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Genetics

New gene locus modifying susceptibility to certain B-tropic murine leukemia viruses

(N- and B-tropism/mouse embryo fibroblasts/genetic control of susceptibility to virus)

ALAIN DECLÈVE, OHTSURA NIWA, JOAN KOJOLA, AND HENRY S. KAPLAN

Cancer Biology Research Laboratory, Department of Radiology, Stanford University School of Medicine, Stanford, California 94305

Contributed by Henry S. Kaplan, October 28, 1975

ABSTRACT **A new gene, *SRV*, the dominant allele of which occurs in mice of strain C57BL, independently modifies the slope ("hitness") and level of sensitivity of the titration curves obtained when one subclass of B-tropic murine leukemia viruses is propagated on mouse embryo cells of nonpermissive *Fv-1* genotypes. Replication of another subclass of B-tropic viruses is not modified with respect to hitness, and that of N-tropic viruses is not affected.**

Susceptibility of mouse embryo cells to murine leukemia virus (MuLV) infection *in vitro* has been reported to be governed by a single gene, *Fv-1* (1–5). MuLV that preferentially replicated on cells of $Fv\text{-}1^{nn}$ genotype were designated "N-tropic", whereas those that replicated better on cells of $Fv\text{-}1^{bb}$ genotype were designated "B-tropic". Heterozygotes were reported to be dominant for resistance. Titration patterns of N- and B-tropic MuLV demonstrated that host cell restriction is determined by two apparently independent parameters: (*1*) the slope of the titration curve at low multiplicity of infection ("hitness"), expressed in only two modes, either 1-hit or 2-hit; and (*2*) the level of sensitivity, a graded response manifested by the relative positions of the titration curves and by the relative endpoint dilution titers (6, 7). N-tropic viruses grown on F_1 hybrid ($Fv\text{-}1^{nb}$) cells exhibited 2-hit kinetics and a level of sensitivity identical to that on nonpermissive homozygous cells. For B-tropic viruses the situation was strikingly different. The WN2226-B virus on (BALB/c × DBA/2)F_1 hybrids (7) and radiation leukemia virus passaged *in vitro* (RadLV*) on (BALB/c × NIH/Swiss)F_1 hybrids (6) yielded titration curves with 2-hit kinetics but the level of sensitivity was intermediate between those of permissive and nonpermissive homozygous hosts. The behavior of RadLV* grown on (C57BL × NIH/Swiss)F_1 hybrids was anomalous: not only was the level of sensitivity intermediate between the levels of the homozygous parental cells, but the titration curve was clearly indicative of 1-hit kinetics (6).

The present report presents evidence that this anomalous behavior is unique to a specific subclass of B-tropic viruses and that, in addition to *Fv-1*, another gene, dominant only in certain strains of mice, also plays a major role in the control of cell restriction. This gene, which interacts with *Fv-1*, has been designated *SRV* because it was first discovered to modify "sensitivity to RadLV".

MATERIALS AND METHODS

Animals. C57BL/Ka and BALB/c mice were obtained from our own colony. NIH/Swiss mice, originally obtained from Dr. Carl Hansen, National Institutes of Health Laboratory Animal Genetic Center, were kindly provided by Dr. Paul Arnstein, National Cancer Institute–California Department of Health. All F_1 hybrid, backcross, and outcross matings were performed in our laboratory. In each cross, the female is designated first. Mice of both sexes were used for intrathymic (IT) injections at 3–4 weeks of age.

Tissue Culture. Primary cultures were prepared as previously described (8) from 13- to 15-day embryos of the above strains and crosses. Cell suspensions of the primary cultures were slow frozen in liquid nitrogen in minimal essential medium (MEM) with 20% fetal calf serum and 10% dimethylsulfoxide, thawed, and incubated at 37° 4–5 days before secondary cultures of mouse embryo fibroblasts (MEF) were plated.

Virus Preparations. Five B-tropic and 5 N-tropic viruses were studied (Table 1). WN 1802-B, passage 2, was kindly provided by Dr. Raymond C. Tennant, Oak Ridge National Laboratory, Oak Ridge, Tenn. Tennant virus, a gift from Dr. Jay A. Levy, University of California, San Francisco, was passaged more than 20 times in our laboratory on C57BL and BALB/c mouse cell lines (Tennant/BL and Tennant/BA, respectively) prior to use in these studies.

