T cells expressing a chimeric antigen receptor that binds hepatitis B virus envelope proteins control virus replication in mice.

Abstract:
Antiviral agents suppress hepatitis B virus (HBV) replication but do not clear the infection. A strong effector T-cell response is required to eradicate HBV, but this does not occur in patients with chronic infection. T cells might be directed toward virus-infected cells by expressing HBV-specific receptors and thereby clear HBV and help to prevent development of liver cancer. In mice, we studied whether redirected T cells can engraft after adoptive transfer, without prior T-cell depletion, and whether the large amounts of circulating viral antigens inactivate the transferred T cells or lead to uncontrolled immune-mediated damage. CD8(+) T cells were isolated from mice and stimulated using an optimized protocol. Chimeric antigen receptors (CARs) that bind HBV envelope proteins (S-CAR) and activate T cells were expressed on the surface of cells using retroviral vectors. S-CAR-expressing CD8(+) T cells, which carried the marker CD45.1, were injected into CD45.2(+) HBV transgenic mice. We compared these mice with mice that received CD8(+) T cells induced by vaccination, cells that express a CAR without a proper signaling domain, or cells that express a CAR that does not bind HBV proteins (controls). CD8(+) T cells that expressed HBV-specific CARs
recognized different HBV subtypes and were able to engraft and expand in immune-competent HBV transgenic mice. After adoptive transfer, the S-CAR-expressing T cells localized to and functioned in the liver and rapidly and efficiently controlled HBV replication compared with controls, causing only transient liver damage. The large amount of circulating viral antigen did not impair or overactivate the S-CAR-grafted T cells. T cells with a CAR specific for HBV envelope proteins localize to the liver in mice to reduce HBV replication, causing only transient liver damage. This immune cell therapy might be developed for patients with chronic hepatitis B, regardless of their HLA type.