Nucleotide Sequences of *gag-pol* Regions That Determine the *Fv-1* Host Range Property of BALB/c N-Tropic and B-Tropic Murine Leukemia Viruses

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Previously, in vitro recombinant DNA studies demonstrated that genetic determinants of N-tropism and B-tropism, or *Fv-1*-related host range properties of murine leukemia viruses, were located in a *Bam*HI-*Hind*III DNA segment derived from the 5' portion of the cloned viral genome. We sequenced this segment and its immediate 5' region from cloned DNA of two BALB/c mouse C-type viruses (WN1802N and WN1802B) and found base differences at 12 positions out of the otherwise identical 1,390-base-pair sequences. Analysis of the most likely reading frame showed that 6 of the 12 base differences would result in four encoded amino acid changes, three of which occur at positions 109 (glutamine in WN1802N versus threonine in WN1802B), 110 (arginine in WN1802N versus glutamic acid in WN1802B), and 159 (glutamic acid in WN1802N versus glycine in WN1802B) of the p30 protein. The remaining one is located at position 36 (threonine in WN1802N versus isoleucine in WN1802B) of the viral polymerase protein. Significant conformational alteration of the p30 protein could be predicted from these amino acid changes.

Most naturally occurring and newly isolated ecotropic murine leukemia viruses (MuLVs) are classified as either N-tropic or B-tropic, depending on the restriction of viral infectivity and leukemogenic activity by different alleles of the *Fv-1* locus of mice (14, 24, 26). N-tropic MuLVs that are infectious in cells of the *Fv-1^{lmm}* genotype are restricted in cells of the *Fv-1^{bb}* and *Fv-1^{nb}* genotypes, whereas B-tropic MuLVs are restricted in cells of the *Fv-1^{lmm}* and *Fv-1^{nb}* genotypes but not in cells of the *Fv-1^{bb}* genotype. The *Fv-1* restriction is not absolute and can be overcome when the restricted viruses are administered at high multiplicities of infection (8, 18, 25).

Phenotypic mixing between N- and B-tropic MuLVs has been shown to result in the production of infectious virus particles with dual sensitivity to *Fv-1* restriction, indicating that a certain virion component may be the target for the restriction (29). *Fv-1* restriction interferes with the proper formation of retroviral DNA forms (6, 20, 38) and thereby blocks provirus integration (19, 34); this virion target molecule apparently plays important roles in the processes of reverse transcription or gene integration or both

(18, 37). Based on previous biochemical and genetic studies, it was hypothesized that the p30 core protein is the target of *Fv-1* restriction (e.g., 2, 12, 16).

We have recently cloned the unintegrated viral DNAs of various N- and B-tropic MuLVs (3), including the paired strains WN1802N and WN1802B originally isolated from the spleen of an 18-month-old BALB/c mouse (13). To determine the location of genetic determinants of N-tropism in two N-tropic MuLVs, WN1802N and Gross passage A, and of B-tropism in WN1802B MuLV, infectious viral DNA recombinants were constructed in vitro by exchanging homologous restriction enzyme DNA fragments from DNA clones of these viruses. Hybrid virus progenies produced from cells transfected with the viral DNA recombinants were examined for their host range property in cells of *Fv-1^{lmm}* and *Fv-1^{bb}* genotypes. This study unequivocally revealed that the viral genetic determinants of N- and B-tropism resided allelically in a *gag-pol* segment bordered by a *Bam*HI site and a *Hind*III site at ca. 1.6-kilobase-pair and ca. 2.9-kilobase-pair distances, respectively, from the left terminus of the linear viral DNA (4). The

FIG. 1. Restriction enzyme map and nucleotide sequencing approaches for the *Bam*HI-*Hind*III fragment and adjacent regions in the pWB5 clone of WN1802B virus and the pWN41 clone of WN1802N virus. A linear retroviral DNA structure, rather than the permuted DNA form of the clones, is depicted and marked with the one *Hind*III (●) and four *Bam*HI sites (○). Arrows indicate the starting points, directions, and extents of sequenced strands. kbp, Kilobase pairs; LTR, long terminal repeat; bp, base pairs.

results are consistent with the findings of previous investigators which demonstrated that N- or B-tropism of various MuLV isolates, as well as of recombinant viruses from them, genetically segregates with characteristic properties of the virion p30 core protein (1, 2, 5, 11, 16, 30, 32) and that specific oligonucleotides associated with N-, B-, and NB-tropism are located in the 5' portion of viral genomic RNA (9, 10, 31). Here we report the nucleotide sequences, as well as the predicted structure, of the encoded polypeptides in this *gag-pol* segment of the paired BALB/c N- and B-tropic MuLVs.

