

## The Immunology of Hepatitis B

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Clearance of the hepatitis B virus (HBV) requires a coordinated innate and adaptive, humoral and cellular immune response.<sup>1</sup> In acute, self-limited hepatitis, most HBV-DNA molecules are cleared in the incubation phase (i.e., prior to the onset of liver damage and clinical symptoms of acute hepatitis B). This rapid reduction in viral load is attributed to inhibition of viral gene expression and replication by cytokines such as IFN- $\gamma$  and TNF- $\alpha$ ,<sup>2</sup> which are detectable in the liver even prior to infiltration of large numbers of HBV-specific T cells. A vigorous, polyclonal and multispecific CD4 and CD8 T cell response then coincides with maximum ALT elevation, clearance of HBe and HBs antigens, and development of neutralizing antibodies. After recovery from hepatitis B, HBV-specific T cells as well as neutralizing antibodies persist for decades.<sup>3</sup> Nevertheless, trace amounts of HBV-DNA remain detectable in serum and PBMC<sup>3</sup> suggesting a balance between T cell- and antibody-inaccessible viral reservoirs and *de novo* induced immune cells that control viral spread.

In chronic hepatitis B, HBV-specific T cells are barely detectable *ex vivo* in circulation, but can be expanded *in vitro* from liver biopsies. Patients with chronic hepatitis who spontaneously clear HBeAg and seroconvert to anti-HBe display a sudden increase in the HBV-specific T cell responses in the peripheral blood.<sup>4</sup> T cell responsiveness remains slightly elevated after HBeAg clearance, because HBeAg-negative patients with low viral load and normal ALT value display stronger *in vitro* responsiveness of circulating HBV-specific T cells than HBeAg-positive patients with high viral load and elevated serum ALT levels.<sup>5</sup> These findings raise the possibility that impaired T cell function may be reversible in chronic HBV infection.

Indeed, antiviral therapy of HBeAg-positive patients restored HBV-specific T cell responses during the first year of treatment,<sup>6</sup> but thereafter, responses decreased and, after 3 years, were no more frequent than in untreated patients.<sup>7,8</sup> Decreased T cell responsiveness during prolonged therapy was associated with increased prevalence of lamivudine-resistant HBV mutants and increased HBV titer.<sup>8</sup> The data provide a rationale for the combination of antiviral and immunostimulatory therapy.

### References

1. Rehermann B, Nascimbeni M. Immunology of hepatitis B virus and hepatitis C virus infection. *Nat. Rev. Immunol.* 2005;5:215-229.
2. Guidotti LG, Chisari FV. Noncytolytic control of viral infections by the innate and adaptive immune response. *Annu. Rev. Immunol.* 2001;19:65-91.
3. Rehermann B, Ferrari C, Pasquinelli C, Chisari FV. The hepatitis B virus persists for decades after patients' recovery from acute viral hepatitis despite active maintenance of a cytotoxic T-lymphocyte response. *Nature Medicine* 1996;2:1104-1108.
4. Tsai SL, Chen MY, Lai MY, Yang PM, Seng JL, Huang JH, Hwang LH, et al. Acute exacerbations of chronic type B hepatitis are accompanied by increased T cell responses to hepatitis B core and e antigens. *J. Clin. Invest.* 1992;89:87-96.
5. Maini MK, Boni C, Lee CK, Larrubia JR, Reignat S, Ogg GS, King AS, et al. The role of virus-specific CD8+ cells in liver damage and viral control during persistent hepatitis B virus (HBV) infection. *J. Exp. Med.* 2000;191:1269-1280.
6. Boni C, Bertoletti A, Penna A, Cavalli A, Pilli M, Urbani S, Scognamiglio P, et al. Lamivudine treatment can restore T cell responsiveness in chronic hepatitis B. *J. Clin. Invest.* 1998;102:968-975.

7. Boni C, Penna A, Bertoletti A, Lamonaca V, Rapti I, Missale G, Pilli M, et al. Transient restoration of anti-viral T cell responses induced by lamivudine therapy in chronic hepatitis B. *J. Hepatol.* 2003;39:595-605.
8. Mizukoshi E, Sidney J, Livingston B, Ghany M, Hoofnagle J, Sette A, Rehermann B. Cellular immune responses to the hepatitis B virus polymerase. *J. Immunol.* 2004;173:5863-5871.