Distinct Intestinal Microbial Signatures Linked to Accelerated Biological Aging in People With HIV

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Abstract Body

Background:

HIV infection disrupts the intestinal barrier, resulting in persistent inflammation, even with antiretroviral therapy (ART). This inflammation contributes to aging-related comorbidities in people with HIV (PWH). However, it remains unclear whether ART-suppressed HIV affects intestinal biological aging and whether microbial dysbiosis and translocation contribute to aging in PWH on ART.

Methods:

Colon and ileal biopsies, blood, and stool were collected from 25 PWH on ART (viral load <50 copies/ml) and 23 age, sex, and ethnicity-matched HIV-negative controls. Accelerated biological aging in colon, ileum, and blood was assessed by regressing biological age estimated by several epigenetic aging clocks (Horvath1, Horvath2, Hannum, PhenoAge, GrimAge, and DunedinPACE) against chronological age. Intestinal integrity was assessed by immunofluorescence staining for tight junction proteins (ZO1, occludin). Markers of microbial translocation (e.g., LBP) and inflammation were measured by ELISA/multiplex arrays. Microbiota profiles of stool, ileum, and colon were determined via 16S rRNA sequencing, and metabolic analyses of plasma and stool were conducted using mass spectrometry.

Results:

Despite similar chronological age (Fig. 1A), PWH exhibited accelerated biological aging of the ileum, colon, and blood (Fig. 1B; e.g., Horvath1 clock; $P<0.002$). Colon and ileum from PWH showed reduced tight junction proteins and increased microbial translocation ($P<0.05$; Fig. 1C-D are examples), significantly associated with accelerated biological aging and higher inflammation ($P<0.05$). Putative pro-inflammatory bacteria like Catenibacterium and Prevotella 2/9 were enriched in PWH, correlating with accelerated aging (FDR<10%). Conversely, short-chain-fatty-acid-producing and anti-inflammatory bacterial genera, like Subdoligranulum and Erysipelotrichaceae UCG-003 were depleted in PWH, correlating with decelerated aging (FDR<10%, Fig. 1E is an example of the colon). Correlation networks revealed associations between specific microbial genera in the colon (Fig. 1F) and ileum (not shown) with accelerated aging, enrichment of pro-inflammatory microbial-related metabolites, and depletion of anti-inflammatory metabolites ($P<0.05$).

Conclusions:

Distinct microbial profiles are linked to intestinal and systemic biological aging in PWH on ART. Further research is needed to understand the mechanisms connecting microbial dysbiosis/translocation to intestinal and systemic biological aging in PWH and to develop preventive strategies.