H-2 EFFECTS ON CELL-CELL INTERACTIONS IN THE RESPONSE TO SINGLE NON-H-2 ALLOANTIGENS

I. Donor *H-2D* Region Control of H-7.1-Immunogenicity and Lack of Restriction In Vivo*

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Immune response (*Ir*)[1] genes determine the ability of hosts to respond immunologically to many antigens, including several cell surface antigens (1–3). The *Ir* control of the response to several non-H-2 histocompatibility antigens, including H-Y, H-4, and H-7 has been documented (4–7). Recent evidence suggests a further role of genes in the *H-2* complex in regulating the immunogenicity, or rejectability, of H-Y-incompatible skin grafts (8, 9), presumably through regulation of H-Y antigen expression.

A considerable number of investigations have centered on the study of restriction of cell-mediated lympholysis with its apparent requirement for H-2 compatibility of effectors and targets for efficient lympholysis. This phenomenon has been described in a variety of responses, including those to chemically-modified syngeneic cells (10, 11), virus-infected syngeneic cells (12, 13, reviewed in 14) and, most important to our studies, non-H-2-histocompatibility (H) antigens (15–17). It has been suggested that *H-2*-linked genes may alter the recognition (presentation) of non-H-2 H antigens by cytotoxic T cells (15). The subsequent demonstration of in vivo cross-priming of F_1 hybrid individuals with non-H-2-incompatible cells possessing either parental *H-2* haplotype (18) suggested that such alteration probably was not the basis for restriction in the response to multiple non-H-2 H antigens. However, the complexity of the array of target non-H-2 H antigens employed in these studies (18) limits their usefulness for elucidation of the mechanism of *H-2* restriction.

We have performed a series of experiments employing skin grafting designed to examine the relevance of the in vitro restriction phenomenon to in vivo skin allograft rejection. To simplify the complexity of target non-H-2 H antigens we chose to study the response to a single alloantigen H-7.1 which has been shown to be under *H-2*-linked *Ir* gene control (7, 19). In the experiments reported in this communication we have (*a*) examined the ability of H-7.1-incompatible

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[1] *Abbreviations used in this paper:* H, histocompatibility; Ir, immune response; MST, median survival time.

TABLE I
Relevant Genotypes of Employed Mouse Strains

Strain	*H-2* Haplotype	*H-2* haplotype origin of										*H-7*
		K	I					*S*	*G*	*D*	*Tla*	
			A	*B*	*J*	*E*	*C*					
C57BL/10	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*a*
B10.C-*H-7*^{b}	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*
B10.A	*a*	*k*	*k*	*k*	*k*	*k*	*d*	*d*	*d*	*d*	*a*	*a*
B10-*H-2*^{a}*H-7*^{b}	*a*	*k*	*k*	*k*	*k*	*k*	*d*	*d*	*d*	*d*	*a*	*b*
B10.D2/o	*d*	*d*	*d*	*d*	*d*	*d*	*d*	*d*	*d*	*d*	*c*	*a*
B10-*H-2*^{d}*H-7*^{b}	*d*	*d*	*d*	*d*	*d*	*d*	*d*	*d*	*d*	*d*	*c*	*b*
B10.A(1R)	*h1*	*k*	*k*	*k*	*k*	*k*	*d*	*d*	*	*b*	*b*	*a*
B10.A(2R)	*h2*	*k*	*k*	*k*	*k*	*k*	*d*	*d*		*b*	*b*	*a*
B10.A(4R)	*h4*	*k*	*k*	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*a*
B10.A(5R)	*i5*	*b*	*b*	*b*	*k*	*k*	*d*	*d*	*d*	*d*	*a*	*a*
B10.A(18R)	*il8*	*b*	*b*	*b*	*b*	*b*	*b*	*b*		*d*	*a*	*a*
B6-*Tla*^{a}	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*a*	*a*

* *H-2G* type presently unknown; therefore, crossover position has not been definitively mapped to either side of *H-2G*.

skin grafts possessing a single parental *H-2* haplotype to cross-prime *H-2* heterozygous recipients for an accelerated second set rejection of H-7.1-incompatible grafts with the opposing parental *H-2* haplotype and (*b*) examined the effect of the donor *H-2*-haplotype on the ability of H-7.1-incompatible skin grafts to efficiently prime recipients. Extensive cross-priming with no evidence of restriction was observed. Further, the survival time of primary grafts and their priming efficiency depended upon the *H-2* haplotype origin of donor genes in the *H-2D* region.

