T Regulatory Cells Disrupt the CCL20-CCR6 Axis Driving Th17 Homing to the Gut

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Background

During HIV-1 infection, the integrity of the intestinal immune barrier is disrupted due to a deep depletion of CD4$^+$ T cells in the gut. The translocation of microbial products from the gut lumen into the bloodstream has been linked with systemic inflammation. Despite long-term effective cART, CD4$^+$ T cells in the *lamina propria* are incompletely restored in most individuals.

Aims

Among the chemotactic axes involved in CD4$^+$ T cell homing to the gut, we focused on the CCR6-CCL20 axis as it governs Th17 cells homing, a T cell subset exerting a major role in antimicrobial immunity. We aimed to assess the factors regulating the expression of CCL20 by the enterocytes, and notably the role of the cytokines produced by Treg and Th17 cells.

Methods

Small bowel biopsies were obtained by endoscopy in 20 HIV-1$^+$ and 10 HIV-1$^-$ individuals. Intestinal lymphocytes phenotype was analyzed by flow cytometry. *CCL20* mRNA was quantified by qRT-PCR. The effect of PRR ligands and cytokines on CCL20 expression was explored using an *ex-vivo* system of human primary enterocytes. A coculture was done between the enterocytes and Th17/Treg cells. The expression of CCL20 by the enterocytes was evaluated by qRT-PCR and ELISA

Results

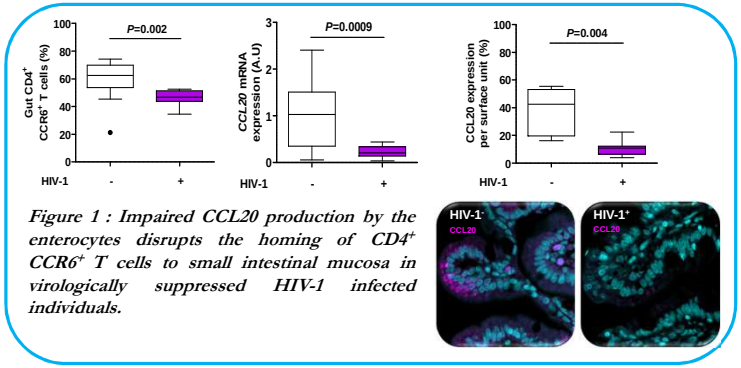

Figure 1 : Impaired CCL20 production by the enterocytes disrupts the homing of CD4$^+$ CCR6$^+$ T cells to small intestinal mucosa in virologically suppressed HIV-1 infected individuals.

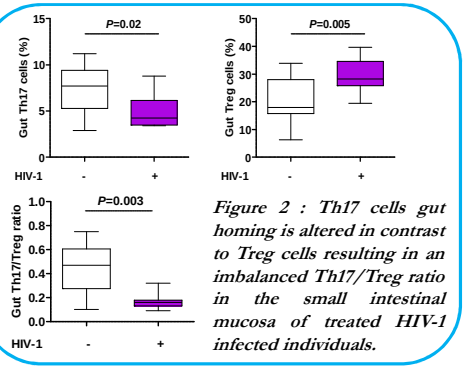

Figure 2 : Th17 cells gut homing is altered in contrast to Treg cells resulting in an imbalanced Th17/Treg ratio in the small intestinal mucosa of treated HIV-1 infected individuals.

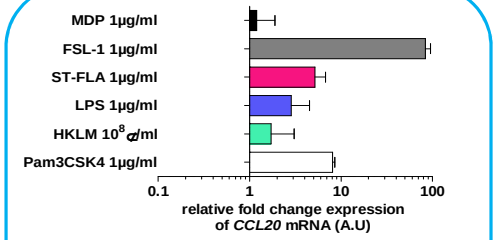

Figure 3 : Microbial sensing induces expression of CCL20 by the small intestine epithelial cells. (Pam3CSK4: TLR1/2 agonist, HKLM: TLR2 agonist, LPS: TLR4 agonist, ST-FLA: TLR5 agonist, FSL-1: TLR6/2 MDP: NOD2 agonist)

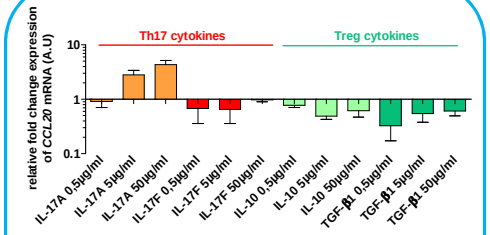

Figure 4 : Th17 cytokines induce expression of the CCL20 chemokine by the small intestine epithelial cells in contrary to Treg cytokines.

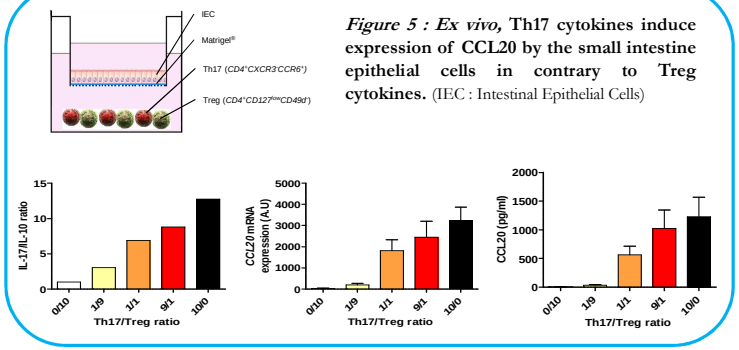

Figure 5 : Ex vivo, Th17 cytokines induce expression of CCL20 by the small intestine epithelial cells in contrary to Treg cytokines. (IEC : Intestinal Epithelial Cells)

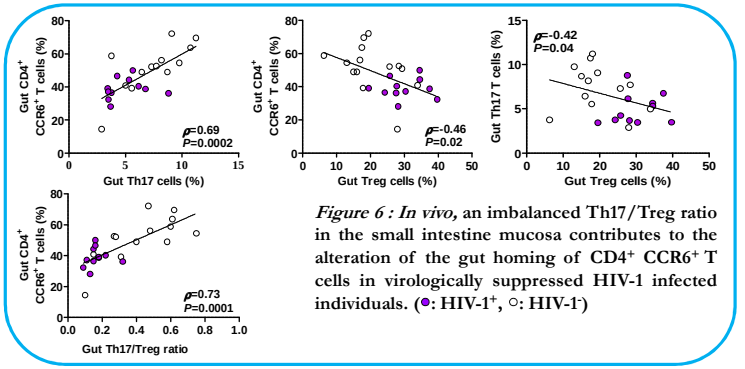

Figure 6 : In vivo, an imbalanced Th17/Treg ratio in the small intestine mucosa contributes to the alteration of the gut homing of CD4$^+$ CCR6$^+$ T cells in virologically suppressed HIV-1 infected individuals. (●: HIV-1$^+$, ○: HIV-1$^-$)

Conclusion