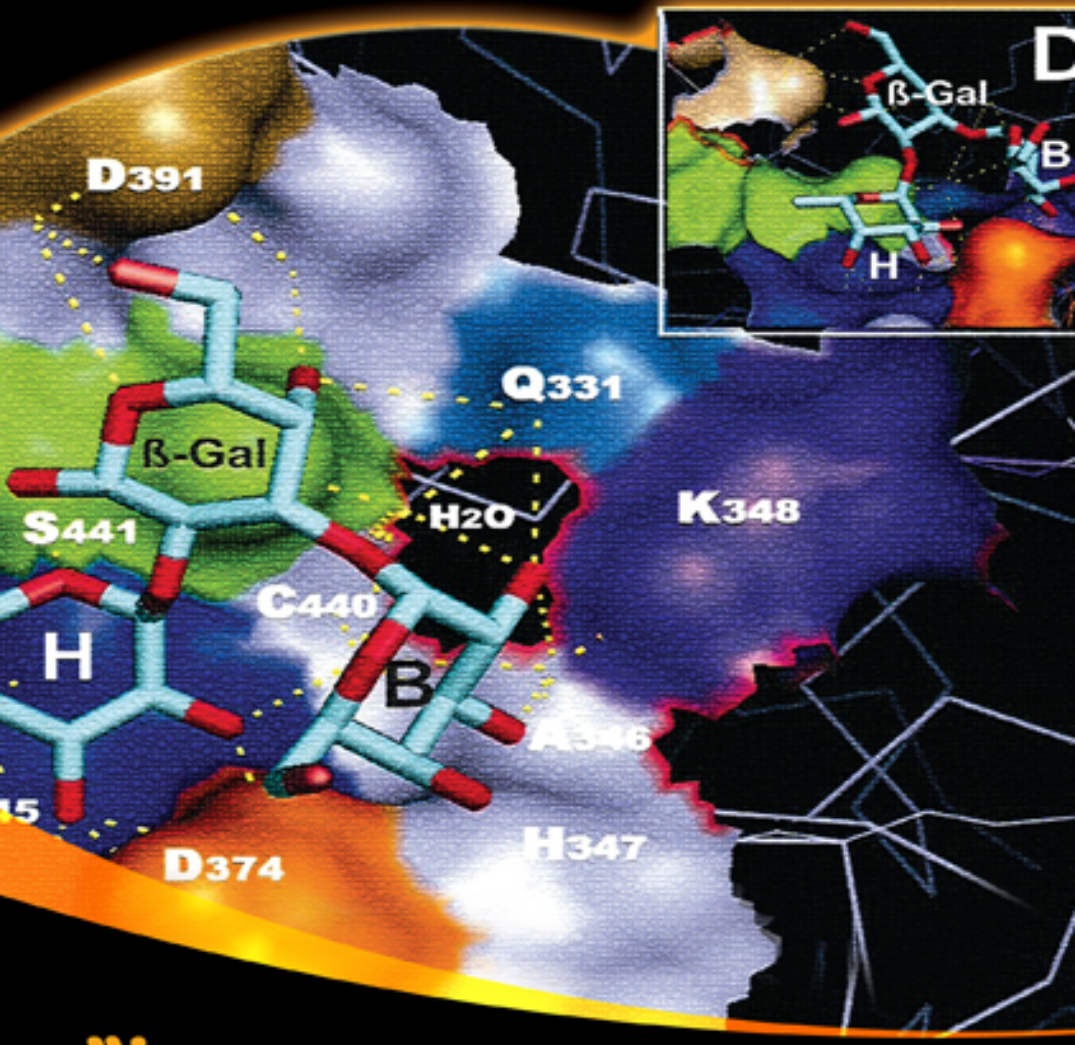
RNA VIRUSES

Host Gene Responses to Infections

edited by

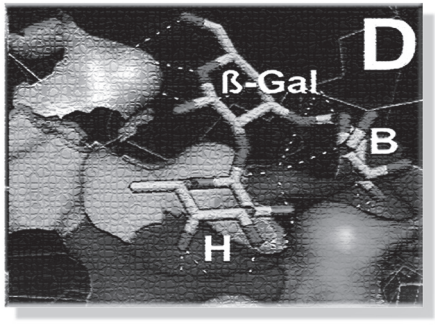
Decheng Yang



World Scientific

RNA VIRUSES

Host Gene Responses to Infections



This page intentionally left blank

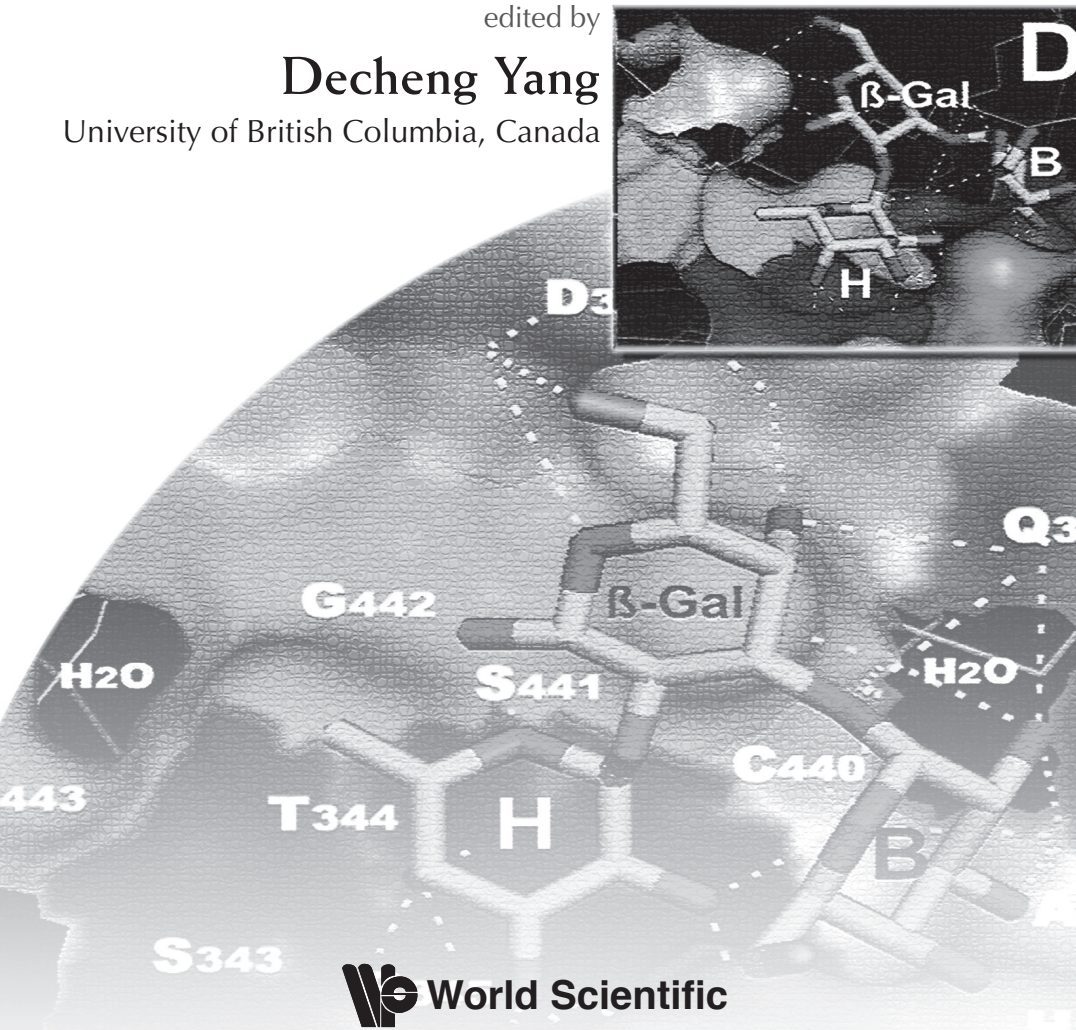
RNA VIRUSES

Host Gene Responses to Infections

edited by

Decheng Yang

University of British Columbia, Canada



World Scientific

NEW JERSEY • LONDON • SINGAPORE • BEIJING • SHANGHAI • HONG KONG • TAIPEI • CHENNAI

Published by

World Scientific Publishing Co. Pte. Ltd.

5 Toh Tuck Link, Singapore 596224

USA office: 27 Warren Street, Suite 401-402, Hackensack, NJ 07601

UK office: 57 Shelton Street, Covent Garden, London WC2H 9HE

Library of Congress Cataloging-in-Publication Data

RNA viruses : host gene responses to infections / editor, Decheng Yang.

p. ; cm.

Includes bibliographical references and index.

ISBN-13: 978-981-283-379-2 (hardcover)

ISBN-10: 981-283-379-X (hardcover)

1. RNA viruses. 2. Viral genetics. I.Yang, Decheng.

[DNLM: 1. Host-Pathogen Interactions. 2. RNA Viruses--physiology. 3. Gene Expression Regulation, Viral. 4. RNA Interference. 5. RNA Viruses--genetics. QW 168 R6268 2009]

QR395.R584 2009

579.2'5--dc22

2008035064

British Library Cataloguing-in-Publication Data

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

Typeset by Stallion Press

Email: enquiries@stallionpress.com

Printed in Singapore.

