

The DNA Provirus Hypothesis

The establishment and implications of RNA-directed DNA synthesis.

Howard M. Temin

The genetic information in RNA is transferred to DNA during the replication of some viruses, including some that cause cancer. This transfer of information from the messenger molecule, RNA, to the genome molecule, DNA, apparently contradicted the "central dogma of molecular biology," formulated in the late 1950's. This mode of information transfer was first postulated and established for the replication of Rous sarcoma virus, a strongly transforming avian C-type ribodeoxyvirus. (Ribodeoxyviruses are RNA viruses that replicate through a DNA intermediate.)

In this article, I discuss the experiments that led to the formulation of the DNA provirus hypothesis; the experiments that established the DNA provirus hypothesis and, therefore, the existence of RNA-directed DNA synthesis; some aspects of the present status of our knowledge of the mechanism of formation of the DNA provirus; and, finally, some implications of this work for the questions of the origin of animal viruses, how cancers may be caused by viruses, and how the majority of cancers, which do not involve infectious viruses, are caused.

The majority of the ideas I discuss came from experiments with Rous sarcoma virus (RSV), the prototype RNA tumor virus. Rous sarcoma virus was originally described by Peyton Rous in 1911. He stated, "A transmissible sarcoma of the chicken has been under observation in this laboratory for the past fourteen months, and it has assumed of late a special interest because of its extreme malignancy and a tendency to wide-spread metastasis. In a careful study of the growth, tests have been made to determine whether it can be transmitted by a filtrate free of the tumor cells. . . . Small quantities of a cell-free filtrate have sufficed to transmit the growth to susceptible fowl" (1).

Although Rous and his associates carried out many experiments with RSV, as the virus is now called, and had many

prophetic insights into its behavior, they and other biologists of that time did not have the scientific concepts or the technical tools to exploit his discovery. And in 1915 Rous himself stopped work with RSV.

The major scientific concepts required to understand the behavior of RSV were that genetic information was contained in and transferred from nucleic acids, developed especially by Avery, MacLeod, and McCarthy (2), and by Watson and Crick (3), as well as the concept that viral genomes could become part of cell genomes, developed especially by Lwoff (4). The major technical tools required were those of quantitative virology and of the study of animal viruses in cell culture, developed especially by Delbrück (5), Enders, Robbins, and Weller (6), and Dulbecco (7).

My first contact with RSV was in 1956 when, as a graduate student at the California Institute of Technology, I was asked by Harry Rubin, a postdoctoral fellow in Professor Dulbecco's laboratory, to try and make more quantitative the observations of Manaker and Groupé (8) that discrete foci of altered chicken embryo cells were associated with Rous sarcoma virus in tissue culture (9).

Assay for Rous Sarcoma Virus

I soon found that addition of RSV to chicken embryo fibroblasts in a sparse layer, rather than in a crowded monolayer as then used for the assay of other animal viruses, led to the appearance of foci of transformed cells (Fig. 1). The number of these foci was proportional to the concentration of virus, and the foci resulted from altered morphology and altered control of multiplication of the infected cells (10). The foci were cell culture analogs of tumors in chickens.

This assay allowed RSV to be studied like other viruses, leading to the demonstration that RSV-infected cells could produce virus and divide (11) and to the

demonstration by Crawford and Crawford (12) that the genome of RSV was RNA. The assay for RSV was also a model for the assay of other transforming viruses, such as polyoma virus, as discussed by Dulbecco (13).

Further observations of RSV-induced foci revealed that some of the foci contained long fusiform cells rather than the rounded cells seen in the focus in Fig. 1 (14). Virus produced by these fusiform foci caused the production of further foci of long fusiform cells, that is, the virus from these foci was a genetic variant.

These and other observations indicated that viral genes controlled the morphology of transformed cells and led to the hypothesis that transformation was the result of the action of viral genes; that is, transformation was a conversion analogous to lysogenic conversion. This hypothesis has been amply confirmed for RSV by the isolation of variant viruses temperature-sensitive for transformation or defective for transformation (15).

These observations also led to the study of differences between transformed and normal cells. At least two important results came from these studies: (i) the concept of an altered requirement of transformed cells for specific multiplication-stimulating factors in serum (16); and (ii) the discovery by Reich and co-workers of increased production by transformed cells of an activator of a serum protease (17).

