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Microfibrillar-associated protein 4: A potential biomarker of chronic obstructive pulmonary disease

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KEYWORDS
Microfibrillar-associated protein 4;
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Summary
Background: Microfibrillar-associated protein 4 (MFAP4) is a matricellular glycoprotein that co-localises with elastic fibres and is highly expressed in the lungs. The aim of this study was to test the hypothesis that plasma MFAP4 (pMFAP4) reflects clinical outcomes in chronic obstructive pulmonary disease (COPD).

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Chronic obstructive pulmonary disease;
Acute exacerbation of COPD;
BODE index;
Modified Medical Research Council score

Methods: pMFAP4 was measured by an AlphaLISA immunoassay in stable COPD ($n = 69$) at baseline and at follow-up until 24 months after inclusion and in acute exacerbations of COPD (AECOPD) ($n = 14$) at baseline and until 6 months after inclusion.
Results: The majority of patients (89%) were in GOLD II and III. Multiple linear regressions showed positive associations between pMFAP4 and the Global initiative for Obstructive Lung Disease (GOLD) grade ($p = 0.01$), modified Medical Research Council score ($p < 0.0001$) and BODE index ($p = 0.04$). Negative associations were found with 6-min walking distance ($p = 0.04$) and bronchodilator-induced reversibility ($p = 0.02$). The pMFAP4 levels varied less than 25% between the baseline and a 3 month follow-up in 83% of the patients. The pMFAP4 levels appeared unaffected in the acute phase of severe AECOPD but rose to an increased stable level within one month after hospitalization.
Conclusion: Increased pMFAP4 was associated to the severity in COPD and has the potential to serve as a stable disease biomarker. This observation warrants confirmation in a larger longitudinal COPD population.

Background

Chronic obstructive pulmonary disease (COPD) is characterised by pulmonary emphysema and a progressive airflow limitation caused by small airway disease [1]. Emphysema results from the degradation of the lung parenchyma, partly due to an inflammation induced protease-antiprotease imbalance [2].

Airflow is quantified using forced expiratory volume in one second (FEV_1) and FEV_1 is currently the only validated biomarker in COPD. However, FEV_1 is poorly correlated with symptom burden and outcomes in COPD, which makes it an inadequate surrogate marker of disease activity, a poor predictor of disease progression and an ineffective tool for the evaluation of treatment responses [3]. Thus, there is a pressing need for new, non-invasive and cost effective biomarkers in COPD [4].

Extracellular matrix turnover products have been suggested as alternative markers of emphysema development and respiratory disease activity [5–7], and microfibrillar-associated protein 4 (MFAP4/MAGP-36) is a matricellular glycoprotein highly expressed in the lung [8]. Immunohistochemistry and immunogold electron microscopy have demonstrated that MFAP4 is colocalised with microfibrils in elastic fibres in pulmonary blood vessels and in the alveolar septae [9,10]. MFAP4 is moreover increased in cirrhotic liver disease [11]. MFAP4 binds to collagen, elastin and the collagen-like regions of pulmonary surfactant proteins A (SP-A) and D (SP-D) [9,10,12] and is suggested with a protective role in photodamaging of the skin through the regulation of metalloproteinase expression [13].

The specific objectives of this pilot-study testing the hypothesis that MFAP4 levels in plasma (pMFAP4) reflect COPD severity were the following: I) to evaluate the association of MFAP4 levels with parameters reflecting disease severity in a stable COPD cohort; II) to evaluate the variability of pMFAP4 expression over time in stable COPD; and, III) to evaluate pMFAP4 variation during and after an acute exacerbation of COPD (AECOPD).

Methods

Ethical considerations

Study protocols were approved by the Regional Scientific Ethics Committee for Southern Denmark, and oral and written informed consent were obtained from the study subjects.

Stable COPD patients

The patients evaluated in this study were from the Danish subpopulation of the ECLIPSE cohort (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points; Clinicaltrials.gov identifier NCT00292552; GSK study code SCO104960) [14] and were followed up after 3, 6, 9, 12, 18 and 24 months. Briefly, patients with stable COPD, aged 40–75 years and with a smoking history of at least 10 pack-years were enrolled [14]. The measured or estimated clinical outcomes were FEV_1; FVC and FEV_1/FVC; a 6-min walking test; the percentage of low attenuation area (LAA%); exhaled carbon monoxide, *eCO*, with *current smoking* defined as an eCO >12 ppm; the modified Medical Research Council (mMRC) dyspnoea scale; and the BODE index calculated according to standards, using the *B*ody Mass Index, *O*bstruction Index, *D*yspnoea score and *E*xercise capacity. COPD subjects were asked about exacerbations 3, 6 and 12 months after enrolment in the study. In addition, they were contacted by telephone every month by the study staff and asked about details of exacerbations during the previous month. Specifically, subjects were asked whether they had been unwell in the last month, whether they had seen a doctor or been to hospital and whether they had taken any medication for exacerbations (oral corticosteroids or antibiotics). The data were analysed 12 months after enrolment into the study as described previously [15].

Control subjects

EDTA-plasma samples were obtained from 54 smoking and 52 non-smoking control subjects who were recruited from