TRANSFER OF MICROBIOME AND IMMUNE PHENOTYPES IN HIV-/+ MSM TO MICE BY FECAL TRANSPLANT

255

Sam Li*, Sharon Sen, Jennifer Schneider, Nichole Nusbacher, Nancy Moreno-Huizar, Charles P. Neff, Michael Shaffer, Abigail Armstrong, Erin Severs, Kristine Kuhn, Catherine Lozupone, and Brent Palmer

*Division of Allergy and Clinical Immunology, Department of Medicine, University of Colorado Anschutz, Aurora, CO *sam.li@ucdenver.edu*

1 Abstract

Background: High-risk men who have sex with men (MSM) have differences in immune activation and gut microbiome composition compared with men who have sex with women (MSW), even in the absence of HIV infection[1,2]. Gut microbiome differences associated with HIV itself when controlling for MSM, as assessed by 16S rRNA sequencing, are relatively subtle. Understanding whether an altered gut microbiome composition drives immune activation in MSM has important implications since immune activation has been associated with both HIV acquisition risk and disease progression.

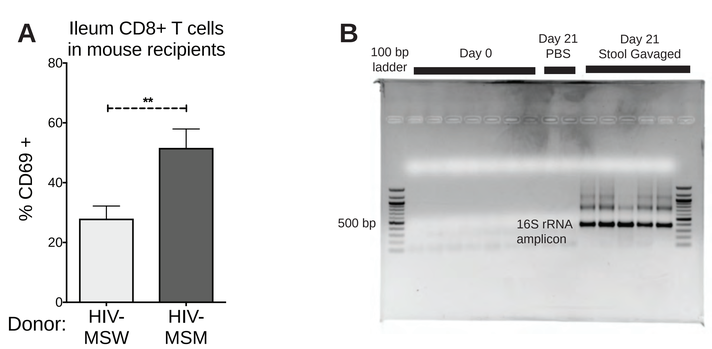
Methods: To investigate the impact of HIV and MSM-associated gut microbes on immune activation, we transplanted feces from HIV- MSW (n=11), HIV- MSM (n=15), and HIV+ untreated MSM (n=9) to gnotobiotic mice. At 21 days post-gavage, CD69 and CD103 expression was evaluated on gut T cells, and fecal microbiome composition in the mice was characterized by 16S rRNA gene sequencing. HLADR and CD38 expression on blood T cells and fecal microbiome composition in the human donors were also analyzed and compared with mouse recipients.

Results: Mouse recipients of HIV-/+ MSM feces had increased T cell activation in the gut compared with recipients of MSW feces. In contrast, there were no immunological differences between recipients of feces from HIV- and HIV+ MSM. Gut CD69+ and CD103+ T cell frequencies in mouse recipients correlated with blood HLADR+ CD38+ CD8+ T cell frequencies in human donors (which was significantly higher in MSM than in MSW), suggesting that immune activation levels in donors were transferred to mice.16S rRNA gene sequencing revealed that the microbiome of MSM and MSW maintained distinct compositions following transplantation to mice and that specific microbiome differences between MSM and MSW donors were replicated. Microbes that correlated with both donor and recipient immune activation were also identified.

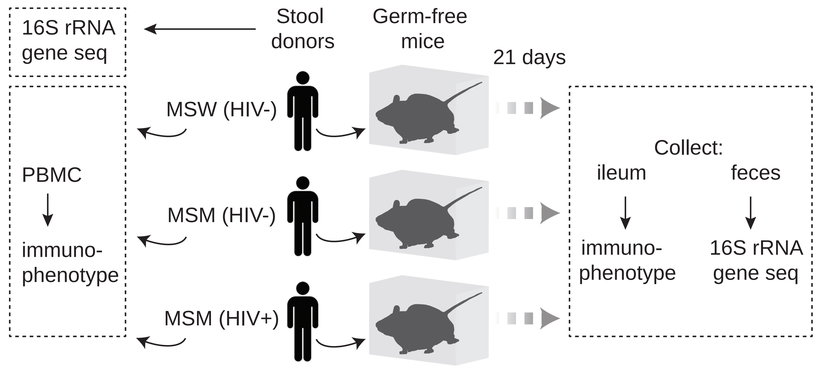
Conclusion: Both microbiome and immune phenotypes in MSM donors are transferrable to mouse recipients through fecal transplantation, suggesting that gut microbes influence immune activation in MSM, which may drive what is seen during HIV infection. These results support the use of gnotobiotic mice as an *in vivo* model to investigate the effects of MSM and HIV-associated microbiome changes on immunology as it relates to transmission and disease.

