CHAPTER 5

Hepatitis Delta Virus RNA Editing

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Summary

The genome of hepatitis delta virus (HDV) is the smallest known to infect man. Encoding just one protein, hepatitis delta antigen (HDAg), 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 in the amber stop codon in the viral gene for the short form of HDAg (HDAg-S) is edited to inosine. As a result, the amber stop codon in the HDAg-S open reading frame is changed to a tryptophan codon; the reading frame is thus extended by 19 or 20 codons and the longer form of HDAg, HDAg-L, is produced. This change serves a critical purpose in the HDV replication cycle because HDAg-S supports viral RNA replication, while HDAg-L is required for virion packaging but inhibits viral RNA replication. This review will cover the mechanisms of RNA editing in the HDV replication cycle and the regulatory mechanisms by which HDV controls editing.

What Is RNA Editing?

RNA editing can be loosely defined as the site-specific modification of an RNA sequence from that of its template by mechanisms other than splicing. The term was first used in the late 1980's to describe an unusual process in which multiple U's are inserted and deleted in trypanosome mitochondrial mRNAs.[1] As a result of the insertions/deletions, the coding capacity of the affected mRNAs is dramatically altered. The usage of the term was subsequently expanded as it was applied to other examples of nucleotide changes in mRNA that changed the coding capacity, including deamination of C to U in apoB100 mRNA in small intestine,[2] deamination of A to I in glutamate receptor subunit B (gluRB) premRNA in brain,[3] and insertion of nontemplated G's in the P gene of paramyxoviruses.[4] While collectively referred to as RNA editing, these sequence revisions involve a wide range of mechanisms. In the two types of editing used by mammalian cells, C to U and A to I, the modified base within the RNA molecule is deaminated and there is no evidence that phosphate backbone is broken during the editing process.

The type of RNA editing used by HDV is adenosine deamination. In this process, the amino group of adenosine is removed and replaced with a keto oxygen. Because this position of

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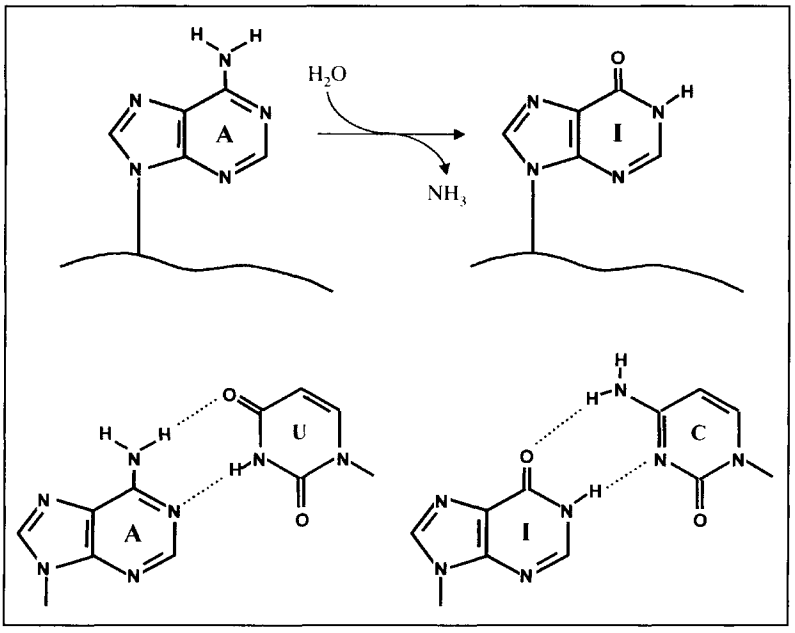

Figure 1. Adenosine deamination. The upper panel shows the replacement of the amino group of adenosine by oxygen to generate inosine. The horizontal line indicates the RNA phosphate backbone, which is not broken during the deamination reaction. The lower panel shows the effects of deamination on base-pairing. Adenosine forms Watson-Crick base-pairs with uracil; whereas inosine base-pairs with cytidine. Hydrogen bonds are designated by dotted lines.

the base is changed from a hydrogen bond donor to an acceptor, the Watson-Crick base-pairing preference of this nucleotide is changed from pairing with U to pairing with C (Fig. 1). Therefore, in any subsequent functions that involve base-pairing (such as translation, RNA-templated transcription, and splice site identification) the edited position will behave as G rather than the original A. Editing has the potential to produce as many as 15 different recodings of an RNA transcript, including the creation of a methionine start codon and the abolition of stop codons. Thus, for example, when the adenosine at the R/G site in the glutamate receptor subunit B mRNA is edited, a CAG arginine codon is changed to CIG, which behaves like CGG, and encodes glycine; as a result of this change, the cation permeability of glutamate receptor channels in mammalian brain are changed. As indicated by this example, sites in RNAs that undergo adenosine deamination have been named according to the coding change brought about by editing. Thus, because editing on the HDV RNA changes an amber stop codon to a tryptophan (W) codon, the position on the HDV RNA at which editing occurs is called the amber/W site.

Mechanism of HDV RNA Editing

HDV Produces Two Forms of HDAg from the Same Gene

Early analyses of HDV proteins showed that there are two electrophoretic forms of HDAg, but it was not clear how these forms differed biochemically and functionally.[5-8] (These forms were sometimes referred to by their apparent molecular weights, p-24 and p-27; they are denoted here as HDAg-S and HDAg-L for short and long, respectively.) Following the cloning of HDV cDNAs,[9,10] a series of studies illuminated the functional roles of HDAg-S and HDAg-L