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Edited by

GEORGE KLEIN

SIDNEY WEINHOUSE

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RETROVIRUSES AND CANCER GENES

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I. Introduction

The possibility that viruses might be tumorigenic materialized at the turn of this century, with reports that erythroleukemia and fibrosarcomas could be induced in chickens by transmissible agents (Ellermann and Bang, 1908; Rous, 1911). Skepticism greeted these reports, dissipated only slowly over the ensuing years, and lingers on in the continuing debate about the possible role of viruses in the genesis of human tumors. But these are needless concerns for most experimentalists: the oncogenic potential of many animal viruses is well established, and the use of tumor viruses now dominates efforts to dissect the mechanisms of tumorigenesis.

Oncogenic viruses are taxonomically diverse. DNA viruses both large (herpes and adenoviruses) and small (papovaviruses), as well as many (but not all) members of the large family of retroviruses, can induce tumors in either experimental or natural hosts (Gross, 1970). Two patterns of viral oncogenesis have emerged. Some viruses possess genetic loci (or "oncogenes") whose actions initiate and maintain the neoplastic phenotype of the infected cell. Other viruses are devoid of specific oncogenes and induce tumors by

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more subtle means, whose particulars we are just beginning to perceive. But both forms of viral oncogenesis are united by the persistence of at least a portion of the viral genome in the host cell, either as an integral part of a host chromosome or as independently replicating units. For the moment, it appears that persistence of the viral genome is a necessary event for viral oncogenesis—to maintain the influence of an oncogene over the host cell, or to sustain the more indirect but equally malicious effects of viruses that induce tumors without benefit of an oncogene. The possibility that transient infection by viruses might trigger an irreversible sequence of events (the "hit-and-run" mechanism) has been posited repeatedly but has gained no substantive experimental support to date.

Although several themes appear to unite oncogenesis by diverse viral agents, and although each family of tumor viruses offers important distinctive features to the experimentalist, it is the retroviruses that have provided the most coherent and penetrating view of tumorigenesis presently available to us. Three features of retroviruses account for this sentiment. First, the oncogenes of retroviruses have proved exceptionally accessible to definition and study, and as a consequence, they have provided our first glimpse of enzymatic mechanisms responsible for neoplastic transformation. Second, the diversity of retrovirus oncogenes has provided a rich set of oncogenic agents whose versatility far exceeds that of DNA tumor virus oncogenes, and whose tumorigenic capacities provide separate experimental models for most major forms of malignancy. Third, oncogenes appear not to be indigenous components of retrovirus genomes, but instead have been transduced from normal genetic loci of the vertebrate hosts in which retroviruses replicate. Moreover, we have reasons to believe that the vertebrate genes from which retrovirus oncogenes derive may participate in tumorigenesis induced by agents other than viruses. Thus while tracking the evolutionary origins of oncogenes, retrovirologists have been led well beyond the confines of tumor virology, to confront what may be a final common pathway of oncogenesis. The genesis and status of this confrontation are the main subjects of this essay.

II. Introducing Retrovirus Oncogenes

Retrovirus oncogenes display a burgeoning diversity that is largely attributable to nature's generosity in providing field isolates, but recent years have also witnessed provisional successes in bringing new oncogenes to view by experimental manipulations (Rapp and Todaro, 1978, 1980; Young *et al.*, 1981). At least 15 retrovirus oncogenes have been identified (Table I). Together, they are known by the generic term v-*onc* (for viral oncogene). Each gene is distinguished by its nucleotide sequence and is designated by a term derived from the name of the virus that bears the gene (hence, v-*src*,

v-*myc*, v-*abl*, etc.; see the table). Many of these genes are represented in more than one viral isolate, and the topographical details of kindred genes may vary from one isolate to another; a few of the genes have been obtained from more than one host species; and a number share similar oncogenic properties and/or biochemical functions (see later).

