLC was assayed 4 d after restimulation.

Target Cells. Spleen cells were cultured for 2 d in the presence of concanavalin A (Con A) and prepared for the cytotoxicity assay as previously described (17).

Haptenation of Stimulator and Target Cells. Trinitrophenyl (TNP) modification was performed according to Shearer (18) by incubating the washed cells for 10 min at 37°C in 10 mM

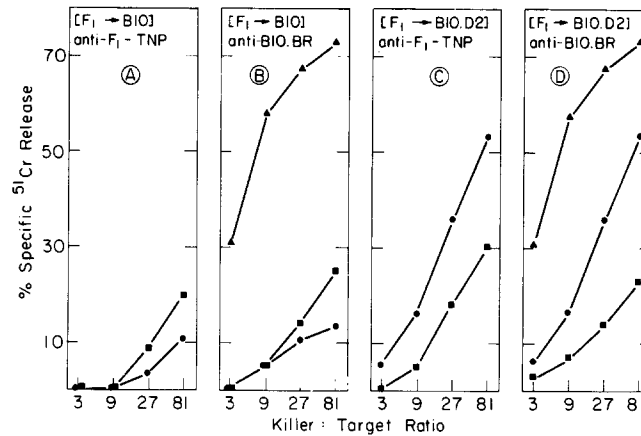


FIG. 1. Lysis of $H-2^b$ -TNP and $H-2^d$ -TNP targets by ($H-2^b \times H-2^d$) F_1 T cells that have matured in irradiated $H-2^b$ or $H-2^d$ hosts. [$F_1 \rightarrow H-2^b$] spleen cells were stimulated for 5 d in MLC with F_1 -TNP cells (A) or B10.BR ($H-2^b$) cells (B). [$F_1 \rightarrow H-2^d$] spleen cells were stimulated with F_1 -TNP (C) or B10.BR cells (D). The ^{51}Cr -labeled targets were B10-TNP (■, spontaneous release: 21.3%), B10.D2-TNP (●, spontaneous release: 17.1%), and B10.BR (▲, spontaneous release: 20.0%). Lysis of unmodified B10 and B10.D2 targets was $<5\%$ in all cases.

trinitrobenzene-sulfonic acid (Eastman Kodak Co., Rochester, N. Y.) in phosphate-buffered saline, pH 7.3, followed by three washes in serum-containing medium. Target cells were haptenated after labeling with [^{51}Cr]sodium chromate (New England Nuclear, Boston, Mass.).

Cytotoxicity Assay. Serial threefold dilutions of cells harvested from MLC were added to 4×10^4 ^{51}Cr -labeled target cells in a final vol of 1 ml medium (17). After 4 h of incubation, specific lysis was assessed according to the formula:

percent specific lysis

$$= 100 \times \frac{\text{counts per minute released in experimental group} - \text{counts per minute spontaneously released}}{\text{detergent releasable counts per minute} - \text{counts per minute spontaneously released}}$$

Cold-Target Competition Assay. 4×10^4 ^{51}Cr -labeled Con A blasts were placed in the assay tubes with 1.6×10^6 identically treated but unlabeled inhibitor blasts. Cytotoxic cells were added last, and the assay performed in the usual way.

Results

Self Preference of Alloreactive CTL from [$H-2^b \times H-2^d \rightarrow$ Parent] Chimeras. Spleen cells from fetal liver radiation chimeras of the types [$F_1 \rightarrow B10$] and [$F_1 \rightarrow B10.D2$] were cultured with TNP-modified syngeneic (F_1), or with unmodified B10.BR ($H-2^k$), stimulator cells. 5 d later, all groups were assayed for cytotoxic activity against B10-TNP and B10.D2-TNP targets; all stimulated cultures were also assayed on B10.BR targets. As shown in Fig. 1A and C, cytotoxic activity generated against TNP-modified F_1 cells was not as markedly restricted to the $H-2$ type of the chimeric host as is usually found for responses to minor H antigens (10) or viral antigens (11, 19). There was, however, a clear host preference, i.e., CTL derived from [$F_1 \rightarrow B10$] chimeras were about threefold more active on B10-TNP than on B10.D2-TNP targets (Fig. 1A), whereas the reverse was true for CTL derived from [$F_1 \rightarrow B10.D2$] chimeras (Fig. 1C).

