IN VolVEMENT OF H-2L GENE PRODUCTS IN VIRUS-IMMUNE T-CELL RECOGNITION

Evidence for an H-2L-Restricted T-Cell Response*

BY WILLIAM E. BIDDISON,† TED H. HANSEN,§ ROBERT B. LEVY,¶ AND PETER C. DOHERTY

From The Wistar Institute of Anatomy and Biology, Philadelphia, Pa. 19104, and the Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014

Recent experiments have identified a new H-2-like cell-surface glycoprotein which is determined by the D region of the murine major histocompatibility complex. This product, designated L (previously called D₇) (1), is distinct from the K and D molecules which bear the H-2 private specificities detected by cocapping (2) and immunoprecipitation (3) techniques. Because D and L are encoded by genes which have yet to be separated by recombination, both remain markers for the D region. However, it was shown that a mutant mouse strain, BALB/c-H-2db (4), had lost the L (but not the D) antigenic specificities from the cell surface (1, 5). In studies of the BALB/c-H-2db strain and the coisogenic strain BALB/c, it was demonstrated that H-2L alloantigens elicit rapid skin graft rejection (4) and a strong primary in vitro cytotoxic T-cell response (6). Therefore, H-2L products appear to function as major transplantation antigens.

Blanden et al. (7) have recently reported that BALB/c-H-2db mice, in contrast to wild-type BALB/c, failed to generate a T-cell response to ectromelia virus in association with products of the D region, whereas BALB/c-H-2db ectromelia-infected target cells could be lysed by D region-compatible ectromelia-immune T cells. The absence of H-2L gene products was thus accompanied by a failure of stimulation, but not of recognition at the level of cytotoxic effector function. This situation does not apply for reactivity to minor transplantation antigens (7) or to trinitrophenyl (TNP), and is unique for all the H-2 mutant strains employed in previous virus studies (8–10). The present study investigates: (a) whether the requirement for H-2L specificities in stimulation of ectromelia virus-immune T cells specific for D region products is unique, or also applies to other viruses; and (b) whether virus-immune T cells recognize viral determinants in association with H-2L as well as H-2D gene products.

Materials and Methods

Mice. BALB/c-H-2db and BALB/cLh (H-2d) mice were bred from stock which was kindly provided by Doctors Henry Kohn and Roger Melvold (Harvard Medical School and Shields

* Supported in part by U. S. Public Health Service grants CA-09140, AI-14162, and NS-11036; and by grant 851-A-4 from the National Multiple Sclerosis Society.
† Present address: Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Md. Recipient of U. S. Public Health Service postdoctoral research award 1 F32 AI05812-01.
§ Recipient of U. S. Public Health Service postdoctoral research award 3 F32 CA05270-02.
¶ Recipient of U. S. Public Health Service postdoctoral research award F32 CA05551-01.
1 Abbreviations used in this paper: SDS, sodium dodecyl sulfate; TNP, trinitrophenyl.
2 R. B. Levy, G. M. Shearer, and T. H. Hansen. 1978. Properties of H-2L locus products in allogeneic and H-2 restricted, trinitrophenyl-specific cytotoxic responses. J. Immuno In press.

1678 THE JOURNAL OF EXPERIMENTAL MEDICINE • VOLUME 148, 1978
Viruses and Immunizations. The influenza type A viruses HK[A/Hong Kong/8/68-X-31(H3N2)] and PR8[A/Puerto Rico/8/34(HON1)] were supplied and grown in embryonated eggs as previously described (11). Mice were immunized in vivo by intraperitoneal inoculation with 200–300 hemagglutination units of virus in allogeneic fluid and spleen cells obtained 5 days later for assay. In vitro induction of secondary influenza-immune T cells was performed by incubation of spleen cells from 4 to 16 wk-primed mice with influenza virus (2–4 HAU/10^7 cells, 37°C, 1 h) and culturing for 5 days in RPMI-1640 medium supplemented with 10% vol/vol fetal bovine serum, 0.01 mM nonessential amino acids, 0.1 mM sodium pyruvate, 0.03% glutamine, 100 U/ml penicillin, and 100 µg/ml streptomycin (Grand Island Biologicals, Grand Island, N. Y.).

