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A Summary of the Second Annual HIV Microbiome Workshop

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Abstract

Commensal organisms appear to play significant roles in normal homeostasis as well as in the pathogenesis of HIV infection in a number of different organ systems. On November 17th and 18th, 2016, leading researchers from around the world met to discuss their insights on advances in our understanding of HIV and the microbiome at the National Institutes of Health (NIH) in Bethesda. Dr. Elhanan Borenstein of the University of Washington gave a keynote address where he discussed new developments in systems biology which hold the promise of illuminating the pathways by which these organisms interact with human physiology. He suggested that we need to get past correlations in microbiome research by using models and informatics which incorporate metagenomics to predict functional changes in the microbiome.

Keywords: HIV, microbial translocation, inflammation, HIV transmission

Pathogenesis

AS OPPORTUNISTIC INFECTIONS become less common, liver disease has become a more prominent cause of morbidity and mortality in HIV.[1] Nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD), which are associated with the metabolic syndrome, are increasingly common in Westerner's, where up to 25% have some evidence of excessive fat in the liver.[2] The liver receives ~75% of its blood supply from the portal vein and so is particularly susceptible to insult from microbial translocation from the gut, which is known to be increased in HIV infection.[3,4] NASH, NAFLD, and cirrhosis have been directly associated with alterations in the gut microbiome.[5] Dr.

Gary Wu of the University of Pennsylvania discussed the potential mechanisms by which diet and microbiota effect risk for fatty liver disease. Dietary fiber is broken down by microbes into oligo and monosaccharides and then fermented to short-chain fatty acids (SCFAs), which have a number of effects on gut physiology. SCFAs serve as an energy source for gut epithelial cells and can be absorbed for use in gluconeogenesis and lipogenesis in the liver; they also regulate metabolism by inhibiting histone deacetylase (HDAC) and through G-protein-coupled receptor (GPCR) signaling.[6]

Low bacterial richness has been linked to marked obesity, insulin resistance, dyslipidemia, and inflammatory phenotype.[7] Energy-restricted and agrarian diets high in fiber have been associated with increased bacterial gene richness.[8]

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High-fiber diet has also been shown to improve glucose tolerance in humans commensurate with an increase in the stool abundance of *Prevotella copri*, transference of microbiota from humans who responded to the high-fiber diet to germ-free mice improved glucose tolerance in those mice.[9] Microbes also effect gut and liver homeostasis through metabolism of bile salts, which can activate the farnesoid X receptor (FXR), thereby enhancing small intestinal barrier function.[10] Obeticholic acid, an FXR activator, has been shown to decrease microbial translocation in rats and improve liver histology in humans with NASH.[11,12] There are several potential targets for therapeutic intervention in NASH, including FXR, diet, the mucosal barrier, and reversal of dysbiosis, and comprehensive treatment may require several modalities.

HIV-infected individuals who suppress their virus without antiretrovirals are termed elite controllers (EC). These individuals tend to have levels of microbial translocation and cellular immune activation similar to healthy controls (HC).[13] Dr. J. Vesterbacka, Karolinska University Hospital (Stockholm, Sweden), discussed the results of his study evaluating gut microbial metabolic pathways in EC, HIV-infected treatment naive and HC participants. They evaluated fecal microbiota composition, functional content of the bacterial 16s ribosomal RNA (rRNA) metagenome, soluble and cellular markers of microbial translocation, and immune activation and tryptophan metabolites. On beta diversity analysis EC were noted to cluster together. At the genus level *Succinivibrio* and *Sutterella* were more abundant in EC, and *Blautia* and *Anaerostipes* were enriched in treatment naives. KEGG level II analysis demonstrated that metabolism of carbohydrates, particularly pentose phosphate, were underrepresented in the EC microbiome compared with either treatment naives or HC. Lipid metabolic pathways were enriched in EC compared with treatment naive, but not significantly different than HC. Genes for metabolism of fatty acids were correlated with lower levels of immune activation. These data suggest that gut microbial metabolism may impact immunologic outcomes in HIV but needs to be confirmed by prospective study.

