Principles of Virology
Molecular Biology, Pathogenesis, and Control of Animal Viruses
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2004. ASM Press, Washington DC, USA
918 pp, 28.5 × 22 cm
Price: US$ 109.95
ISBN 1-55581-259-7

Thus, we cannot reject the assumption that the effect of the filtered lymph is not due to toxicity, but rather to the ability of the agent to replicate.” This quotation from Friedrich Loeffler (1852-1915) opens the first chapter of a new edition of Flint et al.’s textbook Principles of Virology. Molecular Biology, Pathogenesis, and Control of Animal Viruses, a primer that defines and illustrates the basic principles of animal virus biology. Loeffler (1898) was referring to the then still unknown agent responsible for foot-and-mouth disease in cattle, whose etiology he searched for together with Paul Frosch (1860-1928). The choice of these words by Loeffler reflects the complicated history of the science of virology. Although the earliest human records evidence that ancient peoples were aware of the effects of virus infection, and even carried out research into the causes and prevention of viral diseases, viruses have been recognized as distinct biological entities for only a little more than a century. A hundred years of enormous research efforts involving numerous excellent investigators have led to the appreciation that the vast world of viruses encrypts an enormous biologic, genetic and genomic diversity.

A significant part of the virus world consists of animal viruses, an amazing group of infectious agents usually referred to by their ability to cause disease. However, viral pathogenesis is actually fairly rare; rather, the majority of virus infections are silent and do not result in outward signs of disease. Furthermore, viral infection is not a simple process that can be defined by its apparent effects in the host, but instead comprises a very complex, well-regulated and controlled interaction of highly evolved systems. The enormous biological diversity of animal viruses and their multifaceted relationships with their hosts have been finely and skillfully scrutinized in the 20 chapters comprising this book, which is organized into four specific sections: “The science of virology”, “Molecular biology”, “Pathogenesis”, and “Control and evolution”. All chapters are well and clearly structured in short subsections that are very readable and easy to follow. Each chapter ends with an updated and expanded list of relevant books, review articles, and selected research papers. Additional references are listed when a particular experiment is featured in a chapter, and colored text boxes highlight general background information, definitions of terms, and discussions of specific experiments. Furthermore, two handy appendices at the end of the book summarize a wealth of information in a condensed format. Appendix A provides a brief description of the reproductive cycles in single cells of viruses that are frequently mentioned in the main text. Appendix B summarizes the pathogenesis of common viruses that infect humans. It also provides a brief description of the major features of viruses and the diseases associated with them, their epidemiology and the disease mechanism for each virus or virus group.

