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# Transduction of a cellular oncogene: The genesis of Rous sarcoma virus

(recombination/splicing/genetic transposition)

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**ABSTRACT** The oncogene of Rous sarcoma virus (*v-src*) arose by transduction of a cellular gene (*c-src*). In an effort to explore the mechanism of transduction, we have identified the splice acceptor site used in the genesis of mRNA for *v-src*, shown that an equivalent site is used in the splicing of mRNA for *c-src*, and determined the nucleotide sequence from the boundaries of homology between *v-src* and *c-src*. Our data indicate that (i) only a portion of *c-src* is represented within *v-src*, (ii) the leftward recombination between the genome of the transducing virus and *c-src* occurred in an intron of the cellular gene, (iii) *v-src* is in part a spliced version of the corresponding portion of *c-src*, and (iv) nucleotide sequences represented once in the genome of the transducing virus become duplicated to flank *v-src*. These findings indicate that the first step in transduction is probably recombination between DNA forms of the transducing viral genome and *c-src* and otherwise support the prevailing model for transduction by retroviruses. The carboxyl termini of the proteins encoded by *v-src* and *c-src* differ appreciably. An unidentified domain of 127 or 128 nucleotides is located at different positions in the genomes of two strains of RSV and gives evidence of being a foreign element that entered the viral genomes by genetic transposition independent of the transduction of *src*.

The oncogenes of retroviruses arose by transduction of cellular genes (1). The mechanism of transduction has yet to be elucidated but previous comparisons of retroviral oncogenes and their cellular progenitors have engendered several hypothetical models. Chief among these is a scheme in which transduction is mediated by two separate steps of recombination—the first between the DNA forms of a retroviral genome and a cellular gene, the second between a chimeric RNA transcribed from the product of the first recombination and the RNA genome of a retrovirus (see *Discussion*).

The cellular origins of oncogenes were originally recognized from studies of the oncogene (*v-src*) of Rous sarcoma virus (RSV) and its cellular progenitor (*c-src*) (2). In an effort to test the models for transduction by retroviruses, we have identified the splice acceptor site used in the genesis of mRNA for *v-src*, shown that an equivalent site is used in the splicing of mRNA for *c-src*, and determined the nucleotide sequence from the boundaries of homology between *v-src* and *c-src*. Our results provide evidence that the first step in transduction is indeed recombination between viral and cellular DNAs and otherwise support the prevailing model for transduction. In addition, we have found that proteins encoded by *v-src* and *c-src* differ appreciably at their carboxyl termini, and we have identified a domain of 127 or 128 nucleotides (denoted X) that is located at different positions in the genomes of the Schmidt–Ruppin subgroup A (SR-A) and Prague subgroup C (Pr-C) strains of RSV.

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## MATERIALS AND METHODS

We have previously described the preparation of molecular clones of *v-src* (3) and *c-src* (4), the identification of splice junctions (5) by the use of nuclease S1 (6, 7), the isolation of polyadenylated cellular RNA (8), and the determination of the nucleotide sequence (9) by the procedure of Maxam and Gilbert (10). A corrected version (11) of our previous sequence for *v-src* and its environs in SR-A RSV (12) has been used for present purposes. The sequence of the Pr-C RSV genome was provided in advance of publication by D. Schwartz, R. Tizzard, and W. Gilbert (13).

## RESULTS

**The Boundaries of Homology Between *v-src* and *c-src*.** Previous studies with heteroduplexes located the approximate boundaries of homology between *v-src* and *c-src* (4, 14, 15). We used molecular hybridization to identify and isolate DNA encompassing these boundaries within molecular clones of *c-src* (Fig. 1A) and then determined the nucleotide sequence of the isolated DNAs.