Materials and Methods

Mice. The mice employed in this study and their respective genotypes are presented in Table I. Alleles at histocompatibility loci are indicated by superscript, lower case letters as dictated by genetic convention (20). The antigenic specificities determined by these alleles are designated by corresponding arabic numerals following the locus designation (21); for example, the *H-7*^{a} and *H-7*^{b} alleles determine the H-7.1 and H-7.2 antigens, respectively. C57BL/10ScSn, B10.A/Sn, B10.D2/o Sn, and B10.C(47N)/Sn (referred to as B10.C-*H-7*^{b}) mice were derived from breeding stock generously provided by Dr. George D. Snell, The Jackson Laboratory, Bar Harbor, Maine, and were maintained in a quarantined production facility. The B10.A(1R), B10.A(4R), and B10.A(5R) strains were obtained from Dr. Jack Stimpfling, McLaughlin Research Institute, Great Falls, Mont. B10.A(18R) mice were kindly supplied by Edward Clark, Department of Microbiology and Immunology, University of California, Los Angeles, Calif. B6-*Tla*^{a} mice were bred from breeders supplied by Dr. Ron Acton, Department of Microbiology, University of Alabama. The B10-*H-2*^{a}*H-7*^{b} and B10-*H-2*^{d}*H-7*^{b} strains were selected as described previously (7). These two strains differ from B10.A and B10.D2/o, respectively, at the *H-7* locus. These congenic strain combinations define the *H-7*^{a}:*H-7*^{b} allelic combination on the *H-2*^{a} and *H-2*^{d} backgrounds of B10.A and B10.D2/o as does the B10.C-*H-7*^{b}:B10 combination on the background of B10 (22).

Grafting Technique. Orthotopic tail skin was transplanted to 6- to 12-wk-old recipients, according to the technique described previously (23). Donors and recipients were sex-matched. Each recipient received one or two allografts from the same donor and one autograft. The grafts were scored twice a week for the first 10 wk. Grafts were scored for healthy epithelial scale pattern, pigment, and hair, and were scored rejected when no viable signs were observed. Graft survival times within a sample population of recipients are not distributed normally, but are

strongly skewed to the right (24). Therefore, median survival times (MST) and 95% confidence limits were determined for each group of graft recipients. Calculations were made on an IBM 1130 computer (IBM Corp., White Plains, N. Y.) through the use of a computer program employing probit transformation (25). The program was generously provided by Dr. Randy Adams, The Jackson Laboratory. Survival time distributions of different recipient groups were compared by using the nonparametric Mann-Whitney U Test (26). A value of $\alpha \leq 0.01$ was chosen to indicate a significant difference between two distributions.

H-2 heterozygous recipients of primary H-7.1-incompatible grafts possessing a single parental *H-2* haplotype were grafted 14 days after initial graft rejection with secondary H-7.1-incompatible skin grafts from donors with either of the two parental *H-2* haplotypes. Significant accelerated rejection of the secondary graft possessing the parental *H-2* haplotype not shared with the original graft donor was considered evidence of cross-priming.

