

New Applications of Old Drugs as Novel Therapies in Idiopathic Pulmonary Fibrosis

Metformin, Hydroxychloroquine, and Thyroid Hormone

Edward P. Manning, Ashley Losier, Nkiruka Emeagwali, Changwan Ryu*, and Shyoko Honiden*

Section of Pulmonary, Critical Care, and Sleep Medicine, Yale University School of Medicine, New Haven, Connecticut

Recommended Reading from Yale University Pulmonary and Critical Care Medicine Fellows; Shyoko Honiden, M.D., M.Sc., Fellowship Program Director

The current paradigm of the pathogenesis of idiopathic pulmonary fibrosis (IPF) indicates that persistent injury to alveolar epithelial cells (AECs) results in the activation of α SMA (α -smooth muscle actin)-expressing myofibroblasts (1). Although no single mouse model fully recapitulates the human IPF disease state, the bleomycin-induced lung injury model remains the most widely accepted method of translational research despite its limitations, which include a paucity of histological findings of usual interstitial pneumonia and the lack of collagen cross-linking, resulting in reversible fibrosis (2, 3). Therapies that reverse pulmonary fibrosis remain elusive and represent a significant, unmet clinical need; we present three novel studies that highlight recent developments in IPF translational research that forges a path for an innovative approach in treating IPF through the novel application of three well-known drugs. ■

References

1. American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2002; 165:277–304. [Published erratum appears in *Am J Respir Crit Care Med* 166:426.]
2. Herzog EL, Mathur A, Tager AM, Feghali-Bostwick C, Schneider F, Varga J. Review: interstitial lung disease associated with systemic sclerosis and idiopathic pulmonary fibrosis: how similar and distinct? *Arthritis Rheumatol* 2014;66:1967–1978.
3. Blackwell TS, Tager AM, Borok Z, Moore BB, Schwartz DA, Anstrom KJ, et al. Future directions in idiopathic pulmonary fibrosis research: an NHLBI workshop report. *Am J Respir Crit Care Med* 2014;189: 214–222.

Rangarajan S, et al. Metformin Reverses Established Lung Fibrosis in a Bleomycin Model. *Nat Med* (4)

Reviewed by Edward P. Manning

In their groundbreaking work, Rangarajan and colleagues (4) found that reduced activity of AMPK (AMP-activated protein kinase), a known regulator of cellular bioenergetics, is associated with pulmonary fibrosis. After finding decreased AMPK activity in regions of fibrotic human lungs, they examined fibroblasts obtained from these IPF lungs, which displayed reduced AMPK activity that was accompanied by mTOR (mammalian target of rapamycin) activation (which promotes cell growth and proliferation), lactic acid production (an indicator of enhanced glycolysis), and extracellular matrix protein synthesis. Furthermore, activating AMPK in fibroblasts decreased expression of profibrotic genes, including type I collagen, fibronectin, and α SMA, whereas silencing AMPK resulted in increases in their expression.

Subsequently, the authors hypothesized that pharmacologic AMPK activation with metformin could have antifibrotic effects in the setting of pulmonary fibrosis. Among bleomycin-exposed mice, treatment with metformin significantly reduced expression of multiple profibrotic proteins and restored mitochondrial biogenesis, which accelerated the resolution of lung fibrosis. In demonstrating an antifibrotic mechanism via AMPK activation, they are the first to describe the potential for metformin, a well-chronicled drug in the treatment of diabetes, as a new therapy for IPF. Even more exciting is the possibility that this may truly reverse pulmonary fibrosis—currently available drugs only slow disease progression (5).

(Received in original form September 18, 2018; accepted in final form February 27, 2019)

*These authors contributed equally to this work.

Supported by NIH grants T32HL007778 (E.P.M.) and T32HL007778 (N.E.), and by grants from the Parker B. Foundation and the Foundation for Sarcoidosis Research (C.R.).

Author Contributions: E.P.M. reviewed article #1; A.L. reviewed article #2; N.E. reviewed article #3; C.R. provided expertise in idiopathic pulmonary fibrosis translational research, conceived of the review topic, and critically revised the reviews; and S.H. conceived of the review topic and critically revised the reviews.

