GENETIC CONTROL OF CYTOLYTIC T-LYMPHOCYTE
RESPONSES

I. Ir Gene Control of the Specificity of Cytolytic T-Lymphocyte
Responses to Trinitrophenyl-Modified Syngeneic Cells*

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Products of the major histocompatibility complex (MHC) \(^1\) play a key role in
the functional specificity of cytolytic T lymphocytes (CTL). Allogenically
stimulated CTL have specificity primarily for products of the H-2K and H-2D
loci of the mouse histocompatibility 2 (H-2) complex (1). A high proportion of
CTL precursors appear to be committed to react with these allogeneic MHC
gene products (2–4).

The role of MHC products as target specificities for CTL was further
elucidated by the experiments of Doherty et al. (5). These investigators showed
that CTL specific for viral antigens required the presence of the stimulating H-2
product on the target cell, as well as the inducing viral determinants, to effect
cytolysis. This observation also applied to syngeneic systems in which CTL were
induced to chemically modified syngeneic cells (6), non-H-2-linked histocompat-
ability determinants (7), and tumor-specific transplantation antigens (8, 9).
Shearer (10) originally demonstrated that CTL could be induced in vitro by
trinitrophenyl (TNP)-coupled syngeneic cells and showed that these CTL only
lysed TNP-coupled spleen targets sharing H-2K or H-2D gene products with
the responding and stimulating cell populations (H-2 restricted). Burakoff et al. (11)
extended these findings by showing that the observed H-2 restriction was
actually an H-2 preference, as CTL induced by TNP-coupled syngeneic cells
could lyse TNP-modified allogeneic spleen targets (cross-reactive lysis) though
to a lesser extent than the cytolysis of TNP-modified syngeneic spleen targets.
These cross-reacting CTL also had specificity for MHC products on the TNP-
modified allogeneic targets as demonstrated by antiserum and cold target
inhibition experiments (11).

In this communication, we have further examined the cross-reactive CTL
induced by TNP-coupled syngeneic cells in primary in vitro cultures. We
demonstrate that there exists significant interstrain variation among inbred
mouse strains in their ability to produce cross-reactive CTL, and that a

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* Supported by National Institutes of Health grants CA-14723 and AI-13419.

\(^1\) Abbreviations used in this paper: B6, C57BL/6J mice; B10, C57BL/10Sn mice; CTL, cytolytic T
lymphocytes; H-2, histocompatibility; MHC, major histocompatibility complex; TNP, trinitro-
phenyl.
dominant H-2-linked gene(s) controls the ability to produce cross-reactive CTL under these experimental conditions.

Materials and Methods

Mice. 6- to 12-wk-old male and female mice of the following strains were employed for these studies: H-2b: C57BL/6J (B6), C57BL/10Sn (B10); H-2d: B10.D2n, BALB/cJ; H-2f: B10.M; H-2k: B10.BR, C3H/HeJ, CBA/J, AKR/J; H-2q: B10.G; H-2r: B10.RIII; H-2s: B10.S; H-2v: B10.SM. (Additional strains carrying recombinant H-2 haplotypes are listed in Table III.) (B10 × B10.BR)F1 and (B6 × C3H)F1 mice were bred in our colonies. The M523 (H-2<sup>kr</sup>) strain, which carries a mutant H-2<sup>k</sup> haplotype, was a gift from Dr. I. K. Egorov, Moscow, USSR.

Generation of Effector cells. The method used to generate cytotoxic effector T cells to TNP-derivatized stimulator cells has been described previously (12). Briefly, 7 × 10<sup>6</sup> normal spleen cells were co-cultured at 37°C in 16-mm Linbro tissue culture wells (Linbro Chemical Co., New Haven, Conn.) with 6 × 10<sup>6</sup> TNP-derivatized irradiated (1,500 R) spleen cells for 5 days and then assayed. Stimulator and target cells were TNP derivatized by a 10-min incubation at 37°C in a 10-mM solution of trinitrobenzene sulfonic acid (pH 7.4).

51Cr Release Assay. The 51Cr release assay has been described in detail elsewhere (12). A 4-h incubation time was used. Lipopolysaccharide-induced blast targets were used in some experiments. These blasts were produced by 2-day incubation of 4 × 10<sup>6</sup> spleen cells in 2 ml of media containing 5 μg/ml lipopolysaccharide (Difco Laboratories, Detroit, Mich.). Data from experiments with blast targets are quantitatively but not qualitatively different from those experiments with normal spleen targets.

