Rapid gut epithelial repair at the enteroendocrine-immune intersection through microbiota-mediated rescue of tryptophan metabolism during chronic HIV/SIV infection

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GUT: multi-tasking and highly functional organ

- Digestion and nutrient absorption
- Barrier to protect the internal gut microenvironment
- Protection against pathogens
- Largest immune organ in the human body
- Sense and response

GUT MICROBIOTA

- Extended metabolic capacities
- Epithelial barrier integrity
- Exclusion of pathogens
- Modulation of host metabolism
- Maturation and modulation of the immune system
GI tract: unique compartment where the nervous, endocrine and mucosal immune systems converge

Tryptophan (TRP) is a crucial mediator of the immune and endocrine system interactions

* HIV/SIV: HAND and altered TRP metabolism
HIV and the GUT

Major site for early HIV replication, dissemination and persistence

- Severe CD4+ T cell depletion
- Disruption of gut epithelial barriers -> leaky gut
- Microbial translocation
- Gut inflammation and impaired mucosal immunity
- Disturbed host-microbe interaction
Can SIV infection associated gut epithelium damage be reversed/repaired at the intersection of commensal microbes?

The ligated ileal loop model

- Ileum is tied off into 4 – 6 cm loops with intervening 1 cm spacer loops
- Loops allow for multiple bacterial species to be tested in the same animal
- Capture in vivo gut mucosal response in the natural setting
- Anaerobic microenvironment of the gut
- Bacteria can be incubated for up to 8 hours (animal still alive)
- Detect rapid changes in the gut epithelium for repair
ART therapy does not repair epithelial barrier integrity in chronic SIV infection

**Chronic SIV infection**
Exposure to LP and BI repairs gut epithelial barrier within 5 hours independent of CD4+ T cells recovery
LP and BI dampened inflammatory pathways in the gut mucosa during chronic SIV infection

Inflammasome pathway
PPARα/RXRα Activation
Signaling by Rho Family GTPases
Growth Hormone Signaling
mTOR Signaling
PI3K/AKT Signaling
PI3K Signaling in B Lymphocytes
Acute Phase Response Signaling
ILK Signaling
Th1 Pathway
Production of Nitric Oxide and Reactive Oxygen Species in...
CXCR4 Signaling
PTEN Signaling
Fcγ Receptor-mediated Phagocytosis in Macrophages and...
Phospholipase C Signaling
Integrin Signaling
NF-κB Signaling
G Beta Gamma Signaling
ERK/MAPK Signaling
CD28 Signaling in T Helper Cells
IL-8 Signaling
Role of NFAT in Regulation of the Immune Response
Tec Kinase Signaling

SIV+BI+  SIV+LP+  SIV+

Activation Z-score
How do commensals rapidly dampened inflammation and repair gut barrier during chronic SIV infection?

Metabolic profiling of gut luminal contents from chronically SIV infected animals following the exposure to LP and BI

**SIV+ vs. SIV-**
- **Up**: 111 metabolites
  - 41% Lipid
  - 29% Amino Acid
  - 14% Xenobiotics
- **Down**: 56 metabolites
  - 54% Lipid
  - 18% Xenobiotics
  - 16% Amino Acid

**SIV+ LP vs. SIV+**
- **Up**: 29 metabolites
  - 31% Amino Acid
  - 24% Lipid
  - 17% Nucleotide
- **Down**: 7 metabolites
  - 57% Nucleotide
  - 29% Co factors and Vit.
  - 14% Carbohydrate

**SIV+ BI vs. SIV+**
- **Up**: 49 metabolites
  - 31% Xenobiotics
  - 24% Lipid
  - 10% Nucleotide
- **Down**: 19 metabolites
  - 47% Nucleotide
  - 21% Lipid
  - 16% Xenobiotics

FC ± 1.5
- p ≤ 0.05
- q ≤ 0.25
Enteric TRP metabolism is altered during chronic SIV infection.
**Enteric TRP metabolism is altered during chronic SIV infection**

HIV infection is associated with increased IDO1 expression linked to the loss of Th17 cells and gut barrier disruption.

Accumulation of 5-HT and KYN metabolites during SIV infection.

Increased IDO1 expression in the gut.

**Diagram**: Tryptophan (TRP) metabolism during SIV infection. IDO1 and TPH1 are upregulated in the gut, leading to increased production of Kynurenine (KYN) and subsequent metabolites such as 5-Hydroxyindoleacetic acid (5-HIAA). Changes in the expression of enzymes like KATS, KYNU, KNYU, and 3HAO are also observed. SIV infection leads to a decrease in 5-HT levels and increased production of KYN metabolites.
Intestinal mucosal 5-HT is increased during chronic SIV infection due to decreased SERT-mediated 5-HT uptake.

EC cells: major producers of 5-HT in the gut.

No significant differences in EC cells numbers.

No significant differences in the expression of TPH1 and MAOA.
Intestinal mucosal 5-HT is increased during chronic SIV infection due to decreased SERT-mediated 5-HT reuptake

- Serotonin reuptake transporter (SERT)
- Removes intraluminal serotonin

Decreased SERT expression correlates with biomarkers of SIV disease progression
LP and BI shift the metabolism of TRP towards Indolelactate (ILA) biosynthesis during SIV infection

SIV+ vs. SIV-

SIV+ LP vs. SIV+

SIV+BI vs. SIV+
**LP and BI shift the metabolism of TRP towards Indolelactate (ILA) biosynthesis during SIV infection**

Increased levels of ILA (indolic acid derivative of TRP)
Lower levels of KYN metabolites
Decreased IDO1 expression
**Immune modulation effects of ILA**

ILA induce the production of IL-22 by CD4+CD8+ LPLs isolated from the gut

Increased expression of IL-22 related genes *in vivo* after LP and BI exposure
SUMMARY

• LP and BI rapidly restores (5 hours) SIV-induced gut barrier damage and dampens inflammation during SIV infection

• LP and BI rescue the TRP metabolism from SIV-mediated effects and drive towards ILA biosynthesis

• Rapid gut barrier repair through enteric immune-epithelial-commensal axis

• Damaged gut epithelium in SIV infection can be rapidly restored by leveraging commensal metabolites to modulate immune-epithelial interactions

• Novel targets for repair and protection of the gut immunity in HIV disease
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