Correspondence and requests for reprints should be addressed to Shyoko Honiden, M.D., M.Sc., Section of Pulmonary, Critical Care and Sleep Medicine, Yale University School of Medicine, 333 Cedar Street, P.O. Box 208057, New Haven, CT 06520. E-mail: shyoko.honiden@yale.edu.

Am J Respir Crit Care Med Vol 199, Iss 12, pp 1561–1563, Jun 15, 2019

Copyright © 2019 by the American Thoracic Society

Originally Published in Press as DOI: 10.1164/rccm.201809-1700RR on March 1, 2019

Internet address: www.atsjournals.org

Unfortunately, successful therapies in animal models of lung injury have not been particularly efficacious in human studies (6). Although recent work failed to show any significant benefit of metformin usage in IPF (7), it may be possible that AMPK activation is only relevant to certain IPF phenotypes; biomarker studies have demonstrated the heterogeneity of IPF, especially regarding disease pathogenesis and treatment response (8). Incorporating biomarkers in drug development has been an integral component of recent IPF clinical trials (9, 10), and this personalized medicine approach will be instrumental in translating these findings from the bench to the bedside. Drug delivery is another important consideration, as metformin has been traditionally used to treat a systemic illness, whereas IPF is a localized disease; optimizing drug concentrations in the lung, as well as understanding its safety and tolerability as formulated for treating IPF, will require rigorous investigation before proceeding to human studies. Nonetheless, Rangarajan and colleagues provide an exciting rationale for additional translational and clinical investigation for metformin as a potentially novel therapy in IPF. ■

References

- Rangarajan S, Bone NB, Zmijewska AA, Jiang S, Park DW, Bernard K, et al. Metformin reverses established lung fibrosis in a bleomycin model. *Nat Med* 2018;24:1121–1127. [Published erratum appears in *Nat Med* 24:1627.]
- Gan Y, Herzog EL, Gomer RH. Pirfenidone treatment of idiopathic pulmonary fibrosis. *Ther Clin Risk Manag* 2011;7:39–47.
- Kolb M, Bonella F, Wollin L. Therapeutic targets in idiopathic pulmonary fibrosis. *Respir Med* 2017;131:49–57.
- Spagnolo P, Kreuter M, Maher TM, Wuyts W, Bonella F, Corte TJ, et al. Metformin does not affect clinically relevant outcomes in patients with idiopathic pulmonary fibrosis. *Respiration* 2018;96:314–322.
- Guiot J, Moermans C, Henket M, Corhay JL, Louis R. Blood biomarkers in idiopathic pulmonary fibrosis. *Hai* 2017;195:273–280.
- Raghu G, van den Blink B, Hamblin MJ, Brown AW, Golden JA, Ho LA, et al. Effect of recombinant human pentraxin 2 vs placebo on change in forced vital capacity in patients with idiopathic pulmonary fibrosis: a randomized clinical trial. *JAMA* 2018;319:2299–2307.
- Maher TM, van der Aar EM, Van de Steen O, Allamassey L, Desrivot J, Dupont S, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of GLPG1690, a novel autotaxin inhibitor, to treat idiopathic pulmonary fibrosis (FLORA): a phase 2a randomised placebo-controlled trial. *Lancet Respir Med* 2018;6:627–635.

Liu L, et al. Cholesterol-modified Hydroxychloroquine-loaded Nanocarriers in Bleomycin-induced Pulmonary Fibrosis. *Sci Rep* (11)

Reviewed by Ashley Losier

Hydroxychloroquine (HCQ), first described for the treatment of malaria and currently for autoimmune disease (12), has shown promise as an antifibrotic agent. Studies in fibrotic skin disease have demonstrated its ability to inhibit fibroblast activation (13), and recently, HCQ has been shown to slow progression in childhood interstitial lung disease (14). Liu and colleagues (11) have proposed a novel agent consisting of cholesterol-modified HCQ (Chol-HCQ)

as a potential therapy for pulmonary fibrosis; cholesterol modification allows for membrane anchoring, which enhances medication half-life, decreases dosages, and limits toxic effects.

