Endothelial Dysfunction in HIV: Exploring Cytokine and Chemokine Dynamics

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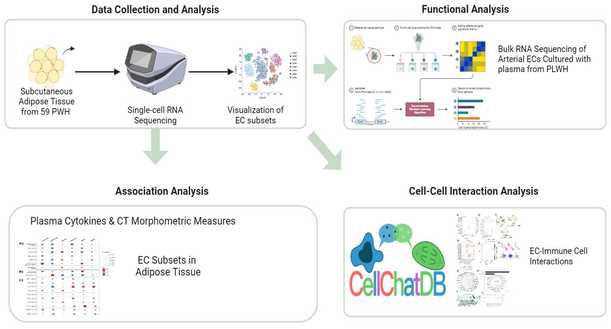
BACKGROUND

- Endothelial dysfunction is a prominent feature in persons living with HIV (PLWH), contributing to their increased risk of cardiovascular disease (CVD).
- Our hypothesis is that elevated levels of pro-inflammatory cytokines and chemokines in the plasma of PLWH directly contribute to endothelial cell activation and dysfunction.
- Understanding the mechanisms driving endothelial dysfunction in HIV is crucial for developing targeted anti-inflammatory interventions beyond statins to reduce cardiovascular risk.

OBJECTIVE

To understand the role of cytokines and chemokines in endothelial cell dysfunction in PLWH with and without diabetes

METHODS



- We used single-cell RNA (scRNA) sequencing to phenotype endothelial cells present in adipose tissue of 59 PLWH.
- We used CellChat analysis to identify predicted interactions between endothelial cells and other cells in the stromal vascular fraction.
- We performed correlation analysis between the proportion of adipose tissue EC subsets and circulating cytokines/morphometric measurements.
- Human arterial ECs (HAECs) were cultured in media or media conditioned with plasma from PLWH and HIV-negative controls. HAECs were cultured under normotensive stretch conditions. We used bulk RNA sequencing to identify changes related to incubation with plasma from patients.

TNF-α signaling via NFKβ is one of the main pathways activated by plasma from PLWH.

RESULTS

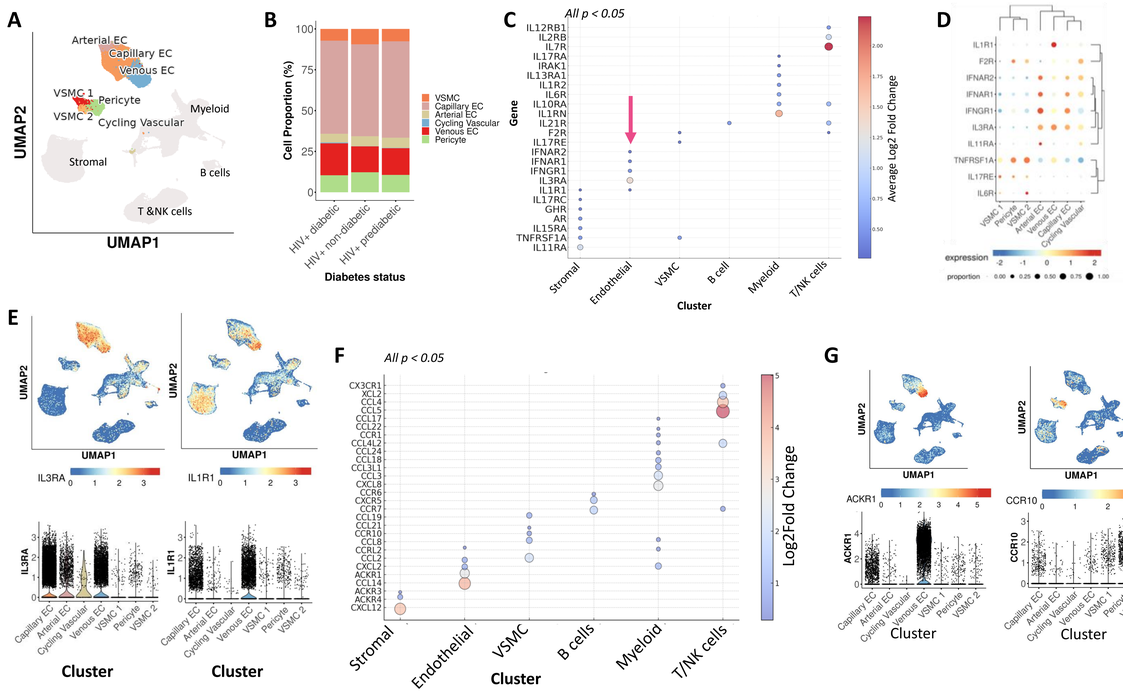


Figure 1. Adipose tissue endothelial cells express higher levels of IFN receptors when compared to other cells in the stromal vascular fraction. UMAP shows the distribution of endothelial cell (EC) subsets (A). There were no differences in the EC subset proportion by diabetes status among PLWH (B). Differential expression of cytokine receptors shows higher expression of interferon (IFN) receptors, IL3RA and IL1R1 compared to other cells in the stromal vascular fraction (C). Arterial and capillary ECs have the highest expression of IFN receptors, while venous ECs had higher expression of IL1R. UMAP and dot plots show expression of IL3RA and IL1R1 on ECs (E). ACKR1 are highly expressed on venous ECs and CCR10 on pericytes (F-G).