The replicative unit in all retrovirus genomes is composed of three genes: *gag* (structural proteins of the virion); *pol* (reverse transcriptase); and *env* (glycoproteins of the viral envelope). An oncogene may be inserted into this unit in at least four distinctive ways (Fig. 1): (1) as an independently expressed

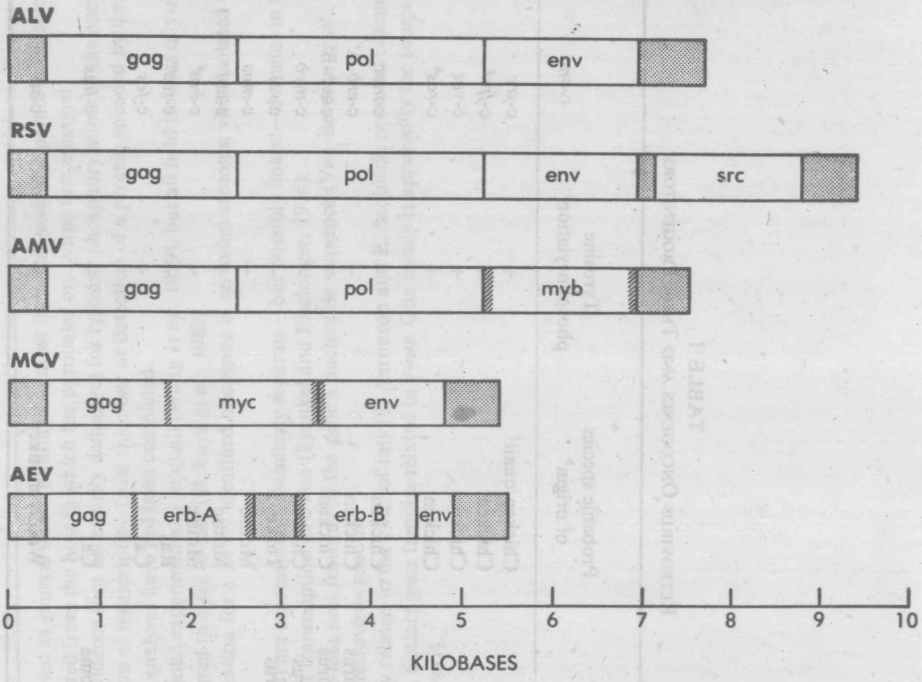

FIG. 1. Styles in retroviruses genomes. Genomes of avian retroviruses are used to illustrate typical dispositions of oncogenes. ALV, avian leukosis virus: contains no oncogene; *gag* encodes structural proteins of the viral core; *pol*, reverse transcriptase; and *env*, the glycoproteins of the viral envelope. RSV, Rous sarcoma virus: the oncogene *src* is expressed from a spliced subgenomic mRNA. AMV, avian myeloblastosis virus: the oncogene *myb* is expressed from a spliced subgenomic mRNA. MCV, MC29 virus: the oncogene *myc* is expressed from a genomic-length mRNA that directs uninterrupted translation from *gag* and *myc*. AEV, avian erythroblastosis virus: the oncogene *erb*-A is expressed from a genomic-length mRNA that directs the uninterrupted translation from *gag* and *erb*-A; the oncogene *erb*-B is expressed from a spliced subgenomic mRNA. Stippling denotes regions that do not encode protein; solid vertical lines denote established gene boundaries; and diagonal shading denotes uncertainty in gene boundaries.

