RESTRICTION OF VIRUS-SPECIFIC T-CELL-MEDIATED EFFECTOR FUNCTIONS IN VIVO

II. Adoptive Transfer of Delayed-Type Hypersensitivity to Murine Lymphocytic Choriomeningitis Virus is Restricted by the K and D Region of H-2

BY ROLF M. ZINKERNAGEL

(From the Department of Immunopathology, Scripps Clinic and Research Foundation, La Jolla, California 92037)

A wide spectrum of effector functions mediated by thymus-derived lymphocytes (T cells) is associated with structures coded in certain regions of the H-2 gene complex. T-helper cells from conventional mice cooperate with bone marrow-derived lymphocytes (B cells) for the production of certain antibody responses only when both share the IA region of H-2 (1-3). This restriction does not apply between allogeneic T and B cells, when the helper T cells are tolerant to the H-2 haplotype of the B cells (4, 5) or are specifically depleted of alloreactive lymphocytes directed against this haplotype (6). Adoptive transfer of delayed-type hypersensitivity (DTH)
1 to fowl-γ-globulin in conventional mice has also been shown to depend upon donor and recipient mice sharing the I region of H-2 (7). The physiological interaction model is the favored, but not the only possible explanation for these findings (3, 8-11).

Different from these models, specific T-cell-mediated lysis of virus-infected (11, 12) or chemically modified target cells in vitro is exclusively associated with structures coded in the K or D regions of H-2 (9, 10, 13). Also, T-cell-mediated immunopathological processes in acute lymphocytic choriomeningitis (LCM) (14) and T-cell-mediated antiviral protection against LCM virus (LCMV) in vivo can be transferred adoptively only within K- or D-region compatible mouse strain combinations, the I region being irrelevant (15, and footnote 2). The H-2K-coded structure can be defined genetically in the B6.H-2β (Hz170) H-2 mutant (16). Most of the evidence explaining lysis of virus-infected cells is compatible with the "altered self" idea or with a physiological interaction model.

DTH is a widely used assay of cell-mediated immunity which is thought to reflect most directly pathophysiological processes (17), especially in infectious diseases. The fact that generation of effector T cells for DTH to fowl-γ-globulin mapped in the I region of H-2 seemed to contradict the finding that T-cell-mediated adoptive transfer of antiviral protection to LCMV mapped in K and D.

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1 Abbreviations used in this paper: DTH, delayed-type hypersensitivity; LCM, lymphocytic choriomeningitis; LCMV, LCM virus; PFU, plaque-forming units.
This investigation reveals that T cells involved in the adoptive transfer of LCMV-specific DTH are, in fact, associated with \( H-2K \) or \( D \), suggesting that, at least in this system, the biological nature of the antigen rather than the T-cell function determines whether T-cell specificity is associated with the \( I \) or with the \( K \) or \( D \) region of \( H-2 \).

Materials and Methods

**Mice.** C3H and BALB/c mice were from L. C. Strong Research Foundation, Inc., San Diego, Calif. D2.GD and A.TL were bred at the Scripps Clinic and Research Foundation from breeding pairs generously donated by Doctors D. C. Shreffler, C. S. David, and R. V. Blanden (18, 19). All other mice were purchased from The Jackson Laboratory.

**Virus.** The WE strain of LCMV was grown in L929 fibroblasts. The virus stock contained \( 1 \times 10^8 \) plaque-forming units (PFU) per ml (20).

**Experimental Protocol for Adoptive Transfer Experiments.** The method described by Blanden was used (21). Approximately \( 3 \times 10^8 \) PFU of LCMV in 0.03 ml were injected into the left footpad and 0.03 ml of control supernate from uninfected L929 fibroblasts into the right footpad of each mouse about 6-8 h before adoptive transfer intravenously (i.v.) of usually \( 1 \times 10^8 \) immune spleen cells (Fig. 1). Donors of immune cells were injected i.v. 7 days previously with about \( 5 \times 10^2 \) PFU of WE LCMV. In groups of 4-6 mice footpad thickness was measured with dial gauge calipers (Schnelltaster, H. C. Kroplin GmbH, Schluchtern, Hessen, Germany). The percent increase in footpad thickness was determined as described by Tosolini and Mires (22). The difference between the average thickness of feet challenged with virus or with control supernate divided by the average thickness of feet of normal untreated mice times 100 yields percent increase.

Control mice were not transfused with cells. At no time did these controls show significant differences in foot swelling whether challenged with LCMV or with control L929 supernate.

