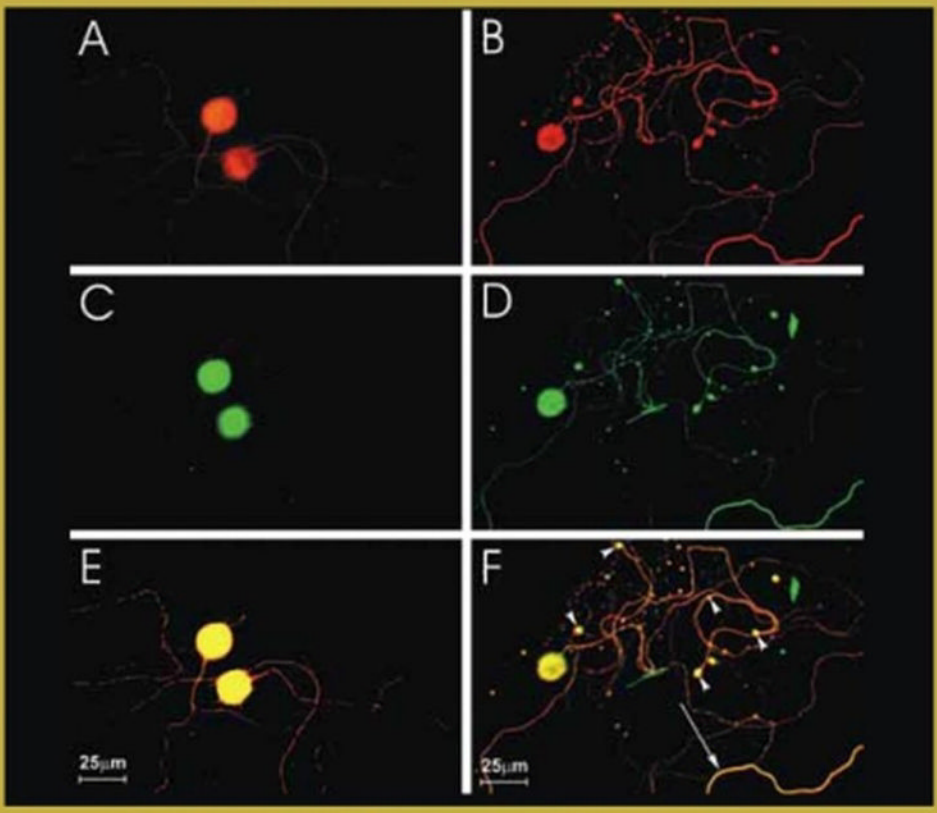
Advances in VIRUS RESEARCH

RESEARCH ADVANCES IN RABIES



79

Edited by
Alan C. Jackson

Advances in
VIRUS RESEARCH

VOLUME 79

Research Advances in Rabies

Advances in
VIRUS RESEARCH

VOLUME 79

Research Advances in Rabies

Edited by

ALAN C. JACKSON
Departments of Internal Medicine (Neurology) and of Medical Microbiology
University of Manitoba
Winnipeg, Manitoba, Canada

ELSEVIER

AMSTERDAM • BOSTON • HEIDELBERG • LONDON
NEW YORK • OXFORD • PARIS • SAN DIEGO
SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO
Academic Press is an imprint of Elsevier

Academic Press is an imprint of Elsevier

32 Jamestown Road, London, NW1 7BY, UK
Radarweg 29, PO Box 211, 1000 AE Amsterdam, The Netherlands
225 Wyman Street, Waltham, MA 02451, USA
525 B Street, Suite 1900, San Diego, CA 92101-4495, USA

First edition 2011

Library of Congress Cataloging-in-Publication Data

A catalog record for this book is available from the Library of Congress

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library

ISBN: 978-0-12-387040-7
ISSN: 0065-3527

Printed and bound in USA
11 12 13 14 10 9 8 7 6 5 4 3 2 1

CONTENTS

CONTRIBUTORS

Aurélie A. V. Albertini
UPR 3296 CNRS, Virologie Moléculaire et Structurale, Gif sur Yvette, France

Ashley C. Banyard
Rabies and Wildlife Zoonoses Group, Department of Virology, Veterinary Laboratories Agency, Weybridge, New Haw, Addlestone, Surrey, United Kingdom

Darryll A. Barkhouse
Center for Neurovirology, Department of Cancer Biology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Denise Bélanger
Faculté de médecine vétérinaire, Département de pathologie et microbiologie, GREZOSP Université de Montréal, Saint-Hyacinthe, Quebec, Canada

Danielle Blondel
UPR 3296 CNRS, Virologie Moléculaire et Structurale, Gif sur Yvette, France

Karl-Klaus Conzelmann
Max von Pettenkofer Institute and Gene Center, Ludwig-Maximilians-University Munich, Munich, Germany

Bernhard Dietzschold
Center for Neurovirology, Department of Microbiology and Immunology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Milosz Faber
Center for Neurovirology, Department of Microbiology and Immunology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Paul Fernyhough
Division of Neurodegenerative Disorders, St. Boniface Hospital Research Centre, and Department of Pharmacology and Therapeutics, University of Manitoba, Winnipeg, Manitoba, Canada