Assays. The *in vitro* and *in vivo* immunofluorescence (IF) assays (16, 17) and the reverse XC plaque assay (18) have been previously described.

RESULTS

IF and XC Titration Patterns in Reciprocal F_1 Hybrid Cells. Titrations of RadLV* and WN 1802-B (both B-tropic viruses) on reciprocal (NIH/Swiss × C57BL)F_1 hybrid MEF displayed 1-hit kinetics with a level of sensitivity intermediate between the levels observed on C57BL MEF and NIH/Swiss MEF, whereas on (NIH/Swiss × BALB/c)F_1 hybrid MEF these viruses exhibited titration curves with 2-hit kinetics at a level intermediate between those of the homozygous ($Fv\text{-}1^{bb}$, $Fv\text{-}1^{nn}$) parent cells (Fig. 1A). The other B-tropic viruses (Tennant/BL and Tennant/BA) yielded 2-hit intermediate titration curves on either (NIH/Swiss × BALB/c) or (NIH/Swiss × C57BL)F_1 hybrid cells (Fig. 1B). All of the N-tropic viruses yielded 2-hit titration curves on both types of F_1 hybrid cells which were almost superimposable on their titration curves on homozygous nonpermissive ($Fv\text{-}1^{bb}$) cells (Fig. 1C). Thus, distinctively different patterns of response are manifested by three different groups of viruses, of which RadLV*, Tennant, and Gross-AKR leukemia virus passaged *in vitro* (GLV*) are typical representatives. Experimental variations were observed with respect to plateau values and displacement of individual curves, but their relative positions remained the same.

Titration Patterns of RadLV *In Vivo*. RadLV was as-

Abbreviations: MuLV, murine leukemia virus; RadLV and RadLV*, wild-type and *in vitro*-passaged radiation leukemia virus; GLV*, *in vitro*-passaged Gross-AKR leukemia virus; IF, immunofluorescence; IT, intrathymic; MEF, mouse embryo fibroblasts.

Table 1. Murine leukemia viruses tested

	Virus	Source	Tissue culture passage history	*Fv-1* tropism	Refs.
1.	RadLV	Radiation-induced lymphoma tissues from C57BL/Ka mice.	Passaged *in vivo* in C57BL mice.	B	9, 10
2.	RadLV*	Radiation-induced lymphoma tissue from C57BL/Ka mice, adapted to replication *in vitro*.	>50 passages in C57BL/Ka MEF.	B	11, 12
3.	WN 1802-B	Spleen from normal 18-month-old BALB/c mouse.	Serial passage in BALB/c MEF.	B	13
4.	Tennant/BA	Leukemic tissue extract from C58 mouse, inoculated into, extracted from, and serially passaged in BALB/c mice.	20th BALB/c MEF passage in our laboratory.	B	14
5.	Tennant/BL	Same as Tennant/BA.	20th C57BL/Ka MEF passage in our laboratory.	B	14
6.	GLV*	Thymus from leukemic C_3H mouse inoculated with Gross passage A virus after long serial passage in C_3H mice.	>50 passages in C_3H MEF.	N	6
7.	RadLV/N	Radiation-induced lymphoma tissue from C57BL/Ka mice.	20th NIH/Swiss MEF passage.	N	15
8.	57B-1(B)	IdUrd-induced *in vitro* from C57BL/Ka MEF.	C57BL (BL-5) cells for 20 + 100 cell generations.	N	a
9.	57B-1(N)	IdUrd-induced *in vitro* from C57BL/Ka MEF.	20 cell generations on C57BL(BL-5) cells, then passaged on NIH/3T3 cells for 100 cell generations.	N	a
10.	57B-2(N)	IdUrd-induced *in vitro* from C57BL/Ka MEF.	NIH/3T3 cells for 20 + 100 cell generations.	N	a

[a] E. Gelmann, A. Declève, O. Niwa, S. Greenspan, and H. S. Kaplan, submitted for publication.

sayed *in vivo* in C57BL/Ka, BALB/c, NIH/Swiss, (C57BL × NIH)F_1 hybrid, and (BALB/c × NIH)F_1 hybrid mice. Despite the poor replication of RadLV in NIH/Swiss mice, the results shown in Fig. 2 indicate that the titration patterns described for RadLV* *in vitro* are also displayed by RadLV *in vivo*. (C57BL × NIH)F_1 hybrid mice exhibited approximately 1-hit kinetics similar to those of C57BL mice and a level of sensitivity intermediate between the levels found in NIH and C57BL parents. In contrast, the (BALB/c × NIH)F_1 hybrids responded to RadLV with multi-hit kinetics and an intermediate level of sensitivity.

