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Immunology of HDV Infection

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Abstract Hepatitis delta virus (HDV) infection may occur as coinfection with hepatitis B virus (HBV) or as superinfection of a chronically HBV-infected patient. A strong antibody response is mounted, which persists for many years; however, it is not able to modulate the course of infection. In most cases the superinfection takes a chronic course. In patients with inactive disease (HDV PCR negative) an oligospecific T-helper cell immune response and a cytotoxic T-cell response were found, which were absent in patients with persistent viremia. The role of the cellular immune response in liver injury during acute infection has not been investigated. Vaccination strategies tested in the woodchuck model induced specific B- and T-cell responses but failed to protect from HDV infection.

1 Introduction

Hepatitis delta virus (HDV) has been recognized to be an important cause of acute or chronic hepatitis in humans. HDV infection may occur as coinfection with hepatitis B virus (HBV) or as superinfection of a chronically HBV-infected patient (Rizetto et al. 1984). The course of simultaneous infection is similar to HBV infection alone and clearance of HBV is accompanied by elimination of HDV. HDV superinfection of chronically HBV-infected patients results in chronic HDV infection in more than 80% of cases. This often progresses rapidly to liver cirrhosis and hepatocellular carcinoma (Fattovich et al. 1987).

The immunopathogenesis of HDV infection has not been investigated in detail so far. Antibodies recognizing both HDV proteins are detected at low titers during acute infection and reach high levels during chronic infection, but are not able to modulate the course of infection. Therefore, antibodies are probably not able to neutralize the virus (Rizetto 1981, 1984). The predictive role of antibodies of the IgM-class for the course of HDV infection has been studied extensively and is somewhat controversial (Aragona et al. 1987; Borghesio et al. 1998; Farci et al. 1986; Govindarajan et al. 1989). Several groups investigated the fine specificity of the antibody response and defined immunogenic epitopes (Bergmann et al. 1989; Seizer et al. 2005; Wang et al. 1990). Knowledge of the cellular immune response in HDV infection is still incomplete. A polyspecific, but weak T helper (Th) cell response is observed in patients with acute self-limiting HDV infection, but is absent in chronically HDV-infected patients (Nisini et al. 1997). The liver damage results in serum alanine and aspartate aminotransferase (ALT and AST) elevation. This observation, as well as the fact that HDV itself is not cytopathic (Guilhot et al. 1994), may indicate that cytotoxic T cells (CTL) are responsible for destruction of hepatocytes; however, little is known about the CTL response in HDV infection. Recently, Huang et al. identified two HLA-A*0201-restricted $CD8^+$ T-cell epitopes on HDV (Huang et al. 2004).

Vaccination studies might also give insight into the role of the immune response in HDV infection. Woodchucks chronically infected with woodchuck hepatitis virus (WHV) can be superinfected with HDV and therefore can be a good model to test vaccine candidates. Different strategies have been investigated to establish a protective vaccine against HDV superinfection. Synthetic peptides, HDAg expressed in *Escherichia coli*, yeast, or baculovirus, infection with vaccinia virus expressing the small or the large hepatitis delta antigen (S-HDAg, L-HDAg), and DNA immunization by gene gun have been studied. So far, none of these protocols has been able to protect woodchucks