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# Analysis of Wild-Derived Mice for *Fv-1* and *Fv-2* Murine Leukemia Virus Restriction Loci: a Novel Wild Mouse *Fv-1* Allele Responsible for Lack of Host Range Restriction

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**Wild-derived mice originally obtained from Asia, Africa, North America, and Europe were typed for in vitro sensitivity to ecotropic murine leukemia viruses and for susceptibility to Friend virus-induced disease. Cell cultures established from some wild mouse populations were generally less sensitive to exogenous virus than were cell cultures from laboratory mice. Wild mice also differed from inbred strains in their in vitro sensitivity to the host range subgroups defined by restriction at the *Fv-1* locus. None of the wild mice showed the *Fv-1*$^n$ or *Fv-1*$^b$ restriction patterns characteristic of most inbred strains, several mice resembled the few inbred strains carrying *Fv-1*$^{nr}$, and most differed from laboratory mice in that they did not restrict either N- or B-tropic murine leukemia viruses. Analysis of genetic crosses of *Mus spretus* and *Mus musculus praetextus* demonstrated that the nonrestrictive phenotype is controlled by a novel allele at the *Fv-1* locus, designated *Fv-1*$^o$. The wild mice were also tested for sensitivity to Friend virus complex-induced erythroblastosis to type for *Fv-2*. Only *M. spretus* was resistant to virus-induced splenomegaly and did not restrict replication of Friend virus helper murine leukemia virus. Genetic studies confirmed that this mouse carries the resistance allele at *Fv-2*.**

Inbred mice contain a number of genetic loci, notably *Fv-1*, *Fv-2*, and *Fv-4*, which restrict the replication and spread of various murine leukemia viruses (MuLVs). Mice carrying the resistance allele at *Fv-4* (*Fv-4*$^r$) are not susceptible to infection by ecotropic MuLVs (27). An endogenous ecotropic proviral sequence was recently identified at *Fv-4*$^r$ (12), and resistance apparently results from the binding of the *Fv-4*$^r$ gene product to ecotropic MuLV cell surface receptors (10, 12, 31). The *Fv-2* locus controls susceptibility to acute erythroblastosis induced by Friend leukemia virus complex (16). Although the resistance allele is known to restrict in vivo replication of the spleen focus-forming virus (SFFV) component of Friend leukemia virus (26), the nature of the *Fv-2* restriction has not been determined. However, it has been suggested that the *Fv-2* gene product may have a normal function in erythropoiesis (1, 17, 23). Finally, alleles at the *Fv-1* locus control the relative sensitivity of cells to different subgroups of ecotropic, amphotropic, and mink cell focus-inducing or dualtropic MuLVs (21). These viruses can be classed as N-tropic if they replicate best in *Fv-1*$^n$ cells, B-tropic if they replicate best in *Fv-1*$^b$ cells, or NB-tropic if they grow equally well in *Fv-1*$^n$ or *Fv-1*$^b$ cells (8). A third restriction allele, termed *Fv-1*$^{nr}$, affects susceptibility to B-tropic viruses as well as certain N-tropic MuLV isolates (W. P. Rowe, J. W. Hartley, and T. Pincus, unpublished data). The *Fv-1* restriction is not absolute but is detected as a 100- to 1,000-fold reduction in plaquing efficiency. Although this restriction is known to affect a postpenetration stage in the viral replicative cycle (9, 14), the underlying molecular mechanism has not been determined. However, it has been shown that the virus *Fv-1* type is determined within the p30 region of the viral *gag* gene (4), and there are some data that suggest that *Fv-1* restricts replication by blocking the formation of closed circular proviral DNA (11, 30).

