Fecal microbiota transplantation reduces inflammation and modulates gene expression in HIV-infected double humanized-BLT (dHu-BLT) mice on antiretroviral therapy

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Introduction: Persistent immune activation and inflammation remain significant barriers to managing comorbidities in people living with HIV (PLWH) on suppressive antiretroviral therapy (ART). While ART substantially reduces plasma viral loads to an undetectable level, it fails to fully restore gut microbial homeostasis and prevent microbial translocation, a critical pathogenic contributor to systemic persistent immune activation and inflammation. To evaluate the potential of human fecal microbiota transplantation (FMT) as an adjunctive therapy to restore gut health and attenuate inflammation and immune activation in PLWH on ART, we utilized a double humanized-BLT (dHu-BLT) mouse model, featuring a functional human immune system and a human-like microbiome.

Methods: Two groups of HIV-infected dHu-BLT mice were used in the study. One group received FMT in addition to ART, while the control group received ART alone. Using both a multi-omics approach (16S rRNA sequencing and RNA-seq) and an immune-based assay, we compared alterations in gut microbial composition, profiled transcriptomic changes in the intestinal tissue, and quantified markers of systemic immune activation and inflammation between the groups.

Result: FMT supplementation in ART-treated mice increased the relative abundance of beneficial bacteria and modulated the transcriptomic profile of both human- and murine-related genes. Notably, genes associated with cellular structure and tissue maintenance, including *Mcpt4*, were upregulated, along with the extracellular matrix organization pathway predicted as the most strongly activated pathway in the FMT-supplemented group compared to ART alone. In contrast, genes and signaling pathways associated with inflammation were downregulated. Importantly, the FMT-supplemented group exhibited a significant reduction of plasma inflammatory markers, including CD62E, sCD14, sCD163, and FABP2, relative to the ART alone group.

Conclusion: These results suggest that FMT may serve as a promising adjunctive strategy for mitigating systemic inflammation by improving gut health, thereby contributing to the reduction of comorbidities in PLWH on ART.