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Nucleotide sequence of the v-*myc* oncogene of avian retrovirus MC29

(leukemia/carcinoma/myelocytomatosis/tumor virus/DNA-binding protein)

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ABSTRACT **Avian myelocytomatosis viruses are retroviruses whose oncogene (v-*myc*) induces an unusually wide variety of tumors, including carcinomas, endotheliomas, sarcomas, and myelocytomatoses. The viral gene v-*myc* arose by transduction of an undetermined portion of a cellular gene known as c-*myc*. In order to facilitate further studies of the functions of v-*myc* and c-*myc* and to permit detailed comparisons between the two genes, we have determined the nucleotide sequence of v-*myc* in the genome of the MC29 strain of myelocytomatosis virus. The v-*myc* domain in MC29 virus encodes a hydrophilic polypeptide with a molecular weight of 47,000, fused to a portion of the polyprotein encoded by the viral structural gene *gag*. The carboxyl-terminal half of the v-*myc* polypeptide is rich in basic amino acid residues. This feature may account for the DNA-binding properties of the hybrid *gag*–*myc*-encoded protein which would have a molecular weight of approximately 100,000, in accord with results from previous studies of the protein encoded by v-*myc*. The junctions between v-*myc* and the genome of the transducing virus are apparent but reveal no clues to the mechanism by which transduction might occur.**

The myelocytomatosis virus MC29 (MC29V) is the prototype for a group of avian retroviruses that induce an unusually broad range of neoplasms, including carcinomas, endotheliomas, mesotheliomas, sarcomas, and myelocytomatosis (1, 2). The versatile pathogenicity of these viruses has been attributed to a single viral oncogene (v-*myc*) which, in turn, is closely related to and probably derived from a cellular gene (c-*myc*) found in vertebrates (3, 4) and in less-advanced metazoan species (5). In addition to its apparent role as evolutionary progenitor for v-*myc*, c-*myc* has now been implicated in the genesis of at least one form of neoplasia—the B-cell lymphomas induced in chickens by infection with avian leukosis viruses (6, 7).

The topography of v-*myc* differs from one myelocytomatosis virus to another. In the prototypic MC29V, v-*myc* is fused to a portion of the viral gene *gag* which encodes the internal structural proteins of the virus (8). The hybrid gene gives rise to a polyprotein with a molecular weight of 110,000 ($p110^{gag\text{-}myc}$), translated from a mRNA that is either identical or very similar to the viral genome (9). The closely related virus CMII encodes a similar polyprotein ($p90^{gag\text{-}myc}$) (10). By contrast, the myelocytomatosis viruses OK-10 and MH-2 contain v-*myc* as an independent genetic unit that is expressed by means of a spliced subgenomic mRNA (11, 12). Tentative identifications of the proteins encoded by v-*myc* in these viruses are now emerging (12).

Several of the better-characterized retroviral oncogene products are plasma membrane proteins with kinase activities that phosphorylate tyrosine in protein substrates (13). Although the $p110^{gag\text{-}myc}$ protein of MC29V is phosphorylated on both serine and threonine, it has given no evidence of being a protein kinase (13). Instead, $p110^{gag\text{-}myc}$ binds with high affinity to double-stranded DNA (14) and is found in the nucleus of infected cells (14, 15), where it may be a component of chromatin (16).

In order to facilitate further dissection of the mechanisms by which the myelocytomatosis viruses induce neoplastic growth, we have determined the nucleotide sequence of v-*myc* and its environs in the genome of MC29V. Our results provide a deduced amino acid sequence for the *myc* domain of $p110^{gag\text{-}myc}$, offer clues to its mechanism of binding to DNA and guideposts for the search for viral and cellular *myc* proteins, reveal the junctions at which v-*myc* has been joined to the genome of the retrovirus that transduced the gene from the host cell, and should eventually assist in elucidation of the mechanism by which the transduction occurred.

