Advances in
VIRUS RESEARCH

Edited by

MAX A. LAUFFER
FREDERIK B. BANG
KARL MARAMOROSCH
KENNETH M. SMITH

VOLUME 24

8

Advances in
VIRUS RESEARCH

Edited by

MAX A. LAUFFER
Andrew Mellon Professor of
Biophysics
University of Pittsburgh
Pittsburgh, Pennsylvania

FREDERIK B. BANG
Department of Pathobiology
The Johns Hopkins University
Baltimore, Maryland

KARL MARAMOROSCH
Waksman Institute
of Microbiology
Rutgers University
New Brunswick, New Jersey

KENNETH M. SMITH
Cambridge, England

VOLUME 24

1979

ACADEMIC PRESS New York San Francisco London

A Subsidiary of Harcourt Brace Jovanovich, Publishers

COPYRIGHT © 1979, BY ACADEMIC PRESS, INC.
ALL RIGHTS RESERVED.
NO PART OF THIS PUBLICATION MAY BE REPRODUCED OR TRANSMITTED IN ANY FORM OR BY ANY MEANS, ELECTRONIC OR MECHANICAL, INCLUDING PHOTOCOPY, RECORDING, OR ANY INFORMATION STORAGE AND RETRIEVAL SYSTEM, WITHOUT PERMISSION IN WRITING FROM THE PUBLISHER.

ACADEMIC PRESS, INC.
111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS, INC. (LONDON) LTD.
24/28 Oval Road, London NW1 7DX

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 53-11559

ISBN 0-12-039824-9

PRINTED IN THE UNITED STATES OF AMERICA

79 80 81 82 9 8 7 6 5 4 3 2 1

CONTENTS

Early Interactions of Viruses with Cellular Membranes

ALEXANDER KOHN

Structural Components and Replication of Arenaviruses

IB RODE PEDERSEN

Polyamines and Virus Multiplication

SEYMOUR S. COHEN AND FRANK P. MCCORMICK

此为试读,需要完整PDF请访问: www.ertongbook.com

ADVANCES IN VIRUS RESEARCH, VOLUME 24

TUMORS AND VIRUSES IN NONHUMAN PRIMATES

S. R. S. Rangan

Delta Regional Primate Research Center, Tulane University, Covington, Louisiana

and

R. E. Gallagher

Laboratory of Tumor Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

I. Introduction

The concept that viruses play a vital and, in some instances, a primary role in neoplastic diseases of vertebrates has been accepted only gradually. Several key discoveries provided the necessary impetus, most notably: the recognition, as early as 1898 by Sanarelli, that the highly contagious myxomatosis in rabbits is infectious in nature; the transmission by filtrates of the erythromyeloblastic form of chicken leukemia by Ellerman and Bang (1908); the cell-free transmission for the first time of a solid chicken sarcoma by Rous (1911); and the later dis-

Copyright © 1979 by Academic Press, Inc.
All rights of reproduction in any form reserved.
ISBN 0-12-039824-9

coveries of the rabbit fibroma and papilloma viruses by Shope (1932, 1933) and of the mouse mammary tumor agent and leukemia virus, respectively, by Bittner (1936) and Gross (1951).

Extensive and methodical studies since then have revealed a number of viruses with the capacity to induce tumors in a variety of animal species. Of these viruses, some induce tumors in the host species which they naturally infect. Examples of such naturally tumorigenic viruses include the Marek's disease virus (MDV) of chickens, Lucké's adenocarcinoma virus of frogs, leukemia and sarcoma viruses of cats, papilloma viruses of human and other animals, and Yaba virus of rhesus monkeys. Other tumorigenic viruses such as simian sarcoma virus (SiSV) from a woolly monkey, and Epstein–Barr virus (EBV) from human Burkitt's lymphoma were originally isolated from spontaneous neoplasms. Although these viruses have been shown to be oncogenic in experimental hosts, their etiological role in naturally occurring neoplasms of the species from which they were derived is yet to be conclusively established. A third group of oncogenic viruses is distinguished by differential pathogenicity in the natural and other experimental hosts. This category is typified by simian vacuolating agent (SV40) and the adenoviruses of human and other animals. SV40 induces a latent infection in rhesus monkeys; however, hamsters often develop malignant tumors following experimental inoculation with the virus. Similarly some members of the adenovirus group are oncogenic in hamsters but remain subclinical or produce acute diseases in their natural hosts.

