

baboons that I could see at the time were not unduly alarmed at my presence once they had reached the top of the cliff.

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*Nature*, 256, 488 (1975).

## H-2 antigen restriction of viral infection

KOSZINOWSKI and Ertl demonstrated<sup>1</sup> that T lymphocytes immunised *in vivo* against virus kill virus-infected target cells only when these share H-2 antigens with the effector cells<sup>2</sup>. The commonly expressed view<sup>3</sup> is that the effector T cells recognise an antigen created by an interaction of H-2K or H-2D antigen molecules with viral protein.

To obtain further support for this notion, Koszinowski and Ertl show convincingly that anti-H-2 serum blocks killing when it is directed against the target cells, but not when directed against the effector cells. An unfortunate nomenclature (for example, anti-H-2<sup>kk</sup> for (H-2<sup>d/k</sup> × H-2<sup>bb</sup>) anti-H-2<sup>kk</sup>) gives the impression that the sera are directed against the antigens of the whole H-2 complex, when in fact both antisera used are directed only against the K end of the H-2 complex. Thus the H-2D antigens of the effector cells are still free, and one cannot rule out the alternative hypothesis<sup>4</sup>, that in order to kill, effector cells have to match up their SD antigens with those of the targets<sup>4</sup>.

On the other hand, cytotoxicity is blocked completely whenever the anti-serum, be it an anti-H-2K or an anti-vaccinia serum, is directed against the target cells, and this is taken as evidence for an interaction product being the target. It is important to know whether a similar blocking could be caused by any antiserum directed against the target cells, or only by anti-H-2 or anti-virus serum. Two points are of particular interest in this respect. First, blocking of cytotoxicity is complete although the antisera cover only the K end—if the blocking is as specific as in allograft reactions, where blocking the target antigens of only one end of H-2 hardly affects the killing<sup>5</sup>, this would mean that vaccinia, unlike LCM and ectromelia virus<sup>2</sup>, modifies only the H-2K antigens. Second, one should note the blocking of F<sub>1</sub> target cells. For example, H-2<sup>k</sup> effectors do not kill H-2<sup>d</sup> targets, but they will kill (d × k)F<sub>1</sub> as well as H-2<sup>k</sup> target cells. Killing of H-2<sup>k</sup> is blocked by anti-H-2K<sup>k</sup>, not by anti-H-2<sup>d</sup>, while killing of F<sub>1</sub> targets are blocked by both

## Matters arising

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antisera. If the H-2<sup>k</sup> effectors interact only with modified H-2<sup>k</sup> antigens on the target cells, one should, again by analogy to the specificity in allograft reactions<sup>6</sup>, not have expected anti-H-2<sup>d</sup> serum to have any effect on the killing of F<sub>1</sub> target cells by H-2<sup>k</sup> effector cells. My comments are based on the assumption that complete blocking is obtained only when all possible effector-target cell interactions are inhibited, and I have overinterpreted the data, if the relationship between percentage <sup>51</sup>Cr-release and number of lytic interactions is less quantitative.

The field of T-cell mediated immunity to virus infected target cells is fruitful and holds promise of information about the evolutionary significance of histocompatibility antigens<sup>3</sup>. It is therefore important, before we make conclusions about mechanisms, to know to what extent the phenomenon is analogous to allograft immunity.

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<sup>2</sup> Blanden, R., *et al.*, *Nature*, 254, 269 (1974).

<sup>3</sup> Lennox, E., *Nature*, 256, 7 (1975).

<sup>4</sup> Zinkernagel, R. M., and Doherty, P. C., *Nature*, 251, 547 (1974).

<sup>5</sup> Nabholz, M., *et al.*, *Eur. J. Immun.*, 4, 378 (1974).

<sup>6</sup> Cerottini, J.-C., and Brunner, K. T., *Adv. Immun.*, 18, 67 (1974).

KOSZINOWSKI AND ERTL REPLY—We think that our data<sup>1</sup> do not allow the interpretation that serum mediated blocking of cell-mediated cytotoxicity (CMC) of virus infected syngeneic cells reflects an inhibition of all possible effector-target cell interactions. We cannot express this opinion since we find inhibitory activities also with antisera directed against vaccinia virus specific surface antigens<sup>2</sup>.

The F<sub>1</sub> fibroblast targets were extremely sensitive for vaccinia infection which led

to high spontaneous and small specific lysis. We are unsure whether the H-2<sup>d</sup> inhibition in these experiments had a significance, since unspecific blocking occurred to some extent (see Fig. 1 of ref. 1). Anyway, xenogenic anti-target cell serum absorbed for H-2 had no specific inhibitory effect.

There are indeed indications that, in the experimental conditions we used the K end is the essential target. When we tested an anti-H-2D<sup>k</sup> serum ((H-2<sup>b</sup> × H-2<sup>d</sup>) anti-K<sup>d</sup> D<sup>k</sup>) we found minimal blocking activities.

These results can be explained by two possible mechanisms. Vaccinia virus alters mainly K-end antigens so that these modified antigens can form a target for the T cell. On the other hand it is possible that T cells predominantly attack K-end alterations. Comparable results concerning different inhibitory activity on T-cell mediated killing by anti-K-end or D-end sera have recently been described in a tumour situation<sup>3</sup>.

In the ectromelia system some mouse strains (B10.A (2R), B10.A (4R)) react more strongly at the K end<sup>4</sup>. Shearer *et al.*<sup>5,6</sup> describe effector cell activity against TNP-modified cells absolutely restricted to the K end in two mouse strains while other strains recognise the TNP-modified D end as well. Restriction of CMC can therefore be dependent on the target cell<sup>5,6</sup>, the modifying agent and the mouse strain used, so that at present no generalised answer about K- or D-end specificity is possible.

We think that the intimacy hypothesis<sup>7</sup> of matching unaltered self antigens is unlikely. In addition to the arguments of Zinkernagel and Doherty<sup>8</sup> we found that the target antigen in the vaccinia infection for the CL has a close physical relationship to SD antigens<sup>1</sup>. Second, enzymatic reduction of H-2 antigens reduces CMC without affecting anti-vaccinia antibody mediated cytotoxicity (Ertl and Koszinowski, unpublished) and third, expression of the H-2 alloantigens is altered detectably by reduced serum absorbing capacity and inhibited allogeneic CMC<sup>9,10</sup>. The latter observation especially, argues against the possibility of matching normal self antigens as a prerequisite for the recognition of new antigenic determinants.

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<sup>10</sup> Koszinowski, U., and Ertl, H., *Nature*, 257, 596 (1975).