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TARGETED INFLAMMATORY PLASMA PROTEOMICS SHOWS UPREGULATION OF DISTINCT PATHWAYS

N. Vadaq[1,2], L. van de Wijer[1], L.E. van Eekeren[1], H. Koenen[1], Q. de Mast[1], L.A.B Joosten[1], M.G. Netea[1], V. Matzaraki[1], A. van der Ven[1]

[1]Radboud university medical center, Nijmegen, The Netherlands, [2]Dr. Kariadi Hospital, Semarang, Indonesia

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BACKGROUND

- Despite long-term suppressive antiretroviral therapy (ART), people living with HIV (PLHIV) display persistent inflammation leading to non-AIDS-related comorbidities.
- To increase our understanding of the underlying mechanisms, we compared plasma inflammatory protein concentration between PLHIV using long-term suppressive ART and healthy controls (HC) and correlated these with markers of inflammation.

METHODS

Discovery cohort (192 PLHIV & 416 HC)

Validation cohort (649 PLHIV & 98 HC)

Targeted proteomics 92 inflammatory proteins by Olink®

Plasma inflammatory markers (n=16) by ELISA

White blood cells population by flow cytometry

PLHIV (n=192) were followed-up for 5 years for clinical events

RESULTS

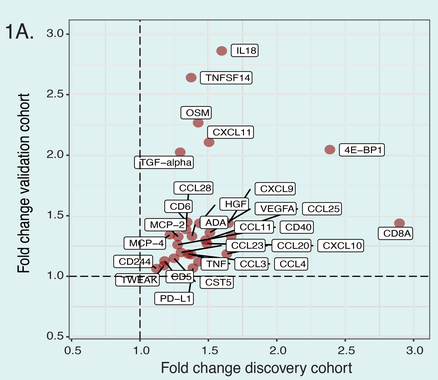


Figure 1. A. Four-quadrant plot of the fold change of differentially expressed proteins (DEP) (n=29) in the discovery (x-axis) and validation cohort (y-axis). Differential expression analysis was performed using a linear regression model with age and sex as covariates. **B.** Results from the network analysis using the DEP between PLHIV and HC. Network analysis was performed by calculating the spearman's rank correlation between pairs of proteins measured in PLHIV of the discovery cohort (n=192), and only those pairs with rho≥0.3 are presented. Proteins are represented as nodes, line colors connecting the nodes represent the degree of correlation for protein linkage; the darker the color, the stronger the correlation. Node color represents the centrality (importance) of protein-based on nodes closeness

Compared to healthy controls, PLHIV exhibited a distinct and upregulated inflammatory protein (n=29; Figure 1A), consisting of mucosal defense chemokines, CCR5 and CXCR3 ligands, and growth factors (Figure 1B).

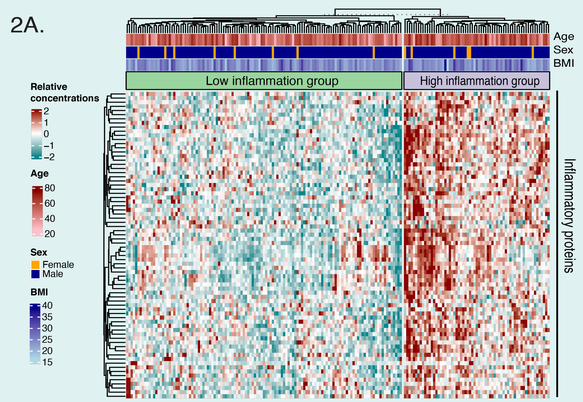


Figure 2. A. Unsupervised k-means clustering of PLHIV using the plasma inflammatory proteins (n=74) measured in PLHIV of the discovery cohort (n=192). The color code indicates the relative concentration of proteins across the samples of the two clusters. Red and green colors indicate high and low protein concentrations, respectively. **B.** Bar plot showing the frequency (y-axis) of a 5-year follow-up clinical events from two clusters of PLHIV of the discovery cohort (n=192).

Unsupervised clustering of plasma inflammatory proteins clearly differentiated PLHIV with high levels of inflammation (n=65) from those with low inflammation (n=123) (Figure 2A).

During five years follow-up, PLHIV in the high inflammation group were at higher risk to develop malignancies (13.8% vs 4%; relative risk 3.4; 95% confidence interval 1.2 to 9.8) and showed a trend for cardiovascular disease events (12.3% vs 7.3%) compared to PLHIV with low inflammation (Figure 2B).

ADDITIONAL FINDINGS

- Differentially expressed proteins correlated strongly with plasma inflammatory markers in PLHIV using long-term suppressive ART.
- Malignancy development associated with higher TNFRSF14 and FGF-23 protein expression, while higher OSM, CCL19, SLAMF1 and HGF associated with cardiovascular disease events

CONCLUSIONS

- Distinct inflammatory proteins and pathways may serve as potential biomarkers and therapeutic targets in PLHIV on long-term ART.
- Clinicians should be aware that PLHIV with a high inflammation endotype are at increased risk to develop malignancies and cardiovascular diseases.

CONTACT INFORMATION

Nadira Vadaq.
N.Nadira@radboudumc.nl
Department of Internal Medicine,
Radboud University Medical Center,
Nijmegen, The Netherlands