Impact of the sequence variability oft he hepatitis B virus genome on the CD8 T cell response

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Worldwide about 240 million people are chronically infected with the hepatitis B virus (HBV). Although efficient therapies targeted to inhibition of the viral reverse transcriptase are available, in most cases lifelong treatment is required to avoid long-term sequelae such as liver cirrhosis and hepatocellular carcinoma. The concept of therapeutic vaccination represents a complementing treatment strategy with the ultimate goal of achieving a cure from HBV-infection. $CD8^+$ T cells play a central role in immune control of HBV-replication. These cells are activated by viral peptides (epitopes) in complex with HLA class I-molecules presented at the surface of infected cells. Persistent infections are associated with a late onset and weak $CD8^+$ T cell response. Moreover, HBV-specific $CD8^+$ T cells from patients with chronic HBV-infection are characterized by a progressive dysfunction - a state termed T cell exhaustion. For the concept of therapeutic vaccination two major challenges exist in the context of hepatitis B. Firstly, CD8 T cell dysfunction needs to be rescued. This can be partially achieved by “check-point” inhibitors that block inhibitory signaling pathways in T cells. A second challenge is the inherent sequence diversity of HBV. In a proof-of-principle study we were able to show that $CD8^+$ T cells select for immune escape mutations in targeted epitopes of the HBV core protein. Upon development of chronic infection HBV seems to systematically adapt its genome sequence to the host-genetically determined cellular immune response. In this project, the extent of the immune adaptation process of HBV will be studied in detail. The overall sequence variability of the full HBV-genome will be characterized, epitopes under reproducible selection pressure by $CD8^+$ T cells will be identified across the complete polyprotein and the functional mechanisms of T cell escape will be defined. Moreover, it will be determined, if T cells targeted to viral escape variants can be activated or if broadly cross-reactive T cells exist in patients and healthy donors. Such T cells directed against different viral variants would be essential for the success of therapeutic vaccination strategies.