Proc. Natl. Acad. Sci. USA
Vol. 78, No. 11, pp. 7101–7105, November 1981
Immunology

Significance of Lyt phenotypes: Lyt2 antibodies block activities of T cells that recognize class 1 major histocompatibility complex antigens regardless of their function

(cytotoxic T cell/helper T cell/T cell receptor/lymphokines)

SUSAN L. SWAIN

Department of Biology, University of California, San Diego, La Jolla, California 92093

Communicated by S. J. Singer, July 27, 1981

ABSTRACT **The effect of anti-Lyt2 on the generation of helper T-cell function and on cytotoxic effects specific for subregions of the major histocompatibility complex (MHC) was determined. The addition of anti-Lyt2 without complement to *in vitro* cultures blocked the generation of allogeneic MHC-induced help and lymphokine production and cytotoxic effects when the response was directed against allogeneic class 1 MHC antigens (*K* and *D* gene products of the mouse *H-2* complex) but had no effect when these responses were specific for class 2 MHC antigens (*I* region gene products). Anti-Lyt2 failed to block the response of help induced to allogeneic mixed lymphocyte-stimulating determinants or the production of lymphokines by T cells specific for class 1 MHC antigens when concanavalin A lectin was used to induce activity. These and earlier results indicate that the ability of anti-Lyt2 antisera to block function is correlated with T cell specificity for class 1 MHC antigens not with the functional activity of the cells.**

The response to allogeneic major histocompatibility complex (MHC) antigens has long provided a useful model for the study of T-cell function. It was shown, in the mouse, that T proliferation (1), T-cell help (2, 3), and the generation of cytotoxic T cells all are stimulated by allogeneic H-2 (the murine MHC complex). There are two classes of MHC antigens, the "serologically defined" antigens (K and D in the mouse) and the "lymphocyte defined" antigens (Ia in the mouse) (4). The serologically defined antigens are now called class 1 MHC antigens (5) and serve as the primary stimulators of the targets for cytotoxic activity. The lymphocyte defined antigens, now called class 2 MHC antigens, are more effective at initiating T-cell proliferation and helper T-cell activity (6). It is thus clear that there is a functional as well as a chemical distinction between the two classes of MHC antigen.

In 1975, the studies by Zinkernagel and Doherty (for review, see ref. 7) led to a crystallization of the concept of the role of MHC antigens in the T-cell recognition of antigen. It was found that the T-cell response to non-MHC antigens is restricted to the allele of the MHC antigens present in the priming environment. In the years immediately following, it became clear that the same correlation between function and subregion found in allogeneic reactions could also be seen in the MHC-restricted responses. Cytotoxic activity to non-MHC antigens was found to be restricted to class 1 MHC antigens (8), and helper T-cell activity against non-MHC antigens was found to be restricted to class 2 MHC antigens (9, 10). It has become generally accepted that most, if not all, helper and cytotoxic T cells recognize MHC antigens.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U. S. C. §1734 solely to indicate this fact.

It was shown concurrently that these two functionally distinct subsets of T cells could be identified by differences in the expression of the cell surface antigens Lyt1, -2, and -3 (11). The cytotoxic subset, with specificity for class 1 antigens, had the $Lyt1^-23^+$ phenotype (Ly23 T cells); the helper subset, with specificity for class 2 antigens, had the $Lyt1^+23^-$ phenotype (Ly1 T cells).

Although this simple picture has been modified by a large number of additional findings that need not be detailed here, the value of the operational distinction between the two subsets remains unchallenged. However, because there was a triple correlation of Lyt phenotype, T-cell function and recognition of class of MHC antigen, it was not possible to determine whether the biologically significant linkage of Lyt phenotype was to function or to MHC subregion.

It has been suggested that the Lyt antigens are obligate markers of functionally distinct T-cell subsets (11). This concept recently has been challenged by the results of a number of investigators (12–15), and an alternate view has been put forward. My colleagues and I (14, 16, 17), and others (12, 15), have suggested that the Lyt phenotype is strongly correlated with the class of MHC antigen that is recognized. I suggest that T cells that recognize class 1 MHC antigens express Lyt2, whereas T cells that recognize class 2 MHC antigens have low or negligible Lyt2 expression regardless of the function of the T-cell subset.

