Editorial

The fecal microbiome directly drives immune activation in HIV infection

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Immune activation is a hallmark of human immunodeficiency virus (HIV) infection: it causes progression to the acquired immunodeficiency syndrome (AIDS), impaired CD4+ T-cell reconstitution on suppressive combination antiretroviral therapy (cART) and contributes to non-infectious comorbidities (1-6). Understanding the mechanisms whereby immune activation arises is thus crucial for the elaboration of novel therapeutic interventions in the setting of HIV infection.

Microbial translocation, i.e., the passage of bacteria and microbial bioproducts through the gastrointestinal (GI) tract to the peripheral circulation, was described as a possible cause of immune activation over a decade ago (7,8). In the attempt to shed light on the mechanisms whereby microbial translocation arises in the context of HIV infection, research studies have proved the existence of anatomical and immune defects within the GI tract of infected individuals (9-14) as well as profound modifications of the intestinal microbiota (15-19). In particular, HIV-related dysbiosis features the depletion of *Bacteroides* and the enrichment for *Proteobacteria*, which, respectively, limit and promote inflammation (15,17), thus implying that precise compositional changes of the microbiota contribute to immune activation in HIV. Consistently, studies have demonstrated that single microbial components are able to induce the activation of adaptive and innate immune cells *in vitro* (20,21) and that HIV-related dysbiosis correlates with markers of immune activation and disease progression (15,22,23). However, whether the fecal microbiome in HIV-infected individuals directly drives peripheral immune activation is currently unknown.

In the paper, "Fecal Microbiota Composition Drives Immune Activation in HIV-infected Individuals" by Neff *et al.* published in *EBioMedicine*, the authors take an interesting approach to the research question by performing *in vitro* stimulation assays with fecal bacteria communities (FBCs) (24) and human cells. Stool and peripheral blood samples were collected from HIV-infected and uninfected individuals: the former was used to develop a novel method for purification of intact microbial cells; the latter were employed to isolate peripheral blood mononuclear cells (PBMCs), monocytes and CD4+ T-cells for a comprehensive study of the inflammatory properties of HIV-associated enteric microbiota.

In contrast to previous findings, HIV infection did not result the predominant factor linked to the reported differences in the composition fecal microbiome: the predominance of *Prevotella*-rich/*Bacteroides*-poor microbiomes was in fact observed in men who have sex with men (MSM) and corroborate previous research on the clustering of the microbiome composition according to sexual behaviour (25). Of note, however, they detected a greater production of pro-inflammatory cytokines in monocyte cultures and the selective activation of peripheral T-cells following culture stimulation with FBCs from HIV-infected MSM and not uninfected MSM, thus demonstrating the pathogenic role of the gut microbiome in HIV disease. From a mechanistic standpoint, tumour necrosis factor (TNF)-α and toll-like receptor (TLR)-2 resulted strong mediators of adaptive immunity activation.

The present paper is noteworthy for several reasons. First, the authors were able to purify FBCs which maintained similar microbiota community membership to whole stool, thus recapitulating *in vitro* the interactions among different components of the microbiome. Second, the finding of higher levels of innate and adaptive immune activation in HIV-infected MSM following FBCs stimulation paves the way to new research questions, such as what is the clinical risk of disease progression/non-infectious comorbidities in this specific patient population. Finally, by demonstrating the mechanisms by which the fecal microbiota induces immune activation, this paper highlights possible targets for new therapeutic interventions in the setting of HIV infection.

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Footnote

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