JOURNAL OF VIROLOGY, Apr. 1993, p. 1747–1751
0022-538X/93/041747-05$02.00/0

Vol. 67, No. 4

MINIREVIEW

3′ Junctions of Oncogene-Virus Sequences and the Mechanisms for Formation of Highly Oncogenic Retroviruses

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Highly oncogenic, or acutely transforming, retroviruses contain host-derived proto-oncogene sequences. All highly oncogenic retroviruses also contain the retroviral *cis* sequences needed for viral replication. However, most highly oncogenic retroviruses contain deletion(s) in their genomes; they are, therefore, replication defective. In contrast, some strains of Rous sarcoma virus have the oncogene *src* located between the *env* gene and the 3′ long terminal repeat (LTR). Thus, these strains of Rous sarcoma virus are both acutely transforming and replication competent.

The 3′ junctions of proto-oncogene-virus sequences in different highly oncogenic retroviruses are located in various regions of *gag*, *pol*, *env*, and the distal untranslated region. Some of these 3′ junction sequences involve different amounts of identity between the presumed parental retrovirus and proto-oncogene sequences. The 3′ junctions of a number of oncogenes are summarized in Fig. 1.

The 3′ oncogene-virus junctions in highly oncogenic retroviruses fall into two groups. The first group has a short region of sequence identity at the junction and comprises 18 of the 31 highly oncogenic viruses. The length of the short sequence identity ranges from 1 bp (BAI avian myeloblastosis virus) (20) to 11 bp (3611 murine sarcoma virus) (32). The second group has an insertion of 2 to 105 bp at the junction and comprises 13 of the 31 highly oncogenic viruses, including, for example, Fujinami sarcoma virus (15).

The numbers of viruses in the first group (having a short region of sequence identity at the junction) relative to the second group (having an insertion at the junction) are different for murine leukemia viruses (MLV), feline leukemia viruses (FLV), and avian leukosis viruses (ALV). Among highly oncogenic retroviruses formed by MLV, six viruses are in the first group (no insertion) and only one virus is in the second group (insertion); among highly oncogenic retroviruses formed by FLV, two viruses are in the first group (no insertion) and six viruses are in the second group (insertion); and among highly oncogenic retroviruses formed by ALV, eight viruses are in the first group (no insertion) and six viruses are in the second group (insertion). (These different distributions are statistically significant [Fisher's test, $P = 0.005$].)

In addition to the viruses listed in Fig. 1, Harvey murine sarcoma virus contains two regions of 30S RNA (VL 30 RNA) located at the 5′ and 3′ ends of the *ras* oncogene (6). This structure suggests at least a two-step origin for this virus, involving recombination of *ras* with a 30S RNA genome and a helper virus.

Many hypotheses have been proposed to explain the formation of highly oncogenic retroviruses. In this review, we present recent results that enable us to compare these hypotheses. We then present an explanation for each form of junction (the two groups) and a rationale for the results with different helper viruses.

In a recently described system (47), chimeric MLV *hyg* RNA and *neo*-containing MLV vector RNA were copackaged. After infection, nonhomologous recombination resulted in the formation of a *hyg* provirus. The junction sequences in the recombinant viruses fell into three groups. Only one is relevant to naturally occurring highly oncogenic retroviruses. This junction, designated general type, involved recombination between *hyg* and *neo* and usually involved a short region of sequence identity. In addition, some general-type recombinants contained an insertion between the two vector sequences. Similar sequence insertion in other types of recombinants indicated that these recombinants were between the *neo*-containing MLV vector and a read-through transcript of the chimeric MLV *hyg*.

Swain and Coffin (42) placed a simian virus 40 (SV40) promoter and a *neo* gene with a polyadenylation signal downstream of an avian leukosis provirus with a mutation in its polyadenylation signal. This mutated polyadenylation signal resulted in most viral transcripts containing the distal SV40 *neo* sequences. Four of six junction sequences were general type. One of the four general-type recombinants contained a short region of sequence identity. Three of the four general-type recombinants contained a 3′ insertion of 1 to 16 bp between the SV40 *neo* cassette and the helper virus sequence. The 16-bp insert was identical to a region in the *pol* gene of the helper virus.

