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## Evolution of different antiviral strategies in wild mouse populations exposed to different gammaretroviruses

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### Abstract

Laboratory mice carry 3 host range groups of gammaretroviruses all of which are linked to leukemia induction. Although polytropic mouse leukemia viruses (P-MLVs) are generally recognized as the proximate cause of MLV-induced leukemias in laboratory mice, wild mice that carry only endogenous P-MLVs do not produce infectious virus and are not prone to disease; these mice carry the permissive XPR1 retroviral receptor and an attenuated variant of the retroviral restriction factor, APOBEC3. In contrast, Eurasian mice carrying ecotropic and xenotropic MLVs have evolved multiple restrictive XPR1 variants, other factors that interfere with MLV entry, and more effectively antiviral variants of APOBEC3. These different antiviral restrictions in *Mus musculus* subspecies suggest that the different virus types found in these natural populations may pose different but largely uncharacterized survival risks in their host subspecies.

### Keywords

mouse gammaretroviruses; XPR1 retrovirus receptor; retrovirus restriction; mouse APOBEC3

### Introduction

The mouse leukemia viruses (MLVs) are simple retroviruses in the gammaretrovirus genus. They are broad host range viruses that lack accessory factors and use ubiquitously expressed host genes as receptors for entry. Inbred strains of laboratory mice and wild mouse species differ in their susceptibility to mouse gammaretrovirus infection and to virus-induced diseases, and they also differ in the types of MLVs they carry. Three MLV host range subgroups contribute to neoplastic disease in laboratory mice. As originally defined, ecotropic (E-MLVs) infect only mouse cells, xenotropic (X-MLVs) infect cells of non-rodent species, and polytropic (P-MLVs) infect both mouse and non-rodent cells [1]. All 3 of these virus types are found as endogenous retroviruses (ERVs) in the germlines of laboratory mice [2–4], and all 3 contribute to the generation of the recombinant infectious P-MLV viruses that have been identified as the proximate cause of disease in laboratory mice [5]. ERVs of the 3 virus types involved in the disease process are found in different subspecies of wild house mice [6] (Figure 1), and this segregation provides the opportunity

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to assess their separate roles in pathogenesis and the evolution of the antiviral responses of their mouse hosts that interfere with replication.

Virus-infected mice carry numerous constitutively expressed antiviral factors that target the various stages of the retroviral life cycle (reviewed for example in [7]). This review will focus on those factors that inhibit early stages of virus replication, and the distribution of restrictive and nonrestrictive genes and allelic variants in virus-infected wild mouse populations that carry different MLVs.

At the level of entry, there are two types of resistance genes that target the receptor-virus interaction. Resistance can result from polymorphisms of the cell surface receptors, or from the presence of ERVs that produce receptor-blocking viral envelope glycoprotein (Env). After the gammaretrovirus enters the receptive cell, reverse transcription and translocation to the nucleus can be inhibited or altered by the virus resistance factors Fv1, APOBEC3, and TRIM5 $\alpha$ . Two of these factors, Fv1 and APOBEC3, are encoded in the mouse genome and are known to have anti-gammaretroviral activity in mice, but no mouse TRIM5 $\alpha$  ortholog with virus restriction activity has been identified [8].

Analyses of these MLVs and host restriction factors in the four house mouse subspecies demonstrate that different restriction genes and alleles evolved in house mice that carry P-MLVs (*Mus musculus domesticus*), and in mice harboring X-MLVs and E-MLVs (*M. m. molossinus*, *M. m. castaneus*, *M. m. musculus*) (Figure 1, 2).

## Restriction of virus entry

Two gammaretrovirus receptors, CAT-1 and XPR1, are used by the three MLV host range groups. Both of these receptors have naturally occurring variants that are responsible for different virus restriction phenotypes. There are two functional variants of the CAT-1 receptor used by E-MLVs [9,10] and 5 variants of the XPR1 receptor for the X-MLVs and P-MLVs, all of which have mutations that alter the virus binding site [2]. These variants are not only important host factors that can restrict infection, but they can also alter virus/host interactions in ways that influence virus-induced pathology.

