Common Inbred Strains of the Laboratory Mouse That Are Susceptible to Infection by Mouse Xenotropic Gammaretroviruses and the Human-Derived Retrovirus XMRV

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Laboratory mouse strains carry endogenous copies of the xenotropic mouse leukemia viruses (X-MLVs), named for their inability to infect cells of the laboratory mouse. This resistance to exogenous infection is due to a nonpermissive variant of the XPR1 gammaretrovirus receptor, a resistance that also limits in vivo expression of germ line X-MLV proviruses capable of producing infectious virus. Because laboratory mice vary widely in their proviral contents and in their virus expression patterns, we screened inbred strains for sequence and functional variants of the XPR1 receptor. We also typed inbred strains and wild mouse species for an endogenous provirus, Bxv1, that is capable of producing infectious X-MLV and that also contributes to the generation of pathogenic recombinant MLVs. We identified the active Bxv1 provirus in many common inbred strains and in some Japanese Mus molossinus mice but in none of the other wild mouse species that carry X-MLVs. Our screening for Xpr1 variants identified the permissive Xpr1sxv allele in 7 strains of laboratory mice, including a Bxv1-positive strain, F/St, which is characterized by lifelong X-MLV viremia. Cells from three strains carrying Xpr1sxv, namely, SWR, SJL, and SIM.R, were shown to be infectable by X-MLV and XMRV; these strains carry different alleles at Fv1 and vary in their sensitivities to specific X/P-MLV isolates and XMRV. Several strains with Xpr1sxv lack the active Bxv1 provirus or other endogenous X-MLVs and may provide a useful model system to evaluate the in vivo spread of these gammaretroviruses and their disease potential in their natural host.

Xenotropic mouse gammaretroviruses were first isolated by Levy and Pincus from the NZB strain of laboratory mice (25). The virus was termed xenotropic because of its inability to infect cells of the various inbred mouse strains, although it could infect rat cells. Subsequent studies isolated this virus type from additional strains of inbred and outbred laboratory mice (23) and showed that these viruses are infectious for cells of multiple mammalian species (24, 33).

The various inbred strains of laboratory mice carry up to 15 endogenous proviruses related to infectious xenotropic mouse leukemia viruses (X-MLVs) (8, 34), and some of these germ line X-MLV proviruses, or XMVs, are capable of producing infectious virus or viral proteins (reviewed in reference 40). These inbred mouse strains differ in their abilities to produce infectious X-MLVs because of the different XMVs that they carry and because of the presence of regulatory genes that alter virus expression and spread. Two strains, F/St and NZB, have a “high-virus” phenotype; that is, they are viremic with X-MLVs from an early age, and virus can readily be isolated from cells and tissues of these strains (6, 25, 31). A second and larger set of inbred strains, which includes common strains such as C57BL and BALB/c, carry XMVs that produce virus after chemical or immunological stimulation (1, 9, 27, 38). A third set of strains, including Swiss strain-derived mice and strains such as A and C3H, are not or are rarely capable of producing infectious X-MLV.

Four active XMVs have been identified in the strains that can produce infectious virus. Two of these proviruses are found in NZB mice (6), a third provirus, termed Bxv1, is found in several common inbred strains (8, 18, 19), and the fourth is found along with the Bxv1 provirus in MA/My mice (16). Only one of these proviruses, Bxv1, has been mapped in the mouse genome; it has been mapped to a position on distal chromosome 1 (Chr 1), where it was first located by conventional linkage analysis of chemically inducible virus production (18). The provirus at this locus was subsequently identified by Southern blotting of somatic cell hybrids and recombinant inbred mouse strains (11, 8). The Bxv1 provirus (also termed Xmv43) is present in the sequenced C57BL mouse genome and maps at 179 MB on Chr 1 (12). This provirus is biologically important for two reasons: not only does Bxv1 reliably produce virus in response to specific inducers (18, 19), but it is also involved in virus-induced leukemias. These diseases are associated with the generation of recombinant leukemogenic polytropic MLVs (P-MLVs), and the Bxv1 provirus has been identified as the source of the long terminal repeat sequences of these pathogenic recombinants (11, 41).