Results

H-2 Determination of Relative Rejectability of H-7.1-Incompatible Skin Grafts. Previously performed dominance testing has revealed that the fast response allele at the *IrH-7.1* locus and associated with $H\text{-}2^b$ is dominant over the slow response alleles associated with $H\text{-}2^a$ and $H\text{-}2^d$ (19). These studies also suggested a difference in the speed with which H-7.1-incompatible skin grafts from donors with different *H-2* haplotypes were rejected by *H-2* heterozygous recipients. To test this possibility, (B10.C($H\text{-}2^b$)-$H\text{-}7^b$ × B10-$H\text{-}2^dH\text{-}7^b$)F_1 female recipients were grafted with skin from either B10, B10.D2, or (B10 × B10.D2)F_1 donors. The results of this experiment are presented in Table II. B10 and (B10 × B10.D2)F_1 grafts were rejected significantly more rapidly than B10.D2 grafts. Similarly, B10, B10.A, and (B10.A × B10)F_1 skin was transplanted to (B10.C($H\text{-}2^b$)-$H\text{-}7^b$ × B10-$H\text{-}2^aH\text{-}7^b$)F_1 male recipients. These results are presented in Table III. B10 and (B10.A × B10)F_1 grafts were rejected more rapidly than B10.A grafts. The results included in Tables II and III clearly demonstrate that (*a*) the *H-2* genotype of donors of H-7.1-incompatible grafts determines their relative rejectability and (*b*) the allele determining greater rejectability is inherited as a dominant trait.

In Vivo Cross-Priming by H-7.1-Incompatible Skin Grafts Possessing Distinct H-2 Haplotypes. We tested the ability of H-7.1-incompatible skin grafts homozygous for a single parental *H-2* haplotype to prime *H-2* heterozygous F_1 recipients for accelerated rejection of secondary, H-7.1-imcompatible skin grafts homozygous for the opposite parental *H-2* haplotype. (B10.C($H\text{-}2^b$)-$H\text{-}7^b$) × B10-$H\text{-}2^dH\text{-}7^b$)F_1 recipients of primary B10, B10.D2, or (B10 × B10.D2)F_1 grafts received secondary B10 and B10.D2 skin 14 days after their rejection of primary grafts. Hosts which did not reject primary grafts within 10 wk received secondary grafts 12 wk after primary grafting. The results of these experiments are included in Table II. B10 primary grafts efficiently primed for the accelerated rejection of both B10 and B10.D2 secondary skin grafts. Further, primary B10 grafts were more effective in priming for accelerated rejection of B10.D2 secondary grafts than were B10.D2 primary grafts. Not unexpectedly, secondary B10 grafts were rejected more rapidly than secondary B10.D2 grafts by recipients of primary B10.D2 grafts. A similar experiment was conducted with (B10.C($H\text{-}2^b$)-$H\text{-}7^b$ × B10-$H\text{-}2^aH\text{-}7^b$)F_1 recipients of primary B10, B10.A, or (B10.A × B10)F_1 grafts. The results of these experiments are shown in Table III. Both primary B10 and B10.A grafts effectively primed for the rejection of secondary B10 grafts. Both B10 and B10.A skin cross-primed; however, second-

TABLE II

The Survival Times of B10, B10.D2/o, and (B10 × B10.D2/o)F_1 Skin Grafts Transplanted to (B10.C-H-7^b × B10-H-2^dH-7^b)F_1 Female Recipients

