

# GI Tract Barrier Breakdown and Adipocyte Inflammation

NIH Workshop on Obesity and Fat Metabolism in Individuals with HIV

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May 22, 2018

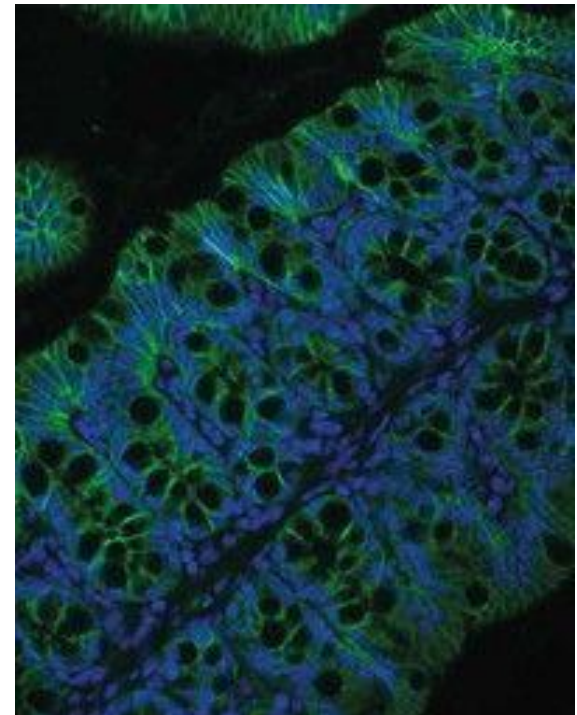
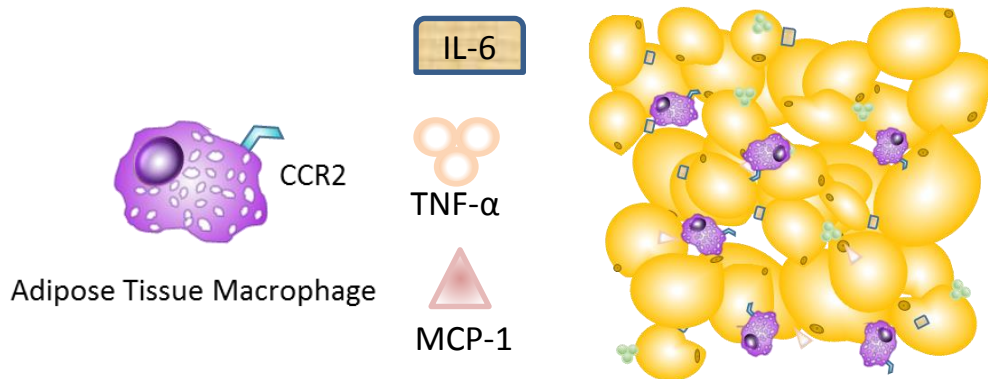


Photo from E. Elinav, Nature Rev Gastro and Hepatology 2018

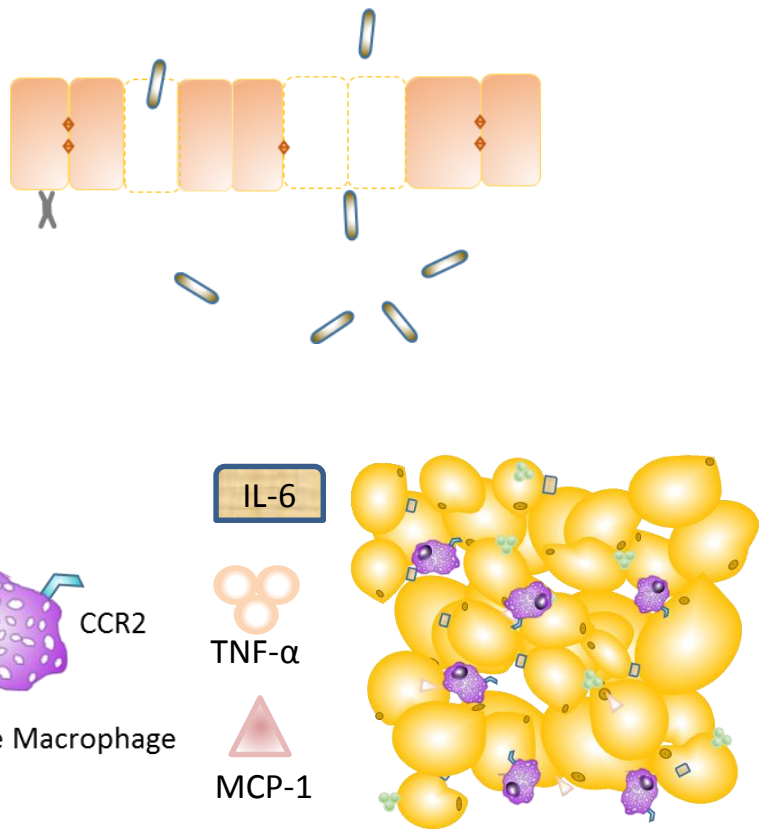
# Inflammation in adipose tissue in PLHIV is a driver of insulin resistance and systemic inflammation

**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**

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**Intestinal microbial translocation**

