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**DOI link to article:**


**Date deposited:**

27/06/2017

**Embargo release date:**

15 December 2018
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<table>
<thead>
<tr>
<th>Journal:</th>
<th>European Respiratory Journal</th>
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<tbody>
<tr>
<td>Manuscript ID</td>
<td>ERJ-00289-2017.R1</td>
</tr>
<tr>
<td>Manuscript Type:</td>
<td>Correspondence</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>22-Feb-2017</td>
</tr>
<tr>
<td>Complete List of Authors:</td>
<td>Sohal, Sukhwinder; University of Tasmania, School of Medicine; Eapen, Mathew; University of Tasmania, NHMRC CRE for Chronic Respiratory Disease and Lung Aging, School of Medicine; Ward, Chris; Newcastle University, Institute of Cellular Medicine Walters, Haydn; University of Tasmania, Discipline of Medicine</td>
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<tr>
<td>Key Words:</td>
<td>COPD, inflammation and airway remodelling, epithelial cells</td>
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</tbody>
</table>
Airway inflammation and inhaled corticosteroids in chronic obstructive pulmonary disease (COPD)

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We read with interest the recent article by Lisette Kunz et al. in the European Respiratory Journal (ERJ), and the appropriately questioning accompanying editorial by Peter Calverley in the same issue, considering airway inflammation and effects of inhaled corticosteroids (ICS) in chronic obstructive pulmonary disease (COPD) (1). Understanding COPD pathology is a hugely important area and it is encouraging that leading respiratory journals are recognising this. We would like to suggest that a broader discussion of new insights into COPD pathology might have been appropriate. Thus, a more integrated consideration of overall airway wall cellularity, vascularity, epithelial mesenchymal transition (EMT), and the effects of ICS on these in COPD is urgently needed to aid discussion of this devastating pathophysiology.

We have previously published that total airway wall cellularity is actually decreased in smokers and COPD patients (2). This change is strongly associated with smoking history and tended to approach normal levels in COPD ex-smokers. We ourselves initially found this surprising because it is at variance with the current “COPD-establishment” paradigm that the pathology is characterised by chronic inflammation in the airways including the airway wall (2), but there are in fact few if any other reports on total airway wall cellularity in the literature. We subsequently found this to be a consistent result over some years of work, and are in the process of publishing a confirmatory follow up study (paper in Press, Respirology), indicating that both small and large airway walls in smokers and mild-moderate COPD patients were hypo-cellular.

Most of the studies in the COPD literature on this area do not seem to take into account total airway wall cellularity, which could have profound implications for the interpretation of differential cell counts. The GLUCOLD study group have a strong and long standing collective history of quantitative studies of airway biopsies. We wonder therefore whether Kunz et al have any information either from their current study or cumulative experience, regarding this big-picture issue to help contextualise their findings? We also noted that their data seemed to indicate that the number of CD4+ cells in the airway wall out-numbered the CD8+ counts; this would be a finding which hasn’t been shown before to our knowledge, and is in marked contrast to our experience in COPD. We therefore wonder if the authors have any comment regarding their unusual CD4+ lymphocyte counts?
Active EMT and epithelial reticular basement membrane (Rbm) fragmentation and hyper-vascularity (with contrasting lamina propria hypo-vascularity) have also been shown to be present in the airway wall in COPD, and we have hypothesised that these changes represent fundamentally important aspects of COPD pathology (3, 4) and may allow a unified understanding of important consequences of basal stem cell reprogramming. Insights into EMT and associated pathology in COPD may have the potential to be translated into a new paradigm for earlier therapy and improved clinical outcomes and may contribute to the very active debates around ICS therapy in COPD. With respect to this, do Kunz et al, have any information from their current study regarding ICS effects on EMT, airway wall vascularity or other manifestations of basal cell reprogramming?

We believe there is a need for debate, and further in-depth studies of what are the fundamental issues with this disease; as Peter Calverley suggests, we have made some progress, but need more. Even major published overviews of COPD largely ignore such important aspects of the disease as the realization that fifty percent of small airways have been obliterated by airway remodeling before the FEV1 has even changed (5), and the lethal association between even early/mild COPD and lung cancer. It is biologically plausible that the link between cancer and COPD, which is an independent risk apart from smoking, may be related to parameters that could be more widely measured, such as markers of EMT or epithelial hyper-vascularity. Progression of this conversation will be helped by discussion of the different approaches from centers that have made great efforts to perform translational quantitative studies in COPD patient airways. We would be very interested in further debate, and indeed collaboration, between centers with access to and experience of working with human COPD tissue, in the spirit of the excellent article by Ratko Djukanović et al, which came out in the same edition of the ERJ. The leading respiratory journals have a key capacity to promote this approach through supporting novel descriptive human tissue studies that provide new insights and paradigms, even when at variance with the respiratory establishment’s current “tenets”.

**Acknowledgments:** This work was supported by Clifford Craig Medical Research Foundation.

**References**


