HelmholtzZentrum münchen
German Research Center for Environmental Health

Scientific Highlight April 2016

☒ co-ordinated with the Director of the Institute / Research Unit

Institute of Lung Biology and Disease

PSP-Element:
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Title of the highlight:
Metabolomics screening identifies reduced L-carnitine to be associated with progressive emphysema.

Keywords:
COPD, metabolome, biomarkers, apoptosis

Central statement of the highlight in one sentence:
The progression of emphysema, a severe chronic lung disease, was found to be associated with reduced lung tissue specific L-carnitine in a clinically relevant mouse model and supplemention with this metabolite improved lung function and impaired disease progression.

Text of the highlight:
Chronic obstructive pulmonary disease (COPD), a leading cause of chronic morbidity and mortality worldwide, is characterized by chronic bronchitis and emphysema. Emphysema is the destruction of alveolar structures, leading to enlarged airspaces and reduced surface area impairing the ability for gaseous exchange.
To further understand the pathological mechanisms underlying progressive emphysema we used mass spectrometry–based approaches to quantitate the lung, bronchoalveolar-lavage fluid (BALF) and serum metabolome during emphysema progression in the established murine porcine pancreatic elastase (PPE) model. Partial Least Square analysis revealed greater changes in the metabolome of lung followed by BALF rather than serum during emphysema progression. Furthermore, we demonstrate for the first time that emphysema progression is associated with a reduction in lung specific L-carnitine, a metabolite critical for transporting long chain fatty acids into the mitochondria for their subsequent β-oxidation and a reported protector against apoptosis.

Moreover, PPE-treated mice demonstrated impaired lung function compared to PBS treated controls, which improved following supplementation with L-carnitine and was associated with a reduction in apoptosis.
In summary, our results provide a new insight into the role of L-carnitine and, importantly, suggest novel therapeutic avenues for COPD.

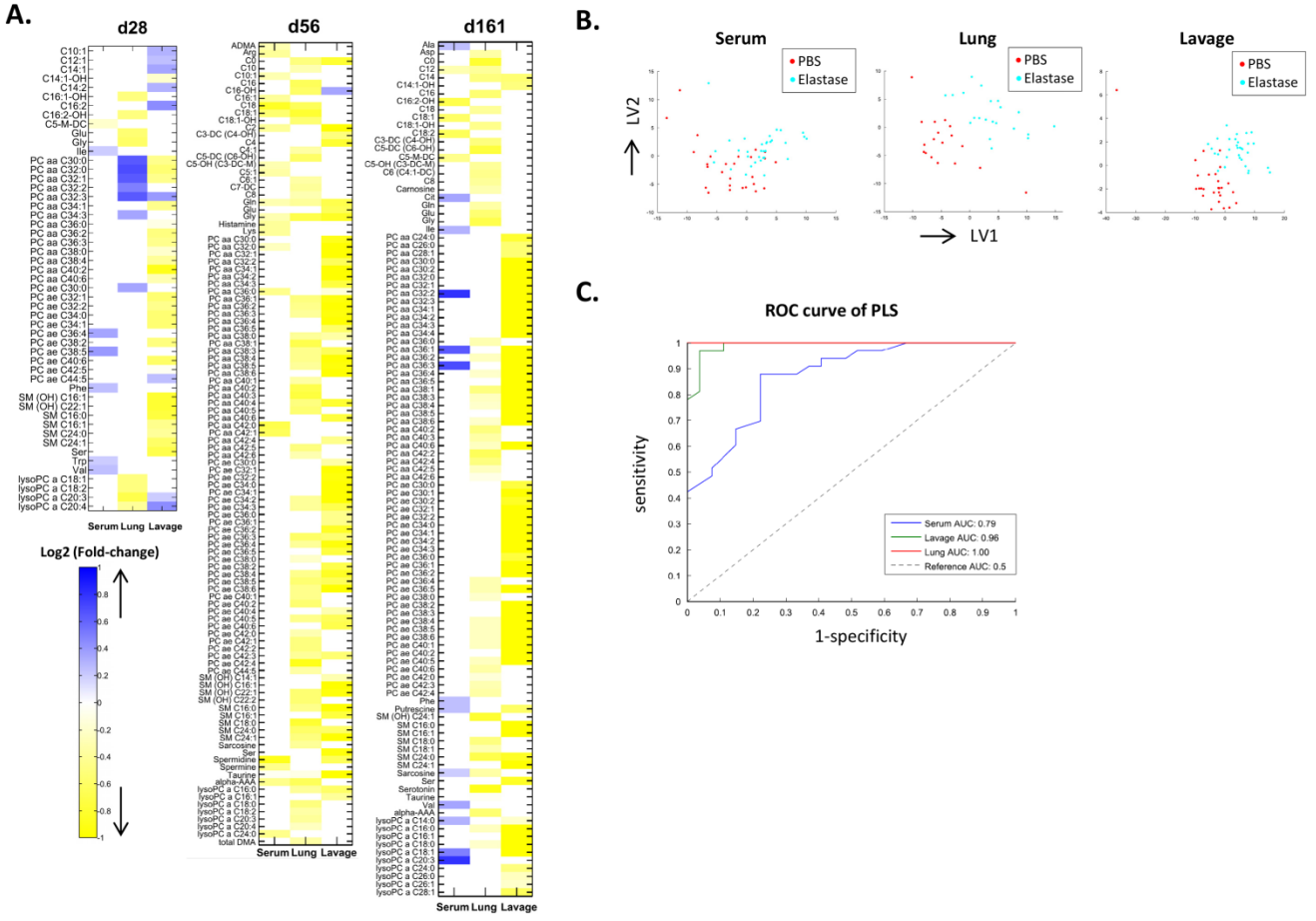
Publication:
Metabolomics screening identifies reduced L-carnitine to be associated with progressive emphysema. Conlon TM, Bartel J, Ballweg K, Günter S, Prehn C, Krumsiek J, Meiners S, Theis FJ, Adamski J, **Eickelberg O, Yildirim AÖ**. Clin Sci (Lond). 2016 Feb 1;130(4):273-87.

