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Editorial Comment

Starting with Volume 156, 1979, the name of the «Zeitschrift für Immunitätsforschung» has been changed to

«Immunobiology»

The «Zeitschrift», founded in 1909 by Paul Ehrlich, was the first immunological journal to be published in the world. The journal has a long-lived reputation as being an important source of scientific information based on the contributions of famous immunologists. The increased use of English as the common scientific language has now prompted the Editorial Board to change the traditional German title to **«Immunobiology»**. With this title change the journal emphasizes its international character as a forum for the publication of a variety of different articles in the broad field of immunology.

The Editorial Board of Immunobiology

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Generation of Virus Specific Cytotoxic T Cells In Vitro. III. Spleen Cells Stimulated by Viral Antigens Generate Alloreactive Cytotoxic T Cells[1])

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Abstract

Cytotoxic T lymphocytes (CTL) from DBA/2 strain mice primed with Sendai virus (SV) in vivo were activated by secondary stimulation of spleen cells with viral antigens in vitro and analyzed for their target antigen specificity. These effector cells lysed syngeneic Sendai virus infected target cells, marginally a variety of non-infected targets and had a strong cytotoxic effect on H-2^b targets. Studies on the antigenic requirements revealed that all SV preparations which generated specific CTL also induced the alloreactive populations. Similar results were found in the response to Newcastle disease virus (NDV) and some influenza A viruses; all these viruses were mitogenic for lymphocytes. Experiments on the cellular requirements indicated that virus specific and alloreactive cells can be separated by their requirements for help and for restimulation. By competition experiments both activities could be attributed to clearly separable T cell subpopulations. The induction mechanism of alloreactive T cells by viral antigens is discussed.

Introduction

H-2 restricted cytotoxic T lymphocytes (CTL) are generally rather specific for the antigen and for the restricting H-2 determinants. However, the discriminatory capacity of these cytotoxic T cells is not absolute. Exceptions have been observed and fall into the following patterns: TNP-specific CTL have exquisite antigen specificity (1) but their specificity for the restricting H-2 antigens is less prominent. On the other hand, the H-2 restriction specificity of cytotoxic effector cells with antigen specificity for viruses or minor H-antigens is clearly demonstrable. They do not lyse allogeneic target cells carrying the same viral antigen (although there is some crossreactivity between H-2^k and H-2^d) and even have the capacity to differentiate between H-2 mutants (2–4). However, they show extensive crossreactivity on target cells carrying antigens of serological distinct viral substrains (5), they lyse syngeneic TNP modified target cells (6) and there is even cytolytic activity on allogeneic target cells without any modification by virus or hapten (7, 8).

Abbreviations: CTL = cytotoxic T lymphocytes; *GM* = growth medium; *NDV* = Newcastle disease virus; *SV* = Sendai virus.

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Based on the crossreactive patterns observed it has been recently proposed that all alloreactive effector cells represent crossreactive cell populations which are generated in the response to environmental antigens which elicit normally H-2 restricted responses (9). In this report we describe the generation of alloreactive T effector cells in the response to three antigenically unrelated viruses. Splenic lymphocytes from DBA/2 strain mice generate upon virus specific restimulation in vitro alloreactive cytotoxic T cells which lyse unmodified $H\text{-}2^b$ target cells. Studies on the induction mechanism and competition experiments demonstrate that these effector cells represent separate subsets of CTL with selective specificity for $H\text{-}2K^b$ or $H\text{-}2D^b$.

Materials and Methods

Animals: Mice from the strains DBA/2, BALB/c, B10.D2, B10.BR, CBA, B10.S, B10, B10.A(2R), B10.A(5) and SWR were raised in our own breeding facility and used at 6–10 weeks of age.

Viruses: Sendai virus and influenza A/Victoria virus (H3N2) were propagated, titrated, purified and inactivated as described (10). Newcastle disease virus strain Italien (NDV) and the influenza virus strains APR/8 (HON1), A/USSR (H1N1) and A/ASIA (H2N2) were kindly supplied by Drs. Klenk and Rott, Gießen. β-propiolactone inactivated Sendai virus (β-pl-SV) (2 mg in 1 ml of the appropriate buffer) was digested with proteolytic enzymes as described previously (11). Trypsin treatment (8 µl, 5 mg/ml; TPCK-treated, Worthington) was for 1 h at 37 °C in 0.5% ammonium bicarbonate buffer, pH 8. Treatment with V8 protease from Staphylococcus aureus: (50 µl, 1 mg/ml; Miles) for 18 h at 37 °C in 50 mM ammonium bicarbonate buffer pH 8. Sendai virus preparations were kindly provided by Dr. M. J. Gething, ICRF, London, UK.

