BACKGROUND & AIMS: The final goal in hepatitis B therapy is eradication of the hepatitis B virus (HBV) replication template, the so-called covalently closed circular DNA (cccDNA). Current antiviral treatment of chronic hepatitis B depends on interferon alpha or nucleoside analogues inhibiting the viral reverse transcriptase. Despite treatment, cccDNA mostly persists in the host cell nucleus, continues to produce hepatitis B surface antigen (HBsAg), and causes relapsing disease. We therefore aimed at eliminating persistently infected hepatocytes carrying HBV cccDNA by redirecting cytolytic T cells toward HBsAg-producing cells. METHODS: We designed chimeric T-cell receptors directed against HBV surface proteins present on HBV-infected cells and used them to graft primary human T cells with antibody-like specificity. The receptors were composed of a single chain antibody fragment directed against HBV S or L protein fused to intracellular signalling domains of CD3xi and the costimulatory CD28 molecule. RESULTS: Our results show that these chimeric receptors, when retrovirally delivered and expressed on the cell surface, enable primary human T cells to recognize HBsAg-positive hepatocytes, release interferon gamma and interleukin 2, and, most importantly, lyse HBV replicating cells. When coincubated with HBV-infected primary human
hepatocytes, these engineered, antigen-specific T cells selectively eliminated HBV-infected and thus cccDNA-positive target cells. CONCLUSIONS: Elimination of HBV cccDNA-positive hepatocytes following antiviral therapy is a major therapeutic goal in chronic hepatitis B, and adoptive transfer of grafted T cells provides a promising novel therapeutic approach. However, T-cell therapy may also cause liver damage and therefore needs further preclinical evaluation.

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