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EDITORIAL

Desmosine, a biomarker for COPD: old and in the way

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In the assessment of clinical presentation and response to therapy in chronic obstructive pulmonary disease (COPD), there is a major need for the identification of suitable and reproducible parameters to evaluate disease progression and changes during interventional trials [1]; in other words, parameters (or markers) associated with clinical outcome.

To date, this need has been met by forced expiratory volume in 1 s (FEV_1), a robust physiological marker that, although a comprehensive and predictive tool, has numerous limitations [2]. The ECLIPSE study (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) exemplifies attempts made to find surrogate markers that are superior to FEV_1 [3]. In ECLIPSE, subtypes from a large number of COPD patients and a variety of predictive/surrogate disease markers are being collected, including longitudinal data on lung physiology, imaging, health outcomes, genetics and biomarkers.

Biomarkers have a special role in this setting. According to the US National Institutes of Health, a biomarker is defined as a ''characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention'' [4], and usually refers to a molecule or material, such as a cell or tissue [5]. As knowledge on the pathogenic processes of COPD broadens, an increasing number of putative biomarkers have been suggested and investigated, but enthusiasm over preliminary results is frequently followed by disappointment due to the lack of reproducibility and frustration due to the increasing number of biomarkers that have failed to live up to initial promises. Consequently, a useful biomarker for COPD is still lacking. Nevertheless, the search for COPD biomarkers is still considered a very promising field: the chance of profiling disease phenotypes and predicting progression by means of a simple, possibly minimally invasive and reproducible examination is an appealing goal.

Desmosine (this term usually includes the isomer isodesmosine) is a special type of amino acid derived from the condensation of four lysine residues, and is unique to mature, cross-linked elastin molecules. This unique characteristic is considered useful in discriminating elastin breakdown-derived peptides from precursor elastin peptides. Based on this feature, desmosine has been extensively evaluated as a potentially attractive indicator of elevated lung elastic fibre turnover and a marker of the effectiveness of agents with the potential to reduce elastin breakdown. Desmosine is probably one of the oldest biomarkers for COPD. It was first developed in the mid-1960s and used in assays to measure desmosine in biological fluids. Later in the early 1980s, the first attempts were made to correlate its urinary excretion with lung elastin content. An historic perspective of technical issues in desmosine measurement and a summary of the information accumulated over the years with respect to its clinical usefulness have been extensively reviewed recently by VIGLIO *et al.* [6], and LUISETTI *et al.* [7], respectively. Around the same time, STOCKLEY [8] outlined the requirements for considering a biomarker valid in the assessment of a slowly progressive condition such as COPD: 1) it must be central to the pathophysiological process; 2) thus, it must be a ''true'' surrogate end-point; 3) it must be stable and vary only with events related to disease progression; 4) its concentration should be directly related to the severity of the condition; 5) it must predict progression; and 6) it must reflect changes induced by effective treatment. Although desmosine can satisfy some of these requirements, particularly 1–3, evidence supporting the last points is still lacking. Thus, desmosine has suffered the same fate as other putative COPD biomarkers: in spite of the extensive amount of data collected, desmosine is still far from being considered a reliable biomarker.

In this issue of the *European Respiratory Journal*, LINDBERG *et al.* [9] present data of a cross-sectional study indicating that desmosine in plasma and urine correlates with lung function. This may not seem like a major advance in our understanding of matrix elastin and COPD, but several minor points taken together support the relevance of this paper. First of all, it is the largest series of subjects (349, approximately one-third of whom had COPD) investigated so far for this characteristic, *i.e.* previous series of subjects investigated were relatively small, and this could be one of the reasons why the correlation between desmosine and FEV_1 was not always reproducible. Interestingly, in the present article, the correlation between FEV_1 and diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) was even stronger in subjects with COPD with respect to those without. In addition, adjustments in desmosine data for age, sex, height, body mass index and smoking habit, provide germane results, since many of these parameters have been significantly associated with desmosine. A significant correlation was found for age, with progressive increases over time, for both sexes. This outcome might explain the contrasting results obtained in the past, when populations with mixed ages were investigated. Another important aspect is that the investigation was performed with liquid chromatography–tandem mass spectrometry, a method that is currently considered the gold standard

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for detection of elastin cross-links in biological fluids [7, 10]. Such a high-throughput platform should minimise the variability seen with other methods, but conversely, it has the disadvantage of requiring expensive instrumentation and skilled personnel, thus precluding wide access to the technique. From a technical point of view, one concern is related to the merging of the measurement of desmosine conjugated to elastin-derived peptides with free desmosine [11, 12]. This might have an impact on the results, since the main goal of measuring desmosine is to monitor only elastin breakdown, as indicated by desmosine contained in elastin fragments; thus, it is not possible to exclude that unbound desmosine is part of the desmosine pool before crosslinking. Last but not least, this study provides evidence that degradation of lung elastic fibres is related to COPD, and confirms once again the validity of the proteinase–antiproteinase hypothesis of emphysema development [13], a mechanism that had been somewhat disregarded due to the increasing number of possible novel pathways [14]. According to such a hypothesis, desmosine would be a true surrogate end-point, directly related to the pathophysiological mechanism of the disease. Interestingly, another biomarker linked to the proteinase–antiproteinase hypothesis has been recently proposed by CARTER *et al.* [15]. They assert that the detection of the fibrinogen cleavage product $A\alpha$–Val^{360} in plasma is specific for pre-inhibition activity of neutrophil elastase (NE) and is a possible biomarker for NE-related COPD. However, it should be emphasised that this marker, which is specific for NE, would not reflect the activity of other proteinases, such as matrix metalloproteinases, that are known to actively take part in the degradation process of lung elastin [13]. From this point of view, desmosine is a less specific marker but with a broader aim, since it captures peptides cleaved by different proteinases.

What should be the next steps to further validate desmosine as a biomarker in COPD? A few months ago, TURINO *et al.* [16] delineated a framework for investigation based on the following requisites. Desmosine should: 1) indicate different phenotypes of COPD; 2) correlate reliably with progression or regression of the clinical course of COPD; 3) rapidly reflect the effects of agents under clinical trial; and 4) be investigated with respect to the influence of comorbidities. A preliminary resolution to requisite 2 was recently presented in the article by FREGONESE *et al.* [17], in which 11 patients with emphysema related to α_1-antitrypsin deficiency presented with plasma and urine levels of desmosine that increased significantly over a period of 14 months, whereas $D_{L,CO}$ significantly deteriorated. Hopefully, the other queries will be answered soon.

The article by TURINO *et al.* [16] ends with the statement that ''large-scale studies of COPD populations…offer the opportunity to further explore the usefulness of elastin degradation as a biomarker in COPD''. The study by LINDBERG *et al.* [9] has started this confirmatory process.

STATEMENT OF INTEREST

None declared.

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