The capacity of the virus preparations to induce target cell formation was measured in the cytolytic assay (11, 12). Haemagglutinin, neuraminidase, haemolytic activities and cell fusion were tested as described previously. As reported in Reference 11 virus preparations treated with trypsin (TRY-SV) had haemagglutination and neuraminidase activities comparable to β-pl-SV, but lacked the fusion capacity and the haemolytic activity (F^-). The preparation digested with V8 protease from Staphylococcus aureus (V8-SA-SV) still contained the F glycoprotein but the haemagglutinin-neuraminidase glycoprotein spikes were removed from the virion ($HANA^-$).

Immunizations: Mice were injected once i.p. with 100 haemaglutination units (HAU) of infectious virus. 3–10 weeks afterwards spleens were removed and lymphocytes were prepared for tissue culture.

Media: Cells were cultured in RPMI 1640 medium with L-glutamine (2 mM final concentration) streptomycin and penicillin (50 units/ml), 2-mercaptoethanol (2×10^{-5} M) and 10% fetal calf serum.

Cell cultures: P-815 ($H\text{-}2^d$) RBL5 ($H\text{-}2^b$) and AKRA ($H\text{-}2^k$) tumor cells were grown in vitro at a concentration of 2×10^5 cells/ml with medium change after every 48 hrs. Mouse spleen cells or lymph node cells were suspended in medium at a concentration of 4×10^6 cells/ml. Cells were cultured in multi-dish culture trays (FB-24 Tc, Linbro Chemicals, New Haven, Conn., USA) or in plastic tissue culture flask of different sizes. If desired, cells were depleted from erythrocytes by lysis in 0.184 M NH_4Cl or by separation on a Ficoll-Hypaque gradient.

Growth medium: DBA/2 spleen cells (4×10^6/ml) were plated in multi dish trays and incubated for 48 hrs in the presence of 10 µg/ml concanavalin A (Pharmacia Uppsala, Sweden). After incubation the supernatant was harvested, centrifuged at 900 g for 10 min., filtered through a 0.45 µm filter (Gelman, Ann Arbor, Mich., USA) aliquoted and stored at -20 °C.

Growth medium was added to long term cultures in a 1:2 dilution with fresh complete medium. Cells in growth medium were seeded at a concentration of 2×10^5/ml and were split when the cell concentration reached 0.5×10^6/ml or routinely after 4 days.

Helper cell culture conditions: Helper cells were generated by first step cultures in a modification of the protocol described by Baum and Pilarski (13). Helper cells were activated either specifically by viral antigens or alloantigens, or received no antigen. Helper cells obtained from a 1 day or 2 day first culture period were transferred into a second step culture to help a cytotoxic response by thymocyte killer precursors. Helper cells were irradiated with 1500 rad before addition to the thymocyte cultures. Controls included: 1. Thymocytes cocultured with irradiated helper cells in absence of viral antigens, 2. Irradiated helper cells in presence of viral antigens, 3. Thymocytes in presence of viral antigens in absence of helper cells. These controls were negative. Cytotoxic T cells were assayed at day 5 of the secondary culture.

^{51}Cr-release assay: The conditions of the ^{51}Cr-release assay and calculation of data are described in a previous paper (10). All values are the mean percent specific ^{51}Cr-release of triplicate wells. The standard errors of the means were always less than ± 5% and are omitted from figures and tables for clarity.