In Part I, “The science of virology”, Chapter 1 is a general introduction to the field and discusses how viruses are classified. It makes note of relevant historic events in the development of the field of virology. Chapter 2 is a practical description of general methods for studying animal viruses in the laboratory. Part II, “Molecular biology”, reviews the molecular processes that take place within infected host cells. Chapter 3 discusses the Baltimore classification system in detail, which makes it easier to understand the genomic complexities when they are presented in the context of the seven major genome strategies. The other ten chapters of Part II describe the organization of viral genomes, provide an overview of viral strategies for genome replication and mRNA synthesis, discuss the main principles of viral architecture, taking into account that virus particles are vehicles for viral genomes, and describe the broad spectrum of molecular processes that integrate the reproductive cycle of viruses in a single cell. Part III, “Pathogenesis” (Chaps. 14-18), addresses issues related to the interplay between viruses and their host organisms. Chapter 14 constitutes a comprehensive study of viral pathogenesis, including the basic concepts of viral dissemination in the host, viral virulence and epidemiology. Viral infection of the host animal is met by a collection of immune responses that, in turn, induce a series of viral countermeasures to host defenses. In Chap. 15, this dynamic interplay is clearly explained using a combination of text and figures. Once viruses have established themselves in host cells, they can maintain different types of relationships with their hosts, as is described in Chap. 16. This chapter is dedicated to pathogenesis and is followed by two updated chapters dealing with extremely important issues in current virol-
This is the first book to summarize current knowledge of the family of proteins called porins and consists of chapters authored by recognized researchers in this field. The volume is edited by Roland Benz, from the University of Würzburg, Germany. Chapter 1, by D. Walthers et al., deals with the regulation of porin expression by the two-component regulatory system EnvZ/OmpR, which controls osmosensing in Escherichia coli. Chapter 2 (G. Schulz) provides an overview of the structure of bacterial porins, while in Chap. 3 J.M. Pagés focuses on one of the most important consequences of porin modification in nature: the role of porins in determining antibiotic resistance in gram-negative bacteria. For example, in Pseudomonas aeruginosa, resistance to some antibiotics, including carbapenems, is due to the loss of certain porins, mainly the outer membrane porin OprD, which is the subject of Chap. 4, by R. Hancock and S. Tamber. Chapter 5 discusses the regulation of porin function, which has been studied using a variety of approaches, including molecular biology and electrophysiology, by the authors A. Baslé and A. Delcour. In Chap. 6, M. Winterhalter and C. Danelon review the methods of reconstitution of general diffusion pores from the bacterial outer membrane. The following chapter, by E. Sugawara and H. Nikaido, provides experimental evidence concerning the channel-formation ability of OmpA/OprF slow porins. The role of channel-tunnel proteins in relation to drug efflux is the subject of Chap. 8, by C. Andersen. Particularly attention is paid to the channel-tunnel protein TolC, whose structure and function have been well studied by several investigators. Chapter 9, authored by T. Schirmer, provides an example of the role of porins in bacterial nutrition by discussing the structure-function relationships of sugar-specific porins, e.g. maltoporin. The editor, R. Benz, and his co-worker F. Orlik describe in Chap. 10 the functional reconstitution of specific porins (the current subject of research in Benz’s laboratory). In Chapter 11, V. Braun and M. Braun review the energy-coupled transport of iron across the outer membrane. The remaining five chapters of the book are devoted to recent knowledge regarding the structure and function of eukaryotic porins, such as the vitamin B₁₂ receptor BtuB (Chap. 12, R. Kadner et al.) and mitochondrial porins (Chap. 13, R. Benz), as well as to their functional roles in mice (Chap. 14, K. Anflous and W. Craigen), intracellular trafficking (Chap. 15, V. De Pinto and A. Messina) and intracellular signalling (Chap. 16, M. Vyssokikh and D. Brdiczka).

This excellent book should be present in all laboratories working in the fields of bacterial outer membranes, bacterial resistance to antibiotics, cell signalling, and intracellular trafficking. In addition, it is suitable for advanced students in microbiology and molecular biology. The information is extremely up-to-date and is supported by high-quality and highly original graphics.

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By three billion years ago, life had changed the color of the inland seas; by two billion years ago, the gross composition of the atmosphere; and by one billion years ago, the weather and the climate. All these profound changes were brought about by microorganisms. In turn, the genes and genomes of extant organisms are the result of these ca. four billion years of evolution.

Insights into the dynamics of bacterial evolution have been facilitated by the new era of comparative sequencing, which has added the dimension of time to the static single-genome sequence. This has led to the recognition that bacteria, far from being clonal, are a mosaic of genetic sequences acquired over time. Thus, the nature of these genome dynamics will likely reflect the lifestyle and selection pressures that acted upon microorganisms.

Microbial Evolution. Gene Establishment, Survival, and Exchange presents topics that are fundamental to understanding microbial evolution. The book is divided into four sections: (i) intracellular mechanisms for generating diversity (six chapters), (ii) intercellular mechanisms for gene movement (four chapters), (iii) mechanisms for gene establishment and survival (seven chapters), and (iv) mechanisms for detecting genomic diversity (four chapters). Each chapter includes didactic aids that are traditionally present in general books, such as study questions and summarizing highlights. The bibliography includes general references, suggested reading, historical references, as well as references specific for a given subject.

Genomic change in microbial evolution operates by two mechanisms, one providing for genome modification and the other for an increase in genomic content. These mechanisms function at the intracellular and intercellular levels, respectively. Processes considered as intracellular include mutations, replication, amplification, and deletion, whereas a major source of extrinsic (intercellular) genome change is the ability of certain bacteria to acquire DNA from other organisms through the processes of transformation, transduction and conjugation (Chaps. 1-11).