TABLE I
*Host Preference of CTL from [F₁ → Parent] Chimeras Induced either with F₁-TNP or with Allogeneic Stimulator Cells**

Responder cells	Experiment number	Ratio of cytotoxic activity on B10-TNP:B10.D2-TNP targets‡	
		Stimulated with F ₁ -TNP	Stimulated with B10.BR
[F ₁ → B10]	1	>25	>25
	2	3	3
	3	ND	>25
	4	ND	10
[F ₁ → B10.D2]	1	ND	0.2
	2	0.3	0.2
	4	ND	0.2
	5	ND	0.5

ND, not done.

* Spleen cells from fetal liver chimeras were stimulated in vitro as given in Materials and Methods; cytotoxic activity was measured either on day 5 of primary or on day 4 of secondary stimulation.

‡ Relative activities were determined from complete titration curves (10).

Spleen cells from these same animals stimulated with H-2-disparate cells gave rise to alloreactive CTL that cross-reacted on TNP-modified targets of both parental strains (Fig. 1 B and D). Interestingly, the relative activities measured against TNP-modified B10 and TNP-modified B10.D2 targets were similar to those of CTL raised against TNP-modified F₁ cells. Thus, alloreactive CTL derived from the [F₁ → B10] chimera cross-reacted more strongly on TNP-modified B10 targets than on TNP-modified B10.D2 targets, whereas alloreactive CTL from the [F₁ → B10.D2] chimera cross-reacted more strongly on haptenated B10.D2 than on haptenated B10 target cells.

From this batch of fetal liver radiation chimeras, eight animals were tested for cross-reactivity of alloinduced CTL on TNP-modified B10 and B10.D2 target cells. Preference for TNP-modified targets of the chimeric host type was found in all animals tested, though to a varying degree (Table I).

Alloinduced CTL Active against TNP-Self Are Allospecific. The cross-reaction of effector cells raised against allogeneic stimulators on haptenated syngeneic targets has been shown before not to result from the costimulation of bystander cells which do not react with the stimulating antigen (13). To confirm this finding for the system employed in our study, spleen cells from an [F₁ → B10.D2] fetal liver chimera were stimulated twice, on day 0 and on day 10 of culture, with B10.BR stimulator cells, and were assayed on day 14 on B10.BR, B10-TNP, and B10.D2-TNP targets. B10.D2-TNP targets were killed about five times more effectively than B10-TNP targets (data not shown). To determine the specificity of the CTL that killed B10.D2-TNP target cells, unlabeled B10.BR, B10.D2-TNP, or B10 inhibitors were added to the assay at a 40-fold excess over the ⁵¹Cr-labeled B10.D2-TNP target cells. The cold B10 targets served as a control for effects unrelated to the antigenic makeup of the inhibitors. As shown in Table II, the lysis of labeled B10.D2-TNP target cells was substantially

TABLE II
Cold-Target Inhibition of $[F_1 \rightarrow B10.D2]$ Anti-B10.BR CTL That Lyse
B10.D2-TNP Targets*

Unlabeled inhibitor blasts	Percent specific ^{51}Cr release from B10.D2-TNP targets at killer:target ratio:	
	30:1	10:1
None	49.3	38.7
B10	47.5	30.1
B10.BR	22.7	11.3
B10.D2-TNP	8.3	0.9

* Spleen cells from an $[F_1 \rightarrow B10.D2]$ fetal liver chimera were stimulated twice in MLC with B10.BR cells. They were assayed on day 4 of secondary MLC against ^{51}Cr -labeled B10.D2-TNP targets in the presence of a 40-fold excess of unlabeled inhibitors. Spontaneous lysis of B10.D2-TNP targets was 16.6%.

reduced in the presence of cold B10.BR targets, although the inhibition was not as effective as observed with B10.D2-TNP inhibitors. Addition of cold B10 blasts had very little effect. The superiority of B10.D2-TNP over B10.BR as inhibitors can be explained by the fact that the killer cells were ~ 10 -fold more active against B10.BR than against B10.D2-TNP targets (data not shown). Therefore, a more rapid loss of the allogeneic competitors during incubation time may have led to a less-pronounced inhibitory effect. We conclude that the cytotoxic activity of allostimulated MLC cells directed against TNP-modified syngeneic target cells is largely a result of allospecific CTL.