These conclusions are based on the study of those alloreactive T cells that are the exception to the general rule that correlates T-cell function with the MHC subregion that is recognized. Only in these situations is it possible to determine whether the Lyt phenotype correlates best with the function of the T cell or with the MHC subregion recognized by the T cells. First, it has been shown that helper T-cell activity and lymphokine production can be generated against class 1 antigens and that here the responding T cell is $Lyt1^+2^+$ (14, 16). Second, it has been shown that cytotoxic T cells can be generated against class 2 MHC antigens (18, 19) and that the T cell responsible is $Lyt1^+2^-$ (20) or expresses relatively low amounts of Lyt2 (this paper).

Recent studies have shown that the presence of anti-Lyt2 can block the cytotoxic activity of cells raised against allogeneic MHC targets (21–24). It has been suggested from these results that Lyt molecules may play an important role in T-cell activity. In this paper these studies are extended by using the presence of anti-Lyt2 antisera to block the induction or execution of several T-cell functions directed at different subregions of the MHC. The results indicate that the activity of those T cells spe-

Abbreviations: Con A, concanavalin A; IL1, interleukin 1; IL2, interleukin 2; LPS, lipopolysaccharide; MHC, major histocompatibility complex; MLC, mixed lymphocyte cultures; SRBC, sheep erythrocytes; TCGF, T-cell growth factor; TRF, helper T-cell replacing factor; PFC, plaque-forming cell(s).

cific for class 1 but not class 2 is blocked by anti-Lyt2 regardless of their function.

MATERIALS AND METHODS

DBA/2, C57BL/6, BALB/c, the B10 congeneic strains B10.T(6R), B10.AQR, B10.G, and B10.BR, and the BDF_1 hybrid (B6 × DBA/2) were bred at University of California, San Diego, from breeding pairs obtained originally from The Jackson Laboratory and from Donald Shreffler.

A monoclonal anti-Thy1.2 (F7D5), a kind gift of Philip Lake, was used in the presence of complement to deplete spleen of T cells for antibody assays. The anti-Lyt2 used for blocking was obtained from culture supernatants of the 53-6.72 hybridoma of Ledbetter and Herzenberg (25). The anti-Lyt2.2 used for complement-mediated depletion was obtained from ascitic fluid of $(BALB/c \times B6)F_1$ mice injected with the AD4.15 cell line (26), a kind gift of Michael Bevan.

Primed allogeneic helper T cells were obtained, as described (27), by culturing 2.5×10^7 spleen cells of the responding strain with 2.5×10^7 mitomycin-treated (25 μg/ml) cells of the stimulating strain in a total volume of 20 ml for 10–14 days. Priming resulted in at least a 10-fold increase in the specific response and loss of third party responses (27).

T-cell growth factor (TCGF) activity was measured as described (28) by adding supernatant to an IL2-dependent cell line. Proliferation of cells was determined by incorporation of ^{125}IdUrd.

Helper T-cell replacing factor (TRF) activity was determined by the ability of the various culture supernatants to provide help for B cells in the primary response to sheep erythrocytes (SRBC). Spleen cells from BDF_1 mice were treated with anti-Thy1.2 plus complement and 6×10^5 cells per culture were incubated with 0.05% SRBC. Mixed lymphocyte culture (MLC) supernatants were added to triplicate cultures on day 0 and the direct (IgM) plaque-forming cells (PFC) responding to SRBC were counted on day 4. Results are shown as the geometric mean ± SEM of triplicate cultures.

Allogeneic help was determined as described (15). Briefly, nylon column-passed, mitomycin-treated spleen cells (T cells) obtained from normal mice were added to triplicate 0.1-ml cultures containing 6×10^5 B cells with 0.05% SRBC. PFC were determined as above.

Cytotoxicity was determined by the ability of effectors to lyse ^{51}Cr-labeled lipopolysaccharide (LPS)-induced (10 μg/ml) blast targets as described (20). MLC for the development of effectors were set up with 2×10^6 responder spleen cells per ml mixed with 8×10^5 mitomycin-treated stimulator cells per ml.