Anthony R. Fooks
Rabies and Wildlife Zoonoses Group, Department of Virology, Veterinary Laboratories Agency, Weybridge, New Haw, Addlestone, Surrey, and National Centre for Zoonosis Research, University of Liverpool, Leahurst, Neston, Wirral, United Kingdom

Richard Franka
Poxvirus and Rabies Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Zhen F. Fu
Departments of Pathology, University of Georgia, Athens, Georgia, USA

Emily A. Gomme
Department of Microbiology and Immunology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Ronald N. Harty
Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

David Hayman
Rabies and Wildlife Zoonoses Group, Department of Virology, Veterinary Laboratories Agency, Weybridge, New Haw, Addlestone, Surrey, and Cambridge Infectious Diseases Consortium, Department of Veterinary Medicine, Cambridge; Institute of Zoology, Regent's Park, London, United Kingdom

Thiravat Hemachudha
Department of Medicine (Neurology) and WHO Collaborating Center in Research and Training on Viral Zoonoses, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

D. Craig Hooper
Center for Neurovirology, Department of Cancer Biology, and Department of Neurological Surgery, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Nipan Israsena
Department of Pharmacology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Alan C. Jackson
Department of Internal Medicine (Neurology), and Department of Medical Microbiology, University of Manitoba, Winnipeg, Manitoba, Canada

Nicholas Johnson
Rabies and Wildlife Zoonoses Group, Department of Virology, Veterinary Laboratories Agency, Weybridge, New Haw, Addlestone, Surrey, United Kingdom

Wafa Kammouni
Department of Internal Medicine (Neurology), University of Manitoba, Winnipeg, Manitoba, Canada

Rhonda B. Kean
Center for Neurovirology, Department of Cancer Biology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Monique Lafon
Unité de Neuroimmunologie Virale, Département de Virologie, Institut Pasteur, Paris, France

Jiraporn Laothamatas
Advanced Diagnostic Imaging and Image-Guided Minimal Invasive Therapy Center (AIMC) and Department of Radiology, Ramathibodi Hospital, Faculty of Medicine, Mahidol University, Bangkok, Thailand

Jianwei Li
Center for Neurovirology, Department of Cancer Biology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Boonlert Lumlertdacha
Queen Saovabha Memorial Institute, Thai Red Cross Society, Bangkok, Thailand

Aekkapol Mahavihakanont
Department of Medicine (Neurology) and WHO Collaborating Center in Research and Training on Viral Zoonoses, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Lorraine McElhinney
Rabies and Wildlife Zoonoses Group, Department of Virology, Veterinary Laboratories Agency, Weybridge, New Haw, Addlestone, Surrey,

and National Centre for Zoonosis Research, University of Liverpool, Leahurst, Neston, Wirral, United Kingdom

Susan A. Nadin-Davis
Centre of Expertise for Rabies, Ottawa Laboratory Fallowfield, Canadian Food Inspection Agency, Ottawa, Ontario, Canada

Xuefeng Niu
Departments of Pathology, University of Georgia, Athens, Georgia, USA

Atsushi Okumura
Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Vijay G. Panjeti
Department of Biology and Center for Disease Ecology, Emory University, Atlanta, Georgia, USA

Bruce A. Pond
Wildlife Research and Development Section, Ontario Ministry of Natural Resources, Peterborough, Ontario, Canada

Leslie A. Real
Department of Biology and Center for Disease Ecology, Emory University, Atlanta, Georgia, USA

Erin E. Rees
Faculté de médecine vétérinaire, Département de pathologie et microbiologie, GREZOSP Université de Montréal, Saint-Hyacinthe, Quebec, Canada

Martina Rieder
Max von Pettenkofer Institute and Gene Center, Ludwig-Maximilians-University Munich, Munich, Germany

Rick Rosatte
Ontario Ministry of Natural Resources, Wildlife Research and Development Section, Trent University, Peterborough, Ontario, Canada

Anirban Roy
Center for Neurovirology, Department of Cancer Biology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Rob W. H. Ruigrok
UMI 3265 UJF-EMBL-CNRS, Unit of Virus Host Cell Interactions, Grenoble, France

Charles E. Rupprecht
Poxvirus and Rabies Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Matthias J. Schnell
Department of Microbiology and Immunology, and Jefferson Vaccine Center, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Prapimporn Shantavasinkul
Queen Saovabha Memorial Institute, The Thai Red Cross Society (World Health Organization Collaborating Center for Research on Rabies Pathogenesis and Prevention), Bangkok, Thailand

Todd G. Smith
Poxvirus and Rabies Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Witaya Sungkarat
Advanced Diagnostic Imaging and Image-Guided Minimal Invasive Therapy Center (AIMC) and Department of Radiology, Ramathibodi Hospital, Faculty of Medicine, Mahidol University, Bangkok, Thailand

Rowland R. Tinline
Department of Geography, Queen's University, Kingston, Ontario, Canada