Specificity of the Anti-TNP Response of CTL from $[H-2^k \times H-2^d \rightarrow \text{Parent}]$ Chimeras. The host preference observed with TNP-induced or alloinduced CTL from $[H-2^b \times H-2^d \rightarrow \text{Parent}]$ chimeras when assayed on TNP-modified targets of the parental strains was often as small as threefold. With another batch of $[H-2^b \times H-2^d \rightarrow \text{Parent}]$ chimeras, used between 6 wk and 3 mo after cell transfer, we occasionally found no self-preference at all in the response to TNP-self or to allogeneic cells (data not shown). Levy and Shearer (20) have shown that the response of normal F_1 ($H-2^k \times H-2^d$) mice to F_1 -TNP stimulator cells is almost exclusively specific for $H-2^k$ -TNP. We repeated our experiments in this system with the notion that the dominance of one haplotype over the other would yield more clear-cut results.

We initially wanted to determine if the dominance of $H-2^k$ - over $H-2^d$ -restricted CTL in the anti-TNP response is dependent on the H-2 type of the environment in which the CTL precursors had matured. Table III shows an experiment in which spleen cells from an AKD2 mouse and from the corresponding $[F_1 \rightarrow \text{Parent}]$ bone marrow radiation chimeras were stimulated with F_1 -TNP cells and assayed for cytotoxic activity 5 d later against haptenated and unhaptenated target cells of the two parental strains. The results show that in both the normal F_1 and in the $[F_1 \rightarrow \text{AKR}]$ chimera, most of the cytotoxic activity was specific for $H-2^k$ -TNP; on the other hand, F_1 cells that matured in a DBA/2 host responded with an equal amount of cytotoxic activity specific for $H-2^d$ -TNP and $H-2^k$ -TNP. The dominance of $H-2^k$ over $H-2^d$ in the cytotoxic response to TNP of $H-2^k \times H-2^d$ mice was thus reduced to a 1:1 ratio in the $[F_1 \rightarrow H-2^d]$ chimera.

Host Influence on the Specificity of Alloinduced CTL from $[H-2^k \times H-2^d \rightarrow \text{Parent}]$

TABLE III
Cytotoxic Response of AKD2 and [F₁ → Parent] Chimera Cells to F₁-TNP Stimulator Cells*

Responder	Percent specific lysis of ⁵¹ Cr-labeled targets:				Ratio of activity on AKR-TNP:DBA/2-TNP‡
	AKR	DBA/2	AKR-TNP	DBA/2-TNP	
Normal AKD2	4/3§	0/0	49/34	23/11	7
[F ₁ → DBA/2]	0/0	0/0	35/19	28/19	1
[F ₁ → AKR]	-1/-3	-5/-3	29/16	9/4	7

* MLC was performed as described in Materials and Methods and cytotoxicity assayed on day 6.

‡ Relative activities were calculated from complete titration curves (10).

§ Results are given for two effector:target ratios, 40:1 and 13:1.

Chimeras. We then went on to determine the cross-reactivity of alloinduced CTL from (H-2^k × H-2^d)F₁ mice and the related [F₁ → Parent] chimeras on TNP-modified parental target cells. In parallel, we wanted to test whether these chimeric mice display a normal pattern of host preference in the H-2-restricted response to minor H antigens.

