GENETIC REGULATION OF
DELAYED-TYPE HYPERSENSITIVITY RESPONSES TO
poly(tTyr,tGlu)-poly(dLAla)-poly(tLys)
I. Expression of the Genetic Defect at Two Phases of
the Immune Process*

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One of the antigens most thoroughly studied in analyzing the molecular and cellular basis of the genetic control of specific humoral immune responses is the multichain synthetic polypeptide poly(tTyr,tGlu)-poly(dLAla)-poly(tLys) [(T,G)-A--L] (1-4). Mice of the H-2b haplotype were found to be high responders to this immunogen, whereas mice bearing the H-2k and H-2a haplotypes were low responders to this immunogen. A third group of mice that are phenotypically nonresponders to (T,G)-A--L are those possessing the H-2a haplotype (5).

Studies on the humoral immune responses to (T,G)-A--L aimed at establishing the cell types in which the genetic defects are expressed in low and nonresponders led to the conclusion that Ir-gene control is expressed in H-2k and H-2a mice at the level of either a B cell or a macrophage or both (6-10). The defect in H-2k nonresponder mice on the other hand is expressed at the T-helper as well as the B cell levels (7, 11).

Whereas the humoral immune responses to (T,G)-A--L have been investigated with different approaches, cellular immune responses were studied mainly by the in vitro antigen-dependent T-cell proliferation (12), which served as a model for T-cell function.

In this work we have studied T-cell function with the delayed-type hypersensitivity (DTH) assay, which we have previously described (13). The method we used dissected the DTH reaction into an either in vivo or in vitro T-cell activation step followed by a step of transferring the educated cells into naive recipients, in which the reaction was manifested.

We report here that educated cells from H-2b mice mediated DTH responses in syngeneic recipients, whereas mice of the a, f, k, d, and s haplotypes were nonresponders to (T,G)-A--L. Further analysis of nonresponsiveness revealed that significant DTH responses could be elicited when educated lymphocytes of the a or k haplotypes
were transferred into hybrids between (high responder × non responder) F1 recipients; however, F1-educated cells could not manifest DTH reaction in the H-2\(^b\) or H-2\(^a\) nonresponder recipients. No DTH responses could be mediated by transferring educated cells of the H-2\(^a\) or H-2\(^b\) origin into the appropriate F1 recipients.

**Materials and Methods**

**Animals.** C3H.SW, C3H/DiSn, CWB, CKB, DBA/1, SJL/J, BALB/c, C57BL/6, C57BL10(B10), B10.A, B10.M, B10.S, A.CA, A.BY, (C3H.SW × C3H/DiSn)F\(_1\), (B10 × B10.A)F\(_1\), (B10 × B10.M)F\(_1\), (A.BY × A.CA)F\(_1\), (SJL × C57BL/6)F\(_1\), B10.A(4R), and B10.A(5R) mice of 2–3 mo of age were used. Inbred and recombinant mice were obtained from the Experimental Animal Unit of our Institute, and F1 hybrid mice were bred in our laboratory.

**Antigen.** The multichain synthetic polypeptide (T,G)-A--L was synthesized and characterized as previously described (14).

**Cell Culture.** In vitro education of lymphocytes to (T,G)-A--L was performed as described before (13). Briefly, splenic lymphocytes were cultured on adherent cells bearing (T,G)-A--L. After 5 d in culture, nonadherent cells were harvested, washed, and transferred intravenously into naive recipients.

**In Vivo Generation of Educated T Cells.** Thymocytes (10\(^6\)) were injected intravenously into syngeneic recipients irradiated with 800 R (Cobalt). Recipients were immunized with 20 \(\mu\)g of (T,G)-A--L in complete Freund's adjuvant (H37 Ra, Difco Laboratories, Detroit, Mich.) intraperitoneally. Spleens that contained the T-educated cells were removed 7 d later, and the single cell suspensions prepared were transferred into naive recipients.