The Provirus Hypothesis

In 1960 I studied the kinetics of mutation of the viral genes controlling cell and focus morphology, the effects of mutation in these viral genes on the morphology of infected cells, and the inheritance of these genes in cells infected with two different Rous sarcoma viruses (18). These studies demonstrated that these viral genes mutated at a high rate, that mutation in a viral gene present in an infected cell often led to change in the morphology of that infected cell, that

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The author is American Cancer Society Professor of Viral Oncology and Cell Biology at the McArdle Laboratory for Cancer Research, University of Wisconsin-Madison, Madison 53706. This article is the lecture he delivered in Stockholm, Sweden, on 12 December 1975 when he received the Nobel Prize in Physiology or Medicine, a prize which he shared with Renato Dulbecco and David Baltimore. Minor corrections and additions have been made by the author. The article is published here with the permission of the Nobel Foundation and will also be included in the complete volume of *Les Prix Nobel en 1975* as well as in the series Nobel Lectures (in English) published by the Elsevier Publishing Company, Amsterdam and New York. The lectures by Drs. Dulbecco and Baltimore appeared in the 30 April and 14 May issues, respectively.

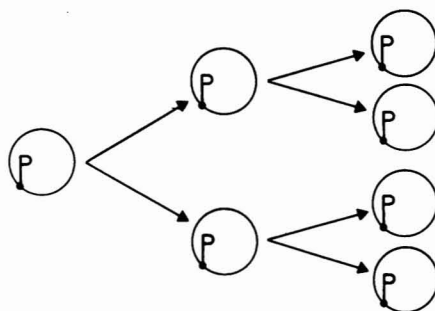
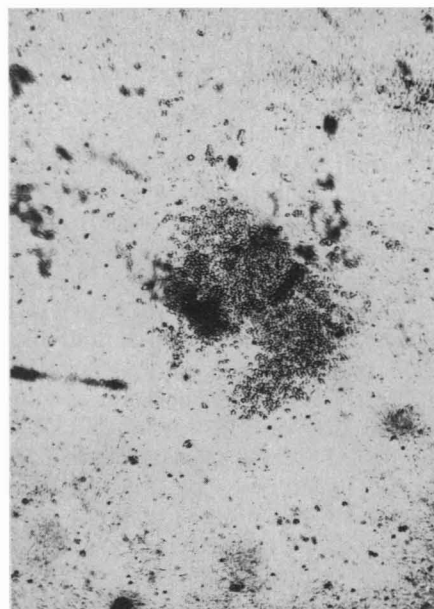


Fig. 1 (left). Focus induced by Rous sarcoma virus in chicken cells. A sparse monolayer of chicken embryo fibroblasts was exposed to Bryan standard Rous sarcoma virus. The cells were overlaid with tissue culture medium and incubated at 38°C for 10 days. This photograph of a single focus was taken with an inverted microscope at a magnification of $\times 25$. Fig. 2 (right). The provirus hypothesis. Virus information (P) is contained in infected cells in one or two copies of a regularly inherited structure with the information for progeny virus and for cell morphology.

two different viruses infecting one cell were stably inherited, and that the intracellular viral genomes were probably located at only one or two sites in the cell genome.

These observations led to the provirus hypothesis (Fig. 2)—infection of chicken cells by RSV leads to the formation of one or two copies of a regularly inherited structure with the information for progeny virus and for cell morphology. [Svoboda *et al.* (19) from studies of RSV-infected rat cells independently postulated the existence of a provirus in RSV-infected cells.] The provirus hypothesis was a genetic hypothesis and contained no implications about the molecular nature of the provirus. However, the regular inheritance of the provirus led me to postulate that the provirus was integrated with the cell genome.

The provirus hypothesis was further supported by the behavior of converted

RSV-infected chicken cells that were not producing infectious virus (20). [Analysis of similar cells by others led to the concept of defectiveness of some strongly transforming RNA tumor viruses (21).]