MATERIALS AND METHODS

Molecular clones of MC29 DNA were obtained as described (17). Various restriction fragments of DNA were cloned into the M13 phage vectors mp7, -8, and -9 (18) and then subjected to sequence analysis by the chain-terminator technique (19). All portions of the reported sequences were obtained from at least two independent, overlapping clones or from both strands of DNA, or from both. Band compression in the sequencing gels in a G+C-rich region was resolved by the substitution of inosine for guanosine in the dideoxy reactions (20). Details of the sequence analysis strategy, complete restriction maps of the DNA analyzed, a summary of codon usage, and documentation of the sequencing gels are available upon request.

RESULTS AND DISCUSSION

The Nucleotide Sequence of v-*myc*. The nucleotide sequence of v-*myc* and adjacent proviral DNA is shown in Fig. 1. We defined the boundaries of v-*myc* in MC29V by comparison to the nucleotide sequence of the Prague-C strain (Pr-C) of Rous sarcoma virus (RSV) (Fig. 2). The leftward junction between v-*myc* and the transducing viral genome is located within the coding domain for the virion protein $p27^{gag}$, as expected from previous descriptions of $p110^{gag\text{-}myc}$ (8) and the genome of MC29V (21). The v-*myc* insert continues from the leftward recombinatory junction for 1,580 nucleotides, after which homology with the genome of Pr-C RSV resumes within the *env*

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Abbreviations: kb, kilobase(s); kbp, kilobase pair(s); MC29V, avian myelocytomatosis virus 29; RSV, Rous sarcoma virus; Pr-C, Prague RSV of subgroup C; *gag*, gene encoding the major structural proteins of the retrovirus core; *env*, gene encoding viral envelope proteins; LTR, long terminal repeat.