The presence of multiple endogenous XMVs in mice that are not susceptible to X-MLV infection can be explained by looking at the wild mouse progenitors of these laboratory strains. The common laboratory strains represent a mosaic of three house mouse species: Mus domesticus, Mus castaneus, and Mus musculus (49). Two of these 3 species carry XMVs (17, 43), and the 3 species carry 3 different alleles of the XPR1 receptor used for entry by X-MLVs, all 3 of which are permis-
sive for X-MLVs (28, 47, 48). In contrast, the XPR1 receptor gene originally cloned from NIH 3T3 cells is not permissive for X-MLV entry (2, 42, 50). This suggests that XMVs were originally acquired by X-MLV-susceptible wild mice and that the receptor variants permissive for this virus were lost in the fancy mouse breeding stocks used to generate laboratory strains.

There are hundreds of strains of laboratory mice. While it is generally recognized that these strains are less genetically diverse than wild Mus species, it is clear that there are distinct lineages of laboratory strains that can be traced to different fancy mouse and wild mouse progenitors. Few of the hundreds of mouse strains have actually been tested for X-MLV susceptibility, and the observations that X-MLV susceptibility is widespread among wild mice and that these inbred strain lineages represent different mosaics of wild mouse species (49) raised the possibility that X-MLV-permissive Xpr1 alleles might have been captured in some of these strains. In this study, we screened inbred strains of laboratory mice for the presence of known and novel variants of the Xpr1 receptor, with the goal of identifying strains susceptible to X-MLV infection. We also identified the inbred strains carrying the inducible Bxv1 provirus and identified the origin of this provirus in the Japanese house mouse species Mus molossinus. The permissive xav allele of Xpr1 (Xpr1xav) was identified in 7 inbred strains, including the high-virus, Bxv1-positive F/St strain. We also demonstrate that cells from laboratory mouse strains carrying Xpr1xav can be efficiently infected with XMRV and X-MLVs.

MATERIALS AND METHODS

Viruses, cells, and virus infectivity. CAST-X is an X-MLV isolated in our laboratory from the spleen of a CAST/Eij mouse (46). Cs252 is a novel MLV isolated from the spleen of a CZECH/Eij mouse (47). The human xenotropic murine leukemia virus-related virus, XMRV (7), was kindly provided by R. Knowles (Institute of Medical Biology, Singapore). Primers used were 5′-ATG AAATTCGCAAGTTGAGATG (Xpr1exon 13) and 5′-ATGCAAGATGAGATGATGATG (Xpr1exon 15). A segment of Xpr1 exon containing the third and fourth putative extracellular loops (ECL3 and ECLA, respectively) was amplified by RTPCR from NIH 3T3 mouse spleen RNA using the forward primer 5′-AGCAGAAGCTTGTGCGTC and the reverse primer 5′-CGCGAAACCTCCTACACCGGC (Xpr1 exon 13, containing ECLA), were amplified from the DNA of multiple strains and used for primer design using primers Ex13F and Ex13R, 5′-AGTG (for 1.8 kb inserts) or 5′-GATCT (for 3′ ends) and 5′-AGTGTTAGCTTCGTCATCTGT (for 5′ ends). The full-length xpr1 genes were amplified by reverse transcription-PCR (RT-PCR) from cells established from SWR tail biopsy specimens and from the cell line SJL/SV, a simian virus 40 (SV40)-transformed line of SJL fibroblasts produced by B. Knowles (Institute of Medical Biology, Singapore). Primers used were 5′-ATG AAATTCGCAAGTTGAGATG (Xpr1exon 13) and 5′-ATGCAAGATGAGATGATGATG (Xpr1exon 15). A segment of Xpr1 containing the third and fourth putative extracellular loops (ECL3 and ECLA, respectively) was amplified by RTPCR from NIH 3T3 mouse spleen RNA using the forward primer 5′-AGCAGAAGCTTGTGCGTC and the reverse primer 5′-CGCGAAACCTCCTACACCGGC (Xpr1 exon 13, containing ECLA), were amplified from the DNA of multiple strains and used for primer design using primers Ex13F and Ex13R, 5′-GCTTACTTACTTGCTG (Ex13R). PCR products were cloned into pCR2.1-TOPO and sequenced.