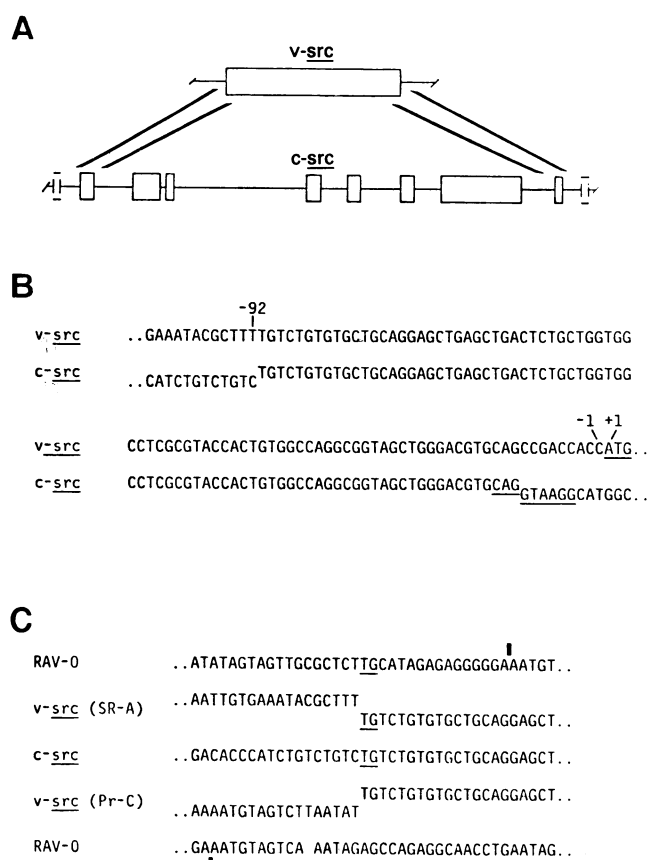
Sequences from *c-src* and the genome of SR-A RSV are aligned across the leftward boundary of homology in Fig. 1B. The two sequences diverge at a point 92 nucleotides upstream from the initiation codon of *v-src* (11, 12), as reported (13). The divergence defines the point of recombination between transducing virus and *c-src* and resides in an intron of *c-src* (see below). To the right of the point of recombination, the nucleotide sequences of *c-src* and the genome of SR-A RSV are homologous to a point 10 nucleotides upstream from the initiation codon of *v-src*, where the sequences again diverge (Fig. 1B). The divergence locates the rightward boundary of an exon in *c-src* (Fig. 1A), manifested by the presence in *c-src* of a consensus sequence for a splice donor site (Fig. 1B).

In a search for homology between transducing virus and *c-src*, we aligned sequences from *c-src*, SR-A RSV, Pr-C RSV, and RAV-0—an endogenous retrovirus of chickens that is closely related to replicative elements in RSV but carries no oncogene (Fig. 1C). Potential sites of recombination with *c-src* were apparent from the alignments. The sites for SR-A and Pr-C were at different but not widely separated positions in the genome of RAV-0. There is no homology between *c-src* and the poten-

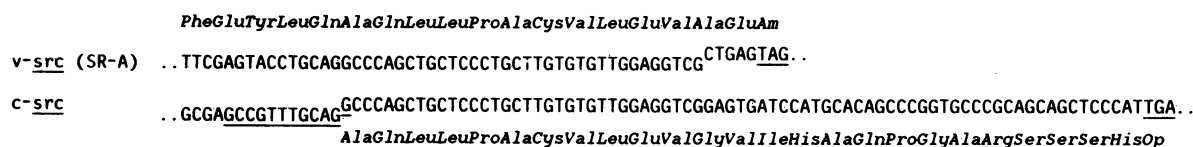
Abbreviations: RSV, Rous sarcoma virus; SR-A, the Schmidt–Ruppin subgroup A strain of RSV; Pr-C, the Prague subgroup C strain of RSV; X, a domain of 127 or 128 nucleotides found at different positions in the genomes of SR-A and Pr-C RSV; U3, a domain at the 3' terminus of the retroviral genome which composes part of the long terminal repeat in the provirus of retroviruses.

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**FIG. 1.** The leftward boundary of homology between *c-src* and *v-src*. (A) Location of the boundary. The topographies of *v-src* and *c-src* are presented schematically. The open boxes represent regions of homology between *v-src* and *c-src*. The homology with *v-src* in *c-src* is interrupted by introns identified previously (4, 14, 15) and perhaps others. The heavy diagonal lines denote the regions of *c-src* that contain the leftward and rightward boundaries of homology with *v-src*. Additional exons may be present in *c-src* outside of the regions of homology with *v-src*, as denoted by the incomplete boxes. (B) Identifying the leftward boundary. The nucleotide sequences of SR-A RSV and *c-src* have been aligned to identify points of divergence (denoted by offsetting of the sequences). The numbering scheme designates the first nucleotide 5' of the initiation codon for *v-src* (underlined) as -1. The underlining of the *c-src* sequence locates a consensus sequence for a splice donor site (16). (C) Searching for homology between transducing virus and *c-src*. The nucleotide sequences of the genomes of RAV-0 (17), SR-A RSV (11, 12), Pr-C RSV (13), and *c-src* have been aligned across the leftward boundary of homology between *v-src* and *c-src*. The boundary is represented by the transition from homology with RAV-0 to homology with *c-src*. A dinucleotide (T-G) shared by *c-src*, *v-src* in SR-A RSV, and RAV-0 at the putative site of recombination for SR-A RSV is underlined. The vertical bar above the RAV-0 sequence denotes the leftward boundary of U3, a domain at the 3' terminus of the viral RNA genome that composes part of the large terminal repeat in the proviruses of retroviruses (18).