The recombinant DNA clone of WN1802N MuLV used in this sequencing study was pWN41 (with pBR322 as the vector), and the clone of WN1802B MuLV was pWB5 (with pBR325 as the vector). These clones were used in the previous fragment exchange study (4). Physical maps of the *Ava*I, *Hpa*II, *Hae*III, *Taq*I, and *Hinf*I restriction endonucleases in the regions between and adjacent to the *Bam*HI (ca. 1.6 kilobase pairs from the left terminus) and *Hind*III (ca. 2.9 kilobase pairs from the left terminus) endonuclease sites were determined,

and the results are shown in Fig. 1. The mapping results demonstrated that pWN41 (WN1802N) and pWB5 (WN1802B) clones were indistinguishable with regard to these restriction sites. Also shown in Fig. 1 is the DNA sequencing strategy carried out by the ^{32} P-end-labeling chemical degradation method of Maxam and Gilbert (22).

Shown in Fig. 2 are the plus-strand sequences of 1,390 base pairs elucidated for the two MuLV DNA clones and the predicted amino acid residues encoded by these sequences. The three possible genetic code reading frames of these sequences contained 1, 26, and 35 termination codons; the latter two were not considered further. The first reading frame generated amino acid sequences which closely matched those previously reported for Moloney MuLV (15, 28, 33, 36). With this reading frame, the plus-strand 1,390-nucleotide sequence encodes 263 amino acids of the p30 protein, 60 amino acids of the p10 protein, an UAG amber termination codon, and 139 amino acids of the amino-terminal portion of the viral polymerase protein.

