ACBP and control of HIV in progressors and elite controllers

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INTRODUCTION

HIV elite controllers (EC) are a rare subgroup of people living with HIV (PLWH) who control HIV replication in absence of antiretroviral therapy (ART). ECs are characterized by an heighten anti-HIV immune response controlling HIV replication. Specific genetic and immunometabolic factors are associated with such control. For instance, certain alleles of human leukocyte antigens (HLA) such as HLA B27 and B57 allow strong CD4 and CD8 T-cell responses. Also, certain immunometabolic pathways are linked with establishment and persistence of such T-cell responses. Autophagy is one such metabolic pathway that contribute to HIV control by potentiating anti-HIV CD4 and CD8 T-cell responses.

Autophagy is a cellular pathway using lysosomal catabolism of cytosolic structures to produce energy independently nutrient input. Acyl-coenzyme A binding protein (ACBP), also known as diazepam binding inhibitor (DBI), is one of the regulators of autophagy. Intracellularly, ACBP favors bioenergetic autophagic reactions by shuttling activated acyl-CoA-bound lipids to cellular organelles. However, when ACBP is secreted in the extracellular space, ACBP inhibits autophagy and increase appetite.

We and other have shown that autophagy and glutaminolysis are linked with IL21 production by CD4 T-cells allowing efficient CD8 T-cell responses (Loucif et al. Autophagy 2021).

As autophagy is elevated in EC and is regulated in part by ACBP, we assessed the influence of ACBP in different groups of people living with HIV (PLWH) receiving or not antiretroviral therapy (ART). We assess extracellular ACBP levels in plasma and intracellular levels in blood cells.

MATERIAL AND METHODS:

Plasma levels of ACBP and inflammatory cytokines were assessed by ELISA in 37 EC, 27 ART-naïve, and 55 ART-treated PLWH, compared to 31 HIV-uninfected controls from the Canadian HIV and Aging Cohort, the Primary HIV infection cohort and the HIV pathogenesis biobank, all in Montreal, QC, Canada. Participant characteristics are indicated below.

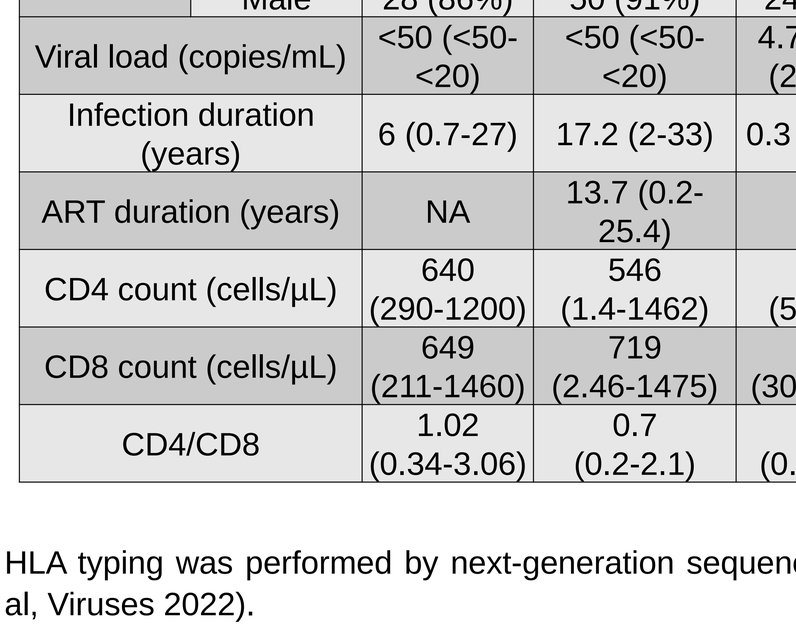
		Elite controlers	HIV ART+	HIV untreated	Control without HIV	P value
Number of participant		37	55	27	31	
Age		45.5 (25-72)	54 (26-74)	34 (21-60)	52 (23-75.5)	<0.001
Sex	Female	9 (24%)	5 (9%)	3 (11%)	8 (26%)	0.09
	Male	28 (86%)	50 (91%)	24 (89%)	23 (74%)	
Viral load (copies/mL)		<50 (<50-<20)	<50 (<50-<20)	4.7 Log10 (2.8-5.9)	NA	NA
Infection duration (years)		6 (0.7-27)	17.2 (2-33)	0.3 (0.1-13)	NA	<0.0001
ART duration (years)		NA	13.7 (0.2-25.4)	NA	NA	NA
CD4 count (cells/µL)		640 (290-1200)	546 (1.4-1462)	310 (57-910)	827 (281-1173)	<0.0001
CD8 count (cells/µL)		649 (211-1460)	719 (2.46-1475)	900 (300-2832)	391 (188-1245)	0.0002
CD4/CD8		1.02 (0.34-3.06)	0.7 (0.2-2.1)	0.4 (0.05-1.2)	2.1 (0.38-3.98)	<0.0001

