

T-CELL POPULATIONS SPECIFICALLY DEPLETED OF ALLOREACTIVE POTENTIAL CANNOT BE INDUCED TO LYSE H-2-DIFFERENT VIRUS-INFECTED TARGET CELLS*

BY JACK R. BENNINK AND PETER C. DOHERTY

(From the Wistar Institute of Anatomy and Biology, Philadelphia, Pennsylvania 19104)

The central question is whether T cells that develop in the context of one set of H-2 specificities can ever be induced to recognize neoantigen presented on an H-2-different cell. Valuable insights are provided by recent experiments with chimeras, generated by reconstituting lethally irradiated parental mice of H-2 type A with A × B F₁ bone marrow cells. The resultant T-cell populations are phenotypically A × B, but can only be induced to recognize minor histocompatibility antigen (or virus) associated with A but not with B (1, 2). This effect seems to be mediated via radiation-resistant cells in the A thymus (2, 3). Such chimeras are apparently tolerant to both A and B in the sense of alloreactivity, but are only able to recognize neoantigen in the context of A. What, however, is the situation if B is not encountered at any stage during physiological differentiation? Can T cells reactive to B+ virus then be generated?

This question can only be examined rigorously in the absence of alloreactive T cells. The procedure used here is to filter either immunologically naive or virus-immune A lymphocytes through uninfected, irradiated (950 rads) A × B F₁ recipients (4, 5). Thoracic duct populations from these mice, which are depleted of alloreactivity for B, are then transferred to a further group of irradiated A × B F₁ mice and stimulated with either influenza virus or with vaccinia virus.

Materials and Methods

Mice. The CBA/J (H-2^k), C57BL/6J (H-2^b), CBA/J × C57BL/6JF₁, A/J (H-2^a), C57BL/6J × A/JF₁, B10.A (H-2^a), B10.D2 (H-2^d), and B10.Br (H-2^k) strains were obtained from The Jackson Laboratory, Bar Harbor, Maine. BALB/c (H-2^d) mice were from the Institute for Cancer Research, Fox Chase, Philadelphia, Pa.

Viruses. The influenza A virus strains PR8 [A/Puerto Rico/8/34 (H0N1)] and NT60 [A/Northern Territory/60/68 (H2N2)] were obtained from Dr. W. Gerhard at the Wistar Institute. HK (A/Hong Kong/X31 [H3N2]), a recombinant between PR8 and a Hong Kong strain that shows antigenic characteristics of the Hong Kong virus (6), was originally supplied by Dr. R. G. Webster, St. Jude Children's Research Hospital, Memphis, Tenn. Virus stocks were stored frozen as allantoic fluid containing between 1,200 and 3,000 hemagglutinating (HA)¹ U/ml (7). Mice were primed intraperitoneally with a single dose at 120-300 HA U (memory mice) or stimulated

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¹ Abbreviations used in this paper: H, influenza virus hemagglutinin antigen; HA, virus hemagglutinating unit; H-2, mouse major histocompatibility complex; i.v., intravenously; M, influenza virus matrix protein; N, influenza virus neuraminidase antigen; PFU, plaque-forming units; T cell, thymus-derived lymphocyte; TDL, thoracic duct lymphocyte; TNP, trinitrophenyl.

intravenously (i.v.) with a single dose of 60–150 HA U. The target cells were exposed to 6–15 HA U of influenza virus per 10^6 cells.

The vaccinia virus (WR isolate) was obtained from Dr. R. Zinkernagel, Scripps Clinic and Research Foundation, La Jolla, Calif., and was propagated in L929 cells (2). Stock virus contains 4×10^7 plaque-forming units (PFU) per milliliter. Mice were infected i.v. with 0.5×10^7 PFU. Target cells were infected with 10^7 PFU per $5\text{--}10 \times 10^6$ cells.

