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Viral Oncogenes and Cellular Prototypes *

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A. Summary

The structural hallmark of retroviral transforming *onc* genes is a specific RNA sequence that is unrelated to the essential retroviral genes but closely related to certain cellular prototypes termed proto-*onc* genes. Two types of *onc* genes have been distinguished. Type I are *onc* genes which utilize elements of specific sequences only to encode a transforming protein. Type II *onc* genes are hybrids which utilize essential viral (typically *gag*) and specific RNA sequences to encode transforming proteins. Comparisons between viral *onc* genes and cellular proto-*onc* genes are reviewed in the light of two competing models for proto-*onc* function: the quantitative model, which holds that viral *onc* genes and cellular proto-*onc* genes are functionally the same and that transformation is the result of enhanced dosage of a cellular proto-*onc* gene; and the qualitative model, which holds that they are different. Structural comparisons between viral *onc* genes and cellular prototypes have demonstrated extensive sequence homologies in the primary structures of the specific sequences. However, qualitative differences exist in the structure and organization of viral *onc* genes and cellular prototypes. These include differences in promoters, minor differences in the primary structure of shared sequences, and absolute differences such as in the presence of sequences which are unique to viral *onc* genes or to corresponding cellular genetic units. For example, type II hybrid *onc* genes of retroviruses share only their specific but not their *gag*-related elements with the cell, and cellular proto-*onc* genes are interrupted by sequences of non-homology relative to viral *onc* genes. In addition, proto-*onc* gene units may include unique cellular coding sequences not shared with viral *onc* genes. There is circumstantial evidence that some proto-*onc* genes are potentially oncogenic after activation (quantitative model) or modification (qualitative model). Activated by an adjacently integrated retroviral promotor, the cellular prototype of the *onc* gene of the avian acute leukemia virus MC29 was proposed to cause lymphoma and activated by ligation with viral promoter sequences two proto-*onc* DNAs, those of Moloney and Harvey sarcoma viruses, were found to transform mouse 3T3 cell lines. Mutations presumably conferred 3T3 cell-transforming ability to the proto-*onc* gene of Harvey sarcoma virus that has been isolated from a human bladder carcinoma cell line. In no case has an unaltered proto-*onc* as yet been shown to be necessary and sufficient for carcinogenesis. Despite this and structural differences between viral *onc* genes and cellular proto-*onc* genes, we cannot at present conclusively distinguish between the quantitative and the qualitative models because a genetic and functional definition of most viral *onc* genes and of all cellular prototypes of viral *onc* genes are not as yet available.

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B. Definition of *onc* Genes

Over *15* transforming *onc* genes have been identified in retroviruses since the discovery of the *src* gene of Rous Sarcoma virus (RSV) in 1970 [3, 8]. The only known function of *onc* genes is neoplastic transformation of normal cells to cancer cells. The structural hallmark of all retroviral *onc* genes is a specific RNA sequence that is unrelated to the three essential virion genes, *gag, pol,* and *env.* Thus, *onc* genes are not essential for retroviruses and instead may be viewed as molecular parasites. Retroviruses with *onc* genes are inevitably and immediately oncogenic in susceptible cells or animals. However, retroviruses with *onc* genes are rare and appear only sporadically in natural cancers [13, 37]. The majority of naturally occurring retroviruses lack *onc* genes and are therefore not directly oncogenic. Retroviruses without *onc* genes carry the three essential virion genes *gag, pol,* and *env* and

