STATIN USE IN ART-TREATED HIV REVEALS AN ALTERED MACROPHAGE TRANSCRIPTOMIC PROFILE

00581

Jeeda Ismail[1], Cheryl M. Cameron[1], Brian Richardson[1], Banumathi Tamilselvan[1], Manomani Kumar[1], Ken Riedl[2], Aya Cannon[2], Emily Bowman[2], Grace A. McComsey[3], Nicholas T. Funderburg[2*], Mark J. Cameron[1*]
[1]Case Western Reserve University, Cleveland, OH, United States, [2]The Ohio State University, Columbus, OH, United States, [3]University Hospitals Cleveland Medical Center, Cleveland, OH, United States. *Equal contribution.

BACKGROUND

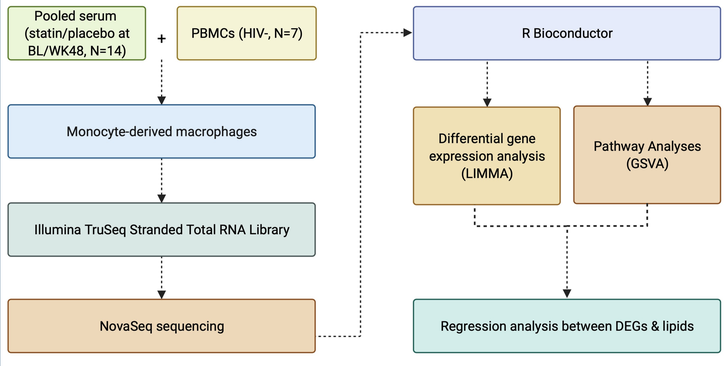
Antiretroviral therapy (ART) treated HIV is associated with an inflammatory profile and increased risk of cardiovascular disease (CVD). Monocytes that home to endothelium and differentiate into macrophages in the vessel wall may contribute to CVD risk in people with HIV (PWH). We reported that statins reduce inflammation in PWH. We hypothesized that rosuvastatin would improve the lipidomes of PWH and reduce the proinflammatory signatures in macrophages.

METHODS

SATURN-HIV, a placebo-controlled trial [NCT01218802], assessed the effects of rosuvastatin (10 mg) on immune activation in ART-treated PWH. Here, we measured the lipidomes (Lipidyzer platform) of participants at baseline (BL) and at 48 weeks (WK48) of statin or placebo treatment.

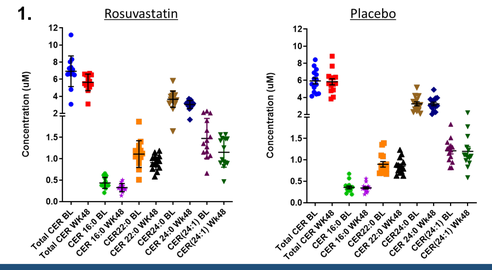
	Sample Size	Mean age	Male	African American
Placebo	14	39 yrs	79%	57%
Statin	14	43 yrs	93%	71%

Pooled serum samples from statin or placebo-treated individuals at BL or WK48 were added to PBMCs from HIV- donors (N=7) to generate monocyte derived macrophages (MDM). MDM RNA was extracted and sequenced. Differential gene expression (DGE) and pathway analyses were performed.



RESULTS

Figure 1. Statin treatment decreases levels of ceramides in PWH. Statins reduce several lipid classes and species, including levels of ceramides (CER), and lipids linked to CVD in PWH (CER16:0, 22:0, 24:0, 24:1, p<0.04).



Rosuvastatin in ART-treated PWH may lead to a **reduced CVD risk** by downregulating *immune activation* signaling in MDMs

