TNFα and IFNγ-producing CD4⁺ T cells modulate gut regeneration in HIV-1 infection

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BACKGROUND

Immune cells in the gastrointestinal tract are critical in host defense against pathogens. Immune cells further contribute to tissue regeneration and can directly interact with intestinal stem cells (ISCs). During HIV-1 infection, mucosal CD4⁺ T cell populations change dramatically. Early after infection CD4⁺ T cells infiltrate the intestine, whereas in chronic infection, CD4⁺ T cells are depleted. How CD4⁺ T cells affect intestinal stem cells and the repercussions for epithelial regeneration during HIV-1 infection is poorly understood.

High levels of TNFα and IFNγ secreted by CD4⁺ T cells inhibit the development of the intestinal cells. Depletion of CD4⁺ T cells impedes the normal regeneration of the epithelial layer

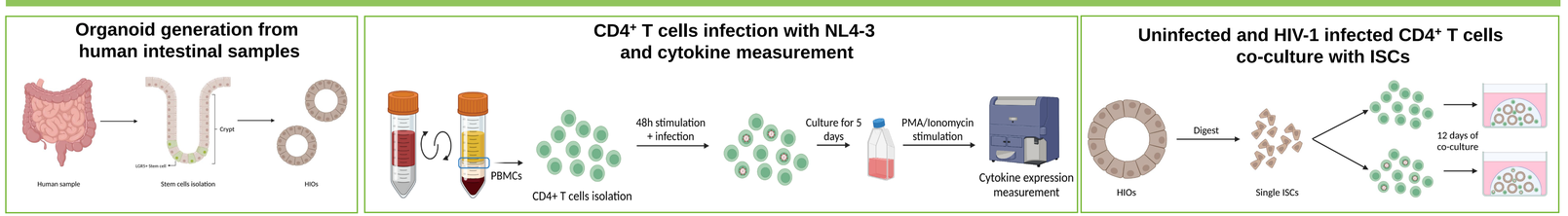
CONCLUSIONS

The number of intestinal cytokine-producing CD4⁺ T cells impact intestinal regeneration. Elevated CD4⁺ T cell numbers producing higher amounts of TNFα and IFNγ, mimicking the situation of acute HIV-1 infection, severely disrupted intestinal development, whereas reduced numbers of CD4⁺ T cells (chronic infection) resulted in impaired intestinal epithelial regeneration. Taken together, these data demonstrate the impact of intestinal CD4⁺T cells on stem cell function and the epithelial barrier during HIV-1 infection.

OBJECTIVE

To mimic acute and chronic HIV-1 enteropathy by using human-derived intestinal organoids (HIOs) in co-culture with HIV-1 infected CD4⁺ T cells

