Circulating HBsAg-specific B Cells are Partially Rescued After Achieving Functional Cure

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BACKGROUND

Hepatitis B virus (HBV) infection remains a major public health issue of great concern. A functional cure of chronic hepatitis B defined as hepatitis B surface antigen (HBsAg) loss is rarely achieved with current therapy(1). Herein, we aimed to characterize circulating HBsAg-specific B cells and identify B-cell epitopes directly associated with HBsAg loss.

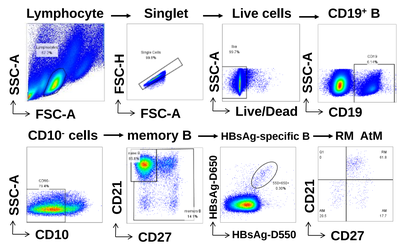
METHODS

Seventy-eight treatment-naïve patients with chronic HBV infection were classified into 4 groups according to the EASL guidelines(2): hepatitis B e antigen (HBeAg) negative chronic infection (n=21), HBeAg-positive chronic infection (n=20), HBeAg-negative chronic hepatitis (n=17), and HBeAg-positive chronic hepatitis (n=20). Forty-six patients who achieved HBsAg loss (n=24) or seroconversion (n=22) following antiviral treatment and 16 hepatitis B vaccinees with normal alanine aminotransferase levels were enrolled. HBsAg-specific B cells phenotypes and function were analyzed by flow cytometry. ELISpot assay was used to measure the ability of B cells to secrete antibodies. HBsAg specific B-cell epitopes associated with functional cure were mapped by ELISA.

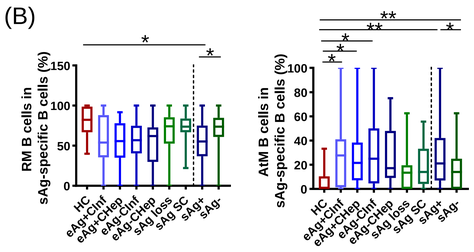
RESULTS

1. The classical resting memory B cell population (RM, $CD21^+CD27^+$) in HBsAg-specific B cells was reduced while the proportion of atypical memory B cells (AtM, $CD21^-CD27^-$), a functionally exhausted subset, was expanded in chronically HBV-infected patients (A and B). An increased proportion of RM B cells and a deceased proportion of AtM B cells were observed in patients after achieving functional cure (C).

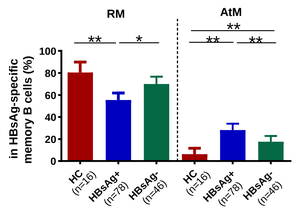
(A)



(B)



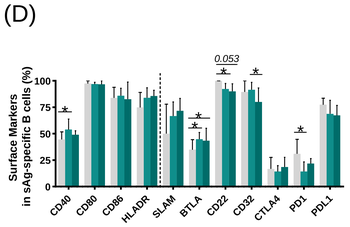
(C)



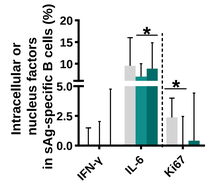
1. HBsAg-specific B cells were partially restored in patients with functional cure.
2. Three functional cure-related epitopes are promising targets for vaccine development.

2. HBsAg-specific B cells expressed lower levels of CD32 and higher levels of IL-6 upon stimulation in patients with HBsAg loss (D and E). The frequency of HBsAb-secreting B cells was significantly increased after achieving functional cure (F).

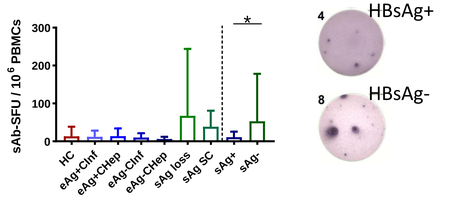
(D)



(E)

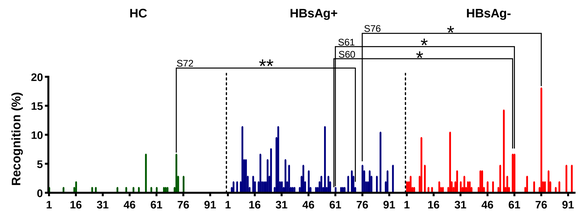


(F)

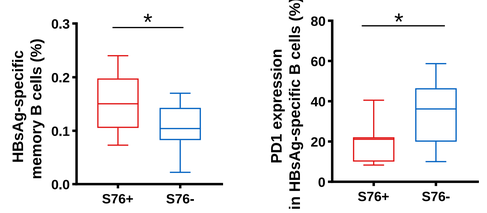


3. Sera from patients with HBsAg loss mainly reacted with peptides S60, S61, and S76, suggesting that they are dominant linear B-cell epitopes relevant for functional cure (G). An expansion of HBsAg-specific B cell was detected in S76-reactive subjects, accompanied by lower PD-1 expression (H).

(G)



(H)



CONCLUSIONS

HBsAg-specific B cells were partially restored in patients after achieving functional cure. Functional cure-related epitopes are promising targets of therapeutic vaccine development for chronic HBV infection to increase the functional cure rate.

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