Single-cell profiling reveals a pathogenic fibroblast phenotype in aortas of Persons living with HIV.

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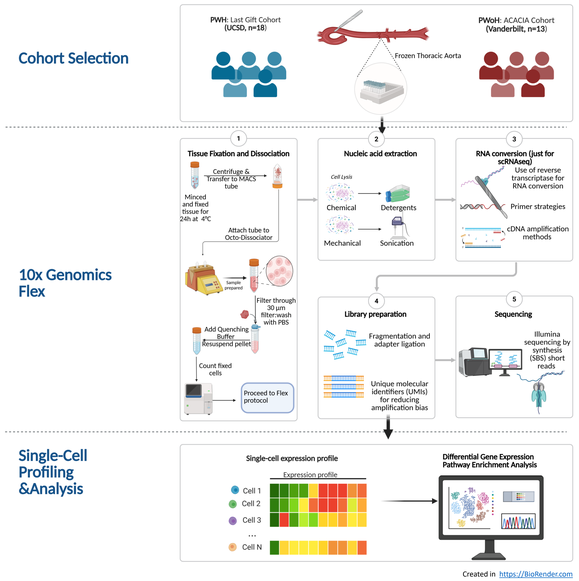
BACKGROUND

- People living with HIV (PWH) have a 1.5–2-fold increased risk of atherosclerotic cardiovascular disease (ASCVD).
- Immune activation is widely studied as the primary driver of HIV-associated ASCVD.
- The role of arterial stromal cells, such as fibroblasts and smooth muscle cells, in HIV-associated ASCVD remains underexplored.
- Fibroblasts regulate extracellular matrix (ECM) remodeling, thrombosis, and vascular inflammation.
- Chronic systemic inflammation in PWH may drive pathogenic changes in fibroblast transcriptional phenotypes, contributing to vascular dysfunction.

OBJECTIVE

To identify transcriptional changes in aortic fibroblasts from PWH that contribute to vascular dysfunction and HIV-associated cardiovascular disease.

METHODS



- Frozen aorta samples from PWH (n=18) and PWoH (n=13) cohorts were analyzed.
- Single-cell RNA sequencing performed using 10x Genomics Flex platform.
- Differential gene expression and pathway enrichment analyzed using edgeR, KEGG, and Reactome databases.

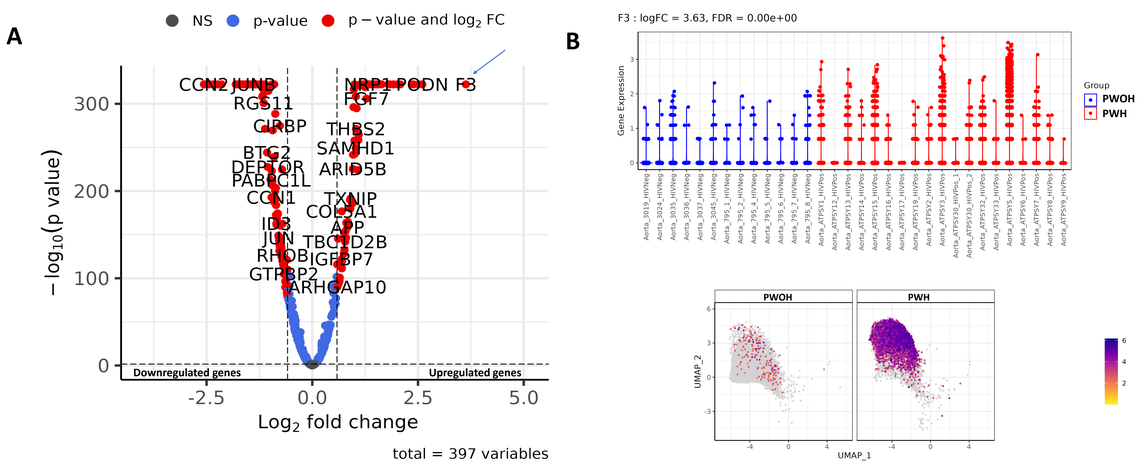
Aortic fibroblasts in PWH adopt a pathogenic transcriptional phenotype characterized by upregulation of coagulation, complement activation, and extracellular matrix remodeling pathways