Since naturally occurring highly oncogenic retroviruses may have formed in more than one round of replication, insertions at the junctions may have been acquired in an additional step of nonhomologous recombination. However, Zhang and Temin (47) saw insertions at the 3′ crossover junctions, even though the viruses replicated for only one round. Therefore, it is possible that the insertions at the junctions in highly oncogenic retroviruses were acquired at the same time as the acquisition of the nonhomologous sequence.

To consolidate information both about recombinants from nature and those from laboratories, we propose a model for the formation of highly oncogenic retroviruses. In our model, we divide the formation of a highly oncogenic retro-

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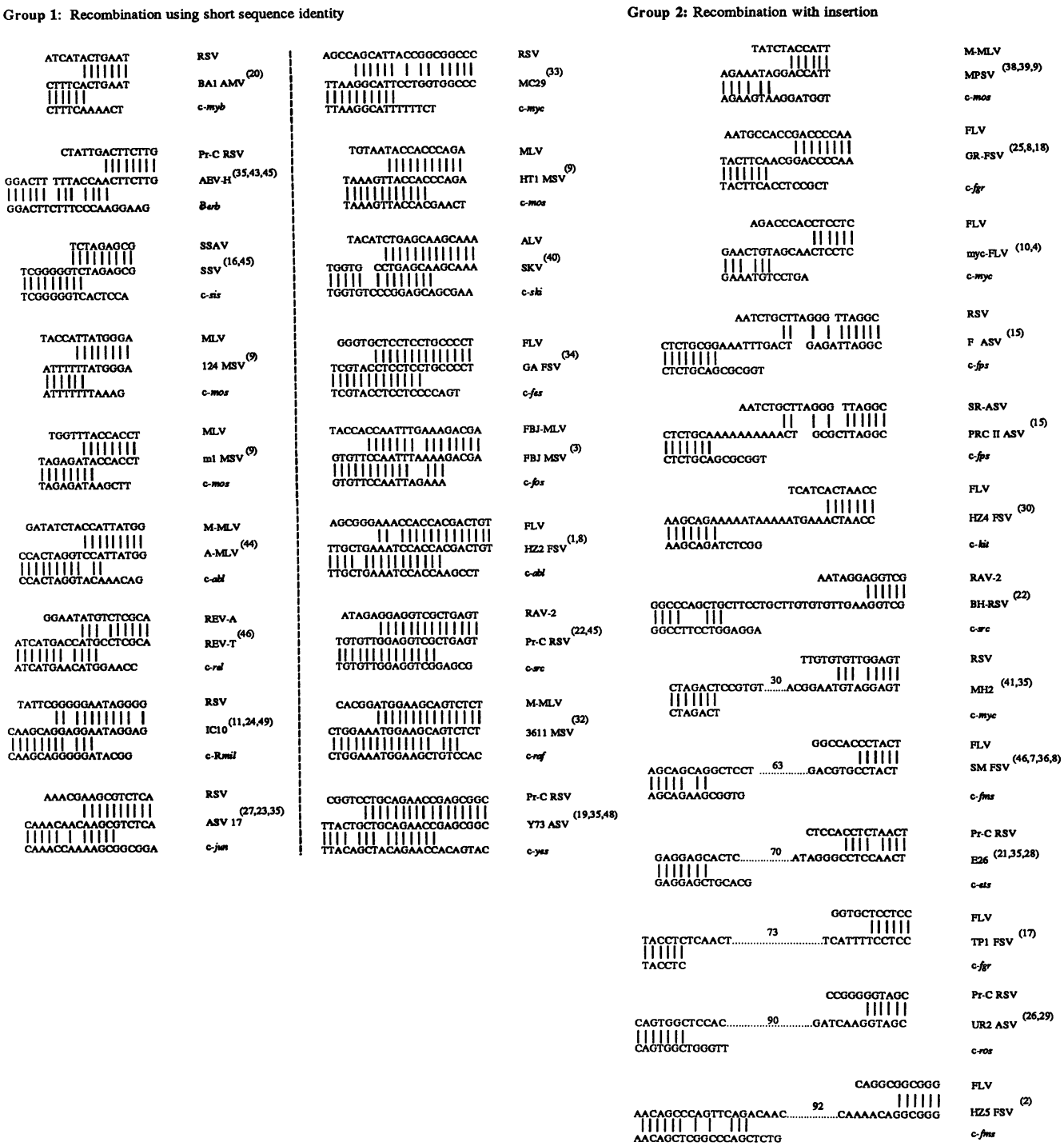

