



Increased Carotid Intima Media Thickness is Associated with Depletion of Circulating Myeloid Dendritic Cells in Patients on Suppressive Antiretroviral Treatment

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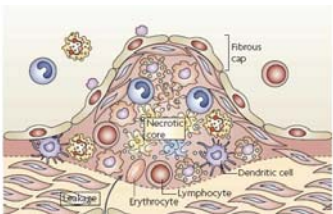
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Abstract

Background: The pathogenesis of accelerated atherosclerosis in HIV-infected patients has not well elucidated. Recent lines of evidence indicate that the accumulation of dendritic cells in the atheroma (DCs), especially myeloid DCs, could stimulate both T-cell recruitment and activation and may facilitate the release of chemokines, cytokines and other inflammatory mediators which are involved in the development and progression of HIV-associated atherosclerosis. We measured in patients on suppressive antiretroviral therapy (ART) circulating mDCs and pDCs and carotid intima media thickness (IMT), as marker for underlying atherosclerosis. **Methods:** The study population included 36 HIV-infected patients (23 M, 13 F; age range 35-61 years) on suppressive ART regimen (median CD4=355 cells/mm³). Controls were uninfected adults matched 1:1 to the HIV infected group by age, gender, race, body mass index (BMI) and traditional cardiovascular risk factors. pDCs and mDCs were assessed by using a new whole blood single-platform based on TruCOUNT assay. The carotid IMT was measured separately in both right and left sides (6 predefined segments per side) using a colour-doppler ultrasonography. The statistical analysis was done by the Mann-Whitney U test and the Spearman rank correlation test. **Results:** The average value of carotid IMT (mean±SE) was significantly higher in the HIV-infected patients versus healthy controls (0.79 vs 0.6) (p<0.01). Despite effective ART, patients exhibited a significant reduction of circulating pDCs and mDCs when compared with healthy donors. The median pDC counts were 2078 cells/ml in patients versus 10179 cells/ml of controls (p<0.001); the median mDC counts were 9453 cells/ml in patients versus 13265 cells/ml of controls (p<0.04). The lowest levels of DCs, especially mDCs, were found in patients who had a greater increase in carotid IMT. The analysis of the correlation showed a statistically inverse association between the carotid IMT and the absolute number of mDCs (r=-0.34; p=0.03). No significant correlation was found between circulating pDCs and carotid IMT. **Conclusions:** The present findings suggest that the depletion of DCs, especially, mDC in peripheral blood correlates with accelerated atherosclerosis in HIV-infected patients in spite of a suppressive ART regimen. It is possible a recruitment of mDCs in the atheroma where these cells contribute to the tissue inflammation and atherosclerotic plaque destabilization.

Background and Objectives

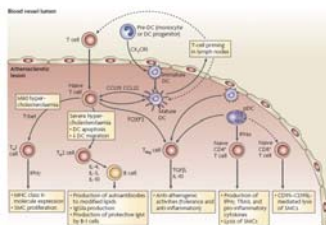


•Antiretroviral drugs, HIV itself and/or HIV-associated immune activation and inflammation have all been implicated in the development of atherosclerosis.

•Interactions between circulating mononuclear cells and vascular endothelium and evidence of infiltrating inflammatory cells are important events in the pathogenesis of atherosclerosis.

Inflamed plaques contain subsets of fully matured and activated DCs (CD11c+), regulating the adaptive and innate immune system during atherosclerotic process and plaque destabilization.

Recently, a significant decrease in circulating mDC precursors with increased detection in atherosclerotic plaques found in patients with cardiovascular disease.



Objectives

We investigated the correlation between circulating pDC and mDC, carotid intima media thickness (IMT) and biomarkers of inflammation in ARV-treated patients with undetectable viremia

Study population

•36 HIV-infected patients (23 males, 13 females; age range 35–61 years) treated with ART since at least 24 months aviremic with a median CD4 of 355 cells/l:

• 5 subjects received a non nucleoside reverse transcriptase (NNRTI)-based regimen (mean duration of therapy 9±2.5 year)
•31 patients were treated with a protease inhibitor (PI)-based regimen. (mean duration of therapy 4±1.5 years)

•36 controls uninfected adults matched 1:1 to the HIV-infected group by age, gender, race, body mass index (BMI) and traditional cardiovascular risk factors.

Current smoking was present in patients, while there was no history of angina, myocardial infarction, cardiovascular medication or other atherogenic risk factors.

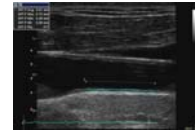
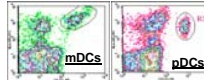
Methods

•DC enumeration: Whole blood Trucount assay with CD45, HLA-DR, Lineage, CD11c, CD123 (BD)

•Levels of hs-CRP were measured by a turbidimetric assay (Tina-quant CRP);

•TNF- α was assessed by ELISA (R&D Systems).

•The carotid IMT (mm) was measured separately in both right and left sides (6 predefined segments per side) using a colour-doppler ultrasonography.

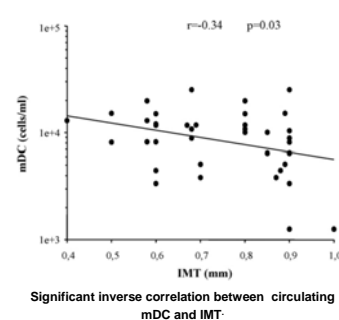
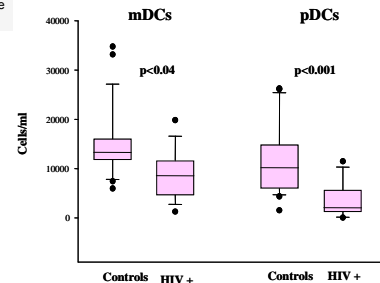


Results

Laboratory values of HIV-infected patients and control subjects (mean \pm S.D.).

	HIV+ patients (n=36)	Controls (n=36)	p
Total cholesterol, mg/dl	197 \pm 58	183 \pm 7.9	0.43
HDL-cholesterol, mg/dl	43 \pm 8.2	22 \pm 3.8	0.31
LDL-cholesterol, mg/dl	114 \pm 51.1	101 \pm 5.9	0.11
Triglyceride, mg/dl	200 \pm 21.1	75 \pm 5.8	<0.001
Blood glucose, mg/dl	93 \pm 18.3	95 \pm 9.1	0.42
Leukocytes/ μ l	6806 \pm 2182	7143 \pm 2078	0.15
hs-CRP, mg/l	7 \pm 3.8	1.3 \pm 0.7	<0.001
Fibrinogen, mg/dl	243 \pm 93.4	240 \pm 87	0.11
D-dimer, ng/ml	140 \pm 13.2	129 \pm 12.2	0.30

HIV-infected patients had higher levels of hs-CRP, while TNF- α was undetectable



Significant inverse correlation between circulating mDC and IMT

Conclusions

- We have shown that the depletion of mDCs in peripheral blood correlates with accelerated atherosclerosis in HIV-infected patients in spite of a suppressive ART regimen.
- It is possible that mDC may be recruited in inflamed tissue, such as atherosclerotic plaques, with the creation of the microenvironment typically encountered in lymphoid tissues.
- The accumulation of DCs in the atheroma could stimulate both T cell recruitment and activation and may facilitate the release of chemokines, cytokines and other inflammatory mediators which are involved in the development and progression of HIV-associated atherosclerosis.
- Future studies are needed to investigate the recruitment and functional profile of DCs in atherosclerotic plaques from patients with HIV infection and the dynamic measurements of DC numbers and IMT at different time points of disease.

References

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