RESULTS

Table 1: Demographics of Last Gift and ACACIA cohort donors

	Last Gift n=18	ACACIA n=13
Age, yrs.	63.5 (58.8, 73.0)	65 (3.0, 68.5)
Gender, % Male	16 (89%)	11 (85%)
Race, % Caucasian	17 (94%)	11 (85%)
HIV Characteristics		
Last CD4⁺ T cell count, cells/µL	292.0 [151.0, 410.0]	N/A
CD4 Nadir, cells/µL	85.5 [44.0, 219.3]	N/A
Last HIV, copies/mL	30.0 [28.3, 38.3]	N/A
Viral suppression, Yes	15.0 (83%)	N/A
ART	Tivicay, Descovy (6); Tivicay, Odefsey (1); Triumeq; d4T, lamivudine (1), viracept (1); Ritonavir, prezista (1); Biktarvy (2); Unavailable (5)	N/A
H/o of Hepatitis B infection	4 (22%)	N/A
H/o of Hepatitis C infection	3 (17%)	N/A
H/o HSV	5 (28%)	N/A
H/o Chlamydia	1 (6%)	N/A
H/o Gonorrhea	7 (39%)	N/A
Syphilis	6 (33%)	N/A
Abbreviations: ART, antiretroviral therapy		

Figure 1. Differential gene expression in aortic fibroblasts from PWH vs PWOH. Volcano plot and UMAPs showing significantly **upregulated genes (right, e.g., *F3, PODN, NRP1*)** or **downregulated (left, *CCN2, JUNB, ID2*)** in fibroblasts from PWH aortas compared with PWOH aortas (edgeR analysis, FDR < 0.05).



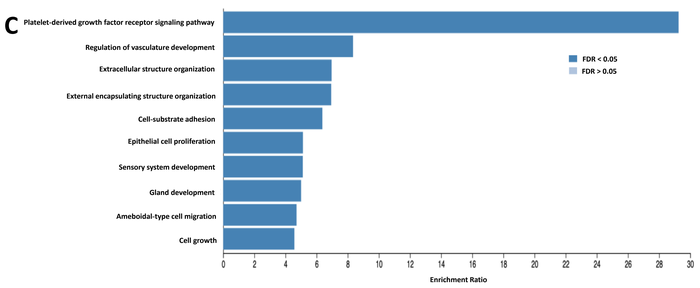


Figure 2. Pathway analysis in aortic fibroblasts from PWH. Bar graph showing enriched pathways in aortic fibroblasts from PWH versus PWoH. **Pathways related to coagulation, complement activation, ECM remodeling, and platelet activation are significantly upregulated (*FDR < 0.01*)**. Bar lengths represent the magnitude of enrichment, and color intensity reflects statistical significance.

CONCLUSIONS

- Aortic fibroblasts in PWH exhibit a pathogenic transcriptional profile.
- Key pathways enriched in PWH fibroblasts include coagulation, complement activation, ECM remodeling, and platelet activation.
- These findings highlight fibroblast activation as a significant stromal mechanism contributing to HIV-associated cardiovascular disease.

REFERENCES

Tieu BC, et al. Aortic adventitial fibroblasts participate in angiotensin-induced vascular wall inflammation and remodeling. PMID: 21099231

Obare LM, et al. . Inflammation in HIV and Its Impact on Atherosclerotic Cardiovascular Disease. PMID: 38781301

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PLAIN LANGUAGE SUMMARY

PWH have a higher risk of heart and blood vessel diseases. Our study found that specific cells in the aorta, called fibroblasts, become activated in harmful ways. These findings highlight mechanisms that might contribute to heart and blood vessel complications in HIV.

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