Deciphering the Hepatitis B virus specific B cell-mediated immune responses in a mouse model of HBV pathogenesis

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Abstract

Humoral responses play a critical role in HBV infection. Indeed, HBsAg seroconversion is regarded as a successful treatment endpoint and B cell-depleting strategies may lead to fatal HBV flares. Recent work characterizing HBs-specific B cells during chronic hepatitis B revealed frequencies that were comparable to those of vaccinated or resolved individuals, but enrichment for a $CD27^{-}$ $CD21^{-}$ $FcRL5^{+}$ $Tbet^{hi}$ "atypical" memory B cell phenotype. These observations raise the possibility that endogenous humoral immunity could be revived by identifying the defects limiting their function. However, further work towards this goal is hampered by the lack of appropriate animal models. Here, we report the generation of a heavy chain and light chain knock-in mouse whose B cells express a BCR recognizing HBsAg (HBs-BCR mice). Furthermore, we have developed a highly sensitive and specific method to detect HBsAg-specific B cells by a dual fishing technique that couples biotinylated HBsAg with fluorescent streptavidins. In vitro experiments indicate that HBsAg-specific B can proliferate and become activated in response to HBsAg. To study their behavior in vivo, HBsAg-specific B cells were adoptively transferred into HBV replication-competent transgenic mice. Data at early time points support the preferential activation and expansion of HBsAg-specific B cells in the liver, rather than the spleen, of HBV transgenic mice and a vigorous production of neutralizing antibodies. Interestingly, virtually all HBsAg-specific B cells showed an activated (CD44+ CD86+) phenotype, and more than half of HBsAg-specific B cells recovered from the liver displayed a germinal-center like (FAS+ GL-7+) phenotype. In line with these results, imaging and functional experiments suggested the presence of organized lymphoid structures within the liver parenchyma. Upcoming scRNAseq and two-photon studies will elucidate the spatiotemporal determinants governing the capacity of Ag-specific B cells to home and function in the virus-bearing liver.