A MAJOR GENETIC LOCUS AFFECTING RESISTANCE TO INFECTION WITH MURINE LEUKEMIA VIRUSES

III. Assignment of the *Fv-1* Locus to Linkage Group VIII of the Mouse

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The *Fv-1* locus of the mouse (1) has been shown to play a major role in the biology of murine leukemia virus (MLV) infection both in vivo and in vitro by determining the sensitivity or resistance of the cells to exogenous infection by the various host-range types of MLV. *Fv-1* type markedly affects the magnitude of response of mice to infection with Friend virus (1) or pseudotypes of murine sarcoma virus (2), the plaquing efficiency of naturally occurring MLV strains when grown in tissue culture (3, 4), and the degree of spread of endogenous, genetically acquired MLV in hybrids between low virus mouse strains and the high virus strain AKR (5, 6). In addition, *Fv-1* appears to have a marked effect on the incidence of spontaneous lymphomas in F_1 hybrids between AKR and low leukemic mouse strains (6).

Two alleles of *Fv-1* have been defined. *Fv-1*^{n} mice and their cells in tissue culture are sensitive to infection with N-tropic MLV strains (2) and are relatively resistant to B-tropic strains; *Fv-1*^{b} mice show the reciprocal pattern. Heterozygotes, *Fv-1*^{nb}, are resistant to both N- and B-tropic strains.

In this report we present evidence that the *Fv-1* locus is on linkage group VIII, about 39 map units from *b*, the locus for brown or black hair color.

In studies of the genetic transmission of the naturally occurring N-tropic MLV infection of AKR mice (5, 6), which are *Fv-1*^{n}, crosses were made between *Fv-1*^{n} and (*Fv-1*^{b} × AKR)F_1 mice, and the progeny were *Fv-1* typed by the spleen focus assay for susceptibility to Friend virus (7). In an extension of these studies, a larger number of C57BR × (BALB/c × AKR)F_1, i.e. BR × (C × AK)F_1, mice have been *Fv-1* typed, and a correlation between *Fv-1* type and black or brown coat color was observed. This coloration is determined by the *b* locus on linkage group VIII, at which the wild type, black (*B*), is dominant to brown (*b*). BALB/c (*Fv-1*^{b}) carries the *b* allele, and AKR the *B*

allele; a cross of (C × AK)F_1 mice with C57BR (*Fv-1^n*, *b*) gives equal numbers of black (*B/b*) and brown (*b/b*) progeny. The association of *Fv-1* type with coat color is shown in Table I, line 1. The correlation was highly significant (χ^2 with 1 degree of freedom = 11.7, $P < 0.001$), indicating that the two genes are linked. The BR × (C × AK)F_1 cross also segregates for *a* (agouti); there was no association of this marker with *Fv-1*.

In crosses with low virus mouse strains, the AKR mouse contributes two unlinked chromosomal loci, either of which results in presence of infectious N-tropic MLV by 2–6 wk of age in *Fv-1^n* progeny (5, 6); thus, in an *Fv-1^n* × (*Fv-1^n* × AKR)F_1 backcross, 75% of the mice are virus positive. In *Fv-1^{nb}* mice, either in the F_1 or segregating generations, detection of virus is less frequent, since titers are suppressed by the inefficient spread of virus from spon-

TABLE I

Association between Inheritance of Fv-1 and Coat Color Markers

Cross	no. of *Fv-1^n* mice/no. in category						Recombinational frequency ± standard error
	Color marker from *Fv-1^n* grandparent		Color marker from *Fv-1^b* grandparent		Total		
	no.	%	*no.*	%	*no.*	%	
C57BR × (BALB/c × AKR)F_1 *Fv-1^n*, *b* × (*Fv-1^b*, *b* × *Fv-1^n*, *B*)	54/85	64	27/79	34	81/164	49	35 ± 3.7
(C57BL/6 × DBA/2)F_1 × DBA/2* (*Fv-1^b*, *B* × *Fv-1^n*, *b*) × *Fv-1^n*, *b*	34/60	57	27/76	36	61/136	45	39 ± 4.2
DBA/2 × (NIH × BALB/c)F_1* *Fv-1^n*, *b* × (*Fv-1^n*, *B* × *Fv-1^b*, *b*)	21/42	50	18/45	40	39/87	45	45 ± 5.3
TOTAL	109/187	58	72/200	36	181/387	47	38.8 ± 2.5

* Includes some mice of the reciprocal mating.

