generation could be beginning life with a smaller endowment of ancient microbes than the last (14), the present study adds the microbiome to the list of possible explanations for the gradual decrease of normal human body temperature in the past 157 years. ■

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Rare to "Ubiquitinous": Alveolar Capillary Dysplasia, FOXF1, and a Sly Approach to Angiogenesis

Originally described by Janney and colleagues in 1981 (1), alveolar capillary dysplasia (ACD) is a rare developmental lung disorder, with more than half of affected infants having other organ systems involved, including major cardiac, gastrointestinal, and genitourinary malformations (2). Clinically, the disease manifests as severe, refractory neonatal pulmonary hypertension, but, in recent years, the spectrum of disease has broadened as children presenting later with milder disease have been increasingly recognized (3). Lung pathology is characterized by a paucity of pulmonary capillaries with pulmonary veins (PVs) located within the same bronchovascular bundle as the pulmonary arteries and bronchioles (2). This abnormal localization of PVs has been referred to as misalignment of the PVs (MPVs) (4), although elegant work by Galambos and colleagues has shown that these actually represent abnormally persistent fetal anastomotic shunt vessels (5), which are observed in other lung disorders. A major advance in the study of ACD came with the identification of pathogenic variants in the gene encoding FOXF1, a transcription factor important for vascular development (6). Genic deletions, deletions of upstream regulatory elements, and single nucleotide and small insertion/deletion variants have all been recognized as causes of ACD. Even with later presentation of relatively milder cases, the prognosis remains poor, often with lung transplant as the only viable therapeutic alternative (7).

In this issue of the *Journal*, Pradhan and colleagues (pp. 1042–1054) report a new potential approach to this disorder (8). Screening a library of compounds, they identified candidates that stabilized the FOXF1 protein expression *in vitro*. In targeting FOXFI, a transcription factor, the authors effectively challenged the longstanding paradigm wherein transcription factors are not considered optimal drug targets. Through a series of elegant experiments bolstered by bioinformatic analysis, the most effective candidate compound, termed TanFe, was shown to act by preventing ubiquitin-mediated degradation of the FOXF1 protein. Treatment with TanFe not only increased FOXF1 levels in a mouse lung injury

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model induced by LPS, but increased expression of downstream FOXF1 target genes important in vascular development, decreased endothelial permeability, and inhibited lung inflammation. Superimposed on the data from the animal studies, the authors demonstrated that TanFe improved angiogenesis in vascular organoids derived from induced pluripotent stem cells from a human patient with ACD. Perhaps most remarkably, prenatal treatment of pregnant mice that were heterozygous for a deleterious FOXF1 variant with TanFe completely rescued the phenotype in affected offspring.

Although the prenatal rescue of ACD in an animal model is exciting, most infants with ACD have *de novo* FOXF1 variants without a family history and are diagnosed postnatally (9). Whether postnatal treatment with TanFe will enhance pulmonary angiogenesis sufficiently to improve the clinical course of infants with ACD is unknown. Interestingly, the induced pluripotent stem cells in this study were derived from a patient with a prenatal genetic ACD diagnosis based on abnormalities identified in other organ systems. The advent of a potential treatment for ACD represents still further motivation for more rapid and earlier genetic testing prenatally and in the acute care setting to expedite diagnosis and therapy. The decreasing cost and increasing efficiency of whole-genome sequencing is yet another reason to champion time-sensitive genetic testing for infants. Not all infants with ACD have major anomalies that might prompt genetic testing, so enhanced methods of prenatal diagnosis of ACD would be necessary to be able to offer this potential therapy prenatally.

Beyond the treatment of a very rare disorder such as ACD, the findings in this study may be more broadly applicable to neonatal lung diseases. Bronchopulmonary dysplasia (BPD), the most common complication of prematurity, is characterized by impaired pulmonary vascular development, pulmonary inflammation, and alveolar simplification. Current treatments for BPD remain limited and largely supportive. Corticosteroids improve lung function and facilitate weaning from mechanical ventilation, but do not reduce mortality rates and possess significant untoward sequelae (10). That TanFe is proangiogenic, reduces inflammation, and decreases endothelial permeability in the LPS-induced lung injury model highlights the viability of this treatment for infants with BPD. Given that lung vascular growth drives alveolar development (11), TanFe represents a novel strategy to enhance pulmonary vascular development and thereby augment postnatal alveolarization. Studies in well-accepted preclinical models of BPD such as neonatal hyperoxia-induced lung injury will be needed to provide important proof of principle. Beyond BPD, impaired pulmonary vascular development is a critical part of the pathophysiology of other neonatal and infant lung disorders, including pulmonary hypoplasia from multiple causes such as congenital diaphragmatic hernia or prolonged oligohydramnios, and lung disease associated with trisomy 21. Thus, should TanFe effectively augment vascular development and consequent alveolarization, it might represent an important new therapeutic tool to address a wide array of neonatal lung diseases.

