CTMI (2006) 307:211–225

The Woodchuck Model of HDV Infection

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Abstract The Eastern woodchuck, *Marmota monax*, has been a useful model system for the study of the natural history of hepadnavirus infection and for the development and preclinical testing of antiviral therapies. The model has also been used for hepatitis delta virus (HDV). In this chapter several new applications of the woodchuck model of HDV infection are presented and discussed. The development of a woodchuck HDV inoculum derived from a molecular clone has facilitated the analysis of viral genetic changes occurring during acute and chronic infection. This analysis has provided insights into one of the more important aspects of the natural history of HDV infection—whether a superinfection becomes chronic. These results could renew interest in further vaccine development. An effective therapy for chronic HDV infection remains an important clinical goal for this agent, particularly because of the severity of the disease and the inability of current hepadnaviral therapies to ameliorate it. The recent application of the woodchuck model of chronic HDV infection to therapeutic development has yielded promising results which indicate that targeting the hepadnavirus surface protein may be a successful therapeutic strategy for HDV.

1 Introduction

The dependence of hepatitis delta virus (HDV) infection on the presence of hepatitis B virus (HBV) imposes restrictions on the types of animal models available to study the natural history of HDV infection and to develop vaccine and therapeutic strategies. Primate models of hepadnavirus infection have included the chimpanzee, which can be infected with HBV, and either the woolly monkey or spider monkey, which can be infected with the closely related woolly monkey hepatitis B virus (WMHBV) (Lanford et al. 1998). The utility of the chimpanzee is severely limited by the scarcity of animals and ethical concerns; similar issues pertain to the woolly monkey, an endangered species. The natural history of WMHBV in spider monkeys is not fully understood, and the ability to establish chronic WMHBV infection followed by HDV superinfection has not been demonstrated. While the duck has been a useful model for HBV, duck hepatitis B virus supports neither HDV packaging nor infection (see the chapter by C. Sureau, this volume). Our efforts have focused on the eastern woodchuck, which has been a valuable naturally occurring animal model of hepadnavirus infection and disease (Tennant and Gerin 1994).

There is no evidence that HDV infection occurs naturally in woodchucks, but several laboratories have shown that woodchucks chronically infected with woodchuck hepatitis virus (WHV) can be infected with HDV. Initially, infection was produced by inoculation of woodchucks with HDV derived from chimpanzees (Ponzetto et al. 1984). Consistent with the requirement of hepatitis B surface antigen (HBsAg) for the HDV replication cycle (Rizzetto et al. 1980), the HBsAg envelope protein was replaced by the WHV surface antigen following the initiation of infection (Ponzetto et al. 1984). It was later demonstrated that WHsAg can efficiently package the HDV genome in cell culture (Ryu et al. 1992). Woodchuck-derived HDV has been passaged serially in woodchucks, and was shown to be infectious in cultured woodchuck hepatocytes (Choi et al. 1988, Taylor et al. 1987). The natural history of HDV infection in woodchucks is similar to that in humans: infection results in acute and chronic infection in a high percentage of animals (Casey et al. 2005, Ponzetto et al. 1984, 1987, Schlipkoter et al. 1990). Finally, HDV replication is restricted to the liver in infected woodchucks (Negro et al. 1989), as it is in chimpanzees and humans. Thus, the woodchuck has been a valuable animal model for HDV.

There are two modes of HDV infection: superinfection of an individual with chronic HBV infection; and coinfection with both viruses of an individual who has not been exposed previously to HBV. While the latter type of exposure