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Suppression of *H-2*^{b}-associated resistance to Friend erythroleukemia virus by a class I gene from the *H-2*^{d} major histocompatibility complex haplotype

(retroviral pathogenesis)

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ABSTRACT **Mice homozygous for the *H-2*^{d} haplotype at the major histocompatibility complex are markedly more susceptible to erythroleukemia induction by the Friend isolate of murine leukemia retrovirus (FV) than are congenic mice homozygous for the *H-2*^{b} haplotype. The resistance conferred by the *H-2*^{b} haplotype is recessive in this cross, since heterozygous F_1 mice are as susceptible as parental strain *H-2*^{d} homozygotes. However, *H-2*^{b}-associated resistance is not an intrinsically recessive trait, since *H-2*^{b}/*H-2*^{dm1} heterozygotes resemble *H-2*^{b} homozygotes in their relative resistance to FV; the mutant *H-2*^{dm1} haplotype lacks the entire *D* region of the parental haplotype except for a single class I gene formed by the fusion of its terminal *D*-region genes to produce a class I gene differing from both parental genes, and thus this finding indicates that one or more *D*-region genes of the *H-2*^{d} haplotype can actively suppress *H-2*^{b}-associated resistance. Unlike *H-2*^{dm1}, the mutant *H-2*^{dm2} haplotype, which retains only the class I *D*^{d} gene in the *D* region of the *H-2*^{d} haplotype, strongly suppresses resistance in *H-2*^{b}/*H-2*^{dm2} heterozygotes, and the presence of *D*^{d} as a transgene significantly reduces the resistance of *H-2*^{b} homozygotes. Since *H-2*^{b}-associated resistance to FV appears to be due mainly to the capacity of L^b (also called D^b), the only class I molecule encoded in the *D* region of the *H-2*^{b} haplotype, to present viral epitopes for recognition by FV-specific cytotoxic T lymphocytes, suppression of resistance to FV by the D^d molecule implies that the presence of one class I molecule of the major histocompatibility complex can interfere with either the presentation of viral epitopes by another class I molecule or the generation of T cells that recognize viral epitopes so presented.**

The murine major histocompatibility complex, *H-2*, is one of several known genetic factors that can influence the resistance or susceptibility to various retrovirus-induced diseases in mice (1, 2). In most studies, the *H-2*^{b} haplotype has proved to confer relatively strong resistance to the virus-induced disease. In the first such study, the capacity of the *H-2*^{b} haplotype to protect against lymphomas induced by Gross murine leukemia virus was a genetically dominant trait, since *H-2*^{b}/*H-2*^{k} heterozygotes in a segregating backcross population showed a much lower lymphoma incidence than that of their *H-2*^{k}-homozygous littermates (3). However, in the second such study, resistance to Friend erythroleukemia virus (FV) appeared to be recessively associated with *H-2*^{b}, since about 1/20th as much virus was required to induce comparable levels of disease in *H-2*^{b}/*H-2*^{d} heterozygotes in a backcross population as in their *H-2*^{b}-homozygous littermates (4).

It has long been clear that *H-2* exerts this protective effect mainly by its capacity to influence the hosts' immune responses to viral antigens; mice producing stronger, more effective immune responses are relatively resistant to viral pathogenesis. In most cases of *H-2*-determined differences in immune responsiveness, haplotypes governing higher levels of response have been genetically dominant in heterozygotes over those governing lower levels (5, 6); thus it has been puzzling that *H-2*^{b}-associated resistance to FV is a recessive trait. The present studies were based on the hypothesis that the *H-2*^{d} haplotype includes one or more genes that suppress *H-2*^{b}-associated resistance. The results show that the determinant(s) of the suppressive effect are located in the *H-2D*^{d} region and that the *D*^{d} gene mediates the effect at least in part.