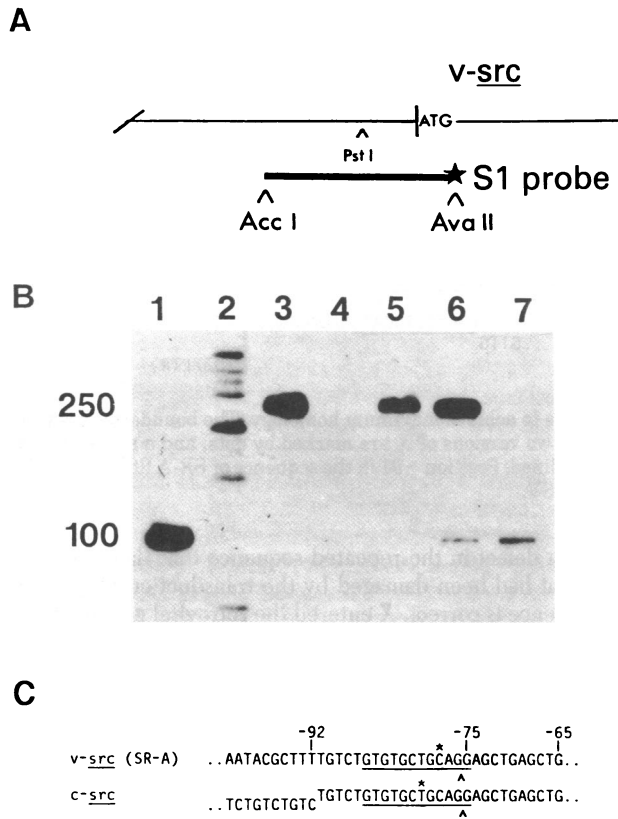


**FIG. 2.** The rightward boundary of homology between *v-src* and *c-src*. Nucleotide sequences from the rightward-most region of homology that we could identify have been aligned. Divergence is indicated by the off-set sequences. Underlining denotes the previously identified termination codon for *v-src* (TAG), a candidate termination codon for *c-src* (TGA), and a consensus sequence for a splice acceptor site (16) in *c-src*. The predicted amino acid sequences are shown above and below the nucleotide sequences.

tial recombinatory site for Pr-C RSV in the genome of RAV-0. By contrast, *c-src* and RAV-0 share a dinucleotide (T-G) at the putative site of recombination for SR-A RSV (Fig. 1C).

When we examined the rightward extreme of homology between *v-src* and *c-src*, ambiguities emerged (Fig. 2). The nucleotide sequences of *v-src* and *c-src* diverge five residues upstream from the previously defined termination codon for *v-src* (11, 12). A potential open reading frame of *c-src* continues for another 12 codons before terminating in TGA. As a consequence, amino acids at the carboxyl terminus of *v-src* are not found in *c-src* and *c-src* must therefore conclude with amino acids not found in *v-src*. These findings pose several problems. First, we cannot account for the origin of the carboxyl terminus of *v-src* in either SR-A or Pr-C RSV. Second, we cannot be certain that we have correctly described the carboxyl terminus of *c-src*. For example, our identification of the termination codon for *c-src* would be incorrect if a splice donor site lies to the left of that codon, or if the splice acceptor site proposed for *c-src* in Fig. 2 is not used. Third, we cannot as yet identify the rightward point of recombination with *c-src*. The nucleotide sequence extending for  $\approx 95$  residues beyond the termination codon in *v-src* can be accounted for only by combining domains of homology with the genomes of RAV-0 and the PRC-II avian sarcoma virus (unpublished data), and it is therefore unlikely that any single retrovirus for which the nucleotide sequence is currently available could be implicated in the rightward recombination with *c-src*. If our interpretation of the available sequences is correct, however, the recombination occurred in the vicinity of the present termination codon for *v-src*—very possibly, to its 5' side.

