DNA TUMOR VIRUSES

MOLECULAR BIOLOGY OF TUMOR VIRUSES

SECOND EDITION

Revised

DNA TUMOR VIRUSES

Edited by
John Tooze
European Molecular Biology Organization

Cold Spring Harbor Laboratory

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Part 2 / Revised

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CONTRIBUTORS

N. H. Acheson *Swiss Institute for Cancer Research*
T. R. Broker *Cold Spring Harbor Laboratory*
S. J. Flint *Princeton University*
B. E. Griffin *Imperial Cancer Research Fund*
T. Grodzicker *Cold Spring Harbor Laboratory*
N. Hopkins *Massachusetts Institute of Technology*
D. Lane *Cold Spring Harbor Laboratory*
B. Padgett *University of Wisconsin*
R. Pollack *Columbia University*
B. Roizman *University of Chicago*
P. G. Spear *University of Chicago*
P. Tegtmeyer *State University of New York, Stony Brook*
W. C. Topp *Cold Spring Harbor Laboratory*
H. zur Hausen *Albert-Ludwigs Universität*

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Preface

In 1970, when the first typescript of *The Molecular Biology of Tumour Viruses* was completed, an attempt to produce a comprehensive and reasonably detailed account of the DNA and RNA tumor viruses and their interactions with their cellular hosts, which could be published in a single book of manageable proportions, was feasible. By early 1973, when the final draft was ready for the printer, its length had increased considerably but not immoderately. The book proved to be timely and useful and in 1975 we began to think seriously about the possibility of producing a revised edition. It quickly became apparent that if a revised edition were to be produced, it could not be published between two covers; and an early decision was taken to separate the book into three volumes: one dealing with transformed animal cells in culture, one with the DNA viruses, and one with the RNA viruses. Perhaps in one sense this was an admission of defeat; none of us felt able to survey the whole field of tumor virology with the authority and critical perception necessary to produce a single comprehensive book to satisfy those who had used its predecessor. The apparent alternatives were a more general text and a more detailed treatise, but in reality, only the latter was feasible.

The inevitable decision to publish three specialized parts, each about the length of the original book but with, we anticipate, a lower circulation, has had one economic consequence as regrettable as it was inescapable. The price has risen, but I wish to dispel any illusions to the contrary: no one involved receives a royalty or personal financial reward. Those who have contributed to this book and to the two others to follow (the book on RNA tumor

viruses will be edited by Robin Weiss and Natalie Teich) have done so for the good of the science and because they believed the venture intrinsically worthwhile.

Groups of individuals willing to contribute sections or chapters to each of the three planned volumes began their work in 1975 and 1976, but a problem that had arisen in 1972-1973 soon became acutely embarrassing. For each volume some chapters arrived punctually, but others failed to materialize as deadline succeeded deadline. Those who had already written watched what they had done become obsolete and with justification felt most frustrated with the whole business. By 1977 it was clear that the three books would not be ready for simultaneous publication, and our efforts concentrated on the one dealing with the DNA tumor viruses for two very good reasons. One was that we had most of the chapters at least in first draft; the other was Joe Sambrook. Joe cajoled reluctant contributors, corrected or rewrote drafts, wrote many missing sections, and then at the end of the day, for reasons that I can understand but do not share, has absolutely refused to have his name appear as coeditor, which is where it ought to be.

As with the first edition, we have used unpublished information where we knew of it. In one particular instance, this policy has greatly enhanced the value of the book. In November 1978, we learned that A. R. Buchman, L. Burnett and P. Berg had gathered into a computer all the published information about the nucleotide sequence of SV40 DNA. This included, of course, the complete sequences obtained by the groups of Fiers and Weissman, the positions of deletion mutations, the sequences of physiologically important segments, and so on, from many sources. Buchman and Burnett had not only collated all this information, but had also devised a system of notation of the SV40 physical map at the nucleotide level. On hearing this news, we decided to contribute to the Stanford group's effort to reduce the existing bewilderment of nomenclatures and asked permission to use the new system. They gave their ready consent and supplied us with successive drafts of their sequence manual. In the text, an effort has been made, where appropriate, to use the map coordinates of the Stanford manual. An abbreviated version is presented in Appendix A, so that readers can for themselves identify the coordinates of any sequence that particularly interests them.

Fortunately, B. E. Griffin and her colleagues, E. Soeda, J. R. Arrand, N. Smolar, and J. Walsh, at the Imperial Cancer Research

Fund Laboratories completed their sequence analysis of polyoma virus DNA early this year, and with B. Barrel and R. Staden of the MRC Laboratory of Molecular Biology, Cambridge, they entered this into a computer in a form similar to that used by the Stanford group. An abbreviated version of their polyoma virus DNA manual is presented in Appendix B.

The nucleotide sequence of the Dunlop strain of the human papovavirus BKV was determined recently by I. Seif, G. Khoury, and R. Dhar of the National Cancer Institute, Bethesda. The nucleotide sequence and analysis that they have generously provided appear in Appendix C.