DNA Provirus Hypothesis

At the time of my formulation of the provirus hypothesis in 1960, the general rules for information transfer in living systems were being clearly established in what was called "the central dogma of molecular biology," that is, genetic information is transferred from DNA to RNA to protein. RNA viruses were an apparent exception to this "dogma." Studies with the newly discovered RNA bacteriophage and with animal RNA viruses, especially with the antibiotic actinomycin D, indicated that RNA viruses

transferred their information from RNA to RNA and from RNA to protein and that DNA was not directly involved in the replication of these RNA viruses (22).

Although I was unable to reconcile the regular inheritance of the provirus with its being RNA, I still tried in 1962, after I had arrived at the University of Wisconsin-Madison, to use actinomycin D to isolate the provirus of Rous sarcoma virus, just as David Baltimore and others were using actinomycin to study the intermediates in the replication of other animal RNA viruses (23).

However, when actinomycin D was added to Rous sarcoma virus-producing cells, it inhibited virus production (Fig. 3). Control experiments demonstrated that this inhibition was neither of early events in infection, as was found by Barry, Ives, and Cruickshank (24) with influenza virus, nor of the ability of the treated cells to support replication of other animal RNA viruses. These results indicated to me that the provirus was DNA.

I carried out further experiments that indicated that new DNA synthesis was required for RSV infection and that new RSV-specific DNA was found in infected chicken cells (25).

On the basis of the results of these experiments, I proposed the DNA provirus hypothesis at a meeting in the spring of 1964 (26)—the RNA of infecting RSV acts as a template for the synthesis of viral DNA, the provirus, which acts as a template for the synthesis of progeny RSV RNA (Fig. 4). At this meeting and for the next 6 years this hypothesis was essentially ignored.

My co-workers and I tried in 1964 and 1965 to obtain direct molecular evidence for the DNA provirus by looking for RNA-directed DNA polymerase activity in cells soon after infection, for infectious DNA in infected cells, and for better systems of nucleic acid hybridization. These initial efforts were unsuccessful (27).

I then developed systems with better controlled cells to study RSV infection—at first, synchronized cells, and later, stationary cells (28). Experiments with these cells indicated that a normal replicative cell cycle was needed for initiation of RSV production.

With this knowledge, I performed experiments that demonstrated more clearly a requirement for new non-S phase DNA synthesis for RSV infection (29), and I demonstrated that this new DNA synthesis was virus-specific (30). Finally, using infection of stationary cells, we demonstrated that the newly

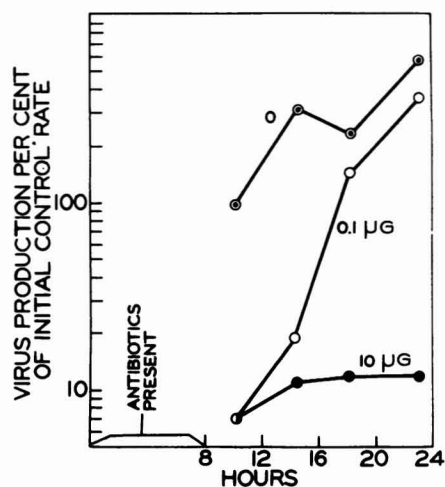


Fig. 3 (left). Effects of actinomycin D on the production of Rous sarcoma virus. Chicken cells producing RSV were exposed to 0, 0.1, or 10 μg of actinomycin D per milliliter. After 8 hours, the medium was removed, the cells were washed, and fresh medium was added. At the indicated times, the medium was harvested and assayed for focus forming units of RSV [from Temin (65)]. Fig. 4 (right). The DNA provirus hypothesis.

synthesized viral DNA could be labeled with 5-bromodeoxyuridine and inactivated by light (Fig. 5) (31). However, our attempts at this time to isolate the bromodeoxyuridine-labeled viral DNA were unsuccessful (32).

RSV Virion DNA Polymerase

In 1969 Satoshi Mizutani came to my laboratory. He demonstrated that no new protein synthesis was required for the synthesis of viral DNA during RSV infection of stationary chicken cells [quoted in (33)], and, therefore, that the DNA polymerase that synthesized viral DNA existed before the infection of the chicken cells. This work was never published completely for, in December 1969, we decided that the experiments indicated that RSV virions contain a DNA polymerase, and we decided to look for the virion polymerase first.

