AUTOPHAGY AND ACYL-COA BINDING PROTEIN INFLUENCE COVID-19 SEVERITY

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BACKGROUND

Autophagy, a cytosolic-structure degradation pathway degrading cellular structures to produce energy and regular cellular pathways.

Autophagy allows the production of IL21 by CD4 T-cells and efficient cytolytic responses by CD8 T-cells (Loucif, Autophagy 2021).

Autophagy is in part regulated by acyl-CoA-binding protein (ACBP) which has two functions.

- Intracellular ACBP favors autophagy by shuttling activated Acyl-coA bound lipids to cellular organelles
- Secreted extracellular ACBP inhibits autophagy and increase appetite.

Herein, we assessed whether autophagy and the ACBP pathway were associated with COVID-19 severity.

METHODS

- Samples and data collected from acute participants during hospitalization through the BQC-19 Quebec biobank. 903 COVID-19 positive participants included (all data available in February 2023), collected between March 2020 and December 2021. Patients were categorized based on WHO severity criteria.
- Somalogic Somascan proteomic assay was performed in plasma: more than 5200 proteins identified and quantified.
- In vitro assays were performed on PBMC from heathy donors, stimulated with phorbol-myristate acetate (PMA) + ionomycine for 16-18h in the presence or absence of brefeldin A (BFA). Recombinant ACBP was added at the indicated concentration for 16-18h. Flow cytometry was used to assess intracellular levels of LC3II, an autophagy marker, as well as IL-21 in CD3+CD4+CD8- T-cells.

DEMOGRAPHICS

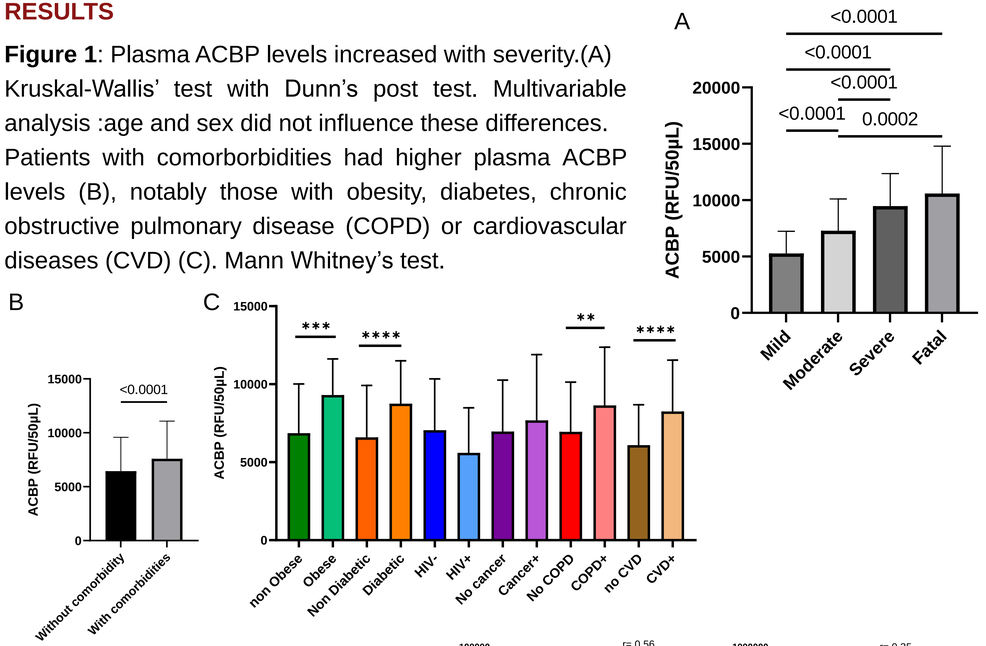
	COVID-19+				
Groups	Mild	Moderate	Severe	Fatal	**All**
n	259	384	236	24	**903**
Age (median, years)	54.3	67.3	65.6	74.3	**61.9**
% Female	58	49	33	42	**48**
% with comorbidities	46	58	55	75	**55**
Plasma ACBP	5.3	7.3	9.5	10.6	**7.0**
Plasma IL6	0.34	0.60	0.85	1.6	**0.54**
Plasma IL21	0.76	0.72	0.66	0.65	**0.71**

Plasma ACBP, IL6 and IL21 levels: medians, RFU/50uL

Plasma ACBP levels were higher with COVID-19 severity, **suggesting that autophagy and IL-21 allow control of SARS-CoV-2 infection**. ACBP is a **targetable autophagy checkpoint** and inhibition of extracellular ACBP could improve SARS-CoV-2 immune control.