Data are expressed as "percent cross-reactive lysis." Within each experiment, specific release was calculated as described elsewhere (12). The equation E-C/FT-C was used, where E is isotope release in tubes containing immune effectors plus targets, C is isotope release in tubes containing normal spleen cells and targets (spontaneous release), and FT is maximum isotope release in tubes containing targets after freeze-thawing three times. A level of specific release (usually 30-50% of specific release) observed with syngeneic TNP-modified targets was chosen for normalization. At the effector to target ratio producing this level of lysis, the 51Cr release on allogeneic TNP-coupled targets was determined. The cross-reactive lysis is the ratio of the specific lysis of allogeneic TNP-modified targets divided by the specific lysis of syngeneic TNP-coupled targets.

Alloantisera. Alloantisera were obtained after four to eight intraperitoneal injections of either tumor or spleen cells. (The donor-recipient combination used is listed in the legend to Table IV). The anti-H-2<sup>k</sup> + Ia<sup>k</sup> serum was a generous gift of Dr. Mark Greene, from this department. This serum, a B10.D2 anti-B10.A, has a lytic titer > 1:640.

The method of antisera blocking has also been previously reported (12). Briefly, 50 μl of a suspension of 51Cr-labeled targets is mixed with 50 μl diluted antisera in a 10 × 75-mm round-bottomed tube for 15 min at 37°C before the introduction of 100 μl of a suspension of effectors.

Results

CTL from H-2<sup>r</sup> Mice Do Not Exhibit Cross-Reactive Lysis. B10.BR CTL induced by TNP-modified syngeneic cell in vitro are unable to lyse TNP-coupled allogeneic B10 (H-2<sup>d</sup>) spleen targets, i.e. these CTL produce no cross-reactive lysis, whereas B10 CTL induced by TNP-modified syngeneic cells demonstrate cross-reactive lysis on TNP-modified B10.BR spleen targets (Fig. 1).

Values or cross-reactive and syngeneic target lysis mediated by the same effector cell pool were obtained from nine separate experiments, and a linear regression analysis plotted as shown in Fig. 2. When H-2<sup>r</sup> CTL generated to TNP-modified syngeneic cells were assayed on H-2<sup>r</sup>-TNP spleen or H-2<sup>r</sup>-TNP spleen targets, the data fit a straight line with a coefficient of correlation (r) = 0.84 and a slope = 0.5 indicating considerable cross-reactivity. However, H-2<sup>r</sup>
CTL generated to TNP-modified syngeneic targets demonstrated little or no lysis of H-2<sup>b</sup>-TNP spleen targets; even when 60-70% specific lysis of H-2<sup>k</sup>-TNP targets was achieved, <10% lysis of H-2<sup>b</sup>-TNP targets was observed.

All animals homozygous for the H-2<sup>k</sup> haplotype, including the congenic B10.BR mice, produce CTL, after TNP-modified syngeneic stimulation, which are restricted, i.e. fail to cross-reactively lyse TNP-modified allogeneic spleen targets (Fig. 3, Experiment 1). This indicates that the noncross-reactive response produced by H-2<sup>k</sup> CTL induced by TNP-modified syngeneic stimulation is an H-2-associated phenomenon as it does not vary with changes in non-H-2-linked background genes.