Titration Patterns of RadLV* on Individual Mouse Embryo Cell Cultures of Selected Outcross and Backcross Genotypes. A tentative model was developed to explain the

Table 2. Segregation of *Fv-1* and *SRV* genotypes in

	Murine strain or cross:	Parental NIH /Sw	Parental C57BL /Ka	Recip. F_1	Individual (NIH × C57BL)F_1 × NIH A_1	A_3	A_4	A_6	A_7	B_1	B_2	B_3	B_6	B_7	C_4	C_5	C_6
Phenotype	Hitness: RadLV*	2	1	1	2	1	1	2	2	1	2	2	2	2	2	1	1
	Hitness: GLV*	1	2	2	1	2	2	2	1	2	2	1	1	2	2	2	2
	Level[a]: RadLV*	L	H	M	L	M	M	M	M	M	M	L	M	M	M	M	M
	Level[a]: GLV*	H	M	M	H	M	M	M	H	M	M	H	H	M	M	M	M
Genotype	*Fv-1* *bb*		√														
	Fv-1 *bn*			√		√	√	√		√	√			√	√	√	√
	Fv-1 *nn*	√			√				√			√	√				
	SRV *MM*		√														
	SRV *Mm*			√		√	√		√	√			√			√	√
	SRV *mm*	√			√			√			√	√		√	√		

Combined *Fv-1*/*SRV* genotypes: *bnMm*, 9; *bnmm*, 10; *nnMm*, 9; *nnmm*, 10.

[a] Levels of sensitivity: H = high, M = medium, L = low.

Table 3. Model for genetic control of susceptibility to RadLV

Mouse strain or cross	Genotype		Phenotype				Percentage of mice with specific genotypes	
			RadLV*		GLV*			
	Fv-1	*SRV*	Hitness	Level[a]	Hitness	Level	Expected	Observed
C57BL/Ka	*bb*	*MM*	1	H	2	M	100	100
BALB/c	*bb*	*mm*	1	H	2	M	100	100
NIH/Swiss	*nn*	*mm*	2	L	1	H	100	100
(C57BL × NIH)F_1	*bn*	*Mm*	1	M	2	M	100	100
(BALB × NIH)F_1	*bn*	*mm*	2	M	2	M	100	100
(BALB × C57BL)F_1	*bb*	*Mm*	1	H	2	M	100	100
(BALB × C57BL)F_1 × NIH	*bn*	*Mm*	1 (1:1)[b]	M	2	M	50	50
	bn	*mm*	2 (1:1)[b]	M	2	M	50	50
(C57BL × NIH)F_1 × NIH	*bn*	*Mm*	1	M	2	M	25	23.6
	bn	*mm*	2 (1:3)	M (1:3)	2 (1:1)	M	25	26.3
	nn	*Mm*	2 (1:3)	M (1:3)	1 (1:1)	H	25	23.6
	nn	*mm*	2 (1:3)	L (1:3)	1 (1:1)	H	25	26.3

[a] Levels of sensitivity: H = high, M = medium, L = low.
[b] 1:2-hit ratios are indicated in parentheses.

anomalous behavior of RadLV* and WN 1802-B in (C57BL × NIH) versus (BALB/c × NIH)F_1 hybrid crosses. This model postulates that an additional gene, *SRV*, modifies the hitness component of the restrictive action of *Fv-1* and thus increases susceptibility to some B-tropic viruses. Its dominant allele *M* (for modifier) is homozygous in strain C57BL mice, and its recessive allele *m* is homozygous in BALB/c and NIH/Swiss mice. The *Fv-1/SRV* genotypes of C57BL/Ka, BALB/c, and NIH Swiss mice would therefore be *bbMM*, *bbmm*, and *nnmm*, respectively, and the genotypes of F_1 hybrids of those strains would be *bnMm* for (C57BL × NIH)F_1, *bnmm* for (BALB/c × NIH)F_1, and *bbMm* for (BALB/c × C57BL)F_1. According to this model, the conversion from 2-hit to 1-hit kinetics occurs only when the *M* allele of SRV is present together with *nb* heterozygosity at the *Fv-1* locus.