Primary graft donor	Secondary graft donor	Recipient	Number of recipients	MST*		95% confidence limits*	
				Primary	Secondary	Primary	Secondary
B10	–	(B10.C-*H-7*^{b} × B10-*H-2*^{d}*H-7*^{b})F_1	13	23.94	–	21.70–26.25	–
B10	B10	(B10.C-*H-7*^{b} × B10-*H-2*^{d}*H-7*^{b})F_1‡	13	–	9.52	–	6.23–12.39
B10	B10.D2/o	(B10.C-*H-7*^{b} × B10-*H-2*^{d}*H-7*^{b})F_1‡	13	–	9.73	–	8.68–10.78
B10.D2/o	–	(B10.C-*H-7*^{b} × B10-*H-2*^{d}*H-7*^{b})F_1	10	61.95	–	54.95–68.95	–
B10.D2/o	B10	(B10.C-*H-7*^{b} × B10-*H-2*^{d}*H-7*^{b})F_1‡	10	–	17.50	–	11.34–23.73
B10.D2/o	B10.D2/o	(B10.C-*H-7*^{d} × B10-*H-2*^{d}*H-7*^{b})F_1‡	10	–	28.77	–	23.24–34.37
(B10 × B10.D2/o)F_1	–	(B10.C-*H-7*^{b} × B10-*H-2*^{d}*H-7*^{b})F_1	6	34.53	–	26.95–43.05	–
(B10 × B10.D2/o)F_1	B10	(B10.C-*H-7*^{b} × B10-*H-2*^{d}*H-7*^{b})F_1‡	6	–	10.50	–	10.50–10.50
(B10 × B10.D2/o)F_1	B10.D2/o	(B10.C-*H-7*^{b} × B10-*H-2*^{d}*H-7*^{b})F_1‡	6	–	12.53	–	9.24–15.82

* Expressed in days.

‡ B10 and B10.D2/o skin grafted to same recipient 14 days after primary graft rejection.

TABLE III

The Survival Times of B10, B10.A, and (B10.A × B10)F_1 Skin Grafts Transplanted to (B10.C-H-7^b × B10-H-2^aH-7^b)F_1 Male Recipients

Primary graft donor	Secondary graft donor	Recipient	Number of recipients	MST*		95% confidence limits*	
				Primary	Secondary	Primary	Secondary
B10	–	(B10.C-*H-7*^{b} × B10-*H-2*^{a}*H-7*^{b})F_1	6	25.97	–	22.05–29.82	–
B10	B10	(B10.C-*H-7*^{b} × B10-*H-2*^{a}*H-7*^{b})F_1‡	6	–	10.08	–	8.61–11.55
B10	B10.A	(B10.C-*H-7*^{b} × B10.*H-2*^{a}*H-7*^{b})F_1‡	6	–	10.99	–	9.59–12.39
B10.A	–	(B10.C-*H-7*^{b} × B10-*H-2*^{a}*H-7*^{b})F_1	8	56.28	–	50.12–62.37	–
B10.A	B10	(B10.C-*H-7*^{b} × B10-*H-2*^{a}*H-7*^{b})F_1‡	8	–	10.99	–	9.59–12.46
B10.A	B10.A	(B10.C-*H-7*^{b} × B10-*H-2*^{a}*H-7*^{b})F_1‡	8	–	21.84	–	17.71–26.04
(B10 × B10.A)F_1	–	(B10.C-*H-7*^{b} × B10-*H-2*^{a}*H-7*^{b})F_1	9	24.78	–	21.77–27.79	–
(B10 × B10.A)F_1	B10	(B10.C-*H-7*^{b} × B10-*H-2*^{a}*H-7*^{b})F_1‡	9	–	9.73	–	8.33–11.06
(B10 × B10.A)F_1	B10.A	(B10.C-*H-7*^{b} × B10-*H-2*^{a}*H-7*^{b})F_1‡	9	–	10.78	–	9.45–12.11

* Expressed in days.

‡ B10 and B10.A skin grafted to same recipients 14 days after primary graft rejection.

ary B10 grafts were rejected more rapidly than secondary B10.A grafts by recipients of primary B10.A grafts. Secondary B10 and B10.A grafts were rejected with equal speed by recipients primed with B10 or (B10.A × B10)F_1 grafts.