*Fv-4*-mediated resistance was first identified in G strain mice and has now been found in various wild mouse populations (13, 20). However, studies on the *Fv-1* and *Fv-2* genes largely have been restricted to the analysis of inbred strains. Because the majority of the older inbred strains were derived from a common source (18), these strains do not represent the full range of genetic diversity within the genus *Mus*. In an effort to extend our knowledge of genes affecting MuLV transmission and disease induction, I tested a variety of wild mouse populations for their in vitro sensitivity to ecotropic MuLVs and for their sensitivity to disease induction by Friend virus complex. Results indicated that the *Fv-2*$^r$ allele, heretofore described only in C57BL and closely related inbred strains, is also carried by the North African mouse, *Mus spretus*. In studies on the *Fv-1* restriction, it was found that many wild mice differ phenotypically from the inbred strains and that two of these wild mice carry a novel allele at the *Fv-1* locus which does not restrict any of the ecotropic MuLV subgroups.

## MATERIALS AND METHODS

**Mice.** BALB/cN and the NIH Swiss inbred line NFS/N were obtained from the Small Animal Section, National Institutes of Health, Bethesda, Md. Inbred strains C57L/J and C57BL/6J were obtained from The Jackson Laboratory, Bar Harbor, Maine. Inbred C57BL/6 mice congenic for *Fv-2*$^s$ (B6.S) were obtained from R. Steeves (Albert Einstein College of Medicine, Bronx, N.Y.) and were maintained in this laboratory by J. Silver. *Mus cervicolor* was obtained from R. Callahan (National Cancer Institute, National Institutes of Health). All other wild-derived mice and the (C57BL/6 × *M. spretus*)Fls and the (C57L × *Mus musculus praetextus*)Fls were kindly provided by M. Potter (National Cancer Institute). All other hybrid mice were bred in our laboratory.

**Viruses and inoculations.** Tissue cultures were prepared from individual mouse embryos or from the tail biopsy tissue of 2- to 4-week-old mice (15). Cultures were maintained for

TABLE 1. Plaquing efficiency of ecotropic MuLVs in inbred strains and wild-derived mice

| Group | *Fv-1* type[a] | Mouse cells (origin)[b] | $Log_{10}$ titer of the following virus[c] | | | |
|---|---|---|---|---|---|---|
| | | | AKV-1 (N-tropic) | AKR-L1 (N-tropic) | WN1802B (B-tropic) | Moloney (NB-tropic) |
| I | n | NFS/N | 3.7 | 4.7 | 1.0 | 4.0 |
| II | b | BALB/c | 1.7 | 2.5 | 3.4 | 3.6 |
| III | nr | 129 | 1.5 | 4.0 | 1.2 | 3.8 |
| | nr-like | *M. musculus musculus* (Denmark) | 1.0 | 3.8 | 1.0 | 3.1 |
| | | *M. musculus musculus* (Czechoslovakia) | 1.0 | 4.0 | 1.0 | 3.0 |
| | | *M. musculus domesticus* (J. J. Downs, Maryland) | 1.8 | 4.1 | 0.8 | 3.1 |
| IV | No *Fv-1* restriction | SC-1 cells | 4.5 | 5.2 | 4.2 | 4.3 |
| | | *M. hortulanus* | 3.9 | 4.7 | 3.2 | 3.9 |
| | | *M. spretus* | 4.0 | 4.2 | 3.7 | 3.5 |
| | | *M. musculus praetextus* | 3.3 | 5.0 | 3.3 | 4.3 |
| | | *M. platythrix* | 3.8 | 5.3 | 4.0 | 4.5 |
| | | *M. caroli* | 3.5 | 4.6 | 4.2 | 4.0 |
| V | | *M. pahari* | 1.5 | 2.2 | 2.5 | 1.4 |
| | | *M. cookii* | 2.8 | 3.0 | 1.7 | 3.3 |
| | | *M. cervicolor* | 2.3 | 3.2 | 2.0 | 3.0 |
| | | *M. musculus domesticus* (Watkins Star, Maryland) | 2.5 | 4.6 | 2.3 | 2.5 |

[a] Mice listed in group V cannot be categorized as a single phenotype.
[b] NFS/N and BALB/c were tested both as embryo fibroblasts and tail cultures; *M. pahari* was tested only as embryo fibroblasts. All other mice were tested only as tail cultures.
[c] Data were taken from seven different experiments.