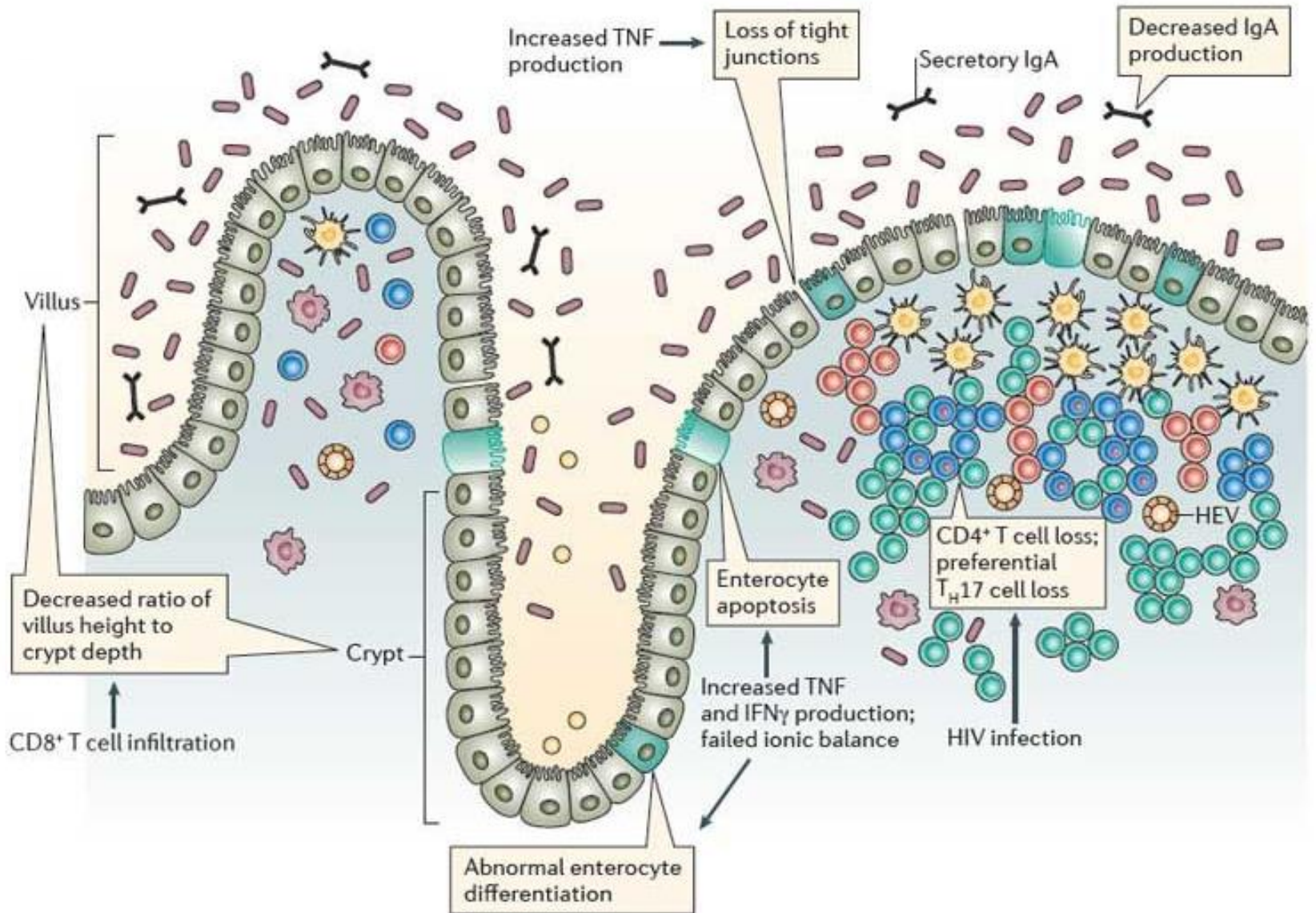
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**Systemic inflammation**

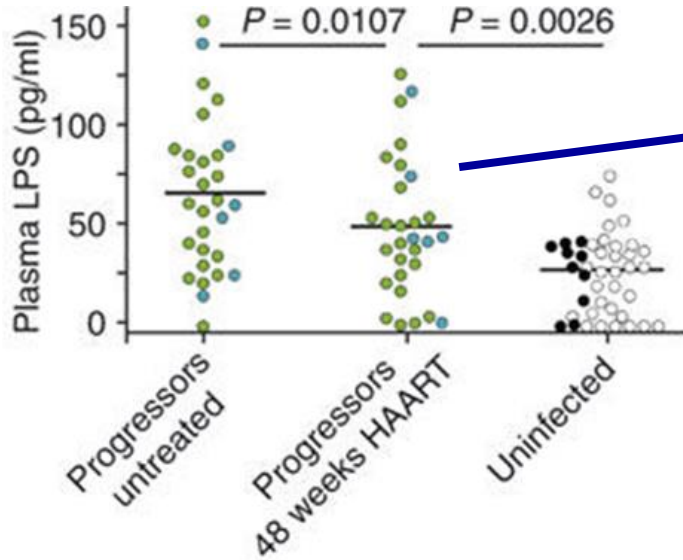
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**Inflammation in adipose tissue**

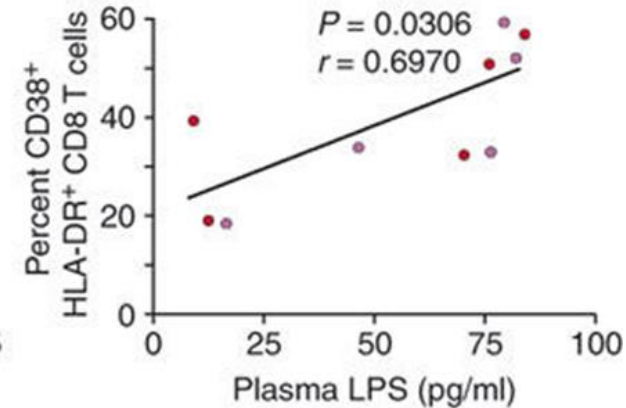
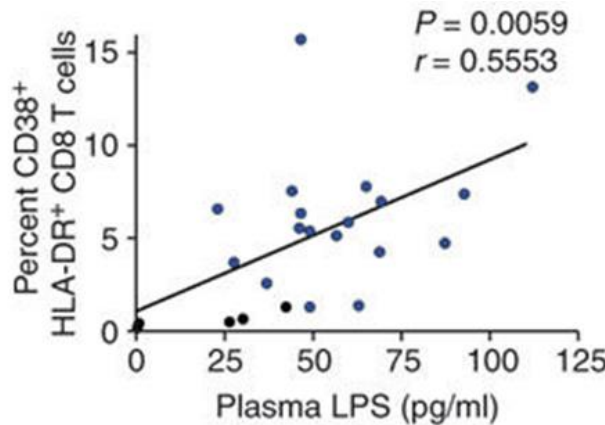
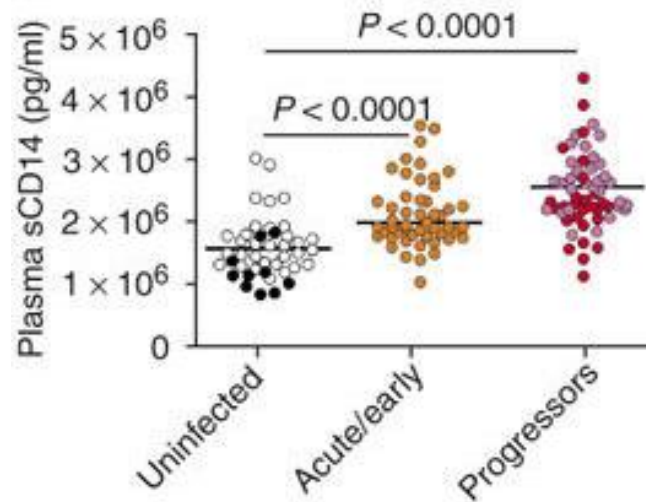
# The intestinal epithelium during HIV infection



