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Abstract

GB Virus C E2 Inhibits PD-1-Mediated T Cell Signaling Dysfunction during Chronic Viral Infection †

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Abstract: Background: Program death receptor 1 (PD-1) is a co-inhibitory receptor that is upregulated and contributes to T cell dysfunction (exhaustion) during chronic viral infections, including HIV and HCV. GB virus C (GBV-C) is a persistent human virus, and co-infection is associated with reduced immune activation and improved clinical outcomes in HIV- and Ebola-infected individuals. Methods: PD-1 levels were measured by flow cytometry on CD38+ T cells from 45 HIV-infected individuals, 20 of whom were co-infected with GBV-C. Jurkat cell lines that stably express GBV-C E2 protein and vector control were used to purify total cellular RNA before, and 24 h following, activation using anti-CD3/CD28 treatment. Gene expression was analyzed by RNA-seq and qRT-PCR. Results: HIV-infected individuals with GBV-C viremia had reduced PD-1 expression on activated CD4+ and CD8+ T cells compared to HIV-infected GBV-C negative individuals. GBV-C particles and GBV-C E2 protein each inhibited PD-1 expression on T cells in vitro. Consistent with this, GBV-C E2 reduced gene expression of *PD-1*, and its ligand *PD-L1*, in both resting and activated T cells. GBV-C E2 regulated transcription of the PD-1 signaling pathway and T cell activation associated genes, without downregulation of the interferon-stimulated and innate immunity-related genes needed to resolve viral infections. Conclusions: Our current understanding of chronic RNA virus infections is that upregulation of PD-1 with T cell exhaustion is critical for viral persistence. However, these data demonstrate that GBV-C infection reduced PD-1 expression on activated T cells during HIV infection, and that the GBV-C E2 protein inhibits PD-1 signaling in T cells. This may preserve T cell function and contribute to the lack of immune deficiency in people with chronic GBV-C infection. Understanding the mechanisms by which GBV-C E2 alters PD-1 signaling may aid in the development of novel immunomodulatory therapeutics to prevent T cell dysfunction (exhaustion) during chronic viral infections.

Keywords: GBV-C; PD-1; T cell exhaustion; HIV