Review

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The hepatitis delta virus: Replication and pathogenesis

Camille Sureau[1,*], Francesco Negro[2,3,*]

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[1] *Molecular Virology laboratory, Institut National de la Transfusion Sanguine (INTS), CNRS INSERM U1134, Paris, France;*
[2] *Division of Gastroenterology and Hepatology, University Hospitals, Geneva, Switzerland;*
[3] *Division of Clinical Pathology, University Hospitals, Geneva, Switzerland*

Summary

Hepatitis delta virus (HDV) is a defective virus and a satellite of the hepatitis B virus (HBV). Its RNA genome is unique among animal viruses, but it shares common features with some plant viroids, including a replication mechanism that uses a host RNA polymerase. In infected cells, HDV genome replication and formation of a nucleocapsid-like ribonucleoprotein (RNP) are independent of HBV. But the RNP cannot exit, and therefore propagate, in the absence of HBV, as the latter supplies the propagation mechanism, from coating the HDV RNP with the HBV envelope proteins for cell egress to delivery of the HDV virions to the human hepatocyte target. HDV is therefore an obligate satellite of HBV; it infects humans either concomitantly with HBV or after HBV infection. HDV affects an estimated 15 to 20 million individuals worldwide, and the clinical significance of HDV infection is more severe forms of viral hepatitis – acute or chronic –, and a higher risk of developing cirrhosis and hepatocellular carcinoma in comparison to HBV monoinfection. This review covers molecular aspects of HDV replication cycle, including its interaction with the helper HBV and the pathogenesis of infection in humans.
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Key point

HDV is a subviral infectious agent and obligate satellite of HBV. HDV biological characteristics do not fulfill the definition of a virus.

Abbreviations: HDV, hepatitis delta virus; RNP, ribonucleoprotein; HBV, hepatitis B virus; HDAg, hepatitis delta antigen; RdRp, RNA-dependent RNA polymerase; ADAR, adenosine deaminase acting on RNA; ORF, open reading frame; S-HDAg, small-HDAg; L-HDAg, large-HDAg; DIPA, delta-interacting protein A; NES, nuclear export signal; SVP, subviral particle; HSPG, heparan sulfate proteoglycan; AGL, antigenic loop; NTCP, sodium taurocholate cotransporting polypeptide; HCC, hepatocellular carcinoma.

* Corresponding author. Addresses: Département des agents transmissibles par le sang, Institut National de la Transfusion Sanguine, 6 rue Alexiandre Cabanel, Paris 75739, France. Tel.: +33 1 44 49 30 56 (C. Sureau), or Divisions of Gastroenterology and Hepatology and of Clinical Pathology, University Hospitals of Geneva, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva 14, Switzerland. Tel.: +41 22 37 95 800 (F. Negro).
E-mail addresses: csureau@ints.fr (C. Sureau), Francesco.Negro@hcuge.ch (F. Negro).

Introduction – life cycle overview

Discovered almost 40 years ago in the liver of individuals chronically infected with the hepatitis B virus (HBV), the hepatitis delta antigen (HDAg) was first considered as a new HBV antigen [1]. It was soon demonstrated that the HDAg protein was associated with a small RNA as a component of a transmissible agent, or defective virus, coated with the HBV envelope proteins (Fig. 1), which could subsist as an obligate satellite of HBV. The cloning and sequencing of the HDAg-associated RNA, now known as the hepatitis delta virus (HDV) genome, revealed that it was unique among known animal virus genomes but sharing common features with some plant subviral agents called viroids [2,3]. HDV characteristics do not fulfill the criteria for the definition of a virus, and it is actually classified as the prototype and sole member of the *Deltavirus* genus. The genome is the smallest among known mammalian viruses, and it bears no homology with that of the helper HBV DNA. It is a single stranded circular RNA, 1700 nucleotides in size, which, unlike plant viroids, encodes a protein (Fig. 2). Since the HDAg protein has no RNA-dependent RNA polymerase (RdRp) function, HDV must rely mostly on cellular enzymes for replication of its genome (Fig. 3), and on the assistance of its helper HBV for propagation. Similar to some plant viroids, HDV RNA replication in the cell nucleus is carried out by cellular RNA polymerase(s), and both genomic HDV RNA and its replication intermediate, the antigenomic RNA strand, include autocatalytic self-cleaving elements, referred to as ribozymes (Fig. 4). Remarkably, HDV manages to produce two forms of HDAg protein from a single open reading frame (ORF); this is achieved using a cellular adenosine deaminase acting on RNA (ADAR) to edit an amber codon on the antigenomic RNA (Fig. 4). The two forms of hepatitis delta protein undergo extensive post-translational modifications to fulfill diverse functions in the processes of genome replication, assembly of the HDV RNP and coating of the latter with HBV envelope proteins. The larger form of hepatitis delta protein manages to establish a physical interaction between the RNP and the HBV envelope proteins leading to assembly HDV virions covered with HBV envelope proteins (Fig. 5). Bearing the same infectivity determinants, HBV and HDV virions also share a common tropism to human hepatocytes (Fig. 6).