### The XPR1 receptor for X-MLVs and P-MLVs

X-MLVs and P-MLVs are viruses capable of infecting cells of non-rodent species and were originally distinguished as separate subgroups because of their different species tropism, their non-reciprocal interference patterns, and by the pathogenicity of P-MLVs [11–16]. The XPR1 receptor for this family of viruses (XP-MLVs) is a multipass transmembrane protein [17–19]. Sequence polymorphisms in the virus envelope and in XPR1 are responsible for the various viral tropisms. The 5 known *Mus Xpr1* variants differentially mediate entry of XP-MLV host range variants due to mutations in two XPR1 extracellular loops (Figure 3A) [11,20–22], and these virus host range variants differ in the receptor determining VRA region of Env [23].

The laboratory mouse carries two of the 5 *Mus Xpr1* alleles, the restrictive *Xpr1<sup>n</sup>* and the permissive *Xpr1<sup>sxv</sup>*; 3 additional restrictive alleles are found in various wild mouse populations and their distribution is subspecies specific (Figure 1). *M. m. domesticus*, which harbors only P-MLVs, carries the permissive *Xpr1<sup>sxv</sup>* allele, whereas the 4 receptor variants that restrict entry of one or more XP-MLVs are found in house mouse subspecies carrying predominantly X-MLVs or in a species (*M. pahari*, which carries *Xpr1<sup>p</sup>*) that is sympatric with X-MLV infected mice [11,22,24] (Figure 2, 3A).

## E-MLVs and their CAT-1 receptor

Infectious E-MLVs of 3 different subtypes have been described: AKV MLV in Asian *M. m. castaneus* and *M. m. molossinus*, HoMLV in *M. spicilegus* of Europe, and CasBrM/Fv4 MLV in Asia and in areas of California where Asian mice were introduced by passive transport by humans [6,25,26]. No endogenous or infectious E-MLVs have been found in European *M. m. domesticus*. One of these three subtypes, AKV MLV, is endogenous in many strains of laboratory mice [3].

The E-MLVs use the CAT-1 receptor [9] which encodes a glycoprotein that functions as a cationic amino acid transporter. It is a multipass transmembrane protein with 14 predicted transmembrane domains. The sites in the mouse protein critical for virus entry lie in the putative third extracellular loop along with two consensus recognition sites for N-linked glycosylation, both of which carry N-glycans [27–29] (Figure 3B).

There are 2 functionally distinct CAT-1 sequence variants in *Mus* (Figure 3B), and both receptors are recognized by the three E-MLV subtypes. The receptor identified in cells from *M. dunni* mice, dCAT-1, differs from the laboratory mouse receptor, mCAT-1, in that it restricts infection by an AKV-type MLV, Moloney MLV, although these cells are fully susceptible to other E-MLV isolates [10]. dCAT-1 differs from mCAT-1 by 4 residues, two of which are in the receptor determining third extracellular loop [10] (Figure 3B). Susceptibility differences are due to polymorphisms in *env* as well as receptor, and these mutations are also associated with cytopathicity [30–32]. Several cytopathic E-MLVs induce syncytia and cell death; in some cases, this response is receptor-specific, and in all 3 cases has been attributed to mutations that alter 2 of the 3 amino acid residues in Env that form the receptor binding pocket [1,33].

Although naturally occurring receptor polymorphisms thus alter both infectivity and cytopathicity, there is no evidence of CAT-1 receptor variation in E-MLV-infected house mouse populations, all of which carry the laboratory mouse variant, mCAT-1 [1].