**Measurement of DTH.** Viable in vivo or in vitro educated cells (25 × 10\(^6\)) were irradiated with 1,200 R before transfer into naive recipients. DTH activity was determined according to Vadas et al. (15). 16 h after, cell transfer recipients were challenged by an injection of 10 \(\mu\)l of 2 mg/ml antigen intradermally in the right ear. Control solution was injected into the left ear. 10 h after challenge, mice received 0.1 ml of a 1.0 mM solution of 5-fluorodeoxyuridine, and, 30 min later, 2 \(\mu\)Ci of \(^{125}\)I-iodo-2'-deoxyuridine (\(^{125}\)I\(\text{UdR}\)). Mice were killed 24–30 h after challenge, ears were cut, and the amount of radioactivity was determined in a gamma spectrometer (Packard Instrument Co., Downers Grove, Ill.). The results are expressed as the ratio of radioactivity in the right (R) ear to that of the left (L) ear (R/L \(^{125}\)I\(\text{UdR}\) uptake). Positive DTH response was considered when the R/L \(^{125}\)I\(\text{UdR}\) uptake was > 1.2. The results are expressed as the arithmetic mean of all mice in the group ± standard error. \(P\) values were calculated by the Student's \(t\) test.

**Histological Examinations.** Ears were taken 24 h after challenging recipients of educated cells, and fixed in Bouin's solution. Serial cuts were stained in hematoxylin and eosin (HE).

**Results**

**Comparison of DTH Responses to (T,G)-A--L of Different Mouse Strains.** To check whether DTH responses to (T,G)-A--L are under genetic control, different mouse strains were screened for their T-cell function. Table I demonstrates that when spleen cells were educated in vitro to (T,G)-A--L only cells of mice possessing the H-2\(^b\) haplotype such as C3H.SW, CWB, C57BL/10, and C57BL/6 could mediate specific DTH responses in syngeneic naive recipients, whereas mice of the k, f, d, and s haplotypes were nonresponders to the synthetic polypeptide.

Table II compares the potential of in vivo educated T cells of different strain of mice to mediate DTH responses. Positive DTH responses were found when 25 × 10\(^6\) viable educated T cells of the H-2\(^b\) haplotypes were transferred into naive syngeneic recipients, whereas educated cells of the a, d, k, q, and s haplotypes failed to elicit significant DTH responses to (T,G)-A--L. The results suggest that cell-mediated immune responsiveness to (T,G)-A--L, similarly to humoral responses, is linked to the H-2 complex. As shown in Table II, F1 hybrids between the parental (nonresponder
TABLE I
(T,G)-A--L Specific DTH Responses of Different Mouse Strains Injected with In Vitro Educated Cells

| Mouse strain | H-2 haplotype | No. of responders/group | R/L $^{32}$UdR* uptake ± SE |
|--------------|---------------|------------------------|-----------------------------|
| C3H.SW       | b             | 9/10                   | 1.41 ± 0.08$\dagger$       |
| CWB          | b             | 5/5                    | 1.30 ± 0.09$\dagger$       |
| C57BL/10     | b             | 4/5                    | 1.35 ± 0.10$\S$            |
| C57BL/6      | b             | 4/5                    | 1.35 ± 0.05$\S$            |
| BALB/c       | d             | 0/4                    | 0.97 ± 0.04                 |
| B10.M        | f             | 1/5                    | 1.08 ± 0.09                 |
| A.CA         | f             | 0/5                    | 1.00 ± 0.10                 |
| C3H/DiSn     | k             | 1/6                    | 1.07 ± 0.06                 |
| SJL/J        | s             | 0/5                    | 0.76 ± 0.08                 |
| B10.S        | s             | 0/5                    | 1.04 ± 0.06                 |

$*$ Significant difference from B10.S group.
$\dagger$ P < 0.01.
$\S$ 0.02 < P < 0.05.

TABLE II
(T,G)-A--L Specific DTH Responses of Different Mouse Strains Injected with In Vivo Educated Cells

| Mouse strain | H-2 haplotype | No. of responders/group | R/L $^{32}$UdR* uptake ± SE |
|--------------|---------------|------------------------|-----------------------------|
| B10.A        | a             | 1/9                    | 0.95 ± 0.04                 |
| C3H.SW       | b             | 6/6                    | 1.74 ± 0.05$\dagger$       |
| C57BL/10     | b             | 11/12                  | 1.52 ± 0.09$\dagger$       |
| C57BL/6      | b             | 7/8                    | 1.64 ± 0.14$\dagger$       |
| CWB          | b             | 4/5                    | 1.38 ± 0.10$\S$            |
| B10.D2       | d             | 0/12                   | 0.99 ± 0.05                 |
| DBA/2        | d             | 0/5                    | 0.90 ± 0.06                 |
| C3H/DiSn     | k             | 2/11                   | 1.01 ± 0.07                 |
| CKB          | k             | 1/5                    | 1.06 ± 0.12                 |
| DBA/1        | q             | 1/5                    | 0.93 ± 0.11                 |
| SJL/J        | s             | 0/6                    | 0.79 ± 0.10                 |
| B10.S        | s             | 0/5                    | 1.04 ± 0.06                 |
| (C3H/DiSn X C3H.SW)F1 | k/b         | 10/13                  | 1.36 ± 0.07$\|$        |
| (B10.A X B10)F1 | a/b         | 13/16                  | 1.36 ± 0.05$\|$        |
| (SJL X C57BL/6)F1 | s/b         | 8/9                    | 1.47 ± 0.06$\|$        |

