Hepatitis B Virus and Liver Disease

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To our mentor Professor Juei-Low Sung
Jia-Horng Kao
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In memory of my parents Ping-Pei Chen and Shiu-Chin Tseng Chen
By Ding-Shinn Chen
To my parents Shi-Yang Kao and Wen-Shu Ho
By Jia-Horng Kao

Foreword

This compact monograph represents a welcomed update on hepatitis B virus (HBV) and the disease it causes. The 17 chapters review the full spectrum of issues regarding HBV—its structure, molecular virology, replicative life cycle, immune pathogenesis, modes of transmission, epidemiology, natural history, complications, prevention, and treatment. Special chapters deal with the important issues of maternal-infant transmission; the disease in children, in immunosuppressed individuals, and in hepatitis C virus-, hepatitis D virus-, and human immunodeficiency virus-coinfected individuals; carcinogenesis; fibrosis progression; noninvasive means of assessment; and the needs for future basic and translational research. The authors are internationally recognized experts from Asia, Australia, the United States, and Europe, reflecting the global distribution and burden of HBV. Importantly, this book goes far beyond what can be covered in standard textbooks of medicine, hepatology, infectious diseases, and even virology.

There are several ways to view this monograph: a big book for a small topic, or a small book for a big topic, or perhaps both. For one thing, the book has two topics—one is small and one big—the hepatitis B virus (small) and the disease that it causes (big).

HBV is small. With its circular, partially double-stranded genome of only 3200 bases, it is the smallest known human DNA virus. This number of bases equates to about ten base pairs per page, or hundreds of words for each base. If HBV had a single open reading frame, it would produce a single moderately sized protein only. HBV, however, produces seven different polypeptides (pre-S1, pre-S2, small HBsAg, HBV polymerase, HBcAg, HBeAg, and X), each with a different structure and distinct function. In addition, the 7 HBV polypeptides contain far more amino acids than could be encoded by 3200 bases. How does this small DNA virus accomplish this big task?

The answer is that the HBV genome is small but efficient. The four open reading frames of HBV (S, C, P, and X) partially overlap each over, but produce different proteins because they are translated in different reading frames. The gene regions also have no introns. By frameshifting and not using introns, the same nucleic acid sequences can produce two or three different amino acid sequences, and each base pair in the genome can be used twice if not three times (particularly in view of the gene regulatory regions). In addition, some of the gene regions have several start sites so that polypeptides of different lengths are produced. The S gene region

possesses three start signals which allow it to encode three forms of HBsAg differing in their length and tertiary structure as well as their functions. The C region has two potential start sites. One start signal encodes the nucleocapsid core antigen (HBcAg) which serves as a structural component of the virus. The second C region start site includes a pre-core region and, after further posttranslational editing, produces HBeAg, a secreted, small molecular weight protein that circulates in the serum. The P region overlaps with the C, S, and X regions and produces a large multifunctional polymerase (both DNA and RNA dependent) and a separate ribonuclease activity. Finally, the small X region produces a polypeptide which is retained intracellularly and probably acts as a transcription factor. Each of the seven HBV polypeptides is essential; deletion of any of them results in a marked decline or termination of replication.

Thus, HBV is small in size but versatile in function and complex in structure. It also has a unique replicative strategy – through an RNA intermediate. Currently, the reasons for the complexity of structure and replicative cycle remain only partially understood. Why does HBV produce such excessive amounts of HBsAg that circulate as incomplete, non-virion forms in microgram amounts during acute and chronic infection? What is the function of HBeAg that circulates in patients with HBV infection with high levels of viral replication and seems necessary to produce chronic infection but not necessarily to sustain it? How does HBV blunt or circumvent the host innate and adaptive immune response to its presence? With its compact structure and multistep replicative cycle, how and when did this virus arise during human evolution?

In contrast to the virus itself, the disease that HBV produces in humans is a very large topic. When HBV was first discovered in the late 1960s, chronic infection with hepatitis B was found to affect 5–10% of the earth's population and to be the major cause of cirrhosis and hepatocellular carcinoma worldwide. Virtually, every human population, even those in the most remote areas of the world, harbored evidence of HBV infection. In China and Southeast Asia, with the highest rates, more than 200 million persons were believed to be chronically infected. In these areas, HBV was the most frequent cause of chronic liver disease and cirrhosis. In these areas and worldwide, hepatocellular carcinoma, the most dreaded long-term consequence of chronic HBV infection, ranked among the most common causes of cancer death. At that time, there was no means of prevention or treatment of this disease. This is not changed: all as a result of the discovery of HBV and the rapid subsequent advances in diagnosis, prevention, and now treatment.

