Reviewer's report

Title: Differential Expression of C-Reactive Protein and Serum Amyloid A in Different Cell Types in the Lung Tissue of Chronic Obstructive Pulmonary Disease Patients.

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Reviewer: Maarten van den Berge

Reviewer's report:

In the present manuscript, the authors aim to identify the nature of the increased systemic inflammation that has been observed in COPD patients. They are particularly interested in CRP as its level has been associated with rate of lung function decline in COPD and Serum amyloid A as higher levels were observed in COPD vs controls. They hypothesize that the origin of the increased systemic inflammation is generated within the lungs and then enters the bloodstream due to 'overflow.' This hypothesis is strengthened by the authors' recent observations that CRP and SAA levels are increased in the lung parenchyma of patients with COPD vs non-COPD controls. In the present study, the authors build further on this by investigating the expression of CRP and SAA in three different lung cell types, epithelial cells, macrophages, and fibroblasts. These cell types were obtained by magnetic separation from lung tissue.

I have the following comments:

Major comments.

1. With respect to the differences between COPD and non-COPD. Do the authors also have data on the total number of cells available in lung tissue? That might be of help in interpreting the data. If not available, it may be a good idea to explain why this could not be a confounding factor.

2. Do they also have data on systemic inflammation available. If so, this should be included in the manuscript.

3. How is the inflammation in lung tissue related to severity of COPD?

4. The authors show differences in inflammatory genes within the different inflammatory cell types in lung tissue. Some are increased in COPD vs non-COPD. Others are decreased. Although systemic inflammation is important, the clinical implications (or possible clinical implications) of these particular findings remain unclear. Which cell type is most relevant for systemic inflammation in COPD? Can it be treated or targeted? This should be better explained in the discussion section.

Minor comments.

5. Table 2. Comorbidities. Which co-morbidities? This may be important in the context of systemic inflammation.
6. Statistical approach. Why the cut-off for alpha of 0.1? This is very unusual even when not taking into account the fact that the authors do not correct their findings for multiple testing. Why not use an alpha of 0.05?

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

'I declare that I have no competing interests’