## Interference Genes

Retrovirus infection can be restricted by specific ERVs that express Env glycoprotein. Resistance genes that function through such an Env-mediated interference mechanism have been identified in chickens, cats and sheep, as well as mice, and thus represent a common survival mechanism in natural populations exposed to endemic infections. In mice, an E-MLV ERV associated with the *Fv4* resistance locus, is a truncated provirus which encodes Env [34]. *Fv4* is found in California and Asian wild mice [35]. These mice also carry E-MLV ERVs that produce at least one pathogenic virus, CasBrM [36]. The *Fv4* Env has a defect in the TM<sub>env</sub> fusion peptide, and its incorporation into virions reduces their infectivity [37]. There is also a family of genes, termed *Rmcf*, linked to resistance to XP-MLVs. These genes represent defective Env-producing XP-MLV ERVs and have been found in laboratory strains and in *M. m. castaneus* [38,39]. The prototype *Rmcf* gene effectively blocks diseases that involve formation of recombinant P-MLVs [40].

Thus, 2 types of entry level restrictions have evolved in mice carrying MLVs. Mice carrying X-MLVs are protected from exogenous infection by multiple restrictive XPR1 receptor variants as well as by interfering Envs. While polymorphic CAT-1 variants are not found in E-MLV infected mice, resistance at entry results from receptor blocks by the widely disseminated Env-producing ERV, *Fv4*.

## Restriction of post-entry replication

Mice carry two restriction genes responsible for post-entry inhibition of MLV replication, *Fv1* and mouse *Apobec3* (*mA3*), both of which have allelic variants with different antiviral phenotypes. *Fv1* is a mouse specific gene that targets the virus capsid, and the allelic variants found in laboratory mice block different subgroups of mouse-tropic MLVs after reverse transcription and before integration [41]. *mA3* encodes a cytidine deaminase that can be packaged in virions and can restrict virus either by causing G to A hypermutation in viral (+) strands during reverse transcription [42], or through a nonenzymatic mechanism involving inhibition of early reverse transcription [43]. There are two allelic variants of *mA3* in laboratory mice, and the C57BL *mA3* is more effectively antiviral than the BALB/c allele [44]. Both *Fv1* and *mA3* have been under positive selection in *Mus* confirming their defensive roles [45,46], but while there are many *Fv1* sequence variants in wild mice [45], there is little information on the antiviral activity of these variants and their distribution in virus-infected wild mouse populations.

### Adaptive evolution of the virus resistance gene *Apobec3* in *Mus*

The BALB/c and C57BL *mA3* alleles differ in expression level, protein sequence and splicing pattern, all of which contribute to antiviral activity. Increased *mA3* expression level in C57BL has been associated with insertion of the long terminal repeat (LTR) of an X-MLV [46], suggesting involvement of the LTR transcriptional enhancer.

Multiple replacement mutations distinguish BALB/c and C57BL *mA3*. Many of these codons are under strong positive selection in *Mus*; 6 of these selected residues lie in two clusters in the N-terminal catalytically active deaminase domain of *mA3*, the region that has also been implicated in virus resistance [46,47]. A structural model of *mA3* positioned these two clusters of positively selected residues on opposite sides of the substrate groove where they have the potential to affect substrate interactions [46,48].

C57BL and BALB/c mice also express *mA3* transcripts with different splicing patterns: C57BL mice preferentially express exon 5-deficient ( $5^-$ ) *mA3* mRNA, while the major *mA3* transcript in BALB/c mice contains exon 5 ( $5^+$ ). *mA3* exon 5 influences protein synthesis at a post-transcriptional level, and inclusion of this exon is effected by two critical polymorphisms: the number of TCCT repeats upstream of exon 5 and a single nucleotide polymorphism within exon 5 [49].

Analysis of wild mouse *mA3* genes for the presence of the LTR, for coding sequence variation and for the splicing signals show that the ancestral *mA3* lacked both the MLV LTR and the polymorphisms that determine exon 5 inclusion [46,49]. These two genetic features were acquired independently at about the time of the house mouse radiation 0.5 million years ago but are found in different *Mus* populations. The more antiviral  $LTR^+Ex5^-$  *mA3* is found largely in X-MLV infected Eastern European *M. m. musculus*, while the  $5^+$  *mA3* allele originated and became fixed in Western European *M. m. domesticus* [49] (Figure 1, 2).

