Proc. Natl. Acad. Sci. USA
Vol. 80, pp. 505–509, January 1983
Genetics

H-2-linked regulation of xenotropic murine leukemia virus expression

(xenotropic viruses/F/St and B10.F mice)

ROBERT A. YETTER, JANET W. HARTLEY, AND HERBERT C. MORSE III*

Laboratory of Microbial Immunity and Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20205

Communicated by Wallace P. Rowe, October 25, 1982

ABSTRACT **A high proportion of lymphocytes from F/St mice produce infectious xenotropic murine leukemia virus (X-MuLV) and express high levels of cell surface antigens, termed XenCSA, related to the major glycoprotein of X-MuLV. In crosses of F/St with AKR, the high-virus phenotype of F/St was found to be recessive and was shown to be governed by a single locus, *Cxv-1*, less than 2 centimorgans from *H-2K*. The close association of *Cxv-1* with the *H-2* complex was confirmed by the observation that B10.F mice, congeneic for the *H-2* region of F/St, expressed high levels of infectious X-MuLV and XenCSA, whereas C57BL/10 mice and other C57BL/10 *H-2* congeneic strains did not. Studies of hybrid mice homozygous for *Cxv-1*^{s}, but segregating for a chromosome 1 X-MuLV induction locus (V locus) of F/St, demonstrated that the high-virus phenotype of F/St was dependent on the interaction between *Cxv-1* and the chromosome 1 V locus.**

Genetic information coding for xenotropic murine leukemia viruses (X-MuLVs) is present in multiple copies in the cellular DNA of all mice (1, 2), but different inbred strains vary greatly in their expression of this information as infectious virus or as virus-coded glycoprotein gp70 (XenCSA, X-MuLV-related cell surface antigens) on the surface of lymphocytes (3, 4). Earlier studies demonstrated that some of the differences in expression of infectious X-MuLV could be attributed to the presence of loci for induction of infectious virus (V loci) in some strains and their absence from others (5–8). For many strains, the X-MuLV loci have been shown to be present on chromosome 1 at or near *Bxv-1* (5, 6, 9). Variations in XenCSA levels among inbred strains were also shown to be influenced by V loci (8), but other differences were attributable to the effects of a locus on chromosome 4 linked to *Fv-1* (10, 11).

Recently, we described another locus that has a major effect on expression of X-MuLV as infectious virus and XenCSA in F/St mice (9). A high proportion of thymocytes and spleen cells from mice of this strain produced infectious ecotropic MuLV and X-MuLV and expressed high levels of XenCSA. Studies of hybrids between F/St and other inbred strains showed that the high ecotropic MuLV phenotype of F/St was governed by three or more dominant, independently assorting V loci. However, the high X-MuLV phenotype of F/St was found to be a recessive trait that was governed by a single locus. This locus was not linked to the X-MuLV V locus of F/St on chromosome 1 or to marker loci on chromosomes 4, 5, 6, 7, 9, or 14. Expression of infectious ecotropic MuLV was not detectably affected by this locus.

In this report, we demonstrate that the locus governing X-MuLV expression in F/St mice is located on chromosome 17 within or tightly linked to the major histocompatibility complex (*H-2*). This locus appears to regulate the levels to which infectious X-MuLV and XenCSA are expressed from loci on chromosome 1.

MATERIALS AND METHODS

Mice. F/St (*H-2*^{p}, *Fv-1*$^{n(r)}$, *Ly-9.2*) mice were bred in our colony. B10.F/Sg (*H-2*^{p}, *Fv-1*^{b}) mice were from a colony established from breeders provided by Jack Stimpfling. C57BL/10SnJ (*H-2*^{b}, *Fv-1*^{b}), AKR/J (*H-2*^{k}, *Fv-1*^{n}), B10.BR/SgSnJ (*H-2*^{k}, *Fv-1*^{b}), and BDP/J (*H-2*^{p}, *Fv-1*^{n}, *Ly-9.1*) mice were purchased from The Jackson Laboratory. P/N (*H-2*^{p}, *Fv-1*^{n}) mice were from the colonies of the National Institutes of Health.