Environmental selection (abiotic and biotic variables) for gene function is ultimately responsible for the maintenance of genome content. Biofilms, terrestrial-subsurface microbiota and host-pathogen interactions are some of the examples of microbial adaptation and evolution, and gene establishment and survival that are described in the book (Chaps. 12-18). Note that bacterial genomes do not vary greatly in size compared to the genomes of eukaryotic organisms. Bacterial genome size is maintained for most "bacterial species", suggesting that, during evolution, gene acquisition is balanced by the parallel processes of gene loss.

Prokaryotic evolution has been historically problematic. Prior to the utilization of molecular genetic approaches, the earliest classification was based on the data collected from microscopy observations [i.e. Ferdinand Cohn (1828-1898)]. Axenic culture and the use of computers to analyze phenotypic data (numerical taxonomy) reinforced the determinative approach. All of this information can be used to calculate coefficients of similarity between strains, and thus prokaryotes were grouped on the basis of phenotypic similarities. However, since the convergence or acquisition of traits through horizontal transfer tend to group organisms together, these empirical methods are not phylogenetic. The suggestion of Zuckerkandl and Pauling, in 1965 [J Theor Biol 8:357-366], that the history of life is recorded in the sequences of nucleic acids and proteins, provided a revolution in microbial taxonomy. The oligonucleotide cataloging of RNA molecules, as proposed by Woese and Fox in 1977 [Proc Natl Acad Sci USA 74:5088-5090], launched a new era in the approach to phylogeny and provided a tool by which all organisms could be compared. We know now that microbial genomes are inherently dynamic; they mutate and undergo gene deletions, acquisitions, and rearrangements over time scales.

The classification of animals, plants and other eukaryotes is based on the "species", a concept that was profoundly discussed by Ernst Mayr [Animal Species and Evolution, 1963]. Species are defined as "groups of actually or potentially interbreeding natural populations which are reproductively isolated from other such groups". But what constitutes a "species" for prokaryotes? This has been and continues to be a difficult question to answer. For bacteria, species has commonly been defined as a group of strains that are distinctly similar to one another. Often, similarity is determined with reference to a designated type strain within the group, even though this strain may not necessarily be the most typical of the group. The Ad Hoc Committee for the Re-Evaluation of the Species Definition in Bacteriology maintains that the criteria of 70% DNA-DNA (hybridization) similarity and a difference of 5°C or less in ΔTm should continue to define bac-
Filoviruses belong to the family Filoviridae, which can cause severe hemorrhagic fever both in humans and non-human primates. So far, only two members of this virus family have been identified: Marburg virus and Ebola virus. There are four species of Ebola virus: Ivory Coast, Sudan, Zaire and Reston. Ebola-Reston is the only known filovirus that does not cause severe disease in humans; however, it can be fatal to monkeys.

The first filovirus was discovered in 1967, when a number of laboratory workers in Germany and Yugoslavia who were handling tissues from green monkeys (Cercopithecus aethiops) developed hemorrhagic fever. A total of 31 cases, including seven deaths, were associated with these outbreaks. The virus was named after Marburg, Germany, the city in which one of the outbreaks took place. It did not reemerge until 1975, when one case occurred in Johannesburg, South Africa. Since then, there have been a few more sporadic cases of Marburg hemorrhagic fever.

Ebola virus was first identified in 1976, when two outbreaks of Ebola hemorrhagic fever occurred in northern Zaire and southern Sudan. The outbreaks involved what eventually proved to be two different species of Ebola virus, although both showed themselves to be highly lethal, as 90% of the Zairian infections and 50% of the Sudanese infections resulted in death. Since 1976, Ebola virus has appeared sporadically in Africa, with small to midsize outbreaks confirmed between 1976 and 1979. Large epidemics of Ebola hemorrhagic fever occurred in Kikwit, Zaire, in 1995, and in Gulu, Uganda, in 2000. Smaller outbreaks were identified in Gabon between 1994 and 1996.