To test this model, an experiment was first performed with outcross embryo cell cultures. Individual embryos from the outcross (BALB/c × C57BL)F_1 × NIH/Swiss would be expected to segregate between two genotype categories: *bnMm* and *bnmm*. If the model is correct, the ratio of 1:2-hit kinetics expected for RadLV* in the individual outcross embryos should be 1:1. That is exactly what was found when RadLV* was titered on MEF cultures from 26 individual embryos of the (BALB/c × C57BL)F_1 × NIH/Swiss outcross; 13 embryo cell cultures replicated RadLV with 1-hit kinetics and 13 with 2-hit kinetics. All titration curves had a level of sensitivity intermediate to those on homozygous BALB/c^{bb}, C57BL^{bb}, and NIH^{nn} MEF cultures. These intermediate curves were similar to curves B and C in Fig. 1A for RadLV* on F_1 hybrids. When cultures of the same 26 individual (BALB/c × C57BL) × NIH/Swiss outcross embryo cells were infected simultaneously with GLV*, all responded with 2-hit kinetics.

NIH/Swiss, C57BL/Ka, F_1 hybrid, and backcross embryo fibroblasts

backcross embryo cell cultures (n = 38)

D_3	D_4	D_5	D_8	D_9	D_{10}	E_2	E_3	E_4	E_5	E_6	E_9	F_1	F_2	F_3	F_4	F_5	F_6	F_7	G_1	G_2	G_3	G_4	G_5	G_6	Totals
2	2	2	2	2	2	2	2	2	2	2	1	2	1	2	2	2	2	1	1	2	2	2	2	2	1-hit:9 2-hit:29
2	1	2	1	1	2	1	1	1	2	1	2	1	2	1	1	2	1	2	2	1	1	1	2	1	1-hit:19 2-hit:19
M	L	M	M	L	M	L	L	M	M	M	M	M	M	M	L	M	L	M	M	L	M	L	M	M	L:10 M:28
M	H	M	H	H	M	H	H	H	M	H	M	H	M	H	H	M	H	M	M	H	H	H	M	H	M:19 H:19
√		√			√				√		√		√			√		√	√				√		*bn*:19
	√		√	√		√	√	√		√		√		√	√		√			√	√	√		√	*nn*:19
			√					√		√	√	√	√	√				√	√		√			√	*Mm*:18
√	√	√		√	√	√	√		√						√	√	√			√		√	√		*mm*:20