Contents

Contributors

Peter Alff
Molecular and Cellular Biology Graduate Program
Department of Medicine, Stony Brook University,
Stony Brook
N.Y. 11794 USA

Robert D. Allison
Infectious Diseases and Immunogenetics Section
Department of Transfusion Medicine
Clinical Center, NIH
Building 10, Room 1C711, 900 Rockville Pike
Bethesda, MD 20892 USA

Aniuska Becerra Artiles
University of Massachusetts Medical School
Center for Infectious Disease and Vaccine Research
55 Lake Ave. North, Worcester
MA 01655 USA

Mario Barro
Global Vaccines, Inc.
7020 Kit Creek Road,
Research Triangle Park,
NC, 27709-4827 USA

Christopher F. Basler
Department of Microbiology
Box 1124, Mount Sinai School of Medicine
1 Gustave L. Levy Place
New York, NY 10029 USA

Thomas. F. Baumert
Inserm, U748, Strasbourg, France
Université Louis Pasteur
Strasbourg
France

Service d'Hépatogastroentérologie
Hôpitaux Universitaires de Strasbourg
Strasbourg
France

Raghavan Bhuvanakantham
Flavivirology Laboratory
Department of Microbiology
5 Science Drive 2
National University of Singapore
117597 Singapore

Irene Bosch
University of Massachusetts Medical School
Center for Infectious Disease and Vaccine Research
55 Lake Ave. North
Worcester, MA 01655 USA

Allan R. Brasier
Departments of Medicine
Biochemistry and Molecular Biology, and the
Sealy Center for Molecular Medicine
The University of Texas Medical Branch
Galveston, TX 77555-1060 USA

Sanjeev Choudhary
Departments of Medicine, Biochemistry, and Molecular Biology, and the
Sealy Center for Molecular Medicine
The University of Texas Medical Branch
Galveston, TX 77555-1060 USA

Vincent T. K. Chow
Infectious Diseases Program
Department of Microbiology
Yong Loo Lin School of Medicine
National University of Singapore
5 Science Drive 2
Kent Ridge 117597, Singapore

Tibor Farkas
Division of Infectious Diseases
Cincinnati Children's Hospital Medical Center
University of Cincinnati, College of Medicine
3333 Burnet Avenue
Cincinnati, OH45229, USA

Friederike Feldmann
Special Pathogens Program
National Microbiology Laboratory
Public Health Agency of Canada
Winnipeg, Manitoba, Canada

Heinz Feldmann
Special Pathogens Program
National Microbiology Laboratory
Public Health Agency of Canada
Winnipeg, Manitoba Canada

Department of Medical Microbiology
University of Manitoba
Winnipeg, Manitoba, Canada

Current address:
Laboratory of Virology
Rocky Mountain Laboratories
National Institute of Allergy and Infectious Diseases
National Institute of Health
903 South 4th Street, Hamilton
Montana 59840 USA

Guang Gao
The James Hogg iCAPTURE
Centre for Cardiovascular and Pulmonary Research
Department of Pathology and Laboratory Medicine
University of British Columbia
Providence Heart + Lung Institute
St. Paul's Hospital
Vancouver, BC V6Z 1Y6, Canada

Irina Gavrilovskaya
Molecular and Cellular Biology Graduate Program
Department of Medicine, Department of Molecular Genetics, and Microbiology
Stony Brook University
Stony Brook, N.Y. 11794

Northport VA Med. Center
Northport N.Y. 11768 USA

Katrina Gee
Department of Microbiology & Immunology
Queen's University, Kingston
Ontario, Canada

Joan Geisbert
National Emerging Infectious Diseases Laboratories Institutes
Boston University School of Medicine,
Boston, MA, USA

Thomas W. Geisbert
National Emerging Infectious Diseases Laboratories Institutes
Boston University School of Medicine
Boston, USA

Bumsuk Hahm
Viral-Immunobiology Laboratory
Department of Immunology and Microbial Science
The Scripps Research Institute
La Jolla, CA 92037, USA

Current Address:
Departments of Surgery and Molecular Microbiology and Immunology
Center for Cellular and Molecular Immunology
University of Missouri-Columbia School of Medicine
One Hospital Dr. Columbia
MO 65212, USA

David N. Irani
Department of Neurology
University of Michigan Medical School
Biomedical Sciences Research Building
Room 4007, 109 Zina Pitcher Place
Ann Arbor
Michigan 48109-2200, USA

Akiko Iwasaki
Department of Immunobiology
Yale University School of Medicine
300 Cedar Street
TAC S655B
New Haven CT 06520 USA

Kuan-Teh Jeang
National Institute of Allergy and Infectious Diseases
National Institutes of Health

Molecular Virology Section, LMM Bethesda
MD, 20892 USA

Xi Jiang
Division of Infectious Diseases
Cincinnati Children's Hospital Medical Center
University of Cincinnati
College of Medicine
3333 Burnet Avenue
Cincinnati, OH45229, USA

Fatah Kashanchi
The George Washington University Medical Center
Department of Immunology
Microbiology and Tropical Medicine
2300 I Street NW
Washington, DC 20037 USA

Zachary A. Klase
The George Washington University Medical Center
Department of Immunology
Microbiology and Tropical Medicine
2300 I Street NW
Washington, DC 20037 USA

Shyam Kottilil
Laboratory of Immunology
National Institute of Allergy & Infectious Diseases
NIH, Building 10, Room 11N204, 900 Rockville Pike
Bethesda, MD 20892 USA