RESULTS

Anti-Lyt2 Blocking of MHC Subregion-Specific Allogeneically Induced Help. A monoclonal rat antibody to murine Lyt2, known to block cytotoxicity (24), was used to study the role of Lyt2 in responses against different MHC subregions. Anti-Lyt2 was added to cultures of T-depleted spleen cells (B cells) in which allogeneic help was provided by unprimed T cells. These T cells differed from the B cells at the whole *H-2* region, *I*, *D*, or *Mls* [Mls, or mixed lymphocyte-stimulating, determinants are non-MHC histocompatibility antigens that stimulate helper activity (29)]. Representative results are shown in Fig. 1. Help was measured by the response of B cells to SRBC as determined by PFC to SRBC on day 4. When help was stimulated by whole *H-2*, *H-2I*, or *Mls* differences, no effect of anti-Lyt2 was observed. However, when help was stimulated by an *H-2D* difference, anti-Lyt2 antibody completely inhibited the response.

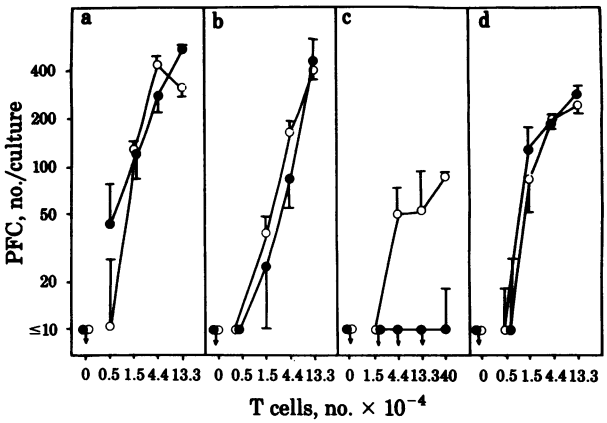

FIG. 1. **Anti-Lyt2 blocking of MHC subregion-specific allohelp. Nylon column-passed, mitomycin C-treated T cells were titrated into triplicate cultures of 6×10^5 anti-Thy1.2-treated B cells. SRBC were added as antigen and direct PFC were determined after 4 days of culture. Strain combinations were used such that T and B cells differed at whole *H-2* (*a*, BALB/c T cells with B10.G B cells); *H-2I* [*b*, B10.T(6R) T cells with B10.AQR B cells]; *H-2D* [*c*, B10.G T cells with B10.T(6R) B cells]; and *Mls* (*d*, BALB/c T cells with DBA/2 B cells). Duplicate series of cultures were set up in the presence (●) or absence (○) of 2% anti-Lyt2 supernatant.**

Similar results were seen in other strain combinations (not shown) and anti-Lyt2 consistently blocked help to K or D but not I or Mls determinants.

To investigate further the role of anti-Lyt2 in blocking helper function, T cells were primed *in vitro* to *K*, *D*, or *I* regions and the effect of anti-Lyt2 on primed helper T cells was determined at the time of restimulation. It has been found that T cells primed in this manner are greatly enhanced in their response to the stimulating alloantigen but have lost reactivity to other alloantigens (27). Such T cells stimulated with cells carrying the priming alloantigen produce large quantities of lymphokines with TCGF activity or with TRF activity in the primary response of B cells to SRBC. The ability of anti-Lyt2 antibody to block the generation of factor(s) with these activities was tested.

A representative of three experiments is shown in Fig. 2. T cells were primed to K^q or I^k and challenged with a single pool of K^qI^k stimulator cells. Anti-Lyt2 was titrated into these cultures. Supernatants were collected after 18 hr and tested for TRF and TCGF activity. Anti-Lyt2 antibody present in cultures over a broad range of concentrations had no effect on the production of lymphokines by I^k primed cells. In contrast, as little as 0.1% of the anti-Lyt2 preparation severely reduced (>90%) the production of lymphokines by K^q primed cells. A mixture of the two types of responding cells was not suppressed by anti-Lyt2 (data not shown).