FIG. 1. Sequences of the 3′ junctions between oncogenes and helper viruses in highly oncogenic retroviruses. The upper nucleotide sequences represent the sequences of the presumed parental replication-competent virus, and the lower sequences represent the sequences of the presumed proto-oncogene. The middle sequences represent the 3′ junctions of highly oncogenic retroviruses. The vertical lines between the sequences indicate identity. The numbers in parentheses are references; the dotted lines with numbers above them represent the numbers of nucleotides not shown. Abbreviations: AEV-H, avian erythroblastosis virus strain H; A-MLV, Abelson murine leukemia virus; ASV, avian sarcoma virus; BAI AMV, BAI avian myeloblastosis virus; BH-RSV, Bryan high-titer Rous sarcoma virus; E26, avian erythroblastosis (myeloblastosis) virus E26; F ASV, Fujinami avian sarcoma virus; FBJ MSV, FBJ murine osteosarcoma virus; FSV, feline sarcoma virus; GA-FSV, Gardner-Arnstein feline sarcoma virus; GR-FSV, Gardner-Rasheed feline sarcoma virus; HT1 MSV, HT1 Moloney murine sarcoma virus; HZ FSV, Hardy-Zuckermann feline sarcoma virus; IC10, IC10 avian lymphomatosis virus; M-MLV, Moloney MLV; MC29, avian myelocytoma virus MC29; MH2, avian carcinoma (myelocytoma) virus MH2; MPSV, myeloproliferative sarcoma virus; MSV, murine sarcoma virus; PRC II ASV, Poultry Research Center avian sarcoma virus II; Pr-C RSV, Prague C Rous sarcoma virus; RAV-2, Rous-associated virus type 2; REV-A, reticuloendotheliosis virus strain A; REV-T, reticuloendotheliosis virus strain T; RSV, Rous sarcoma virus; SKV, Sloan-Kettering virus; SM FSV, McDonough feline sarcoma virus; SR-ASV, Schmidt-Ruppin avian sarcoma virus; SSAV, simian sarcoma-associated virus; SSV, simian sarcoma virus; UR2 ASV, avian sarcoma virus UR2. (All sequences were retrieved from GenBank. Only one sequence was used when the same sequence was found in different retroviral strains.)