Further results in Fig. 3 (experiments 2 and 3) show that (B6 × C3H)<sub>F<sub>1</sub></sub> as well as (B10 × B10.BR)<sub>F<sub>1</sub></sub> CTL when stimulated with either H-2<sup>b</sup> or H-2<sup>k</sup> TNP-coupled stimulator cells cross-reactively lyse TNP-coupled allogeneic targets. It therefore appears that the cross-reactive CTL phenotype is inherited in a dominant fashion. It is evident in Fig. 3 that H-2<sup>k</sup> TNP-modified stimulator cells are capable of inducing CTL that can cross-reactively lyse TNP-coupled allogeneic targets. However, a comparison of the extent of cross-reactive lysis shown by F<sub>1</sub> CTL immunized with TNP spleen cells from each parent revealed that the H-2<sup>k</sup>-TNP stimulator cells elicited more cross-reactive lysis than the H-2<sup>b</sup>-TNP stimulator cells. Thus, H-2<sup>k</sup> TNP-modified stimulator cells bear determinants which can induce cross-reactive CTL, and this suggests that the noncross-reactive CTL phenotype is a characteristic of the H-2 genotype of the effector cell.
Next, we asked whether H-2\textsuperscript{k}-bearing mice were the only animals that produced highly H-2-restricted CTL after TNP-modified syngeneic stimulation. Table I shows three experiments utilizing several strains of C57BL/10 congenic mice. It can be seen that H-2 congeneric mice bearing the H-2\textsuperscript{b}, H-2\textsuperscript{r}, H-2\textsuperscript{s}, and H-2\textsuperscript{d} haplotypes produced cross-reactive CTL. C3H.SW (H-2\textsuperscript{b}), DBA/2 (H-2\textsuperscript{d}), BALB/c (H-2\textsuperscript{d}), DBA/1 (H-2\textsuperscript{d}), and A.SW (H-2\textsuperscript{k}) mice also produce cross-reactive CTL after TNP-modified syngeneic stimulation (results not shown). It thus appears that the production of noncross-reactive CTL after TNP-modified syngeneic primary stimulation is a unique trait common only to mice bearing the H-2\textsuperscript{k} haplotype.

**Cross-Reactive Lysis Is Independent of Target-Cell Haplotype.** Results shown in Table II indicate B10.BR CTL, stimulated with TNP-modified B10.BR spleen cells, produce little or no cross-reactive lysis when tested on TNP-coupled H-2\textsuperscript{b}, H-2\textsuperscript{r}, H-2\textsuperscript{s}, or H-2\textsuperscript{d} targets whereas they lyse syngeneic TNP-modified targets well. In contrast, CTL from B10 or B10.RIII mice stimulated with TNP-modified syngeneic cells demonstrate considerable cross-reactive lysis on all the TNP-modified allogeneic targets tested. Thus, the defect in H-2\textsuperscript{k}...
FIG. 3. Dominant inheritance of the cross-reactive phenotype. In experiment 1 CTL induced to TNP-modified syngeneic cells from several strains homozygous for the H-2k haplotype were assessed for cross-reactive lysis. In experiments 2 and 3 (H-2b × H-2k)F1 CTL were induced by either TNP-modified parental strain and assessed for cross-reactive lysis. Data are expressed as percent cross-reactive lysis as defined in Materials and Methods. Spontaneous release of the target cells ranged from 35 to 40%.

CTL after TNP-modified syngeneic stimulation is also observed when testing other TNP-coupled allogeneic targets. Furthermore, with CTL from TNP-stimulated B10 and B10.RIII mice, which cross-reactively lyse all TNP-modified allogeneic targets tested, the amount of cross-reactive lysis does not correlate with any public serological H-2 specificities on the target cells.

Localization of the Gene(s) Controlling Cross-Reactive Lysis. We have shown that H-2k CTL induced by TNP-coupled syngeneic cells show a highly H-2-restricted specificity in TNP-coupled target lysis, and that the gene(s) controlling this restriction in the specificity of response to TNP-modified cells is H-2 linked. We next asked where, within the H-2 complex, does this gene(s) reside? Table III summarizes several experiments utilizing mice bearing intra-H-2-recombinant haplotypes. To further analyze the gene(s) controlling cross-reactivity in this system, we tested the ability of CTL from several strains of mice carrying portions of the H-2k haplotype to produce cross-reactive CTL (Table III). B10.A and B10.A(4R) CTL were highly H-2 restricted in their response to TNP-modified syngeneic cells, localizing the gene(s) controlling this response to the left of the I-B subregion, i.e. K and/or I-A. C3H.0L CTL produce cross-reactive lysis, also suggesting K-end localization of the gene influencing the cross-reactive response. Both the A.TH and A.TL combination and the B10.T(6R) and B10.AQR recombinant pair produce cross-reactive CTL after TNP-modified syngeneic stimulation. This suggests that the presence of k alleles in the I region is not sufficient for the production of the noncross-reactive cytolytic response.