Results

Virus specific activated lymphocytes are cytotoxic for non-infected allogeneic target cells

Spleen cells from DBA/2 mice primed to Sendai virus were specifically restimulated in vitro and tested in the ^{51}Cr-release assay on various target cells (Fig. 1). Data show that a strong cytotoxic response was generated which could be demonstrated by the lysis of Sendai virus infected syngeneic

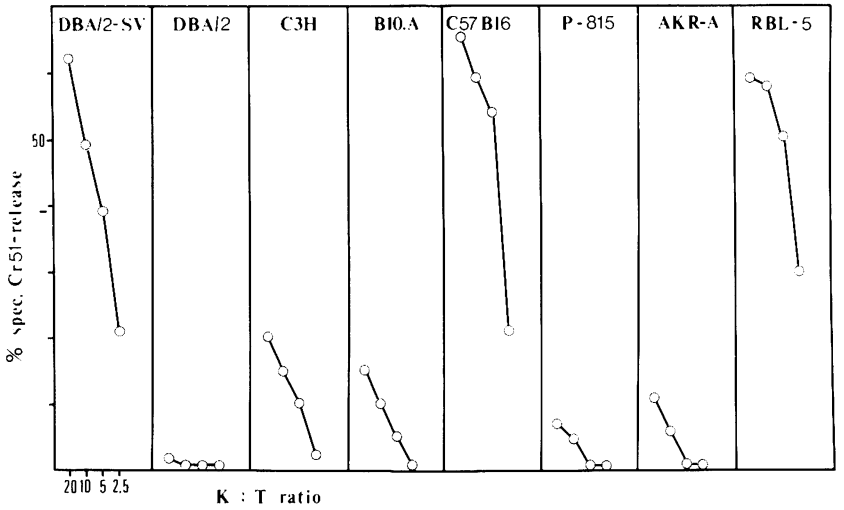


Fig. 1. *DBA/2 spleen cells challenged with Sendai virus lyse non-infected allogeneic cells* Responder cells are derived from DBA/2 strain mice primed with infectious virus 3 weeks previously. Targets are con A blast cells incubated with 10 µg SV antigen for 1 hr at 37 °C or tumor cells p-815 (H-2^d), AKR-A (H-2^k) and RBL-5 (H-2^b) prepared similarly. Assay time 4 hrs.

Table 1. Generation of alloreactive cytolytic activity for H-2^b targets by SV in different mouse strains

Mouse strain[a])	Haplotype	TARGETS % specific ^{51}Cr release[b])	
		syngeneic SV infected blast cells	RBL-5
DBA/2	H-2^d	73	52
B 10.D2	H-2^d	51	24
Balb/c	H-2^d	44	13
CBA	H-2^k	40	6
B 10.BR	H-2^k	47	9
B 10.	H-2^b	38	-2
B 10.S	H-2^s	35	3
SWR	H-2^q	48	5

[a]) Responders were primed in vitro with SV in vivo and restimulated in vitro with 1 μg/ml SV antigen.
[b]) K:T ratio 20:1

con A blasts while non-infected syngeneic target cells were not lysed. When tested on semiallogeneic or allogeneic target cells various degrees of cytolysis were observed. While there was only marginal lysis on H-2^k and H-2^a target cells H-2^b blasts were lysed with an efficiency comparable to the lysis of virus infected syngeneic target cells. Tumor target cells of haplotype H-2^b only were similarly lysed when activity on tumor cells of the haplotypes H-2^d (P-815), H-2^k (AKR-A) and H-2^b (RBL-5) were compared. Both infected and non-infected H-2^b target cells were lysed to the same extent (not shown). In control spleen cell cultures without Sendai virus antigens neither virus specific nor alloreactive cytotoxic activity was generated.

The capacity of Sendai virus to generate alloreactive cytotoxic activity was not restricted to the DBA/2 strain mice. When mice of the strains B10.D2, BALB/c, DBA/2, B10.BR, B10 and SWR were tested (Table 1), it was found that in all H-2^d strain mice some cytotoxic activity with specificity for H-2^b targets was generated which was not found in the other strains tested. The cytotoxic activity on H-2^b target cells could be abrogated by the treatment of effector cells with anti-Thy 1.2 serum and complement or anti-Lyt 2.3 serum and complement indicating the T cell nature of the alloreactive cell population (data not shown).