Cytotoxic Assay. The assay has been described previously (8–10). Briefly, L929 fibroblasts (L cells, C3H, H-2^k), P815 mastocytoma cells (DBA/2, H-2^d), MC57G methylcholanthrene-induced tumor (C57BL/6, H-2^b), and B10.A(5R) SV40-transformed kidney fibroblasts [B10.A(5R), H-2K^b-D^d] were infected with virus subsequent to labeling with Na₂⁵¹CrO₄. The assays were incubated for 12 h at 37°C, and results are expressed as mean percent-specific ⁵¹Cr release for replicates of three or four wells. The formula used for calculating percent specific ⁵¹Cr release is $(It - Mt) \times 100/Dt - Mt$, where *D* is detergent lysis, *t* is the target, *I* is immune lymphocytes, and *M* is spontaneous release for incubation in medium alone.

Negative Selection. Lymphocyte populations specifically depleted of alloreactivity to a particular major histocompatibility complex haplotype were prepared according to procedures fully described elsewhere (4). Briefly, this usually involved acute "filtration" of parental strain (A) lymph node and spleen suspension through irradiated (950 rads) A × B F₁ recipients. Lymph was then collected from the F₁ recipients over the period 15–36 h after injecting the parental cells. Virtually all (98%) of the collected cells at this time have been shown previously by others (4, 5) to be T cells.

Generation of Cytotoxic T Cells. Negatively selected lymphocytes were injected i.v. as $12.5\text{--}20 \times 10^6$ cells per irradiated (950 rads) recipient. Nondepleted populations consisted of mixed F₁ lymph node and spleen cells, which were given i.v. as a dose of 60×10^6 cells for each recipient. All lymphocyte populations were stimulated with virus 3 h after cell transfer. Spleen cells from the irradiated recipients were assayed 5–6 days later. Control, unirradiated mice were also injected with virus, and spleen cells were assayed concurrently.

Results

Primary and Secondary Responses to Influenza A Viruses. A preliminary experiment established that both normal and memory CBA/J (H-2^k) thoracic duct lymphocyte (TDL) populations can be induced to generate a cytotoxic response in virus-infected, irradiated CBA/J recipients (Table I). These effector T cells show cross-reactivity for a variety of type A influenza viruses, regardless of the virus hemagglutinin (H) and neuraminidase (N) antigen subtypes, but do not lyse allogeneic virus-infected cells (9, 10). Furthermore, the stimulator cell in this system is provided by the irradiated, virus-infected recipient rather than by the transferred TDL: both TDL and spleen cells from CBA/J × C57BL/6J F₁ (H-2^{k/b}) develop a virus-immune T-cell response restricted to the recipient H-2 type (Tables II and III).

Immune CBA/J (H-2^k) lymphocyte populations depleted of alloreactivity to H-2^b by passage through irradiated, uninfected CBA/J × C57BL/6J F₁ mice (H-2^{k/b}) cannot be shown to generate influenza-specific cytotoxic T cells in the context of the C57BL/6J (H-2^b, MC57G target) haplotype (CBA_{C57}; Tables III and IV). The constraint applies for both spleen and TDL from the recipients (Tables III and IV). Furthermore, an identical restriction is found if lymphocytes are stimulated with the same (HK → HK, Table IV) or with a heterologous influenza A virus (HK → PR8, Table III).

With this model we are, theoretically, examining two separate possibilities concurrently. The first is that there is cross-priming (11, 12) for recognition of a shared virus component, possibly the internal matrix (M) protein of the PR8 and HK influenza viruses (13, 14), presented in the context of a different set of

TABLE I
Generation of 5-Day Primary and Secondary Syngeneic Cytotoxic T-Cell Responses in 950 rads CBA/J Recipients

Donor TDL‡	Percent of specific ⁵¹ Cr release*					
	HK-infected		PR8	NT60	Normal	
	L cell	P815	L cell	L cell	L cell	P815
	%					
Immune (3.0 × 10 ⁷)	65	0	45	47	0	0
Normal (2.5 × 10 ⁷)	41	6	25	26	3	0
Controls§						
Immune B10.Br (H-2 ^k)	52	3	29	46	0	0
Immune B10.D2 (H-2 ^d)	1	40	8	2	2	0
Normal CBA/J (H-2 ^k)	1	4	3	11	1	0

* Target L929 fibroblasts (L cells, H-2^k) and P815 mastocytoma cells (H-2^d) were infected with HK (H3N2), PR8 (H0N1), or NT60 (H2N2) influenza viruses. Results are calculated as percent of specific ⁵¹Cr release relative to incubation in medium alone.