Bone marrow radiation chimeras from the same batch as used in the previous experiment were immunized to minor H antigens of the B10 series (Materials and Methods) and were stimulated in MLC 3 mo later. A normal AKD2 mouse primed in the same way served as a control. Spleen cells from each animal were divided into two groups: One was boosted with F₁ (B10.BR × B10.D2) spleen cells (anti-minor-H-antigen response), the other group was stimulated with B10 cells. Fig. 2 shows the results of the cytotoxicity assay on day 5 of MLC. The response to minor H antigens is shown in Fig. 2A-C; that to allogeneic stimulator cells in Fig. 2D-F. Spleen cells from the normal mouse primed and boosted with (B10.BR × B10.D2)F₁ stimulator cells developed equal amounts of cytotoxic activity against B10.BR and B10.D2 target cells (Fig. 2A). Effectors raised in the same manner from spleen cells of an [F₁ → DBA/2] chimera had 27-fold more activity against B10.D2 than against B10.BR targets; the reverse was true for CTL derived from the [F₁ → AKR] chimera. Thus, in the response to minor H antigens, the H-2 type of the chimeric host determined the H-2 restriction of the vast majority of the CTL generated in this system, as has been previously reported (10, 12). Unlike the response to F₁-TNP cells, the response of AKD2 mice to B10 minor H antigens is not dominated by one of the two H-2 haplotypes involved.

All three animals tested developed strong cytotoxic responses against allogeneic B10 stimulator cells (Fig. 2D-F). When assayed for their cross-reactivity against TNP-modified target cells of the two parental strains, a pattern very similar to that found in the anti-TNP response (Table III) was observed: Allo-induced CTL from the normal F₁ and the [F₁ → AKR] bone marrow chimera cross-reacted strongly on AKR-TNP targets, although they showed little or no cytotoxic activity against DBA/2-TNP targets. CTL from the [F₁ → DBA/2] chimera, on the other hand, possessed small but equal amounts of cytotoxic activity against haptenated targets of both parental strains. This pattern was observed in two independent experiments.

Therefore, just as in the H-2^b × H-2^d system, we were able to demonstrate that the