Comparison of the DNA sequences of pWN41

→ p30	
CCACTCCGTTGGGGGTAATGGTCAGTTCAGTACTGCGGTTTCTCCTCTGATCTATATACTGGAAAAATAATCCTCTCTTC	90
ProLeuArgLeuGlyGlyAsnGlyGlnLeuGlnTyrTrpProPheSerSerSerAspLeuTyrAsnTrpLysAsnAsnAsnProSerPhe	30
BamH-I	
TCTGAGCATCCAGTAACTGACTGCATTGATTGAATCTGTCTCACCACCCAGCCACCTGGGATGATGCCAGCAATTATTAGGG	180
SerGluAspProGlyLysLeuThrAlaLeuIleGluSerValLeuThrThrHisGlnProThrTrpAspAspCysGlnGlnLeuLeuGly	60
ACTCTGCTTACCGGGGAGAGAAGCAGCGGGTCTCTGGAAGCCGAAAAGCTGTCGGGGGCAACGATGGGCGCCCACTGCCC	270
ThrLeuLeuThrGlyGluGluLysGlnArgValLeuLeuGluAlaValArgGlyAsnAspGlyArgProThrGlnLeuPro	90
AACGAGGTTGACGCTGCTTTCCCTTGAACCTCCCGATTGGGATTACACCACCAAGAGGTAGGAACCACTAGTCTCTATCGCCAG	360
AsnGluValAspAlaAlaPheProLeuGluArgProAspTrpAspTyrThrThrGlnArgGlyArgAsnHisLeuValLeuTyrArgGln	120
TTGCTTTTAGCGGTCTCCAAAACGGGGCGGAGCCCACTTTGGCCAAAGTAAAAGGAATAACCCAGGACCTGATGAGTCCCC	450
LeuLeuLeuAlaGlyLeuGlnAsnAlaGlyArgSerProThrAsnLeuAlaLysValLysGlyIleThrGlnGlyProAspGluSerPro	150
TCAGCCTTCTAGAGACTCAAGCAACCTATCGCAGATACACTCCTTATGATCCTGAGGACCTGGGCAAGAAACGAATGTATCTATG	540
SerAlaPheLeuGluArgLeuLysGlnAlaTyrArgArgTyrThrProTyrAspProGluAspProGlyGlnThrAsnValSerMet	180
TCATTATCTGGCAGTCCGCTCCAGACATTGGTCGAAAGTTAGAGCGGTTAAGAGCTTAAAACTTAGGAGTTTAGTGAGA	630
SerPheIleTrpGlnSerAlaProAspIleGlyArgLysLeuGluArgLeuGluAspLeuLysSerLysThrLeuGlyAspLeuValArg	210
GAAGCCGAAAGGATCTTTAATAAAAGAGAACTCCAGAAGAAAGAGAGCGGTTAGCAGGAGACAGAGAAAAGGAGAGCGGCT	720
GluAlaGluArgIlePheAsnLysArgGluThrProGluGluArgGluGluArgValArgArgGluThrGluGluLysGluGluArgArg	240
AGGGCAGAAGGAGCAGAAAGAGCAAGACCGCTACGAGACATAGAGAAATGAGCAACTTTTGCCACCGTAGTTAGTGACAG	810
ArgAlaGluGluGlnGlnLysGluLysGluArgAspArgArgHisArgGluMetSerLysLeuLeuAlaThrValValSerGlyGln	270
AGACAGGATAGACAGGGGGAGAGCGAAGGAGGCCCACTTGACAAGGATCAATGTGCTACTGTAAAGAAAAGACACTGGGCTAAA	900
ArgGlnAspArgGlnGlyGlyGluArgArgProGlnLeuAspLysAspGlnCysAlaThrCysLysGluLysGlyHisTrpAlaLys	300
GACTGCCAAAGAACCCAGGGGTCGCCAGGACCGGACCCAGACCTCCCTCTGACTTTAGACGACTAGGGGGCTCAGGTCAGGAG	990
AspCysProLysLysProArgGlyProArgGlyProArgProGlnThrSerLeuLeuThrLeuAspAspENDGlyGlyGlnGlyGlnGlu	330
CCCCCCTGAACCCAGGATAACCTCACTGTGGGGGCAACCCGTCACTTCTGGTGGAATACTGGGGCCCAACACTCGTGCTGACT	1080
ProProProGluProArgIleThrLeuThrValGlyGlyGlnProValThrPheLeuValAspThrGlyAlaGlnHisSerValLeuThr	360
CAAAATCTGGGCCCTAAGTGACAGGTGGCTTGGTCCAAGGGGCTACTGGAGGAAGCGGTACTCGTGACACAGATCGCAAGGTA	1170
GlnAspProGlyProLeuSerAspArgSerAlaTrpValGlnGlyAlaThrGlyGlyLysArgTyrArgTrpThrAspArgLysVal	390
CACCTGGCTACCGGTAAGGTCACTCACTCTTCTCCATGTGCCAGACTGCCCTACCCCTTGCTAGGAAGAGACTTGTAACTAACTA	1260
HisLeuAlaThrGlyLysValThrHisSerPheLeuHisValProAspCysProTyrProLeuLeuGlyArgAspLeuLeuThrLysLeu	420
AAAGCCAGATCACTTTGAGGAGTCAAGAGCCAGGTTGTGGGACCAAAAGGACAGCCTCTACAGGTGTTGACCTAAACCTAGAAGAT	1350
LysAlaGlnIleHisPheGluGlySerGlyAlaGlnValValGlyProLysGlyGlnProLeuGlnValLeuThrLeuAsnLeuGluAsp	450
Hind III	
GAGTATCGGCTTCATGACACCTCAGCAGAGCCGGAAGCTT	
GluTyrArgLeuHisGluThrSerAlaGluProGluAla	

FIG. 2. Elucidated 1,390-nucleotide sequence of the plus DNA strand, as well as the inferred amino acid sequences, of two *gag* gene components and the amino-terminal portion of the *pol* gene in WN1802N and WN1802B viruses. Since the two MuLVs showed 99.1% sequence homology in this region, only the complete sequences of WN1802N virus are shown, and base differences found in WN1802B virus are indicated at the top. Base differences leading to encoded amino acid changes are boxed.

