Reviewer's report

Title: Soluble receptor for advanced glycation end-products and progression of airway disease

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Reviewer: S. Vamsee Raju

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Summary

The authors of this study compared plasma concentrations of sRAGE and HMGB1 in healthy non-smokers, smokers, and COPD patients and evaluated their predictive value in estimating pulmonary function. They have analysed baseline demographic data and a longitudinal decline of pulmonary function during a 4-year follow-up period. Baseline plasma sRAGE levels were significantly lower in healthy smokers and COPD patients than in non-smokers. Moreover, plasma sRAGE concentrations were significantly associated with longitudinal declines of FEV1/FVC independent of demographics and baseline lung function. Surprisingly, there was no significant difference in plasma HMGB1 levels across the study groups contradicting what was recently published.

Critiques:

1. As duly noted by the authors, this study is not large enough to make the assertion that sRAGE might be a diagnostic marker for early stage detection of COPD. Based on what was learnt in this study authors are recommended to list the required parameters for a conclusive larger study (required N for COPD patients, duration of follow up study, spirometric characteristics, additional assays like CT etc)

2. Authors proposed to (look at intro) study the relationship between HMBG1 and sRAGE. However, the data figures suggest that these 2 important molecules were studied independent of one another. This is also complicated by the lack of any significant differences in HMBG1. It is recommended that the data for sRAGE and HMBG1 is compared within each study group and discuss their interrelationships, if any.

3. The authors have presented a surprising data set where they contradicted significant differences in HMBG1 in COPD patients. It is important that authors compare the ELISA method used for analysis with earlier work and also discuss how their study differs in terms of inclusion criterion, patient demographics and spirometric differences.

4. The HMBG1 values obtained were very low and were not too distant from the detection limit of the assay. Were their sample processing issues associated?

5. At baseline, there were differences in smokers but not in COPD patients.
Discuss in detail how small sample size of COPD patients contributed to this discrepancy.

6. Subgroup analysis for COPD patients shows a significant association b/w sRAGE and lung function decline. Were their any sex based differences within this group? Fewer females in this group might limit such analysis.

7. Place reference published work for alternate variables like age, BMI, smoking status and baseline FEV1/FVC that were also significantly associated with changes in lung function decline (and also sRAGE in some).

8. One of the great features of this study is that COPD patients were not on any medications prior to this study. Pls state what medications these patients were on during the 4-yr follow up period and how those medications influenced the lung functions analyses.