RESULTS

Figure 1: Plasma ACBP levels increased with severity.(A) Kruskal-Wallis' test with Dunn's post test. Multivariable analysis :age and sex did not influence these differences. Patients with comorbidities had higher plasma ACBP levels (B), notably those with obesity, diabetes, chronic obstructive pulmonary disease (COPD) or cardiovascular diseases (CVD) (C). Mann Whitney's test.



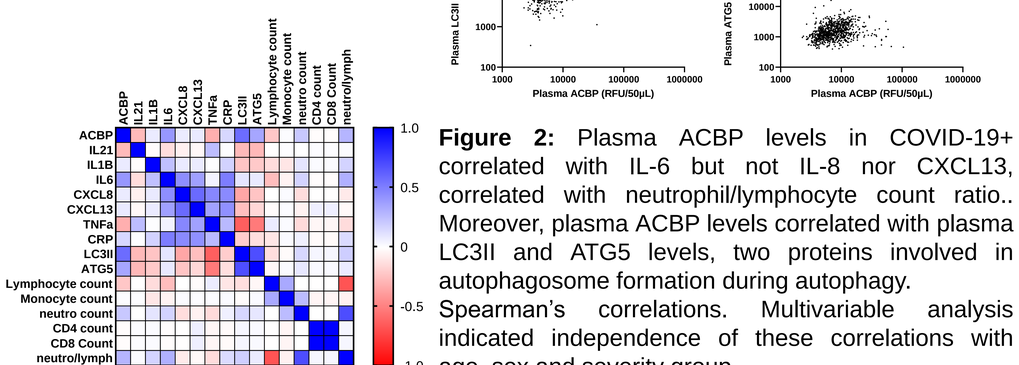


Figure 2: Plasma ACBP levels in COVID-19+ correlated with IL-6 but not IL-8 nor CXCL13, correlated with neutrophil/lymphocyte count ratio.. Moreover, plasma ACBP levels correlated with plasma LC3II and ATG5 levels, two proteins involved in autophagosome formation during autophagy. Spearman's correlations. Multivariable analysis indicated independence of these correlations with age, sex and severity group.

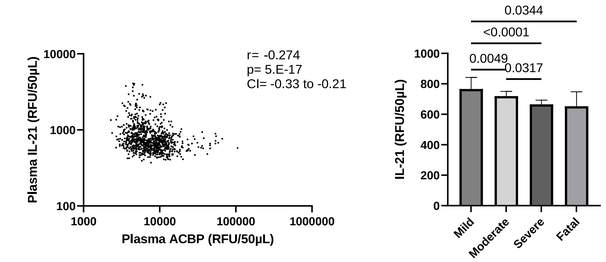


Figure 3: Plasma ACBP levels in COVID-19+ inversely correlated with IL-21 levels. Spearman's correlations. Multivariable analysis indicated independence of these correlations with age, sex and severity group. Plasma IL-21 levels were slightly different between groups. Kruskal-Wallis' test.

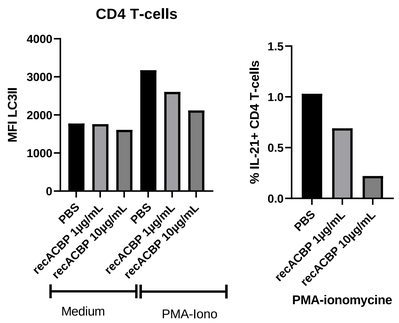


Figure 4: In vitro addition of recombinant ACBP to PBMC culture medium decreased intracellular autophagy marker LC3II and IL-21 production in CD4 T-cells. One experiment representative of 2.

CONCLUSIONS

Autophagy allows efficient immune responses with low inflammation. Extracellular ACBP inhibits autophagy

During acute COVID-19:

↗ plasma levels of ACBP → ↗ inflammation and more severe prognostic.

↗ circulating ACBP levels are associated with ↘ IL-21 levels

→ Targeting extracellular ACBP with blocking antibodies would increase autophagy and promote efficient immune responses in COVID-19

ADDITIONAL KEY INFORMATION

Additional Resources: https://en.quebeccovidbiobank.ca/

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