Figure S1. rHBVvac alone did not eliminate HBV in HBV-carrier mice. HBV-carrier mice were immunized subcutaneously with PBS (Untr), 2 μg rHBV vaccine (rHBVvac), and 2 μg rHBVvac combined with 10 μg CpG M362 (cHBV-vaccine) weekly for 3 weeks, separately. (A) Post-immunization serum levels of HBsAg, measured by ELISA and compared with two-way ANOVA. (B) Post-immunization serum levels of HBeAg, measured by ELISA and compared with two-way ANOVA. (C) Serum anti-HBs levels on day 21 after the treatment. All data represent a mean ± SEM (n ≥ 8). *p < 0.05 versus Untr mice.
Figure S2. CpG M362 promoted the activation of DCs in dLNs. HBV-carrier mice were immunized subcutaneously with PBS (Untr), 2 μg rHBV vaccine (rHBVvac), and 2 μg rHBVvac combined with 10 μg CpG M362 (cHBV-vaccine) weekly for 3 weeks, separately. (A) Proportion of mDCs (Lin−/− MHCII+ CD317− CD11c+) on day 21 post-immunization in dLNs. (B) Flow cytometry results showing expression of CD80, CD86 and CD40 on mDCs in dLNs. (C) Proportion of pDCs (Lin−/− MHCII+ CD317+ CD11cint) on day 21 post-immunization in dLNs. (D) Flow cytometry results showing expression of CD80, CD86 and CD40 on pDCs in dLNs. All data represent a mean ± SEM (n ≥ 8). *p < 0.05, **p < 0.01 versus Untr mice.
Figure S3. HBV-specific CXCR5⁺ CD11a⁺ CD8α⁻ T cells and CXCR5⁺ CD11a⁺ CD4⁺ T cells expressed higher levels of inhibitory molecules LAG-3, TIGIT, PD-1 and Tim-3 than their CXCR5⁻ counterpart during CHB infection. Splenocytes were harvested from HBV-carrier mice on day 21 post-immunization. Cell doublets were gated out using FSC-A vs FSC-H followed by using the Fixable Viability Dyes to exclude the dead cells, and then CD3⁺ CD8⁺ T lymphocytes were gated from these cells. HBV-specific CD11a⁺ CD8α⁻ T cells and HBV-specific CD11a⁺ CD8⁻ T cells (clarified as CD4⁺ T cells) were gated from these cells, then these cells were further separated into CXCR5⁺ cells and CXCR5⁻ cells, and the expression of PD-1, TIGIT, Tim-3, and LAG-3 on these two cells were analyzed by flow cytometry respectively.
Figure S4. cHBV-vaccine partly restored the exhausted HBV-specific CXCR5\(^+\) CD4\(^+\) T cells.

HBV-carrier mice were immunized subcutaneously with PBS (Untr) and 2 \(\mu\)g rHBVvac combined with 10 \(\mu\)g CpG M362 (cHBV-vaccine) weekly for 3 weeks, separately. (A) The frequency of splenic CXCR5\(^+\) CD11a\(^{hi}\) CD4\(^+\) T cells on day 21 post-immunization. (B) PD-1, TIGIT, Tim-3 and LAG-3 expression on HBV-specific CXCR5\(^+\) CD11a\(^{hi}\) CD4\(^+\) T cells on day 21 post-immunization. All data are expressed as mean ± SEM (n ≥ 5). **\(p < 0.01\) versus unvaccinated mice.
Figure S5. The serum ALT remained at the baseline levels in cHBV-vaccine-treated group after HBV re-challenge. HBV-carrier mice were immunized subcutaneously with PBS (Untr) and 2 μg rHBVvac combined with 10 μg CpG M362 (cHBV-vaccine) weekly for 3 weeks, separately. Then, these treated mice were re-challenged with hydrodynamic injection of 8 μg pAAV/HBV1.2 plasmid on day 59 after the first vaccination. Serum levels of ALT monitored on day 7 after the HBV re-challenge (Normal serum ALT levels are < 40 mIU/mL). All data represent a mean ± SEM (n ≥ 7). *p < 0.05 versus Untr mice.
Figure S6. cHBV-vaccine induced long-lasting CXCR5⁺ CD4⁺ T cell response during HBV re-challenge. HBV-carrier mice were immunized subcutaneously with PBS (Untr) and 2 μg rHBVvac combined with 10 μg CpG M362 (cHBV-vaccine) weekly for 3 weeks, separately. Then, these treated mice were re-challenged with hydrodynamic injection of 8 μg pAAV/HBV1.2 plasmid on day 59 after the first vaccination. (A) The frequency of splenic CXCR5⁺ CD11a⁺ CD4⁺ T cells on day 7 after HBV re-challenge. (B) PD-1, TIGIT, Tim-3, and LAG-3 expression on HBV-specific CXCR5⁺ CD11a⁺ CD4⁺ T cells on day 7 after HBV re-challenge. All data are expressed as mean ± SEM (n ≥ 6). *p < 0.05, **p < 0.01 versus unvaccinated mice.