All program: Infectious Diseases

Modelling intestinal HIV-1 transmission using a novel gut-epithelial-immune cell co-culture organoid model

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The gastrointestinal tract is an important entry site for HIV-1 during mother-to-child or sexual transmission and a reservoir in which HIV-1 latently persists and replicates in mucosal target cells, including $CD4^+$ T cells and dendritic cells (DCs). Using cell lines and animal models, several routes for HIV-1 entry into the gastrointestinal mucosa have been proposed, including breakdown of the epithelial barrier by inflammation and/or trauma. However, it remains unknown how HIV-1 crosses the intestinal epithelial barrier and gains entry into the intestinal mucosa.

Here, we showcase a novel human primary gut-epithelial-immune cell co-culture organoid monolayer model generated on transwells. Separate access to apical/lumen and basolateral/mucosa compartments provides the ideal setting to study the interaction between epithelial cells and mucosal DCs, and unravel their role in intestinal HIV-1 infection.

Using confocal imaging and flow-cytometry analyses, we demonstrated that a subset of intestinal epithelial cells are able to internalize HIV-1 into intracellular vesicles, and subsequently transmit HIV-1 across the gut epithelium without affecting tight-junctions. Co-culture of human DCs with gut epithelial monolayers resulted in cell protrusions across the epithelial barrier. Notably, HIV-1 transmission levels further increased after addition of lumen-sampling DCs, as demonstrated by co-culture of basolateral supernatant with HIV-1 permissive cells.

Our findings highlight transcytosis across the epithelial barrier as a mechanism of enteric HIV-1 entry, underscore the relevancy of lumen-sampling DCs in intestinal HIV-1 transmission, and present a novel gut epithelial-DC organoid co-culture system to model the mucosal events in the pathogenesis of intestinal HIV-1 infection and test antiviral drugs.

250/250 words