At the Cold Spring Harbor Symposium in June 1979, A. van der Eb reported the nucleotide sequence of about 14% of the left-hand end of the adenovirus-5 genome, which had been determined by his colleagues, J. Maat, C. P. van Beveren, and H. van Ormondt, at the University of Leiden. The Leiden group willingly agreed to our suggestion that this sequence information also be included, and it is presented in Appendix D. Additionally, R. Dijkema, B. M. M. Dekker, and H. van Ormondt, of the University of Leiden, have determined the nucleotide sequence of the transforming *Bgl*II H fragment of adenovirus-7 DNA. This material appears in Appendix E.

The nucleotide sequence of the transforming *Hin*dIII G fragment of adenovirus-12 DNA, which appears in Appendix F, was determined and kindly provided by H. Sugisaki, K. Sugimoto, and M. Takanami, Institute for Chemical Research, Kyoto University; K. Fujinaga, Y. Sawada, Y. Uemizu, and S. Uesugi, Cancer Research Institute, Sapporo Medical College; and H. Shimojo and K. Shiroki, Institute of Medical Science, University of Tokyo.

Very many people, in addition to the chief contributors, have helped in the production of this book, and I have the privilege of particularly thanking L. B. Chen, L. Chow, B. Clements, P. Gallimore, R. Kamen, J. McDougall, J. McNab, J. Subak-Sharpe, W. Sugden, J. D. Watson, and N. Wilkie. We are all most grateful to Nancy Ford, Chris Nolan, and Joan Ebert of the publications department of Cold Spring Harbor Laboratory for their forebearance in the face of successive revisions of what we hope will prove a useful work.

November 1979 **J. Tooze**

Preface
to Revised Second Printing

Toward the end of 1980 it became obvious that a reprinting of this book would be necessary if it was to remain in print. Reprinting gave us the opportunity to produce a paperback edition that could be more modestly priced than the hardback version. We could also try to bring parts of the book a little more up to date by adding Supplements to several of the chapters and by enlarging the appendixes to include a considerable amount of the new DNA sequence information. The Supplements are not exhaustive reviews of all that has been learned since the manuscript was first sent to the printer 18 months ago. Rather, they summarize, in a few pages, some of the more significant new findings. A number of new figures have also been added, and some of the existing ones have been modified in the light of new data. All this has added another 180 or so pages to the book, and perhaps a word about its organization would not be out of place.

To avoid the delays and costs of repaginating and reindexing the entire book, the Supplements are each independently paginated and have separate reference lists. The index, however, has been revised slightly and covers the material in the Supplements. Several of the enlarged appendixes have been entirely reset.

We had originally intended this book to be one of a set of three, the other two dealing with the RNA tumor viruses and with transformed cells. This is no longer the case. Although the companion volume on the RNA tumor viruses is very close to publication, we have decided, for a variety of compelling reasons, not to attempt to produce the projected third book dealing with

the biology of transformed cells. Of course, it is always sad when a project cannot be brought to completion, and embarrassing if it has been widely advertised, but the decision was unavoidable.

For this printing, Bob Kamen, as well as several of the original contributors, provided material for the Supplements, and it is my great pleasure to thank them and Nancy Ford and her colleagues of the Cold Spring Harbor Laboratory Publications Department for their efforts. Tom Broker took on the arduous task of coordinating the revision of the several appendixes dealing with the adenoviruses. Finally, without the contributions and friendship of Joe Sambrook, this revised edition, like its two forerunners, would, quite simply, never have been produced.

June 1981 **J. Tooze**

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Contents

1

Origins of Contemporary DNA Tumor Virus Research

THE CANCER CELL DEFINED

The evolution of unicellular organisms into multicellular organisms has demanded the emergence of very precise rules to govern both the spatial siting and the multiplication rates of their respective differentiated cells. A given specialized cell does not grow at any site in its multicellular host, but is restricted to have only certain cell types for its neighbors and to proliferate only upon receipt of a message signifying that more of its kind are needed for the orderly growth or maintenance of the complete organism. Given the existence of so many types of multicellular organisms, each with its unique patterns of differentiation, there are likely to exist many, many molecular pathways along which these signals are transmitted. Any of them in turn may fail and lead to one of the many abnormal forms of growth that collectively are called cancer.

Cancer is therefore not a unitary category, but a wide (to some, hopelessly wide) collection of different abnormal conditions, each displaying its own specific properties. In thinking about how to study cancer, most investigators quickly see the need to distinguish the property of excessive cell division from the property of abnormal cellular affinities. The quality of uncontrolled growth is what leads to the localized masses of single cell types often referred to as tumors. When these tumors grow only at the sites of origin, they do not necessarily upset the functioning of their host and frequently are called benign tumors. However, when a cell that has lost the ability to position

itself correctly begins to grow in an inappropriate region, the resulting tumor often quickly leads to disease symptoms and culminates in the eventual death of the afflicted organism. Such growths are known as malignant tumors and quite frequently are the only tumors given the name cancer.

