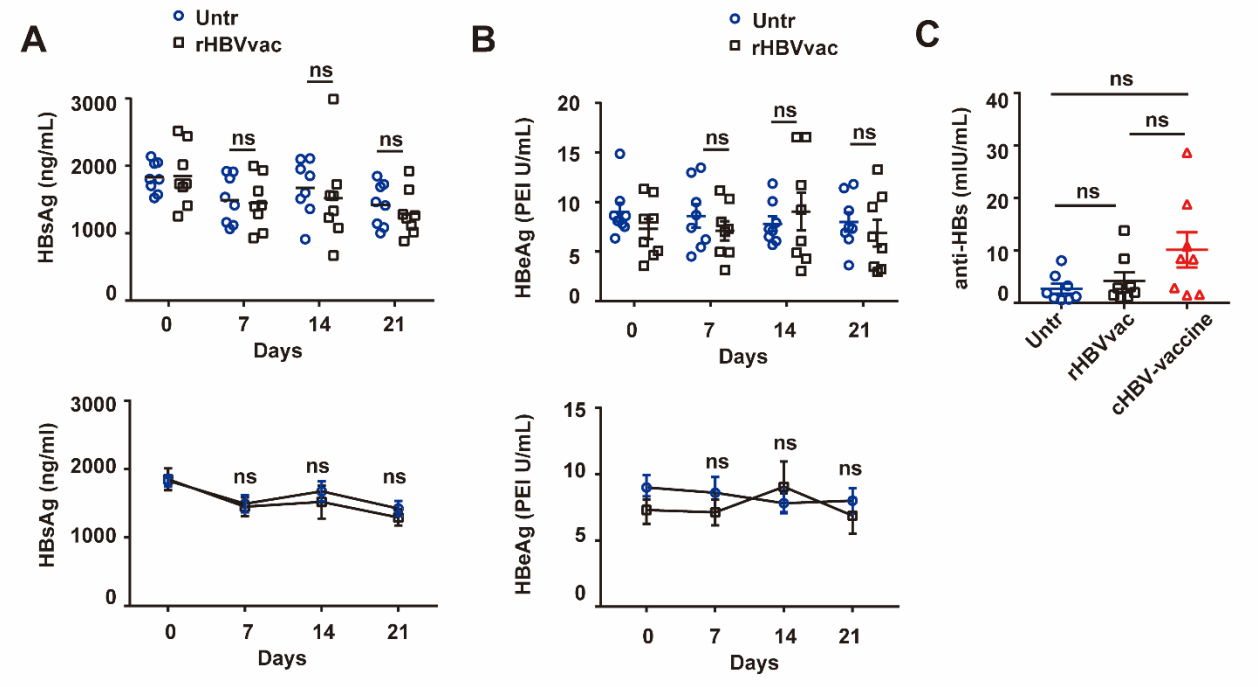

Figure S1. rHBVvac alone did not eliminate HBV in HBV-carrier mice. HBV-carrier mice were immunized subcutaneously with PBS (Untr), 2 μg rHBV vaccine (rHBVvac), and 2 μg rHBVvac combined with 10 μg CpG M362 (cHBV-vaccine) weekly for 3 weeks, separately. (A) Post-immunization serum levels of HBsAg, measured 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.

