

# **CD8<sup>+</sup> T cells of chronic HCV-infected patients express multiple negative immune checkpoints following stimulation with HCV peptides**

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## **Abstract**

Hepatitis C virus (HCV)-specific CD4<sup>+</sup> and CD8<sup>+</sup> T cells are key to successful viral clearance in HCV disease. Accumulation of exhausted HCV-specific T cells during chronic infection results in considerable loss of protective functional immune responses. The role of T-cell exhaustion in chronic HCV disease remains poorly understood. Here, we studied the frequency of HCV peptide-stimulated T cells expressing negative immune checkpoints (PD-1, CTLA-4, TRAIL, TIM-3 and BTLA) by flow cytometry, and measured the levels of Th1/Th2/Th17 cytokines secreted by T cells by a commercial Multi-Analyte ELISArray™ following in vitro stimulation of T cells using HCV peptides and phytohemagglutinin (PHA). HCV peptide-stimulated CD4<sup>+</sup> and CD8<sup>+</sup> T cells of chronic HCV (CHC) patients showed significant increase of CTLA-4. Furthermore, HCV peptide-stimulated CD4<sup>+</sup> T cells of CHC patients also displayed relatively higher levels of PD-1 and TRAIL, whereas TIM-3 was up-regulated on HCV peptide-stimulated CD8<sup>+</sup> T cells. Whereas the levels of IL-10 and TGF-β1 were significantly increased, the levels of pro-inflammatory cytokines IL-2, TNF-α, IL-17A and IL-6 were markedly decreased in the T cell cultures of CHC patients. Chronic HCV infection results in functional exhaustion of CD4<sup>+</sup> and CD8<sup>+</sup> T cells likely contributing to viral persistence.

**Keywords:** Co-inhibitory receptors; HCV; Immune checkpoint; PD-1; T-cell exhaustion; TIM-3

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