Antibodies. Monoclonal anti-H-2K^k was purchased from Becton Dickinson. Fluorescein-labeled monoclonal anti-Ly-9.1 was prepared from supernatants of cultures of the 30C7 cell line, generously provided by Jeff Ledbetter (12). Fluorescein-labeled Fab fragments of goat anti-mouse IgG2 were generously provided by B. J. Fowlkes, National Institute of Allergy and Infectious Diseases. The reagent for assaying XenCSA consisted of fluorescein-labeled F(ab')$_2$ fragments of IgG obtained from the serum of a rabbit (R283) immunized with SIRC cells infected with NZB X-MuLV, prepared as described (4). These antibodies react preferentially with cell surface gp70s related to the envelope gp70s of X-MuLV and mink cell focus-inducing MuLV.

Virus Assays. Suspensions of lymphocytes from thymus and spleen were prepared for infectious center assays of mitomycin C-treated (25 μg/ml for 30 min at 37°C) cells as described (4, 13). X-MuLV was assayed for focus induction in sarcoma virus-positive, leukemia virus-negative (S^+L^-) mink lung cells (14); titers are expressed as focus-forming units (ffu) per 10^7 lymphoid cells. Ecotropic MuLV was assayed by plaque induction in XC cells as described (13); titers are expressed as plaque-forming units (pfu) per 10^7 cells.

Expression of XenCSA was assayed by flow microfluorometry (FMF) using a fluorescence-activated cell sorter (FACS II; Becton Dickinson FACS Systems) and fluorescein-labeled antibodies from rabbit R283 (4). The intensity of staining detected on a population of lymphocytes is expressed as the mean fluorescence value (4) and was determined by using either linear or logarithmic amplification of signals from the photomultiplier tubes. XenCSA values are given as geometric means.

Assays for H-2K^k and Ly-9.1. Single-cell suspensions from spleen (100 μl, 2×10^7 cells per ml) were allowed to react with unlabeled or labeled monoclonal antibodies for 30 min at 4°C.

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Abbreviations: MuLV, murine leukemia virus; X-MuLV, xenotropic MuLV; V locus, a locus governing inducibility of MuLV; S^+L^-, sarcoma virus-positive, leukemia virus-negative; XenCSA, X-MuLV-related cell surface antigens; ffu, focus-forming units; pfu, plaque-forming units; FMF, flow microfluorometry.

* To whom reprint requests should be addressed at: LMI-NIAID-NIH, Building 7, Room 335, Bethesda, MD 20205.

After two washes, cells that had been allowed to react with unlabeled reagents were incubated for an additional 30 min at 4°C with fluorescein-labeled anti-mouse IgG2. Individual animals were designated as being homozygous, heterozygous, or negative for alleles at these loci by comparing the staining detected on their spleen cells by FMF with that detected on positive, negative, and F_1 controls.

RESULTS

Expression of X-MuLV by mice from crosses between AKR and F/St. Previous studies of F_1 mice from crosses between F/St and strains with low spontaneous expression of X-MuLV, such as AKR, showed that the high X-MuLV phenotype of F/St was recessive, whereas the high ecotropic MuLV phenotype was dominant (9). Further analyses of F_1 × F/St mice demonstrated that the high X-MuLV phenotype of this strain was determined by a single recessive gene for which no chromosomal location was established (9). In the present study, crosses between AKR and F/St mice were tested for possible linkage between alleles at the locus governing X-MuLV expression and alleles at *H-2*. Spleen cells and thymocytes from (AKR × F)F_1 × F/St mice were assayed for infectious X-MuLV by cocultivation with mink S^+L^- cells. Cells from the same preparations were also assayed for XenCSA and alleles at *H-2K* by FMF.