The fixation of  $5^+$  *mA3* is surprising, because this allele would seem to be evolutionarily deleterious, with its reduced level of *mA3* expression and lower antiviral activity. The subspecies with this *mA3*, *M. m. domesticus*, carries P-MLV ERVs, which are not known to produce infectious virus and do not cause disease in these populations. However, these P-MLV ERVs have been edited by *mA3* [50], and these P-MLV ERVs do not encode the glycosylated Gag variant (glycogag) carried by all infectious MLVs and most endogenous X-MLVs that is known to antagonize *mA3* [51,52]. This suggests that the  $5^+$  variant of the potentially genotoxic *mA3* enzyme may provide sufficient antiviral benefits in *M. m. domesticus*.

## Conclusions

Acquired retroviral ERVs can alter gene function and genome structure as well as cause disease in their new hosts, but these elements also form stable associations with their hosts over evolutionary time. Host antiviral factors co-evolve with these pathogens, and this “arms race” is responsible for the acquisition of novel antiviral genes and alleles. While most studies on resistance to MLV-induced disease have focused on laboratory mouse strains, the more interesting question is how natural populations deal with endemic infection. Studies on inbred strains of laboratory mice have highlighted the role of P-MLVs in disease-induction, but examination of wild mice produces a different picture in which different antiviral responses have evolved in mice with different ERV profiles (Figure 1,2).

### Eurasian mice

The 3 Eurasian house mouse subspecies carry active E- and X-MLV ERVs that produce infectious virus of both types, but virus spread and virus-induced disease are restricted by several host factors, including restrictive XPR1 receptors, interfering Env genes like *Fv4* and *Rmcf2*, and the more antiviral LTR<sup>+</sup>/Ex5<sup>-</sup> *mA3* subtype.

### Western European mice

Wild mice that carry ERVs related to the leukemogenic P-MLVs, namely *M. m. domesticus*, have low tumor incidence. These mice carry the less antiviral *mA3* gene, have fully functional MLV receptors, and are not known to encode interfering Envs, suggesting that these mice are either not in need of protection or rely on unknown antiviral factors. P-MLV ERVs do not produce infectious virus and, in laboratory mice and wild mice, involvement of P-MLVs in disease is dependent on their rescue by infection with E-MLVs [53,54]. No E-MLVs have been found in wild *M. m. domesticus*; it is tempting to speculate that this absence may be the result of purifying selection.

### Laboratory mice

The classical strains of laboratory mice were created by interbreeding 3 *Mus musculus* subspecies [55]. This interbreeding introduced the 3 MLV types into the same breeding lines, and also removed some natural host restriction factors. Many of the resulting fancy mouse colonies and inbred strains are plagued with tumors that are uncommon in their wild mouse progenitors [56,57].

The fact that multiple types of antiviral factors have evolved in X-MLV, but not P-MLV infected mice suggests that X-MLVs may be more deleterious than appreciated. The pathogenic properties of these viruses are not easily studied, since they are noninfectious in most common strains of laboratory mice [58,59]. The observations detailed here suggest that these viruses may deserve a second look. Further studies on these infected wild mice may also provide insight into the host factors that most influence cross-species and cross-subspecies virus transmission.

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### Highlights

Wild mice carrying XP-MLVs rarely develop virus-induced disease.

Different antiviral host factors are found in mice with X-MLVs and P-MLVs.

Mice with X-MLVs have defective or blocked receptors and a restrictive APOBEC3.