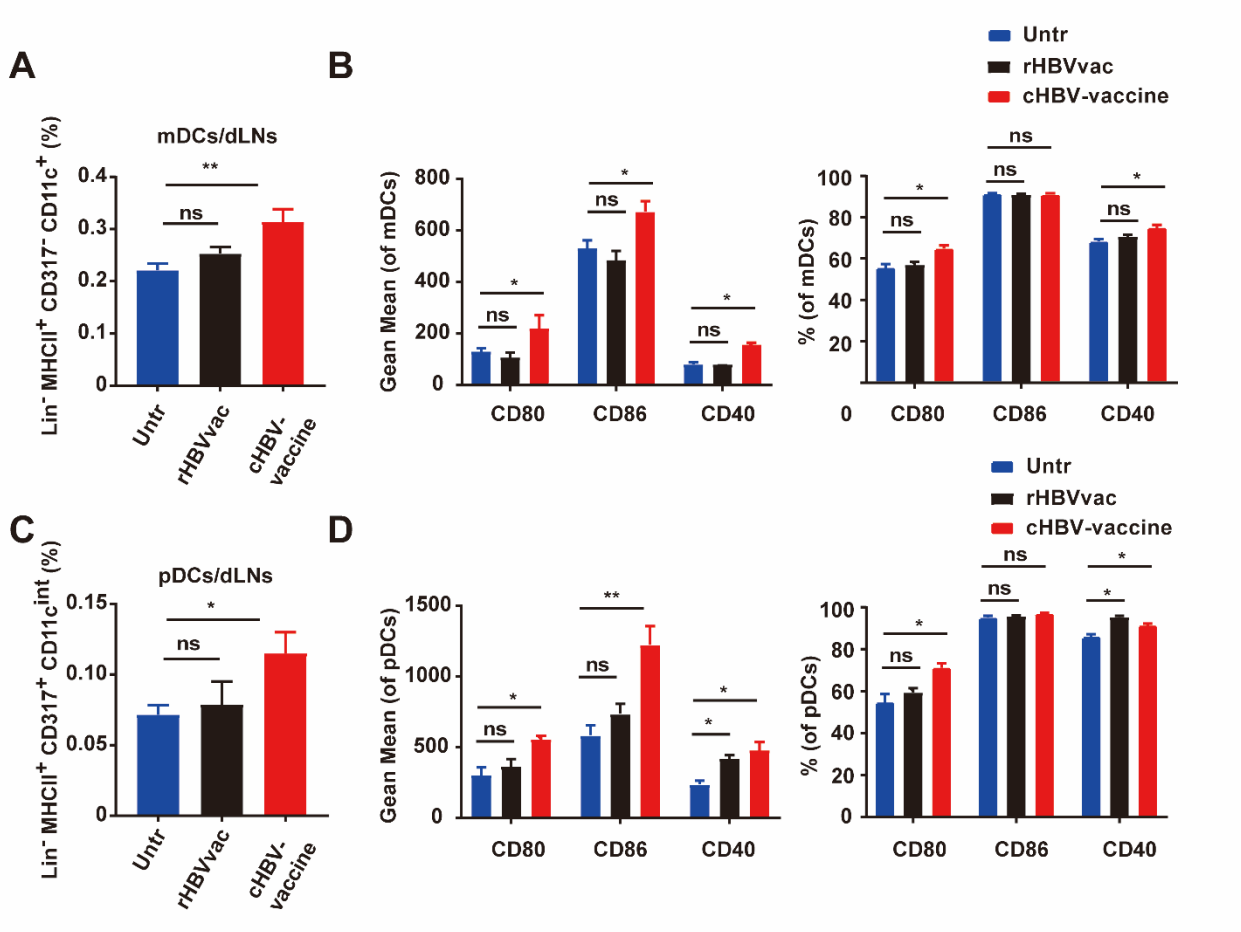

Figure S2. CpG M362 promoted the activation of DCs in dLNs. HBV-carrier mice were immunized subcutaneously with PBS (Untr), 2 μg rHBV vaccine (rHBVvac), and 2 μg rHBVvac combined with 10 μg CpG M362 (cHBV-vaccine) weekly for 3 weeks, separately. (A) Proportion of mDCs ($Lin^{-/-}$ $MHCII^{+}$ $CD317^{-}$ $CD11c^{+}$) 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 ($Lin^{-/-}$ $MHCII^{+}$ $CD317^{+}$ $CD11c^{int}$) 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 ($n \geq 8$). *$p < 0.05$, **$p < 0.01$ versus Untr mice.