TABLE IV

Intra-H-2 Mapping of Gene Determining Relative Rejectability of H-7.1-Incompatible Skin on (B10.C-H-7^b × B10-H-2^{a}H-7^b)F$_1$ Recipients

Primary graft donor	Tertiary graft donor	Number of recipients	MST*	95% confidence limits*
B10	B10	4	8.75‡	2.87–14.63
	B10.A	4	11.34§	0.98–21.63
	B10.A(1R)	4	8.75‡	2.87–14.63
	B10.A(4R)	4	8.75‡	2.87–14.63
	B10.A(5R)	4	11.34§	0.98–21.63
(B10 × B10.A)F$_1$	B10	9	8.75‡	3.43–14.00
	B10.A	9	16.24	13.37–19.11
	B10.A(1R)	9	8.75‡	3.43–14.00
	B10.A(4R)	9	8.75‡	3.43–14.00
	B10.A(5R)	9	20.37	17.29–23.52
B10.A	B10	7	8.75‡	3.29–14.21
	B10.A	7	33.25	28.42–38.08
	B10.A(1R)	7	8.75‡	3.29–14.21
	B10.A(4R)	7	8.75‡	3.29–14.21
	B10.A(5R)	6	21.56	14.14–28.98

* Expressed in days.

‡ All recipients rejected grafts at 10 days.

§ Three of four recipients rejected grafts at 10 days.

These results, therefore, show that in contrast to the expectations from in vitro observations of *H-2* restriction, cross-priming for generation of cytotoxic effectors occurs very efficiently in vivo. Further, in direct contrast to the predictions of restriction, grafts bearing the *H-2^b* haplotype more efficiently primed for accelerated rejection of secondary grafts possessing the *H-2^a* or *H-2^d* haplotypes than did primary grafts from *H-2^a* or *H-2^d* donors.

Mapping the Gene Governing Relative Rejectability. [B10.C(*H-2^b*)-*H-7^b* × B10-*H-2^{a}H-7^b*]F$_1$ recipients of primary and secondary H-7.1-incompatible grafts (Table III) received tertiary H-7.1-incompatible grafts donated by mice carrying *H-2* haplotypes derived from *H-2^a*/*H-2^b* recombinations. Tertiary skin grafts were donated by B10, B10.A, B10.A(1R), B10.A(4R), and B10.A(5R) donors 20–27 wk after secondary grafting. The survival times of tertiary grafts are presented in Table IV. B10 primary grafts were highly effective in accelerating the rejection of all tertiary grafts which were rejected with equal MST's. (B10.A × B10)F$_1$ primary grafts more effectively accelerated the rejection of B10, B10.A(1R), and B10.A(4R) tertiary grafts than rejection of B10.A (α = 0.01) and B10.A(5R) ($\alpha < 0.01$) tertiary grafts. Similarly, B10.A primary grafts more effectively accelerated the rejection of B10, B10.A(1R), and B10.A(4R) tertiary grafts than B10.A (α = 0.001) and B10.A(5R) (α = 0.02) secondary grafts. These results demonstrate that, as in the response to secondary grafts, B10 primary grafts prime for the accelerated rejection of B10.A tertiary grafts more effectively than B10.A primary grafts. Further, the rejectability of tertiary H-7.1-incompatible grafts is apparently determined by genes telomeric to the *H-2^{hl}* recombination site. A more definitive mapping was achieved by grafting four tertiary graft recipients originally primed with (B10.A × B10)F$_1$ skin with skin from B10, B10.A, B10.A(1R), B10.A(2R), B10.A(5R), B10.A(18R),

TABLE V
Mapping of Gene Determining Relative Rejectability of H-7.1-Incompatible Grafts to the H-2D Region

Primary graft donor	Quaternary graft donor	Number of recipients	MST*	95% confidence limits*
(B10 × B10.A)F_1	B10	4	8.75‡	2.87–14.63
	B10.A	4	15.75§	9.87–21.63
	B10.A(1R)	4	8.75‡	2.87–14.63
	B10.A(2R)	4	8.75‡	2.87–14.63
	B10.A(5R)	4	15.75§	9.87–21.63
	B10.A(18R)	4	12.86	11.84–16.24
	B6-*Tla*^{a}	4	8.75‡	2.87–14.63