Marko Kryworuchko
Infectious Disease and Vaccine Research Centre
Research Institute, Division of Virology
Children's Hospital of Eastern Ontario
Departments of Pathology and Laboratory Medicine, and Biochemistry, Microbiology and Immunology
401 Smyth Road, University of Ottawa, Ottawa
Ontario, Canada

Ashok Kumar
Infectious Disease and Vaccine Research Centre
Research Institute, Division of Virology
Children's Hospital of Eastern Ontario
Departments of Pathology and Laboratory Medicine, and Biochemistry, Microbiology and Immunology
401 Smyth Road, University of Ottawa, Ottawa
Ontario, K1H 8L1 Canada

Melanie Lambotin
Inserm, U748, Strasbourg, France
Université Louis Pasteur
Strasbourg, France

Patrick W. K. Lee
Department of Microbiology & Immunology
Faculty of Medicine
Sir Charles Tupper Medical Building
7th floor, Room 7-P 5850 College Street
Halifax, NS B3H 1X5, Canada

W. F. Leong
Infectious Diseases Program
Department of Microbiology
Yong Loo Lin School of Medicine
National University of Singapore
5 Science Drive 2
Kent Ridge 117597, Singapore

Travis Lim
Department of Pathology and Laboratory Medicine
University of British Columbia
The iCAPTURE Center
Providence Heart + Lung Institute
St. Paul's Hospital
Vancouver, BC V6Z 1Y6, Canada

Dennis M. Lindell
Department of Pathology
University of Michigan Medical School
Ann Arbor, MI 48109 USA

Ping Liu
Departments of Medicine, Biochemistry and Molecular Biology and the Sealy Center for Molecular Medicine
The University of Texas Medical Branch
Galveston, TX 77555-1060 USA

Carolina B. López
Department of Microbiology
Mount Sinai School of Medicine
New York, 10029 NY USA

Stephan Ludwig
Institute of Molecular Virology (IMV)
ZMBE, Westfälische-Wilhelms-University
Von-Esmarch Str.
56, D-48149 Münster, Germany

Nicholas W. Lukacs
Department of Pathology
University of Michigan Medical School
Ann Arbor
MI 48109 USA

Honglin Luo
The James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research
Department of Pathology and Laboratory Medicine, University of British Columbia
Providence Heart + Lung Institute, St. Paul's Hospital
Vancouver, BC V6Z 1Y6, Canada

Wei Ma
Biochemistry, Microbiology and Immunology
401 Smyth Road, University of Ottawa, Ottawa
Ontario, Canada

Erich R. Mackow
Molecular and Cellular Biology Graduate Program
Department of Medicine, Department of Molecular Genetics and Microbiology
Stony Brook University
Stony Brook, N.Y. 11794

Northport VA Med. Center
Northport N.Y. 11768 USA

Paola Marcato
Department of Microbiology & Immunology
Faculty of Medicine, Sir Charles Tupper Medical Building
7th floor, Room 7-P 5850 College Street
Halifax
NS B3H 1X5, Canada

Katherine J. Martin
University of Massachusetts Medical School
Center for Infectious Disease and Vaccine Research
55 Lake Ave. North
Worcester, MA 01655 USA

Bruce McManus
The James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research
Department of Pathology and Laboratory Medicine
University of British Columbia
Providence Heart + Lung Institute, St. Paul's Hospital
Vancouver, BC V6Z 1Y6, Canada

Sasmita Mishra
Biochemistry, Microbiology and Immunology
401 Smyth Road, University of Ottawa, Ottawa
Ontario, Canada

Tetsuya Mizutani
Department of Virology I
National Institute of Infectious Diseases
Gakuen 4-7-1, Musashimurayama
Tokyo 208-0011, Japan

Monty Montano
Center for HIV-1/AIDS Care and Research
650 Albany Street, Boston University School of Medicine & Harvard
School of Public Health
Boston, MA 02118 USA

Thomas M. Moran
Department of Microbiology, Mount Sinai School of Medicine
New York, 10029 NY USA

Christoph Neumann-Haefelin
Department of Medicine II
University Hospital Freiburg
Hugstetter Strasse 55
D-79106 Freiburg
Germany

Mah-Lee Ng
Flavivirology Laboratory, Department of Microbiology
5 Science Drive 2
National University of Singapore
117597 Singapore

Michael B.A. Oldstone
Viral-Immunobiology Laboratory
Department of Immunology and Microbial Science and Department of Infectology
The Scripps Research Institute
La Jolla, CA 92037 USA

Da Pan
Department of Microbiology & Immunology
Faculty of Medicine, Sir Charles Tupper Medical Building
7th floor, Room 7-P 5850 College Street
Halifax, NS B3H 1X5, Canada

John T. Patton
Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD 20892 USA

Janusz T. Pawęska
Special Pathogens Unit, National Institute for Communicable Diseases of the National Health Laboratory Service
Modderfontein Road 1, Sandringham-Johannesburg
2131 South Africa