It has been reported that anti-Lyt2 antibodies fail to inhibit concanavalin A (Con A)-mediated cytotoxicity (24). Therefore, the same K^q-primed T cells that were inhibited by anti-Lyt2 when they were challenged with the K^q antigen were induced with Con A. When this alternate mode of induction was used, anti-Lyt2 failed to suppress the production of lymphokines (Fig. 2).

Anti-Lyt2 Blocking of MHC Subregion-Specific Cytotoxic Effects. Because most cytotoxic effectors generated when responder T cells differ from stimulator at the whole *H-2* region are directed against K and D (4), it was likely that the cytotoxicity blocked by anti-Lyt2 in previous reports was directed against these MHC subregions. Therefore, it was of interest to test the effect of anti-Lyt2 on cytotoxicity directed against *Ia* region determinants.

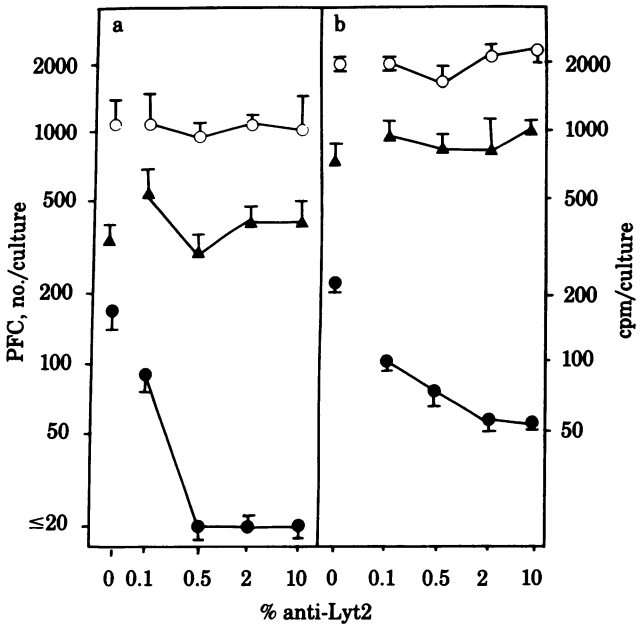

FIG. 2. Anti-Lyt2 blocking of MHC subregion-specific and Con A-stimulated lymphokine production. Primed subregion-specific allohelpers were used after 14 days of *in vitro* culture. Helpers primed to K^q (●, B10.A primed to B10.AQR) and I^k [▲, B10.T(6R) primed to B10.AQR] (5×10^5/ml) were restimulated with anti-Thy1.2-treated spleen cells (5×10^6/ml) in the presence of dilutions of anti-Lyt2 supernatant. After 18 hr, supernatants were harvested and tested for TRF (*a*) or TCGF (*b*) activity. Alternatively, the K^q-primed cells were stimulated with Con A (2 μg/ml) (○) and the effect of added anti-Lyt2 was determined. TRF activity was measured by adding 50% supernatant to anti-Thy1.2-treated BDF_1 spleen cells with SRBC an antigen. Direct PFC to SRBC were determined on day 4. TCGF activity was measured by adding 10% supernatant to 10^4 T cells from a TCGF-dependent line of NK cells.