**A Splice Acceptor Site Shared Between *v-src* and *c-src*.** The genesis of mRNA for *v-src* uses a splice donor site located 389 nucleotides from the 5' end of the viral genome (5, 9) and a previously unidentified splice acceptor site upstream of the initiation codon for *v-src* (19–21). We mapped the position of the splice acceptor site by using an end-labeled restriction fragment of DNA that spans the splice acceptor site in mRNA for *v-src* (Fig. 3A). Hybridization of the fragment to genome RNA of SR-A RSV rendered the DNA resistant to hydrolysis by nuclease S1 (Fig. 3B, lane 5). By contrast, hybridization of the restriction fragment to RNA from cells infected with SR-A RSV produced both DNA that was fully resistant to nuclease S1 and DNA that was reduced to a length of  $\approx 100$  nucleotides by hydrolysis with the nuclease (lane 6). When RNA from uninfected chicken cells was used in the hybridizations, the smaller (and only the smaller) product of hydrolysis was obtained (lane 7). These results were achieved by using RNA from uninfected cells in amounts at least 100 times those used for RNA from infected cells. We therefore attribute the small DNA fragment to hybridization with *v-src* mRNA in the case of infected cells, whereas the fragment of necessity arises from *c-src* mRNA in the case of uninfected cells. We conclude that the size of the smaller fragment defines the approximate location of the splice acceptor site upstream of *v-src* and that an equivalent site is used in the production of mRNA for *c-src*.



**FIG. 3.** Mapping a splice acceptor site shared by *v-src* and *c-src*. (A) The strategy. A fragment of DNA derived from the appropriate domain of the RSV genome and labeled on one end only (star) was used to map the splice acceptor site. Details of our procedures have been described (5) and follow the original design of Weaver and Weissman (7). ATG, The initiation codon for *v-src*. (B) Analysis of DNAs protected from hydrolysis by nuclease S1. The end-labeled DNA (A) was hybridized with viral and cellular RNAs, hydrolyzed with nuclease S1, and analyzed by electrophoresis in a 4% polyacrylamide/8 M urea gel (10). An autoradiograph of the gel after completion of electrophoresis is shown. Lanes: 1, marker DNA,  $\approx$ 100 nucleotides long, obtained by cleaving the end-labeled DNA fragment shown in A with *Pst* I; 2, marker obtained by cleaving the DNA of plasmid pBR322 with *Hin* F and then by end labeling; 3, DNA hybridized with yeast RNA (25  $\mu$ g); 4, DNA hybridized with yeast RNA and hydrolyzed with nuclease S1; 5, DNA hybridized with virion RNA of RSV (unmeasured) and hydrolyzed with nuclease S1; 6, DNA hybridized with 5  $\mu$ g of total RNA from chicken cells infected with RSV and hydrolyzed with nuclease S1; 7, DNA hybridized with 50  $\mu$ g of polyadenylated RNA from uninfected chicken embryos and hydrolyzed with nuclease S1. (C) The splice acceptor site. The sequences illustrated are located upstream of the initiation codons for *v-src* and *c-src*. Nucleotides are numbered as in previous figures. The smallest labeled DNA fragments generated in the splice-mapping procedure terminate at the positions marked with asterisks. Arrows indicate the location of the splice site, which is inferred from the underlined consensus sequence (16).

We located the acceptor site in *v-src* and *c-src* mRNAs with greater precision by fractionating the products of hydrolysis with nuclease S1 in a gel designed for nucleotide sequence analysis (data not shown). As markers, we used fragments of DNA generated by the procedure of Maxam and Gilbert (10) from the same end-labeled DNA as was used for the splice mapping. The results indicated that the splice acceptor site is located 75 nucleotides upstream of the initiation codon for *v-src*, in the midst of a suitable consensus sequence shared by *v-src* and *c-src* (Fig. 3C). We conclude that the domain of *v-src* extending from position -76 to position -91 (Fig. 3C) was derived from an intron of *c-src*.