Oliver Planz
Friedrich-Loeffler-Institute (FLI)
Paul-Ehrlich Str.
28, D-72076 Tübingen
Germany

Stephan Pleschka
Institute for Medical Virology
Justus-Liebig-University
Frankfurter Str.
107, D-35392 Giessen
Germany

Natalie A. Prow
Department of Molecular Microbiology and Immunology
The Johns Hopkins University Bloomberg School of Public Health
Baltimore
Maryland, 21205 USA

Balaji Ramanathan
Department of Biomedical Sciences
Atlantic Veterinary College
University of Prince Edward Island
550 University Ave.
Charlottetown, PE
C1A 4P3, Canada

Carol Shoshkes Reiss
Biology Department
New York University
100 Washington Square East
New York, NY 10003, USA

Paola Sebastiani
Boston University School of Medicine
Department of Biostatistics
Boston, MA 02118 USA

Adrish Sen
Molecular and Cellular Biology Graduate Program
Department of Medicine
Department of Molecular Genetics and Microbiology
Stony Brook University
Stony Brook, N.Y. 11794 USA

Nandini Sen
Molecular and Cellular Biology Graduate Program
Department of Medicine
Department of Molecular Genetics and Microbiology
Stony Brook University
Stony Brook, N.Y. 11794 USA

Maya Shmulevitz
Department of Microbiology & Immunology
Faculty of Medicine
Sir Charles Tupper Medical Building
7th floor, Room 7-P 5850 College Street
Halifax
NS B3H 1X5, Canada

Françoise Stoll-Keller
Inserm, U748, Strasbourg, France
Université Louis Pasteur
Strasbourg, France

Ming Tan
Division of Infectious Diseases
Cincinnati Children's Hospital Medical Center
University of Cincinnati, College of Medicine
3333 Burnet Avenue
Cincinnati, OH45229, USA

Robert Thimme
Department of Medicine II
University Hospital Freiburg
Hugstetter Strasse 55
D-79106 Freiburg, Germany

Bing Tian
Departments of Medicine, Biochemistry and Molecular Biology, and the Sealy Center for Molecular Medicine
The University of Texas Medical Branch
Galveston, TX 77555-1060 USA

Rajas V. Warke
University of Massachusetts Medical School
Center for Infectious Disease and Vaccine Research
55 Lake Ave. North, Worcester
MA 01655 USA

Thorsten Wolff
Robert-Koch-Institute (RKI)
Nordufer 20, D-13353 Berlin
Germany

Decheng Yang
Department of Pathology and Laboratory Medicine
University of British Columbia
The iCAPTURE Center, Providence Heart + Lung Institute
St. Paul's Hospital
Vancouver, BC V6Z 1Y6, Canada

Mary H. Zhang
Department of Pathology and Laboratory Medicine
University of British Columbia
The iCAPTURE Center, Providence Heart + Lung Institute
St. Paul's Hospital
Vancouver, BC 86Z 1Y6, Canada

Preface

With the recognition of the first HIV/AIDS case about 25 years ago, a number of emerging and re-emerging infectious diseases of humans and animals have been reported, such as SARS, bird flu, West Nile virus infection, Ebola virus outbreaks, etc. These diseases have caused the death of millions of lives and uncounted economic loss. Interestingly, these infectious diseases are all caused by viral infections and in particular, by RNA viruses. This is probably due to, at least in part, the high mutation rate of RNA viruses, which is attributed to the lack of proofreading activity of viral RNA-dependent RNA polymerase. Thus, in the recent years, research focusing on understanding the molecular pathogenesis of RNA viruses have been very active and made tremendous advances. In this book, we have organized 27 chapters written by highly respective virologists in the field to review the molecular mechanisms of host-virus interactions, particularly on the host gene responses to RNA viral infections. This book is the first volume ever to focus on such a topic in human and animal RNA viruses. It includes chapters on analyses of host differential gene expressional profiles using cutting edge technologies, host innate and adapted immune responses to viral infections, virus-induced signal transduction pathways related to disease occurrence, and recently discovered novel mechanism on RNA interference in regulation of host-virus interactions. These topics cover a number of representatives of almost all major human and animal RNA virus groups, which are divided into four sections, including retrovirus, positive single strand (ss)RNA virus, negative ssRNA virus and double strand (ds)RNA virus.