HLA typing was performed by next-generation sequencing in PBMCs (see Isnard et al, Viruses 2022).

Plasma levels of cytokines were assessed using multiplexed ELISA. Plasma levels of ACBP (DBI) were assessed using ELISA.

Intracellular ACBP levels were measured by flow cytometry in PBMCs using the BD Biosciences Fortessa X20 cytometer and FlowJo for the analysis.

An alpha levels of 5% was considered for statistical analyses using Spearman's test for correlations, Kruskal Wallis' or Mann-Whitney's tests for comparisons of groups.



RESULTS

Figure 1: Plasma levels of ACBP are lower in ECs compared to ART-naïve or ART-treated PLWH.
Those with protective HLA B27, B57 and/or B58 had a tendency to have lower plasma levels of ACBP.

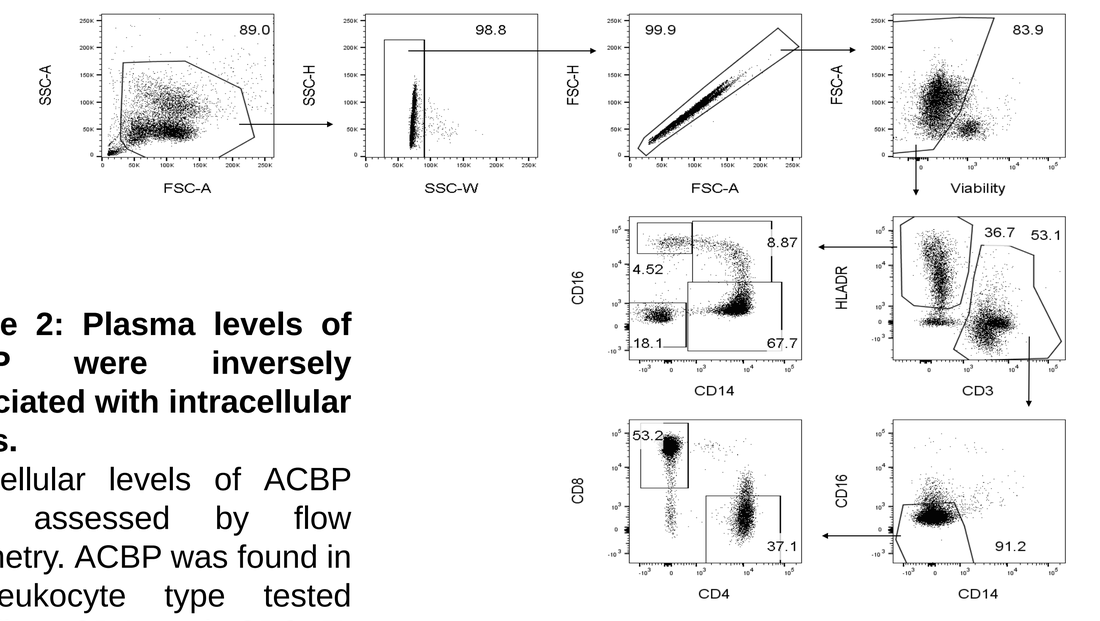


Figure 2: Plasma levels of ACBP were inversely associated with intracellular levels.
Intracellular levels of ACBP were assessed by flow cytometry. ACBP was found in all leukocyte type tested including CD4 and CD8 T-cells, B cells, Dendritic cells (DC), classical, intermediate and non-classical monocytes. Intracellular ACBP levels correlated negatively with levels in intermediate monocytes and CD4 T-cells suggesting that low plasma ACBP levels are associated with cellular retention of the protein.