The results of these tests demonstrated the following points: First, as in earlier studies of (NFS × F)F_1 × F/St and (C57L × F)F_1 × F/St mice (9), the high X-MuLV phenotype of F/St was controlled by a single recessive gene with greater effects on thymocytes than on spleen cells (Table 1, Fig. 1). A high proportion of thymocytes from 23 of 53 (AKR × F)F_1 × F/St mice (43%) produced infectious X-MuLV and expressed high levels of XenCSA (mean fluorescence values greater than 400; Fig. 1*A*). In contrast, thymocytes from the remaining 30 mice produced little or no infectious X-MuLV and expressed low levels of XenCSA. Similar studies of spleen cells from 29 of these mice showed several differences from the studies of thymocytes. First, the proportions of virus producing cells formed a near continuum from $\leq 10^{0.3}/10^7$ cells to $10^{3.9}/10^7$ cells instead of giving two distinct sets. In addition, XenCSA levels on spleen cells from mice with a high proportion of virus-producing cells were not significantly higher than XenCSA levels on spleen cells from mice producing little or no infectious X-MuLV.

Second, studies of the same mice for segregation of alleles at *H-2K* demonstrated that the high-virus phenotype for thymocytes (infectious X-MuLV and XenCSA) was observed only in mice homozygous for the *H-2K* allele of F/St [$H\text{-}2^p$ (15)], whereas thymocytes from $H\text{-}2K^k/H\text{-}2K^p$ heterozygotes, except for one mouse, produced no infectious virus and expressed low levels of XenCSA (Fig. 1*A*). In studies of spleen cells, the majority of mice with low proportions of virus-producing spleen cells ($<10^{1.0}/10^7$ cells) were heterozygous at *H-2K*, whereas spleen cells from mice homozygous at this locus generally had higher proportions of virus-producing cells (Fig. 1*B*). Finally, thymocytes from backcross segregants of both the high and low X-MuLV phenotypes produced equivalent levels of infectious ecotropic MuLV (data not shown).

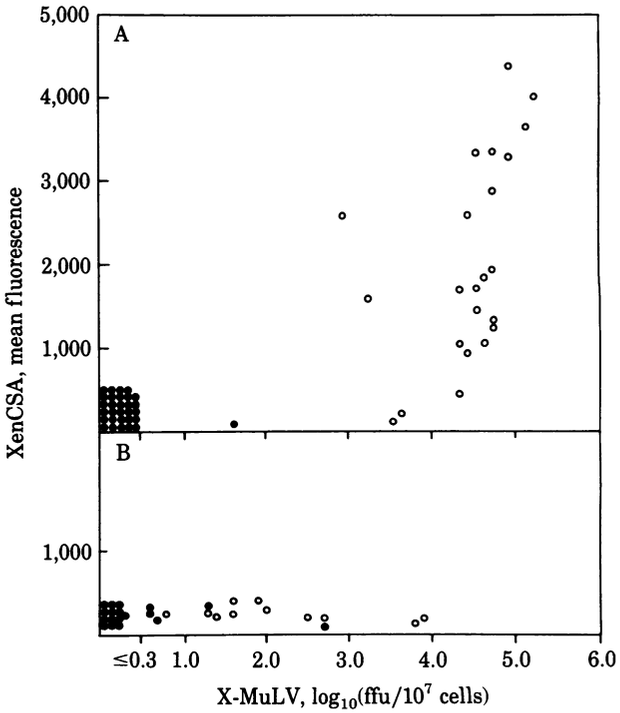

FIG. 1. Thymocytes from 53 (AKR × F)F_1 × F/St mice (*A*) and spleen cells from 29 of the same mice (*B*) were tested for the proportions of virus-producing cells (*x* axis) and expression of XenCSA (*y* axis) and for alleles at *H-2K*. Values for $H\text{-}2K^p/H\text{-}2K^p$ mice are given as ○; values for $H\text{-}2K^k/H\text{-}2K^p$ mice are given as ●. XenCSA values for thymocytes and spleen cells of all heterozygotes at $H\text{-}2^k$ were less than 406.

