A MOUSE GENE ON CHROMOSOME 5 THAT RESTRICTS INFECTIVITY OF MINK CELL FOCUS-FORMING RECOMBINANT MURINE LEUKEMIA VIRUSES

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Mice of the AKR strain are characterized by a high incidence of spontaneous thymic lymphomas occurring after 6 mo of age. Although expression of endogenous ecotropic murine leukemia virus (MuLV)[1] is an essential element for the development of the disease, a crucial step in pathogenesis is the emergence in the thymus, during the preleukemic period, of novel recombinant MuLV, the mink cell focus-forming (MCF) viruses (1). These are genetic recombinants between the endogenous ecotropic MuLV, viral sequences related to xenotropic MuLV, and possibly endogenous sequences unique to MCF MuLV. The MCF viruses found in preleukemic and leukemic AKR thymuses are able to induce thymic lymphomas early in life when inoculated into young AKR mice (2).

The ability of both ecotropic and MCF viruses to spread in mouse cells is determined by alleles at the *Fv-1* locus. Nonpermissive *Fv-1* alleles inhibit the spread of ecotropic virus and the emergence and subsequent spread of MCF viruses, and as a consequence are highly protective against development of spontaneous thymomas. During studies of infection of tissue cultures with MCF viruses we have found an additional gene of the mouse, distinct from *Fv-1*, that inhibits exogenous infection of cells by MCF but not ecotropic viruses. This report describes the characteristics and chromosomal mapping of this gene.

Materials and Methods

Mice. Inbred mice were obtained from The Jackson Laboratory, Bar Harbor, ME and the National Institutes of Health Small Animal Production Section. Hybrids were bred in our laboratories. The AKXD recombinant inbred lines were obtained through the generosity of Dr. Benjamin A. Taylor, The Jackson Laboratory, and were derived by brother-sister mating beginning with the F_2 generation after crossing AKR/J and DBA/2J. NS.*Hm* mice are NFS mice partially congenic for the gene *Hm* (hammertoe), which was derived originally from marker stock from The Jackson Laboratory; the NS.*Hm* congenics were bred in our laboratory. *Hm* is a dominant, fully penetrant gene that produces an easily recognized flexion deformity of the toes.

Viruses and Tissue Cultures. The majority of assays for sensitivity to MCF virus were carried out with MCF AKR-13, an N-tropic isolate obtained from the thymus of a young AKR grafted with thymus from a 6-mo old AKR (2), and the NB-tropic HIX strain of Moloney MCF, isolated by Fischinger et al. (3) from a Moloney MuLV stock passaged in BALB/c. Both of these viruses, as well as other MCF isolates mentioned below, were

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[1] *Abbreviations used in this paper:* MCF, mink cell focus-forming; MuLV, murine leukemia virus.

propagated in the CCL64 mink lung cell line (MiLu) (4), after having been carried through two limiting dilution purification titrations in these cells. In most cases, one or more virus passages in mouse SC-1 cells (5) were also used to eliminate possible contaminating xenotropic virus. Ecotropic virus pools were prepared in infected mouse SC-1 cells. All infections were carried out in medium containing polybrene (16 μg/ml; Abbott Laboratories, North Chicago, IL). Cells were grown and maintained in the Dulbecco-Vogt modification of Eagle's minimum essential medium supplemented with 10% heat-inactivated (56°C, 30 min) fetal calf serum, glutamine, and antibiotics, except for SC-1 cells which were maintained in 5% heated fetal calf serum in Eagle's minimal essential medium. For tests of various inbred and hybrid mice, secondary cultures of either whole mouse embryo or tail fibroblasts from 2–8-wk old animals were used.

Virus Assays. Ecotropic viruses were titrated in tissue culture by the XC plaque procedure (6). Infection of mouse cells by MCF viruses was assayed by a "UV-Mink" procedure: Cultures were infected in the same manner as for plaque titrations except that 3 d later they were UV-irradiated and overlaid with 2×10^5 MiLu cells. Foci of MCF cytopathic changes were scored 5–7 d later, using a dissecting microscope.