Induction requirements of alloreactive cytolytic T cells following virus specific restimulation

A) *Viral antigen requirements*

DBA/2 mice primed to an orthomyxovirus (influenza A/Victoria [H3N2]) or paramyxoviruses (Sendai virus, Newcastle disease virus [NDV]) were restimulated with the sensitizing virus. In the case of NDV and A/Victoria infective virus from allantoic fluid was used as antigen. For

Sendai virus specific restimulation in this experiment, purified non-infectious virus was employed. A part of the SV preparation was treated with trypsin to destroy the functional activity of the fusion protein, while another preparation lacked the haemagglutinin-neuraminidase protein, following V8 protease treatment. The results of Figure 2 show that non-infectious Sendai virus was also able to generate the alloreactive CTL population and inactivation of the F protein or removal of the HN protein was of little effect. Furthermore, it is depicted that generation of NDV specific CTL was also accompanied by generation of an H-2^b specific activity, while an H3N2 subtype of influenza A generated specific CTL which did not contain H-2^b specific alloreactive cells.

Recently BUTCHKO et al. (14) reported that H2N2 subtypes of influenza A viruses are mitogenic for lymphocytes. This effect could be attributed to the haemagglutinin of type 2. Since in our hands (U.K., unpublished) the glycoproteins of paramyxoviruses are also mitogenic for lymphocytes, we tested to see if influenza A strains of H2N2 subtype would also give rise to alloreactive CTL. Four influenza A strains differing with respect to haemagglutinin and neuraminidase type were used for in vitro priming and for secondary stimulation of CTL in vitro. Effector cells were tested on virus infected and non-infected target cells and in addition on non-infected H-2^b targets. As published by other authors (5) lysis of infected cells was specific for orthomyxoviruses but cross-reactive for the different influenza A subtypes (data not shown). When tested on H-2^b target cells (Table 2) only, the H2N2 subtype was active in generation of alloreactive cytolytic activity. However, to give rise to a strong effect on H-2^b target cells in vivo priming with the H2N2 subtype was required. Also, in secondary stimula-

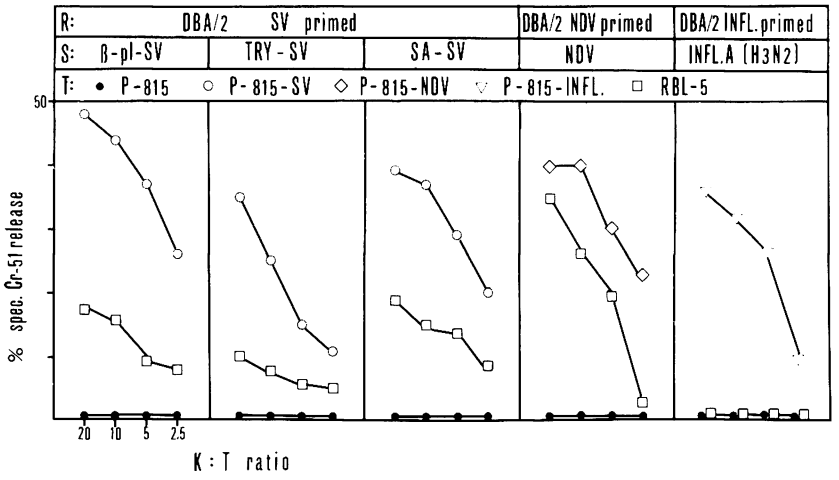


Fig. 2. *Antigenic requirements for CTL activation*
R = responder cells; S = stimulator cells; T = target cells; NDV = Newcastle disease virus, strain Italien; INFL = Influenza A virus, strain Victoria (H3N2).

Table 2. Lysis of RBL-5 (H-2^b) tumor cells by influenza A virus specific activated DBA/2 spleen cells