The WR strain of vaccinia virus (obtained from Dr. R. M. Zinkernagel, Scripps Clinic and Research Foundation, La Jolla, Calif) was grown in mouse L cells as described by Joklik (12). Mice were immunized by intravenous inoculation of 5 × 10^6 plaque-forming units of virus and spleen cells harvested 6 days later for assay.

Target Cells and Cytotoxicity Assays. L cells (C3H, H-2^k), P815 mastocytoma cells (DBA/2, H-2^d), NA neuroblastoma cells (A/J, H-2^o), and B10.A(5R) SV, an SV40 virus-transformed cell line of kidney fibroblasts from B10.A(5R) (H-2^k) mice, respectively (obtained from Dr. Barbara Knowles, Wistar Institute, Philadelphia, Penn.), were maintained in tissue culture. Lipo polysaccharide (LPS)-induced splenic lymphoblasts were prepared, labeled with ^51Cr, and infected with influenza virus as described by Zweerink et al. (13). Influenza virus infection of ^51Cr-labeled tumor target cells was performed as described by Effros et al. (11) and vaccinia virus infection according to Doherty et al. (14). Results of cytotoxicity assays are reported as mean percent specific lysis of quadruplicate or triplicate determinations (11).

Immunoprecipitation Analyses. Radiolabeling, solubilization, precipitation, and sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis were all performed by previously described methods (15).

Alloimmunizations. Alloantisera were raised by primary immunization with a skin graft followed by weekly injections of 2 × 10^7 live lymphoid cells. The titer was assessed in a two-stage microcytotoxicity assay using rabbit serum as a source of complement (16). Anti-D antiserum ([B10.AKMXA.BY] anti-A.AL]) and anti-L antiserum (BALB/c-H-2^db anti-BALB/c) had titers on BALB/c cells of 1:512 and 1:128, respectively. These alloantisera detect specificities on two distinct cell-surface glycoproteins as revealed by immunoprecipitation analysis (Fig. 1).

Alloimmune cytotoxic T cells were generated by 5-day in vitro sensitization as previously described (6).

Results

BALB/c-H-2^db and various control strains of mice were inoculated with influenza or vaccinia viruses and their spleen cells were assayed for cytotoxic activity against virus-infected K and/or D region-compatible target cells. No absolute discrimination was seen in the capacity of influenza- or vaccinia-specific BALB/c and BALB/c-H-2^db lymphocytes to mediate lysis of virus-infected D region-compatible NA (K^d-D^d) or B10.A(5R) (K^d-D^d) target cells (Tables I and II). The vaccinia-immune T-cell populations from BALB/c-H-2^db mice tended to be less effective, but there was no evidence of a total failure of responsiveness (Table II). In addition, secondary influenza-immune BALB/c-H-2^db T-cells generated by in vitro immunization of primed spleen cells were also able to specifically lyse D region-compatible A.TH virus-infected lymphoblasts (Table III). These results imply that L antigens are not required for the generation of D region-restricted influenza- and vaccinia-immune T cells.

To determine if H-2L gene products are recognized by virus-immune T cells, anti-
**FIG. 1.** Electrophoretic patterns of BALB/c antigen sequentially precipitated with antisera against the D and L molecules. [*H*]leucine-labeled antigen was pretreated by precipitation with the reagent indicated on the left and the supernates from this first precipitation step were then tested for residual reactivity with the reagent indicated above the panels. The test precipitates were solubilized with SDS and subjected to disk electrophoresis on 10% polyacrylamide gels. Using this system, H-2 molecules (45,000 mol wt) migrate to 4 cm and a non-specific running front appears at 8 cm of gel. The top two panels indicate that both the anti-D and the anti-L serum precipitate BALB/c molecules with an apparent mol wt of 45,000 daltons. The middle two panels show that although pretreatment with antiserum to L completely removed L molecules (panel IV) the molecules detected by the anti-D serum were unaffected (compare panels I and III). Reciprocally, when the molecules detected by the anti-D serum were removed (panels V and VI), the molecules detected by the anti-L were unaffected (compare panels II and VI). Therefore, these results demonstrate that the anti-L (BALB/c-H-2b* anti-BALB/c) and the anti-D (anti-H-2.4) react with independent populations of molecules.
Table 1

