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Background

HIV-1-specific CD8+ T cell responses play an important role in the control over viral replication. Under persistent antigenic stimulation virus-specific CD8+ T cell become increasingly dysfunctional and upregulate several inhibitory molecules. The interaction and co-regulation of these molecules is largely unknown. The gastrointestinal associated lymphoid tissue (GALT) is one of the major sites of viral replication. Despite a substantial infiltration and expansion of HIV-1-specific CD8+ T cells in the GALT, viral replication appears to be more active in the GALT than in other body compartments. Here we show a distinct mechanism of inhibition of HIV-1-specific CD8+ T cells by soluble epithelial adhesion molecules with increasing viral loads in chronic HIV-1 infection.

Methods

HIV-infected individuals with chronic-progressive or chronic-controlled HIV-1 infection were analyzed. The distribution of E-cadherin in intestinal tissue was determined by immunohistochemistry. Plasma levels of soluble E-cadherin were determined using ELISA. Cytokine secretion by antigen-specific CD8+ T cells in the presence or absence of recombinant soluble E-cadherin was assessed by intracellular cytokine staining and Luminex.

Results

HIV-1 infected individuals had abnormal distribution of E-cadherin in the intestinal mucosa relative to uninfected individuals. These subjects also had significantly increased soluble E-cadherin levels in the plasma relative to HIV-negative subjects ($p < 0.05$). The viral load in chronic HIV-1 infection correlated strongly with E-cadherin levels in the plasma ($R = 0.7$; $p = 0.004$). HIV-1-specific CD8+ T cells in subjects with chronic-progressive HIV-1 infection showed significant elevated levels of KLRG1 expression ($p < 0.05$). In the presence of soluble E-cadherin, a natural ligand for KLRG1, KLRG1hi HIV-1-specific CD8+ T cells showed reduced amounts of cytokine production upon antigenic stimulation, while KLRG1lo expressing cells were not affected.

Conclusion

Our data suggest a novel mechanism by which the disruption of the gastrointestinal epithelium leads to release of soluble E-cadherin, which specifically inhibits KLRG1hi expressing HIV-1-specific CD8+ T cells.