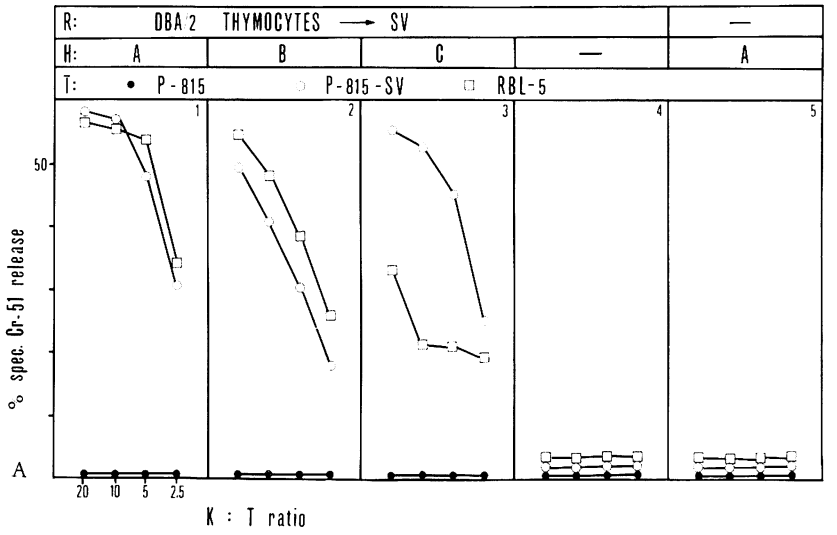
Viruses used for in vivo priming[a])		Viruses used for restimulation in vitro[b]) A/PR/8	A/USSR	A/ASIA	A/VICTORIA
A/PR/8	(H0 N1)	4.99	11.82	3.42	−2.96
A/USSR	(H1 N1)	−2.38	5.79	7.43	1.40
A/ASIA	(H2 N2)	12.80	13.70	82.91	29.37
A/VICTORIA	(H3 N2)	−1.26	0.68	−3.72	1.73

[a]) DBA/2 mice were primed with 100 HAU infective virus containing allantoic fluid at least 3 weeks previous to secondary stimulation in vitro.
[b]) Cytotoxic test on day 6 of in vitro culture; K:T ratio 10:1, incubation time 4 hrs

tion the other subtypes (H0N1), (N1N1) and (H3N2) were active but the most effective response was again induced by challenge with the H2N2 subtype. Thus, the experiments on antigenic requirements for generation of the alloantigen-specific activity revealed that a) different mitogenic viruses and b) the same antigenic preparations of Sendai virus which give rise to H-2 restricted killer cells will also generate effector cells which lyse H-2^b target cells.

B) *Cellular requirements*

In previous experiments we had found that virus specific cytotoxic effector cells could also be generated from thymocytes if antigen primed irradiated spleen cells were present in the culture. For induction of effector cells from thymocytes the experimental protocol described by BAUM and PILARSKI (13) was applied. Three types of cell preparation with helper cell function were prepared: A) DBA/2 spleen cells stimulated with Sendai virus, B) DBA/2 spleen cells stimulated with alloantigen (B10.BR, H-2^k) or C) DBA/2 spleen cells without antigenic stimulation. Cells from type A, B or C were irradiated after 24 or 48 hrs in tissue culture and 1×10^8 of these helper cells were added to the cultures containing 1×10^8 thymocytes from non-primed DBA/2 mice and 1 μg/ml Sendai virus antigen. The activity which was generated after 5 days of in vitro culture was tested on infected and non-infected syngeneic as well as on allogeneic target cells. It was found (Figure 3A 1–3) that in the presence of the irradiated cultured cells A, B and C preincubated for 24 hrs, both syngeneic virus specific activity and alloreactive activity was expressed. However, there was no cytolytic activity generated without helper cells present in the culture (Figure 3A, 4) and the effector cells were generated from thymocytes and not from the helper cell fraction (Figure 3A, 5). After preincubation of helper cells for 48 hrs previous to the addition of thymocytes different results were obtained (Figure 3B). Under these conditions effector cell populations were obtained from thymocytes which had alloreactive cytolytic activity only while there was no generation of virus specific effector cells. This indicates that the