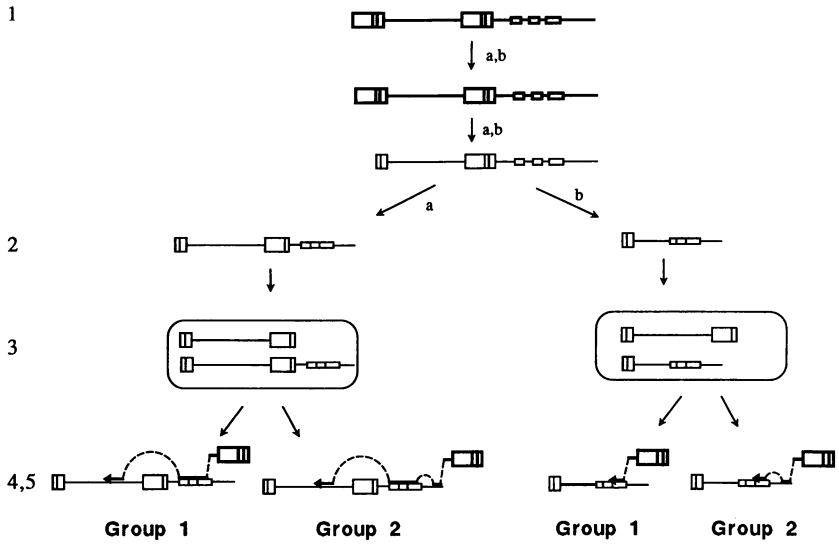

FIG. 2. Model for the formation of highly oncogenic retroviruses. The numbers on the left represent the steps in the formation of a highly oncogenic retrovirus, as discussed in the text. The thin lines represent RNA, and the thick lines represent DNA. The large boxes represent the LTRs of the virus, and the small boxes represent the exon sequences of the proto-oncogenes. (Pathway a) (1) Virus integrates 5′ of proto-oncogene sequence. (2) Read-through transcription occurs, forming a chimeric virus-proto-oncogene RNA containing an internal 3′ LTR sequence. Wild-type viral RNA is formed by normal poly(A) formation. (3) Chimeric and viral RNA are copackaged. (4, 5) After infection, the minus-strand growing point jumps from viral RNA to the proto-oncogene RNA, usually at a short stretch of sequence identity. This process forms the 3′ proto-oncogene-virus junction. A deletion is necessary to remove the internal 3′ LTR sequence. Two deletions result in an insertion junction. The deletion can occur either during minus- or plus-strand DNA synthesis, resulting in a deletion of the internal 3′ LTR sequence and some proto-oncogene sequence. (For simplicity, the figure shows a deletion during minus-strand synthesis.) (Pathway b) (1) Virus integrates 5′ of the proto-oncogene sequence. (2) Read-through transcription occurs, forming a chimeric virus-proto-oncogene RNA containing an internal 3′ LTR sequence. Abnormal splicing deletes the internal 3′ LTR and forms the 5′ virus-proto-oncogene junction. Wild-type viral RNA is formed by normal poly(A) formation. (3) Chimeric and viral RNA are copackaged. (4, 5) After infection, the minus-strand growing point from wild-type viral RNA jumps to the proto-oncogene, usually at a short stretch of sequence identity. Deletion during minus- or plus-strand DNA synthesis in the proto-oncogene sequence forms an apparent insertion at the 3′ proto-oncogene-virus junction. (For simplicity, the figure shows a deletion during minus-strand synthesis.)

virus into five steps, with variations leading to two different pathways (a and b) (Fig. 2).

Step 1. Integration of a retrovirus 5′ to a proto-oncogene.

Step 2. Formation of a chimeric virus-proto-oncogene RNA. After a retrovirus integrates 5′ of a proto-oncogene, a chimeric viral-cellular RNA is formed by read-through transcription (pathway a) or read-through transcription followed by abnormal splicing (pathway b). (A chimeric viral-cellular RNA also can be formed by deletion of the 3′ end of the retrovirus and transcription into the proto-oncogene sequence. However, the rate of mutation on the DNA level is low. If this occurred, subsequent steps would be the same as in pathway b.) (The read-through transcript without abnormal splicing [pathway a] contains an internal 3′ LTR sequence of the virus. This internal 3′ LTR sequence is deleted during reverse transcription [discussed below].)

Step 3. Copackaging with viral RNA. The cells in which the chimeric RNA is formed by read-through transcription (pathways a and b) contain wild-type viral RNA resulting from transcription and normal retroviral polyadenylation. Some abnormal spliced transcripts can be very efficiently packaged (42).

Step 4. Nonhomologous recombination during minus-strand DNA synthesis. In the two pathways (a and b), nonhomologous recombination can be the result of template switching by a copy-choice mechanism during minus-strand DNA synthesis (5). In pathway a, the minus-strand DNA synthesis involves a deletion that removes the 5′ end of the proto-oncogene sequence and the internal 3′ LTR sequence. In pathway b, this process can result in minus-strand DNA with 5′ and 3′ virus-proto-oncogene junctions. Alternatively, in pathway b, a deletion of internal proto-oncogene sequences, which are already fused to 3′ viral sequences, gives rise to an apparent insertion. Depending on the place at which template switching occurs, different amounts of sequence identity are found at the 3′ virus-proto-oncogene junctions formed during the nonhomologous recombination.