$*$ Significant difference from C3H/DiSn group.
$\dagger$ P < 0.01.
$\S$ P < 0.02.
$\|$ P < 0.05.

Comparison of DTH responses in recombinant mouse strains showed that B10.A(5R) mice are responders and B10.A(4R) mice are nonresponders to (T,G)-A--L (Table III). These data suggest that the gene that controls DTH responses is mapped in the K or I-A subregion of the H-2 complex.

Genetic Analysis of DTH Nonresponsiveness to (T,G)-A--L. To examine in which phase of the process leading to the manifestation of the DTH response the defect of the nonresponders to (T,G)-A--L was expressed, educated cells from different nonresponder mice were checked for their ability to mediate DTH responses in F1 hybrids.
Table III

Comparison of DTH Responses to (T,G)-A--L in Recombinant Strains*

| Mouse strain | H-2 subregions | No. of responders/group R/L 125I\textsuperscript{1}UdR uptake ± SE |* |
|--------------|-----------------|-------------------------------------------------|---|
| B10.A (4R)   | k / b b b b b   | 0/6                                             | 0.95 ± 0.09 |
| B10.A (5R)   | b b b / k k d d | 5/7                                             | 1.36 ± 0.09 |

* Cells were educated in vitro.
‡ Significant difference between the groups. 0.01 < \(P < 0.02\).

Table IV

The Ability of Nonresponder (H-2\(^k\)) Lymphocytes to Mediate DTH Responses to (T,G)-A--L in (k X b)\(F_1\) Mice*

| Educated cell donors | Recipient strains Haplotype No. of recipients | No. of experiments | No. of responders/group R/L 125I\textsuperscript{1}UdR index ± SE |
|---------------------|---------------------------------------------|-------------------|-------------------------------------------------|
| C3H.SW              | C3H.SW                                      | b                 | 6/6                                             | 1.74 ± 0.05 |
| C3H.SW              | C3H.SW × C3H/DbSn\(F_1\)                    | b/k               | 5/6                                             | 1.41 ± 0.13 |
| C3H/DbSn            | C3H/DbSn                                    | k                 | 3                                               | 1.01 ± 0.07 |
| C3H/DbSn            | C3H/DbSn × C3H.SW\(F_1\)                    | k/b               | 1/7                                             | 0.91 ± 0.11 |
| C3H/DbSn            | C3H.SW                                    | b                 | 5/6                                             | 1.56 ± 0.15 |

* Cells were educated in vivo.
‡ Significant difference from C3H/DbSn group.
§ \(P < 0.01\).
¶ \(P < 0.001\).
\(\ddagger\) \(P < 0.05\).

between parental (nonresponder × responder) recipients. As shown in Table IV, when educated cells from C3H.SW mice were transferred into (k X b)\(F_1\) recipients, DTH responses could be observed. Significant DTH responses could also be elicited when educated lymphocytes of nonresponder H-2\(^k\) haplotype were transferred into (k X b)\(F_1\) recipients. Also shown in Table IV is that educated H-2\(^k\) lymphocytes did not elicit DTH responses in H-2\(^b\) recipients as a result of H-2 incompatibility between the educated cells and the reactive cells in the recipients. Educated lymphocytes from (k X b)\(F_1\) hybrids could mediate DTH responses only when transferred into syngeneic or to the parental high responder (b haplotype) but not to the parental nonresponder (k haplotype) recipients. The same results were obtained using another strain combination between responder and nonresponder mice, namely, mice of the a and b haplotype. Educated lymphocytes from B10.A mice were able to mediate DTH responses to (T,G)-A--L in (a X b)\(F_1\) recipients, as shown in Table V. Educated cells from (a X b)\(F_1\) hybrids could mediate DTH responses in syngeneic or in the parental high responders (b haplotype) but not in the parental nonresponder (a haplotype) recipients. These results suggest that nonresponder H-2\(^k\) and H-2\(^a\) mice are capable of generating active DTH effector cells to (T,G)-A--L and could mediate responses in a heterozygous high responder environment.