**A Nucleotide Sequence with Variable Locations in the Genomes of RSV.** Comparison of the genomes of SR-A and Pr-C RSV upstream of the transduced domain of *c-src* revealed an absence of homology (Fig. 1C). Further inspection of nucleotide sequences uncovered a sequence of 127 or 128 nucleotides that is located to the left of *v-src* in SR-A RSV but to the right of *v-src* in Pr-C RSV. The enigmatic nature of this sequence prompted us to give it the arbitrary designation of X. Other workers have also noted the presence of X in SR-A and Pr-C RSV, but their definition of the boundaries of X is different from ours (22).

The versions of X and their immediate environs as found in the genomes of SR-A and Pr-C RSV are aligned in Fig. 4. Several notable features are apparent. (i) The two versions of X display more than 85% homology. (ii) It appears that a repetition of 12 nucleotides may have at one time flanked X both in SR-A and Pr-C RSV. The complete sequence (C-G-C-T-C-T-T-G-C-A-T-A) is found at the leftward boundary of X in SR-A RSV and at the rightward boundary of X in Pr-C RSV. In SR-A RSV, the rightward copy of the repeat lacks six nucleotides where X abuts the transduced portion of *c-src*. By contrast, the leftward copy of the repeat in Pr-C RSV lacks three nucleotides and is interrupted by five nucleotides not found in the other versions of the sequence. A single copy of the same sequence of 12 nucleotides occurs in the genome of RAV-0, just upstream from the U3 domain (Fig. 4). Since the genome of RAV-0 does not contain X, we presume that the 12-nucleotide sequence may represent the site at which X was inserted (see Discussion).

We have used a molecular subclone containing a portion of X to search for the sequence in the genomes of other avian retroviruses. By molecular hybridization with cloned viral DNAs immobilized on nitrocellulose, we found evidence for X in the genomes of avian erythroblastosis virus and myelocytomatosis virus but not in the genomes of RAV-0, RAV-1, RAV-2, and PRC-II avian sarcoma virus (data not shown).

**The Viral Boundaries of *v-src*.** Having recognized and defined X, we could now describe the topography surrounding *v-src* in some detail. It appears likely that the same portion of *c-src* has been transduced in both SR-A and Pr-C RSV (Fig. 5). In both strains of virus, the transduced unit is flanked by a large direct repeat recognized previously (12, 13, 23); the same sequence is present as a single copy in the genome of RAV-0. In Pr-C, the repetition situated to the left of *v-src* includes a small portion of the U3 domain ( $\Delta$ U3) and the rightward version of the repeat is interrupted by X. In SR-A, X intervenes between the leftward version of the repeat and *v-src*, whereas the rightward copy of the repeat is undisturbed.

## DISCUSSION

**The Topographies of *v-src* and *c-src*.** We have compared *v-src* and *c-src* to explore the mechanism by which retroviruses transduce cellular genes. Our analysis produced several findings that bear on the relationship between the two genes. First, less than the entire *c-src* gene has been transduced into RSV. The domain between 10 and 75 nucleotides upstream of the initiation codon in *v-src* represents an untranslated exon in *c-src*. To the left of this exon, *v-src* contains a portion of an intron from *c-src* that is joined to the presumed site of recombination with a transducing virus. At least one additional untranslated exon must lie upstream of this intron in *c-src* but it does not appear in *v-src*. Second, the amino acid sequences at the carboxyl termini of *v-src* and *c-src* must differ from each other. This observation extends previous indications that the proteins encoded by the two genes may differ in subtle ways (24) and may offer an explanation for the oncogenic potential of *v-src*.

