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Abstract: T-cell therapy of chronic hepatitis B is a novel approach to restore antiviral T-cell immunity and cure the infection. We aimed at identifying T-cell receptors (TCR) with high functional avidity that have the potential to be used for adoptive T-cell therapy. To this end, we cloned HLA-A*02-restricted, hepatitis B virus (HBV)-specific T cells from patients with acute or resolved HBV infection. We isolated 11 envelope- or core-specific TCRs and evaluated them in comprehensive functional analyses. T cells were genetically modified by retroviral transduction to express HBV-specific TCRs. CD8+ as well as CD4+ T cells became effector T cells recognizing even picomolar concentrations of cognate peptide. TCR-transduced T cells were polyfunctional, secreting the cytokines interferon gamma, tumor necrosis factor alpha and interleukin-2, and effectively killed hepatoma cells replicating HBV. Notably, our collection of HBV-specific TCRs recognized peptides derived from HBV genotypes A, B, C and D presented on different HLA-A*02 subtypes common in areas with high HBV prevalence. When co-cultured with HBV-infected cells, TCR-transduced T cells rapidly reduced viral markers within two days. Our unique set of HBV-specific TCRs
with different affinities represents an interesting tool for elucidating mechanisms of TCR-MHC interaction and dissecting specific anti-HBV mechanisms exerted by T cells. TCRs with high functional avidity might be suited to redirect T cells for adoptive T-cell therapy of chronic hepatitis B and HBV-induced hepatocellular carcinoma.