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The Role of the HBV Envelope Proteins in the HDV Replication Cycle

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Abstract The hepatitis delta virus (HDV) is a subviral agent that utilizes the envelope proteins of the hepatitis B virus (HBV) for propagation. When introduced into permissive cells, the HDV RNA genome replicates and associates with multiple copies of the HDV-encoded proteins to assemble a ribonucleoprotein (RNP) complex. The mechanism necessary to export the RNP from the cell is provided by the HBV envelope proteins, which have the capacity to assemble lipoprotein vesicles that bud into the lumen of a pre-Golgi compartment before being secreted. In addition to allowing the release of the HDV RNP, the HBV envelope proteins also provide a means for its targeting to an uninfected cell, thereby ensuring the spread of HDV. This chapter covers the molecular aspects of the HBV envelope protein functions in the HDV replication cycle, in particular the activity of the small envelope protein in RNP export and the function of the large envelope protein at viral entry.

1 Introduction

In 1977, the initial description of the hepatitis delta antigen (HDAg) by M. Rizzetto, was made from the examination of liver biopsies of hepatitis B virus (HBV) chronic carriers, and it was logically thought to constitute a new HBV antigen (Rizzetto et al. 1977). After its characterization as a nuclear antigen, the immunoreactive material was found to reside in particles coated with the HBV envelope proteins, and was consequently referred to as a virus-like agent that could be transmitted to chimpanzee only in the presence of HBV (Bonino et al. 1984, 1986; Rizzetto et al. 1980a). Because of this absolute requirement for HBV coinfection, it has been considered as a defective virus. The cloning of the hepatitis D virus (HDV)-associated RNA was achieved in 1986 (Chen et al. 1986; Wang et al. 1986), and the nucleotide sequence analysis revealed a genome structure that was unique among animal viruses: it was a circular, single-stranded RNA of negative polarity, with an open reading frame coding for the HDAg-associated protein, the only protein that HDV RNA is known to encode, but it lacked the coding capacity for envelope proteins. Thus, since the very early phase of its discovery, HDV has been closely associated with HBV although its genome sequence presents no homology to that of HBV.

1.1 The Virion Structure

The HDV virions are heterogeneous in size with an average diameter of 36 nm and a buoyant density of 1.25 g/cm^3 in CsCl (Fig. 1), and they display a chimerical structure consisting of an outer lipid membrane in which the HBV envelope proteins are anchored, and an inner ribonucleoprotein (RNP) made of HDV-specific elements (Bonino et al. 1984; He et al. 1989; Rizzetto et al. 1980b). The RNP includes a 1,700-nucleotide single-stranded RNA genome associated with approximately 200 copies of the HDAg protein (Gudima et al. 2002). This protein appears as two isoforms: the small form (S-HDAg) of 195 amino acid residues and the large form (L-HDAg), which is 19 amino acids longer. The difference in size arises as a consequence of an RNA editing event that occurs on a replication intermediate of the viral genome and is copied onto the HDAg mRNA (see the chapter by J.L. Casey, this volume). The examination of the RNP by electron microscopy reveals a spherical, core-like structure, with no apparent icosahedral symmetry and a diameter of approximately 19 nm. The HDV envelope appears undistinguishable from the one of HBV. It consists of a lipid membrane in which the three HBV coat proteins, bearing the hepatitis B surface antigen (HBsAg) and designated small (S-HBsAg),