Viruses which have the capacity to induce proliferative lesions either in the natural host or upon experimental inoculation into a foreign host have been identified in five families (Fenner, 1976), namely: *Papovaviridae, Adenoviridae, Herpetoviridae, Poxviridae,* all of which contain DNA as their genetic material, and *Retroviridae* which contain RNA. Details about the historical aspects of the tumor virology and specific characteristics of individual tumor viruses can be found in several review articles (Gross, 1970; Allen, 1972; Tooze, 1973; Rapp, 1974a,b; Ablashi and Easton, 1977).

The major objective of this chapter is to discuss the current knowledge about tumor viruses belonging to *Retroviridae* and *Herpetoviridae,* isolated from normal and malignant tissues of nonhuman primates. In addition, certain retroviruses of nonprimate origin are considered to a limited extent since they can induce experimental tumors in simian species. SV40 (Eddy, 1964) and simian adenoviruses (Hull *et al.,* 1965; Merkow and Slifkin, 1973) are not included, despite their isolation from monkeys and their ability to induce tumors in rodents since these viruses are not known to induce proliferative diseases in nonhuman primates.

Yaba and Tana poxviruses which are tumorigenic in nonhuman primates likewise are not discussed because relatively little new information has accumulated since the earlier reviews of these agents (Espana, 1971; Yohn, 1972). Table I shows many of the proven and potentially tumorigenic viruses of nonhuman primate origin.

The utilization of nonhuman primates in virus-induced tumorigenesis studies increased subsequent to the demonstration that Rous sarcoma virus (RSV) can induce tumors in rhesus monkeys (Monroe and Windle, 1963). Despite the availability of many virus-induced tumor models in common laboratory animals and despite the fact that many simian species may be either endangered or threatened of becoming extinct, the following considerations warrant the continued, judicious use of nonhuman primates in tumor-virus research related to human malignancies. (i) Due to their phylogenetic closeness, information gathered in one or more virus-induced tumor models in nonhuman primates may be directly applicable to man. (ii) Certain species of nonhuman primates (e.g., marmosets) have proven to be highly susceptible to tumor induction by viruses (e.g., SiSV, EBV) which were originally identified in spontaneous primate malignancies. By analogy, it is conceivable that possible oncogenic viruses associated with human malignancies may also be more readily recognized by studies in a simian host than in other laboratory animals. (iii) Some viruses (e.g., EBV or MPMV) may have a host range restricted to primates requiring the use of nonhuman primates for studies of pathogenesis. (iv) Finally, vaccines produced in nonhuman cell cultures may contain potentially hazardous tumorigenic viruses since many species of nonhuman primates are latent carriers of such viruses. A thorough understanding of the properties of the nonhuman primate tumor viruses would greatly aid in devising methods for their elimination from vaccines, especially those intended for human use.

II. Spontaneous Tumors in Nonhuman Primates

The occurrence of spontaneous neoplasms has been recorded (Ratcliffe, 1940; Lombard and Witte, 1959; Kent, 1960; Newberne and Robinson, 1960; Vadova and Gel'shtein, 1960; Jungherr, 1963; Lapin and Yakovleva, 1963; Ruch, 1967; O'Gara and Adamson, 1972; Seibold and Wolf, 1973) in one or more species (Napier and Napier, 1967) of all the five genera of anthropoid nonhuman primates and in two genera of prosimians. Although a few of the observed tumors were in free-ranging individuals (Maruffo, 1967) the majority of the observations have been from necropsy reports of captive animals exhibited in zoological gardens or those kept under laboratory conditions. Benign and malignant tumors

