Unraveling the role of MUC5B in idiopathic interstitial pneumonias (IIPs)

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The fibrosing IIPs are characterised by progressive scarring of the alveolar interstitium, which leads to significant morbidity and mortality. Idiopathic pulmonary fibrosis (IPF) is the most common and most severe form of IIP with a median survival of 3 years, limited treatment options and an increasing prevalence. The strongest and most replicated risk factor for IPF is the promoter variant located in a highly conserved region of the genome ~3 kilobases upstream of the airway mucin *MUC5B* transcription start site.[1] The *MUC5B* variant rs35705950 has a regulatory role and is associated with increased RNA expression in whole lung tissue in IPF and controls.[2] In mice, transgenic overexpression of Muc5b leads to increased lung fibrosis and decreased mucociliary clearance, supporting the functional role of this airway mucin in lung fibrosis.[3] However, studies of the MUC5B function in human disease have been limited.

The short communication by Stock *et al*[4] is a follow-up to a previous publication by this group in which they characterised MUC5B protein expression in distal airways and honeycomb lesions in a set of surgical lung biopsies of IPF, scleroderma-associated NSIP (SSc-NSIP) and idiopathic NSIP (I-NSIP) lung tissue,[5] showing that the primary site of MUC5B overexpression was in the distal airway and that this was specific to IPF. Nakano *et al* at the same time reported that increased MUC5B expression in the distal airway was associated with the *MUC5B* promoter variant.[6] Stock *et al* have now validated the observation by Nakano *et al* and, for the first time, show that the effect of the alternate T allele is present in IPF distal airway and honeycomb cysts but not in SSc-NSIP, I-NSIP nor in histologically normal control lung tissue. Importantly, the *MUC5B* promoter variant is not associated with increased risk of these other IIPs.[1] Moreover, Stock *et al* demonstrate that individuals with the T allele and higher MUC5B have less severe disease, as assessed by the Composite Physiological Index (CPI).

The main significance of the present study is the replication of previous findings in a larger number of samples and expansion of the variant analysis to other fibrosing IIPs and control tissue, demonstrating specificity to IPF. Stock and Nakano both quantified MUC5B in randomly selected regions of the lung sections to avoid bias. Ideally the entire lung sections will be analysed in the future to further reduce any potential bias. While results of the analysis of the *MUC5B* T allele association with disease severity are intriguing, we view them as preliminary because CPI, although validated against CT,[7] is not a commonly used measure of disease severity. Given the controversy of the protective role of the *MUC5B* variant in survival,[8 9] it will be important to validate these results in larger cohorts with multiple measures of diseases severity. Nevertheless, the work by Stock *et al*[4] provides important further evidence for the functional significance of the *MUC5B* promoter variant to IPF.

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REFERENCES

1 Evans CM, Fingerlin TE, Schwarz MI, *et al*. Idiopathic pulmonary fibrosis: a genetic disease that involves mucociliary dysfunction of the peripheral airways. *Physiol Rev* 2016;96:1567–91.
2 Helling BA, Gerber AN, Kadiyala V, *et al*. Regulation of MUC5B expression in idiopathic pulmonary fibrosis. *Am J Respir Cell Mol Biol* 2017;57:91–9.
3 Hancock LA, Hennessy CE, Solomon GM, *et al*. Muc5B overexpression causes mucociliary dysfunction and enhances lung fibrosis in mice. *Nat Commun* 2018;9:5363.
4 Stock CJ, Conti C, Montero-Fernandez Ángeles, *et al*. Interaction between the promoter *MUC5B* polymorphism and mucin expression: is there a difference according to ILD subtype? *Thorax* 2020;75:902–4.
5 Conti C, Montero-Fernandez A, Borg E, *et al*. Mucins MUC5B and MUC5AC in distal airways and honeycomb spaces: comparison among idiopathic pulmonary fibrosis/usual interstitial pneumonia, fibrotic nonspecific interstitial pneumonitis, and control lungs. *Am J Respir Crit Care Med* 2016;193:462–4.
6 Nakano Y, Yang IV, Walts AD, *et al*. Muc5B promoter variant rs35705950 affects MUC5B expression in the distal airways in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2016;193:464–6.
7 Wells AU, Desai SR, Rubens MB, *et al*. Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography. *Am J Respir Crit Care Med* 2003;167:962–9.
8 Peljto AL, Zhang Y, Fingerlin TE, *et al*. Association between the MUC5B promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis. *JAMA* 2013;309:2232–9.
9 Dudbridge F, Allen RJ, Sheehan NA, *et al*. Adjustment for index event bias in genome-wide association studies of subsequent events. *Nat Commun* 2019;10:1561.