Poster # 845



Dysregulation of Estradiol Signaling Contributes to Mucosal Barrier Dysfunction HIV+ Women

Sumathi Sankaran-Walters[1,2], Anne Fenton[1], Christopher A Gaulke[1], Lauren Nagy[1], Irina Grishina[1], Chantelle Dills[1], Jason Flamm[4], Thomas Prindiville[3], and Satya Dandekar[1]

Departments of Medical Microbiology & Immunology[1], School of Nursing[2], and Internal Medicine[3], University of California, Davis, CA,; Kaiser Permanente Medical Group[4], Sacramento, CA

ABSTRACT

•Background

HIV infection is a leading cause of death in women in Africa. HIV disease progression correlates with immune activation which is higher in women compared to men in both the peripheral blood and gut. Compromised mucosal integrity allows for increased microbial translocation in women which stimulates systemic immune activation. Estradiol improves epithelial integrity but its effects during HIV infection are unknown. The objective of this study was to identify the effects of HIV infection on estradiol signaling in the gut and its impact on gut epithelial integrity.

•Methodology

HIV+ women (n=9) and men (n=12) and HIV- healthy age matched women (n=7) and men (n=7) men were enrolled following IRB approved protocols. Small intestine mucosal samples were obtained by upper GI endoscopy. We compared gene expression profiles in gut epithelium, using laser capture microdissection and gene expression arrays. Plasma levels of microbial products in participants were assayed by real-time PCR. Immunophenotypic analysis was performed using 12 color flow cytometry. The effect of estradiol replacement and HIV infection on epithelial integrity was assayed using 3-D in vitro culture systems.

•Results

A greater proportion of HIV+ women on HAART had sustained levels of GALT CD4+T-cell activation (37.4% vs. 6.5%) and CD8+T-cell activation (42.7% vs. 12.52%) than men (p<.05) as measured by the expression of the surface marker HLA-DR. HIV+ women with and without HAART had lower levels of estrogen receptor β in the jejunum compared to healthy age matched controls. Comparison of gene expression patterns in isolated epithelial cells showed down-regulation of epithelial regeneration pathways and tight junction proteins in postmenopausal women associated with an increase in epithelial inflammation compared to premenopausal HIV+ women and men on HAART. Indicators of microbial translocation, such as plasma LPS, and bacterial 16S rRNA, were increased in women compared to men on HAART.

•Epithelial cells grown in the presence of βE2 had increased proliferation (up to 40% higher) in a dose-dependent manner. Epithelial integrity measured by the trans-epithelial resistance (TER) also decreased by 25% in the presence of SIV infection. Low basal levels of exogenous βE2 restored the TER and increased expression of the tight junction protein, ZO1.

•Conclusions

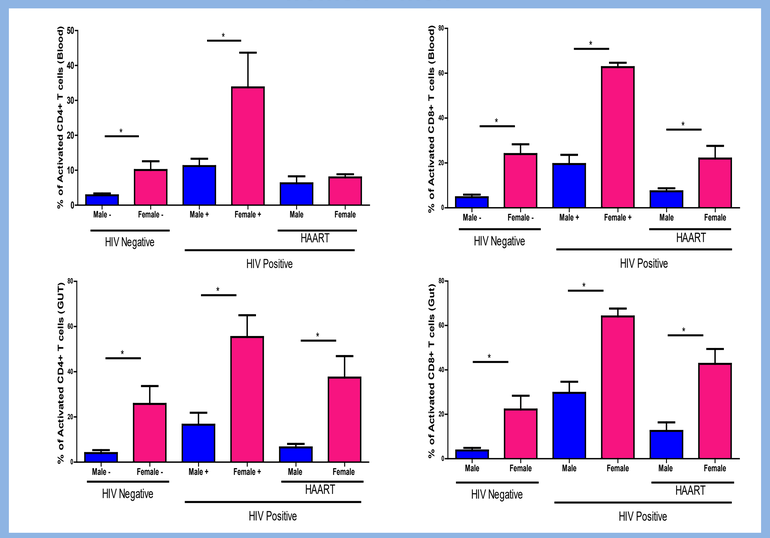
These data suggest that increased inflammation secondary to microbial translocation may explain why women, especially postmenopausal women, have sustained CD4+T-cell activation, despite effective control of viral replication. The decreased expression of ERβ may be a mechanism involved in this effect. Studies investigating the effects of HAART in women should focus on the role of hormones in the maintenance of mucosal integrity and health following menopause. These studies highlight the importance of gut mucosal integrity for maintaining health during HIV infection.