MATERIALS AND METHODS

Mice. BALB/cAn (*H-2*^{d}) and *H-2*-congenic strains BALB.B (*H-2*^{b}), BALB.G (*H-2*^{g}), and BALB.5R (*H-2*^{i5}), as well as C57BL/10Sn (B10, *H-2*^{b}), were from our own colony. B10.D2-H-2^{dm1} (dm1) breeding pairs were a gift from C. S. David (Mayo Clinic, Rochester, MN); these mice carry an *H-2*^{d} haplotype with a mutation in the *D* region. BALB/c-H-2^{dm2} (dm2) breeding pairs were purchased from The Jackson Laboratory; these mice carry an *H-2*^{d} haplotype with a different *D*-region mutation. Breeding pairs of the B6-tD8 (D8) strain, which are C57BL/6 mice (*H-2*^{b}) expressing the *D*^{d} transgene (7), were supplied by the courtesy of G. Jay (American Red Cross, Rockville, MD). These *H-2* haplotypes are represented in Table 1. All experimental mice of these strains and of F_1 crosses among them were bred in our colony.

Virus. Stocks of FV were derived from mixtures of culture fluids from cells producing biologically cloned components of FV. Culture fluids from F_{201}NIH cells [a line of NIH/3T3 into which a molecularly cloned NB-tropic helper component of FV, Friend murine leukemia virus $FMuLV_A$, was introduced (8)] and from SFFV-FRE/FMuLV cells [a line of FRE cells into which the defective pathogenic component of FV, $SFFV_P$, was biologically cloned and which was then superinfected with FMuLV from F_{201}NIH cells (9)] were mixed in a 1:3 ratio; BALB/c mice received 1 ml i.v. of this mixture [≈400 spleen focus-forming units (SFFU)/ml]. The virus was passed *in vivo* twice more from mice infected 12–15 days earlier. Virus stocks used in the present experiments were clarified supernatants from 10% (wt/vol) homogenates of the greatly enlarged spleens of mice of the last passage, stored in 1-ml lots at −70°C for up to 6 months.

Experimental Procedures. Virus stocks were titrated by the spleen focus method (10) in BALB/c mice (usual titer ≈10^4 SFFU/ml) and diluted to produce 10 or 20 SFFU/ml, depending on the experiment. Male or female mice 6–16 weeks of age received 1 ml of the desired virus dilution in the tail

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Abbreviations: FV, Friend erythroleukemia virus; SFFU, spleen focus-forming unit; CTL, cytotoxic T lymphocytes.

Table 1. *H-2* haplotypes used in these studies

Strain	*H-2* type	*H-2* subregion *K*	*A*	*E*	*D*
BALB.B	*b*	*b*	*b*	*b*	*b*
BALB.G	*g*	*d*	*d*	*d*	*b*
BALB.5R	*i5*	*b*	*b*	*k*	*d*
BALB/c	*d*	*d*	*d*	*d*	*d*
B10.D2-dm1	*dm1*	*d*	*d*	*d*	*dm1*
BALB/c-dm2	*dm2*	*d*	*d*	*d*	*dm2*
B6-tD8	*b* + D^{d}*	*b*	*b*	*b*	*b* (+ D^{d})

*Homozygous transgene.

vein. Spleen size was determined by palpation twice weekly from day 7 to 28 and once weekly thereafter for at least 2 months. Mice were deemed splenomegalic if the spleen was ≥0.5 g, but in most cases 0.5-g spleens rapidly progressed in size to at least 1.5–2 g. Results are given in the text and tables as number of mice with splenomegaly/number of mice in the experimental group. Depending on the virus dose and the genetic constitution of the hosts, some mice with the pronounced splenomegaly, which usually peaked around 2–3 weeks after virus administration, showed regression to normal spleen size; after prolonged observation some regressor mice relapsed into splenomegaly again. In experiments including mice of different ages and sexes, older mice (>10 weeks) were slightly more resistant than younger ones, and males were slightly more resistant than females, but in no single experiment did these differences approach statistical significance ($P > 0.20$).

