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Publication Date
1971-04-01

Submitted to Nature New Biology

UCRL-20673
Preprint

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April 1971

AEC Contract No. W-7405-eng-48

LAWRENCE RADIATION LABORATORY
UNIVERSITY of CALIFORNIA BERKELEY

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ORIGIN OF VIRUSES IN THE BIOSPHERE

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Origin of Viruses in the Biosphere

Recent results in cancer virology make it possible to propose a general process whereby viruses enter into the biosphere. From the beginning of the study of the role of viruses in cancer, the phenomenon of latency was noted, and it was observed that these viruses were apparently transmitted through progeny (vertically) but were difficult to transmit between individuals (horizontally) (1). In the past two years two unifying theories of carcinogenesis have appeared, one of Huebner (2) and another of Temin (3). The first of these considers that the genetic information for the production of C-type RNA viruses is present as a normal, but largely repressed, component in the genome of vertebrate cells. The expression of the viral genome (oncogene) is throught to be initiated by a stress which can be external (radiation, mutagens, carcinogens) or internal (aging). The stress acts to derepress the potential of the gene to produce a virus. Temin's theory proposes the information for virus production (the "protovirus") arises de novo in the host cell.

Independently, many years ago, Yamafuji in a series of papers starting in 1943 proposed that viruses originate de novo from host cell DNA (4). He succeeded in inducing formation of polyhedrosis virus in silkworms by means of various mutagenic agents and rejected the conventional explanation that his results were due to activation of a latent virus. He investigated the relation between viral nucleic acid and the nucleic acid of the host worms and concluded that a certain fraction of the host DNA (the "previrus") produced the virus when that fraction was

liberated from the rest of the genome. He was able to observe hybridization of the polyhedral DNA and the viral DNA.

In considering the historical origin of viruses, Luria (5) concluded that they originated as a result of regressive evolution of parts of the cell.

It is important to notice the common denominator of all these theories: the transformation of normal cell constituents into viruses. While the Huebner theory is in terms of genomes, the Temin and Yamafuji theories essentially molecular, and the Luria theory evolutionary, they all agree on this point. The introduction of disorder into the cell nucleus causes the DNA to be expressed in a manner unrelated to the needs of the cell (Fig. 1).

A general means by which viruses might originate in the biosphere is indicated. We suggest that the kind of virus-producing events occurring rapidly in carcinogenesis may have happened repeatedly, though usually very slowly (over many generations) in many lines of descent in the biosphere. Just as ontogney recapitulates phylogeny in the embryonic phase of life, we suggest that a kind of recapitulation also occurs within cells and organs in the degenerative (aging, diseased) phase of life. That is, viruses, both infective and non-infective, may originate directly from the genetic substances of host cells through a kind of regressive evolution within one organism. In fact, episodes of endogenous virus production may be a major means by which new disease-causing agents have been introduced rapidly and repeatedly into the biosphere in the past. Such agents may of course undergo evolutionary change after their

initial input into the biosphere from host genomes. Therefore, the present array of viruses in the biosphere which exhibits a great diversity of host specificity, infectivity, and disease-causing ability would be due to the combined effects of de novo origin and subsequent evolution.

If viruses result from degenerative processes in cells, then several consequences follow. a) All types of cells should contain viruses. Indeed, this is the case. All groups of organisms including Mycoplasma contain viruses (6). b) Since degenerative processes occur in all cells, the production of ciruses should be regarded as a normal process which is intensified in the case of disease. There is evidence that this is the case. Reports of virus-like particles issuing from normal cells are abundant in the literature (7). Even C-type particles have been observed in normal cells (8). c) As the degenerative process proceeds further, larger DNA fragments would be liberated, since more of the host is losing its integrity. Therefore we would expect a wide spectrum of virus dimensions which is indeed the case. d) The conditions for virus formation should increase with aging. Price has observed age-associated changes in the DNA of mouse tissue and interpreted these changes as an accumulation of DNA strand breaks with increasing age (9). He was able to duplicate these changes by x-irradiation (a carcinogenic agent). These results support Yamafuji's conclusions on the de novo origin of viruses since his model requires breaks in the host DNA. e) Infectivity. Since most of the genome is held in common by all members of a given species, we can expect that liberated or derepressed DNA strands will consist largely of material common to the species.

The closer the viral proteins are to proteins originally present in the host cell, the more likely the virus will be able to enter into cells of another member of the species without inducing antibodies against it. Very small viruses (of low nucleic acid content) of de novo origin would contain a smaller proportion of proteins normally present in cells. Therefore, since these viruses would contain a higher proportion of proteins experienced as foreign by the cell, we can predict that small viruses of de novo origin will be less infective than larger viruses. This is indeed the case because a classification of viruses by the parameter of nucleic acid content shows that the smallest viruses are even unable to replicate by themselves (the satellite viruses) unless the cell is infected with a helper virus (10).

