Elite Controllers: Deciphering the Role of the Microbiome and Inflammation

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BACKGROUND

- Elite controllers definition: individuals who mantain controlled viral suppression without treatment.
- **Exceptional Elite Controllers (EECs)** – Our definition: sustained viral suppression for more than 10 years, no treatment and CD4 nadir >350 cells/µL
- **Hypothesis:** The gut microbiome contributes to the virological control of HIV by modulating specific immune responses.

METHODS

- **Participants:**
  - **37 EEC** (mean: **27 years of follow-up** since diagnosis, 568 CD4/µL, and CD4/CD8 ratio of 1.0)
  - 33 chronic progressors (CP): PWH on ART, undetectable VL, CD4 nadir <350/µL).
  - Matched for age, sex, and sexual preferences.
- **Proteomics:** expression profile of 364 inflammatory proteins - (PEA-Olink®). Parametric tests (t-test/ANOVA) on normalized values to compare groups.
- **Stool metagenomics:** taxonomy (mOTUs3) and function (eggNOG-mapper).
- **Immune stimulation assays:** inactivated fecal bacterial communities (FBC) and sterile filtrates (SF). CP's PBMCs were primed with SF or FBC, stimulated with HIV peptides, and gene expression of 9 genes was quantified by qPCR.

	EEC	CP
Age (average)	56 (9)	52 (11)
Sex at birth	65% M 35% W	67% M 33% W
MSM	25%	35%
Nadir CD4 (cells / ul)	583	206
Ratio CD4/CD8	1,08	0,92
Smoker	52%	40%
Past HCV infection	12%	9,4%

Exceptional elite control may be influenced by a microbiome-conditioned immune landscape in which antiviral competence and metabolic functionality predominate over inflammatory and virulence-associated programs.

Plain language summary: people who **naturally keep HIV under control** without treatment ("exceptional elite controllers") show a unique gut microbiome signature:
- Enhanced antiviral capacity
- Reduced inflammation
- Enriched metabolic pathways.

The microbiome may actively contribute to this natural HIV control

CONCLUSIONS

- Bacterial functions in EEC shift to **lower virulence but greater metabolic adaptability**.
- Microbial preparations from EEC primed a **less pro-inflammatory state**, whereas those from CP likely delivered more PAMPs and inflammatory metabolites, reprogramming inflammasome pathways.
- These findings suggest the **microbiome supports long-term HIV control in EEC** by restraining inflammation while preserving antiviral capacity.

ACKNOWLEDGEMENTS

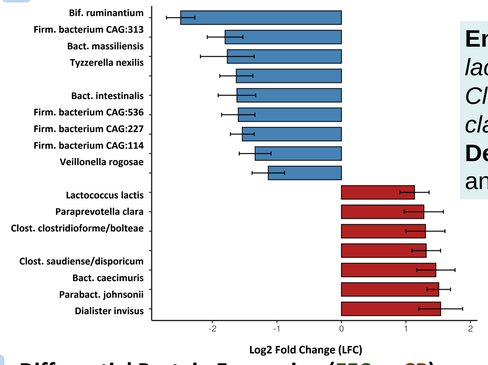
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Study participants

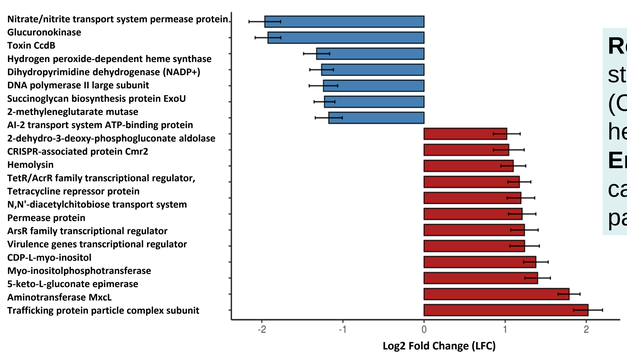
RESULTS

1 Differential Bacterial Abundance (EEC vs CP)



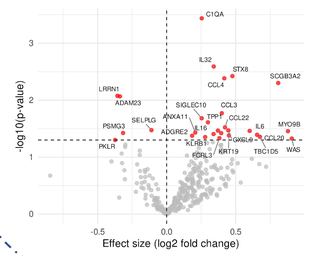
Enriched in EEC: *Lactococcus lactis, Parabacteroides johnsonii, Clostridium* spp., *Paraprevotella clara* and *Dialister invisus*
Depleted in EEC: *Bacteroides* and *Veillonella*

2 Differential Microbial Functions (EEC vs CP)



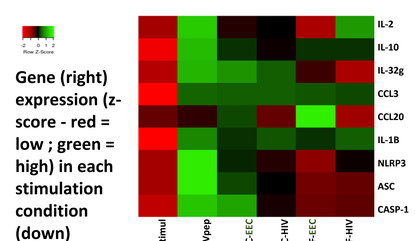
Reduced in EEC: toxin and stress metabolism genes (CdtB, nitrate/nitrite transport, heme synthesis).
Enriched in EEC: regulatory, carbohydrate, and structural pathways.

3 Differential Protein Expression (EEC vs CP)

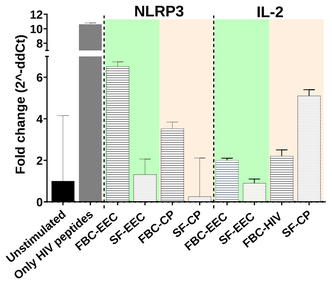


Differential nflammatory profile in EEC: IL32, IL16, IL18, CCL2, CCL3, CCL4, CCL22, CXCL9, and STX8.

4 Immune stimulation assays



Gene (right) expression (z-score - red = low ; green = high) in each stimulation condition (down)



HIV peptides induced all genes. Preconditioning with **SF from EEC or CP blunted NLRP3 and CASP1** compared with FBC.
Attenuated inflammasome activation (NLRP3, CASP1) with SF-EEC stimulation.
Modulates T-cell signaling: IL2 suppressed with SF-EEC.