COPD and biomarkers: the search goes on

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As understanding of cellular and molecular mechanisms underlying disease pathogenesis advances, the opportunities increase to identify specific compounds or molecules which are altered by the disease process or appear de novo. These markers of the pathological process have the potential advantage of indices which are indicative of the existing state or change and can be available non-invasively.1

In this issue of Thorax there is a report of the use of Clara cell secretory protein-16 (CC-16, CC-10 or urotoglobin) as a biomarker for epithelial cell dysfunction (see page 1058).2 CC-16 is a member of the secretoglobin family of secreted disulphide-bridged dimeric proteins.3 It is secreted by non-ciliated Clara cells which reside in respiratory bronchi and by non-ciliated columnar cells of the large and small airways.4 CC-16 also occurs in the epithelial cells of the nose and the urogenital tract of men and women.5 There is evidence, however, that serum levels of CC-16 are largely the result of secretion by cells of the respiratory tract rather than the cells of the urogenital tract.6 Serum levels of CC-16 rise following acute exposure to smoke, chlorine and lipopolysaccharide; in patients with asthma, obliterative bronchiolitis and smokers the serum CC-16 levels are low.7 There is an extensive literature on CC-16 levels in serum and bronchoalveolar lavage fluid in normal individuals, experimental animals and individuals exposed to atmospheric pollutants, as well as asthma.8 The exact function of CC-16 is not known, but it may play a role in reducing inflammation in airways.8

The processes which control serum levels of CC-16 are: (1) the rate of synthesis of CC-16 by Clara cells and secretion into the alveolar fluid; (2) the rate of diffusion from alveolar fluid into the capillary blood, which is influenced by leakiness of the pulmonary epithelial barrier; and (3) renal clearance of CC-16. In normal individuals there is variation as a function of gender, age, body mass index, circadian rhythm, ethnicity, temperature, humidity, pulmonary infection and exposure to allergens.7

The ECLIPSE study, a 3-year longitudinal multicentre study of patients with chronic obstructive pulmonary disease (COPD), provided serum for evaluation of the usefulness of CC-16 as a biomarker to identify characterising clinical features of the disease.5 In this trial of 1888 individuals with COPD, 296 smoking controls with no airflow obstruction and 201 non-smoking controls, there were significant differences between the mean CC-16 levels in current and former smokers with no airflow obstruction. There were also significant differences in mean CC-16 levels between current and former smokers with no airflow obstruction and non-smoking controls. The serum CC-16 levels were significantly reduced in 1888 smokers with no airflow obstruction compared with 296 current and former smokers without airflow obstruction.

A strength of this study is the documentation of serum CC-16 levels in this well-characterised cohort of a large number of patients with COPD, with detailed smoking histories, pulmonary function testing and CT scans of the chest. A disease biomarker should have: (1) high sensitivity, (2) high specificity, (3) biological relevance to the pathogenesis

REFERENCES


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and (4) sufficient information so that changes in the concentration of the biomarkers can be clinically relevant.\textsuperscript{10}

There are significant limitations to CC-16 as a marker of the disease components of COPD. In the cohorts studied, there was no correlation between the presence or severity of emphysema and the serum CC-16 level. Also, there was no correlation between the serum CC-16 level and the symptoms of chronic bronchitis. The use of inhaled corticosteroids or long-acting β\textsubscript{2} agonists in the ECLIPSE cohort was not reflected in significant differences in serum CC-16 levels. We must be aware that, at present, it is not known if the serum CC-16 level is specific for COPD alone or only to exposure to tobacco smoke or ozone. Testing is required of CC-16 serum levels in other diseases of the lung. Also, studies are required in COPD to determine whether CC-16 can indicate disease progression or regression.

This report of CC-16 from the ECLIPSE study does provide baseline data on several patient cohorts in this large-scale study. Additional data are needed to establish whether CC-16 can reflect short-term or long-term progression or regression of COPD parameters of pulmonary function, clinical state or radiological indices of bronchial structure or, possibly, responses to treatment.

We need to establish where CC-16 might be considered in the spectrum of possible biomarkers of COPD. COPD is a systemic disease beyond the lung with inflammation as a significant contributor,\textsuperscript{11} and markers of the inflammatory state such as C-reactive protein (CRP),\textsuperscript{12} 13 and interleukin 8 (IL-8)\textsuperscript{14} have been found to be raised in COPD; significant increases in tumour necrosis factor α (TNFα) in COPD have also been reported.\textsuperscript{15} However, these reflect augmentation of the systemic inflammatory state in COPD which can be influenced by co-morbid conditions in the cardiovascular system or metabolic comorbidities. Thus, biomarkers of the pathological state of patients with COPD may be indicators of extrapulmonary processes as well as pulmonary pathology per se. CC-16 has the advantage that it is an indicator anchored to the Clara cell or Clara cell abnormalities in airway structure and function, and that it is potentially relevant to the Clara cells of the bronchial epithelium, which gives it a potential relevance to effects on the diseased lung.

Competing interests: None.

REFERENCE

RAGE: a biomarker for acute lung injury

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Acute lung injury (ALI), and its more severe counterpart the acute respiratory distress syndrome (ARDS), are syndromes of acute respiratory failure associated with pulmonary oedema caused by increased permeability of the alveolar–capillary membrane. Many clinical scenarios are recognised as being associated with a high incidence of ALI, including the archetypal direct pulmonary and blood borne insults of pneumonia and severe sepsis, respectively. The internationally accepted diagnostic criteria are non-specific to the point of including patients with relatively mild hypoxia and patients with lung pathology that may be different from the classical diffuse alveolar damage.1 ALI is not uncommon but it is challenging to study, partly because the patients are heterogeneous in the causes and severity of their illness. Furthermore,1

Patients were elevated in samples from patients with ALI compared with healthy controls and patients with hydrostatic oedema.6 In this issue of Thorax, Calfee and colleagues7 from the NHLBI ARDS Network report the results of measuring soluble RAGE levels in plasma samples from 676 patients enrolled in the ARMA study, both at entry to the study and after 3 days of standard or protective ventilation (see page 1083). At entry, higher RAGE levels were associated with higher radiographic and physiological indices of ALI severity as well as the non-pulmonary Acute Physiology and Chronic Health Evaluation (APACHE 3) score.7 These data suggest that RAGE may be a marker of disease severity but the potential predictive value of a raised plasma RAGE level needs to be tested in patients at risk of developing ALI in a prospective longitudinal study. Furthermore, in the group randomised to the “standard” mechanical ventilation but not the protective ventilation group, higher baseline RAGE was associated with increased mortality and fewer ventilator-free and organ failure-free days. Because ventilation using 6 ml/kg predicted body weight has a standard of care,8 this observation casts a shadow over the potential usefulness of RAGE although, as the authors state, such subgroup analyses should be viewed with caution.

In both groups plasma RAGE levels decreased 3 days after enrolment, but had fallen by 15% more in the protective ventilation group. Does this mean that RAGE joins the list of potential biomarkers of ventilator associated lung injury?9 The