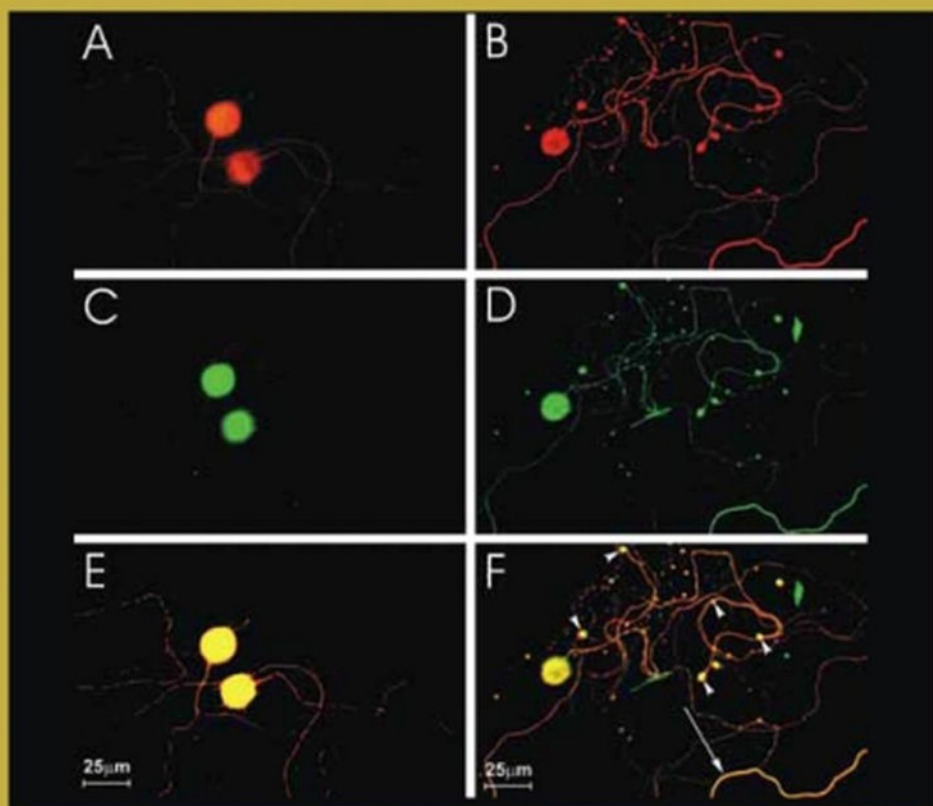


Advances in VIRUS RESEARCH

RESEARCH ADVANCES IN RABIES



79

Edited by
Alan C. Jackson



Advances in
VIRUS RESEARCH

VOLUME **79**

Research Advances in Rabies

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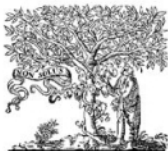
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Research Advances in Rabies

Edited by

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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

Rabies Virus Transcription and Replication

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

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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

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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),