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Early View

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Title: **Broadening concepts of core pathobiology in various aspects of COPD development**

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Dear Editor,

We welcome the innovative paper by Xu et al (1) which investigates in considerable depth the origins of emphysema in smokers. Understandably, given the difficult methodology and harvesting of such tissues, only a small number of demographically variable post-transplant explanted COPD lungs were studied. We would like to contribute to the discussion in the context of known COPD pathophysiology, and in particular thinking about this disease at a much earlier stage.

It seems clear from previous pioneering work (of this group among others), that destruction of small airways is inherently connected to the later development of centrilobular emphysema of smokers (2). This profound injury to the small conducting airways (2, 3), involving their fibrosis and ultimate destruction, causes passive air-trapping in a centrilobular distribution with ultimately over years development of destructive emphysema in this same over-inflated alveolar/respiratory bronchiolar area (1, 4).

We wonder if the pathological “hotspots” which this paper focuses on, with Lm (approximating alveolar diameter) of between 500 and 1000 micron, might represent the disease transition zone between air-trapping and actual emphysema related to this very last phase of full-blown COPD development. Do the authors feel that these two states can be differentiated with the methods used? Further to this, did the authors analyse the range of alveoli from about 750-1250 microns average as their “hotspots”, which in fig 1 seems better related to progressive loss of bronchioles than the Lm range they chose?

We were especially stimulated by two core messages in the paper:

1. There is gene activation in the “hotspots” suggestive of active tissue damage and TGF-related repair/fibrosis. This is consistent with active epithelial-mesenchymal transition (EMT)/plasticity (EMP), full or partial, that we and now many others have demonstrated throughout the airways in smokers. This process is suggested to be crucial to the all-important pathogenic small (conducting) airway remodelling/fibrosis/obstruction in COPD (3), as well as the increased cancer risk in COPD which is over and above that due to smoking exposure per se (5). Indeed, EMT is suggested as active in this investigation, from Fig E3 in the supplement. Further, activation of NOD1, MAPK and caspase 1 as in Fig E4 has also been linked to induction of EMT (6). Inflammasome activation and IL1-beta stimulation due to infection are also involved (7). Specific bacterial colonisation/infection, related to microbial adhesion site upregulation on the luminal epithelium surface is a significant part of COPD pathology (8), and infective exacerbations are a recognised determinant of progressive COPD pathophysiology. Emergent studies also show that regardless of smoking status, lung cancer, presumably associated with EMT, is significantly higher in people with bronchiectasis than in those without bronchiectasis (9). Therefore, we wonder whether the authors have any further information on the microbiome in the airways or lungs they studied?
2. In the hotspots there is also evidence of lymphocyte (and possibly M1 macrophage) recruitment, but this seems quite a small effect and not especially related to bronchioles in the micrographs provided (Fig 2). However, it is interesting that the signal for CD8 cells comes across strongly in most studies of airway wall cellularity even in early COPD; this is in the context of what is a predominantly hypocellular airway wall in COPD (3). We feel more work to define what these cells are doing and why, is to be welcomed. As the authors kindly acknowledge, we have also described a phenotypic

switch to M1 macrophages specifically in the COPD airway wall (in contrast to the lumen) (3) and again the potential significance of this needs further work.

Finally, it is notable that overinflation itself has recently been shown to induce an inflammatory response, and notably made worse by co-presence of infection (10). This combination (peribronchial air-trapping plus infection) may well be operative in the Xu et al paper (1) in the context of the very worse end-stage of COPD being studied.

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