PCR primers for the Bv1 provirus-cell junction fragment and the empty locus at the Bv1 insertion site were designed based on Mus musculus chromosome 1 clone RP24-65D16 (GenBank accession no. AC115995). The Bv1 provirus is present in the reverse orientation at coordinates 107533 to 116189. A Bv1 provirus-cell junction fragment was PCR amplified using primers 5′-AGGACTAGGAAACAGGGAATACAG (Bv1/enFP; nucleotide coordinates 108635 to 108612) and 5′-GATCTTAGGACCCAAG (Bv1/flRP; nucleotide coordinates 106765 to 106740). The empty locus at the Bv1 insertion site was amplified using primers 5′-CCATGCTATACTGCAAGG (Bv1/enFP; nucleotide coordinates 116359 to 116333) and 5′-GATTCTAGGACCCAAG (Bv1/flRP; nucleotide coordinates 106765 to 106740) (Fig. 1). Representative PCR products were cloned into pCR2.1-TOPO and sequenced.

Nucleotide sequence accession numbers. The sequences of the Xpr1 genes for 19 mouse strains (129, AKR, DBA, F1, FVB, HRS, LP, LT, MA/My, NOD, PWD, RBA, RIHS, SOD, SWR, YBR, NZB, SIM/Lt, SJ/Lt) were deposited in GenBank under accession no. HQ323662 to HQ323680. Sequences for the empty Chr1 Bv1 site in N/S/N and the SWR Fv1 gene were deposited in GenBank under accession no. HQ323681 and HQ323682.

RESULTS

Inbred strain distribution of the inducible XMY locus Bv1. We designed primers to identify cell-virus junction fragments diagnostic of the Bv1 provirus, as well as primers to identify the empty locus (Fig. 1). Primers were initially tested on DNAs from mouse strains previously shown to lack Bv1, NFS and NIH 3T3, and on DNAs from C57BL and BALB/c, the strains in which Bv1 was initially discovered (18). We also tested a hamster/mouse somatic cell hybrid, BE 7-2, carrying fragments of two mouse chromosomes, Chr 1 and Chr 15. This hybrid, like mouse cells carrying Bv1, produces infectious X-MLV following induction (14), and it contains a single XMY provirus (11). The 1.8-kb cell-virus junction fragment was identified...
only in DNAs from the hybrid cell line and from mice known to carry Bxv1, whereas the 1.0-kb fragment diagnostic of the empty locus was found only in DNAs from mice or cells lacking Bxv1 (Fig. 1), thus confirming that these primers identify the Bxv1 locus. The sequence of the 1.9-kb cell-virus junction fragment produced by Bxv1 ENFP and Bxv1 FLRP was identical to the corresponding Chr 1 segment in the sequenced C57BL genome (GenBank accession no. AC115959), and the sequence of the Bxv1 FLFP/Bxv1 FLRP product from the Bxv1-negative NFS/N mouse represents the provirus-free insertion site (GenBank accession no. HQ323681).

We analyzed 50 laboratory mouse strains, most of which fall into several inbred strain categories defined by their related breeding histories (3) (Fig. 2). The majority of the analyzed strains originated from the fancy mouse colonies of breeder Abbie Lathrop and from the early lines developed by William Castle; one set of Lathrop mice provided to William Castle gave rise to many common strains, such as DBA and BALB/c, and additional Lathrop mice produced the C57/C58-related strains. A third set of strains was derived from Swiss mice. Additional strains were developed from stocks in New Zealand, and we also included strains of other or uncertain ancestry in this analysis. We did not test the various strains derived by intercrossing other inbred strains.

Bxv1 was identified in 17 strains, most of which are Lathrop or Castle strain-derived mice (Fig. 1, 2). Bxv1 was not found in any of the New Zealand or Swiss strain-derived mice. This distribution is consistent with previous analyses that typed 12 strains for the presence or absence of the Chr 1 Bxv1 induction locus (18, 19, 51) and 7 strains for the presence or absence of diagnostic env fragments by Southern blotting (8) (Fig. 2). Previous testing had also identified a Bxv1-like locus in F/St mice, and although the Chr 1 location initially determined for this virus induction locus did not clearly identify it as Bxv1 (31), the present analysis confirms that Bxv1 is present in F/St (Fig. 1).

