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HIGH-THROUGHPUT TARGETED PLASMA PROTEOMICS SHOWS SYSTEMIC DYSREGULATION IN PLHIV ON ART

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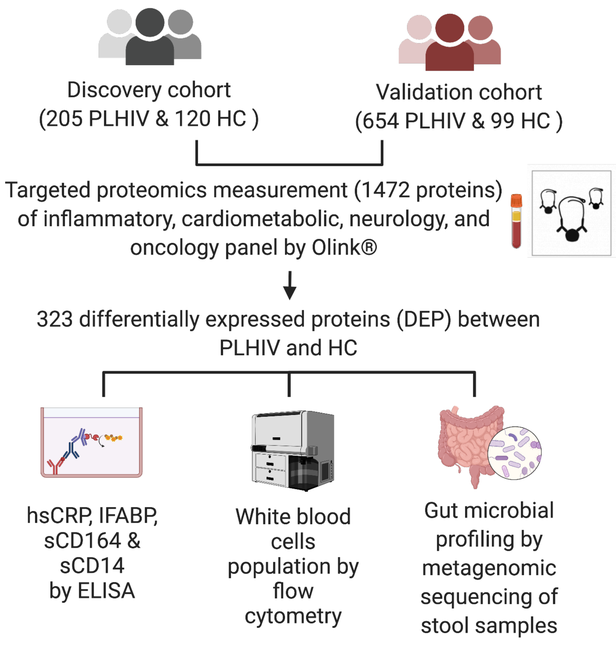
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BACKGROUND

- People living with HIV (PLHIV) on long-term suppressive antiretroviral therapy (ART) are exhibiting an increased prevalence of multi-systemic comorbidities compared to the general population.
- Chronic inflammation and microbial dysbiosis are among the major contributors to these major complications in PLHIV.
- The main objective of this study is to compare multi-systemic, proteomic profiling between virally suppressed PLHIV and healthy controls (HC).

METHODS



RESULTS

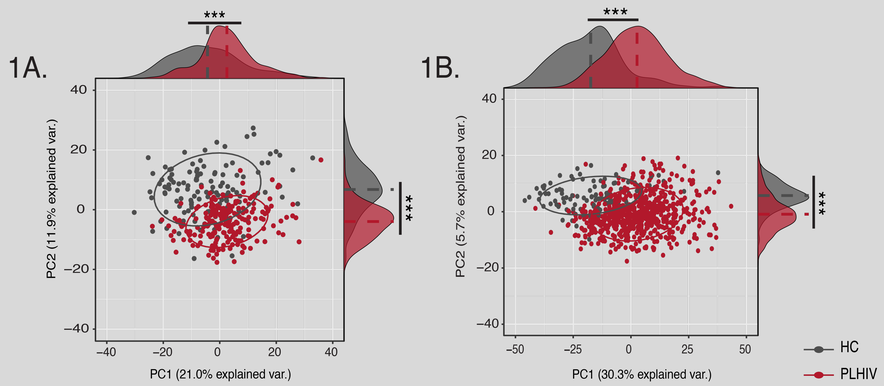


Figure 1. Principle component analysis plot of plasma inflammatory proteins (n=~1400) from the **A.** discovery and **B.** validation cohort of PLHIV and HC using the first two principal components. The ellipses were centered based on the median of the PC1 and PC2 for each group (PLHIV and HC). Protein distributions across PC1 and PC2 for each group are presented in marginal histogram plots. The median differences of the protein distribution across PC1 or PC2 between PLHIV and HC were calculated by the Mann-Whitney-U test. ***P-value<0.0001.

In the discovery and validation cohort, PLHIV displayed distinct systemic dysregulation of protein expression profile compared to HC (Figure 1A and 1B).

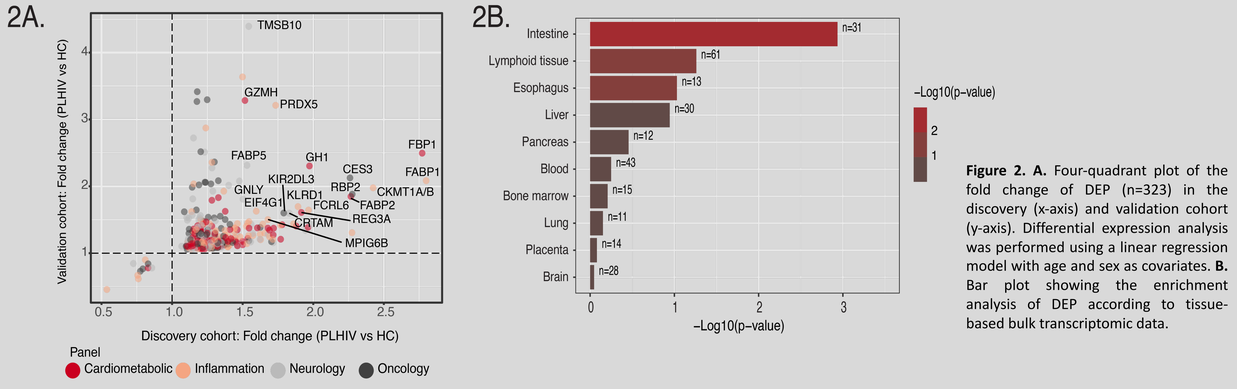


Figure 2. A. Four-quadrant plot of the fold change of DEP (n=323) in the discovery (x-axis) and validation cohort (y-axis). Differential expression analysis was performed using a linear regression model with age and sex as covariates. **B.** Bar plot showing the enrichment analysis of DEP according to tissue-based bulk transcriptomic data.

A total of 313 out of 323 differentially expressed proteins (DEP were upregulated in PLHIV using chronic suppressive ART and equally distributed across the four panels (Figure 2A). Among the top DEP (fold-change >1.5) are the fatty acid-binding protein group (FABP1 and 2), RBP2, and CES3.

Enrichment analysis using publicly available bulk and single-cell transcriptomic data revealed that most of the DEP originated from intestine and lymphoid tissue (Figure 2B).

Pathway analysis of DEP demonstrated lipid and immune-related pathways. The top pathway of lipid metabolism consisted of a number of the fatty acid-binding proteins.

ADDITIONAL FINDINGS

- Microbiome analysis showed a positive influence of microbial species and pathways on DEP originating from enterocytes.
- Across panels, DEP were markedly associated with increased absolute concentrations of hsCRP, IFABP (marker of microbial translocation), sCD14, and sCD163 (monocyte activation markers).

CONCLUSIONS

- Targeted proteomic analysis demonstrated a systemic upregulation of protein expression in PLHIV using long-term ART compared to healthy controls, of which most of the proteins originated from the intestine and lymphoid tissues.
- These upregulated proteins related significantly to markers of systemic inflammation and IFABP, confirming the known link between gut function and inflammation.

CONTACT INFORMATION

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