Desmoplakin: An Important Player in Aging Lung Disease

Idiopathic pulmonary fibrosis (IPF) is a devastating interstitial lung disease characterized by progressive fibrogenesis of unknown cause. The decline in lung function of affected patients causes fatal respiratory insufficiency, and medium survival is just 3–4 years after diagnosis (1). IPF is believed to be caused by a complex interaction between genetic and environmental factors, which is reflected by the set of currently known risk factors (male sex, smoking history, elderly age, and presence of genetic risk loci) (1). Multiple genome-wide association studies identified disease predisposing alleles. The minor allele of rs35705950 in the *MUC5B* (mucin 5B) promoter region confers the highest risk for IPF, the minor G allele of rs2076295 in intron 5 of the *DSP* (desmoplakin) gene is the second in line with an odds ratio of approximately 1.4 (2–4).

DSP is a critical component of desmosomes, which are important for cell–cell adhesion, but the protein has also been shown to influence cell proliferation, differentiation, migration, and apoptosis (5). Immunohistochemical staining localized DSP to the airway epithelia of normal and fibrotic human lungs and to the epithelial cells lining cystic areas of the fibrotic lung but not to the alveoli (4). The rs2076295 risk allele was shown to associate with reduced RNA expression in IPF and control lung tissue (4), although this was difficult to reconcile with the increased RNA expression level in IPF lung tissue when compared with control tissue (4). Furthermore, a direct relation between the polymorphism and DSP expression levels, evidence of differential expression in pulmonary cells, and how this may relate to pathogenic processes in IPF remained unknown.

In this issue of the *Journal*, Hao and colleagues (pp. 1225–1236) follow up on previous observations and provide evidence that the rs2076295 locus is directly responsible for differential RNA expression of DSP in primary epithelial cells and a cell line of human bronchial epithelial cells, and they experimentally confirm that the G allele decreases DSP RNA expression (6). These findings form the basis for further investigations into the localization and differential expression of DSP in pulmonary cells and its role in processes associated with IPF pathogenesis. They show that the loss of DSP in bronchial cells causes increased expression of epithelial–mesenchymal transition and extracellular matrix genes, increased cell migration, and decreased transepithelial electrical resistance. Furthermore, silencing the extracellular matrix genes MMP7 and MMP9 reversed the increased migration (6), thus, providing a direct link between the IPF risk locus, low levels in pulmonary cells, and pathogenic processes characteristic of the remodeling process in IPF.

Desmosomes are typically present in tissues that experience intense mechanical stress or shear stress, such as the heart and skin (7). However, one of the major strengths of the current study is that the authors perform fluorescent *in situ* hybridization costaining of DSP and specific pulmonary cell markers. With this highly sensitive approach, they show that DSP is not only present in airway epithelial cells, but also in the alveolar compartment in both alveolar type I (AT1) and type II (AT2) cells. Furthermore, intracellular localization provided evidence that DSP is most prominently expressed near cell–cell junctions but is also expressed just below the apical cell surface of cultured bronchial epithelial cells and in the apical region of ciliated and club cells in human lung tissue (6), supporting a further prominent role for DSP in maintaining airway epithelial integrity.

To better understand cell type–specific expression levels, the authors analyzed publicly available single-cell RNA-sequencing data from normal and IPF lungs. Interestingly, these data show that the increase in expression of DSP in IPF was caused by epithelial cells only (most prominently by basal cells and to a minor degree by club and secretory cells) (6). This may explain the previously observed increased total lung expression of DSP in IPF. Surprisingly, expression in both AT1 and AT2 cells was already low in control samples and decreased further in IPF. This may well be of major importance because the lowered alveolar cell expression is in line with the low expression conferred by the DSP risk allele. Furthermore, it supports a role for alveolar epithelial cells and underscores the importance of cell-specific analyses.

Bronchial epithelial cells are not the primary suspect in IPF. Most evidence, particularly evidence related to genetic susceptibility, points toward aberrant processes in the AT2 cells initiating the development of pulmonary fibrosis (8). Epithelial integrity of the alveolar compartment, however, will not only involve AT2 cells, but also—and perhaps most importantly—AT1 cells because of their large surface area and extremely flat shape (9). Desmosomes in AT1 cells aid maintenance of the integrity of tissues under mechanical stress, such as at the peripheral portions of the lungs (10). The fact that IPF lungs are typically characterized by fibrogenesis at bibasilar peripheral lung regions is highly suggestive of a causal role of mechanical stress in IPF (11). The involvement of low levels of DSP in the development of IPF and the decreased expression of DSP in AT1 and AT2 cells in IPF support this.

The rs2076295 DSP polymorphism is not only associated with IPF but also associates with chronic obstructive pulmonary disease (COPD). Opposite to IPF, it is the high-expressing major T allele that confers risk for COPD (12) and for the progression of emphysema in COPD (13). Recently we posted the theory of trade-offs in aging pulmonary diseases (14). A trade-off exists when a benefit in one context entails a cost in another (15). Small constitutional differences conferred by common DNA polymorphisms are insignificant in early life but may promote pathogenic processes in aged cells or pulmonary compartments

Originally Published in Press as DOI: 10.1164/rccm.202006-2457ED on July 27, 2020

Am J Respir Crit Care Med Vol 202, Iss 9, pp 1201–1216, Nov 1, 2020
Internet address: www.atsjournals.org

(14). For DSP, a trade-off exists between low levels that predispose to IPF but protect against COPD in aged subjects.

