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Residues in the Murine Leukemia Virus Capsid That Differentially Govern Resistance to Mouse *Fv1* and Human *Ref1* Restrictions

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We identified new residues within a 101-amino-acid stretch of the murine leukemia virus capsid that differentially modulate resistance and susceptibility to the mouse *Fv1* and human *Ref1* genes. Among these residues, aspartate 92 and histidine 117 are both required for *Fv1^b* resistance, whereas the latter is sufficient to confer *Ref1* resistance.

The Friend virus susceptibility gene 1 (*Fv1*) restricts replication of N-tropic and B-tropic murine leukemia viruses (MLV) in laboratory mouse strains harboring the *b* or *n* allele, respectively (15, 29). Several other alleles are present in wild mice (18, 26). Fv1 products are related to retroviral capsids (CA) with closest homologies to human (HERV-L) and mouse (MuERV-L) endogenous retroviral sequences (2, 5). The *Fv1* restriction does not block reverse transcription but prevents proviral DNA integration through unknown mechanisms. Restriction at early stages of retroviral replication has been described in other mammalian species, including monkeys and humans (3, 6, 8, 11, 14, 30, 32). The most studied restriction genes in primates are the human *Ref1* (32) and simian *Lv1* (4, 8) genes. The primate TRIM5α protein, a member of the tripartite motif protein superfamily, unrelated to *Fv1*, has recently been shown to be an early-stage restrictive factor of primate lentiviruses (31) associated with *Ref1* and *Lv1* activities (13, 17, 25, 34). *Ref1* and *Lv1*, in contrast to *Fv1*, target a wide range of mammalian lentiviruses and have been shown to restrict N-tropic but not B-tropic MLV (11, 32).

MLV CA proteins are the main target of the *Fv1*, *Ref1*, and *Lv1* restrictions (9, 12, 22–24). Residue 110 of MLV CA has been identified as the discriminating target determinant between N-tropic, *Ref1*-susceptible MLV and B-tropic, *Ref1*-resistant MLV in murine (18) as well as other mammalian (17, 25, 32, 34) cells. However, under certain conditions, changes at CA residues 105 (10) and 114 (16) have also been reported to modulate *Fv1* restriction.

NB-tropic MLV strains, such as the prototypic Friend and Moloney MLV, are resistant to all tested *Fv1* alleles. Moloney MLV has also been documented to be resistant to *Ref1* and *Lv1* (25, 31, 34), but the status of Friend MLV with respect to these primate restriction systems has not been described. Intriguingly, Friend MLV is NB-tropic despite the presence of the N-tropic hallmark, an arginine at position 110 (Arg110), and conserved residues at positions 105 and 114 (Fig. 1A). Therefore, evasion of the mouse restriction systems, as observed with NB-tropic Friend MLV, appears to involve a residue(s) other than residue 110. To determine the sensitivity of Friend MLV to *Ref1* and more precisely map CA determinants affecting resistance to the mouse *Fv1^b* and *Fv1^n* alleles, we derived Friend MLV CA-based constructs and mutants. Here, we demonstrate that Friend MLV is resistant to the human *Ref1* restriction and identify CA residues that condition N, B, NB, and *Ref1* tropisms. We thereby describe residue combinations that differentially modulate susceptibility and resistance to *Fv1* and *Ref1* restrictions.