Results

Strain Differences in Sensitivity to MCF Virus Infection In·Vitro. In studying the sensitivity of mouse cells in tissue culture to MCF virus infection it was found that cells from three mouse strains known to carry the *Fv-1*^{n} allele were unexpectedly resistant to both N- and NB-tropic MCF isolates. These exceptional strains were DBA/1, DBA/2, and CBA/N. The data for representative tests of various *Fv-1*^{n} strains are shown in Table I. Although all strains are within the expected range of sensitivity to ecotropic virus infection (8), sensitivity to MCF viruses clearly falls into two classes. The restriction is not absolute but is reproducibly 30–100-fold lower for MCF viruses isolated from a variety of sources including AKR, C58, and NFS mice congenic for ecotropic virus loci from these strains, and Friend MuLV stocks; the restriction of the HIX isolate of Moloney-derived MCF is somewhat less, averaging 10–30-fold. The restriction

TABLE I

Relative Sensitivity to Ecotropic and MCF MuLV of Cell Cultures Derived from Selected Fv-1^n *Mouse Strains*

Mouse strain	Percent of virus titer in NFS*											
	Ecotropic MuLV‡				MCF MuLV§							
	AKR L1	AKR Th-2A	Mol	Fr	AKR13	*Akv-1* C36	*Akv-2* C34	C58/J Th-1	GPA MCF-1	PTV-1	HIX	Fr MCF-1
CBA/J	40	13	16	16	25	32	25				50	7
DBA/1					1.6	0.5	0.5				4.0	
DBA/2	63	25	50	90	0.6	0.4	2.0	0.5	1.2	1.2	4.0	0.4
CBA/N	63	63	25	40	1.3	0.3	0.6			0.8	3.2	0.2
(NFS × DBA/1)F$_1$					4.0	2.5	1.0					
(NFS × DBA/2)F$_1$					4.0						6.2	

* Ecotropic viruses were assayed by XC plaque test; MCF viruses were assayed by UV-mink assay except for GPA MCF-1 which was tested by a fluorescent antibody focus assay.

‡ AKR L1 and AKR Th-2a are N-tropic isolates from AKR mice; Mol and Fr are tissue culture-cloned and -passaged NB-tropic Moloney and Friend viruses, respectively.

§ *Akv-1* C36 and *Akv-2* C34 have been described previously (2). C58/J Th-1 was isolated from thymus cells of a 9-mo old C58/J; GPA MCF-1 was isolated from a thymic lymphoma induced in an NFS mouse by a tissue culture stock of Gross passage A ecotropic virus. PTV-1 was the kind gift of Dr. Robert Schwartz, Tufts New England Medical Center, and is an N-tropic MCF-type virus obtained from HRS/J (7). Fr MCF-1 was the kind gift of Dr. Edward Scolnick, National Cancer Institute, and was isolated from a mouse infected with NB-tropic Friend virus.

TABLE II

Characteristics of Resistance of DBA/2 Cell Cultures to MCF Viruses

	Virus	Virus dilution	Helper virus*	Infectious center titer‡ after infection of:	
				NFS	DBA/2
				MCF FFU§ per $10^{5.3}$ cells	
A	Moloney MCF, HIX	$10^{-0.3}$			4.1
		$10^{-0.6}$			4.0
		$10^{-0.9}$		4.8	4.0
				MSV FFU per $10^{5.3}$ cells	
B	Ki MSV (Moloney‖		Moloney	3.3	3.2
	Ki MSV (247 MCF)		Moloney	3.9	2.5
	Ki MSV (247 MCF)		AKR L1	3.9	2.8
	Ki MSV (*AKV1* C44-2 MCF)		AKR L1	3.8	2.2
				MCF FFU per $10^{5.3}$ cells	
C	AKR 13 MCF		—	3.7	2.6
	AKR 13 MCF (Moloney)¶		—	3.9	3.1
	AKR 13 MCF		Moloney	3.7	2.5

* Helper MuLV was added at the time of initial infection at a multiplicity of ~1 plaque-forming unit per cell.

‡ Secondary cell cultures of NFS and DBA/2 embryos were infected and 16–18 h later trypsinized in 0.75% trypsin solution (to inactivate extracellular virus). The cells were washed, mitomycin C-treated (1) diluted in 10% fetal calf serum in Dulbecco's medium and plated as infectious centers on MiLu cells (*A* and *C*) or NRK cells (*B*). MiLu cells were read for MCF foci at 5 or 6 d. NRK cells (maintained on Eagle's medium with 5% fetal calf and 1% dimethyl sulfoxide) were read for MSV foci at 6–8 d.

§ Focus-forming units.

‖ Kirsten (Ki) MSV pseudotype pools were prepared by co-cultivation of Moloney or MCF MuLV-infected cells with the Ki MSV nonproducer cell line KNRK.