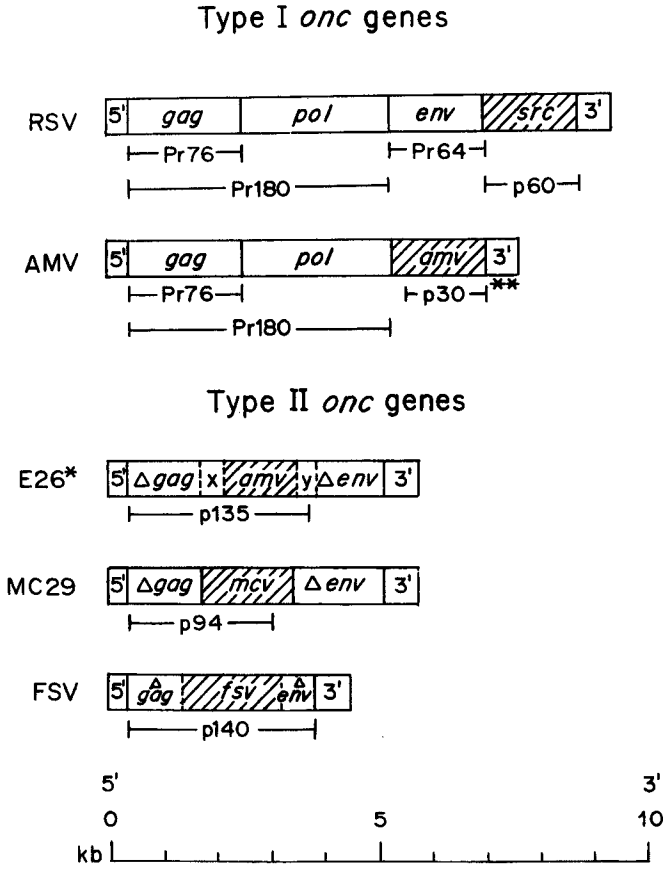

Fig. 1. Genetic structures of oncogenic avian retroviruses with two different types of *onc* genes: Type I *onc* genes utilize specific sequences unrelated to the three essential virion genes *gag, pol,* and *env* [8] to encode transforming proteins. Type II or hybrid *onc* genes utilize specific and virion genes, typically *gag*-related sequences, to encode transforming proteins. *Boxes* indicate the mass of viral RNAs in kilobases (kb) and *segments with in boxes* indicate map locations in kilobases of complete or partial (Δ) complements of *gag* and *env*, of the *onc*-specific sequences (*hatched boxes*) and of the noncoding regulatory sequences at the 5′ and 3′ end of viral RNAs. *Dotted lines* indicate that borders between genetic elements are uncertain. The three-letter code for *onc*-specific RNA sequences extends the one used previously by the authors: *src* represents the *onc*-specific RNA sequences of Rous sarcoma virus (RSV); *fsv* is that of Fujinami sarcoma virus (FSV); *mcv* that of the myelocytomotosis virus (MC29); and *amv* that of the Avian myeloblastosis virus (AMV), which is shared by erythroblastosis virus E26 [3, 4]. Recently, a different nomenclature has been proposed by others, i.e., *myc* (=*mcv*), *myb* (=*amv*), *fps* (=*fsv*) [40]. *Lines and numbers under the boxes* symbolize the complexities in kilodaltons of the precursors (Pr) for viral structural proteins and of the transformation-specific polyproteins (p). For E26 (*) a complete genetic map is not yet available. *X* and *Y* represent unidentified genetic elements of E26 [4]. The protein product of AMV (**) has only been identified in cell-free translation assays (Lee and Duesberg, unpublished), and the size of p30 is deduced from the proviral DNA sequence [29]. The size of the p94 protein of MC29 is deduced from the proviral DNA sequence (Papas et al., this volume) and is at variance with the p110 value reported previously [3]

are found primarily as nonpathogenic parasites which are transmitted horizontally, congenitally, or through the germ line in many animal species. However, certain animals, and, as recently shown, man (Gallo et al., this volume), which carry such viruses turn viremic and develop leukemias and other forms of cancer after long latent periods. Because of their association with leukemias these viruses are often referred to as leukemia viruses [3, 8, 13, 37, 40].

Only one viral *onc* gene, the *src* gene of RSV, is genetically defined by classical deletion and recombination analysis [3, 8]. The *onc* genes of all other retroviruses are associated with defective viruses which lack functional complements of all (or most) essential virion genes. Thus *onc* deletions of defective viruses are not functionally detectable and recombinants cannot readily be distinguished for lack of secondary markers. Consequently all viral *onc* genes except for *src* are not genetically defined.