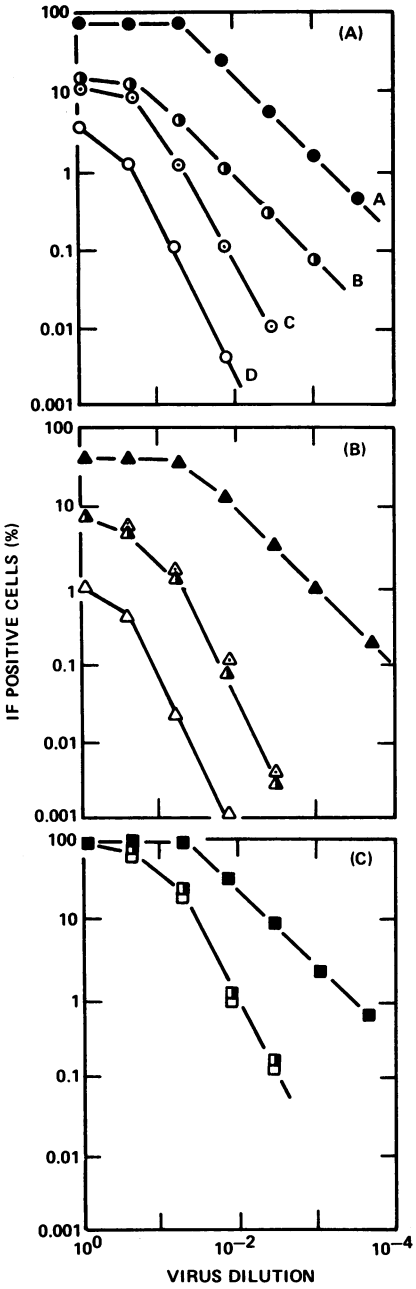

FIG. 1. (A) Titration curves of RadLV*-type B-tropic viruses on MEF of: C57BL/Ka or BALB/c, (●) Curve A; (C57BL × NIH)F_1, (◑) Curve B; (BALB/c × NIH)F_1, (⊙) Curve C; NIH/Swiss, (○) Curve D.

(B) Titration curves of Tennant-type B-tropic viruses on MEF of: C57BL/Ka or BALB/c, (▲); (C57BL × NIH)F_1, (▲); (BALB/c × NIH)F_1, (▲); NIH/Swiss, (△).

(C) Titration curves of N-tropic viruses on MEF of: NIH/Swiss, (■); (C57BL × NIH)F_1 or (BALB/c × NIH)F_1, (◨); C57BL/Ka or BALB/c, (□).

Next, RadLV* and GLV* were assayed in parallel on (NIH × C57BL)F_1 × NIH individual backcross embryo cell cultures. Four different genotypes were expected: *bnMm*, *bnmm*, *nnMm*, and *nnmm*. Since the *M* allele has no apparent effect on infection by GLV*, suggesting that only the *Fv-1* alleles determine hitness for N-tropic viruses, a ratio of 1:2-hit kinetics of 1:1 was expected for GLV*. A 1:2-hit ratio of 1:1 would also be expected for RadLV* if the *M* allele is able to override the repressive effect of the homozygous *Fv-1*^{nn} genotype, whereas a 1:2-hit ratio of 1:3 would be expected if the *M* allele is recessive to the *Fv-1*^{nn} genotype.

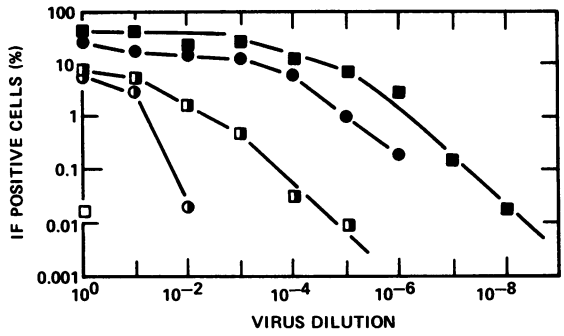

FIG. 2. Dose-response curves of wild-type RadLV *in vivo* in the thymus of 1-month-old C57BL/Ka (■), BALB/c (●), (C57BL × NIH)F_1 (◨), (BALB/c × NIH)F_1 (◑), and NIH/Swiss (□) mice. Thymus cell suspensions were processed for fluorescence 7 days after the virus was injected into both lobes of the thymus.

