PATTERNS OF VIRUS-IMMUNE T-CELL RESPONSIVENESS

Comparison of (H-2k × H-2b) → H-2b Radiation Chimeras
and Negatively Selected H-2b Lymphocytes*

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The vaccinia-immune cytotoxic T lymphocyte (CTL) response associated with the H-2Db allele offers one of the few examples of an immune response (Ir) gene effect in the virus systems (1, 2). A strong virus-specific CTL response in the context of H-2Db is seen in C57BL/6 (B6) or B10 mice (H-2KbI-AkDb), but the B10.A(2R) and B10.A(4R) strains (H-2KkI-AkDb) are low responders in this regard. The Ir gene effect apparently maps to H-2Kk rather than to I-Ak, as the B10.BYR recombinant (H-2KkI-AkDb) is also a high responder (2). Furthermore, low responsiveness to H-2Dp-vaccinia virus is apparently dominant in the (H-2Kk I-AkDb × H-2KbI-AkDb)F1 situation. Does this mean that the virus-immune CTL response associated with H-2Kk is in some way suppressing that occurring at H-2Db?

One approach to the further analysis of this problem has been to first filter (3) high responder B6 T cells through an irradiated low responder B10.A(4R) environment, and to then stimulate these negatively selected (to H-2Kk and I-Ak alloantigen) thoracic duct lymphocytes (TDL) with vaccinia virus in a further set of irradiated B10.A(4R) recipients. The result of this procedure is that the B6 TDL respond strongly to vaccinia virus presented in the context of both H-2Kk and H-2Db (4). Apparently, the aberrant response of the B6 TDL to H-2Kk-vaccinia virus (5), which has obviously not been determined by physiological differentiation (6) in the context of H-2Kk antigens encountered in thymus, does not suppress the generation of CTL that is specific for H-2Db-vaccinia virus.

The present paper describes attempts at suppressing the stimulation of negatively selected (3, 5) high responder TDL by mixing them with low responder [F1] T cells, before priming with H-2Dp-vaccinia virus in a low responder environment. Evidence is also presented that the virus-specific responder phenotype of an F1 → parent radiation chimera (6) may not always be equivalent to that associated with the H-2 type of the irradiated parent.

Materials and Methods

Mice, Viruses, Negative Selection, Immunization, Anti-H-2 Treatment, and Cytotoxic Assay. All materials and procedures were identical to those used previously (1, 3, 5). Recipient mice were...
**TABLE I**

Response of Negatively Selected Parental and F1 T Cells to Vaccinia Virus Presented in the Context of H-2K\(^{\text{b}}\) and H-2D\(^{\text{b}}\)

| Exp. Group | B6 × B10.A(4R) | 850 rad recipient | Percent specific \(^{51}\)Cr release* |
|------------|----------------|-------------------|----------------------------------------|
|            |                |                   | Vacc. N                               | MC57G (bb) N |
| 1 A        | 17 0           | B10.A(4R)         | 57 7                                  | 40 0        |
| B          | 17 17          | B10.A(4R)         | 95 18                                 | 34 0        |
| C          | 0 17           | B10.A(4R)         | 75 4                                  | 15 2        |
| D          | 0 17           | B6 (bb)           | 5 5                                   | 58 0        |
| 2 E        | 20 20          | B10.A(4R)         | 87 25                                 | 28 0        |
| F          |                |                   | 53 —                                  | 25 0        |

Unirradiated controls:

|            |                |                   | Vacc. N                               | MC57G (bb) N |
| 1 G        | B10 (bb)       |                   | 10 4                                  | 48 0        |
| H          | B10.Br (kk)    |                   | 52 3                                  | 0 0         |
| 2 I        | B6             |                   | 17 29                                 | 68 0        |
| J          | B10.Br         |                   | 76 12                                 | 0 0         |
| K          | B6 + B10.Br    |                   | 7 18                                  | 77 0        |

Vacc., cells infected with vaccinia virus; N, normal cells.

* Exp. 1 was assayed at a ratio of 20:1, Exp. 2 at 40:1.

† Treated with antiserum to H-2\(^{\text{b}}\) + complement, the unirradiated control cells were mixed in equal numbers. The treatment killed 72% of cells in group F and 65% in group K.