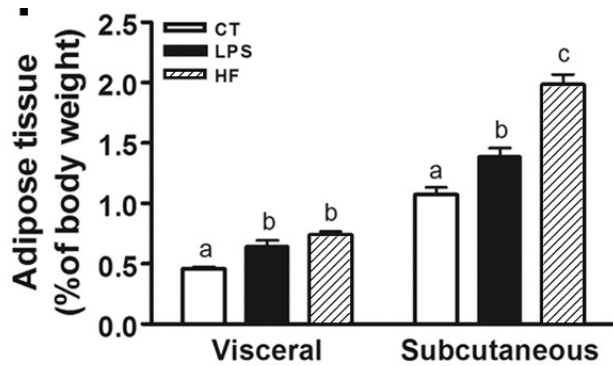
# People with HIV have increased microbial translocation with associated innate and adaptive immune activation



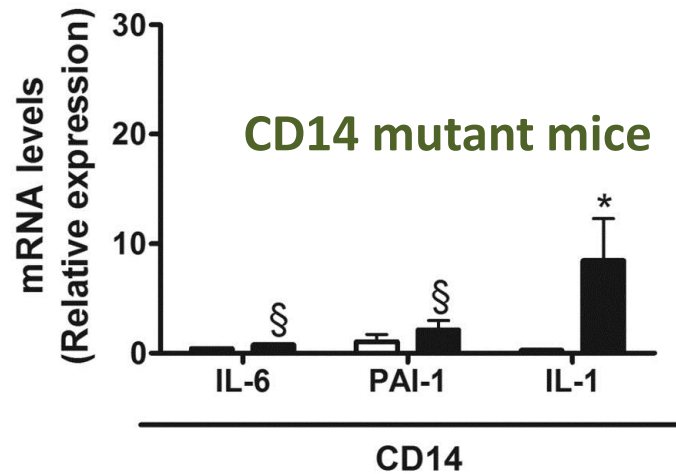
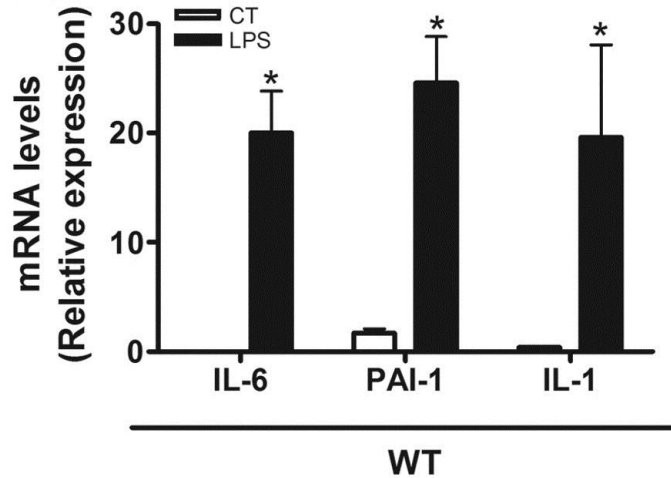
HAART reduces circulating LPS, but plasma LPS still elevated despite viral suppression



# LPS triggers gain in visceral adipose tissue and adipose tissue inflammation in mice



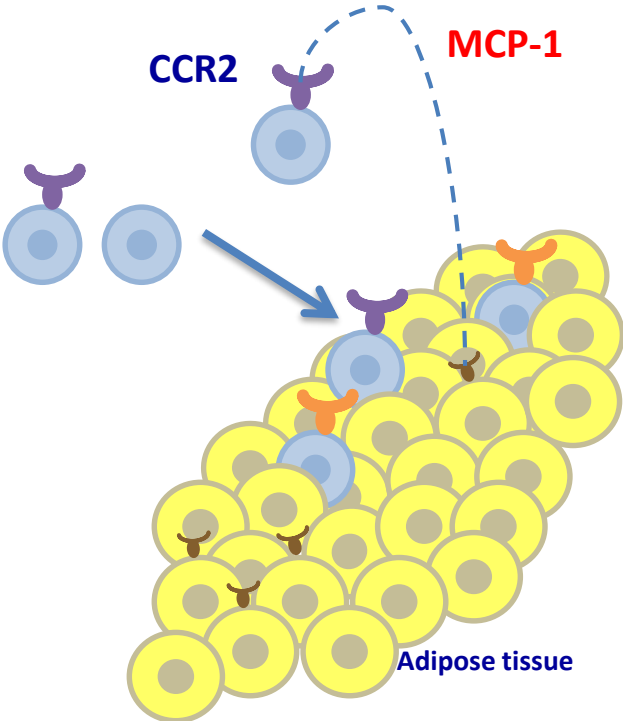
This is mediated via LPS's co-receptor CD14