* Expressed in days.
‡ All recipients rejected grafts at 10 days.
§ All four recipients rejected grafts at 17 days.

and B6-*Tla*^{a} donors. The results of these transplants are shown in Table V. B10, B10.A(1R), B10.A(2R), and B6-*Tla*^{a} quaternary grafts were rejected rapidly with equal MST's of 8.75 days. However, B10.A, B10.A(5R), and B10.A(18R) quaternary grafts were rejected with significantly lower MST's. Statistical comparison of distribution of grafts donated by all *H-2D*^{b} and all *H-2D*^{d} donors demonstrated that at the $\alpha = 0.0001$ level, H-7.1-incompatible grafts from *H-2D*^{b} were rejected more rapidly than similar grafts from *H-2D*^{d} donors. There was no difference ($\alpha = 0.33$) between survival times of grafts from *H-2K*^{b} and *H-2K*^{k} donors. These observations are consistent with mapping of the gene determining relative rejectability to the *H-2D* region as it is defined by the *H-2*^{h1}, *H-2*^{h2}, and *H-2*^{il8}, recombination sites on the centromeric side and the site of recombination which resulted in the separation of the *H-2*^{a} haplotype and *Tla*^{a} in the production of B6-*Tla*^{a} on the telomeric side.

Discussion

H-2-linked *Ir* genes regulate recipient responsiveness to foreign non-H-2 histocompatibility antigens, including H-Y (4, 5), H-4 (6), and H-7 (7) antigens. Of perhaps equal importance in the case of H-Y is the function of *H-2*-linked genes in regulating the relative rejectability of H-Y-incompatible skin grafts (8, 9). In this communication we have reported similar observations in demonstrating that the relative rejectability of H-7.1-incompatible skin grafts depends upon the donor *H-2* genotype, specifically the *H-2D* genotype, of the donor. We have observed more recently that the rejectability of both H-4.2- and H-3.1-incompatible skin grafts is controlled by *H-2*-linked genes (P. J. Wettstein, preliminary observations). In both cases, as in the case of H-7.1, relatively high rejectability associates with the *H-2*^{b} haplotype which cosegregates with fast responsiveness to the respective antigen in allograft recipients. Although the data presented by Kralova and Demant (9) demonstrate that the rejectability of H-Y-incompatible skin grafts is controlled by an *H-2*-linked gene, the variety of *H-2* genotypes of donors and recipients do not allow a definitive intra-*H-2* mapping of the operative regulatory gene. We are presently conducting experiments designed to determine the number, specificity, and intra-*H-2* map positions of genes regulating rejectability of non-H-2-incompatible skin grafts.

It is particularly important to understand the basis for the effect of *H-2D* genes on H-7.1 antigenicity, as inferred from rejectability of H-7.1-incompatible skin grafts. Two plausible explanations come to mind. First, is the possibility that a gene in the *H-2D* region governs the surface density of H-7 molecules. That is, $H\text{-}2D^b$ epidermal cells would carry a high density of H-7 molecules and function as highly efficient stimulators of H-7-specific priming and cytotoxic effector generation in vivo and in vitro. The second possibility is that molecules determined by genes in the *H-2D* region serve as interaction structures, controlling the interactions of effectors with target cells as initial stimulators and/or secondarily as cytotoxic cell targets. Therefore, donor and recipient cells carrying complementary structures coded for by genes associated with $H\text{-}2D^b$ would be expected to interact more efficiently than donor and recipient cells sharing $H\text{-}2D^d$. Differentiation between these two alternatives is experimentally possible. If differences in relative rejectability were due to quantitative differences in antigen density, then one would predict that the rejectability of donor cells would be dependent only upon donor *H-2* genotype regardless of the *H-2* genotype of the responding cells in vivo or in vitro. However, if rejectability differences were the result of varying efficiencies of responder:donor cell interactions, then the observed rejectability of donor cells would be dependent upon *H-2* genotypes of both donor and recipient. One might envisage that such an interaction between responder and H-7-incompatible target cells is analogous to the preferential interaction between antigen-pulsed macrophages and specific subpopulations of T lymphocytes in the guinea pig (27). Experiments are presently in progress to distinguish between these two possibilities with the use of a variety of donor:host combinations.