Nevertheless, on the basis of structural and product analyses, two types of *onc* genes have been distinguished: Type I *onc* genes utilize their specific sequences and viral regulatory sequences to produce unique transforming proteins unrelated to other viral gene products (Fig. 1). Type II *onc* genes are hybrids containing specific sequences and elements of essential virion genes (typically from the *gag* gene, which encodes the core proteins of retroviruses). Together these elements encode hybrid-transforming proteins, which are the basis for the definition of hybrid *onc* genes (Fig. 1) [21]. Examples of type I *onc* genes in the avian tumor virus group are the *src* gene of RSV, which encodes a p60 protein (protein of 60,000 daltons) with an associated kinase function, and the *amv* gene of avian myeloblastosis virus (AMV), which probably encodes a p30 protein (Fig. 1) [29]. Type II *onc* genes are encoded by defective viruses like the acute leukemia viruses MC29 and E26 and like Fujinami sarcoma virus (FSV). The type II *onc* genes of these viruses encode *gag*-related, nonstructural, and probably transforming proteins p94 (MC29), p135(E26), and p140(FSV) (Fig. 1).

To date *onc* genes have not been found in any other group of viruses, such as DNA tumor viruses, which when oncogenic appear to transform with essential virion genes [8]. Genes with exclusive oncogenic function have also not been identified in normal cells. However, genes with oncogenic potential have been isolated from cancer cells (see below).

C. The Qualitative and the Quantitative Model

Retroviruses with *onc* genes represent a paradox among viruses in that they appear only rarely in nature and there is no evidence for horizontal spread. Explanations were offered by the oncogene [15] and protovirus [36] hypotheses which stated that prototypes of *onc* genes exist in some latent form in normal cells and may be induced and transduced by retroviruses without *onc* genes. The original oncogene hypothesis was formulated in 1969, based on sero-epidemiological evidence. Since reverse transcriptase and infectious proviral DNA [37, 40] had not yet been discovered, the hypothesis could not conclusively define the nature of cellular oncogenes and possible mechanisms of transduction by retroviruses. This was first attempted by the protovirus hypothesis [36] and subsequently by a revised oncogene hypothesis [36a].

Using *onc*-specific hybridization probes to test this hypothesis, DNA sequences related to viral *onc* genes have been found in normal animal cells [12, 30, 33]. Some of these sequences, termed proto-*onc* genes, were shown to be highly conserved in different animal species including drosophila [31a, 32, 34]. However, the function of proto-*onc* genes is unknown and proto-*onc* genes, like most viral *onc* genes, have not as yet been genetically defined. Therefore efforts to elucidate the relationship between proto-*onc* genes and viral *onc* genes is, at this time, limited mainly to structural analyses. Analysis of functional relationships has to await genetic definition and functional identification of gene products.

There are two competing views of the role of proto-*onc* genes in normal cells: the *quantitative model,* which postulates that viral *onc* genes and cellular prototypes are the same and the transformation is due to enhaced gene dosage as a consequence of

virus infection [1, 2] and the *qualitative model,* which holds that viral *onc* genes and cellular prototypes are functionally different [3, 8, 10]. The quantitative model sees normal cells as potential cancer cells with switched off *onc* genes. The qualitative model postulates mutational change and possibly deletions of the coding sequence to convert a cellular gene into a viral *onc,* or possibly a non-viral cancer gene. Obviously the two views have very different implications for possible prevention and therapy of tumors caused by such genes, with the qualitative model offering better opportunities for a therapeutic approach. In the following we discuss studies to distinguish between the two models which focus on (a) structural comparisons of molecularly cloned cellular proto-*onc* genes and viral *onc* genes, (b) on measuring expression of proto-*onc* genes in normal and tumor cells, and (c) on testing morphological transforming function of cloned DNAs in transfection assays on cultured mouse 3T3 cell lines.