Wild mouse origin of the Bxv1 provirus. Laboratory mice are a mosaic of the wild mouse species of house mice, and 3 of the 4 house mouse species (M. molossinus, M. castaneus, M. musculus) carry X-MLV-related sequences and are capable of producing infectious virus (4, 17, 26, 43, 46, 47). It is therefore possible that the Bxv1 provirus originated in one of these wild mouse species. A previous attempt to identify Bxv1 in M. molossinus by screening backcross mice for inducible Chr1-linked proviral loci was unsuccessful because these mice carry too many active proviruses (16). We screened house mouse species and several other Mus species that had not been previously typed for endogenous MLVs for the presence of Bxv1 by PCR (Fig. 1, 3). We identified Bxv1 in 4 wild mouse DNAs, all of which were M. molossinus, although 3 additional breeding lines of M. molossinus mice did not have this provirus.

None of the other house mouse species carries Bxv1. M. molossinus is thought to be a natural hybrid of M. castaneus and M. musculus (52), both of which species carry active XMVs; however, the Bxv1 provirus was not found in any mouse of these 2 species (Fig. 1 and 3). The absence of this provirus in these 2 species and the fact that some, but not all, M. molossinus mice carry Bxv1 indicate that this XMV insertion arose relatively recently in Japanese mice. It is likely that Asian mouse X-MLVs, as well as the ecotropic MLVs carried by these mice (17, 39), were introduced into fancy mouse colonies because of inclusion of Japanese mice in fancy mouse colonies;
FIG. 2. Distribution of allelic variants of Bxv1, Fv1, and Xpr1 in inbred strains of the laboratory mouse. The organization of strains into groups based on their related breeding histories is derived from the analysis done by Beck and associates (3). The Bxv1 provirus insertion is identified by + and the empty locus by −; numbers identify strains previously typed for Bxv1 as a Chr 1-linked induction locus (superscript “1”) (18, 19, 51) or by Southern blotting (superscript “2”) (8). Fv1 typing identified the presence of the “n” or “b” restriction fragments that distinguish Fv1n and Fv1b (45). Identical results were obtained for strain sublines SJL/BmJ and SJL/J, for AKR/N and AKR/J, and for C57BL/6 and C57BL/10. Xpr1 variants confirmed by sequencing are indicated with asterisks; all others were typed by PCR. SAMR1 and SAMP8 are hybrids of AKR and an unknown mouse. NOR was derived from a cross between NOD and C57BLKS/J. NZB was derived from NZO; NZM is a hybrid of NZB and NZW. NZL was developed from NZO with contributions from NZB, C57BL, and 129.
in fact, Lathrop started her mouse colony with a pair of Japanese waltzing mice (22, 29, 37). It is also probable that the additional active proviruses found in laboratory mouse strains like NZB and MA/My may have been acquired from these Asian mice.

DNAs from *M. molossinus* and from the common laboratory strains were also typed for alleles of the Fv1 gammaretrovirus restriction gene, a gene that targets the virus capsid and inhibits its replication postentry. DNAs were typed using PCR primers that generate products of different sizes for Fv1\(P\) (1.8 kb) and for Fv1\(P’\) or Fv1\(P”\) (510 bp) (45). Among the laboratory strains, 28 of the 39 mice typed in this way as Fv1\(P’\) were found to lack Bxv1, but 6 of the 10 Fv1\(P”\) mice have Bxv1 (Fig. 2). All *M. molossinus* DNAs tested (MOLC/RkJ, MOLD/RkJ, MSM/Ms, JF1/Ms, MOLF/Eij) produced the longer Fv1\(P’\)-like PCR product, suggesting the possibility that the Bxv1 virus is B tropic. However, *M. molossinus* cells have not been tested for Fv1\(P’\)-type restriction, and although PCR suggests that this Fv1 resembles the longer Fv1\(P’\) at its 3’ end, our previous sequence analysis of the *M. molossinus* Fv1 gene identified Fv1\(P”\) codons at key sites in the coding region (GenBank accession no. FJ603569). Furthermore, the Fv1 tropism of the virus produced by Bxv1 has not been determined, and the Bxv1 capsid sequence has novel substitutions at key Fv1 target sites, so its sensitivity to the laboratory mouse Fv1 variants cannot be predicted. It is therefore not yet clear in what way the acquisition of the Bxv1 provirus was influenced by Fv1.