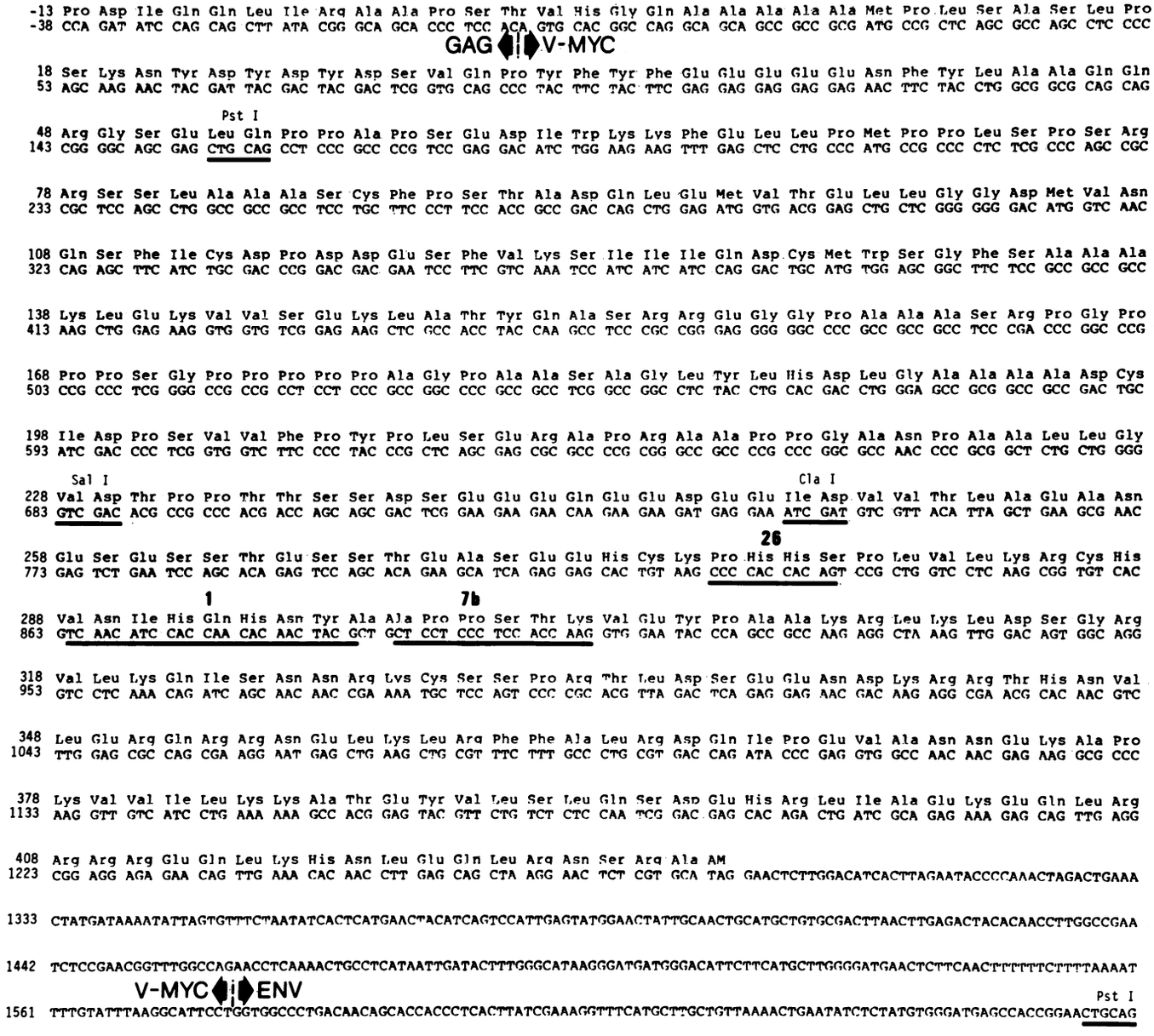

FIG. 1. Nucleotide sequence of v-*myc* and adjacent MC29V proviral DNA. The upper (−13 to 408) and lower (−38 to 1561) numbers at the left of each line refer to the adjacent amino acid and base sequence positions, respectively. The reading frame of v-*myc* continues uninterrupted from the *gag*-p27 reading frame at position +1 until terminated by an amber codon at positions 1277–1279. Recognition sites for cleavage by restriction endonucleases *Pst* I, *Cla* I, and *Sal* I are marked in the sequence. The underlined portions of the sequence with number designations (26, 1, 7b) refer to the v-*myc* specific oligonucleotides characterized by Duesberg *et al.* (21).

gene. The nucleotide sequence adds detail to previous descriptions of the deletion that accompanied insertion of v-*myc* into the genome of MC29V: the deletion extends from a position 87 nucleotides upstream of the termination codon for *gag* to a position 1,393 nucleotides upstream of the termination codon for *env* (assuming that the boundaries of *gag* and *env* in the transducing virus were identical to those in the genome of Pr-C RSV); the deleted regions include nucleotide sequences coding for the carboxyl terminus of $p27^{gag}$, the entire reverse transcriptase gene, the splice acceptor site used in the genesis of mRNA for *env*, and the amino-terminal domain of the envelope glycoprotein $gp85^{env}$ (22).

The nucleotide sequences in the vicinity of the junctions between v-*myc* and adjacent portions of *gag* and *env* reveal no clues to the mechanism by which the transduction of *myc* occurred. There is no notable homology between viral and cellular domains that could have facilitated homologous recombination and no rearrangements of sequence (such as direct repeats) that might evoke the actions of a transposable genetic element (23).

Several convenient landmarks of the v-*myc* sequence are indicated in Fig. 1. The *Pst* I fragment (residues 158–1,676) represents the subclone widely distributed by our laboratory for use as a *myc*-specific probe. As noted previously (17), this fragment also contains a small portion of *env* (nucleotides 1,581–1,676). The left-hand end of the fragment lies 157 nucleotides within v-*myc*, in accord with previous estimates (17).

