Title

Stuck in a Moment: Does Abnormal Persistence of Epithelial Progenitors Drive Pulmonary Fibrosis?

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Authors

Auyeung, Vincent C
Sheppard, Dean

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Dale M. Needham, M.D., Ph.D.
Division of Pulmonary and Critical Care Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland

Outcomes After Surgery and Critical Illness Research Group
Johns Hopkins University
Baltimore, Maryland
and

Department of Physical Medicine and Rehabilitation
Johns Hopkins University School of Medicine
Baltimore, Maryland

ORCID ID: 0000-0002-0293-0549 (A.M.P.).

References

1. Honarmand K, Lalli RS, Priestap F, Chen JL, McIntyre CW, Owen AM, *et al*. Natural history of cognitive impairment in critical illness survivors: a systematic review. *Am J Respir Crit Care Med* 2020;202: 193–201.
2. Fan E, Dowdy DW, Colantuoni E, Mendez-Tellez PA, Sevransky JE, Shanholtz C, *et al*. Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. *Crit Care Med* 2014;42:849–859.
3. Hopkins RO, Suchyta MR, Kamdar BB, Darowski E, Jackson JC, Needham DM. Instrumental activities of daily living after critical illness: a systematic review. *Ann Am Thorac Soc* 2017;14:1332–1343.
4. Sasannejad C, Ely EW, Lahiri S. Long-term cognitive impairment after acute respiratory distress syndrome: a review of clinical impact and pathophysiological mechanisms. *Crit Care* 2019;23:352.
5. Cunningham C. Systemic inflammation and delirium: important co-factors in the progression of dementia. *Biochem Soc Trans* 2011;39:945–953.
6. Fink H, Helming M, Unterbuchner C, Lenz A, Neff F, Martyn JA, *et al*. Systemic inflammatory response syndrome increases immobility-induced neuromuscular weakness. *Crit Care Med* 2008;36:910–916.
7. Witteveen E, Wieske L, van der Poll T, van der Schaaf M, van Schaik IN, Schultz MJ, *et al*.; Molecular Diagnosis and Risk Stratification of Sepsis (MARS) Consortium. Increased early systemic inflammation in ICU-acquired weakness; a prospective observational cohort study. *Crit Care Med* 2017;45:972–979.
8. Griffith DM, Vale ME, Campbell C, Lewis S, Walsh TS. Persistent inflammation and recovery after intensive care: a systematic review. *J Crit Care* 2016;33:192–199.
9. Brummel NE, Hughes CC, Thompson JL, Jackson JC, Pandharipande P, McNeil JB, *et al*. Inflammation and coagulation during critical illness and long-term cognitive impairment and disability. *Am J Respir Crit Care Med* 2021;203:699–706.
10. Leisman DE, Ronner L, Pinotti R, Taylor MD, Sinha P, Calfee CS, *et al*. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. *Lancet Respir Med* [online ahead of print] 16 Oct 2020; DOI: 10.1016/S2213-2600(20)30404-5.
11. Yende S, D'Angelo G, Kellum JA, Weissfeld L, Fine J, Welch RD, *et al*.; GenIMS Investigators. Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. *Am J Respir Crit Care Med* 2008;177: 1242–1247.
12. Griffith DM, Lewis S, Rossi AG, Rennie J, Salisbury L, Merriweather JL, *et al*.; RECOVER Investigators. Systemic inflammation after critical illness: relationship with physical recovery and exploration of potential mechanisms. *Thorax* 2016;71:820–829.
13. Blyth BJ, Farhavar A, Gee C, Hawthorn B, He H, Nayak A, *et al*. Validation of serum markers for blood-brain barrier disruption in traumatic brain injury. *J Neurotrauma* 2009;26: 1497–1507.
14. Heyland DK, Stapleton RD, Mourtzakis M, Hough CL, Morris P, Deutz NE, *et al*. Combining nutrition and exercise to optimize survival and recovery from critical illness: conceptual and methodological issues. *Clin Nutr* 2016;35:1196–1206.
15. Heyland DK, Day A, Clarke GJ, Hough CT, Files DC, Mourtzakis M, *et al*. Nutrition and Exercise in Critical Illness Trial (NEXIS Trial): a protocol of a multicentred, randomised controlled trial of combined cycle ergometry and amino acid supplementation commenced early during critical illness. *BMJ Open* 2019;9:e027893.