A 101-amino-acid fragment recapitulates MLV capsid susceptibilities to *Fv1* and *Ref1* targets. Early studies of *Fv1* MLV target determinants mapped differences between N- and B-tropic MLV to a 302-bp fragment encoding a CA sequence comprised between residues 33 and 133. Residues 109 and 110 were reported to be the MLV NB determinant (9) (Fig. 1A). We constructed a Friend MLV-based Gag-Pol expression vector (pC57GP) that allowed allelic exchanges of this 302-bp MLV CA cassette between BamHI and BstXI restriction sites. These sites were either naturally present or introduced by PCR-directed mutagenesis, in prototypic MLV strains of different NB tropisms. Additional EheI and XhoI sites were also used to swap smaller fragments (Fig. 1A). Prototypic CA sequences were derived from the N-tropic Akr-623 and B-tropic WNB5 MLV clones (7, 19) (kind gifts of A. Rein) and from the NB-tropic Friend MLV 57 and Moloney MLV 8.2 clones (see reference 27 for details). We also PCR amplified and sequenced a BamHI-BstXI fragment from the historical N-tropic Tennant isolate of the Friend complex (NT1; a kind gift of S. Gisselbrecht). NT1 differs from NB-tropic Friend MLV 57 at positions 92 and 124, with glutamate and serine residues substituted for aspartate and alanine, respectively (Fig. 1A).

Single-round infectious retroviral particles with MLV cores were harvested from 293T cell supernatants 48 h after cotransfection of one of the *gag-pol* vectors with the pCSI-G vesicular stomatitis virus G protein expression vector (1) and the pLAPSN retroviral vector carrying the *neo* and human placental alkaline phosphatase reporter genes (20). Viral tropism was assayed on *Fv1*-nonrestrictive *Mus dunni* (dunni) cells or on dunni cells stably transfected with *Fv1^n* (dunni^n) or *Fv1^b* (dunni^b) expression vectors (*Fv1* plasmids were a kind gift of J. Stoye). *Ref1*

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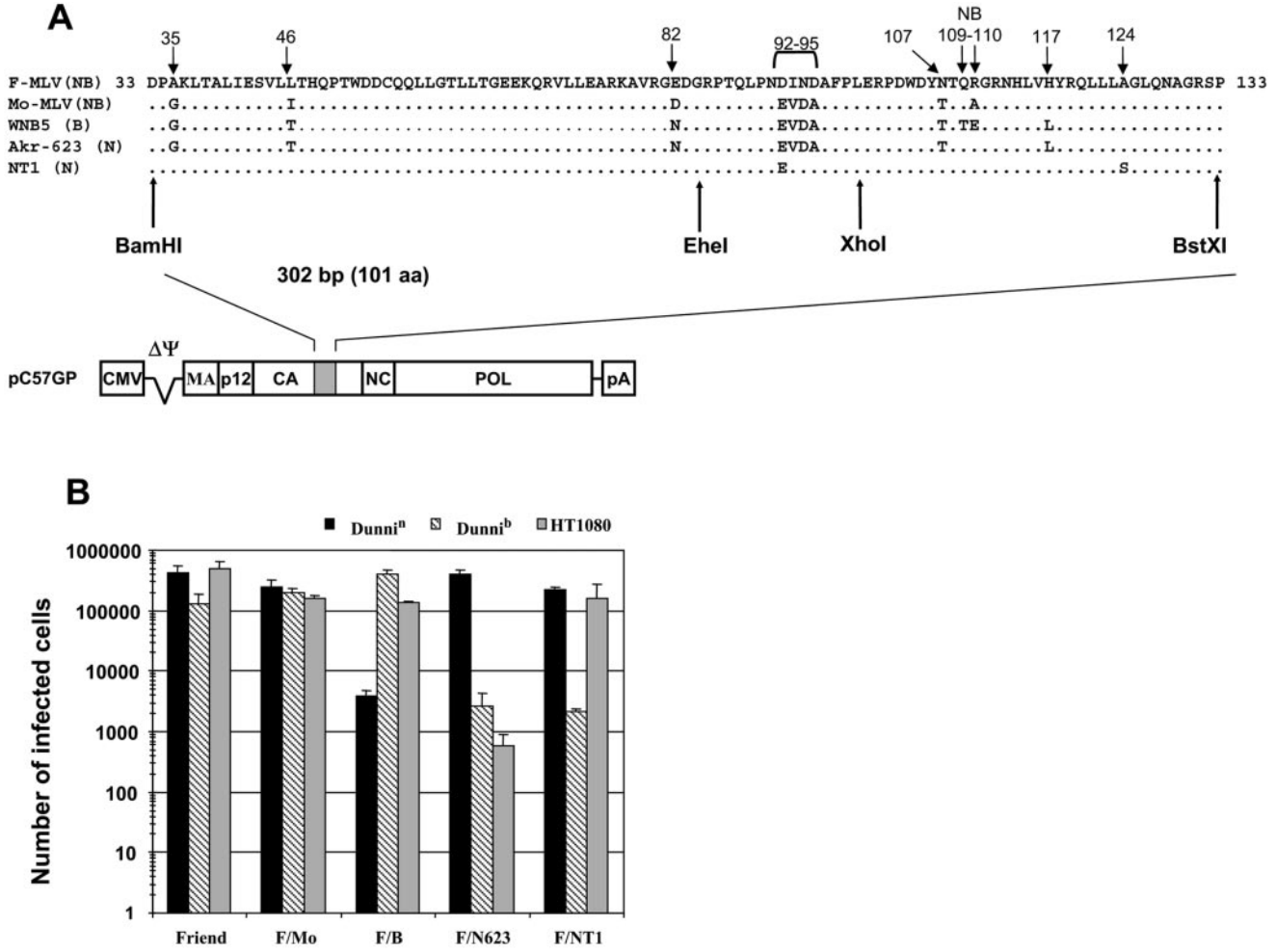