| Exp no. | HK-immune spleen cells | Effector cell: target cell | Percent-specific lysis of target cells* |
|---------|------------------------|---------------------------|----------------------------------------|
|         |                        |                           | HK | N | HK | N | HK | N | HK | N |
| 1       | BALB/c                 | 25:1                      | 10.7 | 0.9 | 11.0 | 2.0 | 0.7 | 1.2 | 19.0 | 1.6 |
|         |                        | 50:1                      | 20.7 | 2.2 | 21.1 | 2.6 | 3.7 | 1.9 | 27.2 | 1.7 |
|         |                        | 100:1                     | 35.8 | 3.4 | 30.0 | 1.3 | 3.4 | 3.0 | 37.8 | 1.9 |
|         | BALB/c-H-2<sup>db</sup> | 25:1                      | 10.3 | 1.9 | 11.1 | 4.3 | 2.1 | 1.4 | 15.3 | 1.3 |
|         |                        | 50:1                      | 18.5 | 3.8 | 15.7 | 5.9 | 4.7 | 4.0 | 27.5 | 1.4 |
|         |                        | 100:1                     | 37.4 | 7.2 | 24.1 | 5.9 | 9.5 | 4.5 | 41.6 | 2.0 |
|         | BALB.K                 | 25:1                      | 32.3 | 1.4 | 4.2 | 2.4 | 45.0 | 0.2 | 4.2 | 1.6 |
|         |                        | 50:1                      | 45.1 | 2.0 | 4.0 | 1.6 | 57.3 | -0.1 | 4.6 | 1.1 |
|         |                        | 100:1                     | 58.1 | 5.0 | 7.1 | 4.2 | 68.3 | 0.9 | 5.3 | 2.7 |
| 2       | BALB/c                 | 25:1                      | 12.3 | -1.7 | 0 | 0.6 | 45.4 | -0.1 |  |  |
|         |                        | 50:1                      | 23.2 | -1.4 | 0.7 | 1.7 | 66.2 | -0.7 |  |  |
|         |                        | 100:1                     | 33.6 | 0.5 | 2.1 | 4.8 | 75.0 | 11.1 |  |  |
|         | BALB/c-H-2<sup>db</sup> | 25:1                      | 4.4 | -0.6 | -0.3 | -1.8 | 28.6 | 3.3 |  |  |
|         |                        | 50:1                      | 11.8 | -1.7 | 1.7 | -0.6 | 46.0 | 5.3 |  |  |
|         |                        | 100:1                     | 23.3 | 0.7 | 1.3 | 1.5 | 65.0 | 1.2 |  |  |
|         | B10.BR                 | 25:1                      | 33.1 | -2.1 | 44.2 | -2.4 | -3.5 | 2.0 |  |  |
|         |                        | 50:1                      | 46.4 | -1.6 | 56.1 | -1.0 | -3.5 | 4.4 |  |  |
|         |                        | 100:1                     | 55.1 | -0.7 | 59.7 | 0.9 | 0.3 | 0.8 |  |  |

* Target cells were either infected with HK influenza virus or uninfected (N). SEM was always <10% of the mean. Cytotoxicity assays were run for 12 h.

† Letters in parenthesis indicate H-2K and D region haplotypes of target cells.