RESULTS

Mapping of Resistance to FV Using Recombinant *H-2* Haplotypes. Groups of mice of various *H-2*-congenic BALB strains and crosses received 10 SFFU of FV and were monitored by palpation for the development of splenomegaly. Three categories of response emerged from these studies according to the latencies and the final incidences for splenomegaly development (Fig. 1 and Table 2, experiment 1). BALB/c and BALB.5R mice and their F_1 crosses with BALB.B were the most highly susceptible, showing pronounced splenomegaly by day 24. The common feature of the *H-2* types of these mice was that none was homozygous for the *D* region of the $H\text{-}2^{b}$ haplotype; otherwise they carried 0, 1, or 2 sets of alleles from the *K* and *I* regions of the $H\text{-}2^{i5}$ haplotype and 0 or 1 set from the *D* region of $H\text{-}2^{b}$. In a category of intermediate susceptibility, BALB.G mice and their F_1 crosses with BALB.B, all homozygous for the *D* region of $H\text{-}2^{b}$ but homozygous or heterozygous for genes in the *K* and *I* regions of $H\text{-}2^{d}$, showed an incidence of splenomegaly of only 36% at day 24, although 100% of these mice had developed disease by day 38. Only the $H\text{-}2^{b}$-homozygous BALB.B mice of the third category showed relatively strong resistance to FV, with a final incidence of 50% attained only on day 38. In all cases the phenotypes of F_1 mice were those of the more susceptible parent strain. Thus the ability of the $H\text{-}2^{b}$ haplotype to confer resistance to FV appears to be a recessive trait in these crosses.

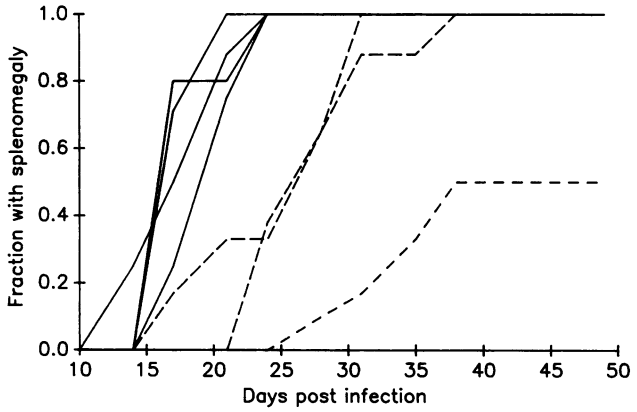

FIG. 1. Cumulative incidences of splenomegaly in female mice of *H-2*-congenic strains and crosses after receiving 10 SFFU of FV on day 0. Group I (solid lines): BALB/c, (BALB/c × BALB.B)F_1, BALB.5R, and (BALB.5R × BALB.B)F_1. Group II (long dashes): BALB.G and (BALB.G × BALB.B)F_1. Group III (short dashes): BALB.B. See Table 2, experiment 1.

Mapping Studies Using Variant $H\text{-}2^{d}$ Haplotypes. To study the effects of certain mutant $H\text{-}2^{d}$ haplotypes and transgenes available only on the C57BL background [which includes a

Table 2. Susceptibility to FV splenomegaly in *H-2*-congenic BALB mice

Group	Strain or cross	*H-2* haplotypes *K/I* region	*D* region	% with splenomegaly 17 days	24 days	31 days	38 days
	Experiment 1: 10 SFFU						
I	BALB/c	*d/d*	*d/d*	17	100	100	100
	(BALB/c × BALB.B)F_1	*d/b*	*d/b*				
	BALB.5R	*bk/bk**	*d/d*				
	(BALB.5R × BALB.B)F_1	*bk/b*	*d/b*				
II	BALB.G	*d/d*	*b/b*	7	36	93	100
	(BALB.G × BALB.B)F_1	*d/b*	*b/b*				
III	BALB.B	*b/b*	*b/b*	0	0	17	50
	Experiment 2: 20 SFFU						
I	BALB/c	*d/d*	*d/d*	33	89	100	100
	(BALB/c × BALB.B)F_1	*d/b*	*d/b*				
II	BALB/c-dm2	*d/d*	*dm2/dm2*	39	77	100	100
	(BALB/c-dm2 × BALB.B)F_1	*d/b*	*dm2/b*				
III	BALB.B	*b/b*	*b/b*	0	35	50	65
	BALB.G	*d/d*	*b/b*				
	(BALB.G × BALB.B)F_1	*d/b*	*b/b*				

Female mice age 7–10 weeks, 8–15 per strain or cross, received FV i.v. on day 0. Splenomegaly was assessed on the indicated days after infection; results are pooled for each group.
*The *K* and *I-A* regions of the $H\text{-}2^{i5}$ haplotype originate from $H\text{-}2^{b}$, and the *I-E* region is from $H\text{-}2^{k}$.