### Xpr1 receptor alleles in viremic strains of laboratory mice.

Multiple host factors can influence the expression of proviral loci and the spread of virus in vivo, and the detection of infectious X-MLVs or viral proteins depends on what proviruses are present and can also be influenced by genes at or near the major histocompatibility complex (MHC) locus and the Fv1 gene (32, 51). For mice carrying active XMVs, another contributing factor is likely to be the XPR1 receptor used by X-MLVs for entry. Because functional variants of the XPR1 receptor for X-MLVs exist in the various mouse species that contributed to the laboratory mouse genome, we screened inbred strains for variants of Xpr1. Two inbred strains, NZB and F/St, are unusual among laboratory strains in that they constitutively express infectious X-MLV throughout life (6, 31). X-MLVs are readily isolated from lymphoid organs of these mice. NZB carries two active XMVs, and the high-virus expression pattern has been attributed to the constitutive expression of one of those XMVs (6), although the presence of a permissive XPR1 variant could also be a contributing factor.

Neither of the XMV loci in NZB loci is Bxv1, as indicated by previous genetic analysis of this strain (16) and by our present study (Fig. 1). To determine if a permissive receptor contributes to the observed high-virus phenotype, we sequenced a segment of the NZB Xpr1 gene encoding the receptor determinants in XPR1 ECL3 and ECL4 (28, 46). This sequencing identified the NZB receptor as the restrictive allele Xpr1\(n\) (GenBank accession no. HQ323678), indicating that the viremia observed in these mice has no contribution from receptor-mediated secondary spread.

The second high-virus strain, F/St, produces detectable levels of X-MLV at 1 week of age and high levels from 4 weeks (31). This mouse carries one active XMV that was identified as the Bxv1 provirus (Fig. 1), but this XMV is not associated with viremia in the other strains that carry it. We sequenced exon 13 of F/St Xpr1, which contains ECL4, and found that these mice carry the permissive Xpr1\(m\) allele (15, 28) (GenBank accession no. HQ323665). While this might suggest an explanation for the F/St high-virus phenotype, analysis of genetic crosses between F/St and other inbred strains have shown that viremia requires Bxv1 and a recessive gene linked to the major histocompatibility locus (51). Xpr1 is closely linked to Bxv1 on Chr 1; its role in viremia cannot be evaluated from the existing data on F/St mice, and this strain has recently become extinct.

### Xpr1 variants in other inbred strains.

Rather than sequence XPR1 from dozens of mouse strains, we first screened DNAs of laboratory mouse strains by PCR for the presence of the permissive Xpr1\(m\) allele. There are five functionally distinct Xpr1 alleles in *Mus*; 4 of these variants are found in the house mouse species and inbred strains, and only 1 of these variants, Xpr1\(m\), encodes a fully permissive receptor (15). The other 3 house mouse receptors (Xpr1\(v\), Xpr1\(b\), and Xpr1\(l\)) restrict 2 or more of the viruses that rely on XPR1 for entry, and all 3 of these restrictive receptors have deletions in the ECL4 segment of the receptor (48) (Fig. 4). The deletion found in *M. castaneus* (Xpr1\(v\)) removes 5 codons, and the different deletions

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**TABLE 3. Distribution of Bxv1 in wild mouse species and wild-derived inbred strains.**

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<td>Other</td>
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FIG. 3. Distribution of Bxv1 in wild mouse species and wild-derived inbred strains. DNAs were screened by PCR for the Bxv1 insertion (+) or for the empty locus (−). A total of four wild-trapped California mice, along with California mouse-derived SC-1 cells, were tested.
found in NIH 3T3 (Xpr1n) and M. musculus (Xpr1m) remove single codons. The m, n, and sxv alleles cannot be reliably distinguished by PCR product size differences, but mixtures of DNAs carrying the m, c, and n alleles with Xpr1sxv DNA produce PCR product doublets. Because we were specifically interested in identifying the permissive Xpr1sxv allele in laboratory mouse strains, we did an initial PCR screen by mixing DNAs from each mouse strain with DNA from a mouse carrying wild-mouse Xpr1sxv (Fig. 4).