L and anti-D alloantiseras were tested for their ability to block the lysis of D region-compatible virus-infected NA (K<sup>k</sup>-D<sup>d</sup>) target cells by BALB/c and BALB/c-H-2<sup>db</sup> influenza-immune T cells. The results in Table IV show that anti-L alloantisera was consistently able to produce significant inhibition of cytotoxicity mediated by virus-immune T cells from BALB/c, but not BALB/c-H-2<sup>db</sup>. The specificity of the inhibiting effect of anti-L alloantisera was shown by its ability to block alloimmune effector cell activity directed against L antigens and the inability of this serum to block the activity of alloimmune effector cells sensitized to D antigens. Anti-D alloantisera inhibited virus-immune cytotoxicity of both BALB/c and BALB/c-H-2<sup>db</sup> T cells, but did not inhibit the activity of effectors directed against L alloantigens on the NA target cells.

Discussion

Although BALB/c-H-2<sup>db</sup> mice do not display detectable cell-surface H-2L gene products, they are able to generate influenza- and vaccinia-immune cytotoxic T-cells which lyse D region-compatible target cells. However, these mice apparently do not make a similar response to ectromelia virus (7). These observations are particularly interesting because vaccinia- and ectromelia-immune cytotoxic T-cell responses are highly cross-reactive (17). Furthermore, these two pox viruses share many serologically defined determinants, detected by both virus neutralization and immunoprecipitation in gels (18, 19). Relatively minor differences between two very similar viruses, together with the presence or absence of a particular H-2 determinant (L), may thus determine
**Table II**

*Cytotoxic Activity Against Vaccinia Virus-Infected Cells*

| Exp. no. | Vaccinia-immune spleen cells | Effector cell: target cell | Percent-specific lysis of target cells* |
|----------|-----------------------------|---------------------------|----------------------------------------|
|          |                             |                           | NA(kd) | B10.A(5R)SV(bd) | L(kk) | P815(dd) |
|          |                             |                           | VAC N | VAC N | VAC N | VAC N |
| 1 BALB/c |                             |                           |        |        |        |        |
| 25:1     | 8.4                         | 2.0                       | 17.0   | 0.6    | 3.6   | 2.0    | 27.9   | 0.5 |
| 50:1     | 18.4                        | 3.0                       | 26.9   | 2.8    | 5.9   | 3.4    | 43.8   | 2.2 |
| 100:1    | 32.1                        | 9.1                       | 36.0   | 3.3    | 8.1   | 7.2    | 63.2   | 1.4 |
| BALB/c-\(c-H^{2}\)^a |                             |                           |        |        |        |        |
| 25:1     | 4.9                         | 2.7                       | 11.0   | 3.6    | 3.4   | 2.1    | 21.3   | 2.7 |
| 50:1     | 10.5                        | 5.4                       | 16.8   | 5.9    | 7.0   | 4.2    | 27.6   | 3.8 |
| 100:1    | 24.8                        | 11.9                      | 23.9   | 7.6    | 9.1   | 6.7    | 37.1   | 3.4 |
| BALB.K   |                             |                           |        |        |        |        |
| 25:1     | 31.9                        | 1.1                       | 4.7    | 4.9    | 48.8  | 1.7    | 3.4    | 4.4 |
| 50:1     | 48.2                        | 3.0                       | 9.8    | 6.0    | 64.3  | 0.8    | 5.4    | 5.3 |
| 100:1    | 57.0                        | 9.8                       | 15.5   | 6.8    | 70.9  | 2.4    | 9.7    | 7.1 |
| 2 BALB/c |                             |                           |        |        |        |        |
| 25:1     | 12.1                        | 0.1                       | 16.7   | -5.5   | -4.0  | 1.4    | 30.9   | -5.9 |
| 50:1     | 27.2                        | 6.0                       | 26.9   | -4.7   | 0.3   | 6.2    | 36.3   | -3.7 |
| 100:1    | 41.1                        | 13.6                      | 38.4   | -0.9   | 5.6   | 10.6   | 45.6   | 10.9 |
| BALB/c-\(c-H^{2}\)^a |                             |                           |        |        |        |        |
| 25:1     | 10.2                        | 5.1                       | 7.6    | 2.4    | 1.5   | 5.6    | 28.1   | 4.8 |
| 50:1     | 18.9                        | 10.5                      | 17.1   | 6.0    | 5.6   | 9.9    | 41.6   | 4.0 |
| 100:1    | 39.0                        | 16.1                      | 25.0   | 8.0    | 15.0  | 14.9   | 46.3   | 15.6 |
| B10.BR   |                             |                           |        |        |        |        |
| 25:1     | 30.5                        | 3.0                       | 0.9    | 1.0    | 41.2  | 3.6    | 7.4    | 7.6 |
| 50:1     | 41.2                        | 5.9                       | 3.2    | 2.3    | 51.7  | 8.7    | 11.9   | 13.9 |
| 100:1    | 50.7                        | 17.5                      | 8.2    | 9.1    | 61.2  | 12.9   | 15.1   | 15.5 |

