HEPATITIS DELTA VIRUS: INFECTION AND DISEASE

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BIOLOGY OF HEPATITIS DELTA VIRUS

Hepatitis delta virus (HDV) is a unique defective agent whose infection is inextricably linked to that of hepatitis B virus (HBV) (Rizzetto et al. 1987; Verme et al. 1983). The virion is a 36 nm spherical particle containing hepatitis delta antigen (HDAg) and RNA (HDV-RNA); its envelope consists of a composition of proteins similar to that of 22 nm defective particles of HBV (Bergman and Gerin, 1986; Bonino et al. 1981, 1986a). Transmission experiments in chimpanzees suggest that HDV is a distinct infectious agent but its expression requires the helper function of HBV (Purcell et al. 1983). An infectious inoculum induced HBV hepatitis and intrahepatic expression of HDAg in HBsAg negative chimpanzees up to a $1 \times 10^{-5}$ dilution whereas a $1 \times 10^{-6}$ dilution caused only an HBV infection (Purcell et al. 1983). No infection occurred in HBsAg negative chimpanzees using higher dilutions of the same inoculum ($>1 \times 10^{-7}$) while dilutions, up to $1 \times 10^{-11}$ induced hepatitis with intrahepatic expression of HDAg in HBsAg carrier chimpanzees. Experimental transmission of HDV to chimpanzees showed also that immunity against HBV protects against HDV (Purcell et al. 1983; Rizzetto et al. 1987).

The genome of the defective agent, has been reverse transcribed to complementary DNA (cDNA), cloned and sequenced (Denniston et al. 1986; Wang et al. 1986). No significant homology has been observed between HDV-RNA, HBV-DNA, host DNA and nucleic acid obtained from serum and liver of HBV or non-A non-B (NANB) infected animals (Weiner et al. 1987).
HDV-RNA contains 1,679-1,683 nucleotides and five open reading frames (ORF) of more than 100 amino acids in its genomic and antigenomic strands. The largest ORF, found on the + strand codes for 214 amino acids, was expressed in bacteria and the resultant fusion protein reacted with human antibodies to HDAg (anti-HD) (Wang et al. 1986). In vitro translation of RNA derived from HDV infected liver produced two HDAg proteins (24 and 27 Kda) which reacted by immunoblot with polyclonal anti-HDV antibody and with a monoclonal antibody obtained from Epstein-Barr virus-transformed human lymphocytes (Pohl et al. 1987). Serum derived HDAg is composed of two major proteins, with a molecular weight of 24-27 Kda and 27-29 Kda while these proteins are detected in the liver together with the other forms of different molecular weight (22, 14 Kda) (Bonino et al. 1986a).

The lack of a +3' poly-(A) tract on the viral RNA, together with its failure to translate HDAg in vitro and the presence of HDAg coding sequences on the antigenomic strand of HDV-RNA, suggests that HDV is a negative strand virus in which the complementary strand of the genome (+) serves as a mRNA (Baroudy et al. 1987). HDV particles contain two RNA species that migrate in gel electrophoresis at 1.75 and 2.0 Kbp, respectively; these forms have the same polarity (genomic, +) and it may be that they represent nicked linear and circular forms of the same RNA molecule. The circular RNA molecule has an extensive secondary structure; its self-annealing properties and high GC content (60%) allow the formation of a double stranded rod-like structure resembling that of a number of different viroid-like RNAs found in plants. Different forms of HDV-RNA are found in infected livers including genomic and antigenomic strands, poly-A RNA and double stranded RNA (dsRNA). The dsRNA species might represent replicative forms of HDV-RNA suggesting that HDV's replicative cycle is somewhat similar to that of the satellites of plant RNA viruses (Kaper and Tousignant, 1984). Satellite RNAs of cucumber mosaic virus (CUMOV) replicate in a rolling circle fashion producing large amounts of double stranded forms which accumulate in the cell and hinder the replication of the helper virus RNA. This determines the attenuation of disease symptoms caused by CUMOV. Occasionally, however, this defensive mechanism turns out to be dangerous for the plant; this happens when a CMV carrier plant is superinfected with satellites containing defective necrotizing genes which caused tremendous epidemics of plant necrosis. Satellite/CUMOV interference in plants closely resembles that of HDV and HBV in humans and animals. Furthermore, some sequence homology of HDV-RNA with plant virusoids (Wang et al. 1986) suggests that HDV and these agents may have a common ancestry.