Step 5. Plus-strand DNA synthesis. In pathway a, depending on whether or not a deletion occurred during minus-strand synthesis, a deletion in plus-strand synthesis could remove the internal 3′ LTR sequence. (It is also possible that a second deletion in plus-strand synthesis occurs, resulting in an internal deletion of proto-oncogene sequences and an apparent insertion at the 3′ junction.) Similarly, in pathway b, the usual plus-strand DNA synthesis results in a highly oncogenic retrovirus with no insertion in the proto-oncogene-virus junction. Alternatively, a deletion of internal proto-oncogene sequences would result in an apparent insertion.

To explain the differences in 3′ junctions among MLV, FLV, and ALV, we note that pathways a and b both involve read-through transcription and that a single deletion results in an insertion junction in pathway b (Fig. 2b, group 2), whereas pathway a requires two deletions (Fig. 2a, group 2). Thus, it appears that highly oncogenic MLV are more likely to be formed by pathway a, highly oncogenic FLV are likely to be formed by pathway b, and ALV are likely to be formed by pathways a and b. (Although we are not sure what the

difference is between FLV and MLV, it can be that the frequency of abnormal splicing is different between the two retroviruses.)

Formation of the 3′ proto-oncogene-virus sequence also has been hypothesized to occur at the DNA level. Goodrich and Duesberg (12, 13) proposed that integration of a second retrovirus at the 3′ end of a proto-oncogene, followed by deletion, forms a highly oncogenic retrovirus. Several lines of evidence suggest that integration of a second retrovirus at the 3′ end of a proto-oncogene is not a necessary step in the formation of highly oncogenic retroviruses. First, in Zhang and Temin's system (47), several different cell clones, which contained a single chimeric vector provirus and a single infectious vector (integrated into different sites), were studied during a single round of virus replication. All of the cell clones produced recombinant viruses at a similar rate. In addition, analyses of recombinants by Zhang and Temin (47) and Swain and Coffin (42) indicated that the 3′ junction sequences of recombinants from the same cell clone are different and that some of the recombinant proviruses are not infectious. These 3′ junctions appear to result from recombination during infection rather than from a preexisting rearrangement in the original virus-producing clone. Third, a poly(A) sequence has been found in one naturally occurring highly oncogenic virus (15) and, in three other experimental systems, some recombinants were found to contain poly(A) sequences (31, 42, 47). The frequency of formation of these naturally occurring highly oncogenic retroviruses containing a poly(A) sequence is low, probably because an internal poly(A) addition sequence within a retrovirus interferes with its infectivity (37, 47). Fourth, the presence of 5′ and 3′ splice sites in reticuloendotheliosis virus strain T (46) provides further evidence that the formation of 3′ proto-oncogene-virus sequences occurs at the RNA level. Furthermore, DNA deletion does not explain insertion junctions.

It has also been proposed that proto-oncogene mRNA is nonspecifically packaged into virions, followed by two nonhomologous recombination events during reverse transcription that place the proto-oncogene sequence into the retroviral genome (14). The frequency of these events depends on how often such RNA is packaged with retroviral RNA. Formation of the 3′ junction would be by a mechanism similar to those discussed here.

Conclusions. Highly oncogenic, or acutely transforming, retroviruses contain host-derived proto-oncogene sequences. The 3′ junctions of the proto-oncogene-virus sequences in different highly oncogenic retroviruses fall into two groups. The first group has a short region of sequence identity at the junction, and the second group has an insertion. The insertion results from read-through transcription followed by deletion(s). The numbers of viruses having a short region of sequence identity at the junction relative to the group having an insertion at the junction are different for MLV, FLV, and ALV. The differences in 3′ junctions among MLV, FLV, and ALV suggest that different retroviruses are likely to have formed highly oncogenic retroviruses by slightly different pathways.

ACKNOWLEDGMENTS

We thank K. Boris-Lawrie, D. Burns, L. Mansky, T. Mitchell, A. Panganiban, and G. Pulsinelli for helpful comments on the manuscript.

This research was supported by Public Health Service research grants CA-22443 and CA-07175 from the National Cancer Institute. J.Z. is a fellow of Leukemia Society of America. H.M.T. is an American Cancer Society research professor.

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