The in vivo cross-priming reported in this communication has strong implications for the study of restriction phenomena, particularly in the restricted cytolytic response to non-H-2 histocompatibility antigens (15, 17). Although cross-priming across multiple non-H-2 H barriers with cell injections has been observed in vivo (18), restriction dogma dictates that effectors subsequently generated from primed lymphocyte populations in vitro are *H-2* restricted in their cytotoxic activity. The results reported here demonstrate that H-7.1-incompatible skin grafts bearing a single parental *H-2* haplotype cross-prime *H-2* heterozygous recipients for accelerated rejection of secondary H-7.1-incompatible grafts bearing the opposite parental *H-2* haplotype. Unlike the in vitro mixed lymphocyte culture of non-H-2-incompatible lymphocytes which results in generation of *H-2*-restricted cytotoxic lymphocytes, in vivo priming with non-H-2-incompatible skin grafts results in generation of cytotoxic lymphocytes, some of which appear to be unrestricted. The efficiency of in vivo cross-priming depends strongly upon the *H-2* genotypes of the primary and secondary graft donor; matching of the primary and secondary graft *H-2* genotypes is absolutely nonessential for accelerated rejection of secondary grafts.

H-2 regulation of the ability of lymphocytes of cross-prime *H-2* heterozygous recipients in vivo has not been reported although extensive cross-priming of precursors of cytotoxic effectors has been documented (18). This cross-priming resulted from immunization of (BALB/c × BALB.B)F_1 mice with challenges of B10.D2 and B10 cells. Such responses were probably specific for more than 30 non-H-2 antigens as inferred from the estimation that BALB/c and C57BL/6

(closely related to B10) differ by more than 30 non-*H-2 H* loci (28). If different *H-2* haplotypes determine relatively high antigenicity of different subsets of non-H-2 H antigens, B10 and B10.D2 would be expected to prime (BALB/c × BALB.B)F_1 recipients preferentially for different, but only partially overlapping, subsets of non-H-2 H antigens. Limited cross-priming would result, the extent of which would be dependent upon the degree of overlap between the subsets of H antigens. Interpretation of data obtained in studies of *H-2* restriction of non-H-2 H antigen-specific cytolysis should include consideration of possible differential effects of *H-2* haplotypes on non-H-2 H antigenicity which may mimic actual *H-2* restriction. Due to the potential importance of an understanding of *H-2*-controlled non-H-2 H antigenicity, we have undertaken an investigation into the differential effects of the $H\text{-}2^b$ and $H\text{-}2^d$ haplotypes on the antigenicity of a wide spectrum of non-H-2 H antigens distinguishing B6 and BALB/c mice.

In an accompanying communication we have described further investigations into the control of H-7.1 immunogenicity employing secondary mixed lymphocyte culture and cell-mediated lympholysis.

Summary

Genes in the *H-2* complex regulate the relative immunogenicity of the H-7.1 histocompatibility alloantigen, as measured by survival times of H-7.1-incompatible skin grafts in vivo. The gene controlling relative rejectability of H-7.1-incompatible grafts has been mapped to the *H-2D* region. H-7.1-incompatible skin grafts donated by $H\text{-}2D^b$ donors were rejected significantly more rapidly by $H\text{-}2^a/H\text{-}2^b$ heterozygous recipients than similar H-7.1-incompatible grafts donated by $H\text{-}2D^d$ donors. Further, there was absolutely no evidence of *H-2* restriction in cytotoxic effector activity. In vivo cross-priming, as indicated by accelerated secondary graft rejection, was extensive. The efficiency of cross-priming was dependent upon the primary and secondary graft donor *H-2* haplotypes.

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