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NOTCH-ing up Surface Tension in the Fibrotic Lung

Why does idiopathic pulmonary fibrosis (IPF) occur in a pattern that is peripheral and lower zone predominant? The paper in this issue of the *Journal* by Wasnick and colleagues (pp. 283–299) sheds some light on this question (1). Mechanical stress plays a key role in development, maturation, and fibrogenesis and exerts effects on endothelial, epithelial, and mesenchymal cells (2). IPF is radiographically evident first in lower zone peripheral regions of the lung where stretch is most manifest when negative pressure is applied to the pleural space during spontaneous respiration (3). Wasnick and colleagues have added to our understanding of the pathobiology of IPF in this study through experimental methods that involve cell culture, human IPF lung specimens including precision-cut lung slices, and a murine model of pulmonary fibrosis to show that Notch1 (Notch receptor 1) activation occurs in type 2 alveolar epithelial cells (AEC2s) and leads to both AEC2 proliferation and plasticity, with diminished maturation of SFB (surfactant protein B) and SFC (surfactant protein C) (1). The latter is important because surfactant reduces cell surface tension and prevents alveolar collapse (4). The most compelling evidence for Notch signaling as an early initiator of fibrosis was the finding of enhanced Notch signaling in regions of IPF lung that appeared histologically normal. Recently, blood SFB concentrations were found to be the most predictive of progression of interstitial lung abnormalities (ILAs) in two prospective cohorts (5). It would be of interest to know whether imaging effects on regional collapse observed by Wasnick and colleagues are present in human subjects with progressive ILAs and whether the elevated blood SFB concentrations represent pro-SFB in ILA cohorts.

Although the observations by Wasnick and colleagues contribute to our understanding of IPF, they do not exclude the profibrotic impact of Notch1 activation on other cell types involved in lung fibrogenesis or other mechanoreceptor-mediated mechanisms of Notch1 activation. Notch1 cleavage has the capacity to transform several pulmonary cell types, including fibroblasts, endothelial cells, and, as shown in this study, AEC2s into cells that have a more fibrogenic phenotype. Notch1 signaling has previously been shown to induce lung fibroblast-to-myofibroblast transition, and conditional mesenchymal cell–specific Notch1 knockout mice exhibit diminished lung fibrosis compared with control animals in response to bleomycin (6). This is consistent with the findings that Notch1 signaling liberates latent TGF-β (transforming growth factor-β) through mechanical forces involving αvβ6 and αvβ1 integrins (7). This is clinically relevant because integrin inhibitors to limit activation of TGF-β are being evaluated as a treatment for IPF in the INTEGRIS (Evaluation of Efficacy and Safety of PLN-74809 in Patients With Idiopathic Pulmonary Fibrosis) clinical trial (NCT 04396756). Furthermore, endothelial cell–to–myofibroblast transition via the Jagged1 (Jagged receptor 1)/Notch1 signaling pathway has been implicated during bleomycin-induced pulmonary fibrosis in rats (8). Others have shown using a repetitive bleomycin lung injury model that there is activation of the Jag1 (Jagged canonical Notch ligand 1) ligand in pulmonary capillary endothelial cells adjacent to augmented Notch1 signaling in adjacent perivascular fibroblasts (9). So, it appears that Notch1 signaling may be involved in multiple pulmonary cell types during lung fibrogenesis, as enhanced Notch1 signaling in lung cells from various lineages appears to mediate profibrotic effects.

The concept of aberrant mechanosensitive signaling was recently extended to a failure of normal alveolar AEC2 differentiation. Inhibition of AEC2 differentiation into AEC1s led to pulmonary fibrosis when combined with stretch induced in the postpneumectomy lung (10). It is notable that peripheral distribution of fibrosis progressing centrally over time was observed in this model, similar to that seen in human IPF (10). Notch signaling is required for activation of lineage-negative stem cell progenitor cells, but a subsequent decrease in Notch1 signaling is necessary for these lung progenitors to differentiate into alveolar epithelial cells (11). This is in keeping with the observations of Wasnick and colleagues that diminishing Notch1 signaling was protective in the murine model and in human lung slices that allowed more normal AEC2 differentiation and function after injury.

Mechanical force–induced ligand binding–induced activation of cell transformation to more fibrotic phenotypes is under the influence of ADAM10 (A disintegrin and metalloproteinase domain 10) and ADAM17, which are Ca^{2+}-regulated transmembrane sheddases in proximity to Notch1. Caolo and colleagues recently reported that Notch 1 signaling is activated by shear stress through a mechanism that involves ADAM10 and Piezo1 (piezo-type mechanosensitive ion channel component 1) in endothelial cells (12). Recently, mass spectroscopic approaches identified higher concentrations of *active* ADAM10/17 in IPF lung tissue (13). Indeed, mechanical forces expose the moiety that ADAMs cleave when there is ligand binding to Notch1. This cleavage event liberates Notch1 from the cell membrane and enables its translocation to the nucleus after further

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cleavage from γ-secretase. Inhibiting MMP-1 (matrix metalloproteinase 1) and ADAM10 using a small-molecule inhibitor in an *in vitro* lung fibrosis assay decreased expression of α-smooth muscle actin, and this may be relevant because α-smooth muscle actin may contribute by further inducing contractile mechanical forces. ADAM10 and ADAM17 have a wide array of cell surface substrates, and *in vivo* effects of their inhibition require further study.

In summary, Wasnick and colleagues' findings support a role for Notch1 signaling in the reduced capacity for AEC2 regeneration and deficient surfactant production. Sustained broad Notch inhibition has been explored as a treatment for cancer, and its tolerability is limited primarily by gastrointestinal side effects (14). It remains to be seen whether the use of Notch1 inhibitors through an inhalational route of administration may be more effective and better tolerated or whether Notch1 signaling can be blocked *in vivo* by downstream inhibition of the Jak (Janus kinase)–Stat (signal transducer and activator of transcription) pathway, as suggested by Wasnick and colleagues (1), or by upstream modulation of HDAC6 (histone deacetylase 6) (15). ■

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Comparing the Incomparable: Identifying Common Themes Across a Diverse Landscape to Address Equity in Lung Allocation

Solid organ allocation policy in the United States has evolved significantly in the past two decades. Since the U.S. Department of Health and Human Services' issuance of its final rule in March 2000, priority has been placed on severity of illness of the transplant recipient, while limiting the impact of geographic location of the organ donor in the allocation algorithm (1). The lung allocation score (LAS) was developed to transition lung allocation away from accrued wait time toward a system that maximizes transplantation benefit. The LAS has met some of its stated goals, with reduction in wait list deaths and increases in transplantation rates (2).

Although the LAS has improved the efficiency of lung allocation, its impact has differed in specific candidate cohorts. The original modeling used for the development of the LAS demonstrated that patients with idiopathic pulmonary fibrosis (IPF) had the highest risk of wait list mortality and a substantially lower risk of post-transplantation mortality than patients with other diagnoses (3),

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