FIG. 1. Sequences, expression vectors, and tropism associated with prototypic MLV capsids. (A) Sequences of the capsid fragment used in the swaps are shown. Amino acid sequence alignment is shown for NB-tropic Friend MLV strain 57 and Moloney MLV (F-MLV and Mo-MLV, GenBank accession no. X02794 and J02255, respectively), B-tropic WNB5 MLV (GenBank accession no. K01190), N-tropic Akr-623 MLV (GenBank accession no. J01998), and the NT1 N-tropic Tennant strain of Friend MLV (this study; GenBank accession no. AY883167). NB, B, or N tropism is indicated in parentheses next to the MLV strain. The amino acid sequence encoded by the BamHI-BstXI 302-bp cassette (positions 1362 to 1664 in the Friend MLV clone 57 sequence), corresponding to amino acids 33 to 133 of the swapped capsid fragment, is shown. Positions corresponding to the EheI and XhoI internal restriction sites are also indicated. Distinctive residues including the NB determinant at positions 109 and 110 and the DIND motif (see text) at positions 92 to 95 are indicated. Dots represent residues identical to the Friend MLV 57 sequence. Each cassette was introduced in the CA gene of the pC57GP gag-pol expression vector from the NB-tropic strain 57 of Friend MLV. CMV, cytomegalovirus promoter; MA, matrix; CA, capsid; NC, nucleocapsid; pA, polyadenylation signal. (B) Evaluation of *Fv1* and *Ref1* MLV restrictions with parental CA cassettes. Virions were produced by transfecting human 293T cells with the vector shown in panel A and complementing vectors as described in the text. Viral supernatants were standardized on permissive *Mus dunni* $Fv1^{-/-}$ cells (dunni). Sensitivity to *Fv1* and *Ref1* restrictions was assayed on dunni^n and dunni^b cells stably expressing the $Fv1^n$ gene or the $Fv1^b$ gene, respectively, and on *Ref1*-positive human HT1080 cells. Cells were infected with serial dilutions of viral supernatant in the presence of Polybrene (8 μg/ml), and 2 days after infection, target cells were fixed and stained for alkaline phosphatase activity (20), and FFU per milliliter were counted. Mean viral titers ± standard errors of the means are shown and were calculated from at least three independent experiments using FFU values obtained in the linear portion of the titration curve.

restriction was tested on human HT1080 cells (Fig. 1B) and TE671 cells as indicated.