2 Background

- Previously, we showed that transplantation of stool from high risk HIV- MSM to gnotobiotic mice promoted T cell activation in the gut, in comparison to stool from low risk HIV- MSW (A)
- However, donors had not been immunophenotyped, and stools from HIV+ MSM donors were not tested in the transfer model
- Though 16S rRNA could be detected by PCR in mouse recipient stool at 21 days post-gavage (B), the composition of the microbiome in mouse recipients was undetermined
- ***Hypothesis: The microbiome composition of HIV-/+ MSM and MSW will remain distinct and be associated with immunological differences in mouse recipients of stool transfer***

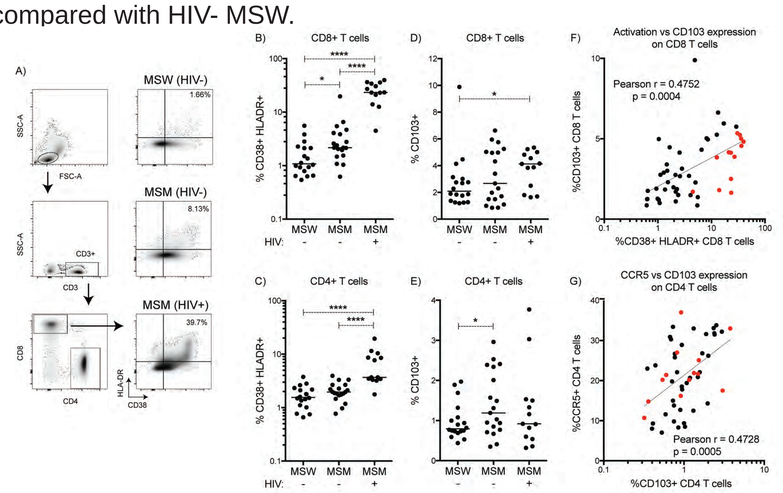


3 Methodology

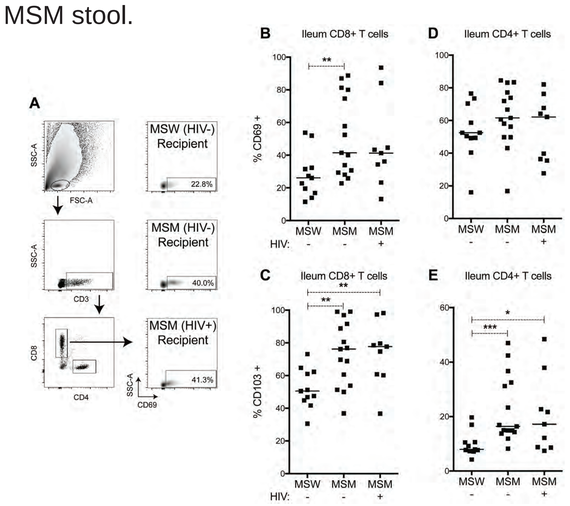


4 Results

HIV- and HIV+ MSM have elevated blood CD8+ T cell activation compared with HIV- MSW.