**Antisera and \(^{51}Cr\) Release Assay.** The sera and tests used have been described in detail (23-25).

Results

**T-Cell Dependence of Primary Footpad Swelling.** 6-8 days after injections of LCMV into the footpads of \( nu/nu \) nude mice on a BALB/c non-H-2 genetic background, the \( nu/+ \) and \(+/+\) littermates and normal BALB/c control mice primary swellings of their footpads clearly demonstrated the reaction's T-cell dependence (Fig. 2). Nude mice failed to develop a primary footpad swelling.

**Cellular Parameters for Adoptive Transfer of DTH.** DTH to LCMV could not be transferred by immune spleen cells treated with AKR anti-\( \theta \) C3H (Table I). This treatment also abrogated any virus-specific T-cell-mediated cytotoxicity in vitro (Table II). Goat anti-mouse IgG-Fab, generously donated by Dr. B. Croker, lysed about 58% of the spleen cells but did not affect the capacity to transfer DTH or cytotoxicity.

Transfer of DTH was dose dependent, with respect to magnitude and time of onset of the footpad swelling (Table I). In no experiment was significant immediate-type hypersensitivity demonstrable at 3-6 h after transfer of immune cells i.v.

The DTH response was specific; vaccinia virus-immune spleen cells did not cause DTH in mice given footpad injections of LCMV. Vaccinia virus-immune spleen cells were lytic in vitro only for vaccinia virus but not for LCMV-infected targets and vice versa (Table I).

The adoptive transfer of LCMV-specific DTH was significant only in \( H-2 \) compatible donor-recipient combinations (Table III), as was the virus-specific cytolytic activity in vitro (Table IV). Footpad swelling in recipients of normal or
DTH TO LCMV IS SPECIFIC FOR H-2K AND H-2D

LCMV-immune H-2 compatible or incompatible spleen cells was significant ($P < 0.05$) only in recipients of $5 \times 10^7$ syngeneic immune spleen cells during the time interval of 2–6 days after transfer (Fig. 3). Recipients of allogeneic immune cells did not differ significantly from recipients of normal allogeneic cells during the observation period and were no different from control mice (not shown) which did not receive cells. The recipients of allogeneic immune cells developed primary footpad swellings from day 7 onwards, which was no different from the swelling in the control mice, indicating that these cells had not conferred appreciable immune protection (Fig. 3).

The accelerated kinetics of the adoptively transferred DTH with a second peak around the time of onset of the primary footpad swelling probably reflects the fact that the high virus dose was not controlled by the transferred immune spleen cells; however, with the host's own developing immune response antigen was cleared more rapidly by day 8 and 9 compared with clearance in recipients of allogeneic immune or normal cells ($P < 0.01$). In other experiments where $1 \times 10^8$ syngeneic immune cells were transferred this second DTH peak was not observed, probably because virus was eliminated earlier.

Mapping of the H-2 Compatibility Requirements. LCMV-immune spleen cells from a great variety of H-2 original type, H-2 recombinant, and H-2 mutant mouse strains were assayed in various strain combinations for their capacities to adoptively transfer DTH (Tables III, IV, and V). Compatibility at the $D$ region alone was sufficient for transfer of significant DTH as for B10 → B10.2A(2r) or B10.D2 → A.TL. Also compatibility at $K$ and $IA$ or $K$, $IA$ and $IB$ allowed efficient transfer of DTH (B10.D2 → D2.GD; C3H → A/J; B10. Br → B10.A(2r)). However, compatibility at the $I + S$ regions alone was not sufficient.
Table I