¶ AKR 13 MCF (Moloney) designates a mixed virus population containing parental viruses and phenotypically mixed virions generated after co-infection of SC-1 cells. The existence in the resulting harvest of AKR 13 MCF genomes (N-tropic) with Moloney MuLV (NB-tropic) virion components was indicated by a >10-fold increase in efficiency of the MCF virus infection of BALB/c cells that are resistant to AKR 13 MCF by virtue of *Fv-1^b* restriction (data not shown).

of both N- and NB-tropic MCF viruses in the resistant cells is further evidence of lack of association of this resistance with the *Fv-1* gene system. It is noteworthy that of the two CBA sublines tested, CBA/J is sensitive while CBA/N is resistant. CBA/J showed a clearcut resistance to the Friend MCF virus, but it was of the same degree as its resistance to ecotropic Friend virus; consequently, we do not relate this to the MCF resistance of the other CBA subline.

Table II shows the results of representative infectivity assays that illustrate some general properties of the restriction of MCF viruses in DBA/2 cell cultures. The dose response of MCF virus infection of resistant DBA/2 secondary embryo cells shows a one-hit pattern (Table II*A*). Second, Kirsten strain (Ki) of murine sarcoma virus when rescued from nonproducer cells by infection with MCF viruses shows the same restriction as the MCF helper (Table II*B*). This observation suggests that the block to efficient infection is a cell surface phenomenon involving a viral envelope protein rather than the viral genome. Third, phenotypic mixtures of MCF viruses and an ecotropic or amphotropic MuLV tend to show less restriction of MCF virus titer in restrictive cells compared with the

MCF virus alone, but titers do not attain the level reached in permissive cells (Table II*C*).

Genetic Analysis. In studies of tissue cultures of hybrids of MCF-sensitive strains (NFS, C57L, and AKR) and DBA/1, DBA/2, or CBA/N, the restriction of infection was seen to be dominant or semidominant; titers were often slightly higher in cultures from heterozygotes as compared with the parental resistant strain (Table I). Tests of backcrosses to the sensitive parent revealed single gene segregation ratios (96/211; 45.5%).

An indication of linkage of the MCF resistance determinant to a chromosome 5 marker was first noted in studies of the AKR × DBA/2 (AKXD) recombinant inbred strains (Table III). Reassortment frequency between *Pgm-1* and MCF resistance in these lines indicated linkage with a recombinational distance of 22 cM. This linkage was confirmed by backcross analysis (Table IV), which estimated the map distance as 20 ± 4.8 cM.

TABLE III

*Distribution of RMcf and Pgm-1 Alleles Among AKXD RI Strains**

Genotype							
Progenitor Type				Recombinant Type			
RMcf[r]	*Pgm-1*[b] (DBA/2)	*RMcf*[c]	*Pgm-1*[a] (AKR)	*RMcf*[a]	*Pgm-1*[b]	*RMcf*[r]	*Pgm-1*[a]
AKXD	1, 3, 4, 5 7, 9, 25	AKXD	6, 10, 14, 17 20, 21, 23, 26, 22	AKXD	8, 11, 12, 16 24, 27	AKXD	13, 15, 18, 22
Dissociations (R) = 10/26‡							

* Typing for *RMcf* alleles was performed by UV-mink testing of tail fibroblast cultures prepared from two mice of each RI strain and inoculated with dilutions of AKR 18 MCF virus. *Pgm-1* typing data were provided by Dr. B. A. Taylor, The Jackson Laboratory.
‡ Using the formula for estimating map distance (r) for linked alleles in RI lines, R = 4r/(1 + 6r) (9), r = 22 cM.

TABLE IV

Linkage Analysis of MCF Resistance and Markers on Chromosome 5

A. Recombination between *Pgm-1* and MCF resistance.

	Number of mice inheriting Pgm-1 allele from indicated parent in progeny of:					
	NS × (NS × DBA/1)F_1		(DBA/2 × C57L)F_1 × C57L		(AKR × DBA/2)F_1 × AKR	
	NS	DBA/1	C57L	DBA/2	AKR	DBA/2
MCF sensitive	6	3	6	1	14	6
MCF resistant	0	7	1	11	3	11
Recombination	3/16		2/19		9/34	
Total	14/69 = 20 ± 4.8					

B. Recombination between hammertoe (*Hm*) and MCF resistance.

	Number of mice with indicated phenotype in progeny of:							
	NS × (CBA/N × NS.*Hm*)F_1		NS × (DBA/2 × NS.*Hm*)F_1		(DBA/2 × NS.*Hm*)F_1 × NS		NS × (NS.*Hm* × DBA/2)F_1	
	+/+	+/*Hm*	+/+	+/*Hm*	+/+	+/*Hm*	+/+	+/*Hm*
MCF sensitive	1	28	1	25	1	16	0	7
MCF resistant	20	2	14	0	18	1	8	0
Recombination	3/51 = 6 ± 3.3				3/91 = 3.3 ± 1.9			

