Circulating Acyl-CoA-Binding Protein abates T-cell function in people living with HIV

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BACKGROUND

Autophagy = degradation pathway degrading cytosolic cellular structures to produce energy and regulate cellular pathways.
Autophagy allows the production of IL21 by CD4 T-cells and efficient cytolytic responses by CD8 T-cells (*Loucif, Autophagy 2021*).
→ Autophagy and IL-21 production → efficient anti-HIV T-cell responses in Elite controllers, as compared to people living with HIV (PLWH) receiving anti-retroviral therapy (ART).
→ Autophagy is in part regulated by the acyl-CoA-binding protein (ACBP) which has two functions.

- Intracellular ACBP ↗ autophagy by shuttling activated Acyl-CoA bound lipids to cellular organelles
- Secreted extracellular ACBP ↘ autophagy and ↗ appetite.

Herein, we assessed whether autophagy and the ACBP pathway were associated with T-cell function in PLWH.

METHODS

- Plasma and peripheral blood mononuclear cells (PBMCs) were obtained from 37 Elite controllers, 55 long term ART-treated PLWH and 31 uninfected controls.
- ACBP and cytokines levels were quantified in plasma by ELISA and multiplexes assays.
- Intracellular levels of cytokines, ACBP and LC3II were assessed by flow cytometry.
- PBMCs from uninfected controls were stimulated with PMA+ionomycin or HIV peptides (Gag, Pol, Env, Nef) for 16-18h in the presence of brefeldin A (BFA). Recombinant ACBP was added at the indicated concentration for 16-18h.
- Metabolites were quantified in serum samples by GC-MS.

DEMOGRAPHICS

		Elite controllers	HIV ART+	Control without HIV
Number of participants		37	55	31
Age		45.5 (25-72)	54 (26-74)	52 (23-75.5)
Sex	Female	9 (24%)	5 (9%)	8 (26%)
	Male	28 (86%)	50 (91%)	23 (74%)
Viral load (copies/mL)		<50 (<20-<50)	<50 (<20-<50)	NA
Infection duration (years)		6 (0.7-27)	17.2 (2-33)	NA
ART duration (years)		NA	13.7 (0.2-25.4)	NA
CD4 count (cells/µL)		640 (290-1200)	546 (1.4-1462)	827 (281-1173)
CD8 count (cells/µL)		649 (211-1460)	719 (2.46-1475)	391 (188-1245)
CD4/CD8		1.02 (0.34-3.06)	0.7 (0.2-2.1)	2.1 (0.38-3.98)

Circulating ACBP levels are elevated in people living with HIV in the chronic phase of the infection, on ART or not. Plasma ACBP levels are linked with inflammation and markers of immune dysfunction. *In vitro*, mimicking extracellular ACBP using recombinant ACBP decreased T-cell responses, including against HIV-peptides. Hence, extracellular ACBP is a target to improve immune function in PLWH, towards an HIV cure.

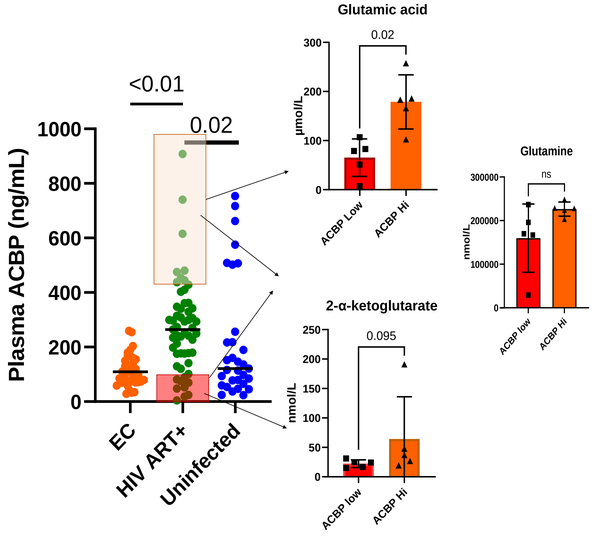


Figure 1: Plasma ACBP levels were higher in ART-treated PLWH, associated with variation in circulating metabolites.
Left: plasma ACBP levels. Kruskal-Wallis' test with Dunn's post test. Multivariable analyses: age, sex and weight did not influence these differences.
Right: metabolomics in serum in 5 participants with high (orange) or low (red) ACBP levels. Mann Whitney's test.

