Comprehensive Virology

Edited by Heinz Fraenkel-Conrat

and Robert R. Wagner

Volume 16

Virus-Host Interactions

Viral Invasion, Persistence, and Disease

Virology

16

Virus-Host Interactions

Viral Invasion, Persistence, and Disease

PLENUM PRESS • NEW YORK AND LONDON

Library of Congress Cataloging in Publication Data

Fraenkel-Conrat, Heinz, 1910-
Virus-host interactions.

(*Their* Comprehensive virology; 16)
Includes bibliographical references and index.
1. Host-virus relationships. I. Wagner, Robert R., 1923- joint author. II. Title. III. Series. [DNLM: 1. Virus diseases. 2. Virus diseases–Immunology. 3. Viruses–Metabolism.
QW160 C737 v. 16]
QR357.F72 vol. 16 [QR482] 576'.64s [576'.64] 80-20780
ISBN 0-306-40488-5

A Division of Plenum Publishing Corporation
227 West 17th Street, New York, N.Y. 10011

Printed in the United States of America

Foreword

The time seems ripe for a critical compendium of that segment of the biological universe we call viruses. Virology, as a science, having passed only recently through its descriptive phase of naming and numbering, has probably reached that stage at which relatively few new—truly new—viruses will be discovered. Triggered by the intellectual probes and techniques of molecular biology, genetics, biochemical cytology, and high resolution microscopy and spectroscopy, the field has experienced a genuine information explosion.

Few serious attempts have been made to chronicle these events. This comprehensive series, which will comprise some 6000 pages in a total of about 18 volumes, represents a commitment by a large group of active investigators to analyze, digest, and expostulate on the great mass of data relating to viruses, much of which is now amorphous and disjointed, and scattered throughout a wide literature. In this way, we hope to place the entire field in perspective, and to develop an invaluable reference and sourcebook for researchers and students at all levels.

This series is designed as a continuum that can be entered anywhere, but which also provides a logical progression of developing facts and integrated concepts.

Volume 1 contains an alphabetical catalogue of almost all viruses of vertebrates, insects, plants, and protists, describing them in general terms. Volumes 2–4 deal primarily, but not exclusively, with the processes of infection and reproduction of the major groups of viruses in their hosts. Volume 2 deals with the simple RNA viruses of bacteria, plants, and animals; the togaviruses (formerly called arboviruses), which share with these only the feature that the virion's RNA is able to act as messenger RNA in the host cell; and the reoviruses of animals and plants, which all share several structurally singular features, the most important being the double-strandedness of their multiple RNA molecules.

Volume 3 addresses itself to the reproduction of all DNA-contain-

ing viruses of vertebrates, encompassing the smallest and the largest viruses known. The reproduction of the larger and more complex RNA viruses is the subject matter of Volume 4. These viruses share the property of being enclosed in lipoprotein membranes, as do the togaviruses included in Volume 2. They share as a group, along with the reoviruses, the presence of polymerase enzymes in their virions to satisfy the need for their RNA to become transcribed before it can serve messenger functions.

Volumes 5 and 6 represent the first in a series that focuses primarily on the structure and assembly of virus particles. Volume 5 is devoted to general structural principles involving the relationship and specificity of interaction of viral capsid proteins and their nucleic acids, or host nucleic acids. It deals primarily with helical and the simpler isometric viruses, as well as with the relationship of nucleic acid to protein shell in the T-even phages. Volume 6 is concerned with the structure of the picornaviruses, and with the reconstitution of plant and bacterial RNA viruses.

Volumes 7 and 8 deal with the DNA bacteriophages. Volume 7 concludes the series of volumes on the reproduction of viruses (Volumes 2–4 and Volume 7) and deals particularly with the single- and double-stranded virulent bacteriophages.

Volume 8, the first of the series on regulation and gentics of viruses, covers the biological properties of the lysogenic and defective phages, the phage-satellite system P 2–P 4, and in-depth discussion of the regulatory principles governing the development of selected lytic phages.