Table 2 summarizes the results. A 1:2-hit ratio of 1:3 was found for RadLV*, indicating that the *M* allele cannot override the *Fv-1*^{nn} genotype to convert 2-hit to 1-hit kinetics. The expected 1:1 ratio was observed for GLV*. In addition, it was found (Fig. 3B) that for GLV* all 1-hit curves in backcross embryos were superimposable on the 1-hit titration curve for GLV* on NIH/Swiss MEF (high level of sensitivity) and all 2-hit curves were superimposable on the 2-hit titration curve for GLV* on C57BL MEF (medium level of sensitivity). With RadLV* the observations were strikingly different; three different families of curves could be observed: (*a*) a low level 2-hit curve (Fig. 3A, Curve D) superimposable on the 2-hit titration curve obtained on NIH/Swiss MEF (Fig. 3A, Curve E); (*b*) a medium level 2-hit curve (Fig. 3A, Curve C) intermediate between the titration curves on the homozygous MEF's (Fig. 3A, Curves A and E); and (*c*) a medium level 1-hit curve (Fig. 3A, Curve B) also intermediate between the titration curves on homozygous parent cells. These findings suggest that the *M* allele not only induces a 2-hit to 1-hit conversion in the presence of the *Fv-1*^{b} allele, as stated earlier, but also acts independently from the *Fv-1*^{b} allele to govern the level of sensitivity. From the observed phenotypes presented in Table 2, one can deduce the *Fv-1/SRV* genotypes if the assumptions of this model for the dual action of the *SRV* gene are correct. In Table 2 the different genotypes are listed in accordance to the phenotypic observations. Of the 38 individual backcross embryos tested, nine exhibited 2-hit kinetics with GLV* and intermediate 1-hit kinetics with RadLV* (corresponding to genotype *Fv-1*^{bn} *SRV*^{Mn}); 10 exhibited 2-hit kinetics with both GLV and RadLV, with an intermediate level of sensitivity for RadLV (*Fv-1*^{bn} *SRV*^{mm}); nine exhibited 1-hit kinetics for GLV and 2-hit medium level curves for RadLV (*Fv-1*^{nn} *SRV*^{Mm}); and 10 exhibited 1-hit kinetics with GLV*, and low level 2-hit kinetics with RadLV (*Fv-1*^{nn} *SRV*^{mm}). Thus, the ratios obtained experimentally, summarized in Table 3, are entirely consistent with the model proposed here for the genetic control of sensitivity to RadLV-type B-tropic viruses.

DISCUSSION

The titration patterns of N-tropic and B-tropic MuLV on mouse embryo cells of homologous, heterologous, F_1 hybrid, outcross, and backcross genotypes indicate that host cell re-

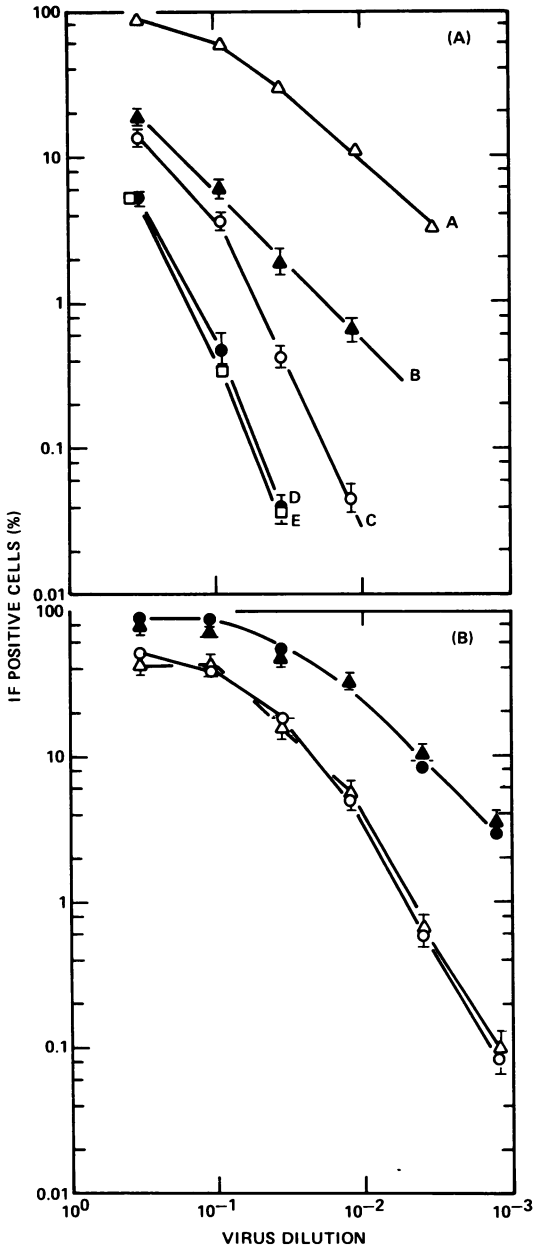

FIG. 3. (A) Titration curves of RadLV* on MEF of: C57BL/Ka ($Fv\text{-}1^{bb}$ SRV^{MM}), Curve A (△); $Fv\text{-}1^{bn}$ SRV^{mn} backcross, Curve B (▲); $Fv\text{-}1^{bn}$ SRV^{mm} and $Fv\text{-}1^{nn}$ SRV^{Mm} backcross, Curve C (○); $Fv\text{-}1^{nn}$ SRV^{mm} backcross, Curve D (●); NIH/Swiss ($Fv\text{-}1^{nn}$ SRV^{mm}), Curve E (□).