Table 1. Expression of infectious X-MuLV and XenCSA by lymphocytes

Mice	Ecotropic MuLV, $\log_{10}$(pfu/10^7 cells)*		X-MuLV (mink S^+L^-), $\log_{10}$(ffu/10^7 cells)*		XenCSA, mean fluorescence†	
	Thymus	Spleen	Thymus	Spleen	Thymus	Spleen
F/St	3.8	4.6	3.8	2.9	2,575	621
AKR	4.0	5.2	0	0	61	114
(AKR × F)F_1	4.9	4.6	0	1	56	117
C57BL/10	0	0	0	0	64	92
B10.BR	0	0	0	0	66	94
B10.F	3.6	4.5	2.7	1	2,730	474
(B10.BR × B10.F)F_1	0	0	0	0	62	97
P	0	0	0	0	51	95
BDP	0	0	0	0	54	93
(BDP × F)F_1	2.8	3.6	4.5	2	2,239	187
(P × F)F_1	3.6	4.6	4.8	3	2,604	280

* Values indicate the mean for two to nine mice 2–5 months of age. The SEM was less than 1.0 ($\log_{10}$) for all strains and F_1s tested.

† Fluorescence values determined by using linear amplification of signals from the photomultiplier tubes. Values indicate the mean for 2 to 15 mice 2–6 months of age. The SEM was less than 22% of the mean for all strains and F_1s tested.

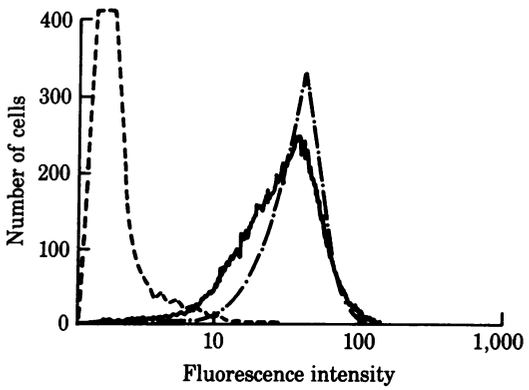

FIG. 2. Fluorescence profiles of thymocytes from F/St (——), B10.BR (– – –), and B10.F mice (–·–) that had reacted with fluorescein-labeled rabbit antibodies to XenCSA. The profiles were generated by using logarithmic amplification of signals from the photomultiplier tubes.

These results demonstrate that, in crosses between AKR and F/St, a single locus, which we will call *Cxv-1*, governs high versus low expression of infectious X-MuLV and XenCSA by thymocytes and, to a lesser extent, high versus low expression of infectious X-MuLV by spleen cells. The locus has no discernible effect on ecotropic MuLV expression. F/St carries a recessive, permissive allele ($Cxv\text{-}1^s$) at this locus, whereas AKR carries a dominant, restrictive allele ($Cxv\text{-}1^r$). The data also indicate that *Cxv-1* is located less than 1.9 ± 1.8 centimorgans from *H-2K*.

Expression of X-MuLV in B10.F Mice. If *Cxv-1* were closely linked to or within *H-2*, it would be expected that mice bearing the same *H-2* haplotype as F/St might express high levels of infectious X-MuLV and XenCSA. To evaluate this possibility, thymocytes and spleen cells from mice of the *H-2* congeneic strains B10.F and B10.BR as well as C57BL/10 were assayed for these two parameters of virus expression; C57BL/10 and the *H-2* congeneics carry a X-MuLV V locus at *Bxv-1* (5). The results of these assays (Table 1) demonstrated that, in comparison to lymphocytes from C57BL/10 and B10.BR mice, a high proportion of thymocytes and spleen cells from B10.F mice produced infectious X-MuLV, equivalent to the levels observed with F/St. In addition, XenCSA levels on thymocytes (Fig. 2, Table 1) and spleen cells (Table 1) were in the range of values observed with cells from F/St. It should be noted that infectious ecotropic MuLV was also produced by a high proportion of thymocytes and spleen cells from B10.F mice. All isolates tested have been B-tropic in host range and the high ecotropic MuLV phenotype of this strain appears to be due to maternal transfer of virus, at least in part through the milk (unpublished observations). Earlier studies have shown that certain other C57BL/10 *H-2* congeneic strains express high levels of ecotropic MuLV as a result of non-*H-2*-linked differences from C57BL/10 (16).

