JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 5, NO. 11, 2020

EDITORIAL COMMENT

SCUBE Diving

Biomarker Discovery for Pulmonary Hypertension From Bench to Bedside*

Jose Gomez-Arroyo, MD, PhD,[a] Norbert F. Voelkel, MD,[b] Antonio Abbate, MD, PhD[c]

For years biomarkers have changed the way we practice medicine by defining a diagnosis, guiding therapy, or simply monitoring a basic biological function. It is not unreasonable to say that irrespective of its function, any clinically relevant biomarker should have at least 4 critical features: it ought to be objective, quantifiable, mechanistically sound, and, most important, reproducible. Interestingly, whereas the knowledge base for pulmonary arterial hypertension (PAH) has expanded almost exponentially in the past 3 decades, few mechanistic biomarkers have fulfilled these criteria and managed to make the transition from bench to bedside. Similarly, the number of biomarkers to diagnose PAH remains limited to invasive hemodynamic parameters described more than 50 years ago, when Cournand and Ranges (1) first pioneered right heart catheterization. Many biomarker candidates have failed in their translation from rodent models to humans, have failed to become readily available clinical laboratory tools, have not been reproducible, or were simply part of a scientific fad.

The complexity of biomarker discovery is what makes the study by Sun et al. (2) in this issue of *JACC: Basic to Translational Science* a rather unique story from a translational science perspective. First, they took advantage of publicly available datasets obtained from induced pluripotent stem cell–derived bone morphogenetic protein receptor type 2 (BMPR2)–deficient human endothelial cells to look for differentially expressed genes in an unbiased manner. Among a short list of differentially expressed genes, they identified signal peptide CUB-EGF-domain containing protein 1 (SCUBE1). At the molecular level, the investigators demonstrate that silencing BMPR2 expression (simulating heterozygosity in humans) was sufficient to decrease the expression of SCUBE1 in pulmonary artery endothelial cells at the transcript and protein levels. Because not all patients with PAH will have mutations in BMPR2, they postulated that alternative triggers involved in the pathogenesis of PAH could impair SCUBE1 expression or function. Indeed, the investigators showed that increased inflammation (by means of interleukin 1-β exposure) or chronic hypoxia were sufficient to down-regulate SCUBE1 expression in a BMPR2-independent fashion. At the cellular level, silencing of SCUBE1 induced endothelial cell apoptosis, a critical "first hit" in the pathobiology of PAH (3,4). To determine the role of SCUBE1 in vivo, Sun et al. measured the tissue expression and serum levels of SCUBE1 in 3 different rodent models of PAH and confirmed low circulating levels and lung tissue expression, a finding that was not present in other models of pulmonary (*Klebsiella pneumoniae* bacterial pneumonia) or nonpulmonary (myocardial infarction) disease. As an attempt to bridge their findings toward a clinically relevant biomarker, they measured circulating levels of SCUBE1 in patients with PAH, pulmonary venous hypertension secondary to left heart

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From the [a]Division of Pulmonary and Critical Care, Department of Internal Medicine, University of Cincinnati, Cincinnati, Ohio, USA; [b]Amsterdam University Medical Centers/Vrije Universiteit Amsterdam, Department of Pulmonology, Amsterdam Cardiovascular Sciences, Amsterdam, the Netherlands, USA; and the [c]Department of Internal Medicine, Division of Cardiology, VCU Pauley Heart Center, Virginia Commonwealth University, Richmond, Virginia, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Basic to Translational Science* author instructions page.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2020.09.009

disease, and other pulmonary and nonpulmonary disease controls. In line with the data from animal models, they showed that levels of SCUBE1 were significantly lower in patients with PAH compared with healthy control subjects in serum and lung tissue samples. In addition, SCUBE1 plasma level correlated with different clinical variables of disease severity (invasive and noninvasive). Interestingly, both tissue and plasma levels of SCUBE1 were not different in patients with chronic obstructive pulmonary disease (although it is unclear whether any of these patients had associated pulmonary hypertension). Last, the investigators not only show that plasma SCUBE1 level was different between PAH and pulmonary venous hypertension but postulate that it could be used to discriminate between these 2 subtypes.

The story told by Sun et al. (2) is to be applauded for the vision and creativity to transform a single data point from a bioinformatics study to a potentially clinically relevant biomarker of disease. Nonetheless, although their study is extensive and comprehensive, many questions remain to be answered. From a biology standpoint, it is unclear what down-regulates the expression of SCUBE1 in patients with PAH. If it is indeed a systemic inflammation and/or hypoxia-inducible factor-dependent phenomenon, why would patients with acute lung injury or chronic obstructive lung disease (assuming they had chronic hypoxic respiratory failure) exhibit normal levels of SCUBE1? Most likely alternative factors drive the change in SCUBE1 expression, none of which were investigated in this study. Is SCUBE1 necessary or even sufficient to cause spontaneous PAH? Although there appears to be a strong association, the most critical experiment is missing: can genetic ablation of SCUBE1 cause pulmonary hypertension? SCUBE1-knockout mice are viable (5), but it is unclear whether they develop pathological lung vascular remodeling. And last, can replacement of SCUBE1 reverse or even prevent the development of PAH?

From a clinical standpoint, the findings need to be reproduced using samples from an external cohort of patients. Although statistically significant, a biomarker with specificity of 85% may not be robust enough to replace the gold-standard diagnostic tools for PAH. However, it will be interesting to know how its discrimination power will change when modeling with other clinically relevant parameters associated with the development of PAH, such as female sex, predisposing conditions (autoimmune disease, liver disease, human immunodeficiency virus infection), and drug exposure history (cocaine, methamphetamine).

Whether SCUBE1 will eventually become a therapeutic target for PAH or plasma levels will be used as a laboratory biomarker to diagnose or discriminate subtypes of pulmonary hypertension remains to be seen. However, one thing is clear: this study should serve as a comprehensive blueprint for researchers interested in the challenging field of biomarker discovery. In the end, anyone can choose to stay in the shallow end of the pool or to dive deep into the ocean, but should you choose the latter, as Sun et al. (2) have done, be sure to bring your vision and creativity.

AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Jose Gomez-Arroyo, Division of Pulmonary and Critical Care, Department of Internal Medicine, University of Cincinnati, 284 Goodman Street, Cincinnati, Ohio 45220. E-mail: gomezaje@ucmail.uc.edu.

REFERENCES

1. Cournand A, Ranges HA. Catheterization of the right auricle in man. Exp Biol Med (Maywood) 1941;46:462–6.

2. Sun W, Tang Y, Tai Y-Y, et al. SCUBE1 controls BMPR2-relevant pulmonary endothelial function: implications for diagnostic marker development in pulmonary arterial hypertension. J Am Coll Cardiol Basic Trans Science 2020;5:1073–92.

3. Hemnes AR, Humbert M. Pathobiology of pulmonary arterial hypertension: understanding the roads less travelled. Eur Respir Rev 2017;26:170093.

4. Voelkel NF, Gomez-Arroyo J, Abbate A, Bogaard HJ, Nicolls MR. Pathobiology of pulmonary arterial hypertension and right ventricular failure. Eur Respir J 2012;40:1555–65.

5. Tu C-F, Yan Y-T, Wu S-Y, et al. Domain and functional analysis of a novel platelet-endothelial cell surface protein, SCUBE1. J Biol Chem 2008;283:12478–88.

KEY WORDS BMPR2, endothelium, pulmonary hypertension, SCUBE1