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

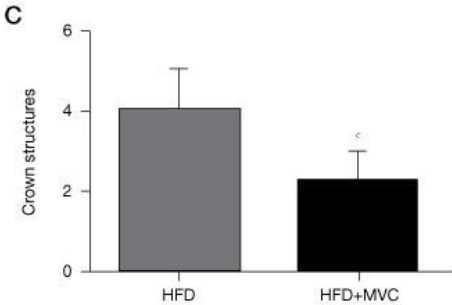
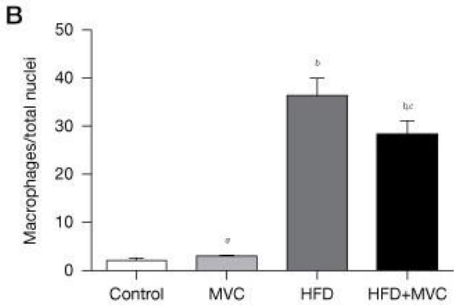
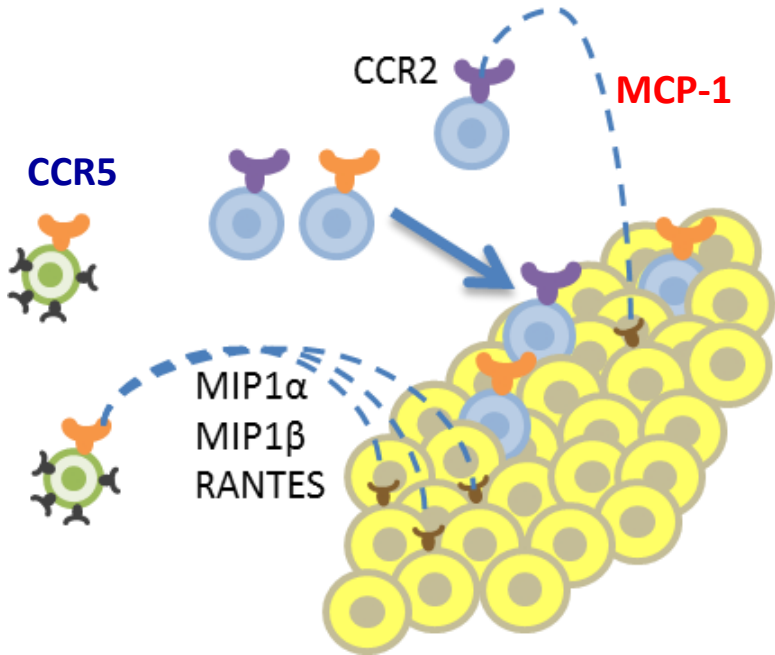
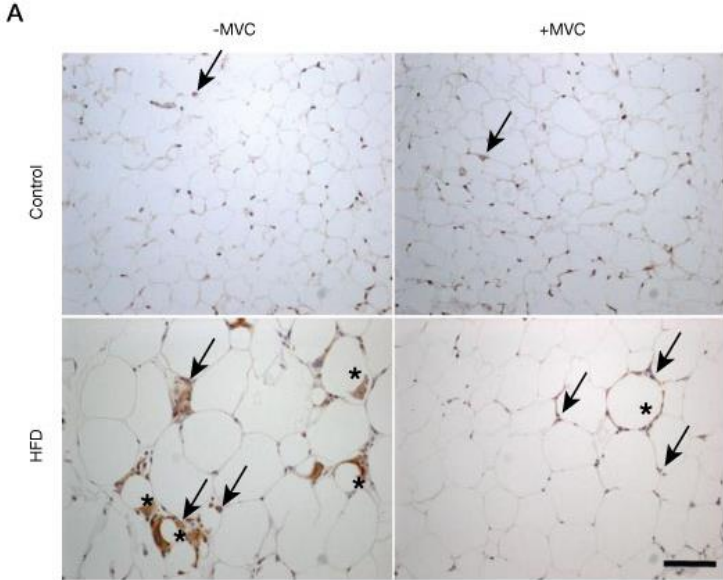
# Higher VAT is associated with increased monocyte chemoattractant protein (MCP-1)(CCL2) in PLHIV

Unpublished data



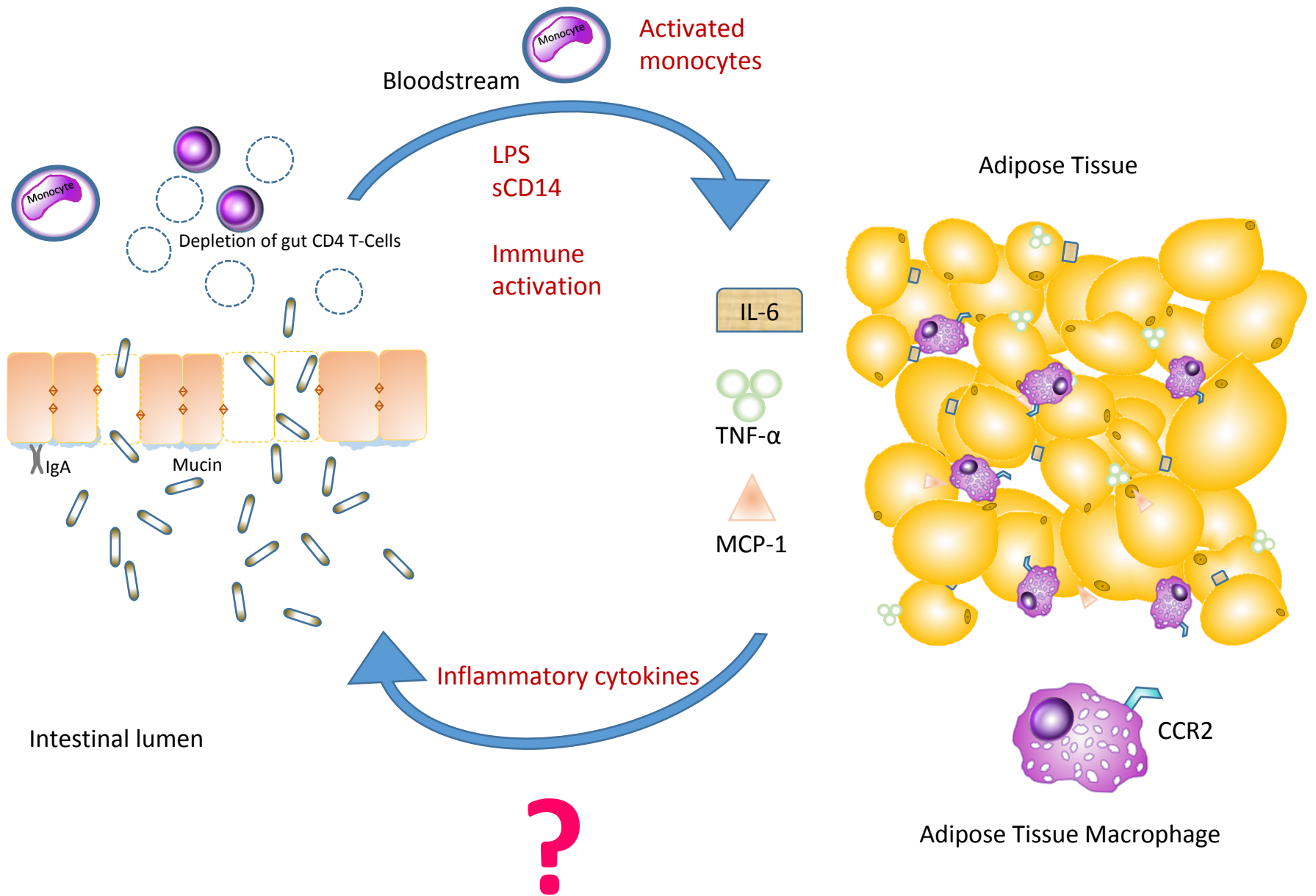
# In addition to CCR2, CCR5 also mediates recruitment of macrophages into adipose tissue

