CANCER 2

A COMPREHENSIVE TREATISE

ETIOLOGY: Viral Carcinogenesis

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Preface

The impact of basic research on oncology has been particularly impressive in the recent search for the cause of malignancy. Equally impressive is our appreciation of the cause of tumors based on observation. Even in the earliest era of the study of infectious diseases, it was proposed that tumorous growth in animals and birds resulted from "minute" infectious particles. Experiments then supported the hypothesis that the etiologic agent in many animal tumors was viral.

The development of molecular biology, supported by technical advances and conceptual understanding of macromolecular action, led to an explosive increase in studies of animal oncogenic viruses. For a decade, new findings emerged from research laboratories revealing the enormous variety of such agents, the complexity of their interactions with cells, and the tantalizingly possible mechanisms by which they might cause malignant transformation of the cell. Repeatedly, clues emerged which suggested the intervention of viral agents in human tumors. A breathless excitement pervaded both the scientific and public communities as highly publicized findings rapidly followed one another. The excitement was no less scientific than it was practical, for implicit in the concept of the viral oncogen is the possibility of specific virostatic or virotoxic agents or of immunization.

Yet, despite the incredible facility of our laboratories and the advances in technique as this volume goes to press, crucial questions remain unanswered: Have we created a "race" of laboratory, viral oncogens, unrelated to wild types? Are there human viral-induced tumors? If so, which are they and how many are there? By what means does the virus integrate into the apparatus of the host cell and later its normal control, resulting in malignancy? Once altered, is that cell capable of directed reversion?

This book presents progress which has been made in the search for the viral etiology of tumors and delineates the vast landscape of future research.

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RNA Viruses

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The Molecular Biology of RNA Tumor Viruses

J. MICHAEL BISHOP AND HAROLD E. VARMUS

1. Introduction

RNA tumor viruses are useful tools for the study of oncogenesis because they rapidly induce tumors in animals and efficiently transform cells in culture. These viruses are distinguished by certain morphological features (Bernhard, 1960; Sarker *et al.*, 1971*a*), an exceptionally large single-stranded RNA genome (about 30,000 nucleotides, Duesberg, 1970) and an RNA-directed DNA polymerase which transcribes the viral genome into single- and double-stranded DNA (Baltimore, 1970; Temin and Mizutani, 1970; Temin and Baltimore, 1972). This transcription, the mechanism by which it occurs, the fate of its products in the infected cell, and the role of the products in both the viral life cycle and virus-induced transformation of the host cell are the principal subjects of our discussion.

The following chapter is not a comprehensive introduction to RNA tumor viruses, but a treatise on the mechanisms which mediate the reproduction and cellular effects of these viruses. Our objective is to prepare the reader to understand the detailed discussions of specific classes of viruses in the subsequent chapters of this volume. We have identified and discussed aspects of viral structure and physiology which appear to be shared by most if not all RNA tumor viruses. The literature citations are not comprehensive and are designed to provide an overview of the major investigative trends in the contemporary study of the molecular biology of RNA tumor viruses.

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4 2. *Taxonomy*

J. M. BISHOP
AND
H. E. VARMUS

RNA tumor viruses are ubiquitous in nature and are associated with a large variety of neoplasms in their natural hosts (Huebner and Gilden, 1971). Consequently, these viruses have become favorite subjects for investigators who are seeking evidence that viruses are involved in the etiology of human tumors. The study of RNA tumor viruses began with the discoveries that avian leukemia (Ellerman and Bang, 1909) and sarcomas (Rous, 1911) can be transmitted horizontally by cell-free infectious agents. However, many viruses which possess both 70S RNA and RNA-directed DNA polymerase are not oncogenic. Some are cytopathic, others are symbiotic with their hosts. Virtually all such viruses, whether oncogenic or not, conform to one of two architectural forms defined by electron microscopy, *viz.*, type B and type C virus particles (Bernhard, 1960; Sarker *et al.*, 1971*a*). These two forms are distinguished by certain features of their morphological maturation and differences in their mature structure (Sarkar *et al.*, 1971*a*), but the outlines of their architectures are quite similar (Fig. 1). A third class of particle—type A—is an intracellular form which appears in two locations: (1) within the cytoplasm, where it is probably a precursor to mature type B particles (Sarkar *et al.*, 1971*a*; Tanaka *et al.*, 1972; for a dissenting opinion, see Smith and Wivel, 1973), and (2) within cisternae, where its nature and function are enigmatic (Wivel and Smith, 1971; Wivel *et al.*, 1973).

There is no universally accepted taxonomic designation for viruses with 70S RNA and RNA-directed DNA polymerase. Since many of these viruses are not oncogenic, we will use the structural designations of B- and C-type particles to denote a single taxonomic class.

For convenience, we can divide the oncogenicity of RNA tumor viruses into three general classes: induction of sarcomas (sarcoma viruses), induction of leukemias and related disorders (leukemia or leukosis viruses), and induction of carcinoma of the breast (mammary tumor viruses, rigorously identified only in mice to date). These categories are outlined here because they have useful

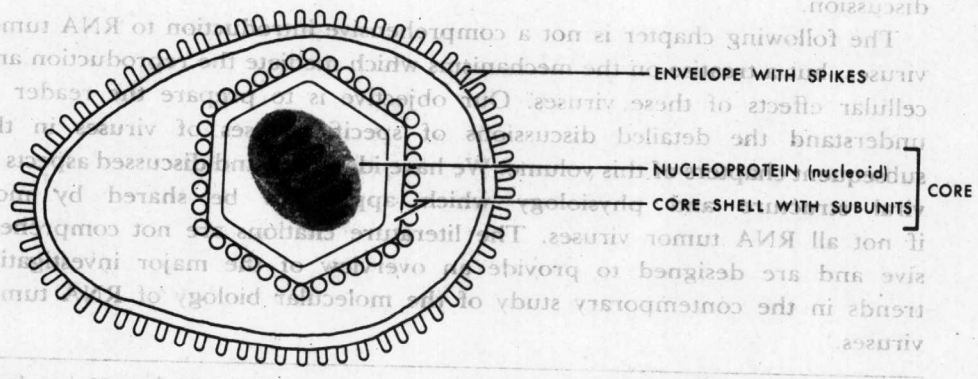

FIGURE 1. The virion of RNA tumor viruses.