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Editorial

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The pivotal role of CD8+ T cells in hepatitis E virus infection

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CD8+ T lymphocytes or cytotoxic T lymphocytes express a range of effector molecules that participate in adaptive host defense and immune memory against pathogens and, upon antigen-dependent stimulation, eliminate infected cells by secreting granzymes and perforins.[1] Importantly, divergent outcomes of many viral infections (*i.e.* HCV; SARS-CoV-2) among individual patients have been linked to differences in virus-specific CD8+ T-cell responses.[2,3] Optimal activation and priming of naïve CD8+ T cells requires recognition of distinct viral peptides through the binding of peptide-MHC adducts by T-cell receptors and co-stimulation by molecules of the CD28 family. Using a combination of *in silico* and *in vitro* approaches, Kemming *et al.* define 25 novel HEV-specific CD8+ T-cell epitopes to examine the immune response in patients with acute, resolved and chronic hepatitis HEV infection.[4]

HEV is a long-neglected RNA virus and the major causative agent of acute viral hepatitis in humans worldwide. At least 20 million HEV infections occur annually, accounting for at least 3.3 million cases of acute illness and 44,000–70,000 deaths.[5,6] Moreover, recent studies reported high seroprevalences across different countries (*i.e.* ∼50% of blood donors in southwestern France).[7] HEV infections are usually self-limiting and asymptomatic in immunocompetent individuals but can progress to chronicity and cause fulminant hepatitis in about 50–70% of immunosuppressed patients.[8] Reduction of immunosuppressive treatment results in viral elimination in approximately 30% of patients. Unfortunately, no specific drugs are approved to treat HEV infections and only ribavirin (RBV) is used for off-label treatment, despite adverse side-effects and the emergence of viral variants that lower sensitivity to RBV treatment.[9] Although recent studies suggested HEV clearance depends on an effective virus-specific CD8+ T-cell response, there is a remarkable deficit in knowledge about the contribution of adaptive T-cell immunity to the control and pathogenesis of HEV infection.[10,11] In particular, little information is currently available about the abundance, phenotype, functional capacity and fate of pre-existing and induced HEV-specific CD8+ T cells, which might determine the divergent outcomes of infection.

Kemming *et al.* performed a high-resolution *ex vivo* analysis of HEV-specific CD8+ T cells using a peptide/HLA class I (pHLA-I) tetramer-based *ex vivo* enrichment strategy with samples from patients with acute, resolved and chronic HEV infection. In line with previous studies, Kemming *et al.* observed a broad and vigorous HEV-specific CD8+ T-cell response within acute patients, with epitope-specific CD8+ T cells accounting for up to one-third of the total circulating CD8+ T-cell count in individual patients, restricted by 9 different HLA class I alleles with most epitopes restricted by HLA-A*02:01 (Fig. 1). This steep increase in CD8+ T-cell activation in combination with previously reported liver infiltration of CD8+ T cells may also partially explain how non-cytopathic HEV may cause liver pathology.[12] Furthermore, following viral clearance, the specific CD8+ T-cell response declined by up to 2 logs within the first months, but then plateaued throughout follow-up for over 5 years after viral clearance in an individual with acute-resolving HEV infection. This long-lasting memory response was further characterized by expression of CD127 and T-cell factor 1 (TCF1), and lowered expression of activation and proliferation markers CD38 and Ki67 (Fig. 1). Conversely, in patients with chronic HEV, only a minor percentage (4/12) displayed a HEV-specific CD8+ T-cell response that focused on only 1 or 2 of the previously defined epitopes, mainly restricted to HLA-A*02:01. In patients with chronic HEV, most epitopes were located in open-reading frame (ORF)1, while in acute patients approximately 50% of HEV-specific CD8+ T-cell responses targeted the smaller viral capsid protein ORF2, implying that ORF2 forms a relatively immunodominant CD8+ T-cell target required during viral clearance. The high genetic homology (85%) of ORF2 amino acid residues across the 4 major human pathogenic genotypes and the observation in neutralization studies that documented a single HEV serotype, imply cross-protection efficacy against different genotypes after self-limiting HEV infection.[13,14] Moreover, a vaccine formulation based on recombinant genotype 1 ORF2 (HEV 239 - Hecolin®), licensed in China, has been reported to protect against symptomatic infections with HEV genotype 4.[15,16] The identification, by Kemming *et al.*, of ORF2-dominant CD8$^+$ T-cell epitopes within acute patients and the absence in chronic patients highlights the importance of ORF2 for the HEV-induced immune response and the potential to develop globally effective HEV antigen-specific immunotherapies. In contrast to patients with acute HEV, HEV-