Antisera Inhibition of Cross-Reactive Lysis. It had been previously reported by Schmitt-Verhulst and Shearer (13) that mice bearing the k alleles in the K end of the H-2 complex were unable to recognize TNP modifications of their own H-2D-coded determinants. This defect was exemplified by the inability of B10.A (Kk, Dd) mice, when immunized with syngeneic TNP-modified spleen cells, to
**Table I**

*Cross-Reactive Lysis Produced by CTL from C57BL/10 Congenic Mice*

| Experiment | Responder cells* | TNP-modified stimulator cells† | TNP-modified target cells | Percent cross-reactive lysis§ |
|------------|-----------------|-------------------------------|--------------------------|-----------------------------|
| 1          | B10(h-2^b)      | B10                           | B10.SM(H-2^b)            | 38                          |
|            | B10.RIII(H-2^b) | B10.RIII                      | B10.SM                   | 55                          |
|            | B10.BR(H-2^b)   | B10.BR                        | B10.SM                   | 4                           |
| 2          | B10.S(H-2^b)    | B10.S                         | B10                      | 45                          |
|            | B10.BR          | B10.BR                        | B10                      | 3                           |
| 3          | B10             | B10                           | B10.RIII                 | 65                          |
|            | B10.D2(H-2^b)   | B10.D2                        | B10.RIII                 | 36                          |
|            | B10.BR          | B10.BR                        | B10.RIII                 | 6                           |

* H-2 haplotypes of various congenic strains are indicated in parentheses.
† Spontaneous release of TNP-coupled normal spleen targets was <40%.
§ Effector to target ratios of 50:1 for B10, 40:1 for B10.RIII, and 38:1 for B10.BR produced 40% TNP-modified syngeneic specific release in experiment 1. In experiment 2, effector to target ratios of 35:1 for B10.S and 25:1 for B10.BR produced 35% TNP-modified syngeneic specific release. In experiment 3, effector to target ratios of 50:1 for B10, 50:1 for B10.D2, and 30:1 for B10.BR yielded 50% TNP-coupled syngeneic specific release.

**Table II**

*Cross-Reactive Lysis of TNP-Modified Allogeneic Targets*

| Responder† | B10.BR (H-2^a) | B10.M (H-2^a) | B10.G (H-2^a) | B10.S (H-2^a) | B10 (H-2^a) | B10.RIII (H-2^a) |
|------------|----------------|---------------|---------------|---------------|-------------|-----------------|
| B10        | 31             | 41            | 53            | 69            | 100         | 35              |
| B10.RIII   | 50             | 38            | 59            | NT            | 35          | 100             |
| B10.BR     | 100            | 12            | 13            | 10            | 10          | 9               |

* Summary of three separate experiments.
† Responder cells were co-cultured with TNP-modified syngeneic cells for 5 days, then assayed on the TNP-modified syngeneic and allogeneic targets.
§ Spontaneous release of TNP-modified normal spleen targets was <40%; H-2 haplotype indicated in parentheses; NT, not tested.

It was conceivable that the inability of mice bearing the k alleles in the H-2 complex to produce cross-reactive responses in our system might be due to the same defect that these authors had described. If this were the case, then most cross-reactivity would be directed at H-2D-end determinants, and the resulting inability of H-2^k haplotype mice to make cross-reactive responses would thus result from the inability of H-2^k CTL to recognize TNP-derivatized H-2D^k determinants. We tested this hypothesis by asking whether CTL from mice that made good cross-reactive responses after TNP-
modified syngeneic stimulation directed these responses at H-2K-coded determinants, H-2D determinants, or both. Specific antisera blocking was used to determine which end of the H-2 complex controlled the target antigens for cross-reactive responses. The results are shown in Table IV. B6 CTL that have been stimulated by TNP-coupled B6 spleen cells lyse A/J (K\(^k\), D\(^d\)), B10.BR (K\(^h\), D\(^k\)), and B10.D2 (K\(^h\), D\(^h\)) TNP-modified targets. Anti-H-2D\(^d\) antisera partially blocks killing of B10.D2-TNP and A-TNP targets. Furthermore, anti-H-2K\(^k\) serum partially inhibits lysis of B10.BR-TNP and A-TNP targets. This indicates that a significant proportion of cross-reactive lytic activity is directed at H-2K-coded products on the cell membranes modified by TNP. Because a significant amount of cross-reactive lytic activity is directed at H-2K-coded products, it is unlikely that the inability to recognize H-2D TNP modifications in the H-2\(^k\) haplotype can fully account for the inability of H-2\(^k\) mice to produce cross-reactive CTL. Therefore, it appears that the genetic defect described by Schmitt-Verhulst and Shearer (13) is not responsible for the inability of the mice bearing the H-2\(^k\) haplotype to display cross-reactive lysis on TNP-modified allogeneic cells.

