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An Integrative Genomic Strategy Identifies Soluble Receptor for Advanced Glycation End-Products as a Causal and Protective Biomarker of Lung Function



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To date, several studies have shown that the serum and plasma levels of the soluble receptor for advanced glycation end-products (sRAGE) are lower in patients with COPD compared with control subjects.^{1,2} Further, sRAGE levels correlated with lung function decline, COPD severity, and emphysema,^{1,2} which makes the circulating levels of sRAGE among the most promising blood biomarkers for COPD and emphysema. However, several factors may complicate the use of sRAGE as a biomarker. First, we previously showed that smoking causes a severe but short-lived decrease of serum sRAGE levels within the first hours after smoking.^{3,4} Second, we found that active smokers display an increased production of endogenous sRAGE, which is a specific form of sRAGE that is produced by alternative splicing, when compared with never smokers.^{3,4} This may be a protective antiinflammatory mechanism to compensate

for the detrimental proinflammatory effects of smoking. However, because endogenous sRAGE only accounts for approximately 10% of the total sRAGE pool in blood, this did not induce significantly higher levels of sRAGE in active smokers compared with never smokers. Another complicating factor is the fact that the missense single-nucleotide polymorphism (SNP) rs2070600, which is present in approximately 5% to 7% of the population, also affects the circulating levels of sRAGE.⁵ This SNP changes a glycine into a serine at the 82nd codon of RAGE, which is located exactly within one of the two N-linked glycosylation-motifs of the ligand-binding V-domain of RAGE, increasing the ligand-binding-capacity of RAGE.⁶ Recently, we have shown that especially the sputum levels of sRAGE are decreased significantly in individuals bearing the minor allele of rs2070600.⁷ Thus, although sRAGE is the most promising biomarker for COPD, there are several factors that affect sRAGE levels, which complicates the usage of sRAGE as a biomarker.

In this issue of *CHEST*, the article by Keefe et al⁸ sheds light on the complicated sRAGE puzzle. They used an integrative genomic strategy to elaborate on the exact pulmonary traits that are associated with plasma sRAGE levels. Furthermore, they investigated the effect of SNPs located near *AGER*, the gene encoding RAGE, on lung function and emphysema parameters. By the use of Mendelian randomization analysis and protein-trait analyses, they showed that plasma sRAGE levels are correlated positively to the FVC. Since longitudinal studies identified that higher sRAGE levels at baseline associated with a reduced decrease in lung function, it was suggested that sRAGE has a protective role on lung function decline. Interestingly, the largest effects of sRAGE levels on lung function were shown in active smokers, which made Keefe et al⁸ suggest that sRAGE may reduce the proinflammatory effects of smoking. Additionally, they identified several SNPs in and around the *AGER* locus that associated with lung function, among which is the well-known SNP rs2070600.

Keefe et al⁸ suggest that sRAGE is involved causally in the pathophysiologic condition of COPD by acting as an antiinflammatory decoy receptor by reducing the amount of circulating RAGE ligands. Although this is a logical idea, one has to consider that the concentration of sRAGE in blood has been reported to be between 0.1