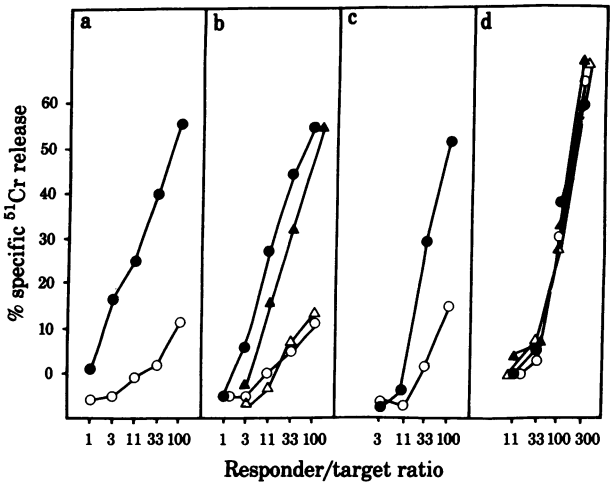

FIG. 3. Anti-Lyt2 blocking of spleen cells cytotoxic to MHC subregions. Spleens of B10.T(6R) primed *in vivo* with 2×10^6 B10.AQR spleen cells and of A.TH primed *in vivo* with 2×10^6 A.TL spleen cells (and of unprimed B10.AQR and A.TL mice) were used as responders. Cytotoxic effectors were generated to whole *H-2* [*a*, B10.T(6R) to B10.BR (anti-$H\text{-}2^k$)]; to *H-2K* [*b*, B10.AQR to B10.A (anti-K^k) (circles), and A.TL to A.AL (anti-K^a) (triangles)]; to *H-2D* [*c*, B10.T(6R) to B10.G (anti D^q)]; and to *H-2I* [*d*, B10.T(6R) to B10.AQR (anti-Ia^k) (circles) and A.TH to A.TL (anti-Ia^k) (triangles)]. ^{51}Cr release assays were incubated in the absence (closed symbols) or presence of 2% anti-Lyt2 (open symbols).

B10.T(6R) mice were primed with 2×10^6 B10.AQR (differing in the *I* region) spleen cells and A.TH mice were primed with spleen cells of A.TL mice. Priming was necessary to generate anti-Ia-specific killing of a magnitude equivalent to that found in unprimed responses to K and D. These primed spleen cells were challenged in MLC with stimulators differing at the whole *H-2* locus, or at *H-2K*, *-D*, or *-I* alone, and the cytotoxic effectors recovered from these cultures were mixed with targets bearing the appropriate stimulating alloantigens. Anti-Lyt2 was added directly to the ^{51}Cr release assays. In each case, cytotoxicity generated to whole *H-2* differences, to *H-2K*, and to *H-2D* was blocked by the presence of anti-Lyt2 antibody (Fig. 3). In contrast, cytotoxicity directed against *H-2I* was unaffected by the presence of anti-Lyt2. Experiments of this design have been repeated three times with similar results. In addition, *in vivo*-primed effectors to K and D have been tested in four experiments and were blocked equally or more efficiently then the unprimed effectors to K or D (data not shown).

The striking failure of anti-Lyt2 to block the *H-2I* directed cytotoxicity raises the question of whether such effectors express Lyt2 molecules. The expression of Lyt2 on the primed T cells responsive to *H-2I* was determined by treatment of cytotoxic effectors with anti-Lyt2.2 plus complement (Table 1). High-titered ($1/10^6$) anti-Lyt2.2 ascites was used as a reagent. This reagent was completely allele-specific under these conditions (lines 1 and 2). Cytotoxic effectors from MLC stimulated with a whole *H-2* difference and with *H-2D* were severely depleted after anti-Lyt2.2 treatment (lines 1 and 3) whereas cytotoxic effectors from cultures stimulated with *H-2I* were more resistant to this treatment. In a series of several experiments, anti-*I*-region killers were more resistant than anti-*K* or *-D*-region killer to lysis with anti-Lyt2.2 but significant depletion was seen in most cases.

DISCUSSION

This paper examines the blocking activity of anti-Lyt2 in two unusual situations: first, in the generation of helper activity in response to class 1 MHC antigens (*K* and *D* regions); and second, in the case in which cytotoxic effector activity is mediated by T cells specific for targets carrying the foreign class 2 MHC (*I* region) alleles.

It had already been shown that, although differences in the *I* region are the strongest inducers of allogeneic help in the mouse, helper cells can be induced by cells that are specific for allogeneic K or D antigens (28). Such cells were shown to have the $Lyt1^+2^+$ phenotype (14, 16).

In the present study, it is shown that both the helper effect of added T cells and the generation of T cell replacing lymphokines is blocked by the presence of anti-Lyt2 in the culture medium but only when the stimulating antigen is allogeneic H-2K or H-2D. The response is not blocked when the stimulators differ at *I* or the whole MHC or at the *Mls* locus (Figs. 1 and 2). In Fig. 1, the helper activity is measured by the direct addition of unprimed T cells to T-depleted B cells. In this experimental model it has been shown that the help can be delivered by TRF (2) which, it is now understood, is a mixture of lymphokines including IL1, IL2, and TRF (30–32). These factors appear to act synergistically on the responding B cell (28).