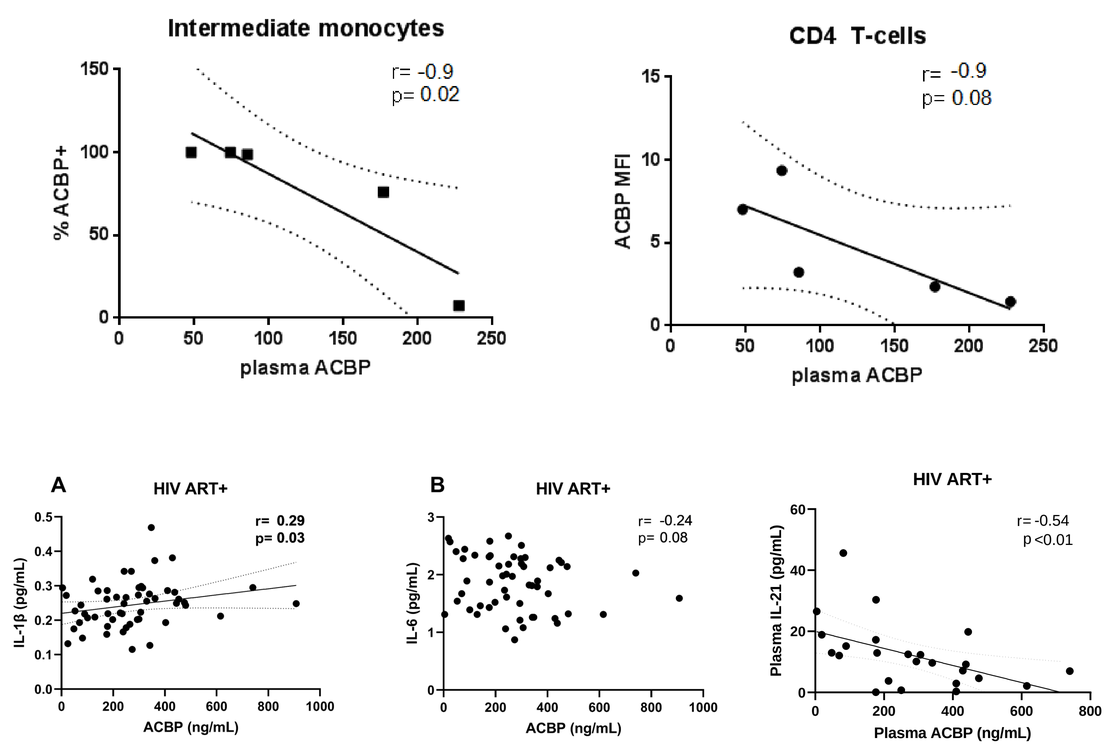


Figure 3: Plasma levels of ACBP were linked with some inflammation markers, and inversely linked with IL21 levels.
Plasma ACBP levels were associated with IL1β levels but not IL6.
Plasma ACBP levels correlated negatively with IL21 levels.

CONCLUSION

Our results suggest that high ACBP levels in ART-treated PLWH seemed associated with lack of cellular retention of the protein and lower autophagy activity. Secretion of ABCP in the extracellular space appeared associated with some innate inflammation markers. Altogether, our results suggest that ART-treated PLWH with high plasma ACBP levels have low levels of autophagy and IL21 production, possibly linked with lower anti-HIV T-cell function. The ACBP pathway represents an interesting target to potentiate anti-HIV immune responses.

Acknowledgments: The authors are highly grateful to the study participants for their contributions, as well as Angie Massicotte, Josée Girouard, Stéphanie Matte, Louise Gilbert, Mario Legault, Cezar Iovi, and Olfa Debbeche for study coordination and assistance

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