**M523 Mutation Does Not Affect the Gene(s) Controlling Cross-Reactive Lysis.** We studied the M523 strain, whose mutation was initially described by Blandova et al. (14). Available data support the assertion that the M523-bearing mouse possesses a point mutation of the H-2K\(^h\) structural gene. Zaleski and Klein (15) have shown that this mutation has also affected the Ir gene which controls the immune response to the cell surface antigen Thy 1.2. We tested cells from M523 mice for their ability to produce cross-reactive CTL after TNP-modified syngeneic stimulation. The results of these experiments could clarify the relationship of the gene controlling cross-reactive lysis to the one described by Zaleski and Klein (15) and might elucidate the role of H-2K structural genes in the control of CTL specificity.

### Table III

**Localization of Gene Controlling Cross-Reactive Lysis**

| Responder cells* | H-2 haplotype | H-2 region formulas‡ | Percent cross-reactive lysis |
|------------------|---------------|-----------------------|-----------------------------|
| B10              | b             | b b b b b b b b      | 50                          |
| B10.D2           | d             | d d d d d d d d      | 34                          |
| B10.BR           | k             | k k k k k k k k      | 7                           |
| A                | a             | k k k k k k d d      | 6                           |
| B10.A(4R)        | h4            | k k k b b b b b b    | 4                           |
| M523             | ka            | k k k k k k k k      | 8                           |
| C3H.OL           | 01            | d d d d d d d d      | 42                          |
| A.TH             | t2            | s s s s s s s d      | 78                          |
| A.TL             | t1            | s k k k k k k k      | 77                          |
| B10.T(6R)        | y2            | q q q q q q q d      | 36                          |
| B10.AQR          | y1            | q k k k k d d d      | 45                          |

* Summary of several experiments. In each case, CTL were stimulated with TNP-modified syngeneic spleen cells and tested on TNP-modified syngeneic and allogeneic spleen cell targets. Spontaneous release of targets was <40% in all cases.

‡ Arrows indicate localization of gene(s) controlling cross-reactivity.
TABLE IV

Antisera Inhibition of Cross-Reactive Lysis by B6 CTL*

| Experiment | TNP-modified target* | Percent specific release§ | Percent antisera inhibition||
|-------------|----------------------|---------------------------|-----------------------------|-----------------------------|
|             |                      |                           | Anti-H-2Kk Anti-H-2Dd       |
| 1           | A                    | 39                        | 62                         | 53                         |
|             | B10.BR               | 28                        | 100                        | 8                          |
|             | B10.D2               | 32                        | 0                          | 71                         |
|             | B6                   | 60                        | 10                         | 14                         |
|             | B6                   | 60                        | 47                         | 6                          |
| 2           | B10.BR               | 15                        | 47                         | 6                          |
|             | B6                   | 28                        | 0                          | 0                          |

* In both experiments B6 CTL were stimulated with TNP-coupled B6 spleen cells.
‡ Spontaneous release of TNP-modified normal spleen cells was <40%.
§ These values are in the absence of antisera. Effector to target ratios of 40:1 in experiment 1 and 15:1 in experiment 2 were used.
|| Anti-H-2Kk serum (B10.D2 anti-B10.A) had a lytic titer 1/500. Anti-H-2Dd serum [(B10 × LP.RIII)FI anti-18R] has a lytic titer 1/1,000. Sera were used at final dilution of 1:12.

Data presented in Table V show that M523 CTL induced by TNP-modified syngeneic cells do not cross-reactively lyse BALB/c or B10 TNP-modified targets and demonstrate very little lysis of TNP-modified C3H.OL targets which theoretically share identical H-2D end determinants, suggesting that this mutation does not affect the gene(s) described by Schmitt-Verhulst and Shearer (13). However, the M523 CTL lyse TNP-modified B10.A(4R) targets that carry the H-2Kk determinants. Similarly, CBA (H-2k) CTL lyse mutant M523 TNP-coupled targets, indicating the H-2k CTL are capable of lysis when tested on targets of the closely related H-2ka TNP-coupled targets, as previously demonstrated by Forman and Klein (16).