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

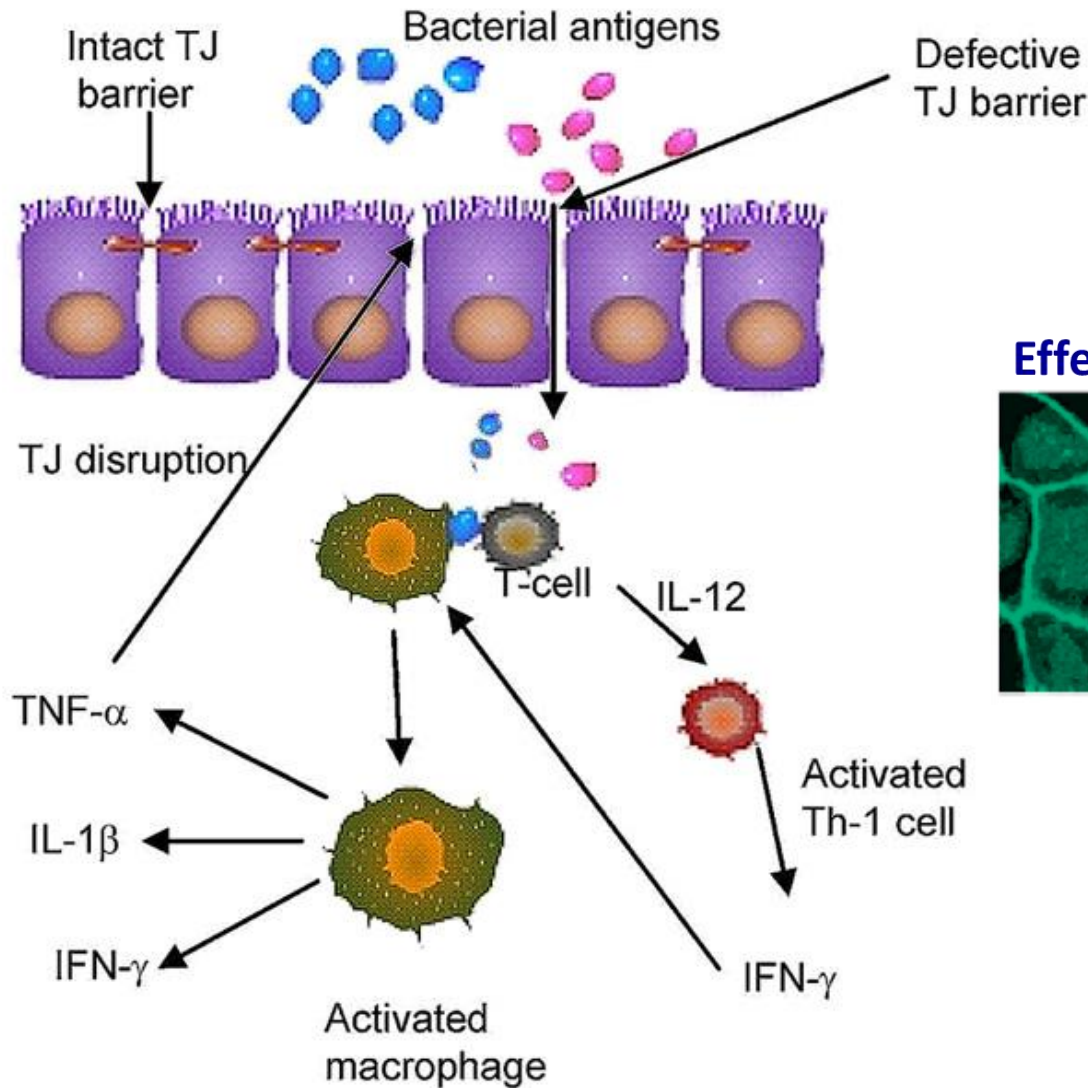


Perez-Matute et al. Antivir Ther 2017

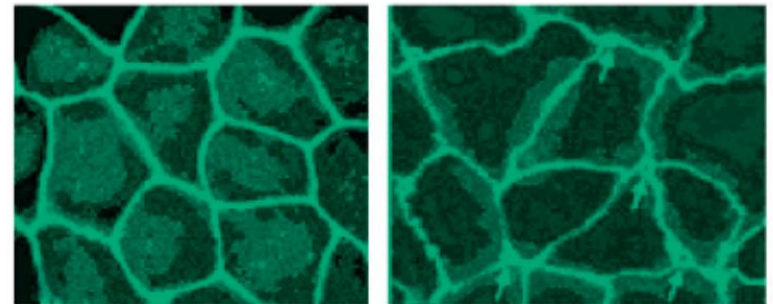