* Target cells were infected with vaccinia virus (VAC) or uninfected (N). SEM was always <20% of the mean. Cytotoxicity assays were run for 12 h.

**Table III**

*Secondary Influenza-Immune Effector-Cell Activity on Virus-Infected H-2K or H-2D Region-Compatible Lymphoblasts*

| HK-immune spleen cells$ | Effector cell: target cell | Percent-specific lysis ± SEM of target cells* |
|------------------------|---------------------------|-----------------------------------------------|
|                        |                           | D2.GD (db) | A.TH (sd) | B10.BR (kk) |
| HK N                   | HK N | HK N | HK N |
| BALB/c                 | 1:1  | 14.9 ± 1.5 | -0.2 ± 0.6 | 10.7 ± 1.7 | -2.5 ± 0.6 | 2.3 ± 2.1 | 5.6 ± 3.4 |
|                        | 5:1  | 27.8 ± 0.8 | 0.1 ± 0.6 | 221 ± 2.2 | -0.6 ± 0.8 | 6.1 ± 2.8 | 8.7 ± 2.5 |
|                        | 20:1 | 37.0 ± 1.0 | 2.7 ± 0.7 | 35.3 ± 3.0 | -1.2 ± 0.7 | 11.1 ± 2.6 | 11.1 ± 2.1 |
| BALB/c-\(c-H^{2}\)^a | 1:1  | 19.2 ± 2.5 | 2.6 ± 1.5 | 6.3 ± 1.8 | 1.1 ± 0.6 | 1.0 ± 3.2 | 1.6 ± 2.1 |
|                        | 5:1  | 34.2 ± 1.1 | 1.2 ± 0.8 | 17.1 ± 1.7 | 2.3 ± 0.8 | 2.0 ± 2.7 | 3.6 ± 2.4 |
|                        | 20:1 | 38.0 ± 1.5 | 0.6 ± 0.3 | 29.8 ± 3.1 | 2.1 ± 1.2 | 4.1 ± 3.0 | 6.3 ± 2.1 |
| B10.BR                 | 1:1  | -0.1 ± 0.8 | 0.3 ± 0.5 | -3.4 ± 1.7 | -1.7 ± 0.8 | 9.8 ± 2.3 | 0.7 ± 1.6 |
|                        | 5:1  | 1.4 ± 0.8 | 1.3 ± 0.9 | -2.3 ± 1.6 | 0.1 ± 0.9 | 23.7 ± 2.2 | 3.3 ± 3.5 |
|                        | 20:1 | 3.5 ± 0.7 | 4.4 ± 1.1 | 1.5 ± 1.6 | 3.9 ± 1.1 | 27.8 ± 2.3 | 0.9 ± 1.8 |

* Target cells were LPS-induced splenic lymphoblasts. Cytotoxicity assay was run for 3 h.
$ Spleen cells from mice primed 7 wk previously with PR8 were restimulated in vitro with HK virus.

the extent to which an animal can respond. Perhaps this reflects a phenomenon similar to that described for Friend leukemia virus by Bubbers et al. (20), where presence or absence of a cytotoxic T-cell response is correlated with whether or not a particular H-2K or H-2D component is incorporated into the virus particle.