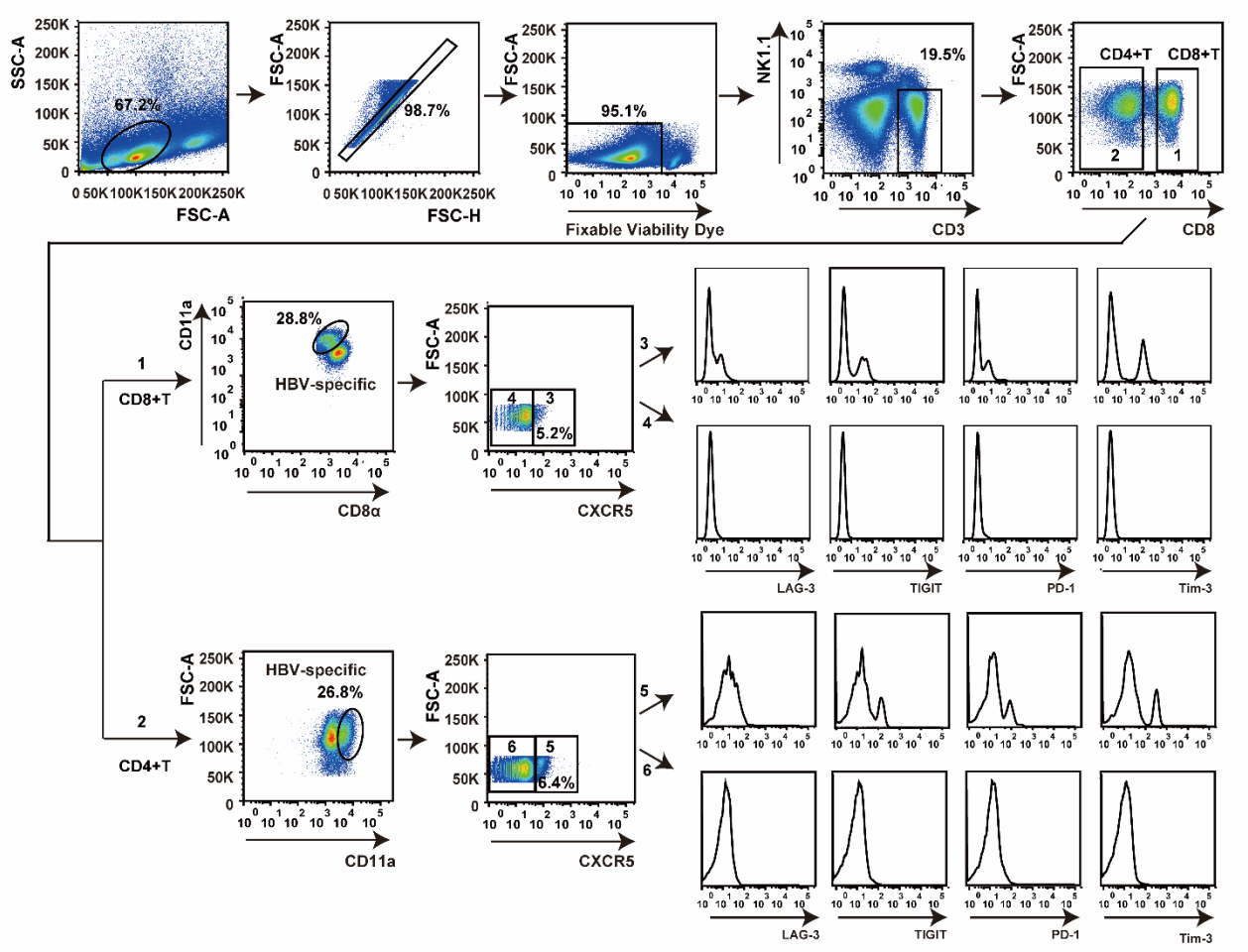

Figure S3. HBV-specific CXCR5^{+} CD11a^{hi} CD8α^{lo} T cells and CXCR5^{+} CD11a^{hi} CD4^{+} T cells expressed higher levels of inhibitory molecules LAG-3, TIGIT, PD-1 and Tim-3 than their CXCR5^{-} counterpart during CHB infection. Splenocytes were harvested from HBV-carrier mice on day 21 post-immunization. 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^{hi} CD8α^{lo} T cells and HBV-specific CD11a^{hi} 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.