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∂ Stuck in a Moment: Does Abnormal Persistence of Epithelial Progenitors Drive Pulmonary Fibrosis?

In idiopathic pulmonary fibrosis (IPF), a fibrotic niche is established that leads to persistent collagen deposition. The mechanisms underlying initiation and persistence of this niche and continuing progression of collagen deposition are poorly understood. In this issue of the *Journal*, Yao and colleagues (pp. 707–717) have developed a new mouse model of pulmonary fibrosis, induced by genetic *Sin3a* loss of function (Sin3a-LOF) in alveolar type 2 (AT2) cells (1). Unlike the single-dose bleomycin model of fibrosis, in which fibrosis peaks 21 days after exposure and then largely resolves, the fibrosis in Sin3a-LOF mice progresses steadily over 4–8 weeks, eventually causing death.

Yao and colleagues show that loss of *Sin3a* causes AT2 cells to adopt a complex cellular phenotype. The cells upregulate genes associated with hypoxia, mitochondrial dysfunction, DNA damage, and senescence. Similar patterns of gene expression were seen in single-cell sequencing of epithelial cells from patients with IPF. These cells expressed p21 protein and were hypoproliferative both *in vivo* and in organoids. Yao and colleagues further showed that the p53 pathway was critically downstream of Sin3a-LOF, as genetic and pharmacological p53 inhibition protected Sin3a-LOF mice from fibrosis. The persistence of dysfunctional epithelial cells was also critical to fibrosis, as a "senolytic" cocktail of dastinib and quercetin decreased the numbers of Sin3a-LOF cells and protected mice from fibrosis.

The transcriptional and functional phenotype of Sin3a-LOF cells has strong similarities to that of a recently described transient population of progenitor cells that emerges after various injuries, including bleomycin exposure, diphtheria toxin ablation, and
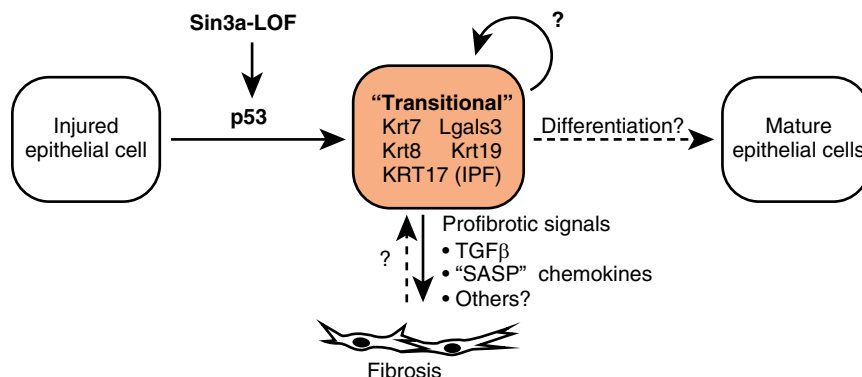
Figure 1. Model for Sin3a loss of function–induced fibrosis and outstanding questions. IPF = idiopathic pulmonary fibrosis; LOF = loss of function; SASP = senescence-associated secretory phenotype.

LPS (2–6). In IPF lungs, KRT17$^+$ cells are probably an analogous population (3, 7). In mice, these cells can be derived from airway or AT2 cells and have the capacity to differentiate into mature AT1 and AT2 cells. The progenitor cells, like Sin3a-LOF cells, are hypoproliferative, and their gene expression phenotype includes upregulation of the p53, TGFβ, hypoxia, and senescence-associated pathways. Sin3a-LOF cells, like these recently described progenitors, upregulate *Krt7*, *Krt8*, *Krt19*, and *Lgals3*, which selectively mark and perhaps contribute (5) to the transient progenitor cell state.

These studies suggest a model in which epithelial cells normally respond to severe injury by entering a transitional state characterized by the activation of pathways often described as pathological. These pathways could actually be homeostatic if injured epithelial cells must transition through this state before then committing to a tissue repair program and differentiating into mature epithelial cells. In this view, pathology would arise when cells get "stuck in a moment"—the transitional state—and cannot get out of it, thereby impairing normal differentiation and repair (Figure 1).

