

---

## 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 syncytial 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 immunosuppression 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<sup>+</sup> and CD8<sup>+</sup> 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