HYPOTHESES

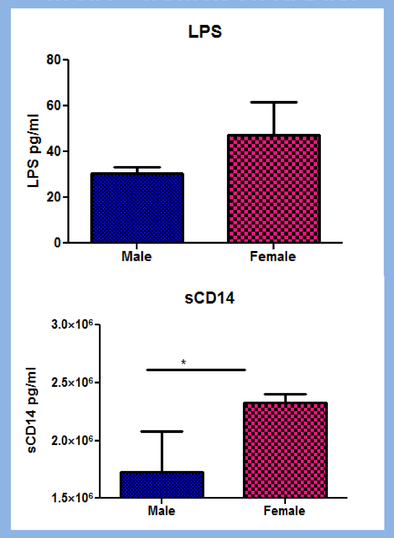
1. ***Estradiol Receptor β is decreased in gut of women with HIV***
2. ***Altered epithelial expression profile may predispose postmenopausal HIV+ women to increased systemic immune activation***

RESULTS 1

HIV infection induced T Cell activation in the blood and gut: women > men



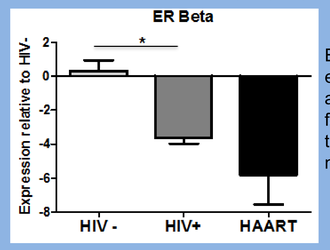
Increased microbial translocation in HIV+ women on HAART



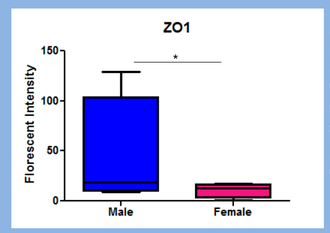
LPS: lipopolysaccharide sCD14 : Soluble CD14

RESULTS 2

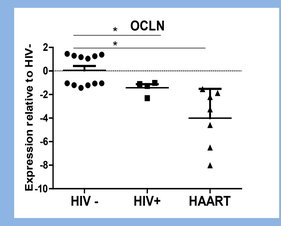
Estrogen receptor β is decreased in HIV+ women and HIV+ women on HAART



Estradiol induces epithelial proliferation and tight junction formation in the gut through signaling mediated by Erβ.
* p<.05

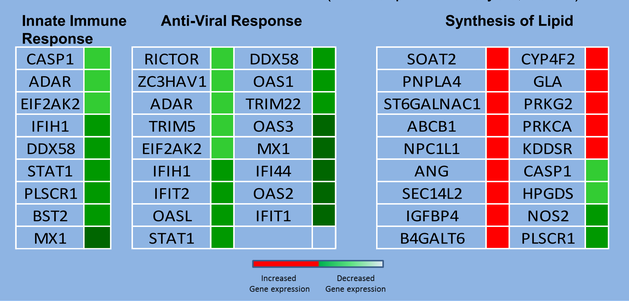


Increased microbial translocation is due to decreased gut epithelial integrity secondary to reduced tight junction protein expression (IHC)
* p<.05



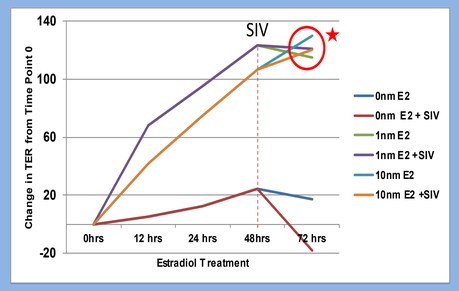
Decreased gut epithelial integrity may be secondary to reduced transcriptional levels of tight junction protein (Occludin) expression in HIV+ and HIV+ women on HAART (Real-time PCR, left). * p<.05

Postmenopausal women on HAART have a altered immune response and metabolic profile compared to premenopausal women on HAART. (Transcriptional analysis, below)



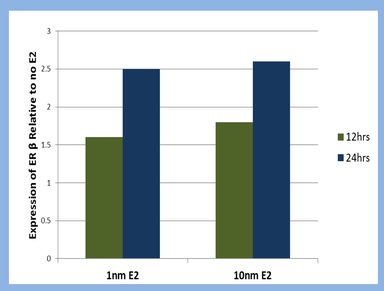
RESULTS 3

E2 protects gut epithelial cells from SIV induced loss of barrier function



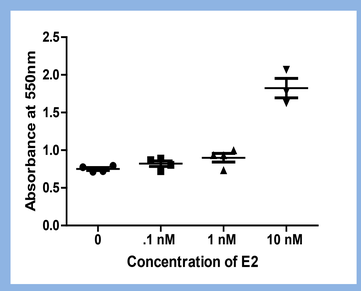
E2 Promotes Maintenance of Gut Epithelial Cell Barrier Function
TER: Trans Epithelial Resistance is a measure of epithelial integrity

In the in-vitro model, E2 treatment increases expression of ERβ



E2 at physiological (1nM) and supraphysiological (10nM) levels increases expression of ERβ in gut epithelial cells

E2 promotes epithelial cell proliferation



E2 at physiological (1nM) and supraphysiological (10nM) levels increases gut epithelial proliferation measured using the MTT assay

CONCLUSIONS

- Decreased gut epithelial integrity may predispose women to higher levels of microbial translocation which contributes to systemic immune activation
- Estradiol protects the gut mucosa by increasing epithelial integrity
- Treatments to improve epithelial integrity and function could decrease microbial translocation and decrease T cell activation in women
- Altered signaling through the E2/Erβ may contribute to the increased immune activation in HIV+ women.
- These studies highlight the role of the gut mucosa in maintenance of health during HIV infection (and other health conditions)

ACKNOWLEDGEMENTS

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This study was approved by the UC Davis IRB