Dr. Y. Guillén, IrsiCaixa Foundation (Barcelona, Spain), discussed the associations between HIV infection, immune status, stool bacterial gene richness, and virome in an unpublished study from the Barcelona cohort. The percentage of individuals falling into the high gene copy subset appeared to decrease gradually with worsening immune status, with HIV negative controls having the highest proportion and late presenters having the lowest. Viral sequences increased with progressive immunosuppression, however, suggesting a loss of immunologic control over viral replication. Longitudinal data following initiation of antiretrovirals will be helpful in corroborating this work.

Pulmonary disease remains common in individuals with HIV with particular increased risk for pneumonia, tuberculosis, pulmonary hypertension, lung cancer, and chronic obstructive pulmonary disease.[14] Dr. Ron Collman of the University of Pennsylvania discussed his study on the lung microbiome in HIV.[15] They performed two bronchoscopy procedures to first identify background contaminants and then to identify lung microbiota with repeated bronchoalveolar lavage (BAL). The microbiome of the lungs was very similar to what was found at the level of the vocal cords

suggesting that microaspirations are the source of the lung microbiota. Interestingly, the pathogen *Tropheryma whipplei* was found more frequently in individuals with HIV (43%) than in HIV-negative (17%) controls and even healthy individuals with HIV had *Aspergillus*, *Cryptococcus*, *Pneumocystis*, and *Microascus* present in BAL fluid. The pulmonary virome, in contrast was not substantially different in HIV-infected versus uninfected individuals with both being dominated by anelloviruses. It is unclear whether these anelloviruses cause pathology in HIV, but there is a negative correlation between anellovirus levels and graft dysfunction after lung transplant.[16] Overall, they were surprised by the similarity of lung microbiome between HIV-positive and HIV-negative individuals, given the increased risk of pulmonary infection that accompanies HIV even with preserved CD4, and suggested that impaired local immune responses may play a role.

Transmission and Prevention

Commensal bacteria affect multiple immune parameters to modulate HIV transmission from mother to child. Mother's microbiome is known to affect the health of the infant, particularly in development of chronic conditions that persist later in life.[17] Dr. Aldrovandi from UCLA discussed her studies correlating components of breast milk to the health of the baby, focusing on HIV-exposed uninfected (HEU) infants. HEU infants experience increased morbidity and mortality compared with age-matched HIV-unexposed uninfected infants. They also develop high risk of bacterial infections that correlates with maternal CD4 counts. Dr. Aldrovandi's group have demonstrated differences between HIV-infected and uninfected mothers in their breast milk oligosaccharide composition (HMO)[18] in a cohort of Haitian women. The HMO component of breast milk is not digestible by infants, but is thought to provide metabolic substrates for gut commensal bacteria. In this study, the relative abundance of 3′-sialyllactose (3′SL), 3-fucosyllactose (3FL), and 2′-fucosyllactose (2′FL) was increased in HIV-infected mothers, whereas Lacto-N-tetraose (LNT) and Lacto-N-neotetraose (LNnT) was increased in HIV-uninfected mothers. HEU infants were shown to have less diverse and less mature stool microbiome, which was significantly associated with LNnT. Furthermore, HEU had less *Bacteroides fragilis* in stool. In germ-free mice, *B. fragilis* seems to be involved in TReg development and a tolerant immune phenotype.[19] Taken together, these data demonstrate that the normal HMO composition of breast milk is disrupted in HIV-infected mothers which can adversely affect infant microbiome and their long-term health.