I have previously shown (27) that helper T cells can be generated in a secondary response to allogeneic K or D and that such primed helper activity is not restricted to the *I* region allele. It is shown here that this primed response to allogeneic cells is also blocked by the presence of anti-Lyt2 but, again, only when the stimulators differ at *K* (shown) or *D* (not shown) alone. The response to *I*, to the whole *H-2*, or to the *Mls* gene product is not blocked (Fig. 2). In this experiment, the production of

Table 1. Lyt phenotype of MHC subregion-specific cytotoxic effectors

Responder strain	Stimulator and target strains	Specificity	Responder/ target ratio	% specific cytotoxicity	
				No treatment	Anti-Lyt2.2
B6	BDF_1	Whole *H-2*	133	16	−2
			44	10	−2
			15	4	−0
B6.Lyt2.1	BDF_1	Whole *H-2*	133	26	27
			44	18	17
			15	10	8
B10.T(6R)	B10.G	D^q	133	42	11
			44	18	−1
			15	16	−1
B10.T(6R)	B10.AQR	Ia^k	133	50	41
			44	40	23
			15	22	10

Cytotoxic effectors specific for whole *H-2* [B6 against BDF_1; B6.Lyt2.1 against BDF_1 (anti-H-2^d)], *H-2D* [B10.T(6R) against B10.G (anti-D^q)], and *H-2I* [B10.T(6R) against B10.AQR (anti-Ia^k)] were raised in MLC. B10.T(6R) mice were primed *in vivo* with 2×10^6 B10.AQR spleen 8 weeks before sacrifice. Cytotoxic effectors were harvested and split into aliquots. One aliquot was treated with complement alone (no treatment) and the other, with a 1:500 dilution of anti-Lyt2.2. After treatment, cytotoxic effectors were determined in a ^{51}Cr release assay.

TCGF (IL2) and the production of helper factor (IL2 plus TRF) were assayed independently and both were affected similarly.

In the second half of this study it was shown that the presence of anti-Lyt2 does not block the effector activity of cytotoxic T cells specific for targets carrying a foreign *I* region allele (Fig. 3). Previous work had shown that the cytotoxic activity of long-term alloreactive T-cell line specific for targets carrying Ia was mediated by $Lyt1^+2^-$ cells (20) and was not blocked by anti-Lyt2 (17).

These studies extended a previous series of observations concerning the correlation between Lyt phenotype and the MHC subregion that is recognized. No exceptions were found to the rule that those T cells that respond to allogeneic K or D are Lyt2 positive and that their activity can be blocked by anti-Lyt2. This is as true for helper cells as for cytotoxic effectors. Those T cells that respond to allogeneic *I* region antigens, be they helpers or a cytotoxic T cells, express less (this paper) or no Lyt2 (20) and their activity is resistant to the presence of anti-Lyt2 (this paper).

There are a number of additional points that can be made. First, it is important to note that the experimental findings presented here and in earlier publications (14, 16, 20) are not in conflict with the previously published data on the Lyt phenotypes of helper and cytotoxic cells. In the usual experimental protocol in which helper cells are raised against whole haplotype differences, helper cells are specific for foreign I and are $Lyt1^+2^-$. Similarly, cytotoxic T lymphocytes raised against stimulators that differ at the whole haplotype are specific for *K* or *D* alleles and are $Lyt1^-2^+$. It is only when the normal association between T-cell functions and the MHC subregion of the target antigen does not hold that it can be revealed that the Lyt phenotype is associated not with T-cell function but with the MHC subregion that is recognized.

Although Lyt phenotypes in these situations in which the normal correlation between function and MHC subregion do not hold have not been extensively studied by other investigators, some such examples have been reported (12, 13, 15).

A number of investigators have shown that the presence of anti-Lyt2 can block cytotoxic T-cell effector function (21–24) and the induction of cytotoxic T cells (33). In these studies, various other antisera to antigens that are or may be expressed on the T cell surface including H-2, Thy1, immunoglobulin, and other non-H-2 antigens (22, 34–36) were shown to be without effect. It seems likely then that the ability of antisera to a surface marker to block function indicates either that the marker is itself involved in function or that it is closely apposed in the membrane to such a molecule.

