

HOST IMMUNE RESPONSE TO HBV: CONTROL VERSUS PATHOGENICITY

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The hepatotropic hepatitis B virus (HBV) is non-cytopathic; liver disease resulting from this infection is therefore thought to be immune-mediated. In order to develop immunotherapeutic strategies for improving the treatment of HBV, there is a pressing need to dissect out the immune components contributing to viral control versus disease pathogenesis.

Defects in many aspects of the coordinated innate and adaptive immune response have been described in patients failing to control HBV infection, but one of the most profound and critical is depletion of the virus-specific CD8 T cell response. We have identified Bim-mediated apoptosis as one of the processes accounting for the failure of HBV-specific CD8 T cells to persist in the face of high antigen load. We are investigating whether T cell tolerance through induction of Bim may relate to inappropriate co-stimulation following intrahepatic antigen presentation and whether blocking this pathway may reconstitute more effective responses *in vivo*. We have also characterized signaling defects attributable to the liver microenvironment that bias the effector function of CD8 T cells in chronic HBV infection.

Data from humans and HBV transgenic mice has pointed to the non-virus-specific lymphocytes infiltrating the liver in the presence of uncontrolled HBV replication as a major contributor to the ensuing damage. We have identified a pathway whereby NK cells, which account for 30-40% of intrahepatic lymphocytes, can mediate hepatocyte death and have shown that this pathway can be stimulated by cytokines induced during flares of HBV-related liver disease.