Volume 9 provides a truly comprehensive analysis of the genetics of all animal viruses that have been studied to date. These chapters cover the principles and methodology of mutant selection, complementation analysis, gene mapping with restriction endonucleases, etc. Volume 10 also deals with animal cells, covering transcriptional and translational regulation of viral gene expression, defective virions, and integration of tumor virus genomes into host chromosomes.

Volume 11 covers the considerable advances in the molecular understanding of new aspects of virology which have been revealed in recent years through the study of plant viruses. It covers particularly the mode of replication and translation of the multicomponent viruses and others that carry or utilize subdivided genomes; the use of protoplasts in such studies is authoritatively reviewed, as well as the nature of viroids, the smallest replicatable pathogens. Volume 12 deals with special groups of viruses of protists and invertebrates which show

properties that set them apart from the main virus families. These are the lipid-containing phages and the viruses of algae, fungi, and invertebrates.

Volume 13 contains chapters on various topics related to the structure and assembly of viruses, dealing in detail with nucleotide and amino acid sequences, as well as with particle morphology and assembly, and the structure of virus membranes and hybrid viruses. The first complete sequence of a viral RNA is represented as a multicolored foldout.

Volume 14 contains chapters on special and/or newly characterized vertebrate virus groups: bunya-, arena-, corona-, calici-, and orbiviruses, icosahedral cytoplasmic deoxyriboviruses, fish viruses, and hepatitis viruses.

Subsequent volumes deal primarily with virus–host interactions and one (Volume 17) with biophysical, biochemical, and serological methods used in virus research. Volume 15 is concerned with immunological reactions to viruses and to virus-infected cells.

The current volume is concerned with viral invasion of cells, factors controlling persistence of viruses in cell cultures and animals, and responses to viral infection of animal and plant cells, as well as certain diseases caused by viruses. At least one additional volume will be devoted to other aspects of cell responses to viral infection, including cell death.

Contents

Chapter 2

Viral Persistence: Evolution of Viral Populations

Julius S. Youngner and Olivia T. Preble

Chapter 3

Defective Interfering RNA Viruses and the Host-Cell Response

John J. Holland, S. Ian T. Kennedy, Bert L. Semler, Charlotte L. Jones, Laurent Roux, and Elizabeth A. Grabau

Chapter 5

Aleutian Disease of Mink: A Model for Persistent Infection

David D. Porter and H. J. Cho

Chapter 6

Role of Viruses in Chronic Neurological Diseases

Jerry S. Wolinsky and Richard T. Johnson

Chapter 7

Host Plant Responses to Virus Infection

R. E. F. Matthews

CHAPTER 1

Viral Invasion: Morphological, Biochemical, and Biophysical Aspects

C. Howe, J. E. Coward, and T. W. Fenger

Department of Microbiology and Immunology
Louisiana State University Medical Center
New Orleans, Louisiana 70112

1. INTRODUCTION

The first encounter of an infectious viral particle with the surface of a susceptible cell initiates a complex series of events, the outcome of which determines whether or not penetration and subsequent takeover of cellular machinery for viral replication ensue. Recognition of factors which govern these interactions derives from knowledge of the molecular structure of virus and target cell, as well as from the effects of the environment in which the interactions occur. This chapter will deal with animal viruses and will be limited to a consideration of the interactions at the cellular membrane which in sequence govern attachment and penetration of the virion up to the point at which the viral genome is uncoated. Early events in the viral replicative cycle have been the subject of several excellent reviews (Dales, 1973; Lonberg-Holm and Philipson, 1974, 1978).

