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Intrahepatic Cross-Presentation and Hepatocellular Antigen Presentation Play Distinct Roles in the Induction of Hepatitis B Virus-Specific CD8$^+$ T Cell Responses

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Abstract

Hepatitis B virus (HBV) causes acute and chronic hepatitis. Approximately 260 million people are chronically infected with HBV and under an increased risk of developing cirrhosis and hepatocellular carcinoma. CD8$^+$ T cells are the key cellular effectors mediating the clearance of HBV infections. However, early immunological events surrounding the priming of HBV-specific CD8$^+$ T cell responses remain poorly understood. This study examined the importance of priming location and the relative contribution of endogenous antigen presentation by hepatocytes versus cross-presentation by bone marrow-derived cells to the induction of functional HBV-specific CD8$^+$ T cell responses using the animal models of acute and chronic HBV infection. Functional HBV-specific CD8$^+$ T cell responses could be induced to intrahepatically expressed HBV even when T cell homing to the lymphoid tissues was severely suppressed, suggesting that functional priming could occur in the liver. The expansion of HBV-specific CD8$^+$ T cells was significantly reduced in the mice whose major histocompatibility complex (MHC) class I expression was mostly restricted to nonhematopoietic cells, suggesting the importance of cross-presentation by hematopoietic cells in the induction of HBV-specific CD8$^+$ T cells. Strikingly, the expansion and cytolytic differentiation of HBV-specific CD8$^+$ T cells were reduced even more severely in the mice whose MHC class I expression was restricted to hematopoietic cells. Collectively, these results indicate that cross-presentation is required but relatively inefficient in terms of inducing the cytolytic differentiation of HBV-specific CD8$^+$ T cells by itself. Instead, the expansion and functional differentiation of HBV-specific CD8$^+$ T cells are primarily dependent on hepatocellular antigen presentation. The information obtained in this study may help to design new immune therapeutic approaches against chronic HBV infections.