and pWB5 revealed base differences at 12 positions out of the 1,390-nucleotide sequence or 99.1% sequence homology. Of the 12 substitutions, 10 involved A-G or T-C transitions; the other 2 (positions 325 and 326) involved A-C transversions. All except two occurred in the middle portion of the p30-encoding region. Of the 12 base substitutions, 6 involved the third base of a codon and resulted in no changes in encoded amino acids. Of the four amino acid changes resulting from the other six base substitutions, three occurred in the p30 protein at amino acid positions 109 (glutamine in WN1802N versus threonine in WN1802B), 110 (arginine in WN1802N versus glutamic acid in WN1802B), and 159 (glutamic acid in WN1802N versus glycine in WN1802B). The fourth amino

acid difference occurred at position 36 of the viral polymerase protein, which is threonine in WN1802N versus isoleucine in WN1802B. The coding sequence of the p10 protein was identical in the two viruses.

A search in the 1,390-nucleotide sequence for corresponding segments of the N-tropic oligonucleotide GAUACACCACCCAAAG(A) and the B-tropic oligonucleotide GAUACACCA CUACAG(AA), elucidated by Rommelaere et al. (31), revealed that they are precisely located at nucleotide positions 343 through 360 of the p30 coding sequence, and thus the last two triplets of these tropic oligonucleotides are responsible for the different amino acid residues 109 and 110 of the p30 protein. The perfect base-to-base matching of these oligonucleotide se-

FIG. 3. Apparent protein conformation properties of WN1802N virus and WN1802B virus p30 proteins as predicted from the inferred amino acid sequences. The amino-terminal ("N") and carboxy-terminal ("C") residues of the p30 polypeptide are designated as positions 1 and 263, respectively. (A) Hydrophilicity curves obtained by the hexapeptide calculation method (17); a dotted line is used for WN1802B virus at positions where differences are present. (B) Probable helical segments (dark solid bar or) , β -sheets (cross-hatched bar or) , and random coil regions (blank or) along the amino acid sequence obtained by probability analysis (7); differences between B-tropic (Bv) and N-tropic (Nv) viruses are shown in expanded graphs, with positions 109, 110, and 159 indicated by arrows.

quences was remarkable since the N-tropic MuLV studied by Faller and Hopkins (9, 10) and Rommelaere et al. (31) presumably represented an independent virus isolate different from WN1802N virus. Furthermore, on the basis of the inferred amino acid sequences, the WN1802N and WN1802B p30 proteins would each produce five tyrosine-containing tryptic peptides, two of which would be detected as being different by fingerprinting analysis. The one containing amino acids 109 and 110 would be 9 residues long from WN1802N and 11 residues long from WN1802B. The one containing amino acid 159 would be four residues long from both viruses and would be more acidic from WN1802N than from WN1802B; however, this peptide of WN1802N is apparently identical to those of Rauscher and Moloney NB-tropic MuLVs (see below). Thus, previously demonstrated N- and B-tropism-associated p30 tryptic peptides (11, 12) are likely to be the ones containing amino acid residues 109 and 110.

The inferred amino acid sequence data could also be employed to explain the differences in

electrophoretic properties of p30s of WN1802N and WN1802B (16, 21, 35). Having a net additional arginine residue, WN1802N p30 is more basic than WN1802B p30, as demonstrated by isoelectric focusing. In sodium dodecyl sulfate-acrylamide gel electrophoresis, WN1802N p30 migrates slightly faster than WN1802B p30; since this evidently cannot be explained on the basis of molecular weight, the difference might be due to protein conformation. Employing a method for calculating peptide hydrophilicity (17), we observed that p30s of these BALB/c viruses had a relatively hydrophobic amino-terminal section, a highly hydrophilic carboxy-terminal section, and a middle section with mixed hydrophobicity and hydrophilicity and also that positions 109 and 110 and position 159 were located in two separate hydrophilic sites (Fig. 3A). Employing a probability method for predicting helix and β -sheet peptide structures (7), we found that positions 109/110 could be placed at the carboxy end of a β -sheet, whereas position 159 could be placed at the carboxy end of a helical segment (Fig. 3B). With the amino