7 to 10 days in minimal essential medium or McCoys medium with 10% fetal calf serum and antibiotics. When the cultures reached confluency, the cells were passaged and infected with virus the next day. Virus stocks were obtained from J. Hartley (National Institute of Allergy and Infectious Diseases, National Institutes of Health) and included the NB-tropic Moloney and Friend ecotropic MuLVs, the N-tropic ecotropic viruses AKV-1 and AKR-L1, and the B-tropic virus WN1802B (22). The NB-tropic virus strains were used to assess virus sensitivity independently of *Fv-1* type, and the two N-tropic strains were used to type for $Fv\text{-}1^{nr}$ which restricts AKV-1 but not AKR-L1.

Virus replication in cultured cells was scored by the XC test 4 to 5 days after inoculation (24). For comparison, viruses were titrated in cultures of SC-1 cells and in tail or embryo fibroblasts prepared from NFS/N ($Fv\text{-}1^{n}$) and BALB/c ($Fv\text{-}1^{b}$).

**Friend virus complex susceptibility.** Mice were typed for *Fv-2* after retro-orbital inoculation of 0.2 ml of a 1% spleen suspension of Friend virus complex. NB-tropic Friend virus complex was originally obtained from F. Lilly (Albert Einstein College of Medicine) and was serially passaged in BALB/c mice. The virus pool used for inoculation contained $3 \times 10^4$ SFFV/ml and $3 \times 10^6$ XC PFU/ml.

Mice were sacrificed 14 days after inoculation, and their spleens were weighed. Because resistance to Friend virus can be attributed to *Fv-4* as well as *Fv-2*, spleens from resistant mice were also typed for infectious helper virus by plating single cell suspensions on SC-1 cells. Virus was scored in these cultures by the XC test 4 to 5 days later. The presence of high titers of ecotropic virus in spleens from resistant mice is characteristic of *Fv-2* restriction but not *Fv-4* restriction (16).

***Gpd-1* typing.** To follow the *Fv-1* locus in genetic crosses, hybrid mice were typed for *Gpd-1* (glucose-6-phosphate dehydrogenase-1), a closely linked isozyme locus (25). Kidney extracts were electrophoresed on cellulose acetate strips, and *Gpd-1* was scored after histochemical staining by the procedure described by Harris and Hopkinson (6).

## RESULTS

**Replication of ecotropic viruses in wild mouse cells.** Susceptibility to ecotropic virus was measured by determining the titers of standard virus stocks in cultured cells of laboratory or wild-derived mice (Table 1). Although a given pool of NB-tropic virus gave the same titer (within a 10-fold range) in cells of different laboratory strains, several wild mice were less susceptible than control cultures to infection by the NB-tropic ecotropic MuLVs (Table 1, group V). Most notably, virus titers were reduced in cells of *Mus pahari* by 2 to 4 logs compared with control SC-1 cells. A less pronounced decrease in sensitivity was noted in other wild mice such as *Mus musculus domesticus* (Watkins Star). These differences were reproducible in repeated assays, suggesting that there is a genetic basis for them.

The wild mice also differed substantially from inbred strains in their susceptibility to the different host range subgroups defined by restriction at the *Fv-1* locus. While cells from $Fv\text{-}1^{n}$ or $Fv\text{-}1^{b}$ inbred strains showed at least a 50-fold difference in susceptibility to N- and B-tropic viruses, none of the wild mouse cells tested reproduced this pattern. However, some of the wild-derived mice from eastern Maryland and Europe (Table 1, group III) restricted B-tropic virus as well as the AKR-L1 N-tropic ecotropic virus. These mice resembled the inbred strains carrying the $Fv\text{-}1^{nr}$ allele.

The remaining wild mice tested generally were equally susceptible to N-tropic and B-tropic ecotropic viruses (Table 1, groups IV and V). For these wild mice, the difference in sensitivity to these two virus subgroups was less than 30-fold. This pattern has not been previously described for any inbred mouse, although it resembles that of SC-1, a cell line established from a wild mouse from California (7).