TABLE I

RETROVIRUS ONCOGENES AND THEIR PROGENITORS

v-*onc*[a]	Protypic virus	Probable species of origin[b]	Tyrosine phosphorylation[c]	c-*onc*	c-*onc* expressed[d]	Protein product of c-*onc*[e]
v-*src*	Rous sarcoma virus	Chicken/quail[f]	+	c-*src*	Yes	$pp60^{c-src}$
v-*fps*	Fujinami sarcoma virus	Chicken	+	c-*fps*[g]	?	?
v-*yes*	Y73 sarcoma virus	Chicken	+	c-*yes*	?	?
v-*ros*[h]	University of Rochester sarcoma virus 2	Chicken	+	c-*ros*[h]	?	?
v-*myc*	Myelocytomatosis virus	Chicken	−	c-*myc*	Yes	?
v-*erb*-A	Avian erythroblastosis virus	Chicken	−	c-*erb*-A[i]	Yes	?
v-*erb*-B	Avian erythroblastosis virus	Chicken	−	c-*erb*-B[i]	Yes	?
v-*myb*	Avian myeloblastosis virus	Chicken	−	c-*myb*	Yes	?
v-*rel*	Reticuloendotheliosis virus	Turkey	−	c-*rel*	Yes	?
v-*mos*	Moloney sarcoma virus	Mouse	−	c-*mos*	—[j]	?[k]
v-*abl*	Abelson leukemia virus	Mouse	+	c-*abl*	Yes	$p150^{c-abl}$
v-*bas*	BALB sarcoma virus	Mouse	−	c-*bas*[l]	?	?
v-*ras*	Harvey sarcoma virus	Rat	−	c-*ras*[m]	Yes	$p21^{c-ras}$
v-*fes*	Gardner-Arnstein feline sarcoma virus	Cat	+	c-*fes*	Yes	$p92^{c-fes}$
v-*fms*	McDonough feline sarcoma virus	Cat	−	c-*fms*	?	?
v-*sis*	Simian sarcoma virus	Woolly monkey	−	c-*sis*	?	?

[a] The names of viral genes are here treated as generic terms, although in most instances several separate viral isolates are known.

[b] The probable species of origin is inferred from the host in which the particular oncovirus first emerged.

[c] A plus sign denotes the existence of evidence (not necessarily definitive) for tyrosine phosphorylation by the oncogene product.

[d] Expression is defined as either detection of transcription from the c-*onc* or detection of a protein encoded by the locus.

[e] Question marks indicate that suitable analyses have not been completed.

[f] Some strains of RSV have been generated experimentally in quail (Wang *et al.*, 1979), but all field isolates of v-*src* have come from chickens.

[g] The c-*fps* of chicken is apparently related to c-*fes* of cats (Shibuya *et al.*, 1980).

[h] The term v-*ros* is a provisional designation for a newly identified oncogene in an avian sarcoma virus isolated at the University of Rochester (P. Balduzzi, personal communication).

[i] The separate domains of *erb* (A and B) are represented by similarly separate—but possibly linked—domains in the chicken genome.

[j] All efforts to date have failed to detect transcription of c-*mos* (Frankel and Fischinger, 1976).

[k] Failure to detect transcription from c-*mos* and features of the gene's nucleotide sequence (Van Beveren *et al.*, 1981) raise the possibility that c-*mos* is inactive unless transferred into a retrovirus genome.

[l] The c-*bas* of mice is apparently closely related to the c-*ras* of rats (S. Aaronson and E. Scolnick, personal communication).

[m] Rat DNA contains at least two small, distinct gene families related to v-*ras*. One family is apparently the source of Harvey and Rasheed v-*ras*, the other of Kirsten v-*ras* (DeFeo *et al.*, 1981).

gene that does not impose on either the structure or function of the replicative genes and is expressed from a subgenomic mRNA (v-*src* of the Rous sarcoma viruses is the sole known example); (2) as an independently expressed gene that replaces part or all of a replicative gene (*env*, for example) and is expressed from a subgenomic mRNA (e.g., v-*myb* of avian myeloblastosis virus); (3) as a fusion between v-*onc* and a portion of *gag* that is accompanied by deletions in one or more of the replicative genes (usually *pol* and portions of *gag* and *env*) and is expressed as a polyprotein produced from a genomic-length mRNA (e.g., v-*myc* of avian myelocytomatosis virus); and (4) as two separately expressed v-*onc* domains—one fused with a portion of *gag*, the other expressed independently, and the two together replacing portions of replicative genes. In this last instance, the *gag–onc* protein is produced from a genomic-length mRNA, the second *onc* protein from a subgenomic mRNA (e.g., *erb*-A and *erb*-B of avian erythroblastosis virus). These themes are varied in yet a further way: the same class of v-*onc* can be fused to *gag* in some viral isolates and occur as an independently expressed locus in others. With the exception of v-*src*, the insertion of oncogenes into retrovirus genomes creates genetic defects that preclude the production of virus unless the defective function(s) is provided by a second "helper" virus.