Antisera-blocking experiments indicated that BALB/c mice possess a subset of
influenza-immune T-cells which recognize H-2L gene products, and that products of the H-2L locus can thus operate in an analogous manner to H-2K/D gene products in virus-immune T-cell recognition. This conclusion is based on the specificity of the anti-L alloantiserum used in this study. As shown by immunoprecipitation studies (Fig. 1 and reference 21), the anti-L serum did not precipitate molecules which bear the K or D region private specificities. The inability to block alloimmune T-cells directed against H-2D alloantigens further confirmed the lack of anti-D reactivity in the anti-L alloantiserum. Thus, the inhibitory effect of the antiserum is most likely due to anti-L antibodies because of the specific inhibition of cytotoxicity and the lack of reactivity with H-2D molecules by immunoprecipitation analysis. Although it could be argued that the inhibitory effect of anti-L alloantiserum on virus-immune T cells is due solely to a steric inhibition of H-2D specificities on the virus-infected target
cell membrane, the inability of anti-L to inhibit lysis mediated by virus-immune 
BALB/c-\(H-2^{ab}\) T cells on these targets makes such an explanation untenable. 
The results, which show that influenza- and vaccinia-immune BALB/c-\(H-2^{ab}\) mice 
are able to lyse \(D\) region-compatible wild-type target cells, are in contrast to those 
obtained using another \(D\) region mutant, B10.D2-\(H-2^{da}\) (22). Zinkernagel and Klein 
(23) observed that lymphocytic choriomeningitis virus- and vaccinia virus-immune 
B10.D2-\(H-2^{da}\) T cells were unable to kill \(D\) region-compatible wild-type targets, a 
result which we have also observed with influenza virus (data not shown). These 
findings imply that B10.D2-\(H-2^{da}\), unlike BALB/c-\(H-2^{ab}\), lack virus-immune T cells 
which recognize both wild type \(L\) and \(D\) molecules. Consistent with this notion are 
recent findings by McKenzie et al. (3) which demonstrated that B10.D2-\(H-2^{da}\) mice 
possess mutations which affect both the \(L\) and \(D\) molecules.
Although influenza-immune T cells apparently recognize \(H-2L\) specificities, current 
studies using the same alloantisera and mouse strains indicate that there is no \(H-2L\)- 
restricted component in the T-cell response to trinitrophenyl (TNP)-modified cells. Blanden and Kees (24) recently reported that T cells generated against ectromelia 
virus and minor histocompatibility antigens do not recognize \(H-2L\) specificities. Thus, 
T cells appear to possess a more selective repertoire of responses associated with \(L\) 
than with \(K\) or \(D\) antigens. The mechanisms which produce this selectivity of 
responsiveness are not known, but an altered self model may most easily explain these 
observations: the minimum requirement for the generation of \(H-2\)-restricted T-cell 
responses is the physical association of foreign antigens with \(H-2K, D,\) or \(L\)-encoded 
self structures. Because TNP most probably is covalently linked to \(L\) molecules, the 
failure to demonstrate a TNP-specific \(H-2L\)-restricted T-cell response would seem to 
argue against the concept that formation of an altered self structure is the only 
requirement for generation of \(H-2\)-restricted cytotoxic responses. Perhaps this result 
may be due to a failure to generate the \(H-2L\)-restricted anti-TNP repertoire during 
differentiation in the thymus (25, 26).

