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T-cell therapy for chronic viral hepatitis

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Abstract

Although therapy for chronic hepatitis C virus infection has delivered remarkable cure rates, curative therapies for hepatitis B virus (HBV) may only be available in the distant future. The possibility to eliminate or at least stably maintain low levels of HBV replication under the control of a functional anti-host response has stimulated the development of specific immunotherapies for HBV infection. We reviewed the development of T-cell therapy for HBV, highlighting its potential antiviral efficiency but also its potential toxicities in different groups of chronic HBV patients.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the only two communicable diseases in which there have been increases in related morbidity and mortality over the past 20 years [1]. Both viruses are chronically infecting about 500 million people (HBV ~350 million, HCV ~150 million) and represent the seventh most frequent cause of death worldwide [1]. HBV and HCV are hepatotropic, non-cytopathic viruses able to establish persistent infections that cause different degrees of hepatic inflammation (chronic hepatitis), leading to the development of liver cirrhosis and hepatocellular carcinoma (HCC).

The two viruses are unrelated and virologically different. HCV remains prevalent in North America and Europe, whereas chronic hepatitis B is prevalent in Asia and sub-Saharan Africa [1,2]. HCV is an RNA virus belonging to the *Flaviviridae* family, and HBV is a DNA virus of the *Hepadnaviridae* family and uses reverse transcriptase to synthesize its DNA from a pre-genomic RNA form [3]. HCV is able to activate in the infected host a classical type I interferon (IFN)-mediated innate response [3], whereas HBV generally escapes innate immune recognition and does not activate type I IFN-mediated immunity. Chronic HBV and HCV infections are both characterized by quantitative and functional defects of virus-specific T-cell response [4,5]. The frequency of virus-specific T cells is extremely low, and virus-specific T cells show features of exhaustion in both chronic HBV and HCV patients [6]. However, the quantitative and functional defects are more pronounced in HBV infections, with T cells virtually undetectable in the blood of many chronic HBV patients by *ex vivo* analysis [7–9]. In addition, while frequency and impact of viral mutations in T cell epitopes are frequently detectable in HCV infections [10], viral mutations affecting CD8 T-cell epitopes are scarcer in chronic HBV patients [6,11,12].

Of extreme practical importance in relation to the potential impact of T-cell therapy for HBV and HCV are the efficacies of currently available treatments. New therapies for HCV have delivered remarkable cure rates, with more than 90% of patients achieving viral clearance with all oral direct-acting antivirals [13]. In contrast, curative therapies for HBV will not be available until the distant future (14). Thus, although it is difficult to see a possible therapeutic advantage of a new T-cell-based therapy in chronic HCV patients, the fact that current therapies for HBV only partially suppress but do not eliminate HBV from the infected host has encouraged research for new and more radical therapies designed to eliminate or at least stably maintain low levels of HBV replication under the control of a functional anti-host response. For these reasons, in this review, we concentrate on the development of T-cell therapy for HBV. T-cell therapy for HCV chronic infection is certainly important for understanding the mechanisms of T-cell antiviral control [15,16], but their use for therapy appears unlikely.

