Latent HHV7 Infection Attenuates Beneficial Host-Microbe Interactions in the Human Gut

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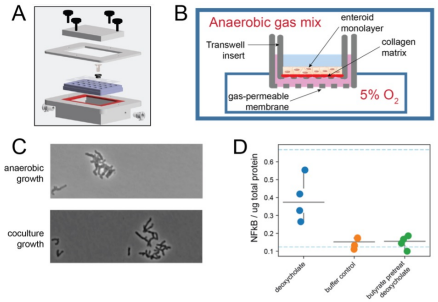
Background

Human Herpes Virus 7 (HHV7) infection results in a lifelong latent infection with over 95% of adults seropositive for HHV7. Lymphocytes are the best understood host cell type for latent HHV7, with the gastric mucosa another site of latent infection. *Herpesviridae* latency affects host processes like interferon signaling, antigen presentation, and proliferation—the same host pathways are implicated in the beneficial responses to commensal microbes.

Methods

Adult human colonic organoids with or without latent HHV7 infection were co-cultured with B. longum in asymmetric oxygen conditions that allow for live interaction (F1). The transcriptional state after 24h of interactions was determined with RNA-sequencing. The transcriptional state was compared between axenic (no microbes) or after co-culture and with or without latent HHV7.



F1: Establishing oxygen gradients across epithelial monolayers. (A) Schematic of oxygen gradient apparatus (B) Closeup view of individual well (C) Growth of the anaerobe B. longum was identical in the apparatus with hypoxic epithelial compared to full anaerobic growth (D) Butyrate administration protects the epithelium from inflammatory effects of deoxycholate.

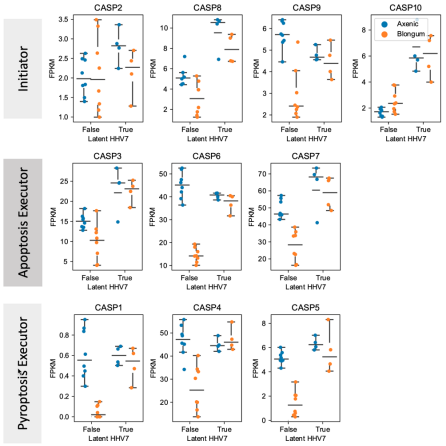
Results

Latent HHV7 is likely mosaic within intestinal stem cells. Screening human intestinal organoids (that lack lymphocytes and are strictly of the endodermal lineage) we have generated evidence that intestinal stem cells (ISC) and IEC can be a host cell for latent HHV7 infection in some but not all people (T1). RNA-sequencing reveals that this is true latency, with ISC and IEC containing HHV7 without transcripts from any of the protein-coding genes in the HHV7 genome. Further we have observed that latent HHV7 is mosaic in the gut, not affecting all of the ISC in an individual (T1).

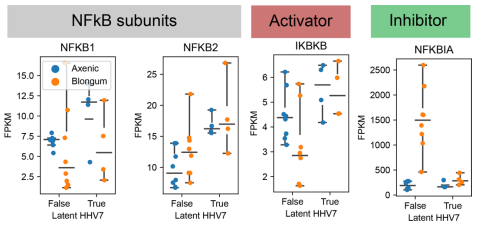
Organoids with latent HHV7 have attenuated transcriptional responses to a commensal microbe. In organoid-derived human IEC we have noted co-culture with the commensal bacteria B. longum suppresses key executors of apoptosis and pyroptosis (F2). These same effects are no longer observed with the B. longum is interacting with IEC latently infected with HHV7. A similar pattern was observed with NFkB regulators (F3).

Donor ID	Organ	Virus Panel Results
81	Colon	virus panel negative
81	Small Intestine	HHV7 positive
87	Colon	virus panel negative
87	Colon	HHV7 positive
88	Colon	HHV7 positive
88	Small Intestine	virus panel negative

T1: Latent HHV7 is found in some intestinal organoids derived from healthy adults. Each donor is assigned a unique numerical ID.



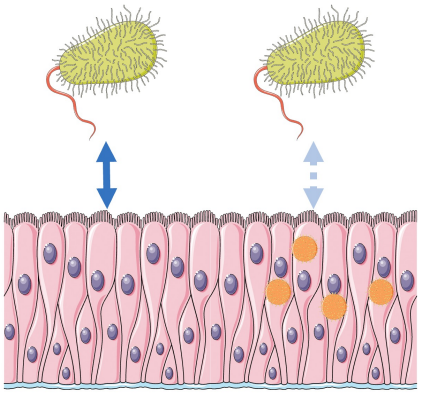
F2: Co-culture with the commensal microbe B. longum suppresses most apoptosis and pyroptosis executors only in an organoid without latent HHV7 infection. Fragments per kilobase per millions of reads (FPKM) from RNA-sequencing of fully-differentiated organoid-derived human intestinal epithelium after 24 hours of co-culture with B.longum (Orange) or remaining axenic (without microbes; Blue). Results from cell without (left) or with (right) latent HHV7.



F3: Stimulation of the NFkB inhibitor NFKBIA by co-culture with the commensal microbe B. longum is absent in organoids with latent HHV7 infection. RNA-sequencing of fully-differentiated organoid-derived human intestinal epithelium after 24 hours of co-culture with B.longum (Orange) or remaining axenic (without microbes; Blue). Results from cell without (left) or with (right) latent HHV7.

Conclusion

Latent HHV7 in the human gut epithelium may attenuate the effect of beneficial microbes like B. longum (F4). The evidence for mosaicism of latent HHV7 in the human gut adds a spatial aspect to these attenuating effects that could be relevant for specific disease processes (e.g. skip lesions in Crohn's disease). Confirmation of these findings, estimating the true prevalence of latent HHV7 in the gut, and identification of the HHV7 latency mechanism will be required to understand the full implications of these findings.



F4: A Model of Latent HHV7 Infection Attenuating Responses to Commensal Microbes. Latent HHV7 infection in the intestinal epithelium may leave the gut mucosa at increased risk for injury by impairing the beneficial response to commensal microbes in a spatially complex manner due to the apparent mosaic nature of latent HHV7 infection in the gut.