CTMI (2006) 307:91–112

Post-translational Modification of Delta Antigen of Hepatitis D Virus

W.-H. Huang · C.-W. Chen · H.-L. Wu · P.-J. Chen (✉)

Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, and Hepatitis Research Center, National Taiwan University Hospital, Taipei, Taiwan
peijer@ha.mc.ntu.edu.tw

1 Introduction 92

2 The Hypothesis 92

3 Isoprenylation of L-HDAg 93
3.1 Role of L-HDAg Farnesylation in the HDV Replication Cycle 95
3.2 Isoprenylation Enhances the *trans*-Suppression Activity of L-HDAg 96
3.3 Other Viral Prenylated Proteins 97

4 Phosphorylation of Delta Antigens 97
4.1 Phosphorylated Delta Antigens in the HDV Life Cycle 98
4.2 Putative Delta Antigen Kinase 100

5 Acetylation of Delta Antigen 100
5.1 Enzyme for Delta Antigen Acetylation 101
5.2 Acetylation Site of Delta Antigen 101
5.3 Functions of Delta Antigen Acetylation 102

6 Methylation of Delta Antigen 103
6.1 Enzyme for Delta Antigen Methylation 103
6.2 Methylation Site of Delta Antigen 105
6.3 Functions of Delta Antigen Methylation 105

7 Prospect 106

References 107

Abstract The hepatitis delta virus (HDV) genome has only one open reading frame, which encodes the viral small delta antigen. After RNA editing, the same open reading frame is extended 19 amino acids at the carboxyl terminus and encodes the large delta antigen. These two viral proteins escort the HDV genome through different cellular compartments for the complicated phases of replication, transcription and, eventually, the formation of progeny virions. To orchestrate these events, the delta antigens have to take distinct cues to traffic to the right compartments and make

correct molecular contacts. In eukaryotes, post-translational modification (PTM) is a major mechanism of dictating the multiple functions of a single protein. Multiple PTMs, including phosphorylation, isoprenylation, acetylation, and methylation, have been identified on hepatitis delta antigens. In this chapter we review these PTMs and discuss their functions in regulating and coordinating the life cycle of HDV.

1 Introduction

Among the animal viruses, hepatitis D virus (HDV) is currently the smallest known. The length of its single-stranded, negative polarity genome, which contains a single open reading frame encoding for delta antigen, contains only 1678 nucleotides. Despite the extreme simplicity of the HDV genome, it replicates and produces progeny even more actively than many RNA viruses. Therefore, many of the fundamental features of the life cycles of viruses can probably be embodied in the simple HDV. In this review, we focus on the role of delta antigen (HDAg). Viral delta antigen has been shown to be essential for viral replication, and its variant, the large delta antigen (L-HDAg), is required for viral assembly. The replication and assembly processes, however, take place in different compartments of infected cells. For example, HDV RNA enters the nucleus and even the nucleolus for replication and transcription. Recent studies have indicated that newly synthesized viral genomic RNA further moves to the cytoplasm. This scenario suggested that different stages of viral RNA replication might take place in several distinct subcellular compartments. As these stages of the HDV life cycle require the presence of viral delta antigen, the protein must be able to traffic to different but appropriate subcellular compartments to synchronize viral replication and assembly. The mechanisms by which the delta antigen orchestrates these complicated steps are the topics of this chapter.

2 The Hypothesis

We propose that the delta antigens are modified post-translationally to produce many different isoforms. Although the amino acid backbone remains unchanged, the modified delta antigens can exert different functions in the viral replication cycle in different subcelluar compartments. Perhaps the post-translational modifications (PTMs) of proteins can draw a similarity with dressing codes for humans. A person has to perform multiple social functions