All reported virion preparations had similar infectious levels as measured on nonrestrictive dunni cells, with titers ranging from 10^5 to 10^6 focus-forming units (FFU)/ml. All parental MLV prototypic tropisms were reproduced when using our chimeric CA-based vector system. Thus, $Fv1^b$ and $Fv1^n$ restrictions resulted in a 20- to 400-fold drop in titers. Strong *Ref1*-mediated restriction, with an average 200-fold drop in titers, was also observed with N-MLV virions (Fig. 1B and 2A). The NB-tropic F-MLV construct was resistant to both $Fv1^b$ and $Fv1^n$, as well as to *Ref1*. Surprisingly though, the $Fv1^b$-susceptible NT1-derived construct was resistant to *Ref1*-mediated restriction (Fig. 1B). This *Ref1* resistance of an N-tropic MLV was observed on HT1080 and TE671, human cell lines that exert strong *Ref1* restriction on other retroviruses (32), as well as on dunni cells stably transduced with human TRIM5α expressed from the pLXSN retroviral expression vector (dunni/TRIM5α) (data not shown). This is the first identified CA sequence that distinguishes between $Fv1^b$ and *Ref1* susceptibilities.

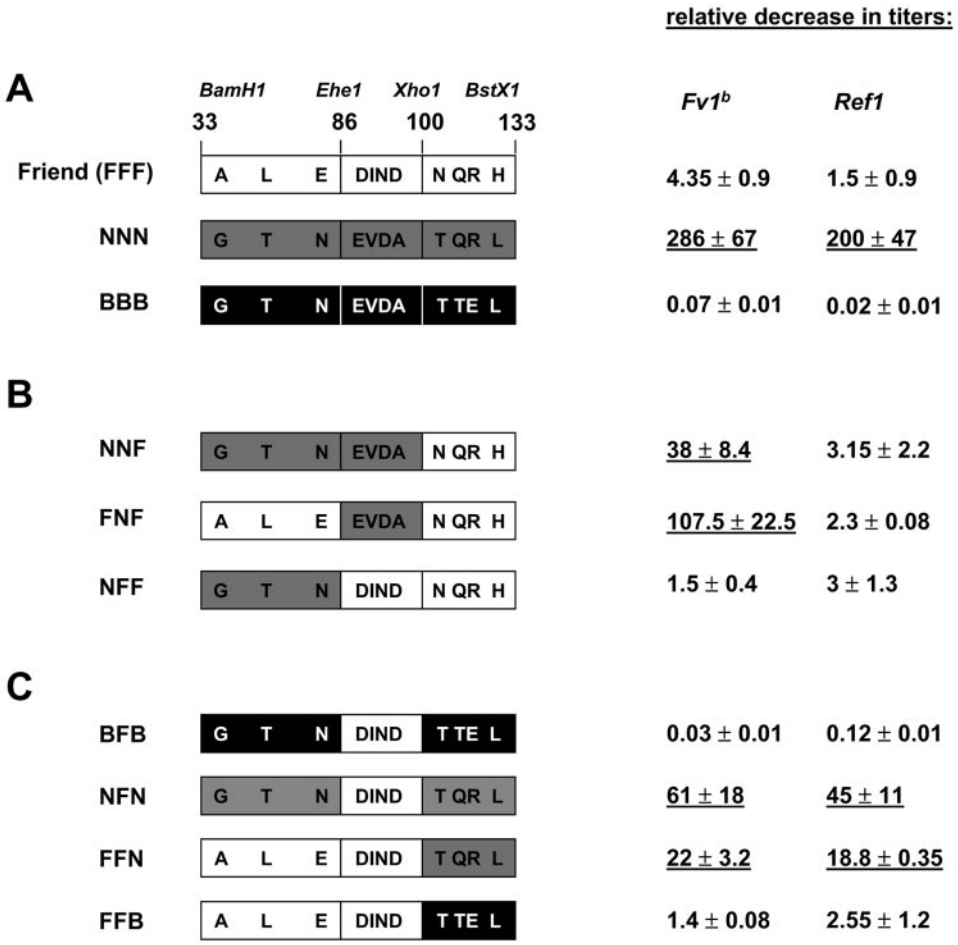

FIG. 2. *Fv1* and *Ref1* restrictions of MLV particles harboring chimeric CA. Allelic fragment exchanges between Friend NB-tropic MLV (F, open boxes), N-tropic Akr-623 MLV (N, grey boxes), and B-tropic WNB5 MLV (B, black boxes) were generated using BamHI, EheI, XhoI, and BstXI restriction sites. Fragment combinations are designated by a three-letter code corresponding to the parental MLV fragments delineated by residues 33 to 86, 87 to 100, and 101 to 133, respectively. Infections were performed as described in Fig. 1. Relative decreases in titers with $Fv1^b$ are shown as mean ratios ± standard errors of the means of viral titers obtained on dunni^n cells over dunni^b cells whereas relative decreases in titers with *Ref1* are shown as mean ratios ± standard errors of the means of titers obtained on dunni^n cells over *Ref1*-positive HT1080 human cells. Data were calculated from at least three independent experiments. Underlined values indicate chimeras that are susceptible to $Fv1^b$ or *Ref1* restrictions.

