

The authors also queried the relevance of our findings on larger airways EMT to COPD. A major feature of COPD, in addition to small airway destruction, is its association with lung (airway) cancer. We have found large airway EMT to be associated with increased angiogenesis; this is a process reminiscent of EMT-type 3, a pro-cancer stroma in contrast with the more specifically profibrotic EMT-type-2 which lacks angiogenesis.<sup>4–6</sup> Active EMT-type-3 in large airways might be the link between COPD and lung cancer development.

For adherens proteins E-cadherin and ZO-1, the authors reported no staining in the smokers/COPD patients' epithelium, suggesting their expression is lost as the part of EMT. It is true that E-cadherin and ZO-1 epithelial expression does decrease during EMT, but if disappeared completely the epithelium would fall apart. Their protein analysis and immunofluorescence data on primary human bronchial epithelial cells does show E-cadherin and ZO-1 expression, albeit decreased. We have also been looking at small airways in smokers and see a lot of E-cadherin staining but also N-cadherin expression, as another likely expression of EMT (figure 1).

Rbm fragmentation<sup>2</sup> which is a vital part of the EMT process<sup>4</sup> is evident in the small airway tissue sections shown in the Milara *et al* paper, as is hypercellularity of the Rbm. However, neither important structural hallmark of EMT is commented upon. The arrows pointing out  $\alpha$ -SMA staining, which is below the Rbm, seem to be in the wrong place.

In spite of our reservations, this study highlights the potential importance of EMT in COPD, which might change the way we think about this disease process and its nasty clinical consequences.

**Sukhwinder Singh Sohal, Eugene Haydn Walters**

NHMRC Centre of Research Excellence for Chronic Respiratory Disease, School of Medicine, University of Tasmania, Hobart, Australia

**Correspondence to** Professor Eugene Haydn Walters, NHMRC Centre for Research Excellence in Chronic Respiratory Disease and School of Medicine, MS1, 17 Liverpool Street, Private Bag 23, Hobart, Tasmania 7000, Australia; haydn.walters@utas.edu.au, ssssohal@utas.edu.au

**Contributors** SSS: literature search, figures, performed the histological analyses, data collection, data interpretation and writing. EHW: design of study, clinical assessments, overview of all analyses, data interpretation and writing.

**Competing interests** None.

**Ethics approval** The Human Research Ethics Committee (Tasmania) Network.

**Provenance and peer review** Not commissioned; internally peer reviewed.



**OPEN ACCESS**



**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/3.0/>

**To cite** Sohal SS, Walters EH. *Thorax* 2013;**68**:783–784.

Received 4 February 2013

Revised 10 February 2013

Accepted 14 February 2013

Published Online First 14 March 2013



► <http://dx.doi.org/10.1136/thoraxjnl-2013-203484>

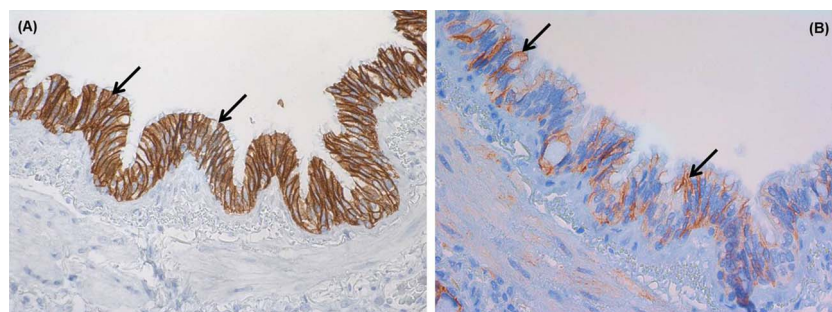
*Thorax* 2013;**68**:783–784.

doi:10.1136/thoraxjnl-2013-203373

## Epithelial mesenchymal transition (EMT) in small airways of COPD patients

We congratulate Milara *et al*<sup>1</sup> for getting a paper suggesting that epithelial mesenchymal transition (EMT) is important in the pathogenesis of chronic obstructive pulmonary disease (COPD) into a top respiratory journal. This is quite a breakthrough.

In the discussion, Milara *et al* were somewhat dismissive of our findings on EMT markers in large airways of COPD patients;<sup>2</sup> commenting that our study was limited by the mesenchymal protein expressions analysed (MMP-9, S100A4, vimentin) being potentially expressed by inflammatory cells. In a follow-up paper<sup>3</sup> we excluded such confounding. Further, our study illustrated that cells in the basal epithelium, and reticular basement membrane (Rbm) in smokers/COPD double-stain for cytokeratin-(s) and the 'EMT marker' S100A4, confirming a likely epithelial origin of these cells. Notably, Milara *et al* also stained their tissue with vimentin.



**Figure 1** Small airways in surgically resected lung sections from smokers undergoing thoracotomy: (A) black arrows indicating E-cadherin expression in the epithelium; (B) black arrows indicating N-cadherin expression in the epithelium.

## REFERENCES

- 1 Milara J, Peiró T, Serrano A, *et al*. Epithelial to mesenchymal transition is increased in patients with COPD and induced by cigarette smoke. *Thorax* 2013;68:410–20.
- 2 Sohal SS, Reid D, Soltani A, *et al*. Reticular basement membrane fragmentation and potential epithelial mesenchymal transition is exaggerated in the airways of smokers with chronic obstructive pulmonary disease. *Respirology* 2010;15:930–8.
- 3 Sohal SS, Reid D, Soltani A, *et al*. Evaluation of epithelial mesenchymal transition in patients with chronic obstructive pulmonary disease. *Respir Res* 2011;12:130.
- 4 Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. *J Clin Invest* 2009;119:1420–8.
- 5 Soltani A, Muller HK, Sohal SS, *et al*. Distinctive characteristics of bronchial reticular basement membrane and vessel remodelling in chronic obstructive pulmonary disease (COPD) and in asthma: they are not the same disease. *Histopathology* 2012;60:964–70.
- 6 Soltani A, Reid DW, Sohal SS, *et al*. Basement membrane and vascular remodelling in smokers and chronic obstructive pulmonary disease: a cross-sectional study. *Respir Res* 2010;11:105.