With few exceptions, the most sensitive criterion of "intactness" of a viral particle is its infectivity, or its capacity to initiate self-replication in a susceptible cell. In order to be infectious, the viral nucleic acid must be associated with the requisite capsid proteins, enzymes, and, in

TABLE 1

Summary[a]

Naked viruses	Viral component(s)	Cell receptor	Viral attachment/ penetration	Associated changes
Adenovirus	Penton fiber (Arg)	3 proteins (KB cells) ?lp; receptor "families"	VP Direct entry	Partial loss of penton fiber; uncoating at NP
Papovavirus (SV40, polyoma)		Ec lp (SV40) Ec gp (polyoma)	VP: Monopinocytotic envelopment, Nu intermembrane fusion (SV40, polyoma)	Increased membrane fluidity (polyoma)
Parvovirus MVM	"*Light*" *particles* activated by cell factor(s)		VP (*Pinocytosis*)	
Reovirus	Nonglycosylated capsid protein = HA (σ^1) (RE03)	?gp	VP	
Picornavirus (enterovirus rhinovirus)	Four capsid proteins	Receptor families ?glp Under genetic control; correlated with susceptibility; *N*-ase insensitive	VP Direct entry	D → A particles Receptor-mediated uncoating; early loss of Vp4; increased membrane fluidity

Abbreviations: Ag, antigen; Arg, arginine; ASA, attachment site activity; ASLV, avian sarcoma leukemia viruses; CEF, chick embryo fibroblasts; Cv, C virus; Ec, erythrocyte; F_0,F_1,F_2, fusion protein complex; Fu, fusion; gl, glycolipids; glp, glycolipoprotein; gp, glycoprotein; HA, H, hemagglutinin; Hc, histocompatibility; HL, hemolysis; HSV-1, Herpes simplex virus type 1; k, kilodalton; lc, fymphocyte; LIS, lithium diiodosalicylate; MLV, murine leukemia virus; MMTV,

Enveloped viruses	Viral envelope component(s)	Cell receptor	Viral		Associated changes
			Attachment	*Penetration*	
Orthomyxovirus (Influenza A)	HA, (gp) → HA_2 (N)	Essential NANA Ec glycophorin cilia	HA	VP (HA cleavage)	Increased membrane fluidity; ?lipid exchange
Paramyxovirus (NDV, Sendai)	HN gp $F_0 \rightarrow F_1, F_2$ (?phosphatase tase) (?host agent)	2 → 3 NANA Ec glycophorin	HN Surface ion rearrangement	Fu, VP (Ec: Fu/HL)	?Membrane dephosphorylation (?Ec band 3); lipid exchange; Ag dispersal
Morbillivirus (measles)	H gp F → F_1, F_2 No N	No NANA required; Rh monkey Ec PAS-2, 4 T lc	H	Fu (Ec: Fu/HL)	Ag dispersal
Pneumovirus (RS)	Spikes No HA, N (1 glycosylated protein)	?		Fu	Ag dispersal
Rhabdovirus (VSV)	G protein Component II (spikes)	?Protein No NANA; ?lipid		VP (Fu)	Viral lipid depletion
Togavirus (Sindbis, SFV)	1 gp, 50 k spikes "Loose" vs. "tight" particles	pI, (gI) CEF:ASA HC ag	Envel. essential	VP pH, ionic strength dependent	Increased membrane fluidity
RNA TV (MLV, MSV, avian TV, MMTV)	Spikes gp71 (MLV)	Transforming strain-specific ASA, LIS-soluble; Cv budding sites; β2-microglobulin	ASLV:CEF gap junctions	VP Direct (? Fu)	
Poxvirus	Vaccinia, lipoprotein envelope DNV (*Amsacta*)	Relatively unspecific	Electrostatic, relatively unspecific	VP, Fu Fu, VP	Ag dispersal
Herpesvirus	HSV-1 Envelope gp (B2, C2) EBV	? EBV:C3, Fc	?Envelope glycoprotein(s); under genetic control	VP, Fu	Regulatory balance (gpB2, C2)

mouse mammary tumor virus; MSV, murine sarcoma virus; MVM, minute virus of mice; N or N-ase, neuraminidase; NANA, *N*-acetylneuraminic acid; NDV, Newcastle disease virus; NP, nuclear pore(s); Nu, nuclear; PAS, periodic acid Schiff; pI, phospholipid(s); Rh, rhesus; RS, respiratory syncytial; SFV, Semliki Forest virus; SV40, simian virus 40; TV, tumor virus(es); VP, viropexis; Vp, viral protein; VSV, vesicular stomatitis virus.