Fifty strains were screened by this method, and 6 strains in addition to F/St were implicated as having Xpr1sxv. Sequencing confirmed the presence of this permissive allele in all 6 strains. Xpr1sxv was found in 3 of the 10 Swiss mouse DNAs and in the 3 mouse strains SOD1, LP, and LT/SvEi. We also sequenced exon 13 in strains expressing high levels of nonocotropic MLV envelope (Env) glycoprotein. For example, DBA mice carry a provirus associated with the Rmcf locus that blocks the entry of viruses that use the Xpr1 receptor (13) and also express high levels of XenCSA and GIX, cell surface antigens related to nonecotropic MLV Env glycoprotein (30). 129-GIX+ mice also express the Env glycoprotein-related GIX antigen. Strains selected for sequencing also included 129, FVB, and NOD, because they are used as human disease models or for genetic manipulations, MA/My, a strain that carries two active XMV proviruses (16), and YBR, a strain produced from a different fancy mouse stock (Fig. 2). No novel sequence variants were identified in these additional mice; all of these strains were found to carry the exon 13 sequence of Xpr1m.

In the last few decades, a number of new inbred strains were derived from wild-trapped mice. These strains are unrelated to the fancy mouse-derived older common inbred strains, and they carry the Xpr1 alleles found in their species of origin. Thus, strains derived from M. molossinus and M. musculus carry Xpr1m and strains derived from M. castaneus carry Xpr1c (48). Two inbred strains derived from wild-trapped M. domesticus mice, PWD and RBA, were found by sequencing to carry Xpr1sxv, as expected (GenBank accession no. HQ323672 and HQ323673).

X-MLV infectivity of cells derived from inbred strains SWR, SJL, and SIM.R. Three of the strains determined to carry the permissive Xpr1sxv receptor based on initial screening and se-
quencing of exon 13 were further characterized. We sequenced the entire Xpr1 gene from SJL and SIM.R. The gene in both strains is identical to that originally cloned from *M. dunni* cells (28). This allele differs from Xpr1sv by one insertion, Δ582T, and two substitutions, E500K and N590D.

The presence of a permissive receptor in these mice does not guarantee infectivity, as failure to infect can result from factors such as receptor interference (reviewed in reference 40). Therefore, we examined cells from all three of these strains for X-MLV infectivity. Cultured tail fibroblasts from SIM.R and SWR and an SV40-transformed line of SJL mouse fibroblasts were tested for susceptibility to LaCZ retroviral vectors incorporating the Env glycoproteins of 2 mouse X-MLVs and 5 other virus isolates known to use the Xpr1 receptor. These 5 additional viruses included 2 polytropic MLVs (P-MLVs), 2 wild mouse virus isolates (CasE#1 and Cz524), and XMRV, an X-MLV-related virus originally isolated from human patients with prostate cancer (7). *Xpr1sv* restricts all these viruses except the P-MLVs, while *Xpr1sv* is permissive for all 7 viruses (47) (Table 1).

The cells from these three inbred mouse strains are susceptible to all viruses (Table 1), confirming that these cells all express a fully permissive XPR1 receptor. Some viruses infected these cells with nearly equal efficiencies, but most of the viruses showed infectivity differences that are consistent with *Fv1* restriction. All MLVs are potentially subject to *Fv1* restriction, including X-MLVs (35), and mouse-tropic MLVs have been typed as N or B tropic based on their restriction by *Fv1* or *Fv1n*, respectively, or as NB tropic if unaffected by either allele. SIM.R was developed as a congenic strain of Swiss noninbred mice and carries the *Fv1b* allele. SIM.R was developed as a congenic strain of Swiss noninbred mice and carries the *Fv1b* allele. SIM.R was developed as a congenic strain of Swiss noninbred mice and carries the *Fv1b* allele. SIM.R was developed as a congenic strain of Swiss noninbred mice and carries the *Fv1b* allele. 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older common inbred lines carry two variants of Xpr1. One of these variants, Xpr1\textsuperscript{aux}, is widespread in wild mouse species, while Xpr1\textsuperscript{au}, has not been identified in any wild-derived or wild-trapped mouse (48). The X-MLV-restrictive allele, Xpr1\textsuperscript{au}, is carried by the majority of these older strains of laboratory mice, while we identified the X-MLV-permissive allele, Xpr1\textsuperscript{aux}, in 3 of 10 Swiss mouse strains and in several strains developed from the Lathrop colonies.