Now there is general agreement that the loss of ability to establish normal cellular affinities reflects fundamental differences between the outer surfaces of a cancer cell and its normal counterpart. But as we shall see later, what these changes are at the molecular level remains almost a total mystery. For the time being, all our operational definitions of a cancer cell are biological, generally being some measure of its ability to grow into a tumor when injected into a suitable recipient organism.

As far as we can tell, cancer is a disease at the cellular level; it starts when a hereditary change somehow transforms a single normal cell into a cancer cell (Lindner and Gartler 1965; Fialkow et al. 1967). When the newly created cancer cell divides, both of its descendants carry the cancer property; and they in turn pass it on to their progeny. How these changes are induced is still a very murky subject, with many highly diverse external agents (e.g., certain viruses, ionizing radiations, ultraviolet light, various chemical compounds), collectively called carcinogens, all increasing the frequency of the cancerous transformation. Given the hereditary property of cancer, it has seemed simplest to believe that most carcinogens act directly by altering the genetic makeup of one or more chromosomes.

Still very debatable is the number of changes necessary to transform a normal cell into a typical cancer cell. Most likely most of the cells isolated from visible tumors are the products of more than one genetic event (Armitage and Doll 1957), and there is general agreement that the increased virulence of many advanced tumors is the result of a progressive series of changes, each of which leads to a greater degree of uncontrolled growth (Burnet 1957).

Because almost all types of differentiated cells give rise to cancer cells, the variety of different cancers, each with its own peculiar biochemical features, is much larger than we would wish to face. Hopefully, however, common features relate many types of cancers so that, in focusing on the origin of one specific

cancer, we will obtain information directly applicable to many others. That this may be so is strongly suggested by the fact that a given tumor virus is often able to transform more than one type of differentiated cell into its cancerous counterpart. For example, the polyoma virus causes tumors of both the salivary and the prostate glands of mice. This may mean that these salivary and prostate cancers, despite their very different morphological appearances, have lost control over cell division and cellular interactions through the misfunctionings of the same molecular processes.

This book is restricted to a survey of the molecular biology of those DNA viruses which either induce tumors in susceptible hosts or transform cells in culture or both. The aim of this first chapter is to introduce the viruses and briefly summarize the history of their discovery and investigation so that the reader can gain an overall impression of the subject before plunging into the considerable detail that follows. We begin with the wart or papilloma viruses because they were the first DNA tumor viruses to be discovered.

INFECTIOUS AGENTS FROM PAPILLOMAS

Warts (papillomas) are commonly found in many species of mammals. They arise by excessive proliferation of epithelial tissue, and they are usually benign growths that only rarely give rise to invasive cancers. Warts are often infectious, and the knowledge that human warts are transmitted by viruses dates to the early part of this century. The first papilloma virus to be well characterized was isolated from wild cottontail rabbits by Shope (1933) of the Rockefeller Institute. Cell-free extracts made from their warts, after passage through filters, caused new warts to appear on the skin of rabbits that had previously been free of warts. The Shope papilloma virus, as it is now usually called, is very specific, infecting only scarified rabbit skin and never causing tumors when inoculated internally.

Purification of the infectious material from the cottontail warts revealed that the virus is relatively stable and spherical in shape, with a diameter of 50 nm. It is present in very large amounts within each wart. The Shope papilloma virus became

the first tumor virus to be studied in detail at the molecular level (Beard et al. 1939); by the late 1940s the molecular weight of the virus and of the viral DNA, a single molecule of 5×10^5 daltons, had been determined (Beard 1948).

Absence of Viral Particles from Proliferating Tissue

Early in his work with this virus, Shope made the then puzzling observation that no infectious viral particles could be recovered from the warts that appeared on inoculated domestic rabbits. Only after infection of wild cottontail rabbits did the resulting warts produce viral particles in significant numbers (Shope 1933; Shope and Hurst 1933). Much subsequent effort went into attempting to detect the virus in warts of domestic rabbits using immunological methods. Although traces of virus-specific antigens were found in most warts, sufficient negative results occurred for people to suggest that the Shope virus might completely disappear after transforming a cell or that it might exist in a latent noninfectious proviral state (Shope 1937; Kidd and Rous 1940).

Partial clarification came first from electron microscopic studies that revealed the complete absence of mature viral particles or their precursors in the proliferating cells of the basal layer (Noyes and Mellors 1957). Multiplication of virus seemed to occur only in older cells that had become keratinized and were destined never to multiply again. Progeny viral particles assembled in the cell nuclei, which often became filled with a million or so mature particles that stuck to each other in crystalline arrays. Multiplication of the Shope papilloma virus thus quickly leads to cellular death.

Most researchers now suspect that the proliferating cells of a wart contain the Shope virus in a proviral form that is normally only converted to the mature form when its host cell starts to become keratinized. At the stage when the host cell is about to die, by a process conceivably analogous to the induction of lysogenic phage, the provirus would leave the chromosomal site and begin a lytic reproductive cycle. Given the general correctness of this scheme, it might further be supposed that the

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