If the Sin3a-LOF cellular phenotype is indeed congruent with the transitional progenitor cell state, then the Sin3a model would be a uniquely valuable model to study the intrinsic signals that instruct epithelial progenitor cells to abnormally remain trapped in the transitional state and the consequences of this entrapment. Sin3a-LOF–induced p53 activation has particular relevance to IPF because a substantial proportion of familial IPF probands have mutations that map to telomerase pathway genes, with attendant activation of DNA damage signaling (8, 9). Telomere maintenance defects may be common in sporadic IPF as well (10). It will be interesting to see if other cell-intrinsic pathways that are activated in the transitional state and in IPF, such as the unfolded protein response (3, 11), would likewise contribute to abnormal persistence of the transitional state. Similar efforts to understand the mechanisms by which extrinsic cues contribute to induction and/or persistence of this state will also be important.

The consequences of cells persisting in the transitional state appear to be profound. Some genes upregulated in Sin3a-LOF cells and described as the "senescence-associated secretory phenotype" are actually familiar intercellular signals that are not unique to senescence. One is TGFβ1, a key activator of collagen-producing fibroblasts. Others are inflammatory chemokines that could help recruit monocyte-derived macrophages that infiltrate fibrotic regions and can, in turn, help support the proliferation and activation of fibroblasts (12, 13). Cells stuck in the transitional state are therefore key players in establishing the fibrotic niche.

To translate these findings into new treatments for pulmonary fibrosis, it will be important to characterize the pathways that physiologically induce the transitional state and those that abnormally maintain it. Therapies that prevent entry into the transitional state or eliminate such cells might also deplete the pool of progenitor cells available for lung repair. For example, Yao and colleagues show that loss of p53 function protects Sin3a-LOF mice from fibrosis by decreasing the profibrotic phenotype of Sin3a-LOF cells. Yet, loss of p53 signaling also impairs progenitor cell differentiation into mature epithelium (4). In the Sin3a-LOF model, the net effect of p53 loss of function does seem to be beneficial, as p53 knockout mice had improved mortality. Whether that is true in other models or in human disease might depend on the nature of the primary injury and perhaps the stage of disease.

It will also be important to determine whether the analogous cells in human IPF are strictly senescent in the classical sense of irreversible cell cycle arrest after stress or injury (14). Though the cells are hypoproliferative and express markers associated with senescence, this state may be reversible. If so, disrupting the signals that maintain entrapment of these epithelial cells in the transitional state could potentially ameliorate fibrosis and promote repair and regeneration at the same time. ∎

Vincent C. Auyeung, M.D., Ph.D.
Dean Sheppard, M.D.
Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine
University of California, San Francisco
San Francisco, California

ORCID IDs: 0000-0001-6273-1595 (V.C.A.); 0000-0002-6277-2036 (D.S.).