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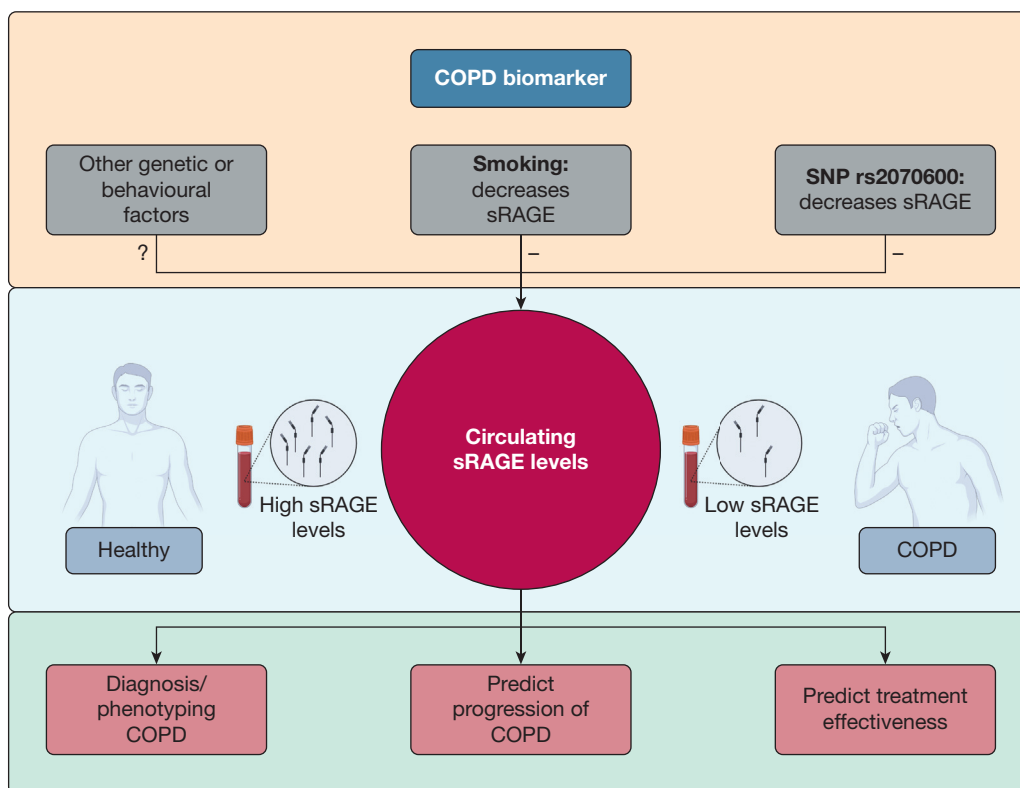


Figure 1 – Circulating soluble receptor for advanced glycation end-products levels as COPD biomarker. The circulating levels of soluble receptor for advanced glycation end-products are lower in patients with COPD compared with healthy control subjects and can be affected by several factors that include the single-nucleotide polymorphism rs2070600, smoking, and, to date, unknown factors. Circulating soluble receptor for advanced glycation end-products levels can be used potentially to diagnose or phenotype patients with COPD, predict the progression of COPD, or predict the effectiveness of specific COPD treatments. SNP = single-nucleotide polymorphism; sRAGE = soluble receptor for advanced glycation end-products.

and 10 ng/mL, whereas the concentration of RAGE ligands in blood easily can be 100 to 1,000 times higher.^{9,10} This extreme excess of RAGE ligands makes it unlikely that a relatively small difference in sRAGE levels affects the capacity of ligands to activate RAGE. Another possible explanation is that sRAGE exerts antiinflammatory properties by preventing RAGE homodimerization, needed for downstream signaling of RAGE, by forming a RAGE:sRAGE heterodimer.¹¹ This would also explain the larger effect of sRAGE levels on lung function in active smokers, because RAGE expression is decreased in lung tissue of active smokers compared with never smokers,⁴ increasing the potential antiinflammatory effect of circulating sRAGE.

It is known that the rs2070600 SNP affects the circulating sRAGE levels⁷ and increases the ligand binding capacity of RAGE.⁶ The study of Keefe et al⁸ shows that other SNPs in proximity of the *AGER* loci significantly affect the FVC and the emphysema parameter %LAA950. Interestingly, besides rs2070600, none of the SNPs used for the Mendelian randomization analysis led to a coding amino acid change. It therefore would be interesting to

investigate the exact mechanism by which these SNPs contribute to changes in lung function.

In the near future, blood biomarkers will be important clinical tools to diagnose and phenotype the condition of patients with COPD, to assess the progression of COPD, and to predict treatment efficiency. To date, sRAGE is still the most promising blood biomarker for COPD; it has been proposed in literature that its discriminating power can be increased by the use of a panel of blood biomarkers in addition to sRAGE.¹² However, more studies that will use a larger cohort with well-characterized patients with COPD are needed before we can use sRAGE clinically as a blood biomarker for COPD. Here, which clinical characteristics of patients with COPD associate most strongly with circulating sRAGE levels and which factors can affect the circulating sRAGE levels must be unraveled. These factors include both genetic factors and behavioral factors such as smoking (Fig 1). The study of Keefe et al⁸ provides an important step to characterize which lung function parameters associate with sRAGE levels and towards characterization of the functional consequences of the presence of SNPs located near the *AGER* loci.

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