There were precedents for virion polymerases. In 1967 Kates and McAuslan and Munyon, Paoletti, and Grace (34) had found a DNA-directed RNA polymerase in poxvirus virions, and in 1968 Borsa and Graham, and Shatkin and Sipe (35) had found an RNA-directed RNA polymerase in virions of reovirus. [The conclusion that RSV virions contained a DNA polymerase could have been deduced in 1967 or 1968 from the DNA provirus hypothesis and the existence of these virion polymerases, but it was not [but see Baltimore (36)].

RSV virions contain an endogenous DNA polymerase activity with the following characteristics (Fig. 6). The virion polymerase activity incorporates deoxyribonucleoside monophosphates into DNA and requires all four deoxyribonucleoside triphosphates, a divalent cation, and a detergent to disrupt the virion envelope. Furthermore, the polymerase activity is inactivated by heat, which denatures the polymerase, and by ribonuclease, which destroys the template, and it is partially resistant to actinomycin D. [All but one of these characteristics, actinomycin D resistance (37), were presented in our original paper (38), which was published together with the paper of Baltimore (39).] We call this virion enzyme activity "endogenous RNA-directed DNA polymerase activity."

The avian RNA tumor virus DNA polymerases are stable and easy to solubilize and study (40). Numerous workers have purified these enzymes, especially from avian myeloblastosis virus, and this DNA polymerase has become a standard reagent for molecular biologists. It is especially useful because it has no deoxy-

ribonuclease activity, but it does have ribonuclease H activity. (Ribonuclease H activity degrades the RNA strand of an RNA-DNA hybrid molecule, but not single-stranded RNA.)

Establishment of the DNA Provirus

Hypothesis

Although the discovery of the RSV virion DNA polymerase immediately provided convincing evidence for the DNA provirus hypothesis, actual proof of the existence of a DNA provirus depended upon later work involving nucleic acid hybridization and infectious DNA experiments.

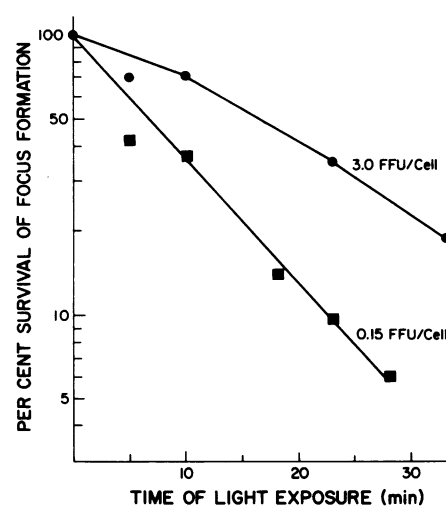


Fig. 5 (left). Light inactivation of focus formation by chicken cells infected with RSV in the presence of 5-bromodeoxyuridine. Stationary chicken cells were exposed to RSV at two multiplicities of infection [0.15 or 3.0 focus forming units (FFU) per cell], incubated in medium containing 5-bromodeoxyuridine, exposed to light, and plated on rat cells to determine the number of focus forming cells surviving [from Boettiger and Temin (31)].

Fig. 6 (right). Endogenous RNA-directed DNA synthesis by avian leukosis virus virions. Purified virions (2 μ g of protein) of an avian leukosis virus were incubated in a complete system (66) with the indicated additions, subtractions, or treatments prior to incubation; the incorporation of label was then measured. *TMP*, thymidine monophosphate; *dATP*, deoxyadenosine monophosphate.