HIV is the most studied virus. As a retrovirus representative, four chapters are prepared in Section I to cover the recent progress on this

important virus. The first chapter reviews the analyses of global gene expression profiles induced by HIV-1 infection in different *in vitro* and *in vivo* models using gene microarray technology and bioinformatic approach. It illustrates the host signatures that can be identified during HIV infection and discusses the utility and significance of these signatures, including an analysis of the types of these genes and biological categories associated with infection. The second chapter discusses the host immune responses to HIV infection. The author highlights the pathogenesis of HIV infection, the nature of innate and adaptive immune responses to HIV in the control of HIV replication and strategies to develop protective immunity in susceptible individuals. The molecular mechanism by which HIV causes cellular immune dysfunction is further discussed in view of molecular signaling in chapter three. As interactions of viral proteins with the signaling molecules in different pathways can result in the modulation of gene expression in a variety of biological process leading to immune suppression and pathogenesis, this third chapter primarily addresses the role of Tat, Nef and Vpr, the best studied HIV proteins, in viral replication, apoptosis, and cytokine expression. In addition, as HIV studies have led the research in the field of virology and made most significant progress comparing with that of other viruses, a fourth chapter on the siRNA/microRNA-mediated host-virus interactions has been added. This chapter discusses the newly emerging mechanism of gene expressional regulation through RNA interference (RNAi), a so called "new arm of immune response", in the host responses to HIV infection.

The representatives of the negative ssRNA viruses in Section II include influenza virus, respiratory syncitial virus (RSV), vesicular stomatitis virus, Hantavirus and measles virus. This group of viruses, particularly the influenza virus, is one of the most dangerous global health threat to man as well as to many other mammals and birds. This virus once caused millions of death of humans during several pandemic outbreaks in the last century; and in recent years, the bird flu caused by avian influenza virus H5N1 strain re-emerges frequently and has a high potential to reassort (antigenic shift) with human influenza virus genome to generate a new mutant that is lethal to the human population**.** Thus, our urgent task is to better understand the viral genetics and pathogenesis to prevent the

outbreak of this deadly virus. Two chapters are arranged to review the recent advances in this field of studies. One chapter provides an overview of the current knowledge of the virus-induced signal pathways, particularly on functional kinase signaling and apoptotic events in influenza virus-infected cells and how these viruses have learned to misuse these cellular responses for efficient replication. The other chapter discusses the multiple elements of immunity that participate in the response to influenza virus infection based on current data obtained from *in vitro* and *in vivo* systems.

The other viruses in this group are also common human and animal pathogens. For example, RSV is a member of the family *Paramyxoviridae* and a leading cause of severe lower respiratory tract infection clinically manifesting as pneumonia and bronchiolitis, particularly in children. The first chapter for this virus reviews the impact of RSV disease, the processes that the virus uses to replicate in airway epithelial cells, the signaling pathways responsive to this virus infection, and how non-structural proteins modulate this process. An additional chapter highlights the literature regarding the host immune responses to RSV infection, including viral recognition by host innate immune cells via pattern recognition receptors, resulting in chemokine and cytokine production and the further development of host adaptive immunity. Hantavirus is another pathogen mainly infecting respiratory systems. This virus was first discovered during the Korean War and re-emerged in many states of US in 1990s. It is transmitted via wild rodents and causes two vascular permeability-based diseases: Hemorrhagic Fever with Renal Syndrome and Hantavirus Pulmonary Syndrome. The viral infection and host innate immunity is reviewed in one chapter with the emphasis on the role of pathogenic Hantavirus G1 or Gn proteins in regulating the early innate cellular responses. Vesicular stomatitis virus, a natural epizootic among farm animals which is spread by sand-flies, is often used for experimental acute infections of mice. Two chapters are included to cover its molecular pathogenesis. One summarizes current understanding of host innate and adaptive immune responses and viral evasion of innate responses. In addition, the potential power of this virus for vaccine platforms and for oncolysis is also addressed. The other chapter makes a detailed expansion on the host immune responses in view of virus recognition and autophagy

signaling pathway. Autophagy is now being appreciated as a pathway used by the innate immune system to recognize and destroy viruses or, in certain viruses, to promote viral replication. This chapter provides a deep discussion on latest studies characterizing novel mechanisms of innate viral recognition and immunity. The last chapter in the negative ssRNA virus section provides updated knowledge on measles virus (MV) pathogenesis with emphasis on virus-induced immunosupression and central nervous system (CNS) diseases. By incorporating outcomes of research on transgenic animal models and clinical studies on host innate immunity as well as data on the MV-dendritic cell interaction and receptor usage, this chapter provides better understanding of the molecular immunology of MV infection.

The host gene responses to positive ssRNA virus are discussed in Section III. This group of viruses contains a number of important human and animal pathogens, such as SARS-CoV, Ebola virus, West Nile virus, hepatitis C virus, Coxsackievirus, dengue virus, norovirus, and Sindbis virus**.** This group of viruses is one of the major sources of emerging and re-emerging pathogens of human and animal diseases. The sudden emerging of Severe Acute Respiratory Syndrome (SARS) in Asia countries in 2002 caused a severe tension on public health worldwide. As the SARS-CoV, a new emerging human coronavirus strain, which is predominantly spread by the respiratory route through aerosol particles and has a high fatality rate, its pandemic outbreak will cause an unimagined severe threat to our society. For this reason, a great effort has been made in a number of laboratories all over the world to study this virus during the past six years. Based on the latest advances available, two chapters have been organized. One focuses on discussion of signal transduction pathways, particularly the virus-induced apoptosis signaling pathway and cell survival signaling pathway, as well as their cross-talk to determine the death and survival of virus-infected cells. The other chapter summarizes the global analyses of host gene expression profiles by genomic and proteomic technologies. These studies have revealed alterations in the transcription and translation of genes belonging to various functional groups, which provide new insights into the host-pathogen interactions and pathophysiology of SARS-CoV infection. Marburg and Ebola viruses, in family *Filoviridae*, are prototype viral hemorrhagic fever pathogens and cause