taneously induced cells (6). *Fv-1* is not linked to either of the virus-inducing loci (6). Since *Fv-1* type is correlated with degree of virus expression, and is also correlated with the *b* locus, it was of interest to examine the correlation between *b* and virus expression in the BR × (C × AK)F_1 mice (Table II). There was a highly significant association between presence of detectable virus and inheritance of the *B* coat color allele from AKR. However, when the analysis was adjusted for *Fv-1* type, it was clear that this association was the result of the *Fv-1* linkage with *b*, and not due to linkage of one of the virus-inducing loci with *b*. This is borne out by the previously reported data on *Fv-1^n* × (*Fv-1^n* × AKR)F_1 crosses (5). In the crosses that segregated for the *b* locus [DBA/2 × (DBA/2 × AKR)F_1, C57L × (C57L × AKR)F_1, and C57-BR × (C57BR × AKR)F_1, and their reciprocal hybrids], of 171 black progeny, 126 (74%) were virus positive, while of 168 brown progeny, 128 (76%) were positive. Thus, in a cross segregating for *Fv-1*, virus detection tends to

TABLE II

Correlation between Coat Color and Presence of Virus in BR × (C × AK)F$_1$ Mice, and the Lack of Such Correlation When Adjusted for Fv-1 Type

Color	*Fv-1* type	Virus testing at 2 wk			Virus testing at 8 wk			*P* value for % of mice with virus‡		
		no. with virus/no. in category		Proportion of positive mice* with titers >10^2	no. with virus/no. in category		Proportion of positive mice* with titers >10^2		2-wk tests	8-wk tests
			%	%		%	%			
Black	*n*	29/54	54	50	41/54	76	81	Black vs. brown		
	nb	7/32	22	24	16/32	50	59	Total	0.08	0.002
Brown	*n*	14/23	61	47	17/26	65	94	*Fv-1^n* mice	0.75	0.30
	nb	5/50	10	15	14/51	27	43	*Fv-1^{nb}* mice	0.25	0.09
Black	N.T.	2/7			2/4			*n* vs. *nb*		
Brown	N.T.	2/5			4/7			Total	$\ll$0.001	$\ll$0.001
Black	Total	38/93	41	42	59/90	66	75	Black mice	$<$0.01	0.03
Brown	Total	21/78	27	36	35/84	42	71	Brown mice	$\ll$0.001	0.005
Total	*n*	43/77	56	49	58/80	72	85			
Total	*nb*	12/82	15	20	30/83	36	52			

* Mice that were positive for virus at either 2 or 8 wk are considered positive mice.

‡ *P* value determined by comparing the proportions positive for virus. Chi-square test with 1 degree of freedom.

correlate with coat color, but there is no such correlation in crosses involving only *Fv-1^n* strains.

A possible objection to the above-described studies is that the *Fv-1* typing results might have been biased by the endogenous MLV infection. On the one hand, the endogenous virus might conceivably act as a helper virus (8), which could increase the spleen focus response to Friend virus and result in a mouse of *Fv-1^{nb}* genotype being classified as *Fv-1^n*. On the other hand, the endogenous infection might produce some protection, resulting in fewer spleen foci and classification of an *Fv-1^n* mouse as *Fv-1^{nb}*. To obviate these difficulties, two crosses between mice of low virus strains were examined for linkage between *Fv-1* and *b* (Table I, lines 2 and 3). There was again correlation between the two markers; for the two groups combined, $\chi^2 = 5.6$, $P = 0.02$.

Analysis of the literature on incidence of spontaneous leukemia in hybrids between AKR and low leukemia strains suggests that the *Fv-1* type of the latter is a major determinant (6). This is compatible with the concept that cell-to-cell spread of virus is important in the pathogenesis of this disease. In attempting to determine whether other types of tumors are caused by endogenous MLV infection, which might be by presently unknown host-range types and affected by unrecognized *Fv-1* subtypes, segregation analysis of tumor occurrence in relation to inheritance of the *Fv-1* locus could be useful, particularly if a closely linked marker can be found.

A preliminary finding suggests that *Fv-1* may be close to the *Gpd-1* locus, which is on linkage group VIII about 32 map units from *b* (9). Axelrad et al.

(10) have produced a line (SIM.R) congenic with SIM mice (*Fv-1*^{n}), but carrying the *Fv-1*^{b} allele from C57BL/6; these mice were inbred after the eighth backcross generation to SIM. We have found that in addition to the *Fv-1* locus, SIM.R carries the *Gpd-1*^{a} allele from C57BL, the SIM strain being *Gpd-1*^{b}.

SUMMARY

The *Fv-1* gene, which regulates sensitivity of mouse cells to infection by naturally occurring host-range types of murine leukemia virus, was shown to be located on linkage group VIII (chromosome 4), 39 map units from *b*.

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