TABLE I

NONHUMAN PRIMATE VIRUSES WITH PROVEN OR POTENTIAL TUMORIGENICITY

Family	Virus designation[a]	Initial detection in species	Source of original isolation[b]	Experimental hosts susceptible to tumor development
Papovaviridae	SV-40	*Macaca mulatta* (rhesus monkey)	Kidney cultures	Rodents[d]
Adenoviridae	Several serotypes	*Macaca mulatta; C. aethiops* (African green monkey)	Kidney cultures, tissues, excreta	Rodents[e]
Herpetoviridae	HVS	*Saimiri sciureus* (squirrel monkey)	Kidney cultures,	New World primates[f], rabbits
	HVA	*Ateles geoffroyi* (spider monkey)	Kidney cultures,	New World primates[f]
	HVP	*Papio hamadryas* (baboon)	Lymphoma cell line	Marmoset[g]
	HVPan	*Pan troglodytes* (chimpanzee)	Oral secretions	Not known[h]
	HVPongo	*Pongo pygmaeus* (orangutan)	Leukemia cell line	Not known[i]
	HVM	*Macaca mulatta*	Blood leukocytes[c]	Not known[j]
Poxviridae	Yaba	*Macaca mulatta*	Subcutaneous tumors	Old World primates[k]
	Tana	*Macaca mulatta*	Skin lesions	Old World primates[l]

Retroviridae	SiSV	*Lagothrix* spp. (woolly monkey)	Fibrosarcoma	Marmoset[m]
	GaLV	*Hylobates lar* (gibbon)	Lymphosarcoma cell line	Gibbon[n],[o]
	BaEV	*Papio cynocephalus* (baboon)	Placental tissue[c]	Not known[p]
	MAC-1	*Macaca arctoides* (stumptail monkey)	Spleen culture[c]	Not known[q]
	OMC-1	*Aotus trivirgatus* (owl monkey)	Kidney cell line[c]	Not known[r]
	MPMV	*Macaca mulatta*	Breast tumor	Not known[s]
	SMRV	*Saimiri sciureus*	Lung culture[c]	Not known[t]
	PO-1-Lu	*Preslytis obscurus* (Langur)	Lung culture[c]	Not known[u]

[a] Names of viruses can be found in the text.
[b] Where not specified isolation from clinically healthy animal.
[c] Isolation by co-cultivation methods.
[d] Eddy, 1964; [e] Hull *et al.*, 1965; [f] Deinhardt *et al.*, 1974a; [g] Deinhardt *et al.*, 1978; [h] Gerber *et al.*, 1977; [i] Rasheed *et al.*, 1977; [j] Frank *et al.*, 1973; [k] Yohn, 1972; [l] Espana, 1971; [m] Wolfe *et al.*, 1971a; [n] Kawakami *et al.*, 1972; [o] Kawakami *et al.*, 1978; [p] Benveniste *et al.*, 1974b; [q] Todaro *et al.*, 1978a; [r] Todaro *et al.*, 1978c; [s] Chopra and Mason, 1970; [t] Heberling *et al.*, 1977; [u] Todaro *et al.*, 1978b.

此为试读，需要完整PDF请访问：www.ertongbook.com

have been recorded in all major anatomical sites and organ structures. Kirk (1972) surveyed the recorded neoplasms in nonhuman primates up to 1972 and compiled over 270 tumors according to the sites and species of origin. Nearly one-half of the tumors were classified as malignant. Since then several additional tumors have been reported in a number of species including macaques (Brown *et al.*, 1971, 1977a,b; Chesney and Allen, 1972, 1973; McClure, 1973; Todd *et al.*, 1973; Manning and Griesemer, 1974; Moe *et al.*, 1975; Schneider, 1975; Sly *et al.*, 1977), gibbons (Johnsen *et al.*, 1971; DePaoli *et al.*, 1973; Snyder *et al.*, 1973; Gallo *et al.*, 1978b), chimpanzees (Graham and McClure, 1977), orangutan (Rasheed *et al.*, 1977), baboons (Lapin, 1975), marmosets (Wolfe and Deinhardt, 1972; Page *et al.*, 1974), and squirrel (Anzil *et al.*, 1977; Reed and Garman, 1977) and owl monkeys (Hunt *et al.*, 1973; Brown *et al.*, 1975; Rabin *et al.*, 1975b).