Finally, among the wild mice typed as having this

nonrestrictive phenotype, there were also some small differences in relative susceptibility to the two virus host range classes. Thus, *Mus caroli* cells were reproducibly more sensitive to infection with B-tropic virus than with N-tropic virus, and although all viruses replicated poorly in cells of *M. pahari*, these cells were clearly more sensitive to B-tropic MuLVs.

**Absence of *Fv-1* restriction maps to chromosome 4.** It is not known whether the absence of *Fv-1* type restriction of N- or B-tropic MuLVs in SC-1 cells is a function of a novel *Fv-1* allele or whether it is due to an unlinked genetic locus or some factor resulting from long-term culture in vitro. However, classical Mendelian crosses could be used to determine the genetic basis for this same phenotype in wild mice. Progeny of genetic crosses between *M. spretus* and *M. musculus praetextus* with various laboratory strains were typed for virus susceptibility (Table 2). Results indicate that F1 hybrids between *M. spretus* and the *Fv-1*$^b$ mouse BALB/c resemble the BALB/c parent in that they are susceptible to B-tropic virus but restrict N-tropic virus. Cells from Fls between *M. musculus praetextus* and the *Fv-1*$^n$ mouse C57L restricted B-tropic virus. In both crosses, the F1 hybrids more closely resembled the resistant parent, although titers of the restricted virus were generally higher in cultures from heterozygotes than from the resistant parental strain. Therefore, resistance is inherited as a semidominant or dominant trait.

Single gene control of this phenotype in *M. musculus praetextus* was established in several crosses. *M. musculus praetextus* was mated with C57L females for one generation and NFS females for five generations. At each generation, mice were typed for virus sensitivity, and heterozygotes were selected for subsequent mating. Of 37 hybrid mice, 15 were more sensitive to B-tropic virus than were their littermates (by 1 to 2 logs), indicating inheritance of a single gene from *M. musculus praetextus* ($P > 0.25$). (C57L × *M. musculus praetextus*)F2 mice were also typed for virus sensitivity (Table 3). Of 36 mice, 7 (19%) were fully sensitive to B-tropic virus, which is consistent with single gene segregation. All seven of these mice were also shown to be homozygous for *Gpd-1*$^b$. Similarly, there was concordance between resistance to B-tropic virus and inheritance of *Gpd-1*$^a$. These data indicate that virus sensitivity is controlled by a gene closely linked to *Gpd-1* (recombination = 1.5 ± 1.4 centiMorgans).

Virus susceptibility and *Gpd-1* were typed in two *M. spretus* crosses (Table 4). The observed pattern of virus susceptibility in the progeny was compatible with single gene control ($P > 0.65$). A heterozygous male from the C57BL/6 × (NFS × *M. spretus*) cross was mated to NFS females for three generations. Combined data from virus typing at each generation also showed single gene segregation since 11 of 26 mice inherited the *M. spretus* phenotype ($P > 0.45$; data not shown). This locus was closely linked to *Gpd-1* (recombination = 8 ± 5.5 centiMorgans).

These data suggest that both *M. spretus* and *M. musculus praetextus* carry a novel *Fv-1* allele which permits the unrestricted replication of N- and B-tropic MuLVs. To establish whether this lack of restriction is controlled by the same genetic locus in these two wild-derived mice, hybrid mice heterozygous for the nonrestrictive alleles from *M. spretus* and *M. musculus praetextus* were mated. Twenty-one progeny of this cross were typed for sensitivity to N- and B-tropic virus (Table 5). *Gpd-1* was not typed since the parental mouse carrying the *M. musculus praetextus* virus restriction locus was homozygous for *Gpd-1*. Results show that six of the progeny showed the nonrestrictive phenotype, seven were typed as *Fv-1*$^n$, and eight were typed as heterozygotes. These data indicate that mice which inherited

