Eur Respir J 2011; 38: 743–748
DOI: 10.1183/09031936.00041711

CORRESPONDENCE

Does RAGE protect smokers from COPD?

To the Editors:

We read with interest the article by SMITH *et al*. [1], which showed a positive correlation between plasma soluble receptor for advanced glycation end-products (sRAGE) and forced expiratory volume in 1 s (FEV_1) in patients with chronic obstructive pulmonary disease (COPD). Here, we outline the results of recent genetic epidemiological studies that suggest the advanced glycosylation end product-specific receptor (*AGER*) gene, which encodes sRAGE, may also have a role in the development of COPD.

Two recent large genome-wide association (GWA) studies conclude that a locus on chromosome 6p21 is associated with lung function (FEV_1 and FEV_1/forced vital capacity) [2, 3], directly implicating the *AGER* gene, which is known to be expressed in alveolar epithelial cells [2]. However, this association was made in populations dominated by nonsmokers and did not specifically examine the effect in chronic smokers. We and others have proposed that COPD results from the combined effect of chronic smoking exposure and the presence or absence of a variable combination of protective and susceptible genetic variants [4, 5]. In this regard, we have examined the same *AGER* variant (single-nucleotide polymorphism (SNP)) reported in the GWA studies (rs2070600) in 484 smokers with normal lung function (''resistant'' smokers) and 455 matched smokers with COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage $\geqslant 2$ on pre-bronchodilator spirometry). We found that the minor allele (T allele or CT/TT genotype) of the *AGER* SNP was more frequently found in resistant smokers compared with those with COPD (15 *versus* 10%; OR 0.60, 95% CI 0.40–0.91; $p=0.01$) [6]. The T allele of this SNP converts glycine to serine at position 82 in the third exon encoding the sRAGE protein (a nonsynonymous change altering polarity at this position) and has been shown to be associated with both reduced serum sRAGE levels and increased sRAGE signalling compared with the more common C allele [1]. This change in sRAGE signalling affects downstream gene expression through mitogen-activated protein kinases and nuclear factor-κB, both of which have been implicated in the inflammatory response in COPD.

Collectively, these studies suggest that the *AGER* gene (encoding sRAGE) may play a role in the development of COPD. sRAGE has systemic anti-inflammatory activity that may have relevance in lung tissue, which is both highly vascular and extensively exposed to various pro-inflammatory aeropollutant insults [1]. Smoking is the most well-known of these aeropollutant exposures and also the most easily quantified, albeit retrospectively. This makes COPD an excellent model with which to examine gene–environment interactions in order to identify genetic variants conferring either protective or susceptibility effects. That COPD is associated with low plasma levels of a ubiquitous systemic anti-inflammatory mediator like sRAGE [1] is somewhat analogous to α_1-antitrypsin deficiency. It is also consistent with the findings that, when compared with resistant smokers, smokers with COPD less frequently carry other SNP variants implicated in pulmonary–systemic anti-oxidant/anti-inflammatory activity (*e.g.* extracellular superoxide dismutase (*SOD3*), protective effect [4]; Hedgehog-interacting protein (*HHIP*), protective effect [6]; and the family with sequence familiarity 13 member A (*FAM13A*), protective effect [6]). These findings suggest that SNPs conferring a resistant (protective) effect maybe just as (or even more) important as susceptible SNPs.

Such an observation has major implications in the genetics of smoking-related lung disease, where exposure to smoking may result in quite different outcomes due to the genetic makeup of the person exposed. First, this is very relevant to study design, as prospective epidemiological studies show 60–70% of chronic smokers maintain normal or near-normal lung function (adjusted FEV_1) despite decades of smoking [7], while the remainder develop COPD of variable severity. In contrast with light smokers or nonsmokers, where the distribution of adjusted FEV_1 is normal, chronic smokers show a trimodal FEV_1 distribution consistent with a moderating genetic effect [8]. Therefore, recruitment of unaffected (resistant) smokers is as important as the recruitment of smokers with COPD to correctly assign smokers as resistant or susceptible. Secondly, if the mechanisms underlying the protective genetic effects can be better understood, then drugs simulating these protective effects (*e.g.* statins [9, 10]) may help prevent the development of COPD. While further genetic studies will be required to establish the functional variant(s) underlying the association of *AGER* with COPD, further discovery of novel pathogenetic pathways underlying responsiveness to smoking exposure (and development of COPD) are likely to emerge through well-designed genetic epidemiological studies.

R.P. Young, B.A. Hay and R.J. Hopkins
Schools of Biological Sciences and Health Sciences, University of Auckland, Auckland, New Zealand.

Correspondence: R.P. Young, Respiratory Genetics Group, University of Auckland, PO Box 26161, 1344 Epsom, Auckland, New Zealand. E-mail: roberty@adhb.govt.nz

Statement of Interest: Statements of interest for R.P. Young and R.J. Hopkins can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

REFERENCES

1 Smith DJ, Yerkovich ST, Towers MA, *et al.* Reduced soluble receptor for advanced glycation end-products in COPD. *Eur Respir J* 2011; 37: 516–522.