The authors successfully synthesized Chol-HCQ-loaded liposomes as nanocarriers that were intravenously administered to bleomycin-exposed rats, which suppressed lung fibroblast proliferation by inhibiting Nf-κB and ERK1/2 signaling pathways. Inflammation was also decreased in these rats treated with Chol-HCQ, as their lungs exhibited significantly less neutrophilic infiltration. More excitingly, Chol-HCQ robustly reduced the amount of lung fibrosis by inhibiting expression of CTGF (connective tissue growth factor) and ERK1/2 signaling. Moreover, Chol-HCQ led to reduced expression of TNF-α, a cytokine associated with highly progressive pulmonary fibrosis, in the lung macrophages and plasma. Finally, serologic and pathologic analyses revealed no obvious organ toxicities associated with Chol-HCQ.

Through innovation in drug delivery, Liu and colleagues are the first to report the mechanistic antifibrotic effects of HCQ in the lung. More importantly, this work provides the needed framework for further investigation of Chol-HCQ in human studies. Both cholesterol modification (15) and nanocarriers (16) have been shown to optimize circulating concentrations of chemotherapy agents and, given extensive history of unsuccessful IPF drug trials to date (17), improvements in drug delivery will be instrumental in optimizing drug efficacy. Thus, combining cholesterol modification with nanocarriers provides a new direction, which is particularly relevant for HCQ given its broad therapeutic range and potential for toxic accumulation (18). Consideration of its therapeutic index, as formulated for IPF, will be an integral step toward successful human studies; such work has been reflected in recent studies on the use of HCQ for the treatment of childhood interstitial lung disease (18, 19). ■

References

- Liu L, Ren J, He Z, Men K, Mao Y, Ye T, et al. Cholesterol-modified hydroxychloroquine-loaded nanocarriers in bleomycin-induced pulmonary fibrosis. *Sci Rep* 2017;7:10737.
- Ben-Zvi I, Kivity S, Langevitz P, Shoenfeld Y. Hydroxychloroquine: from malaria to autoimmunity. *Clin Rev Allergy Immunol* 2012;42:145–153.
- Ramser B, Kokot A, Metze D, Weiss N, Luger TA, Böhm M. Hydroxychloroquine modulates metabolic activity and proliferation and induces autophagic cell death of human dermal fibroblasts. *J Invest Dermatol* 2009;129:2419–2426.
- Dinwiddie R, Sharief N, Crawford O. Idiopathic interstitial pneumonitis in children: a national survey in the United Kingdom and Ireland. *Pediatr Pulmonol* 2002;34:23–29.
- Bakker MH, Grillaud M, Wu DJ, Fransen PKH, de Hingh IH, Dankers PYW. Cholesterol modification of an anticancer drug for efficient incorporation into a supramolecular hydrogel system. *Macromol Rapid Commun* 2018;39:e1800007.
- Yang X, Grailer JJ, Pilla S, Steeber DA, Gong S. Tumor-targeting, pH-responsive, and stable unimolecular micelles as drug nanocarriers for targeted cancer therapy. *Bioconjug Chem* 2010;21:496–504.
- Spagnolo P, Maher TM. Clinical trial research in focus: why do so many clinical trials fail in IPF? *Lancet Respir Med* 2017;5:372–374.
- Braun S, Ferner M, Kronfeld K, Griesse M. Hydroxychloroquine in children with interstitial (diffuse parenchymal) lung diseases. *Pediatr Pulmonol* 2015;50:410–419.
- Kurland G, Deterding RR, Hagood JS, Young LR, Brody AS, Castile RG, et al.; American Thoracic Society Committee on Childhood Interstitial Lung Disease (chILD) and the chILD Research Network. An official American Thoracic Society clinical practice guideline:

classification, evaluation, and management of childhood interstitial lung disease in infancy. *Am J Respir Crit Care Med* 2013;188:376–394.