TABLE 2. Plaquing efficiency of N-, B-, and NB-tropic viruses in primary tail cells of F1 hybrids and parental mice

| Mice | $Log_{10}$ titer of the following virus[a] | | |
|---|---|---|---|
| | AKV-1 (N-tropic) | WN1802B (B-tropic) | Friend (NB-tropic) |
| C57L/J (*Fv-1*$^n$) | 3.8 | ND[b] | 5.8 |
| *M. musculus praetextus* | 2.8 | 3.3 | 5.5 |
| (C57L/J × *M. musculus praetextus*) F1 | 3.4 | 2.0 | 5.7 |
| BALB/c (*Fv-1*$^b$) | 1.6 | 2.7 | 4.7 |
| *M. spretus* | 3.2 | 3.3 | 5.9 |
| (BALB/c × *M. spretus*)F1 | 2.0 | 2.6 | 4.8 |

[a] The titers for each of these viruses in the fully permissive SC-1 cells were as follows: AKV-1, 3.6; WN1802B, 3.2; Friend, 5.4.
[b] ND, Not detectable.

TABLE 3. Segregation of *Gpd-1* and sensitivity to ecotropic virus in (C57L × *M. musculus praetextus*)F2 mice[a]

| *Gpd-1* type[b] | No. of mice | $Log_{10}$ titer of WN1802B (Mean ± SD)[c] |
|---|---|---|
| aa | 14 | 0.4 ± 0.6 |
| ab | 1 | 1.0[d] |
| | 15 | 2.2 ± 0.1 |
| bb | 7 | 3.3 ± 0.02 |

[a] Recombination was 1.5 ± 1.4, as calculated by the method of maximum likelihood (5).
[b] *M. musculus praetextus* was scored as *Gpd-1*$^b$; C57L was scored as *Gpd-1*$^a$.
[c] $Log_{10}$ virus titers in controls were 3.0 to 3.8 in *M. musculus praetextus* cells, 2.0 to 2.5 in the F1 hybrids, and less than 1.1 in C57L.
[d] Single mouse scored as recombinant.

TABLE 4. Segregation of *Gpd-1* and sensitivity to ecotropic viruses in *M. spretus* crosses

| Cross | Inheritance of *M. spretus* *Gpd-1* type[a] | $Log_{10}$ virus titer[b] |
|---|---|---|
| NFS/N × (C57BL/6 × *M. spretus*) | − | 1.0, 1.5, 2.0, 2.0, 2.3, 2.3, 2.6 |
| | + | 3.3, 3.6, 3.7, 3.8 |
| | ND[c] | 3.6, 4.1 |
| C57BL/6 × (NFS × *M. spretus*) | − | 1.3, 1.5, 1.5, 3.4[d] |
| | + | 2.0[d], 2.6, 3.4 |

[a] *M. spretus* carries a unique *Gpd-1* allele which is electrophoretically distinguishable from both *Gpd-1*$^a$ (C57BL/6) and *Gpd-1*$^b$ (NFS/N).
[b] The first cross segregated *Fv-1*$^b$ and therefore was typed for sensitivity to N-tropic virus (virus titer in *M. spretus* cells was 3.2). The second cross segregated *Fv-1*$^n$ and was typed for sensitivity to B-tropic virus (virus titer in *M. spretus* cells was 3.3).
[c] ND, Not done.
[d] Scored as recombinant.

TABLE 5. Plaquing efficiency of ecotropic viruses in the progeny of a cross between mice heterozygous for the nonrestrictive *Fv-1* alleles from *M. spretus* and *M. musculus praetextus*[a]

| $Log_{10}$ titer (Mean ± SD) of the following virus[b] | | No. of progeny | Genotype |
|---|---|---|---|
| AKV-1 | WN1802B | | |
| 3.7 ± 0.7 | 3.1 ± 0.5 | 6 | $Fv\text{-}1^{o/o}$ |
| 3.7 ± 0.3 | 1.8 ± 0.5 | 7 | $Fv\text{-}1^{n/n}$ |
| 3.7 ± 0.5 | 0.7 ± 0.2 | 8 | $Fv\text{-}1^{n/o}$ |

[a] The female parent was the product of a cross between an NFS female and a heterozygous male from the cross: NFS × (C57BL × *spretus*)F1. The male parent was the progeny of a series of crosses in which a *M. musculus praetextus* male was mated with C57L for one generation and with NFS females for three generations. At each generation, males were typed for virus sensitivity, and heterozygotes were used for subsequent mating.