| Mouse strain donor* (H-2 haplotype) | Cell treatment and dose | Recipient§ | Percent increase of footpad thickness at time after transfer (h) |
|-----------------------------------|-------------------------|------------|---------------------------------------------------------------|
|                                   |                         |            | 6       | 24     | 48     | 72     |
| BALB/c LCMV-immune (H-2d)         | Normal AKR + C'         | BALB/c (H-2d) | 2 ± 2  | 27 ± 3  | 33 ± 5  | 27 ± 6  |
|                                   | AKR anti-α C3H + C'     | BALB/c (H-2d) | 2 ± 2  | 2 ± 2   | 2 ± 3   | 2 ± 3   |
|                                   | Anti-Ig + C'            | BALB/c (H-2d) | 2 ± 3  | 22 ± 7  | 34 ± 8  | 24 ± 2  |
|                                   |                         | BALB/c (H-2d) | 2 ± 2  | 20 ± 5  | 47 ± 12 | 54 ± 10 |
|                                   |                         | BALB/c (H-2d) | 4 ± 3  | 12 ± 5  | 19 ± 25 | 48 ± 12 |
|                                   |                         | BALB/c (H-2d) | 2 ± 3  | 2 ± 2   | 6 ± 2   | 12 ± 5  |
|                                   |                         | BALB/c (H-2d) | 2 ± 3  | 2 ± 3   | 6 ± 2   | 2 ± 3   |
|                                   |                         | BALB/c (H-2d) | 2 ± 3  | 2 ± 2   | 7 ± 6   | 5 ± 3   |
|                                   |                         | C3H/St (H-2k) | 2 ± 3  | 20 ± 5  | 62 ± 15 | 69 ± 10 |
|                                   |                         | C3H/St (H-2k) | 2 ± 3  | 8 ± 3   | 20 ± 5  | 59 ± 13 |
|                                   |                         | C3H/St (H-2k) | 2 ± 3  | 2 ± 3   | 3 ± 2   | 2 ± 2   |
|                                   |                         | C3H/St (H-2k) | 2 ± 3  | 6 ± 3   | 4 ± 4   | 5 ± 3   |
|                                   |                         | C3H/St (H-2k) | 2 ± 3  | 4 ± 3   | 3 ± 3   | 3 ± 2   |

* Mice were infected i.v. with 1 × 10⁶ i.c. LD₅₀ of WE LCMV and spleen cells harvested 7 days later. Cytotoxicity was >90% on H-2 compatible L or J774 LCMV-infected targets, as compared with <30% on vaccinia-infected or normal targets.
† Percent of trypan blue positive cells after treatment was normal goat + C': 10%; normal AKR + C': 9%; AKR anti-α C3H + C': 46%; goat-anti-mouse IgG Fab + C': 66%. Cytotoxic activity is recorded in Table II.
§ Recipients were challenged into the left foot with 3 × 10⁶ PFU of WE LCMV and into the right foot with 0.03 ml of control medium 6 h previo to transfusion.
| Means ± SEM of groups of 3-5 mice.
| Significantly greater than controls (P < 0.05).

Table II

Cytotoxicity of Anti-α, or Anti-Ig-Treated, or Control LCMV Immune BALB/c Spleen Cells Used for Transfer Experiments

| Spleen cells and treatment | Percent ⁵¹Cr release from J774 targets |
|----------------------------|-------------------------------------|
|                            | LCMV 30:1 | LCMV 3:1 | Uninfected 30:1 |
| LCMV immune*               |           |          |                |
| Normal AKR + C'            | 100§| 46| 26 |
| AKR anti-α C3H + C'        | 36| 36| 22 |
| Normal goat serum + C'     | 100| 42| 25 |
| Goat anti-mouse IgG + C'   | 100| 44| 23 |
| Normal                     | 33| 30| 26 |
| Medium                     | 31| 31| 24 |

* See Table I.
† The ratio of spleen cells to target cells corresponds to the viable cell numbers before treatment.
§ Means ± SEM of triplicates.
|| Significantly greater (P < 0.05) than anti-α-treated immune spleen cells or normal spleen cells.

as shown for C3H → A.TL. These results correlate with the virus-specific cytotoxic activities measured in vitro (Table IV) and are consistent with previous results (12, 13).

The notion that only K or D but not I-region-coded structures are relevant for this in vivo restriction of DTH-T-cell effector activity is further emphasized by the results in Table V. B10.A(3r) immune spleen cells were able to elicit DTH in
the wild type $H-2^K$ C57BL/6 mice, but not in $B6.H-2^{bK}$ (Hz1), $H-2K$ mutants, which are $IA$ and $IB$ compatible with B10.A(3r).

Discussion

The primary footpad swelling resulting from a local injection of LCMV and the capacity of immune spleen cells to adoptively transfer LCMV-specific DTH are T-cell-dependent phenomena. These results are consistent with the classical observations of DTH in LCM made by Hotchin and Hotchin and Benson (26, 27) and Mims and collaborators (22). They are also compatible with the great amount of evidence indicating that acute, fatal (12, 26, 28) LCM (14), specific antiviral protection by LCMV-immune spleen cells in vivo,2 and cytotoxic activity in vitro (11–13) are all predominantly or exclusively T-cell mediated (9, 10).

