Amare Aregay et al., J Clin Cell Immunol 2017, 8:3(Suppl)
DOI: 10.4172/2155-9899-C1-037

Lack of full re-constitution of exhausted HCV-specific CD8+ T cells following IFN-free DAA therapy is partially reversed upon immune check-point inhibitions during chronic HCV

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Hepatitis C virus (HCV) persists and sets-up chronicity in majority of infected patients. Fortunately, new IFN-free direct-acting antiviral (DAA) therapies resulted in rapid and sustained clearance of HCV from infected patients. However, the impact of HCV clearance on HCV-specific CD8+ T cell responses remain yet to be understood. Owing to the rapid cessation of HCV replication and ensuing abrupt clearance of viral antigens mediated by IFN-free DAAs, we aimed at investigating the possible repercussions thereof on exhausted HCV-specific CD8+ T cells during chronic hepatitis C. We could show, by employing multimer-based magnetic bead enrichment technique that unlike activation markers that increased, *ex-vivo* surface expressions of co-regulatory markers remain unaffected following HCV clearance. Upon 10 day peptide stimulation *in-vitro*, the overall frequency of dextramer positive CD8+ T cells increased from baseline to 24 weeks after treatment in patients without advanced liver disease despite the fact that majority (55%) of patients did not show increase in proliferation. Meanwhile, HCV-specific CD8+ T cells proliferative capacity was not restored in patients with advanced liver disease. In addition, cytokines secretion and degranulation of HCV-specific CD8+ T cells remain unaffected following HCV clearance. Importantly, however, blockade of PDL1 pathway as well as PDL1/TIM3 double blockade resulted in enhanced proliferation and cytokine secretion by HCV-specific CD8+ T cells after IFN-free DAA therapy. Interestingly, HCV-specific CD8+ T cells that did not show increase in proliferation upon peptide stimulation alone could preferentially increase their proliferation and cytokine secretion upon blockade of PDL1 pathway. Taken together, our data implies that despite rapid HCV clearance, IFN-free DAA therapy does not fully re-constitute the altered phenotype and function of HCV-specific CD8+ T cells in chronic HCV. However, combining PDL1 or PDL1/TIM3 blocking therapy with IFN-free DAA therapy might possibly confer a functional and protective virus-specific CD8+ T cell response against re-infection.

Biography

Amare Aregay is currently pursuing his PhD at the Department of Gasteroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany under supervision of Professor Dr. Heiner Wedemeyer. He completed his Master's degree from Wageningen University Research Center. His current PhD work focuses on Cellular Immune Response (specifically T and NK cell response) towards chronic HCV infection in the context of IFN-free DAA therapy and liver transplantation.

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