The available data do not permit a meaningful estimate of the incidence rates of spontaneous neoplasms in nonhuman primates. Past estimates have had one or more biases which might obscure the true incidence rates. For example, the sample size in many of the studies was too small (Klüver and Brunschwig, 1947; Maruffo, 1967) or large numbers of relatively young animals were analyzed (Newberne and Robinson, 1960; Jungherr, 1963), a factor emphasized by O'Conor (1969). Nevertheless from the data of the eight series summarized by O'Conor, 88 (0.075%) neoplasms, 30 (0.026%) being malignant, were observed in a total of 116,120 animals. This suggests that spontaneous tumors are rare in nonhuman primates, but a true estimate awaits prospective studies involving large numbers of animals allowed to reach their natural life span.

That nonhuman primates are not in any way specifically resistant to tumor development is suggested by the reported outbreaks of malignant neoplastic diseases in several primate colonies. The occurrence of malignant lymphomas in baboons at the Sukhumi colony, Georgia, USSR, as well as the retrovirus and herpesvirus associated with these tumors (Lapin, 1975), and the high incidence of a retrovirus-associated leukemia in a colony of gibbons at the SEATO laboratories, Bangkok, Thailand (Johnsen *et al.*, 1971; DePaoli *et al.*, 1973) are discussed in detail later. An outbreak of malignant lymphoma in rhesus monkeys at the Primate Research Center, Davis, California is briefly summarized to illustrate the possible interaction of multiple factors contributing to the disease (Stowell *et al.*, 1971; Manning and Griesemer, 1974; Schneider, 1976).

During a span of about 5 years, 43 cases of malignant lymphoma were recorded in the rhesus colony with an estimated incidence rate of 1000/1,000,000 rhesus per year. The animals that developed the malig-

nant disease included imported animals as well as some that were born in the colony. All animals, except one that died at 6 months of age with a tumor, were nearly a year or more of age. Interestingly, the vast majority of diseased animals were females, leading to speculation of a hormonal-related predisposition to the disease. Although of unknown significance in the outbreak, the rhesus colony had been exposed to several potentially oncogenic factors. These included the possible presence of dibenzanthrazene in the environment, repeated exposure to X-irradiation, impaired immunological functions of animals due to experimental malarial infection or treatment with isoniazid, and a possible infection by a herpes-like virus.

III. Retroviruses of Nonhuman Primates

A. General Characteristics of Retroviruses

1. Taxonomy and Morphology

Retroviridae is a recent name assigned to a family of enveloped RNA viruses which contain an antigenically specific RNA-directed DNA polymerase (reverse transcriptase) (Dalton *et al.*, 1974b; Fenner, 1975). As summarized in Table II, six genera have so far been proposed for this virus family based, primarily, on the earlier morphological classification of Bernhard (1960; Schidlovsky, 1977). Viruses of three genera (A, B, and E) have not been reported in nonhuman primates. Viruses of a fourth genus (F), the so-called foamy viruses, have been isolated in tissue culture from numerous New and Old World primate species (Hooks and Gibbs, 1975). These viruses produce a characteristic type of cytopathic effect on monolayer culture cells. They have not been selectively associated with primate neoplasias *in vivo* nor do they have any transforming effect *in vitro*. Thus, for this chapter on nonhuman primate viruses and tumors, the retroviruses of interest belong to the oncornavirus C and oncornavirus D genera.

Although various electron microscopists have described some pleomorphism of individual viruses and minor differences in ultrastructural details of different viruses, all type-C oncornaviruses, including those of the primate subgenera, have common structural features (Dalton *et al.*, 1974a; DeHarven, 1974; Schidlovsky, 1977). In thin sections these viruses first appear as an out-pouching of the cell membrane accompanied by an electron dense submembranous line. This process is completed by the formation of the viral bud and the circularization of the electron-dense line into the so-called intermediate membrane. The latter structure