Taking account of the HMGU mission:
Currently available treatment for COPD is only able to alleviate symptoms and the exact molecular mechansims underlying disease pathogenesis are yet to be fully elucidated. For the first time, we use targeted metabolomics to assess changes in the metabolome locally to the lung and systemically in serum during disease progression, highlighting novel metabolite changes that could be explored for therapeutic potential in patients.

The internal HMGU co-operation partners with whom the highlight was compiled, if appropriate:
Jörg Bartel, Dr. Jan Krumsiek & Prof. Dr. Fabian J. Theis, Institute of Computational Biology.
Dr. Cornelia Prehn & Prof. Dr. Jerzy Adamski, Institute of Experimental Genetics, Genome Analysis Center.

Metabolomics screening identifies reduced L-carnitine to be associated with progressive emphysema

iLBD/CPC



Targeted metabolomics reveals that there are greater changes in the metabolome local to the lung than in the serum during the progression of PPE-induced emphysema. Metabolomics screening using the AbsoluteIDQTM p180 Kit followed by mass spectrometric analysis of serum, BALF and lung homogenate was undertaken. A: Heat maps demonstrating the mean relative fold change in individual metabolite concentrations in mice exposed to PPE compared to PBS controls at the time points indicated. A white box means the metabolite was not significantly altered in that tissue at that time point ($P > 0.05$, t-test) following univariate analysis. A blue box represents an increase in the metabolite and yellow a decrease. B: Two dimensional partial least square analyses of all metabolites in all mice at every time point. Each dot represents an individual mouse. LV, latent variable. C: Receiver operating characteristics (ROC) curve generated from 5 fold cross validation of the PLS analysis. A representative model for each tissue type is shown plus a reference curve, along with the area under the curve (AUC).

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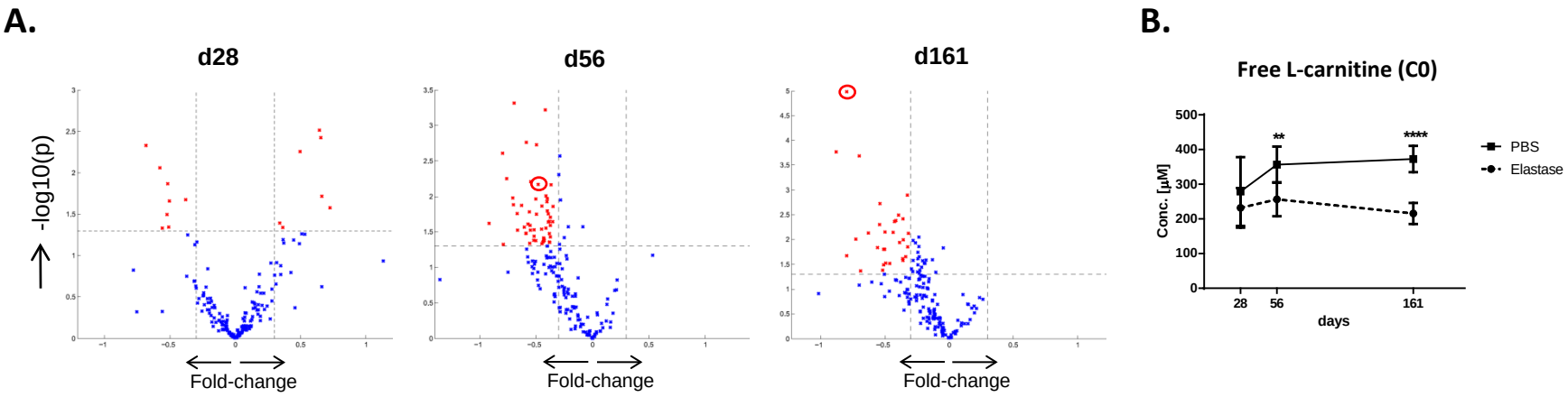