MLV resistance to *Fv1* is due to multiple determinants that modulate position 110. Arg110 is the discriminating determinant between N-tropic, *Ref1*-susceptible MLV and B-tropic, *Ref1*-resistant MLV (17, 18, 25, 32, 34). However, the fact that NB-tropic and N-tropic Friend MLV strains encoding Arg110 are resistant to $Fv1^b$, *Ref1*, or both indicated that other residues in the 101-amino-acid-long capsid region govern $Fv1^b$ and *Ref1* susceptibilities. We therefore further evaluated the bases for the Friend MLV *Fv1* and *Ref1* resistance with smaller domain swaps.

A domain swap introducing N-MLV residues 33 to 100, excluding the canonical 110 residue, into Friend MLV was sufficient to render the latter susceptible to $Fv1^b$ restriction (chimera NNF, Fig. 2B). Friend MLV CA residues 92 to 95 consist of a DIND motif corresponding to an EVDA motif in prototypic N-tropic MLV (Fig. 1A). The swap of this motif was sufficient to convert Friend MLV to N-tropism as shown by a full $Fv1^b$ susceptibility of the corresponding construct (FNF, Fig. 2B). Thus, the DIND motif plays a key role in suppressing the accessibility of the N-tropic target in Friend MLV. Notably though, swapping of this motif did not render Friend MLV susceptible to *Ref1*, and this resistance was maintained even following a larger swap from residues 33 to 100 (NNF, Fig. 2B).

We further assessed the suppressive effect of the Friend MLV DIND motif in a parental B-MLV (BFB) or N-MLV (NFN) context. The sole substitution of this DIND motif was not sufficient to modulate *Fv1* or *Ref1* resistance in either context (Fig. 2C). When this swap was combined with that of the upstream fragment, B-tropic virions became resistant to the $Fv1^n$ restriction. Therefore, glycine, threonine, and/or asparagine at positions 35, 46, and 82, respectively, conditions CA targeting by *Fv1*. Nevertheless, this contribution was not as potent in the N-tropic context, since FFN particles remained susceptible to $Fv1^b$ and *Ref1* restrictions, albeit with a slightly decreased susceptibility (Fig. 2C). The prominent exposure of Asp82, according to the recently published structure of the N-AKV CA amino-terminal domain (21) (Fig. 4B), is in favor of a role for this residue in Fv1 tropism, as also suggested by others (28).

Mutation of histidine to leucine at position 117 is sufficient to render Friend MLV susceptible to $Fv1^b$ and *Ref1* restric-