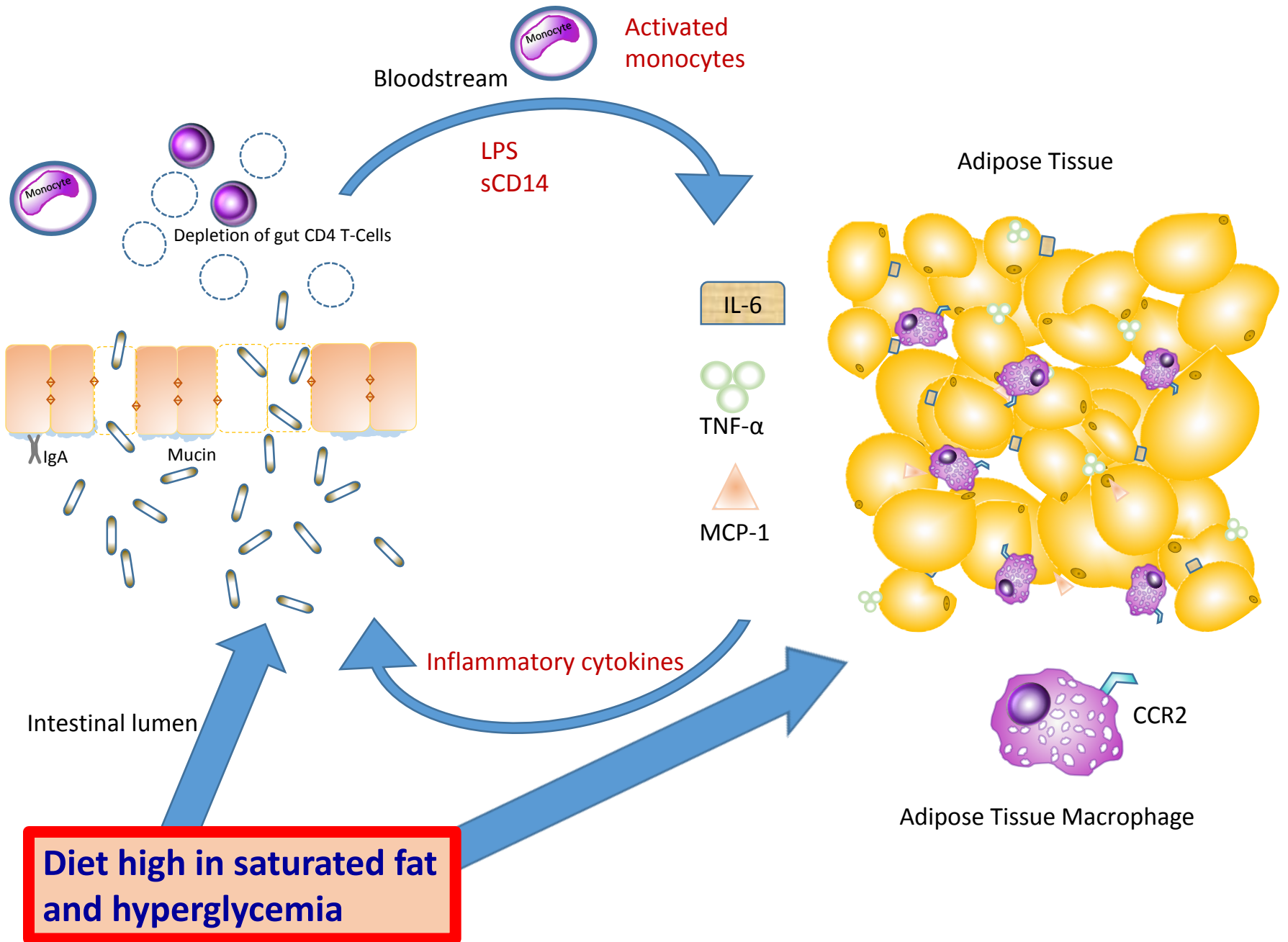
# Intestinal tight junctions can be further disrupted by inflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$ and IFN- $\gamma$