A different pattern of nonresponsiveness was observed in experiments where educated cells of nonresponders of the H-2\(^b\) origin were transferred into F\(_1\) high responder recipients (Table VI). Thus, educated cells of SJL or B10.S mice were unable to mediate DTH responses in (s X b)\(F_1\) recipients and (s X b)\(F_1\)-educated cells could
mediate DTH responses only when transferred into syngeneic and to the parental high responder (b haplotype) but not to the parental nonresponder (s haplotype) recipients (Table VI). Similar pattern was obtained when in vitro educated cells from B10.M and A.CA (both H-2^k) -educated cells could not mediate DTH responses to (T,G)-A--L either in syngeneic environment or in (f × b)F_1 recipients as demonstrated in Table VII. Educated cells of (f × b)F_1 hybrids could mediate DTH responses only when transferred into syngeneic and to the parental high responder (b haplotype) but not to the parental nonresponder (f haplotype) recipients. Cells of B10.S mice (Table VI, Exp. B) and cells of B10.M (Table VII, Exp. A) could be activated in vitro to poly(l-Tyr,l-Glu)-poly(l-Pro)--poly(l-Lys) [(T,G)-Pro--L] and poly(l-Phe,l-Glu)--poly(l-Ala)--poly(l-Lys) [(Phe,G)-A--L], respectively, to mediate DTH responses in syngeneic recipients. These strains are known to produce high antibody levels to the above-mentioned antigens ([16]; and E. Mozes. Unpublished observation.).

Histological examination of ears of (k × b)F_1 mice that were challenged with (T,G)-A--L after receiving in vivo educated cells of the H-2^k mice (Fig. 1a), revealed histological changes that included marked mononuclear infiltration. No such histo-

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**Table V**

*The Ability of Nonresponder (H-2^a) Lymphocytes to Mediate DTH Responses to (T,G)-A--L in (a × b)F_1 Mice*

| Educated cell donors | Recipient strains | Haplotype of recipients | No. of experiments | No. of responders/group R/L IUdR index ± SE |
|----------------------|------------------|------------------------|--------------------|----------------------------------------|
| B10                  | B10              | b                      | 2                  | 15/17                                  | 1.50 ± 0.08§ |
| B10                  | B10.A            | a                      | 1                  | 1/6                                    | 1.06 ± 0.06 |
| B10                  | (B10 × B10.A)F_1 | b/a                    | 1                  | 5/5                                    | 1.32 ± 0.08¶ |
| B10.A                | B10.A            | a                      | 2                  | 1/13                                   | 0.95 ± 0.04 |
| B10.A                | (B10 × B10.A)F_1 | b/a                    | 2                  | 10/12                                  | 1.32 ± 0.11¶ |
| (B10 × B10.A)F_1     | (B10 × B10.A)F_1 | b/a                    | 3                  | 13/16                                  | 1.36 ± 0.05¶ |
| (B10 × B10.A)F_1     | B10              | b                      | 2                  | 7/9                                    | 1.40 ± 0.09¶ |
| (B10 × B10.A)F_1     | B10.A            | a                      | 2                  | 2/10                                   | 1.07 ± 0.07 |

* Cells were educated in vivo.  
‡ Significant difference from B10.A group.  
§ P < 0.01.  
¶ P < 0.05.

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**Table VI**

*The Inability of H-2^a Mice to Mediate DTH Responses to (T,G)-A--L*

| Experiment | Educated cell donors | Recipient strains | Haplotype of recipients | No. of responders/group | R/L IUdR index ± SE |
|------------|----------------------|------------------|------------------------|------------------------|---------------------|
| A          | SJL                  | SJL              | s                      | 0/5                    | 0.79 ± 0.10         |
|            | SJL                  | SJL × C57BL/6F_1 | s/b                    | 1/10                   | 1.01 ± 0.09         |
|            | SJL                  | SJL × C57BL/6F_1 | s/b                    | 1/9                    | 1.47 ± 0.06§       |
|            | SJL × C57BL/6F_1     | C57BL/6          | b                      | 6/6                    | 1.66 ± 0.07¶       |
| B          | B10.S                | B10.S            | s                      | 0/5                    | 1.04 ± 0.06         |
|            | B10.S                | B10.S × B10.SF_1 | s/b                    | 0/5                    | 0.93 ± 0.08         |

