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Hepatitis Delta Virus

With 25 Figures and 12 Tables

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The cover illustration is a simplified structure of hepatitis delta virus showing the internal ribonucleoprotein complex, which contains the circular RNA genome and the two forms of the hepatitis delta antigen; the envelope proteins of hepatitis B virus form the exterior of the virus. The inset is an electron micrograph of purified hepatitis delta virus particles, and was kindly provided by Dr. John Gerin. The background immunofluorescence image is of transfected cells expressing hepatitis delta antigen, and was kindly provided by Dawn Defenbaugh.

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Preface

Since its discovery nearly 30 years ago, hepatitis delta virus (HDV) has continued to surprise and fascinate. Initially thought to be an antigenic variant of hepatitis B virus (HBV), HDV was soon found to be a defective virus that depends on an underlying or simultaneous hepatitis B infection. The clinical significance of HDV infection is more severe acute and chronic liver disease than that caused by the HBV infection alone. The cloning and sequencing of the genome led to the realization that HDV is a unique RNA virus whose closest known relatives are plant viroids, but even that relationship is remote. In the current classification scheme of the International Congress on the Taxonomy of Viruses, HDV remains the sole member of a floating genus, *Deltavirus*. The genome and its replication cycle bear no discernable resemblance to its helper virus, HBV, on which HDV depends for its envelope.

At 1,680 nucleotides the HDV genome is the smallest known to infect man. The virus contains just one gene, which encodes an approximately 25-kDa protein, hepatitis delta antigen (HDAg, also sometimes referred to as delta protein or delta antigen). To compensate for this limited protein coding capacity, HDV relies heavily on host functions and on the structural dynamics of its circular RNA genome.

Although HDV RNA is circular, it forms a characteristic unbranched rod structure in which over 70% of the nucleotides from Watson–Crick base pairs. One of the more remarkable aspects of HDV is that, unlike other RNA viruses, it does not produce a virally-encoded polymerase; rather, it somehow uses host DNA-dependent RNA polymerase to replicate its RNA genome and transcribe its mRNA. At a minimum, this process involves RNA polymerase II; HDAg also plays an as yet undefined role. The potential involvement of another polymerase, such as polymerase I, or of other forms of RNA polymerase II remains an area of active investigation. RNA replication requires the unbranched rod structure of HDV RNA and occurs via a double rolling circle mechanism. Autocatalytic self-cleaving elements, termed ribozymes, in the genome and its complement, the antigenome, play essential roles in the processing of linear transcripts to circular forms. Ribozyme activity occurs via

acid-base catalysis not unlike that accomplished by protein enzymes, and requires a complex double pseudoknot RNA structure. Ribozyme activity is also controlled by the structural dynamics of the RNA: formation of the unbranched rod structure interferes with ribozyme activity and likely prevents cleavage from occurring once the RNA circularized.

HDV produces two forms of HDAg that have different roles in the replication cycle. The longer form has an additional 19 or 20 C-terminal amino acids that facilitate viral particle formation; the shorter form is required for RNA replication. The heterogeneity arises due to highly specific editing of an adenosine in the antigenome RNA by host RNA adenosine deaminase. This process requires particular secondary structure features in the RNA around the editing site. In some cases the unbranched rod structure competes with the configuration required for editing; thus, structural dynamics of the RNA are important not only for HDV ribozyme activity, but for other processes as well.

The functional activity of HDAg is affected by numerous post-translational modifications carried out by host enzymes. These modifications include farnesylation, phosphorylation, methylation and acetylation. Farnesylation is essential for interaction with the hepatitis B virus surface protein (HBsAg), and is thus required for viral particle formation. The specific significance of the other modifications, as well as the nature of their effects on HDAg function, are not yet fully understood.

Being derived from HBV proteins, the outside of the HDV particle is similar to that of HBV, only slightly smaller in size. Although the receptor for neither virus has been identified it is likely that attachment and entry occur by similar processes. Infectivity of both HBV and HDV involves elements of the preS1 and antigenic loop regions of HBsAg.

Molecular genetic analysis of HDV isolates indicates geographical correlations that in some ways mirror those of its helper virus. That the greatest sequence diversity is found among isolates originating in Africa has led to the proposal that HDV might have radiated from that continent. One enigma is that the most distantly related sequences, for both HDV and HBV, come from South America. There is some evidence that infection with certain genotypes, or clades, can influence the severity of HDV disease.

The mechanisms by which HDV thwarts the immune system to produce chronic infection are not yet understood. The woodchuck model of HDV has been the most accessible animal model of HDV infection and has been used both to analyze the natural history of HDV infection and to evaluate the efficacy of vaccine strategies against the virus. Certainly, development of an effective vaccine strategy has been frustrating. Recent work suggests that HDAg may be poorly immunogenic, and may furthermore undergo genetic changes to avoid those limited immune responses that do occur.

There are no effective licensed antiviral therapies for HDV, and although several therapies exist for combating its helper, HBV, none of these treatments affect HDV. This failure is due to the fact that HDV depends only on HBsAg production of the helper, and current anti-HBV therapies are not potent enough to significantly diminish HBsAg levels, which are extraordinarily high. However, two potential therapeutic approaches have shown promise. One targets the host farnesyltransferase activity, which is required for virus production; the other approach advocates reducing HBsAg to levels that are too low to support continued HDV secretion. Both of these approaches are based to varying degrees on an understanding of the molecular virology of HDV, and it is likely that additional therapeutic avenues will be opened as our knowledge of HDV expands.

The more we continue to learn about hepatitis delta virus the more fascinating it becomes. It is my hope that this book will stimulate additional interest in hepatitis delta virus among scientists, academic researchers and advanced students. I would like to thank the authors for their contributions, and the staff at Springer and members of my laboratory for their assistance in preparing this volume.

Washington, DC, March 2006 *John L. Casey*

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List of Contributors

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