Summary

The \(H-2L\) locus is closely linked to \(H-2D\) and codes for antigenic specificities present 
on a \(45,000\) mol wt glycoprotein that is distinct from the molecule which bears the \(D\) 
region private specificity. It was found that BALB/c-\(H-2^{ab}\) mice, which lack detectable 
cell-surface \(H-2L\) gene products, were able to generate influenza- and vaccinia-
imune cytotoxic T cells which lyse \(D\) region-compatible target cells, although they 
have been reported to be incapable of making a similar response to ectromelia virus (7). Thus, the lack of \(H-2L\) antigenic specificities does not produce a general loss of 
responsiveness for other viruses even when a highly cross-reactive pox virus (vaccinia) 
was studied.
Antisera-blocking experiments utilizing sera specific for either \(L\) or \(D\) molecules 
indicated that BALB/c mice generate influenza virus-immune cytotoxic T-cell subsets 
which independently recognize \(H-2L\) and \(H-2D\) gene products in association with 
viral antigens. These results are the first indication that products of the \(H-2L\) locus 
can operate analogously to \(H-2K/D\) gene products in virus-immune T-cell recognition.

Received for publication 21 August 1978.

\(^3\) I. F. C. McKenzie, G. M. Morgan, and R. Melvold. Manuscript in preparation.
References

1. Hansen, T. H., S. E. Cullen, R. Melvold, H. Kohn, L. Flaherty, and D. H. Sachs. 1977. Mutation in a new H-2-associated histocompatibility gene closely linked to H-2D. J. Exp. Med. 145:1550.

2. Morello, D., C. Neuport-Sautes, and P. Demant. 1977. Topographical relationships among H-2 specificities controlled by the D region. Immunogenetics. 4:349.

3. Hansen, T. H., S. E. Cullen, and D. H. Sachs. 1977. Immunochernical evidence for an additional H-2 region closely linked to H-2D. J. Exp. Med. 145:438.

4. Melvold, R. W., and H. I. Kohn. 1976. Eight new histocompatibility mutations associated with the H-2 complex. Immunogenetics. 3:185.

5. McKenzie, I. F. C., G. M. Morgan, R. W. Melvold, and H. I. Kohn. 1976. BALB/c-H-2db: A new H-2 mutant in BALB/c that identifies a locus associated with the D region. Immunogenetics. 4:333.

6. Hansen, T. H., and R. B. Levy. 1978. Alloantigens determined by a second D region locus elicit a strong in vitro cytotoxic response. J. Immunol. 120:1836.

7. Blanden, R. V., I. F. C. McKenzie, U. Kees, R. W. Melvold, and H. I. Kohn. 1977. Cytotoxic T-cell response to ectromelia virus-infected cells. Different H-2 requirements for triggering precursor T-cell induction or lysis by effector T cells defined by the BALB/c-H-2db mutation. J. Exp. Med. 146:869.

8. Blanden, R. V., M. B. C. Dunlop, P. C. Doherty, H. I. Kohn, and I. F. C. McKenzie. 1976. Effects of four H-2K mutations on virus-induced antigens recognized by cytotoxic T cells. Immunogenetics. 3:541.

9. Zinkernagel, R. M. 1976. H-2 compatibility requirement for virus-specific T-cell-mediated cytolysis. The H-2K structure involved is coded for by a single cistron defined by B6(Hz1) and B6(Hz170) H-2Kb mutant mice. J. Exp. Med. 143:437.

10. McKenzie, I. F. C., T. Pang, and R. V. Blanden. 1977. The use of H-2 mutants as models for the study of T cell activation. Immunol. Rev. 35:181.

11. Effros, R. B., P. C. Doherty, W. Gerhard, and J. Bennink. 1977. Generation of both cross-reactive and virus-specific T-cell populations after immunization with serologically distinct influenza A viruses. J. Exp. Med. 145:557.

12. Joklik, W. K. 1966. The pox viruses. Bacteriol. Rev. 30:33.

13. Zweerink, H. J., S. A. Courtneidge, J. J. Skehel, M. J. Crampton, and B. A. Askonas. 1977. Cytotoxic T-cells kill influenza virus-infected cells but do not distinguish between serologically distinct type A viruses. Nature (Lond.). 267:354.