Yu G, et al. Thyroid Hormone Inhibits Lung Fibrosis in Mice by Improving Epithelial Mitochondrial Function. *Nat Med* (20)

Reviewed by Nkiruka Emeagwali

In their pioneering work, Yu and colleagues had previously demonstrated that type II iodothyronine deiodinase (DIO2), a thyroid hormone (TH) activator that converts the prohormone thyroxine (T4) to the active 3,5,3'-triiodothyronine (T3), was significantly expressed in IPF lungs. To further characterize this novel discovery, the authors aimed to understand the role of TH signaling in pulmonary fibrosis, including its effects on mitochondrial function. They found that the expression and enzymatic activity of DIO2 is increased in patients with IPF but negatively correlated with disease severity. They speculated that increased conversion of T4 to T3 improves the metabolic state of AECs in IPF. After finding that DIO2 knockout mice were more susceptible to bleomycin-induced lung fibrosis, they demonstrated that the fibrosis was reversible with aerosolized TH. Using the bleomycin mouse model and a genetically inducible TGF- β 1 (transforming growth factor- β 1) mouse model, they discovered that TH replacement increased survival and resolved lung fibrosis. They used aerosolized TH to minimize its systemic effects on the heart and muscle. In addition, treatment with sobetirome, a thyroid receptor agonist, significantly reduced pulmonary fibrosis in both models.

AECs in IPF lungs have been shown to have abnormal mitochondria resulting from dysregulation of autophagy (21). The authors sought to investigate if thyroid function could be implicated in the abnormalities observed with IPF in both lung bioenergetics and metabolism (22). They showed that TH played an important role in mitochondrial biogenesis and bioenergetics, and in mitochondrial-regulated apoptosis in AECs. They concluded that restoration of mitochondrial function in AECs is

important in promoting the antifibrotic phenotype that they observed. This phenotype was dependent on intact PPARGC1A and PINK1 pathways, known regulators of mitochondrial metabolism, and was associated with the suppression of the death pathways regulated by mitochondria.

TH replacement therapy and its cellular metabolic effects have been well described (23). Interestingly, there is a higher prevalence of hypothyroidism in IPF, and hypothyroidism is a predictor of IPF mortality (24). Taken together, these studies demonstrate a potential role for TH replacement as a therapeutic agent in IPF. Translating these findings into the clinical arena will require additional investigation into the use of inhaled TH in humans; although *in vitro* studies demonstrate its promise as an effective delivery mechanism (25), further understanding of its *in vivo* pharmacodynamic and pharmacokinetic properties is needed. Nonetheless, Yu and colleagues provide the translational rationale to explore the use of this well-known drug in this difficult to treat disease. ■

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

References

20. Yu G, Tzouveleakis A, Wang R, Herazo-Maya JD, Ibarra GH, Srivastava A, et al. Thyroid hormone inhibits lung fibrosis in mice by improving epithelial mitochondrial function. *Nat Med* 2018;24:39–49.
21. Bueno M, Lai YC, Romero Y, Brands J, St Croix CM, Kamga C, et al. PINK1 deficiency impairs mitochondrial homeostasis and promotes lung fibrosis. *J Clin Invest* 2015;125:521–538.
22. Ryu C, Sun H, Gulati M, Herazo-Maya JD, Chen Y, Osafo-Addo A, et al. Extracellular mitochondrial DNA is generated by fibroblasts and predicts death in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2017;196:1571–1581.
23. Wiersinga WM. Paradigm shifts in thyroid hormone replacement therapies for hypothyroidism. *Nat Rev Endocrinol* 2014;10:164–174.
24. Oldham JM, Kumar D, Lee C, Patel SB, Takahashi-Manns S, Demchuk C, et al. Thyroid disease is prevalent and predicts survival in patients with idiopathic pulmonary fibrosis. *Chest* 2015;148:692–700.
25. Agu RU, Mactavish J, K Yeung P, Imran SA. Thyroid hormone (levothyroxine) replacement via the respiratory route by inhalation: *in vitro* exploratory studies. *Expert Opin Drug Deliv* 2016;13:195–205.