The next talk focused on HIV prevention efforts in women by improving vaginal health using live recombinant *Lactobacilli*. Vaginal dysbiosis has been linked to increased genital inflammation and enhanced HIV acquisition in the CAPRISA study.[20,21] Tenofovir disoproxil, a first-line antiretroviral drug, as well as the pre-exposure prophylaxis drug of choice, has been shown to have a 61% efficacy in the prevention of HIV acquisition in a lactobacilli-dominated microenvironment compared with only 18% efficacy in a nonlactobacilli-dominated microenvironment.[22] Laurel Lagenaur from Osel, Inc. discussed the promising development of live biotherapeutic products to prevent HIV acquisition by modulating

vaginal microbiome. Osel's live biotherapeutic product, *Lactobacillus crispatus* CTV-05 (Lactin V), has been shown to restore normal microbiota following antibiotic treatment of bacterial vaginosis, a dysbiotic condition linked to increased HIV acquisition.[23,24] In an attempt to directly modulate HIV infection, they constructed a recombinant *Lactobacillus* strain with a potent broad-spectrum HIV inhibitor Cyanovirin (mCV-N). This product, *Lactobacillus jensenii* 1153–1666, was able to establish vaginal colonization and stable expression of inhibitor protein in rhesus macaque model for up to 6 weeks.

Repeated dose challenge studies showed 63% reduction in HIV acquisition following colonization with this product.[25] Product development was moved forward with formulation of vaginal tablets.[26] The pre-investigational new drug (Pre-IND) meeting has occurred with safety and development of clinical protocol in progress for IND submission later this year.

The final presentation in this section described the characterization of vaginal bacteriome and virome in young women from South Africa, a population that is severely affected by the HIV/AIDS epidemic. Dr. Gosmann from the Ragon Institute at Harvard, discussed microbiome analysis data from the females rising through education support and health study that includes young South African women 18–23 years of age. Vaginal bacteriome in this group of young women consisted of community types (CT) 1–4[27]; whereas CT1 was predominantly characterized by *L. crispatus* and CT2 were characterized by *Lactobacillus inners*, CT3 and CT4 consisted of a diverse non-lactobacilli-dominated profile. Interestingly, there were no differences in the virome profile based on the CT types. Most abundant virome components were *Alphapapillomaviruses* and *Anelloviruses*, which were distributed evenly among CT types. Women with CT3 and CT4 were at a fourfold higher risk for acquiring HIV compared with those in the other CT types. These women were colonized with high abundance of *Prevotella, Veillonella, Mycoplasma,* and *Sneathia* species. However, no risk of HIV acquisition was associated with virome profile. Women in CT3 and 4, including those who acquired HIV during the course of this study, had high levels of cervical CCR5+CD38+HLADR+CD4+ T cells and high levels of inflammatory mediators MIP-1α, MIP-1β, IL-1α, TNF-α, IL1-β, IL-23, and IL-17, indicators of immune activation and inflammation.

Comorbidities

Gastrointestinal infections cause significant morbidity and mortality, particularly in low-income nations, and Yasmine Belkaid of the Mucosal Immunology section of NIAID discussed the long-term consequences of these infections. HIV is well known to cause long-term damage to the gut-associated lymph tissue and there appear to be other pathogens, which cause similar disruption. Yersinia pseudotuberculosis, a foodborne pathogen, can lead to chronic mesenteric lymphadenitis in the absence of chronic infection. The infection appears to cause lasting damage to gut lymphatics and leads to chylous ascites in mice. Postinfection, there is a defect in dendritic cell (DC) migration, CD103+ CD11b+ DCs accumulate in the mesenteric adipose tissue leading to inflammatory remodeling of the adipose compartment similar to what happens in simian immunodeficiency virus (SIV)-infected macaques.[28,29] CD103+ cells may be integral to gut barrier

integrity as they appear to promote IL-17 production.[30] The defect in DC migration appears to be microbiota dependent as it does not occur in germ-free mice and is reversed by antibiotics. Mice postinfection are also no longer able to develop regulatory T cells to food antigen. There is shutdown of Th17, IgA production, and response to oral vaccines. These deficits may later increase risk for inflammatory bowel disease, obesity, and food allergies, thus, it may be necessary to take into account "immunologic scarring" from prior infection when assessing interactions between microbes and the host immune system.