Effector T cells involved in the adoptive transfer of LCMV-specific DTH in vivo are much like those that adoptively transfer antiviral protection or cytotoxicity in vitro in that both groups of T cells are associated with the $K$ and $D$, but not with the $I$ region of $H-2$ (Fig. 4). This is at least circumstantial evidence that immunological processes leading to DTH and those involved in antiviral protection are mediated by T cells of the same specificity.

The clear-cut functional restriction by the $H-2$ gene complex itself strongly indicates T-cell dependence. DTH is the last of the classical T-cell-mediated functions shown to be restricted by regions of the $H-2$ gene complex (7). The previously proposed postulate that $H-2$ restriction may represent a quite generally applicable T-cell marker (11, 29) has so far proven to be true, at least in mice.

As examined so far, all T-cell effector functions involved in immunopathological (acute LCM) or pathophysiological, protective (adoptive transfer of DTH and antiviral protection) processes are at the same time LCMV-specific and specific for the $H-2K$ and $H-2D$ haplotype they carry. This strict rule can, however, be overcome by virus-specific T cells generated in irradiated chimeras reconstituted with parental bone marrow (30–31). An explanation for the apparent association of T-cell specificity with $K$- or $D$-coded cell-surface structures and its biological significance are subject to many speculations (32, 33). Trivial explanations like rejection of $H-2$ incompatible cells or of allogeneic inhibition are unlikely as discussed for the transfer of antiviral protection. DTH was measured before host versus graft reactions could occur, i.e. within 24 or 48 h after transfer, furthermore, F1 into parental strain combinations work very efficiently and $D$-region compatibility alone is sufficient.

Of the two main hypotheses, neither the physiological interaction model, nor the altered self idea, have so far been proven unequivocally (9, 10). Although the results presented do not distinguish between these basic models, they do establish one new point. For adoptive transfer of DTH to LCMV-infected cells, $K$- or $D$-region compatibility is required, even though effector T cells involved in DTH to fowl-$\gamma$-globulin require $I$-region compatibility. It seems unlikely yet

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2 Zinkernagel, R. M., and R. M. Welsh. $H-2$ restriction of virus-specific T-cell-mediated effector functions in vivo. I. Specificity of the T cells conferring anti-viral protection against lymphocytic choriomeningitis virus is associated with $H-2K$ and $H-2D$. J. Immunol. In press.
### Table III
Adoptive Transfer of LCMV-Specific DTH in Various Strain Combinations

| Mouse Strains | H-2 haplotype | Percent increase in footpad thickness at time after cell transfer (h) |
|---------------|---------------|---------------------------------------------------------------------|
|               | Donor*        | H-2 haplotype | 6  | 24  | 48  | 72  |
|               | I:A I-B I-C S |             |    |     |     |     |
| K             | I              |              |    |     |     |     |
|               | k              | kanni(k)     |    |     |     |     |
| B10.BR        | BALB/c        | kanni(d)     |    |     |     |     |
| B10.A(2r)     | B10.BR        | kanni(k)     |    | 24  | 48  | 72  |
| C57BL/10      | BALB/c        | 3 ± 3        | 24 ± 10| 39 ± 10| 47 ± 10|
| B10.BR        | B10.A(2r)     | 3 ± 4        | 2 ± 3  | 2 ± 3  |
| C57BL/10      | BALB/c        | 1 ± 2        | 5 ± 5  | 50 ± 15| 52 ± 13|
| B10.BR        | B10.A(2r)     | 2 ± 2        | 14 ± 4 | 28 ± 4 | 15 ± 4 |
| B10.A(2r)     | BALB/c        | 2 ± 3        | 10 ± 2 | 40 ± 4 | 20 ± 3 |
| C57BL/10      | BALB/c        | 6 ± 2        | 37 ± 3 | 23 ± 5 | 20 ± 2 |
| C57BL/10      | B10.A(2r)     | 3 ± 2        | 12 ± 6 | 50 ± 10| 25 ± 3 |
| B10.D2        | D2.GD         | 1 ± 3        | 23 ± 3 | 41 ± 4 | 21 ± 3 |
| C3H           | B10.D2        | 4 ± 4        | 32 ± 3 | 62 ± 3 | 32 ± 4 |
| B10.D2        | C3H           | 2 ± 1        | 3 ± 3  | 5 ± 2  | 3 ± 3  |
| B10.A(2r)     | C3H           | 5 ± 4        | 35 ± 4 | 40 ± 10| 27 ± 5 |

* Donors were infected with 5 x 10^2 PFU of WE LCMV i.v. 7 or 8 days previously. Cytotoxicity was assayed (Table IV).
† Recipients were challenged with 3 x 10^6 PFU of WE LCMV into the left hind footpad and with 0.03-ml control medium into the right hind footpad 6 h previous to transfusion.
§ Means ± SEM of groups of 4-5 mice.
¶ Statistically significantly different from controls or recipients of neither K or D compatible spleen cells.
NT, not tested.