The recognition sites for several restriction endonucleases in c-*myc* appear to be conserved in v-*myc*. This is apparent from comparison of restriction maps of c-*myc* (7, 17) to the restriction sites in the v-*myc* sequence presented here. The single *Cla* I and *Sal* I sites at positions 744–749 and 683–688, respectively, are of particular interest. They bracket a 1.1-kilobase-pair (kbp)

intron in c-*myc* (24, 25) and must lie within flanking exons because they are retained in v-*myc* and therefore survived the splicing that is an essential step in the transduction of cellular oncogenes into retroviruses (26–28). The splice junction at which the two exons of c-*myc* are fused to generate v-*myc* must lie between *Cla* I and *Sal* I sites, as suggested previously (24, 25). These conclusions conform to the recent demonstration that the exons of cellular oncogenes are joined precisely during transduction into retroviral genomes (29).

The v-*myc* sequence between residues 450 and 700 is exceptionally rich in guanosine and cytidine [(G+C)/(A+T+G+C) = 0.84]. Sequences of this sort may give anomalous reactions in molecular hybridizations. Investigators using v-*myc* as a "probe" in molecular hybridization should be alert to the possibility of spurious interactions with other nucleic acids.

The Reading Frame of v-*myc*. The reading frame of v-*myc* is defined by its continuity with the *gag* reading frame (Fig. 3A). The portion of the open reading frame within v-*myc* extends for 1,276 base pairs before terminating at an amber codon. Thereafter, the v-*myc* insert has a 304-base-pair sequence containing several termination codons and bounded at residue 1,581 by the resumption of homology with the Pr-C RSV genome. Since the v-*myc* terminator is within the inserted cellular sequence, it presumably represents the site at which translation from c-*myc* terminates. Other examples of transduced termination codons in viral oncogenes include the *src* (22, 30), *ras* (31, 32), and *mos* (33) genes; we also know of one exception—the *myb* gene of avian myeloblastosis virus which uses the termination codon of *env* (29).

The deduced amino acid sequence of the v-*myc* domain of p110$^{gag\text{-}myc}$ protein is shown above the nucleotide sequence in Fig. 1. The calculated molecular weight of the v-*myc* polypeptide is 46,936. The complete *gag–myc* polypeptide would have a deduced molecular weight of about 100,000. When allowance is made for modification of electrophoretic mobility due to phosphorylation, the size of the polypeptide corresponds well to the nominal molecular weight of 110,000 assigned on the basis of electrophoresis in polyacrylamide gels. The polypeptide encoded by v-*myc* would yield four tryptic peptides containing methionine, precisely as predicted from previous studies of p110$^{gag\text{-}myc}$ (34). The size of the v-*myc* domain in p110$^{gag\text{-}myc}$ (M_r, 47,000) provides a lower limit for the molecular weight of the product of c-*myc*, but the cellular protein is probably larger: it is unlikely that the entire coding domain of c-*myc* has been transduced into MC29V (see below); and it appears that the v-*myc* domain in the related virus MH-2 may encode a protein with a molecular weight of at least 57,000 (12).

A hydropathic index was calculated for groups of six amino acid residues with overlaps of two residues along the length of the v-*myc* amino acid sequence (Fig. 3*B*). The results indicate that v-*myc* encodes a relatively hydrophilic protein. The predicted polypeptide is devoid of hydrophobic stretches of the sort that mediate insertion of proteins into cellular membranes. The amino acid sequence derived from the v-*myc* coding sequence to the right of the *Cla* I site (i.e., corresponding to the right-hand exon in c-*myc*) is enriched in basic amino acid residues. Moreover, arginine and lysine residues comprise 13% and 10%, respectively, of the carboxyl-terminal 150 amino acids; these numbers have provocative similarities to the amino acid compositions of certain histones. The basic portion of p110$^{gag\text{-}myc}$ may account for its ability to bind to double-stranded DNA (14). Other notable features of the v-*myc* amino acid sequence are clusters of successive proline residues (between residues 164 and 180) derived from a portion of the G+C-rich nucleotide sequence and scattered runs of two to five alanine and acidic amino acid residues.