TABLE II

PROPOSED CLASSIFICATION OF RETROVIRIDAE[a]: NONHUMAN PRIMATE ASSOCIATIONS

Genus	Distinguishing morphological characteristics	Associated biological activity	Nonhuman primate isolates
Cisternavirus A	Intracisternal Double shell Central lucent core	Not reported	Not reported
Oncornavirus B	Complete intracellular core Extracellular Eccentric round core Prominent envelope spikes	Mouse mammary tumor agent	Not reported
Oncornavirus C	Incomplete intracellular core Extracellular Central round core	Highly variable	Endogenous viruses of baboons (BaEV); owl (OMC-1) and stumptail (MAC-1) monkeys; gibbon ape leukemia viruses (GaLV); woolly monkey sarcoma virus (SiSV)
Oncornavirus D	Complete intracellular core Extracellular Central cylindrical core	Most none; fibroblast alteration by MPMV	Endogenous viruses of langurs (PO-1-Lu) and squirrel monkeys (SMRV); MPMV of rhesus monkeys
Lentivirus E	Resemble oncornavirus C	Slow sclerosing diseases; cytopathic effect *in vitro*	Not reported
Spumavirus F	Resemble oncornavirus C Frequently intravacuolar Prominent envelope spikes	Cytopathic effect *in vitro*	Multiple primate isolates

[a] After Dalton *et al.*, 1974b.

delineates the viral nucleoid, which is round and centrally located in all type-C viruses. The nucleoid is separated from the trilamellar viral envelope by an electron lucent perinucleoidal space, which remains present during the entire maturation process of the virion. On the other hand, the nucleoid changes from an electron lucent to a condensed, somewhat irregular, electron-dense structure during the maturation of the virion into secondary extracellular particles.

Type-D oncornaviruses differ morphologically from type-C viruses in two respects (Kramarsky *et al.*, 1971; Schidlovsky, 1977). First, the nucleoid is frequently completely formed prior to the budding process. Thus, as is the case with type-B particles of mouse mammary tumor virus, doughnut-shaped precursor A particles may be observed in the cytoplasm of infected cells. Second, although the nucleoid is centrally located, it is often cylindrical rather than round.

2. Biophysical, Biochemical, and Antigenic Properties

Primate type-C and type-D oncornaviruses have similar biophysical properties. Viruses of both genera are approximately 100 to 120 nm in diameter and contain a nucleoid measuring 60 to 75 nm in diameter. They have a density in the range of 1.14 to 1.17 gm/ml as determined by equilibrium density centrifugation on sucrose gradients. As a rule, density determinations on type-D oncornaviruses have been in the upper range, i.e., 1.16 to 1.17 gm/ml, while those on type-C viruses fall between 1.14 and 1.16 gm/ml. After treatment with detergents, the viral nucleoid or core is released which has a density of 1.23 to 1.28 gm/ml.

Detailed compositional analyses have not been reported for primate oncornaviruses; however, there is no reason to suspect that they would differ from those reported for oncornaviruses from lower species (Green, 1970). Both type-C and type-D primate retroviruses contain in the nucleoid a dimeric molecule of 60 to 70 S RNA, which, under appropriate conditions, can be dissociated to monomeric 30 to 35 S RNA molecules representing the haploid genome. A recent critical report, using a combination of sedimentation techniques and electron microscopy, indicates that a more accurate estimate of high-molecular-weight RNA from primate type-C oncornaviruses has a sedimentation coefficient of 52 S and a molecular length of 16–20 kilobases (Kung *et al.*, 1976). So far there have been no reports related to other RNAs associated with primate oncornaviruses, particularly tRNAs which have been determined to be primers for RNA-directed DNA synthesis in type-C viruses from other species (Dahlberg *et al.*, 1974; Taylor, 1977).

As characteristic of all retroviruses, both type-C and type-D viruses

contain reverse transcriptase in the viral nucleoid. However, consistent differences have been found in the properties of this DNA polymerase from the two oncornavirus genera. Most characteristically, reverse transcriptase from primate type-C viruses is preferentially stimulated by the divalent cation Mn^{2+}, as is the case for this enzyme from all known mammalian type-C viruses (Temin and Baltimore, 1972; Abrell and Gallo, 1973; Sarngadharan *et al.*, 1978). On the other hand, reverse transcriptase from all known primate type-D viruses is preferentially stimulated by the divalent cation Mg^{2+} (Abrell and Gallo, 1973; Heberling *et al.*, 1977; Todaro *et al.*, 1978b). This property is shared by reverse transcriptase from certain avian type-C oncornaviruses (Temin and Baltimore, 1972; Waters and Yang, 1974) and from mouse mammary tumor virus (Howk *et al.*, 1973; Dion *et al.*, 1974). Another important distinguishing property of the reverse transcriptases from the two virus genera is the enzyme molecular weight. In common with reverse transcriptase from other mammalian type-C viruses, the primate type-C viral enzymes have a molecular weight of approximately 70,000 (Temin and Baltimore, 1972; Abrell and Gallo, 1973; Sarngadharan *et al.*, 1978). On the other hand, reverse transcriptase from primate type-D viruses has a molecular weight of 80,000 to 110,000, according to various reports (Abrell and Gallo, 1973; Colcher *et al.*, 1977b; Todaro *et al.*, 1978b).