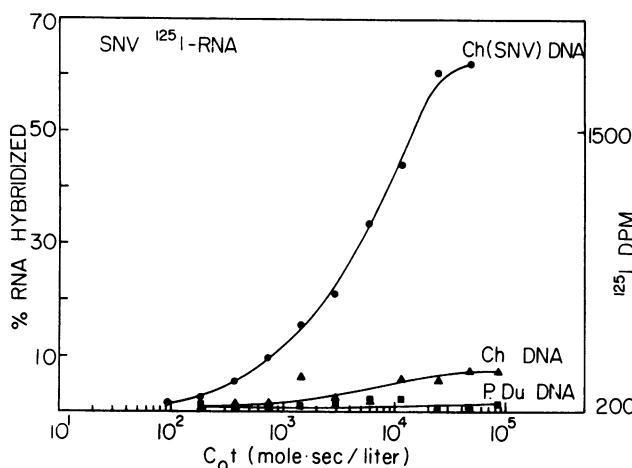
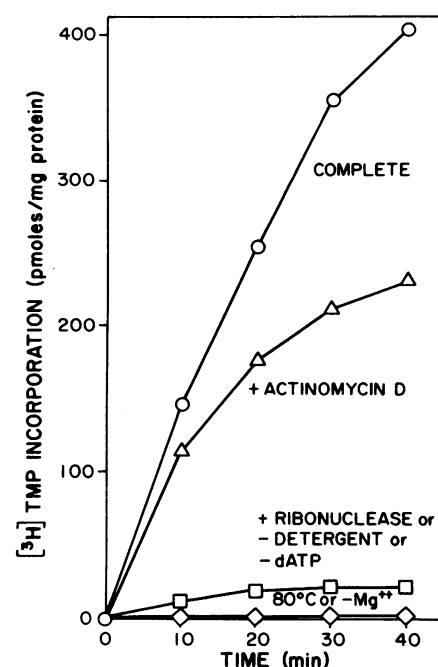


Fig. 7. Hybridization of labeled viral RNA to DNA from infected and uninfected cells. 125 I-labeled RNA from spleen necrosis virus (SNV) was incubated for different times with a large excess of DNA from uninfected chicken (Ch) or Peking duck (*P. Du*) cells or from spleen necrosis virus-infected chicken [Ch(SNV)] cells, and the percentage of RNA that was ribonuclease-resistant was determined (56). DPM, disintegrations per minute.

RSV. We, as well as others, have repeated and extended their work, making it more quantitative (Table 1). Rous sarcoma virus-infected cells, but not uninfected cells, contain a nucleic acid with the information for RSV (the provirus). This information is contained in DNA as shown by its inactivation by deoxyribonuclease, its resistance to alkali, ribonuclease, and Pronase, and its density in equilibrium cesium chloride density gradient centrifugation. A single molecule of about 6×10^6 daltons of double-stranded DNA is sufficient to cause infection, and the efficiency of infection is similar to that of the DNA isolated from animal small DNA viruses (44).

Knowledge of Mechanism of Formation of DNA Provirus to November 1975

The existence of a DNA provirus for RSV has been established. In addition, some knowledge has been gained of the details of the molecular mechanisms for the formation of the RSV provirus. Especially notable has been the work of Bishop and Varmus and their colleagues at

the University of California-San Francisco Medical School (45).

After infection of susceptible cells by RSV, the virion DNA polymerase synthesizes a DNA copy of the viral RNA, probably using a cellular transfer RNA molecule associated with the viral RNA as a primer for the DNA synthesis. After the formation of the RNA-DNA hybrid molecule, there is synthesis of a second strand of DNA, perhaps after degradation of the viral RNA by the ribonuclease H activity of the virion DNA polymerase. Double-stranded closed circular viral DNA appears. Viral DNA becomes integrated with host DNA. However, neither the mechanism for integration nor whether virion-associated enzymes (46) are involved in integration is known.

We have been studying the formation of the provirus of spleen necrosis virus (SNV), a cytopathic member of a species of avian ribodeoxyviruses distinct from the avian leukosis viruses like RSV. Some interesting contrasts, as well as similarities, have been found.

Instead of using only a preformed primer for DNA synthesis, spleen necrosis virus may at times synthesize an

RNA primer de novo (47). The virions of SNV have RNA polymerase activity as well as DNA polymerase activity (48) (Fig. 8). This RNA polymerase activity can initiate synthesis of new RNA chains, and its product RNA, a small molecule, is hydrogen-bonded to viral RNA. Thus, SNV virions have both DNA polymerase and RNA polymerase activities—the only virions so far reported with both of these activities.

We have also studied the kinetics of formation of infectious SNV DNA (49) (Fig. 9). After infection of chicken cells by SNV, infectious viral DNA first appeared in an unintegrated form, found in the supernatant of a Hirt extract (50). Then it appeared in an integrated form, found in the pellet of a Hirt extract. Surprisingly there were large further increases in the amounts of both unintegrated and integrated viral DNA's, and some unintegrated viral DNA persisted for more than a week after infection. In contrast to these results with dividing cells, little infectious viral DNA was formed in stationary cells exposed to SNV. This result indicates that a normal replicative cell cycle is required for formation of infectious viral DNA [also see (51)].