To verify that the differences in X-MuLV expression between B10.F and B10.BR mice were determined by a *H-2*-linked locus, thymocytes from (B10.BR × B10.F)F_1, (B10.BR × B10.F)F_1 × F/St, and F/St × (B10.BR × B10.F)F_1 mice were examined for production of infectious X-MuLV, expression of XenCSA, and segregation of alleles at *H-2K*. As for F/St, the high-virus phenotype was recessive in the F_1 (Table 1); the proportion of virus-producing cells was governed by a single locus (Table 2); and the locus determining the high- or low-virus phenotype was closely linked to *H-2K* (Table 2).

Expression of X-MuLV in Crosses Between F/St and P or BDP Mice. The $H\text{-}2^p$ haplotype, carried by F/St and B10.F, is also borne by strains BDP and P, which are closely related to one another but are not related to F/St. In contrast to F/St and B10.F, these two strains spontaneously produce no infectious X-MuLV and express only low levels of XenCSA on lymphocytes (Table 1). Further, spleen and tail fibroblast cells could not be induced to produce infectious X-MuLV after treatment with *Salmonella* lipopolysaccharide, 5-iododeoxyuridine, or both (data not shown); this is also in contrast to F/St (9). F_1 hybrids between F/St and BDP or P expressed the high X-MuLV and XenCSA levels characteristic of the F/St parent (Table 1), indicating that high virus expression requires $H\text{-}2^p$ homozygosity (or homozygosity at a closely linked gene) and an inducible xenotropic V locus. This was further tested by examining the progeny of the cross BDP × (BDP × F)F_1, in which mice with a chromosome 1 V locus from F/St should be high for X-MuLV expression whereas backcross segregants homozygous for chromosome 1 from BDP should be negative. As shown in Table 3, of 27 BDP × (BDP × F)F_1 mice, 14 animals expressed high levels of infectious X-MuLV and XenCSA in thymus, indicating that the high-virus phenotype was controlled by a single gene. These mice were also tested for segregation of alleles at *Ly-9*, a chromosome 1 linkage marker located 20 centimorgans from the X-MuLV V locus of F/St (9). In 22 of these 27 mice, the virus phenotype assorted in association with alleles at *Ly-9* such that the majority of BDP-type mice (homozygous for *Ly-9.1*) were low for virus expression, whereas the majority of the heterozygotes at this locus were

Table 2. Expression of infectious X-MuLV and XenCSA by thymocytes of mice from crosses between F/St and (B10.BR × B10.F)F_1

F/St × (B10.BR × B10.F)F_1				(B10.BR × B10.F)F_1 × F/St			
*k/p**		*p/p**		*k/p**		*p/p**	
X-MuLV†	XenCSA‡	X-MuLV†	XenCSA‡	X-MuLV†	XenCSA‡	X-MuLV†	XenCSA‡
0	206	5.5	1,062	0	196	4.9	304
1.4	206	4.6	962	0	204	4.7	443
0	257			0	199	4.6	898
1.3	203			0	215	5.1	339
0	209			0	197		
0	205			0	198		
0.7	203			0	215		
				0	198		
				0	208		
				0	199		

* Alleles at *H-2K* determined by FMF using monoclonal anti-H-$2K^k$.
† Values indicate $\log_{10}$(ffu/10^7 cells) on mink S^+L^- cells. Virus titers >2.0 ($\log_{10}$) are considered to be significantly increased.
‡ Mean fluorescence values determined by using logarithmic amplification of signals from the photomultiplier tubes.