It cannot be excluded that the different techniques employed are responsible for the discrepancy between the fowl-y-globulin model and the results with LCMV. Both are T-cell-dependent phenomena that follow the kinetics of DTH reactions. Therefore, the differential association of DTH effector cells with the I or, alter-
DTH TO LCMV IS SPECIFIC FOR H-2K AND H-2D

Table IV

Cytotoxic Activity of Spleen Cells Used For Adoptive Transfer of DTH

| Spleen cells* (H-2 haplotype) | Percent ⁵¹Cr release from targets† |       |       |
|------------------------------|---------------------------------|-------|-------|
|                              | L cells                         | J774  | C57BL/6 macrophages |
|                              | k kkk k k                       | d ddd d d | b bbb b b |
| LCMV Normal                  |       |       |       |
| Experiment 1                 |       |       |       |
| B10                          | LCMV immune                      | 12§   | 13    | 26   | 23   | 60| 35 |
| b bbb b b                    | Normal                           | 15    | 14    | 24   | 23   | 35 | 35 |
| B10.BR                       | LCMV immune                      | 48||   | 14    | 23   | 22   | 37 | 34 |
| k kkk k k                    | Normal                           | 39||   | 14    | 52||  22 | 36 | 36 |
| B10.A                        | LCMV immune                      | 12    | 12    | 63||  22 | 38 | 35 |
| k kkd d d                    | Normal                           | 14    | 13    | 19   | 20   | 35 | 35 |
| BALB/c                       | LCMV immune                      | 14    | 13    | 22   | 21   | 36 | 35 |
| d ddd d d                    | Normal                           |       |       |       |       |    |
| Medium                       | LCMV immune                      | 25    | 23    | 84||  28 |
|                               | Normal                           |       |       |       |       |    |
| Experiment 2                 |       |       |       |
| A.TL                         | LCMV immune                      | 76||   | 24    | 95||  26 |
| s kkk k d                    | Normal                           | 23    | 24    | 28   | 27   |    |    |

* Donor mice were immunized with $10^8$ i.c. LD₉₀ of WE LCMV 7 days previously; spleens from 10-15 animals were pooled and tested (see Table III).
† Spleen cells were assayed at a spleen cell to target ratio of 30:1 for 8 h at 37°C.
§ Means of triplicates. The SEM were between 0.5 and 2.2.
|| Significantly different from immune spleen cells on uninfected targets or normal spleen cells on infected target cells.
¶ NT, not tested.

natively, with the K and D regions may prove to indicate a more fundamental difference. If the assumption is correct, that the phenomena triggered and measured in both models are the same, then the differences may reflect the pronounced biological differences of the antigens used: fowl-γ-globulin and virus. It seems unlikely that I or K and D association of DTH effector cells in these models is due to differential expression of self-recognizer structures for the respective H-2 regions, dependent on the sensitizing antigen. Furthermore, it may be that different subsets of T cells are sensitized by the two antigens (34). Since DTH to fowl-γ-globulin is mediated by Ly-1-positive T cells (35) it will be interesting to determine the Ly type of the T cells eliciting DTH in the LCMV model.

Thus different antigens triggering similar in vivo phenomena apparently sensitize T cells differentially in association with different subregions of H-2. Chemically defined, soluble or particulate antigens that are chemically or
FIG. 3. Footpad swelling in recipients of 5 × 10⁷ syngeneic or allogeneic LCMV immune or normal spleen cells after injection of 10⁶ PFU WE LCMV into the footpad. 7 days LCMV immune BALB/c spleen cells into BALB/c recipients (−Δ−); BALB/c immune into CBA/H (−□−); CBA/H immune into CBA/H (−○−); CBA/H immune into BALB/c (−▽−); normal BALB/c into CBA/H (−●−); normal CBA/H into BALB/c (−▲−).