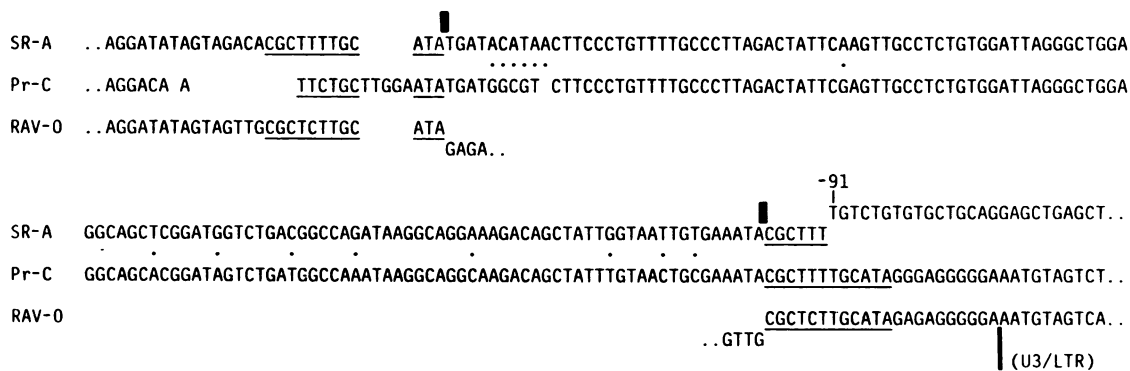


FIG. 4. X units of SR-A and Pr-C RSV. The sequences of X have been aligned so as to achieve maximum homology. The boundaries assigned to X are denoted by bold vertical bars, positions occupied by different nucleotides in two versions of X are marked by dots, and a sequence that brackets X to form direct repeats, and occurs but once in the genome of RAV-0, is underlined. Position -91 in the sequence of SR-A RSV represents the beginning of *v-src*. The leftward boundary of U3 is marked for RAV-1 and Pr-C RSV.

Third, the single splice acceptor site used in the genesis of mRNA for *v-src* was derived from a functional splice site in *c-src*. Moreover, a precise description of the spliced leader in the mRNA for *v-src* has shown that four AUG codons lie upstream of the initiation codon for *v-src* (5, 9). Two of these codons are in the same reading frame as *v-src*. Translation of *v-src* from all four of the upstream AUG codons is precluded by termination codons located short distances downstream. These findings join a growing list of exceptions to the rule that translation from eukaryotic mRNAs generally begins at the AUG closest to the 5' end of the RNA (25).

**A Nucleotide Sequence with Variable Locations in Genomes of RSV.** We have identified a sequence of 127 or 128 nucleotides (designated X) that is found at different positions in the genomes of SR-A and Pr-C RSV. The same or related sequences are present in at least two other (but not all) avian retroviruses. The origins of X and the means by which X reached retroviral genomes are for the moment obscure. Our only clue is the now imperfect repeat of 12 nucleotides that flanks the element in at least two strains of RSV. The repeats apparently arose from a single copy of the same sequence that resides in retroviral genomes devoid of X and may therefore have arisen during the insertion of a transposable genetic element (26).

When did X enter the genome(s) of RSV, and why is it located at different positions in the SR-A and Pr-C strains? The junction between X and the left boundary of *v-src* in SR-A RSV

displays a defect in the repeated sequence that flanks X, as if the repeat had been damaged by the transduction of *c-src*. If this inference is correct, X entered the retroviral genome prior to *src*. The different locations of X in SR-A and Pr-C RSV could then be explained in at least two ways: either one copy of the sequence has been deleted from each strain of virus or the sequence was present in only one of the two retroviruses participating in the separate steps of transduction (see below and Fig. 6).

**Transduction of Cellular Genes by Retroviruses.** The prevailing model for transduction of cellular genes by retroviruses (18, 27–29) is outlined in Fig. 6. Fortuitous insertion of a retrovirus provirus upstream from a cellular oncogene is followed by rearrangement of DNA that joins a leftward domain of the provirus and a portion of the cellular oncogene into a hybrid transcriptional unit. Transcription of the unit and splicing produce chimeric RNA that is suitable for packaging into heterozygous retrovirus virions. Recombination during a subsequent infection generates a retrovirus genome that now includes the transduced portion of the cellular oncogene.

Several features of this model are evident from our comparison of *v-src* and *c-src*. (i) The leftward recombination with *c-src* apparently occurred within an intron, an event that can be easily explained only if the initial step in transduction is a rearrangement of DNA such as the deletion illustrated in Fig. 6. (ii) *v-src* represents in part a spliced version of the homologous regions of *c-src*. (iii) The second recombination is postulated to occur between the spliced chimeric RNA and viral RNA during the course of reverse transcription (Fig. 6). The recombination should therefore occur within an exon of *c-src*, and homology between *c-src* and the transducing virus would facilitate the crossing-over. We were not able to locate the rightward point of recombination with *c-src* with any assurance, but it appears to have taken place within an exon of *c-src*—either a coding domain or an untranslated region of the gene. Previous evidence indicates that recombination of the sort conjectured can occur during the course of retroviral infection (28). (iv) The large direct repeat that brackets *v-src* presumably mirrors the occurrence of two separate recombinatory events, the first downstream of the progenitor for the repeated sequence in transducing virus, the second upstream of the sequence (see asterisks in Fig. 6).