D. Structural Relationship Between Viral *onc* Genes and Cellular Prototypes

Structural comparisons at the nucleic acid sequence level between type I and type II viral *onc* genes and cellular prototypes of different avian tumor virus subgroups have provided the following insights:

The primary sequence of the type I *src* gene of RSV, and of proto-*src,* are very similar if compared by hybridization and heteroduplex analyses [19, 31, 33]. However, scattered single base changes are detected by mismatched regions in *src* RNA-proto-*src* DNA hybrids [19]. By contrast, the organizations of viral and cellular *src* sequences are quite distinct. Heteroduplex analyses of molecularly cloned viral *src* DNA and cellular proto-*src* DNA show that the cellular sequence is interrupted by six to seven sequences of nonhomology compared with the viral counterpart [25, 31, 35]. If one assumes that (i) the coding sequences of the cellular proto-*src* locus and of viral *src* are the same and (ii) that the regions of nonhomology are noncoding introns and (iii) that the single base changes reflect silent or conservative mutations, proto-*src* could have the same function as *src.* Since there is as yet no direct proof for these assumptions, one cannot clearly distinguish between the two models on a structural basis [3, 19]. Basically, the same limitations regarding a distinction between the two models also apply to structural comparisons of other type I *onc* genes with cellular prototypes.

For example, the *onc* gene of Moloney sarcoma virus, v-*mos*, was shown to contain five and its cellular prototype, c-*mos*, 21 unique 5′ codons in addition to 369 codons shared by the two genes [26 a, 38 a].

Recently, we have compared the type II *onc* gene of MC29, the first hybrid *onc* gene identified in retroviruses [21], with its cellular prototype. A heteroduplex formed between molecularly cloned MC29 DNA and a molecular clone of the cellular prototype of the MC29-specific sequence shows that the specific sequence of 1.6 kb termed *mcv* has a complete counterpart in the cellular locus and that the cellular sequence is not flanked at its 5′ end by a *gag*-related element (Fig. 2) [10, 28]. This has been confirmed by biochemical analyses [28]. The heteroduplex also shows that the proto-*mcv* sequence is interrupted by a 1-kb sequence of nonhomology (Fig. 2). Thus, even if one assumes that the internal sequence of nonhomology is a noncoding intron (see Papas et al., this volume), the cellular proto-*mcv* could not encode the p94 *Δgag-mcv* hybrid protein encoded by MC29 (Fig. 1).

The same appears to be true for the cellular prototype of the hybrid *onc* gene of FSV, which also lacks a *Δgag* element (Fig. 3). The cellular prototype of the FSV-specific sequence (*fsv*) is interrupted by only minor sequences of nonhomology if compared with the 5′ 2 kb of the viral counterpart ([20]; Lee, Phares and Duesberg, unpublished). Since the cellular prototypes of type II *onc* genes are not linked to *gag* or other essential retroviral genes, it follows that type II hybrid *onc* genes are qualitatively different from their cellular prototypes.

Due to the absence of direct genetic and biochemical evidence it may be argued that the *Δgag* element of the hybrid *onc* genes found in MC29, FSV, E26 (Fig. 1), and