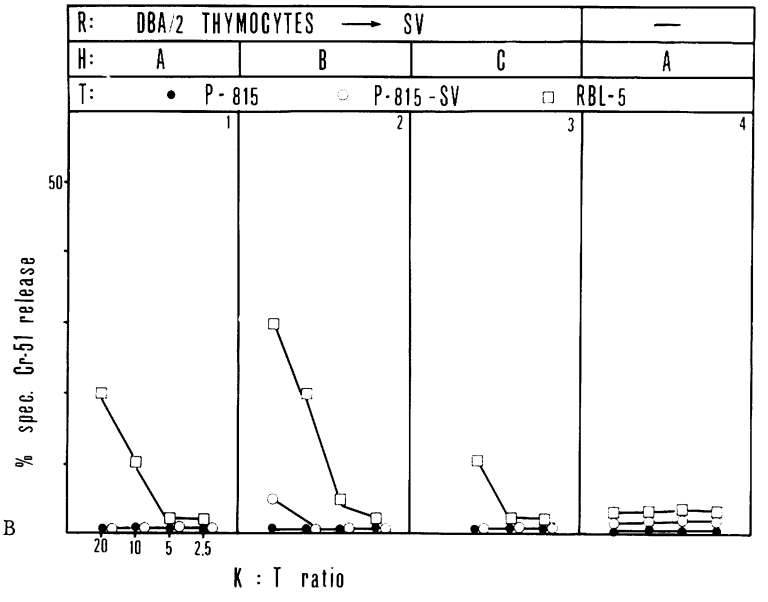


Fig. 3. *A*
H = helper cells, 1500 r irradiated 24 hrs preincubated; A = normal DBA/2 spleen cells preincubated with Sendai virus; B = normal DBA/2 spleen cells preincubated with B10.BR spleen cells; C = normal BBA/2 spleen cells preincubated without antigens added; 4 = no helper cells added to thymocyte responder cultures; 5 = no thymocytes added to helper cell cultures.
B
same helper cells incubated for 48 hrs

generation of virus specific CTL and alloreactive CTL in the presence of Sendai virus can be separated by their different requirements for help. Titration experiments carried out in order to define the quantitative requirements for helper cells (data not shown) also indicated that the generation of alloreactive CTL required smaller numbers of helper cells.

H-2 restricted virus specific CTL and alloreactive CTL are different T cell clones

A) *Competition assays*

The results of the helper cell experiments already indicated that virus specific and alloreactive cytotoxic activity reside in different T cell subsets. By competition experiments the specificity of the effector cells generated was evaluated. Sendai virus specific CTL from the strain DBA/2 were incubated with ^{51}Cr labelled SV infected con A blasts of the strain B10 (H-2^b). The addition of various non-labelled inhibitor cells (SV infected con A blasts of the strain B10.D2 and non-infected con A blasts of the strains B10.D2, B10.BR, B10, B10.A(2R) and B10.A(5R) showed that inhibition of lysis could only be obtained by addition of competitor cells carrying H-2^b antigens, while there was no inhibition of alloreactive killer activity by addition of normal or infected syngeneic cells or by addition of non-infected allogeneic cells of other haplotypes (Figure 4, 2). Similarly, when tested on ^{51}Cr labelled B10.D2 blasts infected with Sendai virus, only H-2^d competitor cells infected with Sendai virus were able to inhibit the lysis of labelled target cells (Figure 4, 1). Thus, separate T cell subsets were

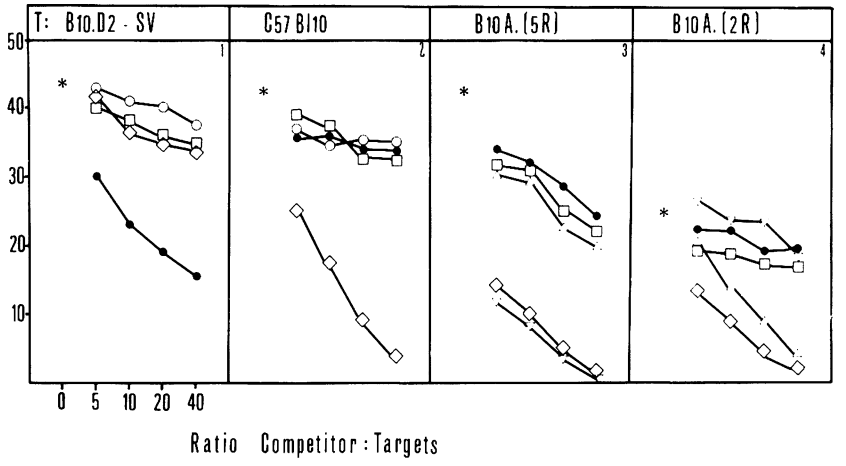


Fig. 4. *Definition of effector cell specificity in competition experiments.*
Responder cells: DBA/2 spleen cells after secondary stimulation in vitro. Responder: target cell ratio 12.5:1. ★ no competitors added.
Competitors (con A blasts): ● B10.D2-SV ○ B10.D2, □ B10.BR, ◇ B10, △ B10.A (2R) (K^k, D^b), ▽ B10.A (5R) (K^b, D^d).