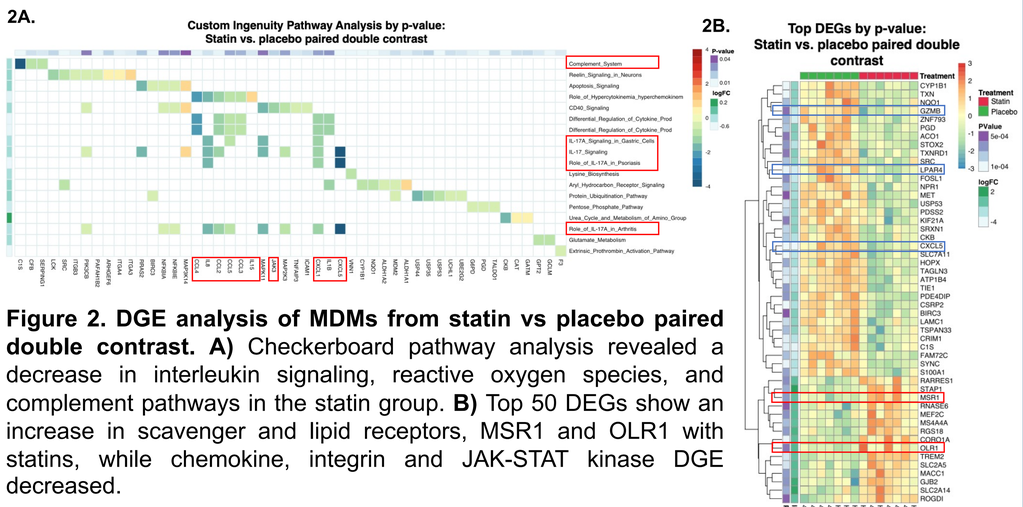


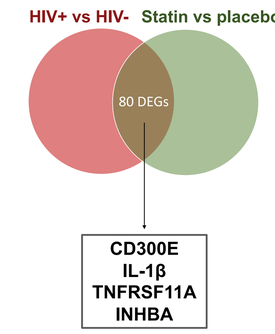
Figure 2. DGE analysis of MDMs from statin vs placebo paired double contrast. A) Checkerboard pathway analysis revealed a decrease in interleukin signaling, reactive oxygen species, and complement pathways in the statin group. **B)** Top 50 DEGs show an increase in scavenger and lipid receptors, MSR1 and OLR1 with statins, while chemokine, integrin and JAK-STAT kinase DGE decreased.

Figure 3. Regression analysis of DEGs and ceramides reveals a unique gene signature. A) DEP analysis from our previous MDM PWH vs HIV- shows increased levels of ceramides are associated with activation of the extrinsic and intrinsic prothrombin pathways, and a decrease in fatty acid metabolism in MDMs. **B)** Statin downregulates inflammatory pathways and upregulates metabolic pathways in MDMs that correlate with decreased total ceramides in pooled serum.



RESULTS

Figure 4. Venn Analysis of top DEGs (p≤0.05) from statin vs. placebo paired double contrast and those from our previous MDM PWH vs HIV- analysis identified genes that are inversely regulated by statin use. INHBA (p=0.005), CD300E (p=0.0006), and IL1B (p=0.03) were downregulated with statins and upregulated in MDMs from PWH vs HIV- subjects.



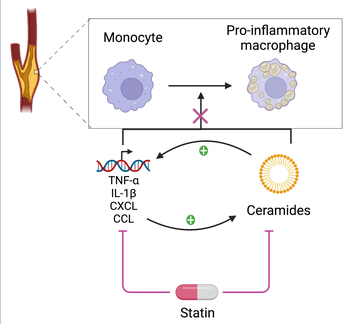


Figure 5. The role of statin in the lipidome and the transcriptome of HIV MDMs. Ceramides act as metabolic signals that contribute to the polarization of monocytes into pro-inflammatory macrophages, reinforced by inflammatory cytokines. Statins reduce ceramides and downregulate inflammatory cytokines, thereby altering macrophage polarization.

CONCLUSIONS

Rosuvastatin in ART-treated PWH may lead to a reduced inflammatory response and CVD risk by downregulating pro-atherosclerotic and immune activation signaling in MDMs, including reduction in levels of ceramides and downregulation of inflammatory cytokines (TNF-alpha, IL-1β and chemokines) and complement signaling.

ACKNOWLEDGEMENTS

We thank the CWRU Applied Functional Genomics Core, CWRU Genomics Core and OSU Comprehensive Cancer Center's Nutrient and Phytochemical Shared Resource for their services. We also thank the clinical trial investigators, study personnel, and participants. Grant support: NIH 1R01HL158592 (MJC and NTF), CWRU/UH Center for AIDS Research (MJC and CMC, 3P30AI036219), R01 NR012642 (GAM), K99/R00 R00HL108743 (NTF).