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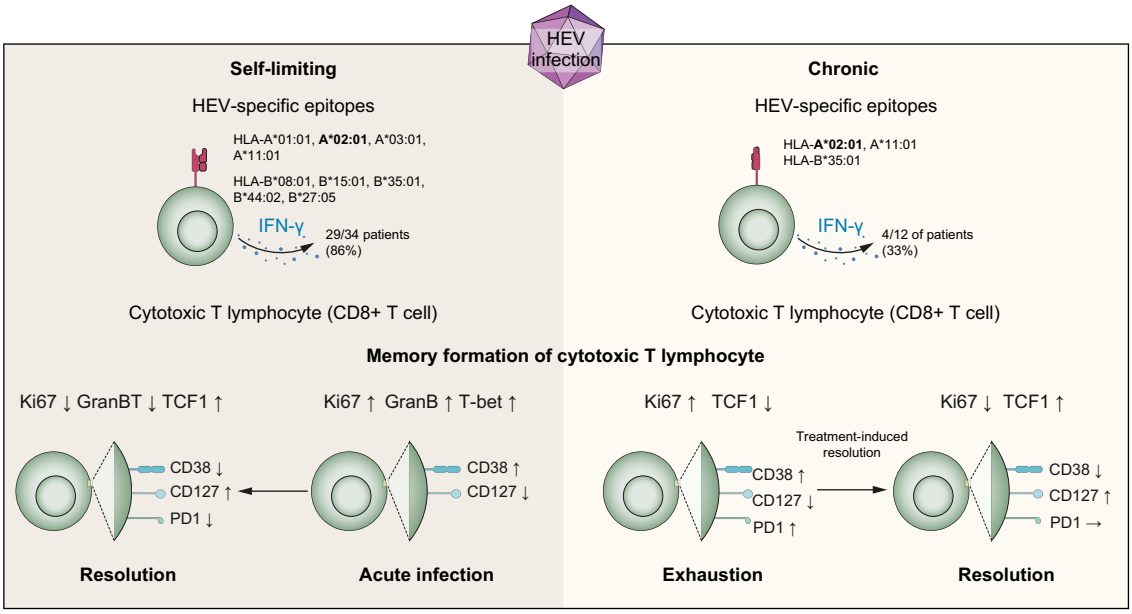

Fig. 1. CD8+ T-cell responses during HEV infection in acute, resolved (left) and chronic (right) patients. Patients with acute, resolved HEV infection display a broad HEV-specific CD8+ T cell, restricted by 9 different HLA class I alleles (mainly HLA-A*02:01), followed by a strong memory response. In contrast patients with chronic HEV infection display a narrow HEV-specific CD8+ T-cell response (mainly restricted to HLA-A*02:01). CD8+ T cell become dysfunctional and exhausted during the course of infection. Nonetheless, treatment-induced viral clearance is accompanied with a partial reinvigoration of HEV-specific CD8+ T-cell function.

specific CD8+ T cells in chronic patients further exhibited an activated (indicated by CD38 and Ki67 expression) yet predominantly CD127- PD-1+ phenotype characteristic of terminally exhausted CD8+ T cells (Fig. 1). A key question in the context of chronic hepatitis E has been whether T-cell immunity recovers after treatment with RBV or reduced immune suppression. In accordance with previous studies, Kemming *et al.* observed at least partial reinvigoration of HEV-specific CD8+ T-cell function as indicated by increased IFN-γ production, following treatment-induced viral clearance.[17] Despite using peripheral blood cells, which do not necessarily reflect the situation of the infected liver, the findings of Kemming *et al.* suggest that immunosuppression does not prevent priming of HEV-specific CD8+ T cells *per se*, but T cells rather become dysfunctional and exhausted during chronic infection. Importantly, HEV-specific CD8+ T cells were found to continually decline with increasing duration of persistent HEV infection, indicating that long-term chronic HEV infection may lower the possibility of, at least partially, reinvigorating CD8+ T-cell functionality. Hence, reduced immunosuppression in combination with antiviral treatment should be started early in persistent HEV infection, as currently recommended by EASL guidelines. In addition, Kemming *et al.* identified a mutation within the HEV genome, which substantially reduced HLA-A*01:01 binding, implying that viral escape may also contribute to CD8+ T-cell failure during chronic HEV infection. An improved understanding of human T cell-mediated immunity during HEV infection, as herein presented by Kemming *et al.*, is not only important to optimize therapeutic strategies in the future, but also to understand HEV pathogenesis.

Although many questions regarding the immunopathology of chronic HEV infection under immunosuppression remain to be answered, the elegant work by Kemming *et al.* published in this issue provides important insights into the mechanisms of CD8+ T-cell failure in persistent HEV infection.[4] The proposed concept of T-cell priming even in the context of immunosuppression, despite dysfunctionality, exhaustion and eventual depletion during continuous antigen recognition, represents a major advance in the field. While the resulting treatment options are already adhering to the EASL guidelines,[18] scanning for viral escape mutants may also become an important component in the clinical management of patients with chronic HEV in the future.

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Conflict of interest

The authors do not have a conflict of interest to report.

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Authors' contributions

YB, DT wrote the initial manuscript. MK prepared the figure. All authors reviewed and agreed to the final version of the manuscript.

Supplementary data

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Author names in bold designate shared co-first authorship

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