2 Repapi E, Sayers I, Wain LV, *et al.* Genome-wide association study identifies five loci associated with lung function. *Nat Genet* 2009; 42: 36–44.
3 Hancock DB, Eijgelsheim M, Wilk JB, *et al.* Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function. *Nat Genet* 2009; 42: 45–52.
4 Young RP, Hopkins R, Black PN, *et al.* Functional variants of antioxidant genes in smokers with COPD and in those with normal lung function. *Thorax* 2006; 61: 394–399.
5 Molfino NA. Genetics of COPD. *Chest* 2004; 125: 1929–1940.
6 Young RP, Hopkins RJ, Whittington CF, *et al.* Individual and cumulative effects of GWAS susceptibility loci in lung cancer: associations after sub-phenotyping for COPD. *PLoS One* 2011; 6: e16476.
7 Løkke A, Lange P, Scharling H, *et al.* Developing COPD: a 25 year follow up study of the general population. *Thorax* 2006; 61: 935–939.
8 Young RP, Hopkins RJ, Eaton TE. Forced expiratory volume in one second: not just a lung function test but a marker of premature death from all causes. *Eur Respir J* 2007; 30: 616–622.
9 Mahajan N, Bahl A, Dhawan V. C-reactive protein (CRP) up-regulates expression of receptor for advanced glycation end products (RAGE) and its inflammatory ligand EN-RAGE in THP-1 cells: inhibitory effects of atorvastatin. *Int J Cardiol* 2010; 142: 273–278.
10 Young RP, Hopkins R, Eaton TE. Pharmacological actions of statins: potential utility in COPD. *Eur Respir Rev* 2009; 18: 222–232.

DOI: 10.1183/09031936.00041711

From the authors:

We thank R.P. Young and co-workers for their comments on our recent article [1]. As we highlighted in our article, there are two recent reports indicating that single-nucleotide polymorphisms in the advanced glycosylation end product-specific receptor (*AGER*) gene, which encodes the receptor for advanced glycation end-products (RAGE), are associated with changes in measurements of airflow obstruction [2, 3]. The findings reported by R.P. Young and co-workers in their correspondence add to these earlier studies and shed light on the genetic basis by which cigarette smoke exposure leads to chronic obstructive pulmonary disease (COPD) in some individuals, while ''resistant smokers'' maintain normal lung function.

Our finding that circulating levels of soluble RAGE (sRAGE) are lower in COPD subjects than healthy controls has since been reproduced in a study reported recently by MINIATI *et al.* [4]. Within an individual, circulating levels of sRAGE may be determined by polymorphisms in the *AGER* gene, but are also susceptible to environmental factors, especially as plasma sRAGE levels are very low during acute exacerbations of COPD and rise during convalescence [1]. There is now a need for longitudinal studies to define the relationship between polymorphisms in the *AGER* gene and circulating levels of sRAGE in patients with COPD, and to assess the extent to which this predicts rate of decline in lung function over time.

J.W. Upham*,#, D. J. Smith#,¶ and S.T. Yerkovich#,¶
*Dept of Respiratory Medicine, Princess Alexandra Hospital, #School of Medicine, The University of Queensland, and ¶The Prince Charles Hospital, Brisbane, Queensland, Australia.

Correspondence: S.T. Yerkovich, The University of Queensland, Level 3, R Wing, Building 1, Princess Alexandra Hospital, Brisbane, QLD 4102, Australia. E-mail: Stephanie_Yerkovich@health.qld.gov.au

Statement of Interest: None declared.

REFERENCES

1 Smith DJ, Yerkovich ST, Towers MA, *et al.* Reduced soluble receptor for advanced glycation end-products in COPD. *Eur Respir J* 2011; 37: 516–522.
2 Hancock DB, Eijgelsheim M, Wilk JB, *et al.* Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function. *Nat Genet* 2010; 42: 45–52.
3 Repapi E, Sayers I, Wain LV, *et al.* Genome-wide association study identifies five loci associated with lung function. *Nat Genet* 2010; 42: 36–44.
4 Miniati M, Monti S, Basta G, *et al.* Soluble receptor for advanced glycation end products in COPD: relationship with emphysema and chronic cor pulmonale: a case–control study. *Respir Res* 2011; 12: 37.

DOI: 10.1183/09031936.00066311

Can dog allergen alone, if combined with indoor pollution, be responsible for asthma in children?

To the Editors:

We read with interest the article by CARLSTEN *et al.* [1] showing the increasing risk of incident asthma in a high-risk birth cohort after early co-exposure to dog allergen (Can f 1) and nitrogen dioxide (NO_2) or environmental tobacco smoke. The topic is highly relevant because most studies on the interaction between allergens and air pollution regard outdoor environments and very few articles have been published on the possible allergen–pollutant relationship in indoor places.

Nevertheless, we think that other limitations to the study should be considered in addition to those already acknowledged by the authors. In their study, they referred to the article of MCCONNELL *et al.* [2] that showed a significant association between ''bronchitis symptoms'' and particulate matter only in the subset of asthmatic children who owned dogs. However, MCCONNELL *et al.* [2] examined the relationship of both dog and cat ownership with air pollution, and reported that effects