TELOMERE ATTENTION IN CIRCULATING WHITE BLOOD CELLS IN COPD RELATES TO LUNG FUNCTION AND OUTCOMES

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Introduction Increasing evidence suggests accelerated ageing as a pathogenic mechanism in COPD.

Methods and results Telomere length in circulating WBC, a marker of biological ageing, was assessed in 200 ex-smoker COPD patients (108 male, age 61.5 ± 6.4 years, FEV1 45.6 ± 17.1% predicted), 50 ex-smokers with normal lung function (27 male, age 59.9 ± 7.3 years, FEV1 109.1 ± 13.4% predicted) and 50 non-smoker healthy subjects (27 male, age 59.3 ± 8.3 years, FEV1 113.2 ± 13.1% predicted). TL was assessed by qPCR and expressed as relative T/S ratio.

TL was shorter in COPD (0.77 ± 0.2 relative T/S ratio) than in both ex-smokers (0.83 ± 0.2 relative T/S ratio) and non-smokers (0.84 ± 0.2 relative T/S ratio) (p < 0.05). Furthermore, TL correlated negatively with age (r = -0.17, p = 0.007), emphysema score (r = -0.217, p = 0.001), number of exacerbations in the previous year to inclusion in the study (r = -0.129, p = 0.04), number of hospitalisations over 3 years follow-up (r = -0.167, p = 0.004) and positively with FEV1 (r = 0.135, p = 0.03) and arterial oxygen saturation (r = 0.161, p = 0.01).

Conclusion COPD patients have evidence of premature ageing (shortened TL) compared to normal subjects irrespective of their smoking history. TL relates to FEV1, SatO2, exacerbation rate and hospitalisations.

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AIRWAY SMOOTH MUSCLE INFLAMMATION IS CONTROLLED BY MICRORNA-145 TARGETING OF SMAD3 IN COPD

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Introduction and objectives Airway smooth muscle cells (ASMCs) may contribute to the pathological airway inflammation and remodelling in COPD through the secretion of inflammatory cytokines and increased proliferation. Our previous work demonstrated that ASMCs from patients with COPD release greater amounts of IL-6 and CXCL8 compared to those from healthy subjects and are in a state of hyperproliferation. MicroRNAs (miRNAs) have recently emerged as important homeostatic regulatory molecules in COPD, and we have previously demonstrated the role of these in controlling ASMC proliferation in asthma. We hypothesise that microRNA-145 (miR-145) controls the aberrant phenotype observed in ASMCs from patients with COPD by targeting SMAD3, an important downstream signalling molecule of the TGF-β pathway.

Methods Human primary ASMCs were grown from individuals classified as being healthy non-smokers, healthy smokers, or those with COPD (n = 9 per group). Cells were stimulated with TGF-β and foetal calf serum, and miRNA and mRNA expression levels were measured by RT-PCR. IL-6 and CXCL8 release was measured by ELISA. Transfection of miR-145 mimics and inhibitors were used to model the effects of miR-145 over-expression and knock-down, respectively.

Results Low concentrations of TGF-β significantly upregulated SMAD3 expression in ASMCs from patients with COPD. Higher concentrations of TGF-β led to a suppression of SMAD3 expression, with a concomitant increase in miR-145 expression in these cells, to a greater degree than in healthy subjects.

Inhibiting miR-145 in ASMCs from COPD patients reduced the increased IL-6 and CXCL8 release and proliferation back to levels comparable to that of healthy individuals.

Conclusions This is the first time that miR-145 has been demonstrated to be important in controlling the increased inflammatory state of ASMCs from COPD patients. This miRNA may not only act as a novel biomarker for COPD, but may also be a novel target for treatment.

CIRCULATING DESMOSINE RELATES TO CARDIOVASCULAR COMORBIDITY, CORONARY ARTERY CALCIFICATION SCORE (CACS), SYSTEMIC INFLAMMATION AND MORTALITY IN PATIENTS WITH COPD

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Introduction and objectives Desmosine is an amino acid that is selectively produced by smooth muscle cells in the cardiovascular system and is a sensitive marker of fibroproliferative processes in the heart and vessel walls. It is considered to be a marker of cardiovascular disease (CVD) due to its association with increased cardiovascular risk.

Methods and results Desmosine and its degradation product isodesmosine were measured in serum from 82 patients with COPD and 63 matched healthy controls. The study population was recruited from the ECLIPSE cohort and the readers were blinded to clinical data.

Results The serum desmosine levels were significantly higher in COPD patients compared to healthy controls (p = 0.002). COPD patients with cardiovascular disease had significantly higher desmosine levels compared to those without cardiovascular disease (p = 0.003). There was a significant association between serum desmosine levels and the CACS (r = 0.24, p = 0.003). No association was found between desmosine and systemic inflammation or mortality in COPD patients.

Conclusion Serum desmosine levels are increased in COPD patients and are associated with increased cardiovascular risk. Further studies are needed to determine the role of desmosine in the pathogenesis of CVD in COPD patients.