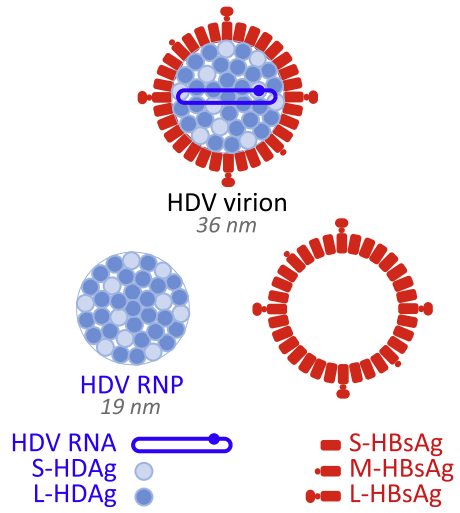

Fig. 1. Schematic representation of the HDV virion. The particle comprises two types of component: i) the viral envelope of HBV origin (in red), including the HBV envelope proteins S-HBsAg, M-HBsAg and L-HBsAg, and ii) the ribonucleoprotein (RNP) (in blue) that comprises the circular genomic HDV RNA associated to multiple copies of the HDV encoded S-HDAg and L-HDAg proteins. The diameters of the HDV virion and HDV RNP are indicated in nanometers (nm).

The HDV genome

The HDV RNA is approximately 1680 nucleotides in size and the smallest genome of the known mammalian viruses [3]. It is present in abundance in infected cells, mostly in the nucleus, along with its replication intermediate, the antigenomic RNA. Both are circular single stranded molecules that adopt a quasi-double-stranded conformation upon self-annealing with 74% of their nucleotides – 60% of which are G or C – forming Watson-Crick base pairs (Fig. 2). The circular nature and self-annealing properties of HDV RNAs are reminiscent of some plant viroids and are important for both genome replication and RNP assembly upon interaction with HDAg proteins [4–9]. The genetic organization of the HDV genome includes several ORFs; one, located on the antigenomic HDV RNA strand, is known to be translated into HDAg proteins [10]. A second ORF coding for a polypeptide referred to as peptide-K, has been reported to be expressed in infected cells, but there is no information about a possible function [11]. The two HDAg proteins are referred to as small-HDAg protein (S-HDAg) of 195 amino acids in length, and large-HDAg (L-HDAg) that differs from S-HDAg by 19 additional amino acid residues at the C-terminus. The difference in size is the consequence of an RNA editing event that occurs on the antigenomic HDV RNA strand during replication (Fig. 4) [12]. S-HDAg is essential to HDV RNA replication but does not possess an RdRp activity, whereas L-HDAg inhibits genome replication and is required for assembly of HDV particles. Some authors have chosen to divide the rod-like structure of the HDV genome into two domains: a small, "viroid-like domain", and a larger "coding domain", including the HDAg ORF sequence and its complementary strand in the rod-like structure (Fig. 2) [13].

Since the initial sequencing of the HDV genotype-1 genome [3], seven additional genotypes have been identified [14], which display a surprisingly extensive divergence of their nucleotide sequences. For instance, the most distant HDV genotype-3 sequence is approximately 40% divergent from that of genotype-1 [15].

HDV RNA replication

Unlike most RNA viruses that replicate their genome by encoding an RdRp, but like some plant viroids, HDV RNA recruits what is normally a host DNA-directed RNA polymerase for replication. HDV and viroid RNAs have structural similarities, and their respective replication mechanisms share common features [3,16–19]. HDV RNA replicates in mammalian cells, as efficiently as viroids do in plants [17,20], and no helper function for HDV RNA synthesis or RNP assembly is provided by HBV. When delivered into the cell nucleus upon infection, the genomic HDV RNA is considered to be replicated through a rolling circle mechanism of antigenomic RNA synthesis carried out by the RNA polymerase II (Pol-II) – a normally DNA-dependent enzyme - that is diverted by HDV to use its RNA as a template. The rolling circle mechanism of RNA synthesis, initially described for replication of some viroids, initiates with the synthesis of multimeric linear transcripts from the circular genomic template. Although multimeric forms of *de novo* synthesized RNA are indeed detected in infected cells, they do not accumulate because they are cleaved into monomers by an autocatalytic self-cleaving sequence, referred to as ribozyme, on the neo-synthesized RNA (Fig. 4). The linear cleavage product is then subjected to intramolecular ligation to form a circular antigenomic molecule, which in turn serves as a template for the synthesis of genomic RNAs through a similar rolling circle mechanism [21]. The HDV rolling circle model differs from that of viroids in including synthesis of a messenger RNA – of antigenomic polarity – for translation into HDAg proteins [22]. Details of the HDV RNA replication mechanism by Pol-II are still missing, but it is clear that S-HDAg is required in this process, and the HDV RNA rod-like conformation is important to substitute for DNA as a substrate for Pol-II [23,24]. Note that Pol-II is also the enzyme that amplifies

Key point

HDV RNA replication is dependent upon cellular RNA polymerase(s) and independent of HBV.

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