Results

**Vaccinia-immune T-Cell Response in the Context of H-2D\(^{\text{b}}\).** Negatively selected B6 (K\(^{\text{b}}\)-A\(^{\text{b}}\)D\(^{\text{b}}\)) T cells mediate a strong virus-immune CTL response in the context of H-2D\(^{\text{b}}\) (4) when sensitized in 850 rads B10.A(4R) (K\(^{\text{b}}\)-A\(^{\text{b}}\)D\(^{\text{b}}\)) recipients (group A, Table I, MC57G target; group L, Table II, HTGSV target). Considerably less effector function is seen when [B10 × B10.A(4R)]F\(_1\); T cells are stimulated in the same way (group C, Table I, MC57G target). Both lymphocyte populations also generate high responses to H-2K\(^{\text{k}}\)-vaccinia virus (groups A, C, and F, Table I, L-cell target).

Mixing the high (B6) and low (F\(_1\)) responder populations together before stimulation does not result in any significant diminution in the level of CTL generation associated with H-2D\(^{\text{b}}\)-vaccinia virus (groups A and B, Table I, MC57G target; groups L and M, Table II, HTGSV target). In fact, removal of the low responder F\(_1\) population with antiserum and complement may enrich for the B6 T cells reacting to virus in the context of H-2D\(^{\text{b}}\) (groups M and N, Table II, HTGSV and MC57G targets). This failure to show suppression could reflect that the suppressor T cells are
**Table II**

Concurrent Stimulation of Negatively Selected B6 and \( [B10 \times B10.A(4R)]F_1 \) TDL in 850 rads B10.A(4R) Recipients

| Group | Population*刺激 | Percent specific ⁶⁷Cr release (30:1) |
|-------|----------------|--------------------------------------|
|       |                | 2RSV (kb)   | HTGSV (db) | MC57G (bb) |
|       |                | Vacc. N    | Vacc. N    | Vacc. N    |
| L     | B6 - B10.A(4R) | 65 0       | 79 4       | 41 2       |
| M     | L + [B10 × B10.A(4R)]F₁| 79 0       | 75 0       | 20 12      |
| N     | M + anti-H-2^a + C'| 79 0       | 100 0      | 36 7       |

Unirradiated controls:

|       |                | 0 0       | 55 17      | 4 2       |
| O     | BALB/c (dd)    | P B6 (bb) | 53 0       | 39 0      |
| Q     | C3H (kk)      | 65 0       | 0 0       |
| R     | [B10 × B10.A(4R)]F₁ (bb × kb) | 93 0       | 1 0      | 45 8      |
| P     | P + R + anti-H-2^a + C'| 60 0       | 44 8      | 67 4      |
| R     | P + R + C'§§    | 69 0       | 20 0      | 52 5      |

Vacc., cells infected with vaccinia virus; N, normal cells.

*15 × 10^⁶ negatively selected TDL and 20 × 10^⁶ F₁ TDL.

§ Equivalent to an effector:target ratio of 15:1 for each lymphocyte population.

§ The level of lysis caused by the P + R population on L cells (kk) infected with vaccinia virus was 16% after treatment with antiserum + C', and 38% after incubation with C' alone. Normal L cells were lysed 7% in each case.

restricted to the H-2K\(^k\) or I-A\(^k\) of the CTL and cannot, therefore, modulate the response of the B6 TDL. We thought that we might circumvent this problem by using the appropriate F₁ → parent radiation chimera.

**The Situation for (CBA × B6)F₁ → B6 Chimeras.** We know, from the studies of Zinkernagel and colleagues (7), that such chimeras respond to H-2Db-vaccinia virus, but not to H-2K\(^k\)-vaccinia virus. This presumably reflects sensitization with virus presented on both H-2\(^b\) and (H-2\(^k\) × H-2\(^b\))\(F₁\) stimulator cells, and latter originating from the transferred bone marrow. Pooled spleen and lymph node or TDL populations from individual chimeras were divided into equal parts and injected into one B6 (K\(^b\)-Ab\(^b\)) or one B10.A(4R) (K\(^k\)-I-A\(^k\)) recipient. Strong virus-immune CTL responses were seen in the context of H-2\(^b\) after priming in the B6 recipients (Table III, MC57G target). However, little, if any, specific lysis was recognized for vaccinia virus associated with either H-2K\(^k\) or H-2D\(^b\) for T cells from 10 of the 11 [(CBA × B6)F₁ → B6] chimeras sensitized in irradiated B10.A(4R) recipients (Tables III and IV). The exception (chimera 11, Table IV) probably reflects carry over of T cells from the bone marrow donor, as only one anti-\(\theta\) treatment was used rather than the two deemed necessary by Zinkernagel et al. (6).