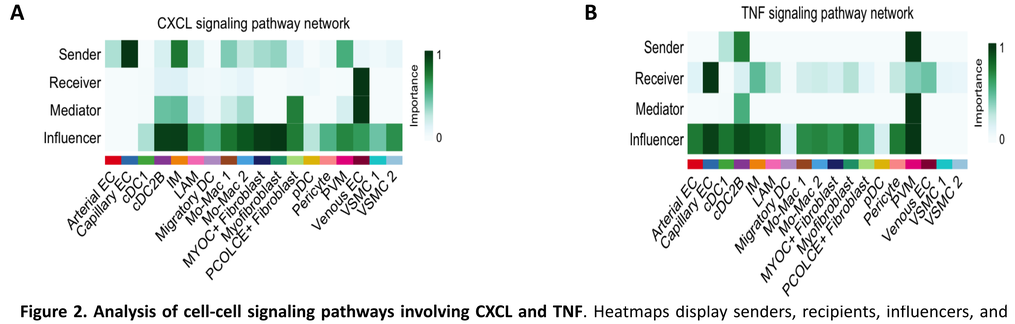


Figure 2. Analysis of cell-cell signaling pathways involving CXCL and TNF. Heatmaps display senders, recipients, influencers, and mediators of CXCL and TNF signaling pathways, along with their relative importance across different cell populations, based on computed network centrality measures.

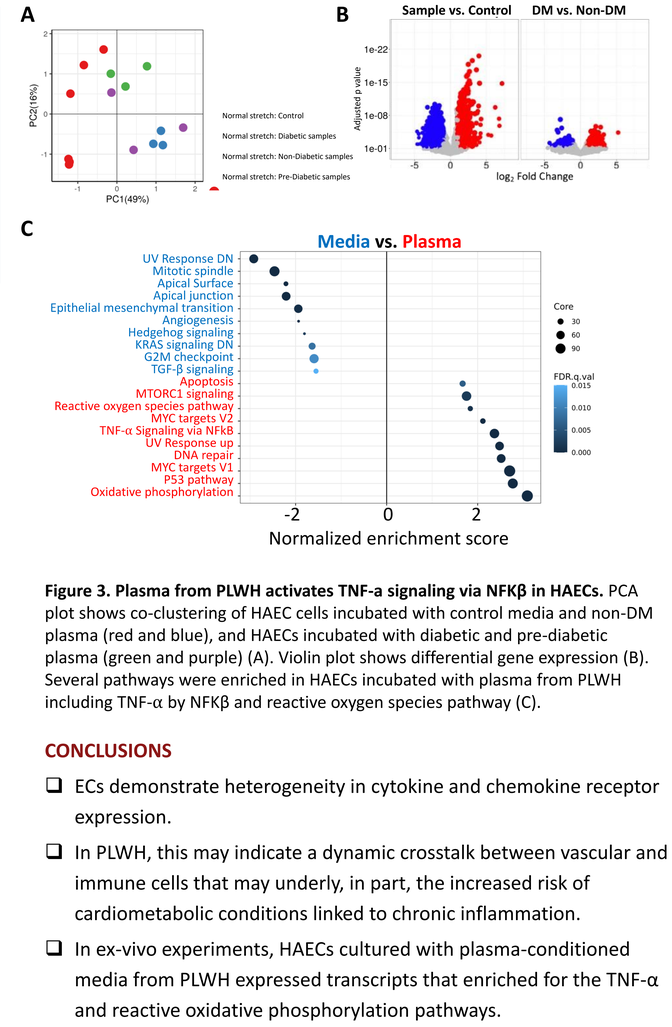


Figure 3. Plasma from PLWH activates TNF-a signaling via NFKβ in HAECs. PCA plot shows co-clustering of HAEC cells incubated with control media and non-DM plasma (red and blue), and HAECs incubated with diabetic and pre-diabetic plasma (green and purple) (A). Violin plot shows differential gene expression (B). Several pathways were enriched in HAECs incubated with plasma from PLWH including TNF-α by NFKβ and reactive oxygen species pathway (C).

CONCLUSIONS

- ECs demonstrate heterogeneity in cytokine and chemokine receptor expression.
- In PLWH, this may indicate a dynamic crosstalk between vascular and immune cells that may underly, in part, the increased risk of cardiometabolic conditions linked to chronic inflammation.
- In ex-vivo experiments, HAECs cultured with plasma-conditioned media from PLWH expressed transcripts that enriched for the TNF-α and reactive oxidative phosphorylation pathways.

FUTURE DIRECTIONS

Mechanistic studies determining the cell-type specific endothelial cell responses to cytokines could inform therapeutic targets in PLWH.

REFERENCES

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