The variety of retrovirus oncogene construction is merely tedious at first glance, but in reality it poses an important challenge because all of these configurations are thought to be products of recombination between a replicating retrovirus and the genome of its host cell (see later). The mechanisms that effect this recombination with its remarkable plurality of outcomes may have no precedent in the annals of molecular genetics.

III. Properties of Retrovirus Oncogenes and Their Products

The oncogenes of retroviruses are genetic luxuries whose actions are highly selective. They are not required for viral replication—indeed they make no known contribution to replication; and their activities may be muted even in cells that sustain vigorous replication, and perhaps chemical expression, of the oncogenes (Graf *et al.*, 1980; Durban and Boettiger, 1981a). This muting underlies one of the cardinal properties of retrovirus oncogenes: the specificity of their pathogenicity. Each oncogene induces tumors in only a limited and characteristic set of tissues; transformation of cells in culture follows the same selective pattern. We cannot at present explain the selectivity of oncogene actions, but the phenomenon has contributed to the view that transformation by retrovirus oncogenes is fundamentally a disturbance of differentiation. According to one prevalent view, oncogenes may act by arresting cellular development within a specific compartment of one or another developmental lineage; tumorigenesis ensues because the immature cells that constitute the compartment continue to divide, as is their nature,

and become a continuously expanding population—a tumor composed of ostensibly normal cells (Graf and Beug, 1978). Other observers have argued that the effects of oncogenes more commonly (or perhaps inevitably) distort the phenotype of susceptible cells to a form that is not representative of a single developmental compartment (Boettiger and Durban, 1979; Durban and Boettiger, 1981b). No matter which view is correct (there appear to be elements of truth in both), the effects of oncogenes on cells, and the selectivity of these effects, point to biochemical functions that in other guises might well direct the course of normal growth and development. Inferences of this sort brook large in present efforts to interpret the evolutionary origins of retrovirus oncogenes (see later).

How do oncogenes evoke the myriad changes that accompany neoplastic transformation? Efforts to answer this daunting question have produced at least dim outlines of several potentially important refrains.

1. Some retrovirus-transforming proteins (but not others; see Table I) apparently mediate the phosphorylation of tyrosine in protein substrates (Hunter and Sefton, 1980b). The best-studied example is the 60,000-MW phosphoprotein encoded by v-*src* ($pp60^{v-src}$), but the products of v-*fps*, v-*yes*, v-*abl*, and v-*fes* also appear to follow suit. Phosphorylation of proteins represents one of the principal devices by which cellular functions are regulated (Rubin and Rosen, 1975) and thus offers an attractive explanation for the pleiotropic effects of retrovirus oncogenes. Moreover, the findings with $pp60^{v-src}$ and other retrovirus-transforming genes have produced unexpected further dividends by alerting cell biologists to the existence of tyrosine phosphorylation. This hitherto unknown reaction is now rapidly emerging as an important regulatory mechanism in normal as well as transformed cells. But efforts to identify cellular proteins that serve as substrates for retrovirus protein kinases have just begun, only a small number of candidate substrates have been sighted, and none of these as yet offers any explanation for the abnormal growth of transformed cells.

2. Several retrovirus-transforming proteins (including $pp60^{v-src}$, $pp21^{v-ras}$, and the product of v-*abl*) appear to act at the periphery of the cell because they are found attached to the plasma membrane of the transformed cell (Hynes, 1980). This inference is for the moment largely circumstantial, however. The techniques used to locate the transforming proteins have limited resolving power and sensitivity; trace amounts of the proteins in presently unappreciated locations might cause major effects.