**Discussion**

We describe here one instance where an F₁ → parent radiation chimera does not assume the complete responder phenotype of the irradiated parent (7-10). Negatively selected B6 (K\(^b\)-I-A\(^k\)) T cells can respond to vaccinia virus presented in the context of both H-2K\(^k\) and H-2D\(^b\) when stimulated in an 850 rads B10.A(4R) (K\(^b\)-I-A\(^k\)) recipient. However, lymphocytes from [(CBA × B6)F₁ → B6] radiation chimeras...
TABLE III

Stimulation of T cells from [(CBA × B6)F1 → B6] Bone Marrow Chimeras in Irradiated Recipients

| Chimera* | 850 rads§ recipient | Cells§ yield (× 10⁶) |  |  |  |  |  |  |  |  |  |  |
|----------|----------------------|----------------------|---|---|---|---|---|---|---|---|---|---|
| No. T cells |  | | | | | | | | | | | |
| | | | L cells (kk) | Normal | Vaccinia | Normal | Vaccinia | Normal | Vaccinia | Normal | Vaccinia | Normal |
| | | | | | | | | | | | | |
| 1 | S + N | B10.A(4R) | 48 | 13 | 25 | 2 | 10 | 6 | 13 | 2 | 4 |
| | B6 | 6 | 5 | 0 | 0 | 54 | 8 | 54 | 8 | 54 | 8 |
| 2 | S + N | B10.A(4R) | 74 | 7 | 16 | 5 | 6 | 3 | 8 | 3 | 4 |
| | B6 | 51 | 2 | 1 | 1 | 3 | 2 | 1 | 3 | 2 | 1 |
| 3 | S + N | B10.A(4R) | 31 | 9 | 10 | 4 | 1 | 1 | 4 | 2 | 7 |
| | B6 | 20 | 2 | 0 | 0 | 66 | 6 | 66 | 6 | 66 | 6 |
| 4 | S + N | B10.A(4R) | 63 | 8 | 16 | 6 | 7 | 4 | 13 | 5 | 7 |
| | B6 | 51 | 2 | 1 | 1 | 62 | 6 | 62 | 6 | 62 | 6 |
| 5 | S + N | B10.A(4R) | 65 | 5 | 9 | 6 | 2 | 7 | 17 | 4 | 10 |
| | B6 | 22 | 0 | 1 | 1 | 43 | 5 | 43 | 5 | 43 | 5 |
| 6 | TDL | B10.A(4R) | 10 | 15 | 0 | 0 | 17 | 3 | 17 | 3 |
| | B6 | 23 | 0 | 1 | 1 | 49 | 3 | 49 | 3 | 49 | 3 |
| 7 | TDL | B10.A(4R) | 20 | 10 | 0 | 0 | 10 | 5 | 10 | 5 |
| | B6 | 15 | 0 | 0 | 0 | 58 | 4 | 58 | 4 | 58 | 4 |
| 8 | TDL | B10.A(4R) | 3 | 10 | 0 | 0 | 12 | 2 | 12 | 2 |

Unirradiated Controls:

| Chimera* | C3H (kk) | B6 (bb) | C3H | BALB/c (dd) |
|----------|----------|---------|-----|-------------|
| 1-5      | 35 44 10 | 8 9 6 7 | 8 50 3 | 8 14 3 |
| 6-8      | 10 13 1 | 10 13 1 |

* Greater than 90% of lymphocytes from each chimera were shown to bear the H-2 k alloantigen using antibody + complement treatment.
‡ Spleen and lymph nodes were pooled for individual chimeras, and equal numbers of spleen and lymph node cells (S + N, at least 4.0 × 10⁷) or TDL (2.0 × 10⁷) were given to one B6 and one B10.A(4R) (kk) recipient. Insufficient TDL were obtained from chimera 8 to allow stimulation in a B6 recipient.
§ Numbers of cells recovered from spleen at 6 d after i.v. inoculation of lymphocytes and vaccinia virus.

