Inhaled corticosteroids attenuate epithelial mesenchymal transition: implications for COPD and lung cancer prophylaxis

To the Editor:

We read with great interest the recent original research article by Raymakers *et al.* [1] published in the *European Respiratory Journal*, regarding the beneficial effects of inhaled corticosteroids (ICS) in reducing the lung cancer risk in patients with chronic obstructive pulmonary disease (COPD). In their discussion, the authors mentioned that the mechanisms by which COPD is associated with an increased risk of lung cancer are not well-established. We do not know which mechanisms ICS inhibit for an appreciable reduction in lung cancer risk. This is a hugely important area and it is encouraging that leading respiratory journals are recognising this. Understanding these interactive mechanisms, we believe, is very important for better future translational approaches to establish early and preventive therapy [2, 3]. We would like to take this further and suggest a broader discussion on the latest findings in COPD pathology involving processes such as epithelial mesenchymal transition (EMT), angiogenesis and airway wall cellularity, and the effects of ICS on these aspects in COPD.

We have previously reported that EMT is an active process in both the small and large airways of smokers and patients with COPD, and has consequential effects on lung physiological parameters in these patients [4, 5]. In the large airways, we observed that EMT-related changes were associated with increased hypervascularity of the underlying reticular basement membrane (Rbm), representing a typical active type-3 EMT process, considered as precursor to malignant conditions and metastasis [3]. It is important to note that it is in the large airways where most squamous cell carcinomas occur and type-3 EMT could be central to this [3]. The other key pathology associated with COPD is small airway or peri-bronchiolar fibrosis and obliteration, which is attributed to active type-2 EMT at this site, but fibrosis in general is also associated with malignancy [3, 5].

In a first proof-of-concept randomised controlled trial, we hypothesised that EMT might be the process through which this effect of ICS occurs. This study reported that inhaled fluticasone propionate delivered in high doses over 6 months did suppress airway epithelial activation and EMT-related changes in large airways of COPD patients [6]. In the same population, we also investigated effects of ICS on vascular remodelling in COPD [7]. However, ICS did not change Rbm vascularity but improved lamina propria vascularity in ex-smokers with COPD [7]. Physiological indices of air trapping showed negative correlations with increased vessel numbers, *i.e.* more vessels, less air trapping [7]. Perhaps for Rbm hypervascularity, longer duration with ICS or intravenous doses are required to attenuate vascular component of EMT.

More recently, in lung resections from cancer patients, we reported active EMT as the leading edge of invasive nonsmall cell lung cancer (both squamous cell and adenocarcinomas), with tumour aggressiveness strongly related to EMT activity [8]. Further, EMT markers within the tumours closely related to EMT activity from non-tumour-affected airway wall epithelium. This work suggests that the level of EMT activity in the airway wall, even in large airways that are acquiescent to bronchoscopic biopsy, could potentially be used as a marker for smokers most likely to develop both COPD and lung cancer.

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Inhaled corticosteroids protect against lung cancer by inhibiting epithelial mesenchymal transition (EMT) in COPD http://bit.ly/2WG682I

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Airway inflammation has also been suggested to be a contributor to lung cancer development in COPD, but careful interpretation is required. Our data from a comprehensive cross-sectional study demonstrated hypocellularity in the lamina propria of both large and small airway walls in COPD compared to never-smokers [9]. There was also no change in the proportions of key immune cell populations such as neutrophils, macrophages (CD68+), and CD8+ and CD4+ cells [9]. The only increase was observed for CD8+ cells in the small airways. We further identified differential macrophage switching in the small airway wall, lumen and alveolar spaces [10]. We observed that the airway wall in never-smokers was predominantly M2 (CD163+), which switched to a more M1 phenotype in COPD patients. In the lumen and alveolar spaces, however, we found an increase in M2 relative to M1 macrophages in both smokers and COPD patients, which was not seen in never-smokers. Bronchioalveolar lavage cytokine profile also matched these findings, and was skewed towards a more M2 profile [10]. Interestingly, M2 macrophages are also the predominant phenotype observed in lung cancer and they are known to promote tumorigenicity [3]. ICS may play a role in suppressing these specific phenotypic changes, thus restricting COPD progression to cancer, but this requires further investigation.

In summary, we believe that EMT with mucosal hypervascularity may represent fundamental important aspects of COPD pathology and a potential novel therapeutic target for prevention of both epithelial malignancy and fibrosis. ICS treatment does attenuate these changes, however, a safer drug than ICS would be ideal for long term use. Indeed, we may now be reaching a position that allows an integrated understanding of this airway disease, with the potential for this understanding to be translated into a new paradigm for earlier, or even preventive, therapy. It is vital to understand fundamental disease mechanisms for early interventions.

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