References

1. Yao C, Guan X, Carraro G, Parimon T, Liu X, Huang G, et al. Senescence of alveolar type 2 cells drives progressive pulmonary fibrosis. Am J Respir Crit Care Med 2021;203:707–717.
2. Kathiriya JJ, Brumwell AN, Jackson JR, Tang X, Chapman HA. Distinct airway epithelial stem cells hide among club cells but mobilize to promote alveolar regeneration. Cell Stem Cell 2020;26: 346–358, e4.
3. Strunz M, Simon LM, Ansari M, Kathiriya JJ, Angelidis I, Mayr CH, et al. Alveolar regeneration through a Krt8+ transitional stem cell state that persists in human lung fibrosis. Nat Commun 2020;11:3559.
4. Kobayashi Y, Tata A, Konkimalla A, Katsura H, Lee RF, Ou J, et al. Persistence of a regeneration-associated, transitional alveolar epithelial cell state in pulmonary fibrosis. Nat Cell Biol 2020;22: 934–946.
5. Jiang P, Gil de Rubio R, Hrycaj SM, Gurczynski SJ, Riemondy KA, Moore BB, et al. Ineffectual type 2-to-type 1 alveolar epithelial cell differentiation in idiopathic pulmonary fibrosis: persistence of the KRT8^{hi} transitional state. Am J Respir Crit Care Med 2020;201: 1443–1447.
6. Choi J, Park JE, Tsagkogeorga G, Yanagita M, Koo BK, Han N, et al. Inflammatory signals induce AT2 cell-derived damage-associated transient progenitors that mediate alveolar regeneration. Cell Stem Cell 2020;27:366–382, e7.
7. Habermann AC, Gutierrez AJ, Bui LT, Yahn SL, Winters NI, Calvi CL, et al. Single-cell RNA sequencing reveals profibrotic roles of distinct epithelial and mesenchymal lineages in pulmonary fibrosis. Sci Adv 2020;6:a1972.
8. Armanios MY, Chen JJL, Cogan JD, Alder JK, Ingersoll RG, Markin C, et al. Telomerase mutations in families with idiopathic pulmonary fibrosis. N Engl J Med 2007;356:1317–1326.
9. Tsakiri KD, Cronkhite JT, Kuan PJ, Xing C, Raghu G, Weissler JC, et al. Adult-onset pulmonary fibrosis caused by mutations in telomerase. Proc Natl Acad Sci USA 2007;104:7552–7557.
10. Alder JK, Chen JJL, Lancaster L, Danoff S, Su SC, Cogan JD, et al. Short telomeres are a risk factor for idiopathic pulmonary fibrosis. Proc Natl Acad Sci USA 2008;105:13051–13056.
11. Korfei M, Ruppert C, Mahavadi P, Henneke I, Markart P, Koch M, et al. Epithelial endoplasmic reticulum stress and apoptosis in sporadic idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2008;178: 838–846.
12. Misharin AV, Morales-Nebreda L, Reyfman PA, Cuda CM, Walter JM, McQuattie-Pimentel AC, et al. Monocyte-derived alveolar macrophages drive lung fibrosis and persist in the lung over the life span. J Exp Med 2017;214:2387–2404.
13. Satoh T, Nakagawa K, Sugihara F, Kuwahara R, Ashihara M, Yamane F, et al. Identification of an atypical monocyte and committed progenitor involved in fibrosis. Nature 2017;541:96–101.
14. Sharpless NE, Sherr CJ. Forging a signature of in vivo senescence. Nat Rev Cancer 2015;15:397–408.

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Predicting Behavioral Problems from Sleep-disordered Breathing Trajectories
Not an Easy Game

Ever since the initial observations of the association between sleep-disordered breathing (SDB) and its negative effect on academic and behavioral functioning in children, the identification of those children at higher risk of being adversely affected, without subjecting them to tedious, time-consuming, laborious, and realistically unimplementable batteries of neuropsychological testing, has been an aspiration among pediatric sleep clinicians.

The seminal observation that the negative effects of SDB on academic performance, with proper early detection and treatment, could pause or reverse (1) otherwise further reinforces the necessity of screening children routinely to obtain clinical elements, which can predict the risk (2–6). The increased awareness in recent years by both the public and health practitioners of the relatively elevated prevalence of SDB during childhood has accentuated the pressing need for early diagnosis and detecting children at higher risk.

Despite such increased awareness, overnight polysomnography remains the gold standard for the diagnosis and severity delineation of SDB. However, current analytical methods used for evaluation of the polysomnogram do not provide any insights as to the downstream adverse consequences of the underlying perturbations associated with it. Furthermore, pediatric sleep laboratories are relatively scarce, leading to long waiting times, which in turn promote the likelihood of many children either going undiagnosed or waiting too long to be diagnosed. Under such circumstances, a significant proportion of children who were considered for treatment and even prescribed psychostimulants based on "behavioral difficulties" could have benefited from polysomnogram assessment and consequent intervention. In parallel with the incremental experience accumulated through several decades, the quest for a well-designed, universally validated, and widely applicable screening tool that can accurately, and as early as possible, identify the most behaviorally vulnerable snoring children, those who are at risk of developing cognitive and behavioral problems associated with SDB, has been a primary line of investigative efforts (7–9). Among the multitude of studies focused on this issue, some initial reports proposed that the temporal trajectory of SDB-related symptoms may reveal susceptibility to behavioral morbidity, though the topic was not assertively tested.

Using a trajectory analysis method, van Eeden and colleagues (pp. 718–725) examined the behavioral outcomes of children in relation to their SDB symptoms over the first 5 years of life in this issue of the Journal (10). The longitudinal dataset consisted of the periodic assessments performed using the 22-item Sleep Related