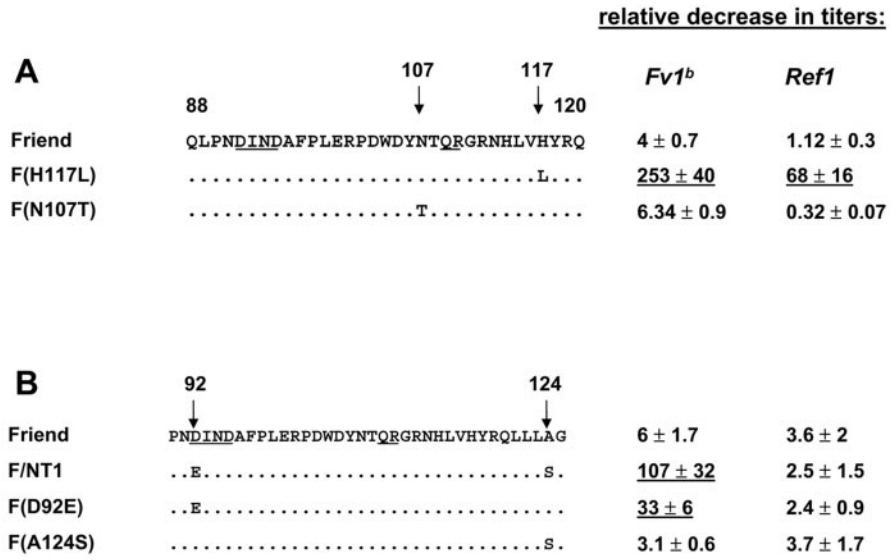

FIG. 3. Residues responsible for resistance of Friend MLV 57 (Friend) to *Fv1*^{b} and *Ref1*. (A) Point mutations were introduced in the NB-tropic Friend MLV CA at positions 107, F(N107T), and 117, F(H117L), to match the N-tropic Akr-623 sequence and (B) at positions 92, F(D92E), and 124, F(A124S), to match the N-tropic F/NT1 sequence. F/NT1 corresponds to the Friend MLV57 CA into which the NT1 residues 33 to 133 have been swapped. All infections were performed as indicated in Fig. 1, and relative mean decreases in titers were calculated from at least three independent experiments as in Fig. 2.

tions. In contrast to Friend MLV virions, FFN virions (Fig. 2C) were susceptible to both *Fv1*^{b} and *Ref1* restrictions. As the difference between these viruses was limited to amino acid changes at positions 107 and 117, we introduced individual substitutions at these positions in the Friend MLV background. Infections on restrictive cell lines showed that the presence of leucine at position 117, F(H117L), was sufficient to induce a susceptibility to *Fv1* and *Ref1* restrictions (Fig. 3A). Charge rather than aromatic properties was crucial for resistance, as mutation of His117 to a lysine in Friend MLV maintained this property whereas mutation to either phenylalanine or tyrosine reversed resistance (not shown).

Loss of *Fv1*^{b} but not *Ref1* restriction in the presence of aspartate 92. As indicated above, suppression of the canonical residue 110 as a target for *Fv1*^{b} is due to the combined presence of His117 and a DIND motif. Interestingly, the N-tropic NT1 strain harbors an EIND motif. The aspartate-to-glutamate change was sufficient to confer *Fv1*^{b} susceptibility with no effect on *Ref1* resistance, as observed with the F(D92E) mutant (Fig. 3B). When introduced alone, the second amino acid difference between the Friend MLV and NT1 strain CA at position 124 did not influence either *Fv1* or *Ref1* susceptibility [F(A124S), Fig. 3B]. Therefore, Glu92 was key to the recognition of the *Fv1*^{b} target in the presence of His117, while it did