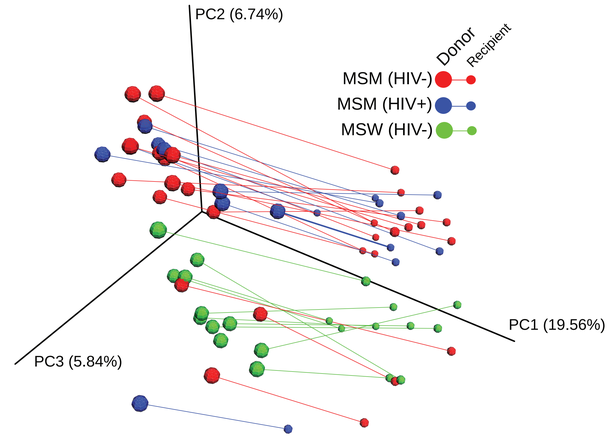


Mouse recipients of stool from HIV-/+ MSM have higher gut T cell activation compared with recipients of stool from HIV- MSW. No immunological differences were detected between recipients of HIV- and HIV+ MSM stool.

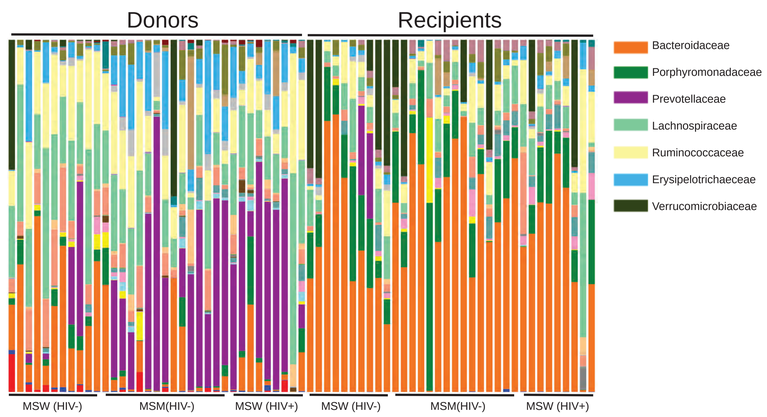


Recipient gut immune phenotype	Correlation with HIV- donor blood CD8 T cell activation	
	Pearson r	p value
% CD69+ CD8 T cells	0.3994	0.0432
% CD103+ CD8 T cells	0.4252	0.0303
% CD103+ CD4 T cells	0.4256	0.0302

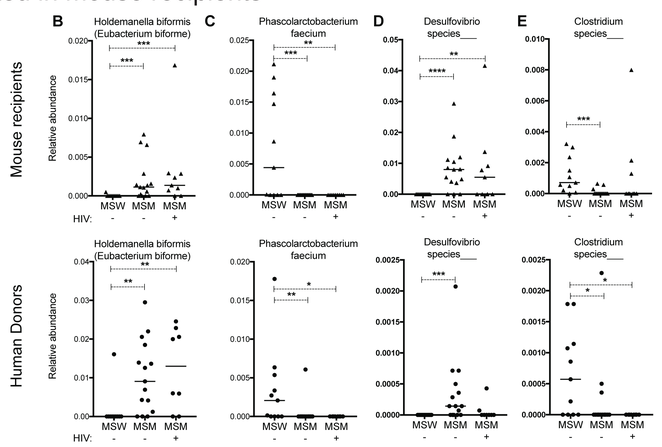
Microbiomes from MSW and MSM maintain distinct compositions following transfer to and colonization of mouse recipients



	%CD69+ CD8 T cells	%CD103+ CD8 T cells	%CD103+ CD4 T cells
PC2	**p=0.016, r=-0.409**	**p=0.003, r=-0.496**	p=0.066, r=-0.319



Differences in relative abundance of specific microbes in donors were replicated in mouse recipients



5 Conclusions

- Microbiome and immune phenotypes in MSM are recapitulated in mice through fecal transplant
- The gut microbiome may influence immune activation in HIV-/+ MSM

References

1) Noguera-Julian M, Rocafort M, Guillén Y, Rivera J, Casadellà M, Nowak P, et al. Gut Microbiota Linked to Sexual Preference and HIV Infection. eBioMedicine. 2016.

2) Kelley CF, Kraft CS, de Man TJ, Duphare C, Lee HW, Yang J, et al. The rectal mucosa and condomless receptive anal intercourse in HIV-negative MSM: implications for HIV transmission and prevention. Mucosal Immunol. 2016.