In conclusion, the increased risk for IPF in carriers of the rs2076295 G allele is conferred by the decreased expression of DSP and associated pathogenic processes in pulmonary cells. Future research should shed further light on the involvement of DSP in specific pulmonary cells and compartments involved in the development of aging lung diseases, IPF, and COPD. However, the presence of trade-offs in aging lung diseases will challenge the translation of findings into therapeutic interventions. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Coline H. M. van Moorsel, Ph.D.
ILD Center of Excellence
St. Antonius Hospital
Nieuwegein, the Netherlands

References

1. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, *et al*.; American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018;198:e44–e68.
2. Allen RJ, Porte J, Braybrooke R, Flores C, Fingerlin TE, Oldham JM, *et al*. Genetic variants associated with susceptibility to idiopathic pulmonary fibrosis in people of European ancestry: a genome-wide association study. *Lancet Respir Med* 2017;5:869–880.
3. Fingerlin TE, Murphy E, Zhang W, Peljto AL, Brown KK, Steele MP, *et al*. Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. *Nat Genet* 2013;45:613–620.
4. Mathai SK, Pedersen BS, Smith K, Russell P, Schwarz MI, Brown KK, *et al*. Desmoplakin variants are associated with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2016;193:1151–1160.
5. Huber O, Petersen I. 150th anniversary series: desmosomes and the hallmarks of cancer. *Cell Commun Adhes* 2015;22:15–28.
6. Hao Y, Bates S, Mou H, Yun JH, Pham B, Liu J, *et al*. Genome-wide association study: functional variant rs2076295 regulates desmoplakin expression in airway epithelial cells. *Am J Respir Crit Care Med* 2020;202:1225–1236.
7. Stokes DL. Desmosomes from a structural perspective. *Curr Opin Cell Biol* 2007;19:565–571.
8. Parimon T, Yao C, Stripp BR, Noble PW, Chen P. Alveolar epithelial type II cells as drivers of lung fibrosis in idiopathic pulmonary fibrosis. *Int J Mol Sci* 2020;21:E2269.
9. Kasper M, Barth K. Potential contribution of alveolar epithelial type I cells to pulmonary fibrosis. *Biosci Rep* 2017;37:BSR20171301.
10. Kulkarni T, de Andrade J, Zhou Y, Luckhardt T, Thannickal VJ. Alveolar epithelial disintegrity in pulmonary fibrosis. *Am J Physiol Lung Cell Mol Physiol* 2016;311:L185–L191.
11. Leslie KO. Idiopathic pulmonary fibrosis may be a disease of recurrent, tractional injury to the periphery of the aging lung: a unifying hypothesis regarding etiology and pathogenesis. *Arch Pathol Lab Med* 2012;136:591–600.
12. Hobbs BD, Putman RK, Araki T, Nishino M, Gudmundsson G, Gudnason V, *et al*. Overlap of genetic risk between interstitial lung abnormalities and idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2019;200:1402–1413.
13. Kim W, Cho MH, Sakornsakolpat P, Lynch DA, Coxson HO, Tal-Singer R, *et al*. DSP variants may be associated with longitudinal change in quantitative emphysema. *Respir Res* 2019;20:160.
14. van Moorsel CHM. Trade-offs in aging lung diseases: a review on shared but opposite genetic risk variants in idiopathic pulmonary fibrosis, lung cancer and chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 2018;24:309–317.
15. Gluckman PD, Low FM, Buklijas T, Hanson MA, Beedle AS. How evolutionary principles improve the understanding of human health and disease. *Evol Appl* 2011;4:249–263.

Inhaled Corticosteroid Withdrawal in Chronic Obstructive Pulmonary Disease: Can IMPACT Help?

The pharmacological strategy to manage chronic obstructive pulmonary disease (COPD), as recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), is to initiate treatment with long-acting bronchodilators, namely long-acting muscarinic antagonists (LAMAs) and long-acting β_2-agonists (LABAs), alone or in combination (1). For patients with frequent COPD exacerbations and significant dyspnea despite these bronchodilators, treatment is intensified to triple therapy by adding inhaled corticosteroids (ICSs) (1). These recommendations have remained quite stable over time, although the 2019 recommendations introduce the use of blood eosinophil levels in the decision to add ICSs (2).

A global phenomenon, however, is the large gap between these recommendations and clinical practice, particularly in respect to the overuse of ICSs. In the United States, the SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) found that 50% of patients were treated with nonindicated ICS-containing regimens (3). The POPE (Phenotypes of COPD in Central and Eastern Europe) study found that over 50% of nonexacerbators were using ICSs, including 37% on triple therapy (4). Apart from the absence of effectiveness, a major concern around such nonindicated ICS overuse is the increased risk of pneumonia and of other adverse events associated with ICS (5).

S.S. is the recipient of a Distinguished James McGill Professorship award. His research is funded in part by infrastructure grants from the Canadian Institutes of Health Research and the Canadian Foundation for Innovation.

Originally Published in Press as DOI: 10.1164/rccm.202006-2600ED on August 6, 2020