Sampling and preservation methods have yet to be standardized across the human microbiome field. Dr. Emily Vogtmann of the National Institutes of Health (NIH), National Cancer Institute discussed her laboratory's work comparing various methods for microbiome sample collection. They compared four different collection media to the gold standard of no solution and immediate freezing: fecal immunochemical test (FIT) tube, fecal occult blood test (FOBT) card, RNA later, and 95% ethanol.[31,32] These samples were then frozen immediately or left at room temperature for 4 days. Microbiota interrogations included relative abundance of three major phyla, alpha diversity, and first principal coordinate of beta diversity matrices. Overall, the collection methods produced similar results and the vast majority of variability was between subjects and not between samples from the same subject. Dr. Vogtmann suggested that these were all valid collection methods as long as they were consistently used within a study. A similar protocol was performed for fecal metabolites and they found that FOBT and 95% ethanol performed similarly to immediate freezing, but that FIT tubes did not perform as well for untargeted metabolomics. There is also a need for quality control samples in microbiome analyses to ensure the validity of outputs. Quality control samples with known composition would allow investigators to periodically check and calibrate equipment and their development should be a priority.

Individuals with HIV suffer disproportionately from a wide variety of oral diseases, particularly dental disease.[33] Dr. Bruce Paster of the Forsyth Institute discussed his oral microbiome work on a cohort of perinatally HIV-infected (PHIV) and perinatally HIV-exposed uninfected (PHEU) adolescents. PHIV adolescents have more dental carries than their exposed but uninfected peers and this may be related to changes in the microbial community of the mouth. Many taxa differed between PHIV and PHEU; PHIV were less diverse but there was no difference in microbes associated with periodontitis. Dr. Malamud of New York University similarly found a clear difference between the oral microbiota of HIV-infected individuals and HIV-negative controls. Bacteroidetes were decreased in HIV and Firmicutes and Proteobacteria were increased in HIV. After antiretroviral therapy, these differences tended to decrease.[34] These findings suggest that the oral mucosal immune system plays a role in selecting symbionts or excluding potential pathogens.

Microbiome and Vaccines

Infancy may be the ideal time for immunization against HIV because infants develop broadly neutralizing antibodies

better than adults, vaccine administration rates are best for infants, and the microbiome is most malleable.[35] Dr. Permar of Duke University discussed data supporting an HIV vaccine strategy focused on infancy.

A comparison of vaccine responses in two studies using the same vaccine (rgp120/MF59), one in infants and one in adults, found that ENV-specific IgG response was higher and more durable in infants.[36,37] This may be related to the rapid changes in the microbiome during the first year of life and acquisition of commensals, in particular *Dialaster* and *Megasphaera*, which divert the anti-HIV ENV humoral response.[38] Manipulating the infant microbiome to prevent this antigen diversion may be a useful strategy to improve antibody responses to HIV ENV proteins.

Dr. Hartigan-O'Connor from UC Davis discussed the influence of microbiota on immune responses to rhesus cytomegalovirus (RhCMV)/SIV vaccines. CMV vectors are being studied in Rhesus macaques as a vaccine delivery mechanism for SIV proteins. These vectors can elicit and maintain high-frequency virus-specific effector T cells and have been shown to protect against pathogenic SIV challenge.[39] CMV latently infects a major portion of human population. CMV affects multiple immune parameters and can be activated in HIV-infected individuals. Dr. Hartigan-O'Connor's group characterized the microbiome and virome in blood and stool of CMV-infected and CMV-uninfected 8–10 months old rhesus macaques. Immune cell development was distinct in the two groups with CMV-infected macaques showing less activated B cells and more naive, effector, and memory T cells. *Anellovirus* was the most abundant component of the virome with increased abundance in CMV-infected macaques. RhCMV infection did not have a dominant effect on infant microbiota. However, CMV-infected and uninfected macaques did show evidence of distinct gut bacteriome with a shift in patterns following vaccination with RhCMV/SIV. There were also alterations in host genes such as alpha defensin 6 in vaccinated macaques. It remains unclear by what mechanism vaccination caused these microbial alterations.

