GI Tract Barrier Breakdown and Adipocyte Inflammation

NIH Workshop on Obesity and Fat Metabolism in Individuals with HIV

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Inflammation in adipose tissue in PLHIV is a driver of insulin resistance and systemic inflammation

So ...what are causes of infiltration of macrophages and other pro-inflammatory cells into adipose tissue of PLHIV?
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Changes in GI epithelium

Intestinal microbial translocation

Systemic inflammation

Inflammation in adipose tissue
The intestinal epithelium during HIV infection

Sandler and Douek, Nature Reviews 2012
People with HIV have increased microbial translocation with associated innate and adaptive immune activation

HAART reduces circulating LPS, but plasma LPS still elevated despite viral suppression

Brenchley et al, Nature Medicine 2006
LPS triggers gain in visceral adipose tissue and adipose tissue inflammation in mice

This is mediated via LPS’s co-receptor CD14

These data provide evidence LPS → innate immune activation → AT inflammation

Cani et al, Diabetes 2007
Higher VAT is associated with increased monocyte chemoattractant protein (MCP-1) (CCL2) in PLHIV

Unpublished data
In addition to CCR2, CCR5 also mediates recruitment of macrophages into adipose tissue.

Maraviroc can reduce adipose tissue macrophage recruitment in obese mice fed high diet.

Perez-Matute et al. Antivir Ther 2017
Depletion of gut CD4 T-cells leads to immune activation in adipose tissue. Activated monocytes release inflammatory cytokines such as IL-6, TNF-α, and MCP-1. These cytokines further activate adipose tissue macrophages through the CCR2 receptor. The intestinal lumen contains IgA and mucin, which play a role in maintaining gut health. The exact mechanism of how these processes are interconnected is still under investigation.
Intestinal tight junctions can be further disrupted by inflammatory cytokines TNF-α, IL-1β and IFN-γ
Diet high in saturated fat and hyperglycemia
Dietary saturated lipids induce adipose tissue inflammation via change in gut microbial composition \( \rightarrow \) LPS \( \rightarrow \) TLR4 signaling and CCL2 (MCP-1)

Caesar et al, Cell Metabolism 2015
High fat diet induces microbial translocation in African Green Monkeys that persist after SIV infection

Xu, Pandrea et al. 21st International AIDS Conf 2016
Hyperglycemia and sugar intake drives intestinal barrier disruption through GLUT-2 dependent transcriptional reprogramming of intestinal epithelial cells and alteration of tight and adherence junction integrity.
Men and women living with HIV consume more than recommended amounts of saturated fat 
(Klassen and Goff, Eur J of Clin Nutrition 2013)

Added sugar intake is also significantly higher among PLHIV 
(Hall et al. OFID 2017)

Saturated fatty acids and added sugar intake in PLHIV are positively associated with increased I-FABP 
(Unpublished data)
Potential Therapeutic Targets

• **Targeting barrier function**
  - Oral bovine immunoglobulin (*Asmuth et al. AIDS 2013*)
  - IL-21 and probiotics enhances T\textsubscript{H17} cell expansion in SIV-infected pigtailed macaques (*Ortiz et al. Mucosal Immunology 2016*)
  - Glucagon-like peptide 2 (teduglutide) (*NHLBI-funded study under way*)

• **Dietary factors that may improve GI barrier function**
  - Reduction in sugar and saturated fats
  - Fruits, nuts and vegetables are ligands of aryl hydrocarbon receptor important in intestinal lymphoid tissue development (*Kiss et al. Science 2011*)
  - Vit A, Vit D

• **Targeting gut microbiota composition**
  - Prebiotics/probiotics
  - Metformin (*Forslund et al. Nature 2015*)
  - Also improves glucose and may activate AMP kinase in intestinal immune cells
  - Ivan Vujkovic-Cvijin talk
  - Alex Soukas’ talk

• **Targeting chemokine receptors to reduce AT inflammation:**
  - CCR2 and CCR5 antagonism with cenicriviroc (ACTG A5363 study in development phase)
Disruption in GI epithelial integrity and GI mucosal immunity drives inflammation.

In turn, adipose tissue inflammation and glucose dysregulation can also increase intestinal permeability.

Treatments to ameliorate GI barrier function may improve metabolic health in PLHIV.