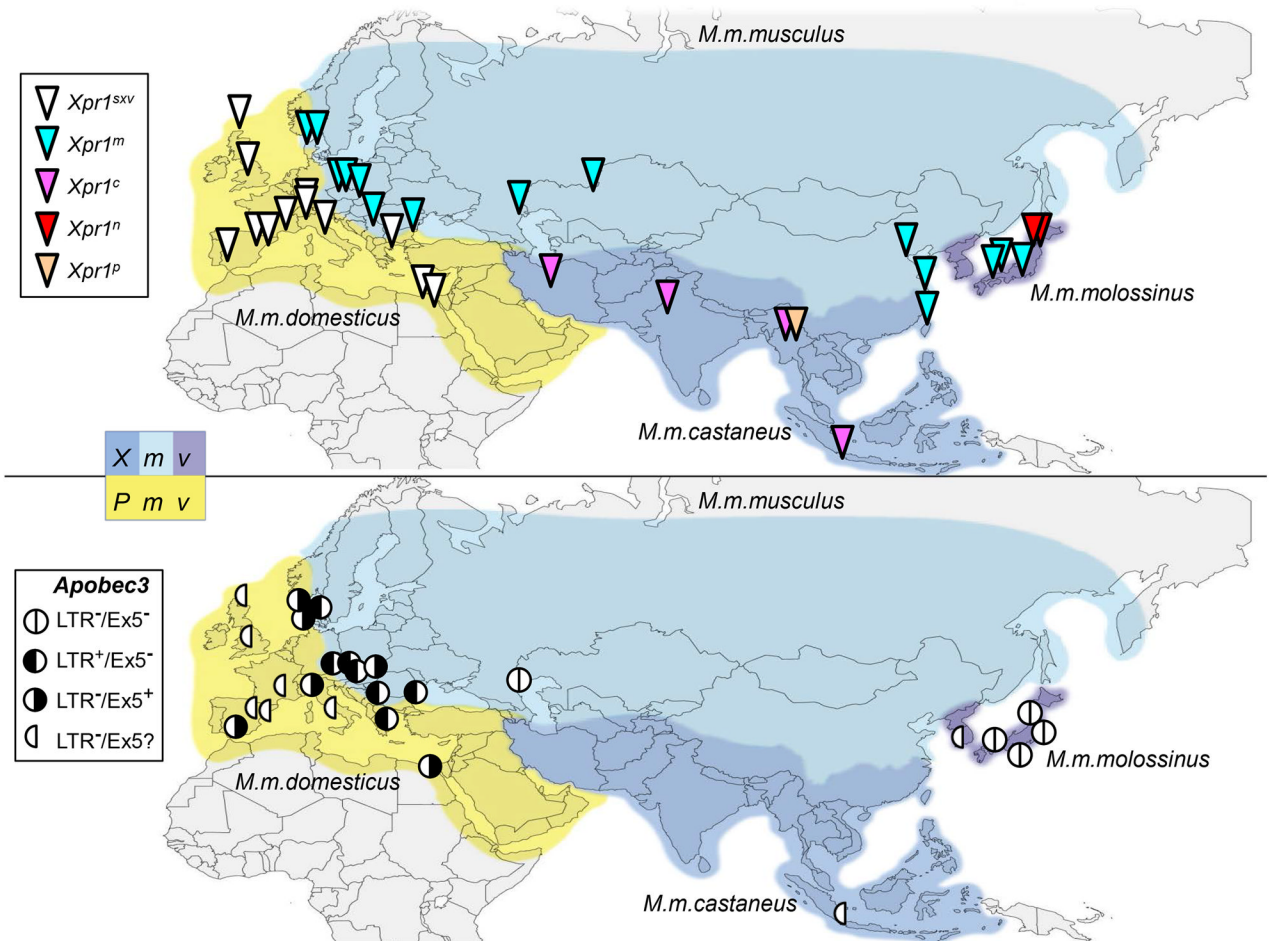
Mice with P-MLVs have a permissive receptor, a weaker APOBEC3, but make no virus.

