# The immune mechanism in HBV viral persistence

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Hepatitis B virus (HBV) is the prototype member of the family *Hepadnaviridae*. Infectious HBV virion (Dane particle) has a spherical structure of 42-44 nm which consists of an outer lipid envelope and an icosahedral nucleocapsid core composed of protein. The nucleocapsid encloses the viral DNA and a DNA polymerase that has reverse transcriptase activity and the outer envelope contains proteins involved in viral binding of, and entry into, susceptible cells. HBV is a partially dsDNA virus, which enters hepatocytes and is converted to covalently closed circular DNA (cccDNA) in the nucleus of the cells. HBV DNA serves as transcriptional template of HBsAg, HBcAg, DNA polymerase, and HBx. According to the envelope proteins or nucleotide sequence variation, HBV can be further divided into four major serotypes (adr, adw, ayr, ayw) and eight genotypes (A-H).

The immune mechanism in HBV viral persistence can be attributed to viral factors and HBV-specific immune suppression in both innate and adaptive immune system. HBx protein may contribute to ongoing expression of HLA class I molecules on hepatocytes and recruitment of inflammatory cells to the liver which lack effective antiviral activity. HBe antigen can acts both as an immunogen and tolerogen, leading to inefficient triggering proinflammatory cytokines via reduction of TLR2 expression on monocytes. HBV-specific CD4+ and CD8+ T-cell response is also significantly diminished. HBV-specific CD8+ T-cells is “partially tolerant”, being unable to bind specific tetramers/HLA-restricted peptide complexes and eliminated of TNF-α and IFN-γ production. HBV-specific CD4+ T-cell is “hyporesponsive”, as consequence of impaired function of HBV-infected DCs, which have reduced IFN-γ,TNF-α and IL-12 production. Mechanisms in the deletion of HBV-specific T cells or in their functional inactivation (exhaustion) can be due to increased expression of PD-1 on virus specific T-cells, down regulation of T cell receptor signaling, or enhanced T cell apoptosis. $CD25^+$ $CD4^+$ T-cells (regulatory T-cells) and Th17 cells also possess a role of limited clearance in chronic viral infection. Other mechanisms of chronic HBV infection include replication of HBV in ‘privileged’ sites, induction of Fas-L on hepatocytes, absence of co-stimulatory signals in the liver, and viral mutations.

In conclusion, the interaction between the HBV virus and both the innate and adaptive immune response promote the HBV viral persistence. Knowing the interaction between viral components and elements of the immune system may further

provide important clues to understand the mechanism of persistent infection, which may potentially lead to novel therapeutics in the future.