recessive allele, *Fv-2*^{r}, that confers essentially complete resistance to FV (11)], we verified that *H-2*^{b}-associated resistance to FV was also recessive in *H-2*^{b}/*H-2*^{d} heterozygotes of the hybrid BALB × C57BL constitution. The recessive nature of this resistance was even more pronounced in these hybrids than in mice of the homozygous BALB genetic background, an effect most likely due to the presence of a dominant independently segregating allele (*Rfv-3*^{r}) in the C57BL genome that augments this resistance (12). After a dose of 20 SFFU of FV, *H-2*^{b} homozygotes of this hybrid genetic background showed 0–3% incidences of splenomegaly in different experiments, whereas *H-2*^{b}/*H-2*^{d} heterozygotes showed incidences of 80–95% (Table 3, experiments 1 and 2).

In sharp contrast to the *H-2*^{d} haplotype, the mutant *H-2*^{dm1} haplotype (13) retained little capacity to abrogate *H-2*^{b}-associated resistance. This mutation consists of a fusion of the two terminal class I genes of the *D* region of *H-2*^{d}, *D*^{d} and *L*^{d} (Fig. 2), such that the only remnant of the parental *D* region is a class I gene encoding a product that differs in its antigen-presenting domains from any class I molecule of the parental haplotype (14–16). Whereas (BALB/c × B10)F$_1$ mice (*H-2*^{b}/*H-2*^{d}) showed a peak incidence of splenomegaly of 53/56 (95%) after a dose of 20 SFFU of FV, only 5/99 (5%) of (BALB.B × B10-dm1)F$_1$ mice (*H-2*^{b}/*H-2*^{dm1}) developed splenomegaly, an incidence comparable to that in (BALB.B × B10)F$_1$ (2/63, 3%) (Table 3, experiment 1). This finding indicates that *H-2*^{b}-associated resistance to FV is not intrinsically recessive, but rather that one or more genes of the *D* region of *H-2*^{d} can suppress the phenotype.

To explore further the effect of the *H-2D*^{d} region on *H-2*^{b}-associated resistance to FV, we studied two additional variant strains. The mutant *H-2*^{dm2} haplotype (16), carried in the congenic BALB/c-dm2 strain, differs from the parental *H-2*^{d} by a deletion comprising all *D*-region class I genes except *D*^{d} (16, 17) (Fig. 2). In a preliminary experiment, BALB/c, BALB/c-dm2, BALB.G, and BALB.B mice and F$_1$ crosses among them were tested for susceptibility to 20 SFFU of FV. No difference was apparent between the *H-2*^{d} and *H-2*^{dm2} haplotypes in their abilities to suppress *H-2*^{b}-associated resistance to FV (Table 2, experiment 2). In a second experiment in congenic mice of the hybrid B10 × BALB genetic background, no *H-2*^{b} homozygotes developed splenomegaly after 20 SFFU of FV, but 80% of *H-2*^{b}/*H-2*^{d} heterozygotes and 72% of *H-2*^{b}/*H-2*^{dm2} heterozygotes did so

Table 3. FV susceptibility of mice of BALB × C57BL crosses of different *H-2* haplotypes

F$_1$ hybrids	*H-2*	Susceptibility	
		Susceptible/ total	%
	Experiment 1		
BALB.B × B10	b/b	2/63	3.2
BALB/c × B10	*b/d*	53/56	94.6
BALB.B × dm1	*b/dm1*	5/99	5.1
BALB/c × dm1	*d/dm1*	49/60	81.7
	Experiment 2		
BALB.B × B10	*b/b*	0/19	0.0
BALB/c × B10	*b/d*	36/45	80.0
B10 × dm2	*b/dm2*	31/43	72.1
BALB.B × D8	*b/b + D*^{d}	13/50	26.0
	Experiment 3		
BALB.B × B10	*b/b*	0/9	0.0
BALB/c × B10	*b/d*	8/8	100.0
BALB.B × D8	*b/b + D*^{d}	5/17	29.4

Mice received 20 (exp. 1), 10 (exp. 2), or 7 (exp. 3) SFFU of FV i.v. from preparation 4 (exps. 1 and 2) or 5 (exp. 3). Susceptible mice had ≥0.5-g spleens on day 14 after virus inoculation.