‡ The immune mice had been primed with PR8 influenza virus 17 days previously. CBA/J recipients were irradiated, given TDL i.v. 24 h later, and dosed with HK virus after an additional 3 h. Recipient spleens were assayed (25:1) on the 5th day after transfer of lymphocytes.

§ Mice had been exposed to PR8 influenza virus 5 wk previously and dosed i.v. with HK virus 5 days before sampling.

TABLE II
Stimulation Is Mediated Via the Recipient Environment Rather Than by the Transferred TDL

Immune population*	Recipient‡	Percent of specific ⁵¹ Cr release					
		HK-infected			PR8	Normal	
		L cell (H-2 ^k)	MC57G (H-2 ^b)	P815 (H-2 ^d)	L cell (H-2 ^k)	L cell (H-2 ^k)	MC57G (H-2 ^b)
		%					
3 × 10 ⁷	CBA × C57F ₁	77	32	4	69	8	1
CBA × C57F ₁	CBA/J (H-2 ^k)	72	0	3	64	4	1
TDL (H-2 ^{k/b})	B10.Br (H-2 ^k)	47	0	2	39	4	2
Controls							
Immune	CBA × C57F ₁	86	46	16	83	2	0
Immune	B10.D2 (H-2 ^d)	11	6	70	7	10	5
Normal	CBA/J	0	5	0	8	0	0

* All mice had been inoculated i.v. with PR8 at least 1 mo previously, dosed i.v. with HK at 3 h after cell transfer, and spleens were assayed after an additional 5 days at a ratio of 50:1.

‡ C57BL mice were also used, but were very young and died from irradiation before the experiment was completed.

H-2 determinants. The second concerns the capacity to mount a 5-day primary response (Table I) to a newly encountered hemagglutinin (15) antigen (H3, Table III) expressed on an H-2-different cell. Neither situation seems to occur. However, previous studies indicate (10, 16) that a concurrent secondary response

TABLE III
Absence of Cross-Priming for Recognition of Allogeneic Influenza-Infected Target Cells

Transferred cells*	Recipient mice†	Percent of specific ⁵¹ Cr release					
		HK-infected targets				Normal	
		L cell (H-2 ^k)	MC57G (H-2 ^b)	NA (H-2 ^a)	P815 (H-2 ^d)	L cell (H-2 ^k)	MC57G (H-2 ^b)
		%					
CBA _{-C57} TDL	CBA × C57F ₁	75	4	63	4	4	0
CBA × C57F ₁ spleen	CBA × C57F ₁	81	57	73	6	0	0
	CBA	83	4	76	6	0	0
	C57	2	74	19	3	2	0
Controls							
Immune	B10.D2 (H-2 ^d)	10	3	67	68	10	5
Immune	C57BL/6 (H-2 ^b)	11	48	9	9	7	3
Immune	B10.A (H-2 ^a)	55	3	64	15	3	1
Immune	CBA × C57F ₁	60	41	72	28	3	0
Normal	CBA × C57F ₁	8	8	21	5	3	5

* The donor lymphocytes were from mice that had been given HK influenza virus 3 wk previously, and the immune controls had been exposed to PR8 influenza virus at least a month before challenge. The CBA × C57F₁ filter mice were irradiated (950 rads) and given 2.0 × 10⁸ CBA/J spleen and lymph node cells 24 h later, the majority being injected i.v. TDL populations were then drained over the next 24-42 h (CBA_{-C57}). The effectiveness of the negative selection procedure is established by the failure to lyse normal MC57G (H-2^b) fibroblasts.

† The recipients and immune controls were all injected i.v. with HK influenza virus on the day of cell transfer. Spleens were assayed 5 days later at a ratio of 50:1.