* Cells of SJL and F_1 mice were educated in vivo, whereas B10.S cells were educated in vitro.  
‡ Significant difference from SJL cells into F_1 recipients.  
§ P < 0.05  
¶ P < 0.001  
† In experiment B, B10.S cells were educated to (T,G)-Pro--L as a positive control, and the R/L index obtained was 1.35 ± 0.06.
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Table VII

The Inability of H-2<sup>k</sup> Mice to Mediate DTH Responses to (T,G)-A--L<sup>*</sup>

| Experiment | Educated cell donors | Recipient strains | Haplotype of recipients | No. of responders/group | R/L, 10<sup>2</sup>U/D index ± SE<sup>†</sup> |
|------------|----------------------|-------------------|-------------------------|------------------------|---------------------------------|
| A B10.M §  | B10.M                | f                 | 0/5                     | 0.99 ± 0.10            |
| B A.CA     | A.CA                 | f                 | 0/5                     | 1.00 ± 0.10            |
| (A.BY × A.CA)F<sub>1</sub> | (A.BY × A.CA)F<sub>1</sub> | b/f                | 0/6                     | 0.98 ± 0.10            |
| (A.BY × A.CA)F<sub>1</sub> | (A.BY × A.CA)F<sub>1</sub> | b/f                | 5/5                     | 1.40 ± 0.08            |
| (A.BY × A.CA)F<sub>1</sub> | (A.BY × A.CA)F<sub>1</sub> | b/f                | 0/6                     | 1.53 ± 0.05            |
| (A.BY × A.CA)F<sub>1</sub> | A.CA                 | f                 | 1/6                     | 0.98 ± 0.07            |

* Cells educated in vitro.
† Significant difference from A.CA group.
§ In experiment A, B10.M cells were educated to (Phe,G)-A--L as a positive control, and the R/L index obtained was 1.56 ± 0.08.
|| P < 0.01.

logical changes could have been observed in ears of H-2<sup>k</sup> mice that received (T,G)-A--L after transfer of educated cells from H-2<sup>k</sup> origin (Fig. 1 b).

Discussion

Our study demonstrates that the DTH response to (T,G)-A--L, likewise the humoral response (5, 17, 18), is linked to the major histocompatibility complex of the mouse and that the genes that regulate these responses are most probably located in the K or I-A subregions of the H-2 complex (Table III). A previous limited strain survey has also suggested a linkage between the ability to manifest DTH responses to (T,G)-A--L and the H-2 complex (19), and similar results were obtained when T-cell responses were measured by the in vitro antigen-dependent T-cell proliferation (12).

Strains of mice can be divided into three groups according to their DTH responsiveness to (T,G)-A--L. The first group is of responders (H-2<sup>b</sup> haplotype), which are capable of mediating DTH reactions in syngeneic recipients as well as in (responder × nonresponder)F<sub>1</sub> hybrids (Tables I and II).

The second class of mouse strains are nonresponders that possess the H-2<sup>s</sup> and H-2<sup>k</sup> haplotypes. T cells of these strains could be activated in a syngeneic environment and could mediate DTH responses in F<sub>1</sub> hybrids between parental (nonresponder × responder), but could not mediate DTH responses in syngeneic naive recipients (Tables IV and V). Thus, it is suggested that for the H-2<sup>k</sup> and H-2<sup>s</sup> nonresponder strains neither accessory cells nor T lymphocytes are expressing the defect in the response to (T,G)-A--L, at least in the activation stage of effector DTH cells. H-2<sup>e</sup> is a natural recombinant that shares the same K-end region as H-2<sup>k</sup> and, as the gene that regulates DTH responses to (T,G)-A--L is mapped to the K-end of the I region of the H-2 complex (Table III), H-2<sup>e</sup> mice were expected to respond as mice of the H-2<sup>k</sup> haplotype.

A third class are nonresponder mice such as those possessing H-2<sup>e</sup> and H-2<sup>f</sup> haplotypes. T cells of these mice could not mediate DTH responses in either syngeneic or in F<sub>1</sub> hybrid recipients (Tables VI and VII). Thus, T cells of H-2<sup>e</sup> and H-2<sup>f</sup> origin could not be activated either in vivo or in vitro for the generation of effector T cells. Cells from such haplotypes could be educated effectively to other synthetic polypeptides like (T,G)-Pro--L and (Phe,G)-A--L, respectively, (Tables VI and VII, footnotes). The results obtained with mice of the H-2<sup>e</sup> haplotype in this study are similar to the observations of Miller et al. (20) who worked with the synthetic copolymer l-glutamic
acid-α-L-alanine-α-L-tyrosine (GAT). In their experiments, DTH to GAT was transferable from sensitized (responder × nonresponder)F₁ mice to naive recipients of the responder but not of the nonresponder haplotypes. Therefore it was suggested that in
the H-2^{a} nonresponder haplotype, macrophages failed to display antigen in a form immunogenic for T cells (20, 21). Our results are also in agreement with reports that T cells of H-2^{a} and H-2^{f} strains cannot be activated into functional (T,G)-A--L specific helper cells (7, 11, 22, 23).