Mapping of tryptic phosphopeptides of p110$^{gag\text{-}myc}$ has revealed that the *myc* domain of the protein is heavily phosphorylated on serine and threonine (36). The amino acid sequence of v-*myc* contains two serine residues (80 and 329) and two threonine residues (344 and 386) in sequences that are characteristically recognized by cyclic nucleotide-dependent protein kinases (X-Y-Z-Ser/Thr, where X and Y are basic residues) (37). There are also a number of serine residues (58, 235, 236, 238, 259, 270, 336, and 394) and some threonine residues (263 and 267) within acidic environments that favor phosphorylation by "casein" kinases or "nuclear acidic" kinases (38). We cannot specify which of these various residues is phosphorylated in p110$^{gag\text{-}myc}$, but two of the three major sites of phosphorylation

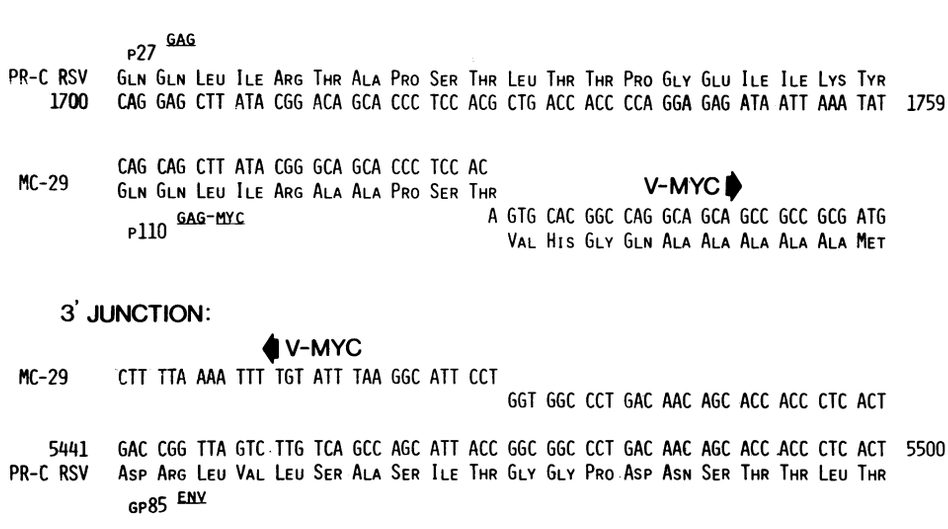

FIG. 2. Finding the junctions between v-*myc* and the genome of a transducing retrovirus. The left-hand (5') and right-hand (3') ends of the sequenced portion of the MC29V provirus were aligned with homologous sequences of Pr-C RSV. Interruption of the almost complete homology between Pr-C RSV and MC29V genomes is indicated by off-setting the MC29V sequence. The deduced amino acid sequences are shown where applicable. Numbers for the Pr-C RSV nucleotide sequence are given according to Schwartz *et al.* (22). For other symbols, see the text for details.

apparently reside within the region deleted in the partially defective mutants described above (36)—i.e., within a domain that includes the *Cla* I site and extends *ca.* 200 nucleotides in the 3′ direction. Since this same domain is required for the binding of $p110^{gag\text{-}myc}$ to DNA (16), phosphorylation may regulate the binding in some way.

It is unlikely that the other two v-*myc* translational reading frames are used because they are frequently closed by termination codons (vertical bars in Fig. 3A). The few initiation codons (ATG) found in these frames (not shown) are followed shortly by stop codons. Cells infected with MC29V contain only a single *myc*-specific mRNA that is of the same length as the viral genome (4). It therefore seems unlikely that any portion of v-*myc* in MC29V is expressed by translation from a spliced subgenomic messenger.

