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Commentary

Microbial Effects on Immunity in HIV: Virus, Gender or Sexual Preference Induced?

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The intestinal microflora has been intensely studied in the context of HIV infection, as alterations in the composition of the microbiome, or microbial dysbiosis, could impact mucosal dysfunction and barrier breakdown, leading to elevated translocation of bacteria into the systemic periphery (Zevin et al., 2016). This in turn could contribute to increased systemic immune activation, which has been associated with enhanced HIV disease progression in untreated individuals, and morbidity and mortality in antiretroviral therapy (ART)-treated, HIV-infected individuals. Initial studies designed to characterize the composition of the intestinal microbiome in HIV-infected individuals demonstrated that bacterial community structure was altered as compared to uninfected individuals. In particular, the relative abundance of genera such as *Prevotella* and *Acinetobacter* as well as the phylum Proteobacteria, were shown to be increased in HIV-infected individuals and these increased abundances were associated with elevated frequencies of mucosal and systemic immune activation and microbial translocation (Dillon et al., 2014; Dillon et al., 2015). In contrast, healthy commensals such as Firmicutes and *Bacteroides* were decreased in HIV infection, potentially contributing to loss of mucosal health.

Critically, more recent data has demonstrated that the microbial alterations previously ascribed to HIV infection may in fact be linked to sexual preference. Indeed, seronegative men who have sex with men (MSM) were shown to exhibit microbiomes rich in *Prevotella,* independent of HIV infection (Kelley et al., 2016, Noguera-Julian et al., 2016). These findings highlight the importance of developing a better understanding of how the microbiome is impacted by disease as well as lifestyle and of defining the exact mechanisms by which alterations in microbial communities as a whole, could contribute to the exacerbated systemic inflammation characteristic of HIV-infection.

In this issue of EBioMedicine, Neff et al. (2018) addressed the question of how entire microbial communities may impact inflammation and immune activation in the context of HIV infection. Here, rather than stimulating with individual bacterial species that have been shown to be dysbiotic as has been done previously (Dillon et al., 2015; Lozupone et al., 2013), the authors developed a method by which whole fecal bacterial communities (FBCs) could be isolated from the stool of representative individuals. Importantly, the authors isolated FBCs from a number of different groups, including (1) ART-naïve HIV-infected MSM, (2) ART-experienced HIV-infected MSM, (3) HIV-uninfected MSM, (4) HIV-uninfected heterosexual males, (5) ART-experienced HIV-infected females, and (6) HIV-uninfected females, in a concerted effort to take into account biological and lifestyle factors including sexual preference, ART treatment and gender. Using this method, the authors demonstrate that peripheral blood mononuclear cells (PBMCs) cultured with FBCs from HIV-infected and seronegative MSM had greater monocyte activation as compared to PBMCs cultured with FBCs from seronegative heterosexual males. In addition, FBC from untreated HIV-infected MSM induced greater pro-inflammatory cytokine production and CD4+ T cell activation as compared to seronegative MSM. Similarly, elevated CD4+ T cell activation and inflammatory cytokine production was observed in PBMC stimulated with FBCs from HIV-infected, ART-treated females, as compared to FBCs from seronegative females. Finally, elevated T cell activation was shown to be mediated by monocytes, which were induced by FBCs mainly through Toll-like receptors (TLRs), specifically TLR-2, to produce elevated levels of cytokines, including TNF-α. Together, these data demonstrate how alterations in microbial community structure due to differential combinations of disease, lifestyle, drug treatment and/or gender could elicit varying immune responses.

Neff et al. (2018) acknowledge that although the overall structure of the microbial communities in FBCs were preserved compared to whole fecal samples, they did observe some significant alterations in specific genera, including loss of *Prevotella*. As even subtle differences in microbial community structure could impact downstream immune responses, especially decreases in species like *Prevotella* that have been associated with increased inflammation, steps to refine the FBC preparation method will be necessary to create whole bacterial communities that exactly mimic that of the initial starting material. Furthermore, although stool is a reasonable representative of intestinal microbial

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communities, it has been shown that mucosa-associated bacterial communities differ somewhat as compared to the stool (Dillon et al., 2014; Zevin et al., 2017). Even given that differences in relative abundances in the fecal and mucosal compartments may be minimal, sheer physical proximity allows for greater interaction between mucosa-associated bacteria and the mucosal immune system and an enhanced possibility for translocation into the systemic periphery. Thus, it will be important in the future to assess whether similar responses are seen when comparing FBCs and whole mucosa-associated bacterial communities.

These findings also underscore the importance of further research into therapeutic strategies aimed towards modulating microbial structures into more beneficial communities. One proposed technique by which intestinal bacterial communities could be adjusted towards more beneficial populations is fecal material transplant (FMT). Previous studies have shown that FMT is well tolerated in HIV-infected ART-treated individuals (Vujkovic-Cvijin et al., 2017) and in SIV-infected macaques was correlated with lower cellular activation (Hensley-McBain et al., 2016). The work presented by Neff et al. (2018) provides interesting insight into a potential mechanism by which altering intestinal microbial communities in their entirety through techniques like FMT may lead to differential mucosal and systemic immune responses, however it will have to be used correctly dependent on sexual preference and gender. Furthermore, the methods developed by Neff et al. (2018) may have wider applications and could be useful in variety of settings to examine the mechanisms by which microbial dysbiosis influences the pathogenesis of other disease states, including inflammatory bowel diseases. Finally, the results here demonstrate that the microbiome could impact not just HIV pathogenesis but also rectal HIV transmission, and assessing how the rectal microbiome may impact pre-exposure prophylactic (PrEP) strategies for HIV prevention will be critical.

Conflict of Interest

The authors declare no conflicts of interest.

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