The positive DTH responses observed when H-2^{k} or H-2^{a}-educated cells were transferred into F1 recipients (Tables IV and V) were not a result of allogeneic effects because: (a) In all the experiments, educated cells were irradiated with a dose of 1,200 R before being transferred into the recipients. (b) The time interval between cell transfer and ear cut was \( \sim 36 \) h, which is too short for the development of graft-vs-host reactions. (c) When allogeneic combinations were tested, such as of C3H/DiSn-educated cells into C3H.SW recipients (Table IV), or when B10-educated cells were transferred into B10.A recipients (Table V) no DTH responses were detected. (d) Transfers of educated cells of H-2^{k} or H-2^{a} origin into their appropriate F1 recipients did not result in positive DTH responses.

Educated cells from H-2^{a} and H-2^{k} haplotypes could not mediate DTH responses in syngeneic recipients. Moreover irradiated (high responder \times nonresponder)F1-educated cells did not mediate DTH reactions in the parental H-2^{k} or H-2^{a} nonresponder naive recipients (Tables IV and V). We, therefore, suggest that these nonresponder recipients bear a defect in another cell population that is needed for the cooperation with the educated T cells to elicit DTH responses to (T,G)-A--L. A different site for the genetic defect in these strains has been suggested from data of in vitro studies on the cellular basis of humoral immune responses to trinitrophenyl- or dinitrophenyl-coupled (T,G)-A--L. It was suggested that the defect is expressed on the antigen-presenting cell (9, 10). However, the results described in this communication agree with data that indicate that the genetic defect in the antibody response of H-2^{k} and H-2^{a} mice is not on the level of the helper T cells but in B cells or at a step of T-B-cell interactions (7, 8, 24).

Histological examinations confirmed the determination by the radioisotopic assay that H-2^{k}-educated cells had the potential to mediate DTH responses in F1 recipients but not in syngeneic naive mice. In preliminary experiments we were able to identify the other cell population that expresses the defect in H-2^{k} recipients as of T origin (G. Strassmann, Z. Eshhar, and E. Mozes. Manuscript in preparation.). However, the possibility of an additional defect on the level of an accessory cell that participates in the different stage of the DTH response has not been excluded.

Summary
Delayed-type hypersensitivity (DTH) responses served in this study as an experimental model for the analysis of genetic regulations of T-cell responses. Educated irradiated cells from H-2^{k} mice mediated responses in syngeneic recipients, whereas mice of the a, d, f, k, and s haplotypes were nonresponders to poly(L-Tyr,L-Glu)--poly(L-Ala)--poly(L-Lys) [(T,G)-A--L]. These results suggest that cell-mediated immune responsiveness to (T,G)-A--L is linked to the H-2 complex, as was shown for humoral responses. Educated irradiated T cells of F1 hybrids between high and low responders mediated DTH responses, which indicates that the gene(s) controlling the DTH responses is dominant.

To analyze the genetic defect in DTH responses to (T,G)-A--L, we separated the T-cell activation phase from the effector phase that was determined in recipient mice.
Two types of nonresponders were observed: (a) When lymphocytes of the a or k haplotypes were educated in a syngeneic environment and then transferred into hybrids between the parental (nonresponder × responder)F1 recipients, DTH responses could have been manifested. (b) On the other hand, no DTH responses could be mediated by transferring educated cells of the H-2a or H-2k origin into the appropriate F1 recipients. In addition, irradiated F1 cells that had been activated to (T,G)-A--L could not mediate DTH responses in both types of nonresponder recipients.

These results suggest that T cells of H-2k or H-2a mice can be activated to generate DTH responses to (T,G)-A--L and that the defect in these mouse strains is expressed in another cell population needed for the manifestation of the DTH reaction in the recipient mice. In contrast, T cells of H-2b and H-2d origin cannot be activated to (T,G)-A--L and, thus, fail to manifest DTH responses.

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