Since viruses, according to this theory, would be a natural product of the degenerative phase of life, we expect that cells would have evolved some means of slowing down the process of virus formation. There is evidence that such mechanisms exist. a) Interferon. The proposed theory would explain the lack of interferon production during the early phases of life. During early embryonic life, we expect that there is very little degeneration of nucleic acids, hence there would not be need of a scavenging agent for broken strands of genetic material, and the cell does not produce interferon. Interferon appears to be produced as a response to the presence of foreign nucleic acid (11). Since broken strands of genetic material would have sort of a semi-autonomous identity, they would be expeienced as foreign nucleic acid to the cell, therefore the need for interferon. b) DNA repair mechanisms. It is known that radiation can induce leukemic viruses which are immunologically identical to those isolated from spontaneous mouse leukemia (12). The

connection between radiation-induced carcinogenesis and defective repair of DNA is shown by the work of Cleaver (13), who worked with skin cells from xeroderma pigmentosum patients. These cells have DNA mechanisms which are very much reduced or absent, and this property appears to be related to the rapid induction of skin cancer in these cases. However, the link between defective DNA repair and the appearance of viruses remains to be shown. In this connection, it is of great interest that the induction of temperate phage is photoreversible (14). If the phage has its origin in a degradation product of the bacterial genome, then the photoreversibility indicates a type of DNA repair mechanism for the host cell.

In summary, we propose that viruses are both products of degenerative processes, as well as causes of degeneration (in infected cells). The origin of viruses is then directly related to those factors which tend to maintain or disrupt hierarchial harmony of the cell.

We gratefully acknowledge helpful discussion with Dr. Eggehard Holler. This work was supported by the National Research Council (Canada) and, in part, by the U. S. Atomic Energy Commission.

References

1. Gross, L., Oncogenic Viruses (Pergamon Press, Oxford, 1970), Chap. 1, p. 23.
2. Huebner, R. J., and Todaro, G. J., Proc. Nat. Acad. Sci. 64, 1087 (1969).
3. Temin, H., Perspect. Biol. Med. 14, 11 (1970); J. Nat. Canc. Inst. 46, No. 2, iii (1971).
4. Yamafuji, K., Enzymologia 35, 131 (1968); Nature 210, 1158 (1966).

5. Luria, S., and Darnell, J., General Virology (Wiley, New York, 1967), Chap. 19.

6. Gourlay, R. N., Bruce, J., and Garwes, D. J., Nature New Biology 229, 118 (1971).

7. Mussay, M., Reczko, E., and Ahl, R., J. gen. Virol. 4, 445 (1969); Kindig, D. A., and Kirsten, W. H., Science 155, 1543 (1967).

8. Tietz, Y., Lennett, E. H., Oshiro, L. S., and Cremer, N. E., J. Nat. Canc. Inst. 46, 11 (1971).

9. Price, G. B., Modak, S. P., Makinodan, T., Science 171, 917 (1971).

10. Almeida, J. D., and Waterson, A. P., Arch. Gesamte Virusforsch. 32, 66 (1970).

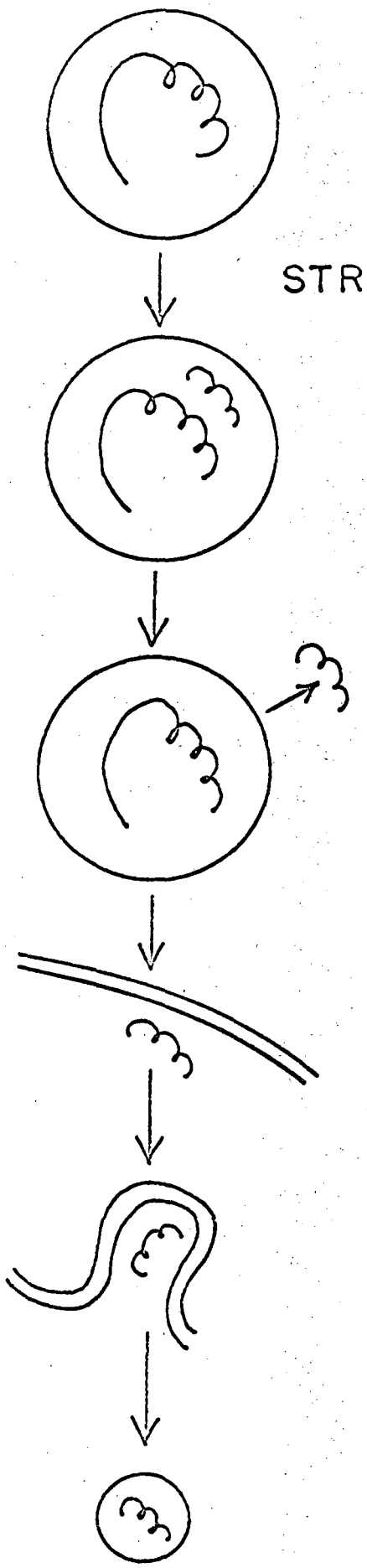
11. Levy, H. B., Baron, S., and Buckler, C. E., in The Biochemistry of Viruses, H. B. Levy, ed. (Dekker, New York, 1969), Chap. 12, p. 579.

12. Kaplan, H. S., Cancer Research 27, 1325 (1967).

13. Cleaver, J. E., Nature 218, 652 (1968).

14. Hanawalt, P. C., in Photophysiology, A. C. Giese, ed. (Academic Press, New York, 1968), p. 203.

Fig. 1. Schematic diagram showing how disordered DNA produces products which are out of harmony with the normal cell functioning. These products are experienced as foreign by the cell and are the start of an independent existence.



NORMAL CELL NUCLEUS

STRESS —

Resulting in strand breakage or derepression. The new DNA is autonomous, and produces proteins for itself.

Some of the resulting products are then experienced as foreign by the cell, and act as antigens. The new fragment is expelled from the nucleus into the cytoplasm.

It is forced to the cell membrane, where it leaves by a type of reverse pinocytosis.

MATURE VIRUS

XBL 714-5110

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