METHODS



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RESULTS

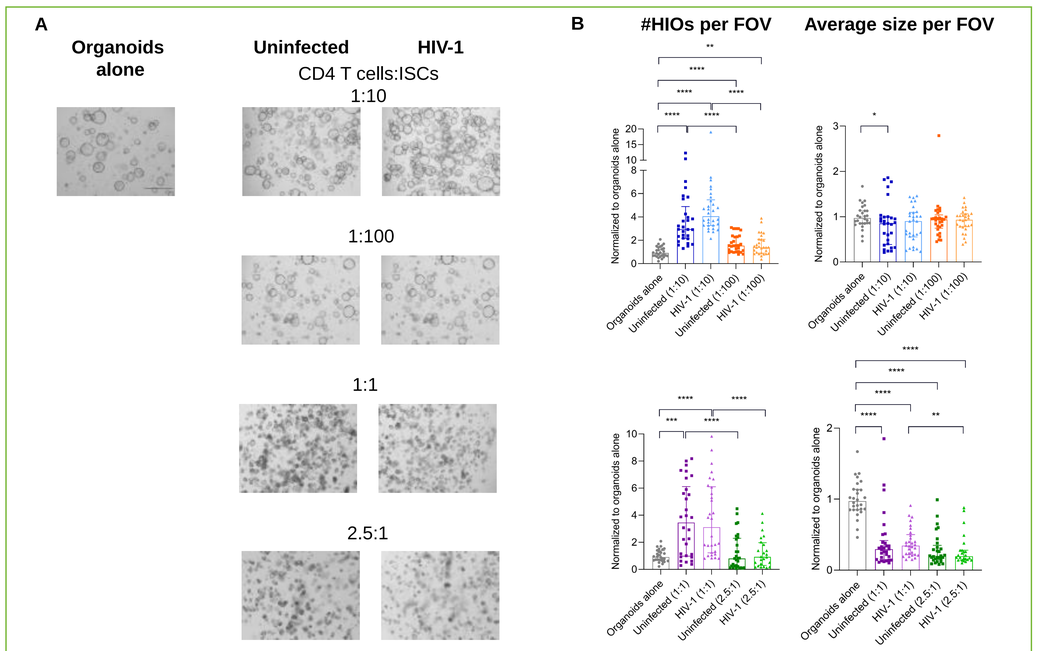

Figure 1. Organoid regeneration is affected in conditions mimicking chronic HIV-1 infection and development is disrupted in conditions mimicking hyperacute HIV-1 infection. A) Representative fields of view (FOV) showing organoids growing alone and with phisiological (1:10), chronic (1:100) and hyperacute (1:1; 2.5:1) amounts of uninfected and HIV-1 infected CD4 T cells. **B)** Number and average size of HIOs per FOV.

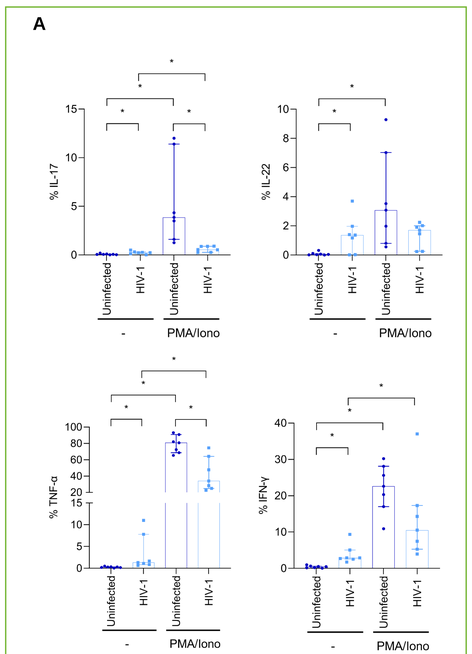

Figure 2. Uninfected and HIV-1 infected CD4 T cells produce IL-17, IL-22, IFNγ and TNFα. A) Media percentages of uninfected and HIV-1 infected IL-17⁺, IL-22⁺, IFN-γ⁺ and TNF-α⁺ CD4 T cells in unstimulated (-) and stimulated (PMA/Iono) conditions.

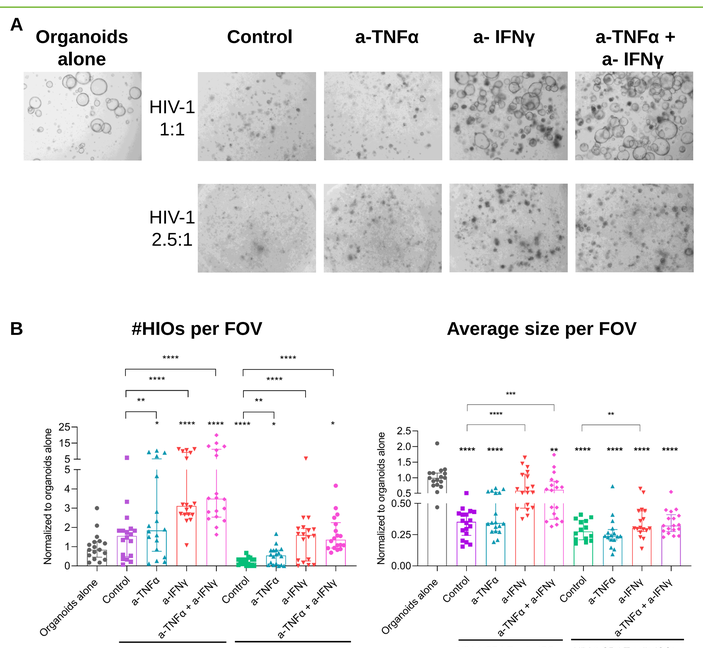

Figure 3. Organoid development is rescued upon the neutralization of IFNγ or/and TNFα. A) Representative FOVs showing organoids growing with HIV-1 infected CD4 T cells in hyperacute (1:1; 2.5:1) mimicking conditions in absence (control) or presence of IFNγ or/and TNFα blockers, **B)** Number and average size per FOV.