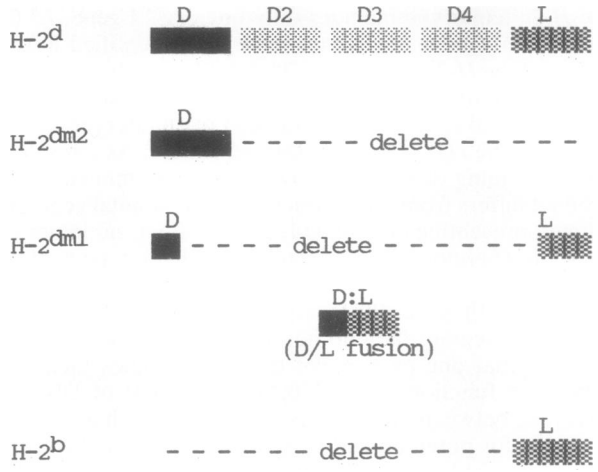

FIG. 2. Schematic representation of the class I genes encoded in the *D* regions of the *H-2*^{d}, *H-2*^{dm1}, *H-2*^{dm2}, and *H-2*^{b} haplotypes. The figure is based on data in ref. 14.

(Table 3, experiment 2). This finding suggests that expression of the *D*^{d} gene—the only known gene remaining in the *D* region of *H-2*^{dm2}—accounts for at least a large part of the ability of the *H-2*^{d} haplotype to suppress *H-2*^{b}-associated resistance to FV.

This conclusion was confirmed in studies utilizing transgenic C57BL/6-D^d (D8) mice. Since these mice are homozygous for both the complete native *H-2*^{b} haplotype and the *D*^{d} transgene, the role of *D*^{d} could be evaluated in the absence of any other portion of the *H-2*^{d} haplotype. In two separate experiments in which *H-2*^{b}-homozygous (BALB.B × B10)F$_1$ mice, which do not carry the *D*^{d} transgene, were completely resistant to 20 SFFU of FV, (BALB.B × B6-tD8)F$_1$ mice (*H-2*^{b}/*H-2*^{b} plus *D*^{d}) showed peak splenomegaly incidences of 31% and 26% (Table 3, experiments 2 and 3). Thus the *D*^{d} gene was capable of partial suppression of resistance to FV even in homozygous *H-2*^{b} mice.

DISCUSSION

In *H-2*-congenic mice on both the inbred BALB and the hybrid BALB × B10 genetic backgrounds, *H-2*^{b}/*H-2*^{d} heterozygotes showed the high susceptibility to FV of homozygous *H-2*^{d} mice rather than the relative resistance to the virus of *H-2*^{b} homozygotes. In studies using recombinant *H-2* haplotypes, comparison of the levels of resistance seen in (BALB.5R × BALB.B)F$_1$, (BALB.G × BALB.B)F$_1$, and BALB.B mice (Fig. 1 and Table 2, experiment 1) suggested that, while genes in both the *K/I* region and the *D* region of *H-2*^{b} confer some degree of resistance, the *K/I*-region gene(s) did so only in mice homozygous for the *D*-region gene(s). This conclusion is consistent with the demonstration that at least two *H-2*^{b}-linked genes influence resistance to FV (17, 18). The critical determinant of *H-2*^{b}-related resistance to FV appeared to be associated with the *D* region of the haplotype, but the resistance was compromised in mice heterozygous for the *D* region of the *H-2*^{d} haplotype. The loss of resistance to FV in *H-2*^{b}/*H-2*^{d} heterozygotes could be due either to the intrinsic recessiveness of the *H-2*^{b}-associated trait or to the presence in the *H-2*^{d} haplotype of a dominant suppressor of the resistance.