Domains Within *myc*. Part or all of two exons of c-*myc* are apparently represented in v-*myc* (24, 25). The 3′ boundary of the leftward exon and the 5′ boundary of the rightward exon may be reproduced faithfully in v-*myc*. The continuity of reading frame across the junction between the domains of the two exons in v-*myc* suggests that the junction was formed by splicing between authentic donor and acceptor sites in c-*myc*. Neither exon may be represented fully in v-*myc*, however. The termination codon for the open reading frame in v-*myc* is apparently contained within the transduced cellular domain, so the 3′ boundary of the rightward exon must lie further downstream.

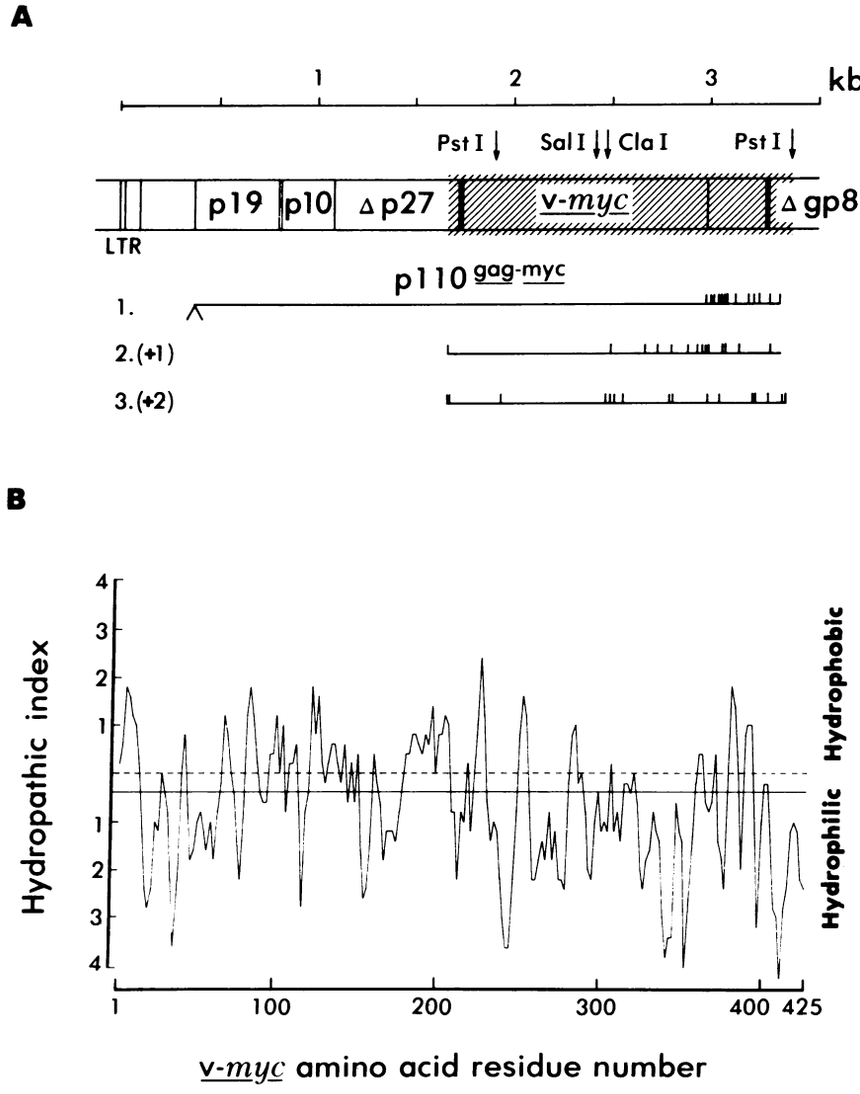

FIG. 3. Topography of v-*myc*. (*A*) Structure of v-*myc* and its translational reading frames in the genome of MC29V. The portion subjected to sequence analysis is shaded. The recombination of *myc* with the genome of a transducing retrovirus has occurred at sites shown as black bars in the diagram of provirus. Δp27 and Δgp85 denote coding domains for the p27 protein of the *gag* gene and the glycoprotein gp85 of the *env* gene that have suffered deletions during the recombination events leading to capture of the v-*myc* insert. The recognition sites in the DNA for *Sal* I and *Cla* I enzymes are shown because they provide landmarks for dividing v-*myc* into portions corresponding to putative exons of c-*myc*. The 1.5-kbp *Pst* I fragment is also shown. The reading frame that engenders $p110^{gag\text{-}myc}$ and the two other reading frames in v-*myc* are shown below the provirus. Vertical bars denote stop codons. The open reading frame for *env* continues in midstream after the stop codons in the second (+1) reading frame. The scale is indicated on top of the figure in kilobases. LTR, left-hand long terminal repeat sequence of the provirus. (*B*) Diagram showing hydropathy along the v-*myc* domain of the $p110^{gag\text{-}myc}$ polypeptide. The hydropathic index is calculated according to Kyte and Doolittle (35) for segments of six consecutive amino acid residues with overlaps of two residues in the v-*myc* sequence. The program was a moving segment approach that continuously determines the average hydropathy within the segment as it advances through the sequence from the amino to the carboxyl terminus. The mean overall relative hydropathy index of an average protein (−0.4) is shown by the continuous line. The mean hydropathy of the *myc* protein is −0.69.