[b] Titers in SC-1 cells were 4.6 (AKV-1) and 3.7 (WN1802B).

both the *M. spretus* and *M. musculus praetextus* recessive genes responsible for the lack of virus restriction show the fully sensitive phenotype. Therefore, this phenotype is controlled by the same genetic locus in both wild mice. The novel nonrestrictive allele at the *Fv-1* locus will be designated $Fv\text{-}1^o$.

***Fv-2*-mediated resistance in wild mice.** Three to five mice from each wild mouse population were tested for sensitivity to induction of erythroleukemia and susceptibility to virus spread after they were inoculated with Friend virus complex. Six of the wild mouse species were found to be resistant to Friend virus-induced splenomegaly: *M. cervicolor*, *M. pahari*, *M. caroli*, *M. cookii*, *M. hortulanus*, and *M. spretus*. Spleens from five of these mice contained no recoverable virus when tested 2 to 4 weeks after they were inoculated. This resistance to helper virus is characteristic of *Fv-4* restriction and, in fact, one of these five mice was found by blot hybridization to contain the resistance allele at the *Fv-4* locus (13).

Spleens from the sixth resistant mouse, *M. spretus*, contained high levels of ecotropic virus after inoculation, despite the absence of splenomegaly. Since this is characteristic of *Fv-2* resistance, genetic crosses were carried out to determine whether *M. spretus* carries the recessive resistance allele ($Fv\text{-}2^r$) at this locus (Table 6). Fls between *M. spretus* and *Fv-2*-sensitive ($Fv\text{-}2^s$) NFS mice were sensitive to virus-induced splenomegaly, whereas the Fls with $Fv\text{-}2^r$ C57BL/6 mice were resistant. Furthermore, all of the progeny between a *spretus* male and females from a C57BL/6 congenic line carrying $Fv\text{-}2^s$ were susceptible to disease induction consistent with the hypothesis that *M. spretus* carries $Fv\text{-}2^r$. Finally, (NFS × *M. spretus*)Fls were crossed with C57BL/6 males. Of the 27 progeny tested, 15 showed the resistance phenotype, which is consistent with single gene segregation. These results indicate that *M. spretus* is resistant to Friend virus-induced disease because these mice carry the resistance allele at the *Fv-2* locus.

## DISCUSSION

A survey of 13 wild-derived mouse populations revealed that many of these mice differ from inbred strains in their sensitivity to MuLVs. Data from Mendelian crosses confirmed that one phenotype found in many of these mice, the absence of *Fv-1* type restriction, is determined by a novel allele at the *Fv-1* locus ($Fv\text{-}1^o$) in two different species. One of the mice typed as $Fv\text{-}1^o$, *M. spretus*, was also shown to carry the rare recessive resistance allele at *Fv-2*.

Although several of the wild mice tested were typed as $Fv\text{-}1^{nr}$, a phenotype which has been identified in a few inbred strains such as F, 129, and NZB (19; W. P. Rowe, J. W. Hartley, and T. Pincus, unpublished data), none of these mice showed the characteristic $Fv\text{-}1^n$ or $Fv\text{-}1^b$ phenotypes found in most inbred strains. However, the absence of $Fv\text{-}1^n$ and $Fv\text{-}1^b$ is not surprising since this survey did not include wild mice from western Europe and Japan. It is these wild mouse populations which most closely resemble the older inbred strains, interbreed readily with laboratory mice, and were present in the colonies which provided the progenitors of the common inbred strains (18).