The discovery of HBV was a major milestone of twentieth-century medicine. Quite aptly, Baruch Blumberg, the discoverer of the Australia antigen, which was later found to be the surface antigen of HBV and named HBsAg, was awarded the 1976 Nobel Prize in Medicine. The global implications of this discovery were immense. Once the Australia antigen was linked to HBV, it was rapidly found to be a reliable diagnostic marker for infection leading to means of screening donor blood and elimination of posttransfusion hepatitis B. More importantly, HBsAg could be purified in high quantities from serum, inactivated by heat and chemical treatment and used as the first, effective vaccine against this disease. Recombinant vaccines

(the first in humans) then followed and are now sensibly priced and used worldwide. Therapies for HBV followed means of prevention, but have now become clearly integral to any attempt to eradicate this disease worldwide. Current oral nucleoside analogues are highly effective in suppressing HBV replication and induce clinically significant remissions in disease in almost all patients. The combined effects of vaccination and treatment have begun to have major effects on the global burden of this disease. Eradication of HBsAg and all evidence of HBV replication by therapy is still limited, but new insights and innovative approaches are now zeroing in on this next step in HBV control.

These considerations make this small, compact monograph a welcome addition to our understanding of this small, compact virus and the very important disease that is causes.

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Preface

Hepatitis B virus (HBV) was identified more than 50 years ago, and it was soon found that the infection is among the most frequent and important in humans. It causes a wide spectrum of liver diseases, spanning from fulminant hepatitis to cirrhosis and hepatocellular carcinoma. In the last couple of decades, the understanding of HBV infection, especially the management of chronic infection, has evolved drastically. The pathogenesis of this virus has become clearer after basic, clinical, and epidemiological studies. More constructively, the infection can now be prevented effectively, and the chronic infection can be suppressed efficiently, shedding light at the end of the tunnel toward the elimination of HBV infection.

However, the rapid progresses are still not well taken by many people in the medical profession. And thus, it is timely and necessary to have a monograph on this subject. We edited a book *Hepatitis B Virus and Liver Disease* which is published by Springer Science + Business Media Singapore Pte Ltd. We aimed to provide a comprehensive, state-of-the-art review of HBV infection and liver disease.

The book updated the results of basic and translational medicine including hepatitis B viral life cycle, immunopathogenesis of HBV-induced chronic liver disease, viral and host genetic factors affecting disease progression, molecular mechanism of HBV-induced hepatocarcinogenesis, and the clinical implications. The clinical aspects of chronic HBV infection were elucidated by experts in epidemiology, natural history, hepatitis B vaccination, coinfection with hepatitis C or D viruses and human immunodeficiency virus, and management of special populations like children, pregnant women, and those under immunosuppressive therapy. The implications of occult HBV infection were also discussed. Finally, the advances and perspectives in the development of novel treatments for the cure of HBV infection were included.

We hope this book can serve as a useful resource for students, health-care providers, and researchers who are interested in the management and study of patients with hepatitis B.

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Molecular Virology and Life Cycle

1

Darren J. Wong and Stephen A. Locarnini

Abstract

The hepatitis B virus is a prevalent human infection with no cure at present. It is a significant cause of global morbidity and mortality and has achieved its persistence in humans via its complex life cycle and ability to use its few protein products in a multifunctional manner to subvert and evade immune detection and clearance. These aspects of the virus are discussed in detail, as are the development of clinically important mutations in the viral genome that develop as a result of host immune selection, as well as those selected by the introduction of antiviral therapy or vaccination.

Keywords

Hepatitis B • Molecular Virology • Lifecycle • Antiviral Resistance

1 Classification

The hepatitis B virus (HBV) is the most well-known member of the virus family *Hepadnaviridae*. The species in this family are split amongst two genera—*Avihepadnavirus* and *Orthohepadnavirus*—with human HBV belonging to the latter. HBV has been further classified into ten genotypes, A to J, which are based

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