IPF: time for the (ciliary) beat generation?

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Idiopathic pulmonary fibrosis (IPF), the most common of the idiopathic interstitial pneumonias remains a disabling, progressive lung disease with extremely poor prognosis, in which no pharmacological intervention significantly alters outcome.1 A relatively poor understanding of the complex pathophysiology of IPF continues to hinder the identification of effective therapies, and of patients most likely to benefit from existing treatments. Universal interstitial pneumonia is the histological hallmark of IPF, characterised by temporospatial heterogeneity in which normal lung is interspersed with areas of subpleural interstitial fibrosis, loss of normal alveolar architecture and the presence of fibroelastic foci.2 Histological sections may also show 'bronchiolisation' of the distal airway with alveolar structures replaced by enlarged airspaces (forming characteristic honeycomb cysts) lined by epithelial cells more akin to proximal airway epithelium, often ciliated and mucus producing.3,4 The potential importance of mucus production in the pathogenesis of IPF has been highlighted by a landmark study demonstrating that a common variant within the putative promoter region of MUC5B (an airway mucin gene) is strongly associated with familial interstitial pneumonia and IPF.5 Moreover, subjects with IPF had significantly higher expression of MUC5B protein levels compared with controls, and this was localised to areas of lung fibrosis. It has been hypothesised that excessive MUC5B may impair the host response to alveolar injury through excess mucus plugging and impaired clearance of inhaled substances and microorganisms. Alternative theories propose that MUC5B may interfere directly with alveolar repair mechanisms, either through disruption of interactions between type II alveolar epithelial cells and extracellular matrix, or by interfering with properties of surfactant and promoting alveolar collapse.

While there has been a proliferation in interest surrounding mucin production in IPF, the importance of cilia has received much less attention. The fascinating gene expression study from Yang et al6 in this edition of Thorax seems set to change this. The authors performed comparative RNA microarray analysis on lung tissue from 119 patients with well-characterised IPF and from patients with brain death whose lungs were considered unusable for lung transplantation. Genes differentially expressed in IPF were interrogated using hierarchical clustering, yielding two subgroups of IPF differentiated by distinct expression profiles. Intriguingly, the strongest signal distinguishing the two cohorts of patients with IPF appeared to come from cilia-associated genes and their structural components (DNAH6, DNAH7, DNAI1 and RPGRIP1L) as well as MUC5B. The authors broadly replicated their findings in lung tissue from an independent cohort with IPF. Interestingly, the two IPF cohorts were indistinguishable clinically, but the 'cilia-high' group had more histological honeycombing in tissue taken from the area immediately adjacent to that used for microarray analysis.

This meticulous study adds important new knowledge in IPF. Consistent findings in two independent cohorts of well-characterised patients, relevant tissue, strong genetics expertise and decent sample sizes represent obvious strengths of the study, and this was localised to areas of lung fibrosis. It has been hypothesised that excessive MUC5B may impair the host response to alveolar injury through excess mucus plugging and impaired clearance of inhaled substances and microorganisms. Alternative theories propose that MUC5B may interfere directly with alveolar repair mechanisms, either through disruption of interactions between type II alveolar epithelial cells and extracellular matrix, or by interfering with properties of surfactant and promoting alveolar collapse.

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Despite these considerations, the potential importance of this study is considerable. Certainly it highlights the ability of good genetic studies to generate new hypotheses and new avenues for exploration. In this particular case it throws attention onto the bronchiolisation process. Considerable focus has centred on epithelial-to-mesenchymal transition in recent years, but perhaps we have ignored the potential of stressed alveolar epithelium to transform into an entirely different epithelial configuration(s). The tantalising possibility, of course, is that secretion of mucin and upregulation of cilia-associated genes may be intrinsically linked. The authors of the present study are ideally placed to begin to focus on this new arena as their clinical studies identify potential genetic polymorphisms in the MUC5B promoter region may be associated with different EPF subtypes in recent years, but perhaps we have ignored the potential of stressed alveolar epithelium to transform into an entirely different epithelial configuration(s). The tantalising possibility, of course, is that secretion of mucin and upregulation of cilia-associated genes may be intrinsically linked. The authors of the present study are ideally placed to begin to focus on this new arena as their clinical studies identify potential genetic polymorphisms in the MUC5B promoter region may be associated with different EPF subtypes.

Of course, we remain frustratingly distant from the day when we can perform something like a transbronchial biopsy and have its transcriptome reliably inform us how best to manage patients with IPF. Nevertheless, a real momentum seems to be building in terms of high quality clinical studies identifying potentially important processes in the biology of IPF. The important next step is obviously to determine whether these can be manipulated to therapeutic advantage. In this regard, we currently await results from the final part of the PANTHER-IPF trial. Assessing whether the mucolytic, antioxidant N-acetylcysteine has beneficial effects in IPF. Meantime, the elegant study from Yang et al suggests that perhaps the ciliary beat is the beat to follow. Perhaps IPF researchers are ready to answer the question Jack Kerouac himself posed in On The Road—‘You boys going to get somewhere, or just going?’

REFERENCES


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