Xpr1\textsuperscript{au} is the only one of the 5 Mus Xpr1 alleles to completely restrict X-MLVs, and its origin is unclear. Studies to determine the wild mouse origins of the common inbred strains have concluded that the largest contribution to the inbred mouse genome is from M. domesticus (49). It makes sense for M. domesticus to carry Xpr1\textsuperscript{au}, as these mice lack endogenous XMVs, consistent with Xpr1\textsuperscript{au} restriction of X-MLVs. However, our survey of wild mouse species failed to find Xpr1\textsuperscript{au} in any M. domesticus mouse or in any wild mouse of any species (48). It is of course possible that Xpr1\textsuperscript{au} is present in some unidentified wild mouse populations that contributed to the laboratory mouse genome. Alternatively, it is possible that this allele arose in the fancy mouse colonies that were maintained by hobbyists for centuries (29). These colonies included mice from multiple species that normally do not interbreed in nature, and these hybrids acquired an increased burden of MLV-endogenous retroviruses of different subtypes that are otherwise segregated in the wild mouse species (17). Artificial breeding protocols might also have resulted in the loss of host factors capable of restricting virus in natural populations, like interfering Env genes. Thus, the appearance of a restrictive receptor allele might have provided a survival advantage leading to its selection and near fixation in these fancy mice.

The XPR1 receptor defines the virus subtypes that can infect the host species. XPR1 therefore controls the type of endogenous retroviruses that accumulate in host genomes and also affects expression of these endogenous viruses in the individual animals. Whether the inbred strains carrying Xpr1\textsuperscript{aux} differ from strains carrying Xpr1\textsuperscript{au} in their expression of endogenous viruses like Bxv1 or whether these strains will permit efficient in vivo replication of exogenous X-MLVs is not yet known but is suggested by the fact that one strain viremic with xenotropic MLV, F/St, carries Bxv1 along with the permissive Xpr1\textsuperscript{au} receptor, although other factors, like MHC haplotype (51), clearly influence this unusual phenotype. While F/St is no longer extant, one additional strain identified here, LT/SvEi, carries the xcv receptor as well as Bxv1 and can be examined for X-MLV expression. The Xpr1\textsuperscript{aux} strains identified here could be used to develop mouse models for the analysis of X-MLV replication, tissue tropism, and pathogenesis and could also be used to determine whether the different host range subtypes in the X/P-MLV infectious-virus family have different in vivo properties. Previous analyses of the disease process in naturally highly leukemic strains, like AKR, while focused on ecotropic and polytropic MLVs, have recognized that at least one XMV, Bxv1, contributes to leukemogenesis by providing LTR sequences to the pathogenic P-MLV recombinants that arise in these mice (11, 41). These studies can now be expanded to determine how polymorphic variants of the XPR1 receptor affect disease type or latency as well as the type of recombinant viruses that appear. Studies on pathogenesis by exogenous X-MLVs can make use of the Swiss strain-derived mice carrying Xpr1\textsuperscript{aux}.

While SIM.R and SJL have not been characterized for their proviral content, SWR and other Swiss strain-derived mice, like NFS, carry only a single XMV copy (11, 34). The near absence of endogenous XMVs in these X-MLV-susceptible mice should simplify analysis of xenogenous-virus infection and pathogenesis. The analysis of X-MLV expression and pathogenesis in such mouse models could have broader relevance, particularly for studies on the origin, pathogenesis, and trans-species transmission of XMRV.

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REFERENCES

can be infected by ectropic, amphotropic, xenotropic, and mink cell focus-forming viruses. J. Virol. 52:695–698.