In addition to reverse transcriptase, all retroviruses contain four or five consistently definable structural proteins. Detailed studies with oncornaviruses from lower mammalian species, particularly mouse type-C viruses, indicate that these structural proteins are translated into two precursor polyproteins (Barbacid *et al.*, 1976a; Jamjoom *et al.*, 1977). One of these, the so-called *gag*-gene product, is cleaved to four proteins which contribute primarily to the internal virion structure. By molecular weight determination, proteins with reasonably consistent masses have been found in all mammalian type-C viruses, including the primate type-C viruses. As summarized in Table III, the major *gag* protein has a molecular weight in the range of 27,000 to 30,000. The other *gag* proteins have molecular weights of 15,000, 12,000, and 10,000. Table III also indicates the predominant antigenic specificity detected by sera obtained after natural immunization by viral infection or by inoculation with whole disrupted virus or with purified viral proteins when the antisera are used to detect viral antigens in a homologous immunological test system. For example, antisera prepared against p30 of a particular gibbon leukemia virus (GaLV) would be strongly cross-reactive with p30s from other viruses of the same *group*, i.e., other GaLV isolates and simian sarcoma associated virus (SiSAV), but not

TABLE III
VIRAL CODED PROTEINS OF PRIMATE RETROVIRUSES

Protein	Molecular weight[a]	Antigenic specificity[b]	Reference
Reverse transcriptase			
Type-C	70,000	Group	*d, e*
Type-D	80,000 to 110,000	Group or type	*f*
Major *gag* protein			
Type-C	27,000 to 30,000	Group	*d, g–j*
Type-D	27,000 (MPMV) 35,000 (SMRV)	Group	*k–n*
Other *gag* proteins			
Type-C	10,000	Group	*o*
	12,000	Group (BaEV); Type (GaLV)	*p* *i, j*
	15,000	Type (BaEV); (GaLV) not reported[c]	*p, q*
Type-D	MPMV SMRV		
	10,000 8,000	Not reported	
	12,000 14,000		
	15,000 20,000		
	20,000 (glycoprotein)		
Surface glycoprotein			
Type-C	69,000 to 71,000	Group and type	*j, r*
Type-D	68,000 (MPMV)	Group and type	*k*
	73,000 to 85,000 (SMRV)	Group or type	*k, n*

[a] See text for references.
[b] Predominant antigenic specificity in a homologous immunoassay.
[c] MuLV p15 has variable antigenic specificities (Strand *et al.*, 1974).
[d] Scolnick *et al.*, 1972; [e] Todaro *et al.*, 1974; [f] Yaniv *et al.*, 1974; [g] Parks *et al.*, 1973; [h] Todaro *et al.*, 1975; [i] Tronick *et al.*, 1975; [j] Krakowar *et al.*, 1978; [k] Todaro *et al.*, 1978b; [l] Tronick *et al.*, 1974; [m] Schochetman *et al.*, 1976; [n] Schochetman *et al.*, 1977; [o] Barbacid *et al.*, 1976b; [p] Stephenson *et al.*, 1976a; [q] Stephenson and Aaronson, 1977; [r] Hino *et al.*, 1975.

with viruses of a different group, e.g., baboon endogenous viruses (BaEV). More broadly reactive antigenic (*interspec*) determinants can, however, be detected by altering the immunological assay system, e.g., by testing the ability of GaLV p30 to compete in an immunoassay using antibody to mouse leukemia virus p30 versus radiolabeled cat endogenous virus (RD114) p30 (Strand and August, 1974; Charman *et al.*, 1976; Barbacid *et al.*, 1977). The use of such a broad assay system

此为试读,需要完整PDF请访问: www.ertongbook.com