Activin-A: active in inflammation in COPD

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Restoring the activin-A/follistatin imbalance is a therapeutic strategy worth pursuing in COPD
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Chronic obstructive pulmonary disease (COPD) is characterised by irreversible airflow limitation in which chronic inflammation of the airways plays a major role. The persistent inflammation is triggered by inhaled toxic substances, such as cigarette smoke. Accumulating evidence indicates the involvement of developmental pathways in chronic lung diseases, including COPD [1]. Signalling pathways such as transforming growth factor (TGF)- β , WNT and Sonic hedgehog have all been linked to COPD, either because of genetic associations or because of differential gene and protein expression in lung tissue [2–4]. Although these pathways were originally primarily known for their role in development, it is now increasingly clear that these pathways also play crucial regulatory roles in tissue inflammation and repair, providing a plausible explanation for the involvement of these pathways in COPD [3].

Activin-A, a member of the TGF- β superfamily, is an important regulator of embryonic development, haematopoiesis and a broad range of tightly regulated biological processes, including immunity and tissue repair [5]. Dysregulation of activin-A may contribute to the development of disease. Recently, increased expression of activin-A has been demonstrated in pulmonary hypertension [6], acute lung injury [7] and asthma [8]. Oxidative stress, Toll-like receptor ligands and inflammatory cytokines stimulate the expression and production of activin-A, which in turn regulates inflammatory cytokine release, explaining its role in inflammatory responses [7]. Accordingly, the endogenous activin-A inhibitor follistatin has attracted great interest in view of its ability to counteract activin-A activity. Due to its involvement in inflammatory responses, it is rational to connect activin-A to the pathogenesis of inflammatory diseases. An imbalance between activin-A and follistatin potentially leads to excess activin-A-mediated inflammatory responses. However, the roles of activin-A and follistatin have not yet been established in COPD.

In this issue, VERHAMME *et al.* [9] demonstrate for the first time that activin-A is an important regulator of cigarette smoke-induced inflammation in COPD. They found that activin-A is elevated and activated in the airway epithelium, airway smooth muscle and alveolar macrophages of COPD patients. These findings were further validated *in vivo*, demonstrating that cigarette smoke induces marked expression of activin-A in the lungs and bronchoalveolar lavage (BAL) fluid of mice. *In vitro*, activin-A expression increased after cigarette smoke exposure of human bronchial epithelial cells, whereas expression of follistatin was reduced. These data suggest that cigarette smoke is a major factor involved in activin-A upregulation. Notably, regardless of airflow limitation, lung tissues of current smokers had a significantly higher level of activin-A mRNA expression compared with nonsmoker subjects, whereas the increased activin-A protein expression in airway epithelium was specific for COPD. Most intriguingly, this study revealed that inhibition of activin-A signalling by administration of its endogenous inhibitor follistatin, attenuates cigarette smoke-induced production of interleukin (IL)-6, monocyte chemoattractant protein-1, tumour necrosis factor (TNF)- α , keratinocyte-derived chemokine and TGF- β ₁, and induces the release of the anti-inflammatory cytokine IL-10. Furthermore, administration of follistatin reduced the number of inflammatory cells, such as monocytes, macrophages, neutrophils, and CD4⁺ and CD8⁺ T-cells, in the BAL fluid of cigarette

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smoke-exposed mice. The authors conclude that activin-A is not an innocent bystander but plays an active role in cigarette smoke induced pulmonary inflammation [9].

The role of activin-A has been widely studied in inflammatory cells and a dual role of activin-A in inflammatory responses has been proposed. On one hand, activin-A promotes alveolar cell death and stimulates the production of pro-inflammatory cytokines, including IL-6. Furthermore, activin-A is increased following pulmonary lipopolysaccharide (LPS) exposure and follistatin reduces LPS-induced pulmonary inflammation in mice [7]. On the other hand, follistatin was shown to augment the production of pro-inflammatory cytokines in concerted action with TNF- α and IL-13 [8]. This dual role was also noted in an LPS model of endotoxaemia, showing that low doses of follistatin augmented IL-6 expression, but reduced TNF- α and IL-1 β concentrations, whereas at higher follistatin concentrations IL-6 expression was normalised [10]. Therefore, the role of activin-A in cigarette smoke-induced inflammation and COPD may be more complex, and studies are warranted to identify its role in more detail. In particular, its potential anti-inflammatory role in the regulation of inflammation in COPD needs to be clarified and the therapeutic potential of activin-A inhibition needs to be explored in more detail.

Several intriguing questions arise from this study that require further investigation. Activin-A regulates expression of its own inhibitor follistatin as a negative feedback mechanism to control the degree of inflammation [11]. Increased expression of follistatin was not observed in COPD, suggesting that this negative feedback mechanism might be altered, leading to uncontrolled inflammatory responses. Therefore, it is important to examine the effect of cigarette smoke on activin-A and follistatin expression in epithelial and inflammatory cells derived from COPD patients. Moreover, it is rational to explore the role of activin-A in remodelling as activin-A shares homology and signalling characteristics with TGF- β ₁. In this respect, follistatin inhibits bleomycin-induced pulmonary fibrosis [12] and ovalbumin induced airway remodelling [13]. Interestingly, activin-A also promotes alveolar epithelial cell death [7]. Hence, it would be worthwhile to explore the role of activin-A in emphysema. Furthermore, although administration of exogenous follistatin was able to inhibit cigarette smoke-induced inflammation, additional study is needed to develop strategies to restore the endogenous activin-A/follistatin imbalance.

In conclusion, the study of VERHAMME *et al.* [9] sheds light on the role of activin-A and follistatin in COPD, and motivates further investigation. Persistent and exaggerated production of activin-A might be a key factor provoking persistent inflammation in COPD. Restoring the activin-A/follistatin imbalance is a therapeutic strategy worth pursuing in COPD.

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