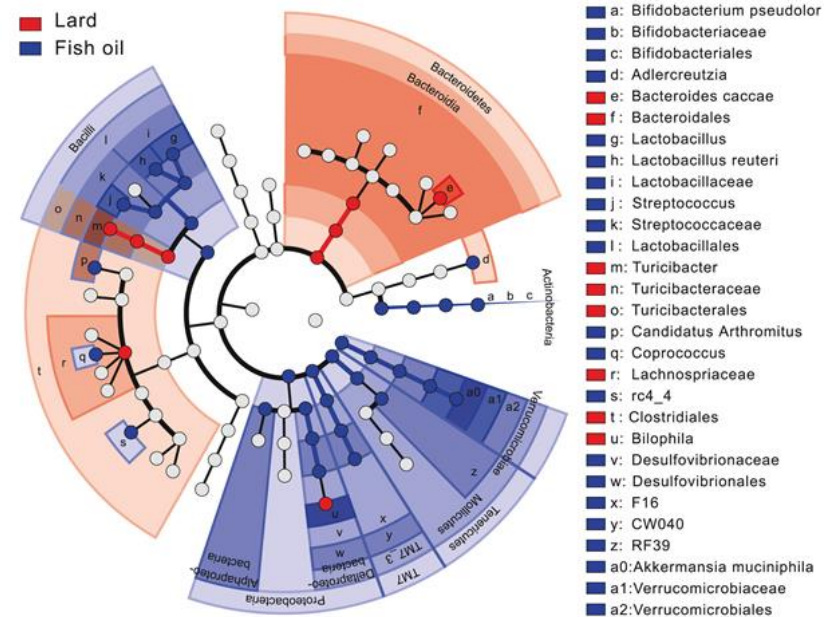
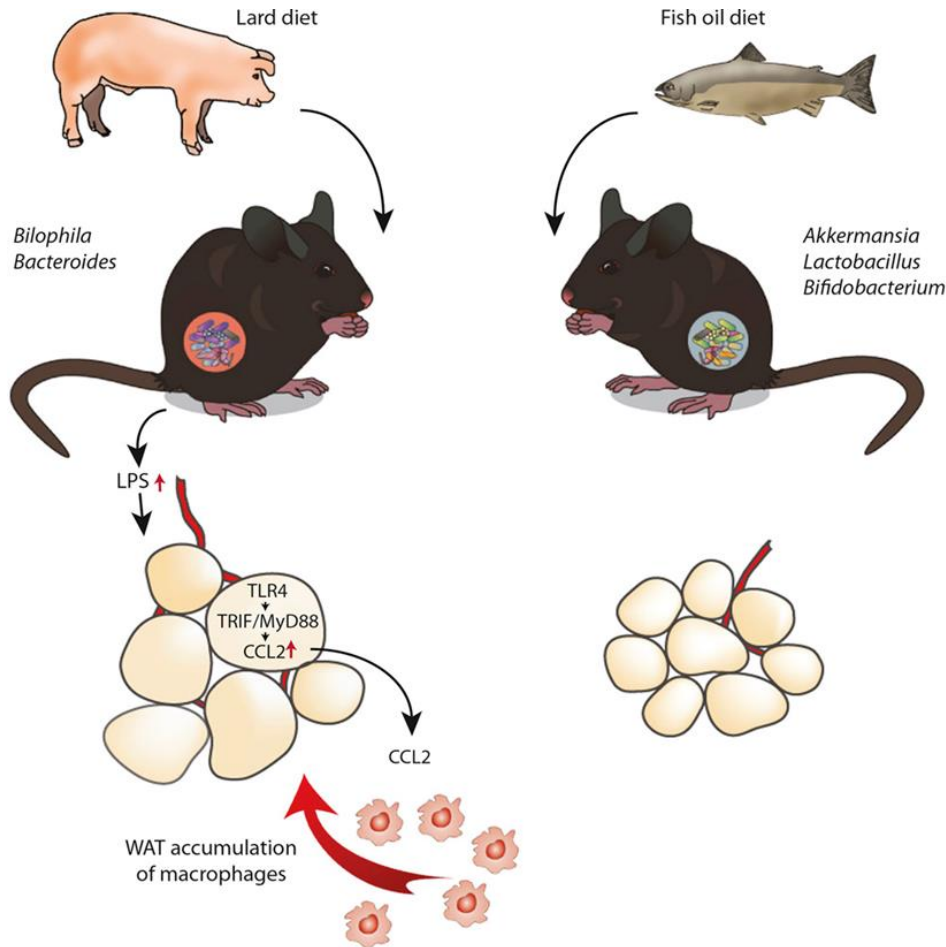
## Effect of TNF- $\alpha$ on ZO-1 proteins



Ma et al. *AJP Gastro Liver* 2005  
Al-Sadi et al. *Am J Pathology* 2016  
Al-Sadi et al. *Front Biosci* 2009



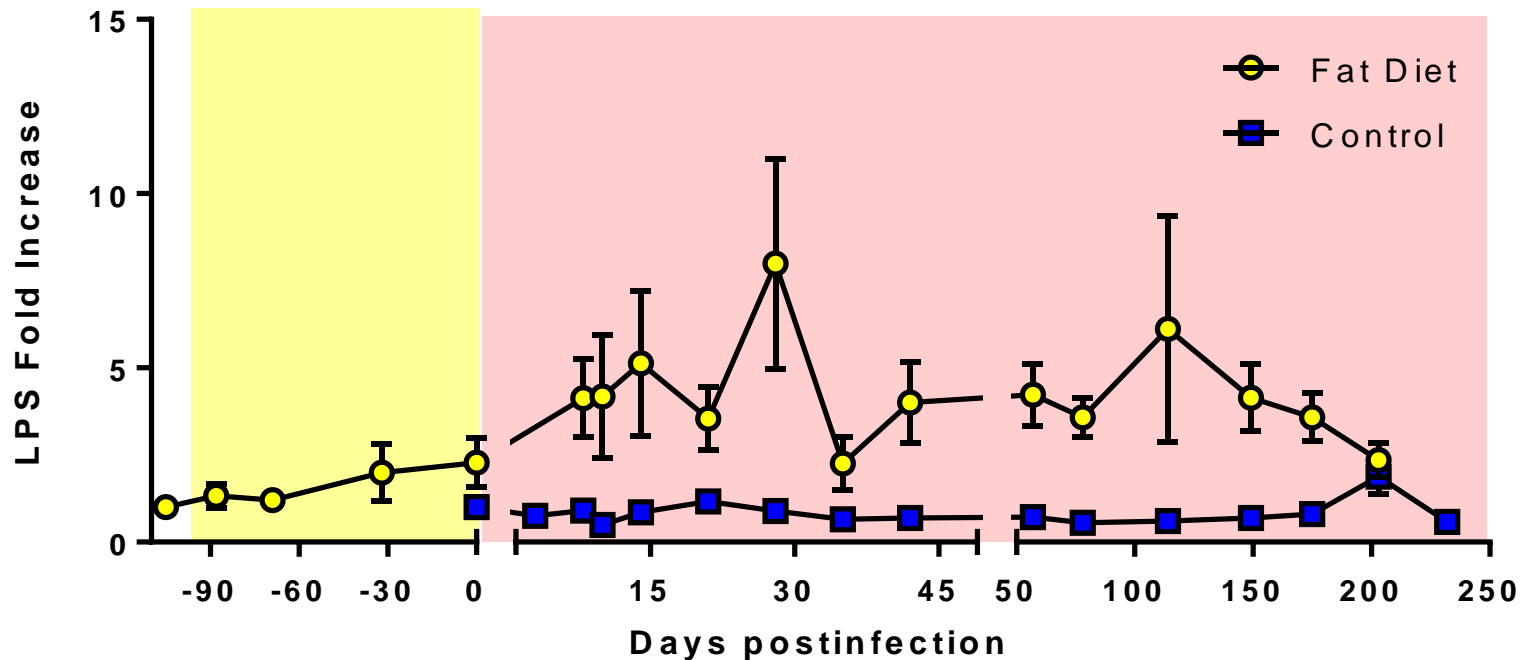
# Dietary saturated lipids induce adipose tissue inflammation via change in gut microbial composition → LPS → TLR4 signaling and CCL2 (MCP-1)