Our present conclusions are in accord with recent findings for *c-myb*—the cellular gene that gave rise to the oncogene (*v-myb*) of avian myeloblastosis virus (30). (i) The leftward recombination with *c-myb* occurred within an intron (ref. 30; unpublished data). (ii) Multiple introns within the transduced por-

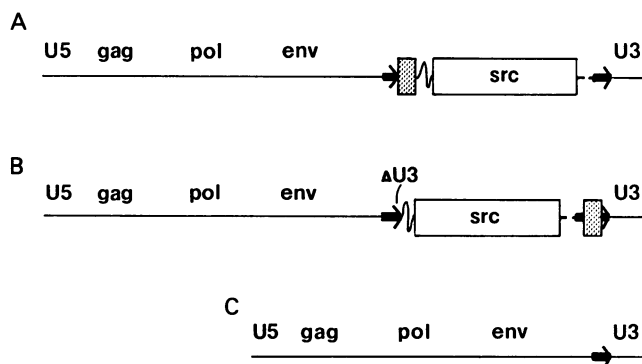


FIG. 5. Topography of avian retrovirus genomes. (A) SR-A. (B) Pr-C. (C) RAV-0. Symbols: heavy arrows, the sequence of  $\approx 120$  nucleotides that is repeated to bracket *src* in RSV but occurs only once in RAV-0; shaded box, the unidentified sequence X; sinusoidal lines, the 5' non-coding region of *c-src* transduced into RSV; broken line, the 3' non-coding region of unknown origin;  $\Delta U3$ , a portion of the U3 domain in the RSV genome.

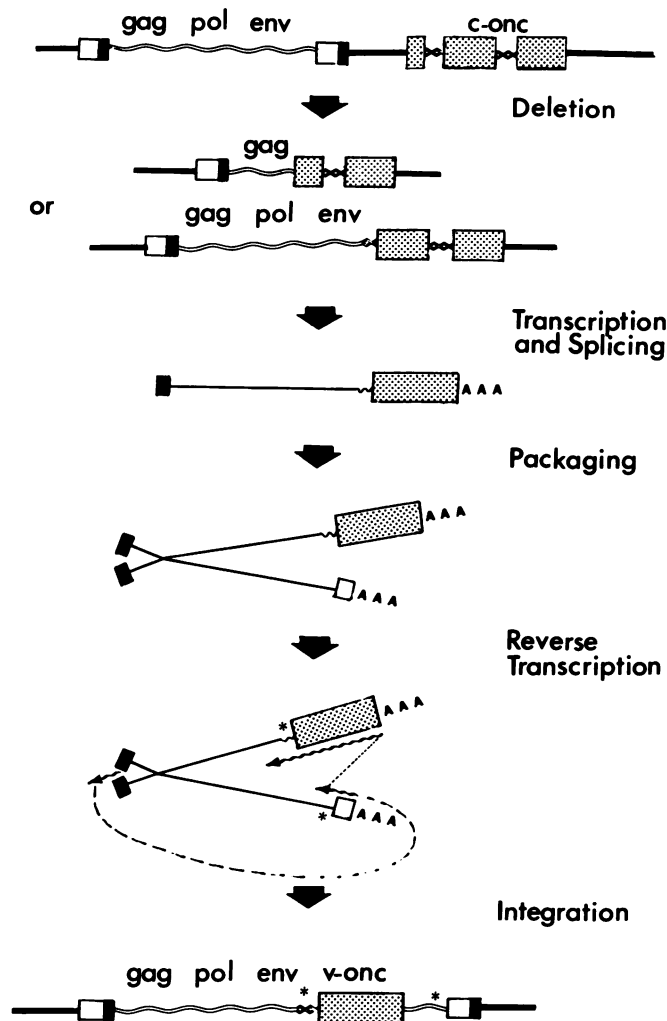


FIG. 6. Model for the transduction of cellular oncogenes by retroviruses.

tion of *c-myb* are precisely spliced out of *v-myb* (30). (iii) The rightward recombination with *c-myb* occurred within an exon of *c-myb* and without benefit of extensive homology between *c-myb* and the genome of the transducing virus.

Were the SR and Pr strains of RSV formed by independent transductions of *c-src*, or were both derived from a single transduction? Although the two strains of virus were isolated separately (31), it is possible that they are merely divergent representations of the same transduction. The data presented above provide circumstantial evidence both for and against this possibility. We see no way to reach a decisive conclusion unless new and more telling information can be obtained.

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