(B) Titration curves of GLV* on MEF of: C57BL/Ka ($Fv\text{-}1^{bb}$ SRV^{MM}), (○); NIH/Swiss ($Fv\text{-}1^{nn}$ SRV^{mm}), (●); ($Fv\text{-}1^{bn}$ SRV^{Mm}) and ($Fv\text{-}1^{bn}$ SRV^{mm}), backcross (△); ($Fv\text{-}1^{nn}$ SRV^{Mm}) and ($Fv\text{-}1^{nn}$ SRV^{mm}), backcross (▲). Standard errors of the means of multiple titrations are indicated for each point in the backcross embryo titration curves.

striction of MuLV replication is determined for RadLV* and WN 1802-B, both B-tropic viruses, by two separate genes, *Fv-1* and *SRV*. The *SRV* alleles are dominant in C57BL mice and recessive in NIH and BALB/c mice. Both loci (*SRV* and *Fv-1*) control the two independent major parameters described earlier (6, 7), namely hitness and level of sensitivity. However, whereas the *Fv-1* gene can operate independently with respect to both hitness and level of sensitivity, the *SRV* gene operates independently only on the level of sensitivity. Its action on hitness operates through *Fv-1*.

These experiments also clearly demonstrate that at least two distinct classes of B-tropic viruses exist; the RadLV type, which respond to the *SRV* gene action for both hitness and level of sensitivity, and the Tennant type, which do not appear to respond to the *SRV* gene. None of the N-tropic viruses appeared to be influenced by the *SRV* gene, although the proximity of their titration curves makes it difficult to exclude small effects on levels of sensitivity.

The nature of the difference between the B-tropic virus classes is not clear. Since RadLV* of C57BL origin (SRV^{MM}) and WN 1802-B of BALB/c origin (SRV^{mm}) responded in the same manner to the *SRV* gene, and since Tennant virus passaged in BALB/c cells did not differ from Tennant virus passaged in C57BL cells, the difference in response to the *SRV* gene of these B-tropic viruses cannot be accounted for by their passage history. The strain C58 ($Fv\text{-}1^{nn}$) origin of Tennant virus may offer an explanation for its failure to respond to *SRV* by conversion from 2-hit to 1-hit kinetics.

Since N-tropic viruses and the two subclasses of B-tropic viruses respond differently to the hitness and level of sensitivity cellular control mechanisms, specific viral attributes determined by differences in these types of viral genomes must be recognized by the cell. It may be, therefore, that it is the relative efficiency of recognition of these distinctive viral traits which differs from one type of virus–host cell interaction to another. In this context, the *SRV* gene might act by modifying the efficiency of the dual restriction mechanism in such a way that the host cells acquire new viral recognition capabilities. The level within the cell at which the *SRV* gene acts is not known. It may involve either a receptor-adsorption penetration type of control mechanism, as has been found with the avian leukosis and sarcoma viruses (19–21) or some step (transcription, translation, or assembly) following integration of the viral genome, as seems to be the case for the *Fv-1* gene control system (22–24).

It is noteworthy that the action of the *SRV* gene could be observed by both the IF and XC assays. This indicates that the *SRV* locus does not act through the induction of infectious xenotropic viruses, since such viruses apparently do not induce plaque formation. A helper type of interaction between ecotropic and xenotropic viruses, or between mixtures of ecotropic viruses, cannot be excluded.

The *SRV* gene effect was also observed *in vivo* after virus inoculation into the mouse thymus. Since earlier studies have suggested a correlation between the *in vivo* IF assay and the leukemogenicity of thymotropic MuLV (17) it will be of interest to evaluate the influence of the *SRV* gene on viral leukemia induction. It will also be desirable to study crosses between other strains of mice to ascertain whether the SRV^{M} allele is present in some $Fv\text{-}1^{nn}$ strains. Such studies may clarify the relationship between *SRV* and other genes known to control susceptibility of mice to leukemia induction by MuLV (1).

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