The forms of unintegrated infectious viral DNA were analyzed by agarose gel electrophoresis (Fig. 10). Three forms were found, reminiscent of the three forms of DNA in papovavirus virions (52). The majority of the infectious DNA was in linear molecules, but there were minor components of closed circular and nicked circular infectious SNV DNA.

Thus, the early events in ribodeoxyvirus infection are complex, and much remains to be learned before we can describe the formation of the provirus in molecular detail.

Origin of Ribodeoxyviruses

Avian RNA tumor viruses undergo a great amount of genetic variation (53, 54). This variation is the result of both mutation and recombination. Recombination takes place not only between viruses, but also between viruses and cells.

The recombination between viruses and cells does not appear to be random, but is primarily with specific cellular genes. These genes are called endogenous ribodeoxyvirus-related genes and are, of course, part of the normal cellular DNA.

Endogenous avian leukosis virus-related genes were first recognized about

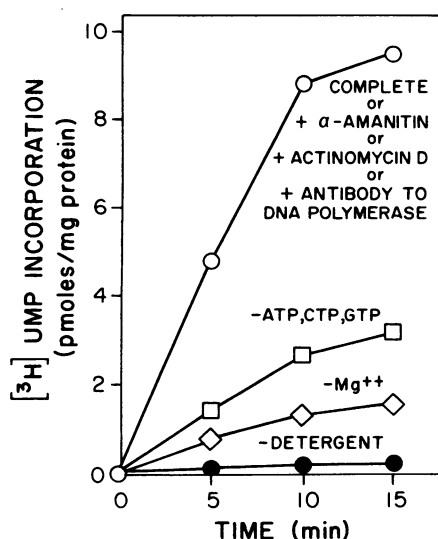


Fig. 8 (left). Endogenous RNA synthesis by reticuloendotheliosis virus virions. Purified virions ($2 \mu\text{g}$ of protein) of SNV were incubated in a complete system with the indicated additions, subtractions, or treatments prior to incubation, and the incorporation of label was measured [from Mizutani and Temin (48)]. ATP, adenosine triphosphate; CTP, cytidine triphosphate; GTP, guanosine triphosphate; UTP, uridine triphosphate.

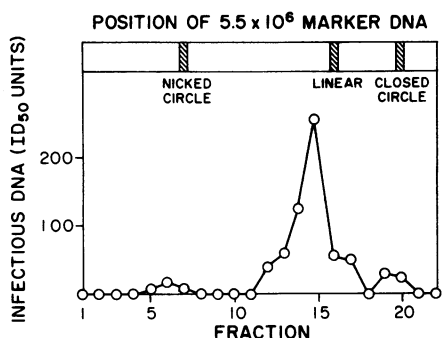
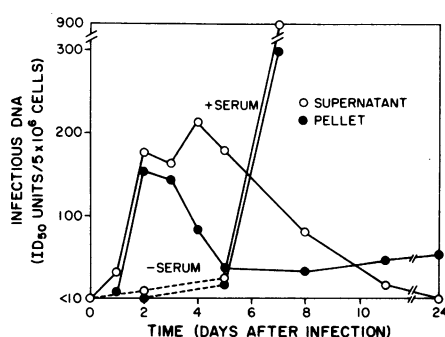


Fig. 9 (top right). Kinetics of formation of infectious DNA in SNV-infected multiplying and stationary chicken cells. Chicken cells were exposed to SNV at a multiplicity of infection of five plaque forming units per cell, and medium with or without serum was added. At different times, the cells were fractionated by Hirt extraction (50), and the DNA's in the supernatant and pellet fractions were assayed for infectivity [from Fritsch and Temin (49)]. Fig. 10 (bottom right). Electrophoresis of unintegrated infectious SNV DNA. The supernatant fraction from Hirt extraction of cells 65 hours after infection by SNV was subjected to electrophoresis in 0.7 percent agarose gels in the presence of ethidium bromide with DNA from plasmid RSF 1010 as a marker. The positions of the marker DNA's were established visually, and each fraction was assayed for infectivity [from Fritsch and Temin (49)].