acid differences at these positions, the β -sheet appeared to comprise eight amino acids (residues 104 through 111) in WN1802N p30 and six amino acids (residues 104 through 109) in WN1802B p30, whereas the helical segment appeared to comprise 11 residues (positions 150 through 160) in WN1802N p30 and 9 residues (positions 150 through 158) in WN1802B p30. These altered C termini of the β -sheet and the helical segment were hydrophilic and hence could be exposed on the surface of the p30 molecule. The exposed segments are likely to be sites for interaction with the *Fv-1* gene product, as well as being responsible for antigenic differences between the p30s of WN1802N and WN1802B viruses (2, 35). The threonine-isoleucine difference at position 36 of the viral polymerase protein could also lead to a protein conformation difference but not one as marked as those in the p30 protein.

Amino acid sequences of p30 proteins of Moloney and Rauscher MuLVs have been determined by direct peptide sequencing of virion protein preparations (15) and by nucleotide sequencing of cloned viral DNA (33). These two MuLVs were isolated after a long and complex passage history in BALB/c mice (23, 27); they are not susceptible to *Fv-1* restriction and hence are designated NB-tropic. We therefore compared their p30 amino acid sequences with the inferred p30 amino acid sequences of WN1802N and WN1802B viruses (Table 1). At positions 109, 110, 159, which distinguish the p30s of WN1802N and WN1802B viruses, Rauscher MuLV p30 is identical to that of WN1802N, and Moloney MuLV p30 differs only at position 110 (alanine) from that of WN1802N. However, of the 263 amino acid residues of p30, Moloney MuLV is different at 11 positions and Rauscher MuLV is different at 14 positions from WN1802 N-tropic virus; 6 of these positions are common to Moloney and Rauscher MuLVs (glutamic acid at position 82, histidine at position 117, asparagine at position 147, lysine at position 214, isoleucine at position 229, and aspartic acid at position 244). Whether these amino acid differences in the middle portion of the p30 polypeptide are related to the NB-tropism property of Rauscher and Moloney MuLVs remains to be investigated.

Analyzing the specific oligonucleotide structures of NB-tropic viral genomes derived from the B-tropic viral genome, Rommelaere et al. (31) concluded that B- to NB-tropism conversion involves changes at genomic sites distinct from but close to those specifying N- or B-tropism. Thus, if Rauscher and Moloney MuLVs originated from N-tropic viruses, as implied by the identical or almost-matching amino acid residues at positions 109, 110, and 159,

TABLE 1. Amino acid sequence variations of MuLV p30s

Position	Amino acid sequence in strain ^a			
	WN1802N	WN1802B	Rauscher	Moloney
4	Leu	—	—	Ala
46	Thr	—	Leu	Ile
82	Asn	—	Glu	Glu
92	Glu	—	Asp	—
93	Val	—	Ile	—
94	Asp	—	Asn	—
95	Ala	—	Asp	—
107	Thr	—	Asn	—
109	Gln	Thr	—	—
110	Arg	Glu	—	Ala
117	Leu	—	His	His
147	Asp	—	Asn	Asn
159	Glu	Gly	—	—
202	Ser	—	—	Asn
214	Arg	—	Lys	Lys
227	Glu	—	Asp	—
229	Val	—	Ile	Ile
242	Ala	—	—	Thr
244	Glu	—	Asp	Asp
247	Lys	—	Arg	—

^a —, Same residue as the amino acid residue of WN1802N, which serves as the basic type of BALB/c endogenous type C retroviruses. Amino acid residues common to both NB-tropic strains but different from N- and B-tropic strains are boldfaced. Of the 263 amino acid residues of p30, WN1802B MuLV was different at 3 positions, Rauscher MuLV was different at 14 positions, and Moloney MuLV was different at 11 positions from WN1802N MuLV.

the NB-tropism could be the result of genetic alterations occurring independently of the N- or B-tropism determinant. However, certain conformational changes due to these amino acid differences located nearby might mask the *Fv-1* determinant by altering the interaction with the *Fv-1* gene product.

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