TABLE IV
Cross-Priming Is Not Seen for Influenza-Immune TDL

Transferred population*	Cells from CBA × C57F ₁ recipients‡		Percent of specific ⁵¹ Cr release				
	Type	Ratio	HK-infected			Normal	
			L cell	MC57G	P815	L cell	MC57G
			%				
CBA _{-C57} TDL (2.0 × 10 ⁷)	TDL	20:1	17	0	—	—	—
	Spleen	20:1	70	0	1	1	0
		40:1	83	0	1	2	2
Immune controls	CBA × C57F ₁	40:1	73	46	6	3	3
	B10.D2	40:1	4	1	33	1	1

* All mice had been dosed with HK influenza virus at least 3 wk previously.

‡ The irradiated recipients were injected with HK influenza virus, and TDL were drained from 4-5 days later.

to cross-reactive influenza virus components tends to suppress a primary response to a heterologous viral H antigen. Thus, it is also necessary to consider the case for immunologically naive T-cell populations that have never been exposed to virus. The influenza model proved insufficiently sensitive for this purpose (unpublished data) so these experiments were done using the poxvirus system.

TABLE V
Stimulation of Negatively Selected TDL and Normal Lymphocytes with Vaccinia Virus

Transferred cells*	Recipient strain	Percent of specific ⁵¹ Cr release from vaccinia targets							
		L cells K ^k .D ^k		MC57G K ^b .D ^b		P815 K ^b .D ^b		B10.A(6R) K ^b .D ^b	
		d5‡	d6‡	d5	d6	d5	d6	d5	d6
		%							
CBA _(-A/J × C57)	A/J × C57F ₁	27	75	0	6	0	8	2	—
A/J × C57F ₁	A/J × C57F ₁	87	82	60	60	51	23	58	51
A/J × C57F ₁	A/J§	70	—	0	—	12	—	41	—
A/J × C57F ₁	C57	4	6	34	60	5	3	41	39
Controls									
	CBA/J	71	76	6	10	10	11	9	16
	C57BL/6J	17	24	62	73	21	20	50	54
	A/J	81	70	0	3	17	16	35	34
	A/J × C57F ₁	83	79	49	51	25	25	62	53
	BALB/cJ	9	—	1	—	21	—	45	—

* CBA/J (H-2K^k.D^k) spleen and lymph node cells were filtered through irradiated A/J × C57F₁ (H-2K^k.D^k × K^b - D^b) mice and then stimulated in a further set of A/J × C57F₁ recipients (1.5 × 10⁷ TDL per mouse). Other mice were injected with 6.0 × 10⁷ spleen and lymph node cells.

‡ Mice were dosed with virus at 3 h after cell transfer and spleens were assayed 5 (30:1) or 6 (25:1) days later, in two separate experiments.

§ The day 6 A/J recipients all died.

Primary Response to Vaccinia Virus. Normal CBA/J (H-2K^k.D^k) lymphocytes were filtered through irradiated A/J × C57BL/6J F₁ (H-2K^k.D^k × H-2K^b.D^b) mice and then stimulated with vaccinia virus in irradiated A/J × C57BL/6J F₁ recipients. These T-cell populations were thus negatively selected to H-2D^d, H-2K^b, and H-2D^b. Two separate experiments were done, and assayed at 5 to 6 days after cell transfer. No evidence was found for any response to virus other than in the context of H-2K^k, the H-2 component shared by donor and recipient (line 1, Table V). Furthermore, stimulation was obviously mediated via the virus-infected recipient, as the cytotoxic activity of A/J × C57F₁ lymphocytes depended on the H-2 type expressed in the sensitizing environment (lines 3-5, Table V). These findings were confirmed in a further experiment, in which TDL and spleen cells were assayed from CBA/J × C57BL/6J recipients (H-2^{k/b}) that had been injected with CBA/J (H-2^k) lymphocytes depleted of alloreactivity for H-2^b (Table VI).

Discussion

Virus-immune cytotoxic T cells cannot be shown to interact with virus-infected target cells expressing H-2 antigens other than those encountered during physiological differentiation. Findings from the influenza and vaccinia systems, where acute tolerance to alloantigen is induced by a filtration procedure (4, 5), thus support evidence generated using chimeras in which long-term tolerance exists (1-3). A similar absence of cross-priming for recognition of the male Y antigen on H-2-different cells has been reported by von Boehmer et al. (17), who used a somewhat less complete negative selection procedure (4).