10 years ago by the presence and Mendelian inheritance of a Rous sarcoma virus virion antigen in some uninfected chicken cells (55). Later an avian leukosis virus virion envelope protein was found in some uninfected chicken cells, and, finally, nucleotide sequences of avian leukosis virus RNA were found in the DNA of all uninfected chicken cells (52, 54). (Similar results have been found with mammalian leukemia viruses and cells.)

Study of the phylogenetic distribution of the endogenous avian leukosis virus-related nucleotide sequences revealed (Table 2) a relationship between the amount of these sequences in cell DNA from a particular species of bird and the closeness of the relationship of that species to chickens; for example, more avian leukosis virus nucleotide sequences were found in pheasant DNA than in duck DNA (56, 57).

This distribution is consistent with a hypothesis (the provirus hypothesis) that I originally proposed in 1970 to explain the origin of ribodeoxyviruses—ribodeoxyviruses evolved from normal cellular components (58). The normal cellular components are the endogenous ribodeoxyvirus-related genes. These genes are involved in normal DNA to RNA to DNA information transfer. This normal process of information transfer in cells could not exist only for its ability to give rise to viruses. It must exist as a result of its role in normal cellular processes, for example, cell differentiation, antibody formation, and memory (59).

One prediction of this provirus hypothesis is that there are relationships between ribodeoxyvirus and cell DNA polymerases. We have demonstrated such

Table 1. Infectious Rous sarcoma virus DNA. DNA was isolated from RSV-infected chicken or rat cells, treated as indicated, and assayed for infectivity in chicken fibroblasts. Infectivity is presented as the amount of DNA required to infect half of the assay cultures [from Cooper and Temin (44)]. The lower the amount of DNA required for infection, the more infectious the DNA was. ID₅₀, infectious dose, 50 percent effective.

DNA	ID ₅₀ (μg)
RSV-infected chicken cell	0.1
RSV-infected chicken cell, deoxyribonuclease	> 10
RSV-infected chicken cell, alkali	1.0
RSV-infected chicken cell, ribonuclease	0.1
RSV-infected chicken cell, Pronase	0.1
RSV-infected chicken cell, cesium chloride density gradient centrifugation	0.1
RSV-infected rat cell	0.1

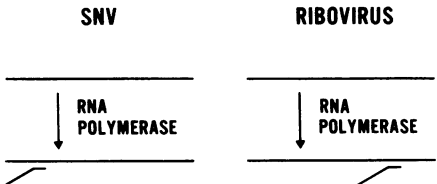


Fig. 11 (left). Initial RNA synthesis by SNV and by other RNA viruses. Fig. 12 (top right). The provirus hypothesis for the origin of the genes for cancer. The heavy lines indicate DNA involved in information transfer of DNA to RNA to DNA. Fig. 13 (bottom right). A hypothesis for the origin of Rous sarcoma virus (RSV). A straight line represents RNA, and a zigzag line represents DNA; ALV is avian leukosis virus.

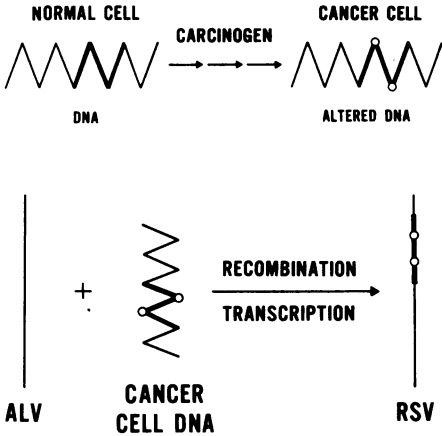
relationships by an antibody blocking test (60). In this test, for example, the activity of an antibody against avian leukosis virus DNA polymerases was blocked by incubation with chicken cell DNA polymerases or a DNA polymerase from an otherwise unrelated avian ribodeoxyvirus.

Therefore, certain predictions of the provirus hypothesis for the origin of ribodeoxyviruses have been verified. But, obviously, much further work must be done to establish or disprove this hypothesis.