Table 3. Expression of infectious X-MuLV and XenCSA by thymocytes of BDP × (BDP × F)F_1 mice

*Ly 9.1/Ly 9.2**		*Ly 9.1/Ly 9.1**	
X-MuLV†	XenCSA‡	X-MuLV†	XenCSA‡
4.2	1,664	0	284
4.0	1,020	0	224
4.0	1,082	0	304
4.0	1,068	0	235
4.0	1,086	4.0§	687
4.2	1,154	0	164
3.8	690	1.0	185
<0.3§	220	0	270
<0.3§	236	0	192
<0.3§	200	0	267
3.3	392		
4.9	1,224		
4.9	1,005		
4.5	991		
<0.3§	207		
5.0	1,080		
4.9	1,035		

* Alleles at *Ly-9* were determined by using monoclonal anti-Ly-9.1.
† Values indicate $\log_{10}$(ffu/10^7 cells) on mink S^+L^- cells. Virus titers >2.0 ($\log_{10}$) are considered to be significantly increased.
‡ Mean fluorescence values determined by using logarithmic amplification of signals from the photomultiplier tubes.
§ Apparent recombinants between alleles at *Ly-9* and the F/St X-MuLV V locus.

high. This gives a linkage estimate of 18.5 ± 7.5, which is compatible with the distance between *Ly-9* and the X-MuLV V locus of F/St as determined by iododeoxyuridine induction studies.

DISCUSSION

The data presented here demonstrate that high expression of X-MuLV by lymphocytes of F/St mice is dependent on the interactions of two loci: *Cxv-1*, closely linked to *H-2* on chromosome 17, and a X-MuLV V locus on chromosome 1. Alternative alleles at *Cxv-1* appear to regulate the extent to which chromosome 1 X-MuLV V loci are expressed as infectious virus and as XenCSA.

The close association between *Cxv-1* and *H-2K* was documented by the observation that among 76 backcross and outcross mice involving F/St or B10.F and mice carrying a chromosome 1 X-MuLV V locus [i.e., AKR or B10.BR, which carry *Bxv-1* (5)] only mice homozygous for $H\text{-}2K^p$ had a high proportion of thymocytes that produced infectious X-MuLV and expressed high levels of XenCSA (Fig. 1, Table 2). These results also showed that the allele at *Cxv-1* associated with $H\text{-}2K^p$ was recessive and permissive for X-MuLV expression, whereas that linked to $H\text{-}2K^k$ in two $H\text{-}2^k$ haplotypes of independent origin was dominant and restrictive for X-MuLV expression.

The finding that lymphocytes from the $H\text{-}2^p$ strains BDP and P produced no infectious X-MuLV and expressed low levels of XenCSA suggested that homozygosity at $H\text{-}2^p$ was not sufficient to produce the high-X-MuLV phenotype expressed by F/St. The necessity for a dominant MuLV V locus was indicated by the observation that a high proportion of thymocytes from (BDP × F)F_1 and (P × F)F_1 mice (homozygous for $H\text{-}2^p$ but heterozygous for the chromosome 1 X-MuLV V locus of F/St) produced infectious X-MuLV and expressed high levels of XenCSA (Table 1). Further, linkage analyses of BDP × (BDP × F)F_1 backcross mice showed assortment of the high X-MuLV phenotype of F/St in association with the chromosome 1 locus *Ly-9* (Table 3).

The view that the alternative alleles at *Cxv-1* determine the extent to which lymphocytes produce infectious X-MuLV or express XenCSA from chromosome 1 X-MuLV V loci is further supported by the studies of C57BL/10 congeneic resistant mice. The C57BL/10 strain has a single X-MuLV V locus, *Bxv-1* (5), on chromosome 1. However, thymocytes from C57BL/10, B10.BR (Table 1), B10.A, or B10.S mice (unpublished observations) produce little or no infectious X-MuLV and express low levels of XenCSA, whereas thymocytes from $H\text{-}2^p$ B10.F (Table 1, Fig. 2) produce high levels of infectious virus and express high levels of XenCSA.

