755: Inflammatory Biomarkers in Chronic HIV Disease Associate With Monocyte Activation

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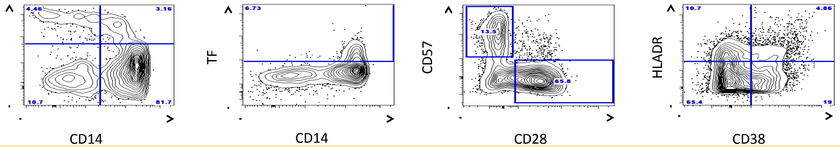
Background

Soluble biomarkers of inflammation independently predict non-AIDS related morbidity and mortality. We explored associations between select biomarkers and cellular immunophenotypes to identify potential mechanisms of excess inflammation among HIV-infected adults.

Methodology

Baseline plasma specimens from SUN Study participants were analyzed for levels of IL-6, hsCRP, soluble (s) CD14, sCD163, and D-dimer. We performed immunophenotyping for markers of T cell activation and maturation (HLA-DR, CD38, CX3CR1, CD28, CD57) and monocyte activation and migration (CCR2, CD14, CD16, tissue factor [TF], CX3CR1, CCR5). Sample plots are shown in Figure 1. We evaluated associations between cellular phenotypes and soluble markers by Spearman rank correlation. Linear regression was used to estimate the percent change in plasma biomarker level for each 5 unit difference in cellular phenotype, after adjustment for age, gender, race, smoking, diabetes, treatment for hypertension or hyperlipidemia, hepatitis, CD4 cell count, and HIV RNA <400 copies/mL. Due to multiple comparisons, we defined significance as p-value ≤0.01.

Figure 1. Sample flow cytometry plots of selected immunophenotypes



Results

Participants' median age was 41 years and CD4 count 471 cells/μL; 76% were male, 44% smokers, 88% on ART, and 72% had HIV RNA <400 copies/mL (Table 1).

Table 1. Clinical Characteristics of study participants

Clinical Characteristic	N=670
Age, median yrs (IQR)	41 (35-47)
Male sex, n (%)	510 (76.1)
Ethnicity, n (%)	
Non-Hispanic white	390 (58.2)
Non-Hispanic black	201 (30.0)
Other	79 (11.8)
BMI, median kg/m^2 (IQR)	25.8 (23.0-29.0)
Current tobacco use, n (%)	288 (44.1)
Intravenous drug use, n (%)	89 (13.6)
Viral hepatitis B or C co-infection, n (%)	112 (17.0)
Diabetes Mellitus, n (%)	59 (8.8)
Hypertension, n (%)	213 (31.8)
Treatment for Hyperlipidemia, n (%)	57 (8.5)
Previous AIDS diagnosis, n (%)	164 (24.5)
Prescribed ART, n (%)	590 (88.1)
Duration of ART, median months (IQR)	32.5 (13.0-64.9)
Plasma HIV RNA <400 copies/mL, n (%)	489 (73.2)
Current CD4 count, median cells/mm^3 (IQR)	471 (336-680)
Nadir CD4 count, median cells/mm^3 (IQR)	206 (90-319)
HIV RNA <400 copies/mL (%)	314 (72)
ART exposure, median years (IQR)	2.8 (1.1-5.4)

Results

Correlations of biomarkers with select cellular phenotypes from univariate models are shown in Figure 2.

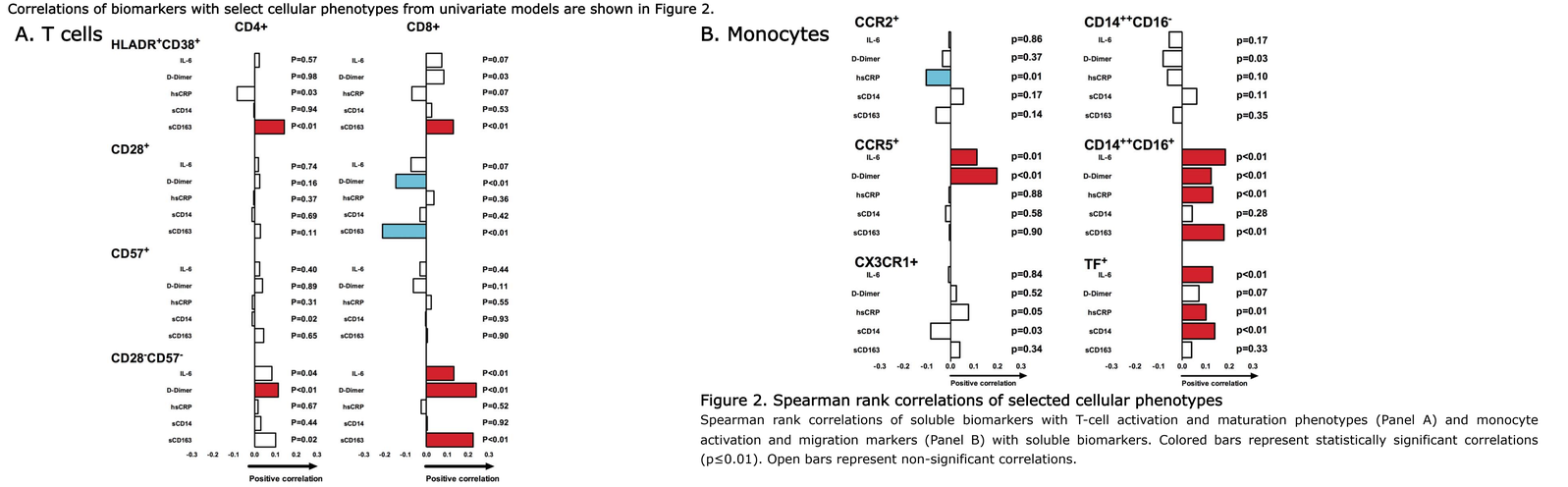


Figure 2. Spearman rank correlations of selected cellular phenotypes

Spearman rank correlations of soluble biomarkers with T-cell activation and maturation phenotypes (Panel A) and monocyte activation and migration markers (Panel B) with soluble biomarkers. Colored bars represent statistically significant correlations (p≤0.01). Open bars represent non-significant correlations.