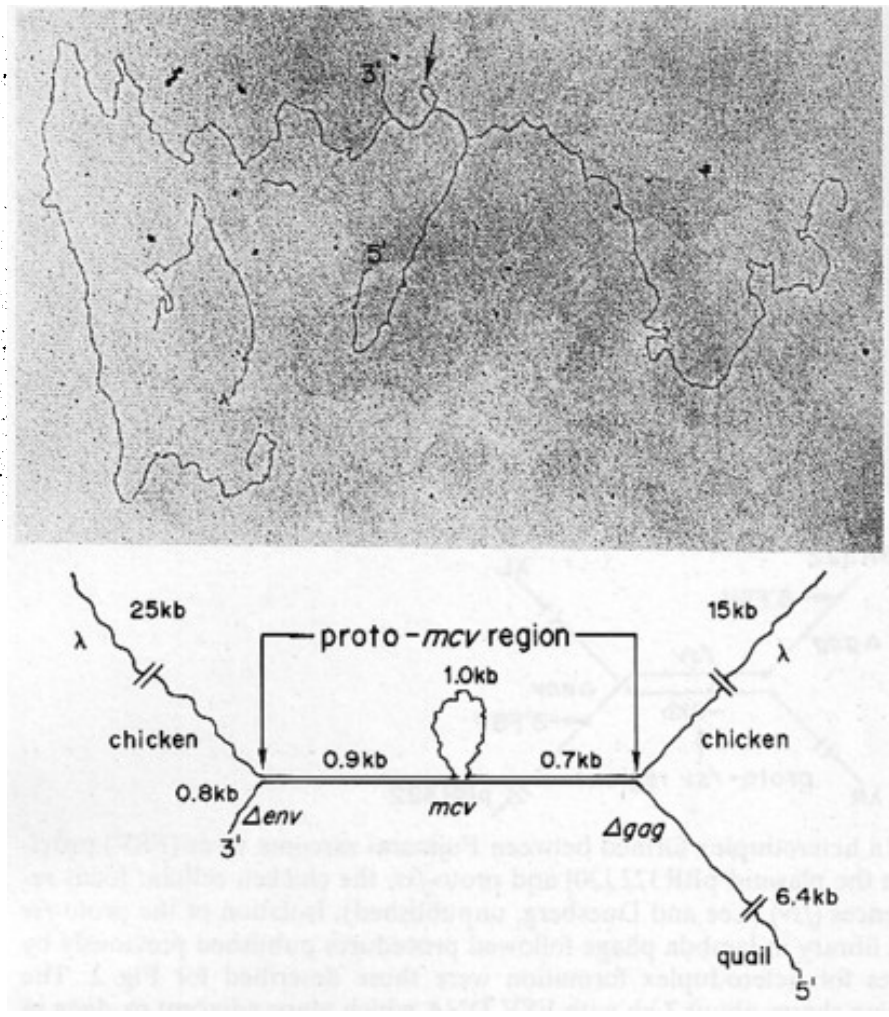

Fig. 2. Electron micrograph of a heteroduplex formed between a fragment of molecularly cloned MC29 proviral DNA and proto-*mcv*, the cellular MC29-related locus of the chicken cloned in lambda phage. Procedures for heteroduplex formation and analysis have been described [28]. The MC29 proviral DNA used was a restriction endonuclease *Eco*RI-resistant DNA fragment that extends from the 5′ end of the viral DNA into *Δenv* (see Fig. 1 for a complete genetic map of MC29). DNA of the proto-*mcv* clone includes the MC29-related locus flanked by about 6–7 kb of chicken DNA at eigher side and then by the two arms of the lambda phage vector. The *arrow* marks the 1-kb sequence of nonhomology that interrupts the MC29-related sequence of proto-*mcv*. The diagram reports length measurements of the respective DNA regions of the heteroduplex in kilobases (data are from Duesberg et al. [10] and Robins et al. [28]

many other avian and murine acute leukemia and sarcoma viruses [3, 40] is not necessary for transforming function. However, several observations lend indirect support to a distinctive role for *Δgag* in hybrid *onc* genes: (a) The genetic *Δgag-x* design is highly conserved in *onc* genes of different taxonomic groups of viruses [3, 40] consistent with a functional role of *Δgag* in hybrid *onc* genes. In support of this view, Temin et al. have recently shown that *gag* may not be essential for packaging of some viral RNAs by helper virus proteins and thus would not necessarily be conserved for this purpose [38 b]. (b) Since *Δgag* together with the specific sequences of a given oncogenic virus forms one genetic unit, i.e., the hybrid *onc* gene which is translated into one nonstructural, probable transforming protein, *Δgag* is also likely to play a direct role in *onc* gene function. If *Δgag* were not necessary for oncogenic function, viruses would have evolved where *Δgag* would not be translated, e.g., spliced out from a mRNA at the posttranscriptional level.

A distinctive role for *Δgag* in *onc* gene function is illustrated by one peculiar pair of *onc* genes which share the same specific sequence but not *Δgag*. One of these, the *onc* gene of AMV, appears to utilize the specific sequence (*amv*) only to encode a