14. Doherty, P. C., W. E. Biddison, J. R. Bennink, and B. B. Knowles. 1978. Cytotoxic T cell responses in mice infected with influenza and vaccinia viruses vary in magnitude with H-2 genotype. J. Exp. Med. 148:554.

15. Cullen, S. E., and B. D. Schwartz. 1976. An improved method for isolation of H-2 and Ia alloantigens with immunoprecipitation induced by protein A-bearing staphylococci. J. Immunol. 117:136.

16. Sachs, D. H., H.-J. Winn, and P. S. Russell. 1971. The immunologic response to xenografts. J. Immunol. 197:481.

17. Gardner, L., N. A. Bowern, and R. V. Blanden. 1974. Cell-mediated cytotoxicity against ectromelia virus-infected target cells. I. Specificity and kinetics. Eur. J. Immunol. 4:63.

18. Burnet, F. M., and W. C. Boake. 1946. The relationship between the virus of infectious ectromelia of mice and vaccinia virus. J. Immunol. 53:1.

19. Downie, A. W., and K. R. Dumbell. 1956. Pox viruses. Annu. Rev. Microbiol. 10:237.

20. Bubbers, J. E., S. Chen, and F. Lilly. 1978. Nonrandom inclusion of H-2K and H-2D antigens in Friend virus particles from mice of various strains. J. Exp. Med. 147:340.

21. Hansen, T. H., and D. H. Sachs. 1978. Isolation and antigenic characterization of the product of a third polymorphic H-2 locus, H-2L. J. Immunol. 121:1469.
22. Egorov, I. K. 1967. A mutation of the histocompatibility-2 locus in the mouse. *Genetika.* 3:136.
23. Zinkernagel, R. M., and J. Klein. 1977. H-2-associated specificity of virus-immune cytotoxic T cells from H-2 mutant and wild-type mice: M523 (H-2K*°) and M505 (H-2K°d) do, M504 (H-2D°d) and M506 (H-2K°b) do not crossreact with wild-type H-2K or H-2D. *Immunogenetics.* 4:581.
24. Blanden, R. V., and U. Kees. 1978. Cytotoxic T-cell responses show more restricted specificity for self than for non-self H-2D-coded antigens. *J. Exp. Med.* 148:1661.
25. von Boehmer, H., H. Werner, and N. K. Jerne. 1978. Major histocompatibility complex-linked immune-responsiveness is acquired by lymphocytes of low responder mice differentiating in thymus of high-responder mice. *Proc. Natl. Acad. Sci. U. S. A.* 75:2439.
26. Zinkernagel, R. M., S. N. Callahan, A. Althage, S. Cooper, P. Klein, and J. Klein. 1978. On the thymus in the differentiation of “H-2 self recognition” by T cells: Evidence for dual recognition? *J. Exp. Med.* 147:882.
Author/s: BIDDISON, WE; HANSEN, TH; LEVY, RB; DOHERTY, PC

Title: INVOLVEMENT OF H-2L GENE PRODUCTS IN VIRUS-IMMUNE T-CELL RECOGNITION - EVIDENCE FOR AN H-2L-RESTRICTED T-CELL RESPONSE

Date: 1978-01-01

Citation: BIDDISON, W. E., HANSEN, T. H., LEVY, R. B. & DOHERTY, P. C. (1978). INVOLVEMENT OF H-2L GENE PRODUCTS IN VIRUS-IMMUNE T-CELL RECOGNITION - EVIDENCE FOR AN H-2L-RESTRICTED T-CELL RESPONSE. JOURNAL OF EXPERIMENTAL MEDICINE, 148 (6), pp.1678-1686. https://doi.org/10.1084/jem.148.6.1678.

Persistent Link: http://hdl.handle.net/11343/260786

File Description: Published version

License: CC BY-NC-SA