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Prenylation of HDAg and Antiviral Drug Development

J. S. Glenn (✉)

Division of Gastroenterology and Hepatology, Stanford University School of Medicine, CCSR 3115, 269 Campus Drive, Palo Alto, CA 94305–5187, USA
jeffrey.glenn@stanford.edu

Abstract Hepatitis delta virus (HDV) is an important cause of acute and chronic liver disease. Current medical therapies are unable to effectively eradicate HDV infections. Research into the molecular virology of the HDV life cycle has revealed a fascinating collection of biology. These insights are now beginning to be translated into new potential treatment strategies. For example, an essential step in the virus assembly process involves the post-translational lipid modification of a specific HDV protein, namely prenylation of large delta antigen. Preventing prenylation abolishes virus particle formation. Drugs capable of specifically inhibiting prenylation have been developed for use in humans. These agents represent a new class of antiviral agents, with HDV as a first target. Here, a brief review of the HDV life cycle emphasizing the role of prenylation is presented along with implications for drug development and therapy.

1 Introduction

1.1 HDV Disease Burden

It has been estimated that at least 15 million of the over 300 million people infected with hepatitis B virus (HBV) also harbor a hepatitis delta virus (HDV) infection and such infections can be found throughout the world (Gerin et al. 2001; Rizzetto et al. 1991). The clinical course associated with HDV is typically more severe than for HBV infection alone. Unfortunately, current therapies are largely ineffective against HDV. The study of HDV molecular virology, however, has revealed exciting new avenues for potential therapeutic intervention. After a brief review of the basic HDV virion composition and life cycle (covered in more detail in other chapters in this volume), this chapter will focus on a special post-translational modification of a key HDV protein. This modification reaction, termed prenylation, turns out to be both a mechanism exploited by the virus to mediate its assembly, and the basis for an exciting new form of antiviral therapy.

HDV can be viewed as a 'parasite virus' of HBV. HDV has its own genome and encodes its own core-like protein, but it requires HBV to provide a source of envelope protein. This provides a molecular explanation for why natural HDV infections are always found in association with hepatitis B. There are two major clinical scenarios: (1) coinfection–acute simultaneous infection of HDV with HBV in a previously uninfected patient; and (2) superinfection–HDV infection of a chronically infected HBV patient (Hoofnagle 1989). This is often manifested by a sudden worsening or 'flare' of previously stable chronic HBV disease.

1.2 The HDV Virion

The HDV particle is composed of a single-stranded circular 1.7 kb RNA genome, small and large delta antigen (S- and L-HDAg), which together are surrounded by a lipid envelope containing the HBV surface antigen proteins (HBsAgs). The fully assembled particle diameter is about 36 nm. Sequencing of isolates from around the world has led to a classification into three genotypes–I, II, and III–based on sequence variation (Casey 1996), and recent data suggests the existence of up to four additional genotypes (Radjef et al. 2004) (see the chapter by P. Dény, this volume). The two major isoforms of delta antigen, termed small and large, are identical in sequence except that L-HDAg has an extra 19 amino acids at its carboxyl (C-) terminus. As detailed