Recently MacDonald *et al.* (37) reported that cytotoxic effectors obtained from the peritoneal exudate of *in vivo*-primed mice are not efficiently blocked with anti-Lyt2 whereas those raised *in vitro* from spleen are blocked. These results may suggest that cells of higher affinity are resistant to such inhibition.

Differences in blocking because of differences in affinity are unlikely to be responsible for the results reported in this paper for several reasons. First, the results are reciprocal. Both the usual (cytotoxicity) and unusual (help) functions are blocked when they are directed to *K* or *D* regions. Furthermore, both primary and secondary responses showed the same pattern of blocking. Thus, the only variable that correlates with the results is the MHC subregion specificity of the responding T cells.

Dialynas *et al.* (38) have shown that three variant clones from a mitogenized cytotoxic T cell line concomitantly lost both Lyt2 surface molecules and cytotoxic activity. These studies provide further evidence that the Lyt2 molecules play some obligatory role in cytotoxic activity although they do not clearly distinguish between models in which the Lyt2 molecule is involved in the recognition event and models in which Lyt has some role in the delivery of the lethal signal. The facts that *Ia*-specific cytotoxic effectors express little or no Lyt2 (Table 1; ref. 20) and that anti-Lyt2 reagents do not block cytotoxic activity argue that Lyt2 is not involved in the delivery of the killing signal.

In these studies and discussion I have considered only the association of the *lyt2* gene product with the recognition of class 1 MHC antigen. It is not clear whether there should be a comparable gene product associated with recognition or response to the class 2 MHC antigen but it seems likely. It is tempting to speculate that the *lyt1* gene product might play such a role and this possibility is somewhat strengthened by the recent finding that anti-Lyt1 can enhance the induction of the T-cell response (33). It is possible, however, that Lyt1 and Lyt2 molecules do not have this type of reciprocal relationship, especially in light of the fact that Lyt1 is expressed on all normal T cells (25) instead of showing expression restricted to class 2 recognizing cells. I would suggest that some other Lyt antigen, not

yet characterized in the mouse, might play this role.

In conclusion, the fact that a T lymphocyte differentiation antigen, Lyt2, is associated in some functional way with the recognition of one of the two basic classes of MHC antigens gives us a probe for further investigations of the significance of the dichotomy of MHC antigens and their role in T-cell recognition and triggering.

I thank M. English and L. Walker for their invaluable technical assistance and K. Wong for her help in preparing the manuscript. I am indebted to the Salk Cell Distribution Center, Dr. Philip Lake, and Dr. Michael Bevan for gifts of cell lines and their products. Dr. R. W. Dutton is thanked for his encouragement and many useful discussions. This work was supported in part by National Institutes of Health Grant AI-08795 and American Cancer Society IM-1N.