The finding that a mutant *H-2*^{d} haplotype, *H-2*^{dm1}, has lost the ability to suppress *H-2*^{b}-associated resistance in heterozygotes (Table 3, experiment 1) indicates that this resistance is not an intrinsically recessive trait. Rather, it appears that the resistance was suppressed in *H-2*^{b}/*H-2*^{d} heterozygotes mainly if not entirely by one or more genes located in the *D* region of the *H-2*^{d} haplotype. Although the *D* region of

the $H\text{-}2^b$ haplotype includes only one class I gene, L^b (also called D^b), five class I genes have been identified in the D region of the $H\text{-}2^d$ haplotype: D^d, $D2^d$, $D3^d$, $D4^d$, and L^d (Fig. 2). The mutation in the $H\text{-}2^{dm1}$ haplotype consists of fusion of the D^d and L^d genes with deletion of all intervening DNA including the $D2^d$, $D3^d$, and $D4^d$ genes (19). As a result, the sole remaining class I gene, $D{:}L^d$, is a recombinant whose product differs from the products of both parental genes in its antigen-presenting domain (14, 15); in effect, no intact gene from the D region of the parental $H\text{-}2^d$ haplotype is present in the $H\text{-}2^{dm1}$ haplotype.

Although these results locate the suppressor gene(s) within the $H\text{-}2D^d$ region, they do not identify the gene. While it is possible that one or more of the class I genes themselves serve this function, the ≈150 kilobases (kb) of DNA that intervene between the five class I $H\text{-}2D^d$ genes have not been analyzed for potential coding sequences of other types, and it is conceivable that the suppressor gene is located there.

The results of our studies using the $H\text{-}2^{dm2}$ haplotype indicate that at least a major portion of the suppressive effect of the $H\text{-}2D^d$ region is due to a gene(s) located in a more narrowly defined portion of the D region. The mutation in the $H\text{-}2^{dm2}$ haplotype consists of a deletion that eliminates a large fraction of the D region, including the class I genes $D2^d$, $D3^d$, $D4^d$, and L^d, leaving only the D^d gene and up to half of the ≈50 kb of DNA between D^d and $D2^d$ (14, 20). Since we observed a similar high level of susceptibility to FV in both $H\text{-}2^b/H\text{-}2^{dm2}$ and $H\text{-}2^b/H\text{-}2^d$ mice, again in contrast to highly resistant $H\text{-}2^b$ homozygotes, it appears that either D^d or an unidentified neighboring gene participates strongly in the suppression of $H\text{-}2^b$-associated resistance to the virus.

That the D^d gene itself is responsible at least in part for the suppression of resistance was indicated by the finding that its presence as a transgene in mice otherwise similar to highly resistant $H\text{-}2^b$ homozygotes conferred a significant level of susceptibility to FV-induced splenomegaly (Table 3, experiments 2 and 3). The fact that these D^d transgene carriers were, however, markedly less susceptible than the $H\text{-}2^b/H\text{-}2^{dm2}$ heterozygotes studied in the same experiment (26% vs. 72% peak incidences, Table 3, experiment 2) could be due to any of several differences between them. Although the only known gene from the $H\text{-}2D^d$ region expressed in both kinds of mice was D^d, the transgenic mice possessed two intact, resistance-conferring $H\text{-}2^b$ haplotypes ($H\text{-}2^b/H\text{-}2^b + D^d$) in contrast to the single one of the $H\text{-}2^b/H\text{-}2^{dm2}$ heterozygotes. In addition, the latter mice possessed an intact K and I region from the $H\text{-}2^d$ haplotype. These differences in dosage of K, I, and D region genes could have reduced the efficacy of D^d-mediated suppression of resistance to the virus in the transgenic mice. It is also conceivable that yet-unidentified D-region genes of the $H\text{-}2^{dm2}$ haplotype, in addition to D^d, contributed to the suppression. On the hypothesis that the D^d gene is solely responsible for the suppression of resistance to FV in $H\text{-}2^b/H\text{-}2^d$ heterozygotes, it would be important to compare the levels of resistance in $H\text{-}2^b/H\text{-}2^{dm1}$ mice that do or do not carry D^d as a transgene; at present both the $H\text{-}2^{dm1}$ haplotype and the D^d transgene are available only in C57BL-background mouse strains, crosses of which would be homozygous for the recessive $Fv\text{-}2^r$ allele and thus absolutely resistant to FV (11). We are currently establishing a BALB.B-D^d transgenic strain for eventual use in this experiment.

