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

We congratulate Milara *et al*[1] 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;[2] 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[3] 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.

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.[4–6] 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[2] which is a vital part of the EMT process[4] 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 α-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.

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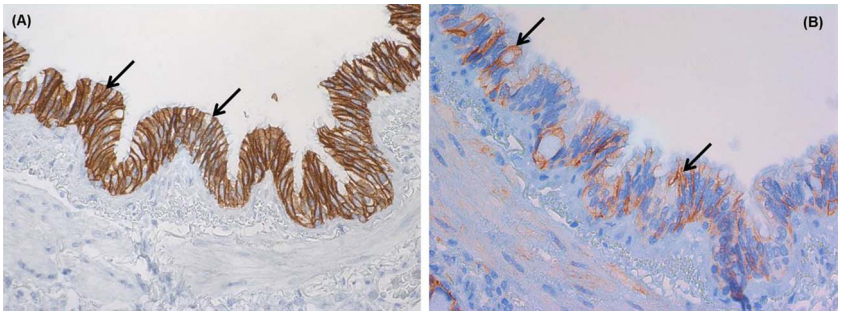

Figure 1 Small airways in surgically resected lung sections from smokers undergoing thoracotomy: (A) black arrows indicating E-cadherin expression in the epithelium; (B) black arrows indicating N-cadherin expression in the epithelium.

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