TABLE V

Distribution of Rmcf^r and Rmcf^s Among Inbred Mouse Strains

Genotype		Strain	Plating efficiency of MCF virus* N-tropic percent of NFS titer	B-tropic percent of BALB/c titer	NB-tropic percent of NFS titer
Fv-1^n	*Rmcf^s*	C57L/J	100		200
		C57Br/cdJ	100		125
		SJL/J	62		
		AKR/J	34		
		C3H/Bi	32		40
		C3H/HeN	32		27
		CBA/J	32		34
		C58/J	25		50
		ST/b	25		
		SEA/J	20		
	Rmcf^r	DBA/1	1.4		4
		DBA/2	0.7		2.7
		CBA/N	0.8		2.5
		CBA/CaJ	0.2		0.2
		CBA/CaHN	0.3		0.2
Fv-1$^{n(r)}$‡	*Rmcf^s*	129/J			200
		NZW			63
		RF/J			40
		F/St			20
		NZB			10
Fv-1^b	*Rmcf^s*	BALB/cAnN			100
		C57BL/6		63	63
		A/J			63
		I/St		80	63

* Virus strains used were AKR 13 MCF (N-tropic), CB208 MCF (B-tropic), and HIX isolate of Moloney MCF (NB-tropic). Mouse embryo or tail tissue cultures were tested for MCF sensitivity by the UV-mink procedure. For the majority of strains the value given represents the mean of two or more tests.

‡ The designation *Fv-1$^{n(r)}$* is given to the subset of *Fv-1^n* strains that show decreased sensitivity to N-tropic MuLV (8; unpublished data).

Further localization of the MCF resistance gene on chromosome 5 was done by crosses involving *Hm*, the hammertoe locus, which is about 18 cM toward the centromere from *Pgm-1*. As shown in Table IV, crosses to this marker showed close linkage (3–6 cM) between *Hm* and the MCF resistance genes of CBA/N and DBA/2. We propose to designate the MCF resistance gene *Rmcf*, with resistance and sensitivity alleles designated *Rmcf^r* and *Rmcf^s*, respectively.

The strain distribution of alleles of *Rmcf* is shown in Table V. As noted above, CBA/J is *Rmcf^s*, while the sublines descended from CBA/Ca (CBA/CaJ, CBA/CaHN, and CBA/N) are all *Rmcf^r*. The *Fv-1$^{n(r)}$* strains appear to be *Rmcf^s* based on their relative sensitivity to NB-tropic virus; a consistent 10-fold reduction in titer on NZB cells has been encountered but we consider this to be a function of the generally reduced permissiveness to exogenous MuLV infection found in cells of this strain. The 4 *Fv-1^b* strains tested were *Rmcf^s*.

Establishment of Rmcf^r Congenic Strains. To facilitate study of the effect of the MCF virus resistance gene on viral leukemogenesis and to permit comparison of

Rmcf^r alleles from different sources on a standard genetic background, the *Rmcf* gene loci from DBA/2 and from CBA/N are being bred into NFS, a strain that is of known sensitivity to several leukemogenic viruses, negative for ecotropic MuLV, and low in expression of xenotropic MuLV and related antigens. To simplify construction of the congenic lines and to provide a morphologic marker by which *Rmcf*^{r} and *Rmcf*^{s} segregants can be scored, a recombinant male that had been typed as carrying the morphologic locus *Hm* and the *Rmcf*^{r} locus in coupling was selected from each of the first backcross populations generated from the mating combinations NFS × (DBA/2 × NS.*Hm*)F_1 and NFS × (CBA/N × NS.*Hm*)F_1. These males were mated to NFS females. For each subsequent generation, mice of *Hm* phenotype are selected for breeding and are typed for MCF virus sensitivity; to date no dissociations have been detected among 135 segregants tested. Lines of NFS partially congenic for *Rmcf*^{r} from DBA/2 and CBA/N, in coupling with *Hm*, are at present at the 7th backcross level.

Discussion

The studies presented here establish that DBA/2, DBA/1, CBA/Ca, and CBA/N mice carry a gene on chromosome 5, closely linked to *Hm*, that specifically decreases the efficiency of infection of their cells by MCF-type recombinant MuLV. The recombinational distance from *Hm*, based on the total experience with first backcross mice (Table IV*B*) and the segregants from the congenic lines, is estimated at 6/277, or 2.2 ± 0.9 cM.

