Endothelial Colony-Forming Cells From People With HIV Display an Interferon Gene Signature

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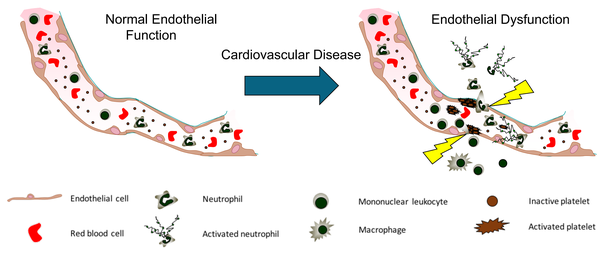
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BACKGROUND

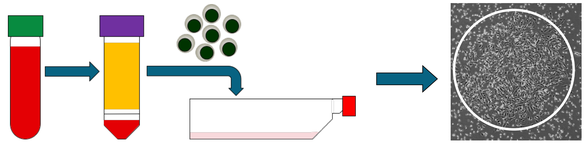
- We aimed to characterise the viral status and gene signature profile of endothelial colony-forming cells (ECFC) in people with HIV

People with HIV have an increased risk of cardiovascular disease (CVD), however, the underlying mechanisms are not fully understood. Endothelial dysfunction is central to CVD pathology. ECFC arise from endothelial progenitors isolated from whole blood and retain the donor's phenotypic characteristics *ex vivo*. ECFC are increasingly used to study disease-specific mechanisms but have been largely overlooked in HIV research. We therefore isolated ECFC from people with HIV and people without HIV either with or without contemporary Pre-Exposure Prophylaxis (PrEP) exposure, to explore differences in ECFC biology



METHODS

- Whole blood was obtained from people with HIV on fully suppressive ART, people without HIV either accessing PrEP or not on PrEP attending Chelsea and Westminster Hospital NHS Foundation Trust.
- ECFC were isolated from peripheral blood mononuclear cells (PBMC)
- DNA and RNA was extracted from ECFC at passage 4
- Proviral HIV DNA was measured by qPCR
- mRNA expression of interferon (IFN) signalling, thrombo-inflammation and metabolic-mitochondrial markers was quantified by RT-PCR

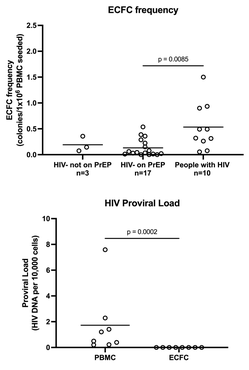


Endothelial colony-forming cells retain an interferon gene signature that positively correlates with inflammatory and metabolic gene expression. This may indicate an interferon-driven dysfunctional endothelial phenotype.

RESULTS

People with HIV Have an Elevated ECFC Frequency Compared to People without HIV and Do Not Contain Integrated Proviral HIV-1 in Genomic DNA in Isolated ECFC

	People without HIV not on PrEP (NP-ECFC)	People without HIV on PrEP (PrEP-ECFC)	People with HIV (HIV-ECFC)
n	3	17	10
Age (mean ±SD)	44 ±12.4 years	34 ±7.5 years	53 ±11.3 years
Sex (M:F)	3:0	17:0	8:2
Ethnicity	Asian (1), Caucasian (2)	Asian (1), Black (2), Caucasian (14)	Black (1), Caucasian (8), Mixed (1)
ART	-	TDF/FTC (17)	TAF/FTC (6), TDF/FTC (3), TDF/3TC (1), ATV (1), BIC (2), DRV/r (1), DOR (2), EFV (2), RAL (1), RIL (1)
Other medications	-	Sertraline (1), simvastatin (1)	Atorvastatin (2), levothyroxine (1), metformin (1), ticagrelor (1)



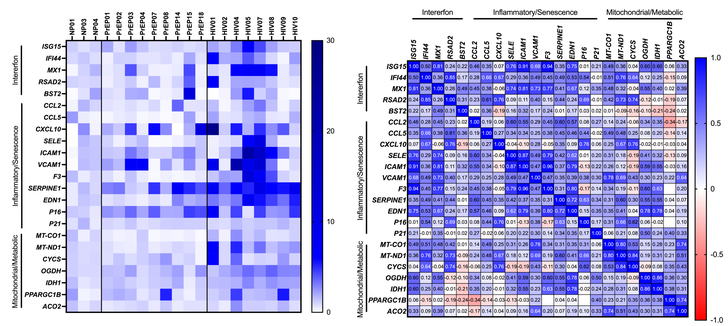
Whole blood was taken from 10 people with HIV, 17 people on PrEP and 3 people without HIV and not on PrEP. ECFC emerged in 10/10, 14/17 and 3/3 donors respectively. People with HIV had higher ECFC frequencies compared to people on PrEP (0.53 vs 0.13 vs colonies/1x10^6 PBMC, p=0.0085). In people with HIV, proviral HIV DNA was detected in matched PBMC but not in ECFC (1.7 vs 0.0 copies/10^4 cells, p=0.0002).

CONCLUSIONS

- People with HIV had higher ECFC frequencies
- Despite the absence of proviral HIV DNA, HIV-ECFC displayed an IFN gene signature
- ECFC IFN gene signature positively correlated with inflammatory and metabolic markers

Collectively, our observations indicate endothelial dysfunction in HIV-ECFC may be driven by IFN signalling. Further investigation is required to fully define mechanisms of endothelial dysfunction and to identify therapeutic targets in people with HIV.

ECFC Display Enriched Inflammatory and Metabolic Gene Expression That Correlates with IFN Gene Expression



HIV-ECFC had elevated IFN signalling, thrombo-inflammatory, mitochondrial and metabolic associated gene expression relative to NP- and PrEP-ECFC. IFN gene expression strongly correlated with inflammatory and metabolic genes.

ADDITIONAL KEY INFORMATION

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