Plasma levels of ACBP vs. other markers			
PLWH ART+	Factor	Slope	P-value
Growth factor	G-CSF	**0.48**	**0.002**
	GM-CSF	**0.44**	**0.006**
Homeostatic factors	IL-7	**0.48**	**0.002**
	IL-15	**0.4**	**0.012**
Inflammation	IFN-α2	**0.37**	**0.02**
	IFN-γ	**0.4**	**0.01**
	IL-1β	**0.43**	**0.007**
	sCD40L	**0.67**	**0.003**
Immune function	**IL-21**	**-0.54**	**<0.001**

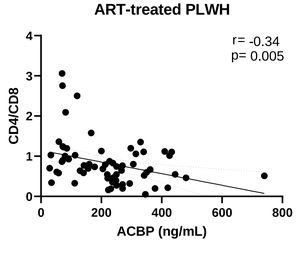
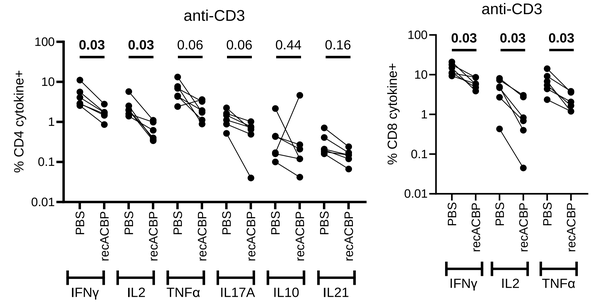


Figure 2: Plasma ACBP levels in ART-treated PLWH correlated with CD4/CD8 ratio and plasma inflammatory markers, but correlated inversely with plasma IL21-levels.
Multivariable analysis indicated independence of these correlations with age and sex. Spearman's test.



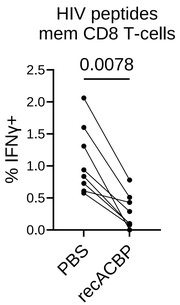


Figure 3: Extracellular ACBP decreases polyclonal and HIV-specific T-cell responses.
10µg/mL of recACBP were added to PBMCs from ART-treated donors, stimulated with anti-CD3 (1µg/mL) or HIV peptides (Gag, Env, Pol, Nef) for 18 hours in the presence of brefeldin A (5µg/mL). Flow cytometry was used to assess intracellular production of indicated cytokines in memory CD4 or CD8 T-cells. Wilcoxon's tests.

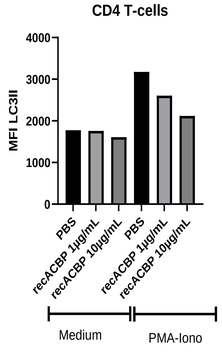


Figure 4: Extracellular ACBP decreases autophagy upon CD4 T-cells activation. PBMCs from health donors were stimulated or not for 18 hours. LC3II(B) fluorescence intensity, a marker of autophagy, was assessed by flow cytometry. One experiment representative of 2.

CONCLUSIONS

Extracellular ACBP inhibits autophagy and prevents efficient immune responses in ART-treated PLWH.
↗ plasma levels of ACBP → ↘ intracellular levels = cellular retention of the protein in EC and some ART-treated PLWH.
↗ plasma levels of ACBP → ↗ inflammation
↗ circulating ACBP levels are associated with ↘ IL-21 levels
➔ Targeting extracellular ACBP with blocking antibodies would increase autophagy and promote efficient immune responses in PLWH.

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