Virome and Mycobiome

Although the study of the human microbiome has moved forward tremendously in the past few years, the focus has mostly been on endogenous bacterial species. Significantly less is known regarding the endogenous viral species (virome) and fungal species (mycobiome) and how they might interact with the bacterial biome. In this section, discussions were focused around the virome and the mycobiome in health and immunodeficiency.

Dr. Bushman from the University of Pennsylvania reviewed current knowledge on gut human virome in health and immunodeficiency. In healthy humans, the gut virome is abundant with $\sim 10^{11}$ particles per gram of stool.[40,41] The gut virome is composed of endogenous retroviruses, persistent/latent viruses (Herpes family viruses, Polyoma viruses, and Adeno-associated viruses), and bacteriophages which infect endogenous bacteria and archaea species.

In an immunodeficient state, components of the virome (such as the latent/persistent viruses) can become pathogenic in the absence of immune control and result in opportunistic infections. For example, low CD4 counts in humans have been associated with adenoviral infections.[42] Fecal microbiome analyzed from SIV-infected and -uninfected macaques showed distinct profile in infected animals with advanced disease, which was not observed in African green monkeys, a species in which SIV is not pathogenic.[43] Interestingly, a recent study with wild chimpanzees showed no virome dysbiosis irrespective of SIV-positive status except when close to death.[44] This might indicate that virome dysbiosis in immunodeficiency is highly species specific or that the really sick SIV-infected chimpanzees die off in the wild and are therefore missed in sampling.

Another level of understanding regarding impact of gut virome on human health comes from children with severe combined immunodeficiency (SCID) syndrome X1, many of whom undergo successful gene therapy treatment.[45–49] Stool analysis of these children has revealed an improvement in microbiota abundance upon successful therapy, which was absent in cases where therapy was not successful.[49] The gut virome of SCID children was enriched for nonpathogenic Anellovirus and Astrovirus while immunocompromised. Similarly, adenovirus was significantly higher in pretransplant SCID patients compared with HC and was reduced following successful gene therapy, an observation that might have future clinical implications.

Study of nonhuman primates in the wild can give us a sense of how SIV affects gut immunity without the artificial conditions of captivity or many of the ever-present confounders in human HIV studies. Dr. D'Arc presented her work on gut virome in wild gorillas. Previous reports have shown no association of bacteriome stability with SIV infection in gorillas.[50] However, enteric virome has been shown to expand dramatically in SIV-infected macaques.[43] The authors in this study investigated enteric virome in SIV-infected and -uninfected gorillas using stool samples. SIV-infected animals had a distinct virome profile with significantly more abundant species of Adenoviridae, which have been previously associated with viremia in infected macaques.[43] SIV-infected status was also associated with Reoviridae and Alloherpesviridae, whereas SIV-uninfected status was associated with Tymoviridae, Microviridae, and Rhabdoviridae. High viral load was associated with Baculoviridae and Picobirnaviridae, whereas low viral load was associated with Alloherpesviridae. Overall, the enteric virome might be a better marker of pathogenesis and disease progression than bacteriome in gorillas. More studies with larger sample size are needed to confirm these data.