generated in the response to Sendai virus. One subset reacted only with syngeneic Sendai virus infected targets while the specificity of the other subsets was exclusively directed to H-2^b alloantigens and did not cross-react with antigens induced by Sendai virus in syngeneic cells. We tried to map the target antigen(s) recognized by the alloreactive CTL. The T cell subset with alloreactivity for H-2^b could be further subdivided into at least two clones, one very likely specific for H-2K^b and the other for H-2D^b as shown by further competition experiments (Figure 4,3, 4,4).

B) *Long term culture conditions*

Long term tissue cultures (15–18) were set up in order to find out if both populations have similar antigen restimulation requirements. Cultures from antigen primed mice were incubated with Sendai virus in order to generate virus specific effector cells. In the same cultures cytolytic activities specific for Sendai and for H-2^b targets was generated. After 14-18 days in vitro the cytolytic activity on both targets started to cease. To these cultures irradiated syngeneic stimulator cells coated with Sendai virus were added in order to generate tertiary cytotoxic effector cells. 6 days after restimulation cytotoxic activity against syngeneic infected target cells could be demonstrated (Table 3, Exp. A) while the cytolytic activity on allogeneic target cells remained low; yet, the potential to generate alloreactive activity was not lost during long term culture. Cells from cultures which previously had demonstrable cytolytic activity on H-2^b target cells were kept in culture

Table 3. Effect of long term tissue culture conditions on alloreactive and virus-specific cytotoxic T cells

Exp.	Day of in vitro[a]) culture	Treatment of cultures	K:T ratio	Target cells (% ^{51}Cr release)		
				P–815	P–815–SV	RBL–5
A	5	test	5:1	4	56	24
	14	test	5:1	3	30	2
	14	3° restimulation with SV infected spleen cells				
	20	test	5:1	13	87	8
B	18	test	5:1	3	26	40
	20	3°restimulation with SV infected spleen cells				
	25		5:1	0	55	48
	32	test and splitting of cultures	5:1	0	6	n.t.
	35	test	5:1	0	0	2
	32	transfer into growth medium				
	35	test	5:1	15	95	80

[a]) DBA/2 spleen cells challenged in vitro with Sendai virus. For restimulation cells were transferred into fresh complete medium. In Exp. B at day 32 cultures were split and 50% of the cells were transferred into medium supplied with con A induced growth medium.

until all cytolytic activity had ceased (Table 3, Exp. B). Upon transfer into tissue culture medium enriched with growth medium without any additional specific antigenic stimulus both alloreactive and H-2-restricted virus specific cytolytic activity was restored. Therefore, the alloreactive T cells remained present under long term culture conditions although they were refractory to the antigenic stimulus by Sendai virus modified stimulator cells indicating different restimulation requirements of both cytolytic T cell populations.

Discussion

Data show that paramyxoviruses and influenza virus strains of the H2N2 subtype induce in H-2^d strain mice T effector cells which lyse syngeneic virus infected target cells and non-infected target cells carrying the haplotype H-2^b. The alloreactive cytolytic activity can be induced with infective influenza virus, Newcastle disease virus (NDV) and Sendai virus (SV). Using SV non-infectious virus preparations, virions devoid of specific glycoproteins and virions carrying functionally inactivated glycoproteins were effective. These induction conditions are identical to that of virus specific effector cells which recognize paramyxovirus antigens on target cells[1]. Viruses which were able to generate alloreactivity had mitogenic effects on lymphocytes.

The alloreactive cell population with cytolytic efficiency comparable to that of the virus specific H-2 restricted effector cells resides in a separate effector cell subset. This is revealed by a) different antigen specificity in cold target cell inhibition tests b) different requirements for help during induction and c) different requirements for restimulation under long term in vitro culture conditions. Altogether we report that alloreactive CTL without crossreactive cytolytic activity on virus infected target cells are generated from spleen cells in vitro upon antigenic stimulation by viral antigens.