Since the common feature of the various MCF viruses is their gp70, it seems likely that the *Rmcf*^{r} restriction operates at the level of the interaction of the viral gp70 with the cell. However, there are no data that directly bear on this point. Sensitivity to the restriction can be conferred by phenotypic mixing, as with MCF pseudotypes of MSV, but this only rules out the viral genome as the target of the restriction.

It seems a distinct possibility that the *Rmcf*^{r} gene could be an endogenous MCF-related MuLV genome, acting by expression of its *env* gene, analogous to the effect of certain defective endogenous avian leukosis proviruses (10). It is now clear that a large proportion of the many biochemically detected endogenous MuLV genomes in the mouse have *env* gene regions that resemble those of MCF viruses (11, 12). It is not yet known whether these genomes are expressed, but if they are, it would be expected that their gp70 products would blockade MCF virus receptors and not affect receptors for ecotropic viruses, as suggested by the studies of Rein (13) which indicate lack of cross-interference between ecotropic and MCF viruses and imply distinct cell surface receptors for these two MuLV classes. Kozak (manuscript submitted for publication) has recently shown that the major cell determinants, presumably receptors, for sensitivity of mouse cells to ecotropic and MCF MuLV, are distinct from one another and are coded by genes on different chromosomes.

Since MCF gp70 are cross-reactive with those of xenotropic MuLV, it might be expected that mice carrying the *Rmcf*^{r} allele would show higher expression of certain xenotropic-related cell surface antigens. While DBA/2 mice do show high level expression of xenotropic-related antigens (XenCSA) on many tissues, DBA/1 and CBA/N mice do not (14). Also, in limited tests of NFS.*Rmcf*^{r}

congenics, we have not found evidence of increased XenCSA expression.

In studies of the interrelationship of resistance to leukemogenesis and failure to generate MCF-type viruses after inoculation of various strains of mice with Friend helper MuLV, Ruscetti et al. (15) and Bassin et al. (16) have reported that expression of an MCF MuLV-related envelope precursor protein ($gPr80^{env}$) is correlated with the resistant phenotype: NIH Swiss and BALB/c are sensitive and are negative for expression of MCF-$gPr80^{env}$, while DBA/2 and C57BL/6 are resistant and positive for expression of this protein. Expression of MCF-$gPr80^{env}$ appears to be dominant in hybrids of DBA/2 and BALB/c. Further, Bassin et al. (16) have presented evidence that the mechanism for MCF virus restriction in DBA/2 cell cultures is analogous to viral interference, with MCF virus infection being blocked in these cells by the constitutively expressed MCF-related $gPr80^{env}$. However, identity of *Rmcf*^{r} and the $gPr80^{env}$ determinant seems unlikely in view of the discrepancy between the two in C57BL/6, which is *Rmcf*^{s} but positive for MCF $gPr80^{env}$ expression.

It is noteworthy that the *Rmcf* gene is located in the same chromosomal region as one of the endogenous ecotropic proviruses, *Cv-1* (17, 18). This provirus is carried by a group of related mice, including BALB/c, C3H, A, and, strikingly, CBA/J. The two CBA substrains that carry *Rmcf*^{r}, CBA/Ca, and CBA/N, do not carry this locus (or any other ecotropic provirus) as judged by biologic and biochemical analyses (unpublished data). *Rmcf* and *Cv-1* are both closely linked to *Hm*, but whether they are allelic has not been determined. It is also of interest that *Rec-1*, the locus for the ecotropic MuLV receptor, is on chromosome 5 (19), but its position is not known.

Both DBA/2 and certain CBA mice have been reported to be anomalously resistant to viral leukemogenesis both with ecotropic Friend helper virus (15) and Moloney virus inoculation (20), and in F_1 hybrids (21) or chimeras (22) with AKR. Whether the *Rmcf* gene is playing a major role in this resistance will require further study, particularly since many reports of studies involving CBA mice unfortunately failed to designate the substrain used.

Perhaps the greatest usefulness of the *Rmcf* gene is its providing a method to evaluate the importance of MCF-type recombinants in various forms of exogenous and endogenous viral leukemogenesis. The NFS congenic lines that we have derived with the gene in coupling with the fully penetrant morphologic marker *Hm* are being used in a variety of studies of this type.

Summary

DBA/1, DBA/2, CBA/N, and CBA/Ca mice carry a gene which specifically restricts infectivity of mink cell focus-forming (MCF) murine leukemia viruses. The gene, designated *Rmcf*^{r}, is dominant or semidominant and maps to chromosome 5; it is closely linked to the morphologic marker gene *Hm*. The *Rmcf* gene may be of much use as a means of determining the role of MCF viruses in various forms of leukemogenesis.

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