TABLE V

DTH in the B6.H-2<sup>nu</sup> (Hzl) H-2 Mutant

| Donor* H-2 haplotype | Recipient† H-2 haplotype | Percent increase of footpad thickness at times after transfer (h) |
|----------------------|--------------------------|---------------------------------------------------------------|
|                      |                          | K<sub>I-A I-B I-C</sub> S D K<sub>I-A I-B I-C</sub> S D       |
| B10.A(3r)<sup.§</sup> | B6.H-2<sup>nu</sup>      | 4 ± 3<sup>||</sup> 4 ± 2 4 ± 2 4 ± 2                        |
| ba bbb b b           | ba bbb b b               |                                                               |
| C57BL/6              |                          | 2 ± 2 25 ± 2<sup>¶</sup> 53 ± 3<sup>¶</sup> 15 ± 2<sup>¶</sup>  |
| b bbb b b            |                          |                                                               |

* Donor mice were infected with 1 × 10<sup>4</sup> i.c. LD<sub>50</sub> of WE LCMV 7 days previous to transfer.
† Recipients were challenged into the left foot with 3 × 10<sup>6</sup> PFU of WE LCMV and 0.03 ml of control supernate into the right foot 8 h previous to transfusion.
§ Cytotoxic activity of B10.A(3r) immune spleen cells assayed at 30:1 for 7 h caused significant (P < 0.05) lysis of C57BL/6 LCMV-infected macrophage targets: 79% vs. 29-30% by normal spleen cells; no significant lysis as compared with controls was detectable against LCMV-infected B6.H-2<sup>nu</sup> macrophage targets.
|| Means ± SEM of groups of 4–5 mice.
¶ Statistically significantly greater than in B6.H-2<sup>nu</sup>.

biologically inert (i.e., nonmultiplying) or intracellular bacteria (29, unpublished results) are passively taken up from interstitium or circulation by phagocytes (36, 37). They may be handled by macrophages, blood monocytes, or other members of the reticuloendothelial system to become associated with structures coded in the I region of H-2. It is unclear how this may happen; a speculative possibility is that phagolysosomes are the processing organelles and that the relevant "antigen-altered" I-coded structures are re-expressed on the cell surface by exocytosis (29, 36-38).
DTH TO LCMV IS SPECIFIC FOR H-2K AND H-2D

Multiplying infectious agents, like viruses, that actively invade cells and interfere in genetic and metabolic pathways of the host cells may, because of these parameters, act quite differently and alter K- and D-coded structures instead of I structures. Altered K or D might be envisaged as complex of viral antigen and K or D structure, as long or short range disturbances of these structures by budding virus, as derepression of regulatory genes determining multigenically defined H-2K or D haplotype expression (though specificity is difficult to envisage in this model [39]), or direct or indirect (e.g., via glycosyltransferases [40]) chemical modification of these self-structures.

Such an interpretation of the various restrictions of T-cell effector functions by the H-2 gene complex and of the DTH phenomena in particular would be consistent with the postulated unifying concept that T cells may be reactive in general (and exclusively?) to altered cell surface structures coded in the K, I, and D region of H-2, to virally altered or chemically modified H-2K or H-2D, antigen altered Ia, and alloantigens (8-10, 32).

Summary

In mice, primary footpad swelling after local infection with lymphocytic choriomeningitis virus (LCMV) and delayed-type hypersensitivity (DTH) adoptively transferred by LCMV immune lymphocytes are T-cell dependent. Nude mice do not develop primary footpad swelling, and T-cell depletion abrogates the capacity to transfer LCMV-specific DTH. Effector T cells involved in eliciting dose-dependent DTH are virus specific in that vaccinia virus-immune lymphocytes could not elicit DTH in LCMV-infected mice.

The adoptive transfer of DTH is restricted to H-2K or H-2D compatible donor-recipient combinations. Distinct from the fowl-γ-globulin DTH model, I-region compatibility is neither necessary nor alone sufficient. Whatever the mechanisms involved in this K- or D-region associated restriction in vivo, it most likely operates at the level of T-cell recognition of "altered self" coded in K or D. T cells associated with the I region (helper T cells and DTH-T cells to fowl-γ-globulin) are specific for soluble, defined, and inert antigens. T cells associated with the K and D region (T cells cytotoxic in vitro and in vivo for acute LCMV-infected cells, DTH effector T cells, and anti-viral T cells) are specific for infectious, multiplying virus. The fact that T-cell specificity is differentially linked...
with the $I$ region or with the $K$ and $D$ regions of $H-2$ may reflect the fundamental biological differences of these antigens. Although it cannot be excluded that separate functional subclasses of T-effector cells could have self-recognizers for different cell surface structures coded in $I$ or $K$ and $D$, it is more likely that the antigen parameters determine whether T cells are specific for "altered" $I$ or "altered" $K$- or $D$-coded structures.

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