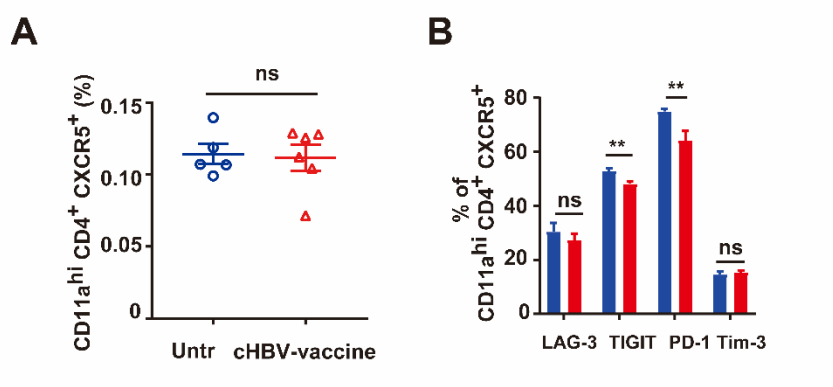

Figure S4. cHBV-vaccine partly restored the exhausted HBV-specific CXCR5$^+$ CD4$^+$ T cells. HBV-carrier mice were immunized subcutaneously with PBS (Untr) and 2 μg rHBVvac combined with 10 μg CpG M362 (cHBV-vaccine) weekly for 3 weeks, separately. (A) The frequency of splenic CXCR5$^+$ CD11a^{hi} CD4$^+$ 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 ($n \geq 5$). $^{**}p < 0.01$ versus unvaccinated mice.

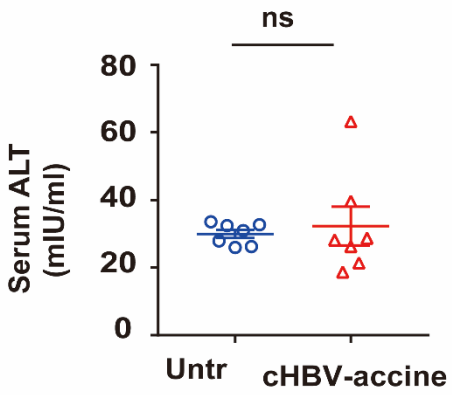

Figure S5. The serum ALT remained at the baseline levels in cHBV-vaccine-treated group after HBV re-challenge. HBV-carrier mice were immunized subcutaneously with PBS (Untr) and 2 μg rHBVvac combined with 10 μg CpG M362 (cHBV-vaccine) weekly for 3 weeks, separately. Then, these treated mice were re-challenged 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 ($n \geq 7$). *$p < 0.05$ versus Untr mice.

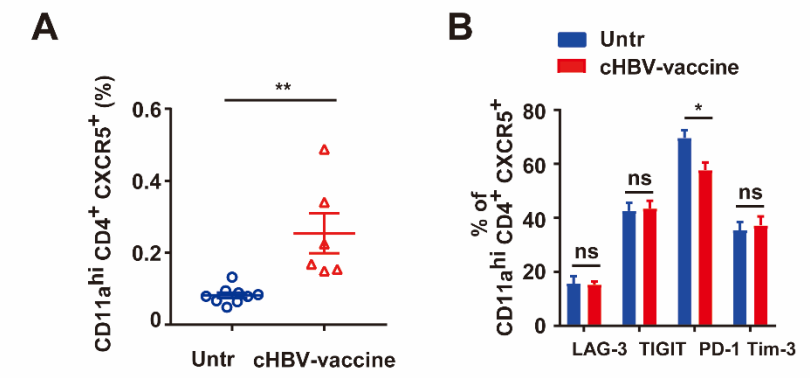

Figure S6. cHBV-vaccine induced long-lasting CXCR5$^+$ CD4$^+$ T cell response during HBV re-challenge. HBV-carrier mice were immunized subcutaneously with PBS (Untr) and 2 μg rHBVvac combined with 10 μg CpG M362 (cHBV-vaccine) weekly for 3 weeks, separately. Then, these treated mice were re-challenged with hydrodynamic injection of 8 μg pAAV/HBV1.2 plasmid on day 59 after the first vaccination. (A) The frequency of splenic CXCR5$^+$ CD11a^{hi} 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^{hi} 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.