The failure of the chimera T cells to respond to H-2Kk-vaccinia virus when primed in an H-2KkI-AkD environment might be thought to reflect an absence of T-cell help originating at the H-2K end (8, 9, 11). It is possible that the response of the negatively selected B6 T cells to H-2Kk-vaccinia virus in some way helps the generation of virus-immune CTL in the context of H-2Dk. However, we have shown previously (4, 5) that filtered B10.A(2R) [KkI-AkD] T cells can respond to H-2Dk-vaccinia virus when primed in B6 recipients, and that B10.D2 [KkI-AkD] lymphocytes recognize H-2Dk-vaccinia virus when stimulated in B10.A(5R) [KkI-AkD] mice: in neither case is any CTL activity detected for H-2Kk-vaccinia virus. The idea that an allogeneic effect...
TABLE IV
Responder Patterns of Chimera T Cells to H-2Kk-Vaccinia Virus in 850 rads B10.A(4R)
Recipients

| Chimera* | Chimera | Percent specific ^51Cr release from L cells |
|----------|---------|-------------------------------------------|
|          |         | Vaccinia 20:1 | Normal 20:1 | Vaccinia 40:1 | Normal 40:1 |
| [(CBA × B6)F1 → B6] | 9 TDL | 13 | — | 5 | — |
|           | S + N  | 4 | 5 | 1 | 1 |
|           | [(CBA × B6)F1 → B10.Br] | 10 TDL | 16 | 23 | 6 | 14 |
|           | S + N  | — | 3 | — | 0 |
|           | [(CBA × B6)F1 → B6] | 11 TDL | — | 32 | — | 0 |
|           | S + N  | — | 16 | — | 6 |
|           | [(CBA × B6)F1 → B10.Br] | 12 TDL | — | 54 | — | 1 |
|           | S + N  | 36 | 45 | 0 | 0 |
|           | [(CBA × B6)F1 → B6] | 13 TDL | 25 | 37 | 2 | 3 |
|           | S + N  | 47 | 61 | 5 | 8 |
|           | (CBA × B6)F1 (kk × bb) | S | 75 | 80 | 6 | 13 |
|           | [(CBA × B6)F1 → B6] | 13 TDL | 22 | 10 | 16 |

* None of the chimera populations caused >12% specific lysis of the vaccinia-infected MC57G (bb) target. However, we are uncertain of the status of the MC57G target in this assay, as the one positive (B10) control caused (40:1) only 21% specific lysis on the vaccinia-infected and 16% lysis on the normal target.

† 2.0 × 10^7 TDL, or 4.0 × 10^7 mixed spleen (S) and lymph node (N) cells.

The chimera and negative selection experiments both approach the same, broad question: in what way does the major histocompatibility complex determine patterns of T-cell effector function? Conceptual problems arise when we try to reconcile the phenomena, and models, derived from these two approaches. It may be that the negatively selected TDL are a very atypical population. However, though as many as 95% of transferred T cells are lost in the filter environment (whether syngeneic or allogeneic, 17), we have not yet found a divergence of self-H-2-restricted responsiveness

(12, 13) mediated by radiation-resistant recipient T cells replaces help in these experiments has also been considered (4, 5, 14), but an identical situation should apply for the [(CBA × B6)F1 → B6] T cells stimulated in the B10.A(4R) recipients. The same is true for arguments that help functions directly between T-cell subsets (14), and is thus independent of the H-2 phenotype of the irradiated mouse, or that help associated with I-A^k and I-A^b is cross-reactive.

The concept that suppression operates in the case where (H-2^k × H-2^b)F1 T cells can respond to vaccinia virus associated with H-2D^k when primed in a B6, but not in a B10.A(4R) recipient, may have some validity (2). However, we have not been able to formally demonstrate such suppression by mixing negatively selected high responder (B6) T cells with excess low responder [B10 × B10.A(4R)]F1 TDL. A possible explanation for this failure to show suppression is that the suppressor T cells are restricted by the H-2K^k or I-A^k antigens on the F1 CTL, and thus do not interact with the B6 responder lymphocytes. Are we to consider, despite experiments to the contrary for a variety of systems (10, 15, 16), that such suppressors are also generated in the [(CBA × B6)F1 → B6] chimeras? Perhaps we are dealing with complex hierarchies of help and suppression, that vary depending on the experience of T cells during physiological differentiation.