| Mice                    | Endogenous MLVs |       |                           | <i>Xpr1</i><br>Allele | <i>Apobec3</i><br>(MLV LTR/Exon5)         |
|-------------------------|-----------------|-------|---------------------------|-----------------------|---|
|                         | X-MLV           | P-MLV | E-MLV (Type) <sup>a</sup> |                       |   |
| Laboratory Strains      | +               | +     | +,- (AKV)                 | <i>n, svv</i>         | LTR-/5 <sup>+</sup> , LTR+/5 <sup>-</sup> |
| <i>M. m. musculus</i>   | +               | Few   | +,- (CasBrM)              | <i>m</i>              | LTR-/5 <sup>+</sup> , LTR+/5 <sup>-</sup> |
| <i>M. m. molossinus</i> | +               | Few   | +,- (CasBrM)              | <i>m</i>              | LTR-/5 <sup>-</sup>                       |
| <i>M. m. castaneus</i>  | +               | Few   | +,- (CasBrM)              | <i>c</i>              | LTR-/5 <sup>?</sup>                       |
| <i>M. m. domesticus</i> | -               | +     | -                         | <i>svv</i>            | LTR-/5 <sup>+</sup>                       |

<sup>a</sup>E-MLVs are present or absent in mouse strains and subspecies.

**Figure 1.**

Distribution of endogenous MLVs and allelic variants of *Xpr1* and *Apobec3* in *M. musculus* subspecies and common strains of laboratory mice. The permissive allele was termed *svv* for susceptibility to xenotropic yirus and the other alleles were named for the cells/species in which they were discovered: *n*, NIH 3T3; *m*, *M. m. musculus* and *M. m. molossinus*; *c*, *M. m. castaneus*, *p*, *M. pahari*.



**Figure 2.** Distribution of functionally distinct alleles of the *Xpr1* receptor and *Apobec3* in Eurasian mice. Blue blocks represent the ranges of *Mus* subspecies carrying X-MLV ERVs (*Xmvs*) and yellow represents the range of *M. m. domesticus*, which carries P-MLV ERVs (*Pmvs*). Top panel: The ancestral permissive *Xpr1<sup>sxv</sup>* allele is in white; different colors indicate the 4 restrictive alleles. Bottom panel: The ancestral *Apobec3* allele, in white, lacks the MLV LTR insertion and Exon 5, features acquired by different *Mus musculus* populations.

**A**

|                           | ECL3, C-term | ECL4          | Virus Susceptibility Patterns |       |       |        |
|---------------------------|--------------|---------------|-------------------------------|-------|-------|--------|
|                           |              |               | X-MLV                         | P-MLV | Cz524 | CasE#1 |
| <i>Xpr1<sup>ssv</sup></i> | KEQNHSDTV    | SITATTFKPHVGD | +                             | +     | +     | +      |
| <i>Xpr1<sup>n</sup></i>   | E.....       | .....-.....N  | -                             | +     | -     | -      |
| <i>Xpr1<sup>m</sup></i>   | .....        | .-...K.....   | +                             | -     | -     | -      |
| <i>Xpr1<sup>c</sup></i>   | .....        | .....-.....   | +                             | -     | +     | -      |
| <i>Xpr1<sup>p</sup></i>   | K...P.YK     | ...V.....     | +                             | -     | -     | +      |

**B**

|        | ECL3                                     | Virus Susceptibility Patterns |       |
|--------|--|-------------------------------|-------|
|        |  | AKV MLV                       | MoMLV |
| mCAT-1 | VKGSIKNWQLTEKN <u>FSCNNND</u> TNVKY-GEGG | +                             | +     |
| dCAT-1 | ...V.....G....                           | +                             | (+)   |

**Figure 3.** Functional polymorphisms in the receptor determining regions of the MLV receptors, CAT-1 and XPR1, in *Mus* species. A) Variation in the C-terminal region of the 3<sup>rd</sup> extracellular loop (ECL3) and in ECL4 of *Xpr1*. B) Variation in the third extracellular loop of CAT-1 (gene name, *Slc7a1*). Consensus sites for N-linked glycosylation are underlined. Susceptibility was determined by infection of fibroblasts with infectious viruses or pseudoviruses carrying the LacZ reporter. Log<sub>10</sub> titer: -, no detectable infection; (+), 1–2; +, 3–6.