Gabriella Ugolini
Neurobiologie et Développement, UPR3294 CNRS, Institut de Neurobiologie Alfred Fessard (INAF), 1 Avenue de la Terrasse, Bât. 32, 91198 Gif-sur-Yvette, France

Hualei Wang
Departments of Pathology, University of Georgia, Athens, Georgia, USA

Celestine N. Wanjalla
Department of Microbiology and Immunology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Henry Wilde
WHO-CC for Research and Training on Viral Zoonoses, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Christoph Wirblich
Department of Microbiology and Immunology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Xianfu Wu
Poxvirus and Rabies Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

PREFACE

Rabies is an ancient disease that unfortunately remains an important public health problem in humans. There have been many important research advances extending from our understanding of how rabies virus replicates and assembles to how the disease can be prevented and treated in humans and how rabies can be controlled in wildlife hosts. The vaccination of Joseph Meister by Louis Pasteur and colleagues in 1885 was just one of many important landmarks of our advances against a truly diabolical virus that infects the brain of its vectors and alters behavior, resulting in transmission by biting at a time when the deadly virus is secreted in the saliva. There has been much progress in many different areas, but many challenges remain involving our understanding of rabies virus infection. Only further basic research will give us a better understanding of mechanisms involved in all aspects of the infection, including at the level of the cell and of the host and also in human and animal populations. This knowledge is needed to develop strategies to better combat all aspects of the disease. In addition, rabies virus is now recognized as the best available tool for the study of neuronal circuits in the nervous system and neuroscientists will certainly use it much more in the future.

I would like to express my appreciation to the series editors, Karl Maramorosch and Frederick Murphy, and to Lisa Tickner at Elsevier for giving me the opportunity of putting together a research volume on rabies and to our many contributors, who are all experts in their fields, for their hard work in preparing insightful and up-to-date chapters that summarize our current state of knowledge in diverse aspects of this very interesting and important viral disease.

ALAN C. JACKSON
Winnipeg, Manitoba, Canada
December 2010

CHAPTER 1

Rabies Virus Transcription and Replication

Aurélie A. V. Albertini,* **Rob W. H. Ruigrok,†** and **Danielle Blondel***

Contents

Abstract

Rabies virus (RABV) is a negative-stranded RNA virus. Its genome is tightly encapsidated by the viral nucleoprotein (N) and this RNA–N complex is the template for transcription and replication by the

* UPR 3296 CNRS, Virologie Moléculaire et Structurale, Gif sur Yvette, France
† UMI 3265 UJF-EMBL-CNRS, Unit of Virus Host Cell Interactions, Grenoble, France

Advances in Virus Research, Volume 79
ISSN 0065-3527, DOI: 10.1016/B978-0-12-387040-7.00001-9

viral RNA-dependent RNA polymerase (L) and its cofactor, the phosphoprotein (P). We present molecular, structural, and cellular aspects of RABV transcription and replication. We first summarize the characteristics and molecular biology of both RNA synthesis processes. We then discuss biochemical and structural data on the viral proteins (N, P, and L) and their interactions with regard to their role in viral transcription and replication. Finally, we review evidence that rabies viral transcription and replication take place in cytoplasmic inclusion bodies formed in RABV-infected cells and discuss the role of this cellular compartmentalization.

I. INTRODUCTION

Rabies virus (RABV) and rabies-related viruses belong to the *Lyssavirus* genus of the *Rhabdoviridae* family, which also includes the *Vesiculovirus* genus with the prototype vesicular stomatitis virus (VSV). However, the natural histories of RABV and VSV are very different. RABV is a prototype neurotropic virus that causes fatal disease in humans and animals, whereas VSV is an arthropod-borne virus that primarily affects rodents, cattle, swine, and horses and can cause mild symptoms upon infection of humans and other species. *Rhabdoviridae* are part of the *Mononegavirales* order, which includes other virus families such as the *Paramyxoviridae*, the *Filoviridae*, and the *Bornaviridae*.

RNA transcription and replication of rhabdoviruses require an intricate interplay of the nucleoprotein N, the RNA-dependent RNA polymerase (RdRp) L, a nonenzymatic polymerase cofactor P, and the RNA genome enwrapped by N, also called the nucleocapsid. During RNA synthesis, P binds L to the N–RNA template through an N–P interaction that involves two adjacent N proteins in the nucleocapsid. L–P binding to the N–RNA probably triggers conformational changes that allow access of the polymerase to the RNA.

II. MOLECULAR ASPECTS OF VIRAL TRANSCRIPTION AND REPLICATION

A. Virion structure

Rabies virions have a bullet-like shape, with a diameter of 75 nm and a length of 100–300 nm depending on the strain (Matsumoto, 1962; Tordo and Poch, 1988b). One end is conical, and the other end is flat (Fig. 1). The viral RNA is encapsidated by the nucleoprotein N (450 amino acids (aa)) to form a helical nucleocapsid in which each N protomer binds to nine nucleotides like for VSV (Iseni *et al.*, 1998; Thomas *et al.*, 1985). The nucleocapsid is associated with a significant amount of phosphoprotein P (297 aa),