Filoviruses are classified as Biological Level 4 agents based on their high mortality rate, person-to-person transmission, potential for aerosol infectivity, and absence of vaccines and chemotherapy. The reservoir of filoviruses remains a mystery. Non-human vertebrate hosts or arthropod vectors have been identified; however, species such as Guinea pigs, primates, bats and hard ticks have also been discussed as possible natural hosts. Due to the difficulty of identifying hemorrhagic fever in tropical settings, where malaria and typhoid fever are the main causes of severe, acute and febrile disease, a wide range of infectious diseases have to be considered before making a diagnosis of filovirus.

Over the last several years, the tools of molecular and cellular biology have been applied in attempts to clarify some of the questions that have arisen about Ebola and Marburg viruses, such as their genome organization, structure, life cycle and pathogenicity. The compilation of data in *Ebola and Marburg Viruses* provides a good basis for understanding these and other issues concerning the mechanism of action of filoviruses. Nonetheless, important matters, such as the reservoir of the viruses, remain unsolved.

The book is divided into 12 chapters. The first three chapters deal with genome organization, the replication and transcription of filoviruses, and the structure of their viral proteins and glycoproteins. Chapters 4-6 discuss the life cycles of the Marburg and Ebola viruses, including the molecular mechanisms of their entry (Chap. 4), the roles of their matrices in their life cycles (Chap. 5), and their maturation (Chap. 6). Pathogenicity in different animal species is addressed in the following three chapters: “Filovirus pathogenesis in non-human primates” (Chap. 7) “Ebola virus infection in the Guinea pig” (Chap. 8), and “Pathogenesis of filovirus infection in mice” (Chap. 9), which also discusses “Recommendations for further research”. Chapters 10-12 focus on cellular and molecular mechanisms of pathogenicity, explaining the “Role of endothelial cells in filovirus hemor-
rhagic fever” (Chap. 10), the “Modulation of innate immunity by filoviruses” (Chap. 11) and the “Cellular and molecular mechanisms of Ebola pathogenicity and approaches to vaccine development” (Chap. 12).

The structure of the book facilitates its reading, due to the division of each chapter into brief and precise sections, and to the length of the chapters, which does not exceed 40 pages each. The language, even though technical in some parts, is not difficult to understand, even for non-scientists. The tables and graphics provide good supporting material for the chapters and help in understanding topics such as the filoviral replication and transcription system (p. 8), the expression strategies of the glycoproteins of filoviruses (p. 61), the molecular model for filovirus entry (p. 115), and the Ebola viral genes and gene products (p. 139). In Chap. 5, devoted to the “Roles of filoviral matrix and glycoproteins in the viral life cycle”, some very interesting electron micrographs of Ebola virus particle formation are shown. Images of the result of Ebola virus infection and its development in non-human primates can be seen in Chap. 7, as well as a “Paradigm showing key cellular events in EBOV (Ebola virus) pathogenesis in non-human primates” (p. 224), which summarizes the steps that take place in the host response to infection such as the “induction of monocytes/macrophages to release a variety of soluble factors that likely trigger a host of downstream events including bystander apoptosis of lymphocytes, activation of the coagulation cascade, and disruption of the vascular endothelium. The end result is loss of homeostasis and dysregulation of the host immune response.”

As a whole, this book is an excellent compilation of all currently available data concerning filoviruses. Ebola and Marburg viruses are of particular public concern due to their ability to cause highly lethal epidemics, especially in countries with limited resources to contain viral infections. Thus, the development of vaccines is crucial to preventing outbreaks of these viruses, while continuing investigations into their biology will help in treating victims of infection.

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CORRIGENDUM

Open access. A turning point in scientific publication
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The last sentence of the Editorial in the September issue (p. 161) should have read:
Otherwise, those authors will be forced, as a researcher from Slovakia stated in a letter to Science on March 5, 2004 [2], “to read the articles from PloS Biology—for free—and try to publish [their] work in Science or Nature—also for free.”

In addition, reference No. 2 should read: Celec P (2004) Open access and those lacking funds. Science 303:1467