IV. The Origin of Retrovirus Oncogenes: Emergence of the Thesis

The virus isolated from a chicken sarcoma by Peyton Rous did not spring quickly or easily into view. Rather, an infectious tumorigenic agent was obtained from extracts of tumor tissue only after the original sarcoma had

been passaged repeatedly from one bird to another (Rous, 1911). It seems possible in retrospect that the original tumor was not the consequence of viral infection; the sarcoma virus that eventually emerged may not have been present in the tissue with which Rous began his work. The isolation of murine sarcoma viruses (Harvey, 1964; Moloney, 1966) and the Abelson murine leukemia virus (Abelson and Rabstein, 1970a,b) decades later raised these issues in a more explicit manner: the new viruses appeared during the passage of leukemia viruses in rodents, as if new capabilities for pathogenesis could be acquired from the host animal.

The discovery of endogenous retroviruses in chickens (Robinson, 1978) and mice (Aaronson and Stephenson, 1976), as well as the development of inbred lines of mice whose predisposition to leukemia appeared to involve genetically transmitted retroviruses (Rowe, 1973), added appreciably to these inferences and engendered the "oncogene hypothesis" of Huebner and Todaro (1969). According to this hypothesis, carcinogens of many sorts act by inducing the expression of otherwise cyrptic retrovirus genes already resident in the genome of the target cells. The oncogene hypothesis is no longer regarded as strictly correct, but it served an important heuristic purpose by prompting experimentalists to ask whether normal cellular DNA might contain retrovirus oncogenes. We now know that vertebrate cells do harbor genetic loci homologous to retrovirus oncogenes (designated here by the generic term "c-*onc*"), but these loci are cellular, not viral genes, and the oncogene hypothesis has been eclipsed by even more sweeping views of the nature of these cellular genes.

V. The Discovery of c-*onc*s

The search for oncogenes in cellular DNA began with the use of molecular hybridization. The strategy exploited naturally occurring deletions that remove most or all of v-*src* (but no other viral gene) from the genome of Rous sarcoma virus (Duesberg and Vogt, 1970, 1971; Martin and Duesberg, 1972; Lai *et al.*, 1973). Viral RNA bearing this class of deletions could be employed to isolate radioactive DNA ($cDNA_{src}$) that hybridized only with nucleotide sequences encoding (or related to) *src* (Stehelin *et al.*, 1976a). The result was a reagent that provided specificity and sensitivity sufficient to detect a single genetic locus among the immense complexity of vertebrate DNA. Similar cDNAs were prepared for replication-defective murine sarcoma viruses (Scolnick *et al.*, 1973, 1975; Frankel *et al.*, 1976), but the genetic definition of these reagents was less rigorous because suitable deletion mutants were not available for isolation of the cDNAs. As a consequence, the experimental strategies had to rely on the assumption that nucleotide sequences not present in the genome of the helper virus must perforce

represent portions of the oncogene—an assumption that proved useful but not inevitably correct (see later).

The initial findings with $cDNA_{src}$ for Rous sarcoma virus prefigured subsequent conclusions for virtually all retrovirus oncogenes. Each family of vertebrates examined—including fish, birds, and mammals—displayed evidence of both DNA and RNA related to the *src* gene (Stehelin *et al.*, 1976a; Spector *et al.*, 1978a,b,c). The DNA related to v-*src* appeared to occur as only one or very few copies in each haploid portion of vertebrate genomes. Retrovirologists had obtained their first glimpse of the cellular gene we now know as c-*src*.