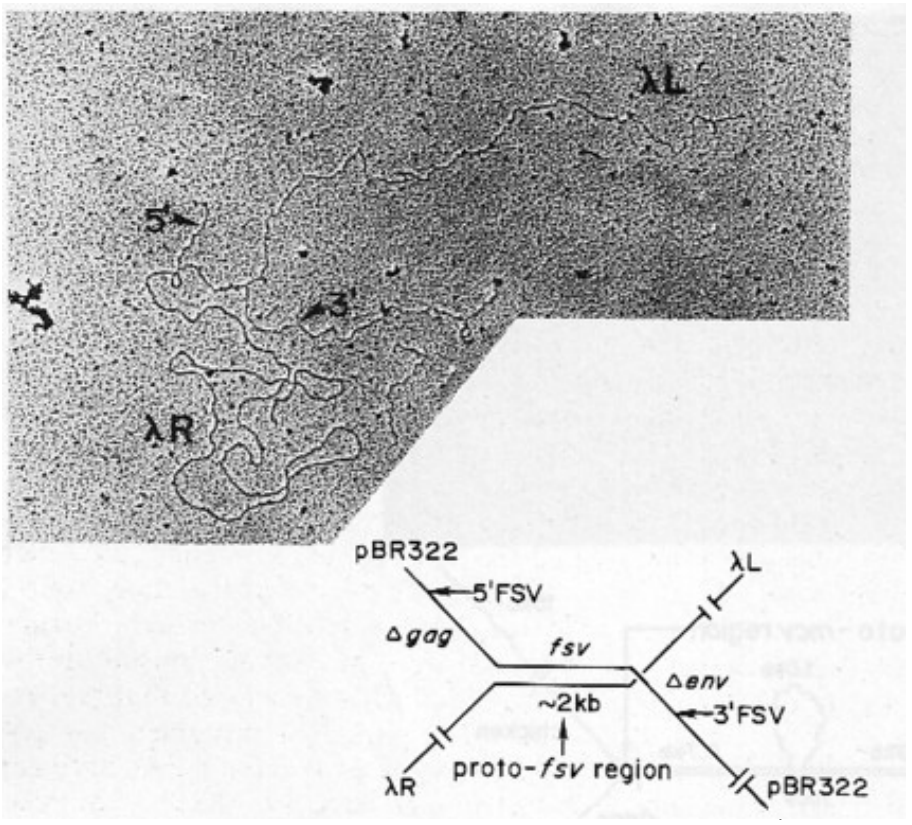

Fig. 3. Electron micrograph of a heteroduplex formed between Fujinami sarcoma virus (FSV) proviral DNA molecularly cloned in the plasmid pBR322 [20] and proto-*fsv*, the chicken cellular locus related to the FSV-specific sequences (*fsv*) (Lee and Duesberg, unpublished). Isolation of the proto-*fsv* sequence from a chicken DNA library in lambda phage followed procedures published previously by this laboratory [28]. Procedures for heteroduplex formation were those described for Fig. 2. The proto-*fsv* lambda phage used here shares about 2 kb with FSV DNA which maps adjacent to *Δgag* in FSV. The 2-kb region of the cellular proto-*fsv* locus appears colinear with its viral counterpart. It is as yet unclear whethter proto-*fsv* represents all FSV-specific sequences, unrelated to essential retrovirus genes, or whether additional proto-*fsv* specific sequences exist that would map between the 2-kb region and *Δenv* of FSV ([20]; Lee, Phares and Duesberg, unpublished)

type I transforming protein although AMV contains a complete *gag* gene (Fig. 1) ([9, 29]; Papas et al., this volume). The other, the *onc* gene of E26, utilizes *Δgag* together with *amv* to encode a type II hybrid-transforming protein (Fig. 1) [4]. The different *onc* gene structures of AMV and E26 correspond to different oncogenic properties. AMV causes exclusively myeloblastosis and E26 causes primarily erythroblastosis [22]. Thus the *onc* genes of AMV and E26 have distinct functions consistent with distinct *onc* gene structures although they share a related specific sequence (*amv*). Extrapolating from this, one can imagine that the proto-*amv* sequence together with adjacent cellular information may be part of a gene with again a distinct cellular function. The same may be true for the functional relationship of all hybrid *onc* genes with their cellular homologs.

Further it appears that related viral *onc* genes and cellular prototypes may differ in the amount of a shared, specific sequence. For example, the specific sequences of the hybrid *onc* genes of MC29 and its relatives MH2 and CMII [3] or of Fujinami and PRCII sarcoma viruses [3, 17, 41] may differ as much as 30% from each other. Likewise the *amv* sequences of AMV and E26 differ in complexity, with E26 lacking both 5′ and 3′ *amv* sequences (Nunn and Duesberg, unpublished). This argues that subsets of a cellular sequence may be sufficient for transforming function as part of a viral transforming gene. By contrast the high degree of conservation of proto-*onc* genes in vertebrates and invertebrates [31a, 32, 34, 40] argues that all cellular sequences, related to a given class of viral hybrid *onc* genes, are necessary for their unknown cellular function including those sequences which

are not shared by all viral *onc* genes of a given class.