L-carnitine is the most significantly altered lung metabolite during emphysema progression. A: A plot of the mean $\log_2$(relative fold change) versus $-\log_{10}$(P) for each individual metabolite at the time point indicated in lung tissue, from PPE-treated mice compared to PBS controls. Significance was taken as $P < 0.05$ (t-test) and a fold change > 0.3 in either direction, as indicated by the red data points and hatched lines. Free L-carnitine (C0) is highlighted by a red circle. B: The concentration of free L-carnitine (C0) in lung tissue. Data shown is the mean value ± SD from 6-11 mice per group at each time point taken from the AbsoluteIDQTM p180 metabolomics screen, with **P < 0.01, ****P < 0.0001 following t-test.

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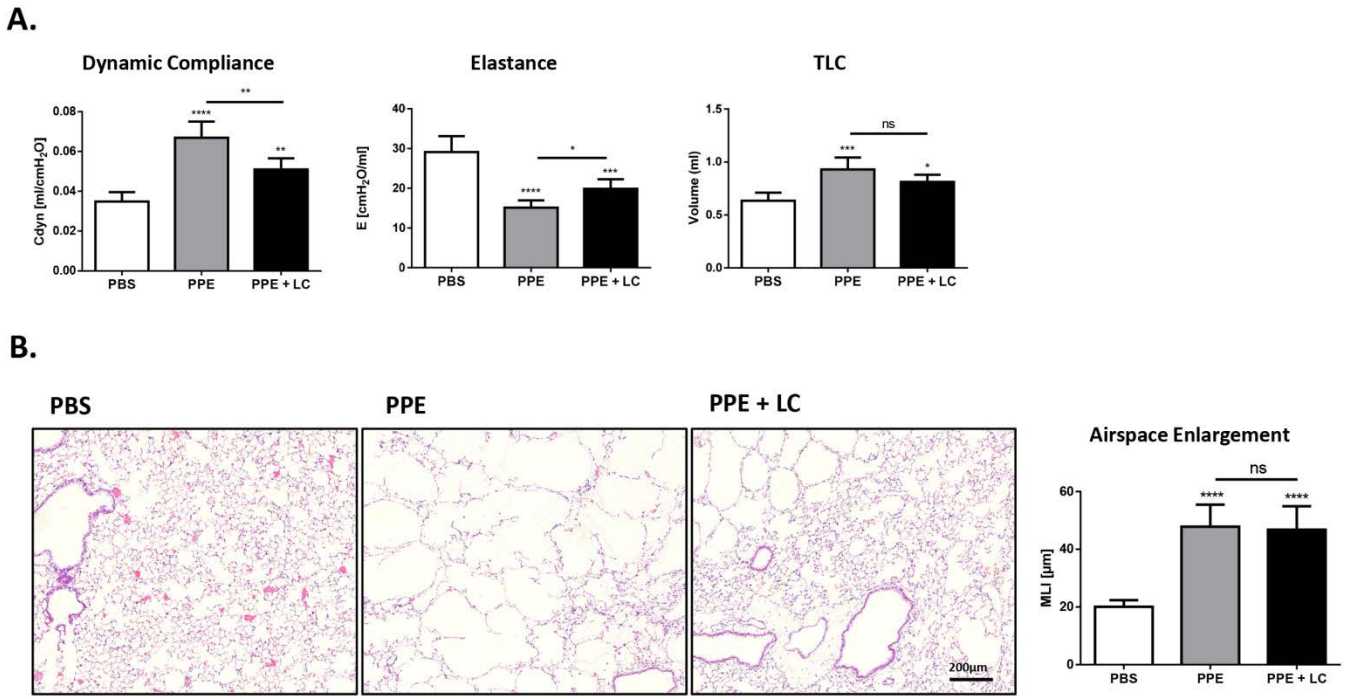

L-carnitine supplementation improves lung function in PPE-induced emphysematous mice. A: Lung function measurements to obtain dynamic compliance, elastance and total lung capacity (TLC) were carried out on day 28 in PBS-treated, PPE-treated and PPE-treated mice supplemented with L-carnitine (LC) every second day at 500mg/kg body weight i.p.. B: Representative photomicrographs of H&E stained lung sections from the three groups of mice. Scale bar 200µm. Airspace enlargement was quantified as the mean linear intercept (MLI) by design-based stereology of the H&E stained lung sections using the newCAST system. All data shown are the mean values ± SD from two experiments, n=4-6 per group, one-way ANOVA following Bonferroni post test with ****P < 0.0001 and ns not significant.