Discussion

To summarize the findings presented in this paper: (a) The specificity of the cytolytic in vitro primary response produced by H-2k CTL, induced by TNP-modified syngeneic cells, is highly H-2 restricted. (b) Mice that bear H-2 haplotypes other than H-2k produce a substantial level of cross-reactive CTL after TNP-modified syngeneic primary stimulation. (c) The gene(s) controlling the specificity of the CTL primary response to TNP-modified syngeneic cells is H-2 linked, and the cross-reactive CTL phenotype is dominant in F1 hybrid mice. (d) Cross-reactive and noncross-reactive CTL maintain their phenotype independent of the H-2 haplotype of the TNP-coupled target. (e) The gene(s) controlling this response maps to the K and/or I-A region of the H-2 complex and can be distinguished from two other genes that map to these regions.

Mice bearing the H-2k haplotype can be induced to exhibit some cross-reactive lysis on TNP-modified allogeneic targets if they are initially primed subcutaneously in vivo and subsequently challenged in vitro with TNP-modified
TABLE V

Cytolytic Activity by the Mutant M523 Strain*

| Responder cells | Modified target cells | Percent cross-reactive lysis $\%$ |
|-----------------|-----------------------|----------------------------------|
| M523 M523       | 100 (60)              |                                  |
| M523 BALB/c     | 5                     |                                  |
| M523 B10        | 12                    |                                  |
| M523 C3H.OL     | 20                    |                                  |
| M523 B10.A(4R)  | 79                    |                                  |
| M523 CBA        | 80                    |                                  |
| CBA M523        | 65                    |                                  |

* M523, a CBA mutant, has an H-2 region of K$, a, I k, S k, and D k. The data represent a summary of two experiments. In each case, M523 or CBA CTL were stimulated with TNP-modified syngeneic spleen cells.

$\dagger$ Spontaneous release of TNP-modified normal spleen cells was <40%.

§ Effector to target ratios of 40:1 and 80:1 gave 60% specific release from the TNP-modified syngeneic target (indicated in parentheses) by M523 and CBA CTL.

syngeneic cells (data not shown). The defect observed in the cross-reactive response of mice of the H-2$k$ haplotype, although highly significant and reproducible, appears to be limited to the primary response.

We have thus described an H-2-linked defect in the H-2$k$ haplotype that limits its ability to cross-reactively lyse TNP-modified targets when stimulated with TNP-coupled syngeneic cells. When these data are considered along with the dominant inheritance of the cross-reactive response and the genetic mapping experiments, we can conclude that an immune response (Ir) gene may be responsible for controlling the specificity of the cytolytic response in the TNP system. We refer to this gene as Ir-X-TNP. This gene(s) regulates the ability to generate cross-reactive CTL after presentation of TNP-modified syngeneic antigens.

In this present report, we localize the Ir-X-TNP gene(s) to the K and/or I-A region by using the B10.A (4R) recombinant strain. In addition, we have shown that the presence of $k$ alleles in the I region is not sufficient for an H-2-restricted cytolytic response to TNP-modified H-2 antigens. However, inasmuch as all Ir gene systems are highly antigen specific, we must note that the TNP-modified stimulating determinants from A.TL and B10.AQR strains do not possess the H-2K$^k$ determinants. Hence, the cross-reactivity observed with these strains was generated with a different stimulating antigen. Further mapping studies will be required to definitively localize the Ir-X-TNP gene.

Several other Ir genes controlling immune responses to cell surface-associated antigens appear to map close to the Ir-X-TNP gene (13, 15). Whether the Ir-X-TNP gene codes for a T-cell recognition defect or rather controls CTL responses by restricting cell-to-cell collaboration or by allowing regulatory cells to be produced is unresolved. Data presented in the following report suggest a possible mechanism by which the Ir-X-TNP gene controls the CTL response to TNP-modified cells.
Summary

The ability of cytotoxic T lymphocytes (CTL) induced in vitro to trinitrophenyl (TNP)-modified syngeneic cells to cross-reactively lyse a TNP allogeneic spleen target varies among inbred mouse strains. The cross-reactive CTL phenotype was found to be histocompatibility 2 (H-2) linked and to be dominant in F1 hybrid mice. All strains investigated demonstrated cross-reactivity except for some strains bearing portions of the H-2k haplotype. The gene(s) controlling this response maps to the K and/or I-A region of the H-2 complex. We have termed the immune response (Ir) gene responsible for controlling the specificity of CTL induced to TNP-modified syngeneic cells Ir-X-TNP.

We wish to thank Dr. Ronald Germain for his stimulating discussions, and Ms. Diane Cannata for her excellent secretarial assistance.

Received for publication 3 April 1978.

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