a fulminant hemorrhagic disease in humans and nonhuman primates. Since the initial discoveries of these agents over 30 years ago, several large outbreaks have occurred in Africa countries. Today, MARV and EBOV are feared worldwide as highly pathogenic agents that pose a biohazard threat to public health. Two chapters have been included in this volume to focus on either viral infection-activated signal transduction pathways or host immune responses to infection. In addition, the authors have also added brief discussion of their first-hand experience on medical responses to control the infection during their trips to the outbreak sites of Africa countries.

West Nile virus, a representative of the family *Flaviviridae,* originally emerged in Africa and was then transmitted to many other countries including recently to United States and Canada. As this virus is maintained in an enzootic cycle between mosquitoes and birds and enters the CNS from blood, it can cause diseases from febrile illness to fatal encephalitis in humans and other vertebrates. Two chapters are devoted either to the genome-wide analysis of gene expression profile related to pathology or to the host innate and adapted immune responses to viral infection. HCV and Dengue virus are another two species of family *Flaviviridae*. HCV infection is a major cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma worldwide. With an increasing large number of infected individuals in the world, HCV has a major impact on public health. Two chapters draw information together on this virus. One provides a review on DNA microarray analyses of gene expression patterns in host gene responses to HCV infection in state-of-the-art model systems and in HCV-infected patients. Specifically, contribution of gene expression profiling for the understanding of HCV-host interactions during the viral life cycle, outcome of viral infection and host responses to antiviral treatment *in vivo* are discussed. The other chapter reviews the recent progress on the understanding of innate, humoral, and $CD4^+$ and $CD8^+$ T cells response to HCV infection and discusses the multiple mechanisms by which HCV evades from these responses. Dengue virus has re-emerged as a major health problem in the tropics, particularly among children. This mosquito-borne flavivirus infection often results in a febrile illness. Less frequently, infections cause dengue hemorrhagic fever, a potentially fatal vascular leakage syndrome. The chapter on this virus

reviews the events of dengue vascular leakage and hypotheses that have been put forth. The authors use their data and many others to discuss the genome-wide identification of host gene expression in response to dengue virus-induced damage as well as the central role of certain selected genes in gene expression network *in vitro* and regulation of disease *in vivo*.

Coxsackie B group viruses are representatives of family *Picornaviridae*. Coxsackievirus B3 (CVB3) and CVB4 are the two most studied serotypes in this group. CVB3 is the primary pathogens of myocarditis and dilated cardiomyopathy, particularly in children and young adults. CVB4 is the major cause of pancreatitis or type I diabetes mellitus. The first chapter for this virus describes the differential gene expression profiles identified using animal models by genomic and proteomic technologies. These genes or gene groups include cytokine/chemokine profiles, antiviral genes, or genes involved in cell survival, apoptosis, fibrosis, immune responses and others. In addition, the roles of certain viral non-structural genes in regulating host-cell macromolecule synthesis and trafficking are also discussed. The second chapter for CVBs covers the virus-activated signal transduction pathways during viral infection, which include the pathways mediated by tyrosine kinases, phosphatases and MAPKs, particularly the pathway associated with the activation of the ubiquitin-proteasome. The authors also added a discussion of the consequences of these coxsackievirus-activated pathways in viral pathogenesis. The host response to norovirus is thoroughly discussed in a chapter by focusing on molecular pathogenesis. Norovirus is recognized as the major cause of epidemics of gastroenteritis worldwide. The high frequency of norovirus disease can be explained by the low infectious dose, the wide genetic and antigenic variations, the high titre, prolonged shedding of viruses by ill and asymptomatic patients, and the high environmental stability of virions. The recent progress on the understanding of viral replication and virus-host interaction, identification of norovirus receptors, and studies of viral pathogenesis by the development of cell culture and reverse genetics systems are discussed. This section concludes with a chapter on the latest available data on sindbis virus. Sindbis virus, a member of Alphavirus in family *Togaviridae*, exhibits a broad host range of animals and humans. This viral infection spans a full range of diseases, including asymptomatic infection, self-limited febrile illness, acute

arthropathy, and rarely, invasion of the central CNS resulting in acute encephalomyelitis. This chapter provides up-to-date knowledge on host responses during sindbis encephalomyelitis in a number of experimental models, with particular emphasis on how they present effective therapeutic targets in these diseases.

