Confounding factors affecting sRAGE as biomarker for COPD

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To the editor:

In a review paper that is currently in press in the *American Journal of Respiratory and Critical Care Medicine*, Stockley et al. provides an excellent overview of the current literature and the necessity and limitations of currently available and future chronic obstructive pulmonary disease (COPD) biomarkers.\(^\text{1}\) In their review, Stockley et al. state that the circulating levels of the soluble Receptor for Advanced Glycation End-products (sRAGE) is the best known biomarker for the COPD phenotype emphysema, yet some limitations prohibit the current use of sRAGE in the clinic, including large inter-individual variation with overlap between healthy controls and COPD patients and limited knowledge on confounding factors such as smoking behavior. Although Stockley et al. provide a thorough overview of the currently available data on sRAGE as biomarker for COPD, they overlooked key publications by our group on the role of sRAGE as COPD biomarker. Stockley et al. speculate about the potential effects of smoking on circulating sRAGE levels and state that this needs to be investigated further. In fact, we have recently addressed these issues, as we have shown that smoking acutely and severely decreases serum sRAGE levels by up to 50% within two hours after smoking 3 cigarettes.\(^\text{2}\) We validated these results using two distinct quantitative sRAGE assays to exclude the possibility of a technical artefact. Furthermore, in a second study we showed that this difference is not caused by chronic smoke exposure, as we did not find significant differences in serum sRAGE levels between age-, gender- and Body Mass Index(BMI)-matched, young and old smokers and never smokers.\(^\text{3, 4}\) These data indicate that smoking acutely and temporarily decreases serum sRAGE levels, which may cause large inter-individual variations in serum sRAGE levels, as reviewed by Stockley et al. Therefore, we proposed that smoking cessation in the hours prior to blood-sampling may decrease the variation in serum sRAGE levels and increase the discriminative value of sRAGE as biomarker for COPD. Furthermore, Stockley et al. state that more studies are needed investigating the effect of COPD exacerbations on serum sRAGE levels. Indeed, we investigated this using serum samples of 14 COPD patients which were in stable disease, and serum samples from the same patients when they were experiencing an exacerbation.\(^\text{5}\) Here, we
showed serum sRAGE levels are significantly decreased during an exacerbation, while there is no difference in the expression of the gene encoding RAGE in granulocytes. In summary, our results are in line with Stockley et al. that more research on confounding factors is needed before sRAGE can be implemented as clinically usable COPD biomarker.

Footnotes

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