Why use T cell therapy in chronic HBV infection

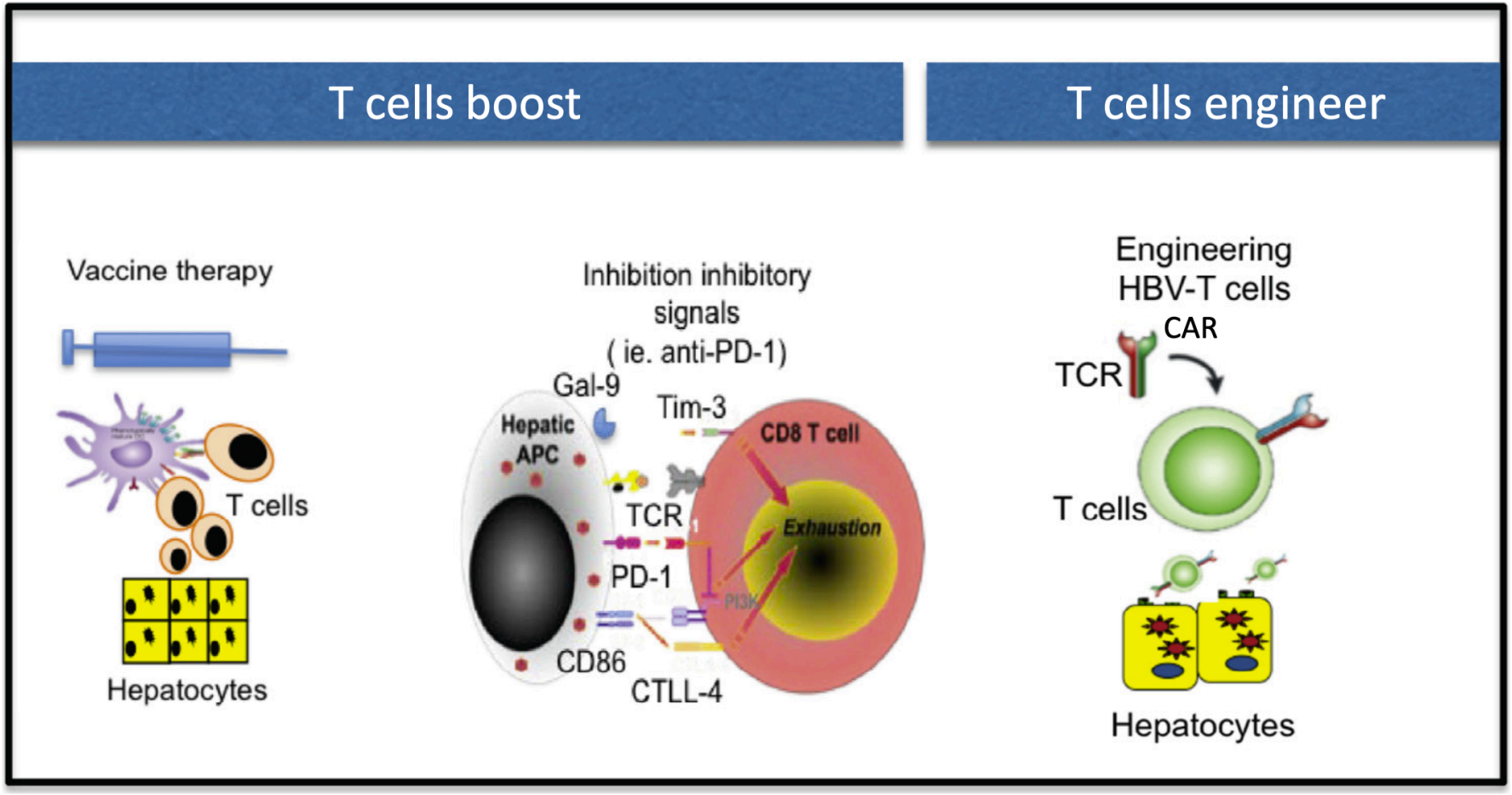
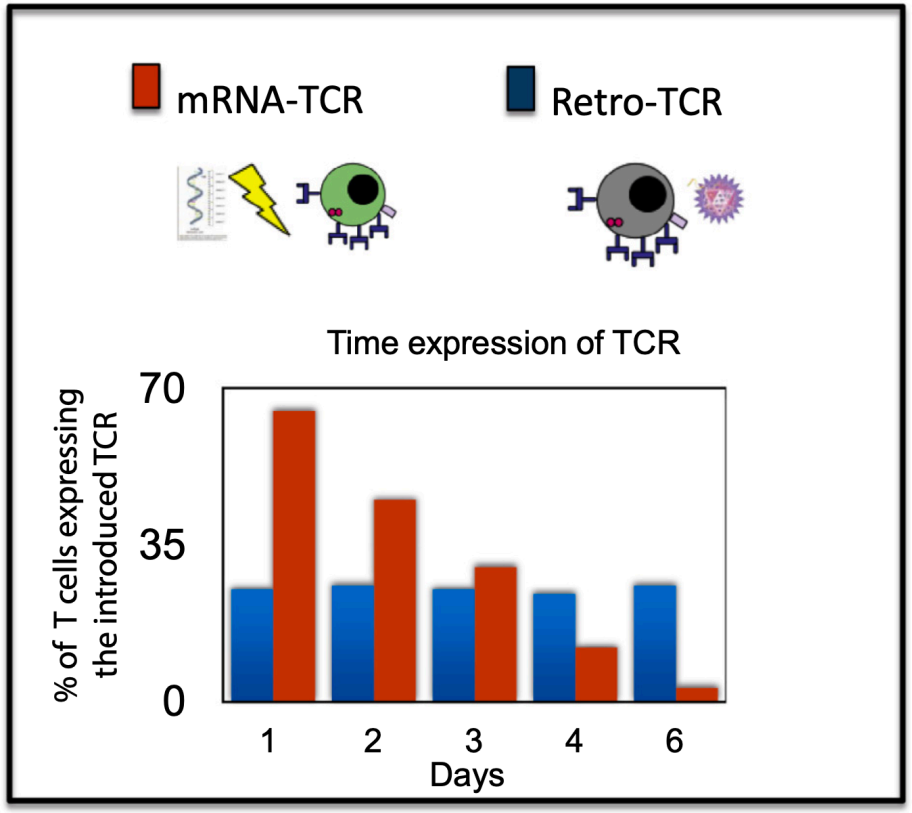


Figure 1. Strategies to boost HBV-specific T cells.