Human studies demonstrate some concordance with findings in gorillas. Dr. Gootenberg from the Ragon Institute at Harvard discussed bacteriome and virome studies being conducted by their group in Uganda.[51] In this cohort, HIV-infected untreated individuals with <200 CD4 count showed significantly higher sCD14, indicative of systemic immune activation. Enteric virome analysis in these individuals showed an abundance of Adenoviridae and Anelloviridae families compared with the HIV-infected treated and HIV-uninfected groups. The Anelloviridae family, particularly the Alphatorquevirus genera that were detected in this group, have been associated with immunosuppression and found to be increased in transplant recipients in other studies.[52–54] The enteric bacterial community in this cohort was also distinct with predominant *Prevotella* colonization in the HIV uninfected, whereas *Bifidobacterium* predominance was noted in

the HIV infected. He suggests immunocompromise as the factor driving changes in the gut virome and bacteriome.

The mycobiome, or commensal fungi, are often overlooked; yet they are critical players in human health and disease. Dr. Ghannoum from Case Western Reserve University, discussed the lesser known world of the mycobiome. His group used a novel pyrosequencing approach to characterize fungi present in the oral cavity of healthy individuals, using the panfungal internal transcribed spacer primers.[55] Eighty-five culturable genera of fungi and 11 unculturable genera of fungi were identified, with highest abundance of Candida species.

It has previously been shown that core oral bacteriome in HIV-positive individuals was distinct from HIV-negative individuals.[55] Data from Dr. Ghannoum's group showed a shift in mycobiome among these groups with evidence for distinct bacterial–fungal interactions in infected versus uninfected individuals.[57] One of the features of the HIV-infected mycobiome was the presence of higher abundance of *Candida* species, whereas the *Pichia* species was completely absent from this group. Interaction analyses revealed that the presence of *Pichia* was associated with the absence of *Candida* and vice versa. Further investigations demonstrated *Pichia* inhibited *Candida* biofilm formation *in vitro* and was a more efficient inhibitor than the current commercially available antifungal Nystatin, in a murine model of oral candidiasis.[56] Other studies with HIV-infected individuals showed lower diversity of microbiome in the immunological failures (IF) compared with immunological successes and healthy uninfected controls (HC). In particular, abundance of *Collinsella stercorsis*, a species associated with alteration in serum lipids and increased risk of heart failure, was found to correlate with body mass index in the IF patients.

Dr. Ghannoum's group have also characterized the gut bacteriome and mycobiome in patients with Crohn's disease (CD) and their nondiseased first-degree relatives in familial clusters.[58] Abundance of *Candida tropicalis*, *Serratia marcescens*, and *Escherichia coli* were elevated in CD patients and positively correlated with each other indicating bacteriome–mycobiome interactions. Functional studies of *in vitro* biofilm formation showed larger and thicker biofilms when all three species were present compared with single and double species biofilms.[58] This may be an example of cooperative evolutionary strategies between commensal bacteria and fungi. Perhaps the fungi aids in host invasion, whereas the bacteria becomes resistant to antibiotics, living under the protection of a complex multispecies biofilm. However, this interkingdom cooperation can negatively impact the host, as the fungi and bacteria produce extracellular enzymes that inflict tissue damage, leading to an increase in proinflammatory cytokines, which results in oxidative damage and apoptotic cell death.[59] Understanding the crosskingdom interactions among commensals is likely to be instrumental in developing a working model of the whole microbiome.

Conclusion

While the current state of microbiome science in HIV remains fairly descriptive, new methods are being developed to study interactions in more controlled settings. We have found mycobiome patterns associated with HIV disease and established links between particular microbes and systemic markers of disease and researchers are pushing to define causality in these relationships. *In vitro* and *ex vivo* model systems will allow us to study interactions between individual microbes, their metabolites, and host epithelial and immune cells. Developing a predictive understanding of the role of microbes in gut physiology will require integration of the virome and mycobiome into a comprehensive model of the commensal ecosystem. New tools and strategies are in development which will allow us to better understand the enzyme pathways and metabolites that link microbes to one another and to host physiology. Systems biology will help us integrate microbial dynamics and metabolism into our understanding of the human body in health and disease.

Author Disclosure Statement

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