Further Implications of These Studies

The provirus hypothesis can explain the origin of ribodeoxyviruses, but it does not help in understanding the origin of other animal viruses. The presence of an RNA polymerase activity in virions of SNV might, however, present a clue to the origin of other animal enveloped RNA viruses. As Baltimore has described, many animal enveloped RNA viruses contain an RNA polymerase activity (36). If there were genetic changes so that the SNV RNA polymerase activity synthesized a complete copy of SNV RNA rather than only a small molecule, the first step in the synthesis of a viral RNA intermediate would occur (Fig. 11). Further genetic changes leading to copying of the newly synthesized RNA strand could complete the replication of the viral RNA. Therefore, I propose that other animal enveloped RNA viruses evolved from ribodeoxyviruses. [The recent reports of DNA intermediates in carrier cultures of some animal enveloped RNA viruses (61) could indicate a vestige of the origin of these viruses from ribodeoxyviruses.]

Animal small deoxyviruses might also have originated from ribodeoxyviruses. As was discussed above, the unin-



tegrated infectious DNA in SNV-infected cells exists in several forms, and the amount of the unintegrated DNA increases for several days after infection. This unintegrated ribodeoxyvirus DNA could represent a precursor of animal small DNA viruses. Continued replication of unintegrated viral DNA and encapsidation in viral proteins would also be required. Therefore, I propose that animal small DNA viruses also evolved from ribodeoxyviruses.

In most of this discussion of virus replication and virus origins, I have not mentioned cancer. In fact, the absence of such discussion makes an important point: RNA tumor virus replication is not sufficient for cancer formation by RNA tumor viruses. Strongly transforming RNA tumor viruses like RSV cause cancer by introducing genes for cancer into cells. But there are viruses that replicate in much the same way as RSV, for example, SNV or Rous-associated virus-O, that do not cause cancer

Table 2. Endogenous avian ribodeoxyvirus-related nucleotide sequences in avian cell DNA's. ¹²⁵I-Labeled RNA's of Rous-associated virus-O, an avian leukosis virus, and of spleen necrosis virus, a reticuloendotheliosis virus, were incubated with an excess of DNA from uninfected cells as described in the legend of Fig. 7. The maximum amounts of hybridization from curves like those in Fig. 7 are listed [from Kang and Temin (56)]. In contrast to RAV-O RNA, SNV RNA hybridized equally to DNA of all the gallinaceous birds. This difference reflects the horizontal transmission of SNV and the vertical transmission of RAV-O.

DNA				
Chick-en	Phea-sant	Quail	Turkey	Duck
RAV-O				
55	20	15	10	< 1
SNV				
10	10	10	10	< 2

because they do not contain genes for cancer (62).

In addition, the majority of human cancers are not caused primarily by infectious viruses like RSV (63), but by other types of carcinogens, for example, the chemicals in cigarette smoke (64). These nonviral carcinogens probably act to mutate a special target in the cell DNA to genes for cancer.

To relate this hypothesis to the existence of animal RNA viruses like RSV, which do cause cancer efficiently, I have suggested that the targets for the nonviral carcinogens are the genes involved in information transfer from DNA to RNA to DNA (Fig. 12) (62, 63). Under this hypothesis, genes for cancer would be formed in a process involving RNA-directed DNA synthesis in both RNA virus-induced and nonvirus carcinogen-induced cancers.

Finally, to end this lecture where it began with Peyton Rous and RSV, we can speculate on the origin of RSV. As I quoted at the beginning of my lecture, Rous noted a change with transplantation in the behavior of the chicken tumor. This change, I propose, was the result of the formation of RSV, that is, the Rous sarcoma appeared before the Rous sarcoma virus. More specifically, other events not involving a virus led to the formation of genes for cancer and the chicken sarcoma. This sarcoma was infected by an avian leukosis virus, and RSV was formed by a rare recombination (Fig. 13).

Summary

I have discussed the observations and experiments that led to the formulation and establishment of the provirus hypothesis and the DNA provirus hypothesis, which includes RNA-directed DNA synthesis for the formation of the provirus.

I have also discussed some aspects of the present status of our knowledge of the mechanism of formation of the DNA provirus both to point out the work remaining to be done and to illustrate hypotheses for the origins of ribodeoxyviruses and the origins of other animal enveloped RNA viruses and of animal small DNA viruses.

Finally, I have indicated that I do not

believe that infectious viruses cause most human cancers, but I do believe that viruses provide models of the processes involved in the etiology of human cancer.

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