This volume also includes two chapters in Section IV on host responses to infections of reovirus or rotavirus, the representatives of dsRNA virus group, in the *reoviridae* family. Although isolated from respiratory and enteric tracts, mammalian reovirus is rarely linked to human disease and thus regarded as benign. Recently, reovirus was found to preferentially kill many types of cancer cells without harming normal cells, raising the prospect of using reovirus as a cancer therapy reagent. Basic studies in reovirus biology reveal that Ras signaling in host cells provides advantages for reovirus replication in transformed cells over normal cells. Thus, the first chapter in this group focuses mainly on reovirus infection in the context of cancer, or transformed cells and highlights the signaling pathways of cancer cells that make them highly infectible by reovirus. Another chapter for this group covers the molecular mechanism of interactions between rotavirus protein and host immune system. Rotavirus is the primary cause of life-threatening diarrhea in young children. Recent studies have revealed that rotaviruses subvert the antiviral effects of interferons through the actions of its NSP1, a viral non-structural protein with a putative N-terminal RING-finger motif and a hypervariable C-terminal region. Its unique structure combined with its manipulation of the proteasomal pathway to degrade the interferon regulatory factors**,** suggests that rotavirus NSP1 is an E3 ubiquitin ligase and serves as a highly effective broad-spectrum antagonist of the innate immune response.

It should be noted that this book is devoted only to human and animal RNA viruses. However, certain aspects of the viral biology and pathogenesis may be useful information for study of other groups of viruses. Since this book is designed primarily as a reference, the authors have attempted to make each chapter comprehensible when read by itself, even though this involves occasional repetition of information in other chapters. In addition, due to the space limitation, I have asked the authors to cite the most recent references, thus I apologise to the authors whose published articles have not been cited in the chapters. I hope that this book will be

of value, not only to biomedical researchers, undergraduate/graduate students and medical students in virology and viral pathogenesis but also for clinicians in infectious diseases.

I thank all of my colleagues who have generously contributed to this book. Particularly, I am grateful to Dr. Bruce McManus for his counsel and encouragement during this work. I would also like to thank the people in my laboratory, particularly Travis Lim and Mary Zhang, for their assistance in editing this book.

Decheng Yang

SECTION I

Retrovirus

This page intentionally left blank

CHAPTER 1

Efforts to Characterize Host Response to HIV-1 Infection

Monty Montano & Paola Sebastiani

ABSTRACT

The human immunodeficiency virus type 1 (HIV-1) continues to expand among vulnerable and resource-limited populations worldwide, with the global prevalence approaching 40 million. Over the past twenty years, substantial progress has been made in the identification and characterization of the role for specific host factors on infection and disease progression. Furthermore, there is wide recognition that both viral and host genetic variation, as well as environmental and behavioral factors underlie the complexity of host transcriptional response and disease outcome. Despite this complexity, a compelling question is whether common features of host genomic response to infection, i.e., an "HIV-1 induced host signature" can be defined, in a form that would be robust under differing experimental models and clinical conditions. If achieved, this might help to synthesize a growing body of data based on genome-wide expression profiles and would be a useful reference frame for the identification of unique gene expression patterns that are associated with favorable response to infection, or alternatively associated with undesired outcomes. In this review, we will attempt, in the context of a growing body of literature that describes human and viral variation, to describe host response to HIV infection *in vitro* and *in vivo*. We will apply methodologies operational in our laboratory to existing HIV infection datasets available in the Gene Expression Omnibus (GEO) database,

derived from expression data obtained *in vivo*. Our goal will be to illustrate the type of host signatures that can be identified and to discuss the utility and significance of these signatures, including an analysis of the types of genes and biological categories associated with infection and their utility. To achieve this we will employ methodologies based on Bayesian modeling of gene expression data for discovering molecular profiles that characterize host signatures. We will provide examples of HIV induced expression profiles that can be derived from these datasets and present host signatures for infection. We will discuss the strengths and weaknesses of this approach and the intrinsic limitations when challenged with the huge diversity of host-pathogen conditions in biological data derived from *in vivo* sampling.

1. INTRODUCTION

The human immunodeficiency virus type-1 (HIV-1) epidemic remains a significant challenge to global health, despite nearly 25 years of research that has led to countless insights into the molecular, pathobiologic and epidemiologic details associated with its infection. Nevertheless, HIV research has provided fundamental insights that have shed light on multiple viral life strategies and host immune mechanisms engaged in response to infection. As new research tools continue to be developed, they have been invariably applied towards a better understanding of this pandemic. Currently, as a research community, we find ourselves firmly within an era of applied genomic biology, i.e., understanding the variation in human genes and the impact of that polymorphism on host response profiles to many disease states and infections, including HIV infection. In the past ten years, genomic approaches have shed much light onto host variation in response to infection by HIV; however, much remains unknown.

A potentially powerful new approach to following pathogenic trajectory in both natural history and drug intervention studies is through the use of genotypic and soluble biomarkers. Biomarkers have the potential for monitoring infection, identifying host correlates for protection, disease progression and profiles for desired treatment outcomes. Identifying and monitoring biomarkers would streamline the testing process for vaccine candidates and therapeutic regimes in current and future trials.