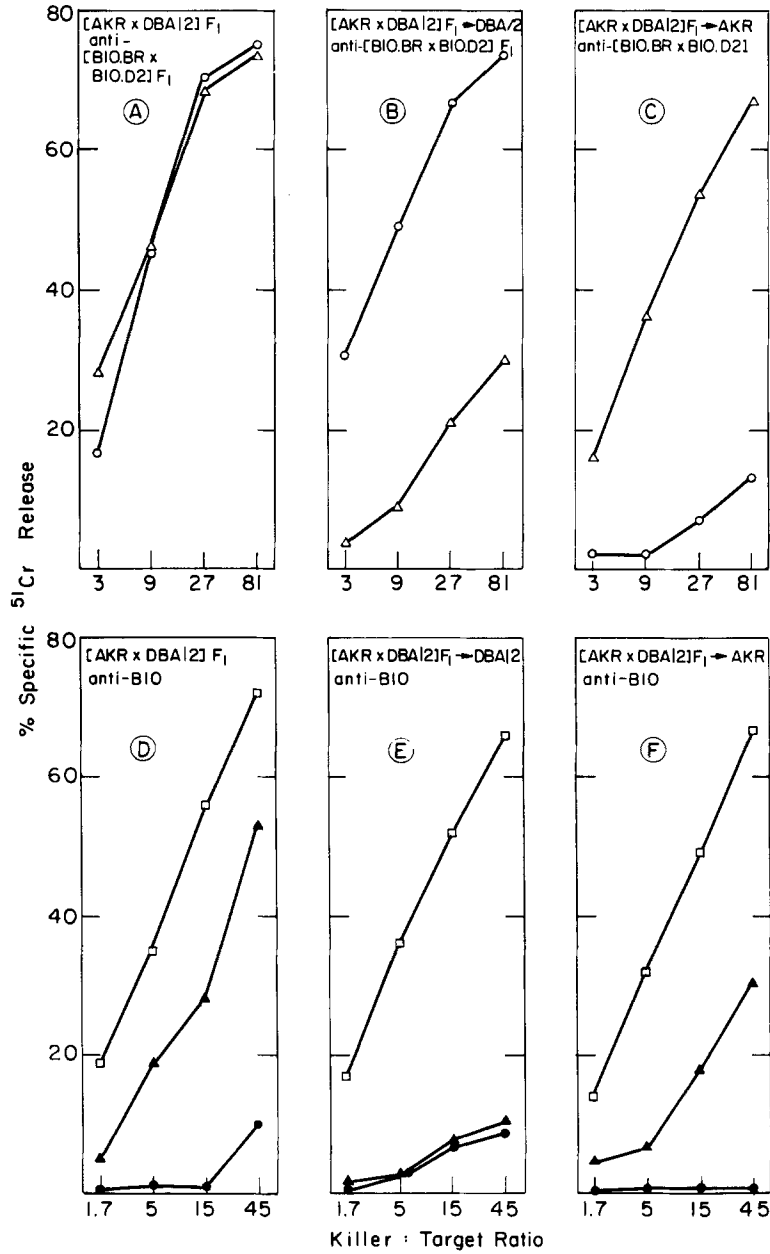


FIG. 2. CTL response of AKD2 cells to minor H antigens and MHC antigens. Normal AKD2 cells stimulated with (B10.BR \times B10.D2) F_1 (A), or B10 (D); [AKD2 \rightarrow DBA/2] chimera cells stimulated with (B10.BR \times B10.D2) F_1 (B), or B10 (E); [AKD2 \rightarrow AKR] chimera cells stimulated with (B10.BR \times B10.D2) F_1 (C), or B10 (F). ^{51}Cr -labeled targets were B10.BR (Δ , spontaneous release: 23.8%), B10 (\square , spontaneous release: 24.5%), B10.D2 (\circ , spontaneous release: 23.0%), AKR-TNP (\blacktriangle , spontaneous release: 27.8%), and DBA/2-TNP (\bullet , spontaneous release: 31.3%). Lysis of unmodified AKR and DBA/2 target cells was $<1\%$ in all cases.

specificity of at least a significant fraction of alloreactive CTL is influenced by the H-2 antigens of the animal in which they mature.

Discussion

The experiments presented in this paper suggest that the receptor specificity of at least a fraction of alloreactive CTL is influenced by MHC antigens on radioresistant cells. Thus, alloreactive CTL from $[A \times B \rightarrow A]$ radiation chimeras are different from those of $[A \times B \rightarrow B]$ chimeras as monitored by their cross-reactivity on TNP-modified targets of the parental strains. Because characterization of the chimeric cells showed that they were exclusively derived from F_1 stem cells, we can state that alloreactive CTL of identical genotype and tolerant to the same set of H-2 antigens display a different spectrum of receptors if they matured under the influence of different H-2 antigens.

The self preference that we describe here for alloreactive cells has been shown before to be a characteristic of CTL specific for conventional antigens such as minor H antigens (10), and viral antigens (11, 19). In these systems, the H-2 type of radioresistant cells of the thymic epithelium determines the MHC restriction of most of the animal's mature T cells (11, 17).

Jerne's theory (9) proposed that whereas T-cells specific for conventional antigens are influenced by self MHC antigens during differentiation in the thymus, alloreactive cells express germline-encoded receptors whose specificity remains unchanged. In terms of our experimental design, the theory predicts that, e.g., $[H-2^b \times H-2^d \rightarrow H-2^b]$ anti- $H-2^k$ CTL possess the same receptor repertoire as $[H-2^b \times H-2^d \rightarrow H-2^d]$ anti- $H-2^k$ CTL. The results presented here contradict this notion: When the two populations of CTL described above were assayed for cross-reactivity against haptenated parental target cells, the influence of host antigens on their receptor repertoire was revealed.