The effect of *Cxv-1* on expression of infectious X-MuLV and XenCSA is greater on thymocytes than on spleen cells; the proportions of virus-producing cells in thymuses of $Cxv\text{-}1^s$ homozygotes are generally 10- to 100-fold higher than in the spleens of the same animals (Fig. 1; Table 1; ref. 9). Preliminary studies comparing infectious X-MuLV production by thymocytes and separated splenic T and B cells indicate that little of this difference is due to the smaller proportion of T cells in spleen than in thymus (unpublished data). The effects of *Cxv-1* on XenCSA expression by thymocytes and spleen cells appear to be related to its effect on infectious X-MuLV. Assays of thymocytes from three sets of backcross mice—(AKR × F)F_1 × F/St (Fig. 1), (NSF × F)F_1 × F/St, and (C57L × F)F_1 × F/St (ref. 11)—showed that XenCSA values were detectably increased only when greater than 0.1% of the cells were producing infectious virus. Because the proportions of virus-producing cells in spleen rarely exceed this level it is perhaps not surprising that XenCSA values for splenocytes are not increased.

The means by which *Cxv-1* exerts its effect on X-MuLV expression is not known, but both intracellular and extracellular mechanisms can be envisioned. Because of the close association with the *H-2* region, we have carried out preliminary tests for indications that *Cxv-1* acts as an immune response gene determining responsiveness to X-MuLV *env* gene products. Samples of SIRC cells infected with NZB X-MuLV were allowed to react with sera from 15 (AKR × F)F_1 × F/St mice (eight high-virus and seven low-virus mice) and then exposed to fluorescein-labeled anti-mouse $F(ab')_2$. FMF assays of the cells gave uniformly low fluorescence levels with sera from both high- and low-virus mice, in tests in which standard positive mouse and rabbit sera gave high levels of fluorescence. Although these results suggest that the low-virus and low-XenCSA phenotype is not simply a function of X-MuLV immune responsiveness, the possibility of absorption of crossreactive antibodies in mice that all express high levels of ecotropic virus has not been ruled out. Further testing of immunological control mechanisms, both humoral and cellular, is indicated, as well as investigations of control at the level of transcription or translation of the viral genome. It will also be of interest to determine the relationship of *Cxv-1* to other retrovirus and leukemia regulatory genes known to be within or closely associated with the *H-2* complex region (17).

It should be noted that the high-expression MuLV locus of NZB mice, *Nzv-1*, is distinct from the xenotropic virus induction and regulation loci described here, because it is not located on chromosome 1 (C. A. Kozak, personal communication) nor is it linked to the *H-2* complex (18).

There was no indication of *Cxv-1*-mediated regulation of endogenous ecotropic MuLV expression in the $H\text{-}2^p$ crosses studied here and in a previous report (9). However, in contrast to X-MuLV, for which endogenous expression without spread of virus is measured, these ecotropic virus phenotypes reflect the amplification by exogenous infection characteristic of the highly inducible multiple V loci of AKR and F/St or of maternally transmitted virus as in the case of B10.F. An $H\text{-}2^p$ mouse strain

carrying a single ecotropic V locus on the restrictive $Fv\text{-}1^b$ background, such as might result from Caesarian derivation of B10.F, could provide an opportunity to determine whether *Cxv-1* affects expression of both ecotropic MuLV and X-MuLV or X-MuLV only.

Finally, it should be noted that of the B10.F mice scored as expressing high levels of X-MuLV and XenCSA a high proportion were also positive for virus of the dual-tropic recombinant MCF class (19). The significance of this finding in relationship to the mechanism of *Cxv-1* regulating activity and the mechanism of generation of MCF viruses is not yet known.

The authors gratefully acknowledge the technical contribution of Ms. E. Rudikoff, Ms. N. Wolford, Ms. J. Chandler, and Mr. C. Shifler and the assistance of Ms. S. Grove, Ms. V. Shaw, and the National Institute of Allergy and Infectious Diseases editorial staff in the preparation of this manuscript. We also thank Drs. W. P. Rowe, W. F. Davidson, and C. A. Kozak for their numerous helpful discussions. R.A.Y. is a recipient of a fellowship from the Cancer Research Institute of New York.

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