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RNA Editing in Hepatitis Delta Virus

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Abstract Hepatitis delta virus (HDV) relies heavily on host functions and on structural features of the viral RNA. A good example of this reliance is found in the process known as HDV RNA editing, which requires particular structural features in the HDV antigenome, and a host RNA editing enzyme, ADAR1. During replication, the adenosine at the amber/W site in the HDV antigenome is edited to inosine. As a result, the amber stop codon in the hepatitis delta antigen (HDAg) open reading frame is changed to a tryptophan codon and the reading frame is extended by 19 or 20 codons. Because these extra amino acids alter the functional properties of HDAg, this change serves a critical purpose in the HDV replication cycle. Analysis of the RNA secondary

structures and regulation of editing in HDV genotypes I and III has indicated that although editing is essential for both genotypes, there are substantial differences. This review covers the mechanisms of RNA editing in the HDV replication cycle and the regulatory mechanisms by which HDV controls editing.

1 Introduction

1.1 HDV Produces Two Forms of HDAg from the Same Gene

Hepatitis delta virus (HDV) is often compared to viroids because of the characteristic unbranched rod secondary structure formed by its RNA and the relatively small size of its genome. However, unlike viroids, HDV does contain one gene that encodes the sole viral protein, HDAg. Early analyses showed two electrophoretic forms of HDAg in liver and viral particles isolated from serum (Bergmann and Gerin 1986; Bonino et al. 1981, 1984, 1986). (These forms were sometimes referred to by their apparent molecular weights, p-24 and p-27; they are denoted here as S-HDAg and L-HDAg for short and long, respectively.) Following the cloning of HDV cDNAs (Makino et al. 1987; Wang et al. 1986), a series of studies illuminated the functional roles of S-HDAg and L-HDAg in HDV replication: S-HDAg is required for replication of HDV RNA, and L-HDAg is required for the formation of HDV particles (Chang et al. 1991; Glenn et al. 1992; Hwang et al. 1992). Early studies found that L-HDAg also inhibits HDV RNA replication (Chao et al. 1990; Kuo et al. 1989), but more recent analyses suggest that this might not always be the case, particularly for antigenome RNA synthesis (Macnaughton and Lai 2002; Modahl and Lai 2000).

Cloning and sequencing of the genome in 1986 indicated heterogeneity at several positions in the 1679 nucleotide (nt) genome (Wang et al. 1986). This variability affected the predicted length of HDAg: some clones contained a UAG (amber) stop as the 196th codon and encoded a 195 amino acid protein, other clones had UGG at this location and encoded a protein 214 amino acids in length (Wang et al. 1986; Xia et al. 1990). Expression of protein from clones that contained either the UAG or UGG sequence showed that the former encoded S-HDAg and the latter L-HDAg (Weiner et al. 1988; Xia et al. 1990). Subsequently, a series of studies in cultured cells and in a chimpanzee infected by injection of an HDV cDNA clone led to the remarkable discovery that the heterogeneity at this position arose during the course of HDV replication. Although transfected cDNAs encoded only S-HDAg, both S-HDAg and L-HDAg were detected (Luo et al. 1990; Sureau et al. 1989). No L-HDAg was detected