It has been shown by several authors that murine spleen cells stimulated by antigens which induce a H-2 restricted response contain CTL, with specificity for the sensitizing antigens, but also additional effector populations which recognize unrelated antigenic determinants (5–9, 18). Since the specificity of the immune repertoire is likely to be defined by various degrees of affinities rather than by subsets of non-overlapping specificity some crossreactivity was to be expected. The T cell subsets with additional reactivity described so far were defined by cloning of effector cells (8, 18) or by competition studies with non-labelled target cells (6, 9). These studies revealed that those effector cells were crossreactive i.e. the same T cell clones seemed to carry receptors specific for the syngeneic antigen-expres-

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[1] KOSZINOWSKI, U., and M. J. GETHING. Generation of virus specific cytotoxic T cells in vitro. II. Induction requirements with functionally inactivated virus preparations (submitted for publication).

sing target cells as well as for allogeneic targets. This indicates that molecules expressed on allogeneic targets may have antigenic determinants which the virusspecific effector cell cannot discriminate from determinants brought about by the antigen specific modification of syngeneic target cells.

Does the interpretation that the induction of the alloreactive T cell clones by viruses is antigen specific and that some sharing of antigenic determinants must exist even when the relatedness is not demonstrable at the effector cell stage also apply to our findings? One possibility may be that the affinity for the shared determinants induced by the virus is high during induction and low at the effector cell level. This is indicated by recent data of BAKER et al. (18). Their effector cell populations were induced against allogeneic cells but showed crossreactivity on syngeneic target cells. Cloning revealed effector cell clones of all three possible specificities: clones with specificity for the alloantigen only, crossreactivity cells and cells with selective specificity for syngeneic cells. If the crossreactive clones had arisen by antigen specific induction it is unlikely that only clones with exquisite specificity for syngeneic determinants were induced by non-antigens specific mechanism. Furthermore, other authors have shown in activation protocols similar to ours (9) that Sendai virus can in fact induce crossreactive effector cells with specificity for alloantigens and also for viral antigens on target cells. We cannot exclude that in our cell cultures, also, some crossreactive activity might have arisen. If so it was too small to be detected by the competition assays. However, it is difficult to envisage how the three viruses which neither serologically nor on the T effector cell level show antigenic crossreactivity all share determinants with H-2^b.

Another possibility which can be advanced to explain the generation of alloreactive clones in virus specific T cell activation is the induction of unrelated third party antigenic determinants by virus. In this case only the immunogenic presentation of determinants is a feature specific for some viruses; not, however, the antigens themselves. The antigens may be derepressed endogenous viral antigens (19, 20) or cell surface antigens (21–23). The failure of the restimulation of the alloreactive clones by virus in the long term cultures could be explained by such mechanisms. Cells capable of expressing relevant antigenic determinants or regulatory T cells required for restimulation to that antigen may not be present under those conditions.

Since a) the alloreactive effector cell population does not show any affinity for determinants induced by the sensitizing antigen which are recognizable by virus specific effector cells and b) antigenically unrelated viruses give rise to similar effector cell populations, it is likely that the lack of affinity at the effector cell level reflects induction by non-antigen specific mechanisms. BEVAN et al. (24) observed that concanavalin A induced in spleen cells from H-2^d strain mice the generation of alloreactive effector cells with specificity for H-2^b. However, the polyclonal activation generates T cells of 10–100 fold less activity than we find by stimulation with viral

antigens, although the mitogenic effect of paramyxoviruses is low. Influenza viruses of the subtype H2N2 have been reported to have mitogenic activities (14). In our experiments the very same subtype induces alloreactive cytolytic activity. Thus, the proliferation data can now be linked for the first time with a T cell function. The effect differs, however, from effector cells generated by con A, since in vivo priming and in vitro restimulation is required. If the process of activation is not antigen specific it is necessary to explain the strong response towards the H-2^d target. Further experiments are required to define if there is a predominant activation of CTL precursors specific for H-2^b or if DBA/2 mice have a high frequency of precursor T cells for this alloantigen.

It has been argued that all alloreactive T cells are crossreactive cell populations induced by environmental antigens (9). Our data seem to extend these observations in showing that viral antigens can even induce effector cells with selective specificity only for the alloantigen. However, we feel that the capacity of some viruses to trigger alloreactive cell clones does not necessarily indicate that this effect accounts for the presence of the large number of alloreactive T cell precursors.

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