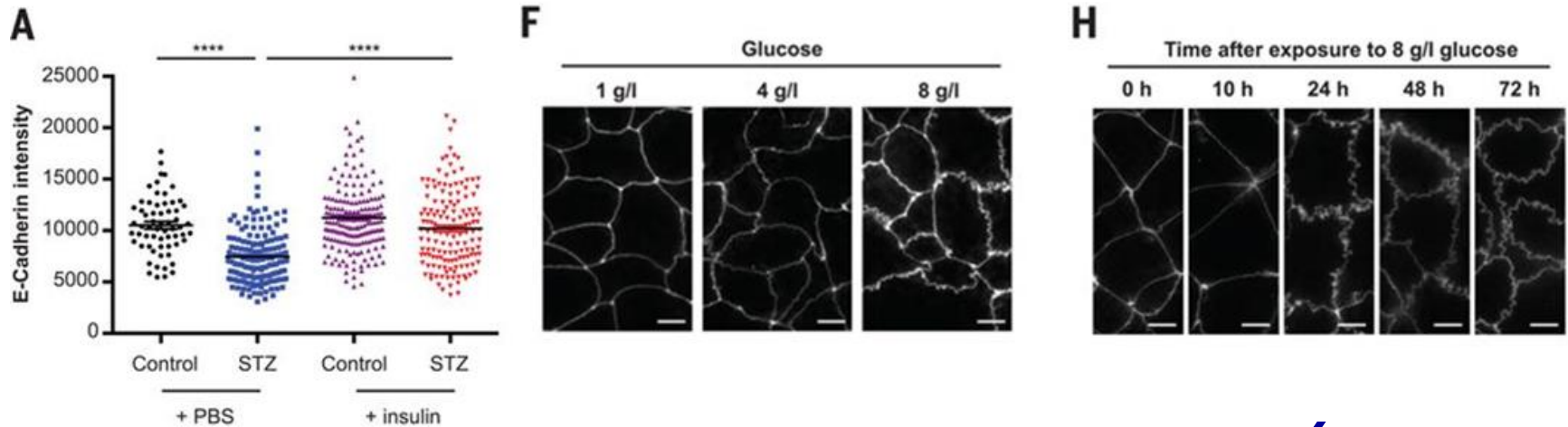
# High fat diet induces microbial translocation in African Green Monkeys that persist after SIV infection



A G M



# 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



Colonic E-cadherin in control mice vs. streptozocin treated mice (model of T1DM)

Z0-1 staining of Caco-2 cells treated with glucose

# **Saturated fat intake and added sugar are high in PLHIV**

**Men and women living with HIV consume more than recommended amounts of saturated fat**

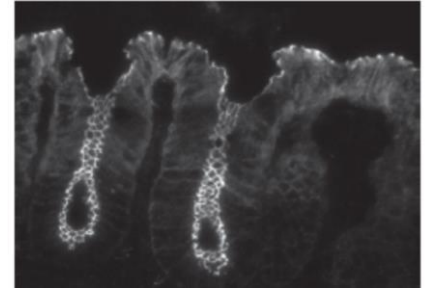
**(Klassen and Goff, Eur J of Clin Nutrition 2013)**

**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<sub>H</sub>17 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 [Ivan Vujkovic-Cvijin talk](#)
- Metformin (*Forslund et al. Nature 2015*) [Alex Soukas' talk](#)
  - Also improves glucose and may activate AMP kinase in intestinal immune cells

## • Targeting chemokine receptors to reduce AT inflammation:

- CCR2 and CCR5 antagonism with cenicriviroc (ACTG A5363 study in development phase)

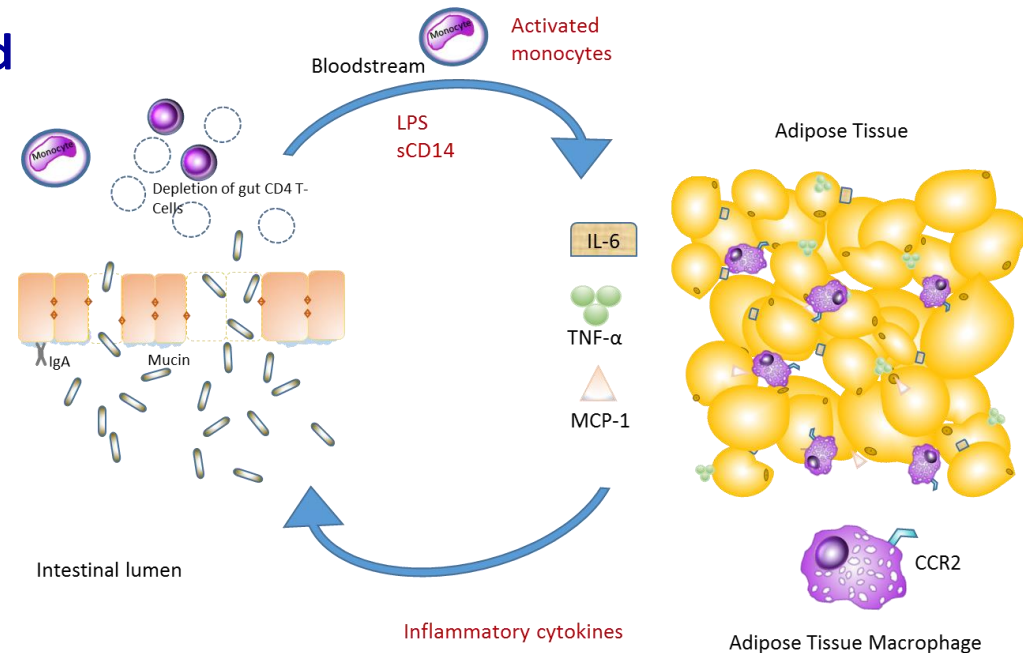


# In summary, breakdown in GI barrier function may play critical role in adipose tissue inflammation in PLHIV

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.



Questions?  
Thank you!