Although in this study a new allele at *Fv-1* was identified, the data failed to identify any additional genetic loci affecting in vitro virus replication in wild mice. However, some of the wild mice tested, particularly *M. pahari*, differed from laboratory mice in their overall lack of virus sensitivity, and the mice typed as $Fv\text{-}1^o$ showed some minor differences in their relative sensitivities to N- and B-tropic viruses. Since most of these wild-derived mice do not interbreed with laboratory strains, the genetic basis for these differences could not be ascertained. However, results of comparable studies on inbred strains have described similar subtle differences among $Fv\text{-}1^n$ strains in their patterns of B-tropic virus restriction (2, 22). While it is possible that these minor differences in virus restriction may be due to the existence of other unlinked loci, a more likely explanation is that *Fv-1* is a complex locus with multiple alleles that cannot be easily distinguished by using assays based on plaquing efficiency.

Results of this survey also show that only one mouse, *M. spretus*, carries the recessive resistance allele at *Fv-2*. This locus is also rare among laboratory mice since it is found only in C57BL/6 and related strains. A comparative analysis of inbred strains has shown that C57BL/6 differs substantially from the other strains in its distribution of alleles at various polymorphic loci (28). However, there is no known ancestral link between this strain and any specific wild mouse population, including *M. spretus*.

As pointed out in an earlier report (13), Friend virus disease resistance patterns in these wild mice suggest that there may be additional genetic loci which affect resistance to virus-induced erythroblastosis. A number of resistant wild mice, including *M. pahari*, *M. caroli*, *M. cookii*, and *M. hortulanus*, do not carry the ecotropic provirus associated with $Fv\text{-}4^r$ (13), nor do they support replication of ecotropic helper virus, suggesting that $Fv\text{-}2^r$ is not responsible for resistance. For *M. pahari*, this in vivo resistance may be due to the fact that, as shown in this report, ecotropic viruses do not replicate well in cells from these mice. However, the basis for resistance in the other mice remains obscure. Since these mice do not interbreed with laboratory strains, it is not possible to determine whether resistance is due to any of the

TABLE 6. Sensitivity to Friend virus-induced splenomegaly

| Mice | No. of mice | Spleen weight range (g) | Ecotropic virus (XC PFU)/no. of spleen cells |
|---|---|---|---|
| NFS | 6 | 0.91–4.6 | $>1{,}000/10^4$ |
| C57BL/6 | 4 | 0.17–0.25 | $>1{,}000/10^3$ |
| *M. spretus* | 3 | 0.02–0.22 | $800/10^4$ |
| (NFS × *M. spretus*)F1 | 6 | 0.71–2.39 | $800/10^4$ |
| (C57BL/6 × *M. spretus*)F1 | 4 | 0.07–0.15 | $600/10^3$ |
| (B6.S × *M. spretus*)F1 | 17 | 0.76–3.3 | ND[a] |

[a] ND, Not done.

same loci described in inbred mice affecting sensitivity to Friend virus (29).

Further studies with these wild mice may help determine the molecular mechanisms affecting virus restriction and virus-induced pathogenesis. Since wild mice carrying *Fv-1$^o$* and *Fv-2$^r$* contain few chromosomally integrated MuLV genomes (3, 13; unpublished data), analysis of exogenous virus replication in these mice should be greatly simplified. Studies on viral leukemogenesis should also benefit from the use of inbred strains congenic for *Fv-1$^o$*, since such mice would provide a common genetic background to study disease induction by N- and B-tropic viruses. Finally, *Fv-1$^o$* congenic mice may also be useful in studies on the expression of endogenous MuLVs. Although most proviral genes are not inducible as infectious virus, these sequences can contribute to the generation of recombinant viruses (12). Since *Fv-1$^n$* and *Fv-1$^b$* restrict the spread of viruses with specific *gag* sequences (4), a broader range of viruses might be recoverable from *Fv-1$^o$* mice.

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