We have searched the downstream region of v-*myc* without success for a splice donor consensus sequence (39). We therefore suggest that the 3′ boundary of v-*myc* lies within an exon of c-*myc*, as predicted by the prevailing model for tranduction by retroviruses (27, 28). The 5′ boundary of v-*myc* is apparently also within an exon of c-*myc*, since a continuous open reading frame spans the junction between *gag* and v-*myc*. This is in contrast to the findings with c-*myb* (29) and c-*src* (unpublished data), in which the leftward boundaries of transduced cellular domains lie within introns, but the model for transduction allows for either possibility at the leftward recombinatory junction (27, 28).

Further evidence that c-*myc* is not completely represented in v-*myc* of MC29V has come from analysis of the RNA transcribed from c-*myc*. The cytoplasm of uninfected chicken cells contains a 2.5-kb RNA that is presumed to be the mRNA for c-*myc* (40, 41). This RNA is substantially longer than v-*myc* in MC29V (1.58 kbp) and must therefore be transcribed in part from portions of c-*myc* not contained in v-*myc*. We will know the full extent of c-*myc* only when we know where transcription from the gene starts and stops.

We used the *Sal* I and *Cla* I sites described above to achieve a conservative division of v-*myc* into domains representing the two exons from c-*myc* (i.e., we excluded the sequence between the restriction sites from analysis). Computer-assisted search of these domains disclosed no significant homologies, suggesting that the two exons did not evolve from a common ancestor by duplication. The hydrophilicity of the right-hand exon domain is somewhat more pronounced and, as noted above, the same domain is substantially more basic than the left-hand exon domain.

The region of v-*myc* immediately to the right of the *Cla* I site may be particularly important to the pathogenicity of the gene. When the *Cla* I site and 200–600 nucleotides to its right are deleted in natural variants of MC29V, the virus loses the ability to transform macrophages in culture and induce carcinomas or endotheliomas in birds, yet it retains the capacity to transform fibroblasts (42–44). The largest deletion has been repaired by propagation of the mutant virus in cell culture, apparently by recombination with c-*myc* (45, 46), but the repaired virus rapidly induces B-cell lymphomas rather than carcinomas, findings that are reminiscent of the role stipulated for c-*myc* in the induction of B-cell lymphomas by avian leukosis viruses (6, 7). The domain of v-*myc* involved in these variations should receive special attention in future studies of *myc* protein and its functions.

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