The study by Pradhan and colleagues also reinforces the concept of treating rare diseases by augmentation of the function of residual protein. Although not directly analogous, the use of correctors has revolutionized the care of patients with cystic fibrosis. Other genetic lung developmental disorders that result from haploinsufficiency of transcription factors include those involving pathogenic variants in TBX4 and NKX2-1. Analogous approaches to reducing protein degradation may provide a pathway for treatment of the lung disease caused by those disorders.

Much more work remains to be done before treatment with TanFe can be translated to the clinic and human infants with ACD or other lung disorders, including further animal studies to better delineate potential off-target effects and potential toxicity and pharmacokinetic studies to determine optimal dosing. Indeed, FOXF1 expression is present in cells beyond the endothelium, which underscores the importance of careful interrogation for any off-target effects. The identification of a compound that inhibits degradation and thus increases functional amounts of a key transcription factor that augments pulmonary angiogenesis provides a potential path forward to treat currently incurable genetic and acquired lung developmental disorders. ■

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SOX17 at the Intersection of Sex, Transcription, and Metabolism in Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) is an incurable and devastating disease characterized by pulmonary vascular remodeling, increased pulmonary vascular resistance, and right heart failure. Genetic mutations account for 23.5% of PAH cases (1). Among known mutations, there is considerable genetic heterogeneity from a diverse collection of rare heterozygous coding-region mutations. One such genetic mutation affects SOX17 (SRY-related HMG-box17) (1). SOX17 is a key endothelial-specific transcription factor involved in angiogenesis (2), induction of tip cell differentiation (3), arteriovenous differentiation (4), and pulmonary endothelial regeneration following vascular injury (5). PAH secondary to deleterious SOX17 variants is associated with congenital heart disease (6) and clinically presents with severe hemodynamic derangements (mean pulmonary arterial pressure of 67 mm Hg and pulmonary vascular resistance of 14.0 Wood units) (7).

Recently, a common genetic variant in the enhancer region of SOX17 was found through a genome-wide association study in an international cohort of patients with PAH (8). This discovery raised the question of the contribution of SOX17 as a risk allele for PAH.

In this issue of the *Journal*, Sangam and colleagues (pp. 1055–1069) proposed that SOX17 deficiency promotes PAH through interactions with hypoxia-inducible factor 2α (HIF2α) and estrogen pathways, as well as dysfunctional mitochondrial metabolism (9). The authors first noted decreased endothelial-specific SOX17 expression in human pulmonary artery endothelial cells isolated from patients with PAH and in rats with chronic hypoxia-induced pulmonary hypertension (PH) and monocrotaline PH. Using an inducible conditional Tie2-Sox17 knockout murine model, the authors found that exposure of Sox17-deficient mice to hypoxia resulted in pulmonary vascular remodeling, increased right-sided pressure, and right ventricular hypertrophy. Conversely, Sox17-transgenic overexpression in mice attenuated hypoxic PH development. Next, the authors demonstrated that Sox17 serves a protective function in the regulation of HIF2α expression and subsequent promotion of normal mitochondrial function in Sox17-deficient mice. *In vitro* studies of SOX17 adenovirus-facilitated overexpression in pulmonary artery endothelial cells resulted in enhanced mitochondrial bioenergetics with increased trichloroacetic acid cycle intermediates. This effect, however, was reversed by the concurrent overexpression of SOX17 and HIF2α. As such, this study adds to the existing body of literature on the pivotal role of HIF2α signaling in PH (a comprehensive review on this topic is provided by Pullamsetti and colleagues [10]). Further work is needed to fully elucidate the mechanism between SOX17 and endothelial HIF2α.

Finally, the authors explored the role of estrogen-mediated transcriptional regulation of SOX17 in murine models. Through *in vitro* and *in vivo* approaches, the authors found an inverse relationship between estrogen metabolite 16αOHE and SOX17 levels in PAH. However, Sox17 only partially attenuated 16αOHE-mediated murine PH, suggesting additional mechanisms in estrogen-mediated PH. Nevertheless, these studies implicate SOX17-mediated sex-dependent differences in PAH susceptibility. On the basis of these current findings, Sangam and colleagues were able to postulate a new link between SOX17 and estrogen-mitochondrial function.

The elegant studies by Sangam and colleagues contribute new knowledge on how estrogen and its metabolites affect SOX17-deficient PAH. Their findings have larger implications given the "estrogen paradox" of PAH whereby sex affects disease penetrance, presentation, progression, and mortality (11). Further work, however, is required to fully elucidate the mechanisms contributing to the pathogenesis of PAH secondary to SOX17. This task is challenging given the limitations in the use of experimental animal models and the difficulties in recapitulating complex human diseases. Moreover, the regulation of SOX17 activity is complex, as SOX17 interacts with transcriptional targets involved in multiple signaling pathways of clinical relevance to PAH, including Notch, TGF-β, Wnt/β-catenin, and HGF/c-Met signaling pathways (12, 13). In tackling this challenge, studies such as the one performed by Sangam and colleagues offer new insights into the molecular pathways underlying genetic variants and illustrate the importance of common genetic variants as potential new therapeutic targets. ■

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