Previous studies have established that FV-specific cytotoxic T lymphocytes (CTL) generated in $H\text{-}2^b$ homozygotes recognize FV antigens only in the context of the D-region L^b (also called D^b) product (21, 22), and it seems likely that this fact is the basis of $H\text{-}2^b$-associated resistance to the virus. Since we have found no significant difference between the levels of cell-surface expression of L^b in $H\text{-}2^b$-homozygous mice that do or do not carry the D^d transgene (unpublished result), the finding that expression of the class I D^d molecule is capable of at least partially suppressing this resistance suggests that it does so either (*i*) at the level of the virus-infected cell by interfering with the antigen-presenting function of the L^b molecule or (*ii*) at the level of the T-cell response by interfering with the ability of mice to produce T lymphocytes with receptors that recognize one or more viral epitopes presented by the L^b molecule. If the interference is at the level of the antigen-presenting function of L^b, it is likely that the D^d molecule competes strongly with L^b for FV peptide epitopes at some point during antigen processing. If the interference is due to the failure to produce T lymphocytes bearing appropriate T-cell receptor molecules, it would appear that the D^d molecule, perhaps armed with some endogenously produced peptide epitope, can mimic the L^b molecule armed with an epitope of FV that is critical for resistance to the virus, so that the L^b-positive host is immunologically tolerant to this important epitope and thus markedly less resistant to the virus.

L^b-restricted anti-FV CTL recognize at least two viral epitopes (22), one of which maps in the viral *env* gene (23) and another in the *gag–pol* region. $H\text{-}2^b/H\text{-}2^d$ heterozygotes do generate a CTL response after immunization with FV-infected $H\text{-}2^b$-homozygous cells, but their response is weak compared with that in $H\text{-}2^b$ homozygotes (D.P., unpublished results) and is apparently inadequate to confer significant resistance to the virus. It is possible that the generation or effectiveness of L^b-restricted CTL specific for a particular one of these epitopes is of overriding importance for conferring resistance to the virus in $H\text{-}2^b$ homozygotes. It would presumably be this component of the response that is suppressed in the presence of the D^d molecule. Further studies in this system will be necessary to elucidate the mechanisms of this suppression of resistance to FV.

It is interesting to note a mirror-image symmetry between the present findings in the FV system and results from studies (24) of $H\text{-}2$-associated resistance to the murine acquired immunodeficiency syndrome (MAIDS) induced by the LP-BM5 virus. In these latter studies (24), homozygosity for the $H\text{-}2^d$ haplotype conferred relative resistance to the disease by comparison with the high susceptibility in $H\text{-}2^b$ homozygotes. As in the present studies, resistance appeared to be recessive in F_1 heterozygotes; the D region of the $H\text{-}2^d$ haplotype determined resistance, and the D^d gene was responsible at least in part for the resistance, since $H\text{-}2^b$-homozygous D8 transgene carriers were significantly more resistant than parental strain mice lacking the transgene. Thus the D^d gene appears to have opposite effects in the two sets of studies, conferring relative resistance to the MAIDS virus and suppressing resistance to FV.

It is also noteable that studies using the D^d transgene-carrying D8 strain have demonstrated that the transgene is a major determinant of the phenomenon of hybrid resistance (25, 26). Whereas classical transplantation rejection depends on recognition by the recipient of antigens present on engrafted cells but absent in the host, the presence of the D^d transgene in $H\text{-}2^b$-homozygous recipients confers the ability to reject hemopoietic grafts from genetically identical donors lacking the transgene (27). In particular, Rauscher murine leukemia virus-induced erythroleukemia cells derived from $H\text{-}2^b$-homozygous mice lacking the transgene were rejected more weakly by syngeneic recipients than by otherwise identical carriers of the D^d transgene (28). However, graft rejection due to the presence of the D^d gene in the host appears to be mediated by natural killer cells, while mature T cells are fully capable of adoptively transferring $H\text{-}2^b$-associated resistance to FV (ref. 29 and D.P., unpublished results). Although the coincidence of two unusual properties of the D^d molecule—the abilities to confer hybrid resistance and to suppress resistance to a retroviral disease—is intrigu-

ing, it is not clear how the mechanisms of the two effects might be related.

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