TABLE VI
Activity of Vaccinia-Specific TDL and Spleen Cells from Recipient Mice

Transferred cells*	Recipient strains	Popula- tion as- sayed‡	Percent of specific ⁵¹ Cr release					
			Vaccinia				Normal	
			L cell 8:1	(H-2 ^k) 25:1	MC57G 8:1	(H-2 ^b) 25:1	L cell 25:1	MC57G 25:1
			%					
CBA _{-c57}	CBA × C57F ₁	Spleen	—	32	—	0	—	—
	CBA × C57F ₁	TDL	0	—	1	—	—	—
CBA × C57F ₁	CBA × C57F ₁	Spleen	60	78	30	55	14	0
	CBA × C57F ₁	TDL	3	—	1	—	—	—
CBA × C57F ₁	CBA	Spleen	71	82	4	3	12	1
CBA × C57F ₁	C57	Spleen	3	7	52	78	6	3

* Mice were given 2.0×10^7 TDL that had been filtered through irradiated CBA × C57F₁ mice (CBA_{-c57}), or a total of 6.0×10^7 spleen and lymph node cells.

‡ TDL were drained from recipient mice at 5–6 days after cell transfer and stimulation with vaccinia virus.

The only other published study dealing with stimulation of immunologically naive T cells in an allogeneic environment gave a rather different result (5), which is at variance with comparable chimera experiments (18). Wilson et al. (5) induced CBA/J (H-2^k) TDL, which had previously been negatively selected to H-2^b, to mediate specific lysis of trinitrophenyl (TNP)-modified H-2^b target cells. A possible explanation is that direct substitution (19) of the H-2^b molecule with TNP leads to expression of a true "altered-self" component (i.e., H-2^b-TNP mimics alloantigen H-2^x) which is recognized via the alloreactive repertoire. Reasonable evidence exists that TNP-self may cross-react with alloantigen, so far as T-cell specificity is concerned (20).

Two general conclusions may be drawn from the present experiments. The first is that cross-priming for recognition of virus on an H-2-different cell does not occur (11, 12). The T-cell response is presumably "locked-in" to a particular spectrum of self (H-2) and nonself (virus). The phenomena described as cross-priming may reflect either antigen processing by host macrophages or T-T help (11). The second is that T-cell precursors capable of recognizing virus in the context of H-2 antigens not encountered during ontogeny cannot be demonstrated. This may reflect either that they do not exist, or are present at too low a frequency to be seen after transfer and stimulation of relatively small numbers of T cells. A third possibility is that T cells that might recognize virus presented on H-2-different cells also possess considerable alloreactive potential, and are thus removed by the biological filtration procedure.

These results can be interpreted as favoring either "one receptor" or "two receptor" models for T-cell recognition (1, 2). The essential constraint would seem to be that the "self-reactive" component is highly conserved, and is probably specific for the H-2 "private" determinants (21). Any mutational model (1, 22, 23) for generating the T-cell repertoire must, therefore, consider that selection operates to allow the emergence of clones in which part of the receptor remains constant while another part varies. Other evidence which indicates

that T cells reactive to influenza virus H antigens possess the same discriminatory capacity as IgG antibody (15, 24) would seem to favor the idea that there are two distinct orders of receptor specificity for self and non-self. Whether these are separate entities or associated with a single recognition unit will need to be approached using techniques for structural analysis.

Summary

Mouse lymphocyte populations of one parental H-2 type (A) were specifically depleted of alloreactive potential by filtration through irradiated A × B F₁ recipients, and thoracic duct cells were then stimulated with virus in an A × B F₁ environment. Experiments using T cells that had previously been exposed to influenza virus in the context of A established that cross-priming for recognition of viral components expressed on H-2-different (B) target cells does not occur. Furthermore, immunologically naive T cells stimulated with vaccinia virus, subsequent to negative selection for reactivity to B, could not be shown to interact with virus-infected cells of type B. Either there is no significant T-cell repertoire for recognition of virus associated with an H-2 determinant not encountered during ontogeny, or such T cells are also alloreactive and are removed during filtration.

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