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for negatively selected and normal TDL. Predicted T-cell specificities seem neither to be enriched for nor depleted (4, 5, 18).

The alternative is that the debate concerning the physiological differentiation of T cells in [(A × B)F₁ → A] radiation chimeras needs to take more account of H-2 antigens (B) present throughout ontogeny on other than radiation-resistant cells in the recipient thymus (A). Specific interaction, even of low affinity, between a developing thymocyte and any antigen (A or B) encountered in thymus may lead eventually to irreversible tolerization. Contact with the same antigen (A) on a stimulator cell (radiation-resistant thymic epithelium) may result in the delivery of a signal which prevents tolerance for low, but not for high, affinity binding. Tolerance in the case of high affinity for A could reflect the delivery of excess signal at a developmental stage before the emergence of T-cell effector function, or operate via some form of positive suppression.

The implication of this model is that the B6 thymocyte which has the potential to recognize H-2K<sup>k</sup>-vaccinia virus does not encounter H-2K<sup>k</sup> during the process of physiological development in the B6 thymus, and would thus not be deleted as a result of low affinity binding to the alloantigen. Thymocytes in the [(CBA × B6)F₁ → B6] radiation chimera could, however, interact with the H-2K<sup>k</sup> alloantigen on adjacent F₁ thymocytes, but not on radiation-resistant B6 thymic epithelium. The existence of a specific hole (19) in the T-cell repertoire of the (H-2<sup>k</sup> × B F₁ → H-2<sup>b</sup>) chimera for H-2K<sup>k</sup>-vaccinia virus (compared with the H-2<sup>b</sup> parent) offers experimental evidence that this deletion model is worth considering. Instances of lack of complete restriction to A in [(A × B)F₁ → A] chimeras (20, 21) may reflect that the affinity of the particular thymocytes for B is insufficient to result in tolerization. Even so, the consequence of the present findings for the (H-2<sup>k</sup> × B F₁ → H-2<sup>b</sup>) chimeras is that tolerization of the developing thymocytes in the chimera operates at a lower level of affinity than that seen for the recruitment of mature B6 T cells in irradiated B10.A(4R) recipients, which results in removal during the filtration procedure.

Summary

Negatively selected H-2K<sup>b</sup>D<sup>b</sup> TDL can be induced to respond strongly to vaccinia virus presented in the context of both H-2K<sup>k</sup> and H-2D<sup>b</sup> when stimulated in irradiated H-2K<sup>k</sup>D<sup>b</sup> recipients. Addition of excess (H-2K<sup>b</sup>D<sup>b</sup> × H-2K<sup>k</sup>D<sup>b</sup>)F₁ TDL, which are low responders to H-2D<sup>b</sup>-vaccinia virus, does not obviously suppress the reactivity pattern of the H-2K<sup>b</sup>D<sup>b</sup> T cells. However, lymphocytes from chimeras made by reconstituting H-2K<sup>b</sup>D<sup>b</sup> mice with (H-2K<sup>b</sup>D<sup>b</sup> × H-2K<sup>k</sup>D<sup>b</sup>)F₁ bone marrow cells make little, if any, cytotoxic T-cell response to vaccinia virus when sensitized in H-2K<sup>b</sup>D<sup>b</sup> recipients. We have thus documented one instance where the responder phenotype of T cells from an F₁ → parent chimera is not equivalent to that associated with the H-2 type of the parental thymus. Lymphocytes from both the chimera and the H-2K<sup>b</sup>D<sup>b</sup> parent (after negative selection) are tolerant to the H-2K<sup>k</sup> and I-A<sup>k</sup> alloantigens encountered in the recipient, but the chimera T cells are also defective in their response to a neoantigen (vaccinia virus) presented in the context of H-2K<sup>k</sup> which the parental T cells invariably recognize. It is thus possible that at least part of the phenomenology associated with the F₁ → parent radiation chimeras reflects deletion of repertoire in the context of H-2 antigens present during thymocyte ontogeny on other than radiation-resistant thymic epithelium.
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