the case of enveloped viruses, lipids, to ensure relatively efficient transport of the viral genome across the host cell membrane. The viral subunits involved in these infectious processes are now quite clearly recognized in a number of major taxonomic groups. The naked nucleic acid of certain positive-stranded RNA viruses (e.g., poliovirus, encephalomyocarditis virus) and a few DNA viruses (e.g., herpesviruses, SV40) can transfect cells not normally susceptible to the corresponding whole virus. Infection initiated in this manner bypasses the receptor components of the cell membrane with which virions must interact in order to penetrate into the cytoplasm. While readily demonstrable experimentally, this mode of genomic entry is not known to have a role in naturally occurring infection and so will not be discussed in detail.

The term "viropexis" was coined to describe the penetration of intact viral particles through the cell membrane by energy-dependent processes assumed to be equivalent to normal phagocytosis (Fazekas de St. Groth, 1948). In the light of accumulated knowledge of endocytotic mechanisms, the present concept of viropexis may now be broadened to include mechanisms of entry by viruses into cells not normally phagocytic. In these instances specialized phagocytic reactions are triggered by the irreversible attachment of viral particles and the "recruiting" of receptor molecules to the attachment site. These specialized processes include receptor-mediated alteration of virions, as with adenoviruses and picornaviruses, or the envelopment of virions by plasma membrane prior to transcytoplasmic migration, as with papovaviruses. Intramembranal events, even though still incompletely understood, are as important as the specificity of surface receptors in governing viropexis and the outcome of initial viral contact. In addition it is apparent that, while most if not all viruses can penetrate by some form of viropexis, only those possessing a lipid-containing envelope can enter the cell by fusion with the plasma membrane.

In considering the susceptible cell, particular attention has been focused on the concept of viral "receptors." This term denotes chemical groupings on the cellular surface, the presence of which determines to a large extent whether viral attachment and penetration can take place. The chemical specificity of receptors underlies the long-recognized "tissue tropisms" of different viruses. It is increasingly clear, however, that receptor specificity alone does not account for the spectrum of susceptibility to viruses, genetic and other biological factors being of equal importance. The reader is referred to recent reviews of these questions (Smith, 1977; Lonberg-Holm and Philipson, 1978). The term "receptor" should be reserved for the attachment function associated with the

cell membrane and should not be used to designate reactive sites on viral surfaces or even viral antigens which may appear at the cell surface during viral maturation. Surprisingly little is known about the biochemical composition of receptors for animal viruses, with the exception of those for orthomyxoviruses and paramyxoviruses. Investigation of cell receptors has broadened to include interrelationships between histocompatibility antigens and susceptibility to viruses, as well as the complex problem of persistent viral infection (e.g., paramyxoviruses, measles virus, and herpesviruses). Problems in the identification of receptors and approaches to their solution have been summarized recently (Gallaher and Howe, 1976; Lonberg-Holm and Philipson, 1978).

Viruses representative of almost every taxonomic group have now been analyzed with respect to the morphology of attachment and penetration. In spite of extensive data available, variation in the strains within a single species, as well as different experimental conditions make it impossible to generalize or even to repeat individual experimental observations, some of which must therefore stand alone. However, interpretations of electron micrographs have in many instances been fortified by other kinds of evidence. We have therefore included results of pertinent biochemical and biophysical analyses, as outlined in Table 1. Only those viruses which have been examined by electron microscopy during early stages of infection are represented in this tabular summary.

2. METHODS

Some of the morphological and biochemical–biophysical approaches toward the elucidation of virus–receptor interactions are listed below, followed by a brief discussion of salient features in each category:

I. Approaches to morphology
   - A. Transmission electron microscopy (TEM)—ultrathin sectioning, negative staining techniques
   - B. Scanning electron microscopy (SEM)
   - C. Freeze-fracture, freeze-etching, immunofreeze-etching
   - D. High-resolution autoradiography

II. Biochemical and biophysical approaches
   - A. Surface and intracellular components analyzed by fluorescence microscopy, fluorescence probes