The self preference of only a fraction of alloreactive CTL can be demonstrated by cross-reactivity on TNP-self. However, Fischer-Lindahl (21) has shown that alloreactive CTL also cross-react on 4-hydroxy-3-nitrophenylacetyl-modified syngeneic targets. This activity is separate from that measured on TNP-self. We assume that (a) additional populations of cross-reactive CTL could be demonstrated using other haptens, and (b) these would also display a self preference. Thus, we suggest that a substantial fraction of alloreactive CTL are self influenced. Still, it has to be considered that two types of alloreactive T cells may exist: those postulated by Jerne (9), expressing germline-encoded anti-MHC receptors, (22-24) and those described here, that by the criterion of self preference, are like T cells specific for conventional antigens.

The cross-reactivity of alloreactive CTL on TNP-modified syngeneic target cells is readily and reproducibly measured and therefore represents a suitable system for studying the influence of self MHC antigens on alloreactive CTL. A disadvantage is the less-pronounced self preference of the anti-TNP responses from $[F_1 \rightarrow \text{Parent}]$ chimeras as compared to responses to minor H antigens (Fig. 2; [10]) or viral antigens (11). The important result for our argument is, however, that alloinduced CTL reactive against TNP-modified parental target cells display the same pattern of lysis as those induced by F_1 -TNP stimulator cells (Fig. 1; Table I).

The cytotoxic response of $[F_1 \rightarrow \text{Parent}]$ chimeras to TNP-modified F_1 cells has been studied previously by Zinkernagel et al. (25). The authors showed that CTL

generated in this manner from $[H-2^d \times H-2^{kd} \rightarrow H-2^{kd}]$ chimeras lyse only haptenated $H-2^k$ targets. This finding was, however, not compared to the response of normal $(H-2^d \times H-2^{kd})F_1$ mice. Levy and Shearer (20) have shown that $(H-2^d \times H-2^k)F_1$ mice respond to syngeneic, TNP-modified cells with predominantly $H-2^k$ -restricted cytotoxic activity. Our experiments confirm this result (Table III). In addition, we found that $[F_1 \rightarrow H-2^k]$ chimeras respond in an identical fashion to the normal F_1 , although anti-TNP CTL from $[F_1 \rightarrow H-2^d]$ chimeras gave about equal amounts of $H-2^d$ - and $H-2^k$ -restricted activity. Thus, the host influence on the TNP response could only be demonstrated in the $[F_1 \rightarrow H-2^d]$ chimeras. Again, the cross-reactivity of alloinduced CTL from $(H-2^d \times H-2^k)F_1$ animals and the related $[F_1 \rightarrow \text{Parent}]$ chimeras followed the same pattern as found in the response to TNP-modified F_1 cells, (Fig. 2; Table III). This supports our view that the specificity of both responses was influenced by self antigens in a similar manner.

The discovery of MHC restriction and of the role that self antigens play in the generation of the T cell repertoire fit well into the framework of Jerne's theory (9). Our findings establish that alloreactive T-cells, which the theory exempts from the influence of self antigens, can also have a self preference.

Summary

We have tested Jerne's hypothesis (9) that the phenomenon of alloreactivity is explained by the existence of T cells that express germline-encoded receptors specific for major histocompatibility complex antigens and that these cells undergo no change in specificity during thymic differentiation. T cells from $[F_1 \rightarrow \text{Parent}]$ bone marrow radiation chimeras reactive to conventional antigens are known to have a self preference, i.e., $[A \times B \rightarrow A]$ chimeras respond better to H-2A-plus-antigen than to H-2B-plus-antigen. We show here that alloreactive cells from such chimeras also have a self preference. Thus, $H-2^k$ -specific alloreactive T cells from $[H-2^b \times H-2^d \rightarrow H-2^b]$ and $[H-2^b \times H-2^d \rightarrow H-2^d]$ chimeras cross-react more on TNP-modified $H-2^b$ or $H-2^d$ targets, respectively. In contrast to Jerne's prediction, the results suggest that the receptor repertoire of alloreactive F_1 cells is influenced by H-2 antigens on radiation-resistant cells present during T cell ontogeny. By this criterion of having a self preference in H-2 restriction, alloreactive T cells appear to be similar to T cells that respond to conventional antigens.

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