In fully adjusted models, shown in Table 2, a 5 unit greater frequency of CD14^{++}CD16^{+} monocytes was associated with 11.4% higher IL-6 (p<0.001), 27.5% higher D-dimer (p<0.001), and 10.9% higher hsCRP (p<0.01); a corresponding difference of monocytes expressing CCR2 was associated with 6.9% lower D-dimer (p<0.01) and CCR5 with 1.4% higher sCD163 (p<0.001). Of T-cell subsets, greater frequencies of CD4^{+}HLADR^{+}CD38^{+} T-cells were independently associated with higher sCD163 (5.1%, p<0.001) and CD8^{+}CD28^{+} T-cells with lower sCD163 (3.0%, p=0.001) and D-dimer (1.2%, p=0.001).

Table 2. Multivariate analysis of percent change in plasma biomarkers for each absolute 5% increase in cellular phenotype

	IL-6			D-dimer			hsCRP			sCD14			sCD163		
	Percent Change	95% Confidence Interval	P	Percent Change	95% Confidence Interval	P	Percent Change	95% Confidence Interval	P	Percent Change	95% Confidence Interval	P	Percent Change	95% Confidence Interval	P
Monocytes															
CD14^{++}CD16^{+}	**11.4**	**4.9 – 18.3**	**<0.001**	2.3	-0.7 – 5.4	0.13	**27.4**	**16.3 – 39.7**	**<0.001**	2.2	-0.6 – 5.0	0.12	**10.9**	**3.3 – 19.1**	**<0.01**
TF+	-0.5	-4.2 – 3.4	0.81	-0.1	-2.0 – 1.8	0.93	1.8	-4.0 – 8.0	0.55	-0.1	-1.8 – 1.7	0.93	-2.6	-6.9 – 1.9	0.25
CCR2+	-2.1	-5.0 – 0.8	0.16	-0.8	-2.3 – 0.7	0.3	**-6.9**	**-11.2 – -2.4**	**<0.01**	0.0	-1.4 – 1.4	0.98	-4.2	-7.5 – -0.7	0.02
CCR5+	0.8	-0.7 – 2.4	0.29	**1.4**	**0.7 – 2.2**	**<0.001**	-0.1	-2.5 – 2.3	0.92	0.0	-0.7 – 0.7	0.96	0.4	-1.5 – 2.2	0.70
T cells															
CD4^{+}HLADR^{+}CD38^{+}	0.0	-2.2 – 2.3	0.97	-0.1	-1.2 – 1.0	0.87	-0.9	-4.3 – 2.7	0.63	0.4	-0.7 – 1.4	0.49	**5.1**	**2.3 – 8.0**	**<0.001**
CD4^{+}CD28^{+}	-0.4	-1.6 – 0.8	0.49	-0.6	-1.2 – 0.0	0.04	1.3	-0.6 – 3.3	0.17	-0.1	-0.6 – 0.5	0.81	-0.4	-1.8 – 1.0	0.56
CD4^{+}CD28^{-}CD57^{-}	2.0	-0.5 – 4.5	0.12	1.5	0.2 – 2.8	0.02	-0.5	-4.4 – 3.5	0.80	1.0	-0.2 – 2.1	0.10	1.7	-1.2 – 4.7	0.26
CD8^{+}HLADR^{+}CD38^{+}	0.5	-0.9 – 1.9	0.50	0.7	0.0 – 1.4	0.05	-0.09	-3.1 – 1.4	0.44	0.5	-0.1 – 1.2	0.12	0.4	-1.3 – 2.1	0.65
CD8^{+}CD28^{+}	-1.5	-2.9 – -0.1	0.04	**-1.2**	**-1.9 – -0.5**	**<0.01**	-0.2	-2.4 – 2.1	0.89	-0.5	-1.1 – 0.2	0.15	**-3.0**	**-4.6 – -1.4**	**<0.001**
CD8^{+}CD28^{-}CD57^{-}	1.4	-0.3 – 3.1	0.10	**2.8**	**1.9 – 3.6**	**<0.001**	0.1	-2.6 – 2.8	0.97	0.1	-0.6 – 0.9	0.71	**3.3**	**1.3 – 5.4**	**<0.01**

In data from the control arms of the ESPRIT/SILCAAT/SMART clinical trials, the degree of the associations with IL-6 levels we described for an absolute difference of 5% in the frequency CD14++CD16+ cells corresponds with a difference of 15% in risk for serious non-AIDS events or all-cause mortality.

Conclusions

Plasma biomarkers that strongly predict clinical risk for non-AIDS morbidity were consistently and strongly associated with monocyte activation phenotypes and modestly with T-cell maturation, but not CD8+ T-cell activation, phenotypes. These findings may help direct treatment strategies to control persistent inflammation in chronic HIV disease.