Comparison with cellular prototypes indicates that hybrid *onc* genes have at least two essential structural domains one represented by the minimal complement of a given class of specific sequences shared with a cellular locus, the other by *Δgag*. Moreover, the cellular genes may in addition to the codons shared with viral *onc* genes consist of other cell-specific codons that together have a function that is different from viral *onc* genes. These differences suggest, but do not prove, that the products encoded by viral hybrid *onc* genes and the genes of the cellular proto-*onc* loci have different functional domains.

E. Expression and Biological Activity of Proto-onc Genes: Evidence for a Role in Carcinogenesis?

A direct assay of the function of cellular proto-*onc* genes is not yet available. In addition it has not as yet been possible to isolate proto-*onc* genes from normal cells that are directly oncogenic. Consequently, no cancer has as yet been shown to be caused by a proto-*onc* gene.

Nevertheless, there is circumstantial evidence that cellular proto-*onc* genes have oncogenic potential. For example, it has been speculated that proto-*onc* genes may be activated by promotors or enhancers of retroviruses without *onc* genes [14, 26]. Such promoters are encoded in viral LTRs, the terminal sequences of proviral DNA and may function like the promotors of bacterial IS-elements [29a]. Applied to retroviruses, the hypothesis states that such activation requires integration of the provirus adjacent to proto-*onc* and subsequent transcription of a hybrid mRNA which includes at its 5′ end viral LTR sequences and cellular proto-*onc* sequences downstream [14, 38]. Thus, the viral promoter would activate cellular genes located downstream of the provirus. This hypothesis would explain how the rather ubiquitous retroviruses without *onc* genes may occasionally become oncogenic. If correct, this would lend direct support to the quantitative model.

Accordingly, virus-negative tumors [11] and tumors induced by nondefective retroviruses without *onc* genes have been screened for the expression of sequences related to viral *onc* genes [14, 16, 26]. Specifically, enhanced expression of proto-*mcv* (Fig. 2) by promoters of avian leukemia viruses without *onc* genes has been proposed to cause bursal lymphoma in chicken after latent periods of over 6 months [14]. However, this proposal raised a number of questions: (a) for example, why does activated proto-*mcv* not cause the acute myelocytomatosis, carcinoma, or sarcoma caused by MC29? This difference may signal qualitative differences between the functions of viral *onc* genes and the hypothetical oncogenic functions of cellular prototypes. These differences may reflect the structural differences, namely linkage of *mcv* to *Δgag* in the viral but not in the cellular gene. It is recognized that this explanation implies that proto-*mcv* has potential oncogenic function, albeit different from the *onc* gene of MC29. However, evidence listed under (c) and (e) suggests that proto-*mcv* may neither be necessary nor sufficient for lymphomagenesis. (b) A recent reinvestigation of proto-*mcv* activation by avian leukemia viruses has revealed that activation also works upstream and as well as in the opposite polarity within a region of about 20 kb flanking proto-*mcv* [26]. Although this does not rule out activation of proto-*mcv* as the cause of the lymphoma, it rules out a common and orthodox mechanism to explain the reportedly causative activation of proto-*mcv*. (c) This work and the original study also raise the questions why proto-*mcv* activation was only observed in 80% of retroviral lymphomas and thus may not be a necessary condition for lymphoma and why the latent period for leukemia virus to cause bursal lymphoma would be at least 6 months [14]. Considering the high multiplicities of infection, the large number of bursal cells, and a complexity of 10^6 kb of the chicken genome, a successful infection within 20 kb of proto-*mcv* should be a rather frequent event consistent with a short, rather than a long, latent period for leukemogenesis. (d) Furthermore, it is unclear why in other cases of viral leukemias, it has not been possible to demonstrate promotion of cellular genes [16] and why a correlation between neoplasia and enhanced expression of