Controlling hepatic toxicity in HBV-specific T-cell therapy



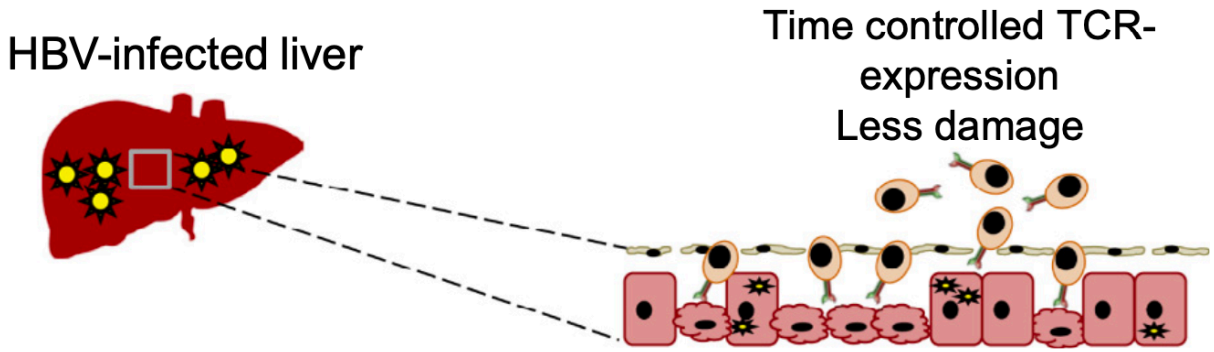


Figure 2. TCR expression on mRNA TCR electroporated T cells is transient. This results in a TCR expression limited by time and a reduced chronic liver damage.

Production of antiviral non-cytolytic HBV- specific T cells

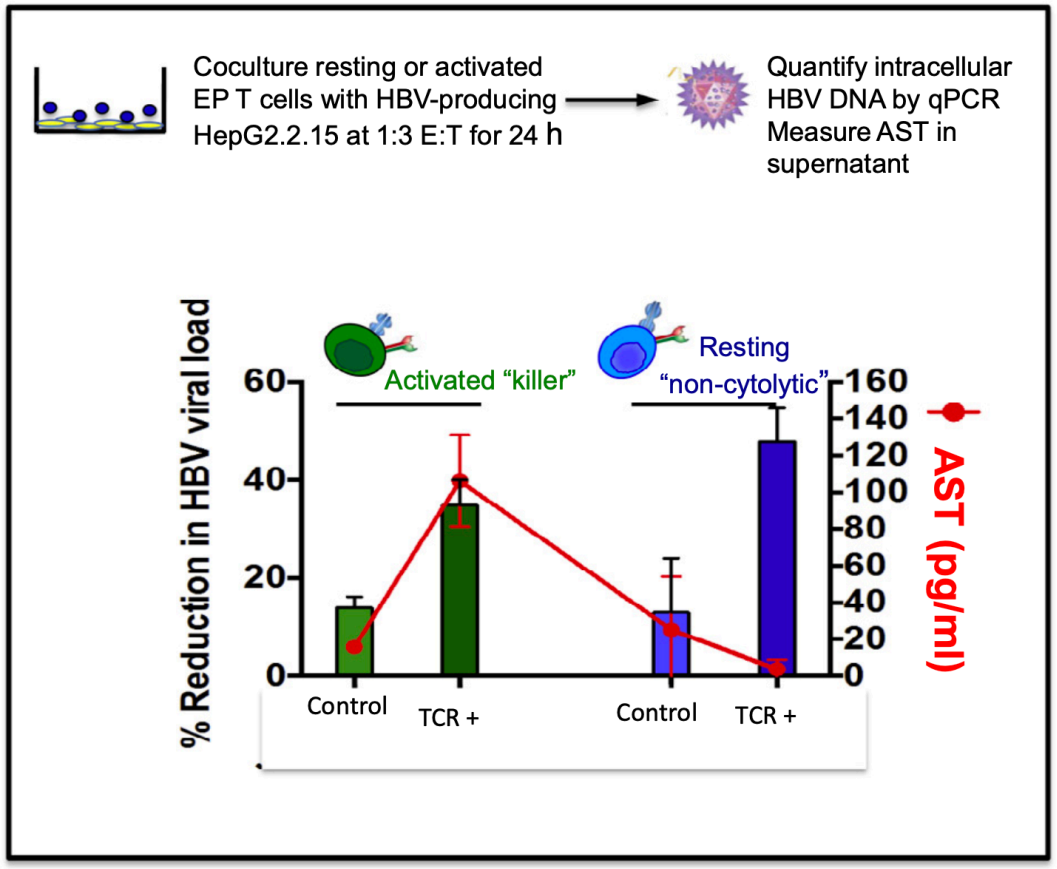


Figure 3. Resting TCR-redirected T cells inhibit HBV replication without lysis. AST, Alanine transaminases; EP, electroporated T cells; qPCR, quantitative polymerase chain reaction.