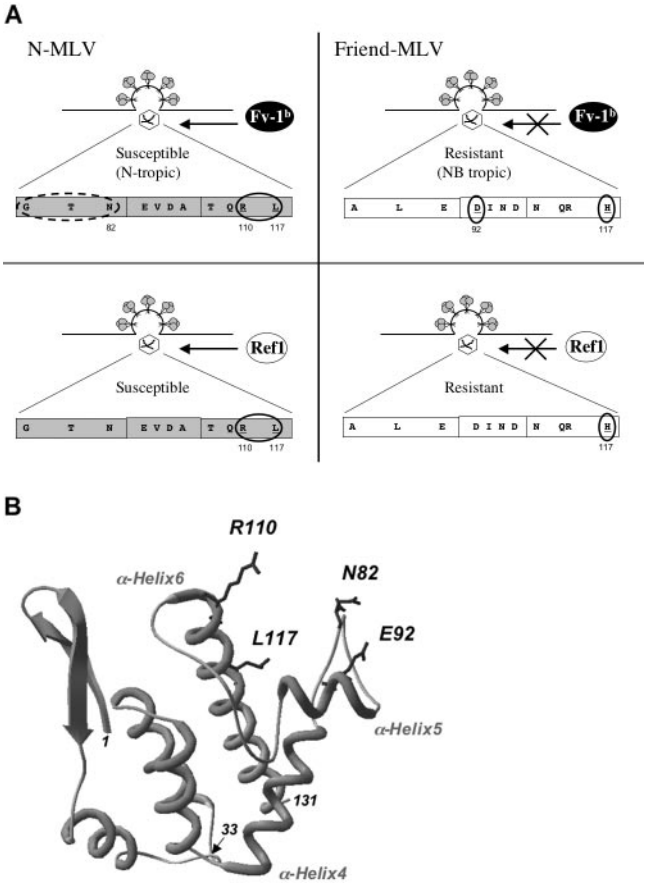

FIG. 4. Schematic representation of the *Fv1* and *Ref1* restriction targets. (A) Target and masking determinants for *Fv1*^{b} (top) and *Ref1* (bottom) restrictions in the MLV CA. Key residues involved in the susceptibility of N-MLV to *Fv1*^{b} and *Ref1* restriction genes are circled (left panels, R110 and L117). The dashed circle indicates a fragment found to modulate the restriction level (see text). Residues sufficient to make the Friend MLV CA target inaccessible to *Fv1*^{b} and/or *Ref1* restrictions are circled (right panels, combined D92 and H117 for *Fv1*^{b}; H117 for *Ref1*). (B) Three-dimensional structure of the amino-terminal domain of N-Akv CA (adapted from reference 21). Amino-terminal (position 1) and carboxy-terminal (position 131) extremities of the crystallized fragment are indicated as well as position 33 corresponding to the BamHI cloning site shown in Fig. 1 and α-helices 4, 5, and 6. Representation of asparagine 82 (N82), aspartate 92 (E92), arginine 110 (R110), and leucine 117 (L117) side chains highlights their potential accessibility to restriction factors.

not modulate *Ref1* restriction. Similar data were obtained using dunni/TRIM5α cells.

In conclusion, while Arg110 is required for both $Fv1^b$ and *Ref1* restrictions, Leu117 is also a major target determinant for both genes (Fig. 4A, left panels). Furthermore, Asp92 is required for efficient resistance to $Fv1^b$ when combined with His117. This is in agreement with a recent report using a different model of *Fv1* restriction (28). However, we found that *Ref1* resistance was not affected by Asp92 (Fig. 4A, right panels). This is compatible with the recently reported crystal structure of the CA amino-terminal domain of an N-tropic MLV in which residue 92, on the one hand, and residues 110 and 117, on the other, are located in two separate neighboring helices, α-helices 5 and 6, respectively (21) (Fig. 4B). Our results suggest that CA MLV recognition by *Fv1* involves both α-helices, which are exposed to the outside of the amino-terminal CA hexamer (21), whereas *Ref1*/*TRIM5*α recognition appears to involve mainly α-helix 6. While α-helices 4 and 6 appear structurally conserved between human immunodeficiency virus type 1 and N-Akv CA, the interconnecting sequence, which includes α-helix 5 of N-Akv CA, displays a variable succession of loops and helices (21). Interestingly, the latter sequence comprises residue 92 of the MLV CA, which we identified as a major Fv1-modulating determinant, and the human immunodeficiency virus type 1 CA CypA-binding loop involved in *Lv1* restriction (12, 23, 33), thus providing differential target patterns recognized by these restrictive cellular mechanisms.

Nucleotide sequence accession number. The GenBank accession number of the BamHI-BstXI fragment from the historical N-tropic Tennant isolate of the Friend complex is AY883167.

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