The mere fact that homologous DNA could be detected across such large phylogenetic distances indicated that the genetic locus or loci in question were highly conserved during the course of evolution. More recent findings have dramatized the extent of this conservation by demonstrating homology with v-*src* (and several other v-*onc*s) in the DNA of the insect *Drosophila* (personal communication, R. Weinberg). Conservation of c-*src* was also explored by evaluating the thermal stability of molecular hybrids formed between $cDNA_{src}$ and DNAs from various sources. The results indicated that the nucleotide sequences of c-*src* might diverge by no more than 10–15% from fish to chicken genomes on the one hand, from chicken to human genomes on the other (Stehelin *et al.*, 1976b; Spector *et al.*, 1978c). The full implications of these findings were not easily sustained at the outset, largely because no assay was available for the protein product of *src*; nevertheless, it appeared that vertebrate species possessed a highly conserved and expressed (i.e., transcribed) gene that is closely related to a viral oncogene. The strong evolutionary conservation of this gene, and the fact that it was found to be expressed in every tissue and every species examined, indicated an essential function in cellular metabolism. Early doubts about the veracity of these deductions were obviated by the eventual identification and characterization of a protein encoded by c-*src* (and known as $pp60^{c-src}$). The characteristics of $pp60^{c-src}$ vindicate and extend all of the original predictions based on molecular hybridization (see later).

Difficulties did arise, however, from the use of a less well-defined cDNA for the oncogene of Harvey/Kirsten murine sarcoma virus (v-*ras*). Initial results indicated that v-*ras* was related to (and presumably derived from) nucleotide sequences in the genome of an endogenous retrovirus of rats (Scolnick *et al.*, 1973; Scolnick and Parks, 1074), a troubling deduction because it stood in striking contrast to the mounting evidence that other retrovirus oncogenes are derived from conserved cellular genes. The advent of molecular cloning to the study of retrovirus genomes quickly resolved the apparent anomaly. It now appears that the genome of Harvey/Kirsten sarcoma virus was constructed with three distinct components (Ellis *et al.*, 1980): one derived from the murine helper virus that was used to initiate

recovery of the sarcoma virus and was isolated together with the sarcoma virus; a second derived in fact from an endogenous virus of rats; and a third, the oncogene proper, derived true to form from a cellular gene of the rat in which the sarcoma virus originally arose.

The principles first enunciated for *src* have since been shown to be widely applicable to retrovirus oncogenes (see table): homologues of these genes (i.e., c-*onc*s) can be found in vertebrate DNA, many (but apparently not all) of which are expressed in phenotypically normal cells. The sole exception at present is the oncogene of the Spleen Focus Forming Virus, which appears to be a recombinant form of the retrovirus *env* gene rather than the derivative of a cellular gene (Oliff *et al.*, 1980). All of the identified c-*onc*s are found in more than one vertebrate species, but the extent of evolutionary conservation varies from one c-*onc* to another: some are readily detectable only in closely related species; others appear to have taken form in primitive vertebrates (or even earlier in evolution) and to have evolved thereafter in concert with speciation. These variations may be only matters of degree, however; it is now reasonable to suppose that every c-*onc* represents a genetic lineage that extends throughout the vertebrate phyla and, in an least some instances, farther down the phylogenetic hierarchy.

The kinship between retrovirus oncogenes and cellular genes is certain. But how can we distinguish parent from progeny? Phylogenetic patterns provide a clue: in contrast to the evolutionary conservation of the cellular genes, the viral oncogenes are usually restricted to single strains of retroviruses that were isolated from particular species (although not inevitably; see later. Moreover, the homology between viral oncogene and cellular DNA is greatest for the species in which the oncogene allegedly originated. The most straightforward interpretation of these findings is that retrovirus oncogenes are derived from cellular genes. Widespread acceptance of this scheme, and the remarkable similarity between retrovirus oncogenes and their cellular homologues (to be described later), have engendered a standard nomenclature that is followed here (Coffin *et al.*, 1981): viral oncogenes are denoted by v, as in v-*src* or v-*myc* (see earlier, and the table); the cellular progenitors of v-*onc*s by c, as in c-*src* or c-*myc* (see the table). The nomenclature is only a convenience, however, and should not be construed as indicating that homologous viral and cellular genes are necessarily identical in either structure or function. The precise relationship between cellular progenitor and viral progeny has yet to be fully explored for any retrovirus oncogene.

VI. Characterizing c-*onc*s

Enumeration of c-*onc*s by molecular hybridization and by mapping with restriction endonucleases has revealed that some may be unique loci within