1. Dutton, R. W. (1965) *J. Exp. Med.* **122**, 759–770.
2. Dutton, R. W., Falkoff, R., Hirst, J. A., Hoffmann, M., Kappler, J. W., Kettman, J. R., Lesley, J. F. & Vann, D. (1971) *Prog. Immunol.* **1**, 355–368.
3. Katz, D. H., Paul, W. E., Goidl, E. A. & Benacerraf, B. (1971) *J. Exp. Med.* **133**, 169–186.
4. Bach, F. H., Bach, M. L. & Sondel, P. M. (1976) *Nature (London)* **259**, 273–281.
5. Klein, J. (1978) *Springer Sem. Immunopathol.* **1**, 31–49.
6. Bach, F. H. (1972) *J. Exp. Med.* **136**, 1430–1444.
7. Doherty, P. C., Blanden, R. V. & Zinkernagel, R. M. (1976) *Transplant. Rev.* **29**, 89–124.
8. Zinkernagel, R. M. & Doherty, P. C. (1975) *J. Exp. Med.* **141**, 1427–1436.
9. Katz, D. H., Hamaoka, T., Dorf, M. E. & Benacerraf, B. (1973) *Proc. Natl. Acad. Sci. USA* **70**, 2624–2628.
10. Kappler, J. W. & Marrack, P. (1976) *Nature (London)* **262**, 797–799.
11. Cantor, H. & Boyse, E. A. (1976) *Cold Spring Harbor Symp. Quant. Biol.* **41**, 23–32.
12. Wettstein, P. J., Bailey, D. W., Mobraaten, L. E., Klein, J. & Frelinger, J. A. (1978) *J. Exp. Med.* **147**, 1395–1404.
13. Bach, F. & Alter, B. J. (1978) *J. Exp. Med.* **148**, 829–834.
14. Swain, S. L. & Panfili, P. R. (1979) *J. Immunol.* **122**, 383–391.
15. Okada, M. & Henney, C. S. (1980) *J. Immunol.* **125**, 300–307.
16. Swain, S. L., Bakke, A., English, M. & Dutton, R. W. (1979) *J. Immunol.* **123**, 383–391.
17. Swain, S. L. (1980) *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **39**, 3111–3113.
18. Wagner, H., Götze, D., Ptschlinzew, L. & Röllinghoff, M. (1975) *J. Exp. Med.* **142**, 1477–1487.
19. Klein, J., Chiang, C. L. & Hauptfield, V. (1977) *J. Exp. Med.* **145**, 450–454.
20. Swain, S. L., Dennert, G., Wormsley, S. & Dutton, R. W. (1981) *Eur. J. Immunol.* **11**, 175–180.
21. Nakayama, E., Shiku, H., Stockert, E., Oettgen, H. F. & Old, L. J. (1979) *Proc. Natl. Acad. Sci. USA* **76**, 1977–1981.
22. Shinohara, N. & Sachs, D. H. (1979) *J. Exp. Med.* **150**, 432–444.
23. Shinohara, N., Hämmerling, U. & Sachs, D. H. (1980) *Eur. J. Immunol.* **10**, 589–594.
24. Hollander, N., Pillemer, N. & Weissman, I. L. (1980) *J. Exp. Med.* **152**, 674–687.
25. Ledbetter, J. A. & Herzenberg, L. A. (1979) *Immunol. Rev.* **47**, 63–90.
26. Raulet, D. H., Gottlieb, P. D. & Bevan, M. J. (1980) *J. Immunol.* **125**, 1136–1143.
27. Swain, S. L. (1981) *J. Immunol.* **126**, 2307–2309.
28. Swain, S. L., Dennert, G., Warner, J. F. & Dutton, R. W. (1981) *Proc. Natl. Acad. Sci. USA* **78**, 2517–2521.
29. Panfili, P. R. & Dutton, R. W. (1978) *J. Immunol.* **120**, 1897–1901.
30. Smith, K. A. (1980) *Immunol. Rev.* **51**, 337–357.
31. Watson, J., Gillis, S., Marbrook, J., Mochizuki, D. & Smith, K. A. (1979) *J. Exp. Med.* **150**, 849–861.
32. Dutton, R. W. & Swain, S. L. (1981) in *Critical Reviews in Immunology* (CRC, Boca Raton, FL), in press.
33. Hollander, N., Pillemer, E. & Weissman, I. L. (1981) *Proc. Natl. Acad. Sci. USA* **78**, 1148–1151.
34. Kimura, A. L. & Wigzell, H. (1977) *Contemp. Top. Mol. Immunol.* **6**, 209–244.
35. Sachs, D. H., Winn, J. & Russell, P. S. (1971) *J. Immunol.* **107**, 481–492.
36. Shiku, H., Kisielow, P., Bean, M. A., Takahashi, T., Boyse, E. A., Oettgen, H. F. & Old, L. J. (1975) *J. Exp. Med.* **141**, 227–241.
37. MacDonald, H. R., Thiernesse, N. & Cerottini, J.-C. (1981) *J. Immunol.* **126**, 1671–1675.
38. Dialynas, D. P., Loken, M. R., Glasebrook, A. L. & Fitch, F. W. (1981) *J. Exp. Med.* **153**, 595–604.