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Epithelial mesenchymal transition (EMT): A necessary new therapeutic target in COPD?

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We read with interest the recent article by Jing Yang et al. in the American Journal of Respiratory and Critical Care Medicine (AJRCCM), considering smoking-induced small airway epithelial cell reprogramming, mediated by exaggerated EGF/EGFR signalling (1). Understanding of smoking-related COPD pathology is hugely important and has recently had a significant surge of new insights, and it is encouraging that leading respiratory journals are recognising this. However, we would like to suggest that a broader discussion of these new insights into COPD pathology might have been appropriate with this opportunity. In particular, a more integrated consideration of epithelial mesenchymal transition (EMT), its relationship to EGFR up-regulation, and perhaps the potential effects of inhaled corticosteroids (ICS) on these facets of COPD is urgently needed to aid discussion of this devastating pathophysiology.

We and several other groups have demonstrated over recent years that both structurally and biochemically, there is active EMT present in the airway epithelium in COPD, in both large and small airways, and that this is closely related to airflow obstruction (2, 3). Furthermore, the Rbm and epithelium in large airways only is hyper-vascular (4) i.e. giving the classic appearance of active EMT type-III, which is a pre-malignant condition (5) which fits in with what we know about the excess risk of lung cancer in COPD. The other prime pathology associated with COPD is small airway fibrosis and obliteration, and this could potentially be related to active Type-II EMT at this site (2). We have shown that these processes are closely associated with epithelial EGFR hyper-expression, which may be major up-stream driver of such novel pathologies, which would fit with the suggestions being made by Yang et al (1) for a central place in COPD for EGFR.

Further, we have reported in a pilot randomized controlled trial that inhaled corticosteroid fluticasone propionate given in high dose over six months suppressed EMT-related changes in large airways of COPD patients (6), along with suppression of EGFR expression. This is the first study reporting anti-EMT/EGFR effects of inhaled corticosteroids in COPD, where of course they are widely used as putative “anti-inflammatory” agent, modelled on their effects in eosinophilic asthma. In human epidemiological studies it is strongly suggested that patients on inhaled corticosteroids, albeit only at high doses (as used in our study), are associated with an appreciable (50%) reduction in the risk of lung cancer. We suggest EMT might be a process through which this effect of ICS occurs. If this is true, it has huge implications for therapeutic and public health policy, since it strongly suggests that ICS or

some other agents having similar effects, should be given early in the natural history of COPD, not just to suppress airway luminal inflammation, but also to suppress epithelial activation, EMT and related fibrotic and malignant consequences.

In summary, we are beginning to recognise that epithelial activation, basal cell reprogramming with EMT and vessel changes, may well represent fundamentally important aspects of COPD pathology in its broadest sense, including the severe sequelae of airway fibrosis and cancer development. At last, we may be getting into a position which allows an integrated understanding of this airway disease, with the potential to be translated into a new paradigm for earlier therapy attacking fundamental disease mechanisms rather than really only symptoms and clinical exacerbations in later-stage patients.

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