known cellular proto-*onc* genes in a number of virus-negative human tumors cannot be demonstrated [11]. (e) An attempt to isolate directly the presumably activated oncogenic proto-*mcv* gene from bursal lymphoma cells has led to the detection of a transforming DNA that is unrelated to MC29 [5]. In these experiments DNA isolated directly from tumor cells has been tested for oncogenic function on the mouse fibroblast 3T3 cell line. Assuming that the 3T3 cell assay is suitable to detect a leukemogenic transforming gene, as has been suggested in some cases ([27]; Lane et al., this volume), this result means that proto-*mcv* was either not responsible for the bursal lymphoma at all [14] or that upon activation it played an indirect role. In the latter scenario, proto-*mcv* could mutate the cellular gene identified in the 3T3 assay to create a maintenance gene for lymphoblast transformation [5]. If correct, the experiments that detected proto-*mcv* activation in lymphoma [14] would have found a lymphoma initiation gene by searching for the presumed maintenance gene with a probe for the acute *onc* gene of MC29. It would appear that available evidence does not prove that proto-*mcv* activation is necessary or sufficient for lymphomagenesis.

There is circumstantial evidence that some other proto-*onc* genes become oncogenic upon activation. Using the techniques of DNA transfection two proto-*onc* genes, i.e., those related to the murine Moloney and Harvey or Kirsten sarvoma viruses, have been shown to transform mouse 3T3 cells after ligation to viral promoter LTR sequences derived from Moloney or Harvey sarcoma virus [6, 23]. Although this does imply that these proto-*onc* genes are potentially oncogenic, the relevance of this result to nonviral cancer is uncertain (a) because the cellular loci are not normally linked to viral LTRs and are only oncogenic after ligation with sarcoma viral LTRs, (b) because the genes of the proto-*onc* loci and their products are not yet genetically and biochemically defined and thus are not directly comparable to their viral counterparts, and (c) because to date the assay has been restricted to the 3T3 cell line, which is pre-neoplastic and transforms spontaneously or can be transformed by a large number of viral and nonviral DNAs [27, 39]. It is on the basis of this assay that the structural differences between the v-*mos* and c-*mos* [26a, 38a] are considered functionally irrevelant [1]. Moreover, to date the same assay has not shown transformation potential for over a dozen other proto-*onc* sequences from normal cells including proto-*src*, which, upon transfection, was expressed at high levels in mouse cells yet failed to transform these cells morphologically (Shalloway and Cooper; Parker and Bishop, personal communication). In particular not a single prototype of a hybrid *onc* gene like proto-*mcv* was shown to have transforming function despite similar efforts (Robins and Vande Woude, personal communication).

Recently, DNA has been isolated directly from cell lines derived from human tumors and has been tested for oncogenic function in the 3T3 cell assay system. In some cases transforming DNA was extracted from bladder carcinoma cells with properties of a proto-*onc* gene. This DNA resembled the *onc* gene of Harvey and Kirsten sarcoma viruses [7, 24]. Since the DNA equivalent of normal cells did not transform 3T3 cells it would follow that a mutational change must have converted this human proto-*onc* gene to become active in the 3T3 cell assay. However, not all cell lines prepared from bladder tumors yielded active DNA, and DNA from primary tumors has not as yet been tested. It remains to be shown that the DNA that was active in the 3T3 cell assay also caused the original cancer.

It would follow that consistent with the qualitative model there is as yet no direct functional or genetic evidence to prove a direct role of proto-*onc* genes in carcinogenesis. Normal proto-*onc* genes have only been shown to be oncogenic on 3T3 cells after modification. In one case proto-*onc* genes were ligated to viral LTRs. In the other case mutation presumably conferred transforming ability to the proto-*onc* gene related to Harvey sarcoma virus isolated from a human bladder carcinoma cell line. Proto-types of type II *onc* genes have not as yet been positive in the 3T3 cell assay and the bursal lymphomas reportedly caused by activation of proto-*mcv* are qualitatively different from the tumors caused by the type II *onc* gene of MC29. Indeed, some